

Table 23: Summary of Plasma Pharmacokinetic Parameters (Safety Analysis Set – SDD Suspension Group)

	Compound of Formula (I) Plasma Concentration		
Parameter (units) Statistic	Reference Capsule (Fed) (N=18)	SDD Suspension (Fed) (N=18)	SDD Suspension (Fasted) (N=18)
AUC_{0-last} (ng×hr/mL)			
Mean (SD)	16600 (7880)	5980 (3960)	737 (417)
Geom CV(%)	46.8	72.8	68.7
AUC_{0-∞} (ng×hr/mL)			
Mean	17400 (8010)	6500 (4180)	893 (480)
Geom CV(%)	45.4	71.7	60.1
C_{max} (ng/mL)			
Mean (SD)	1480 (506)	672 (323)	72.3 (44.9)
Geom CV(%)	32.1	57.9	57.5
t_{max} (hr)			
Median (min,max)	5.0 (3.0, 6.0)	5.0 (5.0, 10)	7.0 (5.0, 12)
T_{lag} (hr)			
Mean (SD)	1.0 (0.31)	0.85 (0.29)	1.2 (0.65)
t_{1/2} (hr)			
Mean (SD)	50 (20)	19 (6.1)	9.0 (0.46)
Geom CV(%)	140	93	23
MRT (hr)			
Mean (SD)	36 (43)	23 (24)	17 (2.9)
Geom CV(%)	84	62	18
CL/F (L/hr)			
Mean (SD)	3.4 (1.4)	11 (8.0)	80 (54)
Geom CV(%)	45	72	63
V_z/F (L)			
Mean (SD)	180 (260)	210 (140)	970 (560)
Geom CV(%)	93	77	53
T_{last} (hr)			

Mean (SD)	170 (140)	77 (110)	31 (7.6)
Geom CV(%)	120	92	30

Table 24: Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by formulation and fed vs fasted (Safety Analysis Set – SDD Suspension Group)

Analyte Parameter (units)	Treatment Comparison	Ratio (%)	90% CI
Compound of Formula (I)			
AUC _{0-tlast} (ng×hr/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	32.2	(26.4%, 39.4%)
AUC _{0-∞} (ng×hr/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	33.5	(27.7%, 40.6%)
C _{max} (ng/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	42.2	(34.8%, 51.2%)
AUC _{0-tlast} (ng×hr/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	4.4	(3.4%, 5.7%)
AUC _{0-∞} (ng×hr/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	5.0	(3.8%, 6.5%)
C _{max} (ng/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	4.5	(3.8%, 5.4%)

5 **Table 25: Summary of Plasma Pharmacokinetic Parameters (Safety Analysis Set – SDD Capsule Group)**

	Compound of Formula (I) Plasma Concentration		
Parameter (units) Statistic	Reference Capsule (Fed) (N=18)	SDD Capsule (Fed) (N=18)	SDD Capsule (Fasted) (N=17)
AUC_{0-tlast} (ng×hr/mL)			
Mean (SD)	19500 (7960)	9470 (4670)	1840 (1650)
Geom CV(%)	50.4	48.0	78.7
AUC_{0-∞} (ng×hr/mL)			
Mean	20100 (7850)	10000 (4610)	2120 (1830)
Geom CV(%)	47.1	44.9	73.7
C_{max} (ng/mL)			
Mean (SD)	1770 (494)	1110 (449)	143 (110)

Geom CV(%)	25.7	44.5	74.1
t_{max} (hr)			
Median (min,max)	5.0 (5.0, 8.0)	5.0 (3.0, 6.0)	7.0 (6.0, 12)
T_{lag} (hr)			
Mean (SD)	1.0 (0.38)	1.3 (0.49)	1.2 (0.88)
t_½ (hr)			
Mean (SD)	35 (18)	26 (20)	14 (11)
Geom CV(%)	69	98	49
MRT (hr)			
Mean (SD)	28 (12)	25 (14)	21 (9.2)
Geom CV(%)	45	55	31
CL/F (L/hr)			
Mean (SD)	3.0 (1.5)	5.9 (2.4)	36 (18)
Geom CV(%)	47	45	74
V_z/F (L)			
Mean (SD)	130 (61)	190 (140)	630 (380)
Geom CV(%)	47	75	72
T_{last} (hr)			
Mean (SD)	170 (96)	100 (89)	44 (32)
Geom CV(%)	91	100	39

Table 26: Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by formulation and fed vs fasted (Safety Analysis Set – SDD Suspension Group)

Analyte Parameter (units)	Treatment Comparison	Ratio (%)	90% CI
Compound of Formula (I)			
AUC _{0-tlast} (ng×hr/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	48.2	(41.4%, 56.1%)
AUC _{0-∞} (ng×hr/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	49.7	(43.1%, 57.2%)
C _{max} (ng/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	59.8	(51.7%, 69.2%)
AUC _{0-tlast} (ng×hr/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	8.0	(5.7%, 11.2%)
AUC _{0-∞} (ng×hr/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	9.0	(6.6%, 12.4%)
C _{max} (ng/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	6.7	(4.9%, 9.2%)

Example 8: Phase 2 study of the compound of Formula (I) in adult subjects with congenital adrenal hyperplasia

A Phase 2 study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of the compound of Formula (I) in adult subjects with classic congenital adrenal hyperplasia (CAH) was designed. The objectives of the study are: to assess the safety and tolerability of two ascending doses of the compound of Formula (I) in adult subjects with CAH; to evaluate the effect of repeated doses of the compound of Formula (I) on endogenous levels of PD biomarkers in adult subjects with CAH; and to evaluate plasma exposures following repeated doses of the compound of Formula (I) administered nightly.

The lower dose strength selected for this study, the compound of Formula (I) 50 mg, was well tolerated in both single and repeat-dose safety and PK studies in healthy volunteers. Doses up to 100 mg were also well tolerated in both single-dose and repeat-dose Phase 1 studies in healthy volunteers, and importantly, in a large Phase 2 study in non-elderly female and male subjects with major depressive disorder receiving the compound of Formula (I) during an 8-week, double-blind treatment period. Furthermore, the anticipated steady state exposures with the selected the compound of Formula (I) doses, using the predicted C_{max} and AUC, are within the acceptable safety margins defined by the nonclinical toxicology studies that have been conducted to date.

Study Design

A Phase 2, open-label, multiple-dose, dose-escalation study to assess the safety, tolerability, PK, and PD of the compound of Formula (I) in approximately 30 adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH was designed. The study will include a sequential-cohort design with four compound of Formula (I) dose cohorts: 50 mg and 100 mg, with each dose administered for 14 consecutive days:

- Cohort 1: compound of Formula (I) 50 mg once daily with a bottle of vanilla-flavored Ensure Plus® (~237 mL) at approximately 2200 hours.
- Cohort 2: compound of Formula (I) 100 mg once daily with a bottle of vanilla-flavored Ensure Plus® (~237 mL) at approximately 2200 hours.
- Cohort 3: compound of Formula (I) 100 mg once daily with the evening meal at approximately 1900 hours.
- Cohort 4: compound of Formula (I) 100 mg twice daily with breakfast at approximately 0700 hours and with the evening meal at approximately 1900 hours.

There will be an approximate 2-week period to evaluate safety and tolerability data before proceeding from Cohort 1 to Cohort 2. Subjects who previously completed the current study in Cohort 1 or Cohort 2 may reenroll to participate in Cohorts 3 or 4 (in addition to new subjects). Table 27 below depicts the dose cohorts, doses, and number of subjects per cohort.

Table 27. Dose cohorts, doses, and number of subjects

Cohort	Compound of Formula (I) Dose	Approximate Dosing Time(s)	Number of Subjects
1	50 mg	2200 hours	8-10
2	100 mg	2200 hours	8-10
3	100 mg	1900 hours	8-10
4	100 mg	0700 and 1900 hours	Up to 8

Subjects will be screened for eligibility to participate in the study for up to approximately 3 weeks (Days -28 to -8). Subjects who reenroll and have had a stable medication regimen for CAH since their last visit in this study do not have to undergo screening; those who reenroll and have had a change to their medication regimen for CAH must undergo a second screening visit. During screening, subjects will provide a single blood

sample in the morning between 0700 and 1000 hours (prior to first morning dose of hydrocortisone) to determine their 17-hydroxyprogesterone (17-OHP) levels for study entry.

Eligible subjects who have a screening 17-OHP level $\geq 1,000$ ng/dL will be admitted to the study center for 1 night and have baseline serial PD samples collected over a 24-hour period beginning in the evening of Day -7. Baseline serial PD samples will be collected at approximately 2145, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, and 2200 hours. The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

Subjects within each dose cohort will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for CYP21A2 genotyping. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. Study drug (the compound of Formula (I) 50 or 100 mg) will be administered at approximately 2200 hours for Cohorts 1 and 2 and at approximately 1845, 2000, 2100, 2200, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1800, 1900, and 2200 hours for Cohorts 3 and 4. The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

Subjects in Cohorts 1 and 2 will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for cytochrome P450 (CYP) 21A2 genotyping. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. Study drug (compound of Formula(I) 50 mg or 100 mg) will be administered at approximately 2200 hours. The subjects' usual morning dose of concurrent steroidal treatments will be administered after the 12-hour post-dose PK/PD samples are collected (at approximately 1000 hours) on Day 2 and after the 16-hour post-dose PK/PD samples are collected (at approximately 1400 hours) on Day 15. Subjects will be discharged from the study center the evening on Days 2 and 15 following completion of all study-related procedures for those days. Prior to this discharge on Day 2, study drug will be administered at the study center at approximately 2200 hours. Study drug will then be self-administered nightly at home at approximately 2200 hours on Days 3 to 13. Subjects will take their usual morning dose of concurrent steroidal treatments at approximately 1000 hours on Days 3 to 14. On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center.

Subjects in Cohorts 3 and 4 will have a blood sample collected on Day 1 for CYP21A2 genotyping (only for subjects who have not previously participated in Cohorts 1 or 2). Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. For Cohort 3, study drug (compound of Formula(I) 100 mg) will be administered at home on Days 1 to 13 at approximately 1900 hours with each subject's evening meal. For Cohort 4, study drug compound of Formula(I) 100 mg) will be administered at home on Days 2 to 14 at approximately 0700 hours with each subject's breakfast and on Days 1 to 13 at approximately 1900 hours with each subjects' evening meal. For both cohorts, the Day 14 evening dose will be administered at the study site. Subjects will take their usual morning dose of concurrent steroidal treatments at approximately 1000 hours on Days 1 to 14. On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center. Subjects will be admitted to the study center on Day 14 (last day of dosing). On Day 14, subjects will receive study drug in the study center at approximately 1900 hours with a standard (moderate fat/moderate caloric) evening meal. The subjects' usual morning dose of concurrent steroidal treatments will be administered after PK/PD samples are collected at approximately 1400 hours on Day 15. Subjects will be discharged from the study center the evening on Day 15 following completion of all study-related procedures.

For all cohorts, follow-up visits on Days 21, 28, and 35 will be conducted at the study center or the subject's home by a qualified home healthcare provider (based on the subject's preference). A final study visit will be conducted at the study site approximately 5 weeks after the last dose of study drug (on Day 49 or early termination). There will be a visit window of -8 hours for Day 7, -8 hours/+3 days for Days 21, 28, and 35, and +7 days for the final study visit. Safety, tolerability, PK, and PD will be assessed at scheduled times throughout the study. The study design schematic is shown in FIG. 11.

Dose escalation procedure

Cohort 1 will consist of approximately 8 to 10 subjects who will receive a daily dose of the compound of Formula (I) 50 mg at approximately 2200 hours for 14 days (subjects will receive study drug at the site on Days 1, 2, and 14, and self-administer study drug at home on Days 3 to 13). Following the completion of Day 15 assessments for all subjects in the Cohort 1, a medical monitor will review the accumulated safety and tolerability results to ensure there are no safety concerns with proceeding to the 100 mg dose (Cohorts 2 and 3), and to determine if a maximum tolerated dose (MTD) has been reached. If the MTD is reached, no

dose escalation will occur. There will be an approximate 2-week period between Cohorts 1 and 2 to accommodate this safety review. A similar procedure will be used prior to proceeding to the 100 mg twice daily dose (Cohort 4).

If the medical monitor determines that it is safe to proceed to the compound of Formula (I) 100 mg, subjects in Cohort 2 will be administered the compound of Formula (I) 100 mg daily for 14 days. Dosing for Cohorts 3 and 4 may begin simultaneously with Cohort 2.

During the 14-day dosing period for any cohort, dosing may be postponed or halted if one or more subjects experience a severe or serious adverse event (AE), or if the type, frequency, or severity of AEs becomes unacceptable. If dosing is postponed, the medical monitor will review all available safety, tolerability, and PK data before allowing any further subjects to receive study drug.

Study Population

Approximately 30 adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH, who meet all protocol eligibility criteria, will be enrolled. Subjects who previously completed the current study in Cohort 1 or Cohort 2 may reenroll to participate in Cohorts 3 or 4 (in addition to new subjects).

Duration of treatment

The expected duration of study participation for each subject is approximately 11 weeks, including up to approximately 3 weeks for screening, a 24-hour PD baseline period (approximately 7 days prior to the first day of dosing), 14 days of dosing, and a follow-up period of approximately 5 weeks. The total duration of the study will be an additional 8 to 11 weeks for subjects who reenroll.

Test product, dose, and mode of administration

The compound of Formula (I) will be supplied as capsules containing 50 mg of the compound of Formula (I) free base for oral administration (see, e.g., Reference 1 formulation as described in Example 9). Doses of the compound of Formula (I) are 50 mg and 100 mg, administered in oral capsule form. Each dose of study drug for Cohorts 1 and 2 is to be administered with a bottle of vanilla-flavored Ensure Plus® (~237 mL). Each dose of study drug for Cohort 3 is to be administered with each subject's evening meal at approximately 1900 hours. Each dose of study drug for Cohort 4 is to be administered with each subject's breakfast at approximately 1900 hours (i.e., a total daily dose of 200 mg).

Criteria for Evaluation

Cohorts 1 and 2

Blood samples to evaluate 24-hour PD baseline will be collected on Days -7 to -6 at approximately 2145, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, and 2200 hours. Blood samples to evaluate PK and PD parameters of the compound of Formula (I) will be collected on Days 1 to 2 and Days 14 to 15 at: 15 minutes pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours post-dose; Day 7 (at approximately 24 hours post-dose); Days 21, 28, and 35 (at approximately 168, 336, and 504 hours post-dose); and at the final study visit (Day 49 or early termination).

Cohorts 3 and 4

Blood samples to evaluate 24-hour PD baseline will be collected on Days -7 to -6 at approximately 1845, 2000, 2100, 2200, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1800, 1900, and 2200 hours. Blood samples to evaluate PK and PD parameters of the compound of Formula (I) will be collected on Days 14 to 15 at the following times (for Cohort 4, all times are relative to evening dosing unless otherwise indicated): 15 minutes predose and at 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 17, 19, 23, 24, and 27 hours postdose; Day 7 (at 24 hours postdose for Cohort 3 or at 12 hours post morning dose but prior to the evening dose for Cohort 4); Days 21, 28, and 35 (at approximately 168, 336, and 504 hours postdose); and at the final study visit (Day 49 or early termination).

Pharmacokinetics

The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0-t_{last}}$)
- Area under the plasma concentration versus time curve from 0 to 24 hours (AUC_{0-24})
- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Terminal half-life ($t_{1/2}$)
- Apparent terminal rate constant (λ_z)

- Apparent mean residence time (MRT)

Additional PK parameters for Day 14 only:

- Average plasma concentration at steady state (C_{avg})
- Percent fluctuation at steady state (% fluctuation)
- Accumulation index at steady state
- Apparent systemic clearance after oral administration (CL/F) (the compound of Formula (I) only)

Pharmacodynamics

Primary: Morning 17-OHP (serum; ng/dL) from the 0600, 0800, and 1000 hour samples (8-, 10-, and 12-hour post-dose samples from Cohorts 1 and 2 and 11-, 13-, and 15-hour postdose samples from Cohorts 3 and 4.

Secondary: 17-OHP at all other times, androstenedione (serum; ng/dL), testosterone (serum; ng/dL), cortisol (serum; μ g/dL), and adrenocorticotrophic hormone (plasma ACTH; pg/mL).

Safety

Safety and tolerability will be monitored throughout the study and will include the following assessments:

- Adverse events
- Clinical laboratory tests - clinical chemistry (including creatine kinase, myoglobin, total and conjugated bilirubin), hematology, coagulation (prothrombin time, aPTT, d-dimer, fibrinogen), and urinalysis (including quantitative myoglobin, casts and crystals)
- Vital signs
- Physical examinations (including musculoskeletal exam)
- 12-lead electrocardiograms (ECGs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Brief Psychiatric Rating Scale (BPRS)

Statistical methods

Safety, PK, and PD variables will be summarized within each dose cohort (the compound of Formula (I) 50 mg and 100 mg) using descriptive statistics. Summaries of PD measures will include both observed values and changes from pre-dose.

Results

Pharmacokinetic results

Eight subjects (four female and four male) were enrolled in this study and completed Cohort 1. Age, sex, and BMI information for the study participants is shown in Table 28, below.

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Table 28. Cohort 1 Subjects

Subject ID	Age (years)	Sex (Male/Female)	BMI (kg/m ²)
001	37	Female	24.9
002	25	Female	32.0
003	49	Male	37.2
004	36	Male	25.0
005	27	Female	25.5
006	19	Male	21.7
007	25	Male	27.5
008	31	Female	34.4

The subjects received a daily dose of the compound of Formula (I) at 50 mg at approximately 2200 hours (~10 p.m. or bedtime) for 14 days. Arithmetic mean values for ACTH (FIG. 12A) and 17-OHP (FIG. 12B) for all 8 Cohort 1 subjects were plotted at each timepoint for Pre-treatment Baseline, Day 1, and Day 14. Both ACTH and 17OHP concentration profiles at day 1 and day 14 show clear reductions from the baseline mean profiles. Cohort 1 mean PK parameters of T_{max} , C_{max} , and AUC_{24} for the compound of Formula (I) are shown in Table 29 below. These PK parameters are consistent with observations from Phase 1 studies in healthy volunteers.

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Table 29. Cohort 1 Mean PK parameters of T_{max} , C_{max} , and AUC_{24}

	Day 1			Day 14		
	T_{max}	C_{max}	AUC_{24}	T_{max}	C_{max}	AUC_{24}
Mean	5.4	1305	10,292	4.4	1349	14,297
CV%	30	25	24	32	15	24

Additional measurements of cohort 1 and cohort 2 mean PK parameters of T_{max} , C_{max} , and AUC_{24} for the compound of Formula (I) on Day 1 of dosing are shown in Table 30 below.

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Table 30: Mean PK parameters of T_{max} , C_{max} , and AUC_{24} on Day 1 of dosing

	Cohort 1 50 mg- Ensure			Cohort 2 100 mg-Ensure		
Day 1	T_{max}^* (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)
G.Mean	6	1,270	10,411	4	2,370	24,725
CV%	-	25	24	-	21	42
N	8	8	8	8	4	4

*Median

5 Additional measurements of cohort 1, cohort 2 and cohort 3 mean PK parameters of T_{max} , C_{max} , and AUC_{24} for the compound of Formula (I) on Day 14 of dosing are shown in Table 31 below.

Table 31: Mean PK parameters of T_{max} , C_{max} , and AUC_{24} on Day 14 of dosing

	Cohort 1 50 mg- Ensure			Cohort 2 100 mg-Ensure			Cohort 3 100 mg w/evening Meal		
Day 14	T_{max}^* (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)
G. Mean	4	1,335	14,070	4	3,379	35,416	3	3,650	34,706
CV%		15	24		31	37		32	15
N	8	8	8	6	6	6	8	8	8

*Median

10 Arithmetic mean values for androstenedione (FIG. 13A) and testosterone (FIG. 13B) for all 8 Cohort 1 subjects were plotted at each timepoint for Pre-treatment Baseline, day 1, and day 14. The androstenedione concentration profile on Day 1 and Day 14 shows a clear reduction from the baseline mean profile.

15 When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of ACTH show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 14A). Arithmetic

mean values across all three timepoints show $\geq 50\%$ reductions from baseline at Day 1 and Day 14 (FIG. 14B).

When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of 17-OHP show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 15A). Arithmetic mean values across all three timepoints show $\geq 40\%$ reductions from baseline at Day 1 and Day 14 (FIG 15B).

When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of androstenedione show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 16A). Arithmetic mean values across all three timepoints show $\geq 30\%$ reductions from baseline at Day 1 and Day 14 (FIG. 16B).

A summary of reduction in 17-OHP and androstenedione in cohort 1 is shown in Table 32. Further, the androstenedione levels of three subjects was normalized by the treatment for the three subjects with Subject ID Nos. 001, 002, and 006).

Table 32. Cohort 1 Summary of Reduction in 17-OHP and Androstenedione at each timepoint in the morning window (6 a.m. to 10 a.m.)

Subject ID	Sex/ Age	Dosing Day	17-OHP % change from baseline			Androstenedione % change from baseline		
			6 AM	8 AM	10 AM	6 AM	8 AM	10 AM
001	F/37	D1 D14	-61.4	14.7	-24.1	-42.0	2.0	-19.5
			-90.3	-67.2	-37.2	-84.6	-58.6	-55.1
002	F/25	D1 D14	-96.0	-95.5	45.4	-68.0	-66.7	-21.7
			-37.7	-58.6	-24.9	-34.2	-47.8	-38.7
003	M/49	D1 D14	-11.8	-46.6	-34.0	-13.4	-47.1	-22.7
			-24.5	-5.2	-22.9	-7.5	-10.8	-16.0
004	M/36	D1 D14	-13.7	17.1	10.1	4.5	15.9	3.0
			-53.6	-46.8	-35.8	-13.8	-15.2	-21.2
005	F/27	D1 D14	-24.4	-83.6	-52.2	-35.6	-50.3	-33.5
			-78.8	-95.1	-86.3	26.7	-13.7	-10.9
006	M/19	D1 D14	-5.1	-1.1	-97.8	-10.0	-18.5	-78.9
			-25.4	-20.4	-98.3	-67.8	-62.7	-92.1
007	M/25	D1 D14	-50.0	-28.0	-27.4	-24.8	-30.0	-15.8
			14.9	4.0	-7.1	-4.8	-36.8	-30.2
008	F/31	D1 D14	-64.5	-80.7	-92.8	-12.2	7.0	-9.3
			-59.0	-65.2	-89.1	74.5	99.4	59.2

Table 33. Cohort 1 Summary of PK parameters of T_{max} , C_{max} , and AUC_{24} for each subject at days 1 and 14

	Day 1			Day 14		
Subject ID	T_{max} (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)
001	6	1830	14,487	6	1570	20,863
002	6	1210	11,829	4	1610	15,494
003	6	1060	11,068	3	1310	15,599
004	4	1670	9,669	3	1160	10,180
005	8	961	9,266	6	1550	15,130
006	4	1030	6,574	3	1090	10,288
007	6	1550	8,239	6	1170	12,880
008	3	1130	11,209	4	1330	13,944
Mean	5.4	1305	10,292	4.4	1349	14,297
CV%	30	25	24	32	15	24
N	8	8	8	8	8	8

After 14 days of once-daily compound of Formula (I) administration, a majority of participants in Cohorts 1-3 showed reduced serum concentrations of adrenal androgens and precursors. Mean changes from baseline ($\pm$ standard deviation) in Cohort 1 were as follows: 17-OHP, -2341.0 ± 1535.0 ng/dL; androstenedione, -98.4 ± 98.7 ng/dL; and ACTH, -157.0 ± 194.9 pg/mL. Mean reductions were larger in Cohort 2 (17-OHP, -4406.0 ± 5516.1 ; androstenedione, -362.8 ± 354.0 ; ACTH, -180.9 ± 155.2) and Cohort 3 (17-OHP, -4760.1 ± 4018.2 ; androstenedione, -210.9 ± 188.6 ; ACTH, -358.9 ± 177.6), suggesting a possible dose response. FIGs. 17A-17C, 18A-18C, and 19A-19C depict results from Cohorts 1, 2, and 3, respectively.

Summary

The results from this ongoing Phase II open-label study demonstrated a reduction of at least 50 percent from baseline in 17-hydroxyprogesterone (17-OHP) and adrenocorticotrophic hormone (ACTH) levels in more than 50 percent of CAH patients in cohort 1 treated with the compound of Formula (I) for 14 days (i.e., 6 of 8 patients in cohort 1 had a reduction of $\geq 50\%$ from baseline levels of 17-OHP during at least one morning window timepoint, see, e.g., Table 32). Meaningful reductions were also observed in other biomarkers, including androstenedione (i.e., 4 of these patients also had a reduction of $\geq 50\%$ from baseline levels of androstenedione during at least one morning window timepoint, see, e.g., Table 32). The greater reductions in biomarkers in cohorts 2 and 3, treated with double the dose of the compound of Formula (I)

compared with cohort 1, suggest a possible dose response. Further, the compound of Formula (I) was well-tolerated with a relatively small number of mild adverse events (AEs) reported (e.g., headache, ovulation pain, fatigue, localized infection (toe), dizziness, nausea, URI, contusion with the most common being headache). No clinically significant findings from routine labs, vital signs, or electrocardiograms were found.

Example 9: Reference Formulation 1 of the compound of Formula (I)

Tables 34A and 34B show Reference formulation 1 of the compound of Formula (I) as used in the clinical studies described in Examples 6 and 8, above. An example manufacturing process is shown in FIG. 20. Another example manufacturing process is shown in FIG. 21.

Table 34A:

Component	Quality Standard	Function	50 mg Capsule	
			Weight (mg/unit)	% (w/w)
Compound of Formula (I), free base	In-house	Active Ingredient	50.0	10.0
Medium-Chain Triglycerides (Labrafac TM Lipophile WL1349)	NF	Oily Phase Vehicle	196.0	39.2
Propylene Glycol Dicaprylate/Dicaprate, (LabrafacTM PG)	NF	Emulsifying Agent	102.0	20.4
Lauroyl Polyoxyl-32 Glycerides (Gelucire® 44/14)	NF	Nonionic Surfactant & Solubilizing Agent	95.0	19.0
Vitamin E Polyethylene Glycol Succinate (Kolliphor® TPGS)	USP/NF	Solubilizing Agent	57.0	11.4
Total Emulsion Weight			500.0	100.0
Gelatin Capsule Shell. Size #00, Swedish Orange cap/body; (Coni-Snap®)	Non-Pharmacopoeial	Capsule Shell	--	--

Gelatin Powder, 220 Bloom	USP	Capsule shell banding agent	---	---
Purified Water	USP	Capsule shell banding solvent	---	---

Table 34B:

Component	Quality Standard	Function	50 mg Capsule	
			Weight (mg/unit)	% (w/w)
Compound of Formula (I), free base	In-house	Active Ingredient	50.0	10.0
Medium-Chain Triglycerides (caprylic:capric acid 60:40; Miglyol 812N)	Ph. Eur./NF	Vehicle	195.85	39.2
Propylene Glycol Dicaprylocaprate, (Labrafac™ PG)	Ph. Eur.	Vehicle	102.15	20.4
Lauroyl macrogolglycerides type 1500-Lauroyl polyoxylglycerides type 1500 (Gelucire® 44/14)	Ph. Eur./NF	Surfactant	95.0	19.0
Vitamin E Polyethylene Glycol Succinate, 260 mg/g <i>d</i> -alpha tocopherol (Vitamin E/TPGS 260)	NF	Surfactant	57.0	11.4
Total Emulsion Weight			500.0	100.0
Orange opaque hard capsule, size 0, composed of gelatin, titanium dioxide and red ferric oxide (Swedish Orange ®)	Non Pharmacopo eial	Capsule Shell	---	---
Ethanol (96%) and Purified Water	USP	Capsule shell banding solvent	---	---

Example 10: Study Evaluating Effect of Ensure Plus, Ensure Pudding, Milk and High Fat Meal on Reference Capsule

Study design

This is a Phase 1, open-label, randomized, four-period crossover study to evaluate the effect of food with different levels of fat and caloric content on the PK, safety, and tolerability of the compound of Formula (I) in healthy adult subjects.

A total of 16 healthy adult subjects (8 males and 8 females) will be randomly assigned to 1 of 4 treatment sequences (4 subjects per sequence [2 males and 2 females per sequence]; see Table 35 below). During each treatment period, subjects will receive a single dose of the compound of Formula (I) 100 mg administered with the appropriate meal, according to the randomization scheme. There will be a washout of at least 21 days between each dose.

Table 35:

Treatment Sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4
1	Reference meal	Test meal 1	Test meal 2	Test meal 3
2	Test meal 1	Test meal 3	Reference meal	Test meal 2
3	Test meal 2	Reference meal	Test meal 3	Test meal 1
4	Test meal 3	Test meal 2	Test meal 1	Reference meal

Reference meal: vanilla-flavored Ensure Plus® Test meal 1: Low fat, low caloric content meal
 1 Test meal 2: Low fat, low caloric content meal 2
 Test meal 3: standard high fat, high caloric content meal

After providing informed consent, subjects will be screened for eligibility to participate in the study. Screening will begin up to 28 days before Day 1 of treatment period 1. Eligible subjects will be admitted to the clinical unit on Day -1 and randomized to 1 of the 4 treatment sequences on Day 1 of treatment period 1. During each treatment period, subjects will fast overnight for at least 10 hours until the start of the assigned meal, according to the randomization scheme, and ingest the study drug at approximately 0800 hours. Subjects must complete the entire meal within the specified time period and should not consume any other food for 4 hours after dosing. For all treatment periods, water will not be permitted for 1 hour before dosing until 2 hours after dosing except for the water provided with study drug dosing and planned meals.

On Day 1 of each treatment period, subjects will be dosed with the compound of Formula (I) 100 mg. Blood samples will be collected for PK analysis over a period of 36 hours during the in-house stay. During each treatment period, subjects will remain in the clinic on the day of dosing and will be discharged on Day 2 after completing all required procedures. On the mornings of Days 8 and 15 of each treatment period, subjects will return for an outpatient visit to the clinic for PK blood sample collection and safety assessments. On Day 21 of treatment periods 1 to 3, subjects will arrive at the site and have Day 21 assessments completed and they will stay overnight at the site and begin Day 1 of the subsequent treatment period the following day. A final follow-up study visit will be conducted on Day 22 of treatment period 4 (21 ± 2 days after treatment period 4 dosing) or upon early termination.

Blood samples for PK d/conducted at scheduled times throughout the study.

Study population

Sixteen healthy adult subjects (8 males and 8 females) between 18 and 55 years of age, inclusive, who meet all protocol eligibility criteria, will be enrolled.

Duration of treatment

The expected duration of study participation for each healthy adult subject will be approximately 16 weeks, including up to 28 days of screening, 4 days of dosing with at least 21 days between consecutive doses, and a final follow-up study visit 21 days (± 2 days) after receiving the last dose of study drug during treatment period 4.

Test product, dose, and mode of administration

The compound of Formula (I) will be supplied as capsules for oral administration (encapsulated, lipidic semi-solid formulation, e.g., Example 9). The compound of Formula (I) capsules will contain 50 mg of the compound of Formula (I) as free base equivalent. During each treatment period, subjects will receive two 50 mg capsules (100 mg) of the study drug along with a meal and water as defined by the randomization scheme. The food, water, and study drug administration are as follows:

Reference meal: Two capsules of study drug will be administered approximately 5 minutes after the start of a liquid dietary supplement (i.e., Ensure Plus® [237 mL container]) and an additional 120 mL of water for study drug dosing.

Test meal 1: Two capsules of study drug will be administered approximately 5 minutes after the start of a low fat, low caloric meal 1 with 120 mL of water for study drug dosing.

Test meal 2: Two capsules of study drug will be administered approximately 5 minutes after the start of a low fat, low caloric meal 2 with 120 mL of water for study drug dosing.

Test meal 3: Two capsules of study drug will be administered approximately 30 minutes after the start of a high fat, high caloric meal with 120 mL of water for study drug dosing.

CRITERIA FOR EVALUATION

Pharmacokinetics

Blood samples for assessment of plasma concentrations of the compound of Formula (I) and metabolites will be collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration (AUC_{0-last})
- Area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0-\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{1/2}$)
- Apparent terminal rate constant (λ_z)
- Apparent mean residence time (MRT)
- Molar AUC ratio of primary metabolite(s) to the parent drug compound of Formula (I). The following plasma PK parameters will be calculated only for the compound of Formula (I):
- Apparent systemic clearance after oral administration (CL/F)

- Apparent volume of distribution during terminal phase after oral administration (V_z/F)

Safety Assessments

- 5 Safety will be monitored throughout the study and will include the following assessments:
- Adverse events (AEs)
 - Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
 - Vital sign measurements (including orthostatic blood pressure and pulse rate)
 - Physical examinations
 - 10 • 12-lead electrocardiograms (ECGs)

Statistical methods

Pharmacokinetic parameters will be calculated using noncompartmental methods and summarized by meal type (test meal/reference meal) using descriptive statistics. Two-sided
 15 90% confidence intervals will be calculated for the ratio of each test meal versus the reference meal for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} for the compound of Formula (I) and metabolites. Safety data will be summarized with descriptive statistics.

Results

20 *Pharmacokinetic results*

Pharmacokinetic results are shown in Table 36 below.

Table 36: Summary of Plasma Pharmacokinetic Parameters

		Compound of Formula (I) Plasma Concentration		
Parameter (units) Statistic	Ensure Plus (Fed) (N=18)	Ensure Pudding (Fed) (N=18)	Whole Milk (Fed) (N=17)	High Fat Meal (Fed) (N=17)
$AUC_{0-t_{last}}$ (ng×hr/mL)				
Mean (SD)	36703 (17400)	34077 (11597)	35561 (15866)	55487 (23242)
Geom CV(%)	58	39.7	44.6	41.9

AUC_{0-∞} (ng×hr/mL)				
Mean	45386 (19648)	40037 (9515)	46737 (17395)	63755 (19139)
Geom CV(%)	43.3	23.8	38.8	31
C_{max} (ng/mL)				
Mean (SD)	3090 (1070)	3038 (984)	2835 (1005)	4336 (1938)
Geom CV(%)	39.7	34.9	34.5	53.6
t_{max} (hr)				
Median (min,max)	5.0 (2.0, 10.0)	5.0 (4.0, 6.0)	5.0 (4.0, 7.0)	5.0 (4.0, 7.0)
T_{lag} (hr)				
Mean (SD)	0.38 (0.46)	0.20 (0.25)	0.16 (0.31)	0.29 (0.37)
t_{1/2} (hr)				
Mean (SD)	361 (263)	373 (196)	373 (143)	326 (120)
Geom CV(%)	61.1	48.6	37.1	33.8
CL/F (L/hr)				
Mean (SD)	2.49 (0.956)	2.636 (0.659)	2.427 (0.975)	1.706 (0.526)
Geom CV(%)	41.2	24.8	38.8	31.1
V_z/F (L)				
Mean (SD)	1254 (906)	1414 (720)	1308 (627)	816 (378)
Geom CV(%)	72.7	58.4	61.3	54.9

Example 11: Spray-dried Dispersion Granule Formulation of the Compound of Formula (I) (SDD-G)

5 Table 37 shows a granule formulation of the compound of Formula (I) using a SDD prepared according to Example 3, above. An example manufacturing process is shown in FIG. 22A and FIG. 22B.

Table 37:

Component	Quality Standard	Function	50 mg Sachet		Batch Weight (g)
			Weight (mg/unit)	% (w/w)	
Example 3, SDD	In-house	Drug Substance	200.0	13.33	40
Calcium Silicate (ZEOPHARM 250)	NF	Glidant	10.0	0.67	2
Mannitol (Pearlitol 200SD)	NF / EP / JP	Filler	832.5	55.5	166.5
Microcrystalline Cellulose (Avicel PH-102)	NF / EP / JP	Filler	300.0	20.0	60
Croscarmellose Sodium (Ac-Di-Sol®) SD711	NF / EP / JP	Disintegrant	150.0	10.0	30
Sodium Stearyl Fumarate	NF / EP / JP	Lubricant	7.5	0.5	1.5
Total			1500	100.0	300

Example 12: Liquid Formulation 1 of the Compound of Formula (I)

Table 38 shows liquid formulation 1 of the Compound of Formula (I) free base. An
 5 example manufacturing process is shown in FIG. 23.

Table 38:

Component	Quality Standard	Function	50 mg/mL Oral Solution		Batch Weight (g)
			Weight (mg/mL)	% (w/v)	
Compound of Formula (I) FB	In-house	Drug Substance	50.0	5	20.03
Saccharin	NF / EP	Sweetener	1.5	0.15	0.61
Butylated hydroxytoluene	NF / EP	Anti-oxidant	1.7	0.17	0.69
FONA orange flavor	NF	Flavor	1.0	0.1	0.41
Labrafac Lipophile WL1349	NF / EP	Liquid Vehicle	to 1 mL	94.58	358.87
Total			1 mL	100.0	380.6

Example 13: Liquid Formulation 2 of the Compound of Formula (I)

Table 39 shows liquid formulation 2 of the Compound of Formula (I) free base. An example manufacturing process is shown in FIG. 24.

5 **Table 39:**

Component	Quality Standard	Function	50 mg/mL Oral Solution		Batch Weight (g)
			Weight (mg/mL)	% (w/v)	
Compound of Formula (I) FB	In-house	Drug Substance	50.0	5	20.17
Saccharin	NF / EP	Sweetener	1.5	0.15	0.61
Butylated hydroxytoluene	NF / EP	Anti-oxidant	1.7	0.17	0.68
LABRAFIL M 1944 CS	NF / EP	Surfactant	200.0	20	80.16
FONA orange flavor	NF	Flavor	1.0	0.1	0.40
Labrafac Lipophile WL1349	NF / EP	Liquid Vehicle	to 1 mL	74.58	278.68
Total			1 mL	100.0	380.7

Example 14: A Phase I, Open-Label Study to Evaluate the Pharmacokinetics, Relative Bioavailability, Effect of Food, Safety and Tolerability of Different Compound of Formula (I) Prototype Formulations in Healthy Adult Subjects.

10

Methodology

15

20

This is a single center, open-label, randomized, single dose 4-period crossover study in healthy adult subjects designed to investigate the pharmacokinetic (PK) and safety of up to 4 compound of Formula (I) liquid lipidic prototype formulations (compound of Formula (I) Oral Solution, Prototype Formulations, 50 mg/mL), a compound of Formula (I) spray dried dispersion formulation (compound of Formula (I) Granule for Sprinkle, 25 – 50 mg) and compound of Formula (I), 50 mg Capsules (Reference). It is planned to enroll 36 subjects to be allocated as 3 cohorts of 12 subjects per cohort, with 6 sub-cohorts of 6 subjects per sub-cohort. In each of these 6 sub-cohorts, 6 subjects will be assigned to one of 3 sub-cohorts where a single oral dose of Investigational Medicinal Product (IMP) is administered in 4 dosing periods (Periods 1 to 4) in multiple fed or fasted states or to one of 3 sub-cohorts where a single oral dose of IMP is administered in 2 dosing periods (Periods 1 and 2) only in

the fed state. Within each sub-cohort, subjects will also be randomized before administration of the first dose of IMP in Period 1 to one of the following treatment sequences (Table 40):

Table 40:

Sub-Cohort	Sequence	Number of Subjects	Total Number of Periods Dosed	Regimen			
				Period 1	Period 2	Period 3	Period 4
1A	ABEF	3	4	Regimen A	Regimen B	Regimen E	Regimen F
	BAEF	3	4	Regimen B	Regimen A	Regimen E	Regimen F
1B	AB	3	2	Regimen A	Regimen B	N/A	N/A
	BA	3	2	Regimen B	Regimen A	N/A	N/A
2A	ADEF	3	4	Regimen A	Regimen D	Regimen E	Regimen F
	DAEF	3	4	Regimen D	Regimen A	Regimen E	Regimen F
2B	AD	3	2	Regimen A	Regimen D	N/A	N/A
	DA	3	2	Regimen D	Regimen A	N/A	N/A
3A	ACEF	3	4	Regimen A	Regimen C	Regimen E	Regimen F
	CAEF	3	4	Regimen C	Regimen A	Regimen E	Regimen F
3B	AC	3	2	Regimen A	Regimen C	N/A	N/A
	CA	3	2	Regimen C	Regimen A	N/A	N/A

5

At informed consent, subjects will agree either to participate in 2 study periods or 4 study periods. Once placed into a sub-cohort, the order in which subjects receive the study treatments will be randomized based on the schedule above.

Subjects will receive up to 4 regimens in up to 4 periods in an order according to the randomization schedule within each sub-cohort.

10

The effect of different prandial states on the PK of the compound of Formula (I) may be explored in Periods 3 and 4 by administering in the fasted state or after an alternative meal (c.g. high fat, standard or light breakfast, etc.).

The proposed regimens are presented in Table 41 below:

15

Table 41:

Regimen	Investigational Medicinal Product	Dose	Route of Administration	Prandial State
A	Compound of Formula (I), 50 mg Capsules (Reference)	50 mg	Oral	Fed (Ensure Plus)
B	Compound of Formula (I) Oral Solution, Prototype Formulation 1, 50 mg/mL	50 mg	Oral	Fed (Ensure Plus)
C	Compound of Formula (I) Oral Solution, Prototype Formulation 2, 50 mg/mL	50 mg	Oral	Fed (Ensure Plus)
D	Compound of Formula (I) Granule for Sprinkle, 25 – 50 mg	50 mg	Oral	Fed (Ensure Plus)
E	Compound of Formula (I) Oral Solution, Prototype Formulation 1	100 mg	Oral	Fed (Ensure Plus)
F	Compound of Formula (I) Oral Solution, Granule for Sprinkle	50 mg	Oral	Fed (alternative meal)

Study Design:

Subjects will be screened for eligibility to participate in the study up to 28 days before the first dose of IMP in Period 1. Each study period will follow the same study design. Subjects will be admitted to the clinical unit on the evening prior to IMP administration (Day -1). For Periods 1 and 2 (Regimen A and one of either Regimens B, C or D), all subjects will receive the compound of Formula (I) formulations in the morning according to the randomization schedule in the fed state with a liquid dietary supplement (Ensure Plus). For Periods 3 and 4 (Regimens E and F), subjects will receive the compound of Formula (I) formulations in the morning according to the randomization schedule in the fed state with a liquid dietary supplement or an alternate prandial state (fasted or alternative meal). IMP administration will be performed on Day 1 with an appropriate interval between subjects based on logistical requirements (approximately 10 min). Meals will be standardized for each treatment regimen across periods.

Subjects will remain in the clinical unit until 36 h post-dose when they will be discharged. Subjects will return to the clinical unit at 168 h (7 days) and 336 h (14 days) post-dose for a PK blood sample and safety assessments. The minimum washout between IMP

dosing occasions will be 14 days between Periods 1 and 2 and 21 days or more to accommodate interim data reviews between Periods 2 and 3 and between Periods 3 and 4.

There will be a follow-up phone call 18 to 24 days post-final visit to ensure the ongoing wellbeing of subjects.

5 Following the completion of Period 2 for all cohorts, there will be an interim data review during which the PK and safety data will be reviewed, plus any relevant emerging Chemistry, Manufacturing and Control (CMC) stability study information, to determine the formulation, dose level and prandial state in which to administer the IMP in Period 3 (Regimen E). There will be a similar interim review following completion of Period 3 (administration of
10 Regimen E) to determine the formulation, dose level and prandial state in which to administer the IMP in Period 4 (Regimen F). The criteria for the interim decisions will be based on available compound of Formula (I) PK data: e.g., C_{max} , T_{max} , AUC(0-36), F_{rel} and safety data.

Number of Subjects Planned:

15 It is planned to enroll 36 healthy male and female (non-pregnant, non-lactating) subjects in 6 sub-cohorts of 6 subjects per sub-cohort. These sub-cohorts will be combined in sets of 2 to create 3 cohorts of $n = 12$ for Periods 1 and 2 to target data in 10 evaluable subjects in each cohort for the primary objectives per formulation variant. A total of 18 subjects, 6 from each of Sub-Cohorts 1A, 2A and 3A participating in Periods 1 and 2, will
20 additionally participate in Periods 3 and 4 with a target of a minimum of 6 evaluable subjects. A subject will be considered evaluable for a particular regimen if they have received an IMP and has completed sufficient planned PK assessments up to 336 h (14 days) after dosing for that regimen to allow for the assessment of study endpoints. A subject will be considered evaluable for a particular comparison (e.g., food effect, relative bioavailability) if they have
25 received both IMPs under comparison and have sufficient PK data up to 14 days after each regimen to allow for assessment of study endpoints.

Subjects withdrawn due to an IMP-related adverse event (AE) will not be replaced. Subjects who are withdrawn for other reasons may be replaced as required by agreement between the principal investigator (PI) and sponsor to ensure sufficient numbers of evaluable
30 subjects at the end of each study period. Replacement subjects may be required to be dosed with specific formulations from the previous regimens in order to obtain the minimum number of evaluable subjects required for interim decisions and to obtain data in any other regimen that is required to fulfil the study objective comparisons, with the exception that any

previously dosed IMP that has been considered sub-optimal will not be dosed. Up to 8 replacement subjects in total may be enrolled into the study. The maximum number of subjects that may be dosed is 44 in total.

If a subject withdraws from Sub-Cohort 1A, 2A or 3A after Period 2, it is acceptable to replace them with a subject from Sub-Cohort 1B, 2B or 3B provided the subject signs an updated consent form agreeing to participate in four treatment periods. At the discretion of the investigator, such a subject may not be required to undergo repeat screening procedures.

Duration of Study:

For subjects enrolled to receive single dose administration on 4 separate occasions in Periods 1 to 4 (Sub-Cohorts 1A, 2A and 3A), the estimated time from screening until the follow-up phone call is approximately 15 to 16 weeks.

For subjects enrolled to receive single dose administration on 2 separate occasions in Periods 1 to 2 only (Sub-Cohorts 1B, 2B and 3B), the estimated time from screening until the follow-up phone call is approximately 8 to 9 weeks.

Pharmacokinetic Assessments:

The plasma concentration data for a compound of Formula (I) will be analyzed for final reporting by Quotient Sciences and for interim reviews by Neurocrine Biosciences, Inc. (NBI), using Phoenix WinNonlin v8.0 or a more recent version (Certara USA, Inc., USA). NBI will be responsible for PK analysis for interim review.

PK analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the following PK parameters (Table 42) where possible and appropriate:

Table 42:

T_{lag}	Time prior to the first measurable (non-zero) concentration
T_{max}	Time to maximum plasma concentration
C_{max}	Maximum plasma concentration
$AUC_{0-tlast}$	Area under the plasma concentration versus time curve (AUC) from 0 h to last measurable concentration

AUC _{0-inf}	AUC from 0 h extrapolated to infinity
AUC _{extrap}	Percentage of AUC _{0-inf} extrapolated beyond the last measurable concentration
Lambda-z	Slope of the apparent terminal phase
T _{1/2}	Apparent terminal half-life
CL/F ^a	Apparent systemic clearance after oral administration
Vd/F ^a	Apparent volume of distribution based on the area after a single oral administration
MRT	Mean residence time
MPR AUC _{0-tlast}	Metabolite to parent ratio based on AUC _{0-tlast}
MPR AUC _{0-inf}	Metabolite to parent ratio based on AUC _{0-inf}

Taste Assessments:

Taste will be assessed for each IMP formulation and vehicle (e.g., Ensure Plus, soft food) using a questionnaire designed for this purpose and adapted for this specific study as required.

The questionnaire will ask subjects to rate the acceptability of smell, sweetness, bitterness, flavor, mouth feel, and aftertaste on a 6-point scale, and overall experience on a 5-point scale for each IMP formulation independently of any previous formulations.

Statistical Methodology:

Descriptive summaries for all safety data, PK assessments and taste questionnaire data will be provided. No hypothesis testing will be performed for the safety or taste questionnaire data.

Periods 1 and 2 – for Each Cohort Separately

Relative Bioavailability

Statistical modelling will be performed on the natural log-transformed compound of Formula (I) PK parameters (AUC(0-tlast), AUC(0-inf) and C_{max}) to assess relative bioavailability (F_{rel}) using a mixed effects model with terms for regimen, period and

sequence as fixed effects and subject within sequence as a random effect. Ratios of geometric means (GMRs) and 90% confidence interval (CI) for the relevant comparison of interest, i.e., between each of the prototype formulations (compound of Formula (I) Oral Solution, Prototype Formulation 1, 50 mg/mL, e.g., Example 12; compound of Formula (I) Oral Solution, Prototype Formulation 2, 50 mg/mL, e.g., Example 13; and compound of Formula (I) Granule for Sprinkle, 25 – 50 mg, e.g. Example 11 [Regimens B, C and D, respectively]) and compound of Formula (I), 50 mg Capsules, e.g., Example 9 (Reference; Regimen A) will be presented.

10 **All Periods (Periods 1 to 4)**

Food Effect

Statistical modelling will be performed on the compound of Formula (I) PK parameters AUC(0-tlast), AUC(0-inf) and Cmax to assess for the effects of food, if relevant. The natural log-transformed PK parameters will be analyzed for bioavailability using a mixed effects model with terms for prandial state (and meal type if applicable) as a fixed effect and subject as a random effect. Ratios of geometric means and 90% CI for the relevant comparisons of interest will be presented where the ratio is defined as fasted/fed or test meal/reference meal (if applicable).

20 ***Relative Bioavailability***

Statistical modelling will be performed on the natural log-transformed compound of Formula (I) PK parameters (AUC(0-tlast), AUC(0-inf) and Cmax) to assess relative bioavailability using a mixed effects model with terms for regimen as a fixed effect and subject as a random effect. Ratios of geometric means and 90% CI for the relevant comparison of interest i.e., between each of the prototype formulations (Regimens E and F, IMPs to be determined by interim reviews following completion of Periods 2 and 3) and compound of Formula (I), 50 mg Capsules (Reference; Regimen A) will be presented.

Results

30 Preliminary PK data is summarized in Table 43 below:

Table 43: Preliminary Data from Periods 1 and 2

	A- Reference	B-Oral Solution 1	C-Oral Solution 2	D- SDD Granule
N	35	12	12	12
Tmax *	5	6	5	5
(h)	(2,6)	(5,7)	(5,7)	(5,7)
Cmax	1361	790	1082	1075
(ng/ml)	(33)	(31)	(46)	(35)
AUC36	9452	5556	7582	6691
(h*ng/ml)	(30)	(34)	(37)	(41)

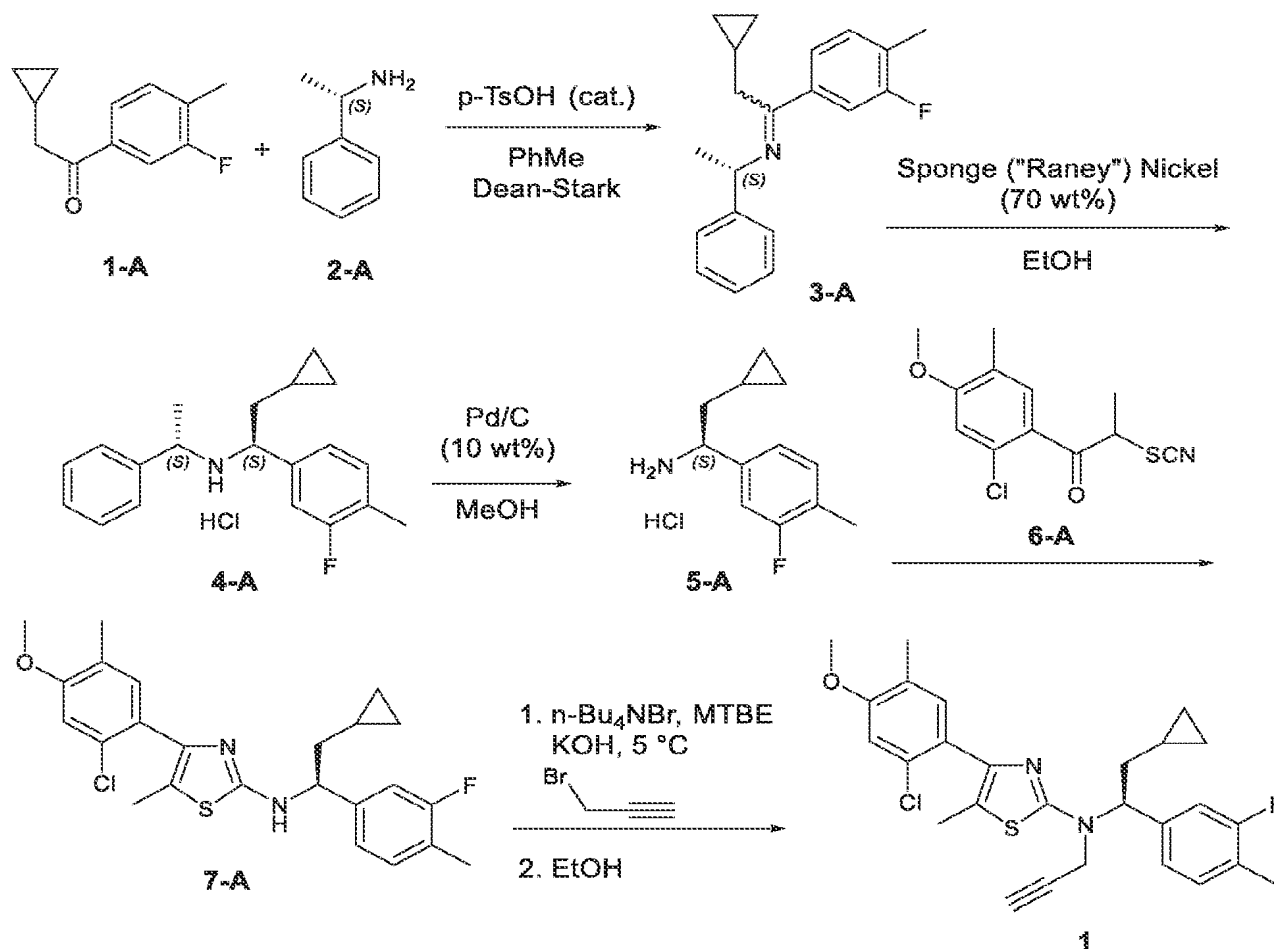
*Geometric Mean /CV% for AUC and Cmax; Median for Tmax

Example 15. Compound of Formula (I) Crystalline Free Base Form I

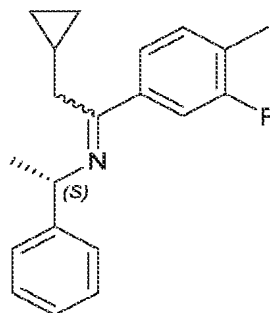
5 Example 15A

Scheme 1: Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I), Form I)

Scheme 1



Step 1: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-N-(1-phenylethyl)ethan-1-imine (Compound 3-A)

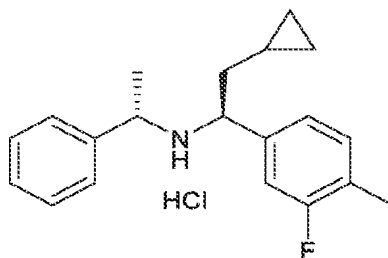


Compound 3-A

A mixture of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (1-A, 150.7 kg, 1 eq., as a 27.6% w/w solution in toluene, Example 15C), (*S*)-(-)-1-Phenylethylamine (2-A, 112.9 kg, 1.19 eq.), and *p*-toluenesulfonic acid (7.4 kg, 0.05 eq.) is refluxed at 110 – 120 °C for 23 – 25 h in a reactor set up in a Dean-Stark configuration. The solvent is then removed

at 125 – 135 °C under atmospheric pressure until distillation halts and a portion of toluene (275 kg, 2.24 w/w) is added to afford a suspension. The suspension is refluxed at 110 – 120 °C for 23 – 25 h. The mixture is cooled to 22 °C and washed twice with aqueous NH₄Cl (10%, 301.2 kg, 0.72 eq.) and once with aqueous NaHCO₃ (5%, 301.2 kg, 0.23 eq., check pH 8 – 9). The solvent is removed at 125 – 135 °C and atmospheric pressure to a target volume of 256 L, the mixture is filtered over celite, the cake is washed with toluene (25 kg). The resulting mixture containing compound 3-A is used directly in the next step without isolation. The yield is determined by correcting for the LOD and GC-FID purity of the sample (208.4 kg, 90.0% corrected, 0.89% Compound 2-A). EI-MS: 294.1 [M-H]⁺, 190.1 [M-C₆H₅CH(CH₃)]⁺, 105.1 [C₆H₅CH(CH₃)]⁺.

Step 2: Preparation of (S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-N-((S)-1-phenylethyl)ethan-1-amine hydrochloride (Compound 4-A)

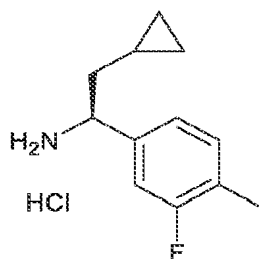


Compound 4-A

Sponge nickel catalyst (144 kg, 0.70 w/w, shipped as a 50% w/w suspension in water) is added to a hydrogenation reactor, equipped with a dip tube capable of removing material from the top of the mass inside, minimizing the amount of water introduced. The supernatant is discarded, ethanol (329.3 kg, 1.58 w/w, anhydrous) is added, the suspension is stirred and then allowed to settle. This process is repeated four more times and the Karl Fisher (KF) of the supernatant is checked ($\leq 1\%$ H₂O w/w). Compound 3-A (208.4 kg, 1 eq., as a 62.6% solution in toluene) is added to the mixture in the hydrogenation reactor and ethanol (387.6 kg, 1.86 w/w) is used to rinse the addition flask into the hydrogenation reactor. The hydrogenation reactor is pressurized/depressurized twice with nitrogen (2 bar) and twice with hydrogen (5 bar) then pressurized with hydrogen (9.8 – 10.2 bar) and heated to 33 – 37 °C and stirred for 17 – 19 h. The system is depressurized/pressurized three times with nitrogen (1 bar) and the suspension is filtered and washed with three times with ethanol (493.8 kg, 2.37 w/w). HCl (concentrated, 83.4 kg, 1.07 eq.) is added and the mixture stirred 25 – 35 min at 20

– 24 °C. The mixture is concentrated by distillation at 78 – 80 °C and atmospheric pressure to remove water with a distillate target volume of 1167 L (5.6 L/kg, Compound 3-A) and the KF of the solution is checked ($\leq 1.5\%$ H₂O w/w). The mixture is stirred at 48 – 52 °C for 55 – 65 min, then 68 – 72 °C for 55 – 65 min, then cooled to 20 – 24 °C at a rate of 12 °C/h and stirred for 25 – 35 min, then cooled to 0 – 4 °C at a rate of 10 °C/h and stirred for 55 – 65 min. The suspension is filtered, the cake is washed twice with precooled ethanol (329.2 kg, 1.58 w/w, 0 °C), and the collected solid is dried at 40 °C to afford compound 4-A (156.5 kg, 66.4% uncorrected). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm -0.33 - -0.06 (m, 2 H) 0.11 - 0.31 (m, 3 H) 1.57 (d, *J*=6.57 Hz, 3 H) 1.95 (br t, *J*=7.07 Hz, 2 H) 2.26 (d, *J*=1.26 Hz, 3 H) 3.68 (br d, *J*=7.83 Hz, 1 H) 3.92 (br t, *J*=6.44 Hz, 1 H) 6.98 (dd, *J*=7.71, 1.14 Hz, 1 H) 7.28 - 7.36 (m, 2 H) 7.37 - 7.50 (m, 5 H). ESI-MS: 298.2 m/z [M+H]⁺.

Step 3: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-amine hydrochloride (Compound 5-A)



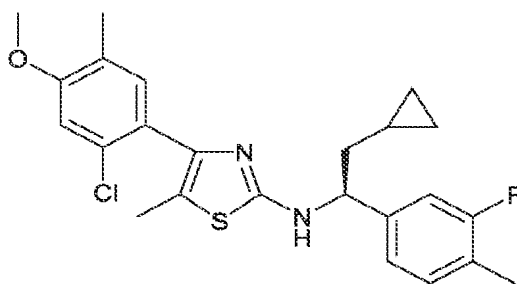
Compound 5-A

Compound 4-A (156.5 kg, 1.00 eq.) and Pd/C (7.8 kg, 10% Pd basis) are added to an inerted hydrogenation reactor. The reactor is then pressurized/depressurized twice with nitrogen (2 bar) and then methanol (494.5 kg, 3.16 w/w) is added. The reactor is depressurized/pressurized three times with nitrogen (2 bar) then three times with hydrogen (5 bar), pressurized with hydrogen (9.8 – 10.2 bar), heated to 58 – 62 °C and stirred for 7 – 9 h. The reaction mixture is cooled to 20 – 24 °C. The reactor is depressurized/pressurized three times with nitrogen (1 bar) and the suspension is filtered and washed three times with methanol (492.9 kg, 3.15 w/w). The solution is concentrated at 63 – 67 °C and atmospheric pressure to a distillate target volume of 1408 L (9.0 L/kg Compound 4-A). *n*-Heptane (1173.8 kg, 7.5 w/w) is added and the mixture is refluxed at 65 – 80 °C and atmospheric pressure in Dean-Stark configuration to remove methanol. The suspension is cooled to 31 – 35 °C and filtered, the cake washed with *n*-heptane (147.1 kg, 0.94 w/w), and the solid dried at 40 °C

(101.0 kg, 93.8% uncorrected, 99.2% *ee*). ^1H NMR (400 MHz, DMSO-*d*₆) δ ppm -0.12 - 0.14 (m, 2 H) 0.26 - 0.42 (m, 2 H) 0.44 - 0.55 (m, 1 H) 1.70 - 1.83 (m, 2 H) 2.23 (d, *J*=1.52 Hz, 3 H) 4.24 (t, *J*=7.33 Hz, 1 H) 7.22 - 7.29 (m, 1 H) 7.29 - 7.36 (m, 1 H) 7.40 (dd, *J*=10.99, 1.39 Hz, 1 H). ESI-MS: 194.2 [M+H]⁺, 177.0 [M-NH₂]⁺.

5

Step 4: Preparation of (*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methylthiazol-2-amine (Compound 7-A)



Compound 7-A

10 A mixture of *n*-heptane (146 kg), water (142 kg), Compound 5-A (57.4 kg), and aqueous sodium hydroxide (30% w/w, 41.0 kg) was stirred together. The layers were partitioned, and the aqueous layer removed. The organic layer was washed with water (170 kg) and the layers partitioned. The organic layer was set aside using *n*-heptane (40 kg) to rinse and *n*-heptane (145 kg) and 1-(2-chloro-4-methoxy-5-methylphenyl)-2-

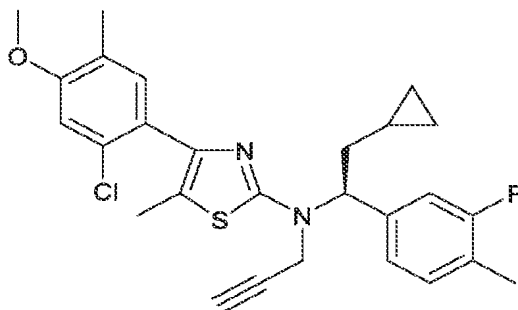
15 thiocyanatopropan-1-one (6-A, 66.1 kg) were added to the reactor and heated to 85 °C. The previously set aside organic layer containing the free base of Compound 5-A was added at 84 – 85 °C to the reactor and rinsed with *n*-heptane (20 kg). The resulting mixture was stirred for 2 h at 83 °C. Subsequently, the solvent was switched to methanol by four put-and-

20 take additions/vacuum distillations of methanol (180 kg) at 55 °C with the target volume being 287 L remaining in the reactor. The suspension was cooled to 5 °C and water (570 kg) was added over 4 h at 5 – 10 °C, with the first 60 kg added very slowly. The suspension was aged 2 h at °C and then isolated by filtration and washed with a mixture of methanol/water (91/115 kg) and then a mixture of methanol/water (134/57 kg). The yellow solid was dried at

25 25 °C and 1 mbar for 17 h then 40 °C and 1 mbar for 22 h to afford Compound 7-A (97.4 kg, 87.5% yield). ^1H NMR (400 MHz, DMSO-*d*₆) δ ppm -0.01 - 0.14 (m, 2 H) 0.29 - 0.42 (m, 2 H) 0.61 - 0.73 (m, 1 H) 1.47 (dt, *J*=13.83, 6.85 Hz, 1 H) 1.76 (dt, *J*=13.89, 7.20 Hz, 1 H) 2.00 (s, 3 H) 2.11 (s, 3 H) 2.19 (d, *J*=1.01 Hz, 3 H) 3.82 (s, 3 H) 4.54 (q, *J*=7.58 Hz, 1 H) 7.00 (s,

1 H) 7.06 (d, $J=0.76$ Hz, 1H) 7.08 - 7.14 (m, 2 H) 7.18 - 7.23 (m, 1 H) 7.89 (d, $J=8.08$ Hz, 1 H). ESI-MS: 445.3 m/z $[M+H]^+$.

Step 5: Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I))



Compound of Formula (I)

A mixture of MTBE (279 kg), tetra-*n*-butylammonium bromide (10.5 kg), and Compound 7-A (95.4 kg) were heated at 60 °C external temperature for 30 min and then cooled to 0 °C. Aqueous potassium hydroxide (52.4% w/w, 364 kg) and propargyl bromide (39.4 kg as an 80% w/w solution in toluene, 1.19 eq.) were added at 0 – 5 °C and the biphasic mixture aged 14.5 h at 4 – 6 °C with vigorous stirring. Subsequently, water (191 kg) was added and the aqueous layer was discharged. The organic layer was washed twice with water (382 kg) and once with aqueous acetic acid (5.26% w/w, 190 kg) at 20 °C. The mixture is polish filtered, rinsed with ethanol (11 kg) and then the solvent switched to ethanol by 3 put-and-take additions/vacuum distillations of ethanol (300 kg) at 25 – 30 °C for the first cycle and then 35 – 40 °C with the target volume of each cycle being 250 L remaining in the reactor. Ethanol (164 kg) was added and the mixture heated at 60 °C external for 0.5 h before it was cooled to 25 °C in 1 h and seeded with authentic compound of Formula (I) (0.340 kg) which may be prepared as described below in Example 15B. The suspension was aged for 5 h, cooled to 0 °C in 2 h, aged 12 h, filtered, and washed twice with ethanol (24 kg each) pre-cooled to 0 °C. The white solid was dried at 40 °C and 1 mbar for 19 h to yield 80.15 kg of the compound of Formula (I), Form I (77.2% yield). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.14 (qt, $J=8.59, 4.42$ Hz, 2 H) 0.29 - 0.48 (m, 2 H) 0.61 - 0.82 (m, 1 H) 1.89 (dt, $J=14.08, 6.98$ Hz, 1 H), 2.07 (br d, $J=7.83$ Hz, 1 H) 2.10 (s, 3 H) 2.14 (s, 3 H) 2.20 (d, $J=1.01$ Hz, 3 H)

3.11 (t, $J=2.27$ Hz, 1 H) 3.83 (s, 3 H) 3.94 - 4.22 (m, 2 H) 5.26 (t, $J=7.58$ Hz, 1 H) 7.05 (s, 1 H) 7.10 - 7.36 (m, 4 H). ESI-MS: 483.2 m/z $[M+H]^+$.

The crystallinity of the crystalline free base Compound of Formula (I), Form I was confirmed by XRPD (Figure 25, Table 44) and further supported by DSC (Figure 26),

- 5 indicating the crystalline compound having an onset of melt at about 84.4 °C (71.9 J/g). TGA of the crystalline free base exhibited about 0.6% of weight loss due to solvent/H₂O.

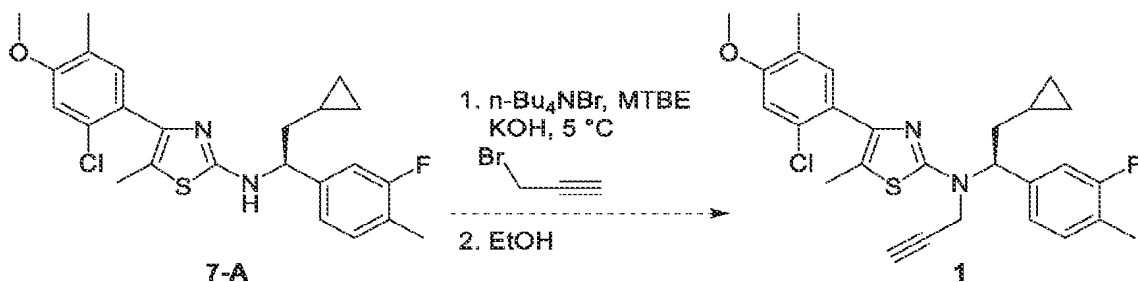
Table 44. XRPD Peak Data for the Compound of Formula (I) Crystalline Free Base Form I

2-Theta (°)	Height (cps)
5.901(15)	1221(101)
10.367(11)	1280(103)
11.762(13)	1377(107)
12.582(11)	1591(115)
13.802(2)	7326(247)
14.1541(16)	20179(410)
15.173(14)	449(61)
15.854(7)	2906(156)
16.746(5)	5113(206)
18.366(7)	1171(99)
19.586(2)	27789(481)
20.100(4)	10759(299)
20.794(4)	5441(213)
21.730(5)	7125(244)
22.239(7)	10370(294)
23.056(11)	3482(170)
23.714(7)	2300(138)
24.115(7)	8402(265)
25.666(4)	26173(467)
26.296(6)	1505(112)
26.752(4)	9919(288)
27.264(7)	1016(92)
27.874(7)	2092(132)
28.623(3)	10560(297)
29.546(6)	5811(220)
30.025(3)	2248(137)
30.737(10)	1333(105)
31.017(19)	1406(108)
31.588(10)	2292(138)
31.809(8)	2212(136)
32.126(13)	593(70)
33.200(16)	839(84)
33.613(13)	2996(158)

2-Theta (°)	Height (cps)
33.914(13)	1156(98)
34.276(16)	1008(92)
34.564(12)	1056(94)
35.397(18)	816(82)
36.073(10)	1928(127)
36.67(3)	562(68)
37.347(9)	1553(114)
37.776(12)	1573(114)
39.070(7)	1890(125)
39.743(15)	1042(93)
40.643(9)	2808(153)
41.106(8)	1107(96)
41.984(11)	2686(150)
42.376(16)	986(91)
42.901(16)	492(64)
43.543(10)	4744(199)
44.419(16)	2810(153)

Example 15B

Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I), seed batch)



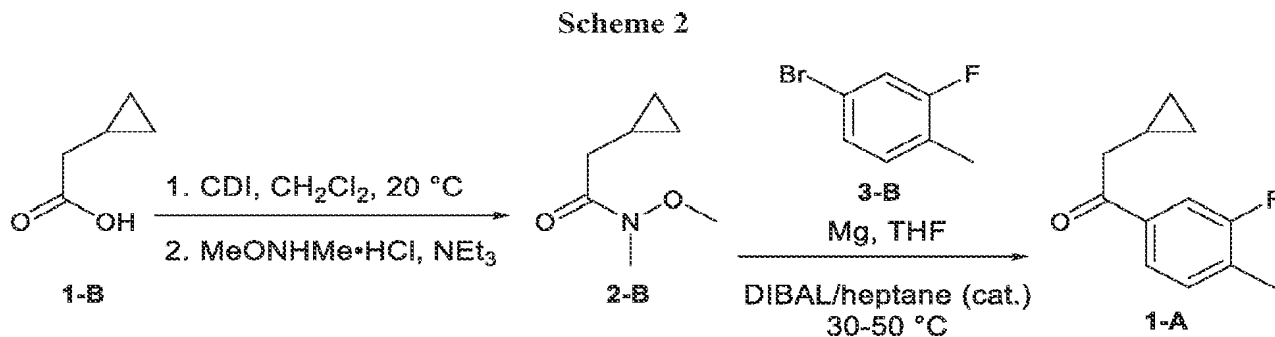
A mixture of MTBE, *tetra*-n-butylammonium bromide, and Compound 7-A cooled to 0 °C is treated with aqueous potassium hydroxide and propargyl bromide maintaining the temperature at 0 – 5 °C. The resulting biphasic mixture is aged 23 h at 4 – 6 °C.

Subsequently, water and MTBE are added and the aqueous layer is discharged. The organic layer is washed twice with water and once with aqueous acetic acid at 20 °C. Ethanol is added and then the solvent switched to ethanol by 3 put-and-take additions/vacuum distillations of ethanol at 35 – 40 °C with a target volume of each cycle remaining in the vessel, except for the third cycle where the mixture is concentrated to dryness. Ethanol is added to the vessel and the mixture heated at 60 °C external for 0.5 h before it is cooled to 20

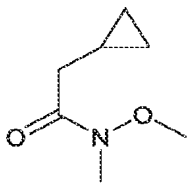
°C in 1 h and aged 18 h affording a suspension. The suspension is cooled to 0 °C, aged 6 h, filtered, and washed twice with ethanol pre-cooled to 0 °C to afford a solid. The solid is dried at 40 °C under vacuum to afford the compound of Formula (I).

Example 15C

5 Scheme 2: Preparation of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (Compound 1-A)



Step 1: Preparation of 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (Compound 2-B)



Compound 2-B

10

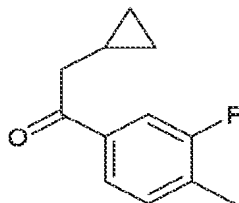
A suspension of 1,1'-Carbonyldiimidazole (152.6 kg, 1.01 eq.) in DCM (682 kg, 513 L, 7.3 w/w relative to 2-cyclopropylacetic acid) was treated with a solution of 2-cyclopropylacetic acid (1-B, 93.6 kg, 1 eq.) in DCM (248 kg, 186 L, 2.65 w/w) over at least 1 h, keeping the temperature ≤ 25 °C and compensating for significant effervescence. The resulting mixture is stirred for 15 min at 22 °C and then *N,O*-dimethylhydroxylamine·HCl (93.3 kg, 1.03 eq.) is added in portions, keeping the temperature ≤ 30 °C. Subsequently, triethylamine (46.4 kg, 0.49 eq.) is added to the stirring mixture at 20 - 25 °C. The resulting mixture is stirred at 22 °C at least 1 h. The mixture is washed once with KHSO₄ solution (0.24 M, 357.1 kg, 0.09 eq.), once with KHSO₄ solution (0.40 M, 365.4 kg, 0.15 eq.), once with KHSO₄ solution (0.80 M, 384.5 kg, 0.30 eq.), and once with NaHCO₃ solution (0.60 M, 393.1 kg, 0.24 eq.). Residual DCM is removed by three put-and-takes of THF (166.6 kg, 1.78 w/w) and vacuum distillation (50 – 60 °C, to minimum volume/until distillation stops). THF (333.2 kg, 3.56 w/w) is added and the yield is determined by correcting for the LOD and GC-

15

20

FID purity of the sample (131.5 kg, 98.2% corrected). $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ : -0.01 – 0.03 (m, 2H) 0.32 – 0.36 (m, 2H) 0.81 – 0.90 (br m, 1H) 2.18 (d, $J=6.80$ Hz, 2H) 2.97 (s, 3 H) 3.53 (s, 3H). ESI-MS: 144.0 $[\text{M}+\text{H}]^+$.

- 5 Step 2: Preparation of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (Compound 1-A)



Compound 1-A

- Mg (turnings, 28.6 kg, 1.37 eq.) are suspended in THF (244.7 kg, 2.0 w/w) and
10 DIBAL-H (1 M in *n*-heptane, 18.9 kg, 0.03 eq.) is added dropwise at 30 °C. The resulting mixture is stirred at 30 °C for at least 10 min and then 4-bromo-2-fluoro-1-methylbenzene (3-B, neat, 21.1 kg, 0.13 eq.) is added over at least 30 min at 30 – 50 °C. Subsequently, the mixture is treated with a solution of 4-bromo-2-fluoro-1-methylbenzene (3-B, 191.6 kg, 1.18 eq.) in THF (414.5 kg, 3.37 w/w) at 30 – 50 °C over 3 h or less. The mixture is stirred at 30
15 °C for at least 1 h. Subsequently, the mixture is treated with 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (2-B, 123.0 kg, 1 eq., 25.9% w/w solution in THF) over at least 1 h at 15 – 25 °C. The resulting mixture is stirred at 20 – 25 °C for at least 1 h. The stirring mixture is then treated with aqueous HCl (3 M, 10.3% w/w, 668.9 kg, 2.24 eq.) at 10 - 25 °C and the resulting mixture is stirred at least 2 h (check pH 3.0 – 3.5). The layers are separated, and the
20 aqueous layer is combined with heptane (290.3 kg, 2.36 w/w). The layers are separated, and the organic layer is washed once with NaHCO_3 solution (0.63 M, 211.6 kg, 0.15 eq.) and once with NaCl solution (2.57 M, 213.0 kg, 0.55 eq.). The residual solvents are removed by vacuum distillation at 58 - 62 °C until distillation stops and then one put-and-take of toluene (275.5 kg, 2.24 w/w) at 107 – 117 °C until distillation stops. Toluene (275.5 kg, 2.24 w/w) is
25 added and the yield is determined by correcting for the LOD and GC-FID purity of the sample (150.7 kg, 91.3% corrected). $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ ppm 0.07 - 0.21 (m, 2 H) 0.40 - 0.54 (m, 2 H) 1.02 (ttt, $J=8.16, 8.16, 6.68, 6.68, 4.86, 4.86$ Hz, 1 H) 2.30 (d, $J=1.77$ Hz, 3 H) 2.91 (d, $J=6.57$ Hz, 2 H) 7.44 (t, $J=7.83$ Hz, 1 H) 7.57 - 7.78 (m, 2 H). ESI-MS: 193.1 $[\text{M}+\text{H}]^+$.

Example 16: Compound of Formula (I) Crystalline Tosylate Salt Form 1

Approximately 20 mg of the Compound of Formula (I) was weighed into a vial. Using a positive displacement pipette, 250 μ L of solvent (IPA) was added to the vial along with a stir bar. The vial was placed in an aluminum block on a Reacti-Therm mixer and heated to 60 °C for ~1 hour. A molar equivalent of para-toluenesulfonic acid was added to the vial (20 μ L of a 2M solution in water) and allowed to stir. The sample was slow cooled back to room temperature along with mild Nitrogen gas for evaporation. Precipitate was collected, left to dry overnight, and then analyzed by XRPD, DSC, and TGA.

The crystallinity of the crystalline tosylate form 1 was confirmed by XRPD (Figure 27, Table 45) and further supported by DSC (Figure 28), indicating the crystalline compound having an onset of melt at about 156 °C (22.2 J/g). TGA of the crystalline compound is provided in Figure 28, and exhibited about 0.5% of weight loss due to solvent/H₂O.

Table 45. XRPD Peak Data for the Compound of Formula (I) Crystalline Tosylate Form 1

2-Theta (°)	Height (cps)
8.112(9)	957(89)
9.124(2)	12296(320)
9.471(2)	4519(194)
10.525(3)	8507(266)
11.316(3)	10211(292)
13.182(5)	6158(227)
13.494(6)	1598(115)
14.249(9)	2197(135)
15.208(9)	1746(121)
15.711(7)	1437(109)
16.252(5)	5723(218)
16.692(3)	3848(179)
17.540(4)	1578(115)
19.031(6)	6774(238)
19.265(4)	6491(233)
19.499(10)	3152(162)
20.401(3)	8581(267)
20.656(4)	3040(159)
21.142(3)	11498(310)
21.703(6)	4979(204)
21.870(11)	5331(211)
22.277(5)	3701(176)
22.769(3)	10159(291)

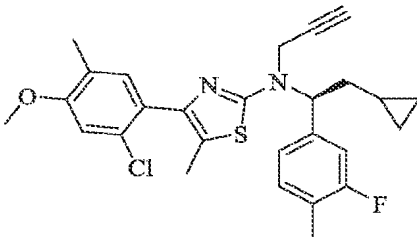
2-Theta (°)	Height (cps)
23.297(3)	14954(353)
23.532(4)	3597(173)
23.810(3)	9590(283)
24.73(2)	2325(139)
25.47(4)	1704(119)
26.087(5)	2413(142)
26.71(3)	422(59)
27.210(6)	1648(117)
27.593(5)	2825(153)
28.472(4)	6417(231)
29.51(3)	1423(109)
29.98(3)	849(84)
30.63(6)	1262(103)
30.77(3)	1121(97)
31.577(3)	5563(215)
32.74(4)	874(85)
33.73(4)	1111(96)
34.415(13)	2054(131)
34.799(11)	706(77)
35.139(15)	1320(105)
35.682(16)	1028(93)
38.39(4)	751(79)
39.743(17)	1790(122)
40.219(16)	762(80)
41.23(3)	925(88)
43.16(3)	1540(113)
44.288(12)	1142(98)

OTHER EMBODIMENTS

It is to be understood that the foregoing description is intended to illustrate and not limit the scope of the disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:
(a) a compound of Formula (I):



(I)

- or a pharmaceutically acceptable salt thereof; and
- (b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.
2. The pharmaceutical composition of claim 1, comprising about 1 wt% to about 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.
 3. The pharmaceutical composition of claim 1, comprising about 5 wt% to about 15 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.
 4. The pharmaceutical composition of claim 1, comprising about 10 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.
 5. The pharmaceutical composition of any one of claims 1-4, comprising an oily phase vehicle.
 6. The pharmaceutical composition of any one of claims 1-5, comprising about 1 wt% to about 50 wt% of the oily phase vehicle.
 7. The pharmaceutical composition of any one of claims 1-5, comprising about 20 wt% to about 50 wt% of the oily phase vehicle.

8. The pharmaceutical composition of any one of claims 1-5, comprising about 35 wt% to about 45 wt% of the oily phase vehicle.
9. The pharmaceutical composition of any one of claims 1-5, comprising about 39 wt% of the oily phase vehicle.
10. The pharmaceutical composition of any one of claims 1-9, wherein the oily phase vehicle is selected from medium-chain triglycerides, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutool.
11. The pharmaceutical composition of any one of claims 1-10, wherein the oily phase vehicle is medium-chain triglycerides.
12. The pharmaceutical composition of any one of claims 10-11, wherein the medium-chain triglycerides are Labrafac TM Lipophile WL1349.
13. The pharmaceutical composition of any one of claims 10-11, wherein the medium-chain triglycerides are Miglyol 812N.
14. The pharmaceutical composition of any one of claims 1-13, comprising an emulsifying agent.
15. The pharmaceutical composition of any one of claims 1-14, comprising about 5 wt% to about 50 wt% of the emulsifying agent.
16. The pharmaceutical composition of any one of claims 1-14, comprising about 10 wt% to about 30 wt% of the emulsifying agent.
17. The pharmaceutical composition of any one of claims 1-14, comprising about 15 wt% to about 25 wt% of the emulsifying agent.
18. The pharmaceutical composition of any one of claims 1-14, comprising about 20 wt% of the emulsifying agent.

19. The pharmaceutical composition of any one of claims 1-18, wherein the emulsifying agent is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcitol.

20. The pharmaceutical composition of any one of claims 1-19, wherein the emulsifying agent is propylene glycol dicaprylate/dicaprate.

21. The pharmaceutical composition of any one of claims 19-20, wherein the propylene glycol dicaprylate/dicaprate is Labrafac TM PG.

22. The pharmaceutical composition of any one of claims 1-21, comprising a nonionic surfactant.

23. The pharmaceutical composition of any one of claims 1-22, comprising about 5 wt% to about 50 wt% of the nonionic surfactant.

24. The pharmaceutical composition of any one of claims 1-22, comprising about 10 wt% to about 30 wt% of the nonionic surfactant.

25. The pharmaceutical composition of any one of claims 1-22, comprising about 15 wt% to about 25 wt% of the nonionic surfactant.

26. The pharmaceutical composition of any one of claims 1-22, comprising about 19 wt% of the nonionic surfactant.

27. The pharmaceutical composition of any one of claims 1-26, wherein the nonionic surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, Gelucire, lauroyl polyoxyl-32 glycerides, Poloxamer, PEG-32 stearate, and PEG-32 hydrogenated palm glycerides.

28. The pharmaceutical composition of any one of claims 1-27, wherein the nonionic surfactant is lauroyl polyoxyl-32 glycerides.

29. The pharmaceutical composition of any one of claims 27-28, wherein the lauroyl polyoxyl-32 glycerides are Gelucire® 44/14.
30. The pharmaceutical composition of any one of claims 1-29, comprising a solubilizing agent.
31. The pharmaceutical composition of any one of claims 1-30, comprising about 1 wt% to about 50 wt% of the solubilizing agent.
32. The pharmaceutical composition of any one of claims 1-30, comprising about 1 wt% to about 20 wt% of the solubilizing agent.
33. The pharmaceutical composition of any one of claims 1-30, comprising about 5 wt% to about 15 wt% of the solubilizing agent.
34. The pharmaceutical composition of any one of claims 1-30, comprising about 11 wt% of the solubilizing agent.
35. The pharmaceutical composition of any one of claims 1-34, wherein the solubilizing agent is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, and Poloxamer.
36. The pharmaceutical composition of any one of claims 1-35, wherein the solubilizing agent is vitamin E polyethylene glycol succinate.
37. The pharmaceutical composition of any one of claims 35-36, wherein the vitamin E polyethylene glycol succinate is Kolliphor® TP GS.
38. The pharmaceutical composition of any one of claims 35-36, wherein the vitamin E polyethylene glycol succinate is Vitamin E/TPGS 260.
39. The pharmaceutical composition of claim 1, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

- (b) an oily phase vehicle;
- (c) an emulsifying agent;
- (d) a nonionic surfactant; and
- (e) a solubilizing agent.

40. The pharmaceutical composition of claim 1, comprising:

- (a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 35 wt% to about 45 wt% of an oily phase vehicle;
- (c) about 15 wt% to about 25 wt% of an emulsifying agent;
- (d) about 15 wt% to about 25 wt% of a nonionic surfactant; and
- (e) about 5 wt% to about 15 wt% of a solubilizing agent.

41. The pharmaceutical composition of claim 1, comprising:

- (a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 39 wt% of an oily phase vehicle;
- (c) about 20 wt% of an emulsifying agent;
- (d) about 19 wt% of a nonionic surfactant; and
- (e) about 11 wt% of a solubilizing agent.

42. The pharmaceutical composition of claim 1, comprising:

- (a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
- (b) a medium-chain triglycerides component;
- (c) a propylene glycol dicaprylate/dicaprate component;
- (d) a lauroyl polyoxyl-32 glycerides component; and
- (e) a vitamin E polyethylene glycol succinate component.

43. The pharmaceutical composition of claim 1, comprising:
- (a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
 - (b) about 35 wt% to about 45 wt% of medium-chain triglycerides;
 - (c) about 15 wt% to about 25 wt% of propylene glycol dicaprylate/dicaprate;
 - (d) about 15 wt% to about 25 wt% of lauroyl polyoxyl-32 glycerides; and
 - (e) about 5 wt% to about 15 wt% of vitamin E polyethylene glycol succinate.
44. The pharmaceutical composition of claim 1, comprising:
- (a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
 - (b) about 39 wt% of medium-chain triglycerides;
 - (c) about 20 wt% of propylene glycol dicaprylate/dicaprate;
 - (d) about 19 wt% of lauroyl polyoxyl-32 glycerides; and
 - (e) about 11 wt% of vitamin E polyethylene glycol succinate.
45. The pharmaceutical composition of any one of claims 1-44, wherein the compound of Formula (I), or pharmaceutically acceptable salt thereof, is in crystalline form.
46. The pharmaceutical composition of any one of claims 1-45, comprising the compound of Formula (I) as a free base.
47. The pharmaceutical composition of claim 45, wherein the crystalline form comprises Form I of the compound of Formula (I).
48. The pharmaceutical composition of any one of claims 1-47, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg, based on the weight of the free base.
49. The pharmaceutical composition of claim 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg, based on the weight of the free base.

50. The pharmaceutical composition of claim 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg, based on the weight of the free base.

51. The pharmaceutical composition of claim 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg, based on the weight of the free base.

52. The pharmaceutical composition of claim 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg, based on the weight of the free base.

53. The pharmaceutical composition of any one of claims 1-52, that is in the form of a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film.

54. The pharmaceutical composition of any one of claims 48-53, wherein the pharmaceutical composition is in tablet form.

55. The pharmaceutical composition of any one of claims 48-53, wherein the pharmaceutical composition is in capsule form.

56. The pharmaceutical composition of any one of claims 48-55, wherein the dosage form is coated.

57. A method for preparing the pharmaceutical composition of any one of claims 1-56, comprising:

- (a) heating a mixture of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent;
- (b) mixing the mixture of step (a) until a homogeneous mixture is achieved; and

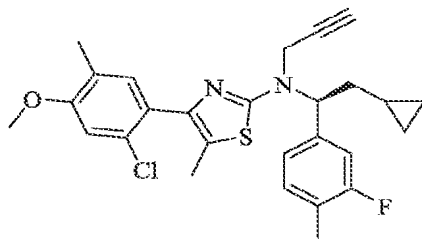
(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the homogeneous mixture of step (b) until the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dissolved, forming a composition.

58. The method of claim 57, further comprising:

- (d) encapsulating the composition of step (c) in a capsule shell to form a capsule; and
- (e) banding the capsule of step (d) in a mixture of banding agent and banding solvent.

59. A pharmaceutical composition in oral solution dosage form comprising:

- (a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

- (b) one or more of a sweetener, an anti-oxidant, and a flavor; and

- (c) a liquid vehicle.

60. The pharmaceutical composition of claim 59, comprising about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

61. The pharmaceutical composition of claim 59, comprising about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

62. The pharmaceutical composition of claim 59, comprising about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

63. The pharmaceutical composition of any one of claims 59-62, comprising a sweetener.

64. The pharmaceutical composition of any one of claims 59-63, comprising about 0.01 w/v% to about 1.5 w/v% of the sweetener.
65. The pharmaceutical composition of any one of claims 59-63, comprising about 0.1 w/v% to about 0.5 w/v% of the sweetener.
66. The pharmaceutical composition of any one of claims 59-63, comprising about 0.15 w/v% of the sweetener.
67. The pharmaceutical composition of any one of claims 59-66, wherein the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and advantame.
68. The pharmaceutical composition of any one of claims 59-67, wherein the sweetener is saccharin.
69. The pharmaceutical composition of any one of claims 59-68, comprising an anti-oxidant.
70. The pharmaceutical composition of any one of claims 59-69, comprising about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant.
71. The pharmaceutical composition of any one of claims 59-69, comprising about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant.
72. The pharmaceutical composition of any one of claims 59-69, comprising about 0.17 w/v% of the anti-oxidant.
73. The pharmaceutical composition of any one of claims 59-72, wherein the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TPGS, butylated hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid.
74. The pharmaceutical composition of any one of claims 59-73, wherein the anti-oxidant is butylated hydroxytoluene.

75. The pharmaceutical composition of any one of claims 59-74, comprising a flavor.
76. The pharmaceutical composition of any one of claims 59-75, comprising about 0.01 w/v% to about 0.5 w/v% of the flavor.
77. The pharmaceutical composition of any one of claims 59-75, comprising about 0.05 w/v% to about 0.2 w/v% of the flavor.
78. The pharmaceutical composition of any one of claims 59-75, comprising about 0.10 w/v% of the flavor.
79. The pharmaceutical composition of any one of claims 59-78, wherein the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetrarome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor.
80. The pharmaceutical composition of any one of claims 59-79, wherein the flavor is FONA orange flavor.
81. The pharmaceutical composition of any one of claims 59-80, comprising about 50 w/v% to about 99.9 w/v% of the liquid vehicle.
82. The pharmaceutical composition of any one of claims 59-80, comprising about 92 w/v% to about 97 w/v% of the liquid vehicle.
83. The pharmaceutical composition of any one of claims 59-80, comprising about 94.6 w/v% of the liquid vehicle.
84. The pharmaceutical composition of any one of claims 59-83, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

85. The pharmaceutical composition of any one of claims 59-84, wherein the liquid vehicle is medium-chain triglycerides.

86. The pharmaceutical composition of any one of claims 84-85, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.

87. The pharmaceutical composition of any one of claims 59-86, further comprising a surfactant.

88. The pharmaceutical composition of claim 87, comprising about 1 w/v% to about 50 w/v% of the surfactant.

89. The pharmaceutical composition of claim 87, comprising about 10 w/v% to about 30 w/v% of the surfactant.

90. The pharmaceutical composition of claim 87, comprising about 20 w/v% of the surfactant.

91. The pharmaceutical composition of any one of claims 87-90, wherein the surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, sodium lauryl sulfate, Poloxamer, corn oil PEG-6 esters, and hydrogenated palm/palm kernel oil PEG-6 esters.

92. The pharmaceutical composition of any one of claims 87-91, wherein the surfactant is oleoyl polyoxyl-6 glycerides.

93. The pharmaceutical composition of any one of claims 91-92, wherein the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS.

94. The pharmaceutical composition of any one of claims 59-93, comprising about 70 w/v% to about 80 w/v% of the liquid vehicle.

95. The pharmaceutical composition of any one of claims 59-93, comprising about 75 w/v% of the liquid vehicle.
96. The pharmaceutical composition of any one of claims 59-95, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcitol.
97. The pharmaceutical composition of any one of claims 59-96, wherein the liquid vehicle is medium-chain triglycerides.
98. The pharmaceutical composition of any one of claims 95-96, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.
99. The pharmaceutical composition of claim 59, comprising:
- (a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
 - (b) a sweetener;
 - (c) an anti-oxidant;
 - (d) a flavor; and
 - (e) a liquid vehicle.
100. The pharmaceutical composition of claim 99, further comprising a surfactant.
101. The pharmaceutical composition of claim 59, comprising:
- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
 - (b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
 - (c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
 - (d) about 0.05 w/v% to about 0.2 w/v% of a flavor; and

- (e) about 92 w/v% to about 97 w/v% of a liquid vehicle.
102. The pharmaceutical composition of claim 59, comprising:
- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
 - (b) about 0.15 w/v% of a sweetener;
 - (c) about 0.17 w/v% of an anti-oxidant;
 - (d) about 0.1 w/v% of a flavor; and
 - (e) about 94.6 w/v% of a liquid vehicle.
103. The pharmaceutical composition of claim 59, comprising:
- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
 - (b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
 - (c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
 - (d) about 0.05 w/v% to about 0.2 w/v% of a flavor;
 - (e) about 15 w/v% to about 25 w/v% of a surfactant; and
 - (f) about 70 w/v% to about 80 w/v% of a liquid vehicle.
104. The pharmaceutical composition of claim 59, comprising:
- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
 - (b) about 0.15 w/v% of a sweetener;
 - (c) about 0.17 w/v% of an anti-oxidant;
 - (d) about 0.1 w/v% of a flavor;
 - (e) about 20 w/v% of a surfactant; and
 - (f) about 75 w/v% of a liquid vehicle.
105. The pharmaceutical composition of claim 59, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) saccharin;

(c) butylated hydroxytoluene;

(d) FONA orange flavor; and

(e) medium-chain triglycerides.

106. The pharmaceutical composition of claim 105, further comprising oleoyl polyoxyl-6 glycerides.

107. The pharmaceutical composition of claim 106, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;

(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;

(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor; and

(e) about 92 w/v% to about 97 w/v% of medium-chain triglycerides.

108. The pharmaceutical composition of claim 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of saccharin;

(c) about 0.17 w/v% of butylated hydroxytoluene;

(d) about 0.1 w/v% of FONA orange flavor; and

(e) about 94.6 w/v% of medium-chain triglycerides.

109. The pharmaceutical composition of claim 59, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-

2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

- (b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
- (c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
- (d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor;
- (e) about 15 w/v% to about 25 w/v% of oleoyl polyoxyl-6 glycerides; and
- (f) about 70 w/v% to about 80 w/v% of medium-chain triglycerides.

110. The pharmaceutical composition of claim 59, comprising:

- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.15 w/v% of saccharin;
- (c) about 0.17 w/v% of butylated hydroxytoluene;
- (d) about 0.1 w/v% of FONA orange flavor;
- (e) about 20 w/v% of oleoyl polyoxyl-6 glycerides; and
- (f) about 75 w/v% of medium-chain triglycerides.

111. The pharmaceutical composition of any one of claims 59-110, comprising the compound of Formula (I) as a free base.

112. The pharmaceutical composition of any one of claims 59-111, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg/mL to about 200 mg/mL, based on the weight of the free base.

113. The pharmaceutical composition of claim 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg/mL to about 150 mg/mL, based on the weight of the free base.

114. The pharmaceutical composition of claim 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg/mL, based on the weight of the free base.

115. The pharmaceutical composition of claim 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg/mL, based on the weight of the free base.

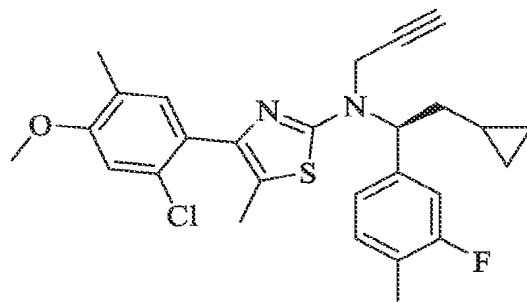
116. The pharmaceutical composition of any one of claims 1-56, having a viscosity between about 15 to about 40 centipoise at about 45 °C.

117. A method for preparing the pharmaceutical composition of any one of claims 59-116, comprising:

- (a) mixing a liquid vehicle with a sweetener;
- (b) mixing the mixture of step (a) with an anti-oxidant and a flavor;
- (c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the mixture of step (b); and
- (d) mixing the mixture of step (c) with an additional portion of the liquid vehicle.

118. The method of claim 117, wherein step (a) comprises mixing a liquid vehicle with a sweetener and a surfactant.

119. A spray-dried dispersion comprising:
a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and
a polymer selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer;

wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:1 to about 1:9.

120. The spray-dried dispersion of claim 119, wherein the neutral polymer is selected from hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

121. The spray-dried dispersion of claim 119, wherein the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer.

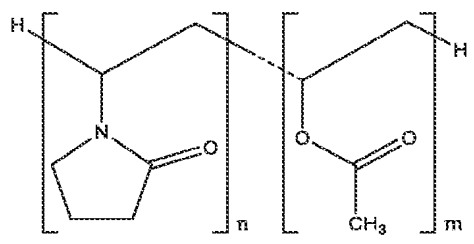
122. The spray-dried dispersion of claim 119, wherein the pyrrolidone polymer is selected from polyvinyl pyrrolidone (PVP) and a polyvinyl pyrrolidone vinyl acetate (PVP/VA).

123. The spray-dried dispersion of claim 122, wherein the pyrrolidone polymer is PVP/VA.

124. The spray-dried dispersion of claim 123, wherein the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 40:60 to about 60:40 by weight.

125. The spray-dried dispersion of claim 124, wherein the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight.

126. The spray-dried dispersion of any one of claims 122-125, wherein the copolymer has the structure:

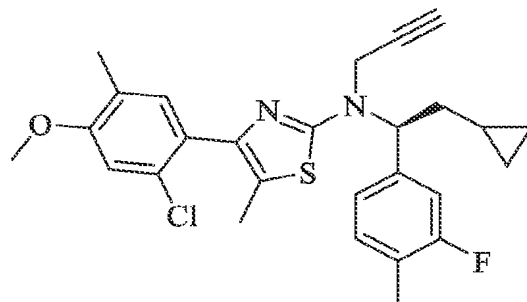


wherein the value of n is about 1 to about 2 times the value of m.

127. The spray-dried dispersion of claim 126, wherein the copolymer is copovidone, wherein the value of n is about 1.16 times the value of m.

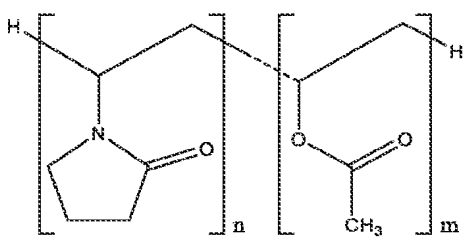
128. The spray-dried dispersion of claim 126, wherein the copolymer is copovidone having an average molecular weight of about 45,000 to about 70,000.

129. A spray-dried dispersion comprising:
a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and
a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



, wherein the value of n is about 1 to about 2 times the value of m and the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight; and
wherein the weight ratio of the compound of Formula (I) to the copolymer is from about 1:1 to about 1:9.

130. The spray-dried dispersion of any one of claims 119-129, wherein the compound of Formula (I) and the polymer together form homogeneous particles.

131. The spray-dried dispersion of any one of claims 119-130, wherein the particles have a particle size distribution D_{50} of about 5 μm to about 100 μm .

132. The spray-dried dispersion of any one of claims 119-131, wherein the particles have a particle size distribution D_{50} of about 10 μm to about 50 μm .

133. The spray-dried dispersion of any one of claims 119-132, wherein the particles have a particle size distribution D_{50} of about 15 μm to about 30 μm .

134. The spray-dried dispersion of any one of claims 119-133, wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:1.5 to about 1:9.
135. The spray-dried dispersion of any one of claims 119-134, wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:2.5 to about 1:4.
136. The spray-dried dispersion of any one of claims 119-135, wherein the weight ratio of the compound of Formula (I) to the polymer is about 1:3.
137. The spray-dried dispersion of any one of claims 119-136, wherein the particles have a residual solvent content less than about 2 wt %.
138. The spray-dried dispersion of any one of claims 119-137, wherein the particles have a residual solvent content less than about 1 wt %.
139. The spray-dried dispersion of any one of claims 119-138, wherein the particles have a residual solvent content of about 0.5 wt % or less.
140. The spray-dried dispersion of any one of claims 119-139, wherein the compound of Formula (I) in the dispersion is substantially amorphous.
141. A pharmaceutical composition comprising the spray-dried dispersion of any one of claims 119-140 and one or more pharmaceutically acceptable excipients.
142. The pharmaceutical composition of claim 141, wherein the spray-dried dispersion is present in an amount of about 20% to about 90% w/w of the composition.
143. The pharmaceutical composition of claim 142, wherein the spray-dried dispersion is present in an amount of about 40% to about 80% w/w of the composition.
144. The pharmaceutical composition of claim 141, wherein the spray-dried dispersion is present in an amount of about 1% to about 20% w/w of the composition.

145. The pharmaceutical composition of claim 144, wherein the spray-dried dispersion is present in an amount of about 13% w/w of the composition.

146. The pharmaceutical composition of any one of claims 141-145, wherein the pharmaceutical excipients are selected from the group consisting of a filler, a lubricant, and combinations thereof.

147. The pharmaceutical composition of claim 146, wherein the filler is selected from the group consisting of a binder, a diluent, a disintegrant, a glidant, a surfactant, and combinations thereof.

148. The pharmaceutical composition of any one of claims 141-147 formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg.

149. The pharmaceutical composition of claim 148, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg.

150. The pharmaceutical composition of claim 149, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg.

151. The pharmaceutical composition of claim 149, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg.

152. The pharmaceutical composition of any one of claims 141-151, wherein the pharmaceutical excipients are selected from the group consisting of a glidant, a filler, a disintegrant, a lubricant, and a combination thereof.

153. The pharmaceutical composition of any one of claims 141-152, comprising a glidant.

154. The pharmaceutical composition of any one of claims 152-153, comprising about 0.1 w/w% to about 5 w/w% of the glidant.

155. The pharmaceutical composition of any one of claims 152-153, comprising about 0.1 w/w% to about 1 w/w% of the glidant.

156. The pharmaceutical composition of any one of claims 152-153, comprising about 0.67 w/w% of the glidant.

157. The pharmaceutical composition of any one of claims 152-156, wherein the glidant is selected from calcium silicate, silicon dioxide, and talc.

158. The pharmaceutical composition of any one of claims 152-157, wherein the glidant is calcium silicate.

159. The pharmaceutical composition of any one of claims 141-158, comprising a filler.

160. The pharmaceutical composition of any one of claims 152-159, comprising about 30 w/w% to about 99 w/w% of the filler.

161. The pharmaceutical composition of any one of claims 152-159, comprising about 50 w/w% to about 90 w/w% of the filler.

162. The pharmaceutical composition of any one of claims 152-159, comprising about 75.5 w/w% of the filler.

163. The pharmaceutical composition of any one of claims 152-162, wherein the filler is selected from mannitol, microcrystalline cellulose, lactose, starch, isomalt, silicified microcrystalline cellulose, Dicalcium Phosphate, maltodextrin, and a combination thereof.

164. The pharmaceutical composition of any one of claims 152-163, wherein the filler is a combination of mannitol and microcrystalline cellulose.

165. The pharmaceutical composition of any one of claims 163-164, comprising about 30 w/w% to about 80 w/w% of mannitol.

166. The pharmaceutical composition of any one of claims 163-164, comprising about 50 w/w% to about 60 w/w% of mannitol.

167. The pharmaceutical composition of any one of claims 163-164, comprising about 56 w/w% of mannitol.

168. The pharmaceutical composition of any one of claims 163-167, comprising about 1 w/w% to about 50 w/w% of microcrystalline cellulose.

169. The pharmaceutical composition of any one of claims 163-167, comprising about 10 w/w% to about 30 w/w% of microcrystalline cellulose.

170. The pharmaceutical composition of any one of claims 163-167, comprising about 20 w/w% of microcrystalline cellulose.

171. The pharmaceutical composition of any one of claims 163-167, comprising about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose.

172. The pharmaceutical composition of any one of claims 141-171, comprising a disintegrant.

173. The pharmaceutical composition of any one of claims 152-172, comprising about 1 w/w% to about 30 w/w% of the disintegrant.

174. The pharmaceutical composition of any one of claims 152-172, comprising about 5 w/w% to about 15 w/w% of the disintegrant.

175. The pharmaceutical composition of any one of claims 152-172, comprising about 10 w/w% of the disintegrant.

176. The pharmaceutical composition of any one of claims 152-175, wherein the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, and sodium bicarbonate.

177. The pharmaceutical composition of any one of claims 152-176, wherein the disintegrant is croscarmellose sodium.
178. The pharmaceutical composition of any one of claims 141-177, comprising a lubricant.
179. The pharmaceutical composition of any one of claims 152-178, comprising about 0.1 w/w% to about 10 w/w% of the lubricant.
180. The pharmaceutical composition of any one of claims 152-178, comprising about 0.1 w/w% to about 1 w/w% of the lubricant.
181. The pharmaceutical composition of any one of claims 152-178, comprising about 0.5 w/w% of the lubricant.
182. The pharmaceutical composition of any one of claims 152-181, wherein the lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid, sodium lauryl sulfate, sodium oleate, glyceryl behenate, and talc.
183. The pharmaceutical composition of any one of claims 152-182, wherein the lubricant is sodium stearyl fumarate.
184. The pharmaceutical composition of any one of claims 141-183, comprising:
- (a) the spray-dried dispersion of any one of claims 119-140;
 - (b) a glidant;
 - (c) a filler; and
 - (d) a disintegrant.
185. The pharmaceutical composition of any one of claims 141-183, comprising:
- (a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of any one of claims 119-140;
 - (b) about 0.1 w/w% to about 1 w/w% of a glidant;

- (c) about 50 w/w% to about 90 w/w% of a filler; and
 - (d) about 5 w/w% to about 0.2 w/w% of a disintegrant.
186. The pharmaceutical composition of any one of claims 141-183, comprising:
- (a) about 13 w/w% of the spray-dried dispersion of any one of claims 119-140;
 - (b) about 0.67 w/w% of a glidant;
 - (c) about 75.5 w/w% of a filler; and
 - (d) about 10 w/w% of a disintegrant.
187. The pharmaceutical composition of any one of claims 141-183, comprising:
- (a) the spray-dried dispersion of Example 3;
 - (b) calcium silicate;
 - (c) a combination of mannitol and microcrystalline cellulose; and
 - (d) croscarmellose sodium.
188. The pharmaceutical composition of claim 187, comprising:
- (a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of Example 3;
 - (b) about 0.1 w/w% to about 1 w/w% of calcium silicate;
 - (c) about 50 w/w% to about 60 w/w% of mannitol and about 10 w/w% to about 30 w/w% of microcrystalline cellulose; and
 - (d) about 5 w/w% to about 0.2 w/w% of croscarmellose sodium.
189. The pharmaceutical composition of claim 188, comprising:
- (a) about 13 w/w% of the spray-dried dispersion of Example 3;
 - (b) about 0.67 w/w% of calcium silicate;
 - (c) about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose; and
 - (d) about 10 w/w% of croscarmellose sodium.
190. The pharmaceutical composition of any one of claims 141-189 that is formulated as a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film.

191. The pharmaceutical composition of claim 190, wherein the pharmaceutical composition is in tablet form.

192. The pharmaceutical composition of claim 190, wherein the pharmaceutical composition is in capsule form.

193. The pharmaceutical composition of claim 190, wherein the pharmaceutical composition is in sachet form.

194. The pharmaceutical composition of claim 190, wherein the pharmaceutical composition is in granule form.

195. The pharmaceutical composition of any one of claims 190-192, wherein the pharmaceutical composition is coated.

196. A method for preparing the spray-dried dispersion of any one of claims 119-140, comprising:

dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and

spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer.

197. The method of claim 196, comprising removing the organic solvent after formation of the spray-dried dispersion by drying the spray-dried dispersion.

198. The method of claim 197, wherein the spray-dried dispersion is dried with a convection tray dryer.

199. The method of any one of claims 196-198, wherein the organic solvent is acetone.

200. The method of any one of claims 196-199, wherein the spray dryer inlet temperature is about 60°C to about 80°C.

201. The method of claim 200, wherein the spray dryer inlet temperature is about 72°C.
202. The method of any one of claims 196-201, wherein the spray dryer outlet temperature is about 25°C to about 45°C.
203. The method of claim 202, wherein the spray dryer outlet temperature is about 35°C.
204. The method of any one of claims 196-203, wherein the homogeneous particles comprise a bulk density of less than about 0.2 g/mL.
205. The method of claim 204, wherein the homogeneous particles comprise a bulk density of less than about 0.15 g/mL.
206. The method of any one of claims 196-205, wherein the homogeneous particles comprise a tapped density of less than about 0.3 g/mL.
207. The method of claim 206, wherein the homogeneous particles comprise a tapped density of less than about 0.25 g/mL.
208. A method for preparing a pharmaceutical composition, comprising combining the spray-dried dispersion of any one of claims 119-140 with one or more pharmaceutically acceptable excipients.
209. The method of claim 208, comprising:
- (a) blending the spray-dried dispersion of any one of claims 119-140, with a glidant;
 - (b) further blending the blend of step (a) with a filler and a disintegrant;
 - (c) screening the blend of step (b) to break up aggregates and assist with blend uniformity;
 - (d) further blending the intragranular blend of step (c);
 - (e) compaction of the intragranular blend of step (d) via roller compaction to form granules;
 - and
 - (f) milling of ribbon from roller compaction into granules of step (e).

210. A method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the spray-dried dispersion of any one of claims 119-140 or the pharmaceutical composition of any one of claims 141-195.

211. The method of claim 210, wherein the spray-dried dispersion or the pharmaceutical composition is administered to the subject in a fed state.

212. The method of claim 210 or claim 211, wherein the spray-dried dispersion or the pharmaceutical composition is administered to the subject with a nutritional composition.

213. The method of claim 212, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

214. The method of claim 212 or claim 213, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

215. The method of any one of claims 212-214, wherein the nutritional composition is administered within 30 minutes of administration of the spray-dried dispersion or the pharmaceutical composition.

216. The method of any one of claims 211-215, wherein administering the spray-dried dispersion or the pharmaceutical composition exhibits a positive food effect.

217. The method of claim 216, wherein the positive food effect is measured in terms of C_{max} , AUC, or combinations thereof when comparing oral administration of the spray-dried dispersion or pharmaceutical composition in the fed and fasting states.

218. The method of any one of claims 211-217, wherein the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10.

219. The method of any one of claims 211-217, wherein the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10.
220. The method of any one of claims 210-219, wherein the subject is a pediatric subject.
221. A method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, comprising orally administering to the subject the pharmaceutical composition of any one of claims 141-195, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.
222. The method of claim 221, wherein the subject is a pediatric subject.
223. A method of improving oral bioavailability of a compound of Formula (I) in a subject, comprising orally administering to the subject the pharmaceutical composition of any one of claims 141-195, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.
224. The method of claim 223, wherein the subject is a pediatric subject.
225. The spray-dried dispersion of any one of claims 119-140, wherein the spray-dried dispersion is formulated for oral administration and exhibits a positive food effect when administered orally.
226. The spray-dried dispersion of claim 225, wherein the spray-dried dispersion has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10.
227. The spray-dried dispersion of claim 225, wherein the spray-dried dispersion has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 5 to about 10.
228. A crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

229. The salt of claim 228, having Form 1 of the Compound of Formula (I).
230. The salt of claim 228 or claim 229, having an X-ray powder diffraction pattern as substantially shown in Figure 27.
231. The salt of any one of claims 228-230, having a DSC thermogram substantially as depicted in Figure 28.
232. The salt of any one of claims 228-231, having a thermogravimetric analysis (TGA) thermogram substantially as depicted in Figure 28.
233. The salt of any one of claims 228-232, having at least one X-ray powder diffraction (XRPD) peak, in terms of 2-theta (± 0.2 degrees), selected 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.
234. The salt of any one of claims 228-232, having at least two X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.
235. The salt of any one of claims 228-232, having at least three X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.
236. The salt of any one of claims 228-232, having at least four X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.
237. The salt of any one of claims 228-232, having characteristic X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), at 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.
238. The salt of any one of claims 228-237, having an endothermic peak having an onset of melt at about 156 °C (22.2 J/g) in a differential scanning calorimetry (DSC) thermogram.

239. A method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in the subject.

240. The method of claim 239, wherein the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

241. The method of claim 240, wherein the circadian release occurs between the hours of 2 a.m. and 10 a.m.

242. The method of any one of claims 239-241, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

243. The method of any one of claims 239-242, wherein the level of 17-hydroxyprogesterone is reduced by at least 25%.

244. The method of any one of claims 239-242, wherein the level of 17-hydroxyprogesterone is reduced by at least 50%.

245. The method of any one of claims 239-244, wherein the level of adrenocorticotrophic hormone is reduced by at least 25%.

246. The method of any one of claims 239-244, wherein the level of adrenocorticotrophic hormone is reduced by at least 40%.

247. The method of any one of claims 239-244, wherein the level of adrenocorticotrophic hormone is reduced by at least 50%.

248. The method of any one of claims 239-247, wherein the level of androstenedione is reduced by at least 25%.

249. The method of any one of claims 239-247, wherein the level of androstenedione is reduced by at least 30%.

250. The method of any one of claims 239-247, wherein the level of androstenedione is reduced by at least 50%.

251. The method of any one of claims 239-250, wherein the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

252. The method of any one of claims 239-251, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

253. The method of any one of claims 239-252, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

254. A method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia,

comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of androstenedione in the subject.

255. The method of claim 254, wherein the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

256. The method of claim 254 or 255, wherein the androstenedione is reduced by at least 25%.

257. The method of claim 254 or 255, wherein the androstenedione is reduced by at least 30%.

258. The method of claim 254 or 255, wherein the androstenedione is reduced by at least 50%.

259. A method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

260. The method of claim 259, wherein the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

261. A method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

262. The method of claim 261, wherein the corticosteroid is a glucocorticoid.

263. A method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof,

wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

264. The method of any one of claims 259-263, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

265. The method of any one of claims 259-264, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

266. The method of any one of claims 259-264, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an

amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

267. The method of any one of claims 259-266, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

268. The method of any one of claims 259-267, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

269. The method of any one of claims 259-268, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

270. A method of treating congenital adrenal hyperplasia in a subject comprising
- (i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
 - (ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
 - (iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

271. The method of claim 270, further comprising (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i).

272. The method of claim 271, further comprising (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

273. The method of claim 271 or 272, wherein steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window.

274. The method of any one of claims 271-273, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m.

275. The method of any one of claims 271-273, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

276. The method of any one of claims 271-275, wherein steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

277. The method of any one of claims 271-275, wherein steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

278. The method of any one of claims 270-277, wherein step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

279. The method of any one of claims 270-278, wherein step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

280. The method of any one of claims 270-279, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

281. The method of any one of claims 270-279, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

282. The method of any one of claims 270-281, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

283. A method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, where in the subject is in a fed state.

284. The method of claim 283, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition.

285. The method of claim 284, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

286. The method of claim 284 or 285, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

287. The method of any one of claims 284-286, wherein the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

288. A pharmaceutical composition of any one of claims 1-56, 59-116 or 141-195 for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

289. The pharmaceutical composition for use according to claim 288, wherein the subject is in a fed state.

290. The pharmaceutical composition for use according to claim 288 or claim 289, wherein the subject is administered the pharmaceutical composition with a nutritional composition.

291. The pharmaceutical composition for use according to claim 290, wherein the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than about 30%.

292. The pharmaceutical composition for use according to claim 290, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

293. The pharmaceutical composition for use according to any one of claims 290-292, wherein the nutritional composition is administered in an amount of about 6 to about 12 fluid ounces.

294. The pharmaceutical composition for use according to any one of claims 290-293, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

295. The pharmaceutical composition for use according to any one of claims 290-294, wherein the nutritional composition is administered within 30 minutes of administration of the pharmaceutical composition.

296. The pharmaceutical composition for use according to any one of claims 289-295, wherein administering the pharmaceutical composition exhibits a positive food effect.

297. The pharmaceutical composition for use according to claim 296, wherein the positive food effect is measured in terms of C_{max} , AUC, or a combination thereof of a compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states.

298. The pharmaceutical composition for use according to any one of claims 289-297, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

299. The pharmaceutical composition for use according to any one of claims 289-297, wherein the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

300. The pharmaceutical composition for use according to any one of claims 289-297, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

301. The pharmaceutical composition for use according to any one of claims 289-297, wherein the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

302. The pharmaceutical composition for use according to any one of claims 288-301, wherein the subject is a pediatric subject.

303. The pharmaceutical composition for use according to any one of claims 289-295, wherein the pharmaceutical composition exhibits a positive food effect when administered orally.

304. The pharmaceutical composition for use according to claim 303, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4 or about 5 to about 10.

305. The pharmaceutical composition for use according to claim 303, wherein the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1 to about 4 or about 5 to about 10.

306. The pharmaceutical composition for use according to claim 303, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1.5 to about 3.

307. The pharmaceutical composition for use according to claim 303, wherein the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1.5 to about 3.

308. The pharmaceutical composition for use according to any one of claims 288-307, wherein the pharmaceutical composition is administered to the subject with a meal.

309. The pharmaceutical composition for use according to claim 308, wherein the meal is a high fat meal.

310. The pharmaceutical composition for use according to claim 308, wherein the meal is a low fat meal.

311. The pharmaceutical composition for use according to any one of claims 308-310, wherein the pharmaceutical composition is administered within about 5 minutes after the start of the meal.

312. The pharmaceutical composition for use according to any one of claims 308-311, wherein the meal is an evening meal.

313. The pharmaceutical composition for use according to any one of claims 308-311, wherein the meal is a morning meal.

314. The pharmaceutical composition for use according to any one of claims 308-313, wherein administering the pharmaceutical composition exhibits a positive food effect.

315. The pharmaceutical composition for use according to claim 314, wherein the positive food effect is measured in terms of C_{max} , AUC, or combinations thereof of the compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states.

316. The pharmaceutical composition for use according to any one of claims 308-315, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

317. The pharmaceutical composition for use according to any one of claims 308-316, wherein the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

318. The pharmaceutical composition for use according to any one of claims 308-315, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

319. The pharmaceutical composition for use according to any one of claims 308-315 or 318, wherein the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

320. The pharmaceutical composition for use according to any one of claims 288-319, wherein the pharmaceutical composition comprises about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

321. The pharmaceutical composition for use according to any one of claims 288-319, wherein the pharmaceutical composition comprises about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

322. The pharmaceutical composition for use according to any one of claims 288-319, wherein the pharmaceutical composition comprises about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

323. The pharmaceutical composition for use according to any one of claims 288-319, wherein the pharmaceutical composition comprises about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

324. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

325. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

326. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

327. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

328. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

329. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

330. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

331. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

332. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

333. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a

dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

334. The pharmaceutical composition for use according to any one of claims 288-333, wherein the subject is concurrently receiving a dose of a glucocorticoid.

335. The pharmaceutical composition for use according to claim 334, wherein the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate.

336. The pharmaceutical composition for use according to claim 334 or 335, wherein the glucocorticoid is cortisol (hydrocortisone).

337. The pharmaceutical composition for use according to claim 334 or 335, wherein the glucocorticoid is cortisone.

338. The pharmaceutical composition for use according to claim 334 or 335, wherein the glucocorticoid is prednisone.

339. The pharmaceutical composition for use according to any one of claims 334-338, wherein the glucocorticoid dose is measured in hydrocortisone equivalents.

340. The pharmaceutical composition for use according to any one of claims 334-339, wherein the glucocorticoid dose is measured as a multiple of the upper limit of normal of physiologic dosing in hydrocortisone equivalents.

341. The pharmaceutical composition for use according to any one of claims 334-340, wherein the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the pharmaceutical composition.

342. The pharmaceutical composition for use according to any one of claims 334-340, wherein the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m²/day as measured after a time period of administration of the pharmaceutical composition.

343. The pharmaceutical composition for use according to any one of claims 334-340, wherein the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m²/day as measured after a time period of administration of the pharmaceutical composition.

344. The pharmaceutical composition for use according to any one of claims 334-340, wherein the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m²/day as measured after a time period of administration of the pharmaceutical composition.

345. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition

346. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

347. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

348. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid

dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

349. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

350. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

351. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

352. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

353. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

354. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

355. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition.

356. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition.

357. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

358. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the pharmaceutical composition.

359. The pharmaceutical composition for use according to any one of claims 288-358, wherein the level of adrenocorticotrophic hormone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotrophic hormone is relative to the level of adrenocorticotrophic hormone prior to administration of the pharmaceutical composition.

360. The pharmaceutical composition for use according to any one of claims 288-358, wherein the level of adrenocorticotrophic hormone is reduced by at least about 40% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotrophic hormone is relative to the level of adrenocorticotrophic hormone prior to administration of the pharmaceutical composition.

361. The pharmaceutical composition for use according to any one of claims 288-358, wherein the level of adrenocorticotrophic hormone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotrophic hormone is relative to the level of adrenocorticotrophic hormone prior to administration of the pharmaceutical composition.

362. The pharmaceutical composition for use according to any one of claims 288-358, wherein the level of adrenocorticotrophic hormone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

363. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of adrenocorticotrophic hormone is within normal limits after a time period of administration of the pharmaceutical composition.

364. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

365. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

366. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

367. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

368. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

369. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

370. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

371. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

372. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

373. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

374. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% and the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the pharmaceutical composition.

375. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal and the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

376. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

377. The pharmaceutical composition for use according to any one of claims 334-376, wherein the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the pharmaceutical composition, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the pharmaceutical composition.

378. The pharmaceutical composition for use according to claim 377, wherein one or more symptoms of glucocorticoid burden selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicality, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the pharmaceutical composition, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the pharmaceutical composition.

379. The pharmaceutical composition for use according to any one of claims 341-378, wherein the time period of administration is at least about 4 weeks.

380. The pharmaceutical composition for use according to any one of claims 341-378, wherein the time period of administration is at least about 24 weeks.

381. The pharmaceutical composition for use according to any one of claims 341-378, wherein the time period of administration is at least about one year.

382. The pharmaceutical composition for use according to any one of claims 288-381, wherein the subject is a pediatric subject.

383. The pharmaceutical composition for use according to claim 382, wherein the pediatric subject is less than or equal to six years old.

384. The pharmaceutical composition for use according to claim 382, wherein the pediatric subject is greater than six years old and less than eleven years old.

385. The pharmaceutical composition for use according to claim 382, wherein the pediatric subject is greater than ten years old and less than fifteen years old.

386. The pharmaceutical composition for use according to claim 382, wherein the pediatric subject is greater than fourteen years old and less than nineteen years old.

387. The pharmaceutical composition for use according to any one of claims 288-381, wherein the subject is an adult subject.

388. The pharmaceutical composition for use according to any one of claims 387, wherein the adult subject is over eighteen years old.

389. The pharmaceutical composition for use according to any one of claims 288-388, wherein the subject is female.

390. The pharmaceutical composition for use according to any one of claims 288-388, wherein the subject is male.

391. The pharmaceutical composition for use according to any one of claims 288-390, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a hydrochloric acid salt or p-toluenesulfonic acid salt.

392. The pharmaceutical composition for use according to any one of claims 288-390, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a p-toluenesulfonic acid salt of any one of claims 228-238.

393. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or a pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in the subject.

394. The compound of claim 393, wherein the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during

the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

395. The compound of claim 394, wherein the circadian release occurs between the hours of 2 a.m. and 10 a.m.

396. The compound of any one of claims 393-395, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

397. The compound of any one of claims 393-396, wherein the level of 17-hydroxyprogesterone is reduced by at least 25%.

398. The compound of any one of claims 393-396, wherein the level of 17-hydroxyprogesterone is reduced by at least 50%.

399. The compound of any one of claims 393-398, wherein the level of adrenocorticotrophic hormone is reduced by at least 25%.

400. The compound of any one of claims 393-398, wherein the level of adrenocorticotrophic hormone is reduced by at least 40%.

401. The compound of any one of claims 393-398, wherein the level of adrenocorticotrophic hormone is reduced by at least 50%.

402. The compound of any one of claims 393-401, wherein the level of androstenedione is reduced by at least 25%.

403. The compound of any one of claims 393-401, wherein the level of androstenedione is reduced by at least 30%.

404. The compound of any one of claims 393-401, wherein the level of androstenedione is reduced by at least 50%.

405. The compound of any one of claims 393-401, wherein the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

406. The compound of any one of claims 393-405, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

407. The compound of any one of claims 393-406, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

408. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound is administered in an amount sufficient to reduce the level of androstenedione in the subject.

409. The compound of claim 408, wherein the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

410. The compound of claim 408 or 409, wherein the level of androstenedione is reduced by at least 25%.

411. The compound of claim 408 or 409, wherein the level of androstenedione is reduced by at least 30%.

412. The compound of claim 408 or 409, wherein the level of androstenedione is reduced by at least 50%.

413. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

414. The compound of claim 413, wherein the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

415. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

416. The compound of claim 415, wherein the corticosteroid is a glucocorticoid.

417. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism,

hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

418. The compound of any one of claims 413-417, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

419. The compound of any one of claims 413-418, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

420. The compound of any one of claims 413-417, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

421. The compound of any one of claims 413-420, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

422. The compound of any one of claims 413-421, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-

2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

423. The compound of any one of claims 413-422, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

424. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject comprising

- (i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
- (ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
- (iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

425. The compound of claim 424, further comprising (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i).

426. The compound of claim 425, further comprising (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-

methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

427. The compound of claim 425 or 426, wherein steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window.

428. The compound of any one of claims 425-427, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m.

429. The compound of any one of claims 425-427, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

430. The compound of any one of claims 425-429, wherein steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

431. The compound of any one of claims 425-429, wherein steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

432. The compound of any one of claims 424-431, wherein step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

433. The compound of any one of claims 424-432, wherein step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

434. The compound of any one of claims 424-433, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-

2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

435. The compound of any one of claims 424-433, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

436. The compound of any one of claims 424-435, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

437. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof for use in a method of treating congenital adrenal hyperplasia (CAH), in a subject, wherein the subject is in a fed state.

438. The compound of claim 437, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition.

439. The compound of claim 438, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

440. The compound of claim 438 or 439, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

441. The compound of any one of claims 438-440, wherein the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

442. The compound of any one of claims 437-441, wherein administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, exhibits a positive food effect.

443. The compound of claim 442, wherein the positive food effect is measured in terms of C_{max} , AUC, or combinations thereof when comparing oral administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the fed and fasting states.

444. The compound of any one of claims 437-443, wherein the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10.

445. The compound of any one of claims 437-443, wherein the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10.

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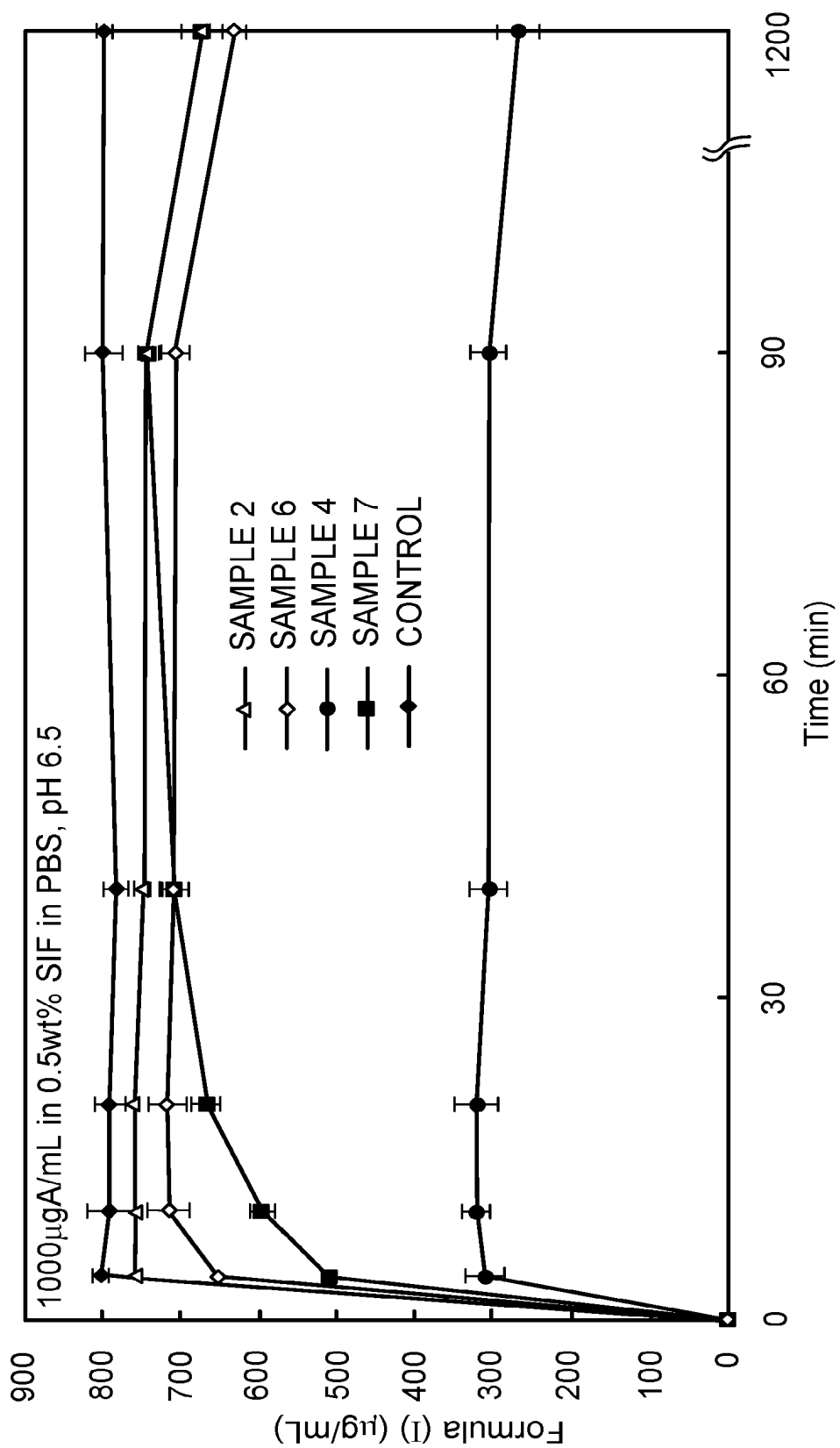


FIG. 1

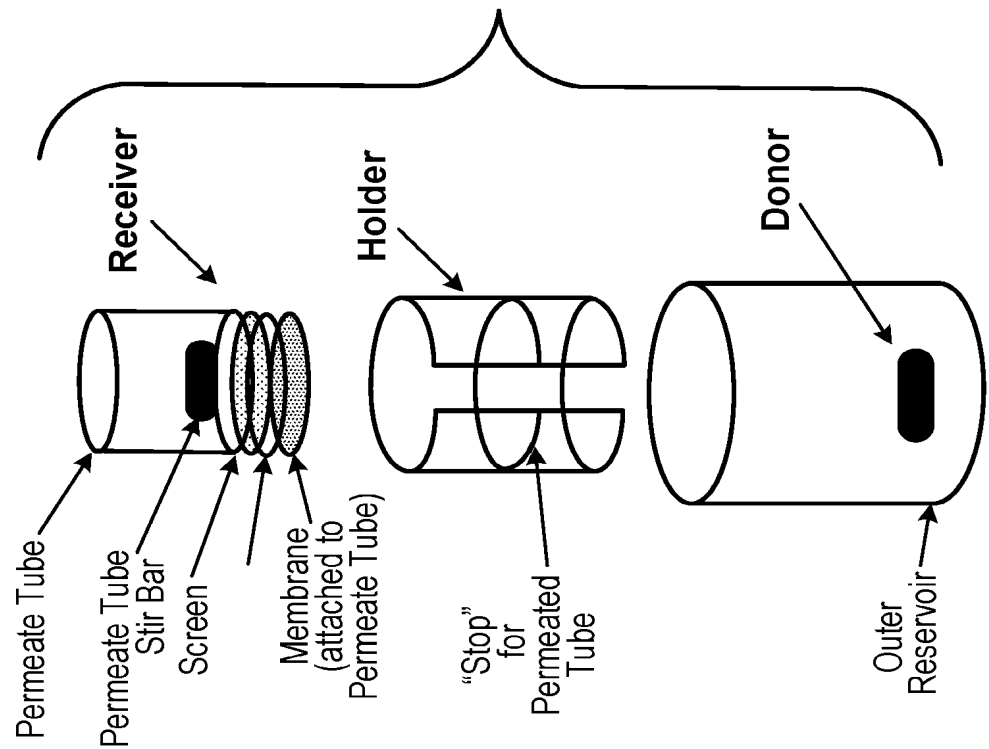
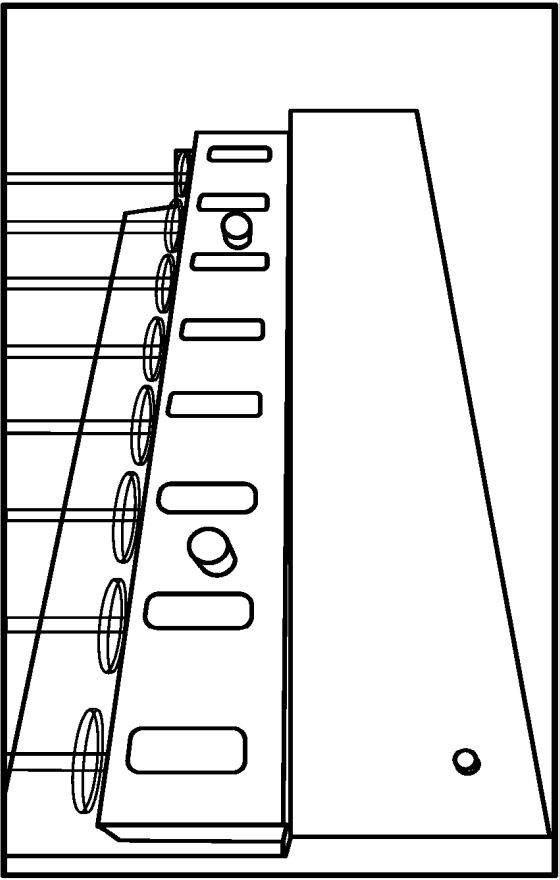


FIG. 2

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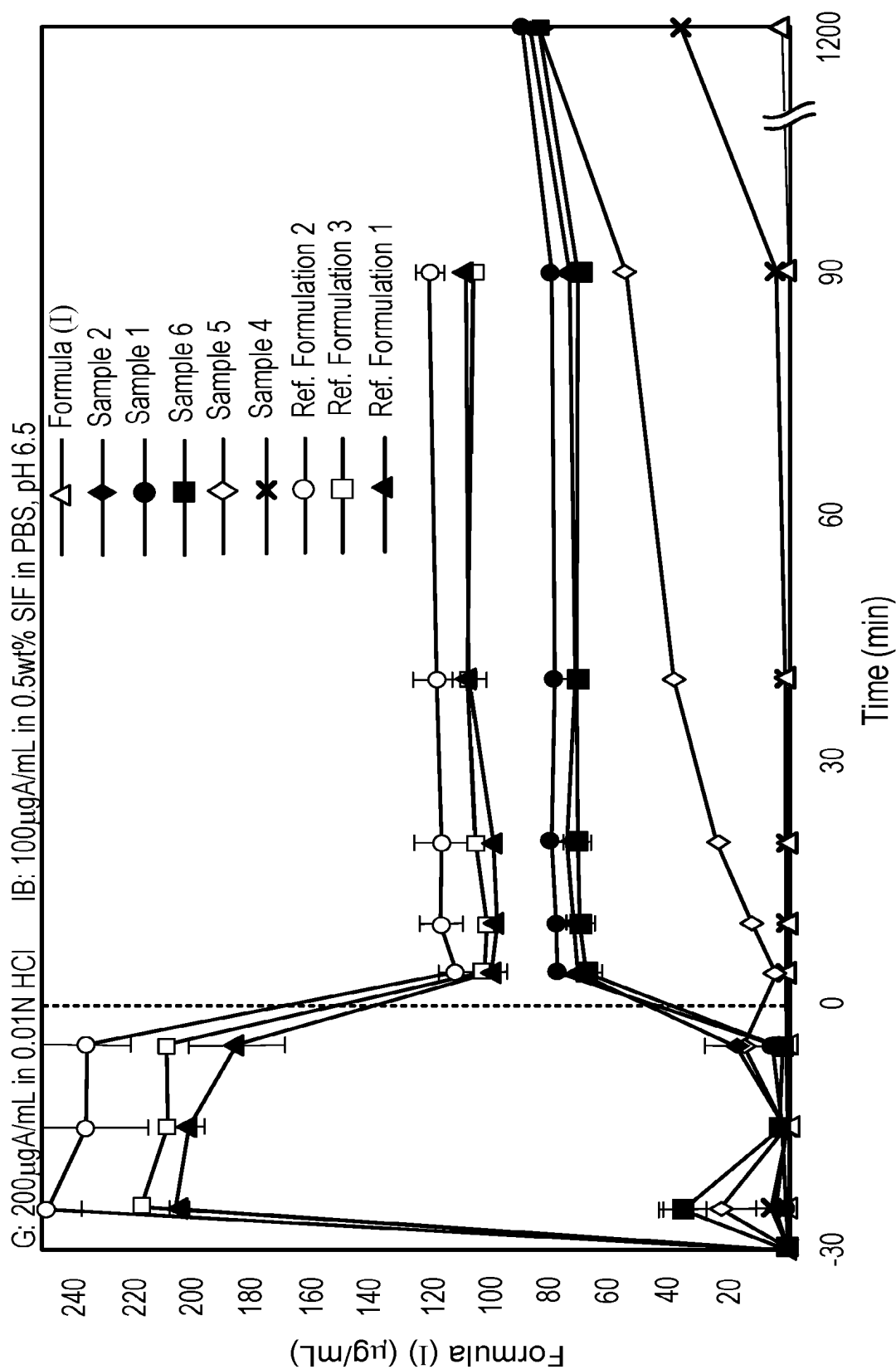


FIG. 3

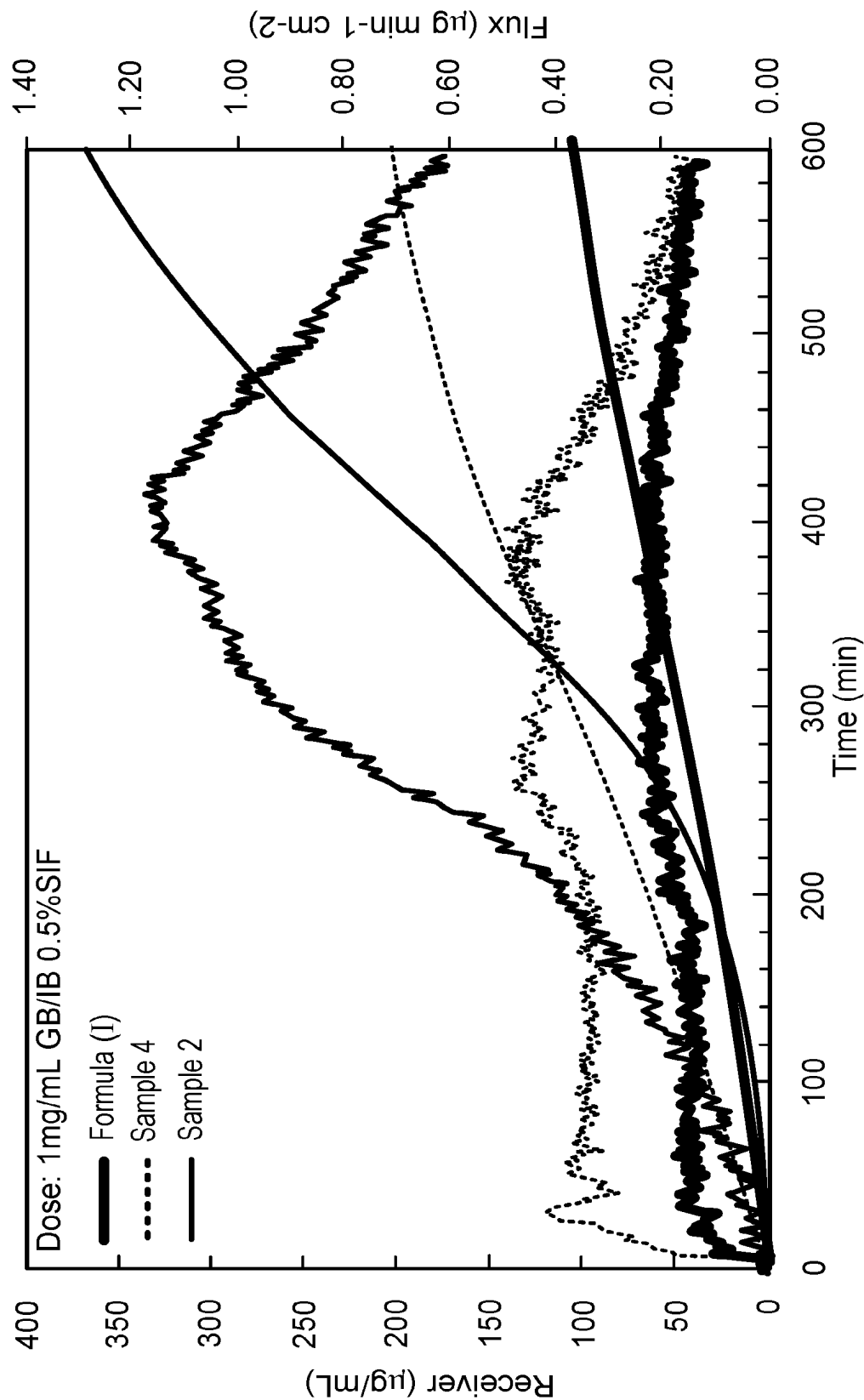


FIG. 4

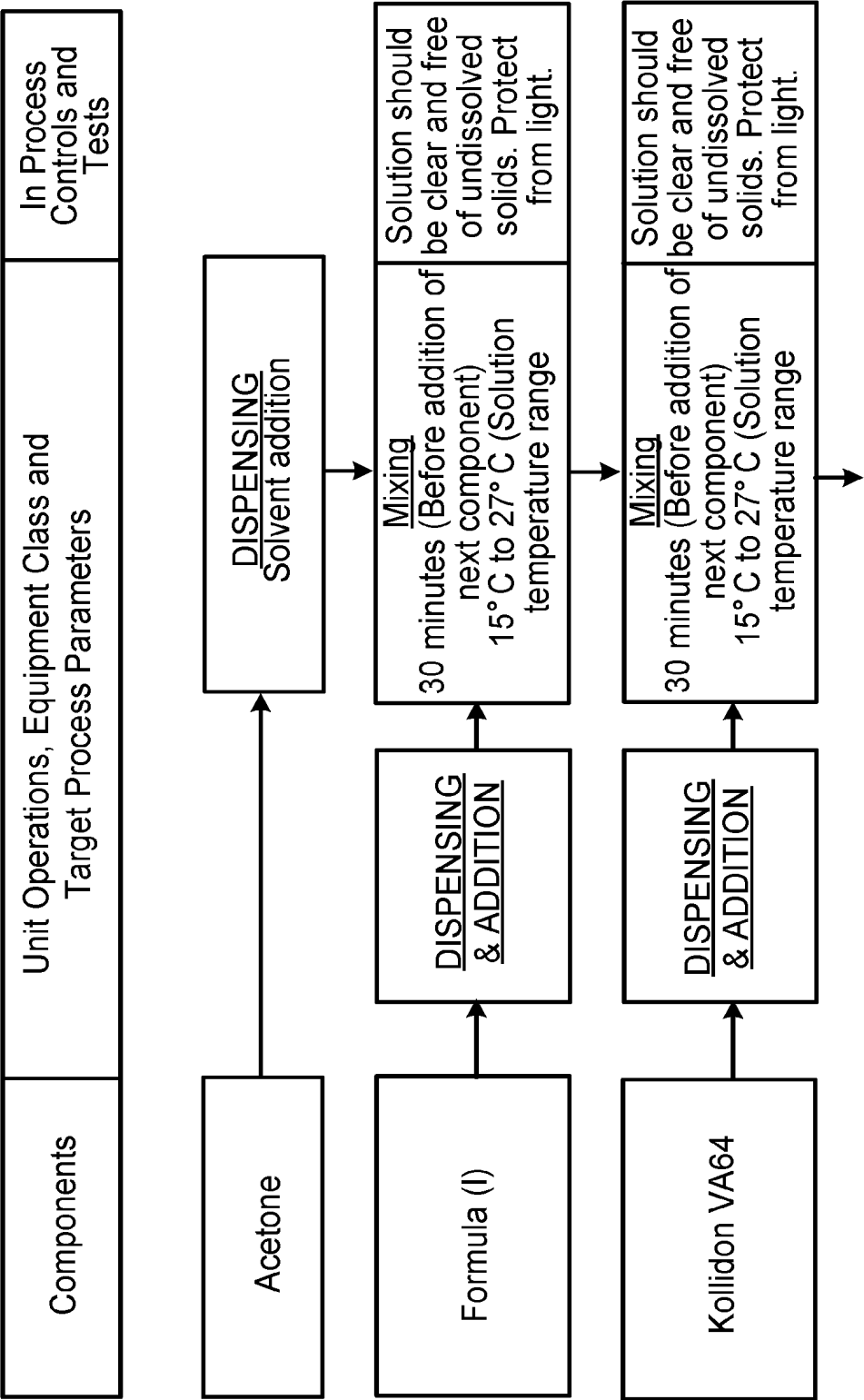
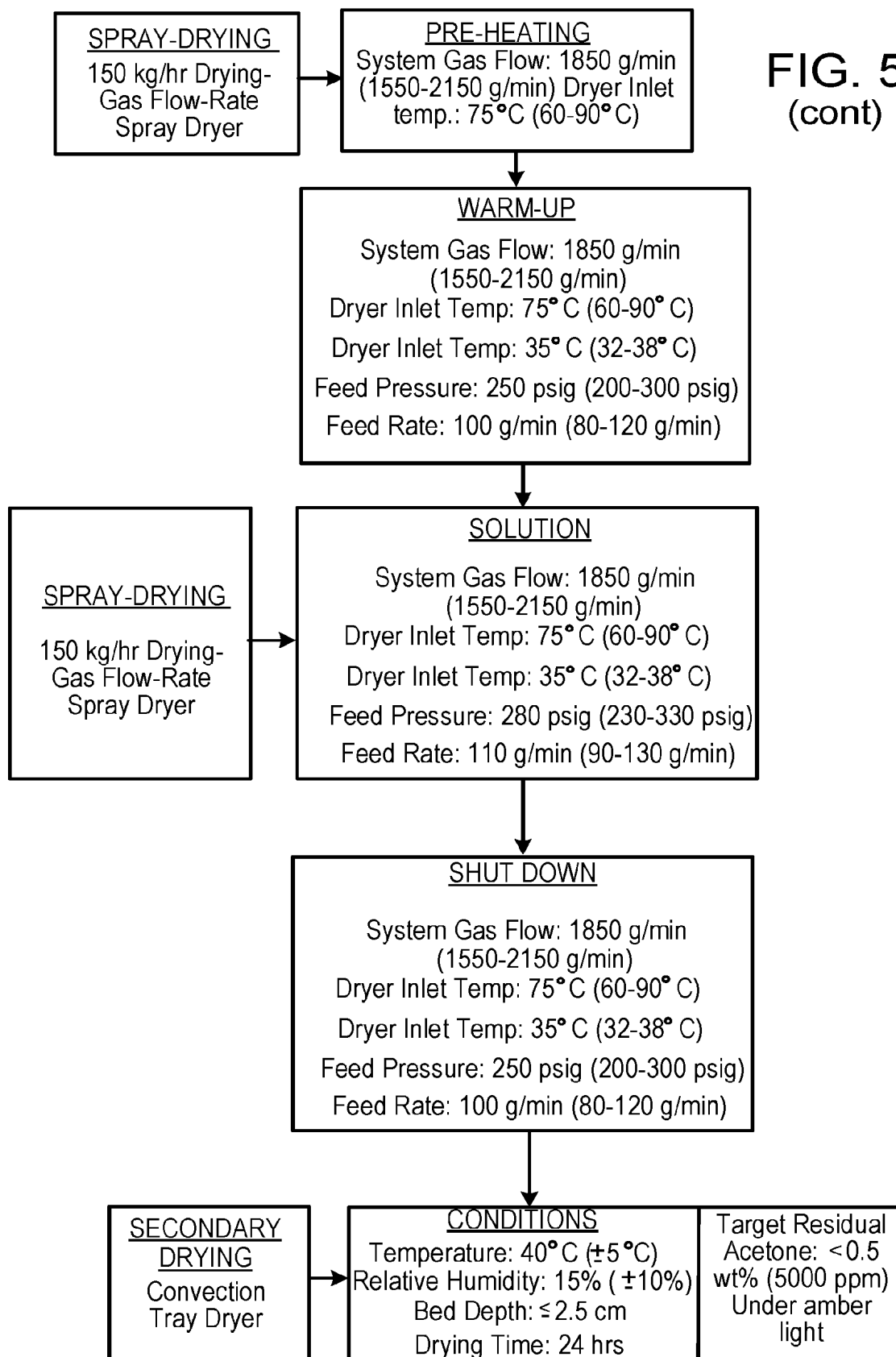


FIG. 5

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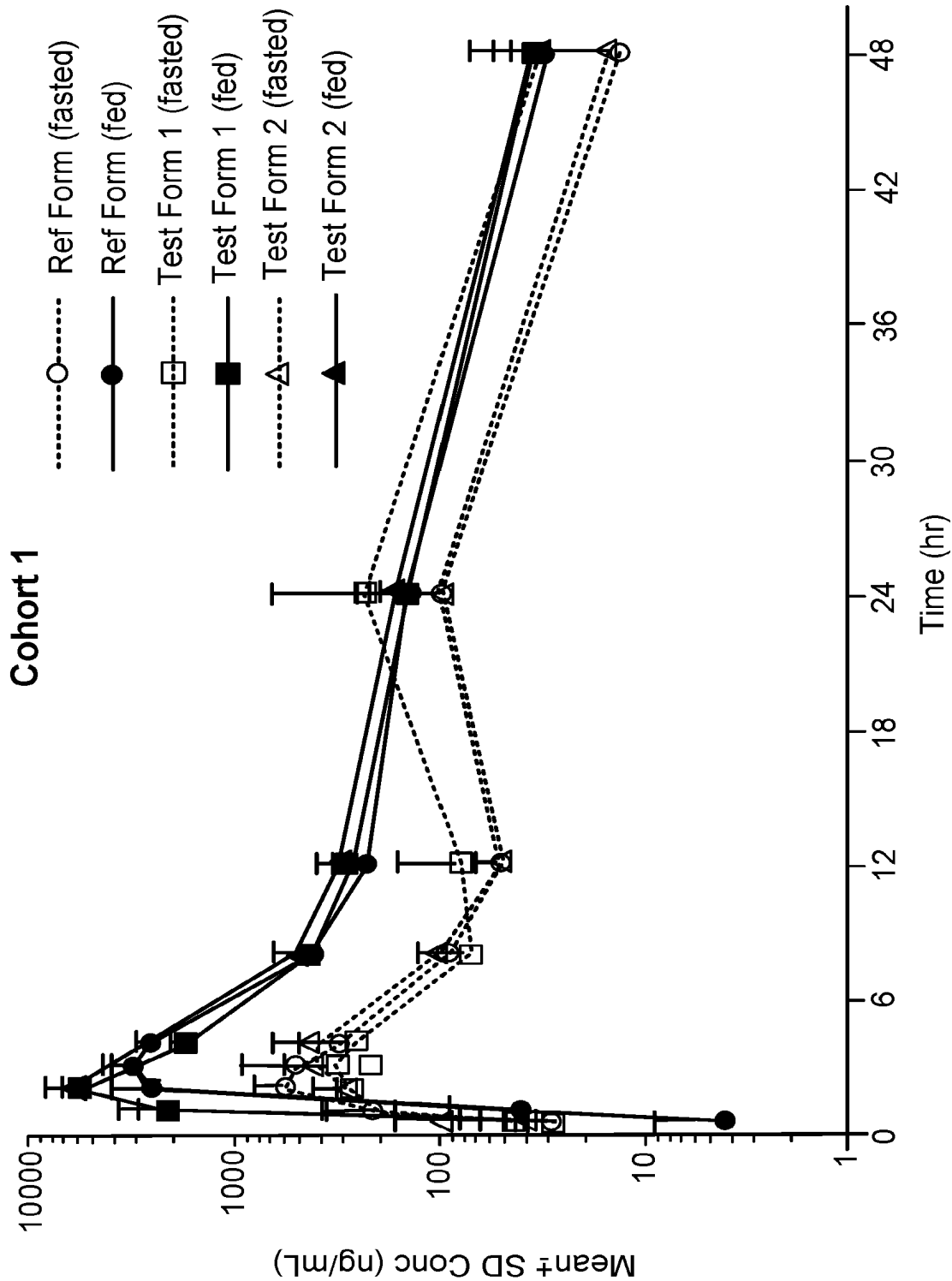


FIG. 6A

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Cohort 2

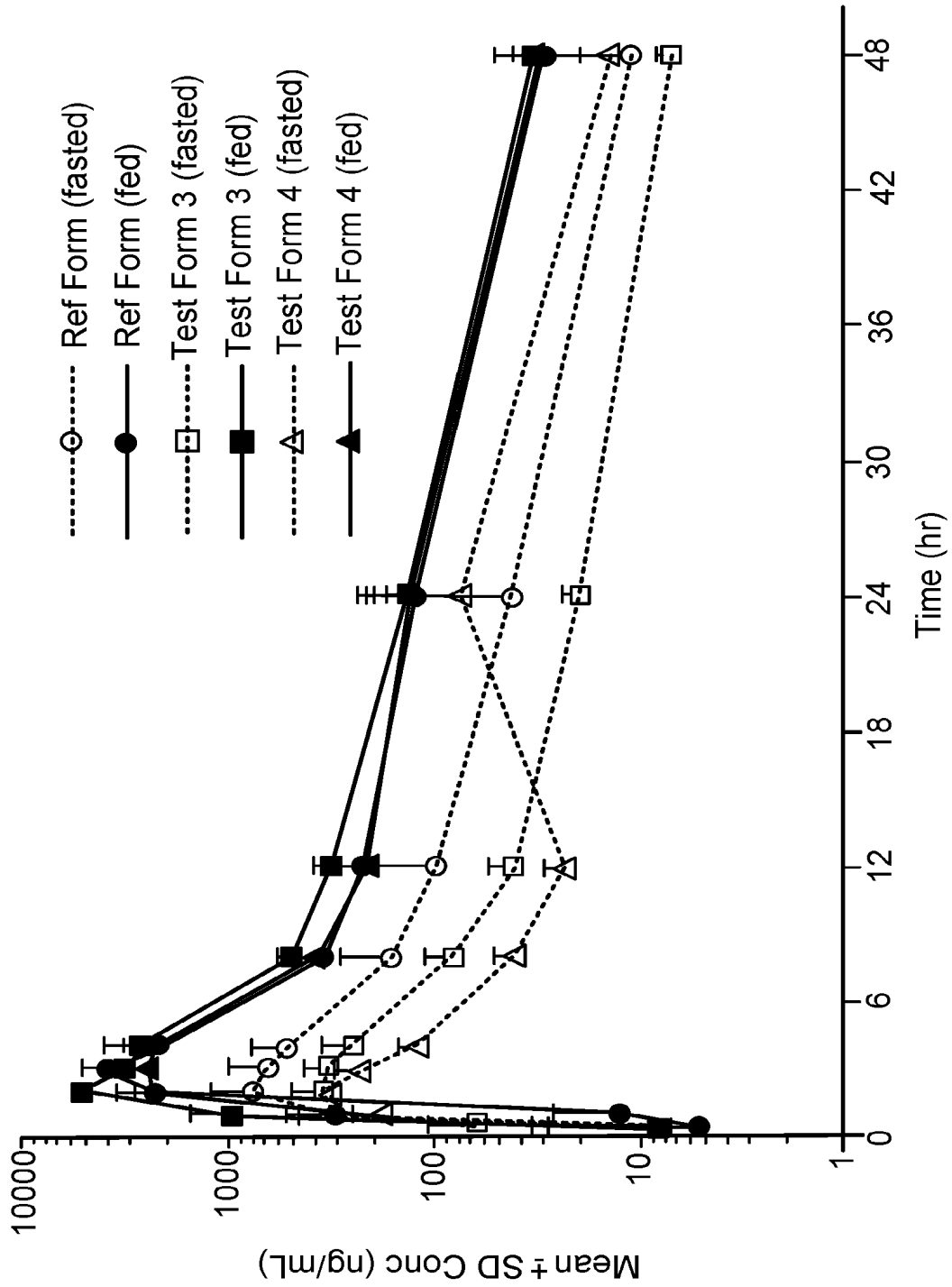


FIG. 6B

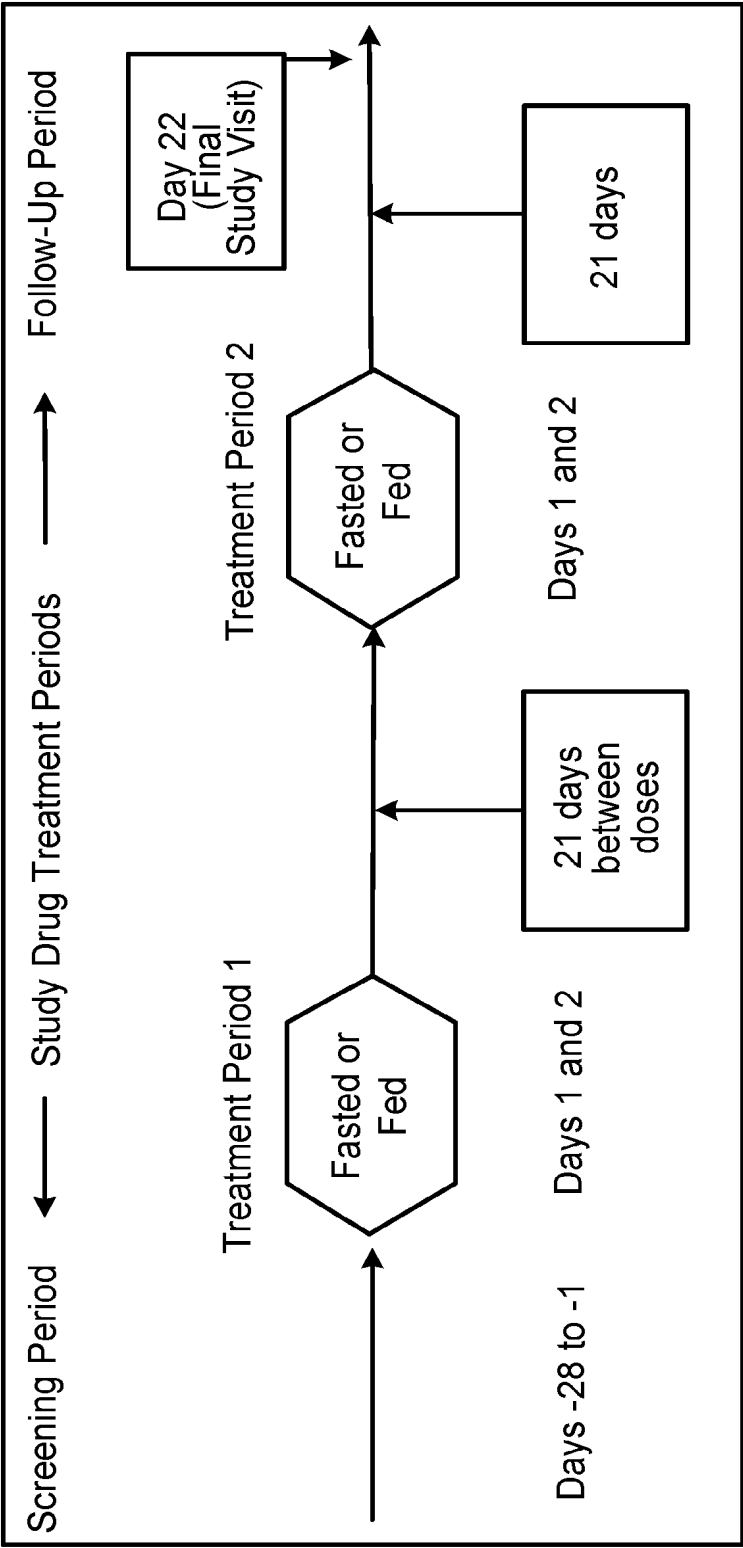


FIG. 7

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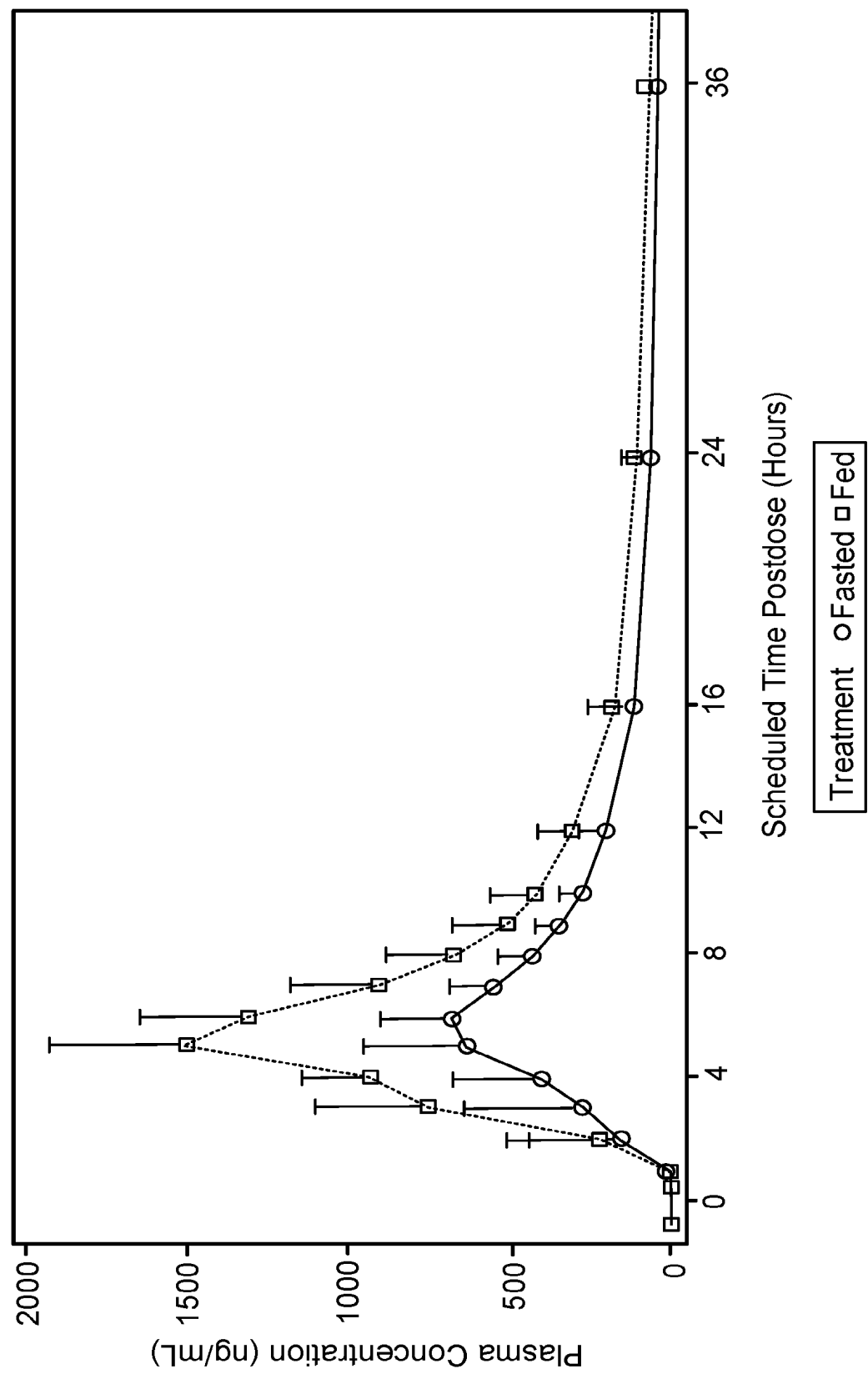


FIG. 8A

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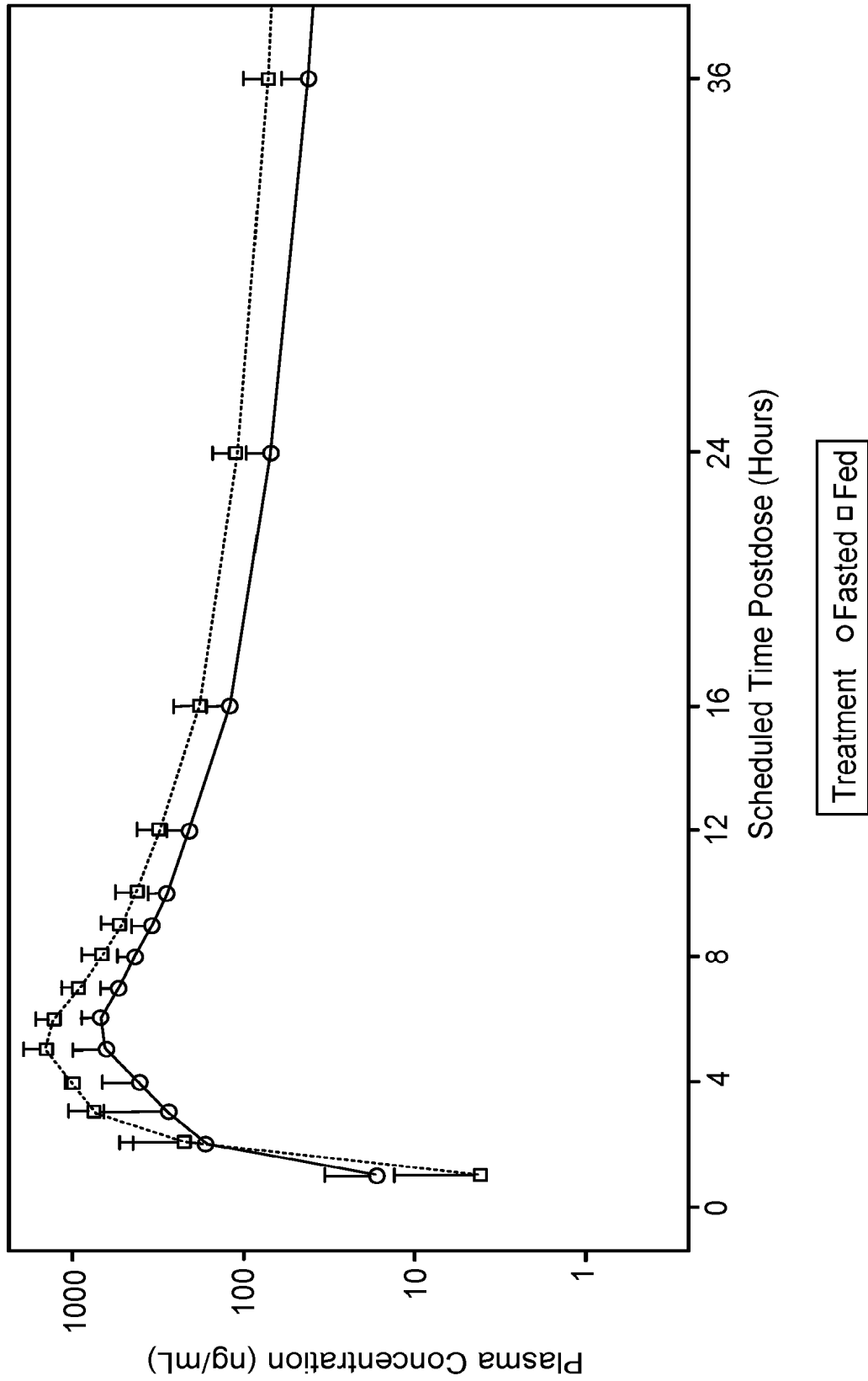


FIG. 8B

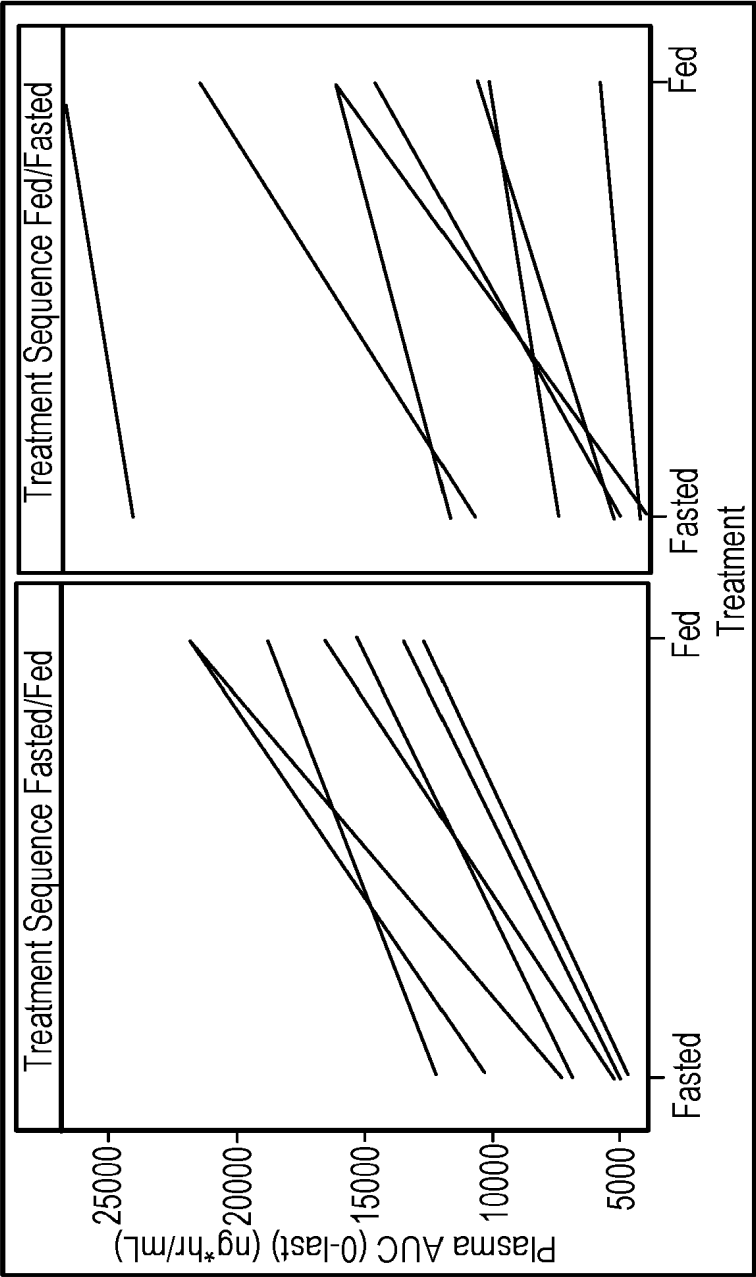


FIG. 9A

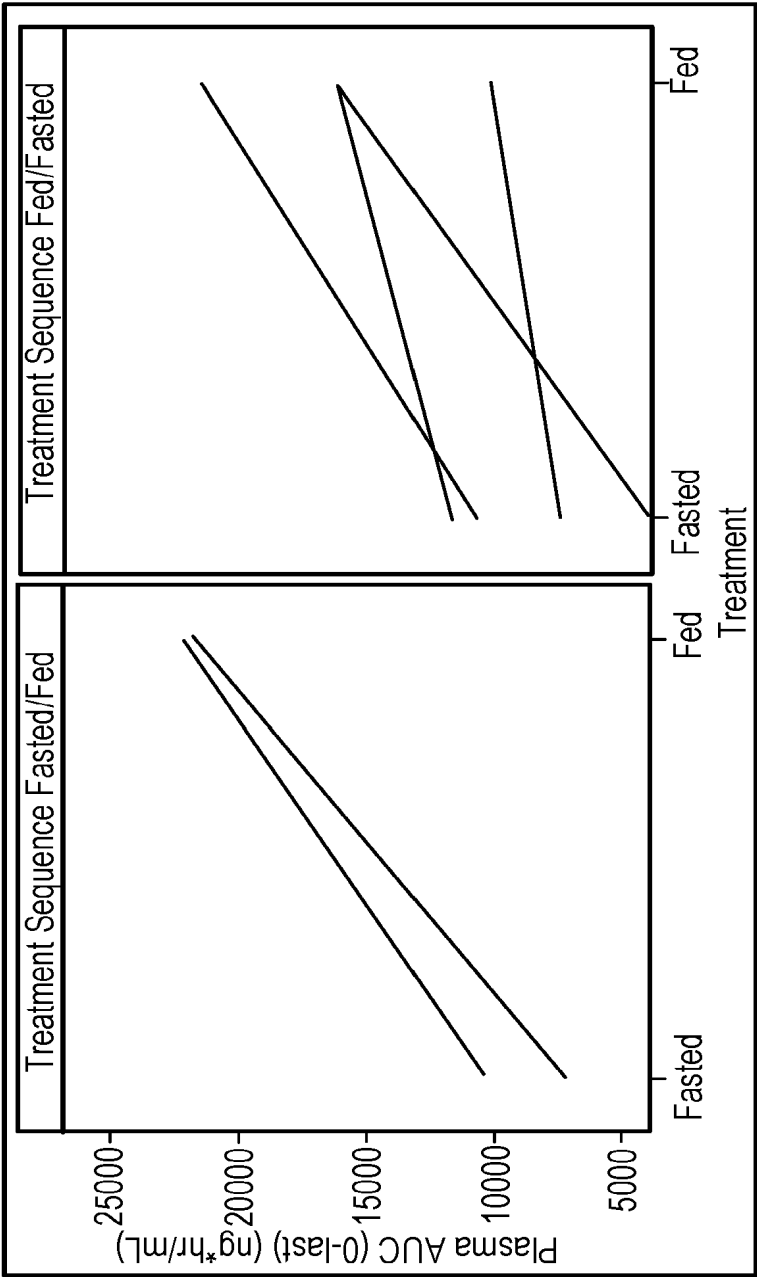


FIG. 9B

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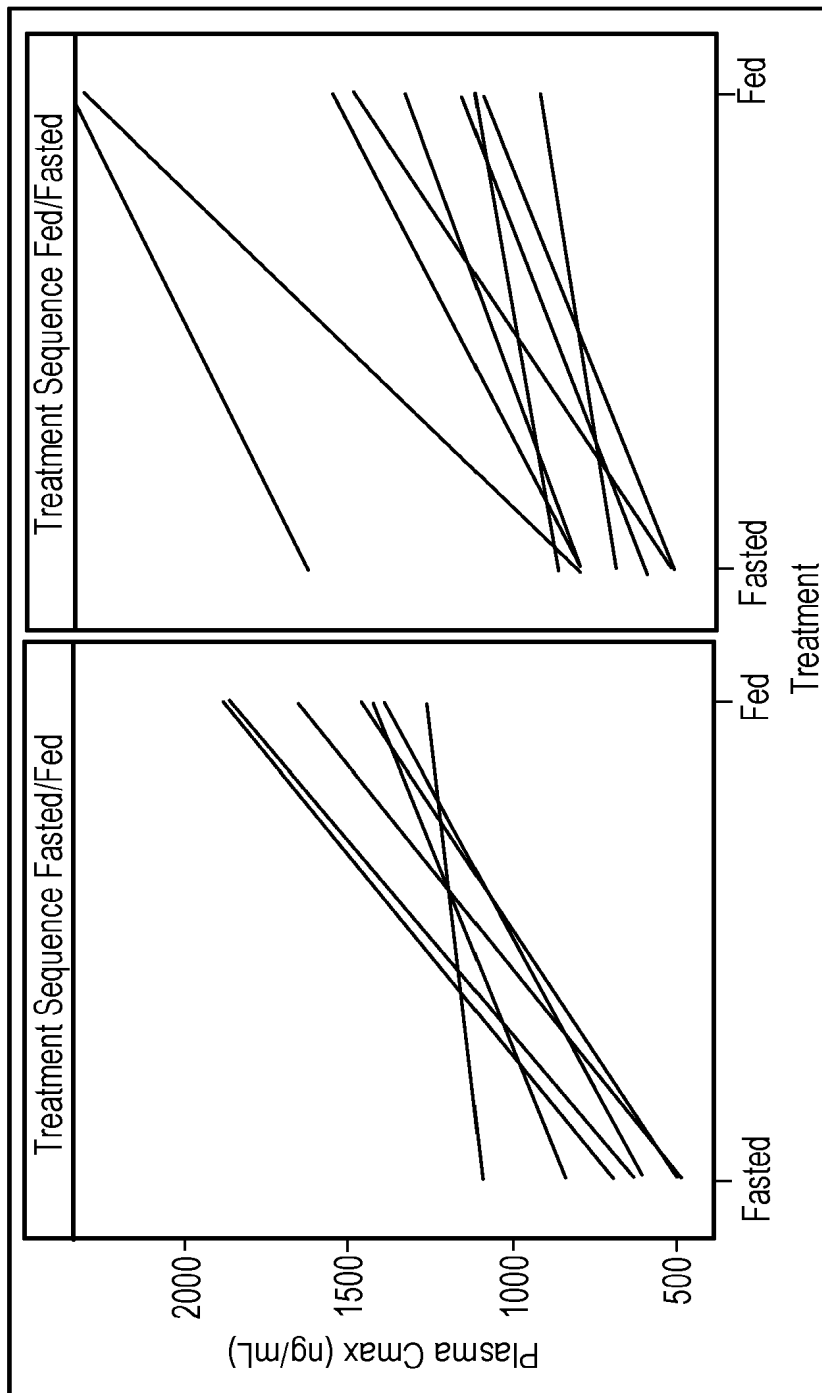


FIG. 9C

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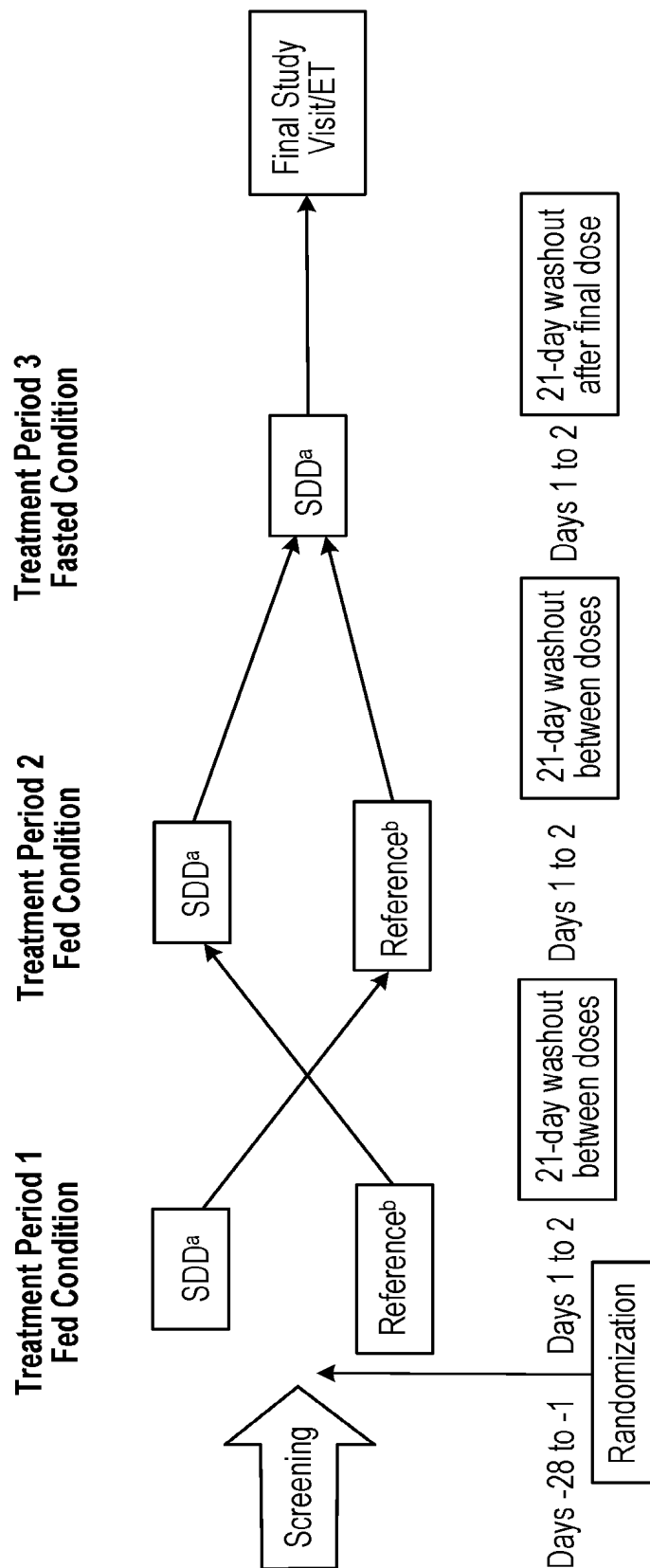


FIG. 10

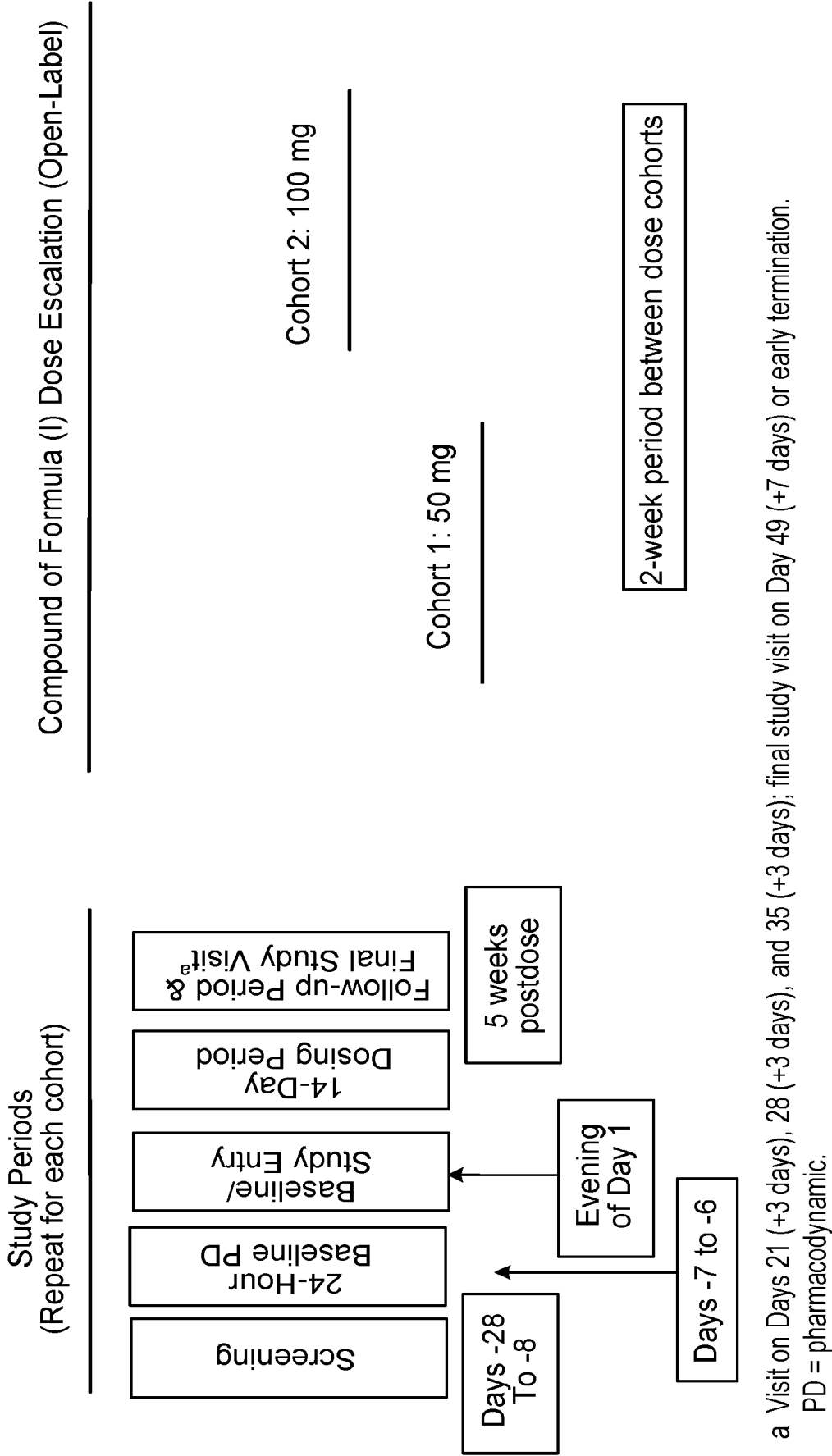


FIG. 11

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ACTH -- Average All Subjects

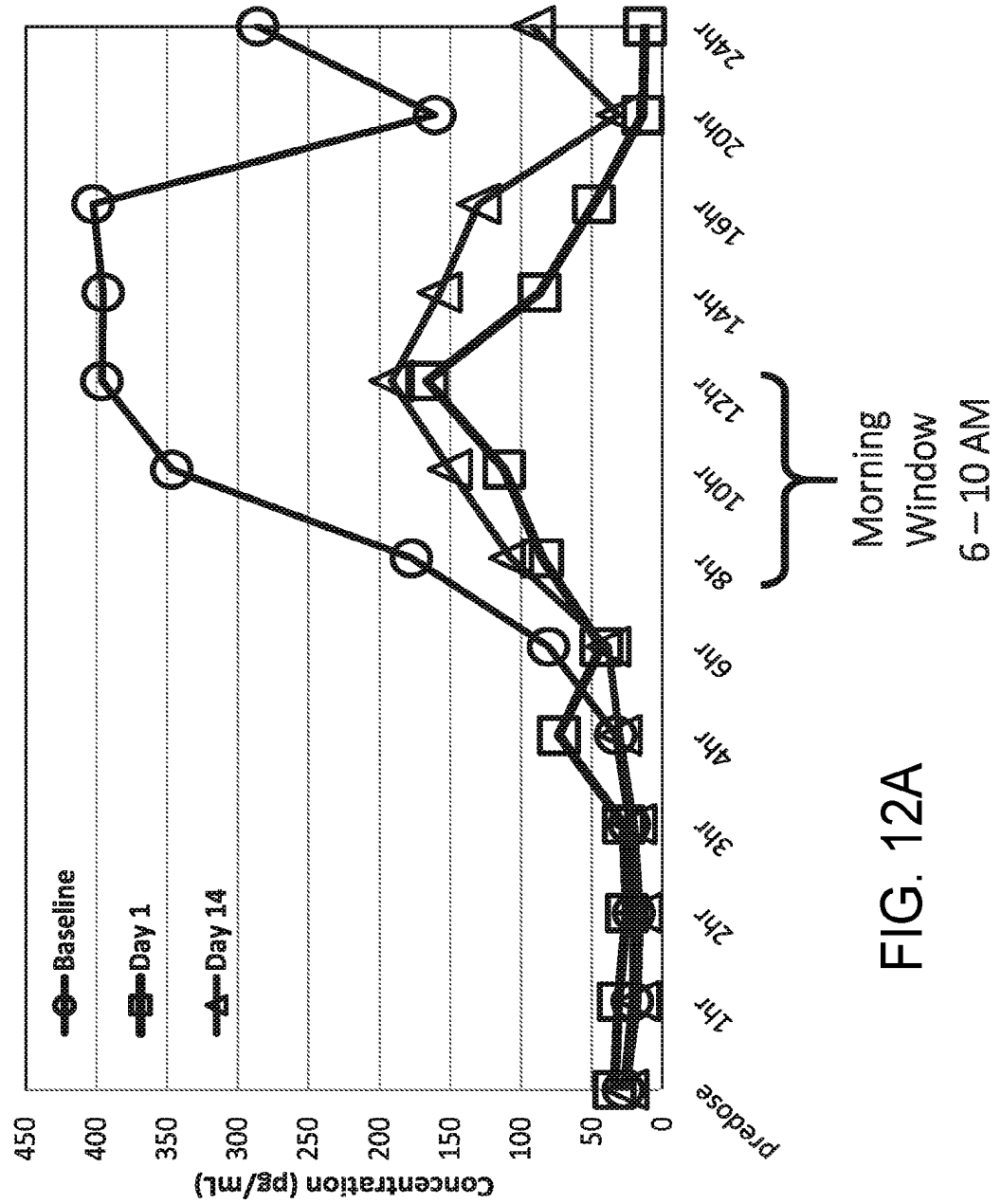


FIG. 12A

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17-OHP -- Average All Subjects

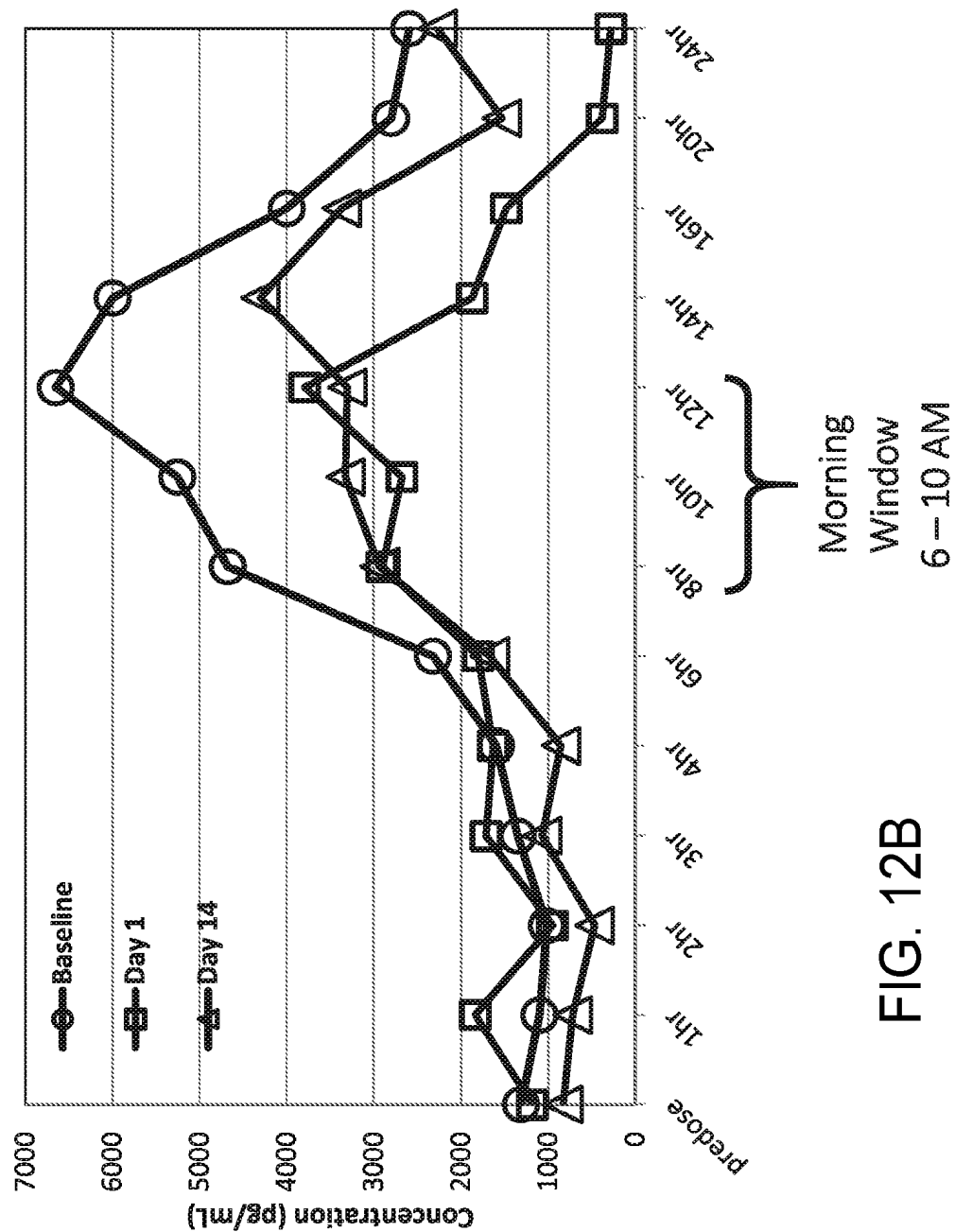


FIG. 12B

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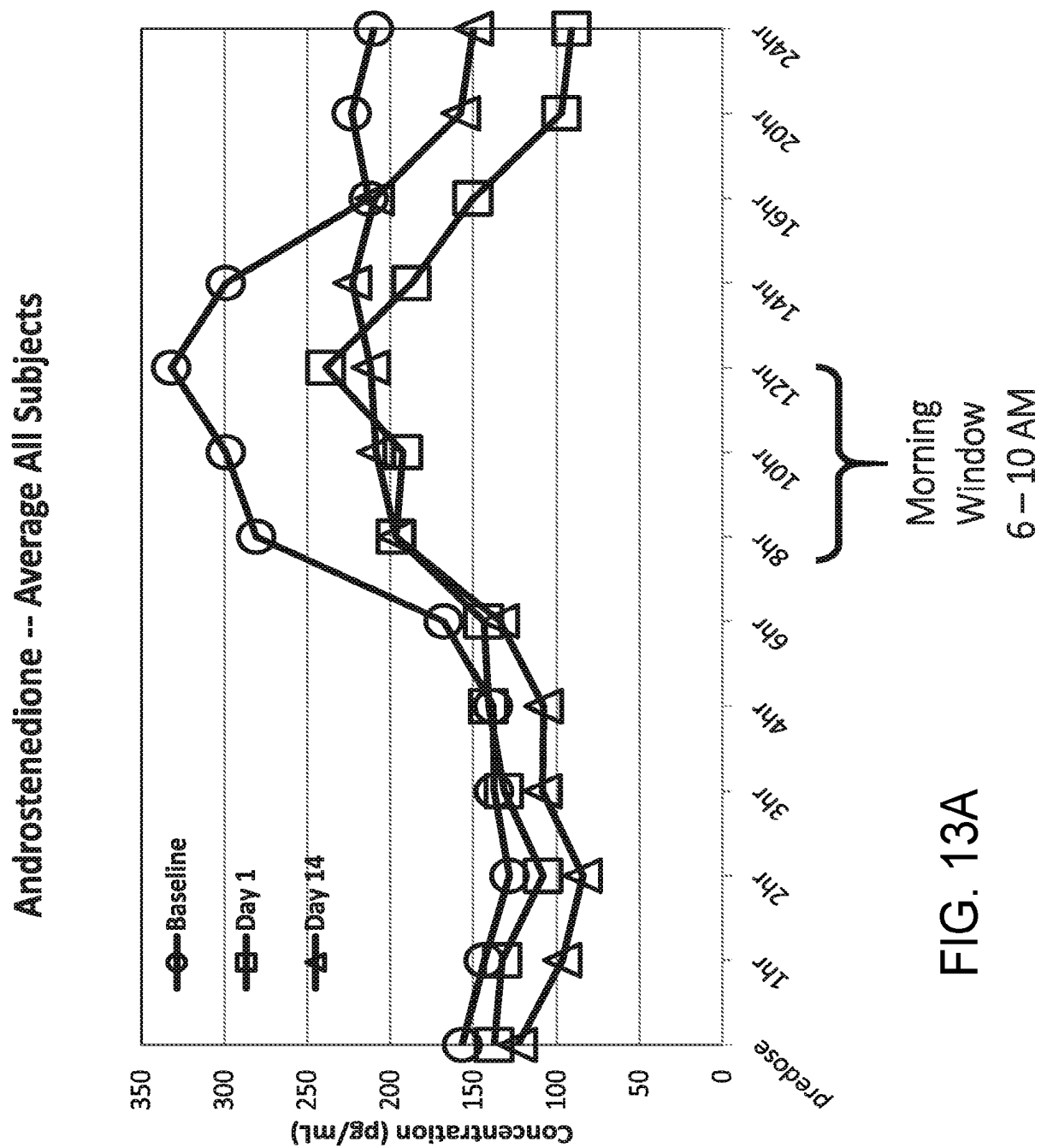


FIG. 13A

Testosterone -- Average All Subjects

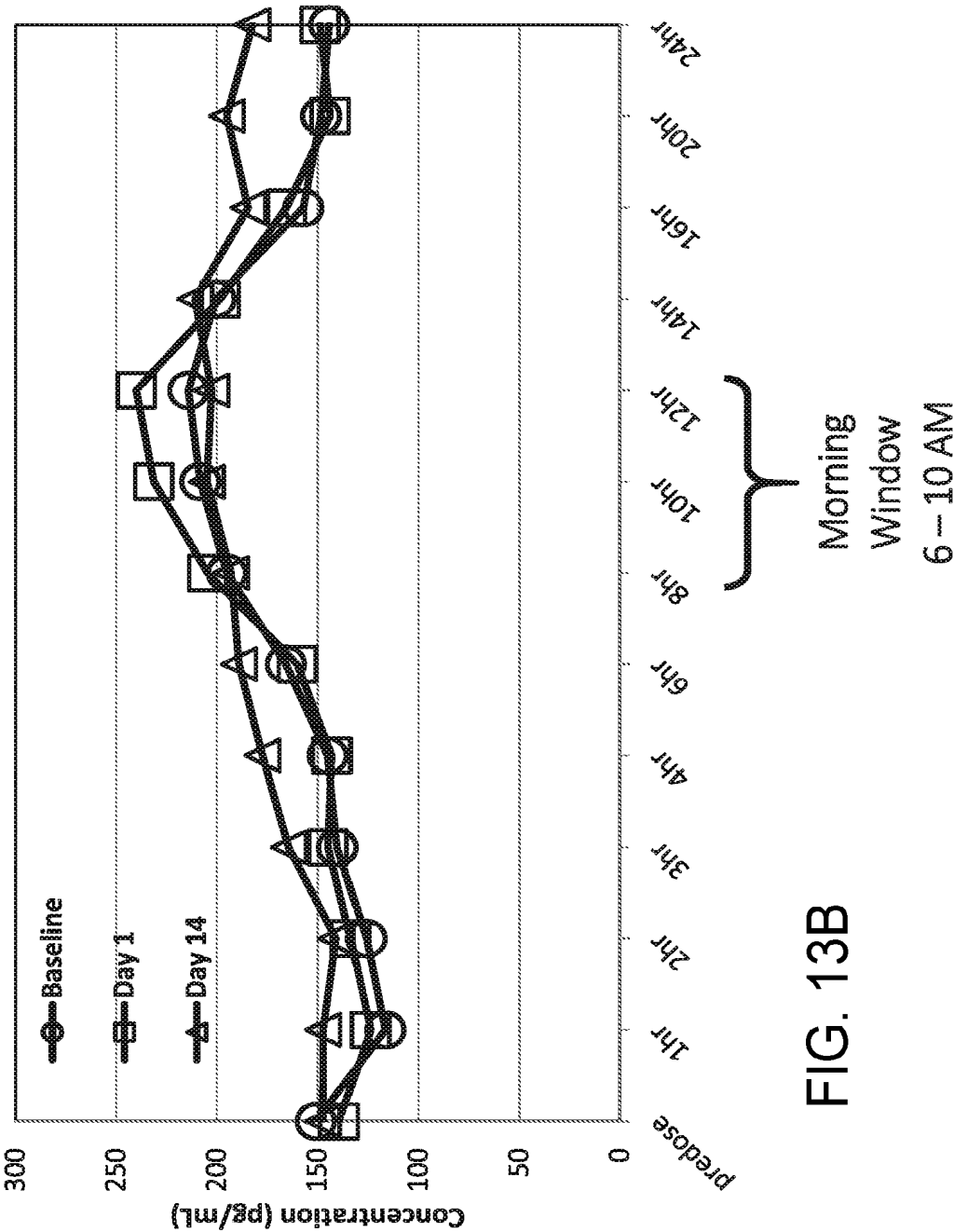


FIG. 13B

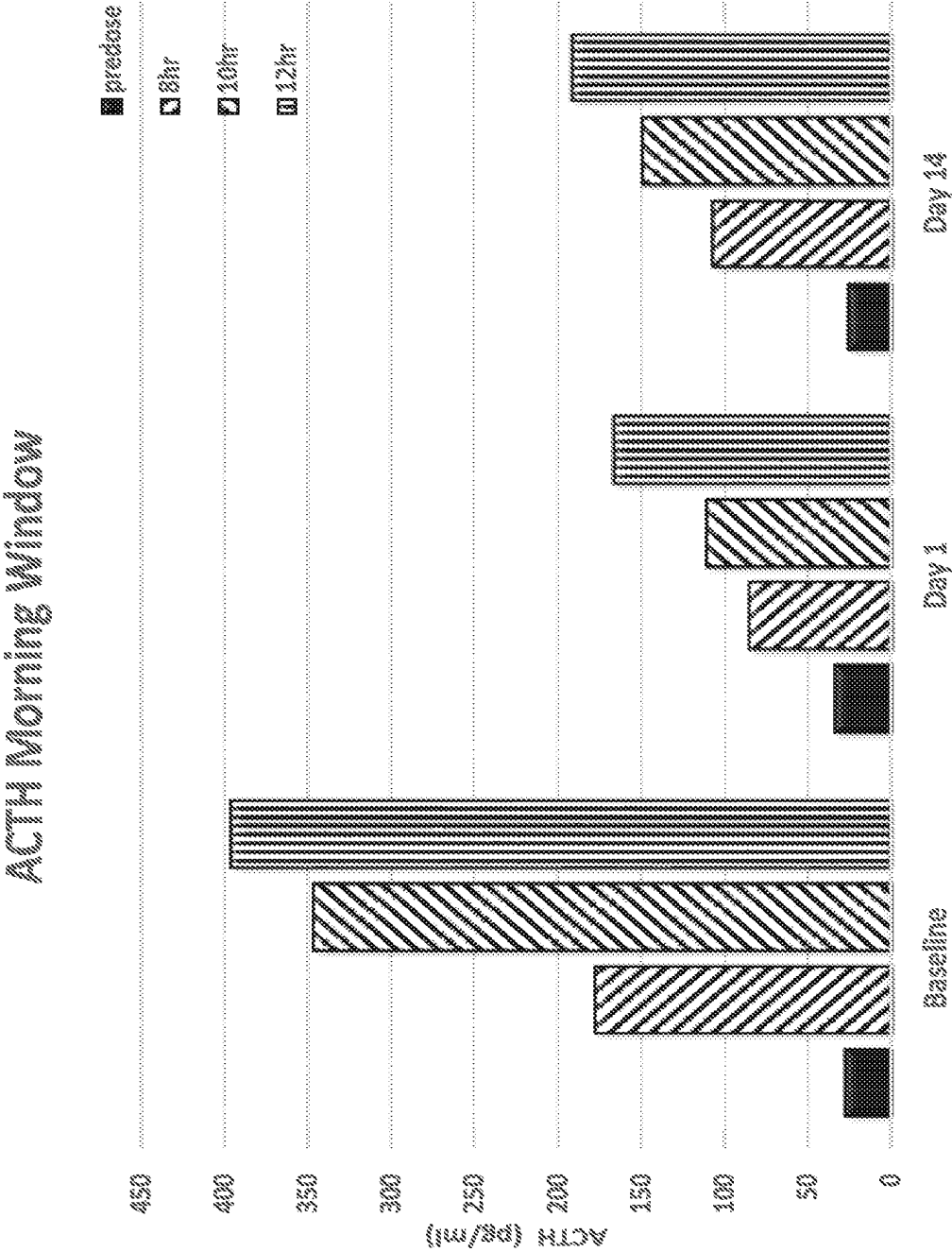


FIG. 14A

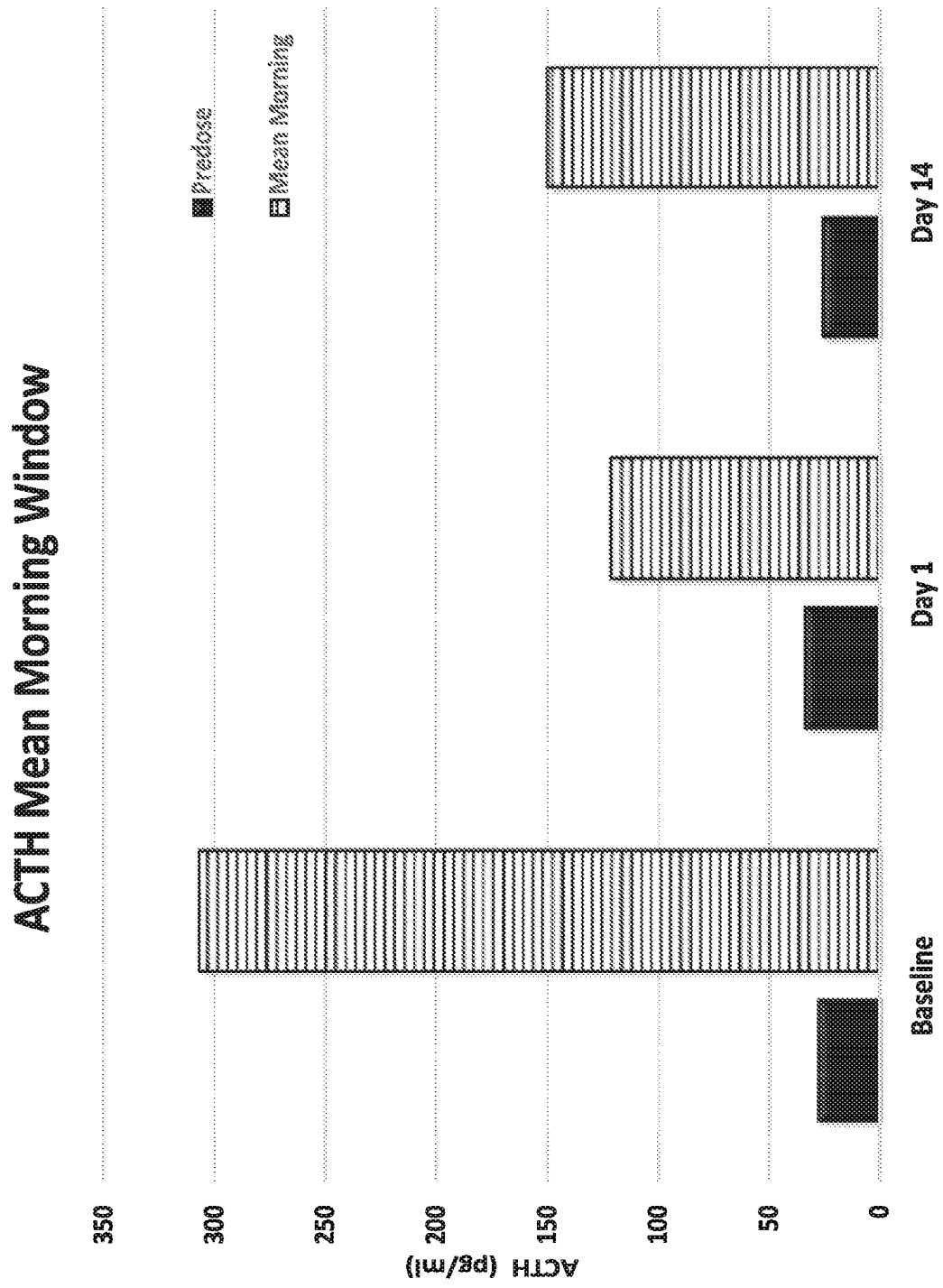


FIG. 14B

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17-OHP Morning Window

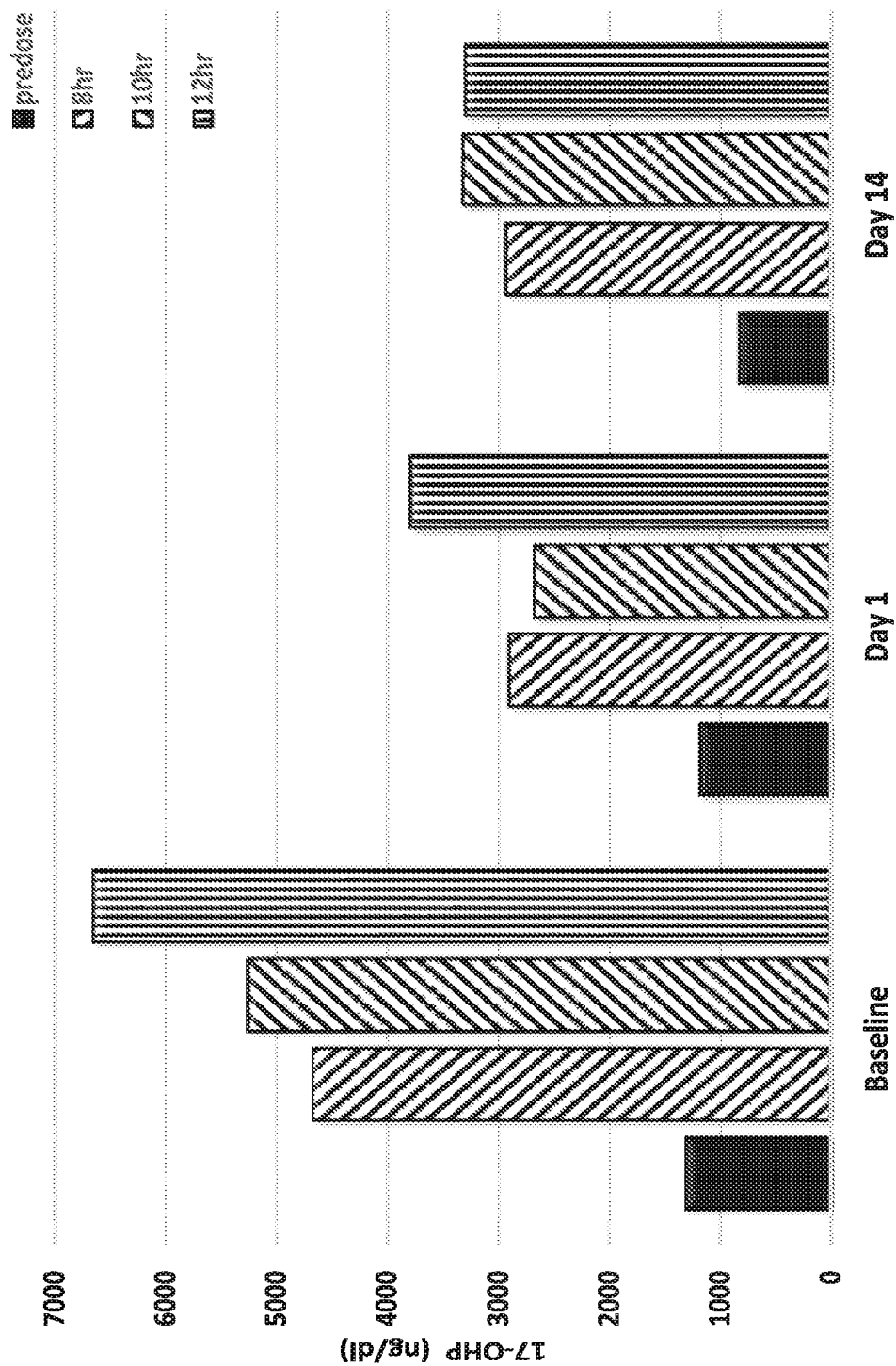


FIG. 15A

17-OHP Mean Morning Window

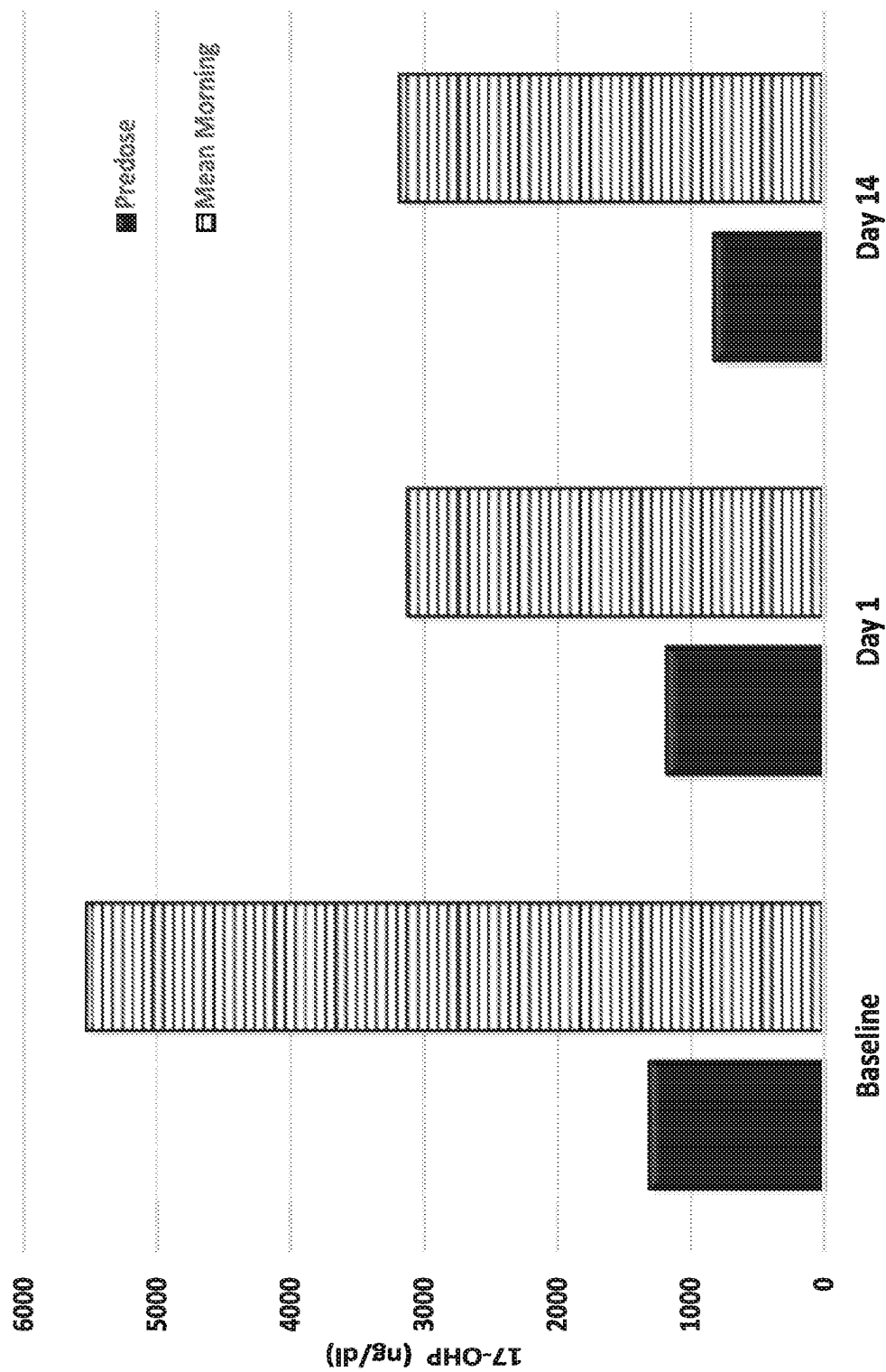


FIG. 15B

Androstenedione Morning Window

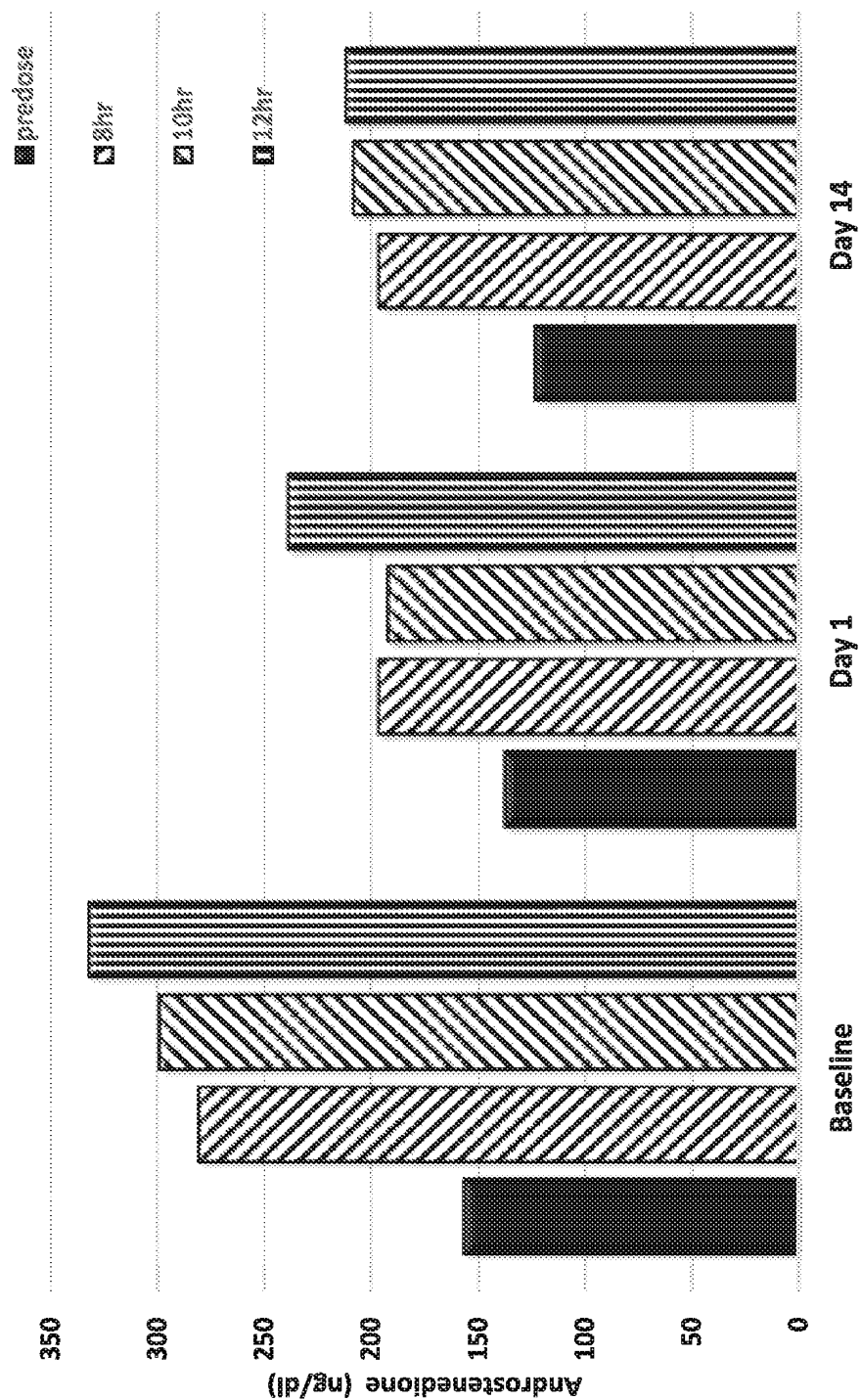


FIG. 16A

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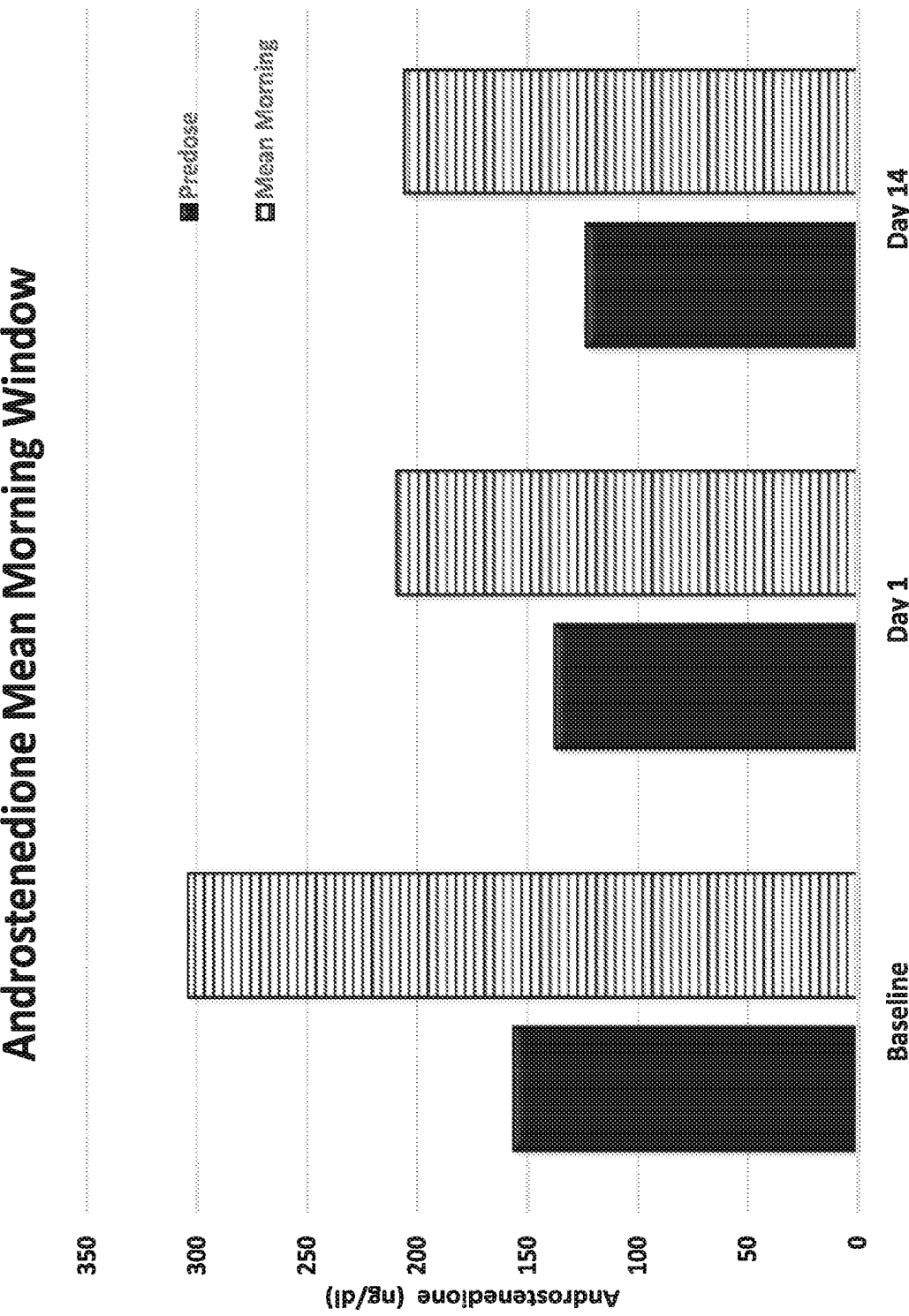


FIG. 16B

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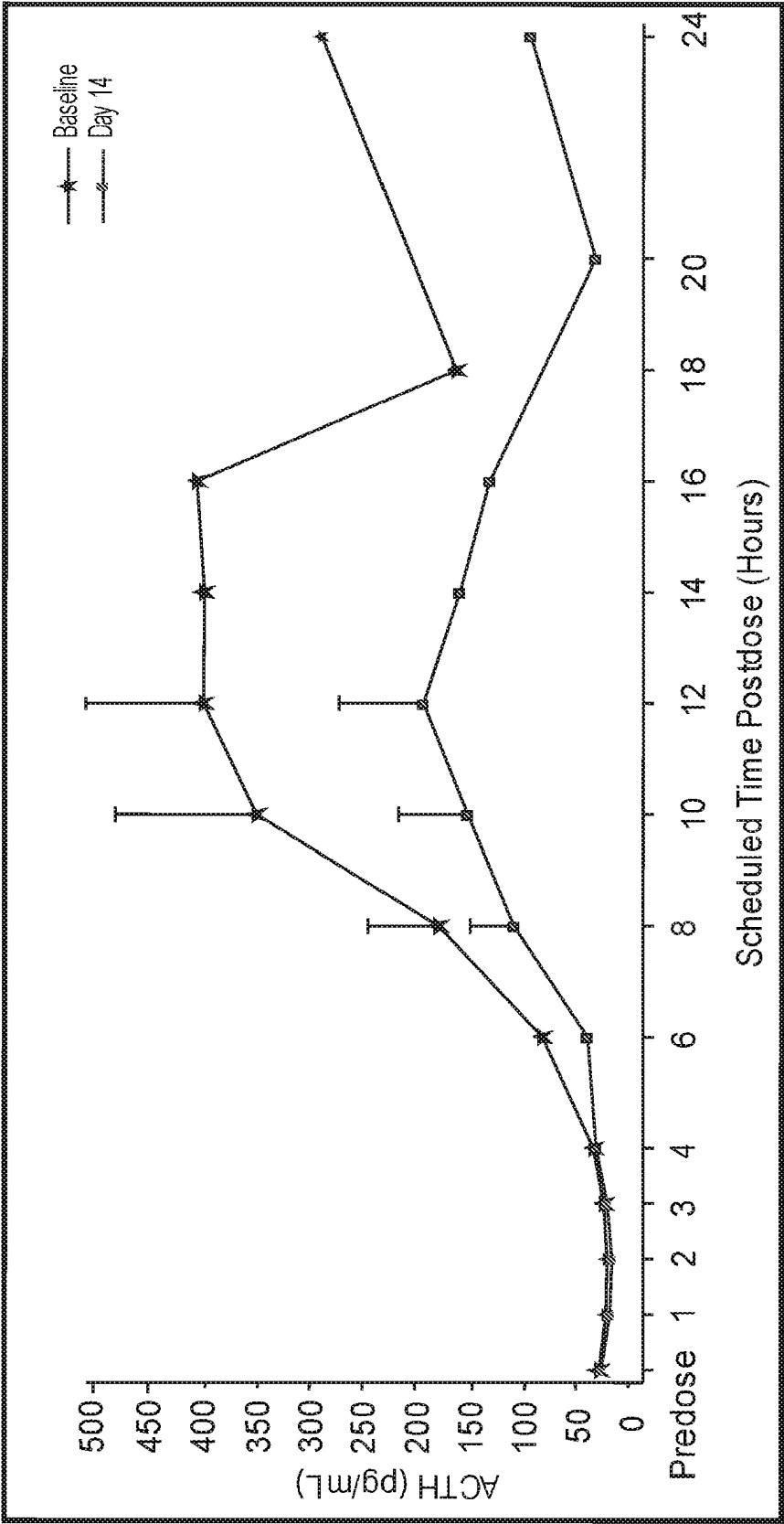


FIG. 17A

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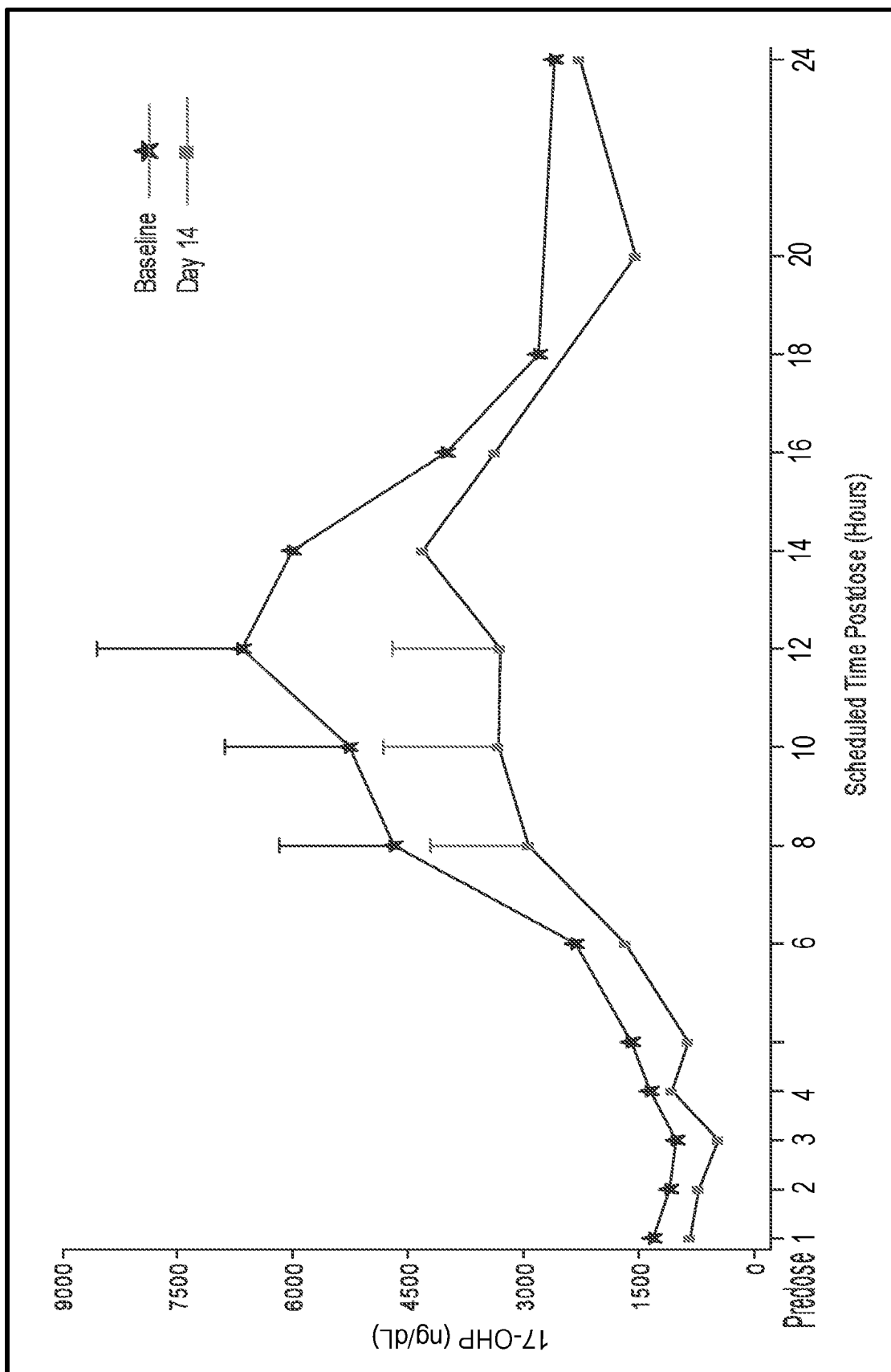


FIG. 17B

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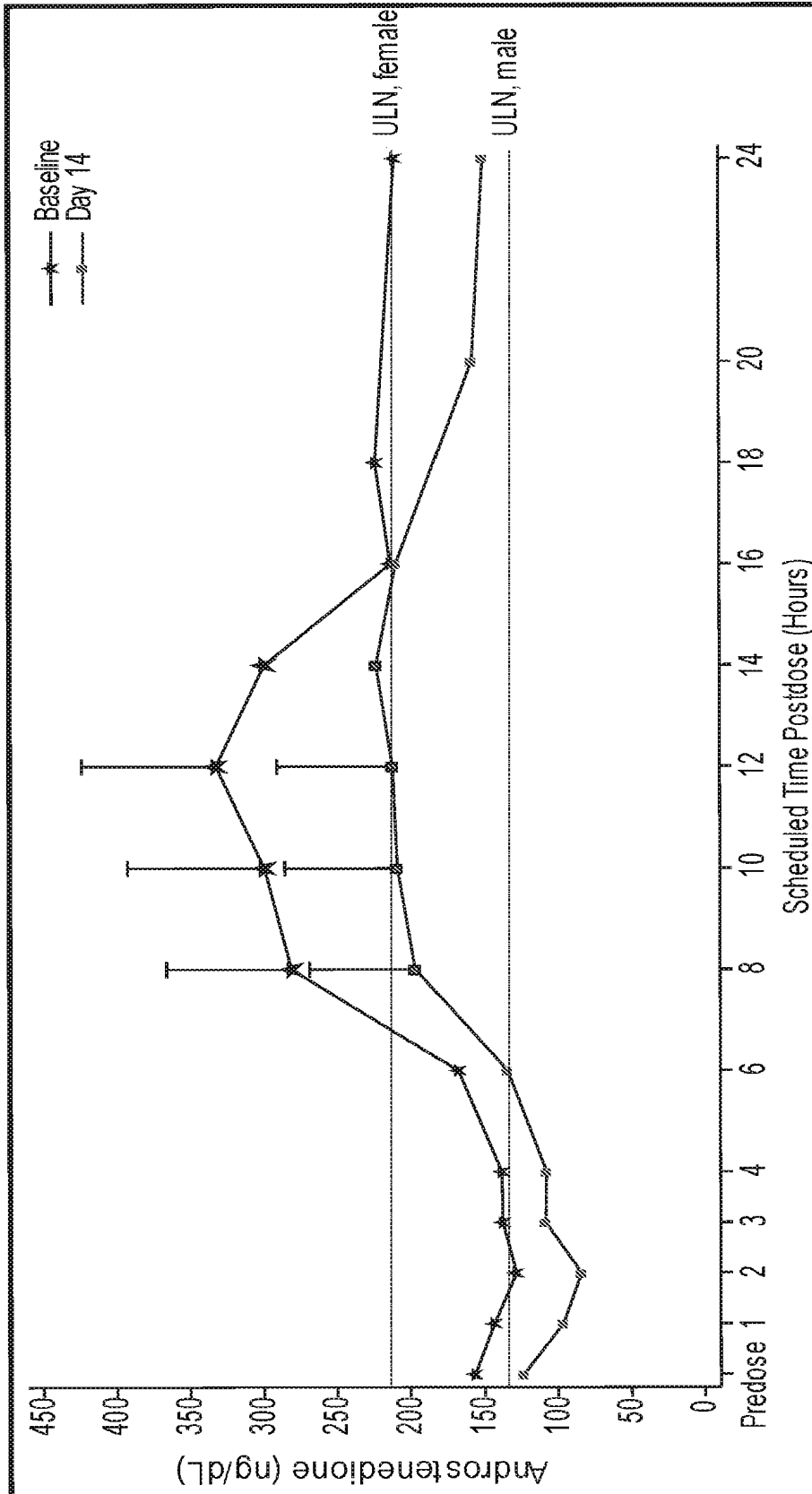


FIG. 17C

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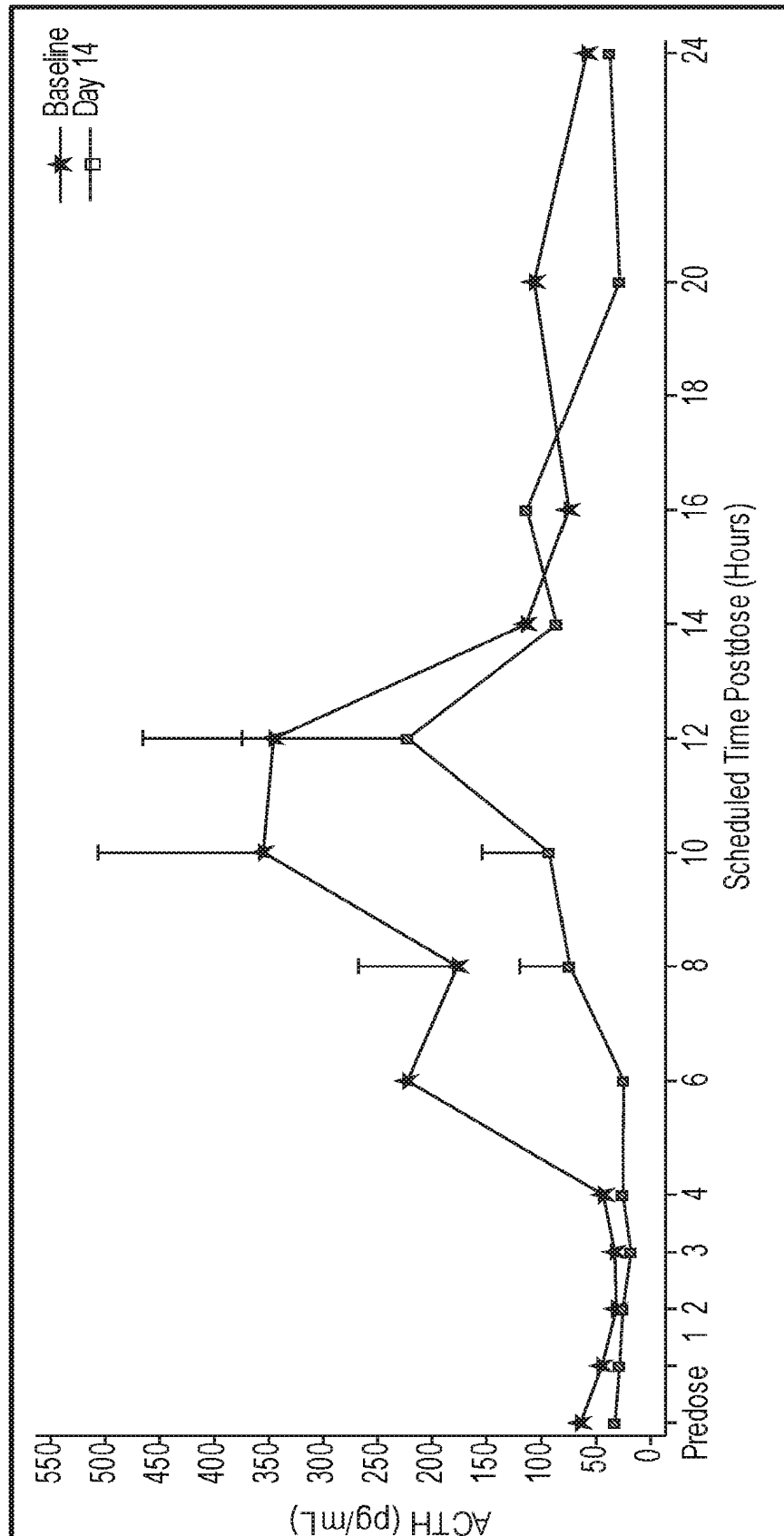


FIG. 18A

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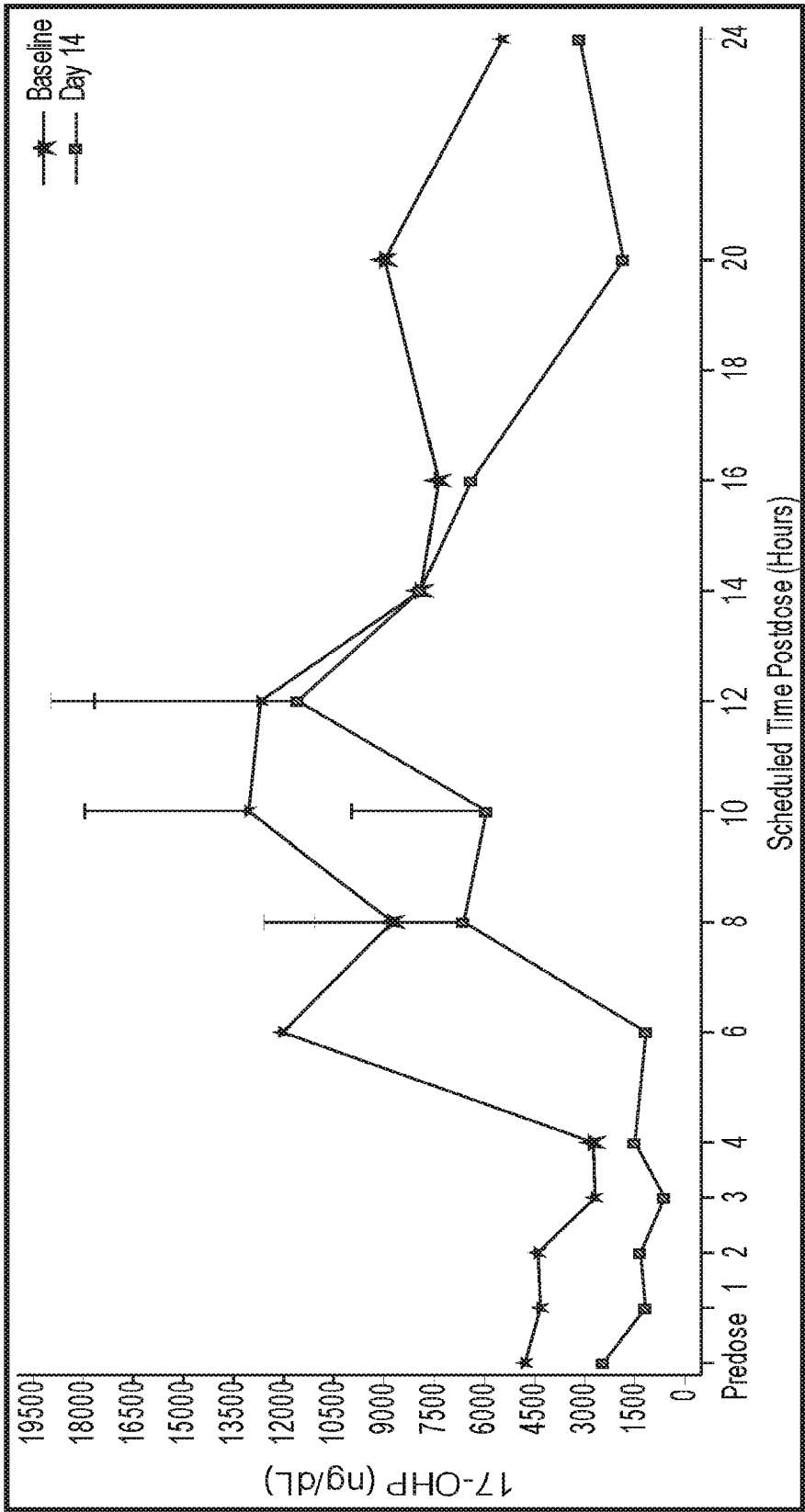


FIG. 18B

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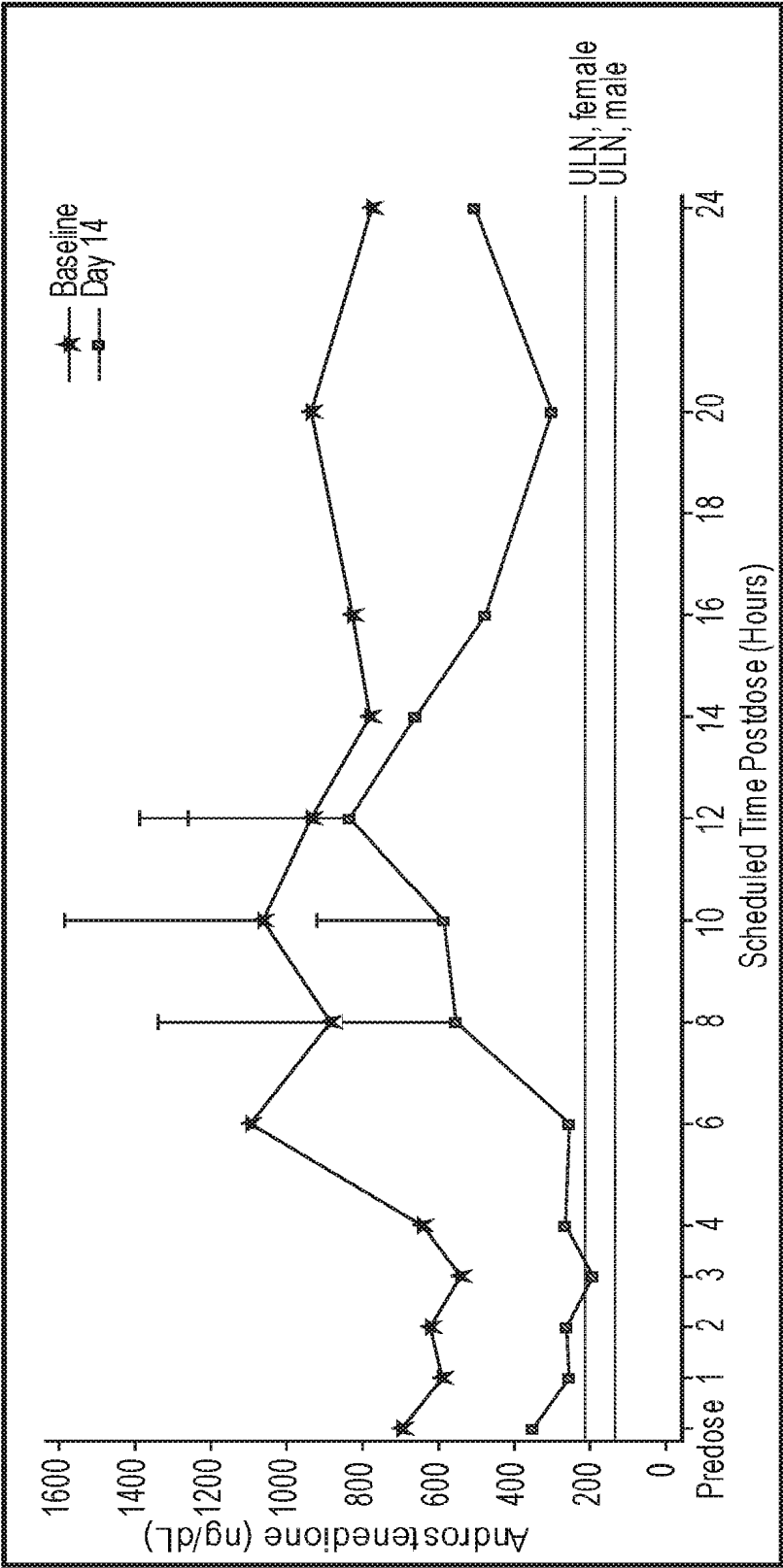


FIG. 18C

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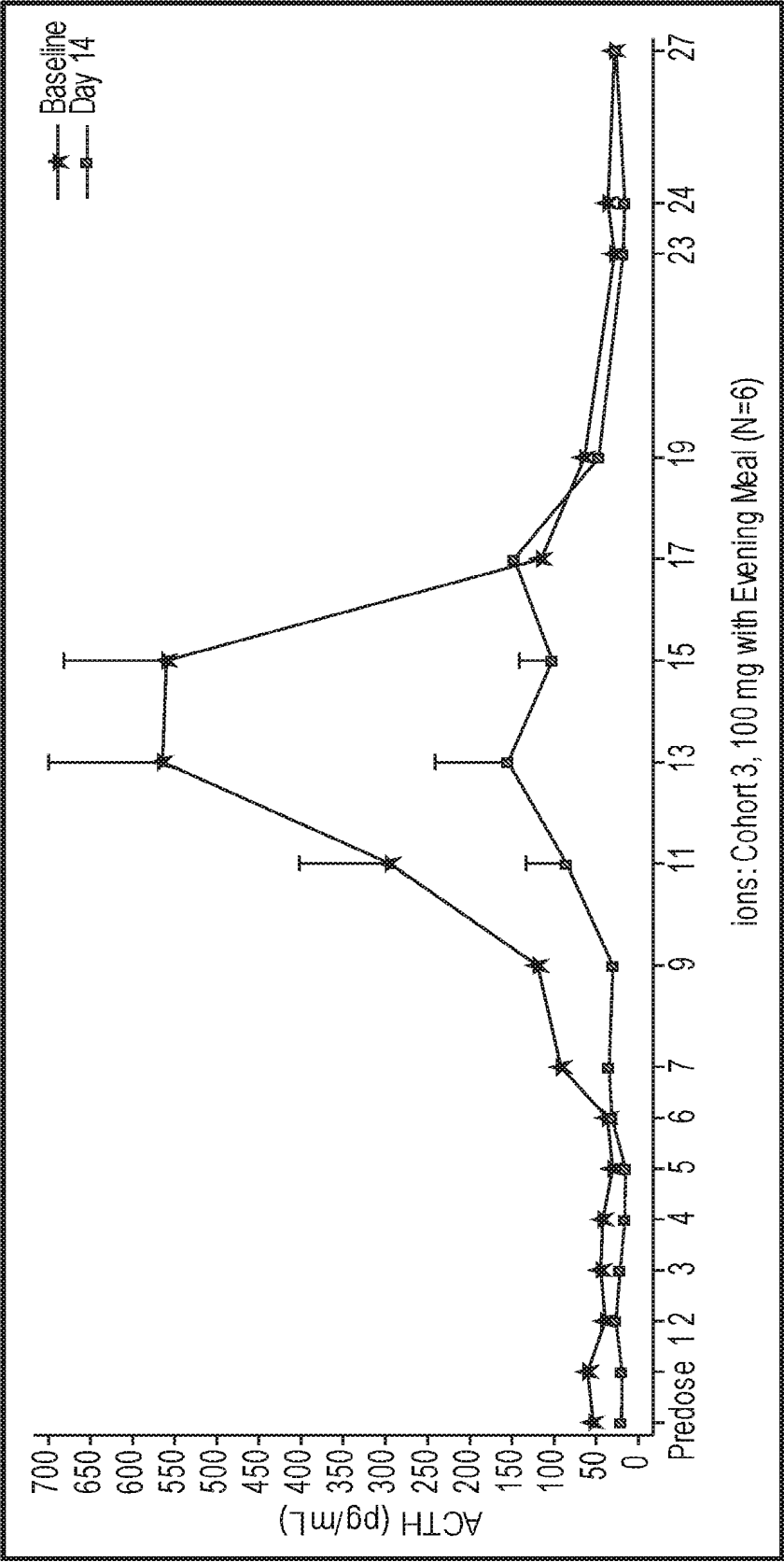


FIG. 19A

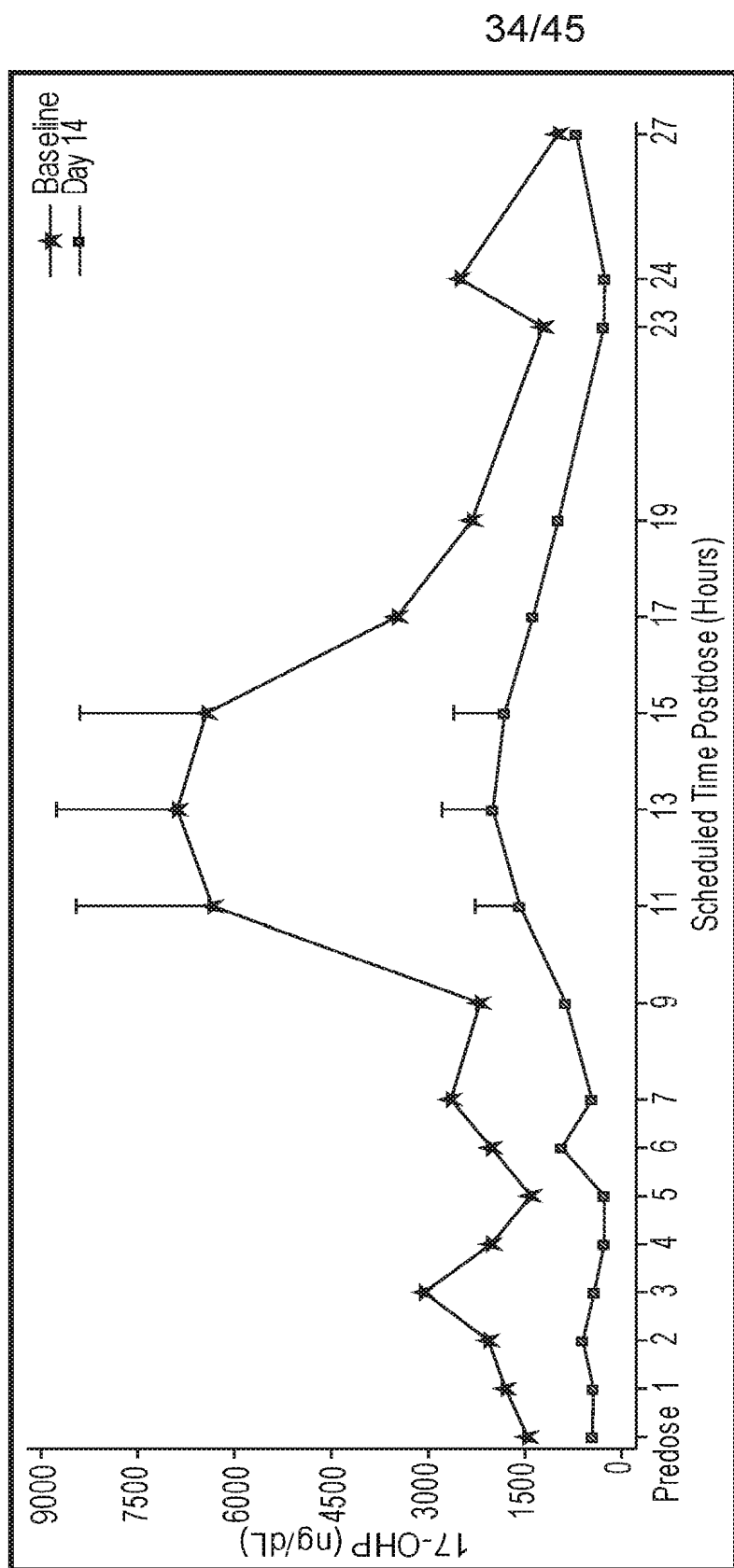


FIG. 19B

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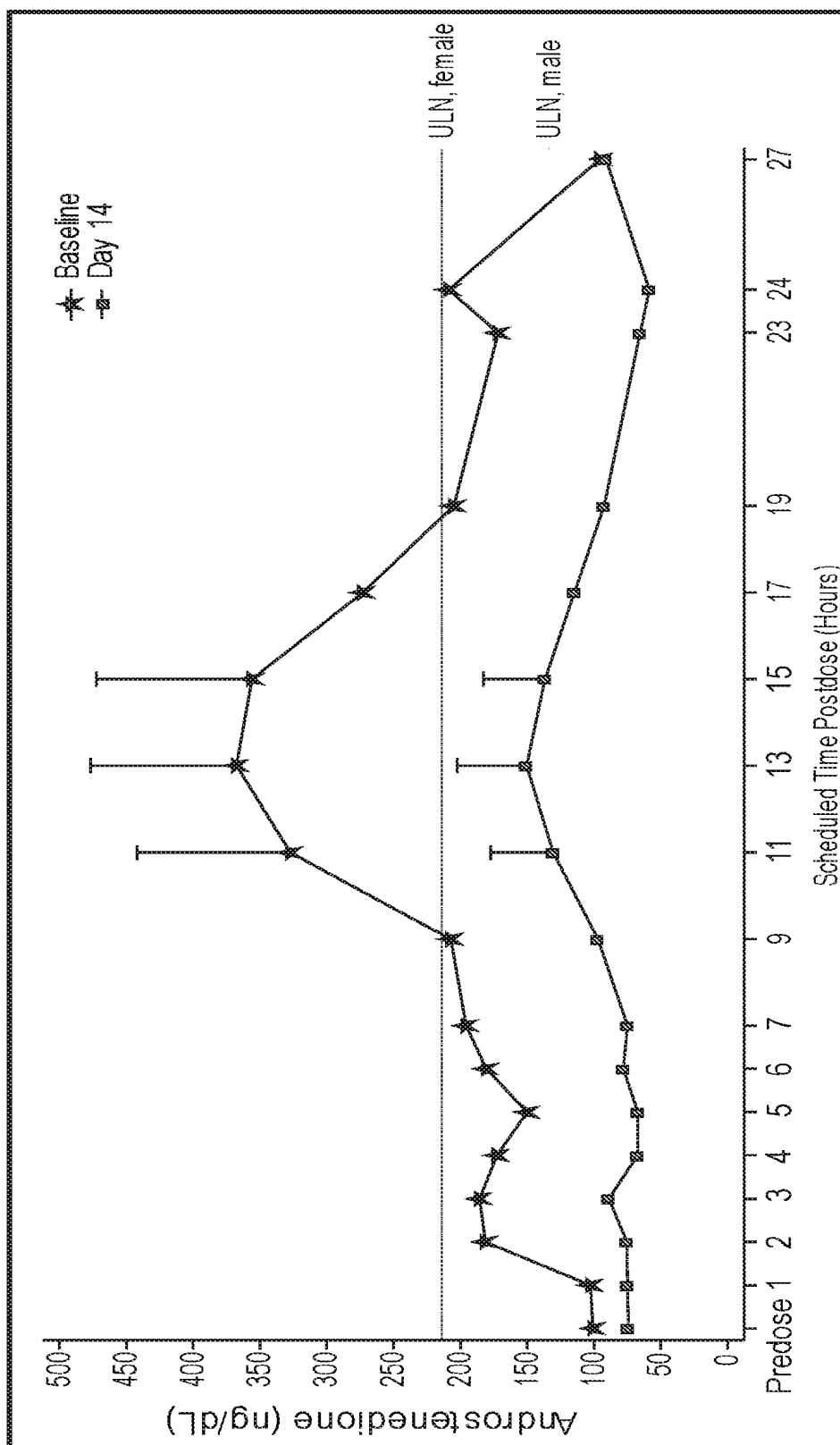


FIG. 19C

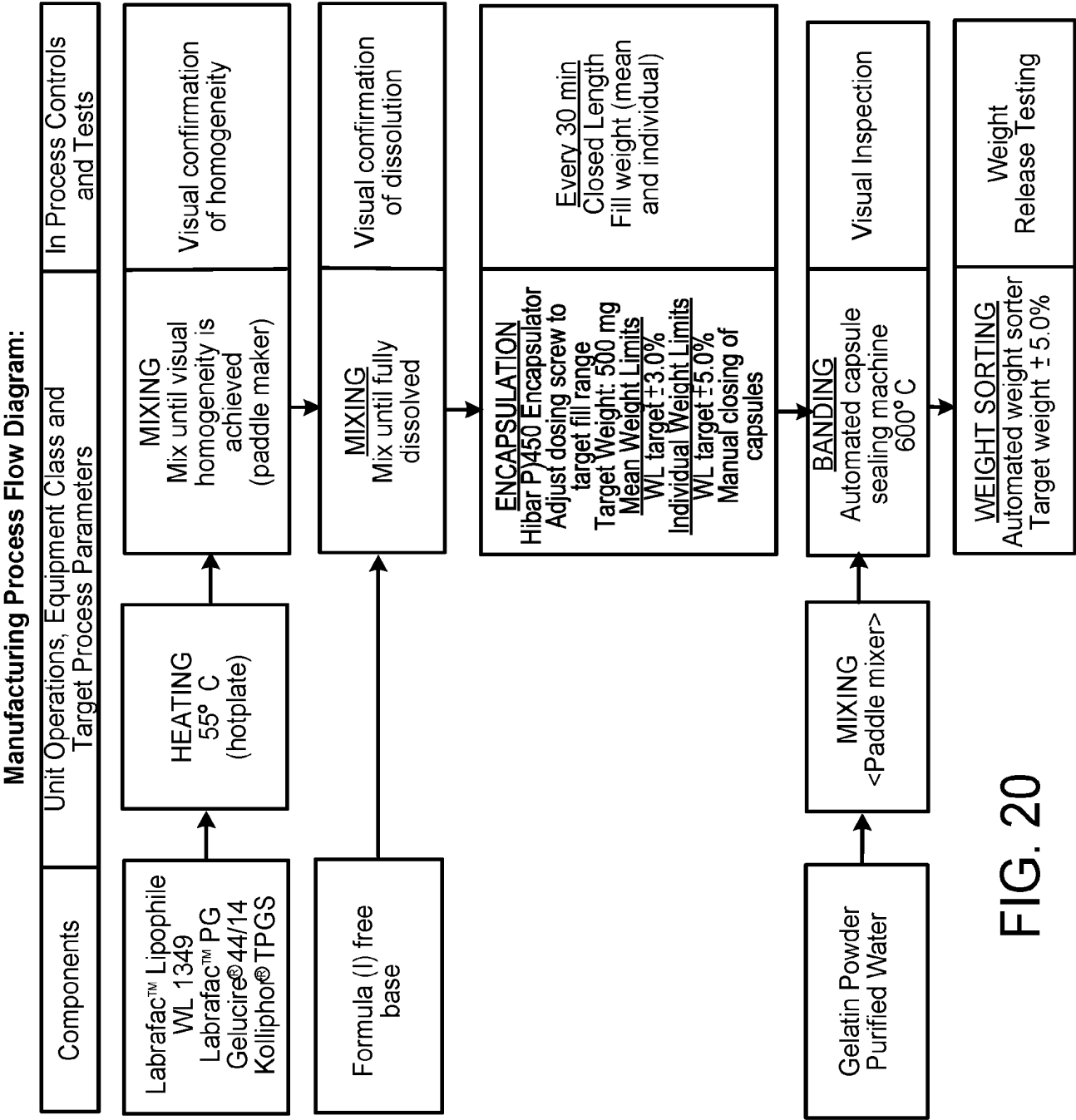
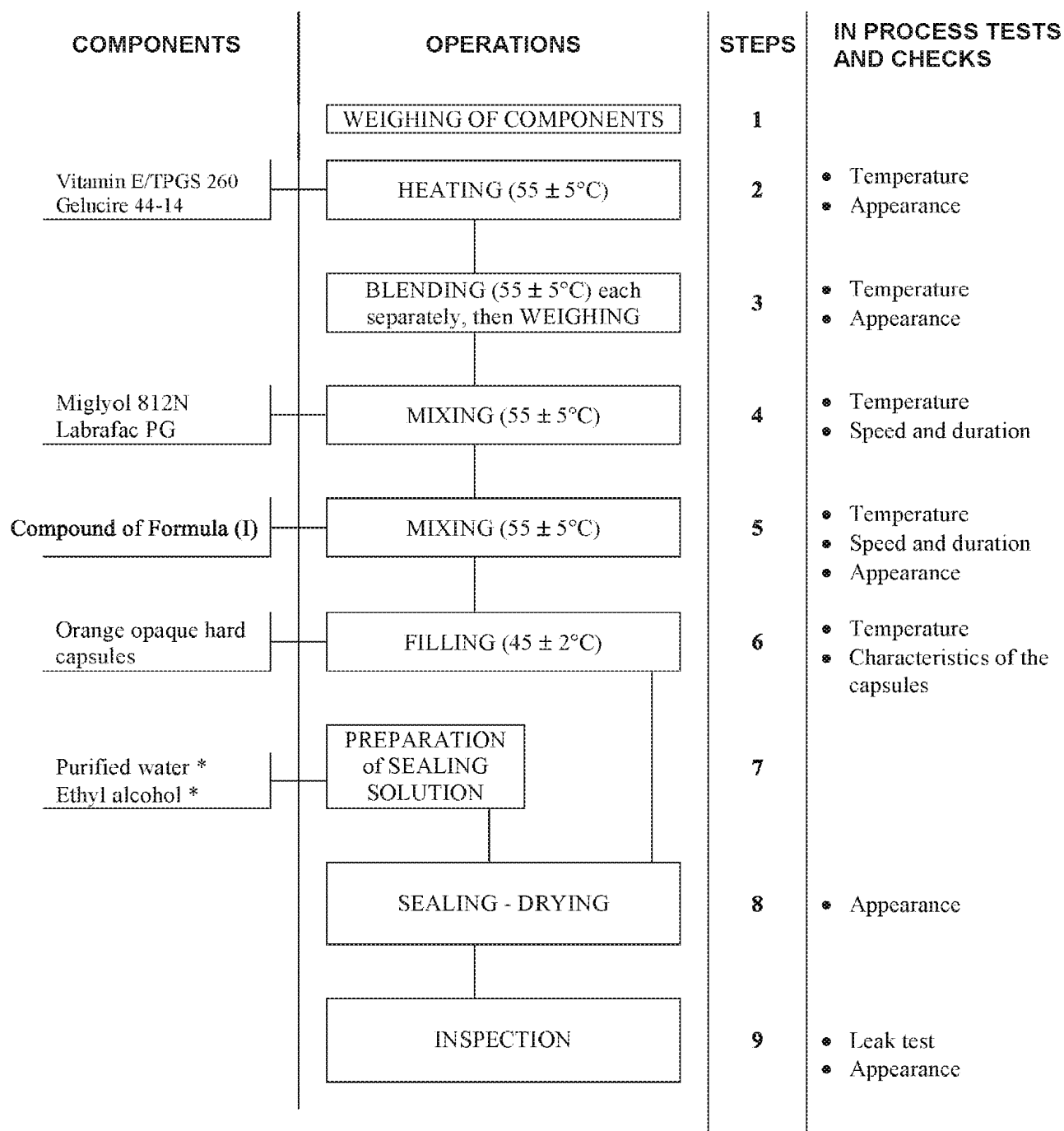


FIG. 20

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* Can be contained in hydro-alcoholic solution ready for manufacturing use

FIG. 21

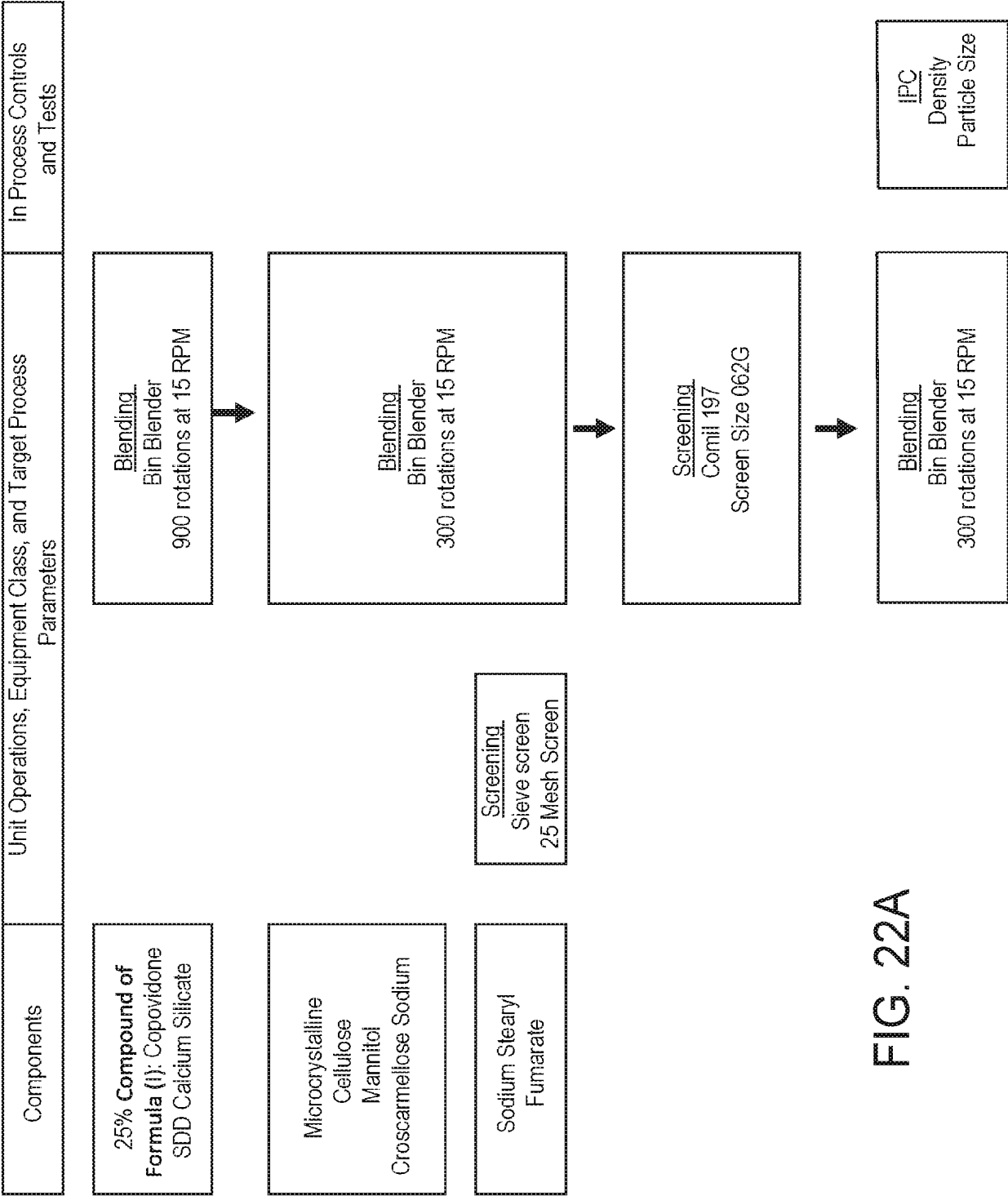


FIG. 22A

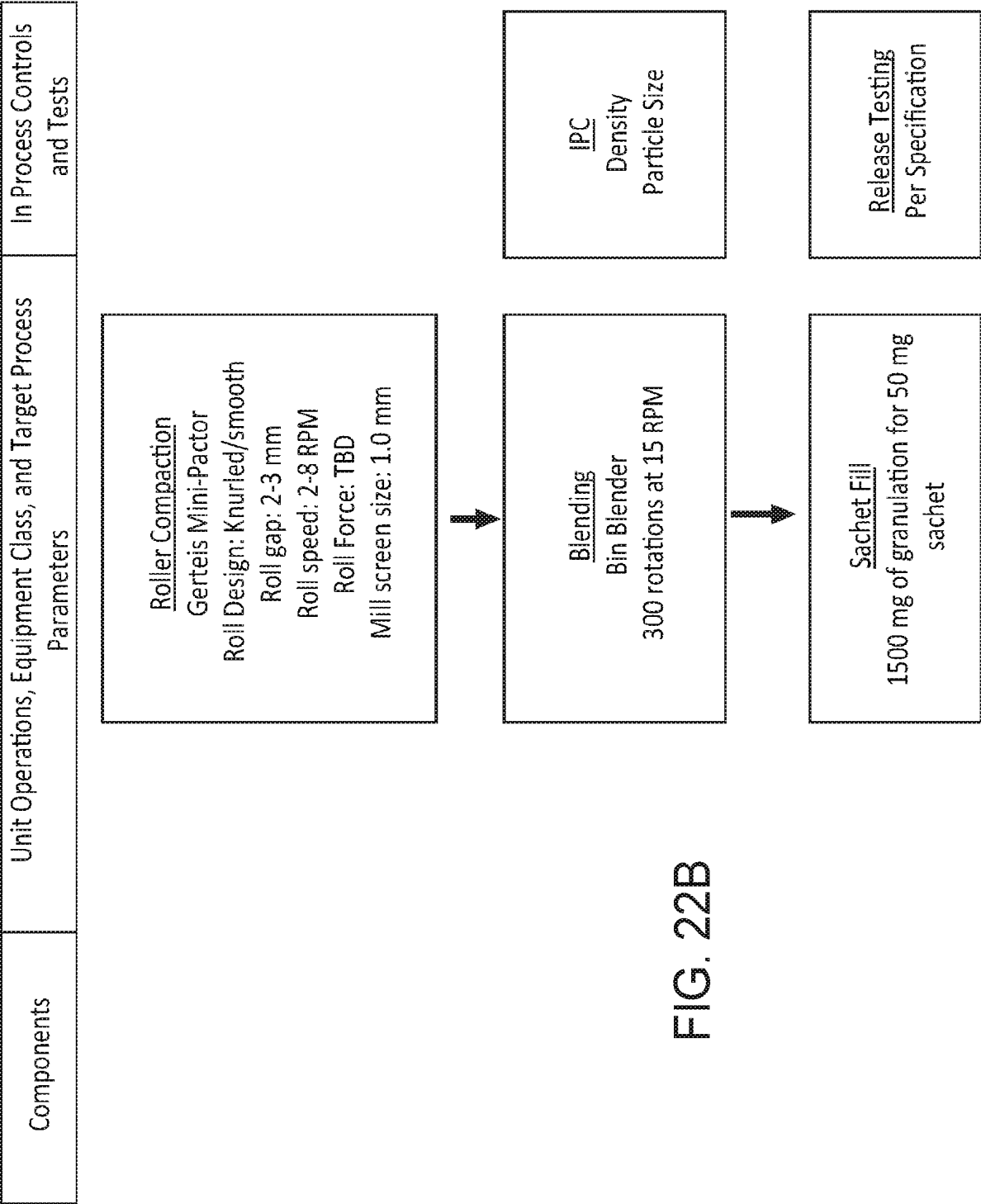


FIG. 22B

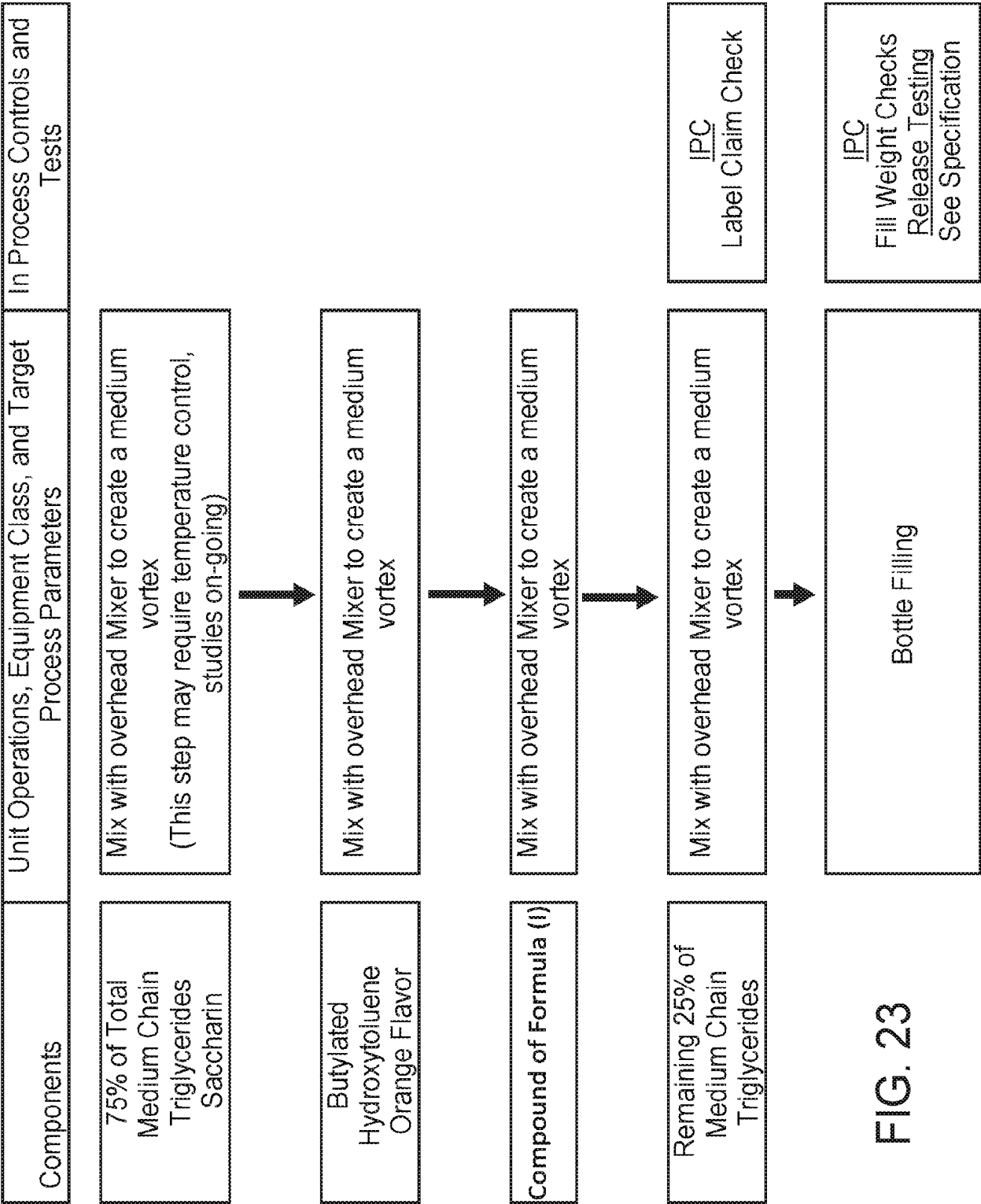


FIG. 23

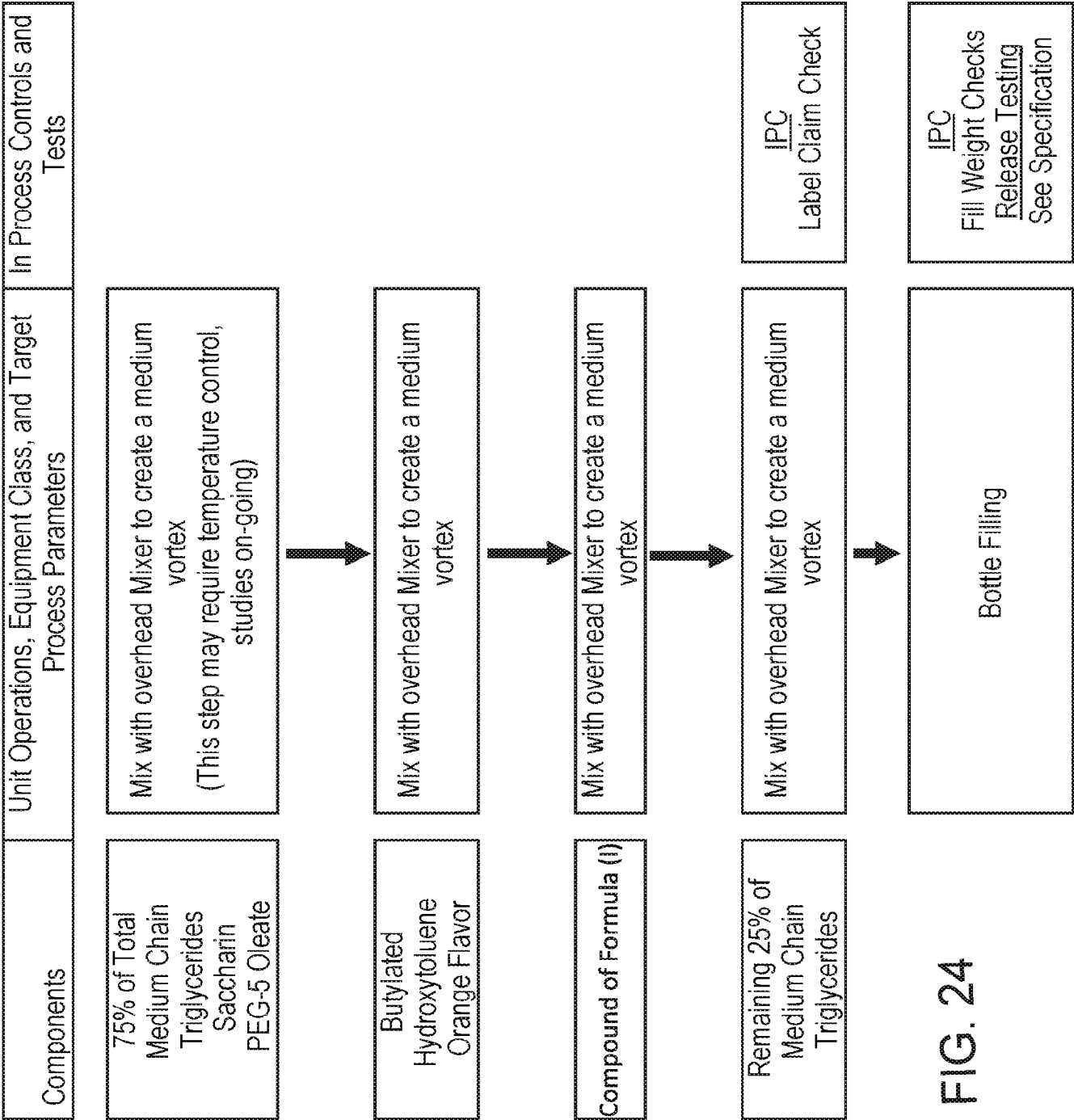


FIG. 24

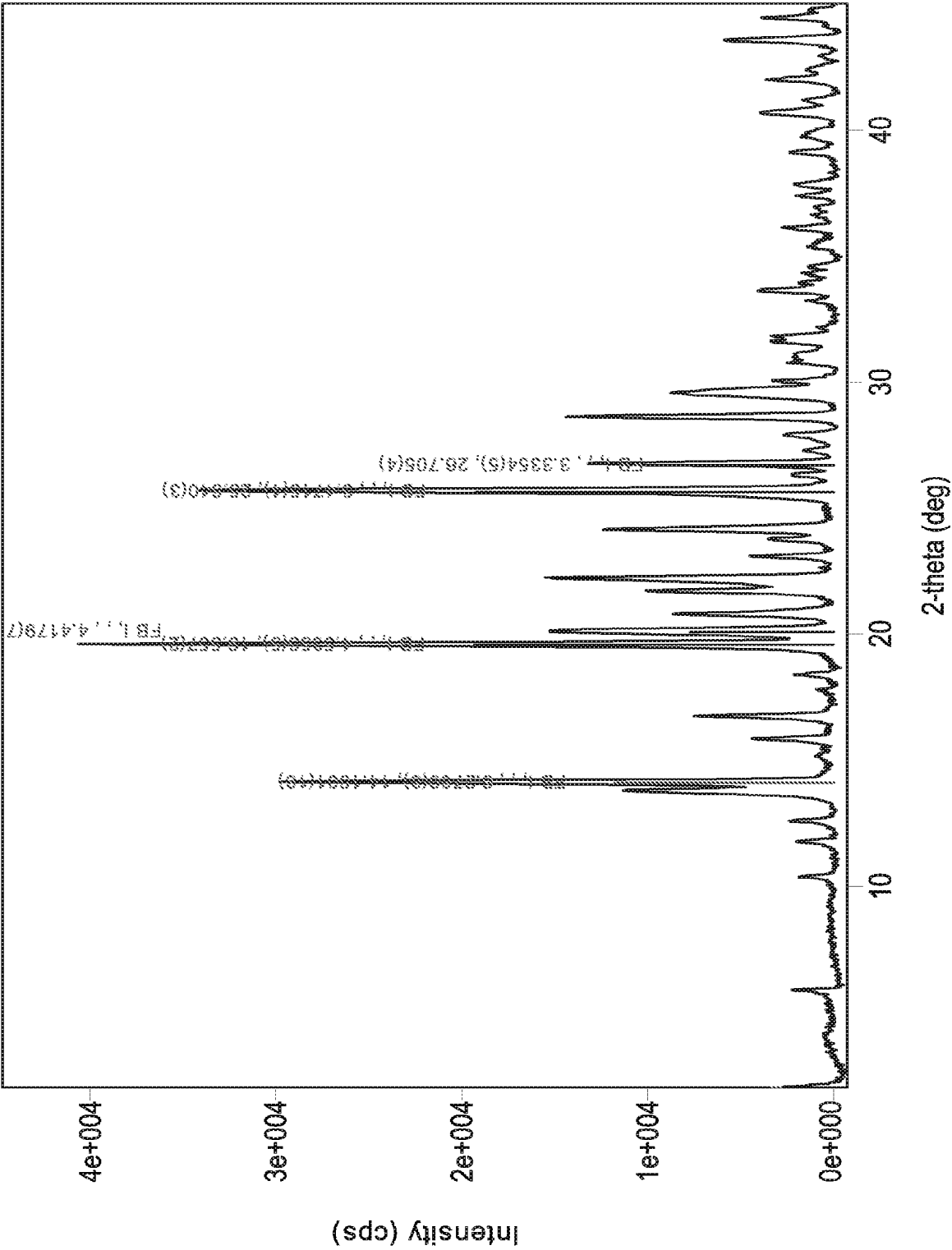


FIG. 25

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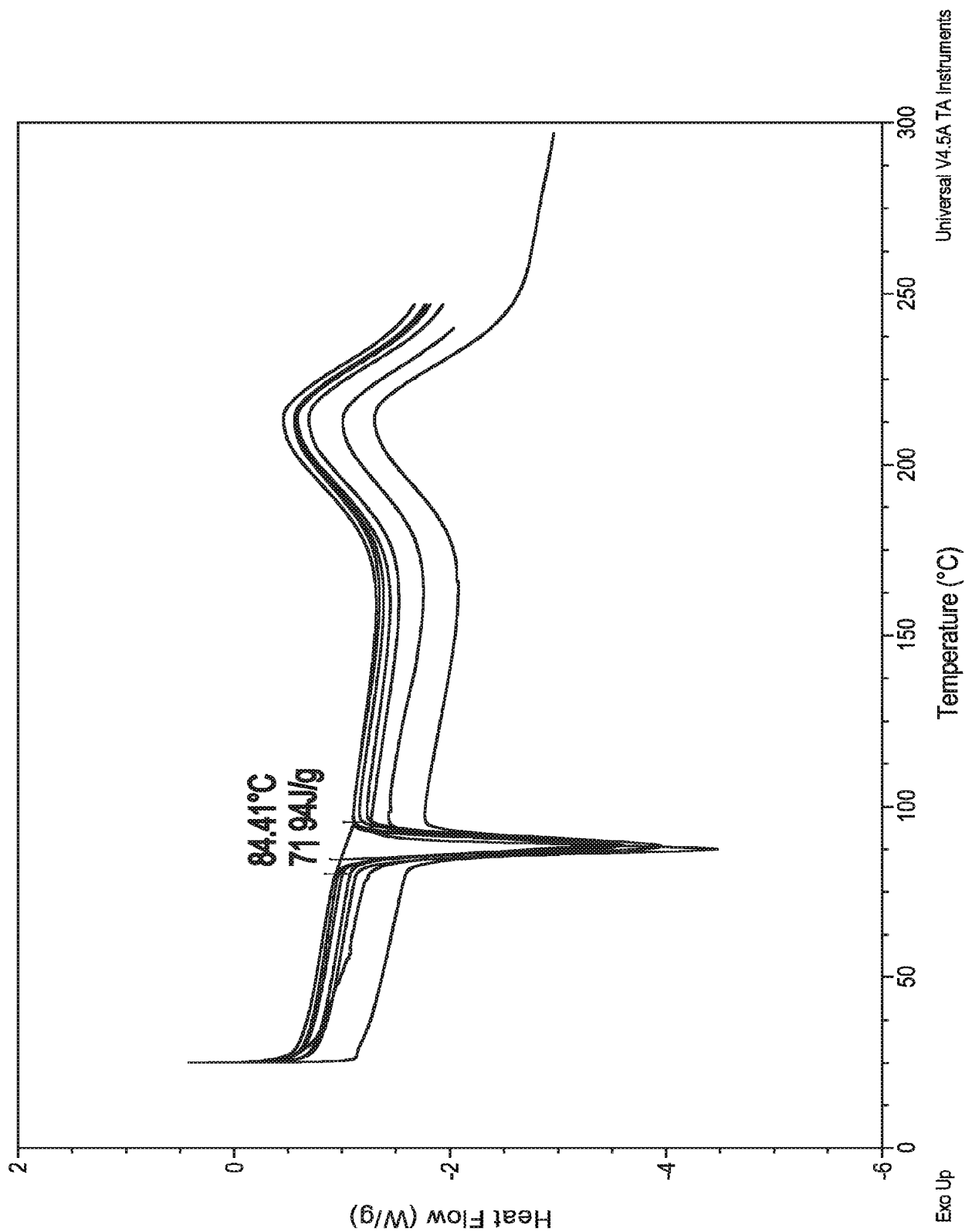


FIG. 26

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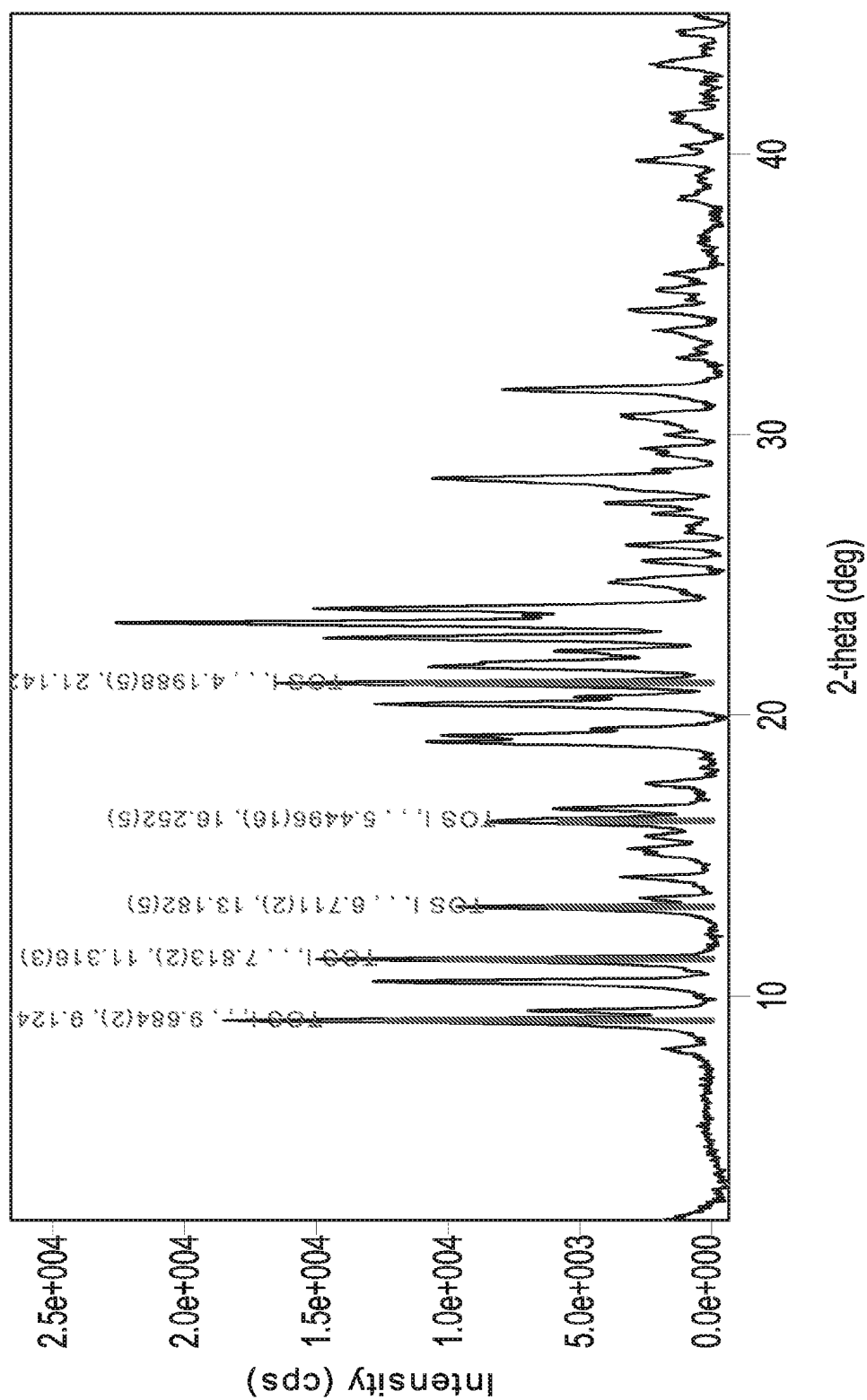


FIG. 27

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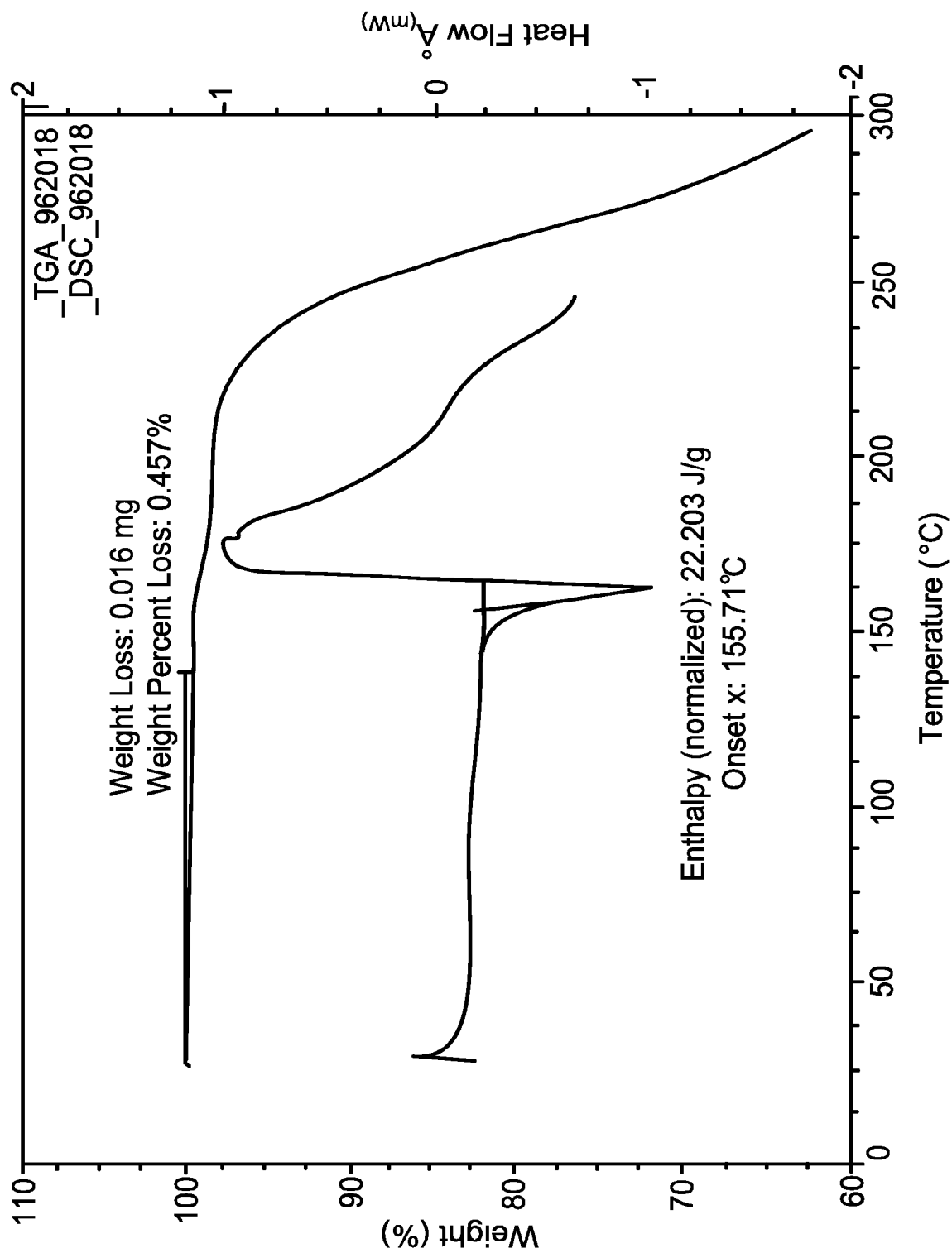


FIG. 28



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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
19/043,264

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50535-710.306

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	Jennifer Vail
PATENT CENTER #	71529866	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

Documents

TOTAL DOCUMENTS: 97

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710_306_IDS.pdf	20	-	388 KB
Spruce 50535-710_306_IDS-TRAN.LET.pdf	(1-4) 4	Transmittal Letter	155 KB
Spruce 50535-710_306_IDS-IDS.pdf	(5-20) 16	Information Disclosure Statement (IDS) Form (SB08)	228 KB
FOR_JP2000302693A_EFS.pdf	14	Foreign Reference	703 KB
FOR_EP2094709B1_EFS.pdf	38	Foreign Reference	1917 KB
FOR_WO0059908A2_EFS.pdf	118	Foreign Reference	3758 KB

2583

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907AE5E236B157E15AB532677AE55CE

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Bibliographic data

Title: Selective androgen receptor modulators, analogs and derivatives thereof and uses thereof
Pub/Pat no: CN101516835A
Pub/Issue Date: 2009-08-26
Inventor(s): IGOR RAKOV[US]|| CASEY BOHL[US]||RAKOV IGOR |BOHL CASEY
Applicant(s): OSURF OHIO STATE UNIVERSITY RE[US]
Classification: C07C255/00AI; C07D207/00AI
Application number: CN20078034701 2007-07-19
Priority number: US20060831988P 20060719;

Abstract of CN101516835A

This invention provides new compounds and uses thereof in treating a variety of diseases or conditions in a subject, including,inter alia, prostate cancer, muscle wasting diseases and/or disorders or a bone-related diseases and/or disorders.

[19] 中华人民共和国国家知识产权局



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[86] 国际申请 PCT/US2007/016311 2007.7.19

[87] 国际公布 WO2008/011072 英 2008.1.24

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权利要求书 32 页 说明书 162 页 附图 19 页

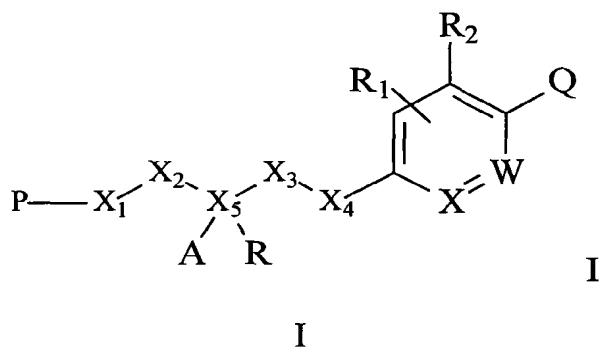
[54] 发明名称

选择性雄激素受体调节剂、它们的类似物和
衍生物以及它们的用途

[57] 摘要

本发明提供新型化合物以及它们在治疗个体的
各种疾病或病症中的用途，所述疾病或病症尤其包
括前列腺癌、肌萎缩疾病和/或病症、或骨相关疾病
和/或病症。

1. 化合物，其由式 I 的结构表示：

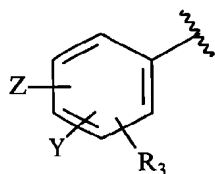


其中

X 是 C 或 N；W 是 C 或 N；

X₁ 是 N、NH、N(C₁₋₄ 烷基)、NAc、NCOOH 或键；或者 X₁ 和 X₃ 与 X₁ 和 X₃ 所连接的 X₂ 和 X₅ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X₁ 和 X₅ 与 X₁ 和 X₅ 所连接的 X₂ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

P 是 H 或式 II：



II

X₂ 是 C₁₋₄ 亚烷基、SO₂、C(O)、CH-[CH₂-(C₄₋₈ 环)]、CH(C₁₋₄ 烷基)、CH(NH₂)、CH(OH)、CH(C₁₋₄ 卤代烷基)、键；或者 X₂ 和 R₃ 与 X₂ 所连接的 X₁ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X₂ 和 X₅ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

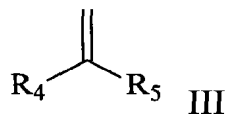
X₃ 是 C₁₋₄ 亚烷基、NH、N、CH(OH)、键；或者 X₁ 和 X₃ 与 X₁ 和 X₃ 所连接的 X₂ 和 X₅ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X₃ 和 X₅ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X₃ 和 X₄ 一起形成双键或一起形成饱和的或不饱和

的、取代的或未取代的 3-6 元环；

X_4 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；或者 X_4 和 X_5 与 X_4 和 X_5 所连接的 X_3 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_3 和 X_4 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

X_5 是碳或者 X_5 和 X_1 与 X_1 和 X_5 所连接的 X_2 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_5 和 X_2 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_5 和 X_3 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_5 和 X_4 与 X_5 和 X_4 所连接的 X_3 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

A 不存在，或是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂；或者 A 和 R 形成式 III 所表示的双键：



Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br；

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO₂、卤化物、CF₃、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHCO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂]；

R 是 H、OH、C₁₋₄ 烷基、CF₃、CH₂OH、O(C₁₋₄ 烷基)或 O(C₁₋₄ 酰基)；

R₁ 是 H、OH、NH₂、F、Cl、Br 或 I；

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基

或 $\text{CH}=\text{CH}-\text{O}$ -对氰基苯基;

R_3 是 H 、 C_{1-4} 烷基、卤化物、 CN 、 NO_2 ; 或者 R_3 和 X_2 与 R_3 所连接的苯环和 X_2 所连接的 X_1 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环;

R' 是 NH_2 、 OH 或 CH_3 ;

R_4 和 R_5 独立地是 H 、 CH_3 、卤化物、 OH 、 C_{1-4} 烷基、 C_{1-6} 环烷基、卤代(C_{1-4} 烷基)、苯基、芳基、 C_{4-8} 杂环烷基或羟基(C_{1-4} 烷基);

R_6 是 CN 、 NO_2 、 $\text{NHC}(\text{O})\text{CH}_3$ 或卤化物;

其中

如果 P 是式 II, X 是 C , X_1 是 NH , X_2 是 $\text{C}(\text{O})$, X_3 是 CH_2 , R 是 OH 并且 A 是烷基或卤代烷基, 那么 X_4 是 $\text{S}(\text{O})[=\text{CHCH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{C}(\text{OH})[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{C}[=\text{CHCH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{N}[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{P}(\text{O})(\text{C}_{1-4}\text{烷基})$ 或 $\text{N}(\text{O})[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$;

或者

如果 P 是式 II, X 是 C , X_1 是 NH , X_2 是 $\text{C}(\text{O})$, X_3 是 CH_2 , R 是 OH 或 OAlk 并且 X_4 是 O 、 S 、 NH 、 S 、 SO 、 SO_2 或亚烷基, 那么 A 是 CN 、 CH_2OH 、 $\text{CH}_2\text{O}(\text{C}_{1-4}\text{烷基})$ 、 $\text{CH}_2\text{O}(\text{C}_{1-4}\text{酰基})$ 、 CH_2CN 、 CH_2N_3 、 CH_2NCS 、 CHO 、 $\text{C}(\text{O})\text{O}(\text{C}_{1-4}\text{烷基})$ 、 CONHR' 、 $\text{C}(\text{O})\text{N}(\text{R}')_2$ 、 $\text{C}(\text{O})\text{O}(\text{C}_{1-4}\text{烷基})$ 、 $\text{C}(\text{O})\text{R}'$ 、 $\text{CH}_2\text{OR}'\text{CH}_2\text{C}(\text{O})\text{CH}=\text{CH}_2$ 或 $\text{C}(\text{O})\text{CH}=\text{CH}_2$;

或者

如果 P 是苯基, X 是 C , X_1 是 NH , X_2 是 $\text{C}(\text{O})$, R 是 OH 并且 A 是 COOH , X_3 是键, X_4 是 CH_2 , R_1 、 R_2 是 H , 那么 Q 不是 H ;

或者

如果 P 是式 II, X 是 C , X_3 是 CH_2 , X_4 是 O 或 NH , R_1 、 R_2 和 R_3 是 H , 并且 X_5 和 X_1 形成 5 元环噁唑烷-2-酮, 那么 Q 不是卤素或 H ;

或者

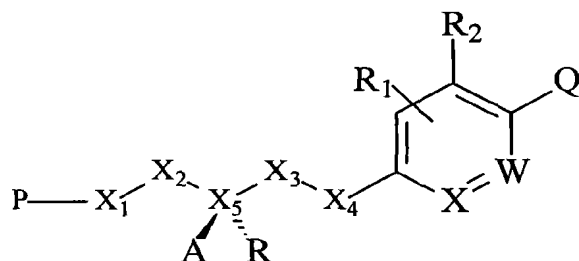
如果 P 是 H , X 是 C , X_1 是 NH , X_2 是 $\text{C}(\text{O})$, R 是 OH , A 是烷基, X_3 是键或 CH_2 并且 X_4 是键或 CH_2 , R_1 和 R_2 是 H , 那么 Q 不是 H 或卤素;

或者

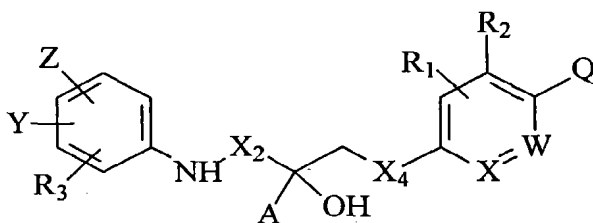
如果 P 是式 II, R_3 是 H , X 和 W 是 C , X_1 和 X_5 与 X_1 和 X_5 所连接的

X_2 一起形成噁唑烷二酮, R 是烷基, X_3 是 CH_2 并且 X_4 是 O 、 NH 、 S 、 SO_2 或 CH_2 , 那么 Q 不是卤化物。

2. 权利要求 1 的化合物, 其由以下结构表示:



3. 权利要求 1 的化合物, 其中所述化合物由式 IV 的结构表示:



IV

其中

X 是 C 或 N ; W 是 C 或 N ;

X_2 是 C_{1-4} 亚烷基、 SO_2 、 $CH-[CH_2-(C_{4-8} \text{ 环})]$ 、 $CH(C_{1-4} \text{ 烷基})$ 、 $CH(NH_2)$ 、 $CH(OH)$ 、 $CH(C_{1-4} \text{ 卤代烷基})$ 、键;

X_4 是 O 、 S 、 SO 、 $C(O)$ 、 $S(O)[=CHCH_2N(CH_3)_2]$ 、 SO_2 、 NH 、 NHR' 、 NO 、 C_{1-4} 亚烷基、 $C(OH)[CH_2CH_2N(CH_3)_2]$ 、 $C[=CHCH_2N(CH_3)_2]$ 、 $PO(C_{1-4} \text{ 烷基})$ 、 $N[CH_2CH_2N(CH_3)_2]$ 、 $NO[CH_2CH_2N(CH_3)_2]$ 或键;

A 是 H 、 OH 、 SH 、 NH_2 、 C_{1-4} 烷基、 CHF_2 、 CH_2F 、 CF_3 、 CN 、 CH_2OH 、 $CH_2O(C_{1-4} \text{ 烷基})$ 、 $CH_2O(C_{1-4} \text{ 酰基})$ 、 CH_2CN 、 CH_2N_3 、 CH_2NCS 、 CHO 、 $C(O)O(C_{1-4} \text{ 烷基})$ 、 $CONHR'$ 、 $C(O)N(R')_2$ 、 $C(O)O(C_{1-4} \text{ 烷基})$ 、 $C(O)R'$ 、 CH_2CF_3 、 CF_2CF_3 、 $CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、CN、NO₂、F、Cl、I 或 Br;

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R 是 H、OH、C₁₋₄ 烷基、CF₃、CH₂OH、O(C₁₋₄ 烷基)或 O(C₁₋₄ 酰基);

R₁ 是 H、OH、F、Cl、Br 或 I;

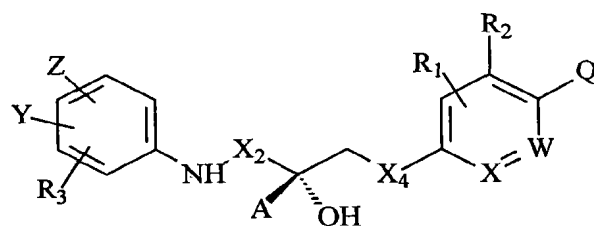
R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

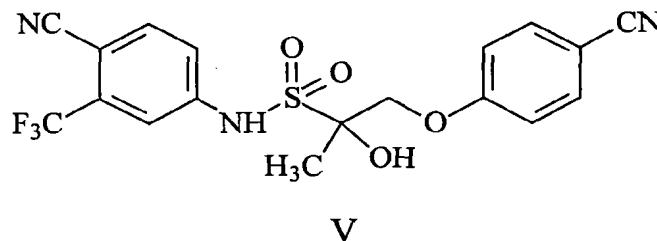
R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

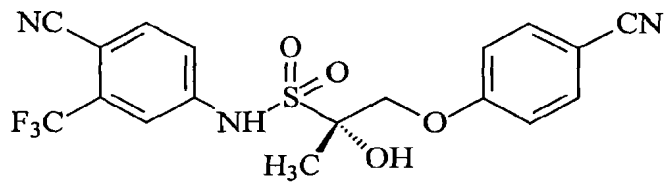
4. 权利要求 3 的化合物, 其由以下结构表示:



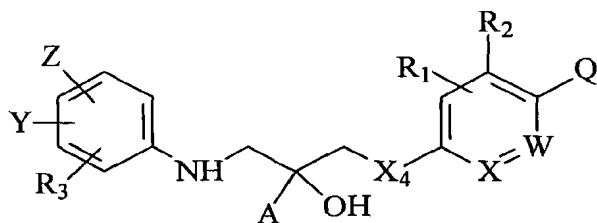
5. 权利要求 2 的化合物, 其中所述化合物由式 V 的结构表示:



6. 权利要求 5 的化合物, 其由以下结构表示:



7. 权利要求 2 的化合物，其中所述化合物由式 VI 的结构表示：



VI

其中

X 是 C 或 N；W 是 C 或 N；

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂；

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br；

Y 是 H、C₁₋₄ 烷基、CF₃、CN、NO₂、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂]；

R 是 H、OH、C₁₋₄ 烷基、CF₃、CH₂OH、O(C₁₋₄ 烷基)或 O(C₁₋₄ 酰基)；

R₁ 是 H、OH、F、Cl、Br 或 I；

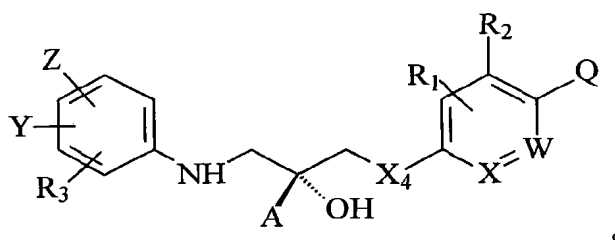
R_2 是 H、由 R_6 取代的苄基、 $(CH_2)_2$ -O-对氰基苯基、 CH_2 -O-对氰基苯基或 $CH=CH$ -O-对氰基苯基；

R_3 是 H、 C_{1-4} 烷基、卤化物、CN 或 NO_2 ；

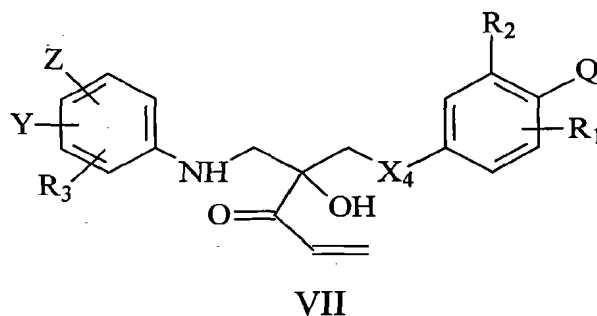
R' 是 NH_2 、OH 或 CH_3 ；并且

R_6 是 CN、 NO_2 、 $NHC(O)CH_3$ 或卤化物。

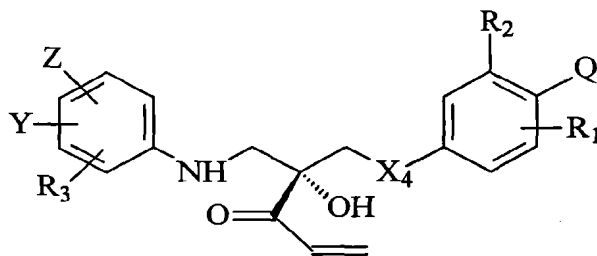
8. 权利要求 7 的化合物，其由以下结构表示：



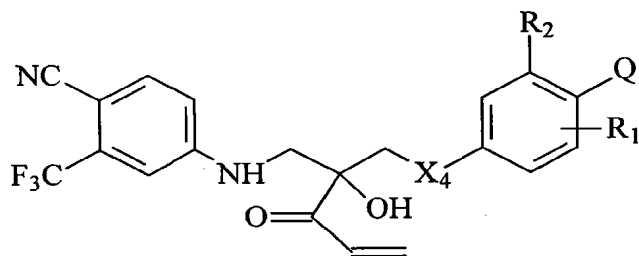
9. 权利要求 7 的化合物，其中所述化合物由式 VII 的结构表示：



10. 权利要求 9 的化合物，其由以下结构表示：

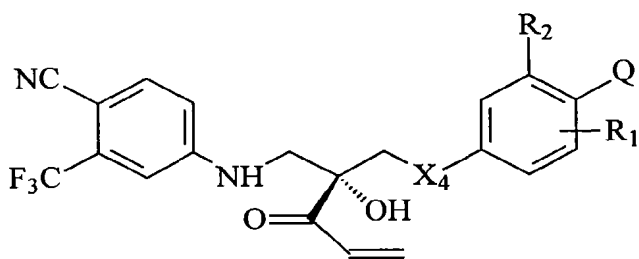


11. 权利要求 9 的化合物，其中所述化合物由式 X 的结构表示：

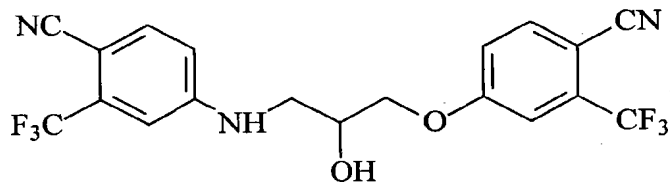


VIII

12. 权利要求 11 的化合物，其由以下结构表示：

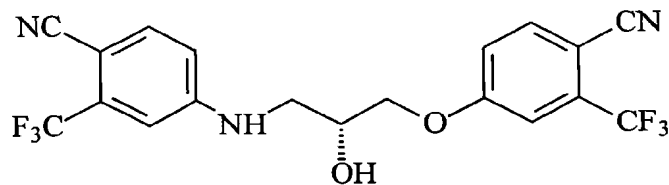


13. 权利要求 7 的化合物，其中所述化合物由式 IX 的结构表示：

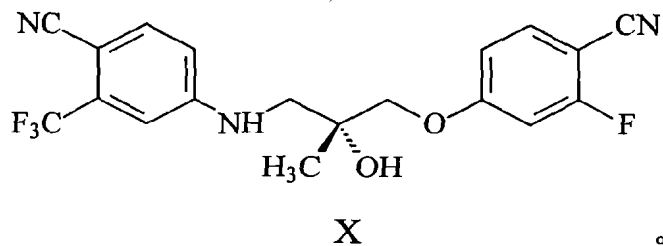


IX

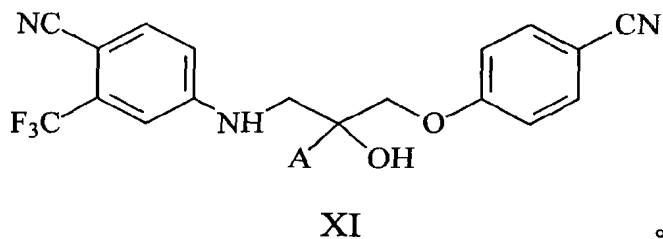
14. 权利要求 13 的化合物，其由以下结构表示：



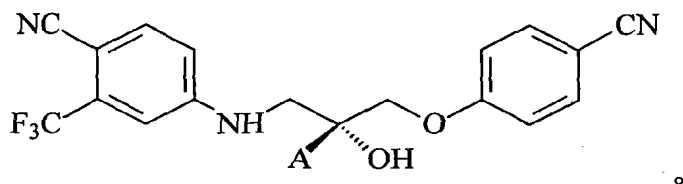
15. 权利要求 7 的化合物，其中所述化合物由式 X 的结构表示：



16. 权利要求 7 的化合物，其中所述化合物由式 X 的结构表示：



17. 权利要求 16 的化合物，其由以下结构表示：



18. 权利要求 15 的化合物，其中 A 是 CH_2OH 。

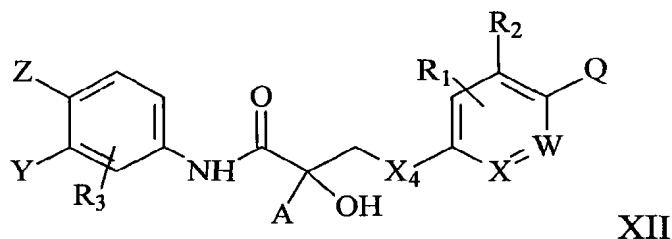
19. 权利要求 17 的化合物，其中 A 是 CH_2OMe 。

20. 权利要求 17 的化合物，其中 A 是 CF_3 。

21. 权利要求 17 的化合物，其中 A 是 CH_3 。

22. 权利要求 17 的化合物，其中 A 是 CN 。

23. 权利要求 1 的化合物，其中所述化合物由式 XII 的结构表示：



其中

X 是 C 或 N; W 是 C 或 N;

X_4 是 O、S、SO、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

A 是 CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、CN、NO₂、F、Cl、I 或 Br;

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R₁ 是 H、OH、F、Cl、Br 或 I;

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

24. 权利要求 23 的化合物, 其中 X_4 是 O。

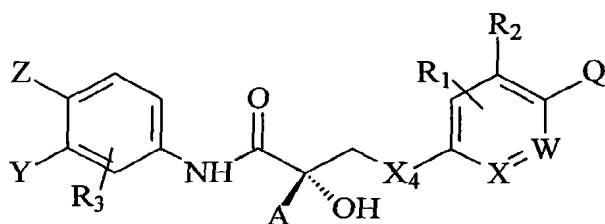
25. 权利要求 24 的化合物, 其中 A 是 CH₂OH。

26. 权利要求 24 的化合物, 其中 A 是 CN。

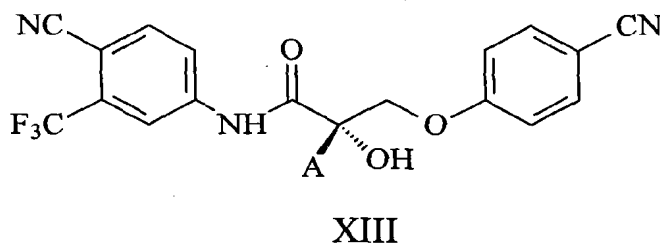
27. 权利要求 23 的化合物, 其中 Q 是 CN, R_1 和 R_2 是 H。

28. 权利要求 23 的化合物, 其中 Q 是 CN, Z 是 CN, Y 是 CF_3 , 并且 R_1 、 R_2 和 R_3 是 H。

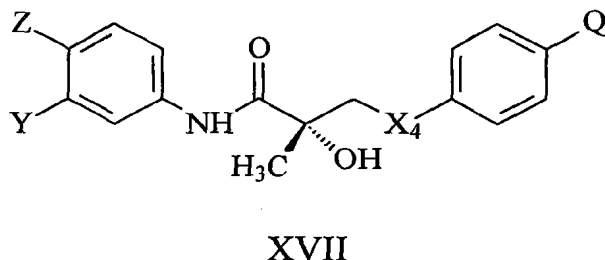
29. 权利要求 23 的化合物, 其由以下结构表示:



30. 权利要求 23 的化合物, 其中所述化合物由式 XIII 的结构表示:



31. 权利要求 1 的化合物, 其中所述化合物由式 XVII 的结构表示:



其中

X_4 是 $S(O)[=CHCH_2N(CH_3)_2]$ 、 $C(OH)[CH_2CH_2N(CH_3)_2]$ 、 $C[=CHCH_2N(CH_3)_2]$ 、 $PO(C_{1-4} \text{ 烷基})$ 、 $N[CH_2CH_2N(CH_3)_2]$ 、

$\text{NO}[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$;

Q 是 H、CN、OH、 NO_2 、卤化物、 C_{2-6} 烯基、 C_{2-6} 炔基、 $\text{C}(\text{O})\text{CH}_2\text{NH}_2$ 、 $\text{C}(\text{O})\text{NH}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{C}(\text{O})\text{N}(\text{C}_{1-4} \text{ 烷基})_2$ 、 $\text{C}(\text{O})\text{NH}_2$ 、 $\text{NH}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{NHC}(\text{O})\text{NH}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{CH}_2\text{C}(\text{O})\text{NH}_2$ 、 $\text{NHC}(\text{O})\text{NH}_2$ 、 $\text{NHCO}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{NH}\text{SO}_2(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{O}[\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2]$ 、 $\text{O}[\text{CH}_2\text{CH}_2(\text{C}_{4-8} \text{ 环烷基})]$ 、 $\text{O}[\text{CH}_2\text{CH}_2(\text{C}_{4-8} \text{ 杂环烷基})]$ 或 $\text{O}[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$;

Z 是 H、CN、 NO_2 、 $\text{NHC}(\text{O})\text{CH}_3$ 、 C_{1-4} 烷基、F、Cl、I 或 Br; 并且

Y 是 H、 C_{1-4} 烷基、 CF_3 、CN、 NO_2 、F、Cl、I 或 Br。

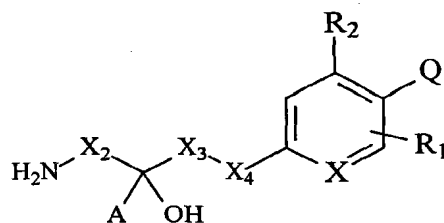
32. 权利要求 31 的化合物, 其中 Q 是 F。

33. 权利要求 31 的化合物, 其中 Q 是 CN。

34. 权利要求 31 的化合物, 其中 Z 是 CN 且 Y 是 CF_3 。

35. 权利要求 31 的化合物, 其中 Q 是 CN, Z 是 CN 且 Y 是 CF_3 。

36. 权利要求 1 的化合物, 其中所述化合物由式 XIX 的结构表示:



XIX

其中

X 是 C 或 N; W 是 C 或 N;

X_2 是 C_{1-4} 亚烷基、 SO_2 、 $\text{C}(\text{O})$ 、 $\text{CH}[\text{CH}_2-(\text{C}_{4-8} \text{ 环})]$ 、 $\text{CH}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{CH}(\text{NH}_2)$ 、 $\text{CH}(\text{OH})$ 、 $\text{CH}(\text{C}_{1-4} \text{ 卤代烷基})$ 、键;

X_3 是 C_{1-4} 亚烷基、NH、N、 $\text{CH}(\text{OH})$ 或键;

X_4 是 O、S、 SO 、 $\text{C}(\text{O})$ 、 $\text{S}(\text{O})[=\text{CHCH}_2\text{N}(\text{CH}_3)_2]$ 、 SO_2 、NH、 NHR' 、NO、 C_{1-4} 亚烷基、 $\text{C}(\text{OH})[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{C}[=\text{CHCH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{PO}(\text{C}_{1-4}$

烷基)、 $N[CH_2CH_2N(CH_3)_2]$ 、 $NO[CH_2CH_2N(CH_3)_2]$ 或键;

A 是 H、OH、SH、 NH_2 、 C_{1-4} 烷基、 CHF_2 、 CH_2F 、 CF_3 、CN、 CH_2OH 、 $CH_2O(C_{1-4}$ 烷基)、 $CH_2O(C_{1-4}$ 酰基)、 CH_2CN 、 CH_2N_3 、 CH_2NCS 、CHO、 $C(O)O(C_{1-4}$ 烷基)、 $CONHR'$ 、 $C(O)N(R')_2$ 、 $C(O)O(C_{1-4}$ 烷基)、 $C(O)R'$ 、 CH_2CF_3 、 CF_2CF_3 、 $CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$;

Z 是 H、CN、 NO_2 、 $NHC(O)CH_3$ 、 C_{1-4} 烷基、F、Cl、I 或 Br;

Y 是 H、 C_{1-4} 烷基、 CF_3 、 NO_2 、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、 NO_2 、 CF_3 、卤化物、 C_{2-6} 烯基、 C_{2-6} 炔基、 $C(O)CH_2NH_2$ 、 $C(O)NH(C_{1-4}$ 烷基)、 $C(O)N(C_{1-4}$ 烷基) $_2$ 、 $C(O)NH_2$ 、 $NH(C_{1-4}$ 烷基)、 $NHC(O)NH(C_{1-4}$ 烷基)、 $CH_2C(O)NH_2$ 、 $NHC(O)NH_2$ 、 $NHCO(C_{1-4}$ 烷基)、 $NHSO_2(C_{1-4}$ 烷基)、 $O-[CH_2CH_2CH(CH_3)_2]$ 、 $O-[CH_2CH_2(C_{4-8}$ 环烷基)]、 $O-[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O-[CH_2CH_2N(CH_3)_2]$;

R_1 是 H、OH、F、Cl、Br 或 I;

R_2 是 H、由 R_6 取代的苄基、 $(CH_2)_2$ -O-对氰基苯基、 CH_2 -O-对氰基苯基或 $CH=CH$ -O-对氰基苯基;

R' 是 NH_2 、OH 或 CH_3 ; 并且

R_6 是 CN、 NO_2 、 $NHC(O)CH_3$ 或卤化物;

其中

如果 X 是 C, X_1 是 NH, X_2 是 C(O), R 是 OH, A 是烷基, X_3 是键或 CH_2 , 并且 X_4 是键或 CH_2 , R_1 和 R_2 是 H, 那么 Q 不是 H 或卤素。

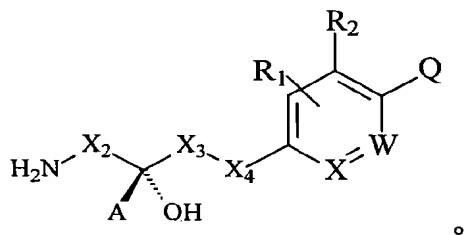
37. 权利要求 36 的化合物, 其中 X_2 是 CH_2 。

38. 权利要求 36 的化合物, 其中 X_2 是 C(O)。

39. 权利要求 36 的化合物, 其中 X_3 是 CH_2 。

40. 权利要求 36 的化合物, 其中 X_4 是 O。

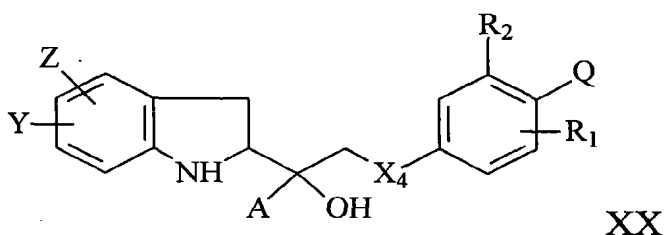
41. 权利要求 36 的化合物, 其由以下结构表示:



42. 权利要求 1 的化合物, 其中 P 是式 II, 并且 X_2 和 X_3 与 X_1 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环。

43. 权利要求 42 的化合物, 其中所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是吡咯烷、吡咯、吗啉、哌啶-4-酮或哌啶。

44. 权利要求 42 的化合物, 其中所述化合物由式 XX 的结构表示:



其中

X_4 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、CF₃、NO₂、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、

NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、
O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R₁ 是 H、OH、F、Cl、Br 或 I;

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基
或 CH=CH-O-对氰基苯基;

R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

45. 权利要求 44 的化合物, 其中 A 是 CH₃。

46. 权利要求 44 的化合物, 其中 X₄ 是 O。

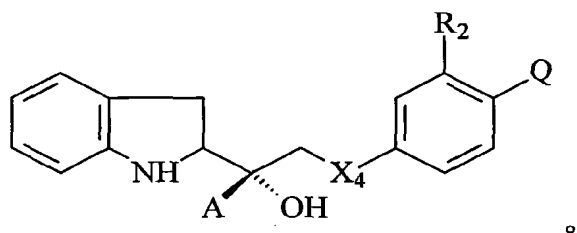
47. 权利要求 44 的化合物, 其中 Q 是 CN。

48. 权利要求 44 的化合物, 其中 Z 是 CN 且 Y 是 CF₃。

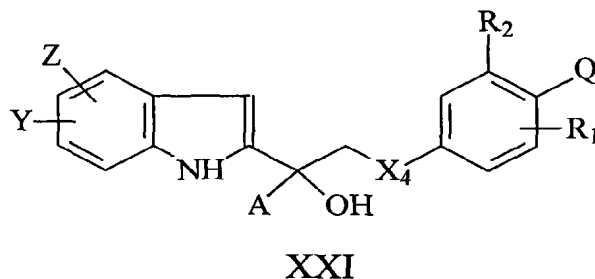
49. 权利要求 44 的化合物, 其中 Z 是 CN, Q 是 CN 且 Y 是 CF₃。

50. 权利要求 44 的化合物, 其中 A 是 CH₃, X₄ 是 O, Z 是 CN, Q
是 CN, R₁ 和 R₂ 是 H, 并且 Y 是 CF₃。

51. 权利要求 44 的化合物, 其由以下结构表示:



52. 权利要求 42 的化合物, 其中所述化合物由式 XXI 的结构表示:



53. 权利要求 52 的化合物, 其中 A 是 CH₃。

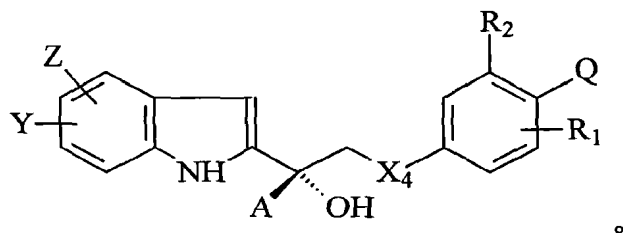
54. 权利要求 52 的化合物, 其中 X₄ 是 O。

55. 权利要求 52 的化合物, 其中 Q 是 CN。

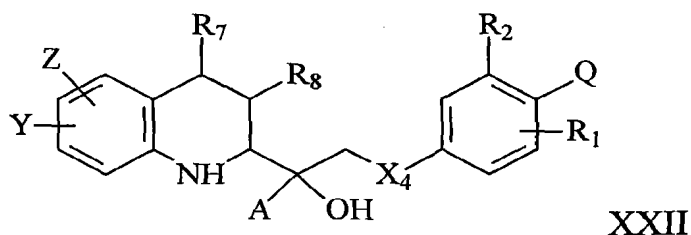
56. 权利要求 52 的化合物, 其中 Z 是 CN 且 Y 是 CF₃。

57. 权利要求 52 的化合物, 其中 A 是 CH₃, X₄ 是 O, Z 是 CN, Q 是 CN, R₁ 和 R₂ 是 H, 并且 Y 是 CF₃。

58. 权利要求 52 的化合物, 其由以下结构表示:



59. 权利要求 42 的化合物, 其中所述化合物由式 XXII 的结构表示:



其中 A、Z、Y、X₄、Q、R₁ 和 R₂ 如式 XX 中所述, R₇ 是 H 或氧代,

并且 R_8 是 H 或 $=CH_2$ 。

60. 权利要求 58 的化合物, 其中 A 是 CH_3 。

61. 权利要求 58 的化合物, 其中 X_4 是 O。

62. 权利要求 58 的化合物, 其中 R_7 和 R_8 是 H。

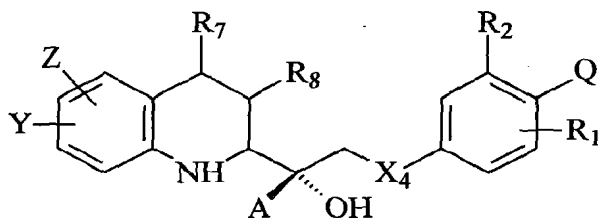
63. 权利要求 58 的化合物, 其中 R_7 是 $=CH_2$ 且 R_8 是氧代。

64. 权利要求 58 的化合物, 其中 Q 是 CN。

65. 权利要求 58 的化合物, 其中 Z 是 CN 且 Y 是 CF_3 。

66. 权利要求 58 的化合物, 其中 A 是 CH_3 , X_4 是 O, Z 是 CN, Q 是 CN, R_1 和 R_2 是 H, 并且 Y 是 CF_3 。

67. 权利要求 58 的化合物, 其由以下结构表示:

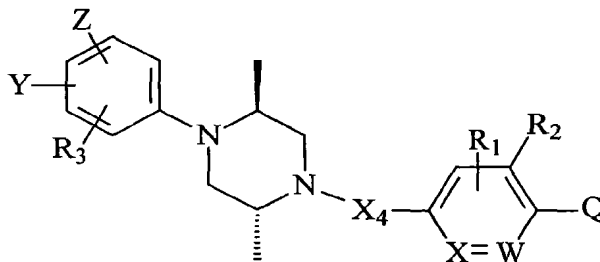


68. 权利要求 1 的化合物, 其中 P 是式 II, 并且 X_1 和 X_3 与 X_1 和 X_3 所连接的 X_2 和 X_5 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环。

69. 权利要求 68 的化合物, 其中所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是哌嗪、哌嗪-2,6-二酮、哌啶、吡咯烷、环己酮、环己烷、环己烯、环戊酮、环戊烷、环戊烯、琥珀酰亚胺、噁唑烷、噁唑烷

二酮或噁唑烷酮。

70. 权利要求 69 的化合物, 其中所述化合物由式 XXIII 的结构表示:



XXIII

X 是 C 或 N; W 是 C 或 N;

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、CF₃、NO₂、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R₁ 是 H、OH、F、Cl、Br 或 I;

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

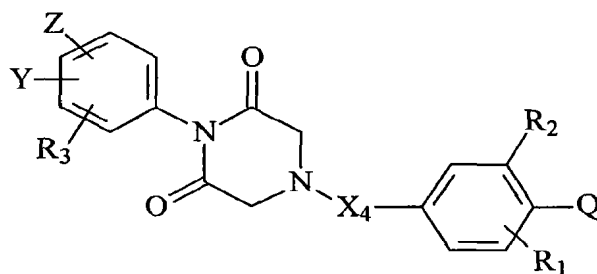
71. 权利要求 70 的化合物, 其中 X₄ 是 O。

72. 权利要求 70 的化合物, 其中 Q 是 CN。

73. 权利要求 70 的化合物, 其中 Z 是 CN 且 Y 是 CF₃。

74. 权利要求 70 的化合物, 其中 X₄ 是 O, Z 是 CN, Q 是 CN, R₁、R₂ 和 R₃ 是 H 且 Y 是 CF₃。

75. 权利要求 68 的化合物, 其中所述化合物由式 XXXIII 的结构表示:



XXXIII

76. 权利要求 75 的化合物, 其中 X₄ 是 O。

77. 权利要求 75 的化合物, 其中 Q 是 CN。

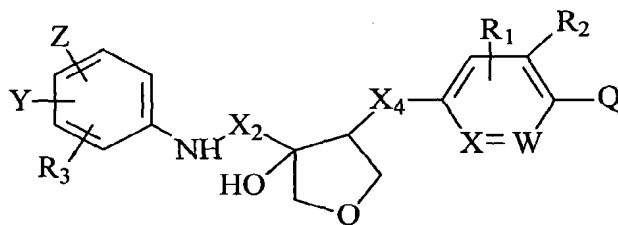
78. 权利要求 75 的化合物, 其中 Z 是 CN 且 Y 是 CF₃。

79. 权利要求 75 的化合物, 其中 X₄ 是 O, Z 是 CN, Q 是 CN, R₁、R₂ 和 R₃ 是 H 且 Y 是 CF₃。

80. 权利要求 1 的化合物, 其中 P 是式 II, X₃ 和 X₅ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环。

81. 权利要求 80 的化合物, 其中所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是四氢呋喃、吡咯烷、哌啶、环己酮、环己烷、环己烯、环己烯酮、环戊酮、环戊烯酮、环戊烷、环戊烯、琥珀酰亚胺、噁唑烷、噁唑烷二酮、噁唑烷酮。

82. 权利要求 80 的化合物, 其中所述化合物由式 XXXIV 的结构表示:



XXXIV

X 是 C 或 N; W 是 C 或 N;

X₂ 是 C₁₋₄ 亚烷基、SO₂、C(O)、CH-[CH₂-(C₄₋₈ 环)]、CH(C₁₋₄ 烷基)、CH(NH₂)、CH(OH)、CH(C₁₋₄ 卤代烷基)、键;

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R₁ 是 H、OH、F、Cl、Br 或 I;

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

83. 权利要求 82 的化合物, 其中 X₄ 是 O。

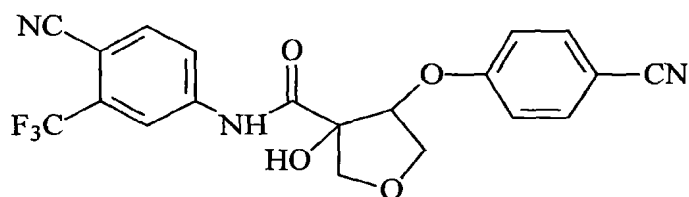
84. 权利要求 82 的化合物, 其中 Q 是 CN。

85. 权利要求 92 的化合物, 其中 X_2 是 CH_2 。

86. 权利要求 82 的化合物, 其中 X_2 是 $C(O)$ 。

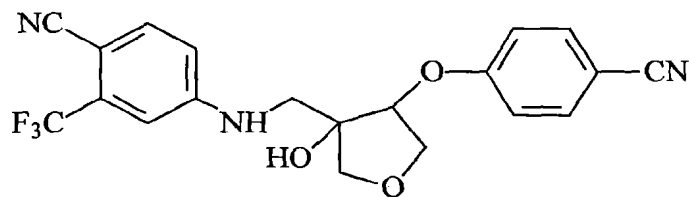
87. 权利要求 82 的化合物, 其中 Z 是 CN 且 Y 是 CF_3 。

88. 权利要求 82 的化合物, 其中所述化合物由式 XXXV 的结构表示:



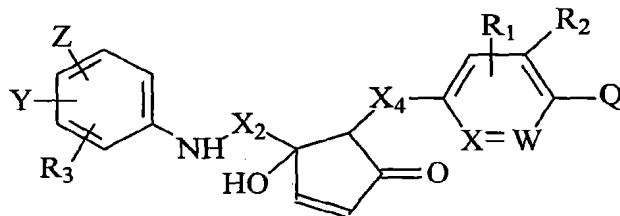
XXXV

89. 权利要求 82 的化合物, 其中所述化合物由式 XXXVI 的结构表示:



XXXVI

90. 权利要求 80 的化合物, 其中所述化合物由式 XXXVII 的结构表示:



XXXVII

91. 权利要求 90 的化合物, 其中 X_2 是 CH_2 。

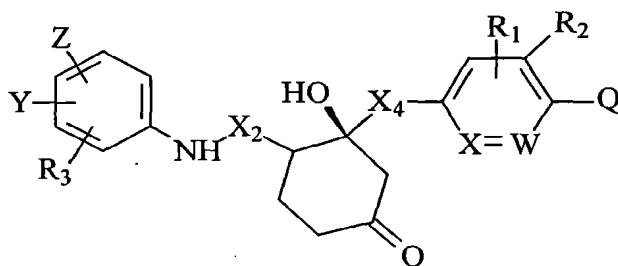
92. 权利要求 90 的化合物, 其中 X_2 是 $C(O)$ 。

93. 权利要求 90 的化合物, 其中 X_4 是 O 。

94. 权利要求 90 的化合物, 其中 Q 是 CN 。

95. 权利要求 90 的化合物, 其中 Z 是 CN 且 Y 是 CF_3 。

96. 权利要求 80 的化合物, 其中所述化合物由式 XXXVIII 的结构表示:



XXXVIII

97. 权利要求 96 的化合物, 其中 X_2 是 CH_2 。

98. 权利要求 96 的化合物, 其中 X_2 是 $C(O)$ 。

99. 权利要求 96 的化合物, 其中 X_4 是 O 。

100. 权利要求 96 的化合物, 其中 Q 是 CN 。

101. 权利要求 96 的化合物, 其中 Z 是 CN 且 Y 是 CF_3 。

102. 权利要求 1 的化合物, 其中 P 是式 II, 并且 X_1 和 X_5 与 X_1 和 X_5 所连接的 X_2 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环;

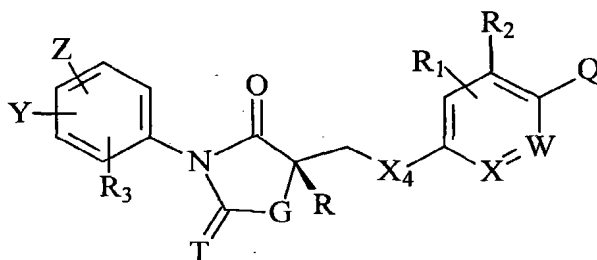
其中

如果 P 是式 II, X 是 C, X_3 是 CH_2 , X_4 是 O 或 NH, R_1 、 R_2 和 R_3 是 H, 并且 X_5 和 X_1 形成 5 元环噁唑烷-2-酮, 那么 Q 不是卤素或 H; 或者

如果 P 是式 II, R_3 是 H, X 和 W 是 C, X_1 和 X_5 与 X_1 和 X_5 所连接的 X_2 一起形成噁唑烷二酮, R 是烷基, X_3 是 CH_2 , 并且 X_4 是 O、NH、S、 SO_2 或 CH_2 , 那么 Q 不是卤化物。

103. 权利要求 102 的化合物, 其中所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是吡咯烷、哌啶、吗啉、琥珀酰亚胺、噁唑烷、噁唑烷二酮、噁唑烷酮。

104. 权利要求 102 的化合物, 其中所述化合物由式 XXXIX 的结构表示:



XXXIX

其中:

X 是 C 或 N; W 是 C 或 N;

G 是 O、NH、 NC_{1-4} 烷基、 NC_{1-4} 酰基、S、 CHC_{1-4} 烷基、 CHC_{1-4} 酰基、 $C(C_{1-4} \text{ 酰基})_2$ 、 $C(C_{1-4} \text{ 烷基})_2$ 或 $(CH_2)_n$, 其中 n 是 1-3;

T 是 S 或 O;

X_4 是 O、S、 SO 、 $C(O)$ 、 $S(O)[=CHCH_2N(CH_3)_2]$ 、 SO_2 、NH、 NHR' 、NO、 C_{1-4} 亚烷基、 $C(OH)[CH_2CH_2N(CH_3)_2]$ 、 $C[=CHCH_2N(CH_3)_2]$ 、 $PO(C_{1-4} \text{ 烷基})$ 、 $N[CH_2CH_2N(CH_3)_2]$ 、 $NO[CH_2CH_2N(CH_3)_2]$ 或键;

Z 是 H、CN、 NO_2 、 $NHC(O)CH_3$ 、 C_{1-4} 烷基、F、Cl、I 或 Br;

Y 是 H、 C_{1-4} 烷基、 CF_3 、 NO_2 、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、 CF_3 、 NO_2 、卤化物、 C_{2-6} 烯基、 C_{2-6} 炔基、 $C(O)CH_2NH_2$ 、

$C(O)NH(C_{1-4} \text{ 烷基})$ 、 $C(O)N(C_{1-4} \text{ 烷基})_2$ 、 $C(O)NH_2$ 、 $NH(C_{1-4} \text{ 烷基})$ 、 $NHC(O)NH(C_{1-4} \text{ 烷基})$ 、 $CH_2C(O)NH_2$ 、 $NHC(O)NH_2$ 、 $NHCO(C_{1-4} \text{ 烷基})$ 、 $NHSO_2(C_{1-4} \text{ 烷基})$ 、 $O-[CH_2CH_2CH(CH_3)_2]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 环烷基})]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 杂环烷基})]$ 或 $O-[CH_2CH_2N(CH_3)_2]$;

R 是 H、OH、 C_{1-4} 烷基、 CF_3 、 CH_2OH 、 $O(C_{1-4} \text{ 烷基})$ 或 $O(C_{1-4} \text{ 酰基})$;

R_1 是 H、OH、F、Cl、Br 或 I;

R_2 是 H、由 R_6 取代的苄基、 $(CH_2)_2$ -O-对氰基苯基、 CH_2 -O-对氰基苯基或 $CH=CH$ -O-对氰基苯基;

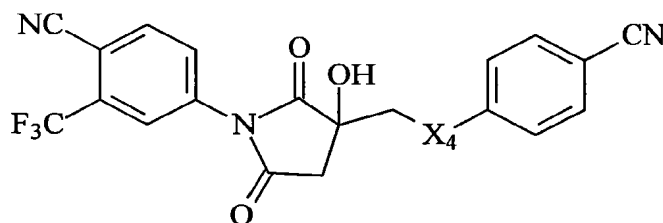
R_3 是 H、 C_{1-4} 烷基、卤化物、CN 或 NO_2 ;

R' 是 NH_2 、OH 或 CH_3 ; 并且

R_6 是 CN、 NO_2 、 $NHC(O)CH_3$ 或卤化物;

其中如果 R_3 是 H, X 和 W 是 C, G 是 O, T 是 O, R 是烷基, X_3 是 CH_2 , 并且 X_4 是 O、NH、S、 SO_2 或 CH_2 , 那么 Q 不是卤化物。

105. 权利要求 104 的化合物, 其中所述化合物由式 XLV 的结构表示:

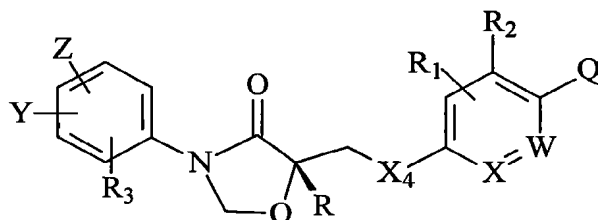


XLV

其中 X_4 如以上关于化合物 XXXIV 所述。

106. 权利要求 105 的化合物, 其中 X_4 是 O。

107. 权利要求 102 的化合物, 其中所述化合物由式 XLII 的结构表示:



XLII

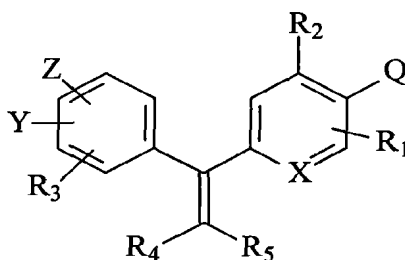
其中:

X、X₄、R、R₁、R₂、R₃、Z、Y 和 Q 如以上关于化合物 XXXIV 所述;

其中

如果 X 是 C, X₄ 是 O、NH 或 S, R₁、R₂ 和 R₃ 是 H 并且 R 是 H, 那么 Q 不是卤素、H 或 CN。

108. 权利要求 1 的化合物, 其中所述化合物由式 XLVII 的结构表示:



XLVII

其中

X 是 N 或 CH;

Z 是 H、CN、NO₂、NHC(O)CH₃、CH₃、F、Cl、I 或 Br;

Y 是 H、CH₃、CF₃、CN、F、Cl、I 或 Br;

Q 是 H、O-(CH₂)₂CH(CH₃)₂ 或 O-(CH₂)₂N(CH₃)₂;

R₁ 是 H、OH、F、Cl、Br 或 I;

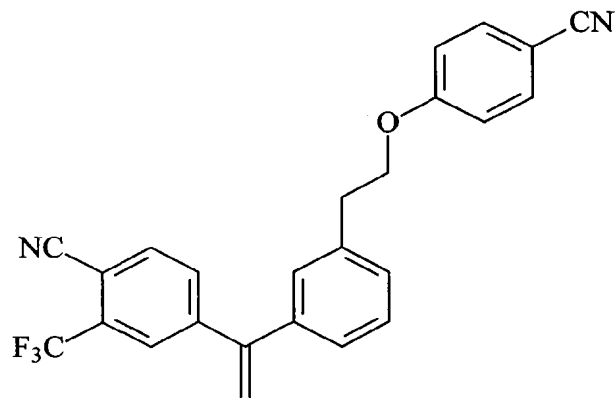
R₂ 是由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、CH₃、卤化物、CN 或 NO₂;

R₄ 和 R₅ 独立地是 H、CH₃、卤化物、OH、C₁₋₄ 烷基、C₁₋₆ 环烷基、卤代-C₁₋₄ 烷基、苯基、芳基、杂环或羟基-C₁₋₄ 烷基; 并且

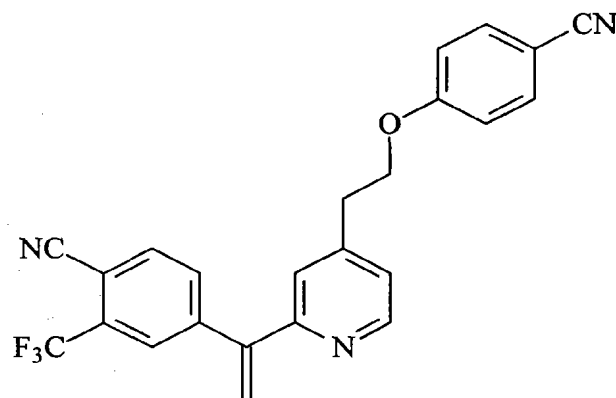
R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

109. 权利要求 108 的化合物, 其中所述化合物由式 XLVIII 的结构表示:



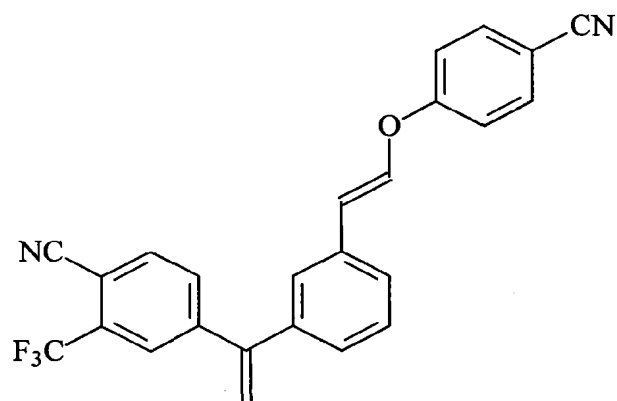
XLVIII

110. 权利要求 108 的化合物,其中所述化合物由式 XLIX 的结构表示:



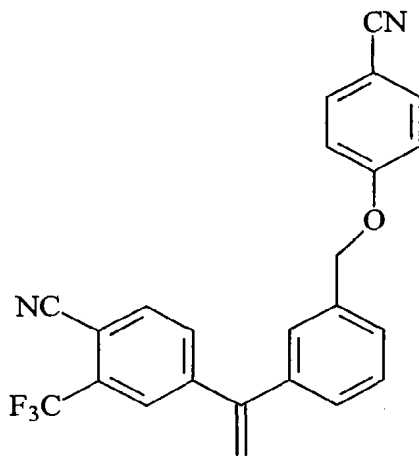
XLIX

111. 权利要求 108 的化合物,其中所述化合物由式 L 的结构表示:



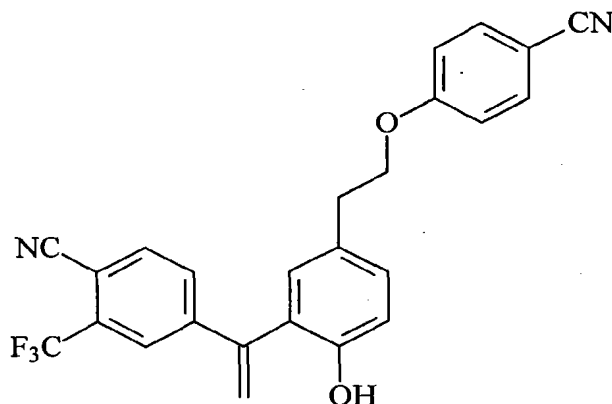
L

112. 权利要求 108 的化合物, 其中所述化合物由式 LI 的结构表示:



LI

113. 权利要求 108 的化合物, 其中所述化合物由式 LII 的结构表示:



LII

114. 药物组合物, 其包含权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、N-氧化物、水合物或它们的任意组合; 以及合适的载体或稀释剂。

115. 药物组合物, 其包含有效量的权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、N-氧化物、水合物或它们的任意组合; 以及药学上可接受的载体、稀释剂或盐。

116. 在雄性个体中避孕的方法, 所述方法包括向所述个体给药有效抑制所述个体中精子产生的量的权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤, 由此实现在所述个体中的避孕。

117. 激素治疗方法, 所述方法包括使个体的雄激素受体与有效实现改变雄激素依赖性病症的量的权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合接触的步骤。

118. 治疗罹患前列腺癌的个体的方法, 所述方法包括向所述个体给药有效治疗所述个体中的前列腺癌的量的权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

119. 延缓罹患前列腺癌的个体的前列腺癌的进展的方法, 所述方法包括向所述个体给药有效延缓所述个体中前列腺癌的进展的量的权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

120. 治疗个体的骨相关的病症、或增加个体的骨量、促进个体的骨形成的方法, 所述方法包括向所述个体给药有效治疗所述骨相关的病症的量的权利要求 1 的化合物或其异构体、药学上可接受的盐、药品、晶体、水合物、*N*-氧化物或它们的任意组合的步骤。

121. 权利要求 120 的方法, 其中所述个体罹患骨质疏松症、骨质减少、骨吸收增加、骨折、骨脆弱、骨矿物质密度 (BMD) 丢失或它们的任意组合。

122. 权利要求 120 的方法, 其中所述方法增加所述个体的骨强度。

123. 权利要求 120 的方法, 其中所述化合物促进或增强成骨细胞生成。

124. 权利要求 120 的方法, 其中所述化合物抑制破骨细胞增殖。

125. 治疗个体的肌萎缩症、降低其发病率、延缓其进展、减轻其严重性或减轻与其相关的症状的方法, 所述方法包括向所述个体给药有效治疗所述个体的所述肌萎缩症的量的权利要求 1 的化合物或其异构体、药学上可接受的盐、药品、晶体、水合物、*N*-氧化物或它们的任意组合的步骤。

126. 权利要求 125 的方法, 其中所述肌萎缩症归因于病状、疾患、疾病或病症。

127. 权利要求 126 的方法, 其中所述病状、疾患、疾病或病症是神经性的、感染性的、慢性的或遗传性的。

128. 权利要求 126 的方法, 其中所述病状、疾患、疾病或病症是肌营养不良症、肌萎缩、伴 X 染色体的脊延髓肌萎缩症 (SBMA)、恶病质、营养不良、麻风病、糖尿病、肾脏病、慢性阻塞性肺疾病 (COPD)、癌症、终末期肾功能衰竭、少肌症、肺气肿、骨软化症、HIV 感染、AIDS 或心脏病。

129. 权利要求 126 的方法, 其中所述肌萎缩症是年龄相关的肌萎缩症, 废用性失调相关的肌萎缩症; 或者所述肌萎缩症归因于慢性下腰痛、烧伤、中枢神经系统 (CNS) 损伤或损害、周围神经损伤或损害、脊髓损伤或损害、化学性损伤或损害、或者酒精中毒。

130. 治疗人类个体的糖尿病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法, 所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

131. 治疗患有的人类个体的葡萄糖耐受不良、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法,所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

132. 治疗人类个体的高胰岛素血症、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法,所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

133. 治疗人类个体的胰岛素抵抗、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法,所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

134. 治疗与糖尿病相关的疾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法,所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

135. 治疗人类个体的脂肪肝症、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法,所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

136. 治疗人类个体的心血管疾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法,所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

137. 治疗个体的恶病质、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

138. 权利要求 137 的方法，其中所述恶病质与所述个体的癌症相关。

139. 治疗个体的类风湿性关节炎、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

140. 治疗个体的慢性肾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

141. 治疗个体的终末期肾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

142. 治疗个体的脆弱、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

143. 治疗个体的性腺功能减退症、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水

合物或它们的任意组合的步骤。

144. 治疗个体的年龄相关的功能减退、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法,所述方法包括向所述个体给药权利要求 1 的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

选择性雄激素受体调节剂、它们的类似物和衍生物以及它们的用途

交叉引用相关申请

本申请要求2006年7月19日提交的美国临时专利申请60/831880和2006年7月19日提交的美国临时专利申请60/831988的利益；这两件申请以其全部通过引用结合于此。

发明领域

本发明提供细胞核激素受体结合化合物、包含它们的组合物以及它们在治疗个体的各种疾病或病症中的使用方法，所述疾病或病症尤其包括前列腺癌、肌萎缩症和与此相关的疾病或病症、和/或骨相关的疾病或病症。

发明背景

细胞核激素受体超家族是最大的一类转录因子，涉及广泛的生理过程。该家族的48个成员分为三类，第1类包括雄激素（AR）、雌激素（ER- α 和ER- β ）、糖皮质激素（GR）、孕酮（PR）和盐皮质激素（MR）的受体。第2类包括类视黄醇、甲状腺和维生素D的受体，而第3类包括其配体有待鉴定的受体（孤儿（orphans））。细胞核激素受体具有功能少有表征的N末端域（NTD）、负责受体与DNA应答元件结合的DNA结合域（DBD）、含有核定位信号的铰链区和结合配体并活化或抑制受体功能的配体结合域（LBD）。而且，存在两个活化功能域，一个位于NTD（AF-1）中，另一个位于LBD（AF-2）中。第I类受体，由于DBD高度的氨基酸序列同源性、LBD的中等同源性以及相似的二级和三级结构特征、和类固醇配体共同的化学特征，经常能与其它第I类受体的配体结合（即交叉反应）。例如，早期对AR和ER的研究表明，类固醇由类固醇A-环与螺旋-3残基接触并且D-环与螺旋-11残基接触而在LBD中的定位，可能对所有类固醇激素受体都是普遍的。

雄激素受体（“AR”）是配体激活的转录调节蛋白，它通过其对内源性雄

激素的活性介导雄性性发育和性功能的诱导。雄激素通常被称为雄性性激素。雄激素是在体内由睾丸和肾上腺皮质产生的类固醇，或者可以在实验室中合成。雄激素类固醇在许多生理过程中起重要作用，包括雄性性征例如肌肉和骨量、前列腺生长、精子发生和雄性毛发模式的产生和维持(Matsumoto, *Endocrinol. Met. Clin. N. Am.* 23:857-75 (1994))。内源性类固醇雄激素包括睾酮和双氢睾酮(“DHT”)。睾酮是睾丸分泌的主要类固醇，而且是雄性血浆中发现的主要循环雄激素。在许多外周组织中，睾酮由 5α -还原酶转化为DHT。因此，DHT被认为是大多数雄激素作用的细胞内介质(Zhou 等人, *Molec. Endocrinol.* 9:208-18 (1995))。其它类固醇雄激素包括睾酮的酯，例如环戊烷丙酸酯(cypionate)、丙酸酯、苯基丙酸酯(phenylpropionate)、环戊基丙酸酯(cyclopentylpropionate)、异己酸酯(isocarporate)、庚酸酯和癸酸酯，以及其它合成雄激素，例如7-甲基-去甲睾酮(“MENT”)及其醋酸酯(Sundaram 等人, "7 Alpha-Methyl-Nortestosterone(MENT): The Optimal Androgen For Male Contraception," *Ann. Med.*, 25:199-205 (1993) ("Sundaram"))。因为AR涉及雄性性发育和性功能，所以AR可能是实现雄性避孕或其它形式的激素替代疗法的靶标。

人类孕酮受体(PR)存在三种不同的亚型：PR-A、PR-B和PR-C(Kastner 等人, *EMBO J* 9:1603-1614, 1990; Wei 等人, *Mol Endo* 10:1379-1387, 1996)，其中，PR-A和PR-B是最丰富的。然而，PR-A亚型对PR-B亚型的比率在靶组织中不恒定，这会改变细胞应答，因为各亚型的活性可以变化。

很少有化合物在很多种条件下都显示出部分孕激素活性。RU-486，最普遍使用的抗孕激素，仅在选定的条件下显示出部分激动剂活性。具有部分激动剂活性的抗孕激素化合物对治疗各种孕激素调节的疾病和病症有用，然而，这些很少的已知抗孕激素仅具有有限的部分激动剂活性，本领域仍需要具有广泛的部分激动剂活性的抗孕激素。

世界人口增长和计划生育的社会意识已经促进了大量的避孕研究。避孕无论如何都是一个困难的课题。它伴有文化和社会的烙印，牵涉宗教，最肯定地，它伴有重要的健康关切。当该课题的焦点集中在雄性避孕时，情况只会恶化。尽管存在合适的避孕器械，但是在历史上，社会期望妇女作出避孕的决定并承担后果。虽然对性传播疾病的忧虑使男人更加认识到需要培养安

全和负责的性习惯，但是妇女仍然经常承担避孕选择的主要压力。妇女们有一些选择，从临时的机械装置（例如海绵和子宫帽）到临时的化学方法（例如杀精子药）。妇女们还有一些可支配的更持久的选择，例如物理装置包括宫内节育器和宫颈帽，以及更持久的化学处理，例如避孕丸和皮下埋植剂。然而，至今，男人们仅有的选择包括使用避孕套和输精管切除术。然而，许多男人不喜欢使用避孕套，因为这会减弱性敏感性，干扰性自发，并很有可能因破裂或使用不当而导致怀孕。输精管切除术也不受青睐。如果有更方便的控制生育的方法供男人使用，特别是在性行为之前无需准备活动的长期方法，那么这些方法就能显著地增加男人承担更多的避孕责任的可能性。

雄性类固醇（例如睾酮及其衍生物）的给药在这方面显得特别有潜力，因为这些化合物具有组合的抑制促性腺激素和代替雄激素的性质(Steinberger 等人, "Effect of Chronic Administration of Testosterone Enanthate on Sperm Production and Plasma Testosterone, Follicle Stimulating Hormone, and Luteinizing Hormone Levels: A Preliminary Evaluation of a Possible Male Contraceptive", *Fertility and Sterility* 28:1320-28 (1977))。长期给药大剂量的睾酮完全停止精子的产生（无精子）或将精子减少至很低的水平（精子减少）。造成不育所需的抑制精子产生的程度还不清楚。然而，世界卫生组织最近的一篇报道显示，每周肌肉注射庚酸睾酮造成 98% 的接受治疗的男性无精子或严重的精子减少（即每毫升小于三百万个精子）和不育(World Health Organization Task Force on Methods And Regulation of Male Fertility, "Contraceptive Efficacy of Testosterone-Induced Azoospermia and Oligospermia in Normal Men," *Fertility and Sterility* 65:821-29 (1996))。

已经开发出多种睾酮酯，它们在肌肉注射后被吸收得更慢，由此产生更大的雄激素效应。庚酸睾酮是这些酯类中使用最广泛的。尽管庚酸睾酮在确定激素药剂用于雄性避孕的可行性方面有很大价值，但是它具有几个缺点，包括需要每周注射和在肌肉内注射后立即出现睾酮的超生理性最高水平(Wu, "Effects of Testosterone Enanthate in Normal Men: Experience From a Multicenter Contraceptive Efficacy Study," *Fertility and Sterility* 65:626-36 (1996))。

雄性和雌性的骨矿物质密度（BMD）都随着年龄而降低。骨矿物质含量

(BMC) 和 BMD 降低的量与骨强度的减小相关, 并容易使患者骨折。

骨质疏松症是全身性骨骼疾病, 其特征是骨量少、骨组织退化并导致骨脆弱 (bone fragility) 和骨折敏感性增加。在美国, 该病症影响超过 0.25 亿人口, 每年造成超过 130 万例骨折, 包括每年 50 万例脊柱骨折、25 万例髋骨折、24 万例腕骨骨折。髋骨折是骨质疏松症最严重的后果, 其中 5-20% 的患者在一年内死亡, 超过 50% 的存活者残疾。老人罹患骨质疏松症的风险最大, 因此, 随着人口老龄化, 预计该问题会显著增加。在接下来的 60 年内, 全世界的骨折发生率预计将增加三倍, 而一项研究估计, 2050 年世界上将有 450 万例髋骨折。

妇女罹患骨质疏松症风险比男性更大。在绝经期后的五年中, 妇女骨丢失急剧加速。增加风险的其它因素包括吸烟、酒精滥用、久坐的生活习惯和低的钙摄入。然而, 骨质疏松症也经常发生于男性身上。十分确定, 男性的骨矿物质密度随着年龄而减少。骨矿物质含量和密度的降低与骨强度的减小相关并容易造成骨折。性激素在非生殖组织中的多效性作用的潜在的分子机制仅仅刚开始为人们所认识, 但是, 清楚的是, 生理浓度的雄激素和雌激素在维持整个生命周期中的骨稳态上起重要作用。因此, 出现雄激素和雌激素剥夺时, 结果是骨重建速度增加, 这使吸收和成形的平衡倾向吸收, 这导致全身性的骨量丢失。在男性, 成熟期性激素的自然减少 (雄激素的直接减少以及由雄激素的外周芳构化产生的雌激素的低水平) 与骨脆弱相关。在去势的男性中也观察到了这种效应。

肌萎缩是指肌肉量的进行性损失和/或肌肉的进行性衰弱和退化, 包括控制运动的骨骼肌或随意肌、控制心脏 (心肌病) 的心肌和平滑肌。慢性肌萎缩是以肌肉量的进行性损失、肌肉衰弱和退化为特征的慢性病症。

肌萎缩过程中发生的肌肉量损失可以通过分解代谢造成肌肉蛋白的降解来表征。发生蛋白质分解代谢的原因是异常地高速度的蛋白质降解、异常地低速度的蛋白质合成或两者的组合。无论是高程度的蛋白质降解还是低程度的蛋白质合成引起的肌肉蛋白分解代谢都会导致肌肉量的减少和肌萎缩。

肌萎缩与慢性的、神经性的、遗传性的或传染性的病状、疾病、疾患或病症相关。它们包括肌营养不良, 例如迪谢内肌营养不良和肌强直性营养不良; 肌萎缩, 例如小儿麻痹症后肌萎缩 (PPMA); 恶病质, 例如心源性恶

病质、艾滋病恶病质和癌症恶病质、营养不良、麻风病、糖尿病、肾脏病、慢性阻塞性肺疾病（COPD）、癌症、终末期肾功能衰竭、少肌症、肺气肿、骨软化症、HIV 感染、AIDS 和心肌病。

此外，其它的情况和病症也与肌萎缩有关并能导致肌萎缩。它们包括慢性下腰痛、高龄（advanced age）、中枢神经系统（CNS）损伤、周围神经损伤、脊髓损伤、化学性损伤、中枢神经系统（CNS）损害、周围神经损害、脊髓损害、化学性损害、烧伤、在四肢固定和因疾病或损伤而长期住院时发生的废用性失调（disuse deconditioning）和酒精中毒。

完整的雄激素受体（AR）信号转导途径对于骨骼肌的适当发育十分关键。而且，完整的 AR 信号转导途径增加瘦肌肉量、肌肉强度和肌肉蛋白的合成。

肌萎缩如果不减弱，会造成可怕的健康后果。例如，在肌萎缩过程中发生的变化会导致身体状况变弱，这对个体的健康有害，导致骨折易感性增强和体能状况虚弱。而且，肌萎缩是患恶病质和 AIDS 的病人发病率和死亡率的强烈预兆。

在基础科学和临床水平都急需新的创新方法以开发用于以下的化合物：

a) 男性避孕；b) 治疗各种激素相关的病症，例如与衰老男性雄激素减退（ADAM）相关的病症，例如疲劳、抑郁、性欲降低、性功能障碍、勃起功能障碍、性腺功能减退症、骨质疏松症、脱发、贫血、肥胖症、少肌症、骨质减少、骨质疏松症、良性前列腺增生、情绪和认知改变以及前列腺癌；c) 治疗与 ADIF 相关的病症，例如性功能障碍、性欲降低、性腺功能减退症、少肌症、骨质减少、骨质疏松症、认知和情绪改变、抑郁、贫血、脱发、肥胖症、子宫内膜异位症、乳腺癌、子宫癌和卵巢癌；d) 治疗和/或预防慢性肌萎缩或少肌症；e) 减少前列腺癌的发病率、中止前列腺癌或引起前列腺癌消退；f) 口服雄激素替代和/或其它临床治疗和/或诊断领域。

很多种疾病和/或病症都受到性腺功能减退症和分解代谢作用的影响，包括肾病、中枢神经系统损伤、烧伤和慢性伤口。

在美国，肾功能衰竭的发病率上升且十分普遍。登记终末期肾脏疾病（ESRD）医疗保险基金项目的患者数量从 1973 年的约 1 万受益人增加至 1983 年的 86354 人，至 2002 年 12 月 3 日达到 431284 人。单是 2002 年，就有 100359 名患者参加美国 ESRD 项目。慢性肾病（CKD）是 ESRD 的先兆，

它在肾脏不能完全从体内排除废物时发生。CKD 是一种缓慢地进行性疾病，其中，糖尿病、高血压和贫血可能是并发的病症。

CKD 使用表示可用肾功能的分期系统来诊断（第 1 期=正常肾功能），而且患者在早期通常不会出现症状。CKD 的第 5 期是 ESRD，它是完全或接近完全的肾衰竭，而且通常发生在肾功能低于基线的 10%时。

与 ESRD 相关的伴随症状包括性腺功能减退症、非意愿体重减轻、疲劳等等。

烧伤导致睾酮减少、氮水平下降和骨矿物质密度（BDM）减少，这些在损伤后甚至可能要持续一年之久，并且与伤口愈合不良、感染风险增大、瘦体重减少、复原受阻和延缓烧伤幸存者重返社会有关。因烧伤而引起的分解代谢作用造成显著的非意愿体重减轻，并进一步使问题复杂化。

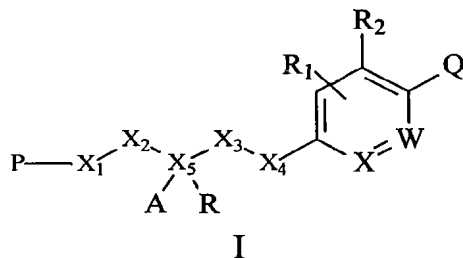
脊髓损伤（SCI）可能会导致改变中枢神经递质的分泌和产生，这继而可能造成下丘脑-垂体-肾上腺轴功能障碍，导致睾酮和其它激素水平的下降。SCI 或其它急性疾病或创伤在特征上包括分解代谢增强伴随合成代谢活动减弱，引发易于损失瘦身体组织的病症。只要分解代谢过程不中断，那么紊乱的营养利用将继续下去。损失瘦体重的影响包括伤口扩展和愈合机制受损。由于营养不良和蛋白缺乏加上固定，脊髓损伤的患者处于高度的患褥疮的风险中。

慢性伤口可以由任意种病症引起，包括糖尿病、循环问题、固定等等。使疾病复杂化（例如在糖尿病中）的是出现神经病，其增加足溃疡的风险。

虽然有许多这些病症的处理和治疗，但是都不理想。由于已显示雄激素受体（AR）信号转导途径增加瘦肌肉量、肌肉强度和肌肉蛋白合成，并且由于性腺功能减退症伴随这些病症，所以靶向 AR 信号转导途径的分子可以用于治疗这些疾病和/或病症。

发明内容

在一个实施方案中，本发明提供由式 I 的结构表示的化合物：

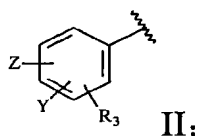


其中

X 是 C 或 N; W 是 C 或 N;

X₁ 是 N、NH、N(C₁₋₄ 烷基)、NAc、NCOOH 或键; 或者 X₁ 和 X₃ 与 X₁ 和 X₃ 所连接的 X₂ 和 X₅ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环; 或者 X₁ 和 X₅ 与 X₁ 和 X₅ 所连接的 X₂ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在;

P 是 H 或式 II:



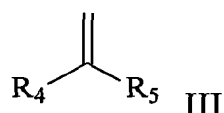
X₂ 是 C₁₋₄ 亚烷基、SO₂、C(O)、CH-[CH₂-(C₄₋₈ 环)]、CH(C₁₋₄ 烷基)、CH(NH₂)、CH(OH)、CH(C₁₋₄ 卤代烷基)、键; 或者 X₂ 和 R₃ 与 X₂ 所连接的 X₁ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环; 或者 X₂ 和 X₅ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在;

X₃ 是 C₁₋₄ 亚烷基、NH、N、CH(OH)、键; 或者 X₁ 和 X₃ 与 X₁ 和 X₃ 所连接的 X₂ 和 X₅ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环; 或者 X₃ 和 X₅ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在; 或者 X₃ 和 X₄ 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环;

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键; 或者 X₄ 和 X₅ 与 X₄ 和 X₅ 所连接的 X₃ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在; 或者 X₃ 和 X₄ 一起形成双键或形成饱和的或不饱和的、取代的或未取代的 3-6 元环;

X_5 是碳或 X_5 和 X_1 与 X_1 和 X_5 所连接的 X_2 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在; 或者 X_5 和 X_2 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在; 或者 X_5 和 X_3 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在; 或 X_5 和 X_4 与 X_5 和 X_4 所连接的 X_3 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在;

A 不存在, 或是 H、OH、SH、 NH_2 、 C_{1-4} 烷基、 CHF_2 、 CH_2F 、 CF_3 、CN、 CH_2OH 、 $CH_2O(C_{1-4}$ 烷基)、 $CH_2O(C_{1-4}$ 酰基)、 CH_2CN 、 CH_2N_3 、 CH_2NCS 、CHO、 $C(O)O(C_{1-4}$ 烷基)、 $CONHR'$ 、 $C(O)N(R')_2$ 、 $C(O)O(C_{1-4}$ 烷基)、 $C(O)R'$ 、 CH_2CF_3 、 CF_2CF_3 、 CH_2OR' $CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$; 或者 A 和 R 形成式 III 所表示的双键:



Z 是 H、CN、 NO_2 、 $NHC(O)CH_3$ 、 C_{1-4} 烷基、F、Cl、I 或 Br;

Y 是 H、 C_{1-4} 烷基、 CH_3 、 NO_2 、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、 NO_2 、卤化物、 CF_3 、 C_{2-6} 烯基、 C_{2-6} 炔基、 $C(O)CH_2NH_2$ 、 $C(O)NH(C_{1-4}$ 烷基)、 $C(O)N(C_{1-4}$ 烷基) $_2$ 、 $C(O)NH_2$ 、 $NH(C_{1-4}$ 烷基)、 $NHC(O)NH(C_{1-4}$ 烷基)、 $CH_2C(O)NH_2$ 、 $NHC(O)NH_2$ 、 $NHCO(C_{1-4}$ 烷基)、 $NHSO_2(C_{1-4}$ 烷基)、O- $[CH_2CH_2CH(CH_3)_2]$ 、O- $[CH_2CH_2(C_{4-8}$ 环烷基)]、O- $[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 O- $[CH_2CH_2N(CH_3)_2]$;

R 是 H、OH、 C_{1-4} 烷基、 CF_3 、 CH_2OH 、 $O(C_{1-4}$ 烷基)或 $O(C_{1-4}$ 酰基);

R_1 是 H、OH、 NH_2 、F、Cl、Br 或 I;

R_2 是 H、由 R_6 取代的苄基、 $(CH_2)_2$ -O-对氰基苯基、 CH_2 -O-对氰基苯基或 $CH=CH$ -O-对氰基苯基;

R_3 是 H、 C_{1-4} 烷基、卤化物、CN、 NO_2 ; 或 R_3 和 X_2 以及与 R_3 相连的苯环和与 X_2 相连的 X_1 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环;

R' 是 NH_2 、OH 或 CH_3 ;

R_4 和 R_5 独立地是 H、 CH_3 、卤化物、OH、 C_{1-4} 烷基、 C_{1-6} 环烷基、卤代(C_{1-4} 烷基)、苯基、芳基、 C_{4-8} 杂环烷基或羟基(C_{1-4} 烷基);

R_6 是 CN、 NO_2 、 $NHC(O)CH_3$ 或卤化物；

其中

如果 P 是式 II，X 是 C， X_1 是 NH， X_2 是 C(O)， X_3 是 CH_2 ，R 是 OH 并且 A 是烷基或卤代烷基，那么 X_4 是 $S(O)[=CHCH_2N(CH_3)_2]$ 、 $C(OH)[CH_2CH_2N(CH_3)_2]$ 、 $C[=CHCH_2N(CH_3)_2]$ 、 $N[CH_2CH_2N(CH_3)_2]$ 、 $P(O)(C_{1-4} \text{ 烷基})$ 或 $N(O)[CH_2CH_2N(CH_3)_2]$ ；

或者

如果 P 是式 II，X 是 C， X_1 是 NH， X_2 是 C(O)， X_3 是 CH_2 ，R 是 OH 或 OAlk 并且 X_4 是 O、S、NH、S、SO、 SO_2 或亚烷基，那么 A 是 CN、 CH_2OH 、 $CH_2O(C_{1-4} \text{ 烷基})$ 、 $CH_2O(C_{1-4} \text{ 酰基})$ 、 CH_2CN 、 CH_2N_3 、 CH_2NCS 、CHO、 $C(O)O(C_{1-4} \text{ 烷基})$ 、CONHR'、 $C(O)N(R')_2$ 、 $C(O)O(C_{1-4} \text{ 烷基})$ 、 $C(O)R'$ 、 $CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$ ；

或者

如果 P 是苯基，X 是 C， X_1 是 NH， X_2 是 C(O)，R 是 OH 并且 A 是 COOH， X_3 是键， X_4 是 CH_2 ， R_1 、 R_2 是 H，那么 Q 不是 H。

或者

如果 P 是式 II，X 是 C， X_3 是 CH_2 ， X_4 是 O 或 NH， R_1 、 R_2 和 R_3 是 H，并且 X_5 和 X_1 形成 5 元环噁唑烷-2-酮，那么 Q 不是卤素或 H；

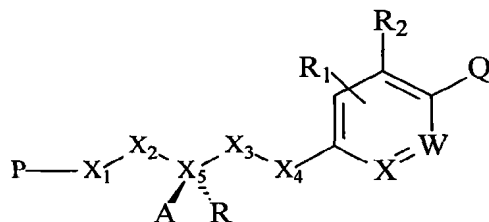
或者

如果 P 是 H，X 是 C， X_1 是 NH， X_2 是 C(O)，R 是 OH，A 是烷基， X_3 是键或 CH_2 ，并且 X_4 是键或 CH_2 ， R_1 和 R_2 是 H，那么 Q 不是 H 或卤素

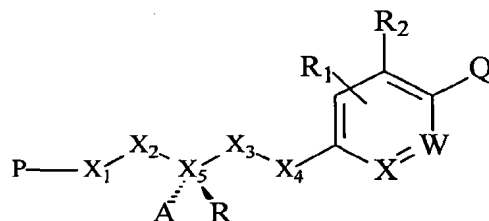
或者

如果 P 是式 II， R_3 是 H，X 和 W 是 C， X_1 和 X_5 与 X_1 和 X_5 所连接的 X_2 一起形成噁唑烷二酮，R 是烷基， X_3 是 CH_2 ，并且 X_4 是 O、NH、S、 SO_2 或 CH_2 ，那么 Q 不是卤化物。

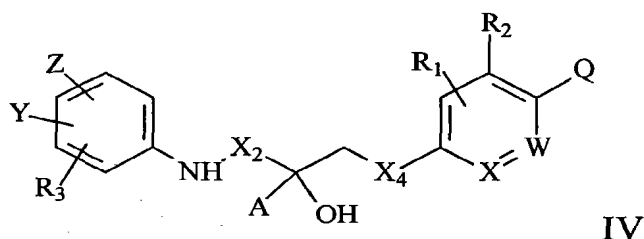
在另一个实施方案中，式 I 的化合物由以下结构表示：



在另一个实施方案中，式 I 的化合物由以下结构表示：



在一个实施方案中，本发明提供由式 IV 的结构表示的化合物：



其中

X 是 C 或 N；W 是 C 或 N；

X₂ 是 C₁₋₄ 亚烷基、SO₂、CH-[CH₂-(C₄₋₈ 环)]、CH(C₁₋₄ 烷基)、CH(NH₂)、CH(OH)、CH(C₁₋₄ 卤代烷基)、键；

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂；

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br；

Y 是 H、C₁₋₄ 烷基、CH₃、CN、NO₂、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、

C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R 是 H、OH、C₁₋₄ 烷基、CF₃、CH₂OH、O(C₁₋₄ 烷基)或 O(C₁₋₄ 酰基);

R₁ 是 H、OH、NH₂、F、Cl、Br 或 I;

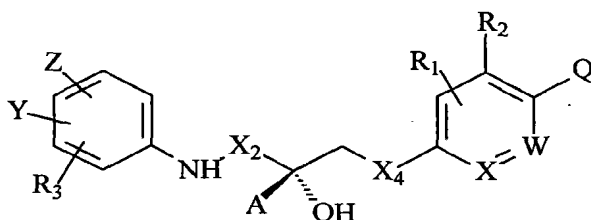
R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

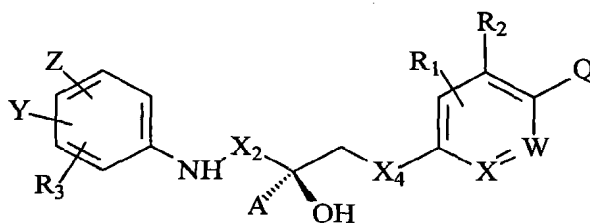
R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

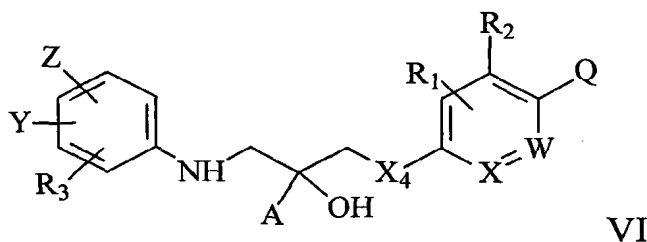
在另一个实施方案中, 式 IV 的化合物由以下结构表示:



在另一个实施方案中, 式 IV 的化合物由以下结构表示:



在一个实施方案中, 本发明提供由式 VI 的结构表示的化合物:



其中

X 是 C 或 N; W 是 C 或 N;

X_4 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂；

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br；

Y 是 H、C₁₋₄ 烷基、CH₃、CN、NO₂、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂]；

R 是 H、OH、C₁₋₄ 烷基、CF₃、CH₂OH、O(C₁₋₄ 烷基)或 O(C₁₋₄ 酰基)；

R₁ 是 H、OH、F、Cl、Br 或 I；

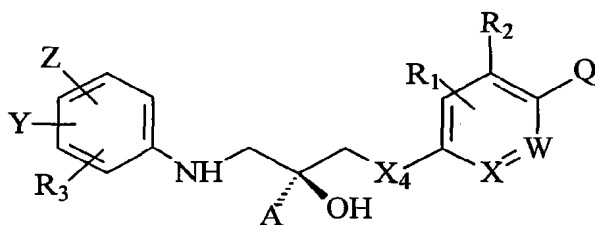
R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂；

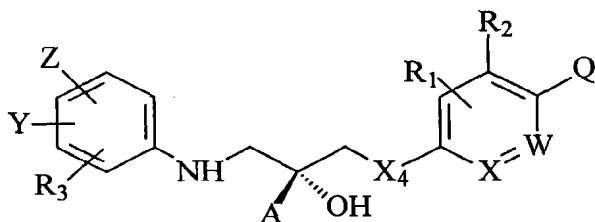
R' 是 NH₂、OH 或 CH₃；并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

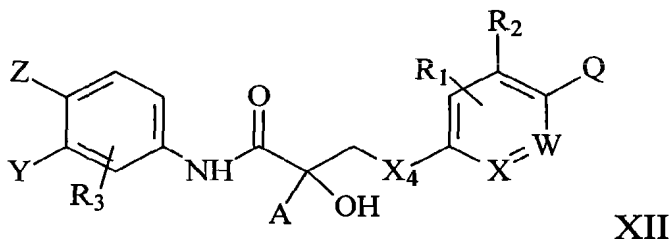
在另一个实施方案中，式 VI 的化合物由以下结构表示：



在一个实施方案中，式 VI 的化合物由以下结构表示：



在一个实施方案中，本发明提供由式 XII 的结构表示的化合物：



XII

其中

X 是 C 或 N；W 是 C 或 N；

X₄ 是 O、S、SO、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

A 是 CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂；

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br；

Y 是 H、C₁₋₄ 烷基、CF₃、CN、NO₂、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂]；

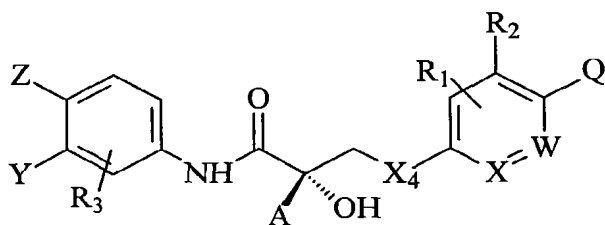
R₁ 是 H、OH、F、Cl、Br 或 I；

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基；

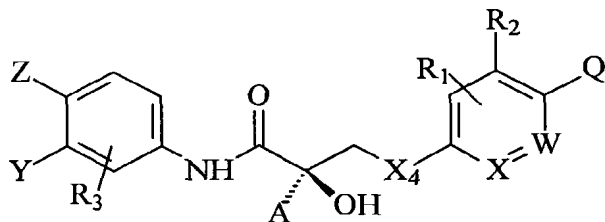
R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂；

R' 是 NH₂、OH 或 CH₃；并且

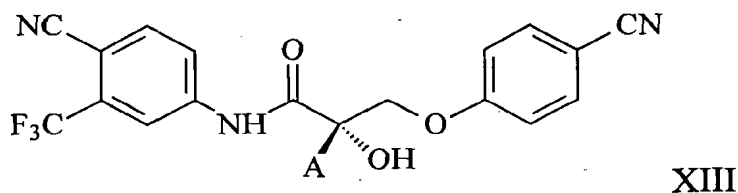
R_6 是 CN、NO₂、NHC(O)CH₃ 或卤化物。在另一个实施方案中，式 XII 的化合物由以下结构表示：



在另一个实施方案中，式 XII 的化合物由以下结构表示：

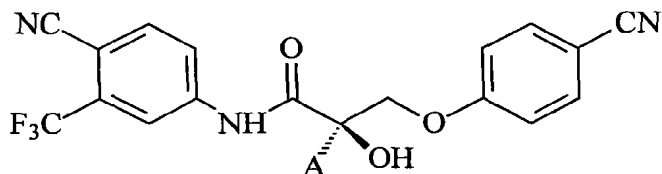


在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：

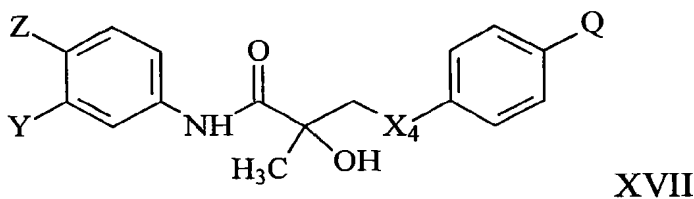


其中 A 如以上在化合物 XII 中所述。

在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：



在一个实施方案中，本发明提供由式 XVII 的结构表示的化合物：



其中

X_4 是 $S(O)[=CHCH_2N(CH_3)_2]$ 、 $C(OH)[CH_2CH_2N(CH_3)_2]$ 、

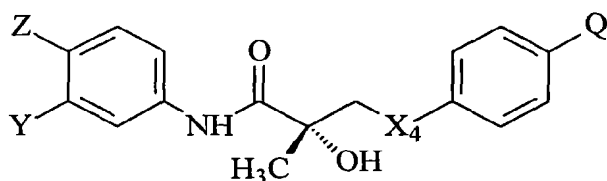
$C[=CHCH_2N(CH_3)_2]$ 、 $PO(C_{1-4} \text{ 烷基})$ 、 $N[CH_2CH_2N(CH_3)_2]$ 、 $NO[CH_2CH_2N(CH_3)_2]$;

Q 是 H、CN、OH、 NO_2 、 CF_3 、卤化物、 C_{2-6} 烯基、 C_{2-6} 炔基、 $C(O)CH_2NH_2$ 、 $C(O)NH(C_{1-4} \text{ 烷基})$ 、 $C(O)N(C_{1-4} \text{ 烷基})_2$ 、 $C(O)NH_2$ 、 $NH(C_{1-4} \text{ 烷基})$ 、 $NHC(O)NH(C_{1-4} \text{ 烷基})$ 、 $CH_2C(O)NH_2$ 、 $NHC(O)NH_2$ 、 $NHCO(C_{1-4} \text{ 烷基})$ 、 $NHSO_2(C_{1-4} \text{ 烷基})$ 、 $O-[CH_2CH_2CH(CH_3)_2]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 环烷基})]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 杂环烷基})]$ 或 $O-[CH_2CH_2N(CH_3)_2]CHF_2$;

Z 是 H、CN、 NO_2 、 $NHC(O)CH_3$ 、 C_{1-4} 烷基、F、Cl、I 或 Br; 并且

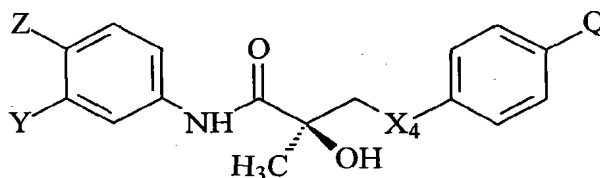
Y 是 H、 C_{1-4} 烷基、 CF_3 、CN、 NO_2 、F、Cl、I 或 Br。

在另一个实施方案中, 式 XVII 的化合物由以下结构表示:

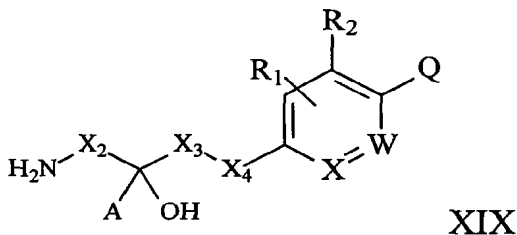


XVII

在另一个实施方案中, 式 XVII 的化合物由以下结构表示:



在一个实施方案中, 本发明提供由式 XIX 的结构表示的化合物:



XIX

其中

X 是 C 或 N; W 是 C 或 N;

X_2 是 C_{1-4} 亚烷基、 SO_2 、 $C(O)$ 、 $CH-[CH_2-(C_{4-8} \text{ 环})]$ 、 $CH(C_{1-4} \text{ 烷基})$ 、 $CH(NH_2)$ 、 $CH(OH)$ 、 $CH(C_{1-4} \text{ 卤代烷基})$ 、键;

X_3 是 C_{1-4} 亚烷基、NH、N、CH(OH)或键；

X_4 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、 C_{1-4} 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C_{1-4} 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

A 是 H、OH、SH、NH₂、 C_{1-4} 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C_{1-4} 烷基)、CH₂O(C_{1-4} 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C_{1-4} 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C_{1-4} 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂；

Z 是 H、CN、NO₂、NHC(O)CH₃、 C_{1-4} 烷基、F、Cl、I 或 Br；

Y 是 H、 C_{1-4} 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO₂、CF₃、卤化物、 C_{2-6} 烯基、 C_{2-6} 炔基、C(O)CH₂NH₂、C(O)NH(C_{1-4} 烷基)、C(O)N(C_{1-4} 烷基)₂、C(O)NH₂、NH(C_{1-4} 烷基)、NHC(O)NH(C_{1-4} 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C_{1-4} 烷基)、NH₂SO₂(C_{1-4} 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C_{4-8} 环烷基)]、O-[CH₂CH₂(C_{4-8} 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂]；

R_1 是 H、OH、F、Cl、Br 或 I；

R_2 是 H、由 R_6 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基；

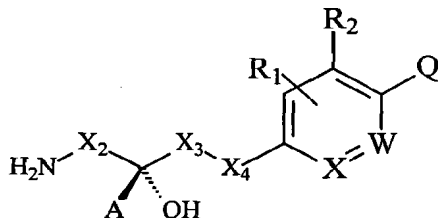
R' 是 NH₂、OH 或 CH₃；并且

R_6 是 CN、NO₂、NHC(O)CH₃ 或卤化物；

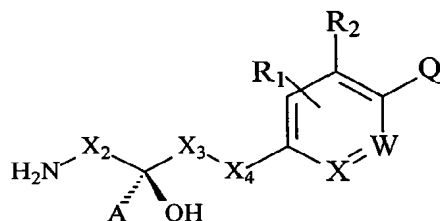
其中

如果 X 是 C， X_1 是 NH， X_2 是 C(O)，R 是 OH，A 是烷基， X_3 是键或 CH₂，并且 X_4 是键或 CH₂， R_1 和 R_2 是 H，那么 Q 不是 H 或卤素。

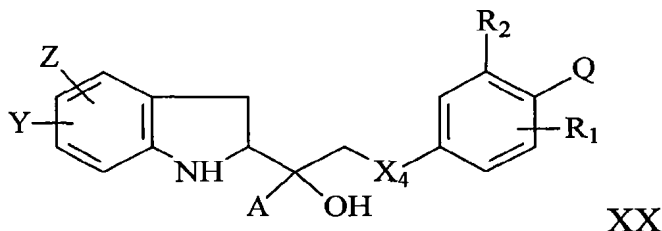
在另一个实施方案中，式 XIX 的化合物由以下结构表示：



在另一个实施方案中，式 XIX 的化合物由以下结构表示：



在一个实施方案中, 本发明提供由式 XX 的结构表示的化合物:



其中

X_4 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHCO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

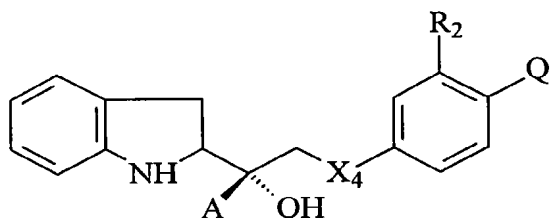
R₁ 是 H、OH、F、Cl、Br 或 I;

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

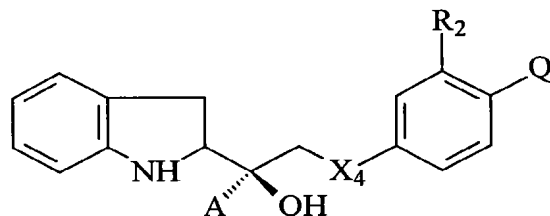
R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

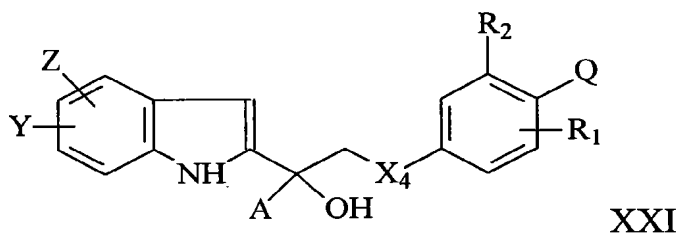
在另一个实施方案中，式 I 的化合物由以下结构表示：



或在另一个实施方案中，

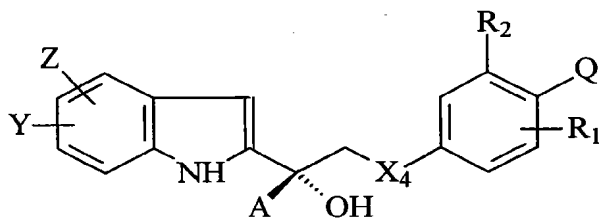


在一个实施方案中，本发明提供由式 XXI 的结构表示的化合物：

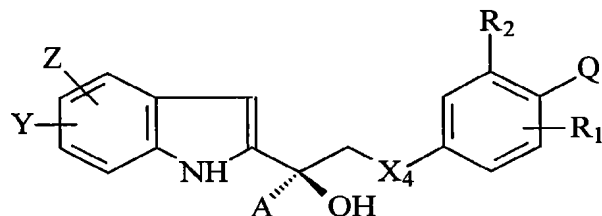


其中 A、Z、Y、X₄、Q、R₁ 和 R₂ 如在化合物 XX 中所述。

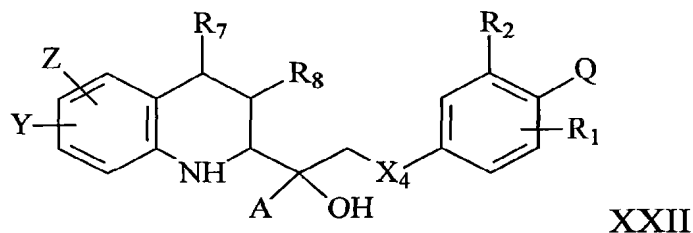
在另一个实施方案中，式 XXI 的化合物由以下结构表示：



或在另一个实施方案中，

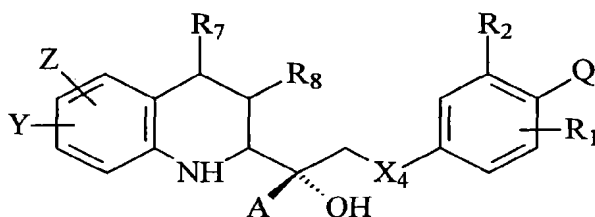


在一个实施方案中，本发明提供由式 XXII 的结构表示的化合物：

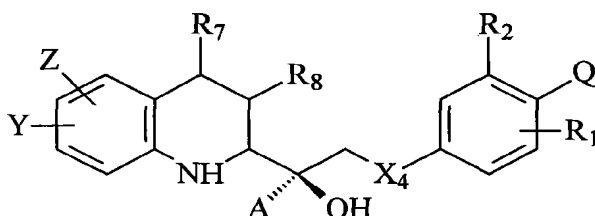


其中 A、Z、Y、X₄、Q、R₁ 和 R₂ 如在化合物 XX 中所述, R₇ 是 H 或氧代, R₈ 是 H 或=CH₂。

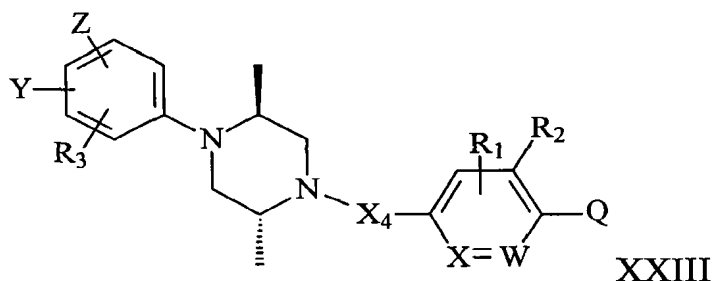
在另一个实施方案中, 式 XXII 的化合物由以下结构表示:



或在另一个实施方案中,



在一个实施方案中, 本发明提供由式 XXIII 的结构表示的化合物:



其中

X 是 C 或 N; W 是 C 或 N;

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、NO₂、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R₁ 是 H、OH、F、Cl、Br 或 I;

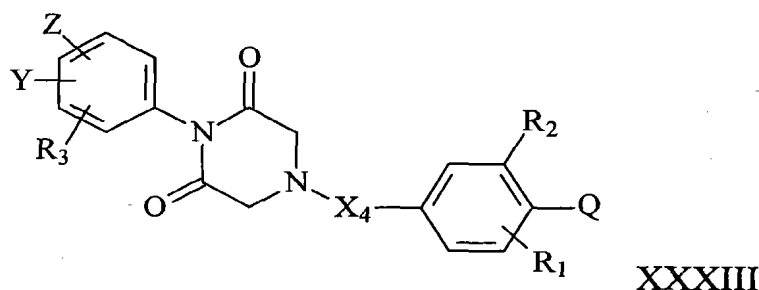
R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

R' 是 NH₂、OH 或 CH₃; 并且

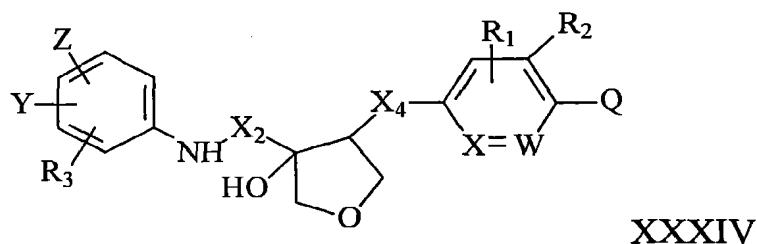
R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

在一个实施方案中, 本发明提供由式 XXXIII 的结构表示的化合物:



其中 Z、Y、X₄、Q、R₁、R₂ 和 R₃ 如在化合物 XXIII 中所述。

在一个实施方案中, 本发明提供由式 XXXIV 的结构表示的化合物:



其中

X 是 C 或 N; W 是 C 或 N;

X₂ 是 C₁₋₄ 亚烷基、SO₂、C(O)、CH-[CH₂-(C₄₋₈ 环)]、CH(C₁₋₄ 烷基)、CH(NH₂)、CH(OH)、CH(C₁₋₄ 卤代烷基)、键;

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR',

NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br；

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂]

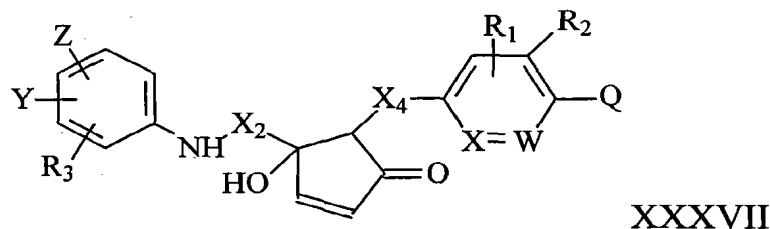
R₁ 是 H、OH、F、Cl、Br 或 I；

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂；

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

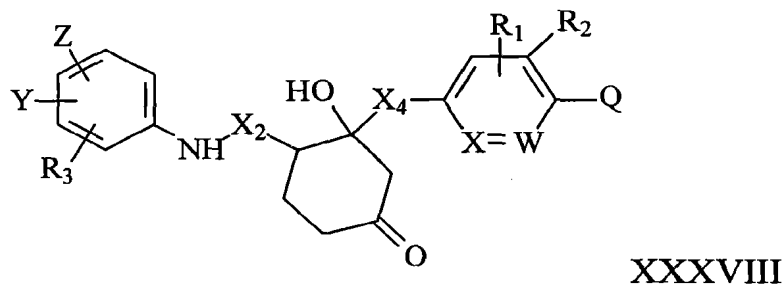
在一个实施方案中，本发明提供由式 XXXVII 的结构表示的化合物：



其中

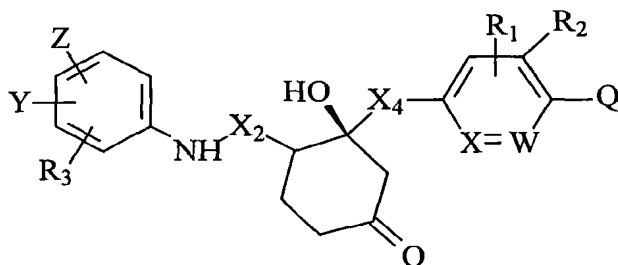
X、X₂、X₄、Z、Y、Q、R₁ 和 R₃ 如以上在化合物 XXXIV 中所述。

在一个实施方案中，本发明提供由式 XXXVIII 的结构表示的化合物：

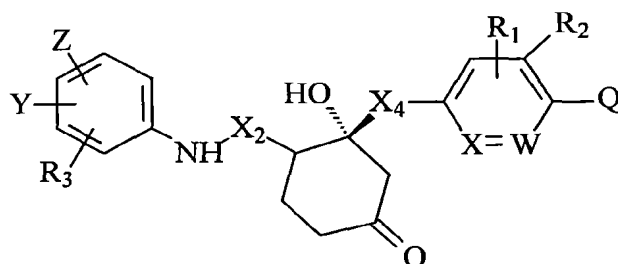


其中 X、X₂、X₄、Z、Y、Q、R₁ 和 R₃ 如以上在化合物 XXXIV 中所述。

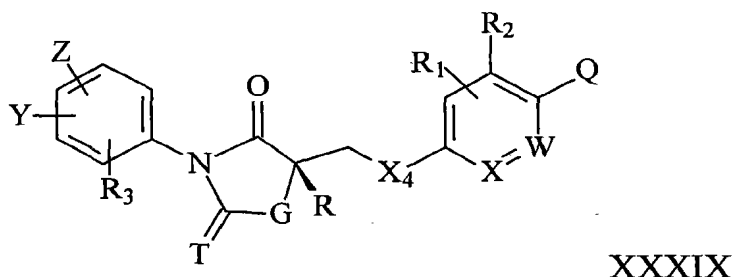
在另一个实施方案中，式 XXXVIII 的化合物由以下结构表示：



或在另一个实施方案中,



在一个实施方案中, 本发明提供由式 XXXIX 的结构表示的化合物:



其中:

X 是 C 或 N; W 是 C 或 N;

G 是 O、NH、NC₁₋₄ 烷基、NC₁₋₄ 酰基、S、CHC₁₋₄ 烷基、CHC₁₋₄ 酰基、C(C₁₋₄ 酰基)₂、C(C₁₋₄ 烷基)₂ 或 (CH₂)_n, 其中 n 是 1-3;

T 是 S 或 O;

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、CF₃、NO₂、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、

NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R 是 H、OH、C₁₋₄ 烷基、CF₃、CH₂OH、O(C₁₋₄ 烷基)或 O(C₁₋₄ 酰基);

R₁ 是 H、OH、F、Cl、Br 或 I;

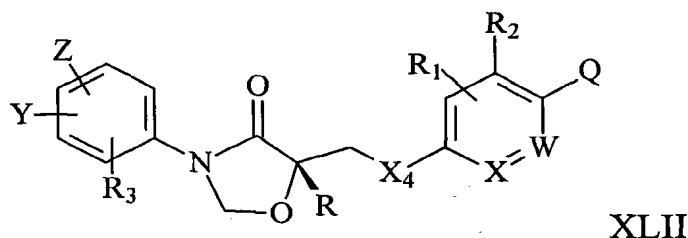
R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

R' 是 NH₂、OH 或 CH₃; 并且

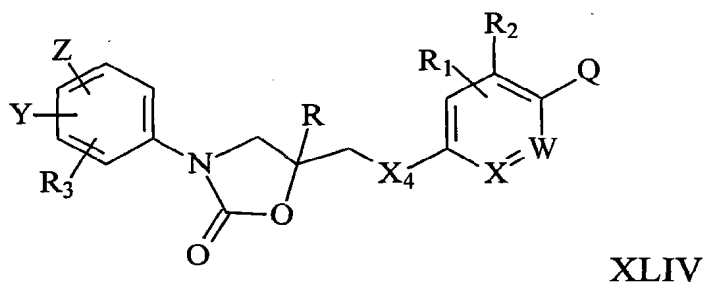
R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

在一个实施方案中, 本发明提供式 XLII 的化合物:



其中 X、X₄、Z、Y、Q、R₁、R₂ 和 R₃ 如以上在化合物 XXXIX 中所述。

在一个实施方案中, 本发明提供式 XLIV 的化合物:



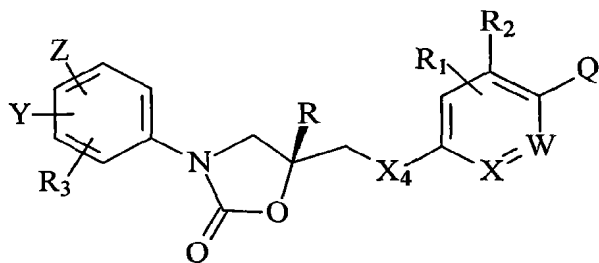
其中:

X、X₄、R、R₁、R₂、R₃、Z、Y 和 Q 如以上在化合物 XXXIX 中所述;

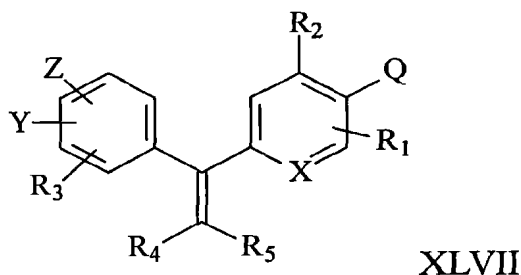
其中

如果 X 是 C, X₄ 是 O、NH 或 S, R₁、R₂ 和 R₃ 是 H 并且 R 是 H, 那么 Q 不是卤素、H 或 CN。

在另一个实施方案中, 式 XLIV 的化合物由以下结构表示:



在一个实施方案中，本发明提供由式 XLVII 的结构表示的化合物：



在一个实施方案中，本发明提供组合物，其包含式(I)的化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合。

在一个实施方案中，所述化合物是选择性雄激素受体调节剂(SARM)。在一个实施方案中，所述 SARM 是部分激动剂。在一个实施方案中，所述 SARM 是组织选择性激动剂，或在一些实施方案中，是组织选择性拮抗剂。

在一个实施方案中，本发明提供一种在雄性个体中避孕的方法，所述方法包括向所述个体给药有效抑制所述个体中精子产生的量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合、或者含有它们的组合物的步骤，由此实现在所述个体中的避孕。

在一个实施方案中，本发明提供激素治疗方法，所述方法包括使个体的雄激素受体与有效实现改变雄激素依赖性病症的量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合、或者含有它们的组合物接触的步骤。

在一个实施方案中，本发明提供治疗罹患前列腺癌的个体的方法，所述方法包括向所述个体给药有效治疗所述个体中的前列腺癌的量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物

或它们的任意组合、或者含有它们的组合物的步骤。

在一个实施方案中，本发明提供延缓罹患前列腺癌的个体的前列腺癌的进展的方法，所述方法包括向所述个体给药有效延缓所述个体中前列腺癌的进展的量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合、或者含有它们的组合物的步骤。

在一个实施方案中，本发明提供治疗个体的骨相关的病症、或增加个体的骨量、促进个体的骨形成的方法，以有效治疗所述骨相关的病症的量给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合、或者含有它们的组合物。

根据这一方面，在一个实施方案中，所述个体罹患骨质疏松症、骨质减少、骨吸收增加、骨折、骨脆弱、骨矿物质密度（BMD）丢失或它们的任意组合。在一个实施方案中，所述方法增加所述个体的骨强度。在一个实施方案中，所述化合物促进或加强成骨细胞分化，或者在另一个实施方案中，所述化合物抑制破骨细胞增殖。

在一个实施方案中，本发明提供治疗个体的肌萎缩症、降低其发病率、延缓其进展、减轻其严重性或减轻与其相关症状的方法，所述方法包括向所述个体给药有效治疗所述个体的所述肌萎缩症的量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合、或者含有它们的组合物的步骤。

根据这一方面，在一个实施方案中，所述肌萎缩症归因于病状、疾患、疾病或病症。在一个实施方案中，所述病状、疾患、疾病或病症是神经性的、感染性的、慢性的或遗传性的。在一个实施方案中，所述病状、疾患、疾病或病症是肌肉营养不良症、肌萎缩、伴 X 染色体的（X-linked）脊延髓肌萎缩症（SBMA）、恶病质、营养不良、麻风病、糖尿病、肾脏病、慢性阻塞性肺疾病（COPD）、癌症、终末期肾功能衰竭、少肌症、肺气肿、骨软化症、HIV 感染、AIDS 或心肌病。

在一个实施方案中，所述肌萎缩症是年龄相关的肌萎缩症，废用性失调相关的肌萎缩症；或者所述肌萎缩症归因于慢性下腰痛、烧伤、中枢神经系统（CNS）损伤或损害、周围神经损伤或损害、脊髓损伤、化学性损伤或损害、或者酒精中毒。

在一个实施方案中，本发明提供治疗人类个体的糖尿病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的葡萄糖耐受不良、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的高胰岛素血症、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的胰岛素抵抗、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗与糖尿病相关的疾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的脂肪肝症、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的心血管疾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗个体的恶病质、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个

体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗个体的眼疾病或病症的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。在一个实施方案中，所述眼疾病或病症包括干燥综合征或干眼病。

在一个实施方案中，本发明提供减少个体脂肪量的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，本发明提供增加个体瘦体重的方法，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供治疗个体的恶病质、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在一个实施方案中，所述恶病质与所述个体的癌症相关。

在另一个实施方案中，本发明提供治疗个体的类风湿性关节炎、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供治疗个体的慢性肾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供治疗个体的终末期肾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供治疗个体的脆弱（frailty）、减轻其严

重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供治疗个体的性腺功能减退症、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供一种治疗个体的年龄相关的功能减退、减轻其严重性、降低其发病率、延缓其发作或减少其发病的方法，所述方法包括向所述个体给药式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤。

在另一个实施方案中，本发明提供以下的方法：抑制精子发生；雄性避孕；激素治疗；治疗前列腺癌；延缓前列腺癌的进展；治疗个体的骨相关的疾病或增加个体的骨量和/或促进个体的骨形成；治疗肌萎缩症、降低其发病率、延缓其进程、减轻其严重性或减轻与其相关的症状；治疗糖尿病、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗葡萄糖耐受不良、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗高胰岛素血症、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗胰岛素抵抗、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗与糖尿病相关的疾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗脂肪肝症、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗心血管疾病、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗恶病质、减轻其严重性、降低其发病率、延缓其发作或减少其发病；治疗眼疾病或病症；减少脂肪量；或增加个体瘦体重，所述方法包括向所述个体给药有效量的式(I)化合物和/或其异构体、药学上可接受的盐、药品、晶体、*N*-氧化物、水合物或它们的任意组合的步骤，如本文所述。

附图简要说明

在说明书的结论部分特别指出并清楚地要求保护作为本发明的主题。但

是, 通过在阅读附图时参照以下的具体描述可以最好地理解关于本发明的组织和操作方法及其目标、特征和优点, 其中:

图 1 描绘了各种选择性雄激素受体调节剂类似物的结构 (图 1A) 和它们的合成路线, 例如化合物 XIII (图 1B)、化合物 V (图 1C)、式 XI 的化合物 (图 1D)、化合物 XXXV (图 1E)、化合物 XXXVI (图 1F)、化合物 XLVI (图 1G)、化合物 X (图 1H)、化合物 XXIV-XXVIII (图 1I)、化合物 XL (图 1J)、化合物 XLI (图 1K)。

图 2 描绘了制备式 XLIII (oxatidylidione) 化合物的合成路线。

图 3 描绘了制备式 XLVIII 化合物的合成路线。

图 4 描绘了制备式 XLIX 化合物的合成路线。

图 5 描绘了制备式 LII 化合物的合成路线。

图 6 描绘了制备式 L 化合物的合成路线。

图 7 描绘了制备式 LI 化合物的合成路线。

图 8 描绘了比卡鲁胺类似物通过野生型雄激素受体的转录激活。在用所示配体处理之前, 用 hAR 和雄激素依赖性萤光素酶报告基因构建体短暂转染 CV-1 细胞。报告相对载体处理的对照的增加倍数 ($n=6$)。

图 9 描绘了表 1 中所示的 S-4 (图 9A) 和睾酮 (图 9B) 在去势的大鼠中的雄激素活性和合成代谢活性。去势的雄性大鼠在 14 天内接受剂量增加的睾酮 (上图) 或 S-4 (下图)。在处死时测定器官重量, 表示为完整对照的百分数。

图 10 描绘了如表 1 中所示的 S-4、S-1、X-2、X-3、X-5 和 X-4 (X 分别为 O、O、S、SO₂、CH₂ 和 NH) 的原子以颜色区分的叠加的碳键合氢隐藏的球-棍模型。激动剂 S-4 和 X-2 以及 S-1 显示出以前未对芳基丙酰胺假定过的六元环状 NH-X 氢键构型。

图 11 描绘 DHT、羟基氟他胺 (HF)、比卡鲁胺 (bical) 和 S-4 通过野生型或突变型雄激素受体的转录激活。用野生型或突变型 AR 和雄激素依赖性报告基因构建体的表达载体短暂转染 CV-1 细胞。报告每一种药物 (100 nM) AR-介导的诱导, 表示为相对萤光素酶单位除以 β -半乳糖苷酶活性 (标准化对照)。

图 12 描绘了雄激素受体配体结合域 (AR LBD) 的晶体结构。图 12A 显

示与 *R*-比卡鲁胺结合的突变型 AR LBD(W741L)的总体结构的主视图。图 12B 显示省略了 *R*-比卡鲁胺的 Fo-Fc 模拟退火省略图中的 W741L-*R*-比卡鲁胺和 *R*-比卡鲁胺的电子密度图。

图 13 描绘野生型 DHT、T877A-HF 和 W741L-*R*-比卡鲁胺的立体重叠，显示类固醇结合平面的概观(图 13A)和类固醇结合平面的侧视图(图 13B)。

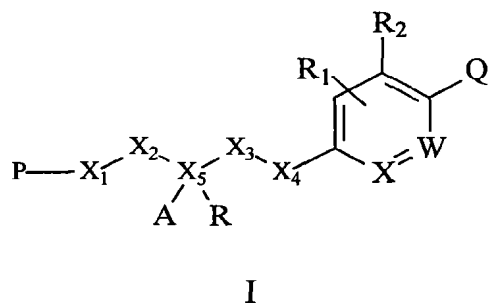
图 14 描绘了与 *R*-比卡鲁胺结合的突变型 W741L 雄激素受体配体结合域。图 14A 显示与 *R*-比卡鲁胺结合的 AR LBD(W741L)的总体结构的侧视图。AF2 区(螺旋 3、4 和 12)以绿色突出显示。保守的电荷-发夹(charge-clamp)残基是 H3 中的 K720 和 H12 中的 E897。图 14B 显示与 DHT 结合的野生型 AR LBD 的 AF2 区的结构细节。W741 侧链显示在充满原子的空间中。

应理解，为了说明的简单清楚，所述图中所示的元件不一定是按比例绘制的。例如，为了清楚，一些元件的尺寸可能相对于其它元件放大。而且，在认为合适的地方，在所述图中可能重复参考数字以指示相应或类似的元件。

发明详述

在以下的具体说明中，叙述了大量的具体细节以提供透彻地理解本发明。然而，本领域的技术人员会理解，没有这些具体细节也可以实施本发明。在其它一些情况下，对众所周知的方法、过程和组分不作详细描述以便不致使本发明变得含混不清。

在一个实施方案中，本发明提供由式 I 的结构表示的化合物：



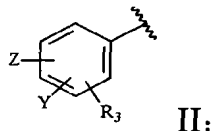
其中

X 是 C 或 N；W 是 C 或 N；

X₁ 是 N、NH、N(C₁₋₄ 烷基)、NAc、NCOOH 或键；或者 X₁ 和 X₃ 与 X₁ 和 X₃ 所连接的 X₂ 和 X₅ 一起形成饱和的或不饱和的、取代的或未取代的

5-或 6-元环；或者 X_1 和 X_5 与 X_1 和 X_5 所连接的 X_2 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

P 是 H 或式 II：



X_2 是 C_{1-4} 亚烷基、 SO_2 、 $C(O)$ 、 $CH-[CH_2-(C_{4-8} \text{ 环})]$ 、 $CH(C_{1-4} \text{ 烷基})$ 、 $CH(NH_2)$ 、 $CH(OH)$ 、 $CH(C_{1-4} \text{ 卤代烷基})$ 、键；或者 X_2 和 R_3 与 X_2 所连接的 X_1 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X_2 和 X_5 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

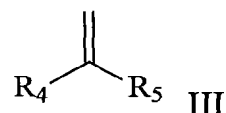
X_3 是 C_{1-4} 亚烷基、 NH 、 N 、 $CH(OH)$ 、键；或者 X_1 和 X_3 与 X_1 和 X_3 所连接的 X_2 和 X_5 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X_3 和 X_5 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_3 和 X_4 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

X_4 是 O 、 S 、 SO 、 $C(O)$ 、 $S(O)[=CHCH_2N(CH_3)_2]$ 、 SO_2 、 NH 、 NHR' 、 NO 、 C_{1-4} 亚烷基、 $C(OH)[CH_2CH_2N(CH_3)_2]$ 、 $C[=CHCH_2N(CH_3)_2]$ 、 $PO(C_{1-4} \text{ 烷基})$ 、 $N[CH_2CH_2N(CH_3)_2]$ 、 $NO[CH_2CH_2N(CH_3)_2]$ 或键；或者 X_4 和 X_5 以及 X_4 和 X_5 所连接的 X_3 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_3 和 X_4 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

X_5 是碳或者 X_5 和 X_1 与 X_1 和 X_5 所连接的 X_2 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_5 和 X_2 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_5 和 X_3 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_5 和 X_4 与 X_5 和 X_4 所连接的 X_3 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

A 不存在，或是 H 、 OH 、 SH 、 NH_2 、 C_{1-4} 烷基、 CHF_2 、 CH_2F 、 CF_3 、 CN 、 CH_2OH 、 $CH_2O(C_{1-4} \text{ 烷基})$ 、 $CH_2O(C_{1-4} \text{ 酰基})$ 、 CH_2CN 、 CH_2N_3 、 CH_2NCS 、 CHO 、 $C(O)O(C_{1-4} \text{ 烷基})$ 、 $CONHR'$ 、 $C(O)N(R')_2$ 、 $C(O)O(C_{1-4} \text{ 烷基})$ 、 $C(O)R'$ 、

CH_2CF_3 、 CF_2CF_3 、 $\text{CH}_2\text{OR}'$ $\text{CH}_2\text{C}(\text{O})\text{CH}=\text{CH}_2$ 或 $\text{C}(\text{O})\text{CH}=\text{CH}_2$; 或者 A 和 R 形成式 III 所表示的双键:



Z 是 H、CN、 NO_2 、 $\text{NHC}(\text{O})\text{CH}_3$ 、 C_{1-4} 烷基、F、Cl、I 或 Br;

Y 是 H、 C_{1-4} 烷基、 CF_3 、 NO_2 、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、 NO_2 、卤化物、 CF_3 、 C_{2-6} 烯基、 C_{2-6} 炔基、 $\text{C}(\text{O})\text{CH}_2\text{NH}_2$ 、 $\text{C}(\text{O})\text{NH}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{C}(\text{O})\text{N}(\text{C}_{1-4} \text{ 烷基})_2$ 、 $\text{C}(\text{O})\text{NH}_2$ 、 $\text{NH}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{NHC}(\text{O})\text{NH}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{CH}_2\text{C}(\text{O})\text{NH}_2$ 、 $\text{NHC}(\text{O})\text{NH}_2$ 、 $\text{NHCO}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{NH}\text{SO}_2(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{O}-[\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2]$ 、 $\text{O}-[\text{CH}_2\text{CH}_2(\text{C}_{4-8} \text{ 环烷基})]$ 、 $\text{O}-[\text{CH}_2\text{CH}_2(\text{C}_{4-8} \text{ 杂环烷基})]$ 或 $\text{O}-[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$;

R 是 H、OH、 C_{1-4} 烷基、 CF_3 、 CH_2OH 、 $\text{O}(\text{C}_{1-4} \text{ 烷基})$ 或 $\text{O}(\text{C}_{1-4} \text{ 酰基})$;

R_1 是 H、OH、 NH_2 、F、Cl、Br 或 I;

R_2 是 H、由 R_6 取代的苄基、 $(\text{CH}_2)_2\text{-O-对氰基苯基}$ 、 $\text{CH}_2\text{-O-对氰基苯基}$ 或 $\text{CH}=\text{CH-O-对氰基苯基}$;

R_3 是 H、 C_{1-4} 烷基、卤化物、CN、 NO_2 ; 或者 R_3 和 X_2 与 R_3 所连接的苯环和 X_2 所连接的 X_1 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环;

R' 是 NH_2 、OH 或 CH_3 ;

R_4 和 R_5 独立地是 H、 CH_3 、卤化物、OH、 C_{1-4} 烷基、 C_{1-6} 环烷基、卤代(C_{1-4} 烷基)、苯基、芳基、 C_{4-8} 杂环烷基或羟基(C_{1-4} 烷基);

R_6 是 CN、 NO_2 、 $\text{NHC}(\text{O})\text{CH}_3$ 或卤化物;

其中

如果 P 是式 II, X 是 C, X_1 是 NH, X_2 是 $\text{C}(\text{O})$, X_3 是 CH_2 , R 是 OH 并且 A 是烷基或卤代烷基, 那么 X_4 是 $\text{S}(\text{O})[=\text{CHCH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{C}(\text{OH})[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{C}[=\text{CHCH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{N}[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{P}(\text{O})(\text{C}_{1-4} \text{ 烷基})$ 或 $\text{N}(\text{O})[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$;

或者

如果 P 是式 II, X 是 C, X_1 是 NH, X_2 是 $\text{C}(\text{O})$, X_3 是 CH_2 , R 是 OH 或 OAlk 并且 X_4 是 O、S、NH、S、SO、 SO_2 或烯基, 那么 A 是 CN、 CH_2OH 、

$\text{CH}_2\text{O}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{CH}_2\text{O}(\text{C}_{1-4} \text{ 酰基})$ 、 CH_2CN 、 CH_2N_3 、 CH_2NCS 、 CHO 、 $\text{C}(\text{O})\text{O}(\text{C}_{1-4} \text{ 烷基})$ 、 CONHR' 、 $\text{C}(\text{O})\text{N}(\text{R}')_2$ 、 $\text{C}(\text{O})\text{O}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{C}(\text{O})\text{R}'$ 、 $\text{CH}_2\text{OR}'\text{CH}_2\text{C}(\text{O})\text{CH}=\text{CH}_2$ 或 $\text{C}(\text{O})\text{CH}=\text{CH}_2$;

或者

如果 P 是苯基, X 是 C, X_1 是 NH, X_2 是 C(O), R 是 OH 且 A 是 COOH, X_3 是键, X_4 是 CH_2 , R_1 、 R_2 是 H, 那么 Q 不是 H;

或者

如果 P 是式 II, X 是 C, X_3 是 CH_2 , X_4 是 O 或 NH, R_1 、 R_2 和 R_3 是 H, 并且 X_5 和 X_1 形成 5 元环噁唑烷-2-酮, 那么 Q 不是卤素或 H;

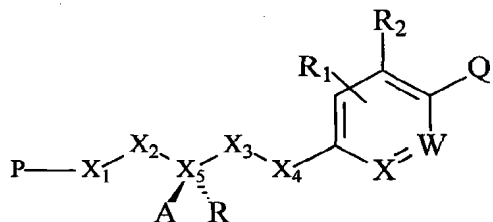
或者

如果 P 是 H, X 是 C, X_1 是 NH, X_2 是 C(O), R 是 OH, A 是烷基, X_3 是键或 CH_2 , 并且 X_4 是键或 CH_2 , R_1 和 R_2 是 H, 那么 Q 不是 H 或卤素;

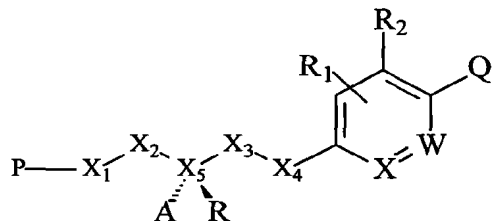
或者

如果 P 是式 II, R_3 是 H, X 和 W 是 C, X_1 和 X_5 与 X_1 和 X_5 所连接的 X_2 形成噁唑烷二酮, R 是烷基, X_3 是 CH_2 , 并且 X_4 是 O、NH、S、 SO_2 或 CH_2 , 那么 Q 不是卤化物。

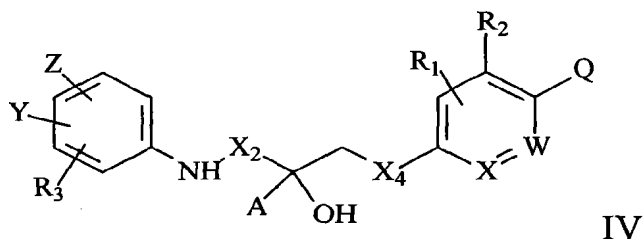
在另一个实施方案中, 式 I 的化合物由以下结构表示:



在另一个实施方案中, 式 I 的化合物由以下结构表示:



在一个实施方案中, 本发明提供由式 IV 的结构表示的化合物:



其中

X 是 C 或 N; W 是 C 或 N;

X₂ 是 C₁₋₄ 亚烷基、SO₂、CH-[CH₂-(C₄₋₈ 环)]、CH(C₁₋₄ 烷基)、CH(NH₂)、CH(OH)、CH(C₁₋₄ 卤代烷基)、键;

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、CN、NO₂、F、Cl、I 或 Br;

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R 是 H、OH、C₁₋₄ 烷基、CF₃、CH₂OH、O(C₁₋₄ 烷基)或 O(C₁₋₄ 酰基);

R₁ 是 H、OH、NH₂、F、Cl、Br 或 I;

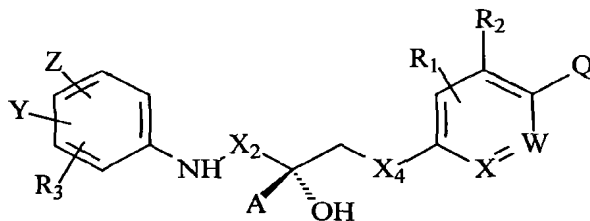
R₂ 是 H、R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

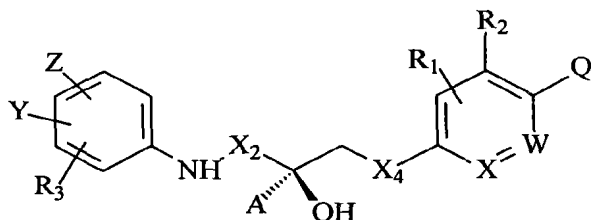
R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

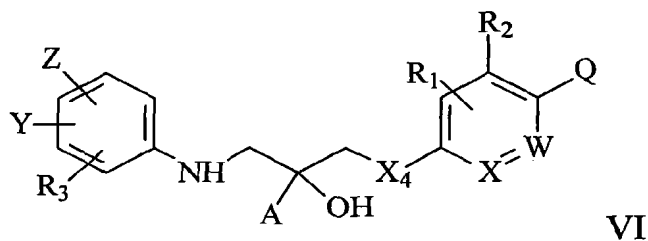
在另一个实施方案中, 式 IV 的化合物由以下结构表示:



在另一个实施方案中，式 IV 的化合物由以下结构表示：



在一个实施方案中，本发明提供由式 VI 的结构表示的化合物：



其中

X 是 C 或 N；W 是 C 或 N；

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂；

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br；

Y 是 H、C₁₋₄ 烷基、CF₃、CN、NO₂、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、

NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R 是 H、OH、C₁₋₄ 烷基、CF₃、CH₂OH、O(C₁₋₄ 烷基)或 O(C₁₋₄ 酰基);

R₁ 是 H、OH、F、Cl、Br 或 I;

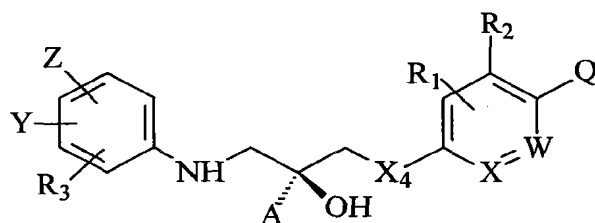
R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

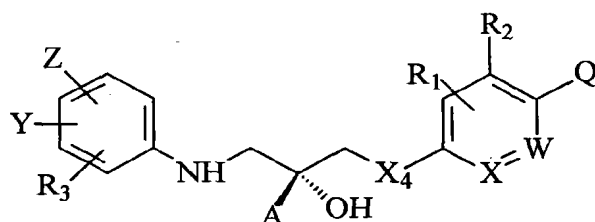
R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

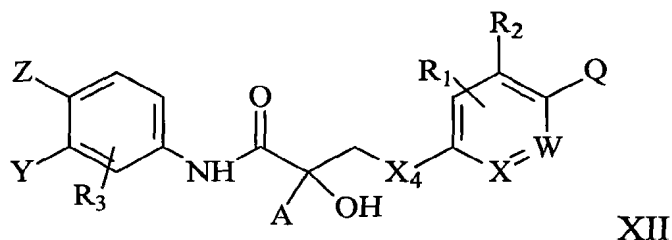
在另一个实施方案中, 式 VI 的化合物由以下结构表示:



在一个实施方案中, 式 VI 的化合物由以下结构表示:



在一个实施方案中, 本发明提供由式 XII 的结构表示的化合物:



其中

X 是 C 或 N; W 是 C 或 N;

X₄ 是 O、S、SO、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、

$N[CH_2CH_2N(CH_3)_2]$ 、 $NO[CH_2CH_2N(CH_3)_2]$ 或键；

A 是 CN、 CH_2OH 、 $CH_2O(C_{1-4} \text{ 烷基})$ 、 $CH_2O(C_{1-4} \text{ 酰基})$ 、 CH_2CN 、 CH_2N_3 、 CH_2NCS 、CHO、 $C(O)O(C_{1-4} \text{ 烷基})$ 、 $CONHR'$ 、 $C(O)N(R')_2$ 、 $C(O)O(C_{1-4} \text{ 烷基})$ 、 $C(O)R'$ 、 $CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$ ；

Z 是 H、CN、 NO_2 、 $NHC(O)CH_3$ 、 C_{1-4} 烷基、F、Cl、I 或 Br；

Y 是 H、 C_{1-4} 烷基、 CF_3 、CN、 NO_2 、F、Cl、I 或 Br；

Q 是 H、CN、OH、 NO_2 、 CF_3 、卤化物、 C_{2-6} 烯基、 C_{2-6} 炔基、 $C(O)CH_2NH_2$ 、 $C(O)NH(C_{1-4} \text{ 烷基})$ 、 $C(O)N(C_{1-4} \text{ 烷基})_2$ 、 $C(O)NH_2$ 、 $NH(C_{1-4} \text{ 烷基})$ 、 $NHC(O)NH(C_{1-4} \text{ 烷基})$ 、 $CH_2C(O)NH_2$ 、 $NHC(O)NH_2$ 、 $NHCO(C_{1-4} \text{ 烷基})$ 、 $NHSO_2(C_{1-4} \text{ 烷基})$ 、 $O-[CH_2CH_2CH(CH_3)_2]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 环烷基})]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 杂环烷基})]$ 或 $O-[CH_2CH_2N(CH_3)_2]$ ；

R_1 是 H、OH、F、Cl、Br 或 I；

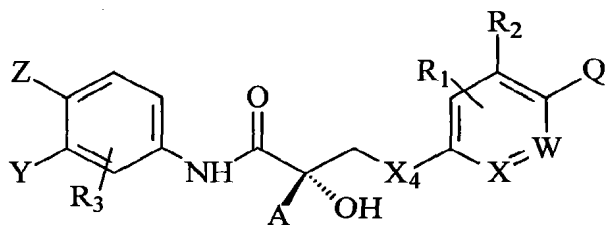
R_2 是 H、由 R_6 取代的苄基、 $(CH_2)_2$ -O-对氰基苯基、 CH_2 -O-对氰基苯基或 $CH=CH$ -O-对氰基苯基；

R_3 是 H、 C_{1-4} 烷基、卤化物、CN 或 NO_2 ；

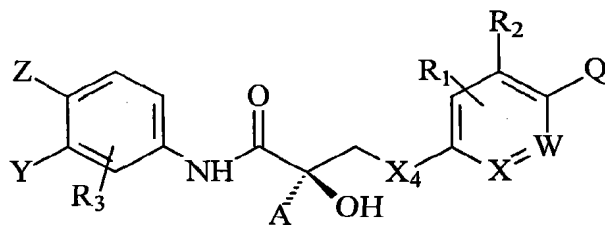
R' 是 NH_2 、OH 或 CH_3 ；并且

R_6 是 CN、 NO_2 、 $NHC(O)CH_3$ 或卤化物。

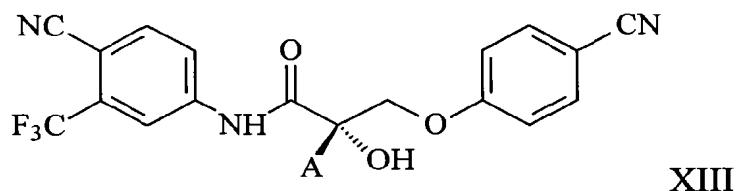
在另一个实施方案中，式 XII 的化合物由以下结构表示：



在另一个实施方案中，式 XII 的化合物由以下结构表示：

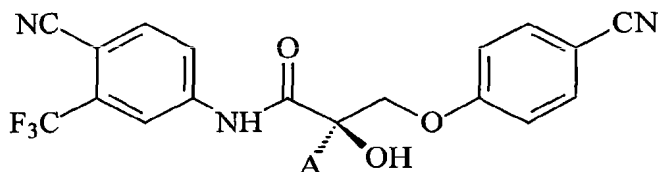


在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：

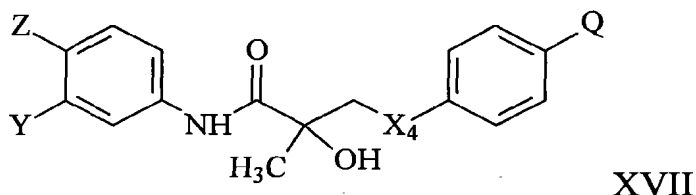


其中 A 如以上在化合物 XII 中所述。

在一个实施方案中, 本发明提供由式 XIII 的结构表示的化合物:



在一个实施方案中, 本发明提供由式 XVII 的结构表示的化合物:



其中

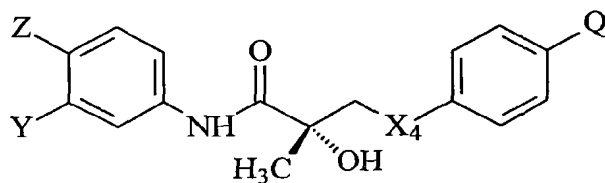
X_4 是 $S(O)[=CHCH_2N(CH_3)_2]$ 、 $C(OH)[CH_2CH_2N(CH_3)_2]$ 、 $C[=CHCH_2N(CH_3)_2]$ 、 $PO(C_{1-4} \text{ 烷基})$ 、 $N[CH_2CH_2N(CH_3)_2]$ 、 $NO[CH_2CH_2N(CH_3)_2]$;

Q 是 H、CN、OH、 NO_2 、 CF_3 、卤化物、 C_{2-6} 烯基、 C_{2-6} 炔基、 $C(O)CH_2NH_2$ 、 $C(O)NH(C_{1-4} \text{ 烷基})$ 、 $C(O)N(C_{1-4} \text{ 烷基})_2$ 、 $C(O)NH_2$ 、 $NH(C_{1-4} \text{ 烷基})$ 、 $NHC(O)NH(C_{1-4} \text{ 烷基})$ 、 $CH_2C(O)NH_2$ 、 $NHC(O)NH_2$ 、 $NHCO(C_{1-4} \text{ 烷基})$ 、 $NHSO_2(C_{1-4} \text{ 烷基})$ 、 $O-[CH_2CH_2CH(CH_3)_2]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 环烷基})]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 杂环烷基})]$ 或 $O-[CH_2CH_2N(CH_3)_2]$;

Z 是 H、CN、 NO_2 、 $NHC(O)CH_3$ 、 C_{1-4} 烷基、F、Cl、I 或 Br; 并且

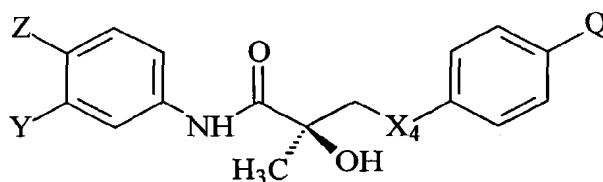
Y 是 H、 C_{1-4} 烷基、 CF_3 、CN、 NO_2 、F、Cl、I 或 Br。

在另一个实施方案中, 式 XVII 的化合物由以下结构表示:

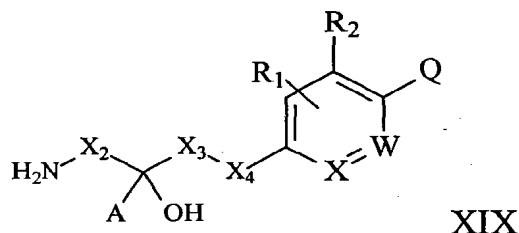


XVII

在另一个实施方案中，式 XVII 的化合物如以下结构表示：



在一个实施方案中，本发明提供由式 XIX 的结构表示的化合物：



XIX

其中

X 是 C 或 N；W 是 C 或 N；

X₂ 是 C₁₋₄ 亚烷基、SO₂、C(O)、CH-[CH₂-(C₄₋₈ 环)]、CH(C₁₋₄ 烷基)、CH(NH₂)、CH(OH)、CH(C₁₋₄ 卤代烷基)、键；

X₃ 是 C₁₋₄ 亚烷基、NH、N、CH(OH)或键；

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂；

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br；

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NH₂SO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R₁ 是 H、OH、F、Cl、Br 或 I;

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

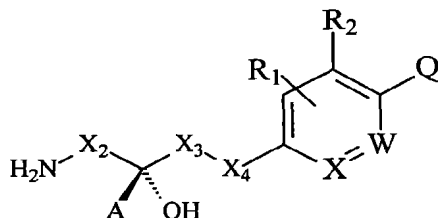
R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物;

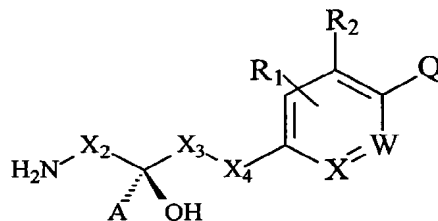
其中

如果 X 是 C, X₁ 是 NH, X₂ 是 C(O), R 是 OH, A 是烷基, X₃ 是键或 CH₂, 并且 X₄ 是键或 CH₂, R₁ 和 R₂ 是 H, 那么 Q 不是 H 或卤素。

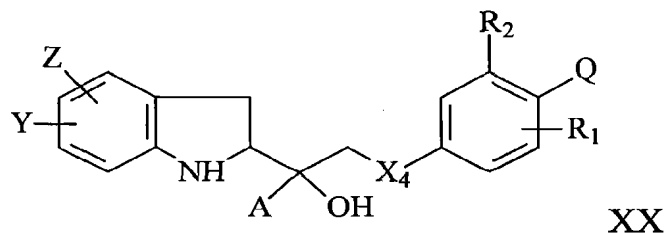
在另一个实施方案中, 式 XIX 的化合物由以下结构表示:



在另一个实施方案中, 式 XIX 的化合物由以下结构表示:



在一个实施方案中, 本发明提供由式 XX 的结构表示的化合物:



其中

X_4 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂；

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br；

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHCO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂]；

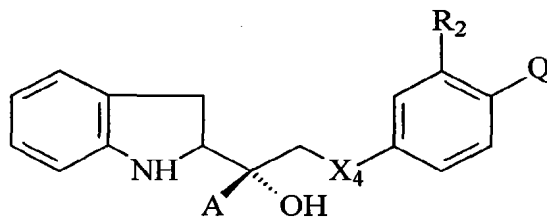
R₁ 是 H、OH、F、Cl、Br 或 I；

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基；

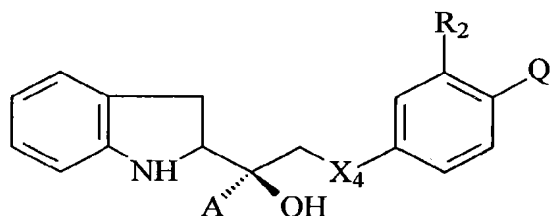
R' 是 NH₂、OH 或 CH₃；并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

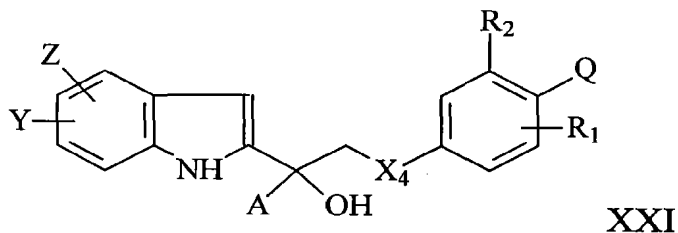
在另一个实施方案中，式 I 的化合物由以下结构表示：



或在另一个实施方案中,

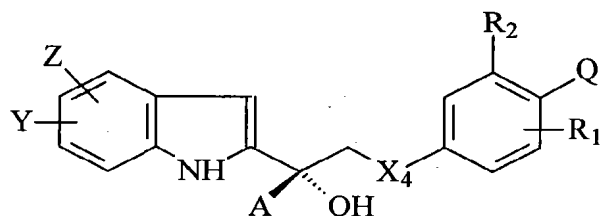


在一个实施方案中, 本发明提供由式 XXI 的结构表示的化合物:

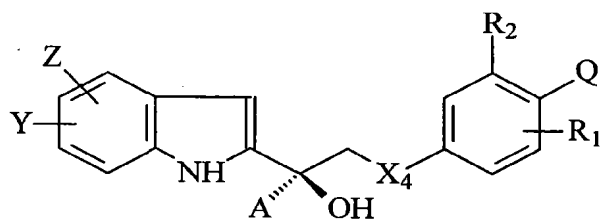


其中 A、Z、Y、X₄、Q、R₁ 和 R₂ 如在化合物 XX 中所述。

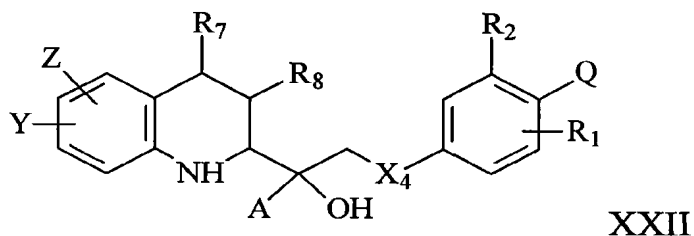
在另一个实施方案中, 式 XXI 的化合物由以下结构表示:



或在另一个实施方案中,

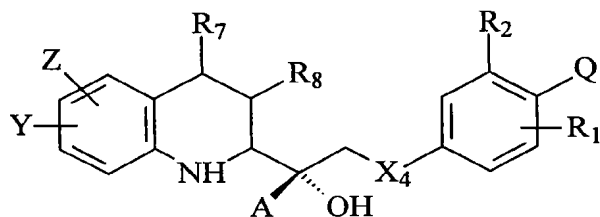


在一个实施方案中, 本发明提供由式 XXII 的结构表示的化合物:

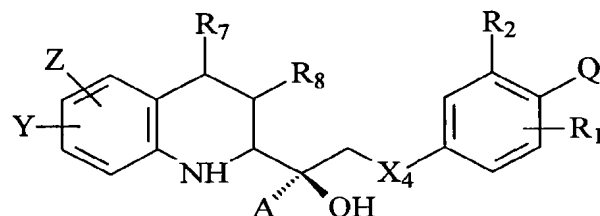


其中 A、Z、Y、X₄、Q、R₁ 和 R₂ 如在化合物 XX 中所述, R₇ 是 H 或氧代, R₈ 是 H 或=CH₂。

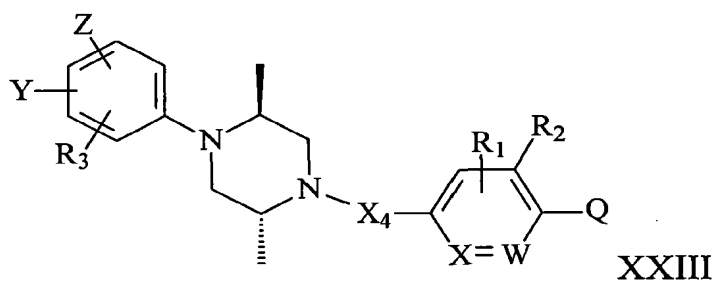
在另一个实施方案中, 式 XXII 的化合物由以下结构表示:



或在另一个实施方案中,



在一个实施方案中, 本发明提供由式 XXIII 的结构表示的化合物:



其中

X 是 C 或 N; W 是 C 或 N;

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、CF₃、NO₂、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R₁ 是 H、OH、F、Cl、Br 或 I;

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基

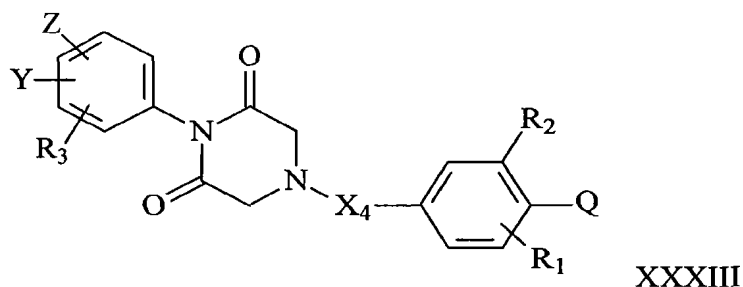
或 $\text{CH}=\text{CH}-\text{O}$ -对氰基苯基;

R_3 是 H 、 C_{1-4} 烷基、卤化物、 CN 或 NO_2 ;

R' 是 NH_2 、 OH 或 CH_3 ; 并且

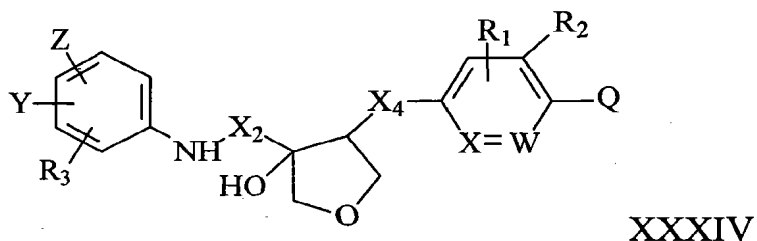
R_6 是 CN 、 NO_2 、 $\text{NHC}(\text{O})\text{CH}_3$ 或卤化物。

在一个实施方案中, 本发明提供由式 XXXIII 的结构表示的化合物:



其中 Z 、 Y 、 X_4 、 Q 、 R_1 和 R_3 如在化合物 XXIII 中所述。

在一个实施方案中, 本发明提供由式 XXXIV 的结构表示的化合物:



其中

X 是 C 或 N ; W 是 C 或 N ;

X_2 是 C_{1-4} 亚烷基、 SO_2 、 $\text{C}(\text{O})$ 、 $\text{CH}[\text{CH}_2-(\text{C}_{4-8} \text{ 环})]$ 、 $\text{CH}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{CH}(\text{NH}_2)$ 、 $\text{CH}(\text{OH})$ 、 $\text{CH}(\text{C}_{1-4} \text{ 卤代烷基})$ 、键;

X_4 是 O 、 S 、 SO 、 $\text{C}(\text{O})$ 、 $\text{S}(\text{O})[\text{=CHCH}_2\text{N}(\text{CH}_3)_2]$ 、 SO_2 、 NH 、 NHR' 、 NO 、 C_{1-4} 亚烷基、 $\text{C}(\text{OH})[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{C}[\text{=CHCH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{PO}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{N}[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$ 、 $\text{NO}[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]$ 或键;

Z 是 H 、 CN 、 NO_2 、 $\text{NHC}(\text{O})\text{CH}_3$ 、 C_{1-4} 烷基、 F 、 Cl 、 I 或 Br ;

Y 是 H 、 C_{1-4} 烷基、 CF_3 、 NO_2 、 CN 、 F 、 Cl 、 I 或 Br ;

Q 是 H 、 CN 、 OH 、 NO_2 、 CF_3 、卤化物、 C_{2-6} 烯基、 C_{2-6} 炔基、 $\text{C}(\text{O})\text{CH}_2\text{NH}_2$ 、 $\text{C}(\text{O})\text{NH}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{C}(\text{O})\text{N}(\text{C}_{1-4} \text{ 烷基})_2$ 、 $\text{C}(\text{O})\text{NH}_2$ 、 $\text{NH}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{NHC}(\text{O})\text{NH}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{CH}_2\text{C}(\text{O})\text{NH}_2$ 、 $\text{NHC}(\text{O})\text{NH}_2$ 、 $\text{NHCO}(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{NHSO}_2(\text{C}_{1-4} \text{ 烷基})$ 、 $\text{O}[\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2]$ 、 $\text{O}[\text{CH}_2\text{CH}_2(\text{C}_{4-8} \text{ 环烷基})]$ 、

O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

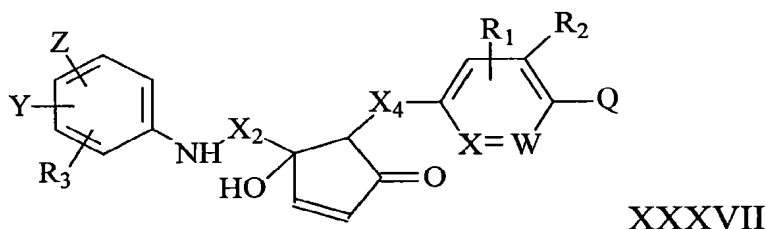
R₁ 是 H、OH、F、Cl、Br 或 I;

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

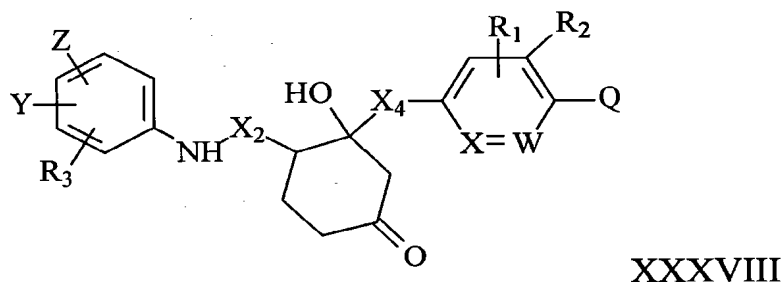
在一个实施方案中, 本发明提供由式 XXXVII 的结构表示的化合物:



其中

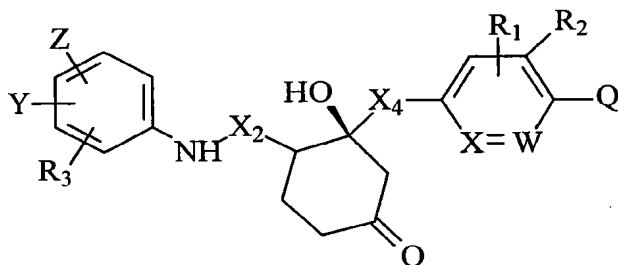
X、X₂、X₄、Z、Y、Q、R₁ 和 R₃ 如以上在化合物 XXXIV 中所述。

在一个实施方案中, 本发明提供由式 XXXVIII 的结构表示的化合物:

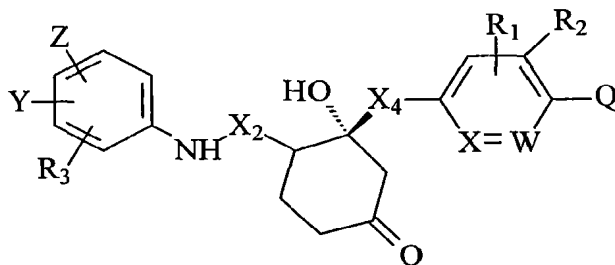


其中 X、X₂、X₄、Z、Y、Q、R₁ 和 R₃ 如以上在化合物 XXXIV 中所述。

在另一个实施方案中, 式 XXXVIII 的化合物由以下结构表示:



或在另一个实施方案中,



在另一个实施方案中, 化合物 XXXVIII 的 X_4 是 O。在另一个实施方案中, 化合物 XXXVIII 的 X_2 是 C(O)。在另一个实施方案中, 化合物 XXXVIII 的 X_2 是 CH_2 。在另一个实施方案中, 化合物 XXXVIII 的 Q 是 CN。在另一个实施方案中, 化合物 XXXVIII 的 Z 是 CN, 并且 Y 是 CF_3 。

在一个实施方案中, 本发明提供式 I 的化合物, 其中 P 是式 II, X_1 和 X_5 与 X_1 和 X_5 所连接的 X_2 一起形成饱和的或未饱和的、取代的或未取代的 5-或 6-元环;

其中

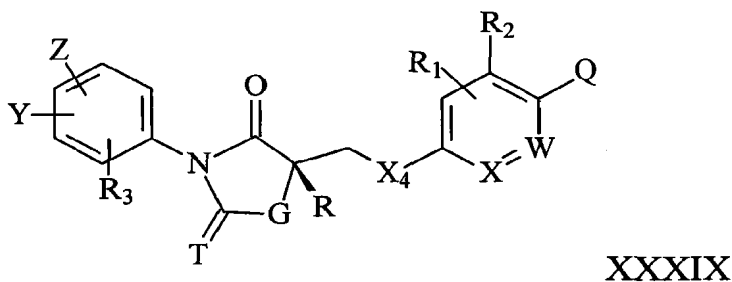
如果 P 是式 II, X 是 C, X_3 是 CH_2 , X_4 是 O 或 NH, R_1 、 R_2 和 R_3 是 H, 并且 X_5 和 X_1 形成 5 元环噁唑烷-2-酮, 那么 Q 不是卤素或 H;

或者

如果 P 是式 II, R_3 是 H, X 和 W 是 C, X_1 和 X_5 与 X_1 和 X_5 所连接的 X_2 一起形成噁唑烷二酮, R 是烷基, X_3 是 CH_2 , 并且 X_4 是 O、NH、S、 SO_2 或 CH_2 , 那么 Q 不是卤化物。

在另一个实施方案中, 所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是吡咯烷、哌啶、吗啉、琥珀酰亚胺、噁唑烷、噁唑烷二酮或噁唑烷酮。

在一个实施方案中, 本发明提供由式 XXXIX 的结构表示的化合物:



其中:

X 是 C 或 N; W 是 C 或 N;

G 是 O、NH、NC₁₋₄ 烷基、NC₁₋₄ 酰基、S、CHC₁₋₄ 烷基、CHC₁₋₄ 酰基、C(C₁₋₄ 酰基)₂、C(C₁₋₄ 烷基)₂ 或(CH₂)_n, 其中 n 是 1-3;

T 是 S 或 O;

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、CF₃、NO₂、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R 是 H、OH、C₁₋₄ 烷基、CF₃、CH₂OH、O(C₁₋₄ 烷基)或 O(C₁₋₄ 酰基);

R₁ 是 H、OH、F、Cl、Br 或 I;

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

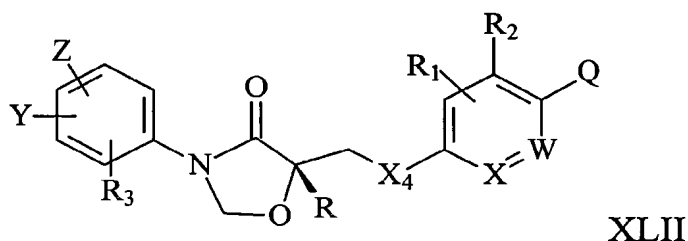
R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

其中

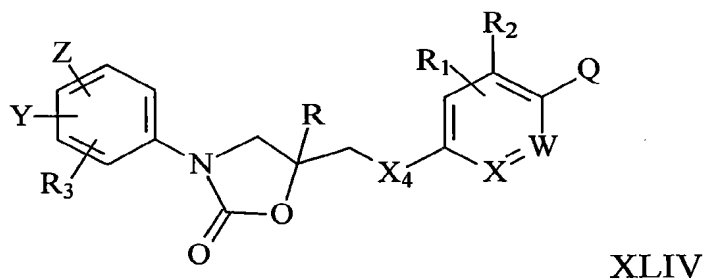
如果 R₃ 是 H, X 和 W 是 C, G 是 O, T 是 O, R 是烷基, X₃ 是 CH₂, 并且 X₄ 是 O、NH、S、SO₂ 或 CH₂, 那么 Q 不是卤化物。

在一个实施方案中, 本发明提供式 XLII 的化合物:



其中 X、X₄、Z、Y、Q、R₁、R₂ 和 R₃ 如以上在化合物 XXXIX 中所述。

在一个实施方案中，本发明提供式 XLIV 的化合物：



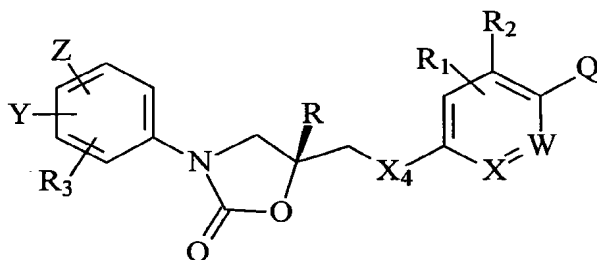
其中：

X、X₄、R、R₁、R₂、R₃、Z、Y 和 Q 如以上在化合物 XXXIX 中所述；

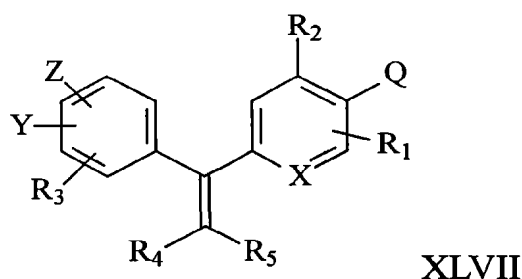
其中

如果 X 是 C，X₄ 是 O、NH 或 S，R₁、R₂ 和 R₃ 是 H 并且 R 是 H，那么 Q 不是卤素、H 或 CN。

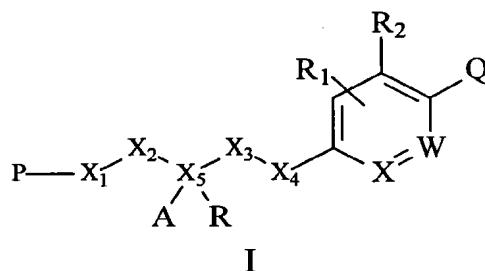
在另一个实施方案中，式 XLIV 的化合物由以下结构表示：



在一个实施方案中，本发明提供由式 XLVII 的结构表示的化合物：



在一个实施方案中，本发明提供由式 I 的结构表示的化合物：

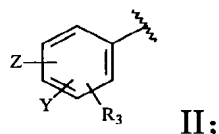


其中

X 是 C 或 N; W 是 C 或 N;

X_1 是 N、NH、N(C₁₋₄ 烷基)、NAc、NCOOH 或键; 或者 X_1 和 X_3 与 X_1 和 X_3 所连接的 X_2 和 X_5 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环; 或者 X_1 和 X_5 与 X_1 和 X_5 所连接的 X_2 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在;

P 是 H 或式 II:



X_2 是 C₁₋₄ 亚烷基、SO₂、C(O)、CH-[CH₂-(C₄₋₈ 环)]、CH(C₁₋₄ 烷基)、CH(NH₂)、CH(OH)、CH(C₁₋₄ 卤代烷基)、键; 或者 X_2 和 R_3 与 X_2 所连接的 X_1 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环; 或者 X_2 和 X_5 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在;

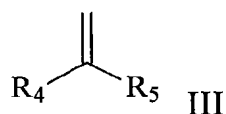
X_3 是 C₁₋₄ 亚烷基、NH、N、CH(OH)、键; 或者 X_1 和 X_3 与 X_1 和 X_3 所连接的 X_2 和 X_5 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环; 或者 X_3 和 X_5 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在; 或者 X_3 和 X_4 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环;

X_4 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键; 或者 X_4 和 X_5 与 X_4 和 X_5 所连接的 X_3 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在; 或者 X_3 和 X_4 一起形成双键或形成饱和的或不饱和的、取代的或未取代的 3 至 6 元环;

X_5 是碳或 X_5 和 X_1 与 X_1 和 X_5 所连接的 X_2 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在; 或者 X_5 和 X_2 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在; 或者 X_5 和 X_3 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在; 或

X_5 和 X_4 与 X_5 和 X_4 所连接的 X_3 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环, 且 A 不存在;

A 不存在, 或是 H、OH、SH、 NH_2 、 C_{1-4} 烷基、 CHF_2 、 CH_2F 、 CF_3 、CN、 CH_2OH 、 $CH_2O(C_{1-4}$ 烷基)、 $CH_2O(C_{1-4}$ 酰基)、 CH_2CN 、 CH_2N_3 、 CH_2NCS 、CHO、 $C(O)O(C_{1-4}$ 烷基)、 $CONHR'$ 、 $C(O)N(R')_2$ 、 $C(O)O(C_{1-4}$ 烷基)、 $C(O)R'$ 、 CH_2CF_3 、 CF_2CF_3 、 CH_2OR' $CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$; 或者 A 和 R 形成式 III 所表示的双键:



Z 是 H、CN、 NO_2 、 $NHC(O)CH_3$ 、 C_{1-4} 烷基、F、Cl、I 或 Br;

Y 是 H、 C_{1-4} 烷基、 CF_3 、 NO_2 、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、 NO_2 、卤化物、 CF_3 、 C_{2-6} 烯基、 C_{2-6} 炔基、 $C(O)CH_2NH_2$ 、 $C(O)NH(C_{1-4}$ 烷基)、 $C(O)N(C_{1-4}$ 烷基) $_2$ 、 $C(O)NH_2$ 、 $NH(C_{1-4}$ 烷基)、 $NHC(O)NH(C_{1-4}$ 烷基)、 $CH_2C(O)NH_2$ 、 $NHC(O)NH_2$ 、 $NHCO(C_{1-4}$ 烷基)、 $NHSO_2(C_{1-4}$ 烷基)、O- $[CH_2CH_2CH(CH_3)_2]$ 、O- $[CH_2CH_2(C_{4-8}$ 环烷基)]、O- $[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 O- $[CH_2CH_2N(CH_3)_2]$;

R 是 H、OH、 C_{1-4} 烷基、 CF_3 、 CH_2OH 、O(C_{1-4} 烷基)或 O(C_{1-4} 酰基);

R_1 是 H、OH、F、Cl、Br 或 I;

R_2 是 H、由 R_6 取代的苄基、 $(CH_2)_2$ -O-对氰基苯基、 CH_2 -O-对氰基苯基或 $CH=CH$ -O-对氰基苯基;

R_3 是 H、 C_{1-4} 烷基、卤化物、CN、 NO_2 ; 或 R_3 和 X_2 以及与 R_3 相连的苯环和与 X_2 相连的 X_1 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环;

R' 是 NH_2 、OH 或 CH_3 ;

R_4 和 R_5 独立地是 H、 CH_3 、卤化物、OH、 C_{1-4} 烷基、 C_{1-6} 环烷基、卤代(C_{1-4} 烷基)、苯基、芳基、 C_{4-8} 杂环烷基或羟基(C_{1-4} 烷基);

R_6 是 CN、 NO_2 、 $NHC(O)CH_3$ 或卤化物;

其中

如果 P 是式 II, X 是 C, X_1 是 NH, X_2 是 C(O), X_3 是 CH_2 , R 是 OH 并且 A 是烷基或卤代烷基, 那么 X_4 是 $S(O)[=CHCH_2N(CH_3)_2]$ 、

$C(OH)[CH_2CH_2N(CH_3)_2]$ 、 $C[=CHCH_2N(CH_3)_2]$ 、 $N[CH_2CH_2N(CH_3)_2]$ 、 $P(O)(C_{1-4}$ 烷基)或 $N(O)[CH_2CH_2N(CH_3)_2]$;

或者

如果 P 是式 II, X 是 C, X_1 是 NH, X_2 是 C(O), X_3 是 CH_2 , R 是 OH 或 OAlk 并且 X_4 是 O、S、NH、S、SO、 SO_2 或亚烷基, 那么 A 是 CN、 CH_2OH 、 $CH_2O(C_{1-4}$ 烷基)、 $CH_2O(C_{1-4}$ 酰基)、 CH_2CN 、 CH_2N_3 、 CH_2NCS 、CHO、 $C(O)O(C_{1-4}$ 烷基)、CONHR'、 $C(O)N(R')_2$ 、 $C(O)O(C_{1-4}$ 烷基)、 $C(O)R'$ 、 $CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$;

或者

如果 P 是苯基, X 是 C, X_1 是 NH, X_2 是 C(O), R 是 OH 并且 A 是 COOH, X_3 是键, X_4 是 CH_2 , R_1 、 R_2 是 H, 那么 Q 不是 H。

或者

如果 P 是式 II, X 是 C, X_3 是 CH_2 , X_4 是 O 或 NH, R_1 、 R_2 和 R_3 是 H, 并且 X_5 和 X_1 形成 5 元环噁唑烷-2-酮, 那么 Q 不是卤素或 H;

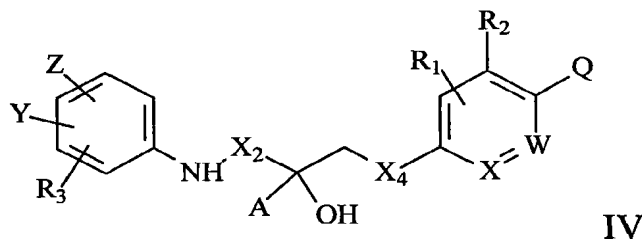
或者

如果 P 是 H, X 是 C, X_1 是 NH, X_2 是 C(O), R 是 OH, A 是烷基, X_3 是键或 CH_2 , 并且 X_4 是键或 CH_2 , R_1 和 R_2 是 H, 那么 Q 不是 H 或卤素;

或者

如果 P 是式 II, R_3 是 H, X 和 W 是 C, X_1 和 X_5 与 X_1 和 X_5 所连接的 X_2 一起形成噁唑烷二酮, R 是烷基, X_3 是 CH_2 , 并且 X_4 是 O、NH、S、 SO_2 或 CH_2 , 那么 Q 不是卤化物。

在一个实施方案中, 本发明提供由式 IV 的结构表示的化合物:



其中

X 是 C 或 N; W 是 C 或 N;

X_2 是 C_{1-4} 亚烷基、 SO_2 、 $CH-[CH_2-(C_{4-8}$ 环)]、 $CH(C_{1-4}$ 烷基)、 $CH(NH_2)$ 、 $CH(OH)$ 、 $CH(C_{1-4}$ 卤代烷基)、键;

X_4 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂；

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br；

Y 是 H、C₁₋₄ 烷基、CF₃、CN、NO₂、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂]；

R 是 H、OH、C₁₋₄ 烷基、CF₃、CH₂OH、O(C₁₋₄ 烷基)或 O(C₁₋₄ 酰基)；

R₁ 是 H、OH、F、Cl、Br 或 I；

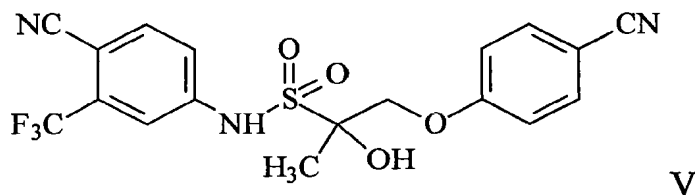
R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂；

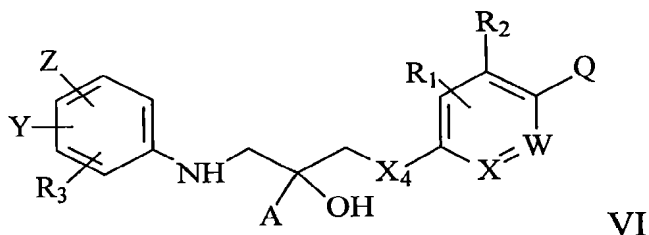
R' 是 NH₂、OH 或 CH₃；并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

在一个实施方案中，本发明提供由式 V 的结构表示的化合物：



在一个实施方案中，本发明提供由式 VI 的结构表示的化合物：



其中

X 是 C 或 N; W 是 C 或 N;

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、CN、NO₂、F、Cl、I 或 Br;

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHCO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R 是 H、OH、C₁₋₄ 烷基、CF₃、CH₂OH、O(C₁₋₄ 烷基)或 O(C₁₋₄ 酰基);

R₁ 是 H、OH、F、Cl、Br 或 I;

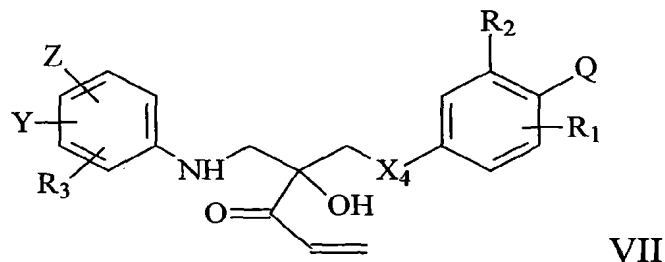
R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

R' 是 NH₂、OH 或 CH₃; 并且

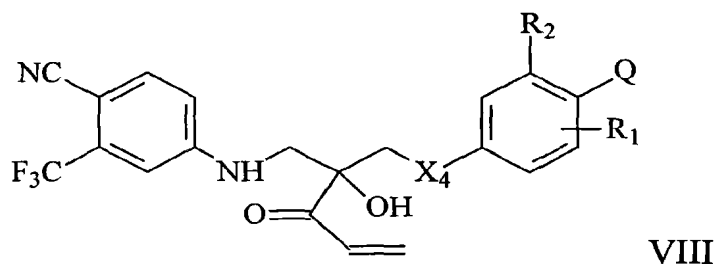
R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

在一个实施方案中, 本发明提供由式 VII 的结构表示的化合物:



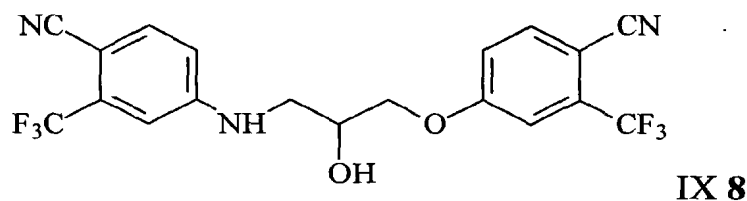
其中 Z、Y、R₁、R₂、R₃、Q 和 X₄ 如以上在化合物 VI 中所述。

在另一个实施方案中，本发明提供由式 VIII 的结构表示的化合物：

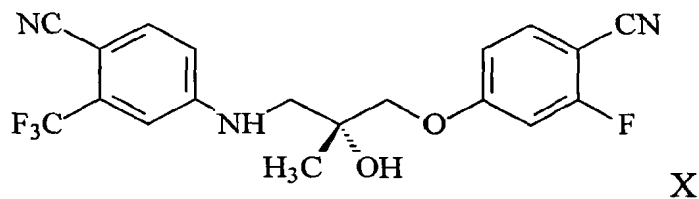


其中 R₁、R₂、Q 和 X₄ 如以上在化合物 VI 中所述。

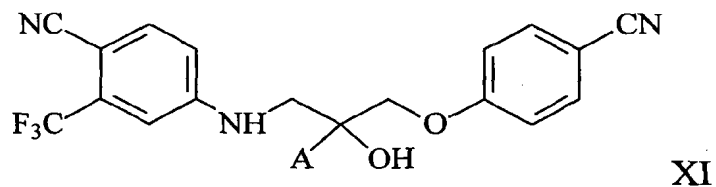
在一个实施方案中，本发明提供由式 IX 的结构表示的化合物：



在一个实施方案中，本发明提供由式 X 的结构表示的化合物：



在一个实施方案中，本发明提供由式 XI 的结构表示的化合物：

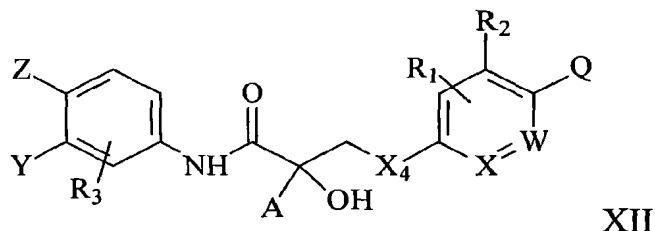


其中 A 如以上在化合物 VI 中所述。

在另一个实施方案中，化合物 XI 的 A 是 CH₂OH。在另一个实施方案中，化合物 XI 的 A 是 CH₂OMe。在另一个实施方案中，化合物 XI 的 A 是

CF₃。在另一个实施方案中, 化合物 XI 的 A 是 CH₃。在另一个实施方案中, 化合物 XI 的 A 是 CN。

在一个实施方案中, 本发明提供由式 XII 的结构表示的化合物:



其中

X 是 C 或 N; W 是 C 或 N;

X₄ 是 O、S、SO、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

A 是 CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、CN、NO₂、F、Cl、I 或 Br;

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHCO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R₁ 是 H、OH、F、Cl、Br 或 I;

R₂ 是 H、R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

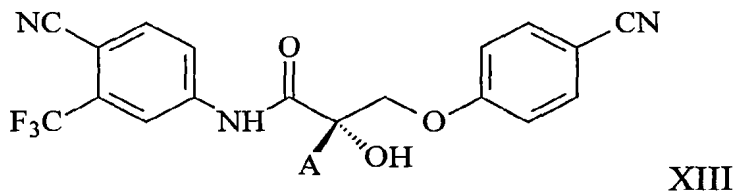
R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

在另一个实施方案中, 化合物 XII 的 X₄ 是 O。在另一个实施方案中, 化合物 XII 的 Q 是 CN, 并且 R₁ 和 R₂ 是 H。在另一个实施方案中, 化合物

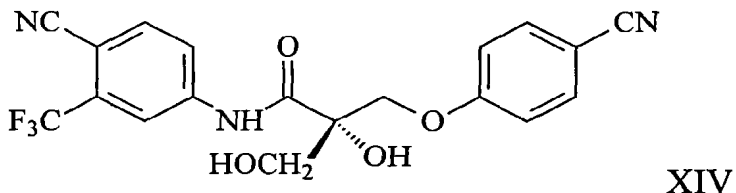
XII 的 Q 是 CN, Z 是 CN, Y 是 CF_3 , 并且 R_1 、 R_2 和 R_3 是 H。在另一个实施方案中, 化合物 XII 的 A 是 CH_2OH 。在另一个实施方案中, 化合物 XII 的 A 是 CN。

在一个实施方案中, 本发明提供由式 XIII 的结构表示的化合物:

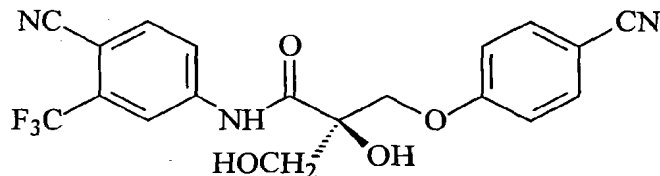


其中 A 如以上在化合物 XII 中所述。

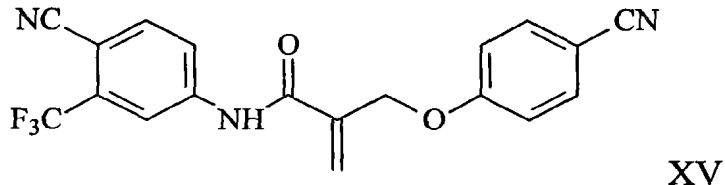
在一个实施方案中, 本发明提供由式 XIV 的结构表示的化合物:



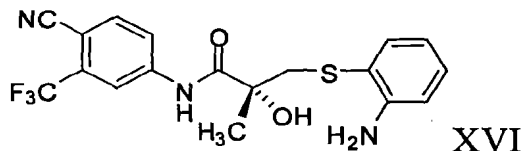
或在另一个实施方案中,



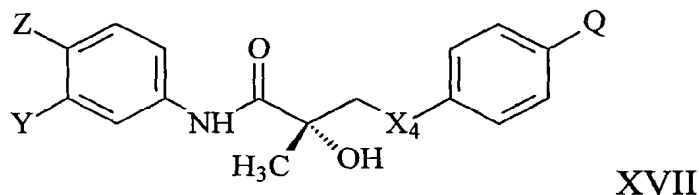
在一个实施方案中, 本发明提供由式 XVI 的结构表示的化合物:



在一个实施方案中, 本发明提供由式 XVII 的结构表示的化合物:



在一个实施方案中, 本发明提供由式 XVIII 的结构表示的化合物:



其中

X_4 是 $S(O)[=CHCH_2N(CH_3)_2]$ 、 $C(OH)[CH_2CH_2N(CH_3)_2]$ 、 $C[=CHCH_2N(CH_3)_2]$ 、 $PO(C_{1-4} \text{ 烷基})$ 、 $N[CH_2CH_2N(CH_3)_2]$ 、 $NO[CH_2CH_2N(CH_3)_2]$;

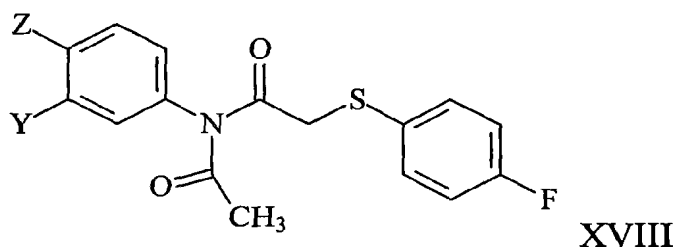
Q 是 H、CN、OH、 NO_2 、 CF_3 、卤化物、 C_{2-6} 烯基、 C_{2-6} 炔基、 $C(O)CH_2NH_2$ 、 $C(O)NH(C_{1-4} \text{ 烷基})$ 、 $C(O)N(C_{1-4} \text{ 烷基})_2$ 、 $C(O)NH_2$ 、 $NH(C_{1-4} \text{ 烷基})$ 、 $NHC(O)NH(C_{1-4} \text{ 烷基})$ 、 $CH_2C(O)NH_2$ 、 $NHC(O)NH_2$ 、 $NHCO(C_{1-4} \text{ 烷基})$ 、 $NHSO_2(C_{1-4} \text{ 烷基})$ 、 $O-[CH_2CH_2CH(CH_3)_2]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 环烷基})]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 杂环烷基})]$ 或 $O-[CH_2CH_2N(CH_3)_2]$;

Z 是 H、CN、 NO_2 、 $NHC(O)CH_3$ 、 C_{1-4} 烷基、F、Cl、I 或 Br; 并且

Y 是 H、 C_{1-4} 烷基、 CF_3 、CN、 NO_2 、F、Cl、I 或 Br。

在另一个实施方案中, 化合物 XVII 的 Q 是 F。在另一个实施方案中, 化合物 XVII 的 Q 是 CN。在另一个实施方案中, 化合物 XVII 的 Z 是 CN, 并且 Y 是 CF_3 。在另一个实施方案中, 化合物 XVII 的 Q 是 CN, Z 是 CN, 并且 Y 是 CF_3 。

在一个实施方案中, 本发明提供由式 XVIII 的结构表示的化合物:

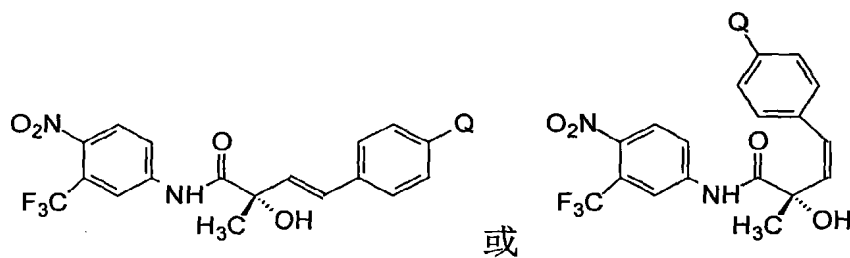


在一个实施方案中, 本发明提供由式 XIX 的结构表示的化合物:

在一个实施方案中, 本发明提供式 I 的化合物, 其中 X_3 和 X_4 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环。在另一个实施方案中, 所述 3-6 元环是环丙基、环丁基、环戊基、环己基、环丁烯基、环戊烯基、环己烯基、苯、哌啶、吡咯、四氢呋喃、吡咯烷、琥珀

酰亚胺、噁唑烷、噁唑烷二酮或噁唑烷酮。

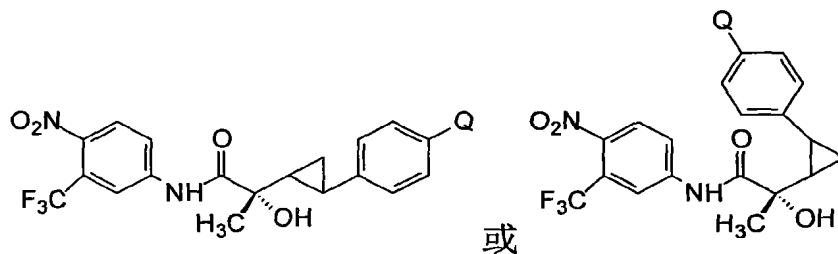
在另一个实施方案中，本发明提供由式 LIII 的结构表示的化合物：



LIII-反式

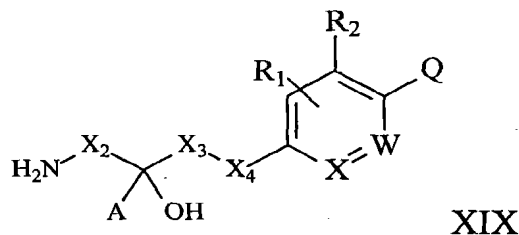
LIII-顺式

在另一个实施方案中，本发明提供由式 LIV 的结构表示的化合物：



LIV

LIV



XIX

其中

X 是 C 或 N；W 是 C 或 N；

X₂ 是 C₁₋₄ 亚烷基、SO₂、C(O)、CH-[CH₂-(C₄₋₈ 环)]、CH(C₁₋₄ 烷基)、CH(NH₂)、CH(OH)、CH(C₁₋₄ 卤代烷基)、键；

X₃ 是 C₁₋₄ 亚烷基、NH、N、CH(OH)或键；

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、

$C(O)O(C_{1-4} \text{ 烷基})$ 、 $CONHR'$ 、 $C(O)N(R')_2$ 、 $C(O)O(C_{1-4} \text{ 烷基})$ 、 $C(O)R'$ 、 CH_2CF_3 、 CF_2CF_3 、 $CH_2OR'CH_2C(O)CH=CH_2$ 或 $C(O)CH=CH_2$;

Z 是 H、CN、 NO_2 、 $NHC(O)CH_3$ 、 C_{1-4} 烷基、F、Cl、I 或 Br;

Y 是 H、 C_{1-4} 烷基、 CF_3 、 NO_2 、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、 NO_2 、 CF_3 、卤化物、 C_{2-6} 烯基、 C_{2-6} 炔基、 $C(O)CH_2NH_2$ 、 $C(O)NH(C_{1-4} \text{ 烷基})$ 、 $C(O)N(C_{1-4} \text{ 烷基})_2$ 、 $C(O)NH_2$ 、 $NH(C_{1-4} \text{ 烷基})$ 、 $NHC(O)NH(C_{1-4} \text{ 烷基})$ 、 $CH_2C(O)NH_2$ 、 $NHC(O)NH_2$ 、 $NHCO(C_{1-4} \text{ 烷基})$ 、 $NHSO_2(C_{1-4} \text{ 烷基})$ 、 $O-[CH_2CH_2CH(CH_3)_2]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 环烷基})]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 杂环烷基})]$ 或 $O-[CH_2CH_2N(CH_3)_2]$;

R_1 是 H、OH、F、Cl、Br 或 I;

R_2 是 H、由 R_6 取代的苄基、 $(CH_2)_2$ -O-对氰基苯基、 CH_2 -O-对氰基苯基或 $CH=CH$ -O-对氰基苯基;

R' 是 NH_2 、OH 或 CH_3 ; 并且

R_6 是 CN、 NO_2 、 $NHC(O)CH_3$ 或卤化物;

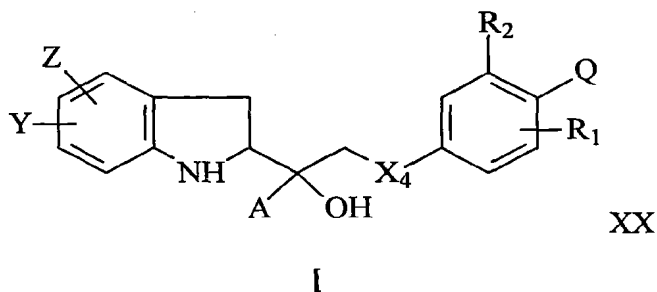
其中

如果 X 是 C, X_1 是 NH, X_2 是 $C(O)$, R 是 OH, A 是烷基, X_3 是键或 CH_2 , 并且 X_4 是键或 CH_2 , R_1 和 R_2 是 H, 那么 Q 不是 H 或卤素。

在另一个实施方案中, 化合物 XIX 的 X_2 是 CH_2 。在另一个实施方案中, 化合物 XIX 的 X_2 是 $C(O)$ 。在另一个实施方案中, 化合物 XIX 的 X_3 是 CH_2 。在另一个实施方案中, 化合物 XIX 的 X_4 是 O。

在一个实施方案中, 本发明提供式 I 的化合物, 其中 P 是式 II, X_2 和 X_3 与 X_1 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环。在另一个实施方案中, 所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是吡咯烷、吡咯、吗啉、哌啶-4-酮或哌啶。

在一个实施方案中, 本发明提供由式 XX 的结构表示的化合物:



其中

X_4 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

A 是 H、OH、SH、NH₂、C₁₋₄ 烷基、CHF₂、CH₂F、CF₃、CN、CH₂OH、CH₂O(C₁₋₄ 烷基)、CH₂O(C₁₋₄ 酰基)、CH₂CN、CH₂N₃、CH₂NCS、CHO、C(O)O(C₁₋₄ 烷基)、CONHR'、C(O)N(R')₂、C(O)O(C₁₋₄ 烷基)、C(O)R'、CH₂CF₃、CF₂CF₃、CH₂OR'CH₂C(O)CH=CH₂ 或 C(O)CH=CH₂；

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br；

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br；

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHCO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂]；

R₁ 是 H、OH、F、Cl、Br 或 I；

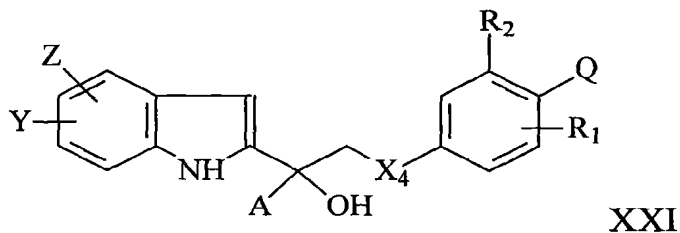
R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R' 是 NH₂、OH 或 CH₃；并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

在另一个实施方案中，化合物 XX 的 A 是 CH₃。在另一个实施方案中，化合物 XX 的 X₄ 是 O。在另一个实施方案中，化合物 XX 的 Q 是 CN。在另一个实施方案中，化合物 XX 的 Z 是 CN，并且 Y 是 CF₃。在另一个实施方案中，化合物 XX 的 Q 是 CN，Z 是 CN，并且 Y 是 CF₃。在另一个实施方案中，化合物 XX 的 A 是 CH₃，X₄ 是 O，Q 是 CN，Z 是 CN，R₁ 和 R₂ 是 H，并且 Y 是 CF₃。

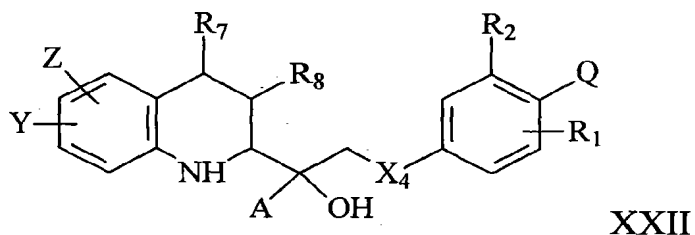
在一个实施方案中，本发明提供由式 XXI 的结构表示的化合物：



其中 A、Z、Y、X₄、Q、R₁ 和 R₂ 如在化合物 XXI 中所述。

在另一个实施方案中, 化合物 XXI 的 A 是 CH₃。在另一个实施方案中, 化合物 XXI 的 X₄ 是 O。在另一个实施方案中, 化合物 XXI 的 Q 是 CN。在另一个实施方案中, 化合物 XXI 的 Z 是 CN, 并且 Y 是 CF₃。在另一个实施方案中, 化合物 XXI 的 Q 是 CN, Z 是 CN, 并且 Y 是 CF₃。在另一个实施方案中, 化合物 XXI 的 A 是 CH₃, X₄ 是 O, Q 是 CN, Z 是 CN, R₁ 和 R₂ 是 H, 并且 Y 是 CF₃。

在一个实施方案中, 本发明提供由式 XXII 的结构表示的化合物:



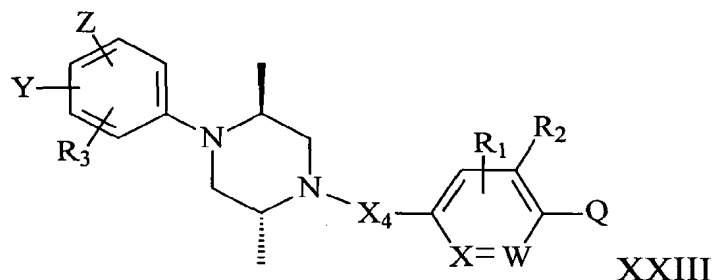
其中 A、Z、Y、X₄、Q、R₁ 和 R₂ 如在化合物 XX 中所述, R₇ 是 H 或氧代, R₈ 是 H 或=CH₂。

在另一个实施方案中, 化合物 XXII 的 A 是 CH₃。在另一个实施方案中, 化合物 XXII 的 X₄ 是 O。在另一个实施方案中, 化合物 XXII 的 R₇ 和 R₈ 是 H。在另一个实施方案中, 化合物 XXII 的 R₇ 是=CH₂, 并且 R₈ 是氧代。在另一个实施方案中, 化合物 XXII 的 Q 是 CN。在另一个实施方案中, 化合物 XXII 的 Z 是 CN, 并且 Y 是 CF₃。在另一个实施方案中, 化合物 XXII 的 A 是 CH₃, X₄ 是 O, Z 是 CN, Q 是 CN, R₁ 和 R₂ 是 H, 并且 Y 是 CF₃。

在一个实施方案中, 本发明提供式 I 的化合物, 其中 P 是式 II, X₃ 和 X₁ 与 X₁ 和 X₃ 所连接的 X₂ 和 X₅ 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环。在另一个实施方案中, 所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是哌嗪、哌嗪-2,6-二酮、哌啶、吡咯烷、环己酮、

环己烷、环己烯、环戊酮、环戊烷、环戊烯、琥珀酰亚胺、噁唑烷、噁唑烷二酮或噁唑烷酮。

在一个实施方案中, 本发明提供由式 XXIII 的结构表示的化合物:



其中

X 是 C 或 N; W 是 C 或 N;

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、CF₃、NO₂、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHCO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R₁ 是 H、OH、F、Cl、Br 或 I;

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

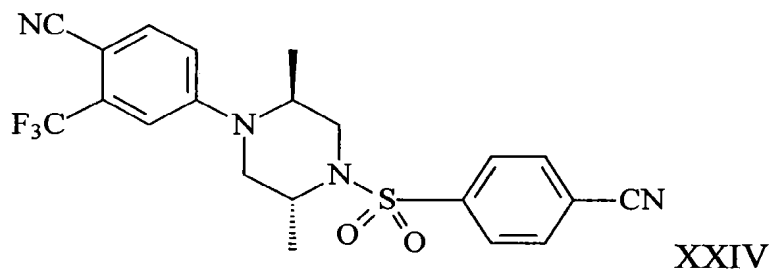
R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

R' 是 NH₂、OH 或 CH₃; 并且

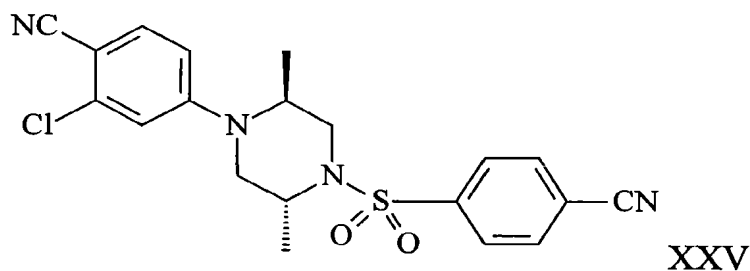
R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

在另一个实施方案中, 化合物 XXIII 的 X₄ 是 O。在另一个实施方案中, 化合物 XXIII 的 Q 是 CN。在另一个实施方案中, 化合物 XXIII 的 Z 是 CN, 并且 Y 是 CF₃。在另一个实施方案中, 化合物 XXIII 的 X₄ 是 O, Z 是 CN, Q 是 CN, R₁、R₂ 和 R₃ 是 H, 并且 Y 是 CF₃。

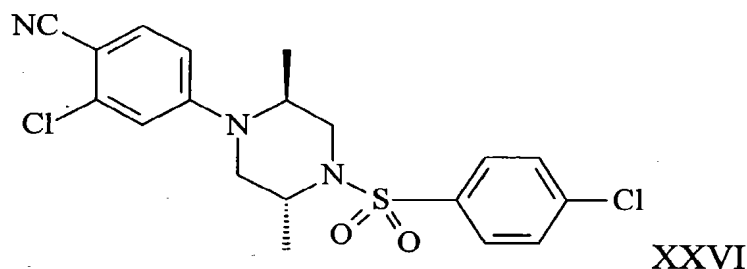
在另一个实施方案中, 本发明提供由式 XXIV 的结构表示的化合物:



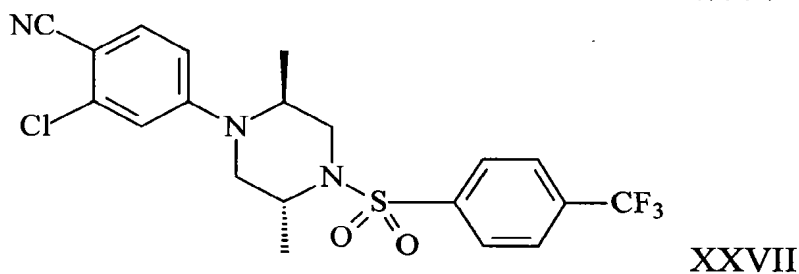
在另一个实施方案中, 本发明提供由式 XXV 的结构表示的化合物:



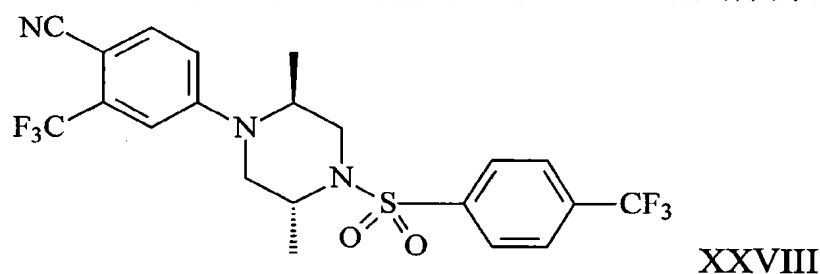
在另一个实施方案中, 本发明提供由式 XXVI 的结构表示的化合物:



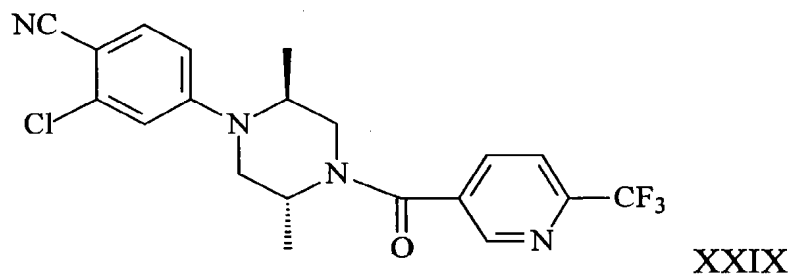
在另一个实施方案中, 本发明提供由式 XXVII 的结构表示的化合物:



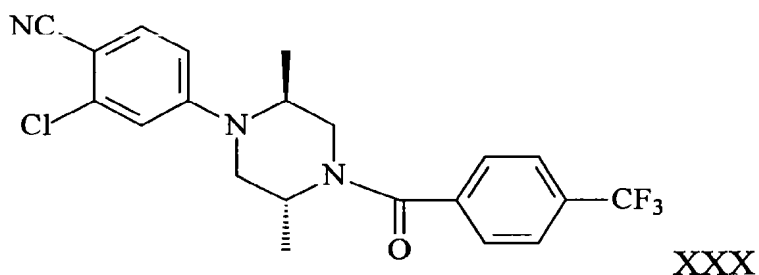
在另一个实施方案中, 本发明提供由式 XXVIII 的结构表示的化合物:



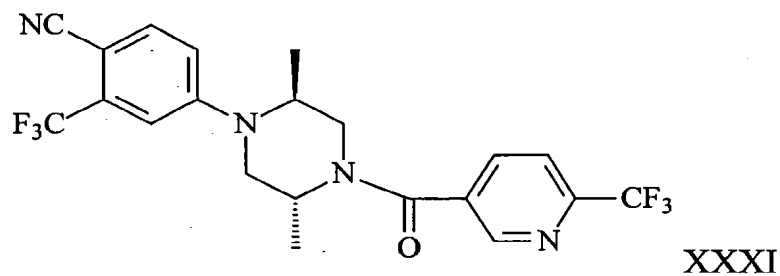
在另一个实施方案中, 本发明提供由式 XXIX 的结构表示的化合物:



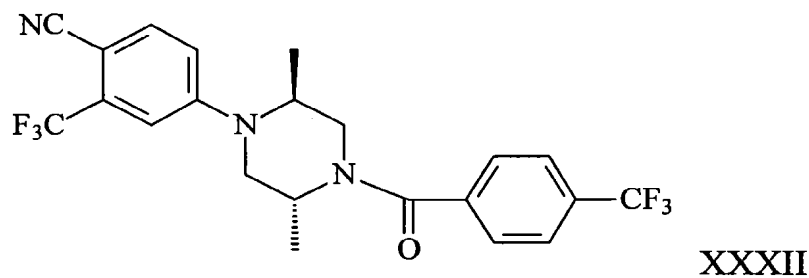
在另一个实施方案中，本发明提供由式 XXX 的结构表示的化合物：



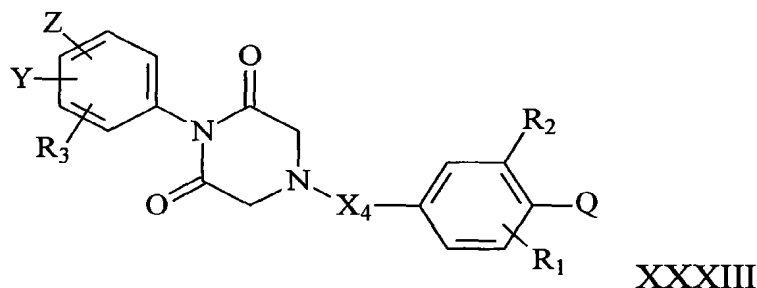
在另一个实施方案中，本发明提供由式 XXXI 的结构表示的化合物：



在另一个实施方案中，本发明提供由式 XXXII 的结构表示的化合物：



在一个实施方案中，本发明提供由式 XXXIII 的结构表示的化合物：

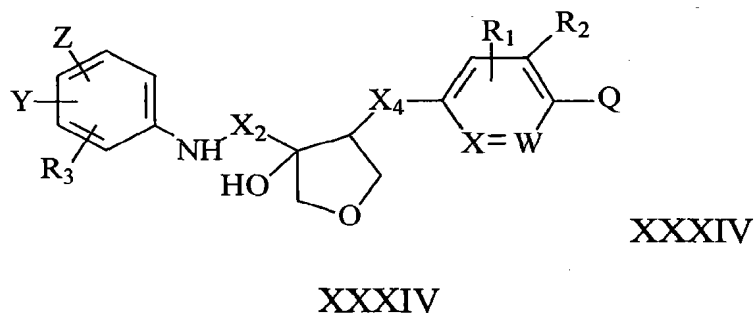


其中 Z、Y、X₄、Q、R₁、R₂ 和 R₃ 如在化合物 XXIII 中所述。

在另一个实施方案中，化合物 XXXIII 的 X₄ 是 O。在另一个实施方案中，化合物 XXXIII 的 Q 是 CN。在另一个实施方案中，化合物 XXXIII 的 Z 是 CN，并且 Y 是 CF₃。在另一个实施方案中，化合物 XXXIII 的 X₄ 是 O，Z 是 CN，Q 是 CN，R₁、R₂ 和 R₃ 是 H，并且 Y 是 CF₃。

在一个实施方案中，本发明提供式 I 的化合物，其中 P 是式 II，X₃ 和 X₅ 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环。在另一个实施方案中，所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是四氢呋喃、吡咯烷、哌啶、环己酮、环己烷、环己烯、环己烯酮、环戊酮、环戊烯酮、环戊烷、环戊烯、琥珀酰亚胺、噁唑烷、噁唑烷二酮或噁唑烷酮。

在一个实施方案中，本发明提供由式 XXXIV 的结构表示的化合物：



其中

X 是 C 或 N；W 是 C 或 N；

X₂ 是 C₁₋₄ 亚烷基、SO₂、C(O)、CH-[CH₂-(C₄₋₈ 环)]、CH(C₁₋₄ 烷基)、CH(NH₂)、CH(OH)、CH(C₁₋₄ 卤代烷基)、键；

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键；

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br；

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、NO₂、CF₃、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NHSO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R₁ 是 H、OH、F、Cl、Br 或 I;

R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

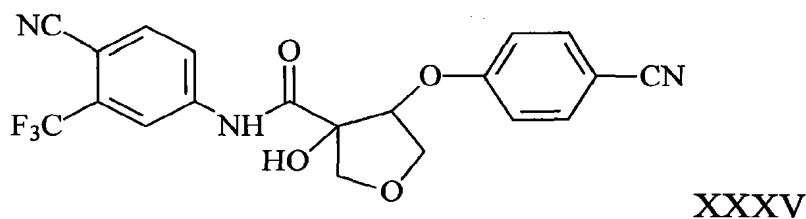
R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

R' 是 NH₂、OH 或 CH₃; 和

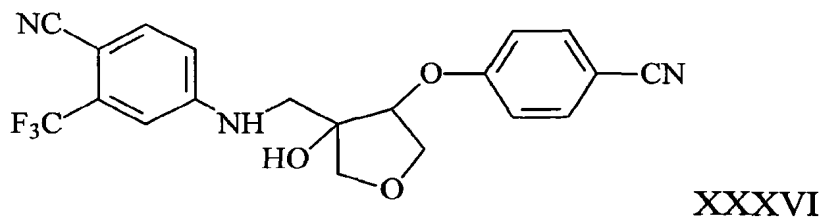
R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

在另一个实施方案中, 化合物 XXXIV 的 X₄ 是 O。在另一个实施方案中, 化合物 XXXIV 的 Q 是 CN。在另一个实施方案中, 化合物 XXXIV 的 X₂ 是 CH₂。在另一个实施方案中, 化合物 XXXIV 的 X₂ 是 C(O)。在另一个实施方案中, 化合物 XXXIV 的 Z 是 CN, 并且 Y 是 CF₃。在另一个实施方案中, 化合物 XXXIV 的 X₄ 是 O, Z 是 CN, Q 是 CN, R₁、R₂ 和 R₃ 是 H, 并且 Y 是 CF₃。

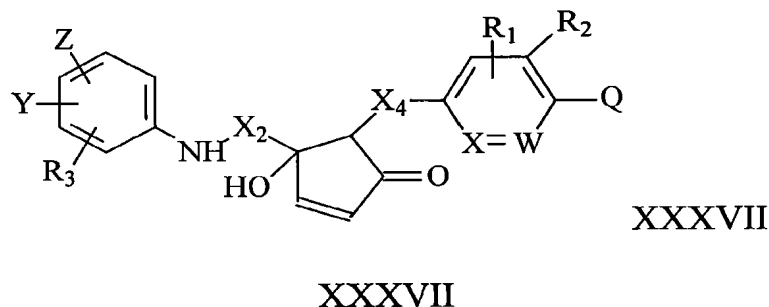
在另一个实施方案中, 本发明提供式 XXXV 的化合物:



在另一个实施方案中, 本发明提供式 XXXVI 的化合物:



在一个实施方案中, 本发明提供由式 XXXVII 的结构表示的化合物:

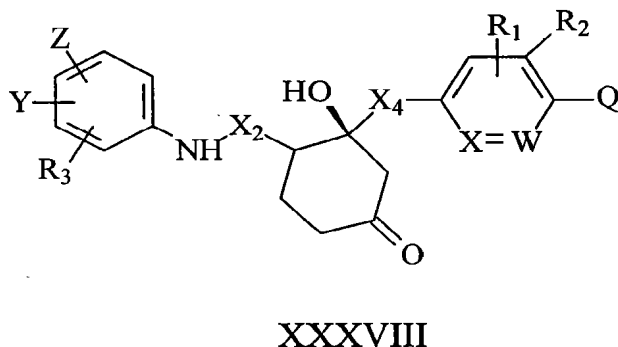


其中

X、X₂、X₄、Z、Y、Q、R₁、R₂和R₃如以上在化合物 XXXIV 中所述。

在另一个实施方案中，化合物 XXXVII 的 X₄ 是 O。在另一个实施方案中，化合物 XXXVII 的 X₂ 是 C(O)。在另一个实施方案中，化合物 XXXVII 的 X₂ 是 CH₂。在另一个实施方案中，化合物 XXXVII 的 Q 是 CN。在另一个实施方案中，化合物 XXXVII 的 Z 是 CN，并且 Y 是 CF₃。

在一个实施方案中，本发明提供由式 XXXVIII 的结构表示的化合物：



其中 X、X₂、X₄、Z、Y、Q、R₁、R₂和R₃如以上在化合物 XXXIV 中所述。

在另一个实施方案中，化合物 XXXVIII 的 X₄ 是 O。在另一个实施方案中，化合物 XXXVIII 的 X₂ 是 C(O)。在另一个实施方案中，化合物 XXXVIII 的 X₂ 是 CH₂。在另一个实施方案中，化合物 XXXVIII 的 Q 是 CN。在另一个实施方案中，化合物 XXXVIII 的 Z 是 CN，并且 Y 是 CF₃。

在一个实施方案中，本发明提供式 I 的化合物，其中 P 是式 II，X₁和 X₅与 X₁和 X₅所连接的 X₂一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；

其中

如果 P 是式 II, X 是 C, X_3 是 CH_2 , X_4 是 O 或 NH, R_1 、 R_2 和 R_3 是 H, 并且 X_5 和 X_1 形成 5 元环噁唑烷-2-酮, 那么 Q 不是卤素或 H。

在一个实施方案中, 本发明提供式 I 的化合物, 其中 P 是式 II, X_1 和 X_5 与 X_1 和 X_5 所连接的 X_2 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环;

其中

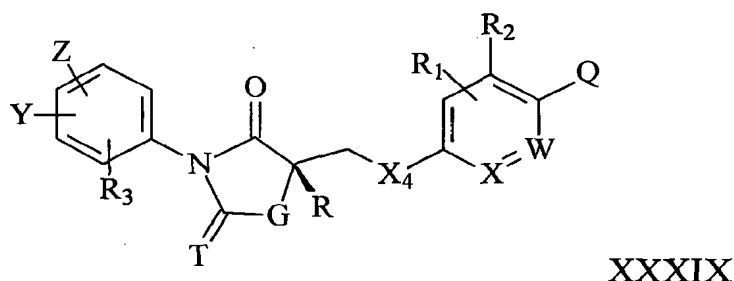
如果 P 是式 II, X 是 C, X_3 是 CH_2 , X_4 是 O 或 NH, R_1 、 R_2 和 R_3 是 H, 并且 X_5 和 X_1 形成 5 元环噁唑烷-2-酮, 那么 Q 不是卤素或 H;

或者

如果 P 是式 II, R_3 是 H, X 和 W 是 C, X_1 和 X_5 与 X_1 和 X_5 所连接的 X_2 一起形成噁唑烷二酮, R 是烷基, X_3 是 CH_2 , 并且 X_4 是 O、NH、S、 SO_2 或 CH_2 , 那么 Q 不是卤化物。

在另一个实施方案中, 所述饱和的或不饱和的、取代的或未取代的 5-或 6-元环是吡咯烷、哌啶、吗啉、琥珀酰亚胺、噁唑烷、噁唑烷二酮或噁唑烷酮。

在一个实施方案中, 本发明提供由式 XXXIX 的结构表示的化合物:



其中:

X 是 C 或 N; W 是 C 或 N;

G 是 O、NH、 NC_{1-4} 烷基、 NC_{1-4} 酰基、S、 CHC_{1-4} 烷基、 CHC_{1-4} 酰基、 $C(C_{1-4} \text{ 酰基})_2$ 、 $C(C_{1-4} \text{ 烷基})_2$ 或 $(CH_2)_n$, 其中 n 是 1-3;

T 是 S 或 O;

X_4 是 O、S、SO、C(O)、 $S(O)[=CHCH_2N(CH_3)_2]$ 、 SO_2 、NH、 NHR' 、NO、 C_{1-4} 亚烷基、 $C(OH)[CH_2CH_2N(CH_3)_2]$ 、 $C[=CHCH_2N(CH_3)_2]$ 、 $PO(C_{1-4} \text{ 烷基})$ 、 $N[CH_2CH_2N(CH_3)_2]$ 、 $NO[CH_2CH_2N(CH_3)_2]$ 或键;

Z 是 H、CN、 NO_2 、 $NHC(O)CH_3$ 、 C_{1-4} 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、CF₃、NO₂、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、C(O)NH(C₁₋₄ 烷基)、C(O)N(C₁₋₄ 烷基)₂、C(O)NH₂、NH(C₁₋₄ 烷基)、NHC(O)NH(C₁₋₄ 烷基)、CH₂C(O)NH₂、NHC(O)NH₂、NHCO(C₁₋₄ 烷基)、NH₂SO₂(C₁₋₄ 烷基)、O-[CH₂CH₂CH(CH₃)₂]、O-[CH₂CH₂(C₄₋₈ 环烷基)]、O-[CH₂CH₂(C₄₋₈ 杂环烷基)]或 O-[CH₂CH₂N(CH₃)₂];

R 是 H、OH、C₁₋₄ 烷基、CF₃、CH₂OH、O(C₁₋₄ 烷基)或 O(C₁₋₄ 酰基);

R₁ 是 H、OH、F、Cl、Br 或 I;

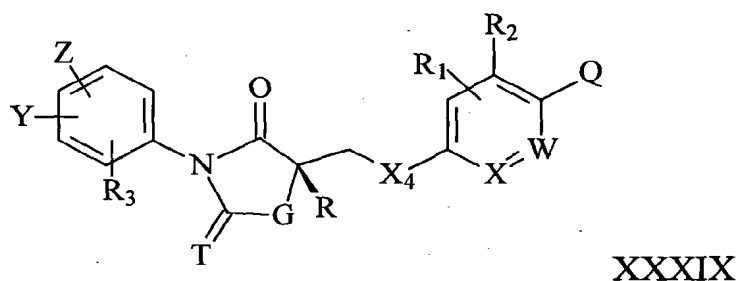
R₂ 是 H、由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、C₁₋₄ 烷基、卤化物、CN 或 NO₂;

R' 是 NH₂、OH 或 CH₃; 并且

R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

在一个实施方案中, 本发明提供由式 XXXIX 的结构表示的化合物:



其中:

X 是 C 或 N; W 是 C 或 N;

G 是 O、NH、NC₁₋₄ 烷基、NC₁₋₄ 酰基、S、CHC₁₋₄ 烷基、CHC₁₋₄ 酰基、C(C₁₋₄ 酰基)₂、C(C₁₋₄ 烷基)₂ 或 (CH₂)_n, 其中 n 是 1-3;

T 是 S 或 O;

X₄ 是 O、S、SO、C(O)、S(O)[=CHCH₂N(CH₃)₂]、SO₂、NH、NHR'、NO、C₁₋₄ 亚烷基、C(OH)[CH₂CH₂N(CH₃)₂]、C[=CHCH₂N(CH₃)₂]、PO(C₁₋₄ 烷基)、N[CH₂CH₂N(CH₃)₂]、NO[CH₂CH₂N(CH₃)₂]或键;

Z 是 H、CN、NO₂、NHC(O)CH₃、C₁₋₄ 烷基、F、Cl、I 或 Br;

Y 是 H、C₁₋₄ 烷基、CF₃、NO₂、CN、F、Cl、I 或 Br;

Q 是 H、CN、OH、CF₃、NO₂、卤化物、C₂₋₆ 烯基、C₂₋₆ 炔基、C(O)CH₂NH₂、

$C(O)NH(C_{1-4} \text{ 烷基})$ 、 $C(O)N(C_{1-4} \text{ 烷基})_2$ 、 $C(O)NH_2$ 、 $NH(C_{1-4} \text{ 烷基})$ 、 $NHC(O)NH(C_{1-4} \text{ 烷基})$ 、 $CH_2C(O)NH_2$ 、 $NHC(O)NH_2$ 、 $NHCO(C_{1-4} \text{ 烷基})$ 、 $NHSO_2(C_{1-4} \text{ 烷基})$ 、 $O-[CH_2CH_2CH(CH_3)_2]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 环烷基})]$ 、 $O-[CH_2CH_2(C_{4-8} \text{ 杂环烷基})]$ 或 $O-[CH_2CH_2N(CH_3)_2]$;

R 是 H、OH、 C_{1-4} 烷基、 CF_3 、 CH_2OH 、 $O(C_{1-4} \text{ 烷基})$ 或 $O(C_{1-4} \text{ 酰基})$;

R_1 是 H、OH、F、Cl、Br 或 I;

R_2 是 H、由 R_6 取代的苄基、 $(CH_2)_2$ -O-对氰基苯基、 CH_2 -O-对氰基苯基或 $CH=CH$ -O-对氰基苯基;

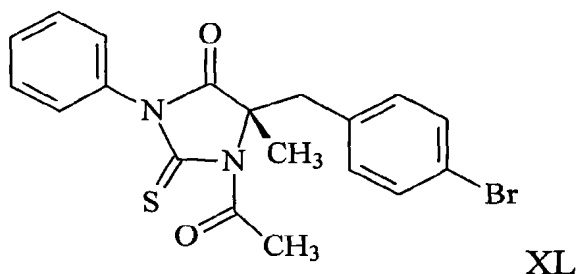
R_3 是 H、 C_{1-4} 烷基、卤化物、CN 或 NO_2 ;

R' 是 NH_2 、OH 或 CH_3 ; 并且

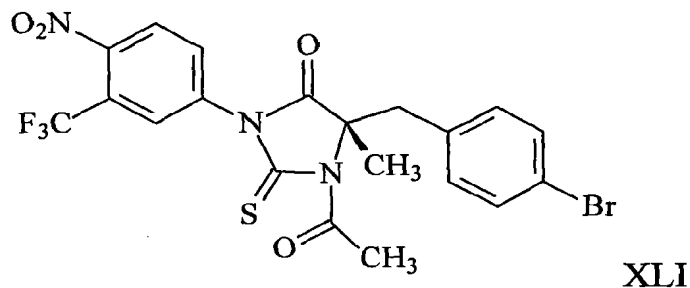
R_6 是 CN、 NO_2 、 $NHC(O)CH_3$ 或卤化物; 其中

如果 R_3 是 H, X 和 W 是 C, G 是 O, T 是 O, R 是烷基, X_3 是 CH_2 , 并且 X_4 是 O、NH、S、 SO_2 或 CH_2 , 那么 Q 不是卤化物。

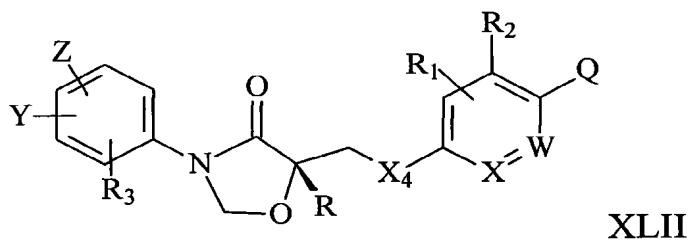
在一个实施方案中, 本发明提供式 XL 的化合物:



在一个实施方案中, 本发明提供式 XLI 的化合物:

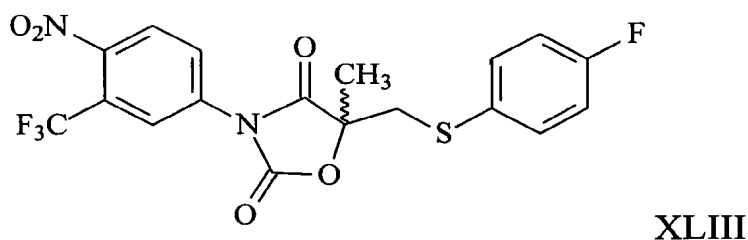


在一个实施方案中, 本发明提供式 XLII 的化合物:

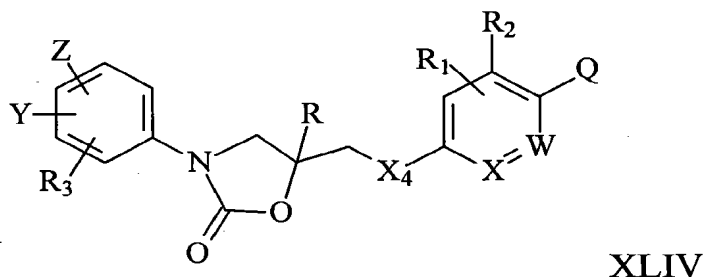


其中 X、X₄、Z、Y、Q、R₁、R₂ 和 R₃ 如以上在化合物 XXXIX 中所述。

在一个实施方案中，本发明提供式 XLIII 的化合物：



在一个实施方案中，本发明提供式 XLIV 的化合物：



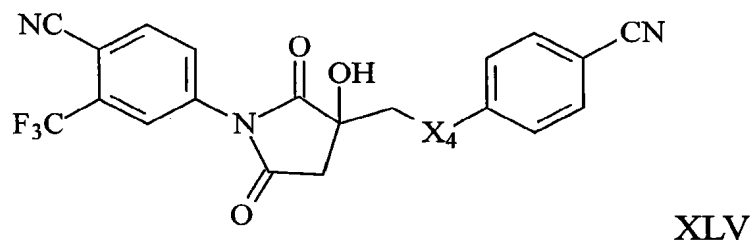
其中：

X、X₄、R、R₁、R₂、R₃、Z、Y 和 Q 如以上在化合物 XXXIXV 中所述；

其中

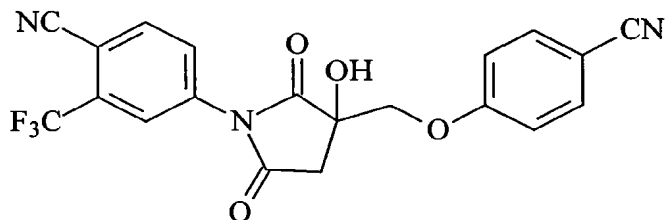
如果 X 是 C，X₄ 是 O、NH 或 S，R₁、R₂ 和 R₃ 是 H 并且 R 是 H，那么 Q 不是卤素、H 或 CN。

在一个实施方案中，本发明提供由式 XLV 的结构表示的化合物：



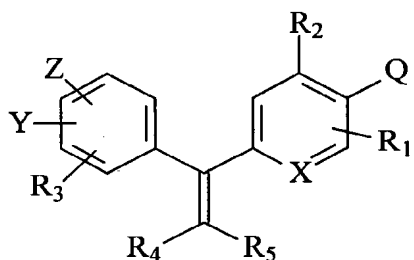
其中 X₄ 如以上在化合物 XXXIX 中所述。

在一个实施方案中，本发明提供由式 XLVI 的结构表示的化合物：



XLVI

在一个实施方案中，本发明提供由式 XLVII 的结构表示的化合物：



XLVII

I

其中

X 是 N 或 CH;

Z 是 H、CN、NO₂、NHC(O)CH₃、CH₃、F、Cl、I 或 Br;

Y 是 H、CH₃、CF₃、CN、F、Cl、I 或 Br;

Q 是 H、O-(CH₂)₂CH(CH₃)₂ 或 O-(CH₂)₂N(CH₃)₂;

R₁ 是 H、OH、F、Cl、Br 或 I;

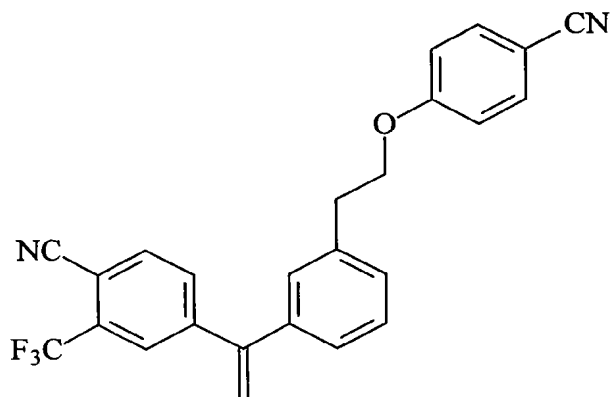
R₂ 是由 R₆ 取代的苄基、(CH₂)₂-O-对氰基苯基、CH₂-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R₃ 是 H、CH₃、卤化物、CN 或 NO₂;

R₄ 和 R₅ 独立地是 H、CH₃、卤化物、OH、C₁₋₄ 烷基、C₁₋₆ 环烷基、卤代(C₁₋₄ 烷基)、苯基、芳基、杂环或羟基-C₁₋₄ 烷基; 并且

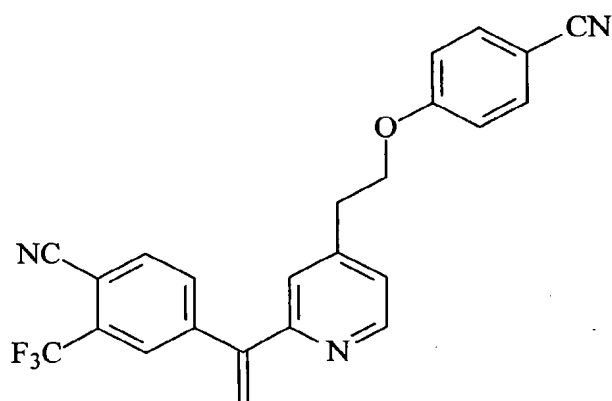
R₆ 是 CN、NO₂、NHC(O)CH₃ 或卤化物。

在一个实施方案中，本发明提供由式 XLVIII 的结构表示的化合物：



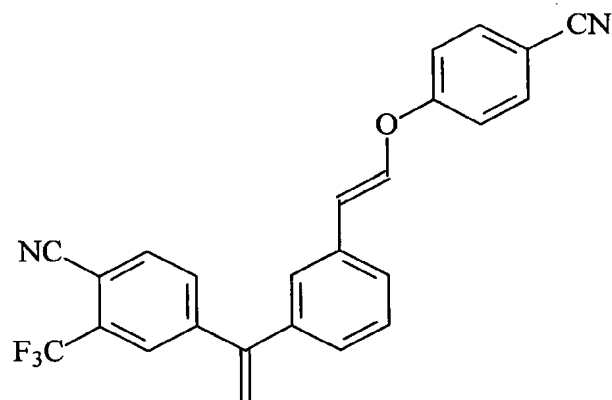
XLVIII

在一个实施方案中，本发明提供由式 XLIX 的结构表示的化合物：



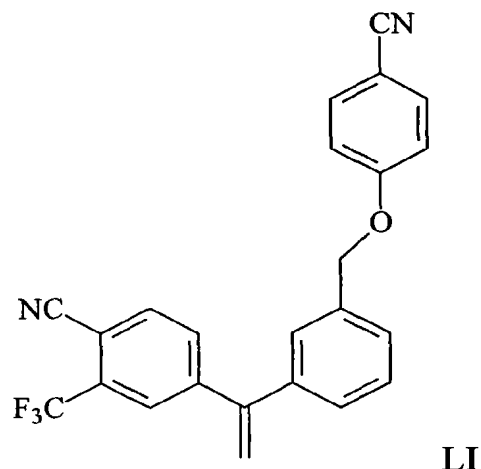
XLIX

在一个实施方案中，本发明提供由式 L 的结构表示的化合物：

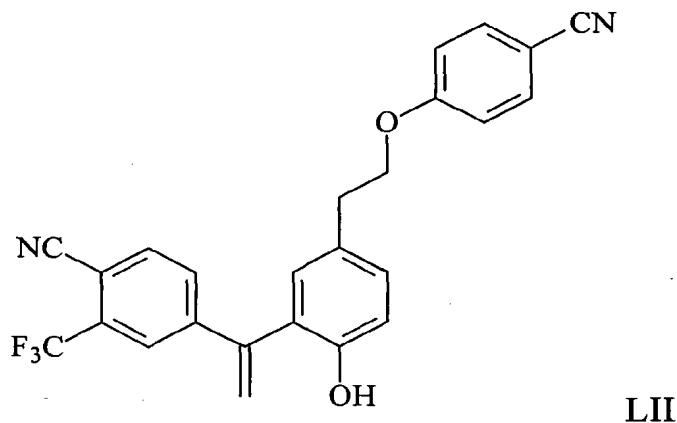


L

在一个实施方案中，本发明提供由式 LI 的结构表示的化合物：



在一个实施方案中，本发明提供由式 LII 的结构表示的化合物：



在另一个实施方案中，本发明提供式 (I)化合物的药学上可接受的盐。在另一个实施方案中，本发明提供式 (I)化合物的药品。在另一个实施方案中，本发明提供式 (I)化合物的水合物。在另一个实施方案中，本发明提供式 (I)化合物的 *N*-氧化物。在另一个实施方案中，本发明提供式 (I)化合物的多晶形物。在另一个实施方案中，本发明提供式 (I)化合物的晶体。在另一个实施方案中，本发明提供式 (I)化合物的任意的代谢产物、异构体、药学上可接受的盐、药品、多晶形物、晶体、不纯物 (impurity)、水合物、*N*-氧化物的组合。

在一些实施方案中，术语“异构体”包括但不限于光学异构体和类似物、结构异构体和类似物、构象异构体和类似物等。在一个实施方案中，术语“异构体”是指包括所述化合物的光学异构体。本领域的技术人员会理解，本发明的化合物含有至少一个手性中心。因此，在本发明的方法中所使用的化合物可以以光学活性形式或外消旋形式存在或被分离。一些化合物也可以

表现为同质多晶。应该理解，本发明包括任意外消旋形式、光学活性形式、多晶型形式或立体异构形式、或者它们的混合物，这些形式具有用于治疗本文所述的雄激素相关病症的性质。在一个实施方案中，所述化合物是纯(*R*)-异构体。在另一个实施方案中，所述化合物是纯(*S*)-异构体。在另一个实施方案中，所述 SARM 是所述(*R*)-异构体和(*S*)-异构体的混合物。在另一个实施方案中，所述 SARM 是包含等量的所述(*R*)-异构体和(*S*)-异构体外消旋混合物。如何制备光学活性形式是本领域公知的（例如，通过重结晶技术拆分所述外消旋形式、通过由光学活性原料合成、通过手性合成或通过使用手性固定相进行色谱分离）。

在另一个实施方案中，本发明的化合物是所述(*R*)-异构体和所述(*S*)-异构体的混合物。在另一个实施方案中，所述混合物包含 60% 的所述(*R*)-异构体和 40% 的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 40% 的所述(*R*)-异构体和 60% 的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 70% 的所述(*R*)-异构体和 30% 的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 30% 的所述(*R*)-异构体和 70% 的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 80% 的所述(*R*)-异构体和 20% 的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 20% 的所述(*R*)-异构体和 80% 的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 90% 的所述(*R*)-异构体和 10% 的所述(*S*)-异构体。在另一个实施方案中，所述混合物包含 10% 的所述(*R*)-异构体和 90% 的所述(*S*)-异构体。

在一个实施方案中，本发明的化合物是 SARM。在一个实施方案中，本发明的化合物与细胞核激素受体例如雌激素受体、孕酮受体或糖皮质激素受体结合。

本发明包括本发明化合物的“药学上可接受的盐”，其可以通过本发明的化合物与酸或碱反应产生。

合适的式 I 的胺的药学上可接受的盐可以由无机酸或有机酸制备。在一个实施方案中，胺的无机盐的例子是硫酸氢盐、硼酸盐、溴化物、氯化物、半硫酸盐（hemisulfates）、氢溴酸盐、盐酸盐、2-羟乙基磺酸盐（羟乙基磺酸盐（hydroxyethanesulfonates））、碘酸盐、碘化物、异硫代硫酸盐（isothionates）、硝酸盐、过硫酸盐、磷酸盐、硫酸盐、氨基磺酸盐、

磺胺酸盐、磺酸（烷基磺酸盐、芳基磺酸盐、卤代烷基磺酸盐、卤代芳基磺酸盐）、磺酸盐和硫氰酸盐。

在一个实施方案中，胺的有机盐的例子包括脂肪族类、脂环族类、芳香族类、芳香脂肪族（araliphatic）类、杂环族类、羧酸类和磺酸类有机酸，它们的例子是乙酸盐、精氨酸、天冬氨酸盐、抗坏血酸盐、己二酸盐、邻氨基苯甲酸盐、链烷羧酸盐、取代链烷羧酸盐、藻酸盐、苯磺酸盐、苯甲酸盐、硫酸氢盐、丁酸盐，碳酸氢盐、酒石酸氢盐、羧酸盐、柠檬酸盐、樟脑酸盐（camphorates）、樟脑磺酸盐、环己基氨基磺酸盐、环戊烷丙酸盐、依地酸钙盐、右旋樟脑磺酸（camsylates）、碳酸盐、克拉微酸钾、肉桂酸盐、二羧酸盐、二葡萄糖酸盐、十二烷基磺酸盐、二氢氯化物、癸酸盐、庚酸盐（enantuates）、乙磺酸盐、乙二胺四乙酸盐、乙二磺酸盐、丙酸酯十二烷基硫酸盐（estolates）、乙磺酸盐、富马酸盐、甲酸盐、氟化物、半乳糖醛酸盐、葡萄糖酸盐、谷氨酸盐、乙醇酸盐（glycolates）、葡萄糖酸盐、葡萄糖庚酸盐（glucoheptanoates）、甘油磷酸盐、葡庚糖酸盐、对羟乙酰氨基苯砷酸盐（glycollylarsanilates）、戊二酸盐、谷氨酸盐、庚酸盐、己酸盐、羟基马来酸盐、羟基羧酸、己基间苯二酚盐（hexylresorcinates）、羟苯酸盐、羟基萘甲酸盐、氢氟酸盐（hydrofluorate）、乳酸盐、乳糖酸盐（lactobionates）、月桂酸盐、苹果酸盐、马来酸盐、亚甲基双（ β -萘酚酸盐）（methylenebis(beta-oxynaphthoate))、丙二酸盐、扁桃酸盐、甲磺酸盐（mesylates）、甲磺酸盐（methane sulfonates）、甲基溴化物、甲基硝酸盐、甲基磺酸盐、马来酸单钾盐、粘酸盐、单羧酸盐、萘磺酸盐、2-萘磺酸盐、烟酸盐、萘磺酸盐、*N*-甲基葡萄糖胺、草酸酯、辛酸盐、油酸盐、双羟萘酸盐、苯乙酸盐、苦味酸盐、苯基苯甲酸盐、新戊酸盐、丙酸盐、邻苯二甲酸盐、果胶酸盐（pectinates）、苯丙酸盐、棕榈酸盐、泛酸盐、多半乳糖醛酸盐（polygalacturates）、丙酮酸盐、奎尼酸盐、水杨酸、琥珀酸盐、硬脂酸盐、磺胺酸盐、碱式醋酸盐、酒石酸、茶碱乙酸盐（theophyllineacetates）、对甲苯磺酸盐、三氟乙酸盐、对苯二酸盐、单宁酸盐、8-氯茶碱盐、三卤代乙酸盐、三乙基碘、三羧酸盐、十一酸盐或者戊酸盐。

在一个实施方案中，羧酸或酚的无机盐的例子包括铵；碱金属，包括

锂、钠、钾、铯；碱土金属，包括钙、镁、铝；锌、钡、氯或季铵。

在另一个实施方案中，羧酸或酚的有机盐的例子包括精氨酸；有机胺，包括脂肪族有机胺、脂环族有机胺、芳香族有机胺、苄星青霉素、叔丁胺、苄乙苄胺(*N*-苄基苄乙胺)、二环己基胺、二甲胺、二乙醇胺、乙醇胺、乙二胺、海巴胺(hydrabamine)、咪唑、赖氨酸、甲胺、三聚氰胺(meglamines)、*N*-甲基-D-葡萄糖胺、*N,N'*-二苄基乙二胺、烟酰胺、有机胺、鸟氨酸、吡啶、甲基吡啶(picolines)、哌嗪、普鲁卡因、三(羟甲基)甲胺、三乙胺、三乙醇胺、三甲胺、氨基丁三醇或尿素。

在一个实施方案中，所述盐可以通过常规方法形成，例如在其中所述盐不溶解的溶剂或介质或者例如水的溶剂中，使产物的游离碱或游离酸形式与一或多当量合适的酸或碱反应来形成，在真空中、通过冷冻干燥或通过将存在的盐的离子交换为另一种离子或合适的离子交换树脂来除去所述盐。

在一个实施方案中，本发明还包括本文所述化合物的氨基取代物的 *N*-氧化物。同样地，可以用脂肪族和芳香族的羧酸制备酚类化合物的酯，例如乙酸酯和苯甲酸酯。

本发明提供所述化合物的衍生物。在一个实施方案中，“衍生物”包括但不限于醚类衍生物、酸类衍生物、酰胺类衍生物、酯类衍生物等。在另一个实施方案中，本发明还包括所述化合物的水合物。

在一个实施方案中，“水合物”包括但不限于半水化合物、一水合物、二水合物、三水合物等。

在另一些实施方案中，本发明提供所述化合物的代谢产物。在一个实施方案中，“代谢产物”指通过代谢或代谢过程由另一种物质产生的任何物质。

在另一些实施方案中，本发明提供所述化合物的药品。在另一些实施方案中，术语“药品”指例如如本文所述的适合制药用途的组合物(药物组合物)。

在一个实施方案中，“烷基”指饱和脂肪族烃，包括直链、支链和环状烷基。在一个实施方案中，所述烷基具有 1-12 个碳原子。在另一个实施方案中，所述烷基具有 1-7 个碳原子。在另一个实施方案中，所述烷基具有

1-6 个碳原子。在另一个实施方案中，所述烷基具有 1-4 个碳原子。所述烷基可以是未取代的或由一个或多个选自以下的基团取代：卤素、羟基、烷氧羰基、酰胺基、烷基酰胺基、二烷基酰胺基、硝基、氨基、烷氨基、二烷基氨基、羧基、硫代(thio)和硫烷基。在一个实施方案中，所述烷基是 CH_3 。

在另一个实施方案中，“烯基”指不饱和的烃，包括具有一个或多个双键的直链、支链和环状基团。所述烯基可以具有一个双键、两个双键、三个双键等。烯基的例子是乙烯基、丙烯基、丁烯基、环己烯基等。在一个实施方案中，所述烯基具有 1-12 个碳原子。在另一个实施方案中，所述烯基具有 1-7 个碳原子。在另一个实施方案中，所述烯基具有 1-6 个碳原子。在另一个实施方案中，所述烯基具有 1-4 个碳原子。所述烯基可以是未取代的或由一个或多个选自以下的基团取代：卤素、羟基、烷氧羰基、酰胺基、烷基酰胺基、二烷基酰胺基、硝基、氨基、烷氨基、二烷基氨基、羧基、硫代和硫烷基。

“卤代烷基”指被一个或多个卤素原子取代的如上定义的烷基，在一个实施方案中被 F 取代，在另一个实施方案中被 Cl 取代，在另一个实施方案中被 Br 取代，在另一个实施方案中被 I 取代。

“芳基”指具有至少一个碳环芳族基团或杂环芳族基团的芳族基团，所述芳基可以是未取代的或由一个或多个选自以下的基团取代：卤素、羟基、烷氧羰基、酰胺基、烷基酰胺基、二烷基酰胺基、硝基、氨基、烷氨基、二烷基氨基、羧基、硫代和硫烷基。芳环的非限制性的例子是苯基、萘基、吡喃基、吡咯基、吡嗪基、嘧啶基、吡啶基、呋喃基、苯硫基、噻唑基、咪唑基、异噻唑基等。在一个实施方案中，所述芳基是 4-8 元环。在另一个实施方案中，所述芳基是 4-12 元环。在另一个实施方案中，所述芳基是 6 元环。在另一个实施方案中，所述芳基是 5 元环。在另一个实施方案中，所述芳基是 2-4 个环的稠环体系。

“羟基”指 OH 基。本领域的技术人员应该理解，当 T 是 OR 时，R 不是 OH。

在一个实施方案中，术语“卤素”在一个实施方案中指 F，在另一个实施方案中指 Cl，在另一个实施方案中指 Br，在另一个实施方案中指 I。在

一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明的外消旋化合物的分离包括结晶技术。在另一个实施方案中，所述结晶技术包括对映异构体的分异结晶(differential crystallization)。在另一个实施方案中，所述结晶技术包括非对映的盐(酒石酸盐或奎宁盐)的分异结晶。在另一个实施方案中，所述结晶技术包括手性辅助衍生物(薄荷醇酯等)的分异结晶。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明的外消旋化合物的分离包括使所述外消旋混合物与另一种手性基团反应，形成非对映的混合物，然后分离非对映异构体并除去其它手性基团以得到纯的对映异构体。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括手性合成。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括生物拆分。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括酶法拆分。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括使用手性固定相的色谱分离。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括亲和色谱法。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括毛细管电泳。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括形成手性碳原子的羟基与光学活性的酸(例如(-)-樟脑酸)的酯基，通过分级结晶或优选通过快速色谱法(flash-chromatography)分离由此获得的非对映异构体的酯，然后将各单独的酯水解为醇。

在另一个实施方案中，通过本发明的方法或通过本发明的外消旋混合物手性分离所获得的对映异构体的纯度和选择性可以通过 HPLC 分析来测定。

在另一个实施方案中，所述方法还包含将式(I)的化合物转化为其异构体、代谢产物、药学上可接受的盐、药品、*N*-氧化物、水合物或它们的任意组合的步骤。

应该理解，所述方法可以包括本文所述的任何实施方案，本领域的技

术人员会理解，所述实施方案会适于制备对应式的化合物。

在一些实施方案中，本文所述的化合物用于预防和治疗肌萎缩症、骨相关的病症和与糖尿病相关的病症。

在一些实施方案中，本文所述的化合物可单独地或作为组合物用于治疗雄性和雌性的各种激素相关的病症，例如性腺功能减退症、少肌症、勃起障碍、缺乏性欲、骨质疏松症和能育性（fertility）。在一些实施方案中，本文所述的化合物用于刺激或促进或恢复对多种过程的功能，这继而导致治疗本文所述的病症，尤其包括促进红细胞生成、骨发生、肌肉生长、葡萄糖摄取、胰岛素分泌，和/或预防脂质生成、凝血、胰岛素抵抗、动脉粥样硬化、破骨细胞活性等。

在一个实施方案中，本发明的方法利用所述化合物与受体接触或结合，并由此介导所述的效应。在一些实施方案中，所述受体是核受体，在一个实施方案中，所述核受体是雄激素受体，或者在另一个实施方案中是雌激素受体，或者在另一个实施方案中是孕酮受体，或者在另一个实施方案中是糖皮质激素受体。在一些实施方案中，所述多种效应可以作为与个体的多种受体结合的功能而同时发生。在一些实施方案中，本文所述的化合物的组织选择性效应提供对不同靶器官的同时作用。

药物组合物

在一些实施方案中，本发明提供使用的方法，所述方法包括给药含有所述化合物的组合物。如本文使用的，“药物组合物”指“治疗有效量”的活性成分（即式 I 的化合物），与药学上可接受的载体或稀释剂。如本文使用的，“治疗有效量”指对于给定的病症和给药方案提供疗效的量。

如本文使用的，术语“给药”指使个体与本发明的化合物接触。如本文使用的，给药可以在体外（即试管内）或体内（即活的有机体例如人类的细胞或组织）中进行。在一个实施方案中，本发明包括向个体给药本发明的化合物。

含有本发明化合物的药物组合物可以通过本领域技术人员已知的任何方法向个体给药，例如口服、肠胃外、血管内、癌旁、经粘膜、经皮、肌肉内、鼻内、静脉内、皮内、皮下、舌下、腹膜内、心室内、颅内、阴道内给药，通过吸入、经直肠、瘤内给药，或者通过其中重组病毒/组合物能被

递送至组织的任何方法（例如穿刺针（**needle**）或导管）给药。或者，对于向粘膜细胞施用、皮肤或眼睛施用，可能需要局部施用。另一种给药的方法是经吸入剂或气雾剂。

在一个实施方案中，所述药物组合物口服给药，因此它被配制成适合口服给药的形式，即作为固体或液体制剂。合适的固体口服制剂包括片剂、胶囊、丸剂、颗粒剂、小丸（**pellets**）、散剂等。合适的液体口服制剂包括溶液剂、混悬剂、分散剂、乳剂、油剂等。在本发明的一个实施方案中，所述 **SARM** 化合物被配制在胶囊中。根据该实施方案，本发明的组合物除含有本发明的化合物和惰性载体或稀释剂之外，还含有硬胶囊。

在一个实施方案中，所述微粒化的胶囊包含含有本发明化合物的颗粒，其中，本文使用的术语“微粒化”指粒径小于 100 微米的颗粒，或者在另一个实施方案中，指粒径小于 60 微米的颗粒，或者在另一个实施方案中，指粒径小于 36 微米的颗粒，或者在另一个实施方案中，指粒径小于 16 微米的颗粒，或者在另一个实施方案中，指粒径小于 10 微米的颗粒，或者在另一个实施方案中，指粒径小于 6 微米的颗粒。

而且，在另一个实施方案中，所述药物组合物通过静脉内、动脉内或肌内注射液体制剂来给药。合适的液体制剂包括溶液剂、混悬剂、分散剂、乳剂、油剂等。在一个实施方案中，所述药物组合物经静脉内给药，因此被配制成适合静脉内给药的形式。在另一个实施方案中，所述药物组合物经动脉内给药，因此被配制成适合动脉内给药的形式。在另一个实施方案中，所述药物组合物肌内给药，因此被配制成适合肌内给药的形式。

而且，在另一个实施方案中，所述药物组合物局部施用于身体表面，因此被配制成适合局部施用的形式。合适的局部制剂包括凝胶剂、软膏、乳剂、洗剂、滴剂等。对于局部施用，本发明的化合物或其生理上耐受的衍生物（例如盐、酯、*N*-氧化物等）被制成在具有或不具有药用载体的生理上可接受的稀释剂中的溶液剂、混悬剂或乳剂，并以这些形式施用。

而且，在另一个实施方案中，所述药物组合物作为栓剂（例如直肠栓剂或尿道栓剂）来给药。而且，在另一个实施方案中，所述药物组合物通过皮下埋植小丸来给药。在另一个实施方案中，所述小丸在一段时间内提供本文所述化合物的控制释放。在另一个实施方案中，所述药物组合物经

阴道给药。

在另一个实施方案中，活性化合物可以在小囊泡、特别是脂质体中递送(参见Langer, Science 249:1627-1633 (1990); Treat等人,于Liposomes in the Therapy of Infectious Disease and Cancer, Lopez- Berestein和Fidler (著者), Liss, New York, pp. 363-366 (1989); Lopez-Berestein, 出处同上, pp. 317-327; 一般地参见出处同上)。

如本文使用的，“药学上可接受的载体或稀释剂”是本领域技术人员熟知的。所述载体或稀释剂可以是用于固体制剂的固体载体或稀释剂、用于液体制剂的液体载体或稀释剂、或它们的混合物。

固体载体/稀释剂包括但不限于胶质、淀粉（例如玉米淀粉、预糊化淀粉（pregeletanized starch））、糖（例如乳糖、甘露醇、蔗糖、葡萄糖）、纤维素材料（例如微晶纤维素）、丙烯酸酯（例如聚甲基丙烯酸酯）、碳酸钙、氧化镁、滑石或它们的混合物。

在一个实施方案中，本发明的组合物可以包括本发明的化合物或其与一种或多种药学上可接受的赋形剂任意组合。

应该理解，本发明包括本文所述化合物（在一些实施方案中被称为“本发明的化合物”）的任何实施方案。

根据本发明的实施方案，合适的赋形剂和载体可以是固体或液体，其类型一般根据使用的给药类型来选择。脂质体也可以用于递送所述组合物。合适的固体载体的例子包括乳糖、蔗糖、明胶和琼脂。口服剂型可以含有合适的粘合剂、润滑剂、稀释剂、崩解剂、着色剂、调味剂、流动诱导剂（flow-inducing agent）和熔解剂。液体剂型可以含有例如合适的溶剂、防腐剂、乳化剂、助悬剂、稀释剂、甜味剂、增稠剂和熔解剂。肠胃外和静脉内形式还应该包含矿物质和其它材料以便使得它们与所选的注射或递药系统的类型相容。当然，也可以使用其它赋形剂。

对于液体制剂，药学上可接受的载体可以是含水的或非水溶液、悬浮液、乳液或油。非水性溶剂的例子是丙二醇、聚乙二醇和可注射的有机酯类例如油酸乙酯。含水载体包括水、醇/水溶液、环糊精、乳液或悬浮液，包括盐水和缓冲介质。油的例子是石油、动物油、植物油或合成来源的油，例如，花生油、大豆油、矿物油、橄榄油、向日葵油和鱼肝油。

肠胃外载体（用于皮下、静脉内、动脉内或肌内注射）包括氯化钠溶液、林格氏葡萄糖、葡萄糖和氯化钠、乳酸林格和固定油。静脉内载体包括流体和营养补充剂、电解质补充剂（例如基于林格氏葡萄糖的电解质补充剂）等。其例子是无菌液体，例如加入和未加入表面活性剂和其它药学上可接受的助剂的水和油。通常，水、盐水、葡萄糖水溶液和相关的糖溶液以及二醇例如丙二醇或聚乙二醇是优选的液体载体，特别是对于可注射溶液剂。油的例子是石油、动物油、植物油或合成来源的油，例如，花生油、大豆油、矿物油、橄榄油、向日葵油和鱼肝油。

而且，所述组合物还可以包含粘合剂（例如阿拉伯胶、玉米淀粉、明胶、卡波姆、乙基纤维素、瓜尔胶、羟丙基纤维素、羟丙基甲基纤维素、聚维酮），崩解剂（例如玉米淀粉、马铃薯淀粉、藻酸、二氧化硅、交联羧甲基纤维素钠（croscarmellose sodium）、交聚维酮、瓜尔胶、羟基乙酸淀粉钠），各种 pH 和离子强度的缓冲剂（例如 Tris-HCl、醋酸盐、磷酸盐），防止吸附到表面的添加剂例如白蛋白或明胶，洗涤剂（例如 Tween 20、Tween 80、Pluronic F68、胆汁酸盐），蛋白酶抑制剂，表面活性剂（例如十二烷基硫酸钠），渗透促进剂，增溶剂（例如克列莫佛（cremophor）、甘油、聚乙烯甘油（polyethylene glycerol）、苯扎氯铵、苯甲酸苄酯、环糊精、失水山梨糖醇（sobitan）酯、硬脂酸），抗氧化剂（即抗坏血酸、偏亚硫酸氢钠、丁基化羟基苯甲醚（butylated hydroxyanisole）），稳定剂（例如羟丙基纤维素、羟丙基甲基纤维素），增黏剂（例如卡波姆、胶体二氧化硅、乙基纤维素、瓜尔胶），甜味剂（例如天冬甜素、柠檬酸），防腐剂（例如 Thimerosal、苄醇、对羟基苯甲酸酯），着色剂，润滑剂（例如硬脂酸、硬脂酸镁、聚乙二醇、十二烷基硫酸钠），助流剂（例如胶体二氧化硅），增塑剂（例如邻苯二甲酸二乙酯、柠檬酸三乙酯），乳化剂（例如卡波姆、羟丙基纤维素、十二烷基硫酸钠），聚合物包衣（例如泊洛沙姆或泊洛沙胺（poloxamines））、包衣剂和成膜剂（例如乙基纤维素、丙烯酸酯、聚甲基丙烯酸酯）和/或辅剂。

在一个实施方案中，本文提供的药物组合物是控释组合物，即在该组合物中，本发明的化合物在给药后的一段时间内释放。控释或缓释组合物包括亲脂性贮库（depots）（例如脂肪酸、蜡、油）中的制剂。在另一个实施方案中，所述药物组合物是速释组合物，即在该组合物中全部量的化合

物在给药后立即释放。

在另一个实施方案中,所述药物组合物可以在控释系统中递送。例如,所述药剂可以使用静脉输注、可植入渗透泵、透皮贴剂、脂质体或其它给药方式给药。在一个实施方案中,可以使用泵(参见 Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald 等人, *Surgery* 88:607 (1980); Saudek 等人, *N. Engl. J. Med.* 321:674 (1989))。在另一个实施方案中,可以使用聚合物材料。在另一个实施方案中,可以将控释系统置于治疗靶(即脑)附近,因此仅需要全身剂量的一部分(参见例如 Goodson, 于 *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 116-138 (1984))。在 Langer 的一篇综述 (*Science* 249:1627-1633 (1990))中讨论了其它控释系统。

所述组合物也可以包括在聚合的化合物,例如聚乳酸、聚乙醇酸、水凝胶等的粉粒制剂之中或之上,或在脂质体、微乳、微胶粒、单层或多层小囊泡、血影或原生质球之上引入活性材料。这种组合物会影响物理状态、溶解性、稳定性、体内释放率和体内清除率。

本发明还包括包被聚合物(例如泊洛沙姆或泊洛沙胺)和与直接抗组织特异性受体、配体或抗原的抗体偶联或与组织特异性受体的配体偶联的化合物的微颗粒组合物。

本发明还包括通过水溶性聚合物,例如聚乙二醇、聚乙二醇和聚丙二醇的共聚物、羧甲基纤维素、葡聚糖、聚乙烯醇、聚乙烯吡咯烷酮或聚脯氨酸的共价连接而修饰的化合物。已知所述修饰的化合物在静脉注射后显示出比相应的未修饰化合物长得多的血液半衰期 (Abuchowski 等人, 1981; Newmark 等人, 1982; 和 Katre 等人, 1987)。这种修饰也可以增加所述化合物在水溶液中的溶解度、消除聚集、提高所述化合物的物理和化学稳定性,并大大降低所述化合物的免疫原性和反应性。因此,与未修饰的化合物相比,通过更低频率地或更小剂量地给药这种聚合物-化合物衍生物,可以实现期望的体内生物活性。

含有活性组分的药物组合物的制备在本领域中很好理解,例如通过混合、造粒或压片的方法。活性治疗成分经常与药学上可接受的并与所述活性成分相容的赋形剂混合。对于口服给药,本发明的化合物或它们的生理上耐受的衍生物例如盐、酯、*N*-氧化物等与为此目的惯用添加剂例如载体、

稳定剂或惰性稀释剂混合，并以常规方法转化为适合给药的形式，例如片剂、包衣片剂、硬或软胶囊、水溶液、醇溶液或油溶液剂。对于肠胃外给药，本发明的化合物或它们生理上耐受的衍生物例如盐、酯、*N*-氧化物等被转化为溶液剂、混悬剂或乳剂（如果需要，用为此目的的惯用的、合适的物质，例如增溶剂等）。

活性组分可以作为中性的药学上可接受的盐的形式被配制成组合物。药学上可接受的盐包括酸加成盐（由多肽或抗体分子的自由氨基形成），其由无机酸例如盐酸或磷酸、或有机酸例如乙酸、草酸、酒石酸、扁桃酸等形成。由自由羧基形成的盐也可以得自无机碱，例如氢氧化钠、氢氧化钾、氢氧化铵、氢氧化钙或氢氧化铁，以及有机碱，例如异丙胺、三甲胺、2-乙胺基乙醇、组氨酸、普鲁卡因等。

为了用于药物，所述化合物的盐是药学上可接受的盐。但是，其它盐也可用于本发明化合物或其药学上可接受的盐的制备中。合适的本发明化合物的药学上可接受的盐包括酸加成盐，其可以通过例如将本发明化合物的溶液与药学上可接受的酸的溶液混合来形成，所述酸例如盐酸、硫酸、甲磺酸、富马酸、马来酸、琥珀酸、乙酸、苯甲酸、草酸、柠檬酸、酒石酸、碳酸或磷酸。

在一个实施方案中，本发明提供包含本发明的化合物的药物组合物。在一个实施方案中，这种组合物用于口服睾酮替代疗法。

在一个实施方案中，本发明还提供包含两种或多种本发明的化合物或它们的多晶型物、异构体、水合物、盐、*N*-氧化物等的组合物。本发明还涉及组合物和药物组合物，所述药物组合物单独包含本发明的化合物，或者包含本发明的化合物与孕激素或雌激素的组合，或者在另一个实施方案中，包含本发明的化合物与化疗化合物、成骨化合物或生肌化合物、或其它适合本文所述的应用的药剂的组合。在一个实施方案中，本发明的组合物包含合适的载体、稀释剂或盐。

在一个实施方案中，本发明的方法可以包括以各种剂量给药本发明的式 I 化合物。在一个实施方案中，以 0.1-200 mg/天的剂量给药本发明的化合物。在一个实施方案中以 0.1-10 mg 的剂量、或在另一个实施方案中以 0.1-26 mg 的剂量、或在另一个实施方案中以 0.1-60 mg 的剂量、或在另一

个实施方案中以 0.3-16 mg 的剂量，或在另一个实施方案中以 0.3-30 mg 的剂量、或在另一个实施方案中以 0.6-26 mg 的剂量、或在另一个实施方案中以 0.6-60 mg 的剂量、或在另一个实施方案中以 0.76-16 mg 的剂量、或在另一个实施方案中以 0.76-60 mg 的剂量、或在另一个实施方案中以 1-6 mg 的剂量、或在另一个实施方案中以 1-20 mg 的剂量、或在另一个实施方案中以 3-16 mg 的剂量、或在另一个实施方案中以 30-60 mg 的剂量、或在另一个实施方案中以 30-76 mg 的剂量、或在另一个实施方案中以 100-2000 mg 的剂量给药本发明的化合物。

在一个实施方案中，本发明的方法可以包括以各种剂量给药本发明的式 I 化合物。在一个实施方案中，以 1 mg 的剂量给药本发明的化合物。在另一个实施方案中，以 3 mg、6 mg、10 mg、16 mg、20 mg、26 mg、30 mg、36 mg、40 mg、46 mg、50 mg、56 mg、60 mg、66 mg、70 mg、76 mg、80 mg、86 mg、90 mg、96 mg 或 100 mg 的剂量给药本发明的化合物。

在一个实施方案中，本发明提供使用方法，该方法包括给药包含以下各项的药物组合物：a) 本文所述的任何实施方案的化合物；和 b) 药学上可接受的载体或稀释剂；所述组合物应理解为包含本文所述化合物的类似物、异构体、代谢产物、衍生物、药学上可接受的盐、*N*-氧化物、水合物或它们的任意组合，并且可以包含式 I 的化合物。

在一些实施方案中，本发明提供药物组合物的使用方法，该药物组合物包含：a) 本文所述的任何实施方案的化合物，包括其类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、*N*-氧化物、水合物或它们的任意组合；b) 药学上可接受的载体或稀释剂；c) 助流剂；和 d) 润滑剂。

在另一个实施方案中，本发明提供药物组合物的使用方法，该药物组合物包含：a) 本文所述的任何实施方案的化合物，包括其类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、*N*-氧化物、水合物或它们的任意组合；b) 乳糖一水合物；c) 微晶纤维素；d) 硬脂酸镁；和 e) 胶体二氧化硅。

在一些实施方案中，本发明的方法利用包含本发明的化合物的组合物，所述方法的优点是所述化合物是雄激素受体的非类固醇类配体并在体内显示出合成代谢活性。根据这个方面，这种化合物不伴有严重的副作用，提

供方便的给药方式和较低的生产成本，并且口服可生物利用，与其它不希望的一类固醇受体没有显著的交叉反应性，并且可能具有很长的生物半衰期。

当施用于哺乳动物，特别是人时，预计医师会确定最适合个体的实际剂量和治疗时间，并且可以根据具体个体的年龄、体重和应答而变化。

在一个实施方案中，用于给药的组合物可以是无菌溶液剂，或者在其它实施方案中，可以是含水或非水溶液、混悬剂或乳剂。在一个实施方案中，所述组合物可以包含丙二醇、聚乙二醇、可注射的有机酯例如油酸乙酯、或环糊精。在另一个实施方案中，组合物也可以包含湿润剂、乳化剂和/或分散剂。在另一个实施方案中，所述组合物也可以包含无菌水或任何其它无菌可注射介质。

在一个实施方案中，本发明提供用于如本文所述的本发明的任何方法的化合物和组合物（包括本文所述的任意实施方案）。在一个实施方案中，使用本发明的化合物或含有它的组合物会有利于抑制、压制、增强或促进个体体内所期望的应答，这一点本领域的技术人员会理解。在另一个实施方案中，所述组合物还可以含有其它活性成分，其活性对给药本发明的化合物所针对的具体应用是有用的。

在一些实施方案中，本发明的方法利用含有本发明的化合物的组合物，所述方法的优点是所述化合物是雄激素受体的非类固醇类配体并在体内显示出合成代谢活性。根据这个方面，这种化合物不伴有严重的副作用，提供方便的给药方式和较低的生产成本，并且口服可生物利用，与其它不希望的一类固醇受体没有显著的交叉反应性，并且可能具有很长的生物半衰期。

当施用于哺乳动物，特别是人时，预计医师会确定最适合个体的实际剂量和治疗时间，并且可以根据具体个体的年龄、体重和应答而变化。

在一个实施方案中，用于给药的组合物可以是无菌溶液剂，或者在其它实施方案中，可以是水性或非水性的溶剂、悬混剂或乳剂。在一个实施方案中，所述组合物可以包含丙二醇、聚乙二醇、可注射的有机酯例如油酸乙酯、或环糊精。在另一个实施方案中，组合物也可以包含湿润剂、乳化剂和/或分散剂。在另一个实施方案中，所述组合物也可以包含无菌水或任何其它无菌可注射介质。

在一个实施方案中，本发明提供用于如本文所述的本发明的任何方法

的化合物和组合物（包括本文所述的任意实施方案）。在一个实施方案中，使用本发明的化合物或含有它的组合物会有利于抑制、压制除、增强或促进个体体内所期望的应答，这一点本领域的技术人员会理解。在另一个实施方案中，所述组合物还可以含有其它活性成分，其活性对给药本发明的化合物所针对的具体应用是有用的。

在一些实施方案中，所述组合物还含有 5 α -还原酶抑制剂（5ARI）、一种或多种 SARM、选择性雌激素受体调节剂（SERM）、芳香酶抑制剂（例如但不限于阿那曲唑（anastrozole）、依西美坦或来曲唑）、GnRH 激动剂或拮抗剂、类固醇或非类固醇 GR 配体、类固醇或非类固醇 PR 配体、类固醇或非类固醇 AR 配体、17-醛酮还原酶抑制剂或 17 β -羟基类固醇脱氢酶抑制剂。在一些实施方案中，这种组合物可以用于治疗激素依赖性病症，例如不育、激素反应性癌例如生殖腺癌或泌尿生殖器癌的瘤形成。

在一些实施方案中，所述组合物包含本文所述的化合物和另一种治疗性化合物，尤其包括 5ARI，例如非那雄胺、度他雄胺、艾宗特来；其他 SARM，例如，RU-58642、RU-56279、WS9761 A 和 B、RU-59063、RU-58841、贝氯特来、LG-2293、L-245976、LG-121071、LG-121091、LG-121104、LGD-2226、LGD-2941、LGD-3305、YM-92088、YM-175735、LGD-1331、BMS-357597、BMS-391197、S-40503、BMS-482404、EM-4283、EM-4977、BMS-564929、BMS-391197、BMS-434588、BMS-487745、BMS-501949、SA-766、YM-92088、YM-580、LG-123303、LG-123129、PMCol、YM-175735、BMS-591305、BMS-591309、BMS-665139、BMS-665539、CE-590、116BG33、154BG31、arcarine、ACP-105；SERM，例如，三苯氧胺（tamoxifene）、4-羟基三苯氧胺、艾多昔芬、托瑞米芬、奥培米芬（ospemifene）、屈洛昔芬、雷诺昔芬、阿佐昔芬，巴多昔芬（bazedoxifene）、PPT（1,3,5-三(4-羟基苯基)-4-丙基-1*H*-吡唑）、DPN（二芳基丙腈）、拉索昔芬、哌喷昔芬（pipendoxifene）、EM-800、EM-652、蔡福昔定、秦噪昔芬、替米利芬、磷酸米泼昔芬、RU 58,688、EM 139、ICI 164,384、ICI 182,780、氯米芬、MER-25、二乙基己烯雌酚、香豆雌酚、染料木黄酮、GW5638、LY353581、珠氯米芬、恩氯米芬（enclomiphene）、地马孕酮醋酸盐、

DPPE、(*N,N*-二乙基-2-{4-(苯基甲基)-苯氧基}乙胺)、TSE-424、WAY-070、WAY-292、WAY-818、cyclocommunol、普林贝瑞(prinaberel)、ERB-041、WAY-397、WAY-244、ERB-196、WAY-169122、MF-101、ERb-002、ERB-037、ERB-017、BE-1060、BE-380、BE-381、WAY-358、[18F]FEDNP、LSN-500307、AA-102、半枝莲(Ban zhi lian)、CT-101、CT-102、VG-101；GnRH激动剂或拮抗剂，例如，亮丙瑞林、戈舍瑞林、曲普瑞林、阿法前列醇、组氨瑞林、地肽瑞里、加尼瑞克、安肽伊妥瑞克、西曲瑞克、雷莫瑞克、加尼瑞克、安雷利克斯、替维瑞克、阿巴瑞克、奥扎瑞克(ozarelix)、舒伐格瑞克(sufugolix)、普拉瑞克、地加瑞克(degarelix)、NBI-56418、TAK-810、脂酰基碱(acyline)；FSH激动剂或拮抗剂、LH激动剂/拮抗剂、芳香酶抑制剂，例如来曲唑、阿那曲唑、阿他美坦、法倔唑、米那美坦、依西美坦、普洛美坦、利阿唑、NKS-01、伏氯唑、YM-51、芬罗唑、4-羟雄烯二酮、氨基苯乙哌啶酮(aminogluethimide)、罗谷亚胺；类固醇或非类固醇糖皮质激素受体配体，例如，ZK-216348、ZK-243149、ZK-243185、LGD-5552、米非司酮、RPR-106541、ORG-34517、GW-215864X、Sesquicillin、CP-472555、CP-394531、A-222977、AL-438、A-216054、A-276575、CP-394531、CP-409069、UGR-07；类固醇或非类固醇孕酮受体配体；类固醇或非类固醇AR拮抗剂，例如氟他胺、羟基氟他胺、比卡鲁胺、尼鲁米特，羟基类固醇脱氢酶抑制剂，PPAR α 配体例如苯扎贝特、非诺贝特、吉非贝齐；PPAR γ 配体，例如，达格列酮、吡格列酮、罗格列酮、伊格列酮(isaglitazone)、利格列酮(rivoglitazone)、萘格列酮(netoglitazone)；双重作用的PPAR配体，例如，naveglitazar、法格立他扎、替格列扎(tesaglitazar)、拉格列扎(ragaglitazar)、奥格列扎(oxeglitazar)、PN-2034、PPAR δ ；17-酮还原酶抑制剂，3 β -DH Δ 4,6-异构酶抑制剂，3 β -DH Δ 4,5-异构酶抑制剂，17,20碳链酶抑制剂，p450c17抑制剂，p450ssc抑制剂，17,20裂合酶抑制剂，或它们的组合。

应该理解，以上给药两种或多种药剂的任何方法、计时、途径或它们的组合应被认为由本文所述的短语“联合给药”所包含。

在一个实施方案中，本发明提供患癌个体的骨骼相关事件(SRE)的治

疗、预防、压制或抑制、或降低罹患它的风险，其包括给药本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合，所述骨骼相关事件(SRE)例如骨折、骨手术、骨辐射、脊髓压迫症、新生骨转移、骨丢失或它们的组合。本发明特别涉及用式(I)的化合物治疗正在进行或已经进行雄激素剥夺治疗(ADT)的罹患前列腺癌个体的 SRE。

在一个实施方案中，用本文提供的方法和/或利用本文提供的组合物治疗的骨骼相关事件是骨折，在一个实施方案中，所述骨折是病理性骨折、非创伤性骨折、脊椎骨折、非脊椎骨折、形态测定骨折(morphometric fractures)或它们的组合。在一些实施方案中，骨折可以是闭合骨折、复合骨折、横骨折、青枝骨折或粉碎性骨折。在一个实施方案中，发生骨折的可以是身体的任何骨，在一个实施方案中，所述骨折是臂、腕、手、指、腿、踝、足、趾、髌、锁骨的任意一块或多块骨中的骨折或它们的组合。

在另一个实施方案中，本文提供的方法和/或组合物有效地治疗、预防、压制、抑制骨骼相关事件、或降低其风险，所述骨骼相关事件例如病理性骨折、脊髓压迫症、高钙血症多、骨相关的疼痛或它们的组合。

在另一个实施方案中，力求用本文提供的方法和/或利用本文提供的组合物治疗的骨骼相关事件包括必要的骨手术和/或骨辐射，其在一些实施方案中，用于治疗在一个实施方案中由骨损害或神经压迫引起的疼痛。在另一个实施方案中，力求用本文提供的方法和/或利用本文提供的组合物治疗的骨骼相关事件包括个体的脊髓压迫症，或有必要改变抗肿瘤疗法，包括改变激素疗法。在一些实施方案中，力求用本文提供的方法和/或利用本文提供的组合物治疗的骨骼相关事件包括治疗、压制、预防骨转移或骨丢失、降低其发病率或延缓其进展或严重性。在一个实施方案中，骨丢失可以包括骨质疏松症、骨质减少或它们的组合。在一个实施方案中，骨骼相关事件可以包括本文所列的实施方案的任意组合。

在一个实施方案中，本文提供的方法和/或利用本文提供的组合物有效地减少骨转移，例如在病灶数量、病灶大小或它们的组合方面。根据本发明的这一方面，在一个实施方案中，本文提供一种预防或抑制个体癌症向骨转移的方法，所述包括向所述个体给药包含托瑞米芬、雷洛昔芬、他莫

昔芬或其类似物、功能衍生物、代谢产物或它们的组合、或它们的药学上可接受的盐的组合物步骤。在一个实施方案中，所述代谢产物可以包括奥培米芬、非培米芬（fispemifene）或它们的组合。在一个实施方案中，所述癌症是前列腺癌。

在一个实施方案中，所述骨骼相关事件是癌症治疗的结果。在一个实施方案中，所述骨骼相关事件是激素剥夺治疗的结果，而在另一个实施方案中，它们是雄激素剥夺治疗(ADT)的结果。

在一个实施方案中，本发明的化合物用于预防或逆转雄激素剥夺治疗(ADT)引起的副作用，例如肌肉量减少、肌肉强度降低、脆弱、性腺功能减退症、骨质疏松症、骨质减少、BMD降低和/或骨量减少。

在雄性，尽管成熟期性激素的自然下降（雄激素直接减少以及由雄激素的外周芳构化产生的雌激素的低水平）与骨脆弱有关，但是这种效应在已接受雄激素剥夺治疗的雄性更明显。

在一些实施方案中，本发明的任意组合物包含任意形式的或本文所述的任意实施方案中的式 I 化合物。在一些实施方案中，本发明的任意组合物由任意形式的或在本文所述的任意实施方案中的式 I 化合物组成。在一些实施方案中，本发明的任意组合物主要由任意形式的或在本文所述的任意实施方案中的式 I 的化合物组成。在一些实施方案中，术语“包含”指包含所指的活性剂（例如式 I 的化合物）以及包含制药产业中已知的其它活性剂和药学上可接受的载体、赋形剂、润滑剂、稳定剂等。在一些实施方案中，术语“主要由...组成”指这样的组合物，其唯一的活性成分是指的活性成分，但是，可以包括用于制剂的稳定、保存等的其它化合物，但是所述其它化合物不直接参与所指的活性成分的疗效。在一些实施方案中，术语“主要由...组成”可以指促进所述活性成分的释放的组分。在一些实施方案中，术语“由...组成”指含有所述活性成分和药学上可接受的载体或赋形剂的组合物。

在一个实施方案中，本发明提供联合制剂。在一个实施方案中，术语“联合制剂”特别地定义为“药盒(kit of parts)”，其意思是如以上定义的组合搭档可以独立地给药，或者通过使用具有不同量的组合搭档的不同的固定组合物给药，即同时地、并发地、分别地或依次地给药。那么，在一些实施方

案中，所述药盒的部件例如可以同时给药，或者按时间先后交替（即对于药盒任何部件在不同的时间点，以相同或不同的时间间隔）给药。在一些实施方案中，可以控制所述联合制剂中的组合搭档的总量的比率。在一个实施方案中，例如为了应对部分待治疗患者亚群的需要或单个患者的需要，所述组合制剂可以变化，所述不同的需要可能归因于具体疾病、所述疾病的严重性、年龄、性别或体重，这可以由本领域的技术人员容易地确定。

应该理解，本发明涉及用于任何适当的疾病、障碍或病症的本文所述的组合物和联合疗法，本领域的技术人员会意识到这一点。上文叙述了所述组合物和联合疗法对特定疾病、障碍和病症的某些应用，它们代表本发明的实施方案，而通过单独或作为所述联合疗法的部分来给药本文所述的化合物或使用本发明的组合物来治疗个体的所述疾病、障碍和病症的方法代表本发明其他的实施方案。

选择性雄激素调节剂化合物的生物活性

在一些实施方案中，本发明的化合物可以用于口服睾酮替代疗法。在其它实施方案中，适当取代的化合物用于：a) 男性避孕；b) 治疗各种激素相关的病症，例如与 ADAM 相关的病症，例如疲劳、抑郁、性欲降低、性功能障碍、勃起功能障碍、性腺功能减退症、骨质疏松症、脱发、肥胖症、少肌症、骨质减少、良性前列腺增生以及情绪和认知改变；c) 治疗与 ADIF 有关的病症，例如性功能障碍、性欲降低、性腺功能减退症、少肌症、骨质减少、骨质疏松症、认知和情绪变化、抑郁、贫血、脱发、肥胖症、子宫内膜异位症、乳腺癌、子宫癌和卵巢癌；d) 治疗和/或预防慢性肌萎缩；e) 治疗前列腺癌、前列腺癌成像、降低前列腺癌的发病率、使其中止或导致其消退；f) 治疗 I 型糖尿病；g) 治疗 II 型糖尿病；h) 压制或抑制糖尿病或降低其发病率；i) 治疗葡萄糖耐受不良；j) 治疗高胰岛素血症；k) 治疗胰岛素抵抗；l) 治疗糖尿病肾病；m) 治疗糖尿病神经病变；n) 治疗糖尿病视网膜病变；o) 治疗脂肪肝症；p) 治疗恶病质；q) 口服雄激素替代和/或其它临床治疗和/或诊断领域，包括本文所述的术语“治疗”所包括的任何实施方案。

在一些实施方案中，本发明的化合物在体内具有组织选择性雄激素活性和合成代谢活性，因此，可用于具体应用，本领域的技术人员会意识到

到这一点。

在一个实施方案中，本发明提供：a) 治疗罹患肌萎缩症的个体的方法；b) 治疗罹患营养不良的个体的方法；c) 治疗个体的骨相关病症的方法；d) 增加个体骨量的方法；e) 改善个体脂质分布的方法；f) 治疗动脉粥样硬化及其相关疾病的方法；g) 改善个体的灵活性和运动的方法；h) 治疗罹患侏儒症的个体的方法；i) 治疗罹患痛经的个体的方法；j) 治疗罹患精神性性交困难的个体的方法；k) 治疗罹患精子生成障碍性不育的个体的方法；这些方法包括向所述个体给药式 I 的化合物和/或所述化合物的类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、不纯物或晶体或它们的任意组合。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于各种应用和治疗其中需要改善认知、减少或治疗抑郁或其它神经保护作用的疾病。

在一个实施方案中，“认知”指认识的过程，特别是保持清醒、认识、思维、学习和判断的过程。认知涉及心理学、语言学、计算机科学、神经科学、数学、习性学和哲学领域。在一个实施方案中，“情绪”指脾气或精神状态。如本文所指的，变化指认知和/或情绪的任何积极或消极变化。

在一个实施方案中，“抑郁”指涉及身体、情绪和思维的疾病，其影响人吃饭、睡觉的方式、自我感知的方式和考虑事物的方式。抑郁的体征和症状包括缺乏活动兴趣、食欲缺乏或进食过量、缺乏表情、空虚、感觉绝望、悲观、内疚或无助、社交退缩（social withdrawal）、疲劳、睡眠障碍、集中、记忆或作决定困难、躁动、易怒、头痛、消化障碍或慢性疼痛。

在一个实施方案中，本发明的方法用于个体，其为人类。在另一个实施方案中，所述个体是哺乳动物。在另一个实施方案中，所述个体是动物。在另一个实施方案中，所述个体是无脊椎动物。在另一个实施方案中，所述个体是脊椎动物。

在一个实施方案中，所述个体是雄性。在另一个实施方案中，所述个体是雌性。在一些实施方案中，尽管本文所述的方法可以用于治疗雄性和雌性，但是，如本文所述和所举例的，对于某些方法，雌性更有利地应答某些化合物的给药。

在一些实施方案中，尽管本文所述的方法可以用于治疗雄性和雌性，但是，如本文所述的，对于某些方法，雄性更有利地应答某些化合物的给药。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于以下各项的应用或治疗：脱发（hair loss）、脱发（alopecia）、雄激素性脱发、斑秃、继发化学疗法的脱发、继发放射疗法的脱发、由瘢痕形成诱导的脱发或由应激诱导的脱发。在一个实施方案中，“脱发（hair loss）”或“脱发（alopecia）”指如极普遍类型的男人型脱发的脱发。脱发通常由头皮的斑块脱发开始，有时发展至全秃，甚至体毛脱落。脱发既影响男性也影响女性。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于与罹患贫血的个体相关的疾病或病症的应用和治疗。在一个实施方案中，“贫血”指具有小于血液中红血细胞的正常数量或小于血液中血红蛋白的正常量、血细胞比容降低、或平均血细胞体积减小或血细胞尺寸减小的病症。在贫血时，血液的携氧能力下降。在一些实施方案中，治疗贫血在本文中也可以指治疗导致贫血的潜在因素，例如：a) 出血；b) 溶血（红血细胞过度破坏）；c) 红血细胞产生不足；和 d) 正常血红蛋白不足。在一些实施方案中，本发明的治疗贫血指治疗贫血的任何形式，包括再生障碍性贫血、苯中毒、范科尼贫血、新生儿溶血病、遗传性球形红细胞增多症、缺铁性贫血、骨质疏松症、恶性贫血、再生障碍性贫血、溶血性贫血、镰状细胞贫血、肾性贫血、地中海贫血、骨髓增生异常综合征和各种骨髓疾病。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于与个体的性欲问题或个体的勃起功能障碍有关的疾病和/或病症的应用和/或治疗。在一个实施方案中，“性欲”可以指性本能。

在一个实施方案中，术语“勃起”指竖立或直立的能力。勃起组织是能够通过其含有的大量血管的膨胀而极大地膨胀并变硬的组织。

在本发明的另一个实施方案中，提供用于个体（即罹患雄激素依赖性病症的个体）的激素治疗的方法，所述方法包括使患者的雄激素受体与本发明的化合物和/或非类固醇激动剂和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合接触的步骤，上述化合物的量有效地使其与所述雄激素受体结合并实现改变雄激素依赖性病症。

在本发明的一个实施方案中，提供用于患者（即罹患雄激素依赖性病症的个体）激素替代治疗的方法，所述方法包括向个体给药足以实现改变所述个体的激素依赖性病症的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合的步骤。

可以用本文所述的化合物和/或组合物，包括本发明的方法治疗的雄激素依赖性病症包括与衰老、性腺功能减退症、少肌症、红细胞生成减少、骨质疏松症和与低雄激素（例如睾酮）或雌激素水平相关的任意的其它病症相关的病症。

可以用本文所述的化合物和/或组合物，包括本发明的方法治疗的雄激素依赖性病症可以包括以雄激素或雌激素水平升高为特征的病症，包括多毛症、不育、多囊卵巢综合征、子宫内膜癌、乳腺癌、男人型脱发、前列腺癌、睾丸癌等，本领域的技术人员会知道这一点。对于这些病症，可以向所述个体单独地或联合其它治疗剂给药本文所述的化合物，本领域的技术人员会理解这一点。

在一个实施方案中，本发明提供治疗个体的癌症、降低其发病率、严重性或发病、延缓其进展、延长缓解期或延缓其发作的方法，所述方法包括向所述个体给药本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合的步骤。在一些实施方案中，这些癌症是与雄性或雌性的生殖组织相关的激素依赖性或雄激素受体依赖性肿瘤（恶性或良性的），例如前列腺癌、卵巢癌、乳腺癌、子宫癌或睾丸癌等。

在一些实施方案中，本发明提供治疗个体癌前兆或病变、降低其发病率的方法，所述方法包括向所述个体给药本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合的步骤。在一些实施方案中，这些癌前兆是见于激素应答组织中的雄激素受体依赖性肿瘤或是与雄性或雌性的生殖组织例如前列腺、卵巢、乳腺、子宫或睾丸等相关。在一些实施方案中，这些癌前兆包括例如前列腺、子宫颈等的任何局部的上皮内瘤样病变。在一些实施方案中，这种方法用于治疗在例如雄性或雌性生殖组织

的组织中的瘤或肿瘤前期、发育异常或增生。

在一个实施方案中，本发明提供化合物、组合物和/或它们在治疗良性前列腺增生(BPH)中的使用方法。“BPH(良性前列腺增生)”是前列腺的良性增大，它是在任何内脏器官中发现的最普通的良性增生性异常，并且是成年男性发病的主要病因。超过75%的大于50岁的男性患BPH，在九十岁的男性中，其患病率达到88%。BPH经常导致逐渐挤压穿过前列腺的尿道部分(前列腺尿道)。因为膀胱的不完全排空和尿急，这造成患者尿频急。尿流的梗阻也能导致一般的排尿失控，包括当希望排尿时排尿启动困难以及因为不能从膀胱排空尿而造成阻止尿流困难(一种称为充溢性尿失禁(overflow urinary incontinence)的病症，它可以导致尿路梗阻和泌尿衰竭(urinary failure))。

在本发明的一个实施方案中，治疗个体的良性前列腺增生(BPH)的方法包括向所述个体给药有效治疗所述个体的BPH的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合的步骤。

在一些实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗个体的恶病质和/或与癌症有关的恶病质、减轻其严重性、降低其发病率或减少其发病的使用方法。在另一个实施方案中，所述癌症包括肾上腺皮质癌、直肠癌、膀胱癌、脑瘤、脑干胶质瘤、脑瘤、小脑星形细胞瘤、大脑星形细胞瘤(cerebral astrocytoma)、室管膜瘤、髓母细胞瘤、幕上原始神经外胚叶瘤(supratentorial primitive neuroectodermal)、松果体瘤、下丘脑胶质瘤、乳腺癌、类癌瘤、癌、子宫颈癌、结肠癌、结直肠癌、子宫内膜癌、食管癌、肝外胆管癌、尤文家族肿瘤(Ewing's family of tumors)(Pnet)、颅外胚细胞肿瘤、眼癌、眼内黑色素瘤、胆囊癌、胃癌、胚细胞瘤、性腺外肿瘤、妊娠滋养细胞肿瘤、头颈癌、下咽癌、胰岛细胞癌、喉癌、白血病、急性淋巴细胞性白血病、口腔癌、肝癌、肺癌、非小细胞肺癌、小细胞肺癌、AIDS相关的淋巴瘤、中枢神经系统(原发性)淋巴瘤、皮肤T细胞淋巴瘤、淋巴瘤(霍奇金病和非霍奇金病)、恶性间皮瘤、黑色素瘤、Merkel细胞癌、转移性鳞癌、多发性骨髓瘤、浆细胞瘤、蕈样肉芽肿病、骨髓增生异常综合征、骨髓增殖性疾病、鼻咽癌、神经

母细胞瘤、口咽癌、骨肉瘤、卵巢上皮样癌、卵巢生殖细胞肿瘤、卵巢低恶性潜在肿瘤、胰腺外分泌癌（*exocrine pancreatic cancer*）、胰岛细胞癌、胰腺癌、鼻旁窦和鼻腔癌、甲状旁腺癌、阴茎癌、嗜铬细胞瘤癌、垂体癌、浆细胞瘤、前列腺癌、横纹肌肉瘤、直肠癌、肾细胞癌、涎腺癌、塞扎里综合征、皮肤癌、皮肤 T 细胞淋巴瘤、卡波西肉瘤、黑色素瘤、小肠癌、软组织肉瘤、软组织肉瘤、睾丸癌、恶性胸腺瘤、甲状腺癌、尿道癌、子宫癌、肉瘤、童年期异常癌、阴道癌、外阴癌、肾母细胞瘤或它们的任意组合。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗肺癌、减轻其严重性、降低其发病率或延缓其发作的用途。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗非小细胞肺癌、减轻其严重性、降低其发病率或延缓其发作的用途。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗霍奇金病（或者在另一个实施方案中，非霍奇金病）、减轻其严重性、降低其发病率或延缓其发作的用途。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗结直肠癌、减轻其严重性、降低其发病率或延缓其发作的用途。

在一些实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗癌症、减轻其严重性、降低其发病率或减少其发病的用途。在另一个实施方案中，所述癌症包括雄激素 AR 依赖性肿瘤（恶性或良性的），例如前列腺癌、乳腺癌（男性或女性、可行手术或不能手术的）。在另一个实施方案中，所述 SARM 化合物是

ADT 的辅药 (adjunct)，所述 ADT 用于治疗前列腺癌、膀胱癌、脑癌、骨肿瘤、结肠癌、子宫内膜癌、肝癌、肺癌、淋巴癌、肾癌、骨肉瘤、卵巢癌、胰腺癌、阴茎癌、皮肤癌、甲状腺癌和/或激素依赖性癌。

在一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合的以下用途：a) 治疗骨相关的病症；b) 预防骨相关的病症；c) 压制骨相关的病症；d) 抑制骨相关的病症；e) 增加个体的骨强度；f) 增加个体的骨量；g) 抑制破骨细胞形成的用途。

在一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合的以下用途：a) 加速骨修复；b) 治疗骨病症；c) 治疗骨密度降低；d) 治疗低骨矿物质密度(BMD)；e) 治疗骨量减少；f) 治疗代谢骨病；g) 促进骨生长或再生；h) 促进骨恢复；i) 促进骨折修复；j) 促进骨重建；k) 治疗成形外科（包括脸部、髌部或关节的）后的骨损害；l) 提高骨强度和功能；m) 增加骨皮质量；n) 增加小梁连接性。

在一个实施方案中，所述骨相关的病症是遗传性病症，在另一个实施方案中，是由特定疾病的治疗方案诱导的结果。例如，在一个实施方案中，本文所述的化合物用于治疗由癌症向骨转移而引起的骨相关的病症，或在另一个实施方案中，治疗例如由给予雄激素剥夺治疗应答个体的前列腺致癌作用而引起的骨相关的病症。

在一个实施方案中，所述骨相关的病症是骨质疏松症。在另一个实施方案中，所述骨相关的病症是骨质减少。在另一个实施方案中，所述骨相关的病症是骨吸收增加。在另一个实施方案中，所述骨相关的病症是骨折。在另一个实施方案中，所述骨相关的病症是骨脆弱。

在另一个实施方案中，所述骨相关的病症是骨矿物质密度(BMD)丢失。在另一个实施方案中，所述骨相关的病症是骨质疏松症、骨质减少、骨吸收增加、骨折、骨脆弱和 BMD 丢失的任意组合。每种病症代表本发明独立的实施方案。

在一个实施方案中，“骨质疏松”指由于钙和骨蛋白的消耗造成的骨变薄和骨量减少。在另一个实施方案中，骨质疏松症是全身性的骨骼疾病，其特

征是骨量低、骨组织退化，并由此导致骨脆弱和骨折易感性增加。在骨质疏松症患者，骨强度是异常的，在一个实施方案中，伴随由此引起的骨折风险增加。在另一个实施方案中，骨质疏松症使通常在见于骨中的钙和蛋白质胶原流失，在一个实施方案中，这导致骨性质异常或骨密度下降。在另一个实施方案中，受骨质疏松症影响的骨可仅仅由于通常不会造成骨折的轻微跌倒或损伤而骨折。在一个实施方案中，骨折可以是裂纹骨折的形式（如在髌骨骨折中）或压缩性骨折的形式（如在脊椎压迫性骨折中）。脊柱、髌和腕是骨质疏松诱发骨折的通常部位，但是，骨折也可以发生于其它骨骼部位。在另一个实施方案中，未加抑制的骨质疏松能够导致体位的改变、身体异常和灵活性下降。

在一个实施方案中，所述骨质疏松症由雄激素剥夺引起。在另一个实施方案中，所述骨质疏松症在雄激素剥夺后发生。在另一个实施方案中，所述骨质疏松症是原发性骨质疏松症。在另一个实施方案中，所述骨质疏松症是继发性骨质疏松症。在另一个实施方案中，所述骨质疏松症是绝经后骨质疏松症。在另一个实施方案中，所述骨质疏松症是幼年骨质疏松症。在另一个实施方案中，所述骨质疏松症是特发性骨质疏松症。在另一个实施方案中，所述骨质疏松症是老年性骨质疏松症。

在另一个实施方案中，所述原发性骨质疏松症是 I 型原发性骨质疏松症。在另一个实施方案中，所述原发性骨质疏松症是 II 型原发性骨质疏松症。每种类型的骨质疏松症代表本发明的独立的实施方案。

根据本发明的这一方面，在一个实施方案中，用本文所述的化合物或其组合治疗所述骨相关的病症。在另一个实施方案中，在给药本文所述的一种或多种化合物之前、同时或之后，可以提供给个体其它骨促进性化合物。在一个实施方案中，所述骨促进性化合物可以包括天然的或合成的物质。

在一个实施方案中，所述骨促进性化合物可以包括骨形态生成蛋白 (BMP)；生长因子，例如表皮生长因子 (EGF)、成纤维细胞生长因子 (FGF)、转化生长因子 (TGF)、胰岛素生长因子 (IGF)、血小板源性生长因子 (PDGF)；Hedgehog 蛋白（例如 *sonic hedgehog*、*indian hedgehog* 和 *desert hedgehog*）；激素，例如促卵泡激素、甲状旁腺素、甲状旁腺激素相关肽、激活素、抑制素、滤泡抑素、*frizzled* 蛋白、*frzb* 蛋白或 *frazzled* 蛋白；BMP 结合蛋白，例

如脊索蛋白和胎球蛋白；细胞因子，例如 IL-3、IL-7、GM-CSF；趋化因子，例如嗜酸细胞活化趋化因子；胶原；骨钙蛋白；骨黏连蛋白等；本领域的技术人员会理解这一点。

在另一个实施方案中，本发明用于治疗骨病的组合物可以包含本文所述的一种或多种化合物、额外的一种或多种骨促进性化合物和骨原细胞。在一个实施方案中，骨原细胞是可以被诱导分化为成骨细胞的干细胞或祖细胞。在另一个实施方案中，所述细胞可以是成骨细胞。在另一个实施方案中，可以向个体给药编码骨促进性化合物的核酸，这应该被认为是本发明的部分。

在一个实施方案中，本发明的方法包括含给药用于治疗骨质疏松症的化合物。在另一个实施方案中，本发明的方法包括给药化合物(与 SERM 联合)，用于治疗骨质疏松症。在另一个实施方案中，所述 SERM 是三苯氧胺、4-羟三苯氧胺、艾多昔芬、托瑞米芬、奥培米芬、屈洛昔酚、雷诺昔芬、阿佐昔芬、巴多昔芬、PPT (1,3,5-三(4-羟基苯基)-4-丙基-1*H*-吡唑)、DPN (二芳基丙腈)、拉索昔芬、哌喷昔芬、EM-800、EM-652、萘福昔定、秦唑昔芬、替米利芬、磷酸米泼昔芬、RU 58,688、EM 139、ICI 164,384、ICI 182,780、氯米芬、MER-25、二乙基己烯雌酚、香豆雌酚、染料木黄酮、GW5638、LY353581、珠氯米芬、恩氯米芬、地马孕酮醋酸盐、DPPE、(*N,N*-二乙基-2- {4-(苯基甲基)-苯氧基} 乙胺)、TSE-424、WAY-070、WAY-292、WAY-818、cyclocommunol、普林贝瑞、ERB-041、WAY-397、WAY-244 ERB-196、WAY-169122、MF-101、ERb-002、ERB-037、ERB-017、BE-1060、BE-380、BE-381、WAY-358、[18F]FEDNP、LSN-500307、AA-102、半枝莲、CT-101、CT-102、VG-101。

在另一个实施方案中，本发明的方法包括与二膦酸盐联合给药所述 SARM 化合物用于治疗骨质疏松症，所述二膦酸盐例如阿屈膦酸盐、替鲁膦酸(tiludronate)、氯屈膦酸钠(clodronate)、帕米膦酸钠、羟乙膦酸盐、阿屈膦酸盐、唑屈膦酸盐(zolendronate)、英卡膦酸二钠(cimadronate)、奈立膦酸钠(neridronate)、米诺膦酸(minodronic acid)、依班膦酸盐、利塞膦酸盐或 homoresidronate。

在另一个实施方案中，本发明的方法包括与降钙素例如鲑精组蛋白

(salmon)、依降钙素、SUN-8577 或 TJN-135 联合给药所述化合物用于治疗骨质疏松症。

在另一个实施方案中，本发明的治疗骨质疏松症的方法包括联合以下物质给药所述 SARM 化合物：a) 维生素 D 或衍生物，例如 ZK-156979；b) 维生素 D 受体配体和类似物，例如骨化三醇、钙三醇(topitriol)、ZK-150123、TEI-9647、BXL-628、Ro-26-9228、BAL-2299、Ro-65-2299 或 DP-035；c) 雌激素、雌激素衍生物或结合型雌激素；d) 抗雌激素药、孕激素或合成雌激素/孕激素；e) RANK 配体单克隆抗体，例如 denosumab(以前称为 AMG162 (Amgen))；f) $\alpha v \beta 3$ 整合素受体拮抗剂；g) 破骨细胞空泡型 ATP 酶抑制剂；h) 结合 VEGF 的破骨细胞受体拮抗剂；i) 钙受体拮抗剂；j) PTh (甲状旁腺素) 和类似物、PTHrP 类似物 (甲状旁腺素相关肽)；k) 组织蛋白酶 K 抑制剂 (AAE581 等)；l) 雷尼酸锶；m) 替勃龙；n) HCT-1026、PSK3471；o) 麦芽糖铈 (gallium maltolate)；p) Nutropin AQ；q) 前列腺素 (用于骨)；r) p38 蛋白激酶抑制剂；s) 骨形态生成蛋白；t) BMP 拮抗抑制剂；u) HMG-CoA 还原酶抑制剂；v) 维生素 K 或衍生物；w) 依普黄酮；x) 氟化盐；y 饮食钙补充剂和 z) 骨保护素。

在一个实施方案中，本发明的方法用于治疗由激素紊乱、破坏或不平衡引起的或与之相关的疾病或病症。在一个实施方案中，所述激素紊乱、破坏或不平衡包括激素过量。在另一个实施方案中，所述激素紊乱、破坏或不平衡包括激素缺乏。在一个实施方案中，所述激素是类固醇激素。在另一个实施方案中，所述激素是雌激素。在另一个实施方案中，所述激素是雄激素。在另一个实施方案中，所述激素是糖皮质激素。在另一个实施方案中，所述激素是皮质类固醇。在另一个实施方案中，所述激素是黄体生成素 (LH)。在另一个实施方案中，所述激素是促卵泡激素 (FSH)。在另一个实施方案中，所述激素是本领域已知的任何其它激素。在另一个实施方案中，所述激素紊乱、破坏或不平衡与绝经有关。在另一个实施方案中，所述激素紊乱、破坏或不平衡与男性更年期、男性更年期血管舒缩综合征、男性更年期乳腺发育、肌肉强度和/或功能下降、骨强度和/或功能下降和发怒有关。在另一个实施方案中，激素缺乏是特定处理的结果，如治疗个体疾病或病症的副产物。例如，所述激素缺乏可以是作为个体前列腺癌疗法的雄激素消耗的结果。

每种可能性代表本发明的独立的实施方案。

在另一个实施方案中，本发明涉及治疗少肌症或恶病质和与其相关的病症（例如骨疾病或病症）。

在一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合的以下用途：1) 治疗肌萎缩症；2) 预防肌萎缩症；3) 治疗、预防、压制、抑制或减少归因于肌萎缩症引起的肌肉损失；4) 治疗、预防、抑制、减少或压制归因于肌萎缩症的肌萎缩；和/或 5) 治疗、预防、抑制、减少或压制归因于肌萎缩症的肌肉蛋白分解代谢；和/或治疗、预防、抑制、减少或压制归因于终末期肾脏疾病或 CKD 的肌萎缩；和/或 6) 治疗、预防、抑制、减少或压制脆弱。

在另一个实施方案中，用于治疗罹患肌萎缩症或本文所述的任何病症的个体的化合物的用途包括给药包含本文所述的化合物的药物组合物。在另一个实施方案中，所述给药步骤包括将液体形式的所述药物组合物经静脉内、动脉内或肌肉内注射给所述个体；在所述个体体内皮下埋植含有所述药物组合物的小丸；口服向所述个体给药液体或固体形式的所述药物组合物；或向所述个体的皮肤表面局部施用所述药物组合物。

肌肉是主要用作动力源的身体组织。身体的肌肉有三种类型：a) 骨骼肌——负责身体的四肢和外部区域运动的肌肉；b) 心肌——心脏肌肉；和 c) 平滑肌——位于动脉和肠壁中的肌肉。

在本文中，消耗性（wasting）病症或障碍定义为至少部分地以体重、器官质量或组织质量的异常的进行性损失为特征的病症或障碍。消耗性病症可以作为疾病例如癌症或感染的结果而发生，或可归因于生理或代谢状态，例如因长期卧床休息或当肢体被固定（例如在铸型中）时发生的废用性失调。消耗性病症也可以是年龄相关的。在消耗性病症过程中发生的体重减少的特征可以是总体重的减少或器官重量的减少，例如归因于组织蛋白减少的骨量或肌肉量的减少。

在一个实施方案中，如本文交替使用的，“肌萎缩（muscle wasting）”或“肌萎缩（muscular wasting）”指肌肉量的进行性损失和/或肌肉的进行性衰减和退化，包括控制运动的骨骼肌或随意肌和控制心脏的心肌和平滑肌。在一

个实施方案中，所述肌萎缩病症或障碍是慢性肌萎缩病症或障碍。“慢性肌萎缩”在本文中定义为肌肉量的慢性（即持续很长一段时间的）进行性损失和/或肌肉的慢性进行性衰减和退化。

肌萎缩过程中发生的肌肉量损失可以是以由于肌肉蛋白分解代谢造成的肌肉蛋白分解或降解为特征。蛋白质分解代谢因为异常高速的蛋白质降解、异常低速的蛋白质合成或这两种的结合而发生。无论是由高度的蛋白质降解还是低度的蛋白质合成引起的肌肉蛋白分解代谢或消耗都会导致肌肉量的减少和肌萎缩。术语“分解代谢”具有本领域中普遍知晓的含义，特别是指能量燃烧形式的新陈代谢。

肌萎缩可以作为病状、疾病、病症或障碍的结果而发生。在一个实施方案中，所述病状、疾患、疾病或病症是慢性的。在另一个实施方案中，所述病状、疾患、疾病或病症是遗传性的。在另一个实施方案中，所述病状、疾患、疾病或病症是神经的。在另一个实施方案中，所述病状、疾患、疾病或病症是感染性的。如本文所述的，为之给药本发明的化合物和组合物的病状、疾病、病症或障碍是直接或间接产生肌肉量的消耗（即损失），即肌萎缩症

的疾病。

在一个实施方案中，个体的肌萎缩由所述个体的肌营养不良症、肌萎缩、伴 X 染色体的脊延髓肌萎缩症（SBMA）引起。

所述肌营养不良症是遗传性疾病，其特征是控制运动的骨骼肌或随意肌的进行性衰减和退化。心脏肌肉和一些其它不随意肌也受到某些形式的肌营养不良的影响。肌营养不良（MD）的主要形式是：迪谢内肌肉营养不良、强直性肌营养不良、迪谢内肌肉营养不良、贝克肌营养不良、肢肌营养不良、面肩胛臂肌营养不良、先天性营养不良症、眼咽肌营养不良、远侧肌营养不良和埃-德二氏肌营养不良。

肌营养不良症可以影响所有年龄的人群。尽管某些形式首先在婴儿或儿童中出现，其它可能直到中年或更晚才出现。迪谢内 MD 是最普通的形式，一般影响儿童。强直性肌营养不良是这些疾病中在成人中的最通常的疾病。

肌萎缩（MA）以肌肉的消耗或减少和肌肉量的减少为特征。例如，小儿麻痹症后期 MA 是作为小儿麻痹小儿麻痹症后期综合征（PPS）的一部分而发生的肌肉萎缩。所述萎缩包括虚弱、肌疲劳和疼痛。

其它类型的MA是伴X染色体的脊延髓肌萎缩症(SBMA,也称为Kennedy病)。该病由X染色体上的雄激素受体基因的缺陷引起,仅影响男性,其在成年期发作。因为主要病因是雄激素受体突变,所以雄激素替代不是流行的治疗策略。有一些调查研究,其中给予外源性丙酸睾酮以提高雄激素的水平,这有希望克服雄激素不敏感性并可能提供合成代谢效应。然而,使用超生理水平的睾酮用于补充会有局限性和其它潜在的严重并发症。

少肌症是折磨老人和慢性病患者的使人衰弱的疾病,其特征是肌肉量和功能的损失。而且,瘦体重的增加与某些肌萎缩症的发病率和死亡率降低有关。而且,其它情况和病症也与肌萎缩症有联系并能导致肌萎缩。例如,有研究显示,在慢性下腰痛严重病例中,出现椎旁肌萎缩。

肌萎缩和其它组织消耗也与高龄有关。相信,在老年人中,全身虚弱归因于肌萎缩。随着身体的老化,更多比例的骨骼肌被纤维组织代替。结果,肌肉的力量、性能和耐力显著下降。

由于疾病或损伤而长期住院或例如当肢体被固定时发生的废用性失调也能导致肌肉萎缩或其它组织消耗。研究显示,在长期住院的罹患损伤、慢性病、烧伤、创伤或癌症的患者中,出现长期单侧肌萎缩和体重减少。

中枢神经系统(CNS)损伤或损害也与肌肉萎缩和其它消耗性病症有关。CNS损伤或损害可由例如疾病、创伤或化学药品引起。其例子有中枢神经损伤或损害、周围神经损伤或损害和脊髓损伤或损害。在一个实施方案中,CNS损害或损伤包括阿尔茨海默氏病(AD)、发怒(情绪)、厌食症、神经性厌食症、与衰老有关的厌食症和/或自信(情绪)。

在另一个实施方案中,肌萎缩和其它组织消耗可能由酒精中毒引起,可以用本发明的化合物和组合物来治疗,这代表它们的实施方案。

在一个实施方案中,本发明提供本文所述的化合物或其类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、N-氧化物、水合物或它们的任意组合用于治疗个体的消耗性疾病、障碍或病症的用途。

在一个实施方案中,所述被治疗的消耗性疾病、障碍或病症与慢性病有关。

在一些实施方案中,本发明涉及治疗可能在肌萎缩、体重减少、营养不

良、饥饿中表现出的任何消耗性病症、或任何归因于组织量减少的功能消耗或缺失。

在一些实施方案中，消耗性疾病或病症，例如恶病质、营养不良、结核病、麻风病、糖尿病、肾脏病、慢性障碍性肺病（COPD）、癌症、终末期肾衰竭、少肌症、肺气肿、骨软化症或心肌病，可以通过本发明的方法，经给药本文所述的 SARM 化合物、包含它的组合物、附加或不附加为所治疗的病症提供疗效的药物、化合物或药剂来治疗。

在一些实施方案中，消耗是由于感染肠道病毒、Epstein-Barr 病毒、带状疱疹、HIV、锥虫、流感（influenza）、柯萨奇病毒、立克次氏体、旋毛虫、血吸虫或分枝杆菌，在一些实施方案中，本发明提供其治疗方法。

恶病质是由疾病引起的或作为疾病副反应的虚弱和体重减少。心源性恶病质，即心肌和骨骼肌的肌肉蛋白消耗，是充血性心力衰竭的特征。癌症恶病质是发生在患有实体瘤和恶性血液病的患者的综合征，其表现为因脂肪组织和瘦肌肉量的大量消耗而导致的体重减少。

恶病质也见于获得性免疫缺陷综合征（AIDS），人类免疫缺陷病毒（HIV）相关肌病和/或肌无力/肌萎缩是 AIDS 比较通变的临床表现。患有 HIV 相关肌病或肌无力/肌萎缩的个体通常经受严重的体重下降、全身的或近端的肌无力、压痛和肌萎缩。

在一些实施方案中，本发明提供用于治疗个体感染、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药包含化合物和免疫调节剂、抗感染剂、基因治疗剂或它们的组合的组合物免疫调节剂。在一个实施方案中，所述抗感染剂可以是抗真菌剂、抗细菌剂、抗病毒剂、或抗寄生虫剂或它们的组合。在一些实施方案中，感染包括放射菌病、边虫病、炭疽、曲霉病、菌血症、细菌真菌病、巴尔通体感染、肉毒中毒、布氏菌病、伯霍尔德杆菌感染、弯曲杆菌感染、念珠菌病、猫抓病、衣原体感染、霍乱、梭菌感染、球孢子菌病、交叉感染、隐球菌病、皮肤真菌病、白喉病、埃里希体病、大肠杆菌感染、坏死性筋膜炎、梭杆菌感染、气性坏疽、革兰氏阴性细菌感染、革兰氏阳性细菌感染、组织胞浆菌病、脓疱病、克雷伯菌感染、军团杆菌病、麻风病、钩端螺旋体病、利斯特菌感染、莱姆病、马杜拉分支菌病、类鼻疽、分枝杆

菌感染、支原体感染、真菌病、诺卡菌感染、甲癣、瘟疫、肺炎球菌感染、假单胞菌感染、鹦鹉热、Q热、鼠咬热、回归热、风湿热、立克次体感染、洛基山斑点热、沙门菌感染、猩红热、恙虫热斑疹伤寒、败血症、性传播疾病、葡萄球菌感染、链球菌感染、破伤风、蜱传播性疾病(tick-borne diseases)、结核病、土拉菌病、伤寒、虱传斑疹伤寒、弧菌感染、雅司病、耶尔森菌感染、人兽互通病、接合菌病、获得性免疫缺陷综合征、腺病毒科感染、甲病毒感染、虫媒病毒传染、Borna病、布尼亚病毒科感染、嵌杯病毒科感染、水痘、冠状病毒科感染、柯萨奇病毒感染、巨细胞病毒感染、登革热、DNA病毒感染、触染性痘疮、脑炎、虫媒病毒、Epstein-barr病毒感染、传染性红斑、汉坦病毒感染、出血热、病毒性肝炎、病毒性人单纯疱疹、带状疱疹、耳部带状疱疹、疱疹病毒科感染、传染性单核细胞增多症、人拉沙热、麻疹、传染性软疣、流行性腮腺炎、副粘病毒科感染、白蛉热、多瘤病毒感染、狂犬病、呼吸合胞体病毒感染、裂谷热、RNA病毒感染、风疹、慢病毒疾病、天花、亚急性硬化性全脑炎、肿瘤病毒感染、疣、西尼罗热、病毒性疾病、黄热病、阿米巴病、异尖线虫病、蛔虫病、巴贝虫病、人芽囊原虫感染、臭虫叮咬、绦虫感染、美洲锥虫病、隐孢子虫病、环孢子虫感染、囊虫病、双核阿米巴病、裂头绦虫病、龙线虫病、包虫病、体外寄生虫感染、丝虫病、贾第虫病、蠕虫病、钩虫感染、幼虫移行症、利什曼病、虱寄生、罗阿丝虫病、疟疾、感染、蝇蛆病、盘尾丝虫病、原虫感染、疥疮、血吸虫病、(寄生虫性)皮肤病、类圆线虫病、绦虫病、弓蛔虫病、弓形体病、旋毛虫病、滴虫感染、锥虫病、非洲锥虫病或者鞭虫感染。

在一些实施方案中，本发明提供用于治疗个体肌骨疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药或它们的组合。在一些实施方案中，肌骨疾病包括软骨发育不全、获得性骨肥大综合征、尖头并指（趾）畸形、关节炎、关节挛缩、关节病、神经源性滑膜炎、软骨疾病、锁骨颅骨发育不良、畸形足、筋膜间隔综合征、颅面骨发育不全、颅缝早闭、皮炎、杜普伊特伦氏挛缩、侏儒症、埃-范二氏综合征、内生软骨瘤病、酸

细胞增多性肌痛综合征、外生骨疣、筋膜炎、疲劳综合征、纤维肌痛、骨纤维性结构不良、多骨纤维性结构不良、扁平足、足畸形、弗莱尔伯格二趾骨远端缺血坏死、漏斗胸、Goldenhar 综合征、痛风、拇外翻、髋脱位、骨肥厚、椎间盘移位、歌舞伎化妆综合征(kabuki make-up syndrome)、克-费二氏综合征、兰-吉综合征、莱-佩二氏病、脊柱前凸、下颌骨颜面发育不全、肢骨纹状肥大、线粒体肌病、肌痛性痉挛、肌痉挛状态、肌营养不良、肌肉骨骼畸形、肌骨疾病、肌炎、骨化性肌炎、肌管性肌病、畸形性骨炎、骨性关节炎、骨软骨炎、成骨不全、骨髓炎、骨坏死、骨硬化症、骨质疏松症、波伦综合征、复发性多软骨炎、风湿性多肌痛、多肌炎、横纹肌溶解、风湿性疾病、鲁-辛二氏综合征、绍伊尔曼氏病、脊柱侧凸、塞佛氏病/跟骨骨突炎、脊柱疾病、脊髓骨赘病、椎管狭窄、强直性脊柱炎、脊椎前移、施普伦格耳畸形、滑膜炎、肌腱病变、网球肘、腱鞘炎、致死性发育不全或 Tietze 综合征。

在一些实施方案中，本发明提供用于治疗个体的消化系统疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗中枢神经系统的药、治疗胃肠系统的药、抗感染药、治疗代谢病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，胃肠疾病包括腺瘤结肠息肉、Alagille 综合征、肛门疾病、阑尾炎、巴雷特食管、胆道闭锁、胆道疾病、卡罗利病、乳糜泻、胆管炎、胆囊炎、胆石症、溃疡性结肠炎、克罗恩病、吞咽障碍、十二指肠的溃疡、痢疾、假膜性小肠结肠炎、食管失弛症、食管闭锁、食管炎、胰腺外分泌功能不全、脂肪肝、大便失禁、胃炎、肥厚性胃炎、胃肠炎、胃食管反流、胃肌轻瘫、痔疮、肝静脉血栓形成、肝炎、慢性肝炎、膈疝、食管裂孔疝、希尔施普龙病、高血压(HTN)、门静脉高压、炎性肠疾病、肠疾病、肠肿瘤、肠神经元发育异常、肠梗阻、肠易激综合征、乳糖不耐受、肝硬化、肝病、梅克尔憩室、胰腺疾病、胰腺肿瘤、胰腺炎、消化性溃疡、杰格斯综合征、直肠炎、直肠疾病、直肠脱垂、短肠综合征、气管食管瘘、惠普尔病或卓林格-艾丽逊综合征。

在一些实施方案中，本发明提供用于治疗个体口颌病、降低其发病率、

延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗感染药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，口顎病包括舌系带过短、夜磨牙症、口灼伤综合征、唇炎、巨颌症、唇裂、含牙囊肿、龈炎、良性迁移性舌炎、唇疱疹、路德维希咽峡炎、巨舌、迈-罗二氏综合征、牙周疾病、皮埃尔·罗班综合征、下颌前突、涎腺疾病、流涎、口疮性口炎、颞下颌关节障碍、颞下颌关节功能紊乱综合征或者口干燥症。

在一些实施方案中，本发明提供用于治疗个体的呼吸道疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗中枢神经系统的药、治疗心血管系统的药、抗感染药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，呼吸道疾病包括气道阻塞、呼吸暂停、石棉沉着病、哮喘、哮喘诱导的肌无力或者骨虚弱、肺膨胀不全、铍中毒、支气管疾病、支气管扩张、细支气管炎、闭塞性细支气管炎机化性肺炎、支气管炎、支气管肺发育不良、慢性阻塞性肺病(COPD)、感冒、咳嗽、胸腔积液、会厌炎、糖皮质激素(GC)引起的肌病或骨质减少、咯血、肺动脉高压、通气过度、卡塔格内综合征、肺脓肿、肺病、胎便吸入综合征、胸腔积液、胸膜炎、肺炎、气胸、肺泡蛋白质沉着症、慢性阻塞性肺病、肺水肿、肺栓塞、肺气肿、肺纤维化、呼吸窘迫综合征、新生儿呼吸过敏症、呼吸道感染、鼻硬结病、弯刀综合征、严重急性呼吸器官综合病、矽肺、睡眠呼吸暂停、中央喘鸣、气管狭窄、归因于哮喘的肌肉量或骨量减少、慢性阻塞性肺病(COPD)中的消耗、韦格纳氏肉芽肿或者百日咳。

在一些实施方案中，本发明提供用于治疗个体耳鼻喉疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗感染药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，耳鼻喉疾病包括中耳胆脂瘤、哮吼、耳聋、鼻出血、听力损失、听觉过敏、迷路炎、喉炎、喉

软化、喉狭窄、乳突炎、梅尼埃病、鼻塞、鼻息肉、耳炎、耳鼻喉病、耳硬化、咽炎、老年性耳聋、咽后脓肿、鼻炎、鼻窦炎、耳鸣、扁桃体炎、鼓膜穿孔、前庭神经元炎、声带麻痹或者语音障碍。

在一些实施方案中，本发明提供用于治疗个体神经系统疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、治疗中枢神经系统的药、抗感染药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，神经系统疾病包括自主神经系统疾病、中枢神经系统疾病、颅神经疾病、脱髓鞘疾病、神经系统畸形、神经病学表现或神经肌肉疾病。

在一些实施方案中，自主神经系统疾病包括灼性神经痛或反射性交感神经营养障碍。

在一些实施方案中，中枢神经系统疾病包括阿尔茨海默氏病、蛛网膜炎、脑脓肿、脑缺血、中枢神经系统感染、大脑性瘫痪、脑血管障碍、皮质基底节变性(corticobasal ganglionic degeneration, CBGD)、Creutzfeldt-Jakob 综合征、丹-沃二氏综合征、痴呆、脑炎、脑脊髓炎、癫痫症、癫痫症诱导的性腺机能减退和/或代谢增进状态、特发性震颤、弗里德赖希共济失调、杰茨曼-斯脱司勒-史茵克病、哈-斯二氏综合征、亨廷顿病、脑积水、缺氧、失眠、脑缺血发作 (ischemic attack)、库鲁病、Landau-Kleffner 综合征、Lewy 体病、马-约病、Meige 综合征、脑膜炎、细菌性脑膜炎、病毒性脑膜炎、偏头痛、运动障碍、多系统萎缩、脊髓炎、橄榄体脑桥小脑萎缩、帕金森病、帕金森障碍、脊髓灰质炎、脊髓灰质炎后综合征、朊病毒病、假脑瘤、希-德二氏综合征、婴儿痉挛、脊髓疾病、核上性麻痹、脊髓空洞症、丘脑疾病、抽搐性运动障碍、多动秽语综合征或葡萄膜脑膜脑炎综合征。在一些实施方案中，所述中枢神经系统疾病是囊性纤维化病诱导的性腺机能减退状态。

在一些实施方案中，颅神经疾病包括 Bell 麻痹、颅神经疾病、面部半侧萎缩、面神经痛、舌咽神经疾病、莫比乌斯综合征或者三叉神经痛。

在一些实施方案中，中枢神经系统疾病包括对中枢神经系统 (CNS) 的损伤或损害。在一些实施方案中，对 CNS 的损伤或损害可能与肌萎缩症有关。

对 CNS 的损伤或损害可以由例如疾病、创伤或化学试剂引起。其例子是中枢神经损伤或损害、周围神经损伤或损害和脊髓损伤或损害。

涉及脊髓损伤 (SCI) 患者的研究已经显示, 在 SCI 后, 中枢神经递质可能会改变, 造成下丘脑-垂体-肾上腺轴功能障碍, 它的破坏导致睾酮和其它激素水平的严重下降。SCI 或其它急性疾病或创伤特征性地包括分解代谢增强和合成代谢活动减低, 导致易于损失瘦身体组织的病症, 并经常伴随紊乱的营养利用。瘦体重的损失的影响包括伤口扩展和愈合机制受损, 使问题进一步复杂化。由于营养不良和蛋白分解代谢加上固定, 脊髓损伤的患者处于高度的患褥疮的风险中。

在一个实施方案中, 本发明的方法可以治疗各种 CNS 损伤。在一个实施方案中, CNS 损伤可以指神经细胞膜的分解, 或者在另一个实施方案中, 指神经不能产生或传播神经冲动, 或者在另一个实施方案中, 指神经细胞的死亡。损伤包括直接或间接影响 CNS 的正常功机能的损害。所述损伤可能是结构性、物理性或机械性损伤, 并可能在挤压、压缩或拉伸神经纤维的情况下由身体冲击造成。或者, 所述细胞膜可能因疾病、化合失调或生理功能障碍, 例如缺氧 (例如卒中)、动脉瘤或再灌注而被破坏或降解。CNS 损伤非限制性地包括例如对视网膜神经节细胞损害、外伤性脑损伤、卒中相关的损伤、脑动脉瘤相关的损伤、脊髓损伤 (包括单瘫、双侧瘫痪、截瘫、偏瘫和四肢瘫痪)、神经增殖性病症或神经性疼痛综合征。

由于对哺乳动物脊髓的损伤, 脊髓中神经之间的连接断裂。这种损伤阻断受该损伤影响的神经束的神经冲动的流动, 结果损害感觉功能和运动功能。对脊髓的损伤可能缘于脊髓的压缩或其它挫伤、脊髓挤压或切断。脊髓切断 (本文中也称为“横切”), 可能是脊髓的完全切断或可能是不完全切断。

在一些实施方案中, 治疗罹患 CNS 损伤 (或在另一个实施方案中为罹患脊髓损伤) 的个体的方法可能伴随用损伤部位的电刺激和给药嘌呤核苷或其类似物 (例如美国专利申请公开 20040214790A1 中所述) 治疗所述个体。

在一些实施方案中, 脱髓鞘疾病包括肾上腺脑白质营养不良、亚历山大病、卡纳万病、脱髓鞘病、Schilder 弥漫性脑硬化、球形细胞脑白质营养不良、异染性脑白质营养不良、多发性硬化或视神经脊髓炎。

在一些实施方案中, 神经系统畸形包括阿-蔡二氏畸形、夏-马-图三氏病、

脑膨出、遗传性运动和感觉性神经病、透明隔-视神经发育不良、隐性脊柱裂或椎管闭合不全。

在一些实施方案中，神经病学表现包括失认症、遗忘症、命名不能症、失语症、失用症、背痛、布朗-塞卡尔综合征、小脑性共济失调、舞蹈症、交流障碍、意识错乱、头晕、诵读困难、张力失常、面神经麻痹、肌束震颤、步态障碍、神经性头痛、偏瘫、记忆障碍、智力低下、缄默症、肌阵挛、颈痛、非语言学习障碍、嗅觉障碍、疼痛、麻痹、幻肢、面容失认症、四肢瘫痪、癫痫发作、痉挛、言语障碍、共同感觉迟发性运动障碍、味觉障碍、斜颈、震颤、牙关紧闭、意识丧失或眩晕。

在一些实施方案中，神经肌肉疾病包括肌萎缩侧索硬化、臂丛神经炎、臂丛神经病、延髓性麻痹、腕管综合征、肘管综合征、糖尿病神经病变、家族性自主神经异常、格-巴二氏综合征、遗传性感觉和自主神经系统神经病、米勒·费希尔综合征、运动神经元病、脊髓性肌萎缩、重症肌无力、先天性结构性肌病、神经卡压综合征、神经痛、神经肌肉疾病、家族周期性麻痹、周围神经系统疾病、POEMS 综合征、多神经病、多发性神经根病、雷夫叙姆病、坐骨神经痛、儿童脊髓性肌萎缩、僵人综合征(stiff-person syndrome)、胸廓出口综合征或尺神经压缩综合征。

在一个实施方案中，治疗罹患神经系统疾病的个体的方法包括治疗所述个体的任何继发性病症，所述病症由所述个体患有神经系统疾病而引起，其中的一些在本文中有叙述。

在一些实施方案中，本发明提供用于治疗个体的眼睛疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、治疗心血管系统的药、抗感染药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，眼睛疾病包括急性区域性隐匿性外层视网膜病变(acute zonal occult outer retinopathy)、埃迪综合征、白化病、眼睛黑蒙(ocular-amaurosis)、弱视(fugax)、弱视(amblyopia)、无虹膜、瞳孔不等、无眼畸形、无晶状体、散光、睑缘炎、眼睑下垂、睑痉挛、盲、白内障、睑板腺囊肿、脉络膜视网膜炎、无脉络膜、眼缺损、色觉缺陷、结膜炎、角膜疾病、角膜营养不良、角膜水肿、

角膜溃疡、糖尿病视网膜病变、复视、双行睫、干眼综合征、Duane 眼球后退综合征、睑外翻、睑内翻、内斜视、虹膜色素剥脱综合征、外斜视、眼出血、眼睛瘤、眼睑疾病、悬浮物、广泛纤维化综合征(general fibrosis syndrome)、青光眼、环状萎缩、偏盲、血小板病-白化病综合征、睑腺炎、霍纳综合征、远视、前房出血、虹膜炎、Kearns-Sayer 综合征、角膜炎、圆锥角膜、泪器疾病、泪管阻塞、晶体疾病、黄斑变性、小眼、近视、病理性眼震、Kearns-Sayer、动眼神经疾病、眼肌麻痹、视神经萎缩、视神经疾病、视神经炎、视神经病变、眶蜂窝织炎、视神经乳头水肿、Peter 异常、老视、翼状胬肉、瞳孔失调、屈光不正、视网膜脱离、视网膜疾病、视网膜静脉闭塞、视网膜色素变性、早产儿视网膜病、视网膜劈裂症、巩膜炎、暗点、斜视、Thygeson 表层点状角膜炎、沙眼、葡萄膜炎、白点综合征、视觉障碍或者玻璃体病症。

在一些实施方案中，本发明提供治疗个体的泌尿道和/或男性生殖器疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗胃肠系统的药、抗感染药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，泌尿系疾病和/或男性生殖器疾病包括抗肾小球基底膜疾病、阴茎头炎、膀胱外翻、膀胱肿瘤、隐睾症、间质性膀胱炎、肾性尿崩症、附睾炎、富尼埃坏疽、肾小球肾炎、古德帕斯丘综合征、血性精液、血尿、溶血尿毒症综合征、肾盂积水、尿道下裂、阳痿、不育、肾结石、急性肾功能衰竭、慢性肾功能衰竭、急性肾小管坏死、海绵肾、多囊性肾发育不良、遗传性肾炎、肾病、肾病综合征、夜尿、少尿、阴茎疾病、阴茎硬结、阴茎肿瘤、包茎、阴茎异常勃起、前列腺疾病、良性前列腺增生、前列腺肿瘤、蛋白尿、肾盂肾炎、赖特病、肾动脉梗阻、精索扭转、睾丸疾病、尿道狭窄、尿道炎、尿潴留、泌尿道感染、排尿障碍、泌尿道和男性生殖器疾病、泌尿系疾病、精索静脉曲张、膀胱或尿道回流。

在一些实施方案中，本发明提供治疗个体的皮肤病症、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明包含给予个体组合物，所述组合物包含化合物和抗癌药、免疫

调节剂、治疗皮肤病症的药、抗感染药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，皮肤病症包括痤疮、光线性角化病、脱发、雄激素性脱发、斑秃、继发化学疗法的脱发、继发放射疗法的脱发、由瘢痕形成诱导的脱发、应激诱导的脱发、血管瘤、足癣、水源性瘙痒症、特应性皮炎、脱发、早年脱发、男人性脱发、雄激素性脱发、基底细胞癌、烧伤、褥疮、白塞氏病、睑缘炎、疖、Bowen 病、大疱性类天疱疮、复发性口腔溃疡、痈、组织蜂窝炎、氯痤疮、手脚慢性皮炎、出汗不良症、感冒疮、接触性皮炎、匍行疹、头皮屑、皮炎、疱疹样皮炎、皮肤纤维瘤、尿布疹、湿疹、大疱性表皮松解症、丹毒、红皮病、擦伤水泡、生殖器疣、化脓性汗腺炎、荨麻疹、多汗症、鱼鳞病、脓疱病、边缘性皮霉菌病、卡波西肉瘤、瘢痕疙瘩、角化棘皮瘤、毛发角化病、虱感染、扁平苔癣、慢性单纯性苔癣、脂肪瘤、淋巴结炎、恶性黑色素瘤、黑斑病、痒、传染性软疣、钱币状皮炎、佩吉特乳头病、虱病、天疱疮、口周皮炎、光变态反应、光过敏、玫瑰糠疹、毛发红糠疹、银屑病、雷诺病、钱癣（ring worm）、酒渣鼻、疥疮、硬皮病、皮脂腺囊肿、脂溢性角化症、脂溢性皮炎、带状疱疹、皮肤癌、皮赘、蜘蛛状血管病、鳞状细胞癌、淤滞性皮炎、蜱叮咬、须癣、头癣、体癣、股癣、脚癣、甲癣、花斑癣、癣、潜蚤病、癜风病或疣。

在一个实施方案中，所述皮肤病症是伤口或烧伤。在一些实施方案中，发现伤口和/或溃疡从皮肤突出或在粘膜表面上或是器官梗死形成的结果。伤口可能是软组织缺损或损害或者潜在疾病的结果。在一个实施方案中，术语“伤口”指具有正常的组织结构完整性的破坏的身体损伤。该术语也包括术语“疮”、“损害”、“坏死”和“溃疡”。在一个实施方案中，术语“疮”指皮肤或粘膜的任何损害，术语“溃疡”指器官或组织表面的局部缺损或陷凹，其由坏死组织的腐离产生。损害一般与任意的组织缺损有关。坏死与由感染、损伤、发炎或梗死形成引起的死亡组织有关。所有这些都由术语“伤口”包括，所述“伤口”指愈合过程中的任意特定阶段的任何伤口，所述阶段包括任何愈合开始前的阶段，或甚至在产生特定伤口（像外科切口）（预防治疗）之前的阶段。

待根据本发明预防和/或治疗的伤口的例子是，例如无菌伤口、挫伤、切伤、撕裂伤、非穿透伤（即其中无皮肤破坏但损伤下面的结构的伤口）、开放性创伤、贯通伤、穿透伤、刺伤、脓毒性伤口、皮下创伤等。疮的例子有

褥疮、口疮、铬毒性溃疡、感冒疮、受压溃疡等。溃疡的例子是消化性溃疡、十二指肠溃疡、胃溃疡、痛风性溃疡、糖尿病性溃疡、高血压缺血性溃疡、淤积性溃疡、小腿溃疡(静脉溃疡)、舌下溃疡、粘膜下溃疡、症状性溃疡、营养不良性溃疡、热带溃疡、软下疳(例如由淋病(包括尿道炎、宫颈内膜炎和直肠炎)引起的)。与伤口或疮有关的可以根据本发明成功治疗的病症是烧伤、炭疽、破伤风、气性坏疽、猩红热(*scalatina*)、丹毒、寻常须疮、毛囊炎、传染性脓胞病或大疱性脓胞病等。术语“伤口”和“溃疡”以及“伤口”和“疮”的使用经常有一定的重叠,而且这些术语常常随机使用。因此,如上所述,在本文中,术语“伤口”包括术语“溃疡”、“损害”、“疮”和“梗死形成”,这些术语是不加区别地使用的,除非另外指出。

待根据本发明治疗的伤口种类还包括: i)一般的伤口,例如外科伤口、外伤、传染性伤口、缺血性伤口、烫伤伤口、化学伤口、大疱伤口; ii)特别针对口腔的伤口,例如拔牙后伤口、特别是与治疗囊肿和脓肿有关的牙髓伤口、细菌、病毒性或自免疫原性溃疡和损害、机械伤口、化学伤口、烫伤伤口、感染性伤口和苔癣样伤口; 具体例子是疱疹溃疡、疱疹性口炎、急性坏死性牙疳和口灼伤综合征; 和 iii)皮肤上的伤口,例如肿疡、烧伤(例如化学烧伤、烫伤)、损害(细菌性、病毒性、自免疫性)、咬伤和外科切口。其他的伤口分类方法是: i)归因于外科切口、轻微擦伤和轻微咬伤的小的组织损失,或 ii)严重的组织损失。后面的类别包括缺血性溃疡、受压溃疡、痙、撕裂、严重咬伤、热烧伤和供区伤(在软组织和硬组织中)和梗死形成。

在本发明的其他方面,待预防和/或治疗的伤口选自无菌伤口、梗死形成、挫伤、切伤、撕裂伤、非穿透伤、开放性创伤、贯通伤、穿透伤、刺伤、脓毒性伤口和皮下创伤。

与本发明有关的其它重要伤口是如缺血性溃疡、受压溃疡、痙、严重咬伤、热烧伤和供区伤的伤口。

在一个实施方案中,本文所述的化合物作为物理治疗/康复的辅药或作为同化剂用于伤口愈合。在另一个实施方案中,本文所述的化合物用于促进前交叉韧带(ACL)或内侧交叉韧带(MCL)损伤的愈合或加速 ACL 或 MCL 术后恢复。在另一个实施方案中,本文所述的化合物用于提高运动能力。在另一个实施方案中,本文所述的化合物用于治疗烧伤。在另一个实施方案中,

本文所述的化合物用于促进软骨再生。在另一个实施方案中，本文所述的化合物用于预防、治疗或逆转与长期的危重病、肺功能障碍、呼吸机依赖、衰老、AIDS、创伤、外科手术、充血性心力衰竭、心肌病、烧伤、癌症、COPD 相关的分解代谢。在另一个实施方案中，本文所述的化合物用于预防或逆转由创伤引起的蛋白质分解代谢。在另一个实施方案中，本文所述的化合物用作：a) 在外科手术中使用的灼烙疗法（cauterization therapy）（激光或辐射）的辅药以促进伤口愈合，b) 冷冻疗法的辅药以促进伤口愈合，c) 化学疗法的辅药以预防副作用，例如脱发、性腺功能减退症、肌萎缩，骨质减少、骨质疏松症、少肌症、LDL、甘油三酯(TG)或总胆固醇增加、HDL 减少。在另一个实施方案中，本文所述的化合物用于慢性分解代谢状态（昏迷、消耗性疾病、饥饿、进食障碍）；并发性骨折和肌肉损害；其中有明显的肌肉或骨消耗的危重病；和/或结缔组织疾病和病症。

缺血性溃疡和压迫溃疡是通常愈合得极慢的伤口，特别在这种情况下，改善而快速的愈合当然对病人很重要。而且，当愈合改善且发生得更快时，治疗罹患这种伤口的患者所涉及的费用显著减少。

供区伤的发生与例如硬组织从身体的一个部位移动至身体的另一个部位（例如移植）有关。由这种手术引起的伤口十分疼痛，因此，改善愈合十分有价值。

术语“皮肤”以非常广泛的意义使用，包括皮肤的表皮层，在皮肤或多或少地损伤的情况下，也包括皮肤的真皮层。除了角质层以外，皮肤的表皮层是外（上皮）层，而较深的皮肤结缔组织层称为真皮。

在一些实施方案中，烧伤与睾酮水平降低相关，而性腺功能减退症与伤口愈合延迟相关。在一个实施方案中，本发明的方法提供治疗罹患伤口或烧伤的个体。

在一些实施方案中，本发明提供用于促进前交叉韧带（ACL）或内侧交叉韧带（MCL）损伤愈合或加速 ACL 或 MCL 术后恢复的方法。

在一些实施方案中，本发明提供用于治疗个体的内分泌病症、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统药、治疗胃肠系统的药、

治疗皮肤病症的药、治疗中枢神经系统的药、抗感染药、治疗肝的药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，内分泌病症包括肢端肥大症、艾迪生病、肾上腺疾病、先天性肾上腺增生、雄激素不敏感综合征、先天甲状腺功能减退症、库欣综合征、尿崩症、糖尿病、1型糖尿病、2型糖尿病、糖尿病酮症酸中毒、空蝶鞍综合征、内分泌腺肿瘤、内分泌系统疾病、巨人症、性腺障碍、格雷夫斯病、两性同体、醛固酮增多症、高血糖高渗性非酮性昏迷、垂体功能亢进、高催乳素血症、甲状腺功能亢进症、性腺功能减退症、垂体功能减退症、甲状腺功能减退症、卡尔曼综合征、纳尔逊综合征、甲状旁腺疾病、垂体疾病、自身免疫性多内分泌腺病、青春期延迟、早熟青春期、肾性骨营养不良、甲状腺疾病、甲状腺激素抵抗综合征、甲状腺肿瘤、甲状腺结节、甲状腺炎、自身免疫性甲状腺炎、亚急性甲状腺炎或者 Wolfram 综合征。

在一个实施方案中，“性腺功能减退症”是由生殖腺功能性活动异常降低导致的或以其为特征的病症，并伴有生长和性发育延迟。

在一些实施方案中，本发明提供用于治疗个体的泌尿生殖器疾病和/或能育性、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明包含给予个体组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗感染药、治疗肾脏的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，泌尿生殖器疾病和/或能育性疾病包括流产、自发性骨盆粘连、外阴阴道念珠菌病、产后抑郁、妊娠糖尿病、精神性性交困难、难产、子痫、子宫内膜异位症、死胎、胎儿生长迟缓、胎盘破裂过早、女性生殖器疾病、女性生殖器肿瘤、葡萄胎、妊娠剧吐、不孕、卵巢囊肿、卵巢扭转、盆腔炎性疾病、胎盘疾病、胎盘功能不全、多囊卵巢综合征、羊水过多、产后出血、妊娠并发症、异位妊娠、外阴瘙痒、产褥期疾病、产褥感染、输卵管炎、滋养层肿瘤、子宫颈功能不全、子宫内翻、子宫脱垂、阴道疾病、外阴疾病、外阴硬化性苔癣（vulvar lichen sclerosis）。

在一些实施方案中，本发明提供用于治疗个体的血液和/或淋巴疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。

在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、抗感染药、治疗肝脏的药、治疗肾脏的药、治疗代谢病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，血液和/或淋巴疾病包括纤维蛋白原缺乏血症、贫血、再生障碍性贫血、溶血性贫血、先天非球形红细胞性贫血（congenital nonspherocytic anemia）、巨幼细胞贫血、恶性贫血、镰状细胞贫血、肾性贫血、血管淋巴样增生伴嗜酸细胞增多、抗凝血酶 III 缺乏、Bernard-Soulier 综合征、血液凝固障碍、血小板疾病、蓝色橡皮疱样痣综合征、切东二氏综合征、冷球蛋白血症、弥漫性血管内凝血、嗜酸粒细胞增多、Erdheim-Chester 病、胎儿幼红细胞增多症、伊万思综合征、因子 V 缺乏、因子 VII 缺乏、因子 X 缺乏、因子 XI 缺乏、因子 XII 缺乏、范科尼贫血、巨淋巴结增生、血液病、血红蛋白病、阵发性血红蛋白尿、血友病 A、血友病 B、新生儿出血病、组织细胞增多病、朗格汉斯细胞组织细胞增生症、非朗格汉斯细胞组织细胞增生症、乔布综合征、白血球减少症、淋巴结炎、淋巴管平滑肌增多症、淋巴水肿、高铁血红蛋白血症、骨髓增生异常综合征、骨髓纤维化、髓样化生、骨髓增殖性疾病、嗜中性白血球减少症、副蛋白血症、血小板存贮池缺乏、真性红细胞增多症、蛋白质 C 缺乏、蛋白质 S 缺乏、紫癜、血小板减少性紫癜症、血栓性血小板减少、RH-同种免疫、结节病、球形红细胞增多症、脾破裂、地中海贫血、血小板无力症、血小板减少、Waldenstrom 巨球蛋白血症或血管性血友病。

在一些实施方案中，本发明提供用于治疗个体的先天性、遗传性或新生儿疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统药物、治疗胃肠系统的药、治疗皮肤病症的药、治疗中枢神经系统的药、抗感染药、治疗肝脏的药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，先天性、遗传性或新生儿疾病包括艾卡迪综合征、羊膜带综合征、无脑畸形、Angelman 综合征、运动失调性毛细血管扩张症、Bannayan-Zonana 综合征、Barth 综合征、基底细胞痣综合征、贝-威二氏综

合征、布卢姆综合征、腮-耳-肾综合征、猫眼综合征、大脑性巨人症联合畸形综合征 (cerebral gigantism-charge syndrome)、染色体 16 异常、染色体 18 异常、染色体 20 异常、染色体 22 异常、Costello 综合征、猫叫综合征、Currarino syndrome 综合征、囊性纤维化病、De Lange 综合征、10q 远侧三体性 (distal trisomy 10q)、唐氏综合征、外胚层发育不良症、胎儿酒精综合征、胎儿疾病、胎儿-胎儿输血、脆 X 综合征、弗-谢二氏综合征、腹裂、先天性遗传性疾病、脐疝、前脑无裂畸形、色素失调症、伊维马克综合征、雅各布斯综合征、黄疸、克兰费尔特综合征、拉尔森综合征、劳-穆二氏综合征、无脑回、小头畸形、9p 单体性、指甲膝盖综合征、神经纤维瘤病、神经元蜡样质脂褐质沉积病、努南综合征、Ochoa 综合征(尿路面容综合征 (urofacial syndrome), 具有古怪面部表情的肾盂积水)、眼脑肾综合征、Pallister-Killian 综合征、帕-魏二氏综合征、Proteus 综合征、梨状腹综合征、Rett 综合征、罗比挠综合征、鲁-塔二氏综合征、脑裂、左右转位、史-伦-奥三氏综合征、Smith-Magenis 综合征、斯特季-韦伯二氏综合征、先天性梅毒、毛发低硫营养不良、三 X 女性、13 三体性(帕塔综合征)、9 三体性、特纳综合征、联体儿、乌谢尔综合征、瓦尔登布尔氏综合征、维尔纳综合征或 Wolf-Hirschhorn 综合征。

在一些实施方案中, 本发明提供用于治疗个体的结缔组织疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中, 所述方法包括向个体给药组合物, 所述组合物包含本发明的化合物和抗癌药物、免疫调节剂、治疗皮肤病症的药、抗感染药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中, 结缔组织疾病包括强直性脊柱炎、Ehlers-Danlos 综合征、亨诺-许兰氏紫癜、川崎病、马方综合征、结节性多动脉炎、多肌炎、银屑病关节炎、反应性关节炎、类风湿性关节炎、硬皮病、干燥综合征、干眼病、斯蒂尔病、系统性红斑狼疮、塔卡亚萨病或韦格纳肉芽肿病。

在一些实施方案中, 本发明提供用于治疗个体的代谢病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中, 所述方法包括向个体给药组合物, 所述组合物包含本发明的化合物和抗糖尿病药、治疗胃肠系统的药、治疗皮肤病症的药、治疗中枢神经系统的

药、抗感染药、治疗肝脏的药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，代谢病包括酸碱平衡失调、酸中毒、碱中毒、尿黑酸尿症、 α -甘露糖苷贮积症、先天性氨基酸代谢障碍、淀粉样变、缺铁性贫血、抗坏血酸缺乏、维生素缺乏症、脚气病、生物素酰胺酶缺乏、碳水化合物缺乏糖蛋白综合征、毒碱病症(carnitine disorders)、胱氨酸贮积症、胱氨酸尿、脱水、法布里病、脂肪酸氧化障碍、岩藻糖苷贮积症、半乳糖血症、戈谢病、吉尔伯特病、葡糖磷酸脱氢酶缺乏、戊二酸血症、糖原贮积病、Hartnup 病、血色素沉着病、血铁质、肝豆状核变性、组氨酸血症、同型胱氨酸尿症、高胆红素血症、高钙血症、高胰岛素血症、高钾血症、高脂血症、高草酸尿、维生素 A 过多症、低钙血症、低血糖症、低钾血症、低钠血症、低磷酸酯酶血症、胰岛素抵抗、碘缺乏、铁超负荷、慢性特发性黄疸、利氏病、莱-奈二氏综合征、亮氨酸代谢障碍、溶酶体贮积病、镁缺乏、枫糖尿病、Melas 综合征、门凯氏卷发综合征、代谢疾病、代谢综合征 X、先天性代谢缺陷、线粒体疾病、粘脂质累积病、粘脂质累积病、尼曼匹克病、肥胖症、鸟氨酸氨甲酰转移酶缺乏症、骨软化症、糙皮病、过氧化物酶体失调、苯丙酮尿、红血球生成性卟啉病、卟啉症、假性早衰、戈谢病、雷夫叙姆病、Reye 综合征、佝偻病、桑德霍夫病、饥饿、丹吉尔病、泰-萨克斯病、四氢生物蝶呤缺乏、三甲胺尿症(trimethylaminuria)、酪氨酸血症、尿素循环障碍、水电解质平衡失调、韦尼克脑病、维生素 A 缺乏病、维生素 B12 缺乏病、维生素 B 缺乏、沃尔曼病或 Zellweger 综合征。

在一些实施方案中，本发明提供用于治疗个体的环境因素诱发疾病(disorder of environmental origin)、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统药物、治疗胃肠系统的药、治疗皮肤病症的药、治疗中枢神经系统的药、抗感染药、治疗肝脏的药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，环境因素诱发疾病包括耳气压伤、咬伤和蜇伤、脑震荡、烧伤、中心核综合征、颅脑损伤、电击伤、骨折、冻伤、

热应激障碍、晕动病、职业病、中毒、惊吓婴儿综合征、肩损伤、太空运动病、脊髓损伤、痹性麻痹或伤口(贯通性和非贯通性)。

在一些实施方案中,本发明提供用于治疗个体的行为机制病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中,所述方法包括向个体给药组合物,所述组合物包含本发明的化合物和治疗心血管系统的药物、治疗中枢神经系统的药物、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一个实施方案中,行为机制病包括攻击、对死亡的态度、共同依赖、自伤行为、性行为或社会行为。

在一些实施方案中,本发明提供用于治疗个体精神障碍、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中,所述方法包括向个体给药组合物,所述组合物包含本发明的化合物和治疗中枢神经系统的药物、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中,精神障碍包括阿斯佩格综合征、注意力缺陷障碍伴多动、注意力缺陷障碍伴多动、双相型障碍、边缘型人格障碍、替身综合征、儿童行为障碍、战时神经症、循环性情感障碍、依赖性人格障碍、抑郁症、分离型精神障碍、心境恶劣障碍、进食障碍、纵火行为、疑病症、冲动控制障碍、克-列二氏综合征、精神障碍、儿童期诊断的精神障碍、多重人格障碍、米肖森综合征、芒氏综合征、代理明肖森综合征(Munchhausen by proxy)、自恋型人格障碍、发作性睡眠、强迫性障碍、性变态、恐怖症、精神病、不宁腿综合征、精神分裂症、季节性情感障碍、性欲和性表现障碍、心理性性功能障碍、睡眠障碍、躯体型障碍、创伤后应激障碍、物质相关性障碍、自杀行为或者拔毛狂。

在一个实施方案中,“抑郁”指涉及身体、情绪和思维的疾病,其影响人吃饭、睡觉的方式、自我感知和考虑事物的方式的想法。抑郁的体征和症状包括缺乏活动兴趣、食欲缺乏或进食过量、缺乏表情、空虚、感觉绝望、悲观、内疚或无助、社交退缩、疲劳、睡眠障碍、集中、记忆或作决定困难、躁动、易怒、头痛、消化障碍或慢性疼痛。

在一个实施方案中,“认知”指认识的过程,特别是保持清醒、认识、思维、学习和判断的过程。认知涉及心理学、语言学、计算机科学、神经科学、数学、习性学和哲学领域。在一个实施方案中,“情绪”指脾气或精神状态。

如本文所指的，变化指认知和/或情绪的任何积极或消极变化。

在一些实施方案中，本发明提供治疗个体的肝病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、治疗胃肠系统的药、抗感染药、治疗肝脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一个实施方案中，肝病包括肝癌、原发性胆汁性肝硬化、自身免疫性肝炎、慢性肝病、肝硬化、肝炎、病毒性肝炎(甲型肝炎、乙型肝炎、慢性乙型肝炎、丙型肝炎、慢性丙型肝炎、丁型肝炎、戊型肝炎、肝炎X)、肝功能衰竭、黄疸、新生儿黄疸、肝细胞瘤、肝癌、肝脓肿、酒精性肝病、血色素沉着病、肝豆状核变性病、门静脉高压、原发性硬化性胆管炎、结节病、绦虫、泡状棘球蚴病、片形吸虫病、血吸虫病、戈谢病、Zellweger综合征、酒精中毒、食物中毒、肺炎球菌性肺炎或者嗜盐弧菌。

在一些实施方案中，本发明提供用于治疗个体的肾疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗胃肠道系统的药、抗感染药、治疗肾脏的药、治疗代谢病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，肾病包括肢端肥大症、急性肾衰竭(ARF)(淀粉样变)、常染色体显性多囊肾病、肾结石、肾脏囊肿、常染色体隐性多囊肾病、慢性肾衰竭(CRF)、慢性肾病、科-勒二氏综合征、肺源性心脏病、冷球蛋白血症、糖尿病肾病、血脂异常、戈谢病、肾小球肾炎、肺出血肾炎综合征、溶血尿毒症综合征、肝炎、肾癌、肾结石、白血病、脂蛋白血症、狼疮、多发性骨髓瘤、肾炎、多动脉性肾囊肿(polyarterial kidney cysts)、链球菌感染后肾小球肾炎、肾小球肾炎、肾痛、先兆子痫、肾结核、肾盂肾炎、肾小管性酸中毒肾病、链球菌所导致的中毒性休克综合征、血栓栓塞、弓形体病、泌尿道感染、膀胱输尿管反流或者威廉斯综合征。

在一个实施方案中，所述肾疾病或病症是急性的，或者在另一个实施方案中是慢性的。在一个实施方案中，其中可以使用所述治疗方法的肾脏疾病或病症的临床适应症包括管型尿、测量的肾小球滤过率或其它肾功能指标。

在一个实施方案中，本发明的方法用于易患肾疾病或病症的个体。在一个实施方案中，关于个体的短语“易患肾疾病或病症”与短语“处于风险的个体”的同义，其包括处于患急性或慢性肾功能衰竭的风险，或如果合理地预计所述个体将罹患与功能性肾单位进行性损失相关的肾功能进行性损失，则所述个体处于需要肾替代疗法的风险。具体的个体是否处于风险是可以由相关医学或兽医学领域的普通技术人员按常规作出的决定。

在一个实施方案中，患有肾病的个体，特别是患有终末期肾脏疾病（ESRD）的男性个体罹患性腺功能减退症，其中一些患有伴发的中度至重度蛋白质能量营养不良（PEM），其造成更高的促红细胞生成素（EPO）需要量，更低的生活质量（QOL）分数和更高的死亡率。许多人具有与性腺功能减退症有关的其它症状，包括疲劳、缺乏食欲、肌无力等。在一些实施方案中，本发明的治疗方法用于治疗与性腺功能减退症有关的症状，所述性腺功能减退症在所述个体中由女性雄激素缺乏（ADIF）引起；由老年男性雄激素缺乏（ADAM）（包括疲劳、抑郁、性欲降低、勃起功能障碍、认知下降、情绪下降）引起；由雄激素不足（男性或女性）、雄激素缺乏（男性或女性）引起。

在一个实施方案中，糖尿病肾病是糖尿病的并发症，其进展得很早，通常在做出糖尿病的临床诊断之前。肾病变最早的临床证据是尿中出现低（但异常）水平（ >30 mg/天或 20 μ g/min）的白蛋白（微量蛋白尿），接着是持续10-15年的蛋白尿（ >300 mg/24 h 或 200 μ g/min）。在1型糖尿病患者，糖尿病性高血压通常在病人罹患微量蛋白尿之前或直到病人罹患微量蛋白尿时就十分明显。一旦出现明显的肾病变，肾小球滤过率（GFR）在一段时间（可能是几年）内下降，造成糖尿病个体的终末期肾脏疾病（ESRD）。

高血压是肾脏病的另一种共病因素。在一些实施方案中，根据本发明治疗肾脏病可以包括用本发明的化合物和治疗高血压的药剂进行同步治疗。

在一些实施方案中，本发明提供用于治疗个体的消耗性疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠道系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的

药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，消耗性疾病包括肌损伤、卧床休养、固定、神经损伤、神经病、糖尿病神经病变、酒精性神经病、脊髓亚急性联合变性、糖尿病、类风湿性关节炎、运动神经元疾病、迪谢内肌营养不良、腕管综合征、慢性感染、结核病、艾迪生病、成人脊髓性肌萎缩（sma）、肢体肌萎缩、酒精性神经病、厌食、神经性厌食、与恶病质相关的厌食、与衰老相关的厌食、后纵隔肿瘤（back tumour）、皮炎、髋关节癌、包涵体肌炎、色素失调症、肋间神经痛、幼年型类风湿性关节炎、累-卡-佩三氏病、肌萎缩、多灶性运动神经病变、肾病综合征、成骨不全、小儿麻痹症后期综合征、肋骨肿瘤、脊髓性肌萎缩、反射性交感神经营养不良综合征或泰-萨克斯病。

在本文中，消耗性病症或障碍定义为至少部分地以体重、器官质量或组织质量的异常的进行性损失为特征的病症或障碍。消耗性病症可以作为疾病例如癌症的结果而发生，或可归因于生理或代谢状态，例如废用性失调，所述废用性失调可以因长期卧床或当四肢被固定（例如在铸型中）时而发生，或因出现多个伤口（包括例如在糖尿病中出现的截肢、和其它病症）而发生，本领域的技术人员会理解这一点。消耗性病症也可以是年龄相关的。在消耗性病症过程中发生的体重减少的特征可以是总体重的减少或器官重量的减少，例如归因于组织蛋白减少的骨量或肌肉量的减少。

在一个实施方案中，术语“肌萎缩（muscle wasting）”或“肌萎缩（muscular wasting）”指肌肉量的进行性损失和/或肌肉的进行性衰减和退化，包括控制运动的骨骼肌或随意肌和控制心脏的心肌和平滑肌。在一个实施方案中，所述肌萎缩病症或障碍是慢性肌萎缩病症或障碍。“慢性肌萎缩”在本文中定义为肌肉量的慢性（即持续很长一段时间的）进行性损失和/或肌肉量的慢性进行性衰减和退化。

肌萎缩过程中发生的肌肉量损失可以是以由于肌肉蛋白分解代谢造成的肌肉蛋白分解或降解为特征。蛋白质分解代谢因为异常高速的蛋白质降解、异常低速的蛋白质合成或这两种的结合而发生。无论是由高度的蛋白质降解还是低度的蛋白质合成引起的肌肉蛋白分解代谢或消耗都会导致肌肉量的减少和肌萎缩。术语“分解代谢”具有本领域中普遍知晓的含义，特别是指能量燃烧形式的新陈代谢。

肌萎缩可以作为病状、疾病、病症或障碍（包括通过本发明的方法治疗的疾病，例如终末期肾功能衰竭）的结果而发生。

在一些实施方案中，本发明提供用于预防抑制素诱导的横纹肌溶解的方法。在一些实施方案中，本发明提供用于预防抑制素诱导的横纹肌溶解、器官衰竭或功能不全的方法。在一些实施方案中，本发明提供用于预防抑制素诱导的肾功能衰竭或肝功能衰竭或不全的方法。在一个实施方案中，所述方法包括向个体给药包含本发明的化合物和抑制素的组合物。

在一个实施方案中，所述消耗性疾病是个体的恶病质或非意愿体重减轻。在另一个实施方案中，本发明提供用于治疗、预防、抑制、减少或压制罹患肾脏病的个体的肌萎缩的方法。在另一个实施方案中，本发明提供用于治疗、预防、抑制、减少或压制罹患肾脏疾病或病症的个体的蛋白质分解代谢的方法。

恶病质是由疾病引起的或作为疾病副反应的虚弱和体重减少。由于疾病或损伤而长期住院或例如当肢体被固定时发生的废用性失调也能导致肌萎缩。研究显示，长期住院的罹患损伤、慢性病、烧伤、创伤或癌症的患者中，出现长期单侧肌萎缩和由此引起的体重减少。神经系统损伤，例如本文进一步叙述的脊髓损伤，也可能是致病因素。

在一些实施方案中，本发明提供用于治疗个体的消耗性疾病或病症、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在另一个实施方案中，所述消耗性疾病和病症尤其包括：a) 获得性免疫缺陷综合征（AIDS）消耗；b) 与卧床休息有关的消耗；c) 贪食症和/或与贪食症有关的消耗；d) 恶病质；e) 癌症恶病质；f) HIV 消耗；g) 由以下因素引起的减轻体重的恶病质和蛋白质损失：长期的危重病、肺功能障碍、呼吸机依赖、衰老、AIDS、创伤、充血性心脏衰竭、心肌病、烧伤、癌症、慢性阻塞性肺疾病（COPD）、进食障碍例如贪食病、神经性厌食、食欲缺乏、饥饿和/或抑郁。

在一些实施方案中，本发明提供用于治疗个体的无效状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述无效状态是小儿麻痹症后期综合征。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和免疫调节

剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠道系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。

在一些实施方案中，本发明用本发明的化合物提供辅助治疗。例如，在一个实施方案中，在疾病、障碍或病症的治疗（其中使用锻炼和限制饮食）中，给药本发明的化合物包括在这种治疗方案中。例如，在一个实施方案中，如本领域的技术人员将认识的，用本发明的化合物进行的辅助疗法或治疗，结合限制饮食和/或锻炼的，可能是用于治疗胰岛素抵抗、葡萄糖耐受不良、体重减轻、糖尿病、心血管疾病、代谢综合征、癌症、肌萎缩等的疗法。

在一些实施方案中，本发明提供用于治疗个体的性腺功能减退状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明提供用于治疗个体的药物治疗诱导的性腺功能减退状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一些实施方案中，性腺功能减退症是由治疗引起的，所述治疗改变激素自女性和男性性腺的分泌。在一些实施方案中，性腺功能减退症可能是“原发性的”或“中枢性的”。在原发性性腺功能减退症中，卵巢或睾丸本身不正常地发挥作用。在一些实施方案中，性腺功能减退症可能是由外科手术、辐射、遗传性病症和发育障碍、肝病和肾病、感染或某些自免疫疾病诱导的。在一些实施方案中，绝经是性腺功能减退症的形式。在一些实施方案中，绝经可能导致闭经、热潮红、阴道干燥或归因于女性雌激素水平下降的易激惹。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素或它们的组合。

在一些实施方案中，本发明提供用于治疗个体的骨质减少状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明提供用于治疗个体的药物治疗诱导的骨质减少状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一些实施方案中，骨质减少是骨量的轻微减少。在一些实施方案中，骨质

减少是骨质疏松症的前兆。在一些实施方案中，骨质减少定义为比正常年青成人的骨密度低 1-2.5 个标准偏差 (SD) 的骨密度。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素或它们的组合。

在一些实施方案中，本发明提供用于治疗个体的少肌状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明提供用于治疗个体的药物治疗诱导的少肌状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一些实施方案中少肌症是严重的肌肉量减少。在一个实施方案中，少肌症的定义是具有比低于正常年青成人的平均值 2 个标准偏差更低的瘦体重。在一些实施方案中，少肌症由以下原因引起：遗传因素、循环系统改变、毛细血管:肌纤维比率降低、运动神经元改变、去神经支配、运动神经末梢板衰退、I 型纤维选择性神经移植术、造成肌肉损害的炎症应答、运动减少、营养不良、低膳食蛋白摄入量、维生素 D 缺乏、年龄相关的维生素 D 减少、氧化性应激、肌肉线粒体突变、特定类型肌纤维的改变、肌肉蛋白减少、致残疾病、卒中、阿尔茨海默氏病、帕金森病、骨质疏松症、动脉粥样硬化、糖尿病、高胰岛素血症、肾功能衰竭或性腺功能减退症。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含 SARM 化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素或它们的组合。

在一些实施方案中，本发明提供用于治疗个体的如上文所述的疾病和/或病症的组合、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的

药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素或它们的组合。

应该理解，如本文所述的本发明的任何方法都包括向个体给药本文所述的化合物或包含它的组合物，以治疗所指的疾病、障碍或病症。每一种本文所述的方法和/或其全部还可能包括给药本文所述的其它治疗剂，本领域的技术人员会理解这一点。

在一些实施方案中，本发明提供用于促进例如乳、精子或卵细胞的产生的方法。在一些实施方案中，本发明提供用于促进瘦肉或卵细胞的产生的方法。在一些实施方案中，本发明提供用于提高饲喂或配种牲畜的生产力的方法，例如增加精子计数、改善精子形态等。在一些实施方案中，本发明提供用于延长农场动物（例如产蛋母鸡、产奶奶牛等）的生产期和/或提高兽群健康（例如改善免疫清除、强壮动物）的方法。

在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素、营养添加剂、激素（每一种和/或全部均如本文所述）、或如本文所述的任何其它治疗剂、或它们的组合。

在另一个实施方案中，本发明提供用于治疗个体的以下疾病的方法：囊性纤维化病及由其引起的诱导性性腺功能减退状态、癫痫及由其引起的诱导性性腺功能减退状和/或代谢亢进状态、遗传性血管性水肿、红斑狼疮及由其引起的 BMD 下降、饮酒和抽烟诱导的骨质疏松症，所述方法包括向所述个体给药本文所述的 SARM。

在另一个实施方案中，本发明提供用于治疗个体的以下疾病的方法：小儿麻痹症和小儿麻痹后综合征及其它无效状态、抑制素诱导的横纹肌溶解症、抑制素诱导的肌无力、抑制素诱导的器官衰竭或功能不全，所述方法包括给药本文所述的化合物和任选适当的抑制素（本领域的技术人员会理解这一点），和/或任何治疗剂。

在另一个实施方案中，本发明提供用于治疗阿片样物质诱导的雄激素缺乏（OPIAD）的方法，所述方法包括向个体给药本文所述的化合物和任选地

阿片剂、阿片样物质、麻醉药等、美沙酮、长效阿片剂/阿片样物质例如 Kadian、缓释吗啡（所有阿片剂/阿片样物质/麻醉药均获得 FDA 批准）、用于治疗海洛因成瘾的阿片剂/阿片样物质、用于治疗恶性肿瘤慢性疼痛的阿片剂/阿片样物质、用于治疗非恶性肿瘤的慢性疼痛综合征的阿片剂/阿片样物质。

在另一个实施方案中，本发明提供用于治疗神经系统疾病、障碍或病症的方法，所述方法包括向所述个体给药本文所述的化合物和任选的抗精神病药（例如佐替平、氟哌啶醇、氨磺必利、利培酮、其它多巴胺 D2 受体拮抗剂）、抗癫痫病药物（例如丙戊酸、卡马西平、奥卡西平（oxcarbamazepine）等）或它们的组合物。

在另一个实施方案中，本发明提供用于治疗激素依赖性疾病、障碍或病症的方法，所述方法包括向所述个体给药本文所述的化合物和任选地化疗剂和治疗（甲氨蝶呤、环磷酰胺、异环磷酰胺、阿霉素、多柔比星、糖皮质激素、环孢菌素、L-甲状腺素、SERM、抗炎药、氟维司群、GnRH 剂、ADT、中止激素替代疗法、颅脑照射、周边照射（peripheral irradiation）等；诱导高催乳素血症（prolactinemia）的药物治疗（通过 5HT2 受体作用的血清素能性的抗抑郁剂、选择性血清素再摄取抑制剂、单胺氧化酶抑制剂、三环抗抑郁剂、抗高血压药例如甲基多巴、利血平、可乐定和维拉帕米；抗多巴胺能的止吐药例如甲氧氯普胺，H2 受体拮抗剂例如西咪替丁和雷尼替丁，雌激素，苯丙胺，AR 部分拮抗剂（酮康唑、螺内酯、依普利酮）

在另一个实施方案中，如本文所述的本发明的化合物和组合物用于促进或加速手术操作后恢复。

在一个实施方案中，本发明提供本文所述的化合物用于减少个体的脂肪量的用途。在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合或者含有它们的组合物的这种使用方法。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合或者含有它们的组合物的以下用途：治疗腹部脂肪累积；治疗肥胖性少肌症；改善身体成分；减少体脂含

量；减少脂肪量；改善血脂谱（profile），增加肌肉量/肌肉强度/肌肉功能；增加骨量/BMD/骨强度/骨功能；减少体脂；先天性高胰岛素血症；库欣病（高皮质醇血症（hypercortisolemia））；个体的与代谢综合征相关的肥胖症或糖尿病。

在另一个实施方案中，所述个体患有激素失调、激素病症或激素疾病。在另一个实施方案中，所述个体处于绝经。

在一个实施方案中，本发明提供本文所述的化合物用于增加个体的瘦体重的用途。在另一个实施方案中，这种用途包括给药本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合。

在一个实施方案中，所述个体患有激素失调、激素病症或激素疾病。在另一个实施方案中，所述个体处于绝经。

实施例 15 显示，式(I)的化合物是合成代谢性的，但是其雄激素性最低，因此，这种化合物可以用于治疗过去雄激素是禁忌的患者群。无论睾酮是否存在，式(I)的化合物都显示促进肌肉生长，同时对前列腺施加抗增殖作用，因此，在一个实施方案中，本发明的方法用于恢复患有少肌症或恶病质的个体损失的肌肉量。

在一个实施方案中，本文所述的化合物改变个体的瘦素水平。在另一个实施方案中，本文所述的化合物降低瘦素的水平。在另一个实施方案中，本文所述的化合物增加个体的瘦素水平。已知瘦素对肥胖症小鼠的食欲、体重减轻有影响，因此其已与肥胖症有关。

在一个实施方案中，本文所述的化合物影响瘦素的循环水平，在另一个实施方案中，影响瘦素的组织水平。在一个实施方案中，术语“瘦素的水平”指瘦素的血清水平。如本文所指的，本发明的化合物对体外和体内的瘦素有影响。瘦素的水平可以用本领域的技术人员已知的方法来测定，例如通过可商购的 ELISA 试剂盒来测定。而且，可以通过本领域技术人员已知的任何方法在体外测定或体内测定中测定瘦素的水平。

由于瘦素与控制食欲、减轻体重、摄取食物和能量消耗有关，所以，调节和/或控制瘦素的水平是治疗、预防、抑制罹患肥胖症个体的肥胖症、降低其发病率的有用的治疗方法。调节瘦素的水平可以导致缺乏食欲、减少食物

摄取、增加瘦素个体的能量消耗，因此，可能有利于控制和治疗肥胖症。

在一个实施方案中，术语“肥胖症”定义为由脂肪在身体内过度累积导致体重增加超过骨骼的限制和身体的需要

在一个实施方案中，术语“肥胖症相关的代谢失调”指由肥胖症引起的、作为肥胖症的后果的、因肥胖症而加重的或继发于肥胖症的病症。这种病症的非限制性的例子是骨关节炎、II型糖尿病、血压增加、卒中和心脏病。

胆固醇、甘油三酯和其它脂质通过脂蛋白在体液中运输，所述脂蛋白可以根据它们的密度划分为例如极低密度脂蛋白（VLDL）、中密度脂蛋白（IDL）、低密度脂蛋白（LDL）和高密度脂蛋白（HDL）。

已显示，LDL-胆固醇在血液中的高水平与动脉粥样硬化有关，动脉粥样硬化是部分地以脂质在动脉特别是冠状动脉的内壁中沉积为特征的进行性疾病。而且已经显示，也 LDL-胆固醇的高血液水平与冠心病有关。而且，HDL 胆固醇的血液水平与冠心病之间存在负相关。

血液中的总胆固醇水平（其为 HDL-胆固醇、LDL-胆固醇、VLDL-胆固醇和乳糜微粒-胆固醇的总和）不一定是冠心病和动脉粥样硬化风险的预兆。

但是，动脉粥样硬化和 LDL 胆固醇水平之间的关联比动脉粥样硬化和总血清胆固醇水平之间的类似关联高得多。

在一个实施方案中，本发明提供将本文所述的化合物用于改善个体的脂质谱和/或减少循环脂质水平的使用方法。在一些实施方案中，根据本发明的这一方面，所述个体罹患选自以下的一种或多种病症：动脉粥样硬化症及其相关疾病、过早衰老、阿尔茨海默氏病、卒中、中毒性肝炎、病毒性肝炎、周围血管功能不全、肾病和高血糖症，而且本发明用于给药本文所述的化合物或含有它的组合物，在一些实施方案中，所述化合物或组合物积极地影响所述个体的脂质谱，这是所述方法用于治疗所指的疾病、障碍和病症的一种手段。

在一个实施方案中，本发明提供治疗动脉硬化症及其相关疾病，例如心血管病症、脑血管障碍、周围血管病症、肠血管病症或它们的组合。

在一个实施方案中，心血管病症包括高血压（HTN）、冠脉疾病（CAD）或心肌灌注。在另一个实施方案中，本发明提供本文所述的 SARM 化合物用于促进主动脉平滑肌细胞增殖的使用方法。在另一个实施方案中，本发明提

供本文所述的化合物用于治疗动脉粥样硬化的使用方法。在另一个实施方案中，本发明提供本文所述的化合物用于降低血压的使用方法。在另一个实施方案中，本发明提供本文所述的化合物用于治疗心脏疾病和病症（包括心脏病、心功能不全例如心肌梗死、心脏肥大和充血性心力衰竭（cognitive heart failure））的使用方法。在另一个实施方案中，本发明提供本文所述的化合物用于保护心脏（包括在胰岛素抵抗中的保护心脏）的使用方；治疗 I 型和 II 型糖尿病、代谢综合征、X 综合征和/或高血压的使用方法。

在一个实施方案中，本发明提供用于治疗、预防个体的心血管和/或脑血管疾病、降低其死亡风险的方法，所述方法包括给药式(I)的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合、或者含有它们的药物组合物。在一个实施方案中，所述化合物以式(I)的结构为特征。

在一个实施方案中，式 I 的化合物降低 LDL 和总胆固醇的水平。在另一个实施方案中，式(I)的化合物降低个体的 LDL 和总胆固醇的水平。

在另一个实施方案中，式 I 的化合物与升高 HDL 的药剂联合给药。在另一个实施方案中，式(I)的化合物与升高 HDL 的药剂联合给药。在另一个实施方案中，升高 HDL 的药剂包括烟酸。在另一个实施方案中，所述升高 HDL 的药剂包括贝特类，所述贝特类包括吉非贝齐（Lopid）、硫脲系吉非贝齐类似物和非诺贝特（TriCor）。在另一个实施方案中，升高 HDL 的药剂包括他汀类药物。在另一个实施方案中，升高 HDL 的药剂包括 1-羟基烷基-3-苯硫脲及其类似物。

在一个实施方案中，本发明提供用于降低个体的循环脂质水平的方法，所述方法包括给药式 I 的化合物或其药学上可接受的盐、水合物、*N*-氧化物或它们的任意组合、或者含有它们的组合物。在一个实施方案中，所述个体罹患动脉粥样硬化及其相关疾病、过早衰老、阿尔茨海默氏病、卒中、中毒性肝炎、病毒性肝炎、周围血管功能不全、肾病、高血糖或它们的任意组合。

在一个实施方案中，本发明提供用于治疗个体的动脉粥样硬化及其相关疾病（例如心血管病症、脑血管障碍、周围血管病症或肠血管病症）的方法，所述方法包括向所述个体给药式 I 的化合物或其药学上可接受的盐、水合物、*N*-氧化物或它们的任意组合、或者含有它们的组合物的步骤。所述方法还可

以包括同时、随后或在先给药已知可用于治疗心血管疾病、脑血管障碍、周围血管病症或肠血管病症的一种或多种药剂。

在一个实施方案中，本发明提供改善个体的灵活性和运动的方法，例如通过治疗所述个体的关节炎。

在另一个实施方案中，术语“关节炎”指主要发生在老年人中的非炎性退行性关节病，它以关节软骨变性、骨头及边缘肥大、滑膜改变等为特征。在另一个实施方案中，它还伴有疼痛和僵硬，特别是在长期活动之后。

在一个实施方案中，术语“糖尿病”指胰岛素的相对或绝对缺乏，导致不受控制的糖代谢。大多数患者在临床上可被划分为患胰岛素依赖型糖尿病（IDDM 或 I 型糖尿病）或非胰岛素依赖型糖尿病（NIDDM 或 II 型糖尿病）。

在其它实施方案中，术语“血压增加”或“高血压”指在超过 90/140 mmHg 的重复性高血压。慢性高血压可以造成眼底血管改变、心肌增厚、肾功能衰竭和脑损害。

在其它实施方案中，术语“卒中”指由于供血不足引起脑神经细胞损害，所述供血不足经常由血管破裂或血凝块造成。在其它实施方案中，术语“心脏病”指心脏正常功能和活动发生障碍，包括心力衰竭。

而且，最近显示，雄激素涉及多能间质细胞定型为肌源性谱系并阻止分化为成脂谱系（Singh 等人, *Endocrinology*, 2003, 7 月 24 日）。因此，所述化合物可用于本文所述的阻止脂肪生成和/或改变干细胞分化的方法。

在另一个实施方案中，本发明涉及加速、增加或促进个体减轻体重的方法，所述方法包括向所述个体给药有效加速、增加或促进所述个体减轻体重的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及降低、压制、抑制或减少个体的食欲的方法，所述方法包括向所述个体给药有效降低、压制、抑制或减少所述个体的食欲的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及改变个体的身体成分的方法，所述方

法包括向所述个体给药有效改变所述个体的身体成分的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。在一个实施方案中，改变所述身体成分包括改变所述个体的瘦体重、去脂体重或它们的组合。

在另一个实施方案中，本发明涉及改变个体的瘦体重或去脂体重的方法，所述方法包括向所述个体给药有效改变所述个体的瘦体重或去脂体重的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及将个体的脂肪转化为瘦肌肉的方法，所述方法包括向所述个体给药有效将所述个体的脂肪转化为瘦肌肉的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及治疗个体的肥胖症相关的代谢失调的方法，所述方法包括向所述个体给药有效治疗所述个体的肥胖症相关的代谢失调的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及预防、压制、抑制或减轻个体的肥胖症相关的代谢失调的方法，所述方法包括向所述个体给药有效预防、压制、抑制或减轻个体的肥胖症相关的代谢失调的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体或它们的任意组合的步骤。

在一个实施方案中，所述肥胖症相关的代谢失调是高血压。在另一个实施方案中，所述病症是骨关节炎。在另一个实施方案中，所述病症是Ⅱ型糖尿病。在另一个实施方案中，所述病症是血压增加。在另一个实施方案中，所述病症是卒中。在另一个实施方案中，所述病症是心脏病。

在另一个实施方案中，本发明涉及降低、压制、抑制或减少个体脂肪形

成的方法，所述方法包括向所述个体给药本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及改变个体的干细胞分化的方法，所述方法包括向所述个体给药有效改变所述个体的干细胞分化的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在一个实施方案中，本文所述的化合物用于：a) 治疗、预防、压制、抑制或减轻肥胖症；b) 加速、增加或促进减轻体重；c) 降低、压制、抑制或减少食欲；d) 改变身体成分；e) 改变瘦体重或去脂体重；f) 将脂肪转化为瘦肌肉；g) 治疗、预防、压制、抑制或减轻肥胖症相关的代谢失调，例如高血压、骨关节炎、糖尿病、青春晚期糖尿病（MODY）、血压增加、卒中或心脏病；h) 降低、压制、抑制或减少脂肪形成；i) 改变干细胞分化；和/或 j) 改变瘦素水平。

在一个实施方案中，本文所述的化合物用于治疗或中止糖尿病的进展或治疗糖尿病症状。在另一个实施方案中，本文所述的化合物用于治疗与糖尿病相关的并发症。这些病症包括：高血压（HNT）、脑血管病、冠状动脉粥样硬化性心脏病、黄斑变性、糖尿病视网膜病（眼病）和失明、白内障一全身性炎症（以炎症指标例如红细胞沉降率或C反应蛋白的增加为特征）、出生缺陷、与妊娠有关的糖尿病、先兆子痫和妊娠高血压、肾病（肾功能不全、肾功能衰竭等）、神经疾病（糖尿病神经病变）、浅表和全身性真菌感染、充血性心力衰竭、痛风/高尿酸血症、肥胖症、高甘油三酯血症、高胆固醇血症、脂肪肝症（非酒精性脂肪性肝炎或NASH）、以及糖尿病相关的皮肤病例如糖尿病脂性渐进坏死（NLD）、糖尿病大水泡（糖尿病性大疱症）、发疹性黄瘤、Digital Sclerosis、播散性环状肉芽肿和黑棘皮病。

在一个实施方案中，本发明提供治疗、压制、抑制以下人类个体的疾病、或降低其发病率的方法：(a) I型糖尿病；(b) II型糖尿病；(c) 葡萄糖耐受不良；(d) 高胰岛素血症；(e) 胰岛素抵抗；(f) 肾病；(g) 糖尿病神经病变；(h) 糖尿病视网膜病；(i) 脂肪肝症；(j) MODY 和(k) 心血管疾病，所述方法包

括向所述个体给药式(I)的化合物的步骤。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于与患糖尿病的个体相关的疾病或病症的应用或治疗。在一个实施方案中，寻求通过本发明的方法治疗的个体是患有 I 型糖尿病的个体。I 型糖尿病以胰腺 β 细胞的自身免疫破坏为特征。90%的个体在诊断时出现所述 β 细胞的免疫破坏标志，所述标志包括胰岛细胞(ICA)抗体、谷氨酸脱羧酶(GAD)抗体和胰岛素(IAA)抗体。尽管这种形式的糖尿病通常发生于儿童和青少年中，但是它可以发生于任何年龄。年轻个体的通常具有快速的 β 细胞破坏并与同时存在酮症酸中毒，而成年人经常保持充足的胰岛素分泌以防止酮症酸中毒达许多年。最终，所有 I 型糖尿患者需要胰岛素疗法以保持血糖量正常。

在一个实施方案中，本发明提供治疗 II 型糖尿病的方法。II 型糖尿病以胰岛素抵抗为特征，而且在该疾病发病的某个阶段以胰岛素分泌相对不足为特征。血浆胰岛素浓度（禁食和膳食刺激的）的绝对值通常增加，但是“相对于”胰岛素抵抗的严重性，血浆胰岛素浓度不足以维持正常的葡萄糖稳态。然而，随着时间推移，出现进行性 β 细胞衰竭，接着发生胰岛素绝对值不足。大多数患有 II 型糖尿病的个体表现出腹内性（内脏性）肥胖症、与胰岛素抵抗的存在密切相关的脂肪肝。所述患者的肝脏变成胰岛素抵抗性，糖原分解不受控制，结果是增加的、非生理性的葡萄糖被输送至血液中。肝脏产生的胆固醇和 VLDL 颗粒也不受控制。而且，这些个体通常存在高血压、血脂异常（高甘油三酯水平和低 HDL-胆固醇水平；餐后高脂血症）和 PAI-1 水平升高。这一连串异常被称为“胰岛素抵抗综合征”或“代谢综合征”或肥胖症相关的病症。由于这些异常，II 型糖尿病的患者罹患大血管并发症例如心肌梗死和卒中的风险增大。

在一个实施方案中，本发明提供治疗糖尿病肾病的方法。糖尿病肾病是糖尿病的并发症，其进展得很早，通常在做出糖尿病的临床诊断之前。肾病变最早的临床证据是尿中出现低（但异常）水平（ >30 mg/天或 20 $\mu\text{g}/\text{min}$ ）的白蛋白（微量蛋白尿），接着是持续 10-15 年的蛋白尿（ >300 mg/24 h 或 200 $\mu\text{g}/\text{min}$ ）。在 I 型糖尿病患者，糖尿病性高血压通常在病人罹患微量蛋白尿之前或直到病人罹患微量蛋白尿时就十分明显。一旦出现明显的

肾病变，肾小球滤过率（GFR）在一段时间（可能是几年）内下降，造成糖尿病个体的终末期肾脏疾病（ESRD）。

在一个实施方案中，本发明提供治疗糖尿病神经病变的方法。糖尿病神经病变是由糖尿病引起的神经病症家族。糖尿病神经病变造成手、臂、足和腿麻木，有时造成它们疼痛和无力。糖尿病中的神经病学问题可能发生于每一个器官系统，包括消化道、心脏和生殖器。糖尿病神经病变划分为周围神经病变、自主神经病变、近端神经病变的和局灶性神经病变。周围神经病变造成趾、足、腿、手和臂的疼痛或感觉缺失。自主性神经病变造成消化、肠和膀胱功能、性反应和出汗的变化，也可影响服务心脏和控制血压的神经。近端神经病变造成股、髋或臀疼痛并导致腿无力。局灶性神经病变导致一条神经或一组神经的突然衰弱，造成肌无力或肌痛。身体内的任何神经都可能受影响。

在一个实施方案中，本发明提供治疗糖尿病视网膜病的方法。糖尿病对眼的影响称为糖尿病视网膜病。糖尿病患者更可能罹患眼疾，例如白内障和青光眼。糖尿病视网膜病对视觉的影响变化很广，取决于该疾病的阶段。糖尿病视网膜病的一些共有症状是视力模糊（这经常与血糖水平有关）、漂浮物（floaters）和闪烁（flashes）以及视力突然丧失。

在一个实施方案中，寻求通过本发明的方法治疗的个体是患有葡萄糖耐受不良的个体。葡萄糖耐受不良是糖尿病前期，其中，血糖高于正常水平，但没有高到确保诊断为糖尿病。

在一个实施方案中，寻求通过本发明的方法治疗的个体是患有高胰岛素血症的个体。高胰岛素血症是导致胰腺分泌过量胰岛素的潜在问题的征兆。高胰岛素血症的最普遍的原因是胰岛素抵抗，在这种病症中，你的身体对抗胰岛素的效应，而胰腺试图通过产生更多胰岛素来补偿。高胰岛素血症与 II 性糖尿病有关。

在一个实施方案中，寻求通过本发明的方法治疗的个体是患有胰岛素抵抗的个体。胰岛素抵抗是其中正常量的胰岛素不足以使脂肪细胞、肌细胞和肝细胞产生正常的胰岛素反应的病症。脂肪细胞中的胰岛素抵抗造成储存的甘油三酯水解，这提高血浆中游离脂肪酸的水平。肌肉中的胰岛素抵抗减少葡萄糖的摄入，而肝脏中的胰岛素抵抗减少葡萄糖储存，这两种效应帮助提

高血糖。归因于胰岛素抵抗的高水平的血浆胰岛素是葡萄糖经常导致代谢综合征和 II 型糖尿病。

糖尿病和肝肥胖症一般与游离脂肪酸 (FFA) 水平升高有关, 游离脂肪酸促进靶组织中的脂质蓄积和胰岛素抵抗, 即主要减弱胰岛素在骨骼肌和肝脏中的作用。胰岛素的突出作用是减少自肝脏的葡萄糖输出。FFA 刺激肝脏糖异生, 只要糖异生与肝糖原分解降低平行进行 (被称为“肝自身调节”的补偿过程), 糖异生本身不会导致肝脏葡萄糖输出增加。FFA 刺激胰岛素分泌, 而胰岛素通过抑制胰高血糖素 (糖原分解的诱导物) 的分泌部分地阻止糖原分解。然而, 长期高水平的 FFA 导致肝脏胰岛素抵抗, 并因此破坏肝自身调节, 导致肝葡萄糖产生增加和罹患 II 型糖尿病。脂肪肝和肝脏胰岛素抵抗是高血糖和 II 型糖尿病的主要驱动力。

在一个实施方案中, 本发明提供抑制 (改善) 脂肪肝的方法, 所述方法肝中的胰岛素抵抗被抑制 (改善), 由此解决 II 型胰岛素的基本问题。

在另一个实施方案中, 所述糖尿病是 I 型糖尿病。在另一个实施方案中, 所述糖尿病是 II 型糖尿病。

在一个实施方案中, 本发明提供治疗、压制、抑制人类个体的糖尿病、降低其发病率的方法, 所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在另一个实施方案中, 所述糖尿病是 I 型糖尿病。在另一个实施方案中, 所述糖尿病是 II 型糖尿病。

在一个实施方案中, 本发明提供治疗患有葡萄糖耐受不良的人类个体的方法, 所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中, 本发明提供治疗人类个体的高胰岛素血症的方法, 所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中, 本发明提供治疗人类个体的胰岛素抵抗的方法, 所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中, 本发明提供治疗人类个体的糖尿病肾病的方法, 所

述方法包括向所述个体给药式 I 的选择性雄激素受体调节剂化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的糖尿病神经病变的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的糖尿病视网膜病的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的脂肪肝症的方法，所述方法包括所述个体给药式 I 的选择性雄激素受体调节剂化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的血管疾病的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供用于 a) 治疗、预防、压制、抑制动脉粥样硬化，b) 治疗、预防、压制、抑制归因于脂肪沉积的肝损害的方法，所述方法包括向所述个体给药有效治疗、预防或抑制动脉粥样硬化和归因于脂肪沉积的肝损害的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体或它们的任意组合、或者含有它们的组合物的步骤。

在一个实施方案中，本文所述的化合物用于：a) 治疗、预防、压制、抑制或减轻动脉粥样硬化；b) 治疗、预防、压制、抑制归因于脂肪沉积的肝损害。

在一个实施方案中，动脉粥样硬化指可能从损害动脉最内层开始的慢性复杂疾病。在另一个实施方案中，损害动脉壁的原因可能包括：a) 血液胆固醇水平提高；b) 高血压；c) 烟草烟雾；d) 糖尿病。在另一个实施方案中，吸烟者的这一病症是可治疗的，尽管烟草烟雾可能会使动脉粥样硬化严重恶化并加速其在冠状动脉、大动脉和腿部动脉中的发展。类似地，在另一个实施方案中，本发明的方法可以用于治疗具有早年心血管疾病家族史的个体（其患动脉粥样硬化的风险增加）。

在一个实施方案中，归因于脂肪沉积的肝损害指脂肪在肝细胞中累积形成脂肪肝，脂肪肝可能与肝脏的炎症有关或可能导致肝脏炎症。这可以导致肝的瘢痕形成和硬化。当结瘢痕形成变为广泛性时，其称为肝硬化。

在另一个实施方案中，脂肪在肝脏中蓄积成为肥胖症。在另一个实施方案中，脂肪肝也与糖尿病、高血甘油三酯和大量饮酒有关。在另一个实施方案中，脂肪肝可能伴随某些疾病例如结核病和营养不良、治疗肥胖症的肠分流术、体内维生素 A 过量或使用某些药物比如丙戊酸（商品名：Depakene/Depakote）和皮质类固醇（可的松、泼尼松）而发生。有时脂肪肝作为妊娠并发症发生。

在一个实施方案中，患有肾病的个体，特别是患有终末期肾脏疾病（ESRD）的男性个体罹患性腺功能减退症，其中一些患有伴发的中度至重度的蛋白质-能量营养不良（PEM），其造成更高的促红细胞生成素（EPO）需要量，更低的 QOL 分数和更高的死亡率。许多人具有与性腺功能减退症有关的其它症状，包括疲劳、缺乏食欲、肌无力等。在一些实施方案中，本发明的治疗方法用于治疗与由所述个体的肾脏疾病或病症引起的性腺功能减退症有关的症状。

在一个实施方案中，糖尿病肾病是糖尿病的并发症，其进展得很早，通常在做出糖尿病的临床诊断之前。肾病变最早的临床证据是尿中出现低（但异常）水平（ >30 mg/天或 20 μ g/min）的白蛋白（微量蛋白尿），接着是持续 10-15 年的蛋白尿（ >300 mg/24 h 或 200 μ g/min）。在 1 型糖尿病个体，糖尿病性高血压通常在病人罹患微量蛋白尿之前或直到病人罹患微量蛋白尿时就十分明显。一旦出现明显的肾病变，肾小球滤过率（GFR）在一段时间（可能是几年）内下降，造成糖尿病个体的终末期肾脏疾病（ESRD）。

高血压是肾脏病的另一种共病因素。在一些实施方案中，根据本发明治疗肾脏病可以包括用本发明的化合物和治疗高血压的药剂进行同步治疗。

可以用本文所述的化合物和/或组合物，包括本发明的方法治疗的雄激素依赖性病症包括与衰老相关的病症。在一个实施方案中，本文所述的化合物用于：a) 年龄相关的功能下降（ARFD）；b) 逆转或预防 ARFD；c) 逆转或预防老年人 ARFD；d) 逆转或预防 ARFD 引发的少肌症或骨质减少；e) 男性更年期、男性更年期血管舒缩综合征；f) 男性更年期乳腺发育、肌肉强度

/功能；g) 骨强度/功能；h) 愤怒；i) 无力；j) 慢性疲劳综合征；k) 认知损害；和/或 l) 改善认知功能。

在一个实施方案中，本文所述的化合物用于治疗炎症和相关病症，例如：a) 预防、治疗或逆转关节炎；b) 预防、治疗或逆转关节炎性病症，例如贝切特氏病(自动免疫性血管炎)、滑囊炎、二羟焦磷酸钙晶体沉积症(或假性痛风)(CPPD)、腕管综合征、结缔组织病症、克罗恩病、埃-当二氏综合征(EDS)，纤维肌痛、痛风、感染性关节炎、炎症性肠病(IBD)、少年关节炎，系统性红斑狼疮(SLE)、莱姆病、马方综合征、肌炎、骨关节炎、结节性多动脉炎、风湿性多肌痛、银屑病、银屑病关节炎、雷诺现象、反射性交感神经营养不良综合征、莱特综合征、类风湿性关节炎、硬皮病、干燥综合征、肌腱炎或溃疡性结肠炎；c) 预防、治疗或逆转自身免疫性疾病。

在一个实施方案中，本文所述的化合物用于预防医源性作用，包括急性疲劳综合征(手术后)或雄激素剥夺治疗(ADT)诱导的副反应，例如肌肉量减少、肌肉强度降低、脆弱、性腺功能减退症、骨质疏松症、骨质减少、BMD 降低和/或骨量减少。

在一个实施方案中，所述化合物和/或组合物和/或它们的使用方法用于治疗人类个体，其中，在一个实施方案中，所述个体是男性，或在另一个实施方案中，所述个体是女性。

在一个实施方案中，本发明的方法包括给药作为唯一活性成分的本发明的化合物。然而，用于以下的方法也包含在本发明的范围内：糖尿病和相关病症、激素疗法、干眼病、肥胖症、治疗前列腺癌、延缓前列腺的进展、以及预防和/或治疗前列腺癌的复发、男性避孕；治疗骨质疏松症、治疗与 AIDF 相关的病症以及治疗和/或预防慢性肌萎缩，所述方法包括联合一种或多种治疗剂给药所述化合物。这些药剂包括但不限于：LHRH 类似物、可逆的抗雄激素、抗雌激素药、抗肿瘤药、5- α 还原酶抑制剂、芳香酶抑制剂、孕激素、通过其它细胞核激素受体作用的药剂、选择性雌激素受体调节剂(SERM)、孕激素、雌激素、PDE5 抑制剂、阿扑吗啡、二碳磷酸盐化合物和一种或多种其它的 SARM。

因此，在一个实施方案中，本发明的方法包括联合糖尿病药物(例如曲格列酮、罗格列酮和吡格列酮)给药本发明的化合物。在另一个实施方案中，

本发明的方法包括联合 LHRH 类似物给药所述的化合物。在另一个实施方案中，本发明的方法包括联合可逆的抗雄激素给药所述的化合物。在另一个实施方案中，本发明的方法包括联合抗雌激素药给药所述的化合物。在另一个实施方案中，本发明的方法包括联合抗癌药给药所述的化合物。在另一个实施方案中，本发明的方法包括联合 5- α 还原酶抑制剂给药所述的化合物。在另一个实施方案中，本发明的方法包括联合芳香酶抑制剂给药所述的化合物。在另一个实施方案中，本发明的方法包括联合孕激素给药所述的化合物。在另一个实施方案中，本发明的方法包括联合通过其它细胞核激素受体作用的药剂给药所述的化合物。在另一个实施方案中，本发明的方法包括联合选择性雌激素受体调节剂 (SERM) 给药所述的化合物。在另一个实施方案中，本发明的方法包括联合孕酮给药所述的化合物。在另一个实施方案中，本发明的方法包括联合雌激素给药所述的化合物。在另一个实施方案中，本发明的方法包括联合 PDE5 抑制剂给药所述的化合物。在另一个实施方案中，本发明的方法包括联合阿扑吗啡给药所述的化合物。在另一个实施方案中，本发明的方法包括联合二碳磷酸盐化合物给药所述的化合物。在另一个实施方案中，本发明的方法包括联合一种或多种其它 SARM 给药所述的化合物。在一些实施方案中，本发明的方法包括联合制剂，所述制剂包含所述的化合物和上文所述的药剂。在一些实施方案中，例如为了应对部分待治疗患者亚群的需要或单个患者的需要，所述联合制剂可以变化，所述不同的需要可能归因于具体疾病、所述疾病的严重性、年龄、性别或体重，这可以由本领域的技术人员容易地确定。在一些实施方案中，本发明的方法包括处理单个患者的需要的个性化用药方法。在一个实施方案中，不同的需要可归因于具体疾病、所述疾病的严重性、患者的整体医学状态或所述患者的年龄。在一些实施方案中，个性化用药是应用基因组数据以更好地定向医学干预的递送。在一些实施方案中，个性化用药方法用作发现和临床测试本发明的新产品的工具。在一个实施方案中，个性化用药包括应用临床上有用的诊断工具，所述工具可能帮助确定病人对具体疾病或病症的易感性。在一些实施方案中，个性化用药是综合性的方法，其在药物和诊断的发现和发展的所有阶段利用患者和健康个体的分子分析来指导决定；通过改善的预防、诊断、治疗和监控方法将这种临床实践的知识应用于更有效地提供准确而高质量的医疗保健。

在一些实施方案中，可以以在动物或人类的雌性升值周期中有效调节能育性的量给药式(I)的化合物，或者在一些实施方案中，以有效控制人类月经周期不规律或有效同步或抑制商品化动物（例如鱼、牛、绵羊、猪、山羊或鸡）、实验室动物（例如猿、黑猩猩、大鼠、小鼠或豚鼠）或家养动物（狗、猫、雪貂、兔或马）的生育期的量给药式(I)的化合物。在一些实施方案中，可以以有效减少月经的量给药式(I)的化合物，由此用于治疗或预防贫血和痛经。在一些实施方案中，可以以有效预防或治疗经前期综合征、子宫内膜异位症、平滑肌瘤（子宫肌瘤）和/或卵巢囊肿的量给药式(I)的化合物。而且，对于患有或以前患有盆腔炎性疾病的个体（其中可能已发生输卵管瘢痕形成），可以使用式(I)的化合物以减少可能发生输卵管妊娠的几率。

在一些实施方案中，可以以有效预防妊娠的量给药式(I)的化合物。在一些实施方案中，这种给药可以在排卵前或性交前、或者在排卵后或性交后。在一些实施方案中，这种给药抑制个体的胚胎植入，或在一些实施方案中抑制个体排卵。

在一些实施方案中，可以以有效诱导雌性宫颈成熟的量给药式(I)的化合物。所述宫颈成熟可以是阵痛和分娩后代的准备、或是刮宫术的准备。在另一个实施方案中，实施这种给药以诱导胚胎或胎儿从个体娩出。

应理解，任何本文所述的化合物的任何用途都可以用于治疗本文所述任何疾病、障碍或病症，而且代表本发明的实施方案。

以下所示的实施例是为了更全面地说明本发明的优选实施方案。但是，它们无论如何都不应该被解释为限制本发明的广泛范围。

实施例

实施例 1

I

化合物 XIII 的合成

2-取代丙烯酸（化合物 46）与 4-氰基-3-三氟甲基苯胺反应，然后进行环氧化。在碳酸钾存在下用对-CN-苯酚使环氧化物开环，产生化合物 XIII，如图 1B 中所示。

实施例 2

化合物 V 的合成

4-氰基-3-三氟甲基苯胺与丙烯-2-磺酰氯 (51) 反应, 进行环氧化, 然后在碳酸钾存在下用 p-CN-苯酚使环氧化物开环, 产生化合物 V, 如图 1C 中所示。

实施例 3

化合物 XI 的合成

用 p-CN-苯酚使环氧乙烷基甲基氨基甲酸叔丁酯 (54) 开环, 得到化合物 55, 然后用 TFA 脱保护, 得到氨基醇 56。将化合物 56 引入与 4-氟-2-三氟甲基苄腈的亲电取代反应中, 形成化合物 58。将 58 氧化成相应的羰基衍生物 59, 将 59 用于进一步的加成反应, 得到化合物 XI, 其如图 1D 中所示。

实施例 4

化合物 XXXV 的合成

由起始化合物 3,6-二氧杂-双环[3.1.0]己烷 (60) 制备 4-亚甲基-四氢呋喃-3-醇(61), 如图 1E 显示。该化合物用于与 p-CN-苯酚(50)进行 Mitsunobu 型反应, 形成化合物 62。用 OsO₄ 进行二羟基化, 然后在 TEMPO 基(2,2,6,6-四甲基哌啶哌啶基氧)的存在下用 NaClO₄ 进行氧化, 形成酸 64。使用亚硫酸二氯和 4-氰基-3-三氟甲基苯胺由化合物 64 产生化合物 XXI, 如图 1E 中所示。

实施例 5

化合物 XXXVI 的合成

如实施例 4 中所述制备化合物 62, 然后进行环氧化, 得到化合物 65, 如图 1F 中所示。用 4-CN-3-三氟甲基苯胺使环氧化物开环, 产生化合物 XXXVI, 如图 1F 中所示。

实施例 6

化合物 XLVI 的合成

4-氰基-3-三氟甲基苯胺与衣康酸酐 (66) 反应, 得到中间体 67。进一步环氧化并用对-CN-苯酚使环氧化物开环, 产生化合物 XLVI, 如图 1G 中所示。

实施例 7

化合物 XLIII 的合成 (图 2)

通过肖登-包曼二氏反应使吡咯烷-2-羧酸 (56) 酰化, 得到异丁烯酰基吡咯烷-2-羧酸 (57), 随后在 *N*-溴丁二酰亚胺的存在下, 将其内酯化, 得到溴内酯 (58)。在回流条件下, 用 24% HBr 溶液将所述溴内酯 (58) 水解 1 h, 随后进行后处理并在乙酸乙酯-己烷混合物中重结晶, 得到高收率的 3-溴-2-羟基-2-甲基丙酸 (59) [59: 白色固体 (收率: 85%) Mp. 108°C $[\alpha]_D^{25} = +10.5$ (c=2.5, 10 MeOH) NMR (^1H , 300MHz, DMSO): 1.35 (s, 3H, CH₃), 3.5 (s, 1H, CH), 3.6 (s, 1H, CH), 4.0 (br, 1H, OH) MS: 205 (M + Na⁺) C₄H₇BrO₃ 已计算出: C, 26.25; H, 3.86 发现: C, 26.28; H, 3.75]。

然后, 通过在氩气氛下冷却至 0°C, 用三溴乙醛保护化合物 59 的羟基和羧基, 在搅拌下滴加浓硫酸。2h 后溶液变暗; 移去冰浴, 反应混合物在室温下搅拌过夜。溶液用冰稀释并用乙酸乙酯萃取, 无水硫酸钠干燥并浓缩, 得到化合物 60, 从乙酸乙酯-己烷中重结晶后, 该化合物的外观为白色晶体。[60: 白色固体 (收率: 89%) Mp. 97°C NMR (^1H , 300MHz, CDCl₃): 1.8 (s, 3H, CH₃), 3.7 (s, 2H, CH₂), 5.8 (s, 1H, CH) C₆H₆Br₄O₃ 已计算出: C, 16.17; H, 1.36; 发现: C, 16.08; H, 1.25]。

将化合物 60 溶解在 1:1 的 2-丙醇与 1M NaOH 的混合物中并在室温下搅拌。3h 后, 当通过 TLC 检测不到原料时, 加入 4'-氟苯硫酚, 反应混合物搅拌过夜。然后, 用浓 HCl 将反应混合物调节至 pH 1, 用乙酸乙酯萃取并用无水硫酸钠干燥。浓缩有机层, 得到油。在己烷-乙酸乙酯-乙酸混合物中对反应混合物进行快速柱层析, 然后在乙酸乙酯-己烷中进行重结晶, 得到无色针状晶体。通过用浓 HCl 酸化反应混合物使该化合物水解以除去保护基, 得到图 2 中所示的手性羟酸 (55) [55: 白色固体 (收率: 65%) M.p. 54°C; $[\alpha]_D^{25} = +24.85$ (c=1.0, MeOH) NMR (^1H , 300MHz, CDCl₃): 1.5 (s, 3H,

CH₃), 3.2 (d, 1H, CH), 3.4 (d, H, CH), 7.0 (m, 2H, Ar, $J = 2.0$ Hz, 8.9 Hz), 7.5 (m, 2H, Ar, $J = 2.0$ Hz, 8.9 Hz) MS: 无母离子峰 C₁₀H₁₁FO₃S, 已计算出: C, 52.16; H, 4.82; 发现: C, 52.05.59; H, 4.76]。

通过于 0℃在氯仿介质中加入硫光气和碳酸氢钠,然后在室温下搅拌过夜,将 4-硝基-3-三氟甲基苯胺转化为相应的异硫氰酸盐 (66)。浓缩反应混合物,将其萃取至乙酸乙酯中,干燥,蒸发,通过使用己烷-乙酸乙酯混合物的快速柱层析进行纯化,得到外观为黄色固体的 66。在搅拌下加入羟酸 55 和 4-硝基-3-三氟甲基苯基异硫氰酸盐 (66)、三氟乙酸银乙腈溶液和三乙胺,反应混合物加热至回流,保持 1h。通过过滤除去硫化银,减压蒸去溶剂,所得剩余物用水洗涤,萃取至乙酸乙酯中,干燥、过滤并浓缩。通过使用己烷-乙酸乙酯混合物的快速柱层析进行分离,所期望的产物呈现为黄色油。鉴定该化合物是噁唑烷二酮 (65),如图 2 中所示。[65: 黄色油(收率: 52%) $[\alpha]_D^{25} = +39.7$ (c=2.5,10 甲醇) NMR (¹H, 500MHz, DMSO): 1.8 (s, 3H, CH₃), 3.2 (s, 1H, 20 CH), 3.3 (s, 1H, CH), 6.9 (m, 2H, Ar, $J = 2.0$ Hz, 8.9 Hz), 7.2 (m, 2H, Ar, $J = 2.0$ Hz, 8.9 Hz), 7.9 (m, 1H, Ar, $J = 2.1$ Hz, 9.0Hz), 8.0 (m, 1H, Ar, $J = 0.5$ Hz, 2.1 Hz) 8.1 (m, 1H, Ar, $J = 0.5$ Hz, 9.0Hz) NMR (¹³C, 500MHz, CDCl₃): 22.8, 43.4, 86.7, 117.0, 117.3, 124.4, 124.5, 124.6, 125.0, 126.8, 129.3, 134.2, 134.3, 135.3, 164.9, 172.8 MS: 无母离子峰 C₁₀H₁₁FO₃S, 已计算出: C, 48.65; H, 2.72; N, 6.30 发现: C, 48.59; H, 2.70; N, 6.31]。

该产物 (65) 在 π 受体/供体(R,R)-Whelk-O1 手性柱上的 HPLC 分析显示比率为 70:30 两个峰,对应两个对映异构体,对映异构体过量值为 40%。噁唑烷二酮形成的发生必定经过羟基从亚胺碳上亲核置换硫化银及随后的协同环重排,这可由中间结构 (67a) 和 (67b) 得到证实;与 Shibuya 等人建立的机制相同的机制。本文考虑,在上述分析型手性柱中获得的对映异构体的良好分离情况可以扩展至相应的制备柱,以便获得所述对映异构体的定量收率,由此用激子偶联振动圆二色性 (exciton coupled vibrational circular dichroism) 测定它们的绝对构型,并用以高斯经验计算法辅助测定红外光谱。本文还考虑,杂环体系的氧原子可以用氨基代换以得到对映性的比卡鲁胺的乙内酰脲类似物,然后所述类似物会为与受体的氢键合相互

作用提供额外的位点。

实施例 8

化合物 XLVIII 的合成 (图 3)

通过重氮化由 4-氰基-3-三氟甲基苯胺制备 4-溴-2-三氟甲基苄腈 (74)。使 4-溴-2-三氟甲基苄腈 (74) 与 BuLi 反应生成 Li 的衍生物 (75)。使 3-溴苄腈与 BuLi 反应生成 Li 的衍生物 (77)。用(2-溴乙氧基)-叔丁基二甲基硅烷 (78) 将 Li 衍生物 (77) 烷基化, 得到衍生物 (79), 79 用 MeMgI 转化为苯乙酮 (80)。随后, 脱保护并与对-CN-苯酚发生 Mitsunobu 反应, 形成苯乙酮 (82)。加入 Li 衍生物 (75), 然后脱水, 得到化合物 XLVIII, 如图 3 中所示。

实施例 9

化合物 XLIX 的合成 (图 4)

将 4-(2-羟基乙基)-吡啶-2-腈 (83) 用叔丁基二甲基硅烷保护, 并用 MeMgI 将其转化为相应的苯乙酮 (85), 然后脱保护, 制备醚 (87)。加入 Li 衍生物 (75), 然后脱水, 得到化合物 XLIX, 如图 4 中所示。

实施例 10

化合物 L 的合成 (图 6)

通过 4-氯甲氧基苄腈 (97) 由对-CN-苯酚 (50) 制备正膦 (98), 在维蒂希反应中 98 与 3-乙酰基苯甲醛 (99) 生成衍生物 (100)。随后, 加入如实施例 8 中所述的 Li 衍生物 (75), 然后脱水, 得到化合物 L, 如图 6 中所示。

实施例 11

化合物 LI 的合成 (图 7)

用叔丁基二甲基硅烷保护 3-羟甲基苄腈 (101), 得到化合物 (102), 随后用 MeMgI 得到相应的苯乙酮 (85)。除去保护基, 进一步与对-CN-苯酚反应以得到 (105)。向 (105) 中加入 Li 衍生物 (75) (如实施例 8 中所

制备), 然后脱水, 得到化合物 LI, 如图 7 中所示。

实施例 12

化合物 LII 的合成 (图 5)

用叔丁基二甲基硅烷保护 5-溴-2-羟基苄腈 (88), 得到化合物 (89)。化合物 (89) 与 BuLi 反应, 得到 Li 衍生物 (90), 其进一步由(2-溴乙氧基)-叔丁基二甲基硅烷烷基化, 得到 (91)。化合物 (91) 与 MeMgI 反应成相应的苯乙酮 (92), 然后脱保护并选择性地保护酚基, 得到衍生物 (94)。衍生物 (94) 与对-CN-苯酚反应, 得到化合物 (95), 然后加入 Li 衍生物 (75) 并脱水 (如实施例 8 中所述), 得到化合物 (96)。随后脱保护, 得到化合物 LII, 如图 5 中所示。

实施例 13

化合物 XXIV 的一般合成 (图 1I)

根据图 1I 制备 4-(4-芳基磺酰-2,5-二甲基哌嗪-1-基)-2-三氟甲基苄腈。于 DMSO-水混合物中在碳酸钾存在下, 用 2,5-二甲基哌嗪亲核取代 4-氟-2-三氟甲基苄腈中的氟原子。在三乙胺存在下, 通过与芳基磺酰氯的反应制备相应的芳基磺酰衍生物。

实施例 14

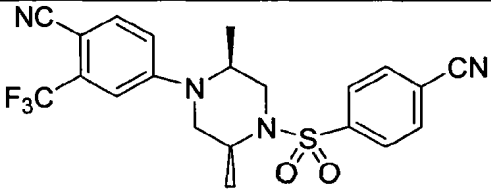
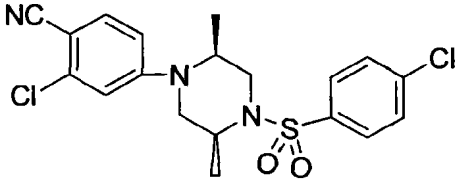
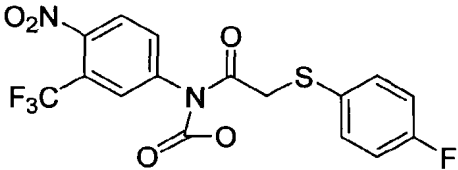
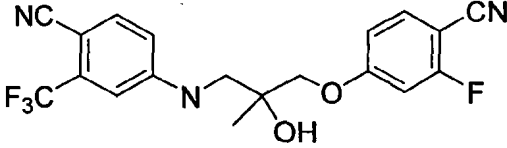
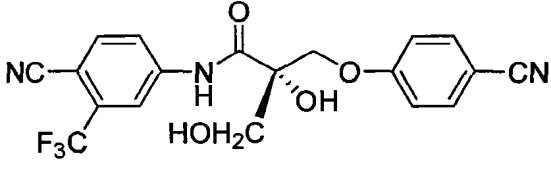
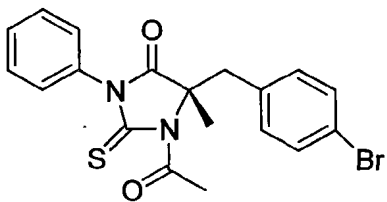
雄激素受体 (AR) 与 SARM 的结合以及 AR-SARM 晶体结构方法

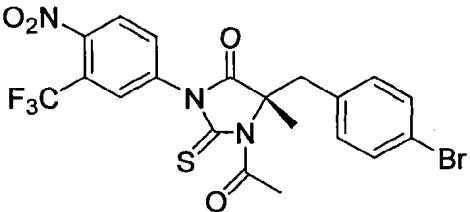
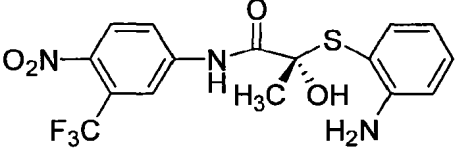
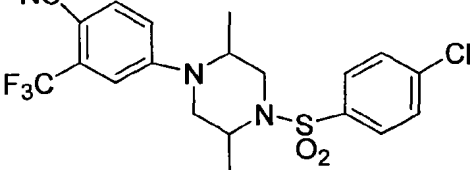
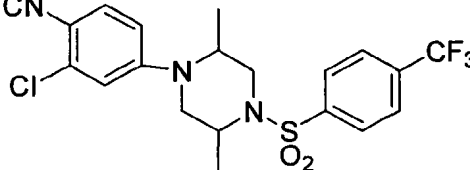
亲合力测定

由斯普拉-道来(氏)大鼠的腹部前列腺得到细胞溶胶 AR。切除前列腺并立即浸没在冰冷的匀浆缓冲液中 (10 mM Tris、1.5 mM EDTA 二钠、0.25 M 蔗糖、10 mM 钼酸钠和 1 mM PMSF)。用剪刀将前列腺切碎, 匀浆并离心 (Model L8-M, Beckman Instruments Inc)。收集上清液 (细胞溶胶) 并储存在 -80°C 下直到使用。在存在或不存在浓度增加的感兴趣的化合物 (10^{-1} nM- 10^4 nM) 的情况下, 于 4°C 下用饱和浓度的 ^3H -MIB (1 nM) 和 1 μM 的曲安奈德培养等份 (50 μL) 的 AR 细胞溶质 18 h。

通过向培养液中加入 1000 nM MIB，测定 ^3H -MIB 的非特异性结合。使用羟基磷灰石分离结合的和游离的放射性配体并测定结合的 ^3H -MIB 的浓度。使用非线性回归测定 IC_{50} ，即抑制 50% ^3H -MIB 的特异性结合的供试化合物的浓度。

测定本发明的化合物的亲和力并显示在下表中：

化合物	抑制常数 (nM)
	633.5
	528.9 nM
	195.81 nM
	412.24 nM
	396.8 nM
	微摩尔范围

	微摩尔范围
	70.7 nM
	2785 nM
	2632 nM

共转染测定

使 CV-1 细胞（绿猴肾细胞）在补充了 10% FBS、2mM 谷氨酰胺和 1% 链霉素和青霉素的达尔伯克氏改良伊格尔氏培养基（DMEM）上生长到在 T175 组织培养烧瓶中融合。无血清 DMEM 中，将细胞用 3 μ g CMVhAR 表达载体、30 μ g 雄激素依赖型萤光素酶报道基因构建体(pMMTV-luc)和 30 μ g β -半乳糖苷酶表达构建体（pSV- β -半乳糖苷酶；Promega, 5 Madison, WI）经 30 mL Plus 试剂（Invitrogen）和 40 mL LipofectAMINE（Invitrogen）转染。4 小时后，将培养基换成补充 0.2 % FBS 和 2 mM 谷氨酰胺的 DMEM。12 小时后，将细胞转移至 24 孔组织培养板，再过 6 小时后，用 0.1 nM-1000 nM 的药物或不加药物（对照）处理。另外 24 小时后，细胞用冷 PBS 洗涤两次，通过用 100 ML 的被动性溶胞解缓冲液（Promega）培养 30 分钟后收集细胞。

将等份（50 mL）溶胞产物加到不透明的 96 孔板，在自动注入 50 mL 萤光素酶底物（Promega）后，用 MicroLumatPlus LB96V 发光计（Berthold Technologies, Oak Ridge, TN）使用 WinGlow 软件包监测萤光素酶的活性。另将等份（50 mL）的溶胞产物和 50 mL β -半乳糖苷酶测定缓冲液一起加到

透明的 96 孔板。在 37℃ 下培养 2 小时后, 在 Dynex MRX 读板器上于 420 nm 测定吸收值。使萤光素酶活性与 β -半乳糖苷酶活性标准化, 以便计算细胞数量和/或转染率损失的差异。

克隆、表达和纯化

由全长 AR 表达构建体 (pCMVhAR) 通过用含有侧翼限制酶切位点的引物进行 PCR 扩增获得 AR-LBD (663-919), 然后将其插入到 pGEX6P-1 质粒载体 (Amersham) 中。通过用 30 μ M IPTG 诱导, 所述 AR LBD 于 15℃ 下在大肠杆菌 BL21 DE3 中表达 16 小时, 为谷胱甘肽-S-转移酶 (GST) 融合蛋白。在含有 150 mM NaCl、50 mM Tris pH 8.0、5 mM EDTA、10% 甘油、1 mg/mL 溶菌酶、10 U/mL DNA 酶 I、10 mM $MgCl_2$ 、10 mM DTT、0.5% CHAPS、100 μ M 配体和 100 μ M PMSF 的缓冲液中, 通过三次冻融循环, 将细胞溶解。由超速离心得到的上清液与谷胱甘肽琼脂糖凝胶 (Amersham) 在 4℃ 下培养 1 h, 并用 150 mM NaCl、50 mM Tris pH 8.0、5 mM EDTA、10% 甘油、10 mM ATP、10 DM 配体、0.1% *n*-辛基- β -葡萄糖苷和 1 mM DTT 洗涤。

于 4℃ 下在含有 150 mM NaCl、50 mM Tris pH 7.0、10% 甘油、0.1% *n*-辛基- β -葡萄糖苷、1 mM DTT 和 5 U/mg 蛋白质 PreScission 蛋白酶 (Amersham) 的缓冲液中过夜切割 GST-LBD 融合蛋白以从谷胱甘肽琼脂糖凝胶中释放 AR LBD。上清液在 10 mM pH 7.2 的羟乙基哌嗪乙磺酸、10% 甘油、10 μ M 配体、0.1% *n*-辛基- β -葡萄糖苷、1 mM DTT 中稀释 3 倍, 然后装载至 HP SP 阳离子交换柱 (Amersham) 上。在相同的稀释缓冲液用 50 mM-500 mM 的 NaCl 梯度洗脱蛋白。在 Millipore 10 kD 截留浓缩器中将缓冲液换成含有 150 mM Li_2SO_4 、50 mM pH 7.2 的羟乙基哌嗪乙磺酸、10% 甘油、100 μ M 配体、0.1% *n*-辛基- β -葡萄糖苷和 10 mM DTT 的缓冲液, 将蛋白质浓缩至大于 4 mg/mL。

结晶、收集数据和结构测定

在一至两天内, 利用悬滴蒸发扩散法于 0.1 M pH 7.5 羟乙基哌嗪乙磺酸和 0.5 M-0.8 M 的柠檬酸钠中形成 AR LBD 晶体。在液氮中快速冷冻之前, 将 AR LBD 晶体转移至由 0.1 M pH 7.5 的羟乙基哌嗪乙磺酸、0.7 M 柠檬酸钠和 20% 乙二醇组成的溶液中。使用 Rigaku RU300 旋转阳极发生器

和 R-轴 IV++成像板 (Rigaku) 收集衍射数据, 并用 Crystal Clear 软件进行处理 (Molecular Structure Corporation)。AR LBD-DHT 复合物 (PDB 编码 1I37) 用作使用 Crystallography & NMR System (CNS) 进行精制的起始结构。在第一轮精制后, 电子密度图使配体准确拟合 (fitting)。使用程序 O 加入模型构建物和水分子, 使用刚性体、扭转角模拟重结晶法和 CNS 的单个温度因子模块进行更多轮的精制。

SARM 的 X 射线研究

将显示 AR 结合低于 100 nM 的 SARM 在萤光素酶测定中进一步分析, 以确定它们是否具有 AR 功能性激动剂活性。随后, 使具有最高活性的 SARM 与 AR 受体共结晶并进行 X 射线分析。

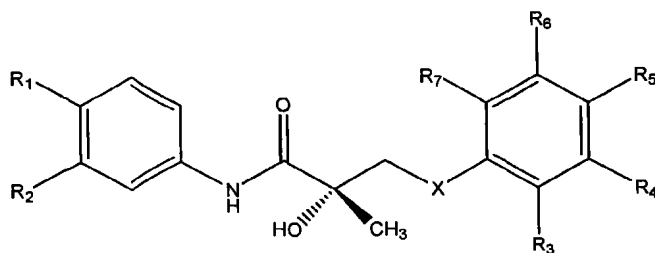
实施例 15

SARM 的功能活性

表 1 描述了所示醚连接化合物 (比卡鲁胺类似物) 的结构和亲合性。所有化合物都使用手性合成方法合成, 包括使用 D-脯氨酸作为手性助剂, 如美国专利 6,995,284 中所公开地, 该专利通过引用结合于此。使用元素分析和波谱数据, 即 ^1H NMR、 ^{13}C NMR、MS 和 IRE 确定合成的化合物的结构。

在本发明的一些方面, 这些化合物的设计充分理解被鉴定为涉及比卡鲁胺类似物的 AR 亲合力的结构元素, 例如: (i) 缺电子的芳香性 A 环, (ii) 在手性中心的 *R*-构型, 和 (iii) 在 B 环的对位的亲电子基团。重要的是要注意, 在这类分子中, 当用醚键代替硫醚或磺酰基连接时, 活性化合物的手性指示从 (*R*) 变为 (*S*)。除了这些对高 AR 结合亲合力所需的结构特征外, B 环取代和连接基 X 的性质是比卡鲁胺类似物的功能活性的关键性决定因素。

表 1:



编号	R1	R2	X	R3	R4	R5	R6	R7	K_i (nM)
比卡鲁胺	CN	CF ₃	SO ₂	H	H	F	H	H	11±2
R-20	NO ₂	CF ₃	SO ₂	H	H	COCH ₃	H	H	9.3±0.8
S-1	NO ₂	CF ₃	O	H	H	F	H	H	6.1±0.19
S-2	NO ₂	CF ₃	O	H	H	COCH ₃	H	H	36.6±2.3
S-3	NO ₂	CF ₃	O	H	H	COCH ₂ CH ₃	H	H	6.1±0.14
S-4	NO ₂	CF ₃	O	H	H	NHCOCH ₃	H	H	4.0±0.70
S-5	NO ₂	CF ₃	O	H	H	CH ₃	H	H	34.8±3.5
S-6	NO ₂	CF ₃	O	H	H	OCH ₃	H	H	13.7±0.68
S-7	NO ₂	CF ₃	O	H	H	NHCO ₂ C(CH ₃) ₃	H	H	336.0±71.1
S-9	NO ₂	CF ₃	O	H	H	H	H	H	4.6±0.26
S-10	NO ₂	CF ₃	O	F	H	F	H	H	3.4±0.34
S-11	NO ₂	CF ₃	O	H	F	F	H	H	3.4±0.56
S-12	NO ₂	CF ₃	O	F	H	F	H	H	3.2±0.30
S-13	NO ₂	CF ₃	O	CH ₃	H	F	H	H	6.0±0.70
S-14	NO ₂	CF ₃	O	H	Cl	F	H	H	10.3±2.0
S-15	NO ₂	CF ₃	O	H	F	Cl	H	H	4.9±0.3
S-16	NO ₂	CF ₃	O	H	Cl	Cl	H	H	1.0±0.088
S-17	NO ₂	CF ₃	O	F	F	F	H	H	11.3±1.1
S-18	NO ₂	CF ₃	O	F	H	F	H	F	10.3±2.0
S-19	NO ₂	CF ₃	O	F	F	H	F	H	9.1±0.6
S-20	NO ₂	CF ₃	O	F	F	F	F	F	1.4±0.34

S-21	NO ₂	CF ₃	O	H	H	Cl	H	H	8.6±1.2
S-22	NO ₂	CF ₃	O	H	H	Br	H	H	12.6±1.8
S-23	NO ₂	CF ₃	O	H	H	I	H	H	22.6±1.6
S-24	NO ₂	CF ₃	O	H	H	NHCSNH ₂	H	H	10.2±1.4
S-25	NO ₂	CF ₃	O	H	H	NHCSNHCH ₃	H	H	271.2±37.2
S-26	CN	I	O	H	H	F	H	H	3.3±0.10
S-27	CN	CF ₃	O	H	H	Cl	H	H	3.4±0.08
S-28	CN	CF ₃	O	H	H	NHCOCH ₃	H	H	12.7±0.02
S-29	CN	Cl	O	H	H	F	H	H	4.5±0.11
S-30	CN	CF ₃	O	H	H	F	H	H	3.3±0.08
S-31	F	CF ₃	O	H	H	F	H	H	32.6±0.10
S-32	Cl	CF ₃	O	H	H	F	H	H	14.5±0.18
S-33	I	CF ₃	O	H	H	F	H	H	15.6±0.19
S-34	Br	CF ₃	O	H	H	Cl	H	H	52.0±0.13
S-35	Br	CF ₃	O	H	H	Br	H	H	25.9±0.04
S-36	H	CF ₃	O	H	H	F	H	H	62.0±0.05

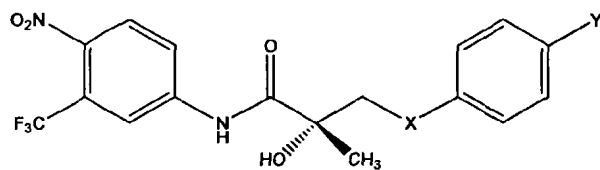
对 AR 介导的转录激活的体外研究（图 8）显示，将 X 连接由砷变为氧或将 B 环对位取代由氟变为乙酰胺基都将纯粹的 AR 拮抗剂转化为激动剂，例如在化合物 S-5 和 R-20 中。在体内试验中，先导化合物 S-1 和 S-4 在体内用作 AR 激动剂并显示出组织选择性（图 9A-9B）。S-1 和 S-4 在前列腺中都是部分激动剂，但是在肛提肌、骨和垂体中是完全激动剂，这些是对理想的选择性雄激素受体调节剂提出的特征。

S-4 的口服生物利用度和安全性已经被证实（数据未显示），确证了这些化合物可能有效治疗雄激素缺乏性疾病或病症的观点。先前已经证明，S-1 和 S-4 不是 5 α -还原酶的底物。本文考虑，这些配体的组织选择性是因

为它们在前列腺中的激动剂活性没有完全被 5 α -还原酶放大, 5 α -还原酶是在前列腺中而不是肌肉中表达的、将睾酮转化为 DHT 的酶。

表2显示最大疗效百分数对表1的各种化合物的X-和Y-位置的依赖性。如实施例13中所述, 使用大鼠腹部细胞溶胶作为 AR 源, 利用竞争性结合测定来测定完整 AR 的亲合力。如实施例13中所述, 使用共转染测定, 检测完整 AR 的体外功能活性。在 10 nM 配体下分析疗效(即转录激活), 将活性表示为对 1 nM 双氢睾酮(DHT)观察到的最大转录激活的百分数。

表 2



ID	X	Y	亲合力 (nM)	疗效 (%最大)
S-1	O	F	6.11 $\pm$ 0.19	43.40 $\pm$ 2.60
X-2	S	F	11 $\pm$ 2	77.4 $\pm$ 5.6
X-3	SO ₂	F	28 $\pm$ 10	18.8 $\pm$ 9.3
X-4	NH	F	7.96 $\pm$ 0.43	21.33 $\pm$ 2.22
X-5	CH ₂	F	9 $\pm$ 0.2	28.9 $\pm$ 2.4
S-4	O	NH(CO)CH ₃	3.98 $\pm$ 0.70	92.92 $\pm$ 7.00
S-23	O	I	23 $\pm$ 1.6	47.2 $\pm$ 1.8

实施例 16

非类固醇配体结合的结构表征

对一系列 4'-氟苯基-2-羟基-2-甲基-N-(4'-硝基-3'-三氟甲基苯基)丙酰苯胺化合物进行构象分析, 这些化合物仅 X 位置的杂原子不同。该分析检

测了 X 位置取代基对溶液中化合物构象的影响以开发构象化合物。将配体溶液 (DMSO- d_6) NMR 构象与它们的来自新近解析的 *R*-比卡鲁胺-W74L-LBD 晶体结构(本文中称为比卡鲁胺-W741L; C. E. Bohl, W. Gao, D. D. Miller, C. E. Bell, J. T. Dalton. Structural basis for antagonism and resistance of bicalutamide in prostate cancer. *Proc Natl Acad Sci U S A* **2005**, 102(17), 6201-6.) 的结合构象作比较。已经预料在连接部位中的分子内氢的键合 (NH-OH), 这在溶液构象中观察到了。然而, 对于一些被分析的化合物, 这种分子内 NH 氢键供予在 OH 和 X 位置间共享。NH-X 氢键导致所述配体在溶液中的总体形状获得意想不到的弯曲, 这种弯曲与在 AR 的同源建模过程中得到的假设性的结合构象明显不同。过去, 对丙酰苯胺没有六元 5 环状 NH-X 氢键合构象的假设。激动剂 S-4(X=O, Y=N-乙酰基)和 X-2(X=S, Y=F)和部分激动剂 S-23(X=O, Y=I)和 S-1(X=O, Y=F)最清楚地显示出这种溶液中苯环的 NH 至-X 加-OH 构象 (图 10), 但是, 对于该系列的拮抗剂 X-3(X=SO₂, Y=F)和 X-4(X=NH, Y=F)和 X-5(X=CH₂, Y=F)没有观察到这种构象。这表明, 所述配体采取这种构象的能力可能对 AR 激活很重要, 这一点通过与非类固醇配体的构象的比较得到确证, 所述非类固醇配体的构象是在随后解析的 *R*-比卡鲁胺-W741L-LBD (AR 突变体, 其中比卡鲁胺用作激动剂) 的 X 射线晶体结构中观察到的。

表 3 提供表 1 中所鉴定的各种化合物的溶液中分子内氢键分析的结果。如表 3 中使用的, 氢键的定义是<3.1Å 的原子间距离, 该距离是在 SYBYL 6.8 中使用分析-»距离命令测得的。

溶液构象使用 NOESY 谱测定。NH-OH 指连接部位酰胺的质子和连接部位羟基的氧之间的原子间距离, NH-X 指连接部位酰胺的质子和连接部位 X 位置的原子之间的原子间距离。S-1 在体外用作部分激动剂, S-4 和 X-2 在体外是激动剂, X-3、X-4 和 X-5 在体外是拮抗剂。

表 3:

ID	NH-OH	NH-X
S-1	2.4	2.3
S-4	2.7	1.9

X-2	2.1	3.0
X-3	2.0	3.6
X-4	2.3	4.4
X-5	2.0	3.9

构建 AR 的位点特异性突变体, 检测 DHT 和三种非类固醇配体即羟基氟他胺 (HF)、比卡鲁胺和 S-4 刺激 AR 介导的转录的能力 (图 11)。在该突变体中, 比卡鲁胺表现为激动剂并刺激 AR 介导的转录激活, 表明结合比卡鲁胺的 W741L 突变体 AR-LBD 采取类似于用结合激动剂的野生型 AR 观察到的构象的活性构象。考虑到纯化结合拮抗剂的野生型 LBD 的困难, 结合比卡鲁胺的 W741L 突变体和结合羟基氟他胺的 T877A 突变体的激动剂构象证明是有用的。本文考虑, 这些突变体复合物会采取更紧凑的构象, 这样会促进在 LBD 的纯化和结晶过程中伴侣蛋白质的解离, 并为我们提供对非类固醇 AR 配体结合机制的首次了解。

使用类似于首先解析与类固醇配体结合的 AR-LBD 晶体结构的科学家所述的方法, 将结合 R1881 和 DHT、DHT-5 的野生型 LBD 和结合比卡鲁胺的 W741L LBD 纯化并结晶。而且, 使用亲和力更高的比卡鲁胺 *R*-异构体。在大肠杆菌中, GST-LBD 与配体共同表达。在亲和层析和裂解融合蛋白后, LBD 的高 pI (等电点) 使杂质蛋白和伴侣蛋白质通过中性 pH 阳离子交换色谱除去。

这两种复合物均采取与结合类固醇的 LBD 非常类似的整体构象 (图 12A)。如由溶液构象的 NMR 研究所预示的, 比卡鲁胺在磺酰基氧和胺类质子之间形成分子内氢键 (图 12B), 这与计算机预测的模型 (图 10) 不同, 指示这是不同于醚连接类似物的构象, 并表明对配体溶液构象的 NMR 研究可能用于预测与 LBD 结合时的配体构象。这种结果说明, 这些突变为非类固醇配体提供更多的空间以嵌入 (fit into) LBD, 并形成由野生型 DHT 复合物观察到的激动剂构象。

大多数 LBD 残基在野生型 DHT 复合物中的位置类似于非类固醇复合物, 尽管配体结构的变化程度惊人 (图 13A)。羟基氟他胺 (HF) 和 *R*-比卡鲁胺具有类似的 A 环和酰胺键结构, 这使类固醇平面完全重叠 (图 13B)。

在 R752 和 A 环的硝基/氰基之间观察到氢键，这模拟了 DHT 中的 3-酮基，而且在 L704 和 N705 和羟基之间也观察到氢键，这模拟了 DHT 中的 17 β -OH。然而，与 DHT 不同的是，在非类固醇配体和 T877 侧链之间没有观察到氢键。

在 R-比卡鲁胺的砒连接基和 B 环区域也观察到残基的位置有很大区别（图 13B），该区域折叠离开类固醇平面并指向口袋（pocket）的顶部，可能占用 W741 吡啶环（在突变体中不存在）的空间。在 T877A-HF 和 WT-DHT 复合物中，W741 吡啶环的位置也区别很大。在 DHT 复合物中，Trp741 侧链与配体接触，而在 T877A-HF 复合物中，该吡啶环距离结合口袋（binding pocket）更远。M745 由 DHT 的 19-甲基置换似乎能解释这些区别。在图 13B 中也看到，与野生型 DHT 和 T877A-HF 相比，R-比卡鲁胺磺酰基造成螺旋 12 残基 M895 的置换。然而，该 M895 侧链被容纳在 T877A-HF 复合物的 W741 吡啶环的位置中。在野生型 LBD 中，W741 和 M895 侧链都可能与比卡鲁胺具有不利的阻止激动剂构象形成的相互作用。另一方面，R-比卡鲁胺的 B 环对位上的氟在 AR 的亲水区域结合，所述区域也提供形成氢键的机会。AR 的这一区域位于螺旋 4 和 5 之间的扭转处并与 H874 咪唑十分接近。在该位置被乙酰胺基 S-4、异硫氰酸盐、氰基或硝基取代的化合物证明对 AR 具有改善的亲合力，表明在该区域它们可能形成有利的氢键。

实施例 17

结合激动剂和拮抗剂的 AR LBD 的结构特征

HSP 的解离是由激动剂诱导的 AR LBD 构象变化引起的初始过程之一。在哺乳动物细胞中，HSP 复合物主要包含 HSP90、HSP70、p60 和 p23。HSP90 直接与受体结合成为同型二聚体，而其它蛋白质主要通过 HSP90 与该复合物结合。AR LBD 中的 HSP90 结合位点还没有被很好地表征。包括环 3-4、H4 和 H5 的残基 720-774 正好形成大部分的 AF2 疏水性凹槽（图 14A-14B），它们被鉴定为可能负责使用截短的结合 HSP90 的区域。

重要地，本文考虑，异常的曝露于溶剂的 HSP90 的 α -螺旋与细胞核受体家族的 H12 非常类似，并可能置换这些受体上的 H12 以促进配体结合。

这个观点尤其可能与 AR 有关，因为 AR 的功能与其它细胞核受体相比似乎有重要的不同。放射标记的 AR 的 IP 和蔗糖梯度离心分析显示，激动剂 R1881（而不是拮抗剂羟基氟他胺和比卡鲁胺）诱导 HSP90 解离，这说明伴侣蛋白质复合物的存在而不是 H12 的 MAEII 模体阻止接近 AF2 区。因此，HSP90 的解离似乎直接与 AR 配体的活性有关。

虽然羟基氟他胺用作野生型 AR 的拮抗剂，但是它对 T877A AR 突变体起激动剂作用。其对突变的 AR 的激动剂活性直接与 HSP90 的解离有关。这与 ER 完全不同，其中 ER 激动剂和拮抗剂都启动 HSP 的解离。与 ER 的情况相比，HSP90 的解离对 AR LBD 似乎是能影响受体的构象的更关键的因素。这说明 AR 拮抗剂活性可能涉及另一种机制。

不同 AR 复合物的限制性蛋白水解分析表明，AR 的配体诱导的激活需要 LBD 的两次连续的构象变化。AR 激动剂，即 T、DHT 和 R1881，稳定了 AR 的 29-KD 片段对抗限制性胰蛋白酶消化，而抗雄激素，即醋酸环丙孕酮、羟基氟他胺、尼鲁米特和比卡鲁胺稳定 35-KD 片段。29-KDa 和 35-KDa 片段都含有完整的 LBD（氨基酸 671-919），35-KDa 片段延伸进入铰链区（氨基酸 621-671）。35-KDa 片段也参与激动剂结合的初始步骤，但是在长时间的消化作用下其不稳定。

这种时间依赖性构象变化被钼酸盐的加入而延迟，这说明 HSP 的解离可能导致铰链区暴露于胰蛋白酶消化。因此，已经提出，激动剂结合启动 AR 的第一次构象变化，这触发 HSP 的解离，然后开始第二次构象变化。然而，尽管拮抗剂能启动第一次构象变化，但是它不能促进 HSP 的解离，这稳定了 LBD 和铰链区并保护铰链区不受进一步的胰蛋白酶消化。

实施例 18

对 SARM 进行基于结构的药物设计（SBDD）的全新方法

在基于激动剂与 AR 的结合构象来设计激动剂方面，与拮抗剂比卡鲁胺结合的 AR 突变体 W741L（bicW741L）使我们洞悉本文提供的化合物的结合模式。这也为区分激动剂和拮抗剂的结合模式特征提供了原理。最近解析的结合激动剂 S-1 的野生型 AR（S1-野生型）的晶体结构确证了在 W741L 突变体中观察到的结合模式。在 1.8 Å 的清晰度下，这些结构都被

解析, 而且这些结构证明了新型的结合模式, 该模式根本上不同于在共晶结构出现之前提出的、由同源模型所表明的模式。

与上述共晶相反, 同源模型沿所对接的 (docked) 类固醇的 α -面具有独特的未被占据的空腔, 所述空穴大到足够能容纳丙酰苯胺的 B 环。

确认全新 SBDD 模型

通过 Spearman 相关系数分析对这些 AR 结构模型进行的经验分析提供了每一种模型预测配体亲合力的等级次序的能力的统计学手段。当使用基于分子对接的方法例如全新设计或虚拟筛选以评价该模型是否能用于按优先次序确定应该沿着哪些经计算机模拟 (*in silico*) 的指导进行时, 这种等级顺序统计量是适当的。将为比较分子场分析 (CoMFA) 模型而编辑的 AR 配体数据库用于以下 AR 模型的 Spearman 分析: CoMFA、结合 S-1 的野生型晶体 (简称为 S1-野生型), 结合比卡鲁胺的 W741L 晶体 (简称为比卡鲁胺 c-W741L) 和同源模型。CoMFA (C. E. Bohl, C. Chang, M. L. Mohler, J. Chen, D. D. Miller, P. W. Swaan, J. T. Dalton. A ligand-based approach to identify quantitative structure-activity relationships for the androgen receptor. *J Med Chem* 2004, 47(15), 3765-76.)、S1-野生型 (C. E. Bohl, D. D. Miller, J. Chen, C. E. Bell, J. T. Dalton. Structural basis for accommodation of nonsteroidal ligands in the androgen receptor. *J Biol Chem* 2005, 280(45), 37747-54.)、比卡鲁胺-W741L (C. E. Bohl, W. Gao, D. D. Miller, C. E. Bell, J. T. Dalton. Structural basis for antagonism and resistance of bicalutamide in prostate cancer. *Proc Natl Acad Sci U S A* 2005, 102(17), 6201-6.) 和 G1 同源模型 ((C. A. Marhefka, B. M. Moore, 2nd, T. C. Bishop, L. Kirkovsky, A. Mukherjee, J. T. Dalton, D. D. Miller. Homology modeling using multiple molecular dynamics simulations and docking studies of the human androgen receptor ligand binding domain bound to testosterone and nonsteroidal ligands. *J Med Chem* 2001, 44(11), 1729-40.)) 的 R_s 值分别为 0.93、0.55、0.29 和 -0.28, 这说明, S1-野生型模型显著的预测值和比卡鲁胺-W741L 模型有限的预测值表明与以前的基于结构的药物设计模型相比有进步。因此, 可以预测这些晶体结构能改善确定由计算机模拟的指导的优先次序的能力, 由此促进药物设计。

实施例 19

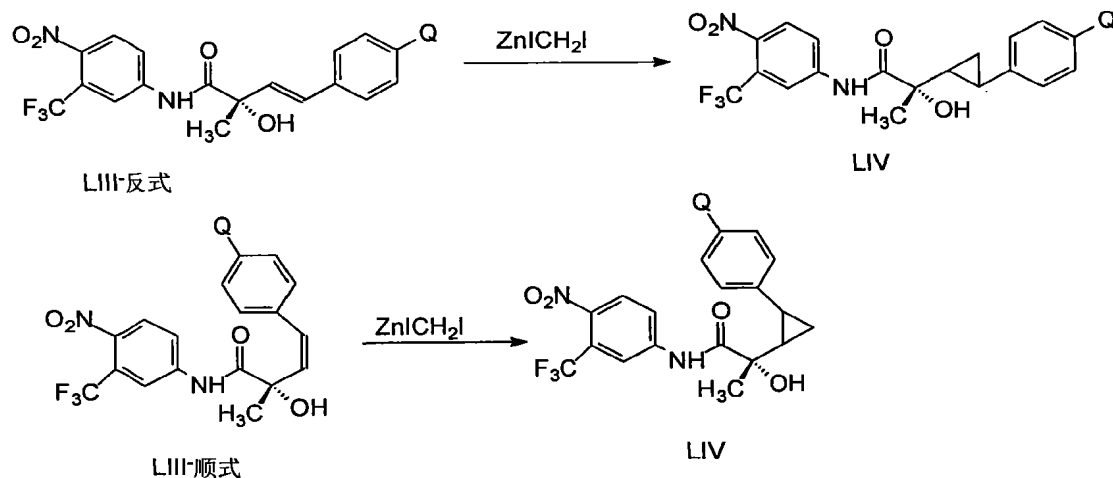
AR 配体结合的计算预测的确认

对实施例 16 中的扭应变参数和氢键相互作用的检验显示, 化合物 XVII 的芳基丙酰胺衍生物化合物采取类似于化合物 XLII 的构象。羟基 α 以这样的方式定位到羰基, 它参与和受体的天冬酰胺 705 的氢键相互作用。该氨基酸与亮氨酸 704 的主链氧形成弱的氢键。所做的计算预测与结合测定得出的结果一致。然而, 为了令人信服地建立上述相互作用和分子采取的构象, 建立了合适的分子模型, 该模型没有自由羟基和酰胺质子, 而且最重要的是, 该模型在构象上局限于类似于化合物 XLII 的结构。因此, 酰胺氮和羟基氧通过羰基官能团连结, 这形成如化合物 XXXIX 中所描绘的噁唑烷二酮衍生物结构。实施芳基丙酰胺衍生物的化合物的合成和这些噁唑烷二酮衍生物的立体选择性合成。

实施例 20

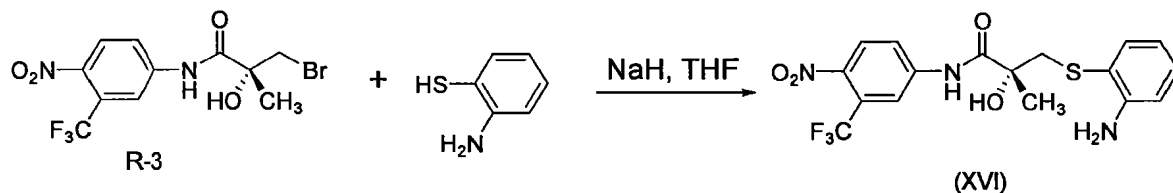
化合物 LIV 的合成

通过化合物 LIII 合成化合物 LIV, 所考虑的第一组化合物是通过西蒙斯-史密斯反应合成的环丙烷系列, 如下路线所示。



实施例 21

化合物 XVI 的合成



根据上述路线合成化合物 XVI。根据 US 06995284 合成 R-3，该专利通过引用结合于此。得到 XVI，为黄色油：计算出的质量 415.08, [M-H] 414.0; $^1\text{H NMR}$ (CDCl_3) 9.13 (bs, 1H, NH), 7.96 (d, $J = 9.0$ Hz, 2H, ArH), 7.88 (dd, $J = 9.0, 2.1$ Hz, 1H, ArH), 7.43 (dd, $J = 7.6, 1.5$ Hz, 1H, ArH), 7.11 (m, 1H, ArH), 6.72 (m, 2H, ArH), 4.15 (bs, 3H, OH & NH₂), 3.59 (d, $J = 14.1$ Hz, 1H, CH₂), 3.02 (d, $J = 14.1$ Hz, 1H, CH₂), 1.56 (s, 3H, CH₃)。

实施例 22

化合物 XL 的合成

如图 1J 中所描绘地合成化合物 XL。向乙醇中的 L-丙氨酸钠盐中加入异硫氰酸苯酯，温热 30 分钟。蒸去溶剂，并向油状剩余物中加入浓 HCl。收集形成的白色固体，在水中洗涤，得到化合物 2。加入乙酸酐，得到化合物 3，在六甲基二硅氮烷钾盐的存在下加入 1-溴-4-溴甲基苯，得到化合物 XL。

化合物 2 的 $^1\text{H NMR}$ (CDCl_3): 7.65, 7.63, 7.61, 7.38, 7.35, 7.25, 4.40, 1.62

化合物 3 的 $^1\text{H NMR}$ (CDCl_3): 7.59, 7.57, 7.56, 7.39, 7.33, 4.92, 2.90, 1.74

化合物 XL 的 $^1\text{H NMR}$ (CDCl_3): 7.53, 7.52, 7.51, 7.50, 7.49, 7.40, 7.39, 7.37, 7.34, 4.38, 1.67, 1.66; 化合物 XL 的熔点: 99°C。

实施例 23

化合物 XLI 的合成

如图 1K 中所描绘地合成化合物 XLI。向乙醇中的 L-丙氨酸钠盐中加入 4-异硫氰基-1-硝基-2-三氟甲基苯，温热 30 分钟。蒸去溶剂并向油状剩余物中加入浓 HCl。收集形成的白色固体，在水中洗涤，得到化合物 2。加入乙酸酐，得到化合物 3，在六甲基二硅氮烷钾的存在下加入 1-溴-4-溴甲基苯，得到化合物 XLI。

化合物 3 的 $^1\text{H NMR}$ (CDCl_3): 10.80, 8.35, 8.18, 7.99, 4.49, 1.43。

化合物 XLI 的 $^1\text{H NMR}$ (CDCl_3): 7.97, 7.47, 7.43, 7.42, 7.19, 7.15, 6.97,

6.92, 3.93, 3.15, 2.88, 1.98。

虽然本文已经说明和描述了本发明的某些特征，但是本领域的普通技术人员现在会得出许多修改、替换、改变和等同形式。因此，应该理解，所附的权利要求书意在覆盖所有落在本发明的真正精神范围内的这种修改和变化。

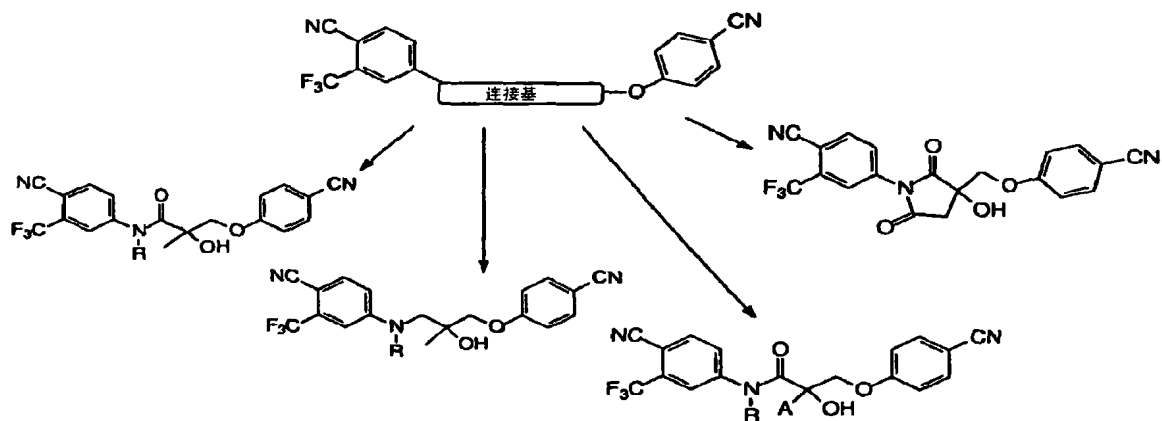


图1A

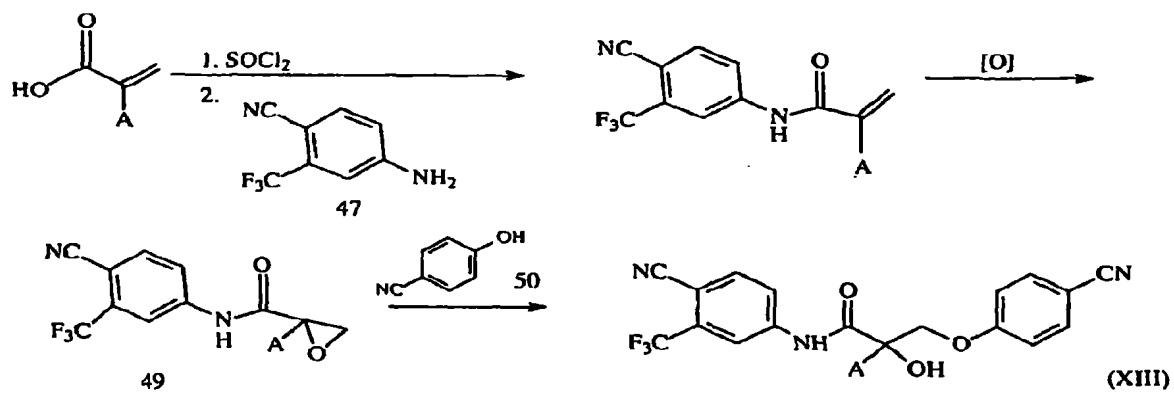


图1B

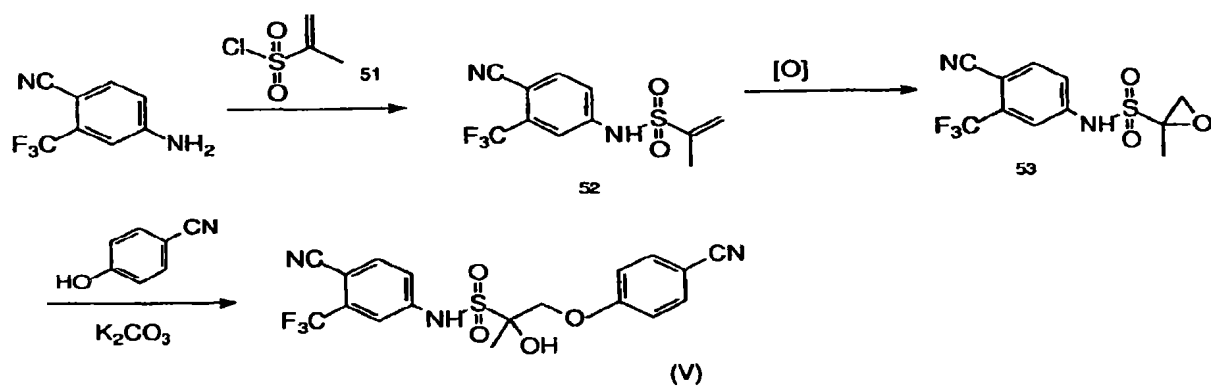


图1C

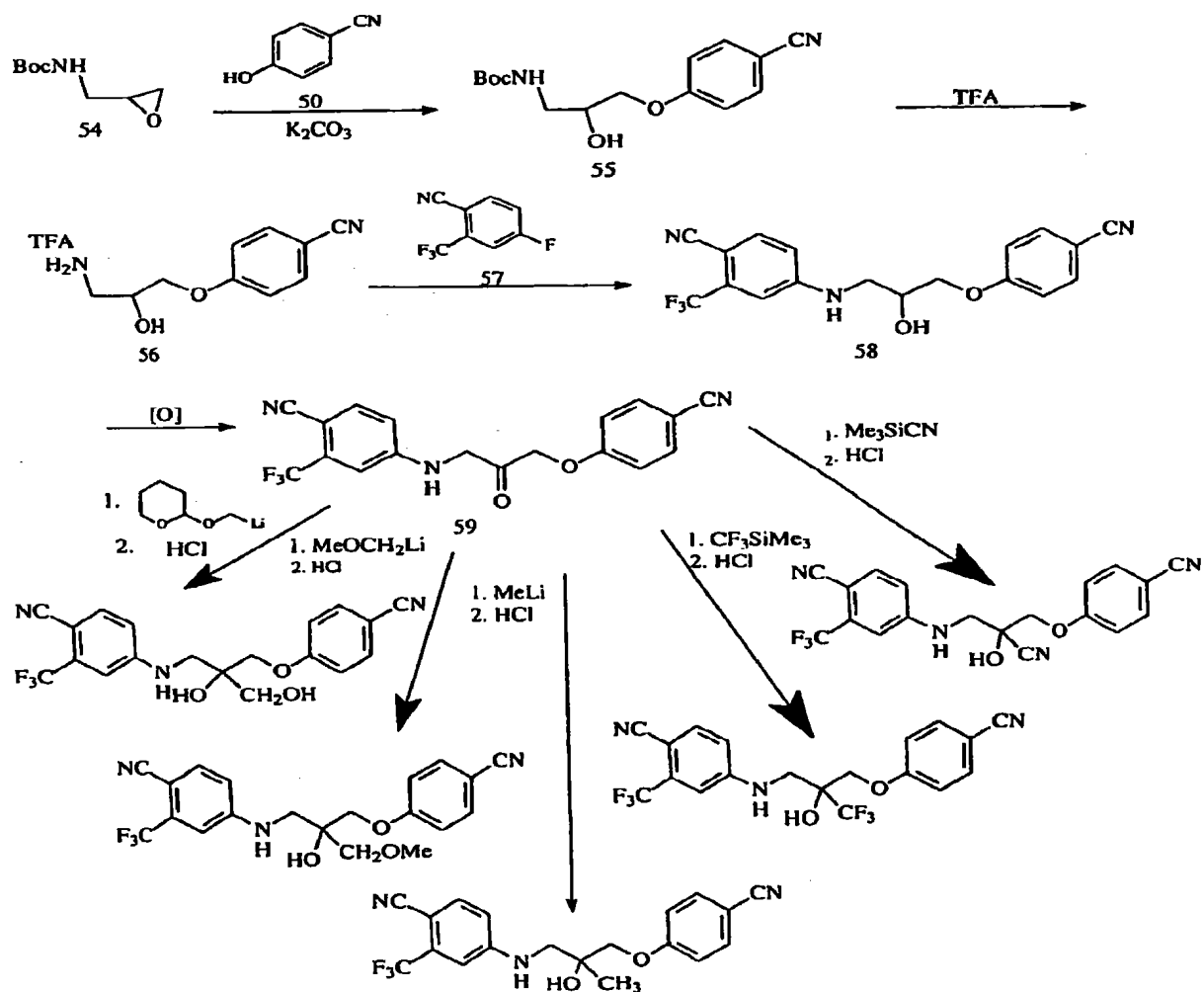


图1D

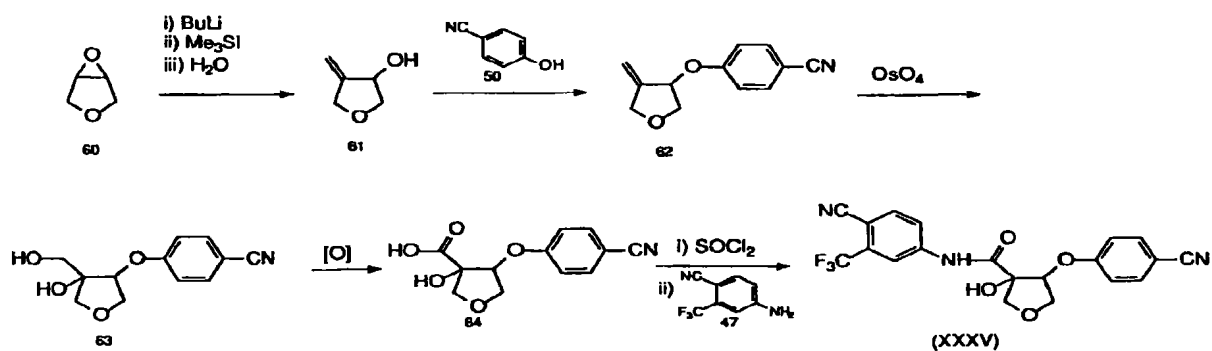


图1E

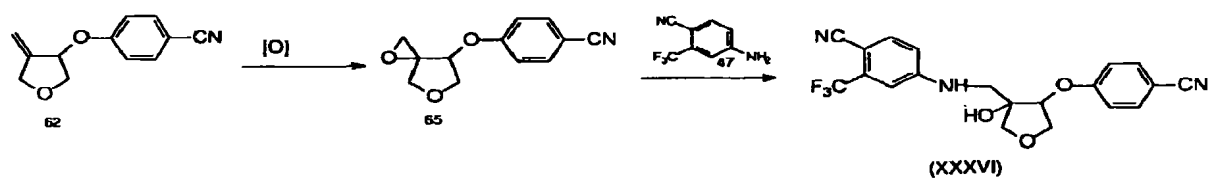


图1F

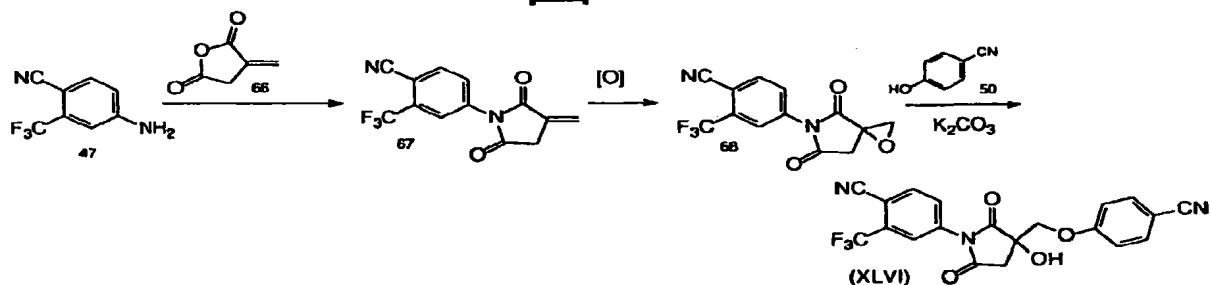


图1G

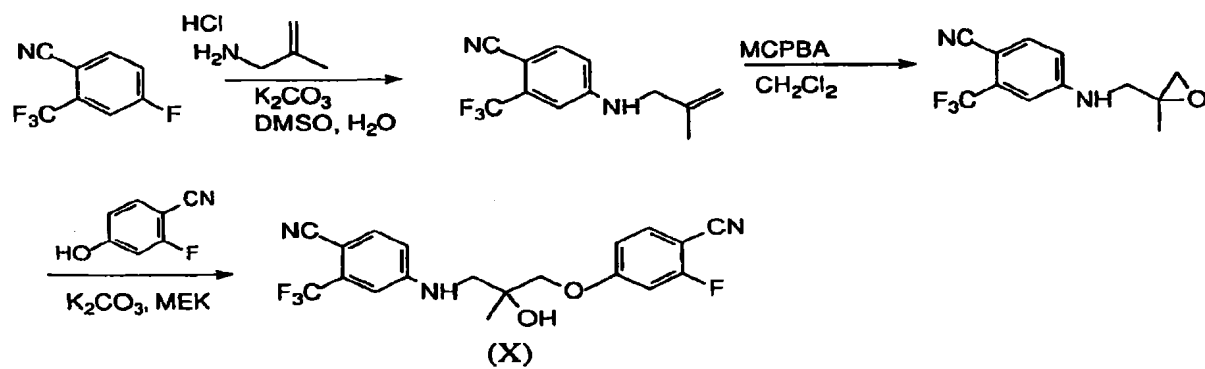
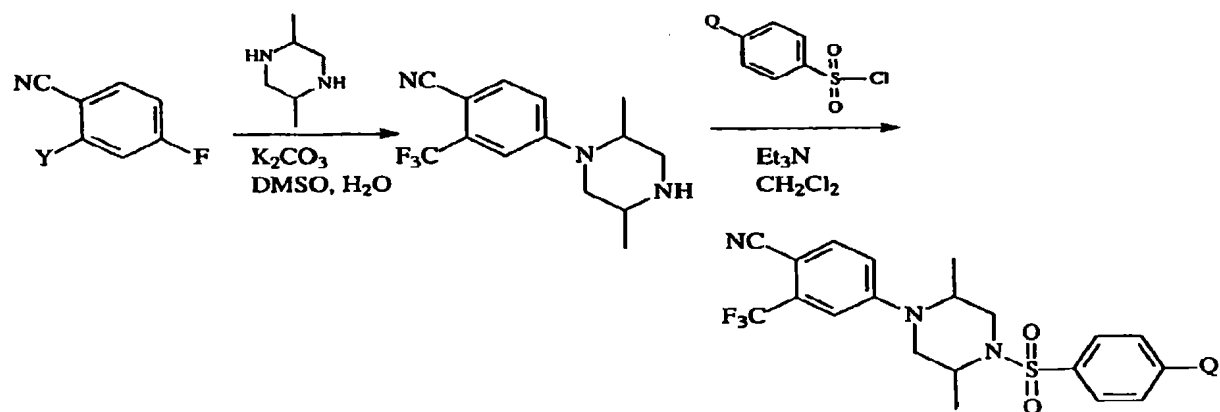


图1H



Q=CN, Y=CF₃ (化合物XXIV)
 Q=CN, Y=Cl (化合物XXV)
 Q=Cl, Y=CN (化合物XXVI)
 Q=CF₃, Y=Cl (化合物XXVII)
 Q=CF₃, Y=CF₃ (化合物XXVIII)

图1I

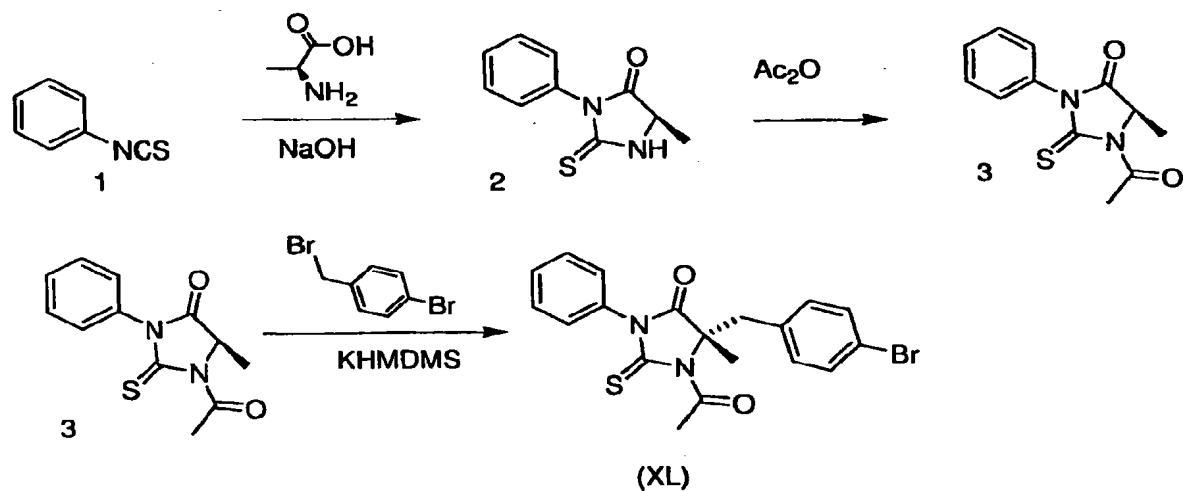


图1J

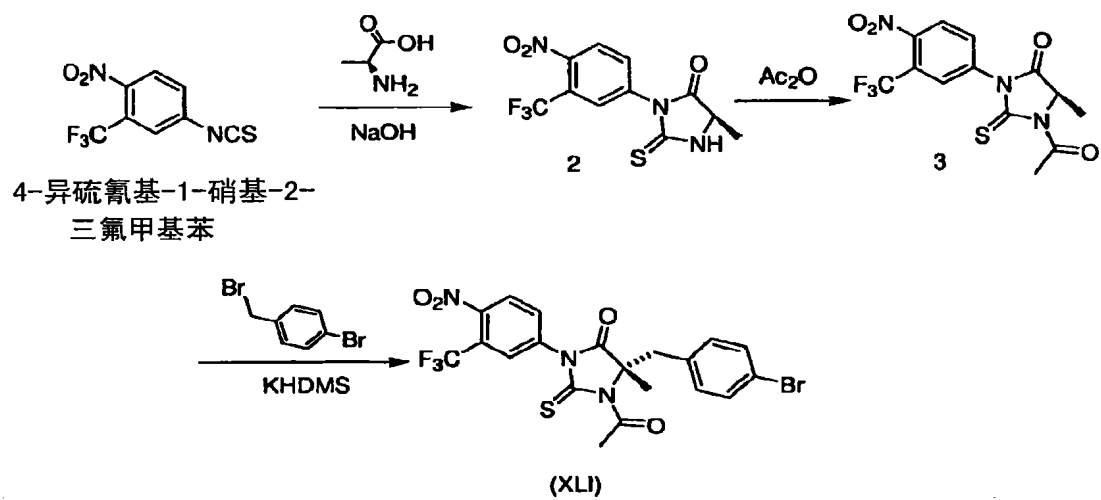
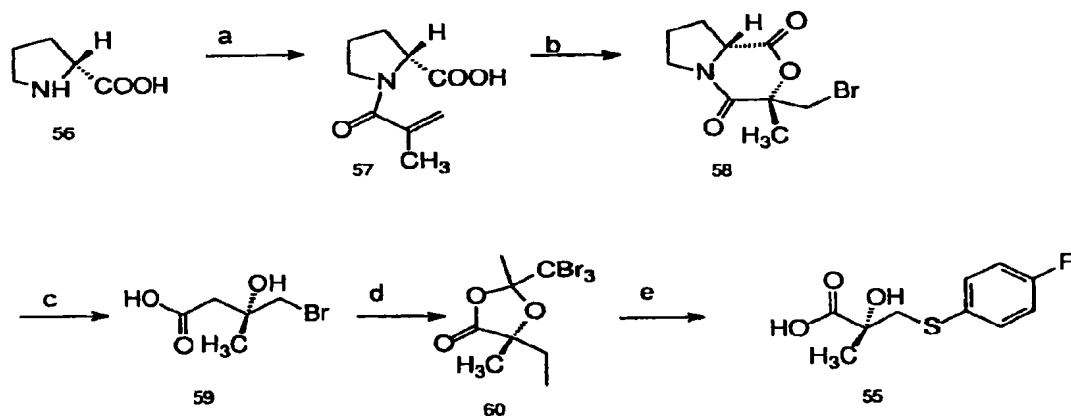
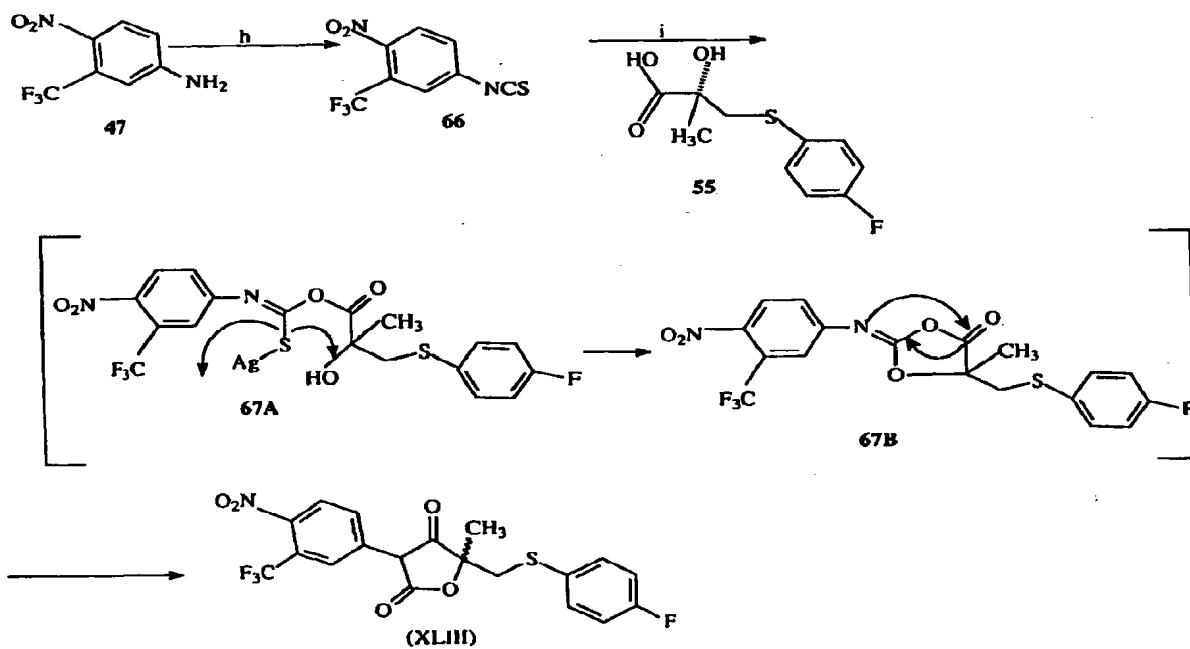


图1K



试剂: a-异丁烯酰氯、NaOH、丙酮; b-NBS、DMF; c-24% HBr ;
d-三溴乙醛、浓硫酸; e- (1) NaOH 、4-氟苯硫酚、2-丙醇, (2) 浓 HCl 。



试剂: h-硫光气、氯仿、 NaCO_3 , i-三氟乙酸银、三乙胺、乙腈。

图2

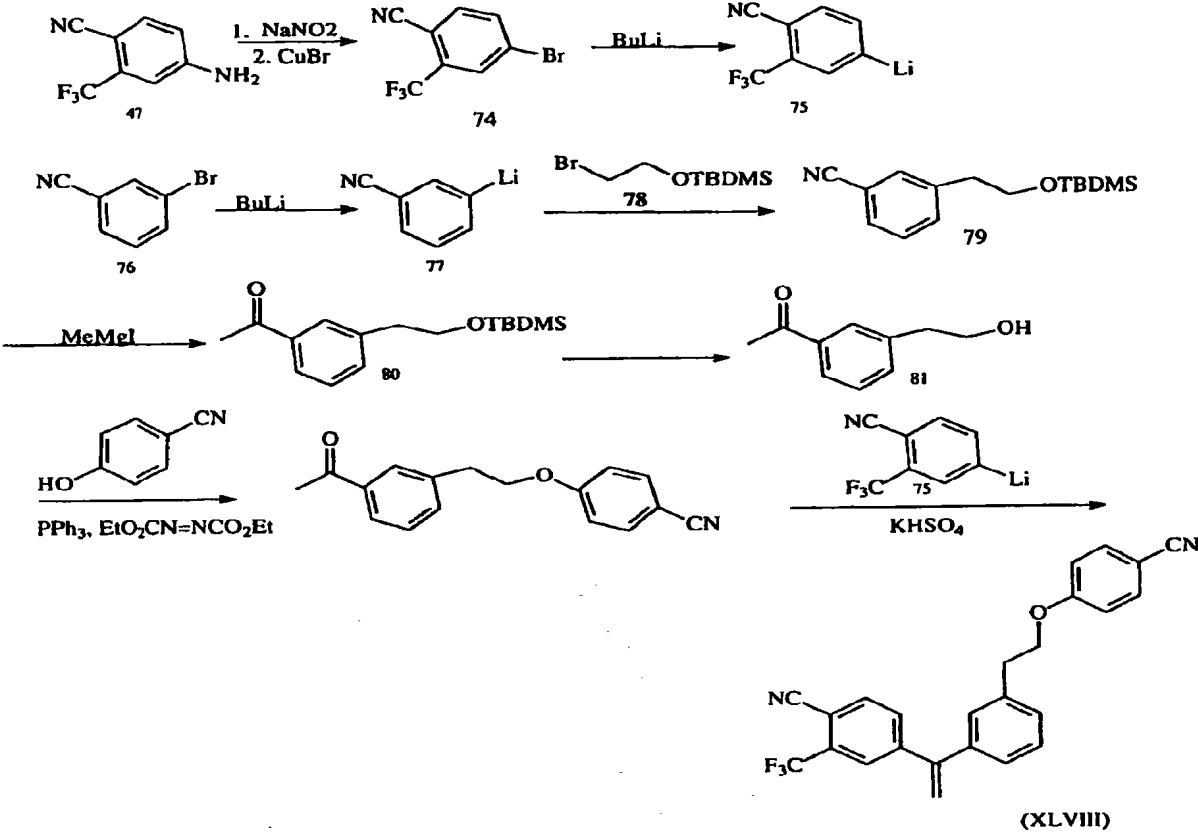


图3

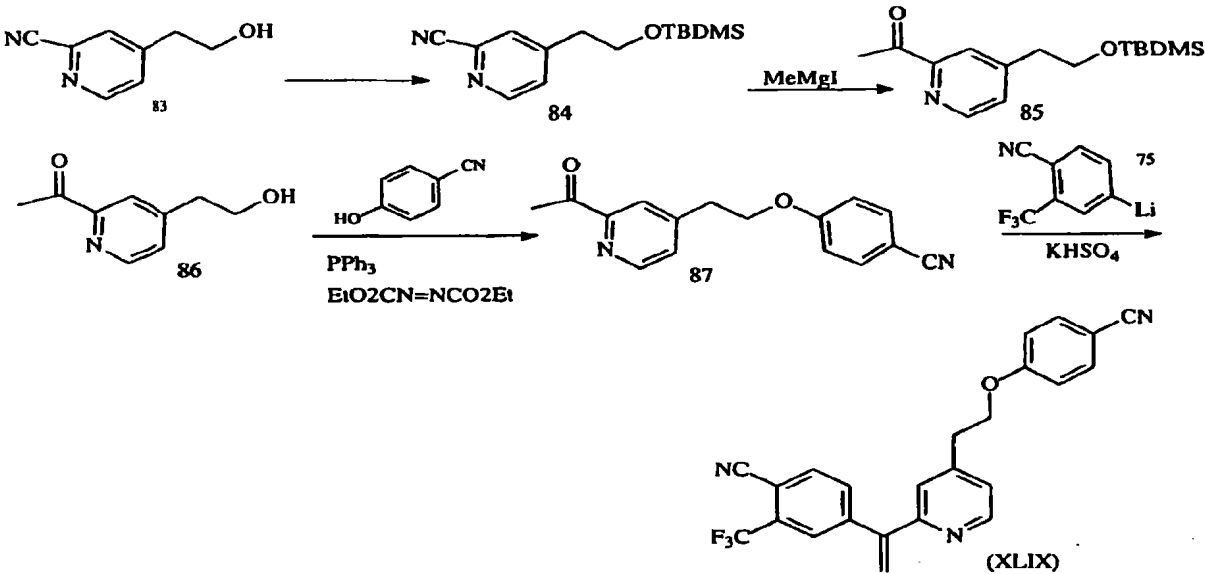


图4

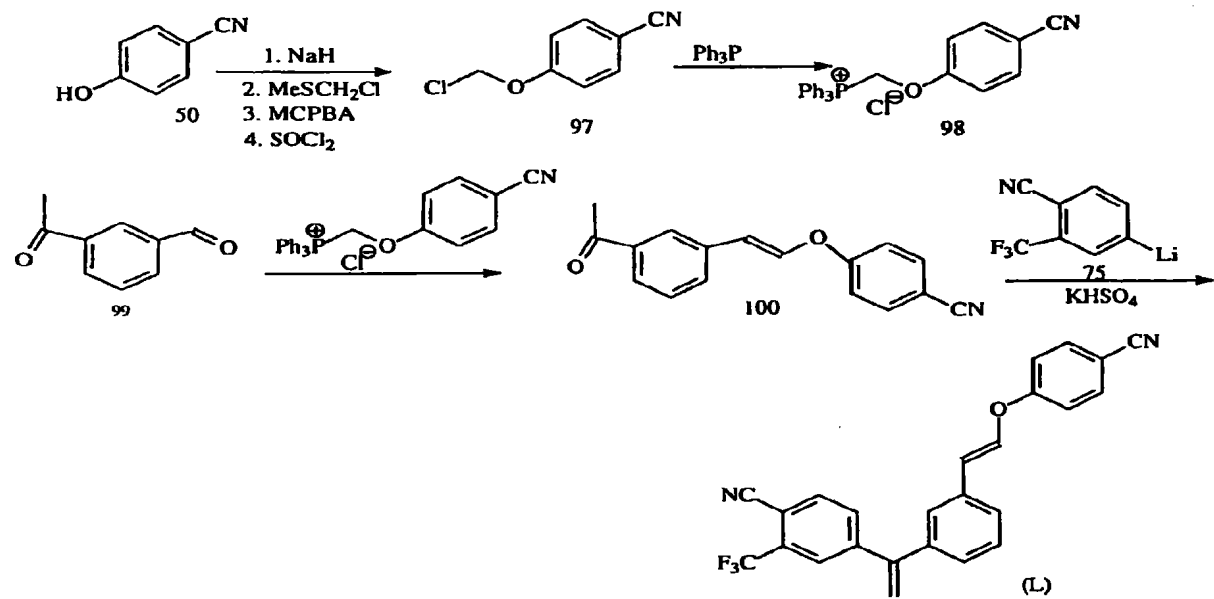


图6

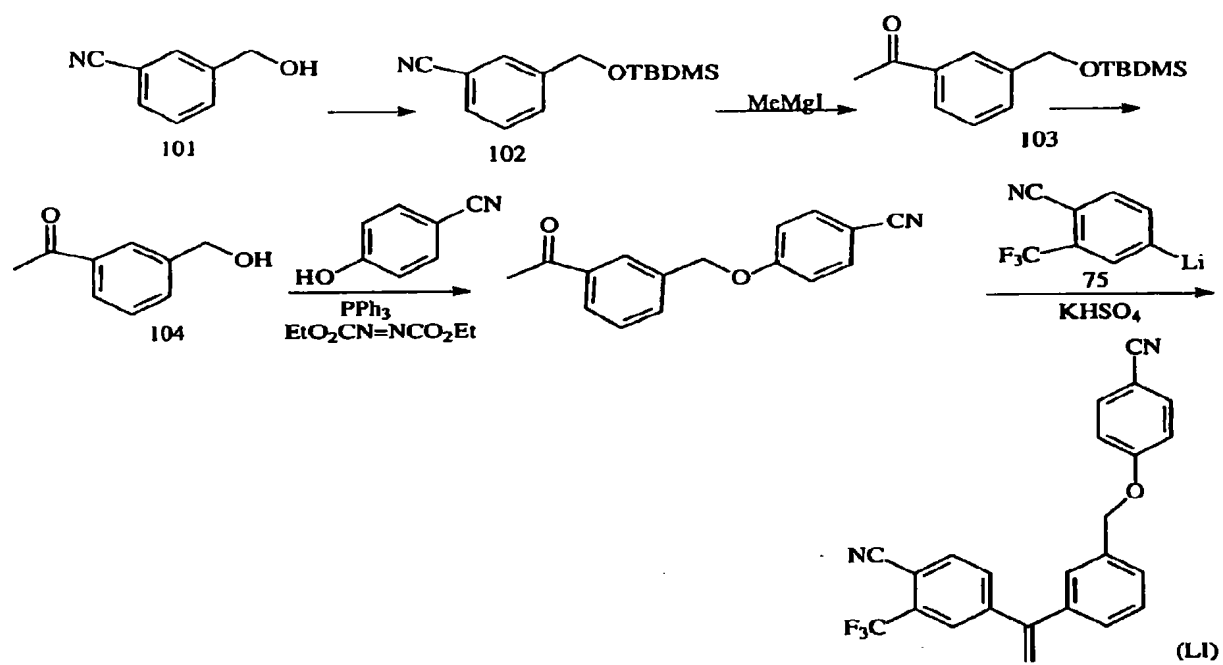


图7

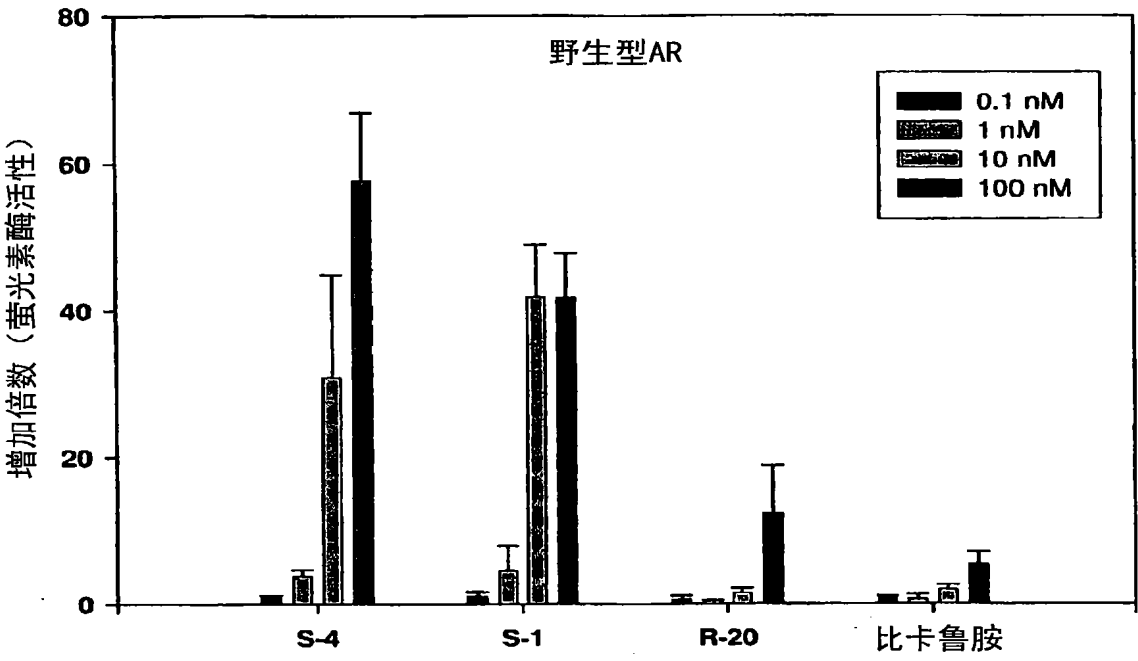


图8

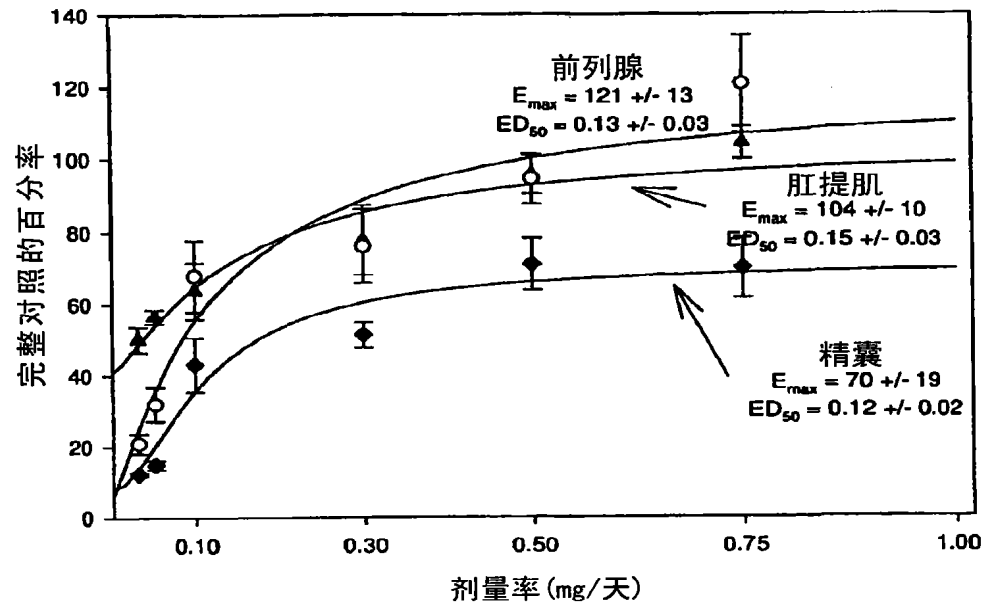


图9A

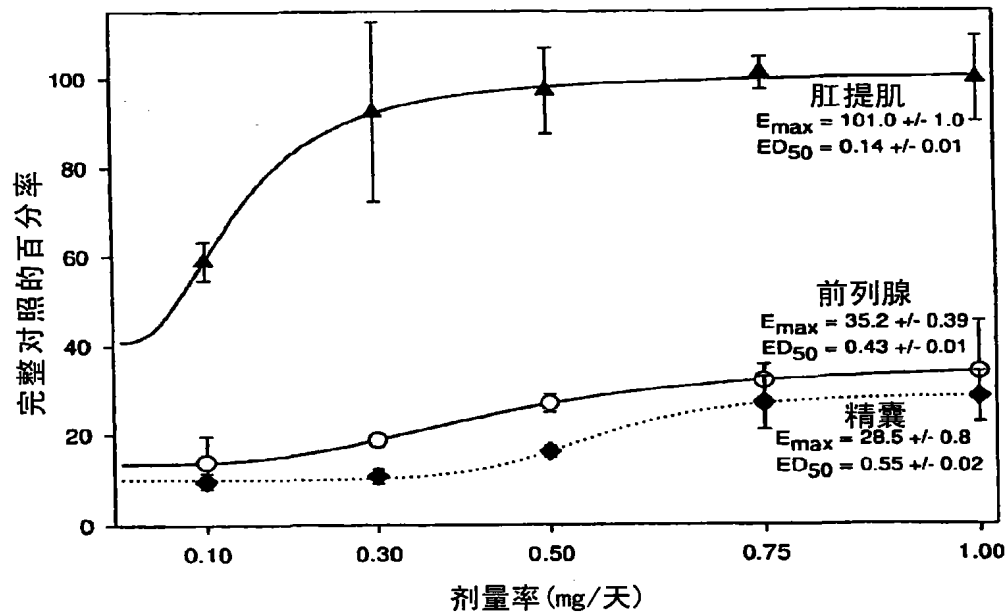


图9B

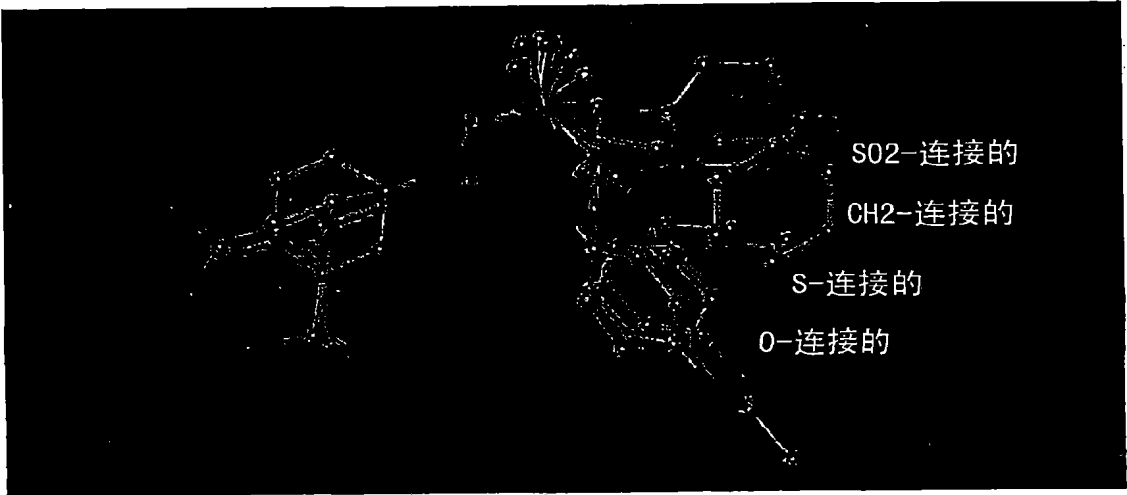


图10

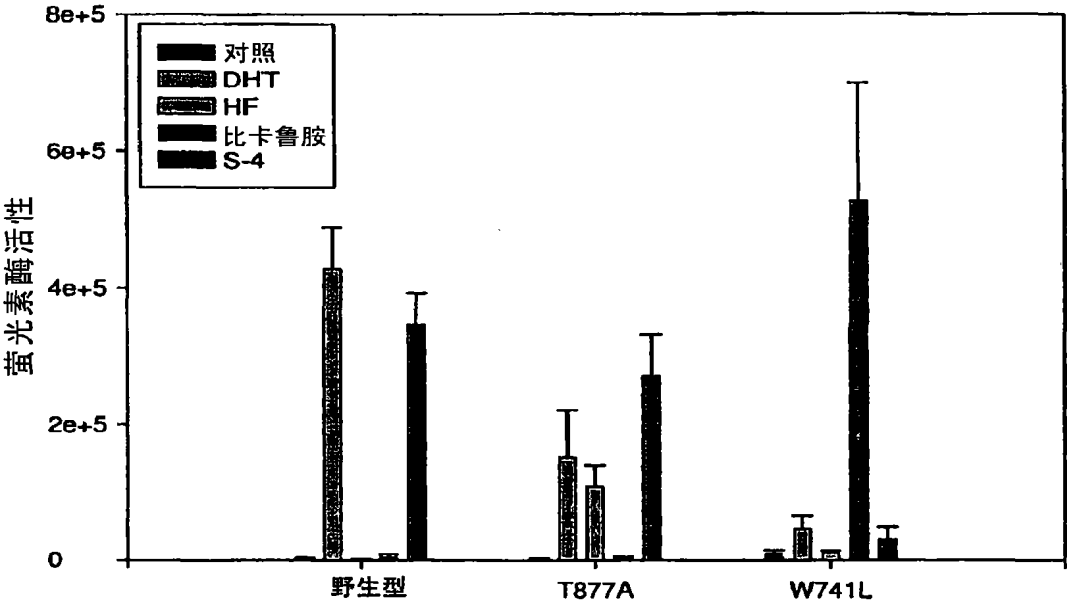


图11

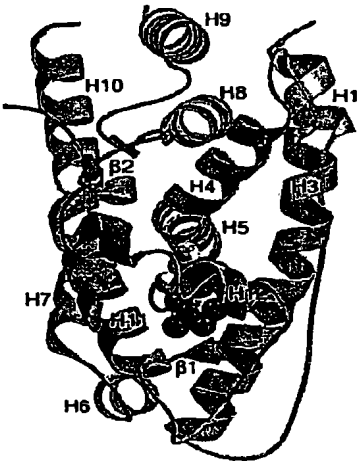


图12A

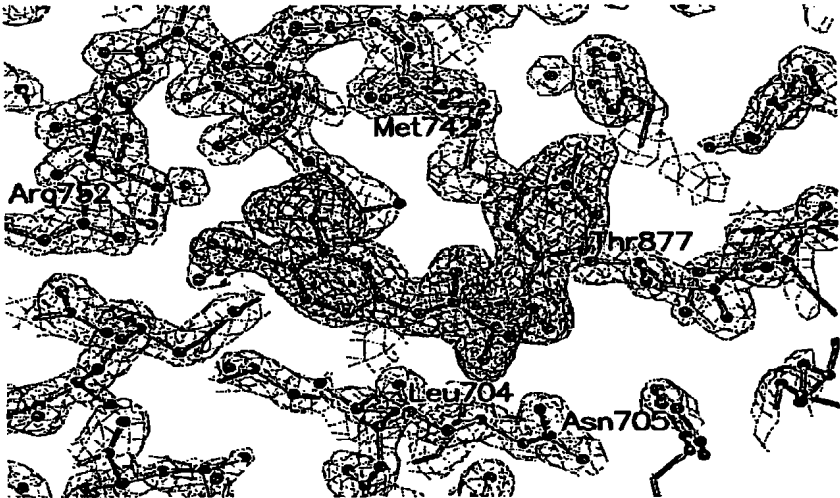


图12B

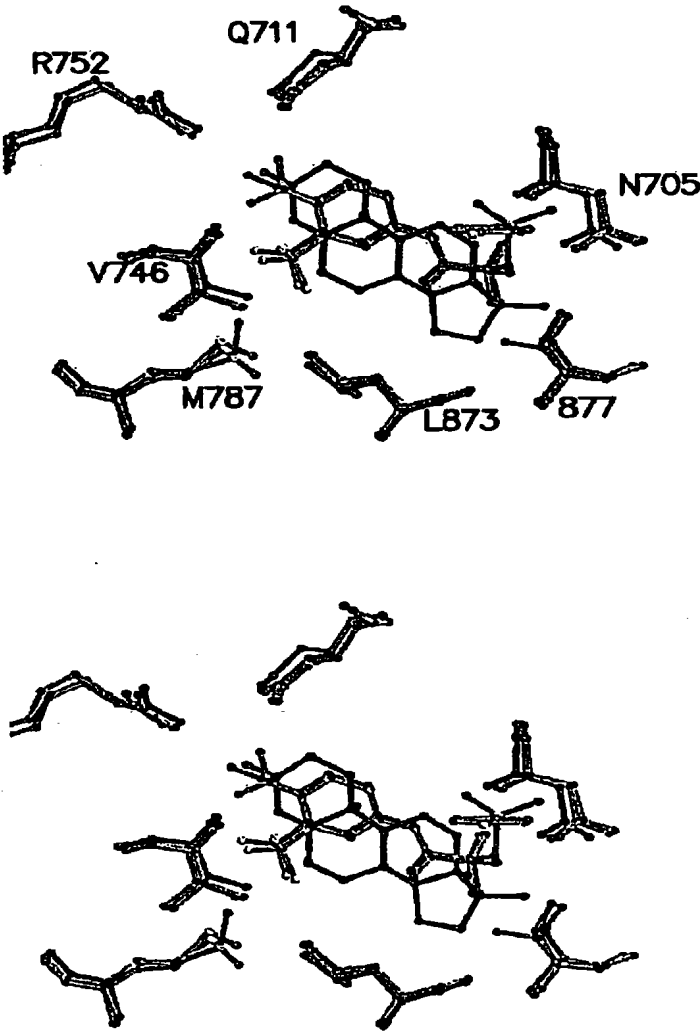


图13A

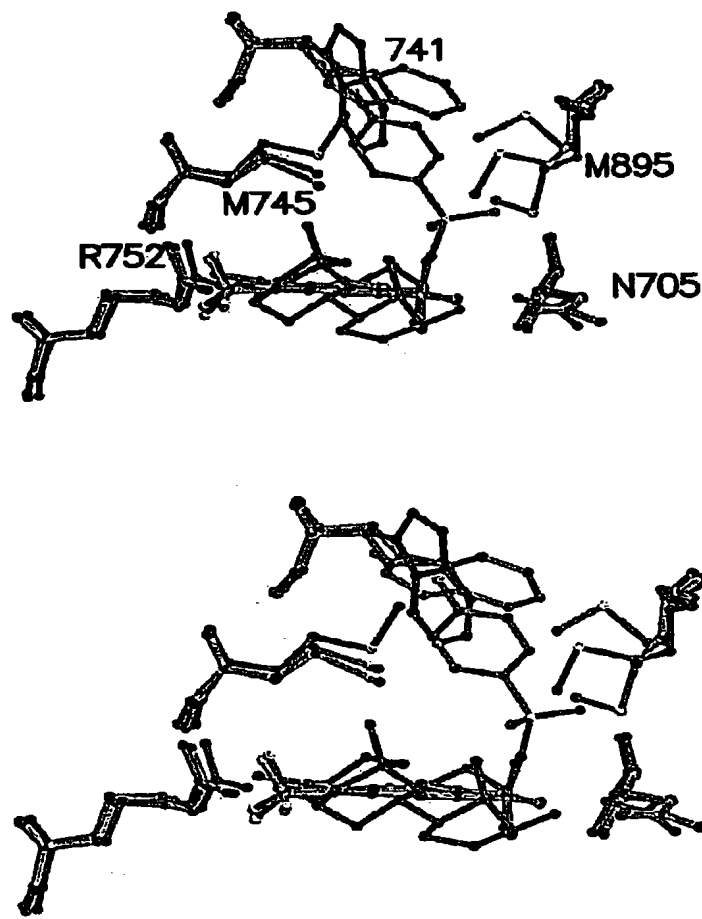


图13B

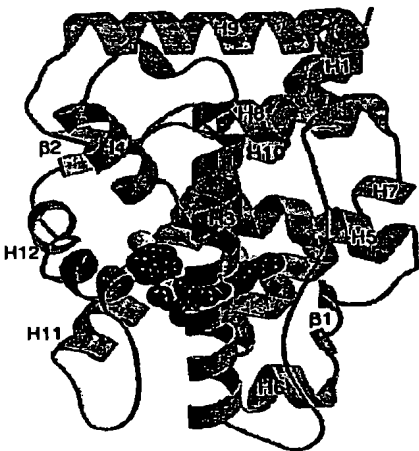


图14A

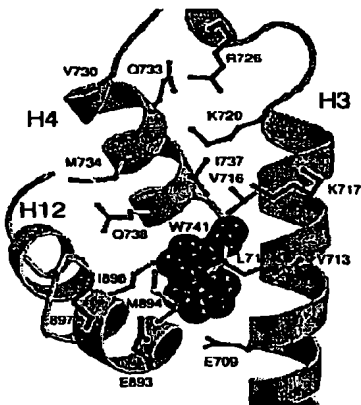


图14B

(19)



(11)

EP 2 094 709 B1

(12)

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WO 2008/036579 (27.03.2008 Gazette 2008/13)

(54) THIAZOLE PYRAZOLOPYRIMIDINES AS CRF1 RECEPTOR ANTAGONISTS

THIAZOLPYRAZOLOPYRIMIDINE ALS ANTAGONISTEN DES CRF1-REZEPTORS

THIAZOLE PYRAZOLOPYRIMIDINES CONVENANT COMME ANTAGONISTES DU RÉCEPTEUR DU CRF1

(84) Designated Contracting States:
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Designated Extension States:
AL BA HR MK RS

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(30) Priority: **20.09.2006 US 826264 P**

(56) References cited:
**WO-A-00/59908 WO-A-01/23388
WO-A-97/29109 WO-A-98/03510
WO-A-02/072202 WO-A-2005/063755**

(43) Date of publication of application:
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- **GEHLERT ET AL: "3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine: a novel brain-penetrant, orally available corticotropin-releasing factor receptor 1 antagonist with efficacy in animal models of alcoholism." THE JOURNAL OF NEUROSCIENCE, vol. 27, no. 10, 7 March 2007 (2007-03-07), pages 2718-2726, XP002465426**
- **HE LIQI ET AL: "4-(1,3-Dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)pyrazolo[1,5-a]-1,3,5-triazine: A Potent, Orally Bioavailable CRF1 Receptor Antagonist" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 43, 2000, pages 449-456, XP002196777 ISSN: 0022-2623**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 2 094 709 B1

- CHEN C ET AL: "DESIGN OF 2,5-DIMETHYL-3-(6-DIMETHYL-4-METHYLPYRIDIN -3-YL)-7-DIPROPYL AMINOPYRAZOLO[1,5-ALPHA] PYRIMIDINE (NBI 30775/R121919) AND STRUCTURE-ACTIVITY RELATIONSHIPS OF A SERIES OF POTENT AND ORALLY ACTIVE CORTICOTROPIN-RELEASING FACTOR RECEPTOR ANTAGONISTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 47, no. 19, 9 September 2004 (2004-09-09), pages 4787-4798, XP001206057 ISSN: 0022-2623

Description

FIELD OF THE INVENTION

[0001] This invention relates to novel thiazole pyrazolopyrimidine compounds, pharmaceutical compositions thereof, and use thereof as CRF¹ receptor antagonists in the treatment of psychiatric and neuroendocrine disorders, neurological diseases, and metabolic syndrome.

BACKGROUND OF THE INVENTION

[0002] Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

[0003] CRF has been implicated in psychiatric disorders and neurological diseases including depression and anxiety, as well as the following: Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis, Parkinson's disease, epilepsy, migraine, alcohol and substance abuse and associated withdrawal symptoms, obesity, metabolic syndrome, congenital adrenal hyperplasia, Cushing's disease, hypertension, stroke, irritable bowel syndrome, stress-induced gastric ulceration, premenstrual syndrome, sexual dysfunction, premature labor, inflammatory disorders, allergies, multiple sclerosis, visceral pain, sleep disorders, pituitary tumors or ectopic pituitary-derived tumors, chronic fatigue syndrome and fibromyalgia.

[0004] CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain thereby suggesting potential functional diversity. For example, widely distributed brain CRF¹ receptors are strongly implicated in emotionality accompanying exposure to environmental stressors. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors. A more discrete septal/hypothalamic distribution and the availability of alternative endogenous ligands suggest a different functional role for the CRF2 receptor. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism. In other cases, CRF2 agonism produces similar effects to those reported for CRF1 antagonists or CRF1 gene deletion. For example, while CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well.

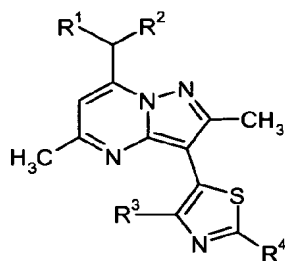
[0005] Certain pyrrolo[2,3-*d*]pyrimidines, pyrrolo[3,2-*d*]pyrimidines, pyrazolo[1,5-*a*]pyrimidines, 1,2,3-triazolo[4,5-*b*]pyridines, and pyrazolo[1,5-*a*]-1,3,5-triazines, useful as CRF antagonists, are described in WO 94/13676, WO 97/29109, WO 98/08847, and WO 98/03510. WO 00/59908 discloses certain pyrazolo[1,5-*a*]pyrimidines which are described as CRF antagonists. WO 2005/063755 discloses a genus of compounds encompassing pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]pyrimidin-2-ones, the compounds in this genus are also described as CRF antagonists. The CRF antagonists 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-*b*]pyridazine and 4-(2-butylamino)-2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)pyrazolo[1,5-*a*]-1,3,5-triazine are disclosed in J. Neuroscience, Vol. 27, No. 10, 2718-2726 (2007) and WO 02/072202, respectively. He et al. describe in J. Med. Chem., Vol. 43, 449-456 (2000) SAR studies in the pyrazolo[1,5-*a*]-1,3,5-triazine series leading to the discovery of the CRF antagonist 4-(1,3-dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)-pyrazolo[1,5-*a*]-1,3,5-triazine. Chen et al. in J. Med. Chem., Vol. 47, 4787-4798 (2004) describe a series of 3-pyridylpyrazolo[1,5-*a*]pyrimidines, which are described as CRF antagonists.

[0006] WO 01/23388 discloses certain amino-substituted pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]-1,3,5-triazines which are described as selective modulators of mammalian neuropeptide Y₁ (NPY₁) receptor.

[0007] The present invention provides novel thiazole pyrazolopyrimidines useful as CRF¹ receptor antagonists. In view of the above, it is desirable to discover new efficacious and selective antagonists of CRF¹ as potentially valuable therapeutic agents for the treatment of psychiatric and neuroendocrine disorders, neurological diseases, and metabolic syndrome. Further, since a majority of commercial CNS and cardiovascular drugs exhibit unfavorable bioavailability and pharmacokinetic profiles, it is also desirable to discover new compounds with favorable bioavailability and pharmacokinetic profiles relative to known CRF antagonists such as CP154526 and NBI30775.

SUMMARY OF THE INVENTION

[0008] In one embodiment, the present invention provides a compound of Formula I



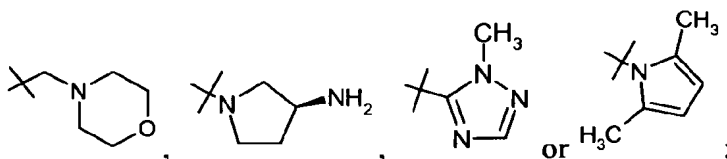
Formula I

wherein:

R¹ and R² are independently ethyl or *n*-propyl;

R³ is hydrogen, Cl, Br, methyl, trifluoromethyl or methoxy;

R⁴ is hydrogen, Br, R^aR^bN-, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



R^a and R^b are independently hydrogen, C₁-C₃alkyl, H₂NCH₂CH₂-, (CH₃)₃COC(O)NHCH₂CH₂-, or CH₃CH₂CH₂NHCH₂CH₂-; or a pharmaceutically acceptable salt thereof.

[0009] In another embodiment, the present invention provides a pharmaceutical composition comprising: a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0010] In another embodiment, the present invention relates to use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, allergy, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, premature labor, stress-induced gastric ulceration, inflammatory disorders, pituitary or ectopic pituitary-derived tumors, chronic fatigue syndrome, fibromyalgia, visceral pain or multiple sclerosis.

[0011] In another embodiment, the present invention relates to a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, allergy, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, premature labor, stress-induced gastric ulceration, inflammatory disorders, pituitary or ectopic pituitary-derived tumors, chronic fatigue syndrome, fibromyalgia, visceral pain or multiple sclerosis.

[0012] In another embodiment, the present invention relates to a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in therapy.

DETAILED DESCRIPTION OF THE INVENTION

[0013] As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Alkyl" means a saturated aliphatic hydrocarbon group, which may be straight or branched, having 1 to 5 carbon atoms in the chain.

"Pharmaceutically acceptable excipient" refers to a pharmaceutically acceptable formulation carrier, solution, or additive to enhance the formulation characteristics. Such excipients must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof and are well known to the skilled artisan (see e.g.

Remingtons Pharmaceutical Sciences, 19th Edition, Mack Publishing Company, 1995).

"Pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed (see e.g. Remingtons Pharmaceutical Sciences, 19th Edition, Mack Publishing Company, 1995).

"Therapeutically effective amount" or "effective amount" means the amount of the compound of formula I of the present invention or pharmaceutical composition containing a compound of formula I of the present invention that will elicit the biological or medical response of or desired therapeutic effect on a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

[0014] The terms "treatment," "treat," "treating," and the like, are meant to include both slowing and reversing the progression of a disorder. These terms also include alleviating, ameliorating, attenuating, eliminating, or reducing one or more symptoms of a disorder or condition, even if the disorder or condition is not actually eliminated and even if progression of the disorder or condition is not itself slowed or reversed. The term "treatment" and like terms also include preventive (e.g., prophylactic) and palliative treatment. Prevention of the disease is manifested by a prolonging or delaying of the onset of the symptoms of the disease.

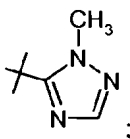
[0015] The symbol "-" in a molecular structure indicates the position of attachment for that particular substituent.

[0016] When any variable occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R¹, R², etc., are to be chosen in conformity with well-known principles of chemical structure connectivity.

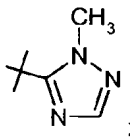
[0017] Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, an arylcarbonylaminoalkyl substituent is equivalent to aryl-C(O)-NH-alkyl-.

[0018] The present invention contemplates the following embodiments, which can alternatively be further combined:

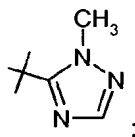
- (a) A compound of Formula I wherein R¹ and R² are ethyl;
- (b) A compound of Formula I wherein R¹ and R² are *n*-propyl;
- (c) A compound of Formula I wherein R³ is Cl, Br, methyl or trifluoromethyl;
- (d) A compound of Formula I wherein R³ is Cl;
- (e) A compound of Formula I wherein R³ is Br;
- (f) A compound of Formula I wherein R⁴ is R^aR^bN-, pyridin-4-yl, morpholin-4-yl, or



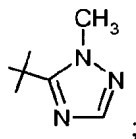
- (g) A compound of Formula I wherein R⁴ is morpholin-4-yl;
- (h) A compound of Formula I wherein R⁴ is



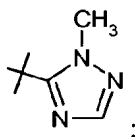
- (i) A compound of Formula I wherein R³ and R^b are independently C₁-C₃alkyl;
- (j) A compound of Formula I wherein R¹ and R² are ethyl, R³ is Cl, and R⁴ is morpholin-4-yl;
- (k) A compound of Formula I wherein R¹ and R² are *n*-propyl, R³ is Cl, and R⁴ is morpholin-4-yl;
- (l) A compound of Formula I wherein R¹ and R² are ethyl, R³ is Br, and R⁴ is morpholin-4-yl;
- (m) A compound of Formula I wherein R¹ and R² are *n*-propyl, R³ is Br, and R⁴ is morpholin-4-yl;
- (n) A compound of Formula I wherein R¹ and R² are ethyl, R³ is Cl, and R⁴ is



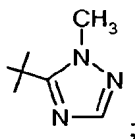
10 (o) A compound of Formula I wherein R¹ and R² are *n*-propyl, R³ is Cl, and R⁴ is



20 (p) A compound of Formula I wherein R¹ and R² are ethyl, R³ is Br, and R⁴ is



30 (q) A compound of Formula I wherein R¹ and R² are *n*-propyl, R³ is Br, and R⁴ is



40 (r) Use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for treating depression or anxiety;
(s) Use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for treating alcohol or substance abuse;

(t) Use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for treating alcohol or substance abuse and associated withdrawal symptoms;

(u) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a K_i value for CRF 1 binding of ≤ 500 nM;

(v) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a K_i value for CRF 1 binding of ≤ 50 nM;

45 (w) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a K_i value for CRF 1 binding of ≤ 5 nM;

(x) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a K_i value for CRF 1 binding of ≤ 500 nM and selectively binding to CRF1 (i.e., lower K_i) relative to CRF2;

(y) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a K_i value for CRF 1 binding of ≤ 50 nM and selectively binding to CRF 1 (i.e., lower K_i) relative to CRF2;

50 (z) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a K_i value for CRF 1 binding of ≤ 5 nM and selectively binding to CRF 1 (i.e., lower K_i) relative to CRF2; and/or

(aa) Particular exemplified compounds with superior bioavailability and pharmacokinetic profiles relative to some known CRF antagonists (e.g., CP 154526 and NBI30775), such as Example 15.

55 **[0019]** The compounds of the present invention are preferably formulated as pharmaceutical compositions administered by a variety of routes. Preferably, such compositions are for oral administration. Such pharmaceutical compositions and processes for preparing same are well known in the art (see, e.g., Remington: The Science and Practice of Pharmacy, A. Gennaro, et al., eds., 19th ed., Mack Publishing Co., 1995).

[0020] The compounds of Formula I are generally effective over a wide dosage range. For example, dosages per day normally fall within the range of about 0.0001 to about 30 mg/kg of body weight. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, and therefore the above dosage range is not intended to limit the scope of the invention in any way. It will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

[0021] The compounds of Formula I are CRF-1 antagonists and, as such, are useful for treating a condition which is treatable by reducing CRF1 receptor tone or stimulation. Corticotropin releasing factor (CRF), a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Natl. Acad. Sci. (USA)* 80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)], has been linked to a number of medical conditions. For example, in addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (1983); G. F. Koob, *Persp. Behav. Med.* 2:39 (1985); E. B. De Souza et al., *J. Neurosci.* 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors [see, e.g., J. E. Blalock, *Physiological Reviews* 69:1 (1989); J. E. Morley, *Life Sci.* 41:527 (1987)].

[0022] CRF is involved in psychiatric disorders and neurological diseases including depression and anxiety [D. M. Nielsen, *Life Sci.* 78:909-919; H. E. Kunzel et al., *J. Psychiatr. Res.* 37:525-533; D. R. Gehlert et al., *Eur. J. Pharmacol.* 509:145-153]. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis, as they relate to the dysfunction of CRF neurons in the central nervous system [for a review, see: E. B. De Souza, *Hosp. Practice* 23:59 (1988)]. Chronic administration of CRF has been shown to produce impairment of the dopamine system suggesting a role in Parkinson's disease [E. Izzo et al., *Pharmacol. Biochem. Behav.* 81:701-708 (2005)]. Other neurological disorders in which CRF is involved include epilepsy [T. Z. Baram et al., *Brain Res.* 770:89-95 (1997)] and migraine [T. C. Theoharides et al., *Endocrinology* 136:5745-5750 (1995)]. CRF has been implicated in alcohol and substance abuse and associated withdrawal symptoms [D. H. Overstreet et al., *Pharmacol. Biochem. Behav.* 77:405-413; Y. Shaham et al., *Psychopharmacology (Berl)* 137:184-190]. Moreover, there is evidence that CRF has a role in various endocrine disorders and cardiovascular diseases such as obesity [E. Timofeeva and D. Richard, *Neuroendocrinology* 66:327-340 (1997)], metabolic syndrome [A. M. Ward et al., *Metabolism* 53:720-726(2004)], congenital adrenal hyperplasia [D. P. Merke and G. B. Cutler Jr., *Endocrinol. Metab. Clin. North Am.* 30:121-135 (2001)], Cushing's disease [M. Labeur et al., *Curr. Drug Targets Immune Endocr. Metabol. Disord.* 4:335-342 (2004)], hypertension [R. J. Briscoe, et al., *Brain Res.* 881:204-207 (2000)], and stroke [S. L. Stevens et al., *J. Cereb. Blood Flow Metab.* 23:1151-1159 (2003)]. Gastric disturbances such as irritable bowel syndrome [Y. Tache et al., *Eur. J. Surg. Suppl.* 1:16-22 (2002)] and stress-induced gastric ulceration [K. E. Gabry et al., *Mol. Psychiatry* 7:474-483, 433 (2002)] have been shown to be related to CRF. In addition, there is indication that CRF has a role in various areas of human female health, for example, premenstrual syndrome [F. Facchinetti et al., *Psychosom. Med.* 56:418-422 (1994)], infertility [L. Ghizzoni et al., *Endocrinology* 138:4806-4811 (1997)], sexual dysfunction [J. E. Jones et al., *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 283:R591-597 (2002)], and premature labor [P. D. Wadhwa et al., *Am. J. Obstet. Gynecol.* 191:1063-1069 (2004)]. There is also evidence that CRF has a significant role in the immune system indicating therapeutic potential for treating inflammatory disorders [A. Gravanis and A. N. Margioris, *Curr. Med. Chem.* 12:1503-1512 (2005)], allergies [L. K. Singh et. al., *Brain Behav. Immun.* 13:225-239 (1999)], multiple sclerosis and other autoimmune disorders [C. Benou et al., *J. Immunol.* 174:5407-5413 (2005)]. In addition to the preceding, CRF has been implicated in visceral pain [M. Nijssen et al., *Neurogastroenterol. Motil.* 17:423-432 (2005)], sleep disorders [T. M. Buckley and A. F. Schatzberg, *J. Clin. Endocrinol. Metab.* 90:3106-3114(2005)], pituitary tumors or ectopic pituitary-derived tumors [K. D. Dieterich et al., *J. Clin. Endocrinol. Metab.* 83:3327-3331 (1998)], chronic fatigue syndrome and fibromyalgia [G. Neeck and L. J. Crofford, *Rheum. Dis. Clin. North Am.* 26:989-1002 (2000)].

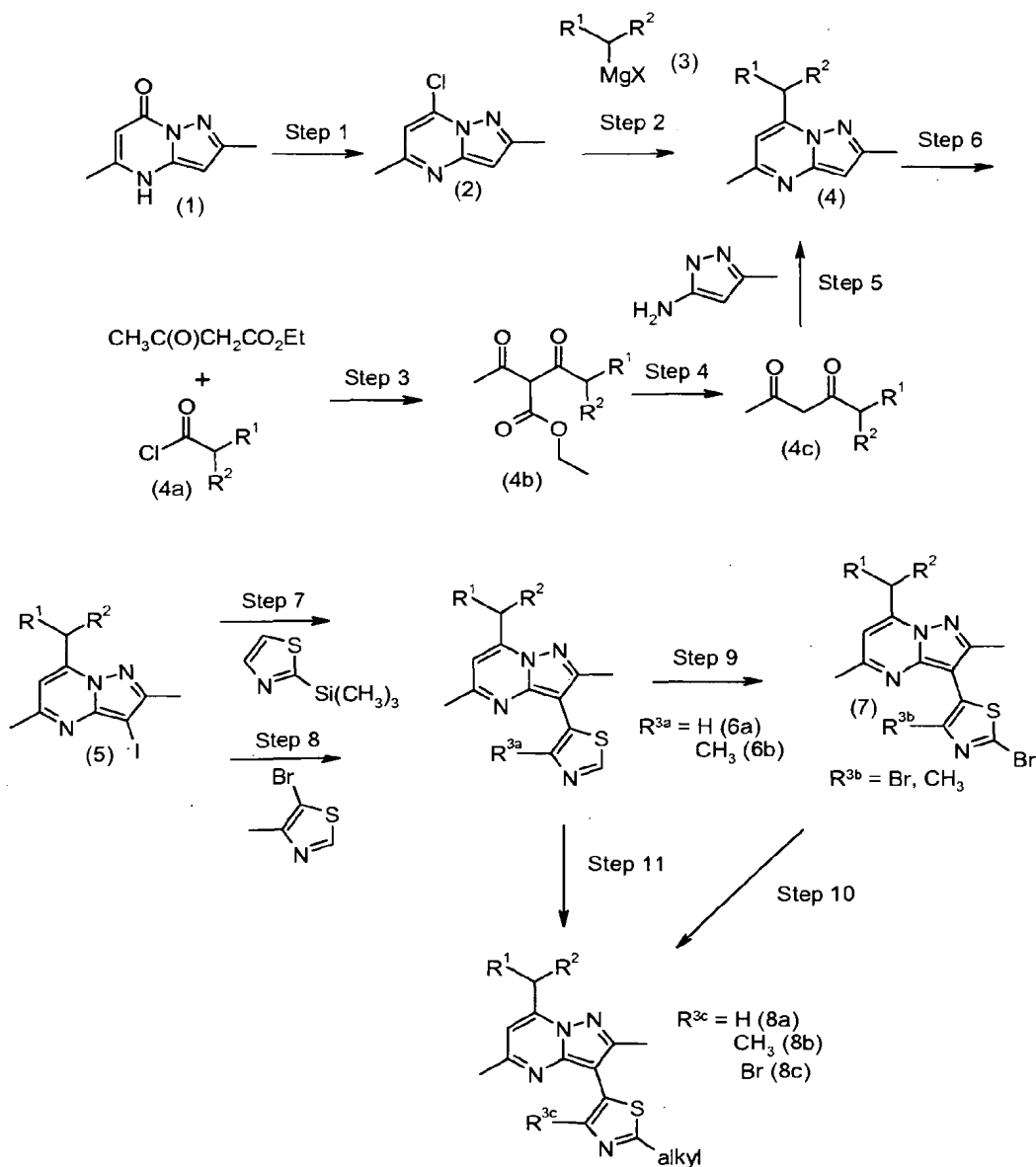
[0023] CRF receptor subtypes, CRF 1 and CRF2, have been identified and are distributed heterogeneously within the brain [D. T. Chalmers et al., *TIPS* 17:166-72 (1996)] thereby suggesting potential functional diversity [S. C. Heinrichs et al., *Regul. Peptides* 71:15 (1997)]. For example, widely distributed brain CRF1 receptor are strongly implicated in emotionality accompanying exposure to environmental stressors [G. Liebsch et al., *Regul. Peptides* 59: 229-39 (1995); D. W. Schulz, *PNAS* 93: 10477-82 (1996)]. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors [Heinrichs et al., 1997]. A more discrete septal/hypothalamic distribution [D. T. Chalmers et al., *J. Neurosci.* 15(10): 6340-50 (1995)] and the availability of alternative endogenous ligands [J. Vaughan et al., *Nature* 378: 287-92 (1995)] suggest a different functional role for the CRF2 receptor [Heinrichs et al., 1997]. For example, a novel CRF-

family neuropeptide with preferential affinity for CRF2 relative to CRF1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism (H. Tezval et al., PNAS 101(25): 9468-9473 (2004)). In some cases, CRF2 agonism produces similar effects to those reported for CRF1 antagonists or CRF 1 gene deletion [S. C. Heinrichs, Trends in Pharmacological Sciences 20(8):311-5 (1999)]. For example, while
5 CRF2 agonists have been proposed as antiobesity agents, CRF 1 antagonists may be an important treatment for obesity as well [C. Contoreggi et al., Neuroendocrinology 80(2):111-23 (2004)].

PREPARING COMPOUNDS OF THE INVENTION

10 **[0024]** All of the compounds of the present invention can be chemically prepared, for example, by following the synthetic routes set forth below. However, the following discussion is not intended to be limiting to the scope of the present invention in any way. For example, the specific synthetic steps for each of the routes described may be combined in different ways, or in conjunction with steps from different schemes, to prepare additional compounds of Formula I. The
15 products of each step can be recovered by conventional methods including extraction, evaporation, precipitation, chromatography, filtration, trituration, crystallization, and the like. In the Schemes below all substituents, unless otherwise indicated, are as previously defined and suitable reagents are well known and appreciated in the art.

Scheme 1



[0025] Formation of a compound of formula (6a,b), (7), or 8(a-c) can be carried out in accordance with reactions as depicted in Scheme 1. An appropriate compound of formula (6a,b), (7), or (8a-c) is one in which R^1 and R^2 are as defined for formula I and $\text{R}^{3a} = \text{H}$ or CH_3 , $\text{R}^{3b} = \text{Br}$ or CH_3 and $\text{R}^{3c} = \text{H}$, CH_3 , or Br .

[0026] In Scheme 1, Step 1, the pyrazolo[1,5-a]pyrimidine-7-one of formula (1) is converted to 7-chloro-2,5-dimethylpyrazolo[1,5-a]pyrimidine using phosphorous oxychloride and dimethylaniline in an inert solvent, such as toluene, at the reflux temperature of the solvent.

[0027] In Step 2, a Grignard reagent of formula (3) ($\text{X} = \text{Cl}$ or Br) is reacted with the chloride of formula (2), in an inert solvent such as toluene, at reflux temperature to provide the 7-alkyl pyrazolopyrimidine of formula (4).

[0028] Alternatively, a 7-alkyl pyrazolopyrimidine of formula (4) can be obtained as shown in Steps 3, 4, and 5. In Step 3 ethyl acetoacetate is acylated with an acid halide of formula (4a) in the presence of magnesium chloride to provide a diketo-ester of formula (4b). The diketo-ester of formula (4b) is decarboxylated under Krapcho conditions to provide the diketone of formula (4c). For example, (4b) is heated in dimethyl sulfoxide at a temperature of about 130 to 170 °C to perform the decarboxylation. In Step 5, the diketone of formula (4c) is cyclized with 3-amino-5-methylpyrazole to give the 7-alkyl pyrazolopyrimidine of formula (4) in a protic solvent such as methanol, ethanol, or acetic acid. Preferred

conditions use acetic acid at a temperature of about 0 to 60 °C.

[0029] The pyrazolopyrimidine of formula (4) is functionalized to an iodo pyrazolopyrimidine of formula (5) in Step 6 using an excess of N-iodosuccinimide in acetonitrile.

[0030] In Scheme 1, Step 7 or 8, the iodo pyrazolopyrimidine of formula (5) is reacted with a thiazole zinc halide in a Negishi cross-coupling reaction to provide a thiazolyl pyrazolopyrimidine of formula (6a) or (6b) (Jensen, J.; Skjaerbaek, N.; Vedso, P. Synthesis 2001, 128). The thiazole zinc halide is generated using methods well known to those skilled in the art. For example, in Step 7, 2-trimethylsilylthiazole is treated with *n*-, *sec*-, or *tert*-butyl lithium, followed by lithium-zinc exchange with ZnCl₂. The organozinc reagent is coupled with the iodo pyrazolopyrimidine of formula (5) in the presence of a palladium catalyst, for example, dichloro[1,1'-bis(diphenyl-phosphino)ferrocene]palladium (II) dichloromethane, in an inert solvent, such as THF, at reflux temperature for about 12 to 36 hours, to provide a thiazole pyrazolopyrimidine of formula (6a).

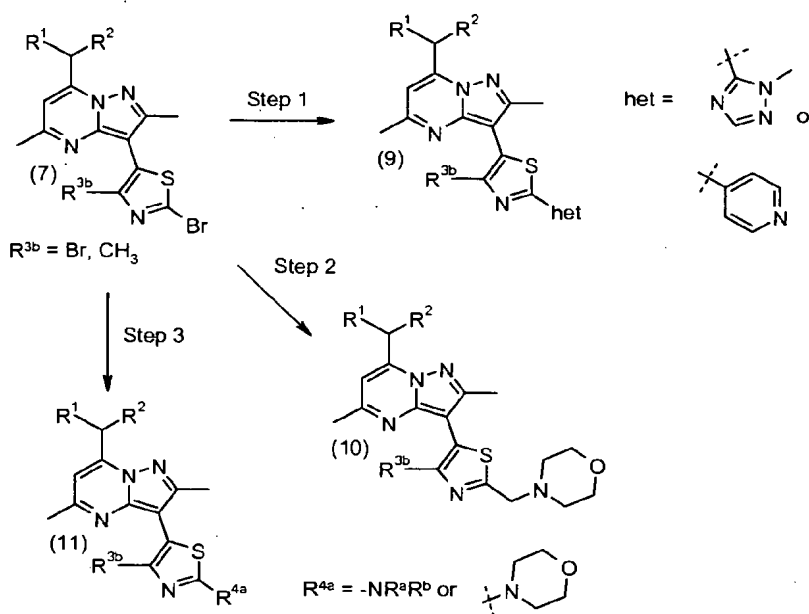
[0031] Alternatively, in Step 8, a thiazole zinc bromide is generated using 5-bromo-4-methylthiazole and zinc metal, and used in the Negishi cross-coupling essentially as described for Step 7, to provide a thiazole pyrazolopyrimidine of formula (6b).

[0032] In Scheme 1, Step 9, a thiazole of formula (6a,b) is brominated to give a bromo or dibromo thiazole of formula (7), wherein R^{3b} = Br or CH₃. The thiazole is brominated with either 1 or 2 eq of N-bromosuccinimide, depending on whether R^{3a} is CH₃ or H, respectively.

[0033] An alkyl thiazole of formula (8a-c) is obtained from either a thiazole of formula (6a,b) in Step 11, or from a bromothiazole of formula (7) in Step 10. In Step 10, halogen-lithium exchange with *n*-, *sec*-, or *t*-butyl lithium provides a thiazole lithium reagent, which is subsequently reacted with electrophiles, such as alkylhalides, like iodomethyl methylether or iodobutane. In Step 11, the thiazole lithium reagent is formed via deprotonation using *n*-, *sec*-, or *tert*-butyl lithium and then subsequently reacted with an electrophile, like iodomethyl methylether or iodobutane.

[0034] It will be appreciated by one skilled in the art that the thiazole ring system is readily functionalized and that thiazole intermediates such as 2-trimethylsilyl-thiazole (Dondoni, A.; et. al. J. Org. Chem. 1988, 53, 1748) can be readily prepared. 5-Bromo-4-methylthiazole is obtained by bromination of 4-methylthiazole with bromine in acetic acid (Collins, I. J., et. al. WO2003093252, 13 Nov 2003). 2,5-Dimethyl-4*H*-pyrazolo[1,5-*a*]pyrimidine-7-one (1) is readily prepared by condensation of ethyl acetoacetate and 5-methyl-2*H*-pyrazol-3-ylamine in refluxing acetic acid.

Scheme 2



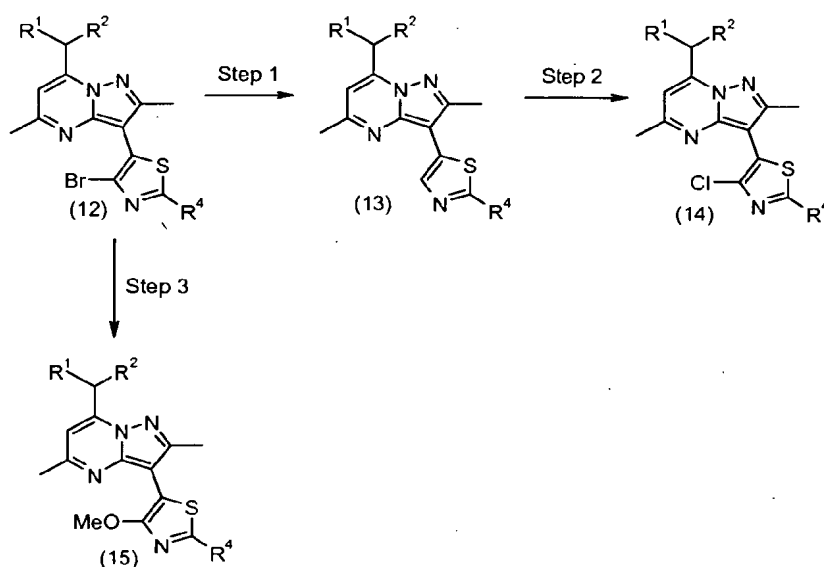
[0035] Formation of a compound of formula (9), (10), or (11) can be carried out in accordance with reactions as depicted in Scheme 2. An appropriate compound of formula (9), (10), or (11) is one in which R^1 , R^2 , R^a , and R^b are as defined for formula I and $R^{3b} = \text{Br}$ or CH_3 , and $R^{4a} = -\text{NR}^a\text{R}^b$ or $-\text{N-morpholinyl}$ and "het" is defined as depicted.

[0036] In Step 1, a bromothiazole of formula (7) is coupled with a heterocyclic zinc reagent in a Negishi cross-coupling reaction to provide a thiazole heterocycle of formula (9). For example, 1-methyl-1,2,4-triazole is treated with *n*-, *sec*-, or *tert*-butyl lithium, followed by zinc chloride, at about -80 to -65 °C, and reacted *in situ* with a bromothiazole of formula (7). The reaction is performed preferentially in an inert solvent, such as THF, in the presence of a palladium catalyst, such as dichloro[1,1'-bis(diphenyl-phosphino)ferrocene]palladium (II) dichloromethane or tetrakis(triphenylphosphine) palladium (0). The reaction is warmed to reflux temperature. Alternatively, the heterocyclic zinc reagent is formed from a haloheterocycle, such as 4-iodopyridine and zinc metal.

[0037] In Scheme 2, Step 2, an intermediate 2-formyl thiazole is formed via halogen-lithium exchange using *n*-, *sec*-, or *t*-butyl lithium followed by reaction with N-formyl morpholine. The formyl thiazole is subjected to a reductive amination in the presence of an organic amine, such as morpholine, to provide a morpholinyl methyl thiazole of formula (10). Reductive aminations are well-known in the art typically using an inorganic borohydride reagent such as sodium borohydride or sodium cyanoborohydride. Preferred conditions use sodium triacetoxyborohydride in an inert solvent such as dichloromethane or THF.

[0038] In Step 3, a bromothiazole of formula (7) undergoes a displacement reaction with an amine of formula $-\text{NR}^3\text{R}^b$ or with morpholine to provide an aminothiazole of formula (11). The reaction is performed in an inert solvent, such as THF or dioxane, using an inorganic base, such as cesium carbonate at 70 to 110 °C.

Scheme 3

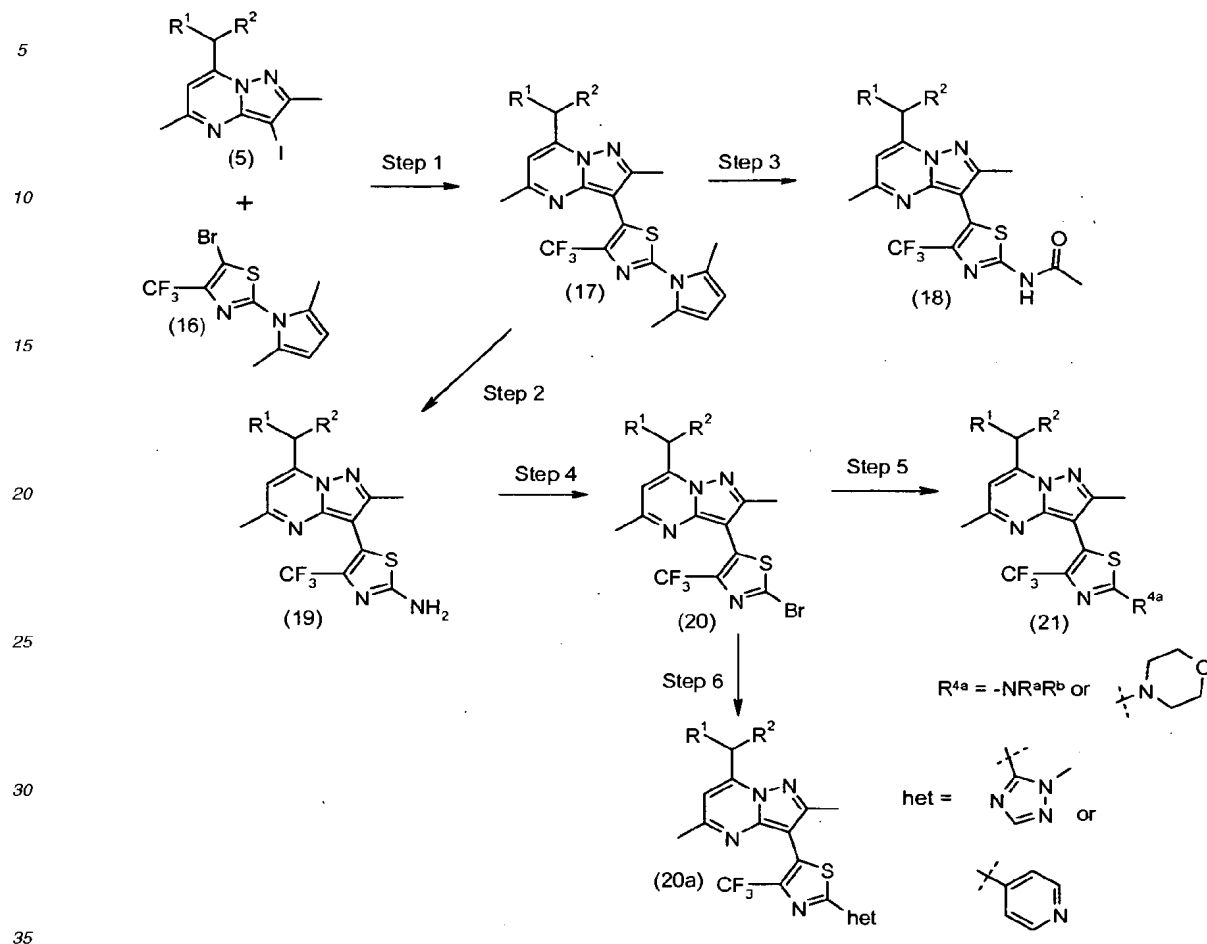


[0039] Formation of a compound of formula (13), (14), or (15) can be carried out in accordance with reactions as depicted in Scheme 3. An appropriate compound of formula (13), (14), or (15) is one in which R^1 , R^2 , and R^4 are as defined for formula I.

[0040] It will be recognized by one skilled in the art that a 4-bromothiazole, such as that of formula (12) is readily manipulated to other functionality. For example, in Step 1, the bromide can be dehalogenated with cuprous chloride to give a thiazole of formula (13) which is subsequently chlorinated with N-chlorosuccinimide to provide a 4-chlorothiazole of formula (14).

[0041] In Scheme 3, Step 3, a 4-bromothiazole of formula (12) is displaced with sodium methoxide in the presence of copper (I) iodide in methanol at about 100 to 120 °C in an inert solvent such as dimethylformamide, to provide a 4-methoxy thiazole of formula (15).

Scheme 4



[0042] Formation of a compound of formula (17), (18), (19), (20), (20a), or (21) can be carried out in accordance with reactions as depicted in Scheme 4. An appropriate compound of formula (17), (18), (19), (20), (20a), or (21) is one in which R^1 , R^2 , R^a , and R^b are as defined for formula I and R^{4a} is $\text{-NR}^a\text{R}^b$ or -N-morpholinyl and "het" is defined as depicted.

[0043] In Scheme 4, Step 1, an iodopyrazolopyrimidine of formula (5) and a 5-bromothiazole of formula (16) undergo a Negishi cross-coupling to form a dimethylpyrrolylthiazole of formula (17). For example, the 5-bromothiazole of formula (16) is treated with *n*-, *sec*-, or *tert*-butyl lithium and then with zinc chloride at about -80 to -65 °C. The organozinc reagent is reacted *in situ* with an iodopyrazolopyrimidine of formula (5). The coupling reaction is performed preferentially in an inert solvent, such as THF, at reflux temperature, in the presence of a palladium catalyst, such as bis(tri-*t*-butylphosphine) palladium (0).

[0044] In Step 2, a dimethylpyrrolylthiazole of formula (17) is deprotected to provide an aminothiazole of formula (19). The dimethylpyrrole is treated with hydroxylamine in acetic acid at a temperature of about 60 to 100 °C, for about 4 to 8 h, preferably for about 6 h. In Step 3, to form the thiazole acetamide of formula (18), the same conditions are used as in Step 2, with the exception that the reaction is continued for about 72 h.

[0045] In Scheme 4, Step 4, a 2-aminothiazole of formula (19) is converted to a 2-bromothiazole of formula (20) using a modified Sandmeyer reaction. Preferred conditions use an alkyl nitrite, such as *t*-butyl nitrite, and copper (II) bromide, in acetonitrile at a temperature of about 60 to 80 °C.

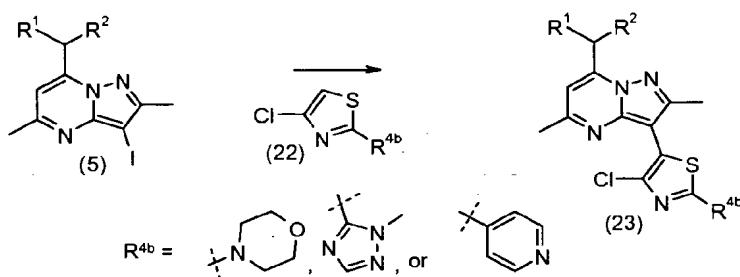
[0046] In Step 5, a 2-bromothiazole of formula (20) undergoes a displacement reaction with an amine of formula $\text{-NR}^a\text{R}^b$ or with morpholine to provide an aminothiazole of formula (21). The reaction is performed in an inert solvent, such as methanol, THF, or dioxane, or is treated neat, with an excess of the amine at a temperature of about 70 to 110 °C. Alternatively the reaction is performed with the reacting amine and an excess of triethylamine, or an inorganic base, such as cesium carbonate. Also contemplated in the synthesis of aminothiazoles of formula (21) are various deprotection steps, such as removal of a *tert*-butyl ester carbamic acid (BOC), as may be required or beneficial for carrying out the

reactions above wherein $-NR^aR^b$ carries additional amine functionality as defined for formula I. The selection and use of suitable protecting groups is well known and appreciated in the art (see for example, *Protecting Groups in Organic Synthesis*, Theodora Greene (Wiley-Interscience)).

[0047] In Scheme 4, Step 6, a 2-bromothiazole of formula (20) is coupled with a heterocyclic zinc reagent in a Negishi cross-coupling reaction to provide a thiazole heterocycle of formula (20a) in a manner similar to that as described for Scheme 2, Step 1.

[0048] It will be appreciated by the skilled artisan that a functionalized thiazole of formula (16) can be prepared by means known in the art. For example, cyclization of thiourea with a bromoketone, such as 3-bromo-1,1,1-trifluoropropan-2-one, provides 4-trifluoromethyl-thiazole-2-ylamine. Subsequent bromination and protection of the amine using hexane-2,5-dione provides (16).

Scheme 5

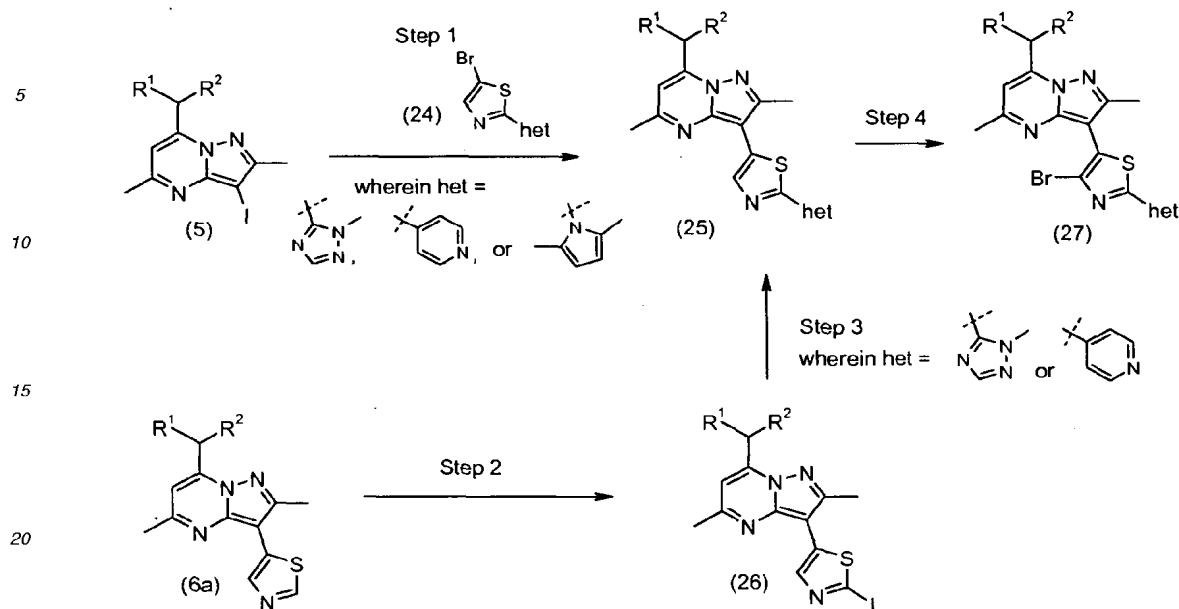


[0049] Formation of a compound of formula (23) can be carried out in accordance with reactions as depicted in Scheme 5. An appropriate compound of formula (23) is one in which R^1 and R^2 are as defined for formula I and R^{4b} is defined as depicted.

[0050] An iodopyrazolopyrimidine of formula (5) and a 4-chloro-2-morpholino-thiazole, for example, of formula (22) undergo cross-coupling to form a pyrazolopyrimidine thiazole of formula (23). For example, the reactants are coupled in the presence of copper iodide, palladium acetate, and triphenylphosphine, with a base such as cesium carbonate. The coupling reaction is performed preferentially in an inert solvent, such as DMF, at about 100 - 150 °C. for 4 - 24 h.

[0051] It will be appreciated by the skilled artisan that a functionalized thiazole of formula (22) can be prepared by means known in the art. For example, 2,4-dichlorothiazole can be reacted with morpholine to give the 2-morpholino-thiazole of formula (22). 2,4-Dichlorothiazole can also be exhaustively brominated to provide 2,5-dibromo-4-chlorothiazole. Subsequent bromine-lithium exchange with *n*-butyl lithium in THF at -90 °C and quench with water provides 2-bromo-4-chlorothiazole [J. Chem. Soc. Perkin Trans 1: Org Bioorg. Chem. (1972-1999), (2):215-219 (1992)]. 2-Bromo-4-chlorothiazole can be subjected to a Negishi cross-coupling reaction with a heterocyclic zinc reagent to obtain the thiazol-2-yl triazole or pyridine.

Scheme 6



[0052] Formation of a compound of formula (27) can be carried out in accordance with reactions as depicted in Scheme 6. An appropriate compound of formula (27) is one in which R¹ and R² are as defined for formula I and "het" is defined as depicted for Step 1 or Step 3, respectively.

[0053] In Scheme 6, Step 1, a heterocyclic thiazole, for example, of formula (25) is obtained by reaction of an iodopyrazolopyrimidine of formula (5) with a bromothiazole of formula (24). The reaction is performed in the presence of N-butylammonium bromide and a base, such as potassium acetate with a palladium catalyst such as palladium acetate with tris(2,4-di-*tert*-butyl-phenyl)-phosphane, in an inert solvent such as N-methylpyrrolidinone at a temperature of about 100 - 150 °C.

[0054] Alternatively, in Step 2, a thiazolyl pyrazolopyrimidine of formula (6a) is iodinated to provide a 2-iodothiazole of formula (26). The thiazole is treated with lithium diisopropylamide at a temperature of -70 to -80 °C for about one hour and then treated with N-iodosuccinimide at about the same temperature in an inert solvent, such as THF. This is followed by Step 3, wherein a triazolyl or 4-pyridyl thiazole of formula (25) is formed using Negishi cross-coupling conditions similar to those described for Scheme 2, Step 1.

[0055] In Scheme 6, Step 4, a thiazolyl pyrazolopyrimidine of formula (25) is brominated to give a bromothiazole of formula (27). The bromination is effected using N-bromosuccinimide in the presence of a small amount of acetic acid in an inert solvent, such as acetonitrile.

[0056] A compound of formula (27), wherein het = 2,5-dimethyl-pyrrol-1-yl, can be further elaborated to obtain compounds of the invention as described in Scheme 4, Steps 2, 3, 4, and 5.

[0057] It will be appreciated by the skilled artisan that heterocycle thiazoles of formula (24) can be readily prepared by means known in the art. For example, thiazole-2-carboxylic acid amide can be cyclized to the triazole with 1,1-dimethoxy-N,N-dimethyl-methanamine, followed by N-methyl-hydrazine to obtain the triazolyl thiazole, which can be subsequently brominated with N-bromosuccinimide. Literature procedures afford 4-thiazol-2-yl-pyridine which can be brominated to provide 4-(5-bromo-thiazol-2-yl)-pyridine. 5-Bromo-2-(2,5-dimethyl-pyrrol-1-yl)-thiazole can be readily obtained by reaction of 2-amino-5-bromothiazole with hexane-2,5-dione.

[0058] As used herein, "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "LC/MS" refers to liquid chromatography/mass spectrometry; "GC/MS" refers to gas chromatography/mass spectrometry; "HR-ToF" refers to high resolution time-of-flight; "APCI" refers to atmospheric pressure chemical ionization; "8" refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "EtOAc" refers to ethyl acetate; "MeOH" refers to methanol; "EtOH" refers to ethanol; "DMF" refers to dimethylformamide.

EXAMPLES

[0059] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following preparations and examples are provided to describe the invention

in further detail. The reagents and starting materials are readily available to, or may be readily synthesized by, one of ordinary skill in the art. Examples 1-35 provide representative compounds and illustrate the preparation thereof. Examples A-D illustrates various biological assays that can be used for determining the biological properties of the compounds of the inventions. Those skilled in the art will promptly recognize appropriate variations from the procedures described in the examples. The names of the compounds of the present invention are provided by ChemDraw Ultra® version 7.0.1. Salts are named as the free base plus the conjugate acid.

Preparation 1

2,5-Dimethyl-4H-pyrazolo[1,5-a]pyrimidin-7-one

[0060] Add ethyl acetoacetate (128 g, 0.98 mol) dropwise to an acetic acid solution (500 mL) of 5-methyl-2H-pyrazol-3-ylamine (100 g, 0.95 mol), keeping the temperature at 25-28 °C. Heat the mixture at reflux for 10 h and then cool to room temperature. Add the reaction to *tert*-butyl methyl ether (5 L) cooled to 5 °C, keeping the temperature below 10 °C. Stir for 1 h at 5 °C, and filter. Dry the resulting material *in vacuo* overnight to provide a white solid (158 g, 96%).

Preparation 2

7-Chloro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

[0061] To a suspension of 2,5-dimethyl-4H-pyrazolo[1,5-a]pyrimidin-7-one (10.0 g, 61.3 mmol) in toluene (150 mL) add *N,N*-dimethylaniline (9.7 mL, 76.7 mmol). Add phosphorus oxychloride (11.2 mL, 122.6 mmol) dropwise to this white suspension. Reflux for 3 h under an inert atmosphere, cool to room temperature, and concentrate the reaction to a brown oil using reduced pressure. Dissolve the oil in ethyl acetate (250 mL) and basify with 1.0 N NaOH. Separate the organic phase and extract the basic aqueous phase with ethyl acetate (2 × 100 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure to yield a brown solid. Purify the material using flash chromatography, eluting with 80% hexane/20% (30% THF/hexane) to 0% hexane/100% (30% THF/hexane) in a step gradient of 20% increments to provide a light green solid (6.65 g, 59%). ES/MS *m/z* (³⁵Cl) 182.3 (M+1)⁺.

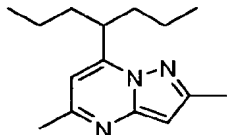
Alternate Procedure:

[0062] Add 2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-one (20 g, 122 mmol) to 1,4-dioxane (60 mL). Stir the mixture at 22 °C for 10 min and then add *N,N*-diethylaniline (20.8 mL, 128 mmol). Stir for an additional 5 min and then add phosphorus oxychloride (11.7 mL, 126 mmol) over 15 min. Stir the mixture at 22 °C for 15 min, then heat to 80-85 °C over 35 min and hold the reaction at this temperature for 1.5 h. Add the cooled reaction mixture slowly to a solution of potassium phosphate dibasic (106.7 g, 612.82 mmol) in water (325 mL) cooled to 0-5 °C, keeping the temperature below 5 °C during the addition. Stir the mixture at 22 °C and then add methyl-*t*-butyl ether (150 mL). Separate the organic layer and extract the aqueous layer with methyl-*t*-butyl ether (2 × 100 mL). Combine the organic portions, dry over sodium sulfate, filter, and evaporate the solvent. Purify by silica gel chromatography, eluting with hexanes/ethyl acetate (2/1) to provide the title compound as a yellow solid (20.7 g, 88%). ES/MS *m/z* (³⁵Cl) 182 (M+1)⁺.

Preparation 3

7-(1-Propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

[0063]



[0064] Charge an oven dried flask equipped with a reflux condenser, with anhydrous THF (40 mL), iodine (catalytic amount), magnesium ribbon (1.92 g, 78.9 mmol) and 4-bromoheptane (9.4 mL, 52 mmol). Heat the reaction to reflux in an oil bath. The temperature of the reaction spikes as the Grignard reaction is initiated. Stir the reaction an additional 4 h at 90 °C and cool to room temperature. Allow the magnesium metal to settle out (can also be centrifuged) and canulate

off the Grignard reagent under positive argon pressure into a flask charged with 7-chloro-2,5-dimethylpyrazolo [1,5-a] pyrimidine (4.80 g, 26.3 mmol) in anhydrous toluene (20 mL). Reflux the reaction under an inert atmosphere overnight. Cool the reaction to room temperature and quench with water. Dilute with ethyl acetate (150 mL), then add water (100 mL) and saturated ammonium chloride (50 mL). Separate and extract the aqueous phase with dichloromethane (75 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 80% hexane/20% (20% ethyl acetate/hexane) to 0% hexane/100% (20% ethyl acetate/hexane) in a step gradient of 20% increments to give yellow crystals (3.08 g, 48%). ES/MS m/z 246.3 (M+1)⁺.

Alternate Procedure:

[0065] Heat a mixture of magnesium turnings (3.5 g, 144 mmol) and a catalytic amount of iodine (100 mg) in THF (100 mL) to 65 °C under a nitrogen atmosphere. Add a few drops of neat 4-bromoheptane and heat the mixture until the reaction starts. Then add a solution of 4-bromoheptane (17.6 mL, 94.9 mmol) in THF (42 mL) keeping the temperature at 65-70 °C over 2 h. Reflux the mixture for an additional hour and then cool the reaction to 22 °C. Add the prepared Grignard reagent to a solution of 7-chloro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (10.2 g; 53.3 mmol) in THF (60 mL) cooled to 0 °C under a nitrogen atmosphere. Add the magnesium reagent solution via cannula over 45 min while keeping the temperature below 10 °C. Then stir the mixture for an additional 30 min at 5 °C. Add to this mixture a 10% aqueous ammonium chloride solution (wt/wt) (125 mL) and stir at 22 °C for 30 min. Separate the organic layer and extract the aqueous layer with ethyl acetate (2 × 25 mL). Combine the organic layers and dry over sodium sulfate. Filter the mixture and evaporate the solvent. Purify the crude material by silica gel flash chromatography using an eluent of hexanes/ethyl acetate (5/1) to provide the title compound (8 g, 62%). ES/MS m/z 246 (M+1)⁺.

Preparation 3a

7-(1-Propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

Alternate Route

Step 1: 3-Acetyl-3-oxo-4-propyl-heptanoic acid ethyl ester

[0066] Add magnesium chloride (14.63 g, 153.70 mmol) to dichloromethane (500 mL) followed by addition of ethyl acetoacetate (19.55 mL, 20.00 g, 153.79 mmol) all at once and stir at room temperature for one hour. Cool the mixture in an ice water bath and add pyridine (24.86 mL, 24.32 g, 307.39 mmol) dropwise. Add di-n-propylacetyl chloride (25.00 g, 153.70 mmoles) dropwise at 0 °C under nitrogen to the white slurry. After the addition is complete remove the cooling bath, warm to ambient temperature, and stir for 16 h. Quench the reaction with 1 N HCl (400 mL) and separate the bottom layer. Dry the organic portion over magnesium sulfate, filter, and concentrate under vacuum to give a yellow oil (34 g, 86%). Use the material directly in the next step without further purification.

Step 2: 5-Propyl-octane-2,4-dione

[0067] Dissolve 3-acetyl-3-oxo-4-propyl-heptanoic acid ethyl ester (32.4 g, 126.39 mmoles) in dimethyl sulfoxide (100 mL) and water (5 mL). Heat the solution at 150 °C for 6 to 8 h or follow the reaction by GC/MS. Cool the reaction and extract with heptane (3 × 100 mL). Wash the combined organic portions with water (100 mL) and brine (100 mL). Concentrate under vacuum at 50 °C to remove most of the heptane. Obtain 23.29g of an oil and use directly in the next step.

Step 3: 7-(1-Propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

[0068] Mix 5-propyl-octane-2,4-dione (15 g, 81.40 mmoles) in acetic acid (15 mL) and cool in an ice bath. Add 5-amino-3-methylpyrazole (7.91 g, 81.40 mmol) portionwise and stir at ambient temperature. Check for completion of the reaction by GC/MS after 3 h. GC indicates correct region isomer in comparison with an authentic sample. Distill off the excess acetic acid. Add water (50 mL) and extract with heptane (50 mL). Wash the heptane with brine (50 mL). Dry the organic layer over MgSO₄, filter, and concentrate under vacuum to give a crude oil (15.8 g, 79%). ¹H NMR (CDCl₃): 6.39 (s, 1H); 6.31 (s, 1H); 3.75 (m, 1H); 2.55 (s, 3H); 2.45 (s, 3H); 1.71 (q, 4H); 1.23 (m, 4H); 0.85 (t, 6H).

[0069] Prepare the following compound essentially as described in Preparation 3, using either procedure. Use 3-bromopentane to prepare the Grignard reagent.

Prep. No.	Chemical name	Physical data
4	7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine	ES/MS m/z 218.1 (M+1) ⁺

Preparation 5

7-(1-Propyl-butyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a] pyrimidine

[0070] Dissolve 7-(1-propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (3.08 g, 12.5 mmol) in anhydrous acetonitrile (25 mL) and add 6 portions (0.70 g each) of N-iodosuccinimide (4.2 g, 18.7 mmol) at 10 minute intervals. Stir over the weekend at room temperature. Strip off the acetonitrile and dilute the oil with dichloromethane (100 mL). Wash with saturated ammonium chloride solution (2 × 50 mL). Collect the organic phase, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure to yield a dark red oil. Purify the oil using flash chromatography, eluting with 100% hexane/0% (20% ethyl acetate/hexane) to 0% hexane/100% (20% ethyl acetate/hexane) in a step gradient of 50% increments to give an orange oil (10.97 g, 87%). ¹H NMR (400 MHz, CDCl₃): 6.42 (s, 1H), 3.74-3.70 (m, 1H), 2.58 (s, 3H), 2.46 (s, 3H), 1.74-1.68 (m, 4H), 1.28-1.14 (m, 4H), 0.84 (t, *J* = 7.0 Hz, 6H).

[0071] Prepare the compound below essentially as described in Preparation 5.

Prep. No.	Chemical name	Physical data
6	7-(1-Ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo [1,5-a]pyrimidine dimethyl-pyrazolo[1,5-a] pyrimidine	¹ H NMR (400 MHz, CDCl ₃): 6.44 (s, 1H), 3.59 (m, 1H), 2.61 (s, 3H), 2.49 (s, 3H), 1.86-1.76 (m, 4H), 0.85 (t, <i>J</i> = 7.5 Hz, 6H).

Alternate procedure for Preparation 6:

[0072] Add acetic acid (1 mL) and N-iodosuccinimide (6.7 g, 29.9 mmol) in one portion to a solution of 7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (6 g, 27.5 mmol) in acetonitrile (60 mL). Stir the mixture at 22 °C for 2 h. Evaporate the solvent and take the residue up in water (50 mL) and methyl-*t*-butyl ether (100 mL). Separate the organic portions, dry over sodium sulfate, filter, and evaporate the solvent to afford the title compound (9.2 g, 96%). ES/MS m/z 344 (M+1)⁺.

Preparation 7

2-Trimethylsilylanyl-thiazole

[0073] Mix *n*-butyl lithium (20.4 mL, 51.0 mmol, 2.5 M in hexane) with diethyl ether (50 mL) in a three-necked flask, equipped with a dropping funnel and thermometer. Cool to -78 °C and add dropwise a solution of thiazole (4.25 g, 50.0 mmol) in diethyl ether (50 mL). After the addition is complete, stir the reaction mixture at -78 °C for 30 min, followed by addition of chlorotrimethylsilane (5.4 g, 50.0 mmol). Stir at -78 °C for an hour and then warm to room temperature. Quench the reaction by adding saturated sodium bicarbonate. Extract the aqueous layer with diethyl ether. Wash the combined organic portions with brine and dry over sodium sulfate. Filter and concentrate under reduced pressure to give a residue. Purify by distillation to give 8.33 g (52-56 °C/ 15 mm Hg) of title compound. ¹H NMR (400 MHz, CDCl₃) 8.13 (d, 1H, *J* = 2.6 Hz), 7.54 (d, 1H, *J* = 2.6 Hz), 0.43 (s, 9H).

Preparation 8

5-Bromo-4-methylthiazole

[0074] Add bromine (9.27 mL, 182 mmol) to a solution of 4-methylthiazole (15.0 g, 152 mmol) in acetic acid (30 mL) at 0 °C. Slowly warm the reaction mixture to room temperature and stir overnight. Dilute with dichloromethane and wash with 1 N NaOH and brine. Dry the organic layer over sodium sulfate, filter, and concentrate under vacuum. Purify the crude product by silica gel column chromatography, eluting with hexanes/ethyl acetate (5/1) to obtain the title compound (9.94 g, 37%). ¹H NMR (400 MHz, CDCl₃): δ 8.69 (s, 1H), 2.43 (s, 3H).

Preparation 9

Thiazole-2-carboxylic acid ethyl ester

[0075] To a mixture of 2-trimethylsilylthiazole (135 g, 858.1 mmol) in toluene (1350 mL) add a solution of ethyl chloroformate (98.4 mL, 1.03 mol) in toluene (1350 mL) over 15 min. Stir the reaction at 22 °C for 2 h. Add the solution over aqueous sodium carbonate 25% (wt/wt) (5 L) and stir for 30 min. Separate the organic layer and re-extract the aqueous layer with methylene chloride (2 × 1 L). Combine the organic layers and evaporate the solvent to provide the title compound (134 g, 99%). ES/MS m/z 158 (M+1)⁺.

Preparation 10

Thiazole-2-carboxylic acid amide

[0076] Add thiazole-2-carboxylic acid ethyl ester (150 g, 0.9 mol) to a mixture of methanol (75 mL) and 30% aqueous ammonium hydroxide (750 mL) and heat the mixture at reflux for 1 h. Then cool to 22 °C and evaporate the methanol under vacuum. Stir the mixture for 30 min at room temperature and filter the solid. Dry the isolated solid under vacuum to afford the title compound (98 g, 85%). ES/MS m/z 129 (M+1)⁺.

Preparation 11

1-Methyl-5-thiazol-2-yl-1H-[1,2,4]triazole

[0077] Cool 1,1-dimethoxy-*N,N*-dimethyl-methanamine (240 mL) to 10 °C and add thiazole-2-carboxylic acid amide (60 g, 421 mmol) in three portions. Stir the mixture at 10 °C for 30 min. Then heat the mixture gradually to reflux in 45 min. Distill off the methanol formed and then heat the reaction to 100 °C for 1.5 h. Cool the mixture to 60 °C and remove the excess 1,1-dimethoxy-*N,N*-dimethyl-methanamine by vacuum distillation. Cool the residue to 22 °C and add hexanes (200 mL). Triturate the mixture for 15 min, filter, and dry the solid to constant weight before using in the next step.

[0078] Add the solid isolated above (68 g) to acetic acid (680 mL) and cool the mixture to 10 °C. Add *N*-methylhydrazine (27 mL, 509 mmol) at such a rate as to keep the temperature below 15°C. Warm the mixture to 20 °C in 30 min and then heat gradually to 90 °C. Stir at 90 °C for 30 min and then cool to 22 °C. Remove the acetic acid by vacuum distillation. Add the residue over water and adjust to pH = 8 by adding 25% aqueous sodium hydroxide solution. Extract the aqueous layer with methyl-*t*-butyl ether (3 × 600 mL). Combine the organic layers and evaporate the solvent. Purify the resulting residue by silica gel chromatography using an eluent of hexanes/isopropanol (9/1) to provide the title compound (49 g, 70%). ES/MS m/z 167 (M+1)⁺.

Preparation 12

5-(5-Bromo-thiazol-2-yl)-1-methyl-1H-[1,2,4]thiazole

[0079] To a mixture of methyl-5-thiazol-2-yl-1H-[1,2,4]triazole (6.55 g; 39.4 mmol) and dimethylformamide (32 mL), add *N*-bromosuccinimide (14 g, 78.8 mmol) in three portions over 1 h. Stir the mixture at 22 °C for 18 h and then add to water (300 mL) chilled to 0-5 °C. Separate the aqueous layer and extract with methyl-*t*-butyl ether (2 × 200 mL). Combine the organic layers and wash with 7% aqueous sodium hydrogen carbonate (100 mL) and then dry over sodium sulfate. Filter and evaporate the solvent to afford the title compound (9.5 g, 93%). ES/MS m/z ⁷⁹Br/⁸¹Br 245/247 (M+1)⁺.

Preparation 132,5-Dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-7-(1-propyl-butyl)-pyrazolo[1,5-*a*]pyrimidine

[0080] Combine 5-(5-bromo-thiazol-2-yl)-1-methyl-1H-[1,2,4]triazole (6.5 g, 23.8 mmol) and 2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*]pyrimidine (6 g, 24.5 mmol) in *N*-methylpyrrolidinone (58 mL) and stir to complete solution under nitrogen. Then add tetra-*N*-butylammonium bromide (5.47 g, 16.7 mmol) and potassium acetate (11.8 g, 119 mmol) and heat the mixture to 100 °C under a nitrogen atmosphere. Degas the hot mixture by three cycles of vacuum/nitrogen purge. Then add palladium acetate (216 mg, 0.94 mmol) and tris(2,4-di-*tert*-butyl-phenyl)-phosphane (787 mg, 1.2 mmol). Heat the mixture 4 h at 125 °C under nitrogen. Cool the mixture to 22 °C and add to water (750 mL). Extract the aqueous layer with methyl-*t*-butyl ether (3 × 200 mL), combine the organic portions, and evaporate. Purify the residue by filtration through a silica gel pad eluting with hexanes/ethyl acetate (4/1). Combine the product containing fractions

and evaporate the solvent to afford the title compound (7 g, 72%). ES/MS m/z 410 ($M+1$)⁺.

Preparation 14

2,5-Dimethyl-7-(1-propyl-butyl)-3-thiazol-5-yl-pyrazolo[1,5-a] pyrimidine

[0081] Charge an oven dried flask with 2-trimethylsilanylthiazole (1.765 g, 11.24 mmol) dissolved in anhydrous THF (30 mL) and chill under an inert atmosphere to -78 °C. Slowly add *n*-butyl lithium (2.5 M hexane solution, 4.5 mL, 11.24 mmol) and stir 30 min at -78 °C. Add anhydrous zinc chloride (2.26 g, 16.58 mmol) in one aliquot and stir 30 min at -78 °C. Allow the reaction to rise to room temperature, stir 30 min, and add 7-(1-propyl-butyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a] pyrimidine (1.624 g, 5.18 mmol) and dichloro[1,1'-bis(diphenylphosphino) ferrocene] palladium (II) dichloromethane (0.423 g, 0.518 mmol). Reflux overnight in an oil bath (90 °C) under an inert atmosphere. Cool the reaction to room temperature, quench with saturated sodium bicarbonate, and dilute with ethyl acetate (150 mL). Separate and extract the aqueous with ethyl acetate (75 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 100% hexane/0% (30% THF/hexane) to 0% hexane/100% (30% THF/hexane) in a step gradient of 10% increments to give a white solid (0.720 g, 42%). ES/MS m/z 329.0 ($M+1$)⁺.

[0082] Prepare the compound below essentially as described in Preparation 14.

Prep. No.	Chemical name	Physical data
15	7-(1-Ethyl-propyl)-2,5-dimethyl-3-thiazol-5-yl-pyrazolo[1,5-a]pyrimidine	¹ H NMR (400 MHz, CDCl ₃): δ 8.75 (s, 1H), 8.75 (s, 1H), 8.28 (s, 1H), 6.47 (s, 1H), 3.62-3.55 (m, 1H), 2.65 (s, 3H), 2.61 (s, 3H), 1.89-1.75 (m, 4H), 0.85 (t, 6H, <i>J</i> = 7.5 Hz), 0.85 (t, 6H, <i>J</i> = 7.5 Hz).

Alternate procedure for Preparation 15:

[0083] Add *n*-butyl lithium (76.5 mL, 191 mmol, 2.5 M in hexanes) to a solution of 2-trimethylsilylthiazole (30 g, 191 mmol) in THF (450 mL) at -78 °C under nitrogen, keeping the temperature below -74 °C during the addition. Stir the mixture at -78 °C for 30 min and then add zinc chloride, dry powder, (39.9 g, 286 mmol) in one portion and warm the mixture to 22 °C over one hour. Add 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine, (30 g, 87 mmol) and 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride (6.5 g, 8 mmol) and heat the mixture to reflux under nitrogen for 8 h. Cool the mixture to 22 °C and add 10% aqueous ammonium chloride (450 mL). Separate the organic layer and wash the aqueous layer with methyl-*t*-butyl ether (2 × 100 mL). Combine the organic portions, dry over sodium sulfate, filter, and evaporate the solvent to afford the title compound (20.4 g, 78%). ES/MS m/z 301 ($M+1$)⁺.

Preparation 16

7-(1-Ethyl-propyl)-3-(2-iodo-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

[0084] Add a freshly prepared solution of lithium di-*i*-propylamide (150 mL; 62.4 mmol, 0.6 M in THF) to a mixture of 7-(1-ethyl-propyl)-2,5-dimethyl-3-thiazol-5-yl-pyrazolo[1,5-a]pyrimidine, (17.8 g, 62.4 mmol) in THF (100 mL) at -78 °C under a nitrogen atmosphere, keeping the temperature below -74 °C during the addition. Stir the mixture at -78 °C for one hour and then add a solution of *N*-iodosuccinimide (15 g, 63 mmol) in THF (100 mL) keeping temperature below -74 °C. Warm the reaction gradually to 22 °C and then add a 10% aqueous solution of ammonium chloride (300 mL). Separate the organic layer and wash the aqueous layer with methyl-*t*-butyl ether (2 × 200 mL). Combine the organic layers, dry over sodium sulfate, filter, and evaporate the solvent. Purify the resulting residue by silica gel chromatography, eluting with hexanes/acetone (5/1) to afford the title compound (15 g, 60%). ES/MS m/z 427 ($M+1$)⁺.

Example 1

7-(1-Ethyl-propyl)-2,5-dimethyl-3-(4-methyl-thiazol-5-yl)-pyrazolo[1,5-a]pyrimidine

[0085] Add Rieke® zinc (10 g in 100 mL of THF, 13.2 mL, 18.48 mmol) to 5-bromo-4-methylthiazole (2.13 g, 18.48 mmol) and heat at reflux for 2 h. Cool the mixture to room temperature and settle the zinc down by centrifuge. Bubble nitrogen gas through 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (900 mg, 2.62 mmol) in dry tet-

rahydrofuran (10 mL) and add the organozinc bromide solution followed by addition of [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (106 mg, 0.13 mmol). Stir the reaction mixture under reflux overnight and cool to room temperature. Add ammonium chloride solution to the reaction mixture and extract with dichloromethane. Dry the organic portion over sodium sulfate, filter, and remove the solvent under vacuum. Purify the crude product by silica gel column chromatography, eluting with hexane/ethyl acetate (3/1) to obtain the title compound (652 mg, 79%). ¹H NMR (400 MHz, CDCl₃): δ 8.80 (s, 1H), 6.48 (s, 1H), 3.63 (m, 1H), 2.57 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, *J* = 7.3 Hz). ES/MS *m/z* 315 (M+1)⁺.

Preparation 17

3-(2,4-dibromo-thiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine

[0086] Dissolve 2,5-dimethyl-7-(1-propyl-butyl)-3-thiazol-5-yl-pyrazolo[1,5-*a*] pyrimidine (3.15 g, 9.59 mmol) in acetonitrile (100 mL) and add N-bromosuccinimide (4.27 g, 24.0 mmol) in one aliquot. Stir overnight under an inert atmosphere and confirm the reaction is complete using TLC. Concentrate under reduced pressure, dilute the oil with dichloromethane (150 mL), and wash with water (75 mL). Dry the organic phase over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting oil using flash chromatography, eluting with 100% hexane/0% (30% THF/hexane) to 0% hexane/100% (30% THF/hexane) in a step gradient (0-10-15-20-25-30-35-40-45-50-100% of 30% THF/hexane) to give yellow crystals (3.70 g, 79%). ES/MS *m/z* (⁷⁹Br⁸¹Br) 486.7 (M+1)⁺.

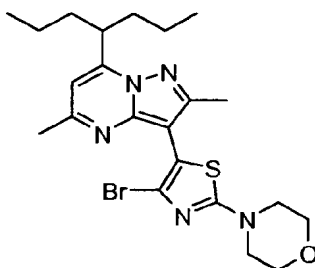
[0087] Prepare the compounds below essentially as described in Preparation 17, with the exception that dichloromethane is used as the solvent.

Ex. No.	Chemical name	Physical data
2	3-(2,4-Dibromo-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidine	MS (APCI) <i>m/z</i> (⁷⁹ Br ⁸¹ Br) 459.1 (M+1) ⁺
3*	3-(2-Bromo-4-methyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidine	ES/MS <i>m/z</i> (⁷⁹ Br) 393 (M+1) ⁺
*Use 1.1 eq NBS and stir for 3 days.		

Example 4

3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine

[0088]



[0089] Charge an oven dried flask with 3-(2,4-dibromothiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine (0.973 g, 2.00 mmol), anhydrous dioxane (20 mL), morpholine (0.872 g, 10.0 mmol), and cesium carbonate (1.95 g, 6.00 mmol). Reflux in an oil bath (105 °C) under an inert atmosphere overnight. Confirm the reaction is complete using LC/MS. Dilute with ethyl acetate (100 mL), wash with water (50 mL), and back extract the aqueous with ethyl acetate (50 mL). Combine the organic phases, dry over magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 100% hexane/0% (40% dichloromethane/20% ethyl acetate/2% 7 N ammonia in methanol/38% hexane) to 0% hexane/100% (40% dichloromethane/20% ethyl acetate/2% 7 N ammonia in methanol/38% hexane) in a step gradient of 10% increments to yield an off-white solid

(0.878 g, 89%). ES/MS m/z (^{79}Br) 491.7 ($M+1$) $^+$.

[0090] Prepare the following examples essentially as described in Example 4, using as the amine either 2,0 dimethylamine/THF or morpholine, and using THF or dioxane as the solvent. Run reactions in a sealed vessel or Schlenk tube.

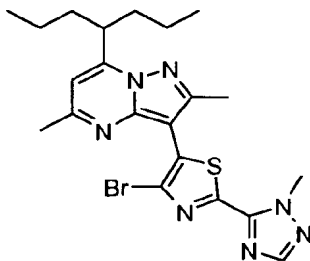
Ex. No.	Chemical name	Physical data
5 $^+$	{4-Bromo-5-[2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-thiazol-2-yl}-dimethylamine	ES/MS (^{79}Br) 449.8 ($M+1$) $^+$.
6	3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidine	MS (APCI) m/z (^{81}Br) 466.5 ($M+1$) $^+$
7	{4-Bromo-5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-thiazol-2-yl}-dimethyl-amine	MS (APCI) m/z (^{81}Br) 424.4 ($M+1$) $^+$
8	{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-4-methyl-thiazol-2-yl}-dimethyl-amine	ES/MS m/z 358 ($M+1$) $^+$
9	7-(1-Ethyl-propyl)-2,5-dimethyl-3-(4-methyl-2- morpholin-4-yl-thiazol-5-yl)-pyrazolo[1,5- <i>a</i>]pyrimidine	ES/MS m/z 400 ($M+1$) $^+$

*Use 6 eq of cesium carbonate.

Example 10

3-[4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propylbutyl)-pyrazolo[1,5-*a*]pyrimidine

[0091]



[0092] Charge an oven dried flask with 1-methyl-1,2,4-triazole (0.498, 6.00 mmol) and anhydrous THF (20 mL) and chill under an inert atmosphere to -78 °C. Slowly add *n*-butyl lithium (2.5 M hexane solution, 2.4 mL, 6.0 mmol) and stir 30 min. Add anhydrous zinc chloride (1.36 g, 10.0 mmol) in one aliquot and stir 30 min at -78 °C. Allow the reaction to warm to room temperature, stir 30 min, and add 3-(2,4-dibromothiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo [1,5-*a*] pyrimidine (0.973 g, 2.00 mmol) and dichloro[1,1'-bis(diphenylphosphino) ferrocene] palladium (II) dichloromethane (0.163 g, 0.200 mmol). Reflux the reaction overnight in an oil bath (90 °C) under an inert atmosphere. Cool the reaction to room temperature, quench with water, and dilute with ethyl acetate (100 mL). Separate and extract the aqueous portion with dichloromethane (50 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 100% hexane/0% (10% acetonitrile/40% THF/50% hexane) to 0% hexane/100% (10% acetonitrile/0% THF/50% hexane) in a step gradient of 10% increments to give a white solid (0.090 g, 9%). ES/MS m/z (^{79}Br) 487.7 ($M+1$) $^+$.

Alternate preparation:

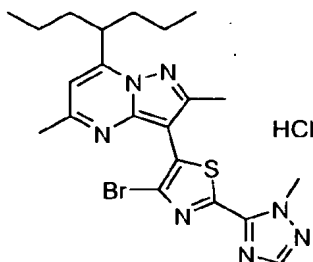
[0093] To a solution of 2,5-dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-7-(1-propyl-butyl)-pyrazolo [1,5-*a*]pyrimidine (6 g, 14.65 mmol) in acetonitrile (60 mL) add N-bromosuccinimide (2.74 g, 15.4 mmol) in one portion and stir at 22 °C for 10 h. Evaporate the solvent and dissolve the residue in a mixture of water (50 mL) and methyl-*t*-butyl ether (100 mL). Separate the organic layer and extract the aqueous layer with additional methyl-*t*-butyl ether (2 × 50 mL). Combine the organic portions and evaporate the solvent. Purify the resulting material by filtration through a silica

gel pad, eluting with hexanes/ethyl acetate (3/1). Combine the product containing fractions and evaporate the solvent. Add heptanes (25 mL) and triturate the solid. Filter the solid and dry under vacuum to afford the title compound (5.5 g, 77%). ES/MS m/z ($^{79}\text{Br}/^{81}\text{Br}$) 488/490 ($M+1$) $^+$.

Example 10a

3-[4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propylbutyl)-pyrazolo[1,5-a]pyrimidine, hydrochloride

[0094]



[0095] Dissolve 3-[4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)- pyrazolo [1,5-a]pyrimidine (750 mg, 1.54 mmol) in acetone (5 mL) and add 1 M HCl in diethyl ether (1.84 mL, 1.84 mmol). Stir the mixture at room temperature for 3 h and concentrate *in vacuo*. Dissolve the residue in diethyl ether/hexane = 1/1 (5 mL) and crystallize the desired HCl salt (526 mg, 65%). ES/MS m/z (^{81}Br) 490 ($M+1$) $^+$; $^1\text{H-NMR}$ (CDCl_3): 8.20 (s, 1H), 6.82 (s, 1H), 4.21 (s, 3H), 3.64 (m, 1H), 2.49 (m, 3H), 2.44 (s, 3H), 1.75 (m, 4H), 1.96(m, 4H), 0.81 (m, 6H).

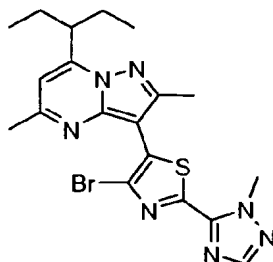
[0096] Prepare the following compound essentially as described in Example 10.

Ex. No.	Chemical name	Physical data
11*	7-(1-Ethyl-propyl)-2,5-dimethyl-3-[4-methyl-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-pyrazolo[1,5-a]pyrimidine	ES/MS m/z 396 ($M+1$) $^+$
* Use 0.5 M zinc chloride in THF instead of anhydrous zinc chloride. Heat at 80 °C for 3 days.		

Example 12

3-(4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

[0097]



[0098] Under nitrogen atmosphere, add *n*-butyl lithium (2.5 M in hexane, 0.6 mL, 1.5 mmol) to a solution of 1-methyl-1,2,4-triazole (124.5 mg, 1.5 mmol) in THF (3 mL) at -78 °C and stir for 30 min. Add anhydrous zinc chloride (409 mg, 3.0 mmol), continue stirring for 30 min, warm up to room temperature and stir for 2 h. Add 3-(2,4-dibromothiazol-5-yl)-

7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (229 mg, 0.5 mmol), followed by tetrakis(triphenylphosphine)pal-
ladium (58 mg, 0.05 mmol) and reflux overnight. Cool to room temperature, dilute with ethyl acetate, and wash with
saturated ammonia chloride. Dry the organic portion over sodium sulfate, filter, and concentrate to a residue. Purify the
crude material by flash chromatography, eluting with hexanes:ethyl acetate (10:2.5) to give the title compound as a
yellow foam (77 mg). MS (APCI) m/z (⁷⁹Br) 460.4 (M+1)⁺.

Alternate preparation from Example 21:

[0099] Add acetic acid (1 mL) and N-bromosuccinimide (4.1 g, 22 mmol) to a solution of 7-(1-ethyl-propyl)-2,5-dimethyl-
3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-pyrazolo[1,5-a]pyrimidine (8 g, 21 mmol) in acetonitrile (80 mL). Stir
the mixture 2 h at 22 °C. Then evaporate the solvent and add water (50 mL) and methyl-*t*-butyl ether (100 mL) to the
resulting residue. Separate the organic portion, dry over sodium sulfate, filter, and evaporate the solvent. Recrystallize
the resulting residue from isopropyl alcohol to afford the title compound (8.7 g, 90%). ES/MS (m/z): (⁷⁹Br/⁸¹Br) 460/462
(M+1)⁺.

Example 12a

3-(4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine,
p-toluene sulfonic acid

[0100] Dissolve 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethyl-pyrazolo
[1,5-a]pyrimidine (50 mg, 0.109 mmol) in acetone (3 mL). Add a 0.25 M aqueous solution of *p*-toluene sulfonic acid
(434.4 μL, 0.109 mmol) and evaporate the resulting mixture to dryness. Add ethyl acetate (12 mL) to get partial dissolution
of the solids. Add methanol (1 mL) to achieve a clear solution. Concentrate the solution by slow evaporation until crystals
are observed. Isolate the crystals by filtration and dry under vacuum at 25 °C to obtain about 50 mg of the title compound.

[0101] Determine the stoichiometry of the salt by ion chromatography using the following HPLC conditions: column:
Phenomenex Phenosphere SAX, 4.6 × 150 mm at 30 °C; mobile phase: 50% acetonitrile/50% 0.025 M sodium phosphate
buffer at pH = 4.5; flow rate = 1.5 mL/min; detection: UV at 205 nm; injection volume = 5 μL; run time = 3 min. Theoretical
amount calc: 27.2% tosylate; found: 28.4% tosylate (average of three HPLC runs).

Example 13

{4-Chloro-5-[2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-a] pyrimidin-3-yl]-thiazol-2-yl}-dimethylamine

[0102] Charge an oven dried flask with {4-bromo-5-[2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-a] pyrimidin-3-yl]-thi-
azol-2-yl}-dimethylamine (0.20, 0.44 mmol) and anhydrous THF (3.0 mL) and chill under an inert atmosphere to -78 °C.
Slowly add *n*-butyl lithium (1.6 M hexane solution, 0.42 mL, 0.67 mmol) and stir 30 min. Add N-chlorosuccinimide (0.120
g, 0.889 mmol) in one aliquot and stir 30 min at -78 °C. Allow the reaction to warm to room temperature, and stir for 5
h, checking the progress using LC/MS. Dilute with ethyl acetate (100 mL), wash with saturated ammonium chloride (50
mL), and back-extract the aqueous with dichloromethane (50 mL). Combine the organic phases, dry over anhydrous
magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatog-
raphy, eluting with 100% hexane/0% (25% THF/hexane) to 0% hexane/100% (25% THF/hexane) in a step gradient of
10% increments to give a white solid (0.087 g, 48%). ES/MS m/z (³⁵Cl) 406.0 (M+1)⁺.

[0103] Prepare the following examples essentially as described in Example 13 using the appropriate bromothiazole
prepared above.

Ex. No.	Chemical name	Physical data
14	3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-a] pyrimidine	ES/MS m/z (³⁵ Cl) 448.0 (M+1) ⁺
15	{4-Chloro-5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a] pyrimidin-3-yl]-thiazol-2-yl}-dimethyl-amine	MS (APCI) m/z (³⁵ Cl) 378.0 (M+1) ⁺

Preparation 18 2,4-dichlorothiazole

[0104] Cool to 5 °C a mixture of thiazolidine-2,4-dione (50 g, 0.43 mol) in phosphorus oxychloride (240 mL) and add
pyridine (34 mL, 0.43 mol) over 15 min. Heat the mixture to 125 °C for 4 h and then cool to 22 °C. Remove the excess

phosphorus oxychloride by vacuum distillation and add the residue to water (1 L) chilled to a temperature of 5 °C. Extract the mixture with methylene chloride (3 × 400 mL). Combine the organic portions and evaporate the solvent to afford the title compound (50 g, 76%). EI/MS m/z : (^{35}Cl / ^{35}Cl / ^{35}Cl / ^{37}Cl / ^{37}Cl / ^{37}Cl) 153/155/157 ($M+1$)⁺.

Preparation 19

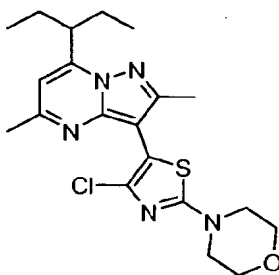
4-chloro-2-morpholino-thiazole

[0105] To a mixture of 2,4-dichlorothiazole (34 g, 0.22 mol) in acetonitrile (425 mL) add potassium carbonate (60.9 g, 0.44 mol) and then morpholine (21.2 mL, 0.225 mol) dropwise over 30 min. Reflux the mixture at 40 °C and then cool to 22 °C. Filter the mixture and evaporate the filtrate. Triturate the residue with *i*-propyl alcohol (60 mL) at 22 °C for one hour. Filter the solids and dry under vacuum to a constant weight to afford the title compound (34.5 g, 76%). ES/MS m/z (^{35}Cl) 205 ($M+1$)⁺.

Example 16

3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0106]



[0107] Under a nitrogen atmosphere dissolve 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (116 mg, 0.25 mmol) in THF (1.5 mL) and chill to -78 °C. Add *n*-butyl lithium (0.1 mL, 2.5 M in hexane, 0.25 mmol) and stir at -78 °C for 30 min. Add *N*-chlorosuccinimide (33.4 mg, 0.25 mmol) and stir for another 30 min, slowly warming to room temperature. After stirring overnight, quench the reaction by adding a solution of saturated ammonia chloride and extract with ethyl acetate. Wash the organic layer with brine, dry over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with hexanes:dichloromethane:ethyl acetate (5:5:2) to provide the title compound (54 mg). MS (APCI) m/z (^{35}Cl) 420.6 ($M+1$)⁺; ^1H NMR (400 MHz, CDCl_3): 6.44 (s, 1H), 3.79 (t, 4H, $J=4.8$ Hz), 3.63-3.56 (m, 1H), 3.47 (t, 4H, $J=4.8$ Hz), 2.55 (s, 3H), 2.45 (s, 3H), 1.88-1.75 (m, 4H), 0.87 (t, 6H, $J=7.5$ Hz).

Alternate Preparation from Preparation 6:

[0108] Combine 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine, (9 g, 26.2 mmol) and 4-chloro-2-morpholino-thiazole (7.5 g, 36.7 mmol) in dimethylformamide (90 mL) previously degassed with nitrogen. Add cesium carbonate (17.8 g, 55 mmol), copper iodide (250 mg, 1.31 mmol), triphenylphosphine (550 mg, 2.09 mmol) and palladium acetate (117 mg, 0.52 mmol). Heat the mixture to 125 °C for 16 h and then cool to 22 °C. Add water (900 mL) and extract with methyl-*t*-butyl ether (3 × 200 mL). Combine the organic portions and evaporate the solvent. Purify by silica gel chromatography eluting with hexanes/ethyl acetate (4/1) to afford the title compound (6.4 g, 62%). ES/MS m/z (^{35}Cl) 420 ($M+1$)⁺.

Example 16a

3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine, hydrochloride

[0109] Dissolve 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (1.40 g, 3.33 mmol) in acetone (10 mL) at 50 °C and cool to room temperature. Add hydrogen chloride (2 M in diethyl

ether, 2.0 mL, 4.0 mmol) and stir well in a sonicator. Concentrate the solution a little and add a minimal amount of diethyl ether to crystallize the HCl salt. Cool the mixture in a refrigerator overnight. Add additional hydrogen chloride (2 M in diethyl ether, 2.0 mL, 4.0 mmol) and cool in a refrigerator. Filter the crystalline material and dry to obtain the title compound (1.15 g, 75%). ES/MS m/z (^{35}Cl) 420 ($M+1$)⁺; ^1H NMR(CDCl_3): 9.18 (br, 1H), 6.86 (s, 1H), 3.72 (m, 4H), 3.49 (m, 1H), 3.39 (m, 4H), 2.48 (s, 3H), 2.38 (s, 3H), 1.79 (m, 4H), 0.79 (m, 6H).

Example 17

3-(4-Bromo-2-butyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0110] Under a nitrogen atmosphere, add *n*-butyl lithium (2.5 M in hexane, 0.2 mL, 0.5 mmol) to a solution of 3-(2,4-dibromo-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (230 mg, 0.5 mmol) in THF (3 mL) at -78 °C. After 30 min, add 1-iodobutane (138 mg, 0.75 mmol) and continue stirring for 1 hour. Warm up to room temperature and stir for one hour. Quench the reaction by adding saturated ammonia chloride solution and extract with ethyl acetate. Dry the organic portion over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with hexanes/ethyl acetate (10/1.5) to give the title compound as orange foam (78 mg). ES/MS m/z (^{81}Br) 437.4 ($M+1$)⁺.

[0111] Prepare the following example essentially as described in Example 17.

Ex. No.	Chemical name	Physical data
18	3-(4-Bromo-2-methoxymethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidine	MS (APCI) m/z (^{81}Br) 424.6 ($M+1$) ⁺

Example 19

7-(1-Ethyl-propyl)-3-(2-methoxymethyl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0112] Under a nitrogen atmosphere, add *n*-butyl lithium (2.5 M in hexane, 0.4 mL, 1.0 mmol) to a solution of 7-(1-ethyl-propyl)-2,5-dimethyl-3-thiazol-5-yl-pyrazolo[1,5-*a*]pyrimidine (300 mg, 1.0 mmol) in THF (3 mL) at -78 °C. Stir 30 min and add 1-iodomethyl methyl ether (205 mg, 1.2 mmol). Continue stirring for one hour and then slowly warm up to room temperature and stir overnight. Quench the reaction by adding saturated ammonium chloride solution and extract with ethyl acetate. Wash the organic layer with brine, dry over sodium sulfate, filter, and concentrate under vacuum to a residue. Purify the crude material by flash chromatography, eluting with hexanes/ethyl acetate (10/2) to give the title compound as a yellow foam (184 mg). MS (APCI) m/z 345.3 ($M+1$)⁺.

Example 20

3-(4-Chloro-2-methoxymethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0113] Add *n*-butyl lithium (2.5 M in hexanes, 174 mL, 0.43 mmol) to a stirred solution of 7-(1-ethyl-propyl)-3-(2-methoxymethyl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (150 mg, 0.43 mmol) in THF (3 mL) at -78 °C. Stir for 30 min and add N-chlorosuccinimide (87 mg, 0.653 mmol). Stir 30 min and then warm the reaction slowly to room temperature allowing the reaction to continue overnight. Quench the reaction by adding saturated ammonium chloride solution, extract with ethyl acetate, dry over sodium sulfate, filter, and concentrate to a residue. Purify by flash chromatography, eluting with hexanes/ethyl acetate (10/2) to give the title compound (7 mg). MS (APCI) m/z (^{35}Cl) 379.3 ($M+1$)⁺.

Example 21

7-(1-Ethyl-propyl)-2,5-dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-pyrazolo[1,5-*a*]pyrimidine

[0114] Mix 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (175 mg, 0.38 mmol) and copper(I) chloride (132 mg, 1.33 mmol) in DMF (5 mL) and heat to 120 °C for 24 h. Cool to room temperature, dilute with ethyl acetate, and wash with brine. Dry the organic layer over sodium sulfate, filter, and concentrate under vacuum to a residue. Purify by flash chromatography, eluting with hexanes and then hexanes/EtOAc (10/1.8) to give a yellow-orange solid (45 mg). ES/MS m/z 382.0 ($M+1$)⁺.

Alternate Preparation:

[0115] Add *n*-butyl lithium (2.5 M in hexanes, 57.6 mL, 144 mmol) to a solution of N-methyltriazole (11.95 g, 144 mmol) in THF (600 mL) at -78 °C under a nitrogen atmosphere, keeping the temperature below -74 °C during the addition. Then add zinc chloride, dry powder, (26 g, 192 mmol) in one portion and warm the mixture to 22 °C in one hour. Add 7-(1-ethyl-propyl)-3-(2-iodo-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (12.5 g, 29 mmol) and tetrakis(triphenyl) phosphine palladium catalyst (1.15 g, 0.01 mol) in one portion and heat the mixture to reflux under nitrogen for 8 h. Cool the mixture to 22 °C and add water (300 mL). Separate the organic layer and extract the aqueous layer with methyl-*t*-butyl ether (2 × 200 mL). Combine the organic portions, dry over sodium sulfate, filter, and evaporate the solvent. Purify by passing over a silica gel pad eluting with hexanes/ethyl acetate (4/1) to afford the title compound (8 g, 72%). ES/MS *m/z* 382 (M+1)⁺.

Example 22

3-(4-Chloro-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0116] Stir a mixture of 7-(1-ethyl-propyl)-2,5-dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-pyrazolo[1,5-*a*]pyrimidine (20 mg, 0.052 mmol) and N-chlorosuccinimide (7.6 mg, 0.0569 mmol) in dichloromethane (0.5 mL) and acetonitrile (0.5 mL) at room temperature overnight in a vial. Concentrate to a residue. Purify by flash chromatography, eluting with hexanes and then with hexanes/ethyl acetate (10/1.5) to give the title compound (16 mg). ES/MS *m/z* (35Cl) 416.0 (M+1)⁺.

Example 23

7-(1-Ethyl-propyl)-3-(4-methoxy-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0117] Stir a mixture of 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (162 mg, 0.35 mmol), sodium methoxide (57 mg, 1.05 mmol) and copper(I) iodide (67 mg, 0.35 mmol) in methanol (3 mL) in a sealed 4-mL vial for 15 h at 120 °C. Cool to room temperature, remove the solid by filtration, and concentrate the filtrate under vacuum. Purify the residue by flash chromatography, eluting with hexanes/THF (10/2). Recrystallize the material from methanol to give the title compound (20 mg). ES/MS *m/z* 416.0 (M+1)⁺.

Preparation 20

4-Bromo-5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-thiazole-2-carbaldehyde

[0118] Under a nitrogen atmosphere, add *n*-butyl lithium (1.6 M in hexanes, 0.312 mL, 0.50 mmol) to a THF solution (2.5 mL) of 3-(2,4-dibromo-thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (230 mg, 0.50 mmol) at -78 °C and stir for 30 min. Add a THF (0.5 mL) solution of N-formyl morpholine (58 mg, 0.50 mmol). Stir for one hour, then store the reaction at -20 °C overnight. Warm the reaction to room temperature, dilute with ether, and quench by adding 4 N HCl (4 mL). Separate and extract the organic phase with 4 N HCl (2 × 4 mL). Combine the aqueous portions, treat with solid sodium bicarbonate to pH = 8 to 9 and then extract with diethyl ether. Combine all the organic layers, wash with brine, dry over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with hexanes/dichloromethane/ethyl acetate (5/5/1) to give the title compound (154 mg). MS (APCI) *m/z* (81Br) 409.0 (M+1)⁺.

Example 24

3-(4-Bromo-2-morpholin-4-yl-methyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0119] Combine 4-bromo-5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-thiazole-2-carbaldehyde (150 mg, 0.368 mmol), morpholine (35 mg, 0.405 mmol) and sodium triacetoxyborohydride (97 mg, 0.46 mmol), in dichloromethane (3 mL) and methanol (0.5 mL). Stir overnight, add additional morpholine (35 mg, 0.405 mmol), and sodium triacetoxyborohydride (97 mg, 0.46 mmol), and stir 4 h more. Remove the solvent under vacuum, dilute with dichloromethane, and wash with brine. Dry the organic phase over sodium sulfate, filter, and concentrate under vacuum. Purify the resulting material using flash chromatography, eluting with dichloromethane:2 M ammonia in methanol (10:1) to give a mixture. Purify the mixture using a reverse phase column, eluting with water/acetonitrile (80/20) to water/acetonitrile (10/90) to give the title compound (20 mg). ES/MS *m/z* (81Br) 480.0 (M+1)⁺.

Example 25

3-(4-Bromo-2-pyridin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

[0120] Under a nitrogen atmosphere, add *n*-butyl lithium (1.6 M in hexane, 0.312 mL, 0.5 mmol) to a solution of 3-(2,4-dibromo-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (229 mg, 0.5 mmol) in THF (4 mL) at -78 °C. After stirring for 30 min, add anhydrous zinc chloride (264 mg, 1.5 mmol) and continue stirring for 30 min. Warm the reaction to room temperature and stir for one hour. Add 4-iodopyridine (103 mg, 0.5 mmol), followed by 1,1'-bis (diphenylphosphino)ferrocene palladium (II) chloride (dichloromethane adduct) (0.40.8 mg, 0.05 mmol). Heat the reaction to reflux overnight. Cool to room temperature, dilute with ethyl acetate, and wash with water and brine. Dry the organic layer over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with dichloromethane:2 N ammonia in methanol (10:0.75) to give a mixture. Purify the mixture using a reverse phase column, eluting with water:acetonitrile = 80:20 to water: acetonitrile = 10:90, to give the title compound (19 mg). ES/MS m/z (^{79}Br) 456.0 ($M+1$)⁺.

Preparation 21

4-Trifluoromethyl-thiazole-2-ylamine

[0121] Add thiourea (4.0 g, 52.3 mmol) and 3-bromo-1,1,1-trifluoropropan-2-one (5.5 mL, 10 g, 52.3 mmol) to ethanol (100 mL) and heat at 50 °C for 2 h. Cool to room temperature and concentrate to dryness. Dissolve the residue in water and adjust the pH to >12 with 2 M NaOH. Extract with diethyl ether (4×). Dry the combined organic extracts with sodium sulfate, filter, and concentrate under vacuum. Purify the resulting material by silica gel chromatography (CH_2Cl_2) to obtain the title compound (6.9 g, 79%). ES/MS m/z 169 ($M+1$)⁺.

Preparation 22

5-Bromo-4-trifluoromethyl-thiazol-2-ylamine, hydrobromide

[0122] Add bromine (2.0 mL, 6.28 g, 39.3 mmol) dropwise to an ice-bath cooled solution of 4-trifluoromethyl-thiazole-2-ylamine (6.0 g, 35.7 mmol) in diethyl ether (60 mL). Stir for one hour after the addition is complete and then warm to room temperature. Collect the solids by filtration and wash with diethyl ether to obtain the title compound (10.5 g, 90%). ES/MS m/z ($^{79}\text{Br}/^{81}\text{Br}$) 247/249 ($M+1$)⁺.

Preparation 23

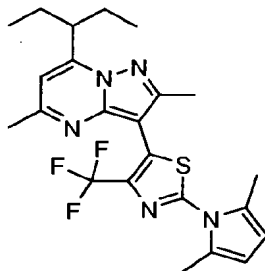
5-Bromo-2-(2,5-dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazole

[0123] Add hexane-2,5-dione (3.5 mL, 3.4 g, 30.2 mmol) to a solution of 5-bromo-4-trifluoromethyl-thiazol-2-ylamine hydrobromide (9.0 g, 27.4 mmol) in methanol (60 mL). Stir at room temperature overnight. Add phosphate buffer (50 mL, pH = 7). Collect the resulting precipitate by filtration, washing with water. Dissolve the filter cake in CH_2Cl_2 and dry over sodium sulfate. Filter and concentrate under vacuum to obtain the title compound (8.2 g, 92%). ^1H NMR (400 MHz, CDCl_3) δ 5.91 (s, 2H), 2.27 (s, 6H).

Example 26

3-[2-(2,5-Dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazol-5-yl]-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

[0124]



[0125] Cool a solution of 5-bromo-2-(2,5-dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazole (2.2 g, 6.6 mmol) in THF (25 mL) in a dry ice bath. Add *t*-butyl lithium (1.7 M in pentane, 8.5 mL, 14.5 mmol) dropwise. Stir for 45 min and then add zinc chloride (0.5 M in THF, 14.6 mL, 7.3 mmol) dropwise. Stir 5 min and remove the cooling bath. Stir 30 min and then add 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (1.5 g, 4.4 mmol) and bis(tri-*t*-butylphosphine)palladium (0) (450 mg, 0.9 mmol). Reflux for 24 h. Cool the reaction, pour the mixture into diethyl ether, and wash with water (2×). Extract the combined water layers with diethyl ether. Dry the combined organic portions over sodium sulfate, filter, and concentrate to dryness under vacuum. Purify the resulting residue by silica gel chromatography (75-100% CH₂Cl₂ in hexanes) to give the title compound (1.47 g, 72%). HR-ToF-MS *m/z* calcd for C₂₃H₂₆F₃N₅S+H⁺: 462.1939, found: 462.1915.

Example 27

5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-ylamine

[0126] Add hydroxylamine (2 mL, 50% in water) to a solution of 3-[2-(2,5-dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazol-5-yl]-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (1.1 g, 2.3 mmol) in acetic acid (10 mL). Heat the reaction to 80 °C for 6 h. Cool to room temperature. Pour into diethyl ether and wash with 2 M NaOH (2×) and then once with water. Dry the organic portion over sodium sulfate, filter, and concentrate to dryness under vacuum. Purify the resulting residue by silica gel chromatography (40% ethyl acetate in hexanes) to give the title compound (0.76 g, 87%). ES/MS *m/z* 384 (M+1)⁺.

Preparation 24

3-(2-Bromo-4-trifluoromethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0127] Heat a mixture of copper(II) bromide (540 mg, 2.4 mmol) and *t*-butylnitrite (0.36 mL, 310 mg, 3.0 mmol) in acetonitrile (20 mL) to 60 °C. Add 5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-ylamine (755 mg, 2.0 mmol) as a solid. Heat the reaction to 80 °C for 2 h. Cool the reaction, pour into diethyl ether and extract with water (3×). Dry the organic layer over sodium sulfate, filter, and concentrate to dryness under vacuum. Purify the resulting residue by silica gel chromatography in CH₂Cl₂ to give the title compound (0.77 g, 87%). ES/MS *m/z* (⁷⁹Br/⁸¹Br) 447, 449 (M+1)⁺.

Example 28

{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-dimethyl-amine

[0128] Heat a sealed tube containing 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (313 mg, 0.7 mmol), and dimethyl amine (2 M in THF, 4 mL, 8 mmol) in methanol (4 mL) to 80 °C for 2 h. Cool the reaction and concentrate under vacuum. Purify the resulting residue by silica gel chromatography, eluting with 0-30% ethyl acetate in CH₂Cl₂, to give the title compound (0.28 g, 97%). HR-ToF-MS *m/z* calcd for C₁₉H₂₄F₃N₅S+H⁺ 412.1770, found: 412.1783.

[0129] Prepare the following example essentially as described for Example 28 with the exception that the reaction is refluxed for 8 h.

Ex. No.	Chemical name	Physical data
29	7-(1-Ethyl-propyl)-2,5-dimethyl-3-(2-morpholin-4-yl-4-trifluoromethyl-thiazol-5-yl)-pyrazolo[1,5-a]pyrimidine	HR-ToF-MS m/z calcd for C ₂₁ H ₂₆ F ₃ N ₅ OS+H ⁺ : 454.1873, found: 454.1873, found: 454.1888

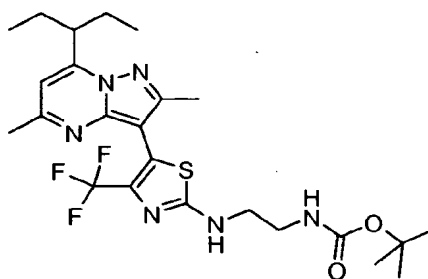
Example 30

N-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-acetamide

[0130] Add hydroxylamine (50% in water, 5 mL) to a solution of 3-[2-(2,5-dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazol-5-yl]-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (2.4 g, 5.2 mmol) in acetic acid (25 mL). Heat the reaction to 80 °C for 72 h. Cool the reaction to room temperature, pour into diethyl ether and wash with 2 M NaOH (2×) and then once with water. Dry the organic portion over sodium sulfate, filter, and concentrate to dryness. Purify the resulting residue by column chromatography, eluting with 40% ethyl acetate in hexanes to give the title compound (0.28 g, 13%). HR-ToF-MS m/z calcd for C₁₉H₂₂F₃N₅OS+H⁺ 426.1575, found: 426.1565.

Example 31

[0131] (2-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}amino)-ethyl)-carbamic acid *tert*-butyl ester



[0132] Add (2-amino-ethyl)-carbamic acid *tert*-butyl ester (0.5 mL, 506 mg, 3.2 mmol) to a solution of 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (100 mg, 0.22 mmol) and triethylamine (0.3 mL, 222 mg, 2.2 mmol) in methanol (1 mL). Evaporate off the methanol and heat to 80 °C overnight. Cool the reaction to room temperature and concentrate under vacuum. Purify the resulting residue by column chromatography, eluting with 10-50% ethyl acetate in CH₂Cl₂, to give the title compound (0.11 g, 97%). ES/MS m/z 527.2 (M+1)⁺.

[0133] Prepare the compounds below as essentially described in Example 31 using the appropriate amine.

Prep. or Ex. No.	Chemical name	Physical data
Prep. 25*	[2-({5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-propyl-amino)-ethyl]-carbamic acid <i>tert</i> -butyl ester	ES/MS m/z 569.3 (M+1) ⁺
Prep. 26**	(S)-(1-{5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-pyrrolidin-3-yl)-carbamic acid <i>tert</i> -butyl ester	ES/MS m/z 553.3 (M+1) ⁺
Ex. 32***	<i>N</i> -{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}- <i>N,N</i> -dipropyl-ethane-1,2-diamine, hydrochloride	ES/MS m/z 511.2 (M+1) ⁺
* Heat at reflux in EtOH overnight. Evaporate EtOH and heat at 110 °C for 24 h. ** Heat at 80 °C in EtOH overnight. *** Make the HCl salt and recrystallize from EtOAc/hexanes.		

Example 33

*N*¹-[5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl]-ethane-1,2-diamine, hydrochloride

[0134] Add (2-{5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-ylamino}-ethyl)-carbamic acid *tert*-butyl ester (101 mg, 0.192 mmol) to 1 M HCl in methanol (1 mL). Heat the reaction at 70 °C overnight. Cool the reaction and concentrate under vacuum from methanol/ethyl acetate. Triturate the resulting residue with ethyl acetate to obtain the title compound (64 mg, 78%). ES/MS *m/z* 427.0 (*M*+1)⁺.

[0135] Prepare the following examples essentially as described for Example 33.

Ex. No.	Chemical name	Physical data
34	<i>N</i> ¹ -[5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl]- <i>N</i> ¹ -propyl-ethane-1,2-diamine, hydrochloride	ES/MS <i>m/z</i> 469.2 (<i>M</i> +1) ⁺
35	(<i>S</i>)-1-[5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl]-pyrrolidin-3-ylamine, hydrochloride	ES/MS <i>m/z</i> 453.0 (<i>M</i> +1) ⁺

Example A

In Vivo Potency Assessment Using Ex Vivo Binding

[0136] To assess in vivo potency, a compound of the present invention is evaluated using ex vivo binding. Using the procedures as provided in D. R. Gehlert et al., EJP 509: 145-153 (2005), a compound is administered to a rat via the oral route. The binding of ¹²⁵I-sauvagine to the cerebellum is then assessed ex vivo as described in Gehlert *et al.* For example, Example 15 provides 65% inhibition at 10 mg/kg.

Example B

CRF1 Filter Binding Assay

[0137] The limitations of plasmid-based human CRF 1 expression, in terms of generating a recombinant cell line with sufficient receptor density to develop a binding assay, are overcome by using a Phoenix retroviral expression system licensed from Stanford. The stable HEK-hCRF1 cell line is used to prepare membranes and binding reactions (200 μL) are set up as follows: 50 μL of ¹²⁵I-sauvagine (0.2 nM final), 50 μL compound and 100 μL CRF1 membrane (25 μg/reaction). The reactions are incubated at room temperature for 2 h and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are washed twice with ice-cold assay buffer (50 mM tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM MgCl₂, 0.05% BSA, pH 7.2), air dried over night and counted with 100 μL Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 μM non-labeled sauvagine. Triplicate determinations are typically run and the median data points plotted by Graph Pad Prism.

[0138] Using this assay, the exemplified compounds of the present invention inhibit the binding of ¹²⁵I-Sauvagine (4 nM) in roller/adherent cells with a K_i (inhibition constant) below 1 μM. For example, Example 15 exhibits a K_i of 6.2 nM.

Example C

CRF2 Filter Binding Assay

[0139] The limitations of plasmid-based human CRF2 expression, in terms of generating a recombinant cell line with sufficient receptor density to develop a binding assay, are overcome by using a Phoenix retroviral expression system licensed from Stanford. The stable HEK-hCRF2 cell line is used to prepare membranes and binding reactions (200 μL) are set up as follows: 50 μL of ¹²⁵I-sauvagine (0.2 nM final concentration), 50 μL compound and 100 μL CRF2 membrane (25 μg/reaction). The reactions are incubated at room temperature for 2 hours and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are washed twice with ice-cold assay buffer (50 mM tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM MgCl₂, 0.05% BSA, pH 7.2), air dried over night and counted with 100 μL Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 μM non-labeled sauvagine. Alternatively, compounds are evaluated using a Scintillation Proximity assay. This assay is set up as follows: 50 μL of ¹²⁵I-Sauvagine (0.2 nM final concentration), 50 μL compound or non-labelled sauvagine (NSB) and 100 μL

containing 250 μ g wheat germ agglutinin (WGA) SPA beads and CRF2 membrane (1.5 μ g/reaction). Plates are incubated for 4-5 h at room temperature and then centrifuged at 200 X g for 10 min. Bound radioactivity is assessed using a Wallac Trilux scintillation counter. Binding is assessed typically using triplicate determinations and the median data points plotted by Graph Pad Prism. Compounds are initially screened at a fixed concentration and, if sufficient activity is noted, subsequent concentration-response curves are generated.

[0140] Particular exemplified compounds of the present invention are tested in the CRF2 binding assay and exhibit weak affinity for the CRF2 receptor. For example, Example 15 exhibits 11% inhibition at a concentration of 50 μ M. This result suggests that the compounds of the present invention are selective for the CRF 1 receptor, (relative to CRF2).

Example D

Bioavailability and Pharmacokinetic Properties

[0141] The volume of distribution (Vdist) relates the amount of the drug in the body to the concentration of the drug in the blood or plasma. The volume of distribution refers to the fluid volume that would be required to contain the total amount of the drug in the body at the same concentration as in the blood or plasma: $V_{dist} = \text{amount of drug in the body} / \text{concentration of drug in blood or plasma}$ (Goodman and Gillman's). For a 10 mg dose and a plasma concentration of 10 mg/L, the volume of distribution would be 1 liter. The volume of distribution reflects the extent to which the drug is present in the extravascular tissue. A large volume of distribution reflects the tendency of a compound to bind to the tissue components compared with plasma protein binding. In a clinical setting, Vdist can be used to determine a loading dose to achieve a steady state concentration.

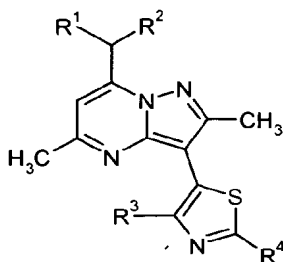
[0142] To test for volume of distribution, Male Sprague Dawley rats (N=3) are administered a single 1 mg/kg intravenous dose of compound. Multiple plasma samples are collected at time points from 0.08 to 24 hours post-dose. The plasma samples are analyzed by LC/MS/MS to determine the plasma concentrations. Plasma pharmacokinetic calculations are performed to determine the pharmacokinetic parameters including Vdist and plasma clearance (CLp).

[0143] Compounds of the present invention preferably have favorable bioavailability profiles. For example, a majority of commercial CNS and cardiovascular drugs exhibit a human Vdist of <10 L/Kg. In comparison with CRF antagonists, CP154526 (Schulz et al., Proc. Natl. Acad. Sci. (USA), 93:10477 (1996)) and NBI30775 (Chen et al., Drug Development Research, 65:216 (2005)), which exhibit a rat Vdist of 114 L/Kg and 76 L/Kg, respectively, when analyzed separately. Example 15 of the present invention, when analyzed separately, exhibits a rat Vdist of only 7.2 L/Kg following a single intravenous dose of 1 mg/kg.

[0144] Further, the plasma clearance (CLp) is a measure of the rate of removal of the drug from the body. Following an intravenous dose and first-order kinetics, the plasma clearance may be determined using the following equation: $CLp = \text{Dose} / \text{AUC}$, where AUC is the total area under the curve that describes the concentration of the drug in the plasma as a function of time from zero to infinity. Reference CRF antagonists CP154526 and NBI37582 exhibit rat clearance (CLp) of 83 and 306 mL/min/kg, respectively, when analyzed separately, following a single intravenous dose, while Example 15 of the present invention, when analyzed separately, exhibits a rat CLp of only 23.6 mL/min/kg.

Claims

1. A compound of Formula I



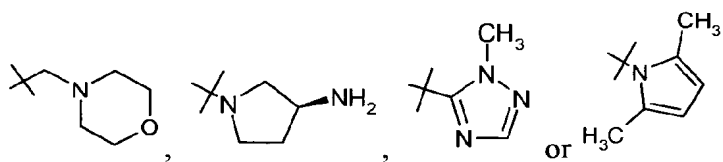
Formula I

wherein:

R¹ and R² are independently ethyl or *n*-propyl;

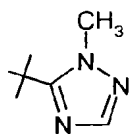
R³ is hydrogen, Cl, Br, methyl, trifluoromethyl or methoxy;

R⁴ is hydrogen, Br, R^aR^bN-, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,

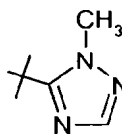


R^a and R^b are independently hydrogen, C₁-C₃alkyl, H₂NCH₂CH₂-, (CH₃)₃COC(O)NHCH₂CH₂-, or CH₃CH₂CH₂NHCH₂CH₂-; or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R³ is Cl, Br, methyl or trifluoromethyl.
3. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R³ is Cl or Br.
4. The compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R⁴ is R^aR^bN-, pyridin-4-yl, morpholin-4-yl, or



5. The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R⁴ is morpholin-4-yl or



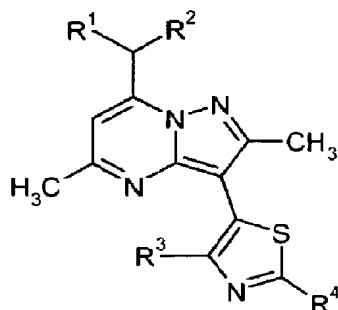
6. The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R⁴ is R^aR^b- and R^a and R^b are independently C₁-C₃alkyl.
7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is 3-[4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)- pyrazolo[1,5-*a*]pyrimidine.
8. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.
9. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.
10. A pharmaceutical composition comprising: a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
11. A compound according to any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in therapy.

12. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in the treatment of anxiety or depression.

13. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in the treatment of alcohol or substance abuse.

Patentansprüche

1. Verbindung der Formel I



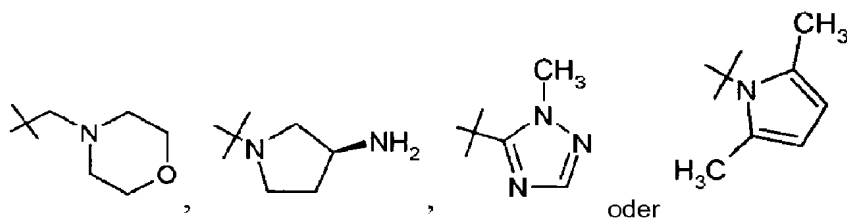
Formel I

worin

R¹ und R² unabhängig voneinander für Ethyl oder n-Propyl stehen;

R³ für Wasserstoff, Cl, Br, Methyl, Trifluormethyl oder Methoxy steht;

R⁴ für Wasserstoff, Br, R^aR^bN-, Methoxymethyl, n-Butyl, Acetamido, Pyridin-4-yl, Morpholin-4-yl,



steht;

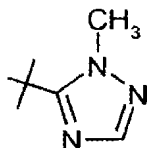
R^a und R^b unabhängig für Wasserstoff, C₁-C₃Alkyl, H₂NCH₂CH₂-, (CH₃)₃COC(O)NHCH₂CH₂- oder CH₃CH₂CH₂NHCH₂CH₂- stehen;

oder ein pharmazeutisch akzeptables Salz hiervon.

2. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salz hiervon, worin R³ für Cl, Br, Methyl oder Trifluormethyl steht.

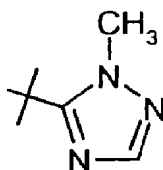
3. Verbindung nach Anspruch 1 oder 2 oder ein pharmazeutisch akzeptables Salz hiervon, worin R³ für Cl oder Br steht.

4. Verbindung nach einem der Ansprüche 1 bis 3 oder ein pharmazeutisch akzeptables Salz hiervon, worin R⁴ für R^aR^bN-, Pyridin-4-yl, Morpholin-4-yl oder



steht.

5. Verbindung nach einem der Ansprüche 1 bis 4 oder ein pharmazeutisch akzeptables Salz hiervon, worin R⁴ für Morpholin-4-yl oder

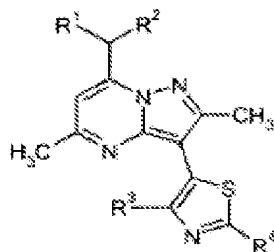


steht.

6. Verbindung nach einem der Ansprüche 1 bis 4 oder ein pharmazeutisch akzeptables Salz hiervon, worin R⁴ für R^aR^bN- steht und R^a und R^b unabhängig für C₁-C₃Alkyl stehen.
7. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salz hiervon, nämlich 3-[4-Brom-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-α]pyrimidin.
8. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salz hiervon, nämlich 3-(4-Brom-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-α]pyrimidin.
9. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salz hiervon, nämlich 3-(4-Chlor-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin.
10. Pharmazeutische Zusammensetzung, die eine Verbindung nach einem der Ansprüche 1 bis 9 oder ein pharmazeutisch akzeptables Salz hiervon und einen pharmazeutisch akzeptablen Hilfsstoff umfasst.
11. Verbindung nach einem der Ansprüche 1 bis 9 oder ein pharmazeutisch akzeptables Salz hiervon zur Verwendung in der Therapie.
12. Verbindung nach einem der Ansprüche 1 bis 9 oder ein pharmazeutisch akzeptables Salz hiervon zur Verwendung bei der Behandlung von Angst oder Depression.
13. Verbindung nach einem der Ansprüche 1 bis 9 oder ein pharmazeutisch akzeptables Salz hiervon zur Verwendung bei der Behandlung von Alkohol- oder Substanzmissbrauch.

Revendications

1. Composé répondant à la formule I



Formule I

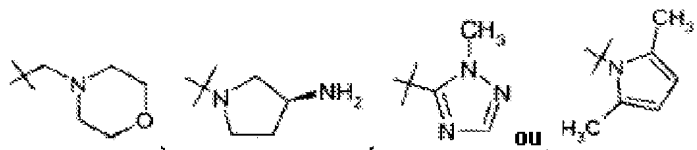
dans laquelle :

R¹ et R² représentent, de manière indépendante, un groupe éthyle ou un groupe *n*-propyle ;

R³ représente un atome d'hydrogène, un atome de chlore, un atome de brome, un groupe méthyle, un groupe trifluorométhyle ou un groupe méthoxy ;

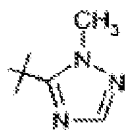
R⁴ représente un atome d'hydrogène, un atome de brome, un groupe R^aR^bN-, un groupe méthoxyméthyle, un groupe *n*-butyle, un groupe acétamido,

un groupe pyridin-4-yle, un groupe morpholin-4-yle,

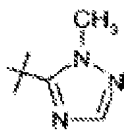


R^a et R^b représentent, de manière indépendante, un atome d'hydrogène, un groupe alkyle en C₁-C₃, un groupe H₂NCH₂CH₂-, un groupe (CH₃)₃COC(O)NHCH₂CH₂-, ou un groupe CH₃CH₂CH₂NHCH₂CH₂-; ou un de ses sels pharmaceutiquement acceptables.

2. Composé selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables, dans lequel R³ représente un atome de chlore, un atome de brome, un groupe méthyle ou un groupe trifluorométhyle.
3. Composé selon la revendication 1 ou 2, ou un de ses sels pharmaceutiquement acceptables, dans lequel R³ représente un atome de chlore ou un atome de brome.
4. Composé selon l'une quelconque des revendications 1 à 3, ou un de ses sels pharmaceutiquement acceptables, dans lequel R⁴ représente un groupe R^aR^bN-, un groupe pyridin-4-yle, un groupe morpholin-4-yle ou un groupe



5. Composé selon l'une quelconque des revendications 1 à 4, ou un de ses sels pharmaceutiquement acceptables, dans lequel R⁴ représente un groupe morpholin-4-yle ou un groupe



6. Composé selon l'une quelconque des revendications 1 à 4, ou un de ses sels pharmaceutiquement acceptables, dans lequel R⁴ représente un groupe R^aR^bN- et R^a et R^b représentent, de manière indépendante, un groupe alkyle en C₁-C₃.
7. Composé selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables, qui est la 3-[4-bromo-2-(2-méthyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-diméthyl-7-(1-propyl-butyl)-pyrazolo[1,5-a]pyrimidine.
8. Composé selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables, qui est la 3-(4-bromo-2-(2-méthyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-éthylpropyl)-2,5-diméthyl-pyrazolo[1,5-a]pyrimidine.
9. Composé selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables, qui est la 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-éthyl-propyl)-2,5-diméthyl-pyrazolo[1,5-a]pyrimidine.
10. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptables, et un excipient pharmaceutiquement acceptable.
11. Composé selon l'une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptables, à utiliser en thérapie.
12. Composé selon l'une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptables, à utiliser dans le traitement de l'anxiété ou de la dépression.
13. Composé selon l'une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptables, à utiliser dans le traitement de l'abus d'alcool ou d'autres drogues.

REFERENCES CITED IN THE DESCRIPTION

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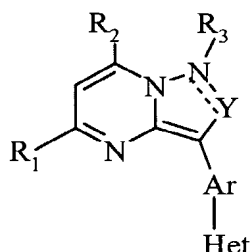
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(54) Title: CRF RECEPTOR ANTAGONISTS AND METHODS RELATING THERETO



(I)

(57) Abstract: CRF receptor antagonists are disclosed which have utility in the treatment of a variety of disorders, including the treatment of disorders manifesting hypersecretion of CRF in a warm-blooded animals, such as stroke. The CRF receptor antagonists of this invention have the following structure (I), including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof, wherein R₁, R₂, R₃, Y, Ar, and Het are as defined herein. Compositions containing a CRF receptor antagonist in combination with a pharmaceutically acceptable carrier are also disclosed, as well as methods for use of the same.



CRF RECEPTOR ANTAGONISTS AND METHODS RELATING THERETO

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Application Serial No. 60/532,031, filed December 12, 2003, the entire disclosure of which is incorporated by
5 reference herein.

FIELD OF THE INVENTION

This invention relates generally to CRF receptor antagonists and to methods of treating disorders by administration of such antagonists to a mammal in need thereof.

10 BACKGROUND OF THE INVENTION

The first corticotropin-releasing factor (CRF) was isolated from ovine hypothalami and identified as a 41-amino acid peptide (Vale et al., *Science* 213:1394-1397, 1981). Subsequently, sequences of human and rat CRF were isolated and determined to be identical but different from ovine CRF in 7 of the 41 amino acid
15 residues (Rivier et al., *Proc. Natl. Acad. Sci. USA* 80:4851, 1983; Shibahara et al., *EMBO J.* 2:775, 1983).

CRF has been found to produce profound alterations in endocrine, nervous and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotrophic hormone ("ACTH"), β -endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the
20 anterior pituitary (Vale et al., *Science* 213:1394-1397, 1981). Briefly, CRF is believed to initiate its biological effects by binding to a plasma membrane receptor which has been found to be distributed throughout the brain (DeSouza et al., *Science* 224:1449-1451, 1984), pituitary (DeSouza et al., *Methods Enzymol.* 124:560, 1986; Wynn et al.,
25 *Biochem. Biophys. Res. Comm.* 110:602-608, 1983), adrenals (Udelsman et al., *Nature* 319:147-150, 1986) and spleen (Webster, E.L., and E.B. DeSouza, *Endocrinology* 122:609-617, 1988). The CRF receptor is coupled to a GTP-binding protein (Perrin et al., *Endocrinology* 118:1171-1179, 1986) which mediates CRF-stimulated increase in intracellular production of cAMP (Bilezikjian, L.M., and W.W. Vale, *Endocrinology*
30 113:657-662, 1983). The receptor for CRF has now been cloned from rat (Perrin et al., *Endo* 133(6):3058-3061, 1993), and human brain (Chen et al., *PNAS* 90(19):8967-8971, 1993; Vita et al., *FEBS* 335(1):1-5, 1993). This receptor is a 415 amino acid protein comprising seven membrane spanning domains. A comparison of identity

between rat and human sequences shows a high degree of homology (97%) at the amino acid level.

In addition to its role in stimulating the production of ACTH and POMC, CRF is also believed to coordinate many of the endocrine, autonomic, and behavioral responses to stress, and may be involved in the pathophysiology of affective disorders. Moreover, CRF is believed to be a key intermediary in communication between the immune, central nervous, endocrine and cardiovascular systems (Crofford et al., *J. Clin. Invest.* 90:2555-2564, 1992; Sapolsky et al., *Science* 238:522-524, 1987; Tilders et al., *Regul. Peptides* 5:77-84, 1982). Overall, CRF appears to be one of the pivotal central nervous system neurotransmitters and plays a crucial role in integrating the body's overall response to stress.

Administration of CRF directly to the brain elicits behavioral, physiological, and endocrine responses identical to those observed for an animal exposed to a stressful environment. For example, intracerebroventricular injection of CRF results in behavioral activation (Sutton et al., *Nature* 297:331, 1982), persistent activation of the electroencephalogram (Ehlers et al., *Brain Res.* 278:332, 1983), stimulation of the sympathoadrenomedullary pathway (Brown et al., *Endocrinology* 110:928, 1982), an increase of heart rate and blood pressure (Fisher et al., *Endocrinology* 110:2222, 1982), an increase in oxygen consumption (Brown et al., *Life Sciences* 30:207, 1982), alteration of gastrointestinal activity (Williams et al., *Am. J. Physiol.* 253:G582, 1987), suppression of food consumption (Levine et al., *Neuropharmacology* 22:337, 1983), modification of sexual behavior (Sirinathsinghji et al., *Nature* 305:232, 1983), and immune function compromise (Irwin et al., *Am. J. Physiol.* 255:R744, 1988). Furthermore, clinical data suggests that CRF may be hypersecreted in the brain in depression, anxiety-related disorders, and anorexia nervosa. (DeSouza, *Ann. Reports in Med. Chem.* 25:215-223, 1990). Accordingly, clinical data suggests that CRF receptor antagonists may represent novel antidepressant and/or anxiolytic drugs that may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF.

The first CRF receptor antagonists were peptides (see, e.g., Rivier et al., U.S. Patent No. 4,605,642; Rivier et al., *Science* 224:889, 1984). While these peptides established that CRF receptor antagonists can attenuate the pharmacological responses to CRF, peptide CRF receptor antagonists suffer from the usual drawbacks of peptide therapeutics including lack of stability and limited oral activity. Some published patent documents include US6313124, WO 01/23388, and WO 97/29109, all of which disclose pyrazolopyrimidine compounds as CRF antagonists. Published

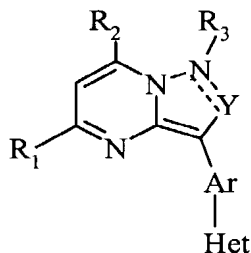
application WO 98/54093 described certain pyrazolopyrimidine compounds as tyrosine kinase inhibitors.

Due to the physiological significance of CRF, the development of biologically-active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF receptor remains a desirable goal. Such CRF receptor antagonists would be useful in the treatment of endocrine, psychiatric and neurological conditions or illnesses, including stress-related disorders in general.

While significant strides have been made toward achieving CRF regulation through administration of CRF receptor antagonists, there remains a need in the art for effective small molecule CRF receptor antagonists. There is also a need for pharmaceutical compositions containing such CRF receptor antagonists, as well as methods relating to the use thereof to treat, for example, stress-related disorders. The present invention fulfills these needs, and provides other related advantages.

SUMMARY OF THE INVENTION

In brief, this invention is generally directed to CRF receptor antagonists, and more specifically to CRF receptor antagonists having the following general structure (I):



(I)

and pharmaceutically acceptable salts, esters, solvates, stereoisomers and prodrugs thereof, wherein R₁, R₂, R₃, Y, Ar, and Het are as defined below.

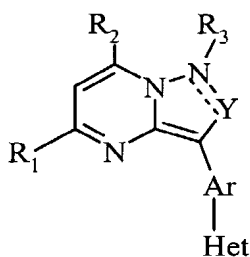
The CRF receptor antagonists of this invention may have utility over a wide range of therapeutic applications, and may be used to treat a variety of disorders or illnesses, including stress-related disorders. Such methods include administering a pharmaceutically effective amount of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition, to an animal in need thereof. Accordingly, in another embodiment, pharmaceutical compositions are disclosed containing one or more CRF receptor antagonists of this invention and a pharmaceutically acceptable carrier and/or diluent.

These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain procedures, compounds and/or compositions, and are hereby incorporated by reference in their entirety.

5 DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to corticotropin-releasing factor (CRF) receptor antagonists.

In a first embodiment, the CRF receptor antagonists of this invention have the following structure (I):



(I)

or a pharmaceutically acceptable salt, ester, solvate, stereoisomer or prodrug thereof, wherein:

“---” represents the second bond of an optional double bond;

R₁ is hydrogen, alkyl, substituted alkyl, heteroaryl, substituted heteroaryl, -NH₂, or halogen;

R₂ is alkyl, substituted alkyl, -C(O)NR₇R₈, aryl, substituted aryl, aryloxyalkyl, substituted aryloxyalkyl, heteroarylalkoxyalkyl, substituted heteroarylalkoxyalkyl, heterocyclealkyl, substituted heterocyclealkyl, arylalkyl, substituted arylalkyl, heteroaryl, or substituted heteroaryl, wherein said heteroaryl or substituted heteroaryl is connected to the pyrimidine ring via a carbon-carbon bond;

R₃ is null, hydrogen, or alkyl;

Y is =(CR₄)- or -(C=O)-;

R₄ is hydrogen, alkyl, substituted alkyl, thioalkyl, alkylsulfinyl, or alkylsulfonyl;

Ar is phenyl, phenyl substituted with 1 or 2 R₅, pyridyl or pyridyl substituted with 1 or 2 R₅;

R₅ at each occurrence is hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, halogen, alkylsulfonyl, or alkylsulfinyl;

Het is heteroaryl optionally substituted with 1 or 2 R₆;

R₆ at each occurrence is hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, or halogen; and

R₇ and R₈ are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, arylalkyl, substituted arylalkyl, heterocyclealkyl or substituted heterocyclealkyl; or

R₇ and R₈ taken together with the nitrogen to which they are attached form a heterocyclic ring or a substituted heterocyclic ring.

As used herein, the above terms have the following meaning:

10 "Alkyl" means a straight chain or branched, acyclic or cyclic, unsaturated or saturated hydrocarbon containing from 1 to 10 carbon atoms, while the term "lower alkyl" has the same meaning as alkyl but contains from 1 to 6 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, sec-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Representative saturated cyclic alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclopentyl, -CH₂-cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like. Cyclic alkyls, also referred to as "homocyclic rings," and include di- and poly-homocyclic rings such as decalin and adamantyl. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an "alkenyl" or "alkynyl", respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 3-methyl-1 butyne, and the like.

"Alkylidene" represents a divalent alkyl from which two hydrogen atoms are taken from the same carbon atom, such as =CH₂, =CHCH₃, =CHCH₂CH₃, =C(CH₃)CH₂CH₃, and the like.

30 "Aryl" means an aromatic carbocyclic moiety such as phenyl or naphthyl.

"Arylalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with an aryl, such as benzyl (*i.e.*, -CH₂-phenyl), -CH₂-(1- or 2-naphthyl), -(CH₂)₂-phenyl, -(CH₂)₃-phenyl, -CH(phenyl)₂, and the like.

"Aryloxyalkyl" means an aryl attached through an oxygen bridge to an alkyl (*i.e.*, aryl-O-alkyl-) such as -methyl-O-phenyl, and such.

"Heteroaryl" means an aromatic heterocycle ring of 5- to 10-members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and bicyclic ring systems. Representative heteroaryls include (but are not limited to) furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinoliny, isquinoliny, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnoliny, phthalazinyl, and quinazolinyl.

"Heteroarylalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heteroaryl, such as -CH₂-pyridinyl, -CH₂-pyrimidinyl, and the like.

"Heterocycle" (also referred to herein as a "heterocycle ring") means a 5- to 7-membered monocyclic, or 7- to 14-membered polycyclic, heterocycle ring which is either saturated, unsaturated or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring as well as tricyclic (and higher) heterocyclic rings. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Thus, in addition to the aromatic heteroaryls listed above, heterocycles also include (but are not limited to) morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperizinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Heterocyclealkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heterocycle, such as -CH₂-morpholinyl, and the like.

The term "substituted" as used herein refers to any group (e.g., alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle or heterocyclealkyl) wherein at least one hydrogen atom is replaced with a substituent. In the case of a keto substituent ("C(=O)-") two hydrogen atoms are replaced. "Substituents" within the context of this invention include halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, alkyl, alkoxy, thioalkyl, haloalkyl, hydroxyalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, -NR_aR_b, -NR_aC(=O)R_b, -NR_aC(=O)NR_aR_b, -NR_aC(=O)OR_b, -NR_aSO₂R_b, -OR_a, -C(=O)R_a, -C(=O)OR_a, -C(=O)NR_aR_b, -OC(=O)NR_aR_b, -SH, -SR_a,

-SOR_a, -S(=O)₂R_a, -OS(=O)₂R_a, -S(=O)₂OR_a, wherein R_a and R_b are the same or different and independently hydrogen, alkyl, haloalkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl.

"Halogen" means fluoro, chloro, bromo or iodo.

"Haloalkyl" means an alkyl having at least one hydrogen atom replaced with halogen, such as trifluoromethyl and the like. Haloalkyl is a specific embodiment of substituted alkyl, wherein alkyl is substituted with one or more halogen atoms.

"Alkoxy" means an alkyl attached through an oxygen bridge (*i.e.*, -O-alkyl) such as -O-methyl, -O-ethyl, and the like.

"Thioalkyl" means an alkyl attached through a sulfur bridge (*i.e.*, -S-alkyl) such as -S-methyl, -S-ethyl, and the like.

"Alkylamino" and "dialkylamino" mean one or two alkyl moieties attached through a nitrogen bridge (*i.e.*, -NHalkyl or -N(alkyl)(alkyl)) such as methylamino, ethylamino, dimethylamino, diethylamino, and the like.

"Hydroxyalkyl" means an alkyl substituted with at least one hydroxy group.

"Mono- or di(cycloalkyl)methyl" represents a methyl group substituted with one or two cycloalkyl groups, such as cyclopropylmethyl, dicyclopropylmethyl, and the like.

"Alkylcarbonylalkyl" represents an alkyl substituted with a -C(=O)alkyl group.

"Alkylcarbonyloxyalkyl" represents an alkyl substituted with a -C(=O)Oalkyl group or a -OC(=O)alkyl group.

"Alkoxyalkyl" represents an alkyl substituted with a -O-alkyl group.

"Alkylthioalkyl" represents a alkyl substituted with a -S-alkyl group.

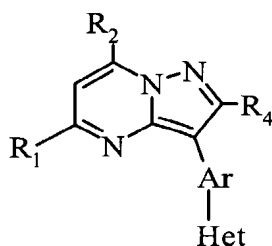
"Mono- or di(alkyl)amino represents an amino substituted with one alkyl or with two alkyls, respectively.

"Mono- or di(alkyl)aminoalkyl" represents an alkyl substituted with a mono- or di(alkyl)amino.

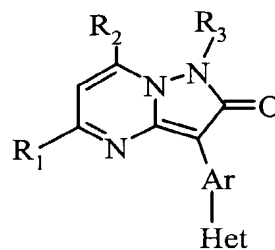
"Alkylsulfonyl or alkylsulfinyl" represents an alkyl substituted with a (-S(=O)₂-) or (-S(=O)-) functionality, respectively.

Embodiments of this invention presented herein are for purposes of example and not for purposes of limitation. In a first embodiment of the invention, R₃ is

null and Y is $=(\text{CR}_4)-$ in the following structure (II), and in a further embodiment Y is $-(\text{C}=\text{O})-$ in the following structure (III).

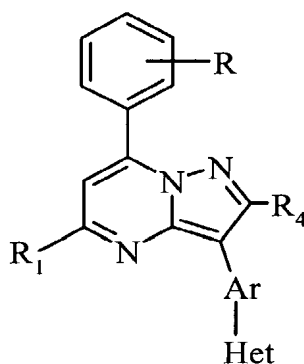


(II)



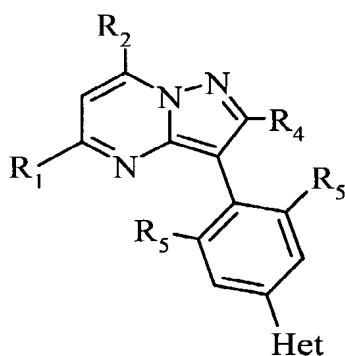
(III)

5 Further embodiments of this invention have structure (IV) when R_2 is phenyl, R is an optional substituent of said phenyl, and Y is $=(\text{CR}_4)-$.

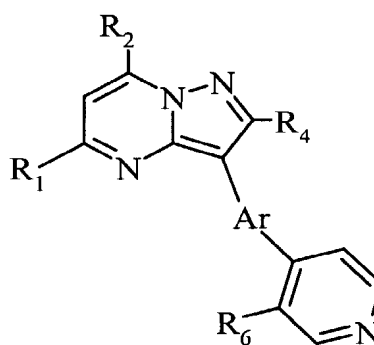


(IV)

10 In further embodiments of this invention wherein Y is $=(\text{CR}_4)-$, Ar is phenyl substituted with 2 R_5 in structure (V) and Het is pyridyl substituted with 1 R_6 in structure (IV).



(V)



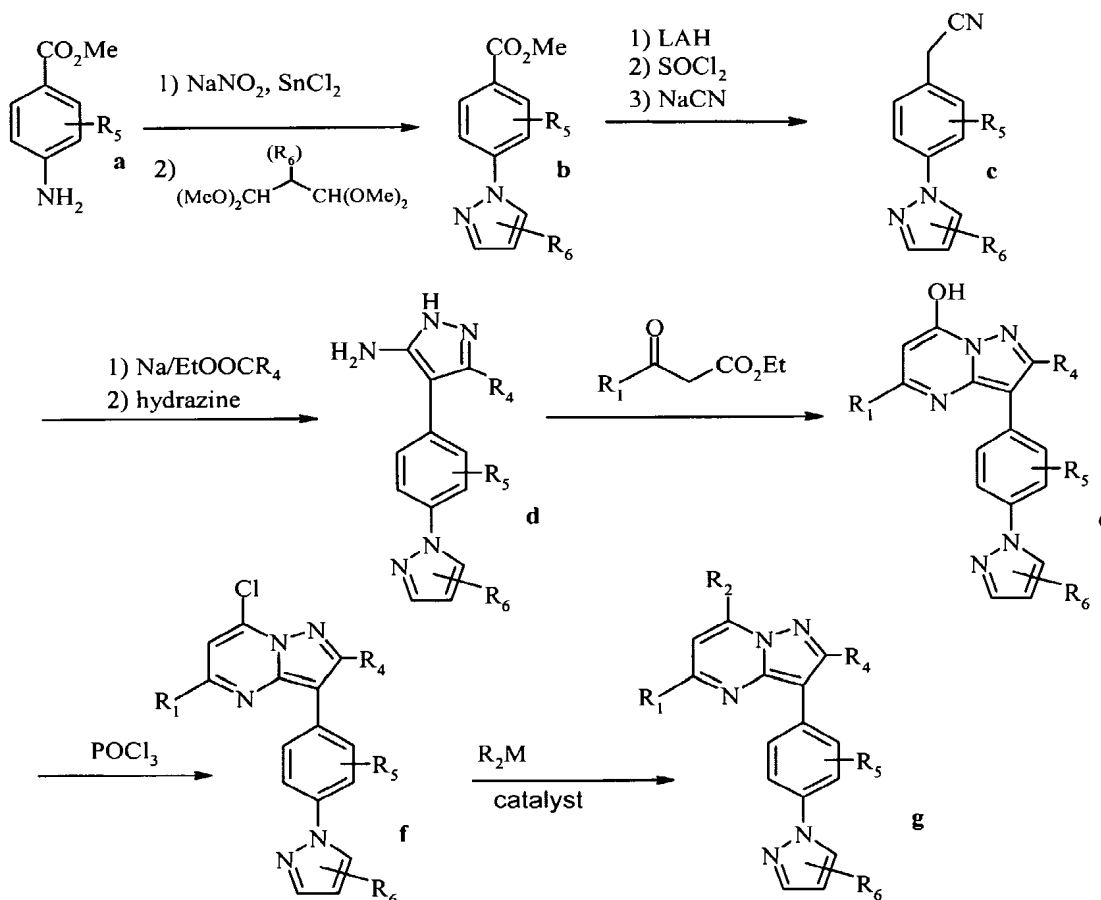
(VI)

15 The compounds of the present invention may generally be utilized as the free base. Alternatively, the compounds of this invention may be used in the form

of acid addition salts. Acid addition salts of the free base amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Thus, the term "pharmaceutically acceptable salt" of structure (I) is intended to encompass any and all pharmaceutically acceptable salt forms.

In general, the compounds of structure (I) may be made according to the organic synthesis techniques known to those skilled in this field, as well as by the representative methods set forth in the Examples. Examples of synthetic procedures which may be used to prepare compounds according to the invention are illustrated in Reaction Schemes 1-3.

Reaction Scheme 1

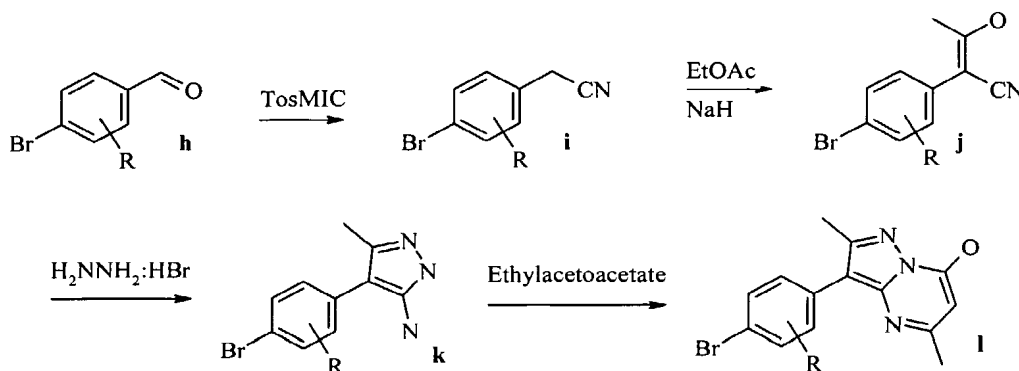


The amino functionality of 4-aminobenzoate **a** may be condensed with an, optionally, substituted malonaldehyde to give the corresponding 4-pyrazol-1-yl benzoate **b**. After reaction with LAH, SOCl₂, and NaCN to give conversion to the pyrazolophenylacetonitrile compound **c**, reaction with Na/ethyl carboxylic acid ester and hydrazine yields the bis-pyrazole **d**. Reaction with the appropriately substituted β-keto ester gives pyrazolopyrimidine **e** which reacts with POCl₃ to give the chloride **f**. Reaction of the chloride **f** with an appropriate organometallic reagent R₂M in the presence of a suitable catalyst or promoter gives compound **g**. Examples of suitable organometallic reagents and suitable catalysts/promoters include:

1. (substituted) alkyl grignard reagents R₂MgX (Fe(acac)₃ promoter);
2. aryl, heteroaryl, or alkenyl boronic acids or esters (Pd(PhP)₄ catalyst); and
3. aryl or heteroaryl zinc reagents (Pd(PhP)₄ catalyst).

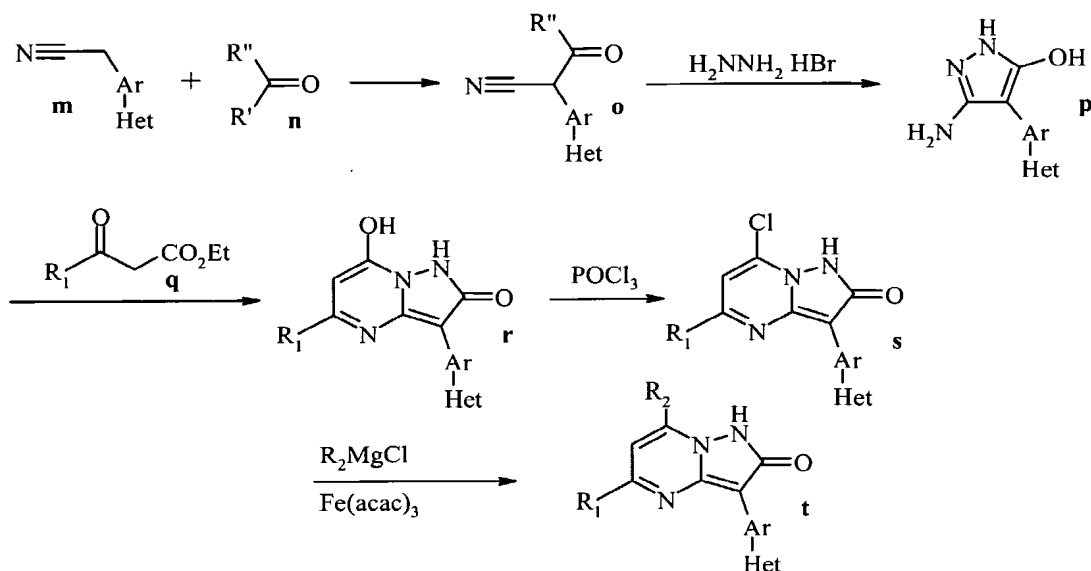
The R₂ groups thus installed may be further manipulated or reacted, using standard methods known to those skilled in the art (for example oxidation/reduction, hydrolysis, and the like), to provide further examples of the invention.

Reaction Scheme 2



Multiple synthetic routes to the pyrazolopyrimidine core of the invention are available. In Reaction Scheme 2, the optionally substituted halobenzaldehyde **h** reacts with tosylmethyl isocyanide (TosMIC) to form the phenylacetonitrile **i**. Reaction of **i** with NaH and EtOAc gives the 3-hydroxy but-2-enenitrile **j** which undergoes ring closure in reaction with hydrazine HBr to give the 3-amino 2-phenyl pyrazole **k**. Addition of the β-keto ester gives the pyrazolo[1,5-a]pyrimidin-7-ol **I**. Substitution of the oxygen as in Reaction Scheme 1 and substitution of the distal bromine with Het gives compounds according to the invention.

Reaction Scheme 3



- Reaction of substituted acetonitrile **m** with ketone **n**, where R' is a good leaving group such as alkoxy, cyano, or halo and where R'' is a group such as hydroxy or alkoxy gives cyanoketone **o** which reacts with hydrazine to give substituted pyrazole **p**. Reaction of **p** with β-keto ester **q** gives pyrazolopyrimidine **r**. Reaction with POCl₃ gives the chloride **s**, and substitution of chloride by R₂ gives compound **t**.

- The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention may be capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of structure (I) may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (*J. Neuroscience* 7:88, 1987) and Battaglia et al. (*Synapse* 1:572, 1987). As mentioned above, suitable CRF antagonists include compounds which demonstrate CRF receptor affinity. CRF receptor affinity may be determined by binding studies that measure the ability of a compound to inhibit the binding of a radiolabeled CRF (e.g., [¹²⁵I]tyrosine-CRF) to its receptor (e.g., receptors prepared from rat cerebral cortex membranes).
- The radioligand binding assay described by DeSouza et al. (*supra*, 1987) provides an assay for determining a compound's affinity for the CRF receptor. Such activity is typically calculated from the IC₅₀ as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the receptor, and is reported as a "K_i" value calculated by the following equation:

$$K_i = \frac{IC_{50}}{1 + L / K_D}$$

where L = radioligand and K_D = affinity of radioligand for receptor (Cheng and Prusoff, *Biochem. Pharmacol.* 22:3099, 1973).

In addition to inhibiting CRF receptor binding, a compound's CRF receptor antagonist activity may be established by the ability of the compound to antagonize an activity associated with CRF. For example, CRF is known to stimulate various biochemical processes, including adenylate cyclase activity. Therefore, compounds may be evaluated as CRF antagonists by their ability to antagonize CRF-stimulated adenylate cyclase activity by, for example, measuring cAMP levels. The CRF-stimulated adenylate cyclase activity assay described by Battaglia et al. (*supra*, 1987) provides an assay for determining a compound's ability to antagonize CRF activity. Accordingly, CRF receptor antagonist activity may be determined by assay techniques which generally include an initial binding assay (such as disclosed by DeSouza (*supra*, 1987)) followed by a cAMP screening protocol (such as disclosed by Battaglia (*supra*, 1987)).

With reference to CRF receptor binding affinities, CRF receptor antagonists of this invention have a K_i of less than 10 μ M. In a preferred embodiment of this invention, a CRF receptor antagonist has a K_i of less than 1 μ M, and more preferably less than 0.25 μ M (*i.e.*, 250 nM). As set forth in greater detail below, the K_i values may be assayed by the methods set forth in Example 27.

CRF receptor antagonists of the present invention may demonstrate activity at the CRF receptor site, and may be used as therapeutic agents for the treatment of a wide range of disorders or illnesses including endocrine, psychiatric, and neurological disorders or illnesses. More specifically, CRF receptor antagonists of the present invention may be useful in treating physiological conditions or disorders arising from the hypersecretion of CRF. Because CRF is believed to be a pivotal neurotransmitter that activates and coordinates the endocrine, behavioral and automatic responses to stress, CRF receptor antagonists of the present invention may be used to treat neuropsychiatric disorders. Neuropsychiatric disorders which may be treatable by CRF receptor antagonists of this invention include affective disorders such as depression; anxiety-related disorders such as generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, cardiovascular abnormalities such as unstable angina and reactive hypertension; and feeding disorders such as anorexia nervosa, bulimia, and irritable bowel syndrome. CRF antagonists may also be useful in treating stress-induced immune suppression

associated with various diseases states, as well as stroke. Other uses of CRF antagonists of this invention include treatment of inflammatory conditions (such as rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and G.I. motility), pain, Cushing's disease, infantile spasms, epilepsy and other seizures in both infants and adults, and various substance abuse and withdrawal (including alcoholism).

In another embodiment of the invention, pharmaceutical compositions containing one or more CRF receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a CRF receptor antagonist of the present invention (*i.e.*, a compound of structure (I)) and a pharmaceutically acceptable carrier and/or diluent. The CRF receptor antagonist is present in the composition in an amount which is effective to treat a particular disorder--that is, in an amount sufficient to achieve CRF receptor antagonist activity, and preferably with acceptable toxicity to the patient. Preferably, the pharmaceutical compositions of the present invention may include a CRF receptor antagonist in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more preferably from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a CRF receptor antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the CRF receptor antagonist in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, PA 1990.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (I) *in vivo* when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound.

With regard to stereoisomers, the compounds of structure (I) may have chiral centers and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present

invention, including mixtures thereof. Furthermore, some of the crystalline forms of the compounds of structure (I) may exist in alternative crystalline, amorphous or polymorphic forms as polymorphs, all of which are included in the present invention. In addition, some of the compounds of structure (I) may also form solvates with water or other organic solvents. Such solvates are similarly included within the scope of this invention.

In another embodiment, the present invention provides a method for treating a variety of disorders or illnesses, including endocrine, psychiatric and neurological disorders or illnesses. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the disorder or illness. Such methods include systemic administration of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of CRF receptor antagonists include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention may be prepared in aqueous injection solutions which may contain, in addition to the CRF receptor antagonist, buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

In another embodiment, the present invention permits the diagnostic visualization of specific sites within the body by the use of radioactive or non-radioactive pharmaceutical agents. Use of a compound of the present invention may provide a physiological, functional, or biological assessment of a patient or provide disease or pathology detection and assessment. Radioactive pharmaceuticals are employed in scintigraphy, positron emission tomography (PET), computerized tomography (CT), and single photon emission computerized tomography (SPECT.) For such applications, radioisotopes are incorporated of such elements as iodine (I) including ^{123}I (PET), ^{125}I (SPECT), and ^{131}I , technetium (Tc) including ^{99}Tc (PET), phosphorus (P) including ^{31}P and ^{32}P , chromium (Cr) including ^{51}Cr , carbon (C) including ^{11}C , fluorine (F) including ^{18}F , thallium (Tl) including ^{201}Tl , and like emitters of positron and ionizing radiation. Non-radioactive pharmaceuticals are employed in magnetic resonance imaging (MRI), fluoroscopy, and ultrasound. For such applications, isotopes are incorporated of such elements as gadolinium (Gd) including ^{153}Gd , iron (Fe), barium (Ba), manganese (Mn), and thallium (Tl). Such entities are

also useful for identifying the presence of particular target sites in a mixture and for labeling molecules in a mixture.

As mentioned above, administration of a compound of the present invention can be used to treat a wide variety of disorders or illnesses. In particular, compounds of the present invention may be administered to a warm-blooded animal for the treatment of depression, anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, unstable angina, reactive hypertension, anorexia nervosa, bulimia, irritable bowel syndrome, stress-induced immune suppression, stroke, inflammation, pain, Cushing's disease, infantile spasms, epilepsy, and substance abuse or withdrawal.

The following examples are provided for purposes of illustration, not limitation.

EXAMPLES

The CRF receptor antagonists of this invention may be prepared by the methods disclosed in Examples 1 to 26. Example 27 presents a method for determining the receptor binding affinity, and Example 28 discloses an assay for screening compounds of this invention for CRF-stimulated adenylate cyclase activity.

Analytical HPLC-MS Method 1

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (APCI);

HPLC column: YMC ODS AQ, S-5, 5 μ , 2.0 x50 mm cartridge;

HPLC gradient: 1.0 mL/minute, from 10 % acetonitrile in water to 90 % acetonitrile in water in 2.5 minutes, maintaining 90 % for 1 minute. Both acetonitrile and water have 0.025% TFA.

Analytical HPLC-MS Method 2

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (APCI);

HPLC column: Phenomenex Synergi-Max RP, 2.0 x 50 mm column;

HPLC gradient: 1.0 mL/minute, from 5 % acetonitrile in water to 95 % acetonitrile in water in 13.5 minutes, maintaining 95 % for 2 minute. Both acetonitrile and water have 0.025% TFA.

Analytical HPLC-MS Method 3

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (electrospray);

HPLC column: XTerra MS, C₁₈, 5 μ , 3.0 x 250 mm column;

5 HPLC gradient: 1.0 mL/minute, from 10 % acetonitrile in water to 90 % acetonitrile in water in 46 minutes, jump to 99% acetonitrile and maintain 99 % acetonitrile for 8.04 minutes. Both acetonitrile and water have 0.025% TFA.

Analytical HPLC-MS Method 4

10 Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (APCI) and Berger FCM 1200 CO₂ pump module;

HPLC column: Berger Pyridine, PYR 60A, 6 μ , 4.6 x 150 mm column;

15 HPLC gradient: 4.0 mL/minute, 120 bar; from 10 % methanol in supercritical CO₂ to 60% methanol in supercritical CO₂ in 1.67 minutes, maintaining 60 % for 1 minute. Methanol has 1.5% water. Backpressure regulated at 140 bar.

Preparative HPLC-MS

Platform: Shimadzu HPLC equipped with a Gilson 215 auto-sampler/fraction collector, UV detector and a PE Sciez API150EX mass detector;

HPLC column: BHK ODS-O/B, 5 μ , 30x75 mm

20 HPLC gradient: 35 mL/minute, 10% acetonitrile in water to 100 % acetonitrile in 7 minutes, maintaining 100 % acetonitrile for 3 minutes, with 0.025% TFA.

Abbreviations:

25 AA: Acetyl acetate
LAH: Lithium aluminum hydride
DCM: Dichloromethane
DMSO: Dimethyl sulfoxide
EAA: Ethyl acetoacetate
LC-MS: liquid chromatography-mass spectroscopy
30 NaBH(OAc)₃: Sodium Triacetoxyborohydride
Pd-C: Palladium (10 %) on Carbon
TFA: Trifluoroacetic acid
Tosmic: Tosylmethyl isocyanide
acac: acetylacetonate

EDCI: N-ethyl-N'-(dimethylaminopropyl)carbodiimide hydrochloride

THF: tetrahydrofuran

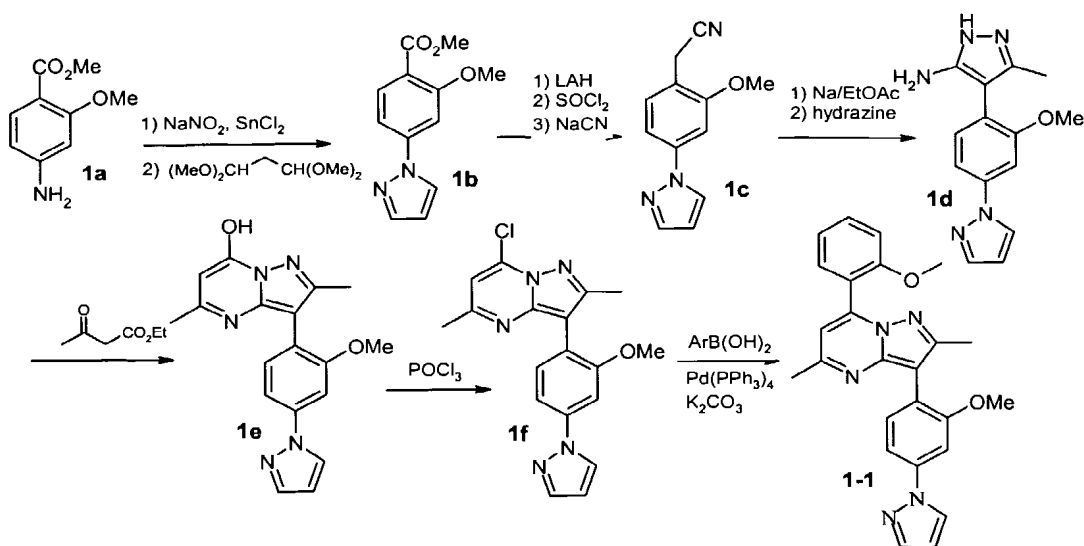
TEA: triethylamine

 t_R : Retention time

5

EXAMPLE 1

7-(2-METHOXY-PHENYL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE

**Step 1A:**

- 10 To a cooled suspension of methyl 4-amino-2-methoxybenzoate (6.82 g, 37.7 mmol) in 6N HCl (aqueous) was added a solution of sodium nitrite (2.60 g, 37.7 mmol) dropwise. After stirring at 0 °C for 20 min, stannous chloride dihydrate (24.7 g, 109.3 mmol) was added portionwise. The resulting suspension was stirred at 0 °C for 1.5 hr prior to filtration. The collected solid was suspended in EtOH to which
- 15 malonaldehyde bis(dimethyl acetal) (7.5 mL, 45.7 mmol) was added, and this reaction mixture was subjected to reflux overnight. After evaporation of EtOH, the residue was extracted between EtOAc and water, and the organic phase was dried and evaporated to dryness. The residue was passed through a silica gel plug (25% EtOAc/hexane) to yield Cmpd **1b** (7.43 g) as a mixture of the methyl and ethyl benzoate.

Step 1B:

To a solution of **1b** (10.6 g) in dry diethyl ether (200 mL) was added LAH powder (1.74 g) slowly at 0 °C. After stirring for 45 min at 0 °C the reaction mixture was decanted onto ice-water, and the aqueous phase was acidified to pH 4.0. After isolation, the alcohol (8.8 g) was refluxed with thionyl chloride (10 mL) in DCM for 2.5 hr, decanted onto ice-water, and extracted with DCM. The crude benzyl chloride (8.26 g) was heated with NaCN (3.65 g, 74.4 mmol) in DMSO (100 mL) at 80 °C for 45 min. After removal of DMSO, Cmpd **1c** (5.98 g) obtained after column chromatography with 30% EtOAc/hexane.

10 Step 1C:

To a solution of **1c** (5.98 g, 28.1 mmol) in EtOAc (150 mL) was added metallic sodium (1.0 g, 43.5 mmol) portionwise, and the mixture was refluxed overnight. The resulting suspension was decanted onto ice-water and acidified to pH 4.0. The organic phase was dried and evaporated to dryness. The resulting compound (9.5 g) was mixed with hydrazine monohydrobromide (15.3 g, 135.4 mmol,) and refluxed in EtOH/H₂O (6:1) for 5 hr. After evaporation of EtOH and extraction with EtOAc, the organic phase was dried and evaporated to dryness to yield Cmpd **1d** (7.5 g.)

Step 1D:

A mixture of **1d** (7.5 g, 27.9 mmol) was refluxed with ethyl acetoacetate (5.0 mL) in AcOH (100 mL) for 3 hr. After evaporation of AcOH and precipitation in diethyl ether, Cmpd **1e** (10.4 g) obtained after filtration.

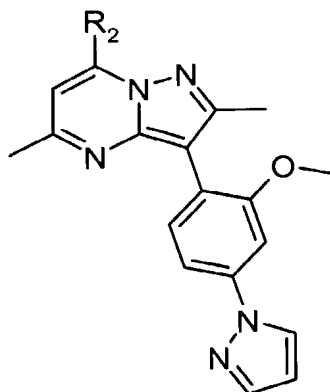
Step 1E:

To a suspension of **1e** (2.1 g, 6.3 mmol) in acetonitrile was added POCl₃ (2.2 mL, 24.1 mmol,) and this mixture was refluxed for 5 hr, decanted to ice-water, and extracted with EtOAc to yield Cmpd **1f** (1.88 g) after chromatographic purification.

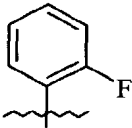
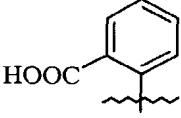
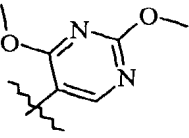
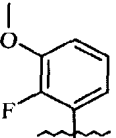
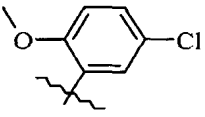
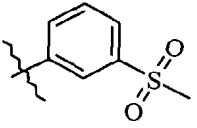
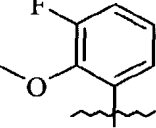
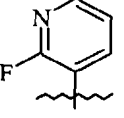
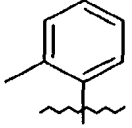
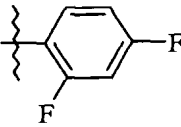
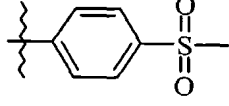
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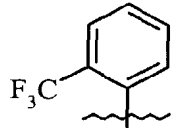
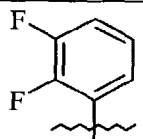
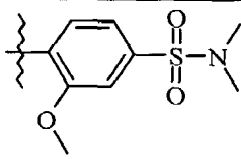
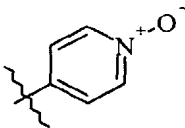
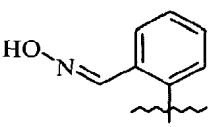
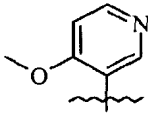
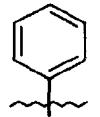
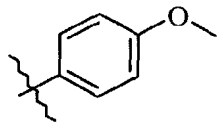
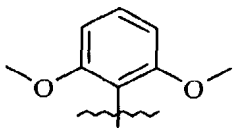
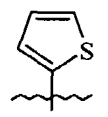
A mixture of Cmpd **1f** (1.0 mmol), 2-methoxyphenylboronic acid (1.2 mmol), K₂CO₃ (2.0 mmol) and Pd(PPh₃)₄ (0.05 mmol) was heated in 1,4-dioxane/H₂O (2:1) at 110 °C overnight. After evaporation of solvent, the mixture was extracted between CHCl₃/H₂O, and the organic phase was dried and evaporated to dryness. Cmpd **1-1** (402 mg) was obtained after column chromatography. Depending on the

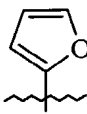
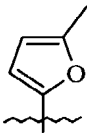
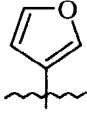
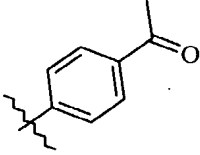
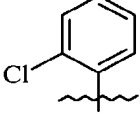
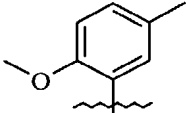
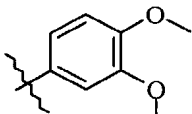
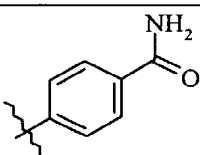
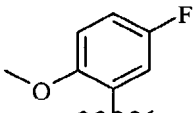
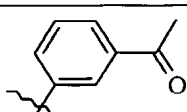
aryl functionality in the arylboronic acid reagent, the compounds listed in the following table were synthesized and purified by preparative LC-MS:

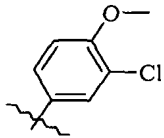
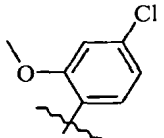
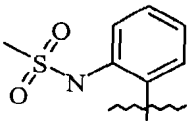
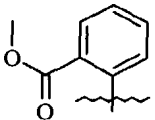
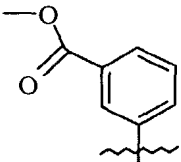
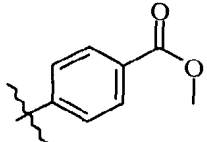
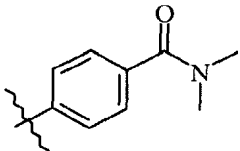
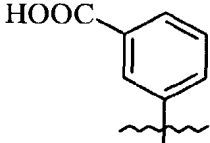
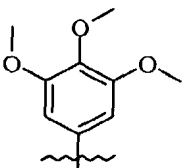
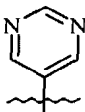


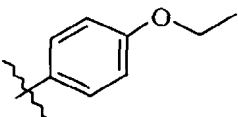
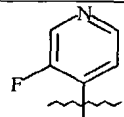
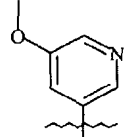
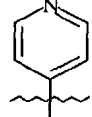
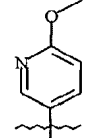
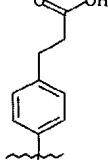
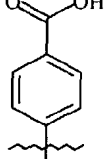
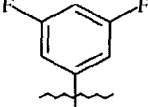
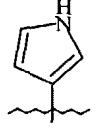
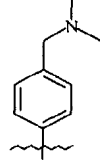
Cmpd	R ₂	MW	MS	t _R	HPLC Method
1-1		425.49	425	1.315	4
1-2		414.47	414	1.586	4
1-3		443.48	443	1.335	4
1-4		455.52	455	1.32	4
1-5		439.47	439	1.353	4
1-6		413.45	413	1.25	4
1-7		425.49	425	1.317	4

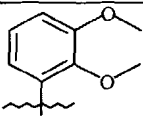
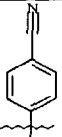
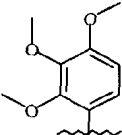
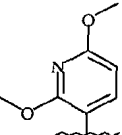
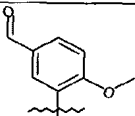
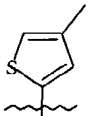
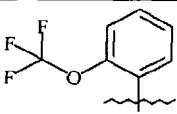
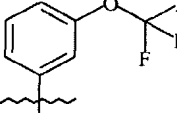
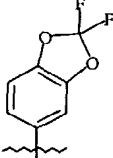
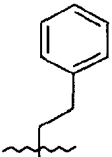
Cmpd	R ₂	MW	MS	t _R	HPLC Method
1-8		413.45	413	1.236	4
1-9		439.47	439	5.625	2
1-10		457.49	457	7.09	2
1-11		443.48	443	1.226	4
1-12		459.94	459	1.188	4
1-13		473.56	473	1.446	4
1-14		443.48	443	1.120	4
1-15		414.44	414	1.242	4
1-16		409.49	409	1.088	4
1-17		431.44	431	1.071	4
1-18		473.56	473	1.514	4

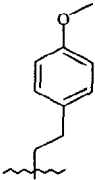
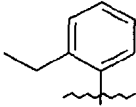
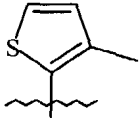
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1-19		463.46	463	1.030	4
1-20		431.44	431	1.165	4
1-21		502.60	502	1.469	4
1-22		412.45	412	1.506	4
1-23		438.49	438	6.463	2
1-24		426.48	426	4.405	2
1-25		395.46	396	8.240	2
1-26		425.49	425.9	8.260	2
1-27		455.52	456	7.550	2
1-28		401.49	401.9	8.490	2

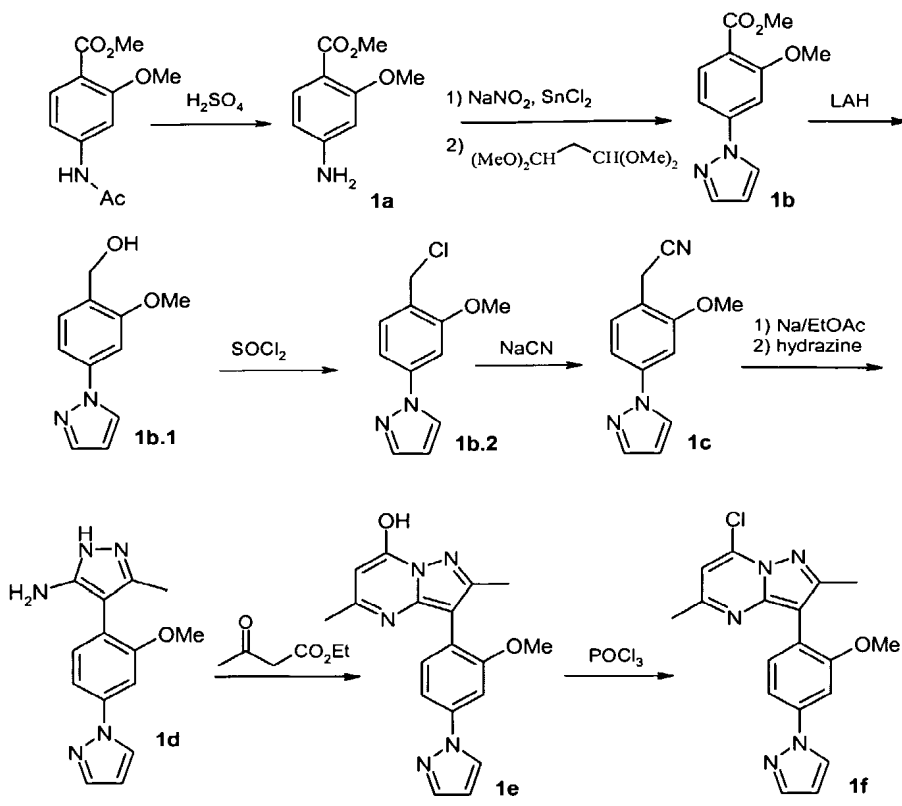
Cmpd	R ₂	MW	MS	t _R	HPLC Method
1-29		401.49	401.9	8.530	2
1-30		385.42	385.9	8.410	2
1-31		399.45	335.9	4.700	2
1-32		385.42	385.9	8.300	2
1-33		437.50	437	7.861	2
1-34		429.912	429	8.229	2
1-35		439.512	439	8.320	2
1-36		455.52	455	7.718	2
1-37		438.49	438	6.153	2
1-38		443.48	443	1.218	4
1-39		437.50	437	7.807	2

Cmpd	R ₂	MW	MS	t _R	HPLC Method
1-40		459.94	459	8.956	2
1-41		459.94	459	8.598	2
1-42		488.57	488	7.216	2
1-43		453.50	454	7.601	2
1-44		453.50	454	8.310	2
1-45		453.50	454	8.380	2
1-46		466.54	467	6.690	2
1-47		439.47	440	7.010	2
1-48		485.54	486	8.000	2
1-49		397.44	398	6.270	2

Cmpd	R ₂	MW	MS	t _R	HPLC Method
1-50		439.52	439	8.288	2
1-51		414.44	414	5.640	2
1-52		426.48	426	5.910	2
1-53		396.45	396	4.920	2
1-54		426.48	426	6.630	2
1-55		467.53	468	6.970	2
1-56		439.47	440	6.710	2
1-57		431.44	432	8.660	2
1-58 ¹		384.44	385	5.390	2
1-59		452.56	453	4.590	2

Cmpd	R ₂	MW	MS	t _R	HPLC Method
1-60		455.52	455	6.170	2
1-61		420.47	420	1.410	4
1-62		485.54	486	7.540	2
1-63		456.50	456	8.120	2
1-64		453.50	454.3	5.710	2
1-65		415.52	415	6.770	2
1-66		399.46	399	6.430	2
1-67		479.46	479	6.740	2
1-68		479.46	479	7.260	2
1-69		475.45	475	6.970	2
1-70		423.52	423	6.370	2

Cmpd	R ₂	MW	MS	t _R	HPLC Method
1-71		453.54	453	6.280	2
1-72		423.52	423	8.420	2
1-73		415.52	415	8.080	2

EXAMPLE 1A**ALTERNATE SYNTHESIS OF INTERMEDIATE 1F****Step 1A-A:**

- 5 To a 3-neck flask equipped with a mechanical stirrer was charged 250 g (1.12 mol) of 2-methoxy-4-acetylaminobenzoic acid methyl ester followed by 1L of methanol. Agitation was started and 94 mL (3.36 mmol, 3 eq.) of concentrated sulfuric acid was slowly added creating a slight reflux. The mixture was stirred for 24 hr. The mixture was concentrated *in vacuo* affording
- 10 a thick slurry. The slurry was filtered using a Buchner funnel and washed with 300 mL of cold methanol. The filter cake was collected and dried in *vacuo* at 45 °C for 24 hr affording 302 g of **1a** as a hemi-sulfate salt in a 96% yield.

Step 1A-B:

- 15 In a 2L three-neck Morton flask equipped with a mechanical stirrer and thermocouple was charged 200 g (716 mmol) of methyl 4-amino-2-methoxybenzoate

- 1a.** The solid was slurried with 700 mL of 6N hydrochloric acid and chilled in an ice-bath. To the mixture was charged dropwise 54.3 g (788 mmol, 1.1 eq.) of sodium nitrite in 100 mL of water maintaining a temperature of <15 °C during the addition. The mixture was stirred an additional 1.5 hr affording a light yellow, homogeneous solution.
- 5 To the mixture was carefully added 272 g (1432 mmol, 2 eq.) of anhydrous stannous chloride. The temperature during the addition was kept <10 °C. The mixture was stirred at 0 °C for 1 hr, and then stored at 5 °C for 16 hr. The precipitate was collected by filtration through a Buchner funnel and the filter cake air dried for 2 hr. The filter cake was transferred to a 2 L round bottom flask equipped with a magnetic stir bar and
- 10 diluted with 600 mL of ethanol. To the slurry was charged 142 mL (859 mmol, 1.2 eq.) of malonaldehyde bis(dimethyl acetal) and the mixture refluxed for 6 hr. After evaporation of ethanol, the residue was diluted with ethyl acetate and neutralized with sodium hydroxide. The organic phase was separated, dried and concentrated in vacuo. The crude product was passed through a silica gel plug eluting with 25% ethyl
- 15 acetate in hexane affording 96 g of Cmpd **1b** in a 58% yield as a mixture of the methyl and ethyl esters.

Step 1A-C:

- To a 1L round bottom flask containing 500 mL dry THF was added LAH (14.5 g, 380 mmol, 0.95 eq), and the mixture was cooled to 0 °C. To this mixture was
- 20 added dropwise a solution of **1b** (96 g, 400 mmol, 1.0 eq) in 300 mL THF. The temperature was maintained below 15 °C during the addition. After the addition was complete, the mixture was stirred for 1 hr, then the reaction mix was carefully quenched with water (14.5 mL), 10% aq. sodium hydroxide (14.5 mL), and water (43.5 mL). The resulting mixture was filtered through a pad of Celite® and concentrated to
- 25 provide **1b.1** as a slightly yellow oil (63.9 g, 75.7%), which was used without further purification.

Step 1A-D:

- Thionyl chloride (95 mL, 1.30 mol, 3.1 eq) was added dropwise over 1 hr to a solution of **1b.1** (85.0 g, 0.42 mol) in 400 mL DCM, keeping the rate of addition
- 30 such that a gentle reflux was maintained. A precipitate formed, which re-dissolved upon completion of the addition. The resulting dark solution was refluxed for 4 hr. The cooled reaction mixture was poured onto 500 g of ice, and the resulting mixture was extracted with 2 x 700 mL of DCM. The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and

concentrated to provide **1b.2** (76.5 g) as a brown solid, which was used without further purification.

Step 1A-E:

A solution of **1b.2** (76 g, 340 mmol, 1.0 eq.) in DMF (100 mL) was added
5 dropwise over 20 min. to a mixture of sodium cyanide (24.5 g, 500 mmol, 1.5 eq) and
DMF (300 mL) heated to 100 °C. The mixture was heated at 100 °C for 4 hr, then the
cooled mixture was filtered through Celite®. The filtrate was concentrated, then the
residue was taken up in 300 mL DCM and washed with saturated aqueous sodium
bicarbonate solution (200 mL). The organic layer was dried over sodium sulfate,
10 filtered, and concentrated to provide a dark brown solid residue. This residue was
slurried in ethanol (100 mL), then the solid was collected by filtration and washed with
cold ethanol and ether, providing **1c** (48.0 g) as an off-white solid. The mother liquid
was concentrated and purified by silica gel chromatography, eluting with 1:1
hexane/ethyl acetate, to provide an additional 15.4 g of **1c** as a white solid. Combined
15 yield 63.4 g.

Step 1A-F:

To a solution of **1c** (63.4 g, 0.30 mol, 1 eq) in ethyl acetate (800 mL)
was added metallic sodium (10.3 g, 0.45 mmol, 1.5 eq) portionwise, and the mixture
was refluxed for 16 hr. The cooled suspension was poured onto 500 g ice, acidified to
20 pH 5, then extracted with 2 x 300 mL ethyl acetate. The organic phase was dried over
sodium sulfate, filtered, and concentrated to a crude yellow oil (86.5 g).

The crude yellow oil (86.5 g) was dissolved in ethanol (480 mL) and
water (80 mL), then hydrazine monohydrobromide (100 g, 0.88 mol, 3 eq) was added
and the mixture was heated at 85 °C for 16 hr. The solvents were evaporated, brine
25 (200 mL) was added, and the mixture was extracted with 2 x 300 mL ethyl acetate.
The combined organic layers were dried over sodium sulfate, filtered, and concentrated
to provide **1d** (68 g) as a crude brown foam, which was used without further
purification.

Step 1A-G:

30 A mixture of **1d** (68 g, 250 mmol, 1.0 eq), ethyl acetoacetate (100 mL),
acetic acid (150 mL), and ethanol (150 mL) was refluxed for 24 hr. The cooled mixture
was concentrated to provide a solid residue, which was then deposited onto a fritted
glass filter and washed with ether, providing **1e** (52.0 g, 51.2%) as an off-white solid.

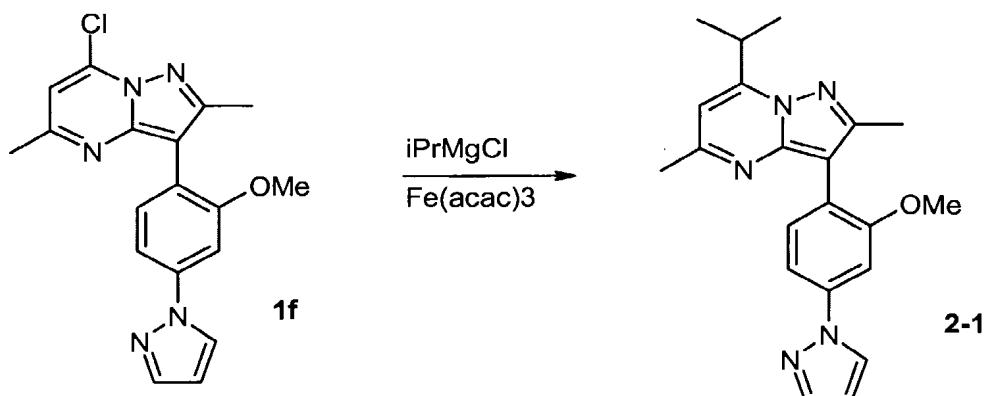
The mother liquor was concentrated, then chromatographed on silica gel using 10% methanol in DCM as eluent. The solid product thus obtained was washed with ether to provide an additional 17.0 g of **1e** as an off-white solid (combined yield 69 g).

Step 1A-H:

- 5 To a suspension of **1e** (41.2 g, 123 mmol) in acetonitrile (200 mL) was added POCl₃ (45.0 mL, 493 mmol,) and this mixture was refluxed for 16 hr. The cooled reaction mixture was poured onto ice-water, and the resulting mixture was extracted with chloroform. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography,
10 eluting with 3:1 hexanes/ethyl acetate, to yield **1f** (29.0 g) as a tan solid.

EXAMPLE 2

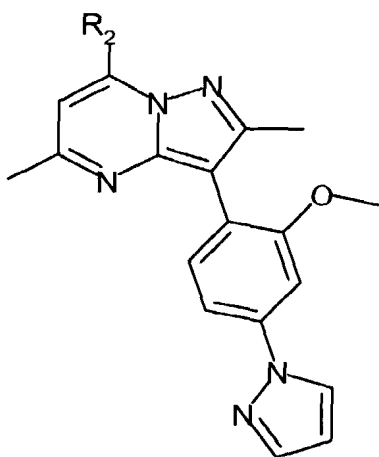
7-ISOPROPYL-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE



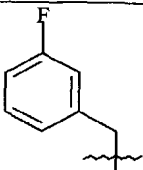
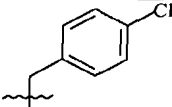
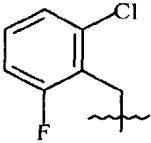
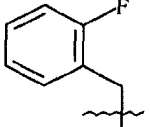
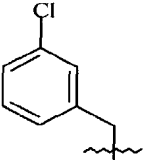
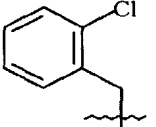
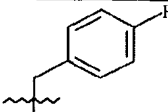
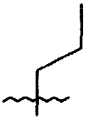
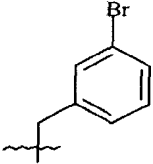
15 Step 2A:

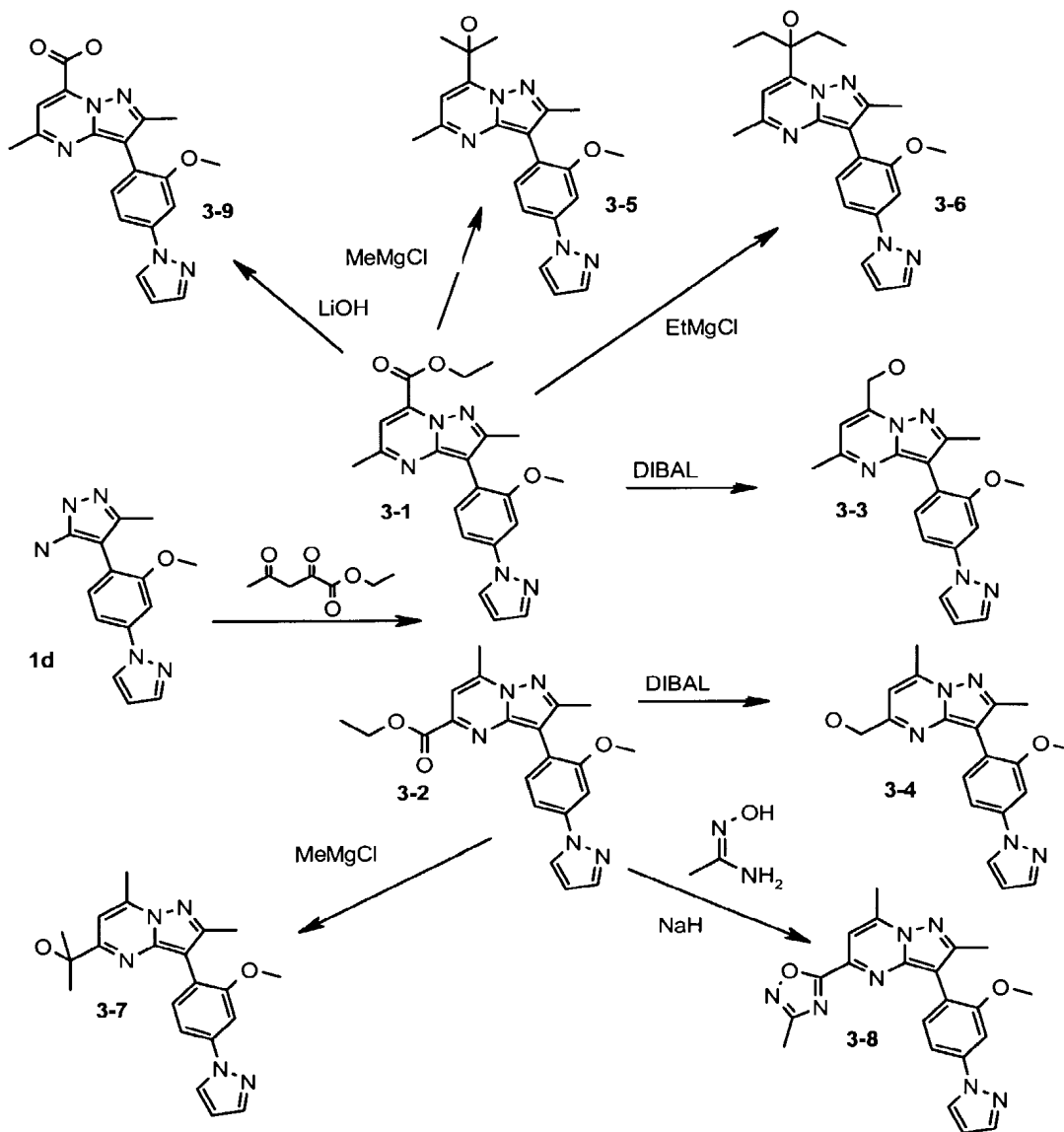
- To a solution of Cmpd **1f** (1.41 g, 4.0 mmol) and Fe(acac)₃ (424 mg, 1.2 mmol) in THF/NMP (v/v = 8:1) was added iPrMgCl (2.0 M in THF, 4.0 mL) slowly at room temperature. The reaction mixture was stirred for 1.5 hr before quenched with 1N HCl (aq.). After extraction with EtOAc, the crude product was purified by column
20 chromatography (25% EtOAc/Hexane) to yield Cmpd **2-1** (628 mg.)

Depending on the alkyl functionality in the alkyl magnesium halide, the compounds listed in the following table were synthesized:



Cmpd	R ₂	MW	MS	t _R	HPLC Method
2-1		361.447	361	1.286	4
2-2		375.474	375	1.499	4
2-3		333.393	333	1.542	4
2-4		375.474	375	1.278	4
2-5		389.5	390.2	8.490	2
2-6		347.42	348	6.514	2
2-7		415.417	415	7.880	2
2-8		409.491	409	6.280	2

Cmpd	R ₂	MW	MS	t _R	HPLC Method
2-9		427.481	428	8.240	2
2-10		443.936	444	8.790	2
2-11		461.926	462	8.740	2
2-12		427.481	428	8.240	2
2-13		443.936	444	8.750	2
2-14		443.936	444	8.660	2
2-15		427.481	428	8.240	2
2-16		361.447	361	2.700	1
2-17		488.387	488	8.920	2

EXAMPLE 3**3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE-7-CARBOXYLIC ACID ETHYL ESTER****5 Step 3A:**

To 20 mL EtOH were added Cmpd **1d** (1.0 g, Example 1, Step 1C) and ethyl-2,4-dioxovalerate (0.82 g) followed by 0.5 mL acetic acid. The reaction mixture was heated at 80 °C for 12 hr. Concentration and purification by silica gel column

chromatography yielded Cmpd **3-1** (0.66 g, 46.1% yield) and the inverted addition Cmpd **3-2** (0.47 g, 32.2% yield.)

Step 3B:

To Cmpd **3-1** (30 mg) dissolved in THF (1.5 mL) was added DIBAL (150
5 uL of 2 M DIBAL in hexane.) The reaction mixture was stirred at room temperature for 2 hr and quenched with water (0.4 mL.) After purification via LC-MS, Cmpd **3-3** (3.3 mg) obtained. Following the same procedure, the reduction of Cmpd **3-2** afforded Cmpd **3-4** (2.6 mg) after purification.

Step 3C:

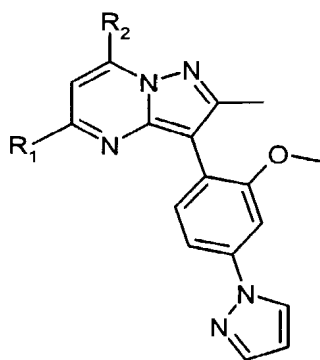
10 To 1.5 mL THF was added Cmpd **3-1** (30 mg) followed by CH₃MgBr (150 uL of 2 M CH₃MgBr in THF.) The reaction mixture was stirred at room temperature for 2 hr and quenched with water. The resulting material was purified by LC-MS to yield Cmpd **3-5** (3.8 mg.) Following this procedure with Cmpd **3-1** and CH₃CH₂MgBr yielded Cmpd **3-6** (4.1 mg.) after purification. Following the same
15 reaction procedure employing Cmpd **3-2** as the starting reagent and CH₃MgBr as nucleophile afforded Cmpd **3-7** (4.0 mg) after purification.

Step 3D:

To THF (1.5 mL) was added acetamidoxime (20 mg) and NaH (10 mg) with stirring at room temperature for 30 min. Cmpd **3-2** (40 mg) was added, and the
20 mixture was heated at 90 °C for 2 hr in a sealed tube. After purification via LC-MS, Cmpd **3-8** obtained (5.5 mg.)

Step 3E:

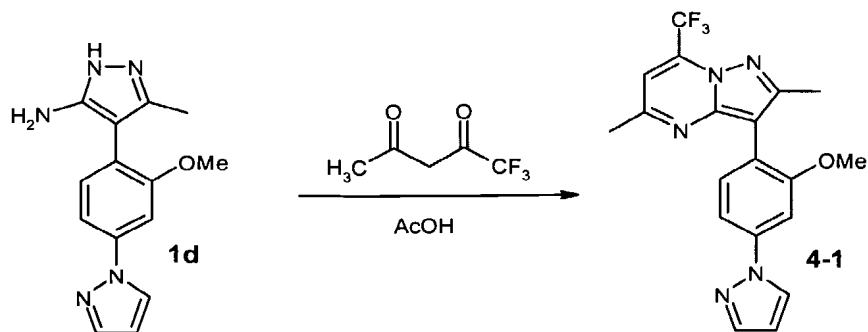
To Cmpd **3-1** (200 mg) in dioxane:water (9:1) was added LiOH (30 mg.) The reaction proceeded with stirring for 6 hr at room temperature followed by
25 quenching to pH 4 (HCl, 4 N) and extraction between H₂O (20 mL) and EtOAc (20 mL.) The organic phase was dried over Na₂SO₄ and concentrated. The resulting concentrate was purified by silica gel column chromatography (50:50 EtOAc/hexane) to yield Cmpd **3-9** (180 mg.) Compounds presented in Example 3 are tabulated in the following table:



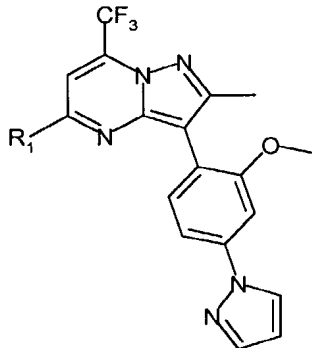
Cmpd	R ₁	R ₂	MW	MS	t _R	HPLC Method
3-1			391.429	392	2.681	1
3-2			391.429	392	6.850	2
3-3			349.392	350	5.060	2
3-4			349.392	350	5.030	2
3-5			377.446	378	6.880	2
3-6			405.499	406	7.980	2
3-7			377.446	378	1.264	4
3-8			401.428	402	6.990	2
3-9			363.375	364	5.740	2

EXAMPLE 4

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-TRIFLUOROMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE

**5 Step 4A:**

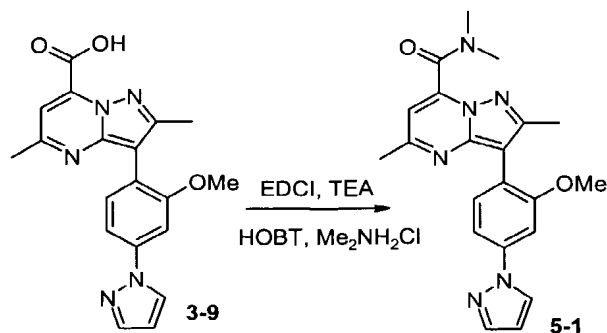
A mixture of Cmpd **1d** (40 mg, Example 1, Step 1C) and 1,1,1-trifluoropentane-2,4-dione (excess) was heated in AcOH at 150 °C for 15 min with microwave to afford after purification via LC-MS Cmpd **4-1** (29 mg.) Depending on the trifluorodione, the compounds in the following table were synthesized:



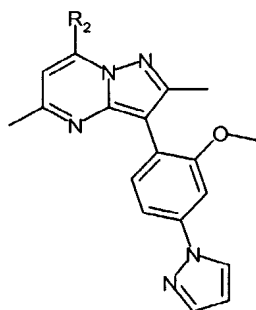
10

Cmpd	R ₁	MW	MS	t _R [*]
4-1		387.363	387	6.215
4-2		415.417	415	6.928

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 5**3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE-7-CARBOXYLIC ACID DIMETHYLAMIDE****5 Step 5A:**

To a solution of Cmpd **3-9** (50 mg, 0.14 mmol, 1 eq) in DCM (1 mL) was added HOBT (57 mg, 0.42 mmol, 3 eq), TEA (0.12 mL, 0.84 mmol, 6 eq), dimethylamine hydrochloride (34 mg, 0.42 mmol, 3 eq) and EDCI (79 mg, 0.42 mmol, 3 eq). The mixture was stirred at room temperature for 16 hr, then the solvent was evaporated, and the crude reaction mixture was purified by preparative HPLC/MS, providing Cmpd **5-1** (10 mg) as a TFA salt. Depending on the amine employed in the amidation step above, the compounds in the following table were synthesized:

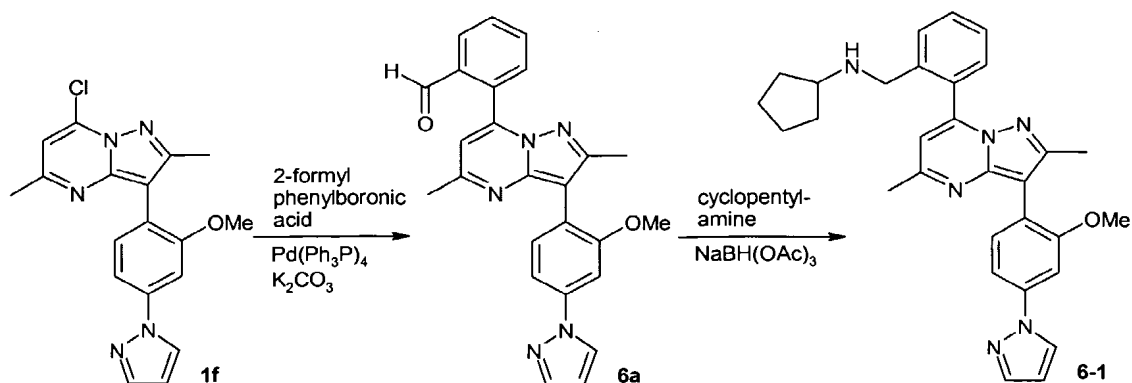


Cmpd	R ₂	MW	MS	t _R [*]
5-1	-C(O)N(CH ₃) ₂	390.44		5.17
5-2	-C(O)N(CH ₂ CH ₃) ₂	418.50	419.2	6.22
5-3	-C(O)N(CH ₃)CH ₂ CH ₃	404.47	405.2	5.66

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 6

CYCLOPENTYL-{2-[3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDIN-7-YL]-BENZYL}-AMINE

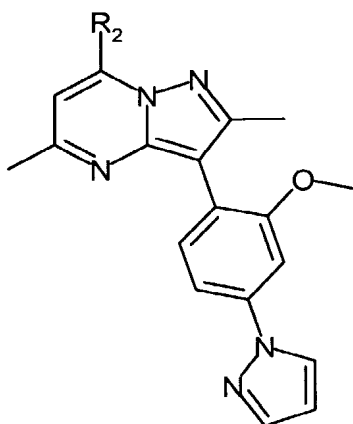
**5 Step 6A:**

To a solution of **1f** (500 mg, 1.4 mmol, 1 eq) in 1:1 dioxane/water (6 mL) was added 2-formylphenylboronic acid (255 mg, 1.7 mmol, 1.2 eq), followed by potassium carbonate (390 mg, 2.8 mmol, 2.0 eq) and tetrakis(triphenylphosphine)palladium(0) (82 mg, 0.07 mmol, 0.05 eq). The mixture was heated in a sealed tube at 100 °C for 3 hr, then the solvent was removed under vacuum. The residue was taken up in ethyl acetate and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, concentrated, and the residue was purified by silica gel column chromatography using 1:1 hexanes/ethyl acetate as eluent, to afford **6a** (500 mg, 85%) as a yellow solid.

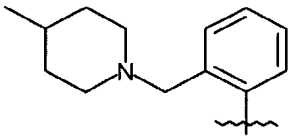
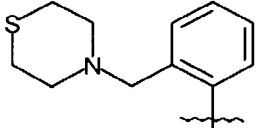
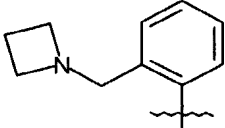
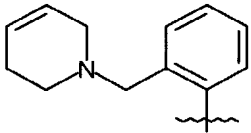
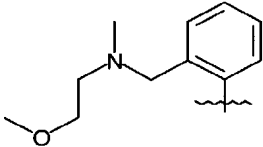
15 Step 6B:

Sodium triacetoxyborohydride (80 mg, 0.38 mmol, 2 eq) was added at RT to a solution of **6a** (80 mg, 0.19 mmol, 1 eq) and acetic acid (0.011 mL, 0.19 mmol, 1 eq) in dichloroethane (1 mL). The mixture was stirred at RT for 16 hr, then the mixture was concentrated, taken up in methanol, and purified directly by preparative HPLC/MS, providing **6-1** (36 mg, 38 % yield) as a TFA salt.

Depending on the amine employed in the reductive amination step above, the compounds of the following table were synthesized:



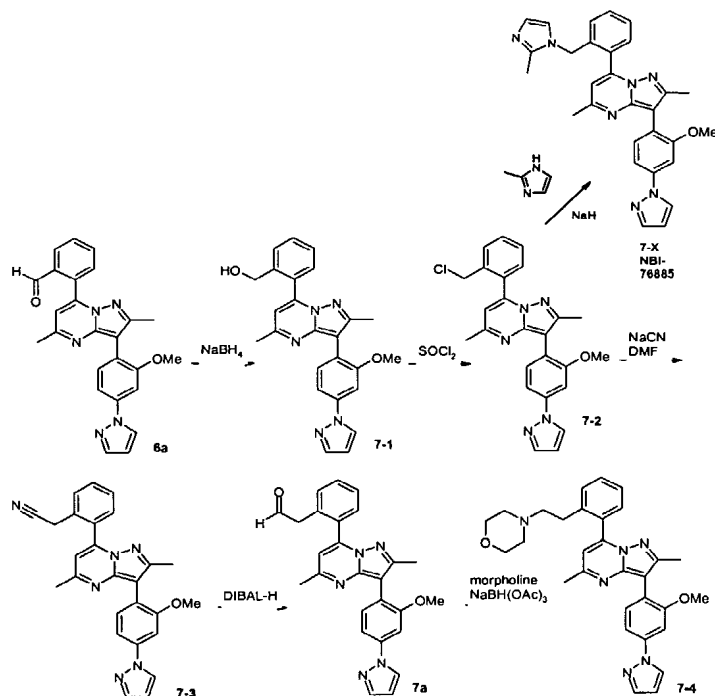
Cmpd	R ₂	MW	MS	t _R
6-1		492.62	493.4	5.69
6-2		506.65	507.4	5.95
6-3		478.60	479.1	5.49
6-4		466.59	467.1	5.33
6-5		452.559	452	4.40
6-6		478.597	478	4.70
6-7		492.624	492	4.85
6-8		506.651	506	4.74

Cmpd	R ₂	MW	MS	t _R *
6-9		506.651	506	4.82
6-10		510.663	510	4.60
6-11		464.57	464	4.38
6-12		490.608	490	4.60
6-13		496.612	496	4.57

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 7

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-[2-(2-MORPHOLIN-4-YL-ETHYL)-PHENYL]-PYRAZOLO[1,5-A]PYRIMIDINE

**5 Step 7A:**

To a suspension of **6a** (345 mg, 0.82 mmol) in 1:1 THF/methanol (4 mL) at RT was added carefully sodium borohydride (62 mg, 1.6 mmol, 2 eq). The mixture was stirred for 30 min, then water was added and the mixture was extracted with DCM. The combined organic layers were washed with water and brine, then dried over sodium sulfate, filtered, and concentrated to provide **7-1** (450 mg, 90 %) as a solid, which was used without further purification.

10

Step 7B:

Thionyl chloride (0.17 mL, 2.3 mmol, 2.2 eq) was added to a solution of **7-1** (450 mg, 1.05 mmol, 1 eq) in DCM (5 mL) at RT. The mixture was stirred at RT for 30 min, then water was added and the mixture was extracted with DCM. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated to provide **7-2** (420 mg, 90 %) as a yellow solid.

15

Step 7-C

Sodium hydride (11 mg of 60 % dispersion in mineral oil, 0.28 mmol, 4 eq) was added to a solution of 2-Methylimidazole (17 mg, 0.21 mmol, 3 eq) in 2 ml DMF at rt. The mixture was stirred for 10 min, then a solution of 7-2 (30 mg, 0.07 mmol, 1 eq) in 0.2 ml DMF was added and the mixture was stirred at rt for 17 h. The mixture was diluted with methanol, then purified directly by preparative HPLC/MS, providing 7-X (6 mg) as a TFA salt.

Step 7D:

Sodium cyanide (3.3 mg, 0.067 mmol, 3 eq) was added to a solution of 7-2 (10 mg, 0.023 mmol, 1 eq) in DMSO (3 mL) at RT. The mixture was stirred at RT for 2 hr, then water was added and the mixture was extracted with DCM. The combined organic layers were washed with water and brine, then dried over sodium sulfate, filtered, and concentrated to provide crude 7-3 (8 mg, 80 % yield) as a solid.

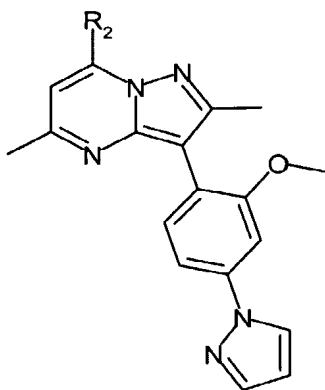
Step 7E:

DIBAL-H (0.23 mL of a 1.5 M solution in toluene, 0.35 mmol, 3 eq) was added to a solution of 7-3 (50 mg, 0.11 mmol) in DCM (1 mL) at -78 °C. The mixture was stirred at -78 °C for 20 min, then was allowed to warm to RT. Water was added and the mixture was stirred for 10 min, then the aqueous layer was extracted with two additional portions of DCM. The combined organic extracts were washed with water and brine, were dried over sodium sulfate, filtered through Celite®, and concentrated. The residue was purified by prep HPLC/MS to provide 7a (15 mg) as a TFA salt.

Step 7F:

Sodium triacetoxyborohydride (15 mg, 0.069 mmol, 2 eq) was added to a room temperature solution of 7a (15 mg, 0.034 mmol, 1 eq) and acetic acid (0.002 mL, 0.034 mmol, 1 eq) in DCM (1 mL). The mixture was stirred at RT for 16 hr, then the mixture was concentrated, taken up in methanol, and purified directly by preparative HPLC/MS, providing 7-4 (11 mg, 50% yield) as a TFA salt.

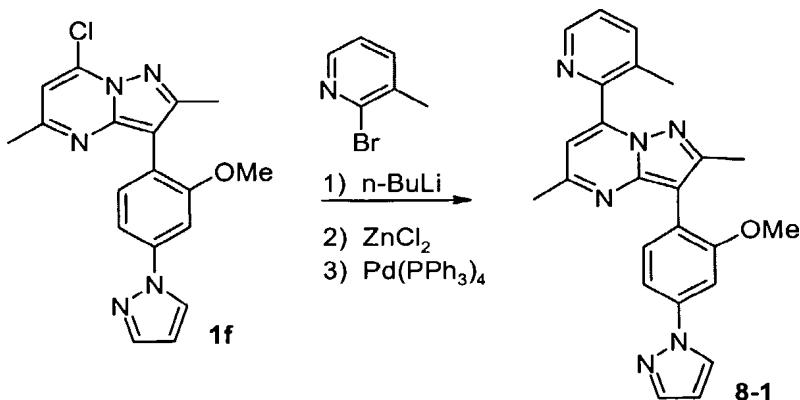
The following table summarizes the compounds of Example 7. By varying the amine employed in the reductive amination step above, Cmpds 7-5 and 7-6, included in the table, were synthesized by the methods of Step 7E:



Cmpd	R ₂	MW	MS	t _R	HPLC Method
7-1		425.49	425	5.41	2
7-2		443.94	444.1	1.15	4
7-3		434.50	435.4	7.05	2
7-4		506.82	509.2	5.13	2
7-5		524.69	525.2	5.48	2
7-6		496.612	497.2	5.18	2
7-7		489.58	490.2	4.94	

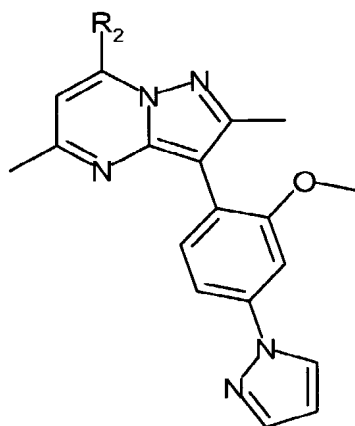
EXAMPLE 8

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-(3-METHYL-PYRIDIN-2-YL)-
PYRAZOLO[1,5-A]PYRIMIDINE

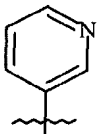
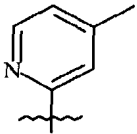
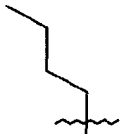
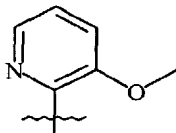
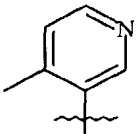
**5 Step 8A:**

To a solution of 2-bromo-3-methylpyridine (4.85 g, 28.2 mmol) in dry THF (8.0 mL) cooled to -70°C was added n-BuLi (1.6 M solution in hexane, 17.6 mL, 28.2 mmol) dropwise. The reaction mix was stirred at -70°C for 30 min, then ZnCl_2 (0.5 M solution in THF, 66.0 mL, 34 mmol) was added over 5 min. The mixture was
 10 allowed to warm to 0°C over 1 hr, then Cmpd 1f (1.66 g, 4.70 mmol) and tetrakis(triphenylphosphine)palladium(0) (326 mg, 0.28 mmol) were added. The mixture was then heated to reflux for 4 hr. The cooled reaction mixture was quenched with water, the THF was evaporated and the resulting aqueous mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered,
 15 concentrated, and the residue was chromatographed on silica gel using 1:3 hexanes/ethyl acetate to give 8-1 free base (1.6 g, 83 %) as a yellow solid. To a solution of 8-1 (1.6 g, 3.9 mmol) in 7:1 ethyl acetate/chloroform (100 mL) was added hydrogen chloride (4.0 mL of a 2.0 M solution in ether, 8.0 mmol) at 0°C . The suspension was diluted with ether, then the solid was collected on a fritted glass filter
 20 and rinsed with ether to obtain 8-1 HCl salt (1.7 g, 98 %) after drying under high vacuum.

Depending on the halide employed in Step 8A above, the compounds of the following table were synthesized:



Cmpd	R ₂	MW	MS	t _R
8-1		410.48	411	5.400
8-2		410.48	411	5.770
8-3		426.48	427	5.690
8-4		440.51	441	6.240
8-5		399.456	399	4.130
8-6		426.478	426	6.410
8-7		396.452	396	5.720

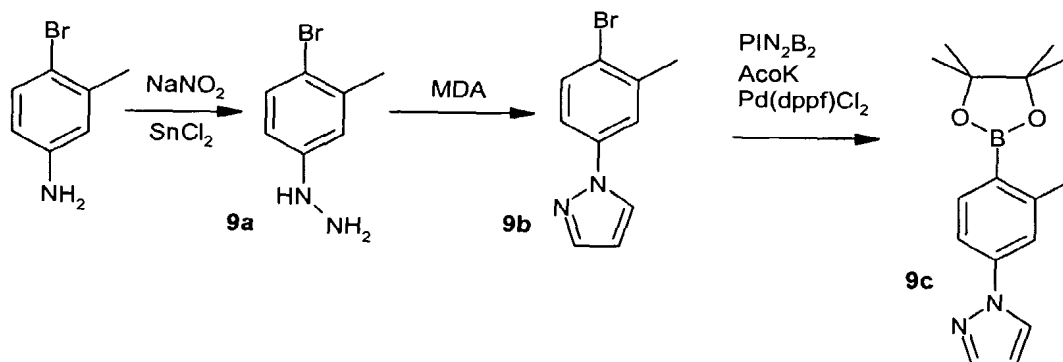
Cmpd	R ₂	MW	MS	t _R [*]
8-8		396.452	396	4.940
8-9		410.479	410	5.640
8-10		375.474	375	6.260
8-11		426.478	426	5.850
8-12		410.479	410	4.700

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 9

SYNTHESIS OF REAGENT 2-METHYL-4-(PYRAZOL-1-YL)PHENYLBORONIC ACID PINACOL
ESTER

5



Step 9A:

4-Bromo-3-methylaniline (10.2 g) was suspended in 6N HCl (85 mL) and cooled to 0 °C. A solution of sodium nitrite (4 g in 40 mL H₂O) was added over 10 min. The reaction was stirred for 15 min at 0 °C followed by the addition of stannous chloride dihydrate (36 g in 25 mL 12N HCl.) The reaction was stirred for 2 hr at 0 °C. The reaction was filtered and the filter cake washed with cold H₂O to afford 4-bromo-3-methylphenylhydrazine hydrochloride (Cmpd **9a**, 20 g) as a tan solid.

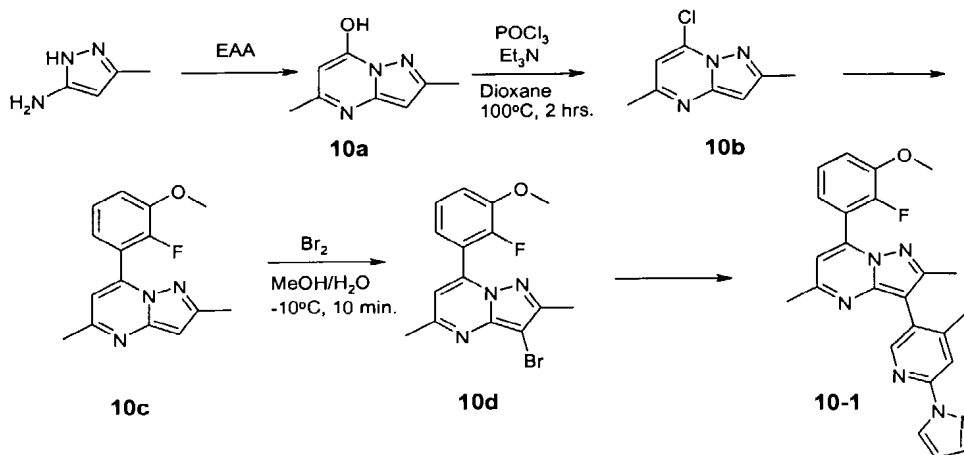
Step 9B:

The compound resulting from Step 9A (20 g) was suspended in 50 mL ethanol. Malondialdehyde bis-dimethylacetal (11.0 mL, 67 mmol) was added and the reaction was heated to 85 °C for 2 hr. The reaction mixture was neutralized with sodium bicarbonate and extracted by washing with DCM. The combined organic layers were dried over magnesium sulfate and concentrated. The residue was taken up in ethyl acetate and the mixture filtered through a pad of Celite®. The filtrate was evaporated, and the oily residue was purified by column chromatography (1:1 ethyl acetate: hexanes) to afford 1-(4-bromo-3-methylphenyl)pyrazole (Cmpd **9b**, 9.6 g, 73%) as an amber oil.

Step 9C:

To a solution of Cmpd **9b** (2.0 g in 15 mL dioxane) was added bis(pinacolato)diboron (2.4 g), potassium acetate (2.4 g) and 1,1'-bis(diphenylphosphino) ferrocene dichloropalladium (II) (500 mg.) The reaction was heated to 85 °C for 12 hr. The reaction mixture was filtered through a pad of Celite® and the filter cake washed with ethyl acetate. The filtrate was concentrated to a brown liquid which was purified by column chromatography (20% ethyl acetate:hexanes) to afford 2-methyl-4-(pyrazol-1-yl)phenylboronic acid pinacol ester (Cmpd **9c**, 1.8 g, 75%) as a yellow oil; LC/MS: [M+H] = 285.0.

Also prepared by the methods above were 2-chloro-4-(pyrazol-1-yl)phenylboronic acid pinacol ester (**9d**) and 2-methyl-3-(pyrazol-1-yl)phenylboronic acid pinacol ester (**9e**).

EXAMPLE 10**7-(2-FLUORO-3-METHOXY-PHENYL)-2,5-DIMETHYL-3-(4-METHYL-6-PYRAZOL-1-YL-PYRIDIN-3-YL)-PYRAZOLO[1,5-A]PYRIMIDINE****5 Step 10A:**

A solution of 3-amino-5-methylpyrazole (20.0 g, 206 mmol), ethyl acetoacetate (32.0 g, 247 mmol), acetic acid (6 mL), and dioxane (150 mL) was refluxed for 16 hr. A white solid precipitated, which was collected by filtration. The filter cake was washed with ether to provide **10a** (29.0 g, 86 %) as a white solid.

10 Step 10B:

To a suspension of compound **10a** (5.0 g, 31 mmol) in 1,4-dioxane (30 mL) was added triethylamine (8.50 mL, 62 mmol) and phosphorous oxychloride (7.4 mL, 77 mmol). The reaction was heated under nitrogen at 100°C for 2 hr. The reaction mixture was cooled in an ice bath, then treated successively with water and aqueous sodium bicarbonate solution (final pH 8). Dichloromethane was added and the mixture was washed 3x with water. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to a dark brown oil. The crude product was purified by silica gel chromatography using 30% ethyl acetate in hexanes as eluent, providing **10b** (3.8 g, 70%) as a white solid.

20 Step 10C:

To a mixture of 80 mL dioxane and 8 mL water were added compound **10b** (3.3 g, 18 mmol, 1 eq), 2-fluoro-3-methoxyphenylboronic acid (4.3 g, 26 mmol, 1.4 eq), potassium carbonate (5.0 g, 36 mmol, 2 eq), and

tetrakis(triphenylphosphine)palladium(0) (1.5 g, 1.3 mmol, 0.07 eq). The mixture was stirred and heated at 100 °C for 16 hr, then was allowed to cool and water (75 mL) was added. The mixture was extracted with ethyl acetate, then the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 4:1 hexane/ethyl acetate to provide Cmpd **10c** (3.78 g, 76 %) as white solid.

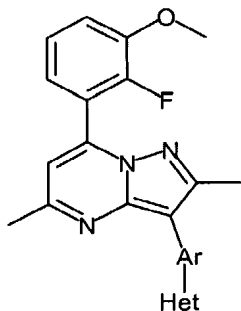
Step 10D:

Bromine (1.77 g, 11 mmol) was added to a solution of **10c** (3.0 g, 11 mmol) in methanol (30 mL) at -10 °C. After 10 min, the mixture was filtered to collect the precipitate that had formed. The filter cake was washed with cold methanol, and was then dried under vacuum to yield **10d** (3.15 g, 83 %) as a yellow solid.

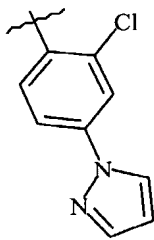
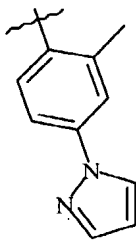
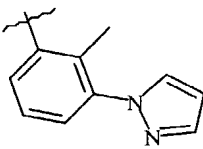
Step 10E:

Suzuki reaction of Cmpd **10d** (460 mg, 1.3 mmol) according to the procedure of Step 10C above, using Cmpd **12-1** in place of 2-fluoro-3-methoxyphenylboronic acid, yielded Cmpd **10-1** (15 mg, solid) following purification by prep HPLC/MS and silica gel chromatography (4:1 hexane/ethyl acetate eluent).

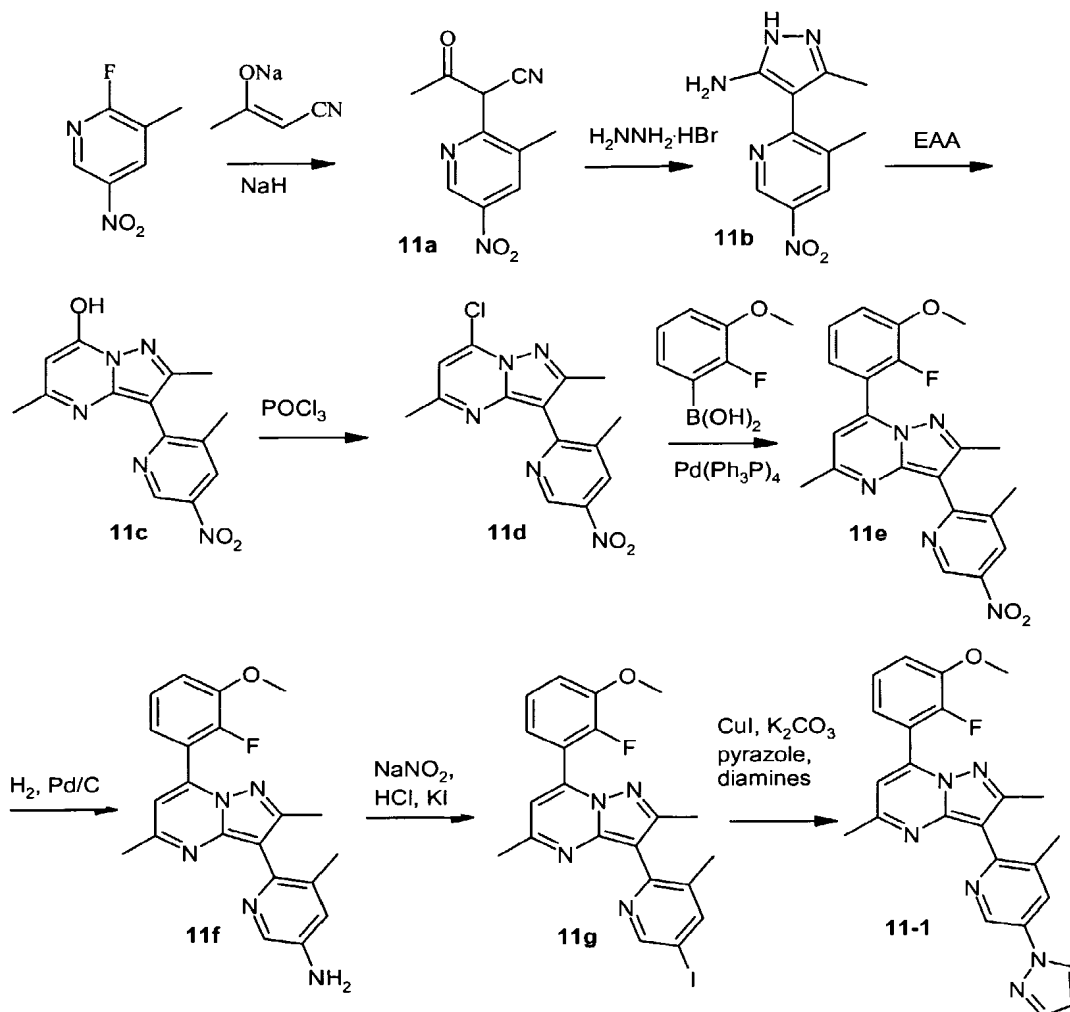
Depending on the boronate ester or acid employed in the final Suzuki reaction, the compounds listed in the following table were synthesized and purified by preparative LC-MS:



Cmpd	AR-HET	MW	MS	t _R
10-1		428.469	429	8.110

10-2	 <chem>Clc1ccc(cc1)n2cc[nH]2</chem>	447.899	447	6.390
10-3	 <chem>Cc1ccc(cc1)n2cc[nH]2</chem>	427.481	427	6.330
10-4	 <chem>Cc1ccccc1n2cc[nH]2</chem>	427.481	427	7.670

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 11**7-(2-FLUORO-3-METHOXY-PHENYL)-2,5-DIMETHYL-3-(3-METHYL-5-PYRAZOL-1-YL-PYRIDIN-2-YL)-PYRAZOLO[1,5-A]PYRIMIDINE****5 Step 11A:**

Sodium hydride (1.54 g of 60 % dispersion in oil, 38.5 mmol, 2 eq) was added to a solution of cyanoacetone sodium salt (2.5 g, 23 mmol, 1.2 eq) in DMF (40 mL) at RT. The mixture was stirred for 15 min, then a solution of 2-fluoro-3-methyl-5-nitropyridine (3.0 g, 19.2 mmol, 1.0 eq) in 10 mL DMF was added dropwise. The reaction mixture was stirred at RT for 6 hr. The reaction was quenched with 5 g ice, followed by 150 mL water and 10 mL acetic acid. The mixture was extracted with ethyl acetate, then the combined organic extracts were dried over sodium sulfate, filtered,

and concentrated. The residue was purified by silica gel chromatography using 30% ethyl acetate in hexanes as eluent, providing **11a** (1.85 g, 44 % yield) as an orange oil.

Step 11B:

5 A mixture of **11a** (1.8 g, 8.2 mmol, 1.0 eq), hydrazine monohydrobromide (1.0 g, 8.8 mmol, 1.1 eq), ethanol (30 mL) and water (3 mL) was heated at reflux for 17 hr. The solvent was evaporated, and the residue was purified directly by silica gel chromatography using 1:1 hexanes/ethyl acetate as eluent, obtaining **11b** (1.8 g, 94 % yield) as a yellow foam.

Step 11C:

10 A mixture of **11b** (1.8 g, 7.7 mmol, 1.0 eq), ethanol (15 mL), acetic acid (15 mL), and ethyl acetoacetate (1.6 g, 12.4 mmol, 1.6 eq) was heated in a sealed tube at 105 °C for 19 hr. The solvent was evaporated, and the residue was deposited on a fritted glass filter, rinsing with ether, to provide **11c** (1.0 g, 43 % yield) as a yellow solid.

Step 11D:

15 A mixture of **11c** (800 mg, 2.7 mmol, 1.0 eq), phosphorous oxychloride (900 mg, 5.9 mmol, 2.2 eq), and acetonitrile (15 mL) was refluxed for 3 hr. The reaction was poured onto ice, then the mixture was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with aqueous sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to provide **11d** (640 mg, 76 %) as a
20 yellow solid.

Step 11E:

A suspension of **11d** (640 mg, 2.0 mmol, 1 eq), 2-fluoro-3-methoxyphenylboronic acid (480 mg, 3.8 mmol, 1.4 eq), potassium carbonate (555 mg, 4.0 mmol, 2.0 eq), tetrakis(triphenylphosphine)palladium(0) (230 mg, 0.2 mmol, 0.1 eq)
25 in 20 mL dioxane and 2 mL water was stirred and heated at 100 °C for 16 hr. Water (50 mL) was added and the mixture was extracted with ethyl acetate (50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was triturated with methanol to obtain **11e** (300 mg, 37 %) as a yellow solid.

Step 11F:

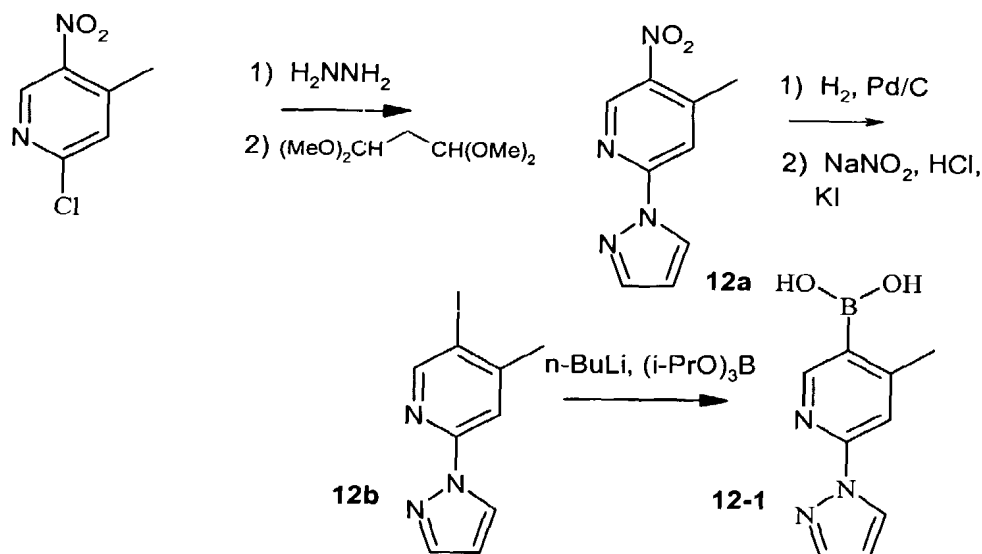
10 % Pd/C (100 mg) was added to a nitrogen-sparged solution of **11e** (300 mg, 0.74 mmol, 1.0 eq) in 20 mL ethanol and 10 mL THF. The mixture was shaken in a Parr shaker under 40 psi hydrogen gas at RT for 6 hr. The mixture was
5 purged with nitrogen and filtered. The filtrate was concentrated to provide **11f** (260 mg, 94% yield) as a yellow oil.

Step 11G:

A solution of sodium nitrite (60 mg, 0.87 mmol, 1.3 eq) in water (10 mL) was added dropwise to an ice-cold solution of **11f** (260 mg, 0.69 mmol, 1.0 eq) in 4N
10 hydrochloric acid (5 mL). The mixture was stirred at 0 °C for 1 hr, followed by addition of 10 mL of half-saturated aqueous potassium iodide. The mixture was stirred at RT for 16 hr, then 50 mL saturated aqueous sodium bicarbonate solution was added and the mixture was extracted 2x 50 mL ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, concentrated and the residue purified by silica gel
15 chromatography using 4:1 hexanes/ethyl acetate as eluent, providing **11g** (170 mg, 51 % yield) as a yellow solid.

Step 11H:

To a solution of **11g** (170 mg, 0.35 mmol, 1.0 eq) in dioxane (6 mL) were added potassium carbonate (200 mg, 1.45 mmol, 4.1 eq), pyrazole (60 mg, 0.89
20 mmol, 2.5 eq), copper(I) iodide (60 mg, 0.32 mmol, 0.9 eq), trans-1,2-diaminocyclohexane (36 mg, 0.32 mmol, 0.9 eq), and N,N'-dimethylethylenediamine (28 mg, 0.32 mmol, 0.9 eq). The mixture was stirred and heated in a sealed tube at 100 °C for 19 hr. The reaction mixture was filtered through a Celite® pad, concentrated, and purified by prep HPLC/MS to obtain Cmpd **11-1** (70 mg, 37 % yield)
25 as a TFA salt; MW: 428.47; LC/MS: 429 [MH]⁺; t_R: 5.390, Anal. Meth. 2.

EXAMPLE 12**4-METHYL-2-PYRAZOL-1-YL-5-PYRIDYLBORONIC ACID****Step 12A:**

5 2-Chloro-4-methyl-5-nitropyridine (5.0 g, 29 mmol, 1.0 eq) was dissolved in 50 mL hydrazine solution (1M solution in THF) and the mixture was stirred and heated in a sealed tube at 80 °C for 22 hr. The cooled reaction mixture was filtered, and the solid obtained was washed with ether to provide 5.7 g of a greenish brown solid.

10 A mixture of this solid (5.7 g, 24 mmol, 1.0 eq), malonaldehyde bis(dimethylacetal) (5.9 g, 31 mmol, 1.3 eq), and acetic acid (50 mL) was stirred and heated in a sealed tube at 80 °C for 5 hr. The solvent was evaporated, then aqueous sodium bicarbonate solution (200 mL) was added and the mixture was extracted with 2 x 200 mL ethyl acetate. The combined organic layers were dried over sodium sulfate,

15 filtered, and concentrated. The residue was recrystallized from ethanol to obtain **12a** (2.6 g, 53 % yield) as a yellow solid.

Step 12B:

20 A mixture of **12a** (2.6 g, 13 mmol) and 10 % Pd/C (200 mg) in 30 mL of 1:1 THF/methanol was shaken in a Parr apparatus under 40 psi hydrogen at RT for 2 hr. The reaction mixture was filtered through a Celite® pad and the filtrate concentrated to a light green oil. The oil was resuspended in 10 mL of 3N hydrobromic acid, cooled

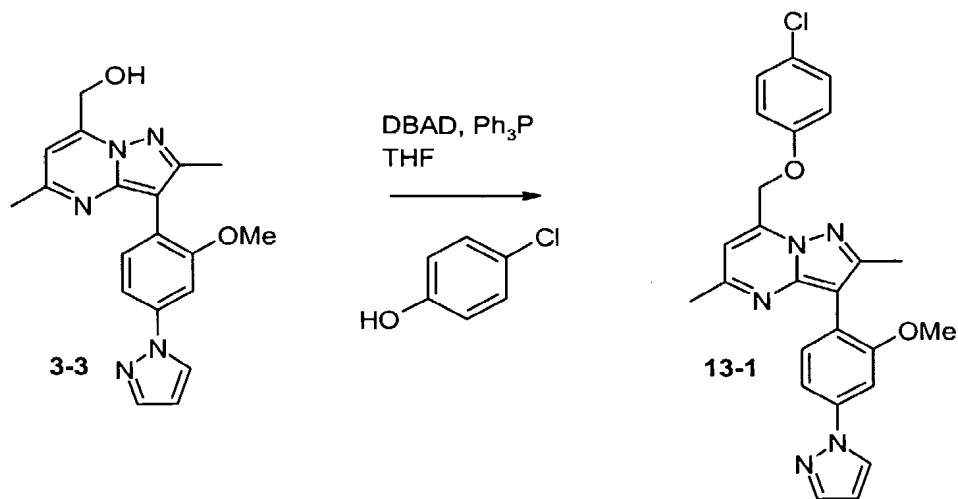
to 0 °C, then treated dropwise with a solution of sodium nitrite (835 mg, 12 mmol, 1.1 eq) in 2 mL water. The mixture was stirred at 0 °C for 1 hr, then 2 mL of half-saturated potassium iodide was added and the mixture was stirred at RT for 22 hr. Saturated aqueous sodium bicarbonate solution was added, then the mixture was extracted with 5 2x 100 mL ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography using 4:1 hexanes/ethyl acetate as eluent, to provide **12b** (1.23 g, 33 %) as a yellow solid.

Step 12C:

10 n-Butyllithium (1.8 mL of a 2.0 M solution in pentane, 3.6 mmol) was added dropwise to a solution of Cmpd **12b** (600 mg, 2.1 mmol) and triisopropylborate (900 mg, 4.8 mmol) in 5 mL THF at -78 °C. The mixture was allowed to warm to RT over 1 hr, then the mixture was cooled to -78 °C and treated with additional triisopropylborate (400 mg, 2.1 mmol), followed by additional n-butyllithium (0.5 mL of a 15 2.0 M solution in pentane, 1.0 mmol). The mixture again was allowed to warm to RT over 1 hr, then 0.8 mL of 1N hydrochloric acid was added and the mixture was stirred for 1 hr. The mixture was filtered, rinsing the solid with methanol and ethyl acetate, then the filtrate was concentrated. The residue was chromatographed on silica gel, eluting with 1:1 hexanes/ethyl acetate to provide Cmpd **12-1** (220 mg, 52 % yield) as a 20 red solid.

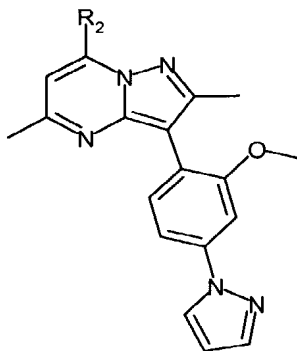
EXAMPLE 13

7-(4-CHLORO-PHENOXYMETHYL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE

**5 Step 13A:**

To a solution of Cmpd **3-3** (25 mg, 0.072 mmol, 1 eq) in THF (1.5 mL) were added di-*tert*-butylazodicarboxylate (30 mg, 0.11 mmol, 1.5 eq), triphenylphosphine (30 mg, 0.11 mmol, 1.5 eq) and 4-chlorophenol (30 mg, 0.023 mmol, 3.3 eq). The mixture was stirred at RT for 17 hr, then the solvent was evaporated and the residue was purified by silica gel chromatography, eluting with hexanes/ethyl acetate to provide Cmpd **13-1** (8 mg) as a solid.

Depending on the phenol employed, the compounds listed in the following table were synthesized and purified by preparative LC-MS:

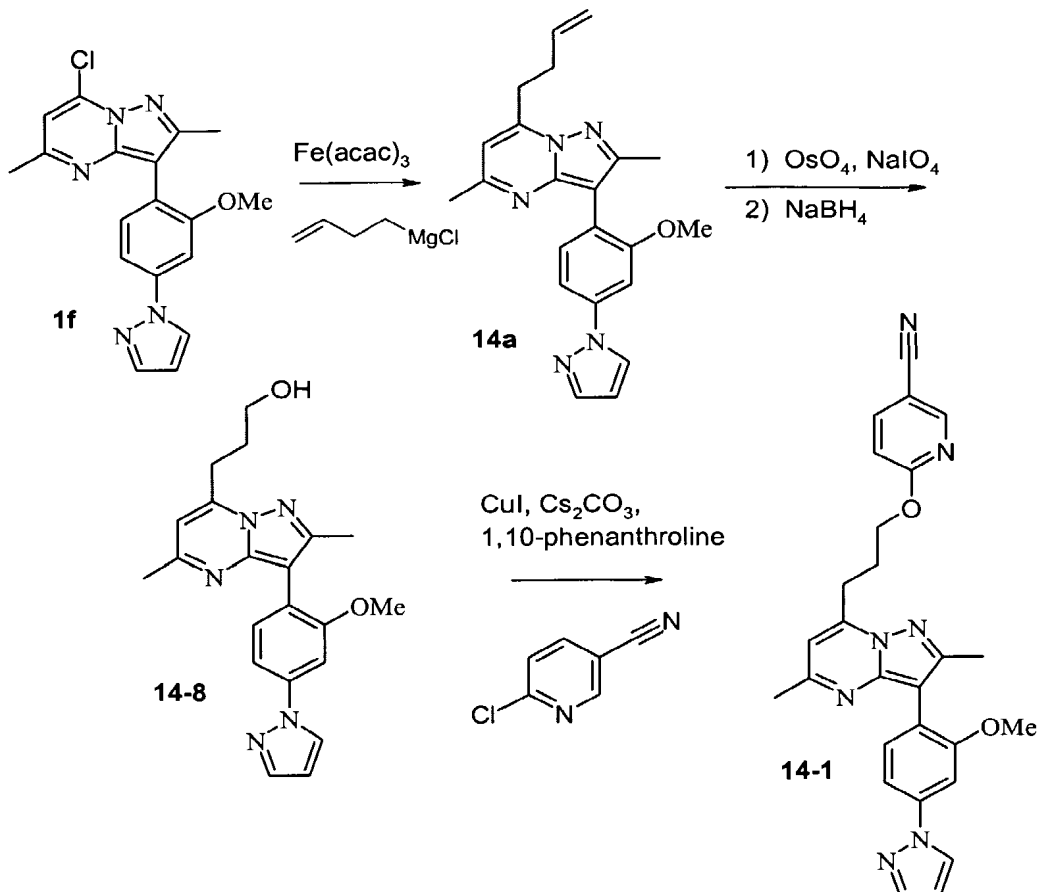


Cmpd	R ₂	MW	MS	t _R *
13-1		459.935	460	9.090
13-2		493.487	494	7.690
13-3		477.925	478	9.210
13-4		450.5	451	7.850
13-5		477.925	478	9.170
13-6		425.49	426	8.420

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 14

6-{3-[3-(2-Methoxy-4-pyrazol-1-yl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-propoxy}-nicotinonitrile

**5 Step 14A:**

To a solution of Cmpd **1f** (1.06 g, 3.0 mmol) and iron(III)acetylacetonate (353 mg, 1.0 mmol) in 10 mL anhydrous THF/NMP (7:1) was added slowly 3-butenylmagnesium chloride (9.0 mL of a 0.5 M solution in THF, 4.5 mmol). The reaction mixture was stirred at RT for 1 hr, then more iron(III)acetylacetonate (1.0 g, 2.8 mmol) and Grignard reagent (6.0 mL, 3.0 mmol) were added. The reaction mixture was stirred for 2 hr, then water was added. The mixture was extracted with ethyl acetate, then the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent to provide **14a** (538 mg, 48 % yield).

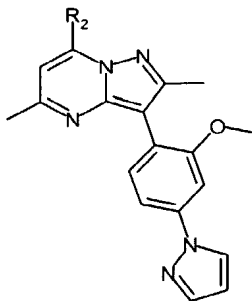
Step 14B:

To a solution of **14a** (380 mg, 1.02 mmol) in 10 mL THF/water (4:1) was added osmium tetroxide (26 mg, 0.10 mmol) followed by sodium periodate (642 mg, 3.0 mmol) at RT. The mixture was stirred at RT for 1 hr, then ethyl acetate and water were added. The organic layer was dried over sodium sulfate, filtered, and evaporated to provide the crude aldehyde, which was dissolved in methanol (20 mL). Sodium borohydride (152 mg, 4.0 mmol) was added portionwise. After stirring at room temperature for 20 min, the reaction mixture was concentrated. The residue was purified by silica gel chromatography, eluting with hexanes/ethyl acetate to provide Cmpd **14-1** (230 mg, 60 % yield).

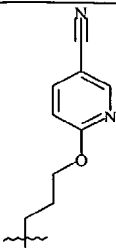
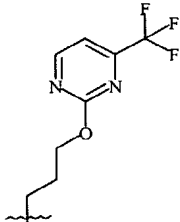
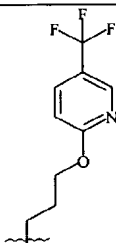
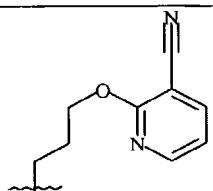
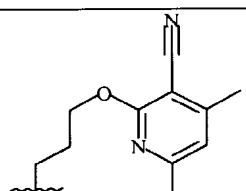
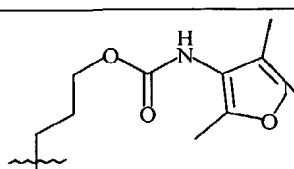
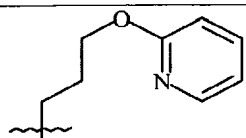
Step 14C:

A mixture of **14-1** (30 mg, 0.08 mmol, 1 eq), copper(I) iodide (15 mg, 0.08 mmol, 1 eq), cesium carbonate (52 mg, 0.16 mmol, 2 eq), and 1,10-phenanthroline (14 mg, 0.08 mmol, 1 eq) was heated in 1 mL of toluene in a sealed vial at 110 °C for 17 hr. The cooled mixture was filtered through Celite®, then concentrated. The residue was purified by silica gel chromatography using hexane/ethyl acetate as eluent to provide **14-2** (5 mg) as a solid.

Depending on the aryl halide used in the method of Step 14C, the compounds listed in the following table in addition to Cmpd **14-1** were synthesized and purified by preparative LC-MS.



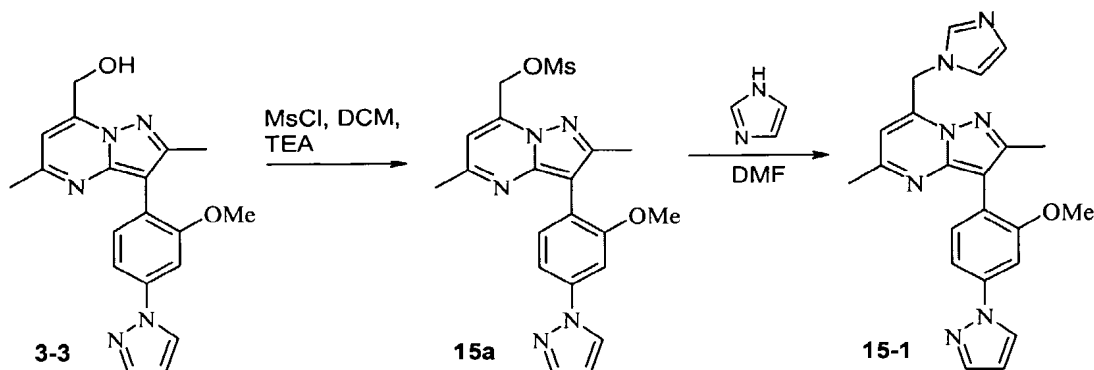
Cmpd	R ₂	MW	MS	t _R ⁺
14-1		377.446	377	5.170

Cmpd	R ₂	MW	MS	t _R *
14-2		479.542	479	7.570
14-3		523.517	523	8.020
14-4		522.529	522	6.620
14-5		479.542	479	7.350
14-6		507.595	507	8.320
14-7		515.571	515	6.510
14-8		454.531	454	6.690

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 15

7-IMIDAZOL-1-YLMETHYL-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE

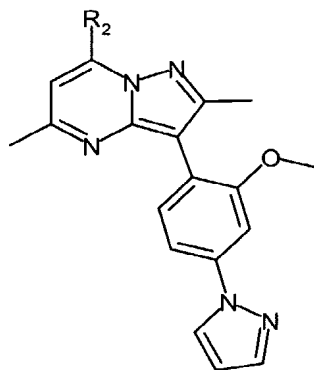
**5 Step15A:**

A solution of methanesulfonyl chloride (100 mg, 0.86 mmol, 1.5 eq) in DCM (0.5 mL) was added dropwise to a 0 °C solution of Cmpd 3-3 (200 mg, 0.57 mmol, 1 eq) in 5 mL DCM. The mixture was allowed to warm to RT over 1 hr, then saturated aqueous sodium bicarbonate solution was added and the mixture was
 10 extracted with 2 x 20 mL DCM. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to obtain **15a** (180 mg, 49 % yield) as a yellow foam.

Step 15B:

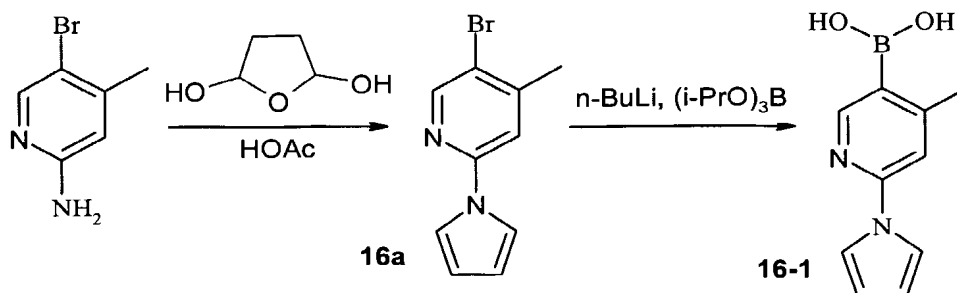
Potassium carbonate (20 mg, 0.14 mmol, 2.6 eq) and imidazole (20 mg, 0.30 mmol, 5.5 eq) were added to a solution of **15a** (23 mg, 0.054 mmol, 1 eq) in DMF
 15 (1 mL). The reaction mixture was stirred at RT for 16 hr, then methanol (1 mL) was added and the reaction mixture was purified directly by preparative HPLC/MS, providing **15-1** (10 mg) as a TFA salt.

Depending on the nucleophilic heterocycle or amine employed, the compounds listed in the following table were synthesized and purified by preparative
 20 LC-MS:



Cmpd	R ₂	MW	MS	t _R *
15-1		399.456	400	4.190
15-2		467.453	468	6.320
15-3		399.456	400	5.520
15-4		402.499	403	4.110
15-5		376.462	377	3.880
15-6		400.444	401	5.330

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 16**4-METHYL-2-PYRROL-1-YL-5-PYRIDYLBORONIC ACID****Step 16A:**

- 5 A solution of 2-amino-5-bromo-4-methylpyridine (1 g, 5.4 mmol) and 2,5-dihydroxytetrahydrofuran (2.8 g, 27 mmol) in acetic acid (10 mL) was heated at 90 °C in a sealed tube for 2 hr. The reaction mixture was concentrated and the residue was purified by silica gel chromatography using 4:1 hexanes/ethyl acetate, providing **16a** (900 mg, 71 % yield) as a light yellow oil.

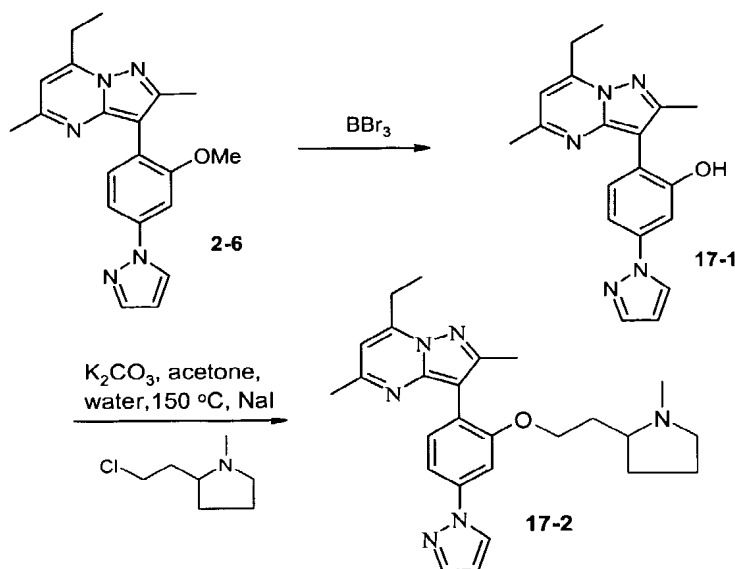
Step 16B:

- 10 n-Butyllithium (3.6 mL of a 2.0 M solution in pentane, 7.2 mmol) was added dropwise to a solution of Cmpd **16a** (860 mg, 3.6 mmol) and triisopropylborate (1.4 g, 7.3 mmol) in 6 mL THF at -78 °C. The mixture was allowed to warm to RT over 1 hr, then 0.5 mL of 4N hydrochloric acid was added and the mixture was stirred for 10
- 15 min. The mixture was extracted 2x 25 mL DCM, then the organic layer was dried over sodium sulfate, filtered, and concentrated to provide **16-1** (250 mg) as a yellow oil. The aqueous layer was concentrated, then the solid residue was washed with ethanol. The combined ethanol filtrates were concentrated to provide additional **16-1** (500 mg) as a yellow oil.

20

EXAMPLE 17

7-ETHYL-2,5-DIMETHYL-3-{2-[2-(1-METHYL-PYRROLIDIN-2-YL)-ETHOXY]-4-PYRAZOL-1-YL-PHENYL}-PYRAZOLO[1,5-A]PYRIMIDINE

**5 Step 17A:**

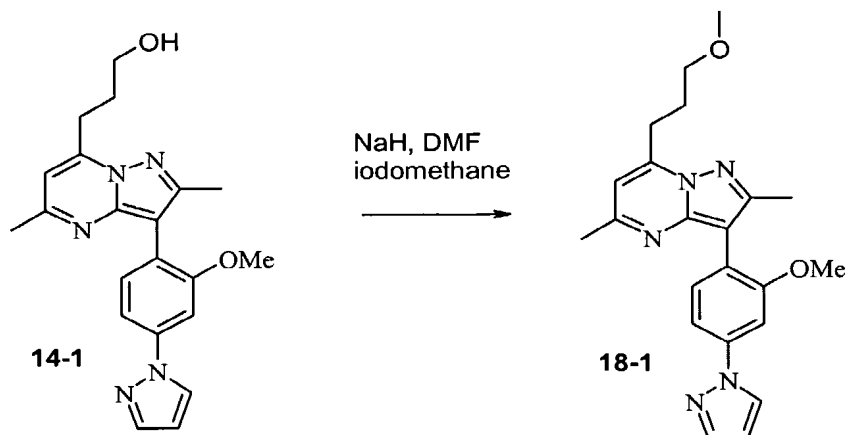
To a solution of Cmpd 2-6 (350 mg) in chloroform (5 mL) was added BBr_3 (1.0 M in DCM, 5 mL.) The mixture was stirred overnight at room temperature and quenched with water. The mixture was extracted with chloroform (2x 10 mL), then the combined organic extracts were dried over sodium sulfate, filtered, and concentrated to provide Cmpd 17-1 (280 mg) as an oil. An aliquot (10 mg) was purified by prep HPLC/MS to provide purified Cmpd 17-1 (2.9 mg.)

Step 17B:

A mixture of Cmpd 17-1 (45 mg, 0.14 mmol, 1 eq), potassium carbonate (56 mg, 0.41 mmol, 3 eq), sodium iodide (20 mg, 0.13 mmol, 1 eq), 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride (39 mg, 0.21 mmol, 1.5 eq), acetone (1 mL) and water (1 mL) was heated in a sealed tube in a microwave reactor at 150°C for 25 min. The acetone was evaporated, then the residue was diluted with methanol, filtered, and subjected directly to preparative HPLC/MS purification, yielding Cmpd 17-2 (14 mg, 20%) as a TFA salt; MW: 444.58; LC/MS: 444 $[\text{MH}]^+$; t_R : 6.010, Anal. Meth. 2.

EXAMPLE 18

7-(3-METHOXY-PROPYL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE



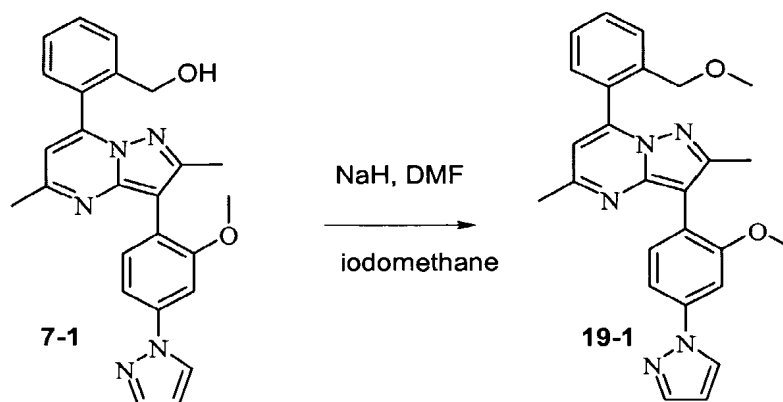
5 **Step 18A:**

To a solution of **14-1** (30 mg) in dry DMF was added NaH (10 mg, 60% dispersion). After stirring at RT for 10 min, methyl iodide (0.015 mL) was added. The mixture was stirred for 1 hr, then methanol (1 mL) was added and the mixture was subjected directly to prep HPLC/MS purification, providing Cmpd **18-1** (12 mg) as a

10 TFA salt; MW: 391.47 LC/MS: 391 [MH]⁺; t_R: 7.050, Anal. Meth. 2.

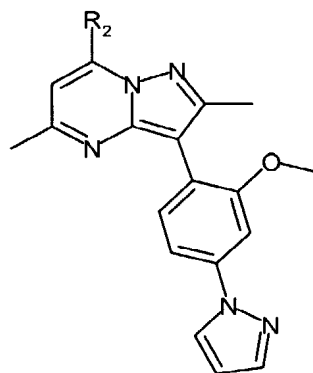
EXAMPLE 19

2-[7-(2-METHOXYMETHYL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDIN-3-YL]-5-PYRAZOL-1-YL-PHENOL

**5 Step 19A:**

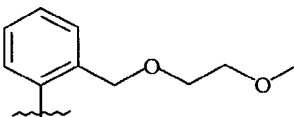
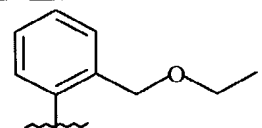
The procedure of Example 18 was followed using Cmpd 7-1 as starting material

Depending on the alkyl halide employed, the compounds listed in the following table were synthesized and purified by preparative LC-MS.



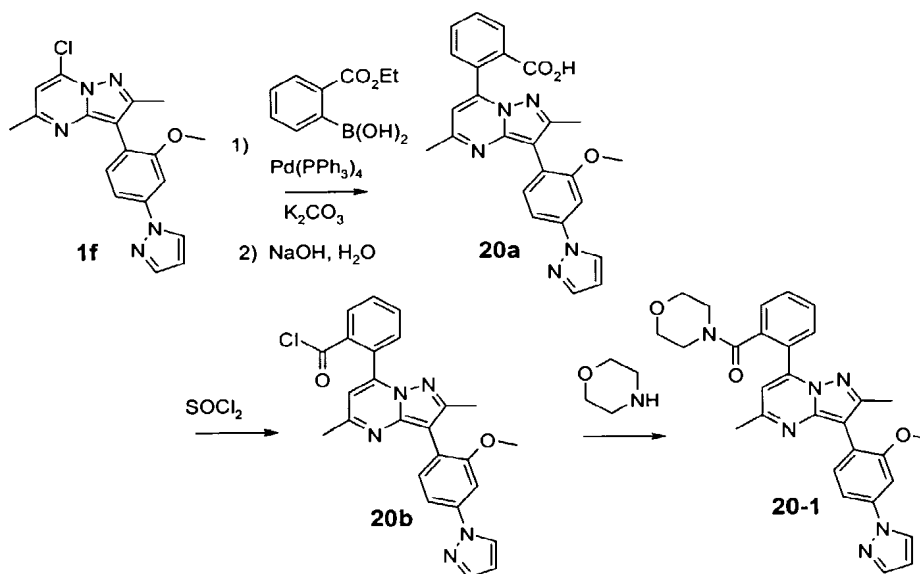
Cmpd	R ₂	MW	MS	t _R ⁺
19-1		439.517	439	6.130

10

Cmpd	R ₂	MW	MS	t _R [*]
19-2		483.569	483	5.980
19-3		453.543	453	6.290

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 20



5 Step 20A:

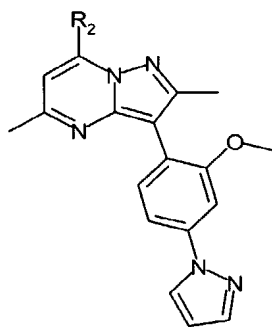
A mixture of Cmpd **1f** (710 mg, 2.0 mmol), (2-ethoxycarbonyl)phenylboronic acid (470 mg, 2.4 mmol), tetrakis (triphenylphosphine)palladium(0) (116 mg, 0.1 mmol), and potassium carbonate (550 mg, 4.0 mmol) was heated in 9:1 dioxane/water (10 mL) at 100 °C for 2.5 hr. Sodium hydroxide solution (3N, 10 mL) was added, and the mixture was stirred at 100 °C for an additional 30 min. The cooled mixture was concentrated, then water was added and the pH adjusted to 2 with hydrochloric acid. The mixture was extracted with chloroform, then the combined chloroform extracts were dried over sodium sulfate, filtered, and concentrated to provide a crude solid, which was recrystallized from chloroform to provide Cmpd **20a** (420 mg, 48 % yield) as a yellow solid.

Step 20B:

Compound **20a** (420 mg, 0.96 mmol) was heated in 10 mL chloroform with thionyl chloride (1.0 mL, 14 mmol) at 70 °C for 2 hr. Volatiles were evaporated to provide Cmpd **20b** (450 mg) as a dark solid.

5 Step 20C:

A solution of **20b** (32 mg, 0.07 mmol) in chloroform (1 mL) was treated with morpholine (0.1 mL, 1 mmol) at RT. The mixture was allowed to sit at RT for 30 min, then the solvent was evaporated. The residue was taken up in methanol, filtered and purified directly by preparative HPLC/MS to provide **20-1** (13 mg, 30 %) as a TFA salt. Depending on the amine used, the compounds listed in the following table were synthesized and purified by preparative HPLC-MS:

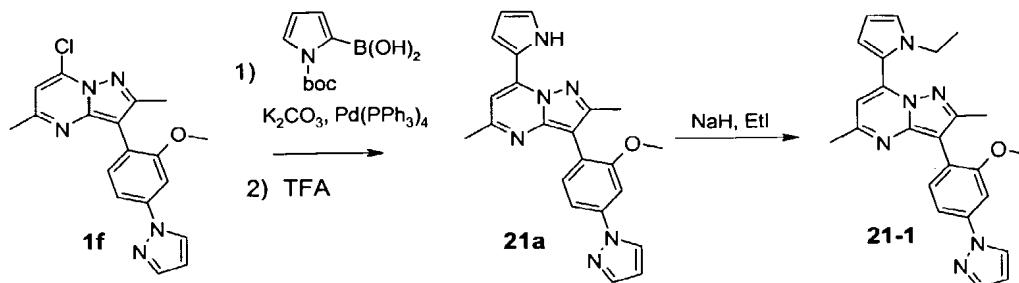


Cmpd	R ₂	MW	MS	t _R [*]
20-1		508.579	508	6.180
20-2		506.607	506	7.050
20-3		492.58	492	6.710
20-4		491.552	491	5.840

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 21

7-(1-ETHYL-1H-PYRROL-2-YL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE

**5 Step 21A:**

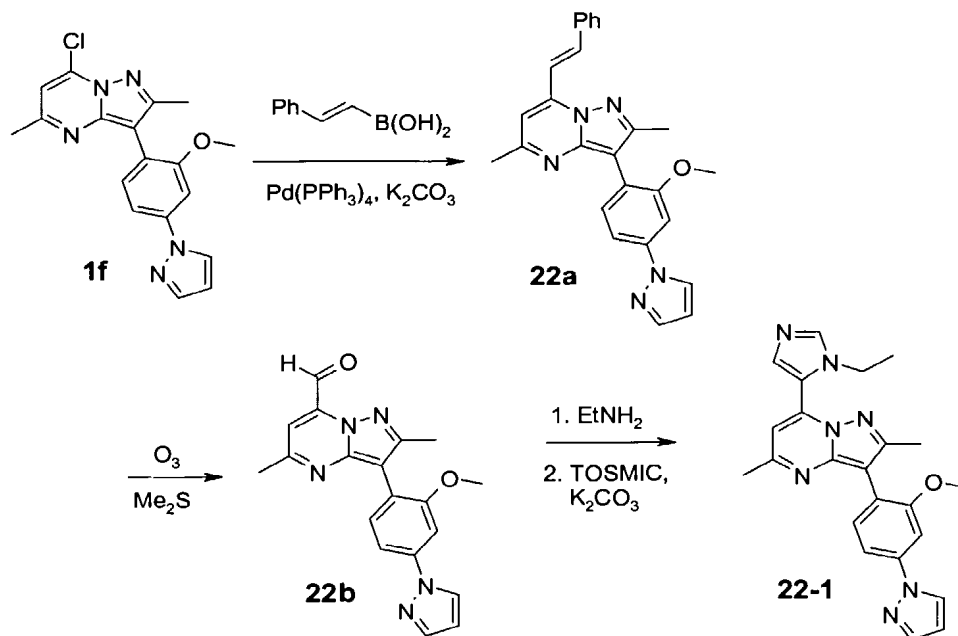
A mixture of Cmpd **1f** (210 mg, 0.6 mmol), N-Boc-pyrrole-2-boronic acid (158 mg, 0.75 mmol), tetrakis(triphenylphosphine)palladium(0) (40mg, 0.035 mmol), and potassium carbonate (166 mg, 1.2 mmol) was heated in 9:1 dioxane/water (5 mL) at 110 °C for 3 hr in a sealed tube. The cooled mixture was concentrated, then water was added and the mixture was extracted with chloroform. The combined chloroform extracts were dried over sodium sulfate, filtered, and concentrated to provide a crude solid, which was stirred in 1:1 TFA/DCM (3 mL) for 16 hr. The mixture was diluted with ethyl acetate, then treated with aqueous ammonia. The organic layer was dried over sodium sulfate, filtered, and concentrated, then the residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent to provide **21a** (110 mg, 48 % yield) as a yellow solid.

Step 21B:

To a solution of **21a** (110 mg, 0.28 mmol) in dry DMF (2 mL) was added sodium hydride (20 mg of a 60% dispersion in mineral oil, 0.5 mmol) at RT. The mixture was stirred for 5 min, then ethyl iodide (0.050 mL, 0.60 mmol) was added and the mixture was stirred at RT for 2 hr. Water and ethyl acetate were added, then the ethyl acetate layer was washed with water and brine, then dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluent to provide Cmpd **21-1** (84 mg, 73 % yield) as a yellow solid; MW: 412.50 LC/MS: 412 [MH]⁺; t_R: 7.630, Anal. Meth. 2.

EXAMPLE 22

7-(3-ETHYL-3H-IMIDAZOL-4-YL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE

**5 Step 22A:**

A mixture of Cmpd **1f** (1.50 g, 4.25 mmol), 2-phenylethenylboronic acid (692 mg, 4.68 mmol), potassium carbonate (1.17 g, 8.50 mmol), and tetrakis (triphenylphosphine)palladium(0) (250 mg, 0.22 mmol) in dioxane (9 mL) and water (1 mL) was heated at 105 °C for 16 hr. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated, and the residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent to afford **22a** (1.60 g, 89 % yield) as a yellow solid.

Step 22B:

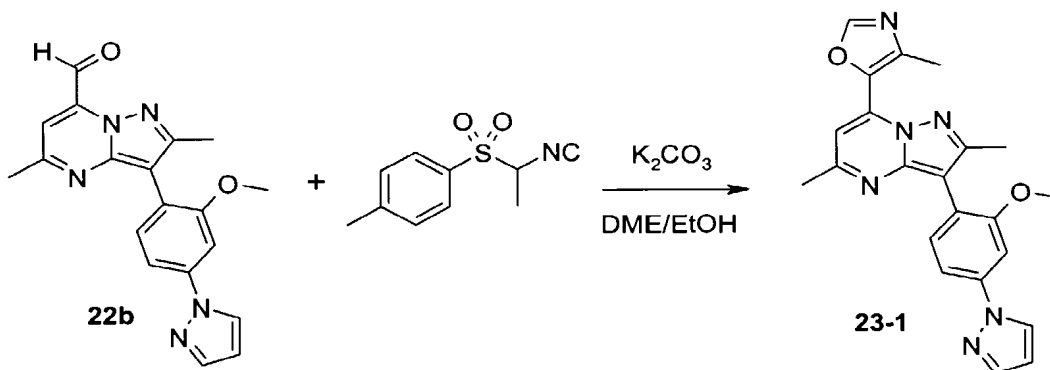
An ozone/oxygen mixture was bubbled through a solution of **22a** (1.60 g, 3.8 mmol) in dry 2:1 DCM/methanol (20 mL) at – 70 °C for 8 minutes. Dimethyl sulfide (1.5 mL) was added and the mixture was stirred and allowed to warm to RT over 16 hr. The solvent was evaporated and the residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent, providing Cmpd **22b** (1.0 g, 76 % yield) as a yellow solid.

Step 22C:

A mixture of **22b** (35 mg, 0.10 mmol), ethylamine (1.0 mL of a 2.0M solution in THF, 2.0 mmol), and magnesium sulfate in 1,2-dichloroethane was stirred at RT for 15 hr. The mixture was filtered, then the filtrate was evaporated to dryness. The residue was taken up in 1:1 ethanol/DME (2 mL), then TOSMIC (38 mg, 0.19 mmol) and potassium carbonate (55 mg, 0.4 mmol) were added and the mixture was refluxed for 17 hr. Water was added and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluent, providing Cmpd **22-1** (5 mg) as an oil; MW: 413.48 LC/MS: 413 [MH]⁺; t_R: 5.000, Anal. Meth. 2.

EXAMPLE 23

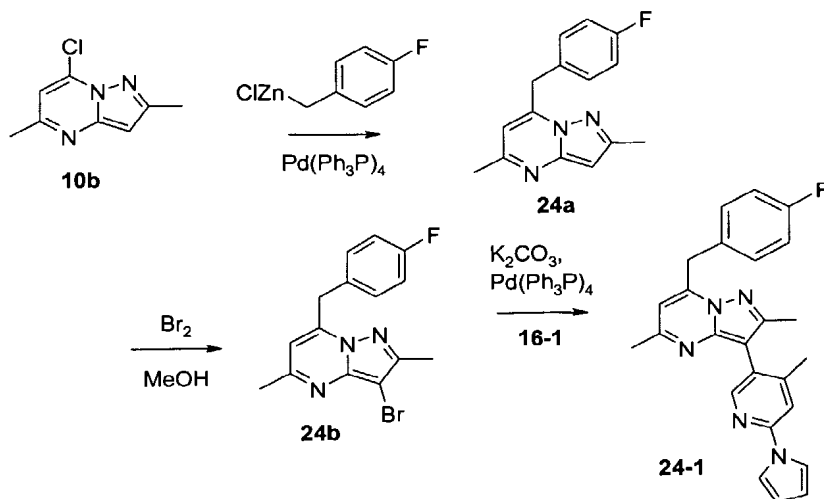
3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-(4-METHYL-OXAZOL-5-YL)-
PYRAZOLO[1,5-A]PYRIMIDINE



A mixture of **22b** (208 mg, 0.60 mmol), alpha-methyl-TOSMIC (251 mg, 1.2 mmol) and potassium carbonate (248 mg, 1.8 mmol) was heated in 5 mL 1:1 DME/ethanol at 80 °C for 14 hr. Water was added and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluent, providing **23-1** (60 mg, 23 %) as an oil; MW: 400.44 LC/MS: 400 [MH]⁺; t_R: 5.250, Anal. Meth. 2.

EXAMPLE 24

7-(4-FLUORO-BENZYL)-2,5-DIMETHYL-3-(4-METHYL-6-PYRROL-1-YL-PYRIDIN-3-YL)-
PYRAZOLO[1,5-A]PYRIMIDINE

**5 Step 24A:**

To a solution of 4-fluorophenylzinc chloride (20 mL of a 0.5 M solution in THF, 10 mmol) were added Cmpd **10b** (1.0 g, 5.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.26 mmol). The reaction mixture was heated at 90 °C in a sealed tube for 3 hr. The cooled reaction mixture was treated with 4N hydrochloric acid (4 mL), then water was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with 30% ethyl acetate in hexanes to obtain **24a** (1.0 g, 71 % yield) as an off-white solid.

15 Step 24B:

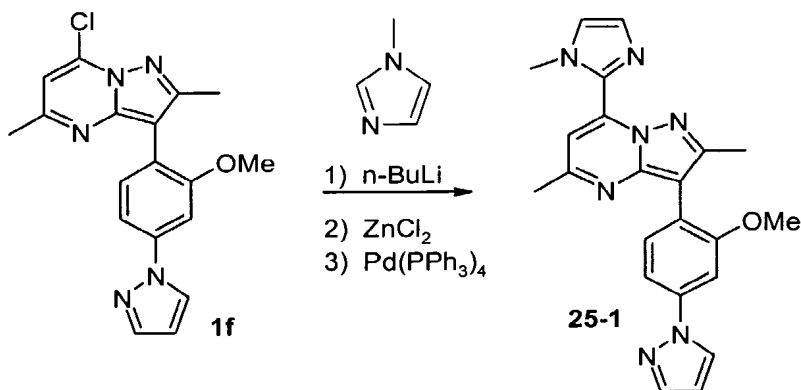
Compound **24a** (1.0 g, 3.9 mmol) was dissolved in 15 mL methanol. Bromine (0.62 g, 3.9 mmol) was added dropwise to the solution, resulting in formation of a white precipitate. The solid was collected on a fritted glass filter and rinsing with methanol. This compound was further purified by silica gel column chromatography, eluting with 4:1 hexanes/ethyl acetate to provide first a dibromination product (110 mg, 7 % yield), followed by **24b** (1.0 g, 77 % yield) as a white solid.

Step 24C:

A mixture of Cmpd **24b** (800 mg, 2.4 mmol), Cmpd **16-1** (500 mg, 2.5 mmol), tetrakis(triphenylphosphine)palladium(0) (280 mg, 0.24 mmol), and potassium carbonate (600 mg, 4.3 mmol) was heated in 9:1 dioxane/water (3.5 mL) at 95 °C for 3 hr in a sealed tube. Aqueous sodium bicarbonate solution (5 mL) was added to the cooled mixture, which was then extracted twice with DCM. The combined DCM extracts were dried over sodium sulfate, filtered, and concentrated to provide a crude oil, which was partially purified by prep HPLC/MS. The partially purified product was then chromatographed on silica gel using 4:1 hexanes/ethyl acetate as eluent, providing Cmpd **24-1** (3 mg) as a yellow solid; MW: 411.48 LC/MS: 412 [MH]⁺; t_R: 9.160, Anal. Meth. 2.

EXAMPLE 25

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-(1-METHYL-1H-IMIDAZOL-2-YL)-PYRAZOLO[1,5-A]PYRIMIDINE

Step 25A:

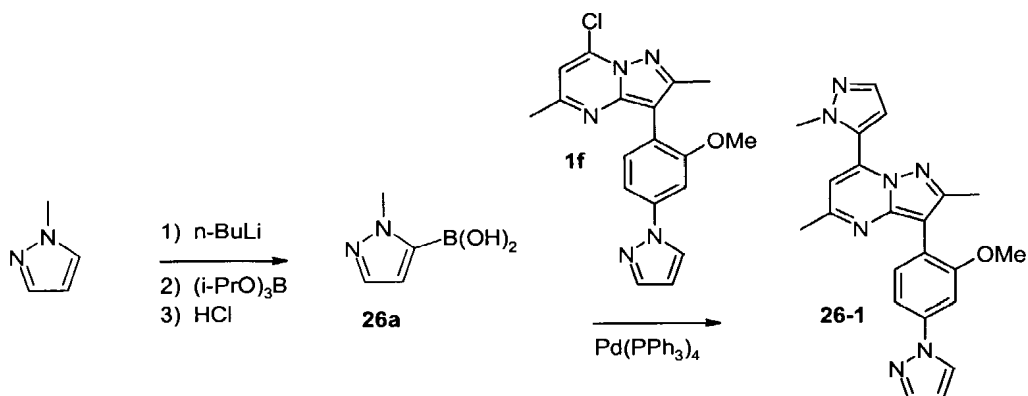
To a solution of 1-methylimidazole (246 mg, 3.0 mmol) in dry THF (3 mL) cooled to -70 °C was added n-BuLi (2.5 M solution in hexane, 1.7 mL, 4.2 mmol) dropwise. The reaction mix was stirred at -70 °C for 10 min, then ZnCl₂ (0.5 M solution in THF, 20 mL, 10 mmol) was added over 5 min. The mixture was stirred at -70 °C for 1 hr, then was warmed to 0 °C. Cmpd **1f** (106 mg, 0.30 mmol) and tetrakis(triphenylphosphine)palladium(0) (70 mg, 0.06 mmol) were added. The mixture was then heated to reflux for 3 hr. The cooled reaction mixture was quenched with water, the THF was evaporated and the resulting aqueous mixture was extracted with

ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, concentrated, and the residue was chromatographed on silica gel using ethyl acetate as eluant to give **25-1** (15 mg) as a yellow solid; HPLC retention time 4.13 min (method 2); MW 399.5; observed MS 399.

5

EXAMPLE 26

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-(2-METHYL-2H-PYRAZOL-3-YL)-PYRAZOLO[1,5-A]PYRIMIDINE



10 Step 26A:

To a solution of 1-methylpyrazole (820 mg, 10 mmol) in dry THF (20 mL) cooled to -70°C was added n-BuLi (1.6 M solution in hexane, 6.3 mL, 10 mmol) dropwise. The reaction mix was stirred at -70°C for 5 min, then triisopropyl borate (2.5 mL, 11 mmol) was added over 5 min. The mixture was allowed to warm to RT over 1 hr, then 6N hydrochloric acid (5 ml) was added. The mixture was stirred for 30 min, then was evaporated to dryness to provide crude **26a** as a solid, which was used without further purification.

Step 26B:

20 Cmpd **1f** (530 mg, 1.5 mmol) and crude **26a** (entire amount, approximately 10 mmol) were subjected to Suzuki reaction according to the procedure of Example 1. The reaction mixture was concentrated, then water was added and the mixture was extracted with chloroform. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated, then the residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluant. The product was further

purified by crystallization from acetonitrile, providing Cmpd **26-1** (280 mg) as a yellow solid; HPLC retention time 6.42 min (method 2); MW 399.5; observed MS 399)

EXAMPLE 27

CRF RECEPTOR BINDING ACTIVITY

The compounds of this invention may be evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by Grigoriadis et al. (*Mol. Pharmacol* vol50, pp679-686, 1996) and Hoare et al. (*Mol. Pharmacol* vol63 pp751-765, 2003.) By utilizing radiolabeled CRF ligands, the assay may be used to evaluate the binding activity of the compounds of the present invention with any CRF receptor subtype.

Briefly, the binding assay involves the displacement of a radiolabeled CRF ligand from the CRF receptor. More specifically, the binding assay is performed in 96-well assay plates using 1-10 μ g cell membranes from cells stably transfected with human CRF receptors. Each well receives about 0.05 mL assay buffer (e.g., Dulbecco's phosphate buffered saline, 10 mM magnesium chloride, 2mM EGTA) containing compound of interest or a reference ligand (for example, sauvagine, urocortin I or CRF), 0.05 mL of [¹²⁵I] tyrosine - sauvagine (final concentration ~150 pM or approximately the K_D as determined by Scatchard analysis) and 0.1 mL of a cell membrane suspension containing the CRF receptor. The mixture is incubated for 2 hr at 22 °C followed by separation of the bound and free radioligand by rapid filtration over glass fiber filters. Following three washes, the filters are dried and radioactivity (Auger electrons from ¹²⁵I) is counted using a scintillation counter. All radioligand binding data may be analyzed using the non-linear least-squares curve-fitting programs Prism (GraphPad Software Inc) or XLfit (ID Business Solutions Ltd).

EXAMPLE 28

CRF-STIMULATED ADENYLATE CYCLASE ACTIVITY

The compounds of the present invention may also be evaluated by various functional testing. For example, the compounds of the present invention may be screened for CRF-stimulated adenylate cyclase activity. An assay for the determination of CRF-stimulated adenylate cyclase activity may be performed as

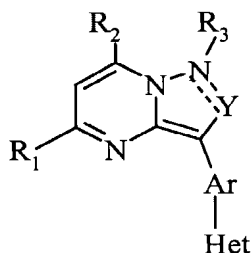
generally described by Battaglia et al. (*Synapse* 1:572, 1987) with modifications to adapt the assay to whole cell preparations.

More specifically, the standard assay mixture may contain the following in a final volume of 0.1 mL: 2 mM L-glutamine, 20 mM HEPES, and 1 mM IMBX in DMEM buffer. In stimulation studies, whole cells with the transfected CRF receptors are plated in 96-well plates and incubated for 30 min at 37 °C with various concentrations of CRF-related and unrelated peptides in order to establish the pharmacological rank-order profile of the particular receptor subtype. Following the incubation, cAMP in the samples is measured using standard commercially available kits, such as cAMP-Screen™ from Applied Biosystems. For the functional assessment of the compounds, cells and a single concentration of CRF or related peptides causing 50% stimulation of cAMP production are incubated along with various concentrations of competing compounds for 30 min at 37°C, and cAMP determined as described above.

It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

WHAT IS CLAIMED IS:

1. A compound having the following structure:



or a pharmaceutically acceptable salt, ester, solvate, stereoisomer or prodrug thereof,

wherein:

“---” represents the second bond of an optional double bond;

R₁ is hydrogen, alkyl, substituted alkyl, heteroaryl, substituted heteroaryl, -NH₂, or halogen;

R₂ is alkyl, substituted alkyl, -C(O)NR₇R₈, aryl, substituted aryl, aryloxyalkyl, substituted aryloxyalkyl, heteroarylalkoxyalkyl, substituted heteroarylalkoxyalkyl, heterocyclealkyl, substituted heterocyclealkyl, arylalkyl, substituted arylalkyl, heteroaryl, or substituted heteroaryl, wherein said heteroaryl or substituted heteroaryl is connected to the pyrimidine ring via a carbon-carbon bond;

R₃ is null, hydrogen, or alkyl;

Y is =(CR₄)- or -(C=O)-;

R₄ is hydrogen, alkyl, substituted alkyl, thioalkyl, alkylsulfinyl, or alkylsulfonyl;

Ar is phenyl, phenyl substituted with 1 or 2 R₅, pyridyl or pyridyl substituted with 1 or 2 R₅;

R₅ at each occurrence is hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, halogen, alkylsulfonyl, or alkylsulfinyl;

Het is heteroaryl optionally substituted with 1 or 2 R₆;

R₆ at each occurrence is hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, or halogen; and

R₇ and R₈ are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, arylalkyl, substituted arylalkyl, heterocyclealkyl or substituted heterocyclealkyl; or

R₇ and R₈ taken together with the nitrogen to which they are attached form a heterocyclic ring or a substituted heterocyclic ring.

2. A compound according to claim 1 wherein R_1 is hydrogen, alkyl, substituted alkyl, $-NH_2$, or halogen.

3. A compound according to claim 1 wherein R_2 is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, wherein said heteroaryl or substituted heteroaryl is connected to the pyrimidine ring via a carbon-carbon bond.

4. A compound according to claim 1 wherein R_3 is null.

5. A compound according to claim 4 wherein Y is $=(CR_4)-$.

6. A compound according to claim 5 wherein R_4 is hydrogen, alkyl, or substituted alkyl.

7. A compound according to claim 1 wherein R_3 is hydrogen or alkyl.

8. A compound according to claim 7 wherein Y is $-(C=O)-$.

9. A compound according to claim 1 wherein Ar is phenyl substituted with 1 R_5 .

10. A compound according to claim 9 wherein R_5 is alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, halogen, alkylsulfonyl, or alkylsulfinyl.

11. A compound according to claim 1 wherein Het is substituted with 1 R_6 .

12. A compound according to claim 11 wherein R_6 is alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, or halogen.

13. A compound according to claim 1,

wherein:

R₁ is hydrogen, alkyl or substituted alkyl;
R₃ is null;
Y is =(CR₄)-;
R₄ is hydrogen, alkyl or substituted alkyl;
Ar is phenyl substituted with one R₅;
R₅ is alkyl, substituted alkyl, alkoxy or substituted alkoxy; and
Het is heteroaryl.

14. A compound according to claim 13,

wherein:

R₁ is lower alkyl;
R₄ is lower alkyl;
R₅ is alkoxy; and
Het is pyrazolyl.

15. A compound according to claim 14,

wherein:

R₁ is methyl;
R₄ is methyl; and
R₅ is methoxy.

16. A compound according to claim 15,

wherein:

R₂ is alkyl, substituted arylalkyl, substituted aryl, heteroaryl, substituted heteroaryl, substituted heteroaryloxyalkyl, heteroarylalkyl or substituted heteroarylalkyl.

17. A compound according to claim 16,

wherein:

R₂ is substituted arylalkyl, substituted aryl, heteroaryl or substituted heteroaryl.

18. A compound according to claim 17,

wherein:

R₂ is substituted benzyl, substituted phenyl, substituted pyrazolyl, pyridinyl or substituted pyridinyl.

19. A compound according to claim 18,
wherein:

R₂ is substituted pyrazolyl, pyridinyl or substituted pyridinyl.

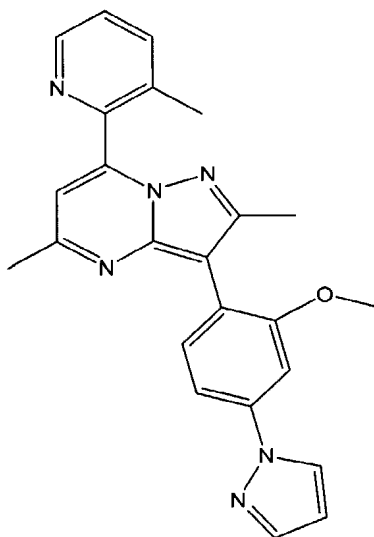
20. A compound according to claim 19,
wherein:

R₂ is substituted pyridinyl.

21. A compound according to claim 20,
wherein:

R₂ is methyl substituted pyridinyl or methoxy substituted pyridinyl.

22. A compound according to claim 21, wherein said compound is represented by the formula:



23. A pharmaceutical composition comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier or diluent.

24. A method for treating a disorder manifesting hypersecretion of CRF in a mammal comprising administering to the animal an effective amount of a pharmaceutical composition according to claim 23.

25. A method according to claim 24, wherein the disorder is stroke.

26. A method according to claim 24, wherein the disorder is depression.

27. A method according to claim 24, wherein the disorder is an anxiety-related disorder.

28. A method according to claim 24, wherein the disorder is obsessive-compulsive disorder.

29. A method according to claim 24, wherein the disorder is irritable bowel syndrome.

30. A method according to claim 24, wherein the disorder is anorexia nervosa.

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/IB2004/004234

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	US 6 313 124 B1 (HE LIQI ET AL) 6 November 2001 (2001-11-06) cited in the application column 10, lines 24ff	1-30
Y	WO 97/29109 A (JANSSEN PHARMACEUTICA N.V; NEUROCRINE BIOSCIENCES INC; CHEN, CHEN; WEB) 14 August 1997 (1997-08-14) cited in the application claim 1 and p.5, line 26	1-30

☐ Further documents are listed in the continuation of box C☒ Patent family members are listed in annex.

* Special categories of cited documents

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

20 June 2005

Date of mailing of the international search report

27/06/2005

Name and mailing address of the ISA

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Authorized officer

Wolf, C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/004234

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: claims 24-30 in respect of industrial applicability
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 24-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No
PCT/IB2004/004234

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
US 6313124	B1	06-11-2001	US	6124289 A	26-09-2000
			AT	264860 T	15-05-2004
			AU	748818 B2	13-06-2002
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			CA	2314613 A1	05-08-1999
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			CN	1542010 A	03-11-2004
			DE	69916578 D1	27-05-2004
			DE	69916578 T2	31-03-2005
			DK	1049699 T3	05-07-2004
			EP	1344779 A1	17-09-2003
			EP	1049699 A1	08-11-2000
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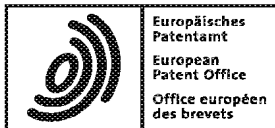
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(54) **CRF1 RECEPTOR ANTAGONIST, PHARMACEUTICAL FORMULATIONS AND SOLID FORMS THEREOF FOR THE TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA**

(57) Provided are methods related to treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine (Formula I), or a pharmaceutically acceptable salt thereof. Further provid-

ed are pharmaceutical formulations and solid forms of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and their use in the treatment of congenital adrenal hyperplasia (CAH).

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(52) Cooperative Patent Classification (CPC): (Cont.)

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Description

TECHNICAL FIELD

[0001] The present disclosure relates to 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for the treatment of congenital adrenal hyperplasia (CAH). The present disclosure further relates to pharmaceutical formulations and solid forms of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and their use in the treatment of congenital adrenal hyperplasia (CAH).

BACKGROUND

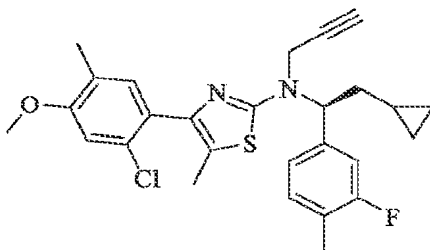
[0002] Classic congenital adrenal hyperplasia (CAH) is a disease that includes a group of autosomal recessive disorders that result in an enzyme deficiency that alters the production of adrenal steroids due to 21-hydroxylase deficiency, a condition that results in little or no cortisol biosynthesis. One clinical manifestation of the absence of cortisol is the lack of feedback inhibition of pituitary adrenocorticotrophic hormone (ACTH) secretion. Increased ACTH levels cause adrenal hyperplasia and the enzyme mutation causes a shunting of cortisol precursor steroids to alternate pathways. Most notably, the shunting of androgens leads to virilization and other developmental complications in females and the over-accumulation of ACTH is associated with the formation of testicular adrenal rest tumors in males. In addition, since the same enzyme (21-hydroxylase) is used in the pathway for the biosynthesis of the mineralocorticoids, a number of these patients suffer from aldosterone deficiency which can result in dehydration and death due to salt-wasting. The prevalence of classic 21-hydroxylase deficiency CAH in the US general population, based on newborn screening, has been documented as 1:10,000 to 1:20,800 (Trakakis et al., "An update to 21-hydroxylase deficient congenital adrenal hyperplasia," *Gynecol. Endocrinol.* (2010) 26(1):63-71; Hertzberg et al., "Birth prevalence rates of newborn screening disorders in relation to screening practices in the United States," *J. Pediatr.* (2011) 159(4):555-560).

[0003] Pediatric patients from birth through adolescence, and females in particular, appear to be the most vulnerable population of CAH sufferers and represent the subgroup of patients with the greatest unmet medical need (Cheng and Speiser, "Treatment outcomes in congenital adrenal hyperplasia," *Adv. Pediatr.* (2012) 59(1):269-281; Merke and Poppas, "Management of adolescents with congenital adrenal hyperplasia," *Lancet Diabetes Endocrinol.* (2013) 1(4):341-352). Excessive androgen production in these younger patients results in early onset puberty and adrenarche, changes in skeletal maturation patterns, short stature caused by premature growth plate fusion, as well as significant hirsutism and acne problems. While survival is properly ensured through steroid replacement strategies based on physiologic dosing of glucocorticoids (e.g., hydrocortisone) and mineralocorticoids (e.g., fludrocortisone), these doses are often inadequate to suppress the accumulating ACTH and overproduction of progestogens and androgens (e.g., 17-hydroxyprogesterone [17-OHP], androstenedione, and testosterone). The uncontrolled symptoms of androgen excess, indeed, have a substantial impact on the day-to-day functioning and development of these patients.

[0004] Currently, exogenous corticosteroids are the standard of care for treating patients with classic CAH. This treatment is used to correct the cortisol deficiency and reduce the excessive ACTH levels and androgen excess. However, the dose and duration of steroid use required to suppress ACTH are typically well above the normal physiological level used for cortisol replacement alone (as in patients with Addison's disease). This increased exposure to glucocorticoids can lead to iatrogenic Cushing's syndrome, increased cardiovascular risk factors, glucose intolerance, reduced growth velocity, and decreased bone mineral density in CAH patients (Elnecave et al., "Bone mineral density in girls with classical congenital adrenal hyperplasia due to CYP21 deficiency," *J. Pediatr. Endocrinol. Metab.* (2008) 21(12):1155-1162; King et al., "Long-term corticosteroid replacement and bone mineral density in adult women with classical congenital adrenal hyperplasia," *J. Clin. Endocrinol. Metab.* (2006) 91(3):865-869; Migeon and Wisniewski, "Congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. Growth, development, and therapeutic considerations," *Endocrinol. Metab. Clin. North Am.* (2001) 30(1):193-206).

[0005] Corticotropin releasing factor (CRF) is a hypothalamic hormone released directly into the hypophyseal portal vasculature and acts on specific corticotropin releasing factor 1 (CRF1) receptors on corticotropes in the anterior pituitary to stimulate the release of ACTH. Blockade of these receptors has been shown to decrease the release of ACTH in both animals and humans. Therefore, compounds that block CRF1 receptors have the potential to directly inhibit the excessive ACTH release that occurs in CAH and thereby allow for normalization of androgen production while using lower, more physiologic doses of hydrocortisone.

[0006] The compound of Formula (I)



(I)

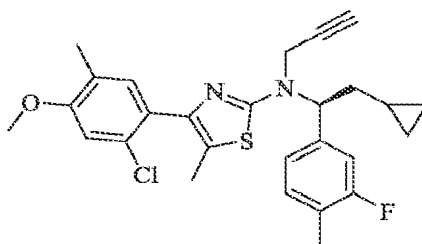
4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, is a selective CRF1 receptor antagonist. The compound of Formula (I) can be prepared according to the methods described in U.S. Patent Nos. 6,586,456 and 8,314,249, each of which is hereby incorporated by reference in its entirety. The compound of Formula (I) is a low solubility compound with low bioavailability. Partially due to its low solubility, attempts at formulating the compound of Formula (I) have proven to be difficult, particularly for formulations suitable for pediatric administration.

[0007] Thus, there is a need for a treatment for CAH that avoids the severe complications associated with corticosteroid therapy. There is also a need for a formulation of the compound of Formula (I) with increased bioavailability and a need for a formulation of the compound of Formula (I) that is suitable for pediatric administration. The formulations and methods of the present invention help address these and other needs.

SUMMARY

[0008] Provided herein is a pharmaceutical composition comprising:

(a) a compound of Formula (I):



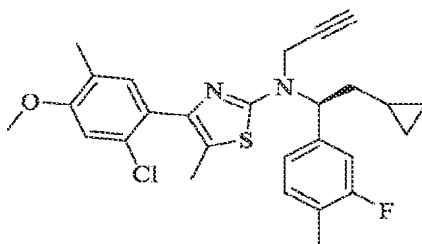
(I)

or a pharmaceutically acceptable salt thereof; and

(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

[0009] Provided herein is a pharmaceutical composition in oral solution dosage form comprising:

(a) a compound of Formula (I):

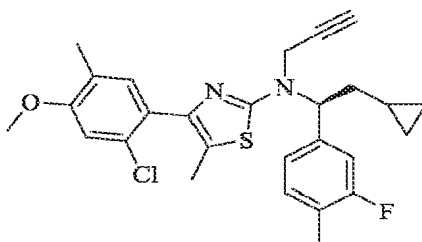


(I)

or a pharmaceutically acceptable salt thereof;
 (b) one or more of a sweetener, an anti-oxidant, and a flavor; and
 (c) a liquid vehicle.

[0010] Also provided herein is a pharmaceutical composition of the present disclosure (e.g., a pharmaceutical composition in oral solution dosage form of the present disclosure) for use in therapy, for example, for use in any of the methods disclosed herein.

[0011] Provided herein is a method for treating congenital adrenal hyperplasia (CAH) comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

[0012] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject.

[0013] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject.

[0014] Provided herein is a method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in the subject.

[0015] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in the subject.

[0016] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic

hormone (ACTH); and (c) androstenedione in the subject.

[0017] In some embodiments, the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof. In some embodiments, the circadian release occurs between the hours of 2 a.m. and 10 a.m.

[0018] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

[0019] In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25%. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50%.

[0020] In some embodiments, the level of adrenocorticotrophic hormone is reduced by at least 25%. In some embodiments, the level of adrenocorticotrophic hormone is reduced by at least 40%. In some embodiments, the level of adrenocorticotrophic hormone is reduced by at least 50%.

[0021] In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

[0022] In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

[0023] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

[0024] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

[0025] Provided herein is a method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of androstenedione in the subject. In some embodiments, the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

[0026] Also provided herein is a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of androstenedione in the subject.

[0027] Also provided herein is use of a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of androstenedione in the subject.

[0028] In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

[0029] Provided herein is a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

[0030] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

[0031] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable

salt thereof, in the manufacture of a medicament for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

[0032] In some embodiments, the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

[0033] Provided herein is a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof. In some embodiments, the corticosteroid is a glucocorticoid.

[0034] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

[0035] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

[0036] Provided herein is a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

[0037] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

[0038] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

[0039] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

[0040] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

[0041] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

[0042] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

[0043] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

[0044] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

[0045] Provided herein is a method of treating congenital adrenal hyperplasia in a subject comprising

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

[0046] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject comprising

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

[0047] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the method comprises:

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

[0048] In some embodiments, the method further comprises (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i). In some embodiments, the method further comprises (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

[0049] In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

[0050] In some embodiments, steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

[0051] In some embodiments, steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

[0052] In some embodiments, step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

[0053] In some embodiments, step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

[0054] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

[0055] Provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, where in the subject is in a fed state.

[0056] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject, wherein the subject is in a fed state.

[0057] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject, wherein the subject is in a fed state.

[0058] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1500 calories per liter with a caloric distribution of about 14.7% protein, about 32% fat and about 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

[0059] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

[0060] In some embodiments, administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max} , AUC, or combinations thereof when comparing oral administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the fed and fasting states.

[0061] In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10.

[0062] Provided herein is a method of reducing glucocorticoid burden in a subject as measured after a time period of administration of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

[0063] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing glucocorticoid burden in a subject, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

[0064] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing glucocorticoid burden in a subject, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

[0065] Provided herein is a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

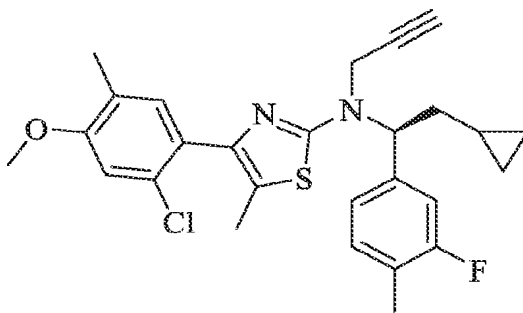
[0066] Also provided herein is a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

[0067] Also provided herein is use of a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

[0068] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof for use in therapy, for example, for use in any of the methods disclosed herein.

[0069] Also provided herein is use of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for use in any of the methods disclosed herein.

[0070] Also provided herein is a spray-dried dispersion containing 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



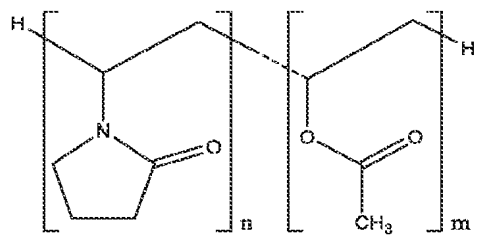
(I)

or a pharmaceutically acceptable salt thereof, and a polymer. In some embodiments, the polymer is selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:9 to about 1:1.

[0071] In some embodiments, the polymer is a neutral polymer. In some embodiment, the neutral polymer is selected from hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

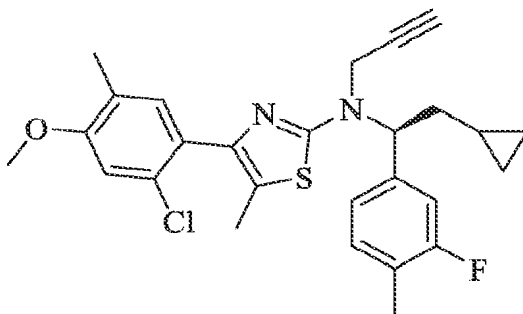
[0072] In some embodiments, the polymer is an enteric polymer. In some embodiments, the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer.

[0073] In some embodiments, the polymer is a pyrrolidone polymer. In some embodiments, the pyrrolidone polymer is selected from polyvinyl pyrrolidone (PVP) and a polyvinyl pyrrolidone vinyl acetate (PVP/VA). In some embodiments, the pyrrolidone polymer is PVP/VA. In some embodiments, the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 40:60 to about 60:40 by weight. In some embodiments, the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight. In some embodiments, the copolymer has the structure:



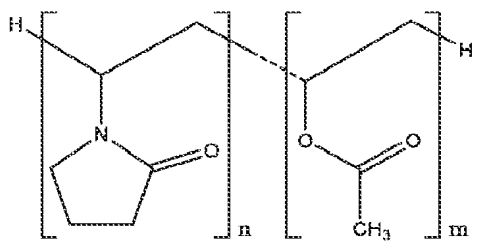
wherein the value of n is about 1 to about 2 times the value of m . In some embodiments, the copolymer is copovidone, wherein the value of n is about 1.16 times the value of m . In some embodiments, the copolymer is copovidone having an average molecular weight of about 45,000 to about 70,000.

[0074] Provided herein is a spray-dried dispersion comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



wherein the value of n is about 1 to about 2 times the value of m and the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight; and wherein the weight ratio of the compound of Formula (I) to the copolymer is from about 1:1 to about 1:9.

[0075] In some embodiments of the spray-dried dispersions of the present disclosure, the compound of Formula (I) and the polymer together form homogeneous particles. In some embodiments, the particles have a particle size distribution D_{50} of about 5 μm to about 100 μm . In some embodiments, the particles have a particle size distribution D_{50} of about 10 μm to about 50 μm . In some embodiments, the particles have a particle size distribution D_{50} of about 15 μm to about 30 μm .

[0076] In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:1.5 to about 1:9. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:2.5 to about 1:4. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is about 1:3.

[0077] In some embodiments, the particles have a residual solvent content less than about 2 wt %. In some embodiments, the particles have a residual solvent content less than about 1 wt %. In some embodiments, the particles have a residual solvent content of about 0.5 wt % or less.

[0078] In some embodiments, the compound of Formula (I) in the dispersion is substantially amorphous.

[0079] Also provided herein is a method for preparing a spray-dried dispersion of the present disclosure, comprising: dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer.

[0080] In some embodiments, the method comprises removing the organic solvent after formation of the spray-dried dispersion by drying the spray-dried dispersion. In some embodiments, the spray-dried dispersion is dried with a convection tray dryer. In some embodiments, the organic solvent is acetone.

[0081] In some embodiments, the spray dryer inlet temperature is about 60°C to about 80°C. In some embodiments, the spray dryer inlet temperature is about 72°C.

[0082] In some embodiments, the spray dryer outlet temperature is about 25°C to about 45°C. In some embodiments, the spray dryer outlet temperature is about 35°C.

[0083] In some embodiments, the homogeneous particles comprise a bulk density of less than about 0.2 g/mL. In some embodiments, the homogeneous particles comprise a bulk density of less than about 0.15 g/mL.

[0084] In some embodiments, the homogeneous particles comprise a tapped density of less than about 0.3 g/mL. In some embodiments, the homogeneous particles comprise a tapped density of less than about 0.25 g/mL.

[0085] Also provided herein is a pharmaceutical composition comprising the spray-dried dispersion of the present disclosure and one or more pharmaceutically acceptable excipients. In some embodiments, the spray-dried dispersion is present in an amount of about 20% to about 90% w/w of the composition. In some embodiments, the spray-dried dispersion is present in an amount of about 40% to 80% w/w of the composition.

[0086] In some embodiments, the pharmaceutical excipients are selected from the group consisting of a filler, a lubricant, and combinations thereof. In some embodiments, the filler is selected from the group consisting of a binder, a diluent, a disintegrant, a glidant, a surfactant, and combinations thereof.

[0087] In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg.

[0088] In some embodiments, the pharmaceutical composition is formulated as a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film. In some

embodiments, the pharmaceutical composition is in tablet form. In some embodiments, the pharmaceutical composition is in capsule form. In some embodiments, the pharmaceutical composition is coated.

[0089] In some embodiments, the spray-dried dispersion is formulated for oral administration and exhibits a positive food effect when administered orally. In some embodiments, the spray-dried dispersion has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10. In some embodiments, wherein the spray-dried dispersion has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 5 to about 10.

[0090] Also provided herein is a method for preparing a pharmaceutical composition, comprising combining the spray-dried dispersion of the present disclosure with one or more pharmaceutically acceptable excipients.

[0091] Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure.

[0092] Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

[0093] Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

[0094] In some embodiments, the spray-dried dispersion or the pharmaceutical composition is administered to the subject in a fed state. In some embodiments, the spray-dried dispersion or the pharmaceutical composition is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than 30%. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the spray-dried dispersion or the pharmaceutical composition.

[0095] In some embodiments, administering the spray-dried dispersion or the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max} , AUC, or combinations thereof when comparing oral administration of the spray-dried dispersion or pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 10 to about 20. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 10 to about 20.

[0096] In some embodiments of the disclosed methods, the subject is a pediatric subject.

[0097] Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in therapy, for example, for use in any of the methods disclosed herein.

[0098] Also provided herein is use of a spray-dried dispersion of the present disclosure for manufacture of a medicament for use in any of the methods disclosed herein.

[0099] Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0100] Also provided herein is a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

[0101] Also provided herein is use of pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

[0102] Also provided herein is pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy, for example, for use in any of the methods disclosed herein.

[0103] Also provided herein is use of pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for use in any of the methods disclosed herein.

[0104] Also provided herein is a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, comprising orally administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared

as a spray-dried dispersion.

[0105] Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

[0106] Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

[0107] In some embodiments, the subject is a pediatric subject.

[0108] Also provided herein is a method of improving oral bioavailability of a compound of Formula (I) in a subject, comprising orally administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

[0109] Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in a method of improving oral bioavailability of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

[0110] Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of improving oral bioavailability of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

[0111] In some embodiments, the subject is a pediatric subject.

[0112] Also provided herein is a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

[0113] Also provided herein is a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt, for use in therapy, for example, for use in any of the methods disclosed herein.

[0114] Also provided herein is use of a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt, for manufacture of a medicament for use in any of the methods disclosed herein.

[0115] Other features and advantages of the methods, processes, formulations, and uses provided herein will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

[0116]

FIG. 1 shows the dissolution performance of several spray-dried dispersion formulations in 0.5 wt% simulated intestinal fluid (SIF) in phosphate buffered saline (PBS), pH 6.5.

FIG. 2 shows the vertical membrane flux cell integrated in the μ Diss Profiler™ used for the membrane flux assay.

FIG. 3 shows non-sink dissolution data for several spray-dried dispersion formulations and the compound of Formula (I) in 0.5 wt% SIF in PBS, pH 6.5.

FIG. 4 is a graph showing membrane flux of 1 mg/mL GB/IB 0.5 wt% SIF doses of the compound of Formula (I) and various spray-dried dispersion formulations over time. The solid lines indicate flux ($\mu\text{g min}^{-1} \text{cm}^{-2}$) and the broken lines indicate concentration ($\mu\text{g/mL}$) in 0.5% SIF.

FIG. 5 is a flow diagram of the spray drying manufacturing process used to prepare a 1000 g batch of a SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64.

FIGS. 6A and 6B are line graphs showing the pharmacokinetic results of a bioavailability and food effect study in dogs. FIG. 6A shows the results from Cohort 1 and FIG. 6B shows the results from Cohort 2.

FIG. 7 is a flow chart showing the study design of a Phase 1 study of the pharmacokinetics and food effect of the compound of Formula (I) in healthy adult subjects.

FIGS. 8A and 8B are line graphs showing the mean plasma concentration versus time profiles for the compound of Formula (I) under fasted and fed conditions, respectively, in healthy adult subjects.

FIGS. 9A-9C are spaghetti plots of the pharmacokinetics of the compound of Formula (I) in healthy adult subjects under fasted and fed conditions. FIG. 9A shows the $\text{AUC}_{0-\text{tlast}}$ values. FIG. 9B shows the $\text{AUC}_{0-\infty}$ values. FIG. 9C shows the C_{max} values.

FIG. 10 is a flow chart showing the study design of a Phase 1 study of the bioavailability, pharmacokinetics and food effect of the compound of Formula (I) in healthy adult subjects.

FIG. 11 shows the study design of a Phase 2 study of the compound of Formula (I) in adult subjects with congenital adrenal hyperplasia.

FIGs. 12A and 12B show the arithmetic mean values for adrenocorticotrophic hormone (ACTH) (FIG. 12A) and 17-hydroxyprogesterone (17-OHP) (FIG. 12B) for all 8 Cohort 1 subjects plotted at each time point for pre-treatment baseline (circles), day 1 (squares), and day 14 (triangles).

FIGs. 13A and 13B show arithmetic mean values for androstenedione (FIG. 13A) and testosterone (FIG. 13B) for all 8 Cohort 1 subjects were plotted at each timepoint for pre-treatment baseline (circles), day 1 (squares), and day 14 (triangles).

FIGs. 14A and 14B show the reduction of ACTH at timepoints 8-, 10-, and 12-hours postdose. FIG 14A shows the values for each time point as compared to baseline. FIG. 14B shows the mean values across all three timepoints. FIGs. 15A and 15B show the reduction of 17-OHP at timepoints 8-, 10-, and 12-hours postdose. FIG 15A shows the values for each time point as compared to baseline. FIG. 15B shows the mean values across all three timepoints. FIGs. 16A and 16B show the reduction of androstenedione at timepoints 8-, 10-, and 12-hours postdose. FIG 16A shows the values for each time point as compared to baseline. FIG. 16B shows the mean values across all three timepoints.

FIG. 17A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 17B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 17C: shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 18A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 18B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 18C shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 19A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 19B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 19C shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 20 is a scheme showing the manufacturing process for forming 50 mg capsules of the compound of Formula (I). FIG. 21 is an alternative scheme showing the manufacturing process for forming 50 mg capsules of the compound of Formula (I).

FIGs. 22A and 22B show a scheme showing the manufacturing process for forming SDD granules of the compound of Formula (I).

FIG. 23 is a scheme showing the manufacturing process for forming 50 mg/mL liquid formulation 1 of the compound of Formula (I).

FIG. 24 is a scheme showing the manufacturing process for forming 50 mg/mL liquid formulation 2 of the compound of Formula (I).

FIG. 25 is an XRPD spectrum of the compound of Formula (I) free base crystalline form I.

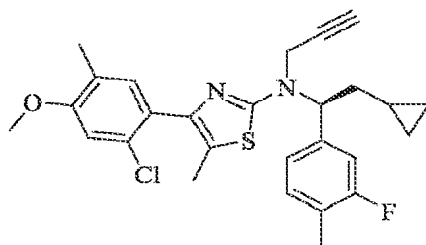
FIG. 26 is a DSC spectrum of the compound of Formula (I) free base crystalline form I.

FIG. 27 is an XRPD spectrum of the compound of Formula (I) tosylate crystalline form 1.

FIG. 28 is a DSC and TGA spectrum of the compound of Formula (I) tosylate crystalline form 1.

DETAILED DESCRIPTION

[0117] As described herein, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, is a selective CRF1 receptor antagonist that has been found to be effective treating congenital adrenal hyperplasia. Specifically, the compound of Formula (I) has been found to effectively reduce several biomarkers associated with congenital adrenal hyperplasia.

[0118] Newborn screening for CAH is performed by immunoassay to measure 17-OHP levels in heel-stick capillary blood specimens obtained within the first 72 hours of life. The blood sample is analyzed for 17-OHP by commercially available dissociation-enhanced lanthanide fluoroimmunoassay (DELFA; PerkinElmer, Waltham Massachusetts) (White et al., J. Pediatr. 163:10-12 (2013)). Second-tier screening tests utilizing biochemical and molecular genetic testing methods, performed between 8 and 14 days of life, are employed by nine states in the United States and strongly recommended by an additional 5 states. The biochemical method includes immunoassay with organic solvent extraction or liquid chromatography followed by tandem mass spectrometry to measure steroid ratios of 17-OHP, androstenedione, and 21-deoxycortisol to cortisol (see, e.g., Speiser et al., Int. J. Pediatr. Endocrinol. 2010:494173, 2010). The genetic screen looks for *CYP21A2* mutations that are associated with CAH. While not widely employed in the U.S., the addition of a second screening could potentially improve the sensitivity of the overall screening process, where sensitivity of the first screen alone is approximately 72%.

[0119] In absence of results from the newborn screening, female infants with classical CAH are typically identified due to the presence of ambiguous genitalia. Males have normal genitalia at birth and therefore are not diagnosed unless newborn screening is conducted or other medical complications come to attention. Infants who are not initially diagnosed with CAH and suffer from the salt-wasting form of the disease are later diagnosed in the setting of poor weight gain, vomiting, hyperkalemia and hyponatremia within the first few weeks of life.

[0120] Treatment of CAH is based on normalization of hormone and steroid levels using a variety of medications from diagnosis in infancy through adulthood. Glucocorticoids are the current standard treatment in CAH and are used both to correct the endogenous cortisol deficiency and for reducing the elevated ACTH levels from the pituitary, which drives increased androgen production. Unlike the treatment of Addison's disease (adrenal insufficiency), in which cortisol replacement is sufficient, the treatment of CAH must also reduce ACTH production, to control the subsequent androgen excess as well. Thus, the goals of glucocorticoid treatment include cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women and to inhibit testicular adrenal rest tumors in men. Mineralocorticoid replacement is needed to achieve normal plasma renin activity for maintenance of regular blood pressure, electrolyte balance, and volume status in those patients with the salt-wasting form of CAH.

[0121] The regimen of glucocorticoid treatment must support normal physiology and also ensure that sufficient cortisol is available during events that may elicit a strong stress response (e.g., intercurrent illness, exercise, hypotension). Careful monitoring is also necessary to avoid the development of iatrogenic Cushing's syndrome due to glucocorticoid overtreatment in an effort to adequately suppress androgen production, or Addisonian syndrome due to under-treatment.

[0122] Overtreatment with mineralocorticoids may cause hypertension while under-treatment may lead to low blood pressure, salt loss, fatigue and increased requirements for glucocorticoids. Typical laboratory tests for monitoring treatment efficacy include measurement of plasma concentrations of 17-OHP, androstenedione, testosterone, renin activity, and electrolytes. Adult patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension, and insulin resistance (see, e.g., Kim et al., Semin. Reprod. Med. 27(4):316-21 (2009)). A study of a large cohort of pediatric and adult CAH patients (n=244) demonstrated that patients are prescribed a variety of glucocorticoid treatment regimens yet frequently suffer from poor hormonal control and the aforementioned adverse outcomes (see, e.g., Finkelstein et al., J. Clin. Endocrinol Metab. 97(12):4429-38 (2012)).

[0123] Treatment of CAH includes efforts to normalize the cortisol deficiency with glucocorticoids (usually hydrocorti-

tisone in children but often more potent agents with narrow therapeutic indices, such as dexamethasone, in adults) and, if necessary for salt-wasting, mineralocorticoids (usually fludrocortisone). The glucocorticoid doses required to achieve sufficient suppression of excess androgens, however, are usually well above the normal physiologic dose used for cortisol replacement alone as in patients with Addison's disease. This increased exposure to glucocorticoids can lead to iatrogenic Cushing's syndrome, increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients (see, e.g., Elneave et al., J. Pediatr. Endocrinol. Metab. 21:1155-62 (2008); King et al., J. Clin. Endocrinol. Metab. 91(3):8656-59 (2006); Migeon et al., Endocrinol. Metab. Clin. North Am. 30:193-206 (2001)). Recently, best practices for the clinical management of congenital adrenal hyperplasia were published in the *Journal of Clinical Endocrinology and Metabolism* (Speiser, P.W., et al. J. Clin. Endocrinol Metab. November 2018, 103(11): 1-46). This article is incorporated by reference in its entirety.

[0124] Corticotropin-releasing factor (CRF) was isolated from ovine hypothalamus and identified as a 41-amino acid peptide. CRF has been found to produce profound alterations in endocrine, nervous, and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-induced release of adrenocorticotrophic hormone ("ACTH"), β -endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (see, e.g., Vale et al., Science 213:1394-1397, 1981). Secretion of CRF causes release of ACTH from corticotrophs in the anterior pituitary via binding to the CRF₁ receptor, a member of the class B family of G-protein coupled receptors.

[0125] Due to the physiological significance of CRF, the development of biologically-active small molecules having significant CRF₁ receptor binding activity and which are capable of antagonizing the CRF₁ receptor remains a desirable goal and has been the subject of ongoing research and development for the treatment of anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse.

[0126] The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. Deficiencies in these enzymes as a result of mutation or deletion cause the substrate concentrations to increase. In the most common form of CAH resulting from mutations or deletions in the 21-hydroxylase gene (CYP21A2), potent androgens are produced by the adrenal because of the accumulation of the steroid precursors, progesterone and 17-hydroxyprogesterone (17-OHP). Plasma levels of 17-OHP can reach 10-1000 times the normal concentration in these cases. These increases result in the overproduction of androgens, specifically androstenedione, testosterone, and dihydroxytestosterone causing virilization in females. In addition, 21-hydroxylase deficiency in CAH causes insufficient biosynthesis of glucocorticoids and mineralocorticoids, specifically cortisol and aldosterone. Cortisol is a critical negative feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates the restraint on the hypothalamus and pituitary, which causes ACTH levels to increase. The excessive ACTH stimulation causes hypertrophy of the zona fasciculata and zona reticularis resulting in adrenal hyperplasia.

Definitions

[0127] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

[0128] The term "about" preceding a value for DSC, TGA, or T_g, which are reported as degrees Celsius, have an allowable variability of $\pm 5^{\circ}\text{C}$. In all other instances, unless otherwise specified, the term "about" preceding a stated value includes the stated value and also includes $\pm 20\%$ of the stated value, and includes more specifically values of $\pm 10\%$, $\pm 5\%$, $\pm 2\%$, and $\pm 1\%$ of the stated value.

[0129] To provide a more concise description, some of the quantitative expressions herein are recited as a range from about amount X to about amount Y. It is understood that when a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any range therein.

[0130] "Room temperature" or "RT" refers to the ambient temperature of a typical laboratory, which is typically around 25°C .

[0131] "Spray-drying" refers to the method of producing a dry powder from a solution or slurry. The solution or slurry is atomized or rapidly dried with a hot gas, e.g., air or nitrogen, that causes the solvent to evaporate quickly and uniformly. A "spray-dried dispersion" refers to the powder obtained from the spray-drying process.

[0132] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, co-solvents, complexing agents, dispersion media, coatings, antibacterial and antifungal agents, isotonic

and absorption delaying agents, and the like, which are not biologically or otherwise undesirable. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic formulations is contemplated. Supplementary active ingredients can also be incorporated into the formulations. In addition, various excipients, such as are commonly used in the art, can be included. These and other such compounds are described in the literature, e.g., in the Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (2010); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 12th Ed., The McGraw-Hill Companies.

[0133] "Subject," as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate. In some embodiments, the subject is a human.

[0134] In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the subject has been identified or diagnosed as having congenital adrenal hyperplasia (CAH). In some embodiments, the subject is suspected of having CAH. In some embodiments, the subject has a clinical record indicating that the subject has CAH (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein). In some embodiments, the subject is a pediatric subject.

[0135] The term "pediatric subject" as used herein refers to a subject under the age of 21 years at the time of diagnosis or treatment. The term "pediatric" can be further divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman et al., Textbook of Pediatrics, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph et al., Rudolph's Pediatrics, 21st Ed. New York: McGraw-Hill, 2002; and Avery et al., Pediatric Medicine, 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

[0136] As used herein, the terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

[0137] The term "preventing," as used herein, means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

[0138] The term "administration" or "administering" refers to a method of giving a dosage of a compound or pharmaceutical formulation to a vertebrate or invertebrate, including a mammal, a bird, a fish, or an amphibian. The preferred method of administration can vary depending on various factors, e.g., the components of the pharmaceutical formulation, the site of the disease, and the severity of the disease.

[0139] As used herein, "therapeutically effective amount" is an amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or an amount of a pharmaceutical composition comprising the compound of Formula (I), which is sufficient to achieve the desired effect and can vary according to the nature and severity of the disease condition, and the potency of the compound. A therapeutic effect is the relief, to some extent, of one or more of the symptoms of the disease, and can include curing a disease. "Curing" means that the symptoms of active disease are eliminated. However, certain long-term or permanent effects of the disease can exist even after a cure is obtained (such as, e.g., extensive tissue damage).

[0140] The term "amorphous" means a solid in a solid state that is a non-crystalline state. Amorphous solids are disordered arrangements of molecules and therefore possess no distinguishable crystal lattice or unit cell and consequently have no definable long range ordering. The solid state form of a solid may be determined by polarized light microscopy, X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), or other standard techniques known to those of skill in the art.

[0141] As used herein, "time of day window" refers to a period of time defined by a window start time and a window stop time. These times all refer to local times where a sample was taken. The phrase "same time of day window" when

referring to samples taken from the subject mean, e.g., that a sample taken at 8:15 a.m. and a sample taken at 9:15 a.m. are considered to be taken in the same time of day window of, e.g., 2 a.m. to 10 a.m. or 6 a.m. to 10 a.m.

Methods

[0142] The present disclosure relates to methods of treating congenital adrenal hyperplasia (CAH). The methods include administering to a subject a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a subject a therapeutically effective amount of a SDD of the present disclosure that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a subject a therapeutically effective amount of pharmaceutical composition of the present disclosure that contains a SDD that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0143] Provided herein is a method of treating congenital adrenal hyperplasia (CAH) comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof to normalize or partially normalize levels of biomarkers associated with congenital adrenal hyperplasia. In some embodiments, normalizing or partially normalizing levels of biomarkers comprises reducing levels of elevated biomarkers or increasing levels of depressed biomarkers as compared to subject without CAH.

[0144] Provided herein is a method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers associated with congenital adrenal hyperplasia. In some embodiments, the biomarkers are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in the subject.

[0145] In some embodiments, the reduction in level of any of the biomarkers (e.g., any of 17-OHP, ACTH, and androstenedione) is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof. A day prior to administering the compound of Formula (I) applies to a subject that has not previously been administered the compound of Formula (I) within at least the past 24 hours.

[0146] In some embodiments, the circadian release of biomarkers associated with CAH occurs between the hours of 2 a.m. and 10 a.m. In other embodiments, the circadian release of biomarkers associated with CAH occurs between the hours of 6 a.m. and 10 a.m.

[0147] In some embodiments of any of the methods disclosed herein, the compound of Formula (I), or a pharmaceutically acceptable salt, is administered to the subject at nighttime or administration prior to sleep (i.e., bedtime administration). In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered six to eight hours prior to the circadian release of the biomarker. Administration prior to the circadian release may be adapted for shift workers (e.g., those who work at night and sleep during the day), in which case administration will not necessarily occur at nighttime. Administration is therefore dependent upon the expected circadian release of the biomarker, and can vary depending upon the individual's (i.e., subject, patient) particular work and sleep patterns.

[0148] In some embodiments of the methods provided herein, the level of 17-hydroxyprogesterone is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25%. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50%. In some embodiments of the methods provided herein, the level of 17-hydroxyprogesterone is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

[0149] In some embodiments, the level of 17-hydroxyprogesterone is reduced to a level within the range of 17-hydroxyprogesterone expected for a subject without CAH, i.e., less than 1,000 ng/dL or less than 200 ng/dL.

[0150] In some embodiments of the methods provided herein, the level of adrenocorticotrophic hormone is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of adrenocorticotrophic hormone is reduced by at least 25%. In some embodiments, the level of adrenocorticotrophic hormone is reduced by at least 40%. In some embodiments, the level of adrenocorticotrophic hormone is reduced by at least 50%.

[0151] In some embodiments of the methods provided herein, the level of adrenocorticotrophic hormone is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

55% to about 90%, or about 60% to about 90% from pre-administration levels.

[0152] In some embodiments, the level of adrenocorticotrophic hormone is reduced to a level within the range of adrenocorticotrophic hormone expected for a subject without CAH.

[0153] In some embodiments of the methods provided herein, the level of androstenedione is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

[0154] In some embodiments of the methods provided herein, the level of androstenedione is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

[0155] In some embodiments, the level of androstenedione is reduced to a level within the range of androstenedione expected for a subject without CAH, i.e., less than 200 ng/dL.

[0156] Also provided herein is a method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce one or more biomarker of CAH in a subject, e.g. reduce the androstenedione in the subject. Growth impairment can refer to, e.g., accelerated height velocity, accelerated weight velocity, and/or accelerated bone age.

[0157] Provided herein is a method for reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

[0158] Provided herein is a method for reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the corticosteroid is a glucocorticoid.

[0159] Also provided herein is a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. The long-term effects of glucocorticoid treatment are well documented in the art (see, e.g., Oray, M. et al. (2016): Long-term effect of glucocorticoids, Expert Opinion on Drug Safety. DOI: 10.1517/14740338.2016.1140743). Such side effects are associated with every biological system, e.g., musculoskeletal (e.g., osteoporosis, avascular necrosis of bone, and myopathy), endocrine and metabolic (e.g., hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression), gastrointestinal (e.g., gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis), cardiovascular (e.g., hypertension, coronary heart disease, ischemic heart disease, heart failure), dermatologic (e.g., dermatoprosia, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, and hair loss), neuropsychiatric (e.g., mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, and delirium), ophthalmologic (e.g., cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, and central serous chorioretinopathy), and immunologic (e.g., suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections).

[0160] Accordingly, in some embodiments, the side effects of glucocorticoid treatment are selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosia, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, reactivation of latent infections, and any combination thereof.

[0161] Provided herein is a method of treating congenital adrenal hyperplasia in a subject comprising

- (i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
- (ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
- (iii) administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof if the subject

is determined to have elevated levels of the one or more biomarkers.

[0162] In some embodiments, the method further comprises (iv) measuring the level of the one or more biomarkers after administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i). In some embodiments, the method further comprises (v) continuing the administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

[0163] In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

[0164] In some embodiments, steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

[0165] In some embodiments, steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

[0166] In some embodiments, step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

[0167] In some embodiments, step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

[0168] In some embodiments of the methods of the present disclosure, the compound of Formula (I) is administered at an amount equivalent to from about 25 mg to about 150 mg of the compound of Formula (I) free base. In some embodiments, compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at an amount equivalent to about 50 mg or about 100 mg of the compound of Formula (I) free base.

[0169] In some embodiments of the methods disclosed herein, compound of Formula (I) is administered in the free base form.

[0170] In some embodiments of the methods disclosed herein, the compound of Formula (I) is administered once daily.

[0171] Also provided herein is a method of treating CAH in a pediatric subject. The methods include administering to a pediatric subject a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a pediatric subject a therapeutically effective amount of a SDD of the present disclosure that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a pediatric subject a therapeutically effective amount of pharmaceutical composition of the present disclosure that contains a SDD that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pediatric subject is a neonate. In some embodiments, the pediatric subject is an infant. In some embodiments, the pediatric subject is a child. In some embodiments, the pediatric subject is an adolescent.

[0172] In some embodiments of the methods of the present disclosure, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject in a fed state. The term "fed state," as used herein, refers to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof from about 1 hour before consumption of food or a nutritional composition to about 1 hour after consumption of food or a nutritional composition. The term "fasted state," as used herein, refers to a gap of at least two hours between consumption of food or a nutritional composition and administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject with food or a nutritional composition, such as a nutritional supplement or formula, a meal replacement beverage, a liquid dietary supplement, or a high caloric liquid meal. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject within about 1 hour before the subject has consumed food or a nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject within about 1 hour after the subject has consumed food or a nutritional composition. Examples of suitable nutritional compositions include, but are not limited to, infant formulas, dietary supplements, dietary substitutes, and rehydration compositions. In some embodiments, the food is a product containing concentrated calories and protein. In some embodiments, the nutritional composition is a composition utilized for enteral and parenteral supplementation for infants, specialty infant formulas, supplements for the elderly, and supplements for those with gastrointestinal difficulties and/or malabsorption. Adult and pediatric nutritional formulas are well known in the art and are commercially available (e.g., Similac®, Ensure®, Jevity® and Alimentum® from Ross Products Division, Abbott Laboratories, Columbus, Ohio).

[0173] In some embodiments, the nutritional composition is in liquid form. The energy density of the nutritional compositions, when in liquid form, can range from about 0.6 Kcal to about 3 Kcal per mL. In some embodiments, the nutritional composition is in solid or powdered form. When in solid or powdered form, the nutritional supplements can contain from

about 1.2 to more than 9 Kcals per gram, such as about 3 to 7 Kcals per gram.

[0174] In some embodiments, the nutritional composition is a meal replacement bar. Examples include PowerBar®, Glucerna® bars, Choice DM® bars, Ensure® bars, and Boost® bars. In some embodiments, the nutritional composition is a nutrition shake or meal replacement beverage. Commercially available examples include the Ensure® branded adult products (such as Ensure® Original, Ensure® Plus, Ensure® Enlive, Ensure® High Protein, Ensure® Clear, and Ensure® Light), Glucerna®, Choice DM®, Slim Fast®, Pediasure®, Glytrol®, and Resource®. In some embodiments, the nutritional composition is Ensure® Plus. In some embodiments, the nutritional composition is vanilla-flavored Ensure® Plus. Ensure Plus® is a high calorie liquid dietary supplement that contains 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

[0175] In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

[0176] In some embodiments of the methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject before administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject at the same time as administration of the nutritional composition.

[0177] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject, followed by administration of the nutritional composition. In some embodiments, the nutritional composition is administered about 1 minute, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 40 minutes, about 45 minutes, or about 60 minutes, or within a range defined by any of the preceding values after administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the nutritional composition is administered 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, or 60 minutes, or within a range defined by any of the preceding values after administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the nutritional composition is administered within 30 minutes of administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

[0178] In some embodiments, the nutritional composition is administered to the subject, followed by administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered about 1 minute, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 40 minutes, about 45 minutes, or about 60 minutes, or within a range defined by any of the preceding values after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, or 60 minutes, or within a range defined by any of the preceding values after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered within 30 minutes of administering the nutritional composition. In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

[0179] In some embodiments of the methods, a food effect is observed between administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof in a fed state versus a fasted state. The term "food effect," as used herein, refers to the relative difference in AUC (area under the curve AUC_(0-t) and/or AUC_(0-∞)) or C_{max} (maximum plasma concentration or peak plasma concentration) of an active substance, when the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally to a subject, concomitantly with food or in a fed state as compared to the same values when the same compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered in a fasted state. The food effect (F) is calculated as:

$$F\% = [(X_{\text{fasted}} - X_{\text{fed}}) / X_{\text{fasted}}] \times 100$$

where X_{fed} and X_{fasted} are the values of AUC (AUC_(0-t) and/or AUC_(0-∞)) or C_{max} in the fed and fasted state, respectively. In some embodiments, an increased, or positive, food effect is observed when the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to a subject in a fed state. In some embodiments, administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in an increased, or positive, food effect, whereby an increased C_{max} and/or AUC are observed when administered orally in the fed state as compared to the fasting state.

[0180] In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10, such as about 5 to about 9, about 5 to about 8, about 5 to about 7, about 5 to about 6, about 6 to about 10, about 6 to about 9, about 6 to about 8, about 6 to about 7, about 7 to about 10, about 7 to about 9, about 7 to about 8, about 8 to about 10, about 8 to about 9, or about 8 to about 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5, about 6, about 7, about 8, about 9, or about 10, or within a range defined by any of the preceding values. In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is about 10 to about 20.

[0181] In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is 5 to 10, such as 5 to 9, 5 to 8, 5 to 7, 5 to 6, 6 to 10, 6 to 9, 6 to 8, 6 to 7, 7 to 10, 7 to 9, 7 to 8, 8 to 10, 8 to 9, or 8 to 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is 5, 6, 7, 8, 9, or 10, or within a range defined by any of the preceding values.

[0182] In some embodiments of the methods, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10, such as about 5 to about 9, about 5 to about 8, about 5 to about 7, about 5 to about 6, about 6 to about 10, about 6 to about 9, about 6 to about 8, about 6 to about 7, about 7 to about 10, about 7 to about 9, about 7 to about 8, about 8 to about 10, about 8 to about 9, or about 8 to about 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5, about 6, about 7, about 8, about 9, or about 10, or within a range defined by any of the preceding values. In some embodiments, the mean C_{max} of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is about 1.5 to about 3 times higher in the fed state compared to the fasted state. In some embodiments of the methods, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is 5 to 10, such as 5 to 9, 5 to 8, 5 to 7, 5 to 6, 6 to 10, 6 to 9, 6 to 8, 6 to 7, 7 to 10, 7 to 9, 7 to 8, 8 to 10, 8 to 9, or 8 to 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is 5, 6, 7, 8, 9, or 10, or within a range defined by any of the preceding values. In some embodiments, the mean C_{max} of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is 1.5 to 3 times higher in the fed state compared to the fasted state. In some embodiments, the mean C_{max} of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is about 2 times higher in the fed state compared to the fasted state. In some embodiments of the methods, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 10 to about 20.

[0183] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a meal. In some embodiments, the meal is a high fat, high caloric meal. In some embodiments, the meal is a low fat, low caloric meal. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered within approximately 5 minutes after the start of the meal. In some embodiments, the meal is an evening meal. In some embodiments, the meal is a morning meal.

[0184] In some embodiments, the fed state is with a high fat meal. In some embodiments, the fed state is with a low fat meal. The FDA has provided draft guidelines regarding high fat and low fat meals ("Assessing the Effects of Food on Drugs in INDs and NDAs - Clinical Pharmacology Considerations Guidance for Industry," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), February 2019, Clinical Pharmacology). Table 1 shows test meal definitions provided by the FDA guidance.

Table 1

Meal Type	Total Kcal	Fat		
		Kcal	Grams	Percent
High-Fat	800-1000	500-600	55-65	50
Low-Fat	400-500	100-125	11-14	25

[0185] The composition of a high fat meal provided by the FDA guidance is depicted in Table 2.

Table 2. Composition of a High Fat Meal*

Total Calories	800-1000
Calories from Protein	150
Calories from Carbohydrates	250
Calories from Fat	500-600

(continued)

An Example of a High Fat Breakfast	<ul style="list-style-type: none"> • Two eggs fried in butter • Two strips of bacon • Two slices of toast with butter • Four ounces of hash brown potatoes • Eight ounces of whole milk
*50 percent of calories are derived from fat. Substitutions can be made to this meal, if the content, volume, and viscosity are maintained.	

[0186] The composition of a low fat meal provided by the FDA guidance is depicted in Table 3.

Table 3. Composition of a Low Fat Meal

Total Calories	400-500
Fat (g)	250
Percent Calories from Fat	25
An Example of a Low Fat Breakfast*	<ul style="list-style-type: none"> • Eight ounces milk (1 percent fat) • One boiled egg • One packet flavored instant oatmeal made with water
*This low-fat breakfast contains 387 calories and has 10 grams of fat.	

[0187] In some embodiments, a high fat meal contains 800-1000 total Kcal and 500-600 fat Kcal. In some embodiments, a low fat meal contains 400-500 total Kcal and 100-125 fat Kcal.

[0188] Also provided herein is a method of improving gastrointestinal absorption of a compound of Formula (I), or pharmaceutically acceptable salt thereof, in a subject. The method includes orally administering to the subject a pharmaceutical composition of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I), or pharmaceutically acceptable salt thereof, which has not been prepared as a spray-dried dispersion. In some embodiments, the subject is a pediatric subject.

[0189] Also provided herein is a method of improving oral bioavailability of a compound of Formula (I), or pharmaceutically acceptable salt thereof, in a subject. The method includes orally administering to the subject a pharmaceutical composition of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I), or pharmaceutically acceptable salt thereof, which has not been prepared as a spray-dried dispersion.

[0190] In some embodiments of the methods provided herein, the subject is a pediatric subject.

[0191] Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition is a lipidic semi-solid formulation. In some embodiments, the pharmaceutical composition is a liquid formulation. In some embodiments, the pharmaceutical composition is administered to the subject in a fed state.

[0192] Also provided herein is a pharmaceutical composition of the present disclosure for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject. In some embodiments, the subject is in a fed state.

[0193] In some embodiments, the pharmaceutical composition is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than about 30%. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 6 to about 12 fluid ounces. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the pharmaceutical composition.

[0194] In some embodiments, the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max} , AUC, or a combination thereof of a compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the

fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1.5 to 3. In some embodiments, the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is 1.5 to 3.

[0195] In some embodiments, the subject is a pediatric subject.

[0196] In some embodiments, the pharmaceutical composition is formulated for oral administration and exhibits a positive food effect when administered orally. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the $C_{\max}$ in the fed state to the $C_{\max}$ in the fasted state of about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 10 to about 20. In some embodiments, the compound of Formula (I) has a ratio of the $C_{\max}$ in the fed state to the $C_{\max}$ in the fasted state of about 10 to about 20. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4 or about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the $C_{\max}$ in the fed state to the $C_{\max}$ in the fasted state of about 1 to about 4 or about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4. In some embodiments, the compound of Formula (I) has a ratio of the $C_{\max}$ in the fed state to the $C_{\max}$ in the fasted state of about 1 to about 4. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1.5 to about 3. In some embodiments, the compound of Formula (I) has a ratio of the $C_{\max}$ in the fed state to the $C_{\max}$ in the fasted state of about 1.5 to about 3. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1 to 4 or 5 to 10. In some embodiments, the compound of Formula (I) has a ratio of the $C_{\max}$ in the fed state to the $C_{\max}$ in the fasted state of 1 to 4 or 5 to 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1 to 4. In some embodiments, the compound of Formula (I) has a ratio of the $C_{\max}$ in the fed state to the $C_{\max}$ in the fasted state of 1 to 4. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1.5 to 3. In some embodiments, the compound of Formula (I) has a ratio of the $C_{\max}$ in the fed state to the $C_{\max}$ in the fasted state of 1.5 to 3.

[0197] In some embodiments, the pharmaceutical composition is administered to the subject with a meal. In some embodiments, the meal is a high fat meal. In some embodiments, the meal is a low fat meal. In some embodiments, the pharmaceutical composition is administered within about 5 minutes after the start of the meal. In some embodiments, the meal is an evening meal. In some embodiments, the meal is a morning meal.

[0198] In some embodiments, administering the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of $C_{\max}$, AUC, or combinations thereof of the compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound

of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1.5 to 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1.5 to 3.

[0199] For the avoidance of doubt, also provided herein is the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, or corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the corresponding methods, as described herein.

[0200] For the avoidance of doubt, also provided herein is use of the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

[0201] For the avoidance of doubt, also provided herein is use of the corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

Reduction in glucocorticoid burden, adrenal androgens and precursors

[0202] Glucocorticoids are a class of corticosteroids, which are a class of steroid hormones. Glucocorticoids are corticosteroids that bind to the glucocorticoid receptor that is present in almost every vertebrate animal cell. In some embodiments, the subject is concurrently receiving a dose of a glucocorticoid. In some embodiments, the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate. In some embodiments, the glucocorticoid is cortisol (hydrocortisone). In some embodiments, the glucocorticoid is cortisone. In some embodiments, the glucocorticoid is prednisone. In some embodiments, the glucocorticoid is dexamethasone.

[0203] In some embodiments, the glucocorticoid dose is measured in hydrocortisone equivalents. In some embodiments, the glucocorticoid dose is measured as a multiple of the upper limit of normal of physiologic dosing in hydrocortisone equivalents. Any glucocorticoid can be given in a dose that provides approximately the same glucocorticoid effects as normal cortisol production; this is referred to as physiologic, replacement, or maintenance dosing.

[0204] In some embodiments, the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m²/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m²/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m²/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0205] In some embodiments, the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m²/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m²/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m²/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0206] In some embodiments, the glucocorticoid dose concurrently given to the subject is a normal physiological dose of hydrocortisone equivalents. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 2 to about 16 mg/m²/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 4 to about 12 mg/m²/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 5 to about 11 mg/m²/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 6 to about 10 mg/m²/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 7 to about 9 mg/m²/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 4 to about 9 mg/m²/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 8 mg/m²/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 12 mg/m²/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is less than about 8 mg/m²/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15 or about 16 mg/m²/day, or within a range defined by any of the preceding values.

[0207] In some embodiments, the glucocorticoid dose concurrently given to the subject is at the upper limit of normal of a normal physiological dose of hydrocortisone equivalents. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the upper limit of normal is 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 2 times the normal physiological dose. In some embodiments, the upper limit of normal is about 2.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, or about 3.0 times the normal physiological dose, or within a range defined by any of the preceding values.

[illegible]

pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[illegible]

[0210] In some embodiments, the glucocorticoid dose of the subject is reduced within a range defined by any of the preceding values.

[0211] In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In

[0222] In some embodiments, the level of testosterone of the subject is reduced within a range defined by any of the preceding values.

[0223] In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than 1.5 times the upper limit of normal and the level of androstenedione is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0224] In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 50% and the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal and the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0225] In some embodiments, the level of 17-hydroxyprogesterone and androstenedione of the subject is reduced within a range defined by any of the preceding values.

[0226] In some embodiments, the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0227] In some embodiments, the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, one or more symptoms of glucocorticoid burden selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0228] In some embodiments, the quality of life as measured by the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) in the subject is improved after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) is relative to the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) results prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0229] In some embodiments, fatigue is reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in fatigue is relative to the fatigue prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0230] In some embodiments, sleep is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in sleep is relative to the sleep prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0231] In some embodiments, insulin resistance is reduced in the subject after a time period of administration of the

compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of insulin resistance is relative to the insulin resistance prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0232] In some embodiments, glucose tolerance is reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in glucose tolerance is relative to the glucose tolerance prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0233] In some embodiments, glucose control is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in glucose control is relative to the glucose control prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0234] In some embodiments, lipid levels reflecting dyslipidemia are reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in lipid levels is relative to the lipid levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0235] In some embodiments, lipid levels reflecting hyperlipidemia are reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in lipid levels is relative to the lipid levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0236] In some embodiments, bone mineral density is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in bone mineral density is relative to the bone mineral density prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0237] In some embodiments, bone turnover is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in bone turnover is relative to the bone turnover prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0238] In some embodiments, fat mass is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in fat mass is relative to the fat mass prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0239] In some embodiments, body weight is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in body weight is relative to the body weight prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0240] In some embodiments, central obesity is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in central obesity is relative to the central obesity prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0241] In some embodiments, blood pressure is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in blood pressure is relative to the blood pressure prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0242] In some embodiments, the severity of hirsutism is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in the severity of hirsutism is relative to the severity of hirsutism prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0243] In some embodiments, menstrual cyclicity is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in menstrual cyclicity is relative to the menstrual cyclicity prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0244] In some embodiments, control of testicular adrenal rest tumor is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in control of testicular adrenal rest tumor is relative to the control of testicular adrenal rest tumor prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0245] In some embodiments, fertility is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in fertility is relative to the fertility prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0246] In some embodiments, gonadotropin levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in gonadotropin levels is relative to the gonadotropin levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0247] In some embodiments, progesterone levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in progesterone

levels is relative to the progesterone levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0248] In some embodiments, semen levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in semen levels is relative to the semen levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0249] In some embodiments, LH (luteinizing hormone) levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in LH levels are relative to the LH levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0250] In some embodiments, the time period of administration is at least about 4 weeks. In some embodiments, the time period of administration is at least about 24 weeks. In some embodiments, the time period of administration is at least about one year. In some embodiments, the time period of administration is at least 4 weeks. In some embodiments, the time period of administration is at least 24 weeks. In some embodiments, the time period of administration is less than about 1 day. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6 or 7 days, or within a range of any of the preceding values. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 weeks, or within a range of any of the preceding values. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, or within a range of any of the preceding values. It is understood that comparative measurements occur preferably during the morning.

[0251] In some embodiments, the subject is a pediatric subject. In some embodiments, the pediatric subject is less than or equal to six years old. In some embodiments, the pediatric subject is greater than six years old and less than eleven years old. In some embodiments, the pediatric subject is greater than ten years old and less than fifteen years old. In some embodiments, the pediatric subject is greater than fourteen years old and less than nineteen years old.

[0252] In some embodiments, the subject is an adult subject. In some embodiments, the subject is over eighteen years old. In some embodiments, the subject is female. In some embodiments, the subject is male.

[0253] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described herein. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 9. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 11. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 12. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 13. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a hydrochloric acid salt or p-toluenesulfonic acid salt.

[0254] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a p-toluenesulfonic acid salt described herein.

[0255] For the avoidance of doubt, also provided herein is the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, or corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the corresponding methods, as described herein.

[0256] For the avoidance of doubt, also provided herein is use of the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

[0257] For the avoidance of doubt, also provided herein is use of the corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

p-Toluenesulfonic Acid Salt

[0258] In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt thereof is 4-(2-chloro-4-methoxy -5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

[0259] In some embodiments, the 4-(2-chloro-4-methoxy -5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt is a crystalline salt. In some embodiments, the p-toluenesulfonic acid crystalline salt has Form 1.

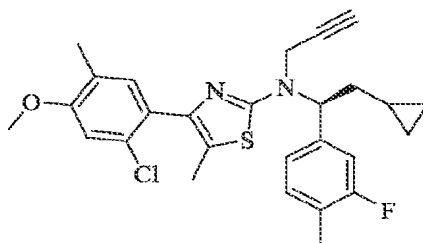
[0260] In some embodiments, the p-toluenesulfonic acid crystalline salt has an X-ray powder diffraction pattern as substantially shown in Figure 27. In some embodiments, the p-toluenesulfonic acid crystalline salt has a DSC thermogram substantially as depicted in Figure 28. In some embodiments, the p-toluenesulfonic acid crystalline salt has a thermogravimetric analysis (TGA) thermogram substantially as depicted in Figure 28.

[0261] In some embodiments, the p-toluenesulfonic acid crystalline salt has at least one X-ray powder diffraction (XRPD) peak, in terms of 2-theta (± 0.2 degrees), selected 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least two X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least three X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least four X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has characteristic X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), at 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has an endothermic peak having an onset of melt at about 156 °C (22.2 J/g) in a differential scanning calorimetry (DSC) thermogram.

Lipidic Semi-Solid Formulation

[0262] Provided herein is a lipidic semi-solid formulation, which is a pharmaceutical composition comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and

(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

[0263] In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 15 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 10 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base, or within a range of any of the preceding values.

[0264] In some embodiments, the pharmaceutical composition comprises an oily phase vehicle. An oily phase vehicle is a solvent that is poorly miscible with water. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 50 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 20 wt% to about 50 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 35 wt% to about 45 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 39 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 wt% of the oily phase vehicle, or within a range of any of the preceding values.

[0265] In some embodiments, the oily phase vehicle is selected from medium-chain triglycerides, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutool. In some embodiments, the oily phase vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides are Labrafac TM Lipophile WL1349. In some embodiments, the medium-chain triglycerides are Miglyol 812N.

[0266] In some embodiments, the pharmaceutical composition comprises an emulsifying agent. An emulsifying agent is a compound or substance that acts as a stabilizer for emulsions. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 50 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 10 wt% to about 30 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 15 wt% to about 25 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 20 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises

about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 wt% of the emulsifying agent, or within a range of any of the preceding values.

[0267] In some embodiments, the emulsifying agent is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutool. In some embodiments, the emulsifying agent is propylene glycol dicaprylate/dicaprate. In some embodiments, the propylene glycol dicaprylate/dicaprate is Labrafac TM PG.

[0268] In some embodiments, the pharmaceutical composition comprises a nonionic surfactant. A nonionic surfactant is a substance with a hydrophilic head and a hydrophobic tail that has no charge that is a formulation component added to improve solubility or emulsion properties. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 50 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 10 wt% to about 30 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 15 wt% to about 25 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 19 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 wt% of the nonionic surfactant, or within a range of any of the preceding values.

[0269] In some embodiments, the nonionic surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, Gelucire, lauroyl polyoxyl-32 glycerides, Poloxamer, PEG-32 stearate, and PEG-32 hydrogenated palm glycerides. In some embodiments, the nonionic surfactant is lauroyl polyoxyl-32 glycerides. In some embodiments, the lauroyl polyoxyl-32 glycerides are Gelucire® 44/14.

[0270] In some embodiments, the pharmaceutical composition comprises a solubilizing agent. A solubilizing agent is a solvent that assists with solubilizing the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 50 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 20 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 15 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 11 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 wt% of the solubilizing agent, or within a range of any of the preceding values.

[0271] In some embodiments, the solubilizing agent is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, and Poloxamer. In some embodiments, the solubilizing agent is vitamin E polyethylene glycol succinate. In some embodiments, the vitamin E polyethylene glycol succinate is Kolliphor® TPGS. In some embodiments, the vitamin E polyethylene glycol succinate is Vitamin E/TPGS 260.

[0272] In some embodiments, the pharmaceutical composition comprises:

- (a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
- (b) an oily phase vehicle;
- (c) an emulsifying agent;
- (d) a nonionic surfactant; and
- (e) a solubilizing agent.

[0273] In some embodiments, the pharmaceutical composition comprises:

- (a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 35 wt% to about 45 wt% of an oily phase vehicle;
- (c) about 15 wt% to about 25 wt% of an emulsifying agent;
- (d) about 15 wt% to about 25 wt% of a nonionic surfactant; and
- (e) about 5 wt% to about 15 wt% of a solubilizing agent.

[0274] In some embodiments, the pharmaceutical composition comprises:

- (a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 39 wt% of an oily phase vehicle;
- (c) about 20 wt% of an emulsifying agent;

- (d) about 19 wt% of a nonionic surfactant; and
- (e) about 11 wt% of a solubilizing agent.

[0275] In some embodiments, the pharmaceutical composition comprises:

- (a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
- (b) a medium-chain triglycerides component;
- (c) a propylene glycol dicaprylate/dicaprate component;
- (d) a lauroyl polyoxyl-32 glycerides component; and
- (e) a vitamin E polyethylene glycol succinate component.

[0276] In some embodiments, the pharmaceutical composition comprises:

- (a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
- (b) about 35 wt% to about 45 wt% of medium-chain triglycerides;
- (c) about 15 wt% to about 25 wt% of propylene glycol dicaprylate/dicaprate;
- (d) about 15 wt% to about 25 wt% of lauroyl polyoxyl-32 glycerides; and
- (e) about 5 wt% to about 15 wt% of vitamin E polyethylene glycol succinate.

[0277] In some embodiments, the pharmaceutical composition comprises:

- (a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
- (b) about 39 wt% of medium-chain triglycerides;
- (c) about 20 wt% of propylene glycol dicaprylate/dicaprate;
- (d) about 19 wt% of lauroyl polyoxyl-32 glycerides; and
- (e) about 11 wt% of vitamin E polyethylene glycol succinate.

[0278] In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 15 to about 40 centipoise at about 45 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 26 to about 30 centipoise at about 45 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 5 to about 25 centipoise at about 60 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 14 to about 18 centipoise at about 60 °C.

[0279] In some embodiments, the pharmaceutical composition does not comprise a combination of mannitol, croscarmellose sodium, maize starch, hydroxypropyl methylcellulose, and magnesium stearate.

[0280] In some embodiments, the pharmaceutical composition does not comprise at least one of mannitol, croscarmellose sodium, maize starch, hydroxypropyl methylcellulose, and magnesium stearate.

[0281] In some embodiments, the pharmaceutical composition comprises a compound of Formula (I), or pharmaceutically acceptable salt thereof, in crystalline form. In some embodiments, the pharmaceutical composition comprises a compound of Formula (I), or pharmaceutically acceptable salt thereof, in amorphous form. In some embodiments, the pharmaceutical composition comprises a compound of Formula (I) as a free base. In some embodiments, the crystalline form of the compound of Formula (I) is of Form I.

[0282] In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 75 mg to about 150 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 100 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 25 mg, based on the weight of the free base.

[0283] In some embodiments, the pharmaceutical composition is in the form of a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film. In some embodiments, the pharmaceutical composition is in tablet form. In some embodiments, the pharmaceutical composition is in capsule form. In some embodiments, the dosage form is coated.

[0284] Some embodiments provide a method for preparing the pharmaceutical composition, comprising:

- (a) heating a mixture of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent;
- (b) mixing the mixture of step (a) until a homogeneous mixture is achieved; and
- (c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the homogeneous mixture of step (b) until the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dissolved, forming a composition.

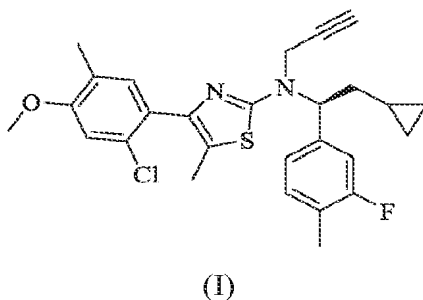
[0285] In some embodiments, the method further comprises:

- (d) encapsulating the composition of step (c) in a capsule shell to form a capsule; and
- (e) banding the capsule of step (d) in a mixture of banding agent and banding solvent.

Liquid Formulations

[0286] Provided herein is a pharmaceutical composition in oral solution dosage form comprising:

- (a) a compound of Formula (I):



- or a pharmaceutically acceptable salt thereof;
- (b) one or more of a sweetener, an anti-oxidant, and a flavor; and
- (c) a liquid vehicle.

[0287] In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base, or within a range of any of the preceding values.

[0288] In some embodiments, the pharmaceutical composition comprises a sweetener. A sweetener is a formulation component added to improve taste. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 1.5 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.1 w/v% to about 0.5 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.15 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.1, 0.2, 0.3, 0.4, or 0.5 w/v% of the sweetener, or within a range of any of the preceding values.

[0289] In some embodiments, the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and advantame. In some embodiments, the sweetener is saccharin.

[0290] In some embodiments, the pharmaceutical composition comprises an anti-oxidant. An anti-oxidant is a formulation component included to improve stability by preventing oxidation. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.17 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.1, 0.2, 0.3, 0.4, or 0.5 w/v% of the anti-oxidant, or within a range of any of the preceding values.

[0291] In some embodiments, the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TPGS, butylated

hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid. In some embodiments, the anti-oxidant is butylated hydroxytoluene.

[0292] In some embodiments, the pharmaceutical composition comprises a flavor. A flavor is a formulation component added to mask taste through aromatics. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 0.5 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.05 w/v% to about 0.2 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.10 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19 or 0.2 w/v% of the flavor, or within a range of any of the preceding values.

[0293] In some embodiments, the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetarome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor. In some embodiments, the flavor is FONA orange flavor.

[0294] A liquid vehicle is a solvent capable of dissolving or partially dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the purposes of delivery as an oral dosing solution. In some embodiments, the pharmaceutical composition comprises about 50 w/v% to about 99.9 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 90 w/v% to about 99 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 92 w/v% to about 97 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 94.6 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 w/v% of the liquid vehicle, or within a range of any of the preceding values.

[0295] In some embodiments, the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the liquid vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides is Labrafac Lipophile WL1349.

[0296] In some embodiments, the pharmaceutical composition further comprises a surfactant. A surfactant is a formulation component added to improve solubility or emulsion properties. In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 50 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 10 w/v% to about 30 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 20 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 w/v% of the surfactant, or within a range of any of the preceding values.

[0297] In some embodiments, the surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, sodium lauryl sulfate, Poloxamer, corn oil PEG-6 esters, and hydrogenated palm/palm kernel oil PEG-6 esters. In some embodiments, the surfactant is oleoyl polyoxyl-6 glycerides. In some embodiments, the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS.

[0298] In some embodiments, the pharmaceutical composition comprises about 50 w/v% to about 90 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 70 w/v% to about 80 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 75 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 74.6 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 w/v% of the liquid vehicle, or within a range of any of the preceding values.

[0299] In some embodiments, the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the liquid vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides is Labrafac Lipophile WL1349.

[0300] In some embodiments, the pharmaceutical composition comprises:

- (a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
- (b) a sweetener;
- (c) an anti-oxidant;
- (d) a flavor; and
- (e) a liquid vehicle.

[0301] In some embodiments, the pharmaceutical composition further comprises a surfactant.

[0302] In some embodiments, the pharmaceutical composition comprises:

- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
- (c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
- (d) about 0.05 w/v% to about 0.2 w/v% of a flavor; and
- (e) about 92 w/v% to about 97 w/v% of a liquid vehicle.

[0303] In some embodiments, the pharmaceutical composition comprises:

- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.15 w/v% of a sweetener;
- (c) about 0.17 w/v% of an anti-oxidant;
- (d) about 0.1 w/v% of a flavor; and
- (e) about 94.6 w/v% of a liquid vehicle.

[0304] In some embodiments, the pharmaceutical composition comprises:

- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
- (c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
- (d) about 0.05 w/v% to about 0.2 w/v% of a flavor;
- (e) about 15 w/v% to about 25 w/v% of a surfactant; and
- (f) about 70 w/v% to about 80 w/v% of a liquid vehicle.

[0305] In some embodiments, the pharmaceutical composition comprises:

- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.15 w/v% of a sweetener;
- (c) about 0.17 w/v% of an anti-oxidant;
- (d) about 0.1 w/v% of a flavor;
- (e) about 20 w/v% of a surfactant; and
- (f) about 75 w/v% of a liquid vehicle.

[0306] In some embodiments, the pharmaceutical composition comprises:

- (a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
- (b) saccharin;
- (c) butylated hydroxytoluene;
- (d) FONA orange flavor; and
- (e) medium-chain triglycerides.

[0307] In some embodiments, the pharmaceutical composition further comprises oleoyl polyoxyl-6 glycerides.

[0308] In some embodiments, the pharmaceutical composition comprises:

- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
- (c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
- (d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor; and

(e) about 92 w/v% to about 97 w/v% of medium-chain triglycerides.

[0309] In some embodiments, the pharmaceutical composition comprises:

- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.15 w/v% of saccharin;
- (c) about 0.17 w/v% of butylated hydroxytoluene;
- (d) about 0.1 w/v% of FONA orange flavor; and
- (e) about 94.6 w/v% of medium-chain triglycerides.

[0310] In some embodiments, the pharmaceutical composition comprises:

- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
- (c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
- (d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor;
- (e) about 15 w/v% to about 25 w/v% of oleoyl polyoxyl-6 glycerides; and
- (f) about 70 w/v% to about 80 w/v% of medium-chain triglycerides.

[0311] In some embodiments, the pharmaceutical composition comprises:

- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.15 w/v% of saccharin;
- (c) about 0.17 w/v% of butylated hydroxytoluene;
- (d) about 0.1 w/v% of FONA orange flavor;
- (e) about 20 w/v% of oleoyl polyoxyl-6 glycerides; and
- (f) about 75 w/v% of medium-chain triglycerides.

[0312] In some embodiments, the pharmaceutical composition comprises the compound of Formula (I) as a free base.

[0313] In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg/mL to about 200 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 75 mg/mL to about 150 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 50 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 100 mg/mL, based on the weight of the free base.

[0314] In some embodiments, the liquid pharmaceutical composition has a viscosity between about 1 to about 50 centipoise at about 25 °C.

[0315] Some embodiments provide a method for preparing a pharmaceutical composition comprising:

- (a) mixing a liquid vehicle with a sweetener;
- (b) mixing the mixture of step (a) with an anti-oxidant and a flavor;
- (c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the mixture of step (b); and
- (d) mixing the mixture of step (c) with an additional portion of the liquid vehicle.

[0316] In some embodiments, step (a) of the method comprises mixing a liquid vehicle with a sweetener and a surfactant.

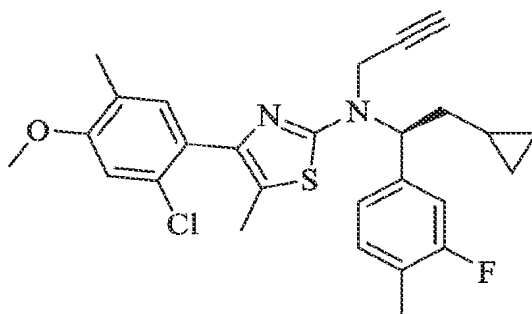
Spray-dried dispersions

[0317] The methods and uses of the present disclosure may comprise administering a spray-dried dispersion (SDDs) of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-

ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and to the use of the SDDs in the treatment of congenital adrenal hyperplasia (CAH).

[0318] In some embodiments, concentration and bioavailability enhancement in an aqueous environment of a low-solubility drug in a spray-dried dispersion is achieved if the SDD exhibits one or more properties, including, for example: (1) the solid dispersion is substantially homogeneous; (2) the drug is substantially amorphous; (3) the SDD has a relatively high drug loading; and (4) the SDD has a low residual solvent content. In some embodiments, the dispersion, when administered to an aqueous environment, provides at least a temporary dissolved drug concentration in the aqueous environment that is greater than the solubility of the crystalline form of the drug in the same environment. The aqueous environment can be, for example, an *in vitro* environment, such as a dissolution test media (e.g., phosphate buffered saline (PBS) solution), or an *in vivo* environment, such as the gastrointestinal (GI) tract of an animal, for example, a human. In some embodiments, the aqueous environment is the lower GI tract, such as the small intestine and large intestine.

[0319] Provided in the present disclosure is a spray-dried dispersion that contains a polymer and a compound having the structure of Formula (I):



or a pharmaceutically acceptable salt thereof. In some embodiments, the SDD includes a polymer selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from about 1:1 to about 1:9.

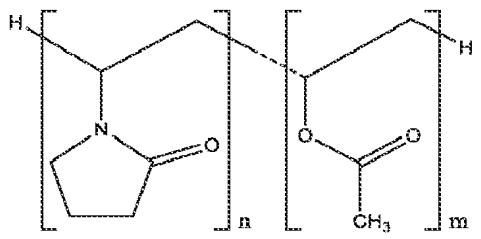
[0320] In some embodiments, the polymer is a neutral polymer. For example, the polymer does not contain any charged functional groups. In some embodiments, the neutral polymer is a cellulosic polymer. For example, the cellulosic polymer can be a polymer with at least one ester- and/or ether-linked substituent in which the polymer has a degree of substitution of at least 0.05 for each substituent. Examples of suitable neutral polymers include, but are not limited to, hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

[0321] In some embodiments, the polymer is an enteric polymer. An "enteric polymer," as used herein, is a polymeric substance that is substantially insoluble and/or substantially stable under acidic conditions exhibiting a pH of less than about 7 and which is substantially soluble or can decompose under conditions exhibiting a pH of about 7 or more. Examples of suitable enteric polymers include, but are not limited to, carboxymethyl ethyl cellulose (CMC), cellulose acetate phthalate (CAP), cellulose acetate succinate (CAS), methylcellulose phthalate, hydroxymethyl ethyl cellulose phthalate, hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), polyvinyl alcohol phthalate, polyvinyl butyrate phthalate, polyvinyl acetal phthalate, a copolymer of vinyl acetate/maleic anhydride, a copolymer of vinylbutylether/maleic anhydride, a copolymer of styrene/maleic acid monoester, a copolymer of methyl acrylate/methacrylic acid, a copolymer of styrene/acrylic acid, a copolymer of methyl acrylate/methacrylic acid/octyl acrylate, a copolymer of methacrylic acid/methyl methacrylate, an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, a methacrylic copolymer, and mixtures thereof. In some embodiments, the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer. In some embodiments, the enteric polymer is a Eudragit® polymer sold by Evonik Industries (Essen, Germany). In some embodiments, the enteric polymer is an amino methacrylate copolymer. In some embodiments, the amino methacrylate copolymer is Eudragit® E PO/100. In some embodiments, the enteric polymer is an ammonioalkyl methacrylate copolymer. In some embodiments, the ammonioalkyl methacrylate copolymer is Eudragit® RLPO. In some embodiments, the enteric polymer is a methacrylic copolymer. In some embodiments, the methacrylic copolymer is Eudragit® L100 or Eudragit® S100.

[0322] In some embodiments, the polymer is a pyrrolidone polymer. For example, the pyrrolidone polymer can be a vinyl pyrrolidone polymer, such as polyvinyl pyrrolidone (PVP) or polyvinyl pyrrolidone vinyl acetate (PVP/VA), including

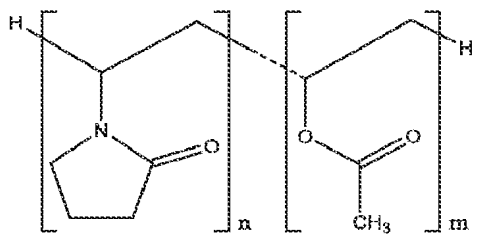
homopolymers and copolymers of PVP and homopolymers and copolymers of N-vinyl pyrrolidone. In some embodiments, the pyrrolidone polymer is PVP/VA. In some embodiments, the PVP/VA is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 30:70 to about 70:30 by weight, such as about 40:60 to about 60:40 by weight, or about 45:55 to about 55:45 by weight. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 30:70, about 35:65, about 40:60, about 45:55, about 50:50, about 55:45, about 60:40, about 65:35, or about 70:30 by weight. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight.

[0323] In some embodiments, the pyrrolidone polymer has the structure:



where the value of n is about 1 to about 2 times the value of m . For example, the value of n can be about 1, about 1.05, about 1.1, about 1.15, about 1.16, about 1.2, about 1.25, about 1.3, about 1.35, about 1.4, about 1.45, about 1.5, about 1.55, about 1.6, about 1.65, about 1.7, about 1.75, about 1.8, about 1.85, about 1.9, about 1.95, or about 2 times the value of m , or a value within a range defined by any of the preceding values. In some embodiments, the value of n is about 1.16 times the value of m . In some embodiments, the copolymer is copovidone, and the value of n is about 1.16 times the value of m .

[0324] In some embodiments, the pyrrolidone polymer has the structure:



where the value of n is 1 to 2 times the value of m . For example, the value of n can be 1, 1.05, 1.1, 1.15, 1.16, 1.2, 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, or 2 times the value of m , or a value within a range defined by any of the preceding values. In some embodiments, the value of n is 1.16 times the value of m . In some embodiments, the copolymer is copovidone, and the value of n is 1.16 times the value of m .

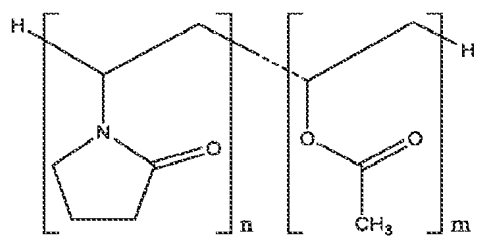
[0325] In some embodiments, the polymer used in the disclosed SDDs is present in an amount sufficient to increase the maximum drug concentration of the amorphous form of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the environment of use (e.g., aqueous environment) relative to a control composition that contains an equivalent amount of a crystalline form of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, but without polymer. In some embodiments, once the SDD is introduced into an environment of use (e.g., aqueous environment), the polymer increases the aqueous concentration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, relative to the control composition. It is to be understood that the control composition is free from solubilizers or other components that would materially affect the solubility of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and that the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is in solid form in the control composition.

[0326] In some embodiments of the SDDs, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from about 1:1 to about 1:9. For example, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer can be about 1:1 to about 1:8, about 1:1 to about 1:7, about 1:1 to about 1:6, about 1:1 to about 1:5, about 1:1 to about 1:4, about 1:1 to about 1:3, about 1:1 to about 1:2, about 1:1 to about 1:1.5, about 1:1.5 to about 1:9, or about 1:2.5 to about 1:4. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:9, about 1:8, about 1:7.5, about 1:7, about 1:6, about 1:5, about 1:4, about 1:3, about 1:2.5, about 1:2, about 1:1.5, or about

1:1, or a weight ratio within a range defined by any of the preceding values. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:9. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:1.5. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:1.

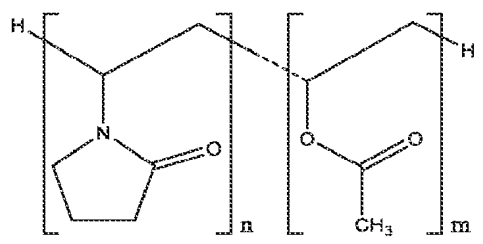
[0327] In some embodiments of the SDDs, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from 1:1 to 1:9. For example, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer can be 1:1 to 1:8, 1:1 to 1:7, 1:1 to 1:6, 1:1 to 1:5, 1:1 to 1:4, 1:1 to 1:3, 1:1 to 1:2, 1:1 to 1:1.5, 1:1.5 to 1:9, or 1:2.5 to 1:4. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:9, 1:8, 1:7.5, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2.5, 1:2, 1:1.5, or 1:1, or a weight ratio within a range defined by any of the preceding values. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:9. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:1.5. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:1.

[0328] In some embodiments, the spray dried dispersion includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



where the value of n is about 1 to about 2 times the value of m and the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight, and the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the copolymer is from about 1:1 to about 1:9.

[0329] In some embodiments, the spray dried dispersion includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



where the value of n is 1 to 2 times the value of m and the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of 60:40 by weight, and the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the copolymer is from 1:1 to 1:9.

[0330] In some embodiments of the SDDs, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer together form homogeneous particles. In some embodiments, the particles are a substantially homogeneous composition that includes the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer. As used herein, "substantially homogeneous" means that the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dispersed as homogeneously as possible throughout the polymer and can be thought of as a solid solution of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, dispersed in the polymer. While the dispersion can have some concentrated domains of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, the dispersion itself has a single glass transition temperature (T_g) which demonstrates that the dispersion is substantially homogeneous. This contrasts with a simple physical mixture of pure amorphous particles of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and pure amorphous polymer particles, which generally displays two distinct T_g s, one of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one of the polymer.

thereof, and one of the polymer. "T_g," as used herein, is the characteristic temperature where a glassy material, upon gradual heating, undergoes a relatively rapid (e.g., 10 to 100 seconds) physical change from a glass state to a rubber state.

[0331] In some embodiments, the particles have a particle size distribution (D-value, D₅₀), of about 5 μm to about 100 μm, such as about 5 μm to about 95 μm, about 5 μm to about 90 μm, about 5 μm to about 85 μm, about 5 μm to about 80 μm, about 5 μm to about 75 μm, about 5 μm to about 70 μm, about 5 μm to about 65 μm, about 5 μm to about 60 μm, about 5 μm to about 55 μm, about 5 μm to about 50 μm, about 5 μm to about 45 μm, about 5 μm to about 40 μm, about 5 μm to about 35 μm, about 5 μm to about 30 μm, about 5 μm to about 25 μm, about 5 μm to about 20 μm, about 5 μm to about 15 μm, about 5 μm to about 10 μm, about 10 μm to about 100 μm, about 10 μm to about 95 μm, about 10 μm to about 90 μm, about 10 μm to about 85 μm, about 10 μm to about 80 μm, about 10 μm to about 75 μm, about 10 μm to about 70 μm, about 10 μm to about 65 μm, about 10 μm to about 60 μm, about 10 μm to about 55 μm, about 10 μm to about 50 μm, about 10 μm to about 45 μm, about 10 μm to about 40 μm, about 10 μm to 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about 75 μm to about 100 μm, about 75 μm to about 95 μm, about 75 μm to about 90 μm, about 75 μm to about 85 μm, about 75 μm to about 80 μm, about 80 μm to about 100 μm, about 80 μm to about 95 μm, about 80 μm to about 90 μm, about 80 μm to about 85 μm, about 85 μm to about 100 μm, about 85 μm to about 95 μm, about 85 μm to about 90 μm, about 90 μm to about 100 μm, about 90 μm to about 95 μm, or about 95 μm to about 100 μm. In some embodiments, the D₅₀ is about 5 μm, about 10 μm, about 15 μm, about 16 μm, about 20 μm, about 25 μm, about 30 μm, about 35 μm, about 40 μm, about 45 μm, about 50 μm, about 55 μm, about 60 μm, about 65 μm, about 70 μm, about 75 μm, about 80 μm, about 85 μm, about 90 μm, about 95 μm, or about 100 μm. In some embodiments, the D₅₀ is about 10 μm, about 11 μm, about 12 μm, about 13 μm, about 14 μm, about 15 μm, about 16 μm, about 17 μm, about 18 μm, about 19 μm, or about 20 μm, or a value within a range defined by any of the preceding values. In some embodiments, the D₅₀ value is about 16 μm. The D₅₀ value can be measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, laser diffraction and

disc centrifugation.

[0332] In some embodiments, the particles have a particle size distribution (D-value, D_{50}), of 5 μm to 100 μm , such as 5 μm to 95 μm , 5 μm to 90 μm , 5 μm to 85 μm , 5 μm to 80 μm , 5 μm to 75 μm , 5 μm to 70 μm , 5 μm to 65 μm , 5 μm to 60 μm , 5 μm to 55 μm , 5 μm to 50 μm , 5 μm to 45 μm , 5 μm to 40 μm , 5 μm to 35 μm , 5 μm to 30 μm , 5 μm to 25 μm , 5 μm to 20 μm , 5 μm to 15 μm , 5 μm to 10 μm , 10 μm to 100 μm , 10 μm to 95 μm , 10 μm to 90 μm , 10 μm to 85 μm , 10 μm to 80 μm , 10 μm to 75 μm , 10 μm to 70 μm , 10 μm to 65 μm , 10 μm to 60 μm , 10 μm to 55 μm , 10 μm to 50 μm , 10 μm to 45 μm , 10 μm to 40 μm , 10 μm to 35 μm , 10 μm to 30 μm , 10 μm to 25 μm , 10 μm to 20 μm , 10 μm to 15 μm , 15 μm to 100 μm , 15 μm to 95 μm , 15 μm to 90 μm , 15 μm to 85 μm , 15 μm to 80 μm , 15 μm to 75 μm , 15 μm to 70 μm , 15 μm to 65 μm , 15 μm to 60 μm , 15 μm to 55 μm , 15 μm to 50 μm , 15 μm to 45 μm , 15 μm to 40 μm , 15 μm to 35 μm , 15 μm to 30 μm , 15 μm to 25 μm , 15 μm to 20 μm , 20 μm to 100 μm , 20 μm to 95 μm , 20 μm to 90 μm , 20 μm to 85 μm , 20 μm to 80 μm , 20 μm to 75 μm , 20 μm to 70 μm , 20 μm to 65 μm , 20 μm to 60 μm , 20 μm to 55 μm , 20 μm to 50 μm , 20 μm to 45 μm , 20 μm to 40 μm , 20 μm to 35 μm , 20 μm to 30 μm , 20 μm to 25 μm , 25 μm to 100 μm , 25 μm to 95 μm , 25 μm to 90 μm , 25 μm to 85 μm , 25 μm to 80 μm , 25 μm to 75 μm , 25 μm to 70 μm , 25 μm to 65 μm , 25 μm to 60 μm , 25 μm to 55 μm , 25 μm to 50 μm , 25 μm to 45 μm , 25 μm to 40 μm , 25 μm to 35 μm , 25 μm to 30 μm , 30 μm to 100 μm , 30 μm to 95 μm , 30 μm to 90 μm , 30 μm to 85 μm , 30 μm to 80 μm , 30 μm to 75 μm , 30 μm to 70 μm , 30 μm to 65 μm , 30 μm to 60 μm , 30 μm to 55 μm , 30 μm to 50 μm , 30 μm to 45 μm , 30 μm to 40 μm , 30 μm to 35 μm , 35 μm to 100 μm , 35 μm to 95 μm , 35 μm to 90 μm , 35 μm to 85 μm , 35 μm to 80 μm , 35 μm to 75 μm , 35 μm to 70 μm , 35 μm to 65 μm , 35 μm to 60 μm , 35 μm to 55 μm , 35 μm to 50 μm , 35 μm to 45 μm , 35 μm to 40 μm , 40 μm to 100 μm , 40 μm to 95 μm , 40 μm to 90 μm , 40 μm to 85 μm , 40 μm to 80 μm , 40 μm to 75 μm , 40 μm to 70 μm , 40 μm to 65 μm , 40 μm to 60 μm , 40 μm to 55 μm , 40 μm to 50 μm , 40 μm to 45 μm , 45 μm to 100 μm , 45 μm to 95 μm , 45 μm to 90 μm , 45 μm to 85 μm , 45 μm to 80 μm , 45 μm to 75 μm , 45 μm to 70 μm , 45 μm to 65 μm , 45 μm to 60 μm , 45 μm to 55 μm , 45 μm to 50 μm , 50 μm to 100 μm , 50 μm to 95 μm , 50 μm to 90 μm , 50 μm to 85 μm , 50 μm to 80 μm , 50 μm to 75 μm , 50 μm to 70 μm , 50 μm to 65 μm , 50 μm to 60 μm , 50 μm to 55 μm , 55 μm to 100 μm , 55 μm to 95 μm , 55 μm to 90 μm , 55 μm to 85 μm , 55 μm to 80 μm , 55 μm to 75 μm , 55 μm to 70 μm , 55 μm to 65 μm , 55 μm to 60 μm , 60 μm to 100 μm , 60 μm to 95 μm , 60 μm to 90 μm , 60 μm to 85 μm , 60 μm to 80 μm , 60 μm to 75 μm , 60 μm to 70 μm , 60 μm to 65 μm , 65 μm to 100 μm , 65 μm to 95 μm , 65 μm to 90 μm , 65 μm to 85 μm , 65 μm to 80 μm , 65 μm to 75 μm , 65 μm to 70 μm , 70 μm to 100 μm , 70 μm to 95 μm , 70 μm to 90 μm , 70 μm to 85 μm , 70 μm to 80 μm , 70 μm to 75 μm , 75 μm to 100 μm , 75 μm to 95 μm , 75 μm to 90 μm , 75 μm to 85 μm , 75 μm to 80 μm , 80 μm to 100 μm , 80 μm to 95 μm , 80 μm to 90 μm , 80 μm to 85 μm , 85 μm to 100 μm , 85 μm to 95 μm , 85 μm to 90 μm , 90 μm to 100 μm , 90 μm to 95 μm , or 95 μm to 100 μm . In some embodiments, the D_{50} is 5 μm , 10 μm , 15 μm , 16 μm , 20 μm , 25 μm , 30 μm , 35 μm , 40 μm , 45 μm , 50 μm , 55 μm , 60 μm , 65 μm , 70 μm , 75 μm , 80 μm , 85 μm , 90 μm , 95 μm , or 100 μm . In some embodiments, the D_{50} is 10 μm , 11 μm , 12 μm , 13 μm , 14 μm , 15 μm , 16 μm , 17 μm , 18 μm , 19 μm , or 20 μm , or a value within a range defined by any of the preceding values. In some embodiments, the D_{50} value is 16 μm . The D_{50} value can be measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, laser diffraction and disc centrifugation.

[0333] The SDDs of the present disclosure have a low residual solvent content. "Residual solvent content," as used herein, refers to the amount of solvent present in the SDD following spray drying, immediately upon exit from the spray dryer. The presence of solvent in the SDD lowers the glass transition temperature (T_g) of the dispersion. In some embodiments, mobility of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the SDD and its propensity to phase separate and crystallize decreases as the amount of residual solvent in the SDD decreases. In some embodiments, the SDDs have a residual solvent content of not more than about 10 wt%, such as not more than about 5 wt%, or not more than about 1 wt%. For example, the SDDs have a residual solvent content of about 2 wt%, about 1.9 wt%, about 1.8 wt%, about 1.7 wt%, about 1.6 wt%, about 1.5 wt%, about 1.4 wt%, about 1.3 wt%, about 1.2 wt%, about 1.1 wt%, about 1 wt%, about 0.9 wt%, about 0.8 wt%, about 0.7 wt%, about 0.6 wt%, about 0.5 wt%, or less. In some embodiments, the SDDs have a residual solvent content of less than about 2 wt%. In some embodiments, the SDDs have a residual solvent content of less than about 1 wt%. In some embodiments, the SDDs have a residual solvent content of about 0.5 wt% or less. In some embodiments, the SDDs have a residual solvent content of not more than 10 wt%, such as not more than 5 wt%, or not more than 1 wt%. For example, the SDDs may have a residual solvent content of 2 wt%, 1.9 wt%, 1.8 wt%, 1.7 wt%, 1.6 wt%, 1.5 wt%, 1.4 wt%, 1.3 wt%, 1.2 wt%, 1.1 wt%, 1 wt%, 0.9 wt%, 0.8 wt%, 0.7 wt%, 0.6 wt%, 0.5 wt%, or less. In some embodiments, the SDDs have a residual solvent content of less than 2 wt%. In some embodiments, the SDDs have a residual solvent content of less than 1 wt%. In some embodiments, the SDDs have a residual solvent content of 0.5 wt% or less.

[0334] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the spray-dried dispersion is substantially amorphous. As used herein, "substantially amorphous" means that the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in amorphous form is at least 60 wt% and that the amount of crystalline form present does not exceed 20 wt%. In some embodiments, the compound of Formula (I),

or a pharmaceutically acceptable salt thereof, in the dispersion is "almost completely amorphous," meaning that at least 90 wt% of the drug is amorphous, or that the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the crystalline form does not exceed 10 wt%. Amounts of crystalline drug can be measured by powder X-ray diffraction (PXRD), scanning electron microscope (SEM) analysis, differential scanning calorimetry (DSC), polarized light microscopy (PLM), or any other standard quantitative or qualitative measurement used to detect crystalline material. Without wishing to be bound by any theory, it is believed that the amorphous, or non-crystalline form, in combination with the polymer, leads to greater ease of dissolution and absorption in the desired location, for example, the intestines, resulting in enhanced bioavailability as compared to a crystalline form of the compound of Formula (I) without polymer.

Process for preparing spray-dried dispersions

[0335] Provided in the present disclosure are methods for preparing a spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof, such as the SDDs described herein. In some embodiments, the method includes dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer. In some embodiments, the product obtained by spray-drying is dried to remove the solvent or solvent mixture. In some embodiments, the organic solvent is acetone.

[0336] The SDDs disclosed herein can be obtained by spray-drying a mixture comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, one or more polymer(s), and an appropriate solvent or solvent mixture. Spray-drying involves atomization of a liquid mixture containing, for example, a solid and a solvent or solvent mixture, and removal of the solvent or solvent mixture. Atomization can be done, for example, through a two-fluid or pressure or electrosonic nozzle, or on a rotating disk.

[0337] Spray-drying converts a liquid feed to a dried particulate form. In some embodiments, spray-drying involves the atomization of a liquid feed solution into a spray of droplets and contacting the droplets with hot air or gas in a drying chamber. The composition to be spray-dried can be any solution, coarse suspension, slurry, colloidal dispersion, or paste that can be atomized using the selected spray-drying apparatus. In some embodiments, the composition is a solution that is clear and free of undissolved solids. In some embodiments, the sprays are produced by either rotary (wheel) or nozzle atomizers. Evaporation of moisture from the droplets and formation of dry particles proceed under controlled temperature and airflow conditions. Commercially available types of apparatus can be used to conduct the spray-drying. For example, commercial spray dryers are manufactured by Buchi Ltd. and Niro (e.g., the PSD line of spray driers manufactured by Niro). Techniques and methods for spray-drying can also be found in Perry's Chemical Engineering Handbook, 6th Ed., R. H. Perry, D. W. Green & J. O. Maloney, eds., McGraw-Hill Book Co. (1984); and Marshall, "Atomization and Spray-Drying" 50, Chem. Eng. Prog. Monogr. Series 2 (1954).

[0338] In some embodiments, the spray-drying is conducted with an inlet temperature of from about 40°C to about 100°C, for example, from about 60°C to about 80°C, or from about 70°C to about 75°C. In some embodiments, the spray-drying is conducted with an inlet temperature of about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 70°C, about 72°C, about 75°C, about 80°C, about 85°C, about 90°C, about 95°C, or about 100°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is about 60°C to about 80°C. In some embodiments, the spray-drying is conducted with an inlet temperature of about 61°C, about 63°C, about 65°C, about 67°C, about 69°C, about 71°C, about 73°C, about 75°C, about 77°C, about 79°C, about 81°C, about 83°C, or about 85°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is about 72°C.

[0339] In some embodiments, the spray-drying is conducted with an inlet temperature of from 40°C to 100°C, for example, from 60°C to 80°C, or from 70°C to 75°C. In some embodiments, the spray-drying is conducted with an inlet temperature of 40°C, 45°C, 50°C, 55°C, 60°C, 70°C, 72°C, 75°C, 80°C, 85°C, 90°C, 95°C, or 100°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is 60°C to 80°C. In some embodiments, the spray-drying is conducted with an inlet temperature of 61°C, 63°C, 65°C, 67°C, 69°C, 71°C, 73°C, 75°C, 77°C, 79°C, 81°C, 83°C, or 85°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is 72°C.

[0340] In some embodiments, the spray-drying is conducted with an outlet temperature of from about 20°C to about 75°C, for example, from about 25°C to about 50°C, or from about 30°C to about 40°C. In some embodiments, the spray-drying is conducted with an outlet temperature of about 20°C, about 25°C, about 30°C, about 35°C, about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 65°C, about 70°C, or about 75°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is about 25°C to about 45°C. In some embodiments, the spray-drying is conducted with an outlet temperature of about 24°C, about 26°C, about 28°C, about 30°C, about 32°C, about 34°C, about 36°C, about 38°C, about 40°C, about 42°C, about 44°C, or about 46°C, or within a range

defined by any of the preceding values. In some embodiments, the outlet temperature is about 35°C.

[0341] In some embodiments, the spray-drying is conducted with an outlet temperature of from 20°C to 75°C, for example, from 25°C to 50°C, or from 30°C to 40°C. In some embodiments, the spray-drying is conducted with an outlet temperature of 20°C, 25°C, 30°C, 35°C, 40°C, 45°C, 50°C, 55°C, 60°C, 65°C, 70°C, or 75°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is 25°C to 45°C. In some embodiments, the spray-drying is conducted with an outlet temperature of 24°C, 26°C, 28°C, 30°C, 32°C, 34°C, 36°C, 38°C, 40°C, 42°C, 44°C, or 46°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is 35°C.

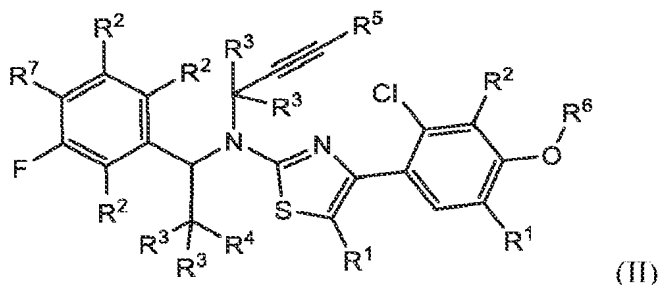
[0342] In some embodiments, the method involves removing the organic solvent after formation of the spray-dried dispersion. In some embodiments, the organic solvent is removed by drying the SDD. In some embodiments, a secondary drying process, such as fluidized bed drying, vacuum drying, tray drying, microwave drying, rotary drum drying or biconical vacuum drying is used to remove or reduce residual solvents, such as the organic solvent, to pharmaceutically acceptable levels. In some embodiments, the SDD is dried with a convection tray dryer.

[0343] In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of less than about 0.2 g/mL, or less than about 0.15 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of about 0.19 g/mL, about 0.18 g/mL, about 0.17 g/mL, about 0.16 g/mL, about 0.15 g/mL, about 0.14 g/mL, about 0.13 g/mL, about 0.12 g/mL, about 0.11 g/mL, about 0.1 g/mL, about 0.09 g/mL, about 0.08 g/mL, about 0.07 g/mL, about 0.06 g/mL or about 0.05 g/mL, or within a range defined by any of the preceding values. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of less than 0.2 g/mL, or less than 0.15 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of 0.19 g/mL, 0.18 g/mL, 0.17 g/mL, 0.16 g/mL, 0.15 g/mL, 0.14 g/mL, 0.13 g/mL, 0.12 g/mL, 0.11 g/mL, 0.1 g/mL, 0.09 g/mL, 0.08 g/mL, 0.07 g/mL, 0.06 g/mL or 0.05 g/mL, or within a range defined by any of the preceding values. The term "bulk density," as used herein, refers to a property of powders and is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume.

[0344] In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of less than about 0.3 g/mL, or less than about 0.25 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of about 0.29 g/mL, about 0.28 g/mL, about 0.27 g/mL, about 0.26 g/mL, about 0.25 g/mL, about 0.24 g/mL, about 0.23 g/mL, about 0.22 g/mL, about 0.21 g/mL, about 0.2 g/mL, or about 0.19 g/mL, or within a range defined by any of the preceding values. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of less than 0.3 g/mL, or less than 0.25 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of 0.29 g/mL, 0.28 g/mL, 0.27 g/mL, 0.26 g/mL, 0.25 g/mL, 0.24 g/mL, 0.23 g/mL, 0.22 g/mL, 0.21 g/mL, 0.2 g/mL, or 0.19 g/mL, or within a range defined by any of the preceding values. The term "tap density" or "tapped density," as used herein, refers to a measure of the density of a powder. The tapped density of a pharmaceutical powder is determined using a tapped density tester, which is set to tap the powder at a fixed impact force and frequency. Tapped density by the USP method is determined by a linear progression of the number of taps.

Deuterated Compounds

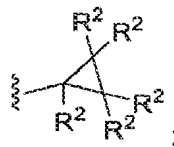
[0345] Also disclosed herein are compounds having the structure of the following formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

- each R¹ is independently C(R^A)₃;
- each R^A is independently hydrogen or deuterium;
- each R² is independently hydrogen or deuterium;

each R^3 is independently hydrogen or deuterium;
 R^4 is



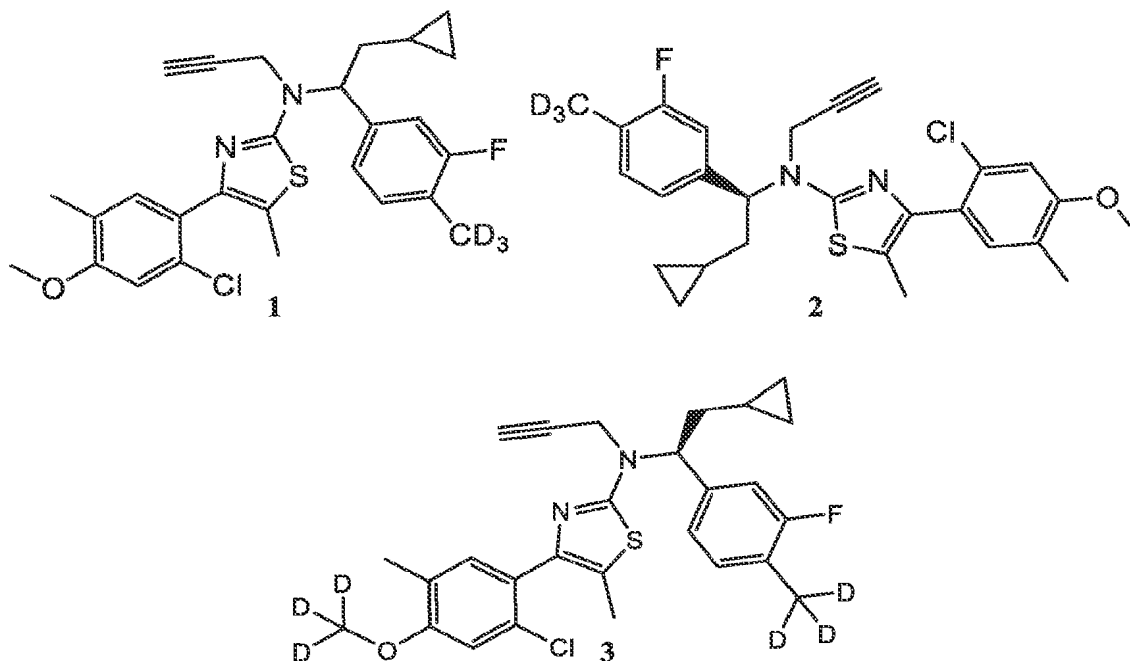
R^5 is hydrogen or deuterium;

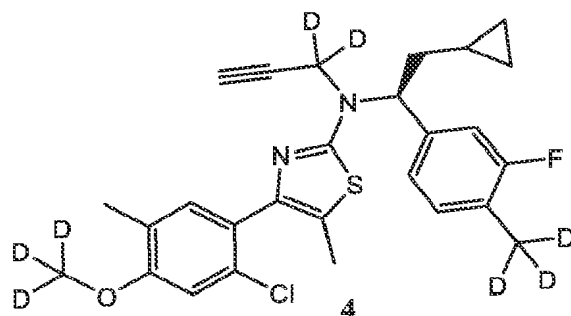
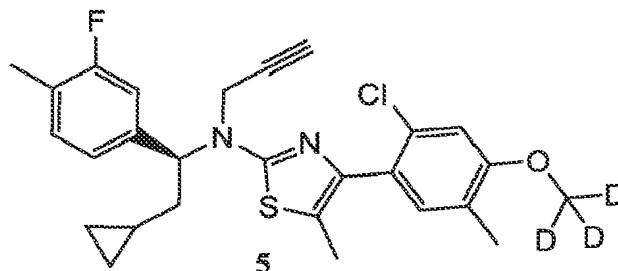
R^6 is $C(R^A)_3$; and

R^7 is $C(R^B)_3$, wherein at least one of R^A , R^B , R^2 , R^3 and R^5 is deuterium.

[0346] With regard to the compounds provided herein, when a particular atomic position is designated as having deuterium or "D" or "d", it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is about 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor of, in certain embodiments, at least 3500 (52.5% deuterium incorporation), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation) at each designated deuterium position.

[0347] In some embodiments, the compound of Formula (II) may be one of the following, or a pharmaceutically acceptable salt thereof:





Pharmaceutical compositions

[0348] The methods and uses disclosed herein can comprise administering the compound of Formula (I) as a pharmaceutical composition.

[0349] In some embodiments of the methods described herein, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered in a pharmaceutical composition further comprising one or more pharmaceutically acceptable excipients.

[0350] Also provided herein is a pharmaceutical composition comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in any of the methods described herein.

[0351] In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that does not comprise a spray-dried dispersion of the compound of Formula (I), as specified, e.g., in Example 1. Accordingly, in some embodiments, the pharmaceutical composition does not comprise any of the following polymers: hydroxypropylmethylcellulose acetate succinate-L (HPMCAS-L); polyvinyl pyrrolidone vinyl acetate 64 (PVP/VA 64); HPMCAS-M; and methyl methacrylate copolymer (1:1) (Eudragit® L100).

[0352] In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is not the reference formulation described in Example 9. Accordingly, in some embodiments, the pharmaceutical composition does not comprise at least three of the excipients selected from caprylic/capric triglyceride (Labrafac® Lipophile, Gattefossé, France); propylene glycol dicaprate/dicaprylate (Labrafac® PG, Gattefossé, France); oleoyl polyoxyl-6 glycerides (Labrafil® M 1944 CS, Gattefossé, France); polysorbate 20; polyoxyl castor oil (Kolliphor® RH 40, BASF, Germany); polyoxyl 15 hydroxystearate (Kolliphor® HS 15, BASF, Germany); lauroyl polyoxyl-32 glycerides (Gelucire® 44/14, Gattefossé, France); d- α -tocopheryl polyethylene glycol 1000 succinate (TPGS); and diethylene glycol monoethyl ether (Transcutol®, Gattefossé, France).

[0353] In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 9. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 11. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 12. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 13.

[0354] In some embodiments, the pharmaceutical compositions include a spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0355] In some embodiments, the pharmaceutical composition includes the SDD comprising a compound of Formula (I) and one or more pharmaceutically acceptable excipients. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 20% to about 90% w/w of the composition, such as about 20% to about 85%,

about 20% to about 80%, about 20% to about 75%, about 20% to about 70%, about 20% to about 65%, about 20% to about 60%, about 20% to about 55%, about 20% to about 50%, about 20% to about 45%, about 20% to about 40%, about 20% to about 35%, about 20% to about 30%, about 20% to about 25%, about 25% to about 90%, about 25% to about 85%, about 25% to about 80%, about 25% to about 75%, about 25% to about 70%, about 25% to about 65%, about 25% to about 60%, about 25% to about 55%, about 25% to about 50%, about 25% to about 45%, about 25% to about 40%, about 25% to about 35%, about 25% to about 30%, about 30% to about 90%, about 30% to about 85%, about 30% to about 80%, about 30% to about 75%, about 30% to about 70%, about 30% to about 65%, about 30% to about 60%, about 30% to about 55%, about 30% to about 50%, about 30% to about 45%, about 30% to about 40%, about 30% to about 35%, about 35% to about 90%, about 35% to about 85%, about 35% to about 80%, about 35% to about 75%, about 35% to about 70%, about 35% to about 65%, about 35% to about 60%, about 35% to about 55%, about 35% to about 50%, about 35% to about 45%, about 35% to about 40%, about 40% to about 90%, about 40% to about 85%, about 40% to about 80%, about 40% to about 75%, about 40% to about 70%, about 40% to about 65%, about 40% to about 60%, about 40% to about 55%, about 40% to about 50%, about 40% to about 45%, about 45% to about 90%, about 45% to about 85%, about 45% to about 80%, about 45% to about 75%, about 45% to about 70%, about 45% to about 65%, about 45% to about 60%, about 45% to about 55%, about 45% to about 50%, about 45% to about 50%, about 50% to about 90%, about 50% to about 85%, about 50% to about 80%, about 50% to about 75%, about 50% to about 70%, about 50% to about 65%, about 50% to about 60%, about 50% to about 55%, about 55% to about 90%, about 55% to about 85%, about 55% to about 80%, about 55% to about 75%, about 55% to about 70%, about 55% to about 65%, about 55% to about 60%, about 60% to about 90%, about 60% to about 85%, about 60% to about 80%, about 60% to about 75%, about 60% to about 70%, about 60% to about 65%, about 65% to about 90%, about 65% to about 85%, about 65% to about 80%, about 65% to about 75%, about 65% to about 70%, about 70% to about 90%, about 70% to about 85%, about 70% to about 80%, about 70% to about 75%, about 75% to about 90%, about 75% to about 85%, about 75% to about 80%, about 80% to about 90%, about 80% to about 85%, or about 85% to about 90% w/w of the composition. In some embodiments, the SDD is present in an amount of about 40% to about 90% w/w of the composition. In some embodiments, the SDD is present in an amount of about 40% to about 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 60% to about 80% w/w of the composition. In some embodiments, the SDD is present in an amount of about 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 1% to about 20% w/w of the composition, such as about 13% w/w of the composition.

[0356] In some embodiments, the pharmaceutical composition includes the SDD comprising a compound of Formula (I) and one or more pharmaceutically acceptable excipients. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of 20% to 90% w/w of the composition, such as 20% to 85%, 20% to 80%, 20% to 75%, 20% to 70%, 20% to 65%, 20% to 60%, 20% to 55%, 20% to 50%, 20% to 45%, 20% to 40%, 20% to 35%, 20% to 30%, 20% to 25%, 25% to 90%, 25% to 85%, 25% to 80%, 25% to 75%, 25% to 70%, 25% to 65%, 25% to 60%, 25% to 55%, 25% to 50%, 25% to 45%, 25% to 40%, 25% to 35%, 25% to 30%, 30% to 90%, 30% to 85%, 30% to 80%, 30% to 75%, 30% to 70%, 30% to 65%, 30% to 60%, 30% to 55%, 30% to 50%, 30% to 45%, 30% to 40%, 30% to 35%, 35% to 90%, 35% to 85%, 35% to 80%, 35% to 75%, 35% to 70%, 35% to 65%, 35% to about 60%, 35% to 55%, 35% to 50%, 35% to 45%, 35% to 40%, 40% to 90%, 40% to 85%, 40% to 80%, 40% to 75%, 40% to 70%, 40% to 65%, 40% to 60%, 40% to 55%, 40% to 50%, 40% to 45%, 45% to 90%, 45% to 85%, 45% to 80%, 45% to 75%, 45% to 70%, 45% to 65%, 45% to 60%, 45% to 55%, 45% to 50%, 50% to 90%, 50% to 85%, 50% to 80%, 50% to 75%, 50% to 70%, 50% to 65%, 50% to 60%, 50% to 55%, 55% to 90%, 55% to 85%, 55% to 80%, 55% to 75%, 55% to 70%, 55% to 65%, 55% to 60%, 60% to 90%, 60% to 85%, 60% to 80%, 60% to 75%, 60% to 70%, 60% to 65%, 65% to 90%, 65% to 85%, 65% to 80%, 65% to 75%, 65% to 70%, 70% to 90%, 70% to 85%, 70% to 80%, 70% to 75%, 75% to 90%, 75% to 85%, 75% to 80%, 80% to 90%, 80% to 85%, or about 85% to 90% w/w of the composition. In some embodiments, the SDD is present in an amount of 40% to 90% w/w of the composition. In some embodiments, the SDD is present in an amount of 40% to 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of 60% to 80% w/w of the composition. In some embodiments, the SDD is present in an amount of 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 1% to about 20% w/w of the composition, such as about 13% w/w of the composition.

[0357] In some embodiments of the pharmaceutical compositions disclosed herein (e.g., a composition including an SDD), the pharmaceutically acceptable excipient is selected from the group consisting of a filler, a lubricant, and combinations thereof. In some embodiments, the pharmaceutical excipients are selected from the group consisting of a glidant, a filler, a disintegrant, a lubricant, and a combination thereof.

[0358] In some embodiments, the pharmaceutical composition includes a filler. In some embodiments, the filler is selected from among binders, diluents, disintegrants, glidants, surfactants, and combinations thereof.

[0359] In some embodiments, the filler include saccharides (e.g., sugars, starch, and cellulose), gelatin, calcium carbonate, and synthetic polymers (e.g., polyvinylpyrrolidone, polyethylene glycol, and poloxamers (e.g., Poloxamer 188, a copolymer of polyoxyethylene and polyoxypropylene)). Exemplary fillers include, but are not limited to, glucose,

sucrose, lactose, a starch, including modified starches such as sodium starch glycolate (e.g., Explotab®), xylitol, dextrin, saccharose, sorbitol, mannitol (e.g., Parteck® M 200 (mannitol with an average particle size of about 50 µm to about 500 µm) or Parteck® M 100 (mannitol with an average particle size of less than 212 µm)), a cellulose, a polyvinylpyrrolidone, a polyethylene glycol, a polyvinyl alcohol, a polymethacrylate, dibasic calcium phosphate, magnesium stearate, calcium stearate, sodium stearate, stearic acid, hydrogenated vegetable oils, a mineral oil, sodium lauryl sulfate, magnesium lauryl sulfate, glyceryl palmitostearate, sodium benzoate, sodium stearyl fumarate, colloidal silicon dioxide, sodium benzoate, sodium oleate, sodium acetate, alginic acid, alginates (e.g., sodium alginate), calcium silicate, and ion exchange resins. Exemplary cellulose fillers include microcrystalline cellulose (e.g., Avicel® PH-101 (microcrystalline cellulose with an average particle size of approximately 50 µm) or Avicel® PH 200 (microcrystalline cellulose with an average particle size of approximately 180 µm)), methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethylcellulose. Exemplary fillers include cross-linked polyvinylpyrrolidone such as with an average particle size of 90 µm to 130 µm or with an average particle size of 10 µm to 30 µm). Other fillers known to those of skill in the art are also contemplated as being useful when formulated in the pharmaceutical compositions described herein.

[0360] In some embodiments, the filler is a binder. Binders include agents that hold the active pharmaceutical ingredient (e.g., spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof) and inactive ingredients together in a cohesive mix. Exemplary binders include, but are not limited to, glucose, sucrose, lactose, a starch, including modified starches such as sodium starch glycolate (Explotab®), xylitol, dextrin, saccharose, sorbitol, mannitol (e.g., Parteck® M 200 (mannitol with an average particle size of about 50 µm to about 500 µm), Parteck® M 100 (mannitol with an average particle size of less than 212 µm)), gelatin, gum tragacanth, acacia mucilage, a cellulose, a polyvinylpyrrolidone, a polyethylene glycol, a polyvinyl alcohol, a polymethacrylate, and sodium starch glycolate. Exemplary cellulose fillers include microcrystalline cellulose (e.g., Avicel® PH-101 (microcrystalline cellulose with an average particle size of approximately 50 µm) or Avicel® PH 200 (microcrystalline cellulose with an average particle size of approximately 180 µm)), cellulose ethers, methyl cellulose, ethyl cellulose, croscarmellose sodium, sodium carboxy methyl cellulose starches, hydroxypropyl cellulose, and hydroxypropyl methyl cellulose. Exemplary polyvinylpyrrolidone fillers include cross-linked polyvinylpyrrolidone such as Kollidon® CL (crospovidone with an average particle size of 90 µm to 130 µm) or Kollidon® CL-SF (crospovidone with an average particle size of 10 µm to 30 µm). Other binders known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

[0361] In some embodiments, the filler is a diluent. Suitable diluents include, but are not limited to, lactose, mannitol, isomalt, sucrose, dextrose, and sorbitol.

[0362] In some embodiments, the filler is a disintegrant. Disintegrants include any agent that promotes breakup of the formulation in an aqueous environment, for example, to promote more rapid release of the active pharmaceutical ingredient (e.g., the compound of Formula (I), or a pharmaceutically acceptable salt thereof). Exemplary disintegrants include, but are not limited to, starch and modified starches, such as corn starch, potato starch, sodium starch glycolate or croscarmellose sodium, alginic acid, alginates, such as sodium alginate, polyvinylpyrrolidone, bentonite, methylcellulose, agar, carboxymethylcellulose, crospovidone, acid-carbonate effervescent systems, such as citric acid with bicarbonate salts, and ion exchange resins. Other disintegrants known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

[0363] In some embodiments, the pharmaceutical composition comprises a disintegrant. In some embodiments, the pharmaceutical composition comprises about 1 w/w% to about 30 w/w% of the disintegrant. In some embodiments, the pharmaceutical composition comprises about 5 w/w% to about 15 w/w% of the disintegrant. In some embodiments, the pharmaceutical composition comprises about 10 w/w% of the disintegrant. In some embodiments, the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, and sodium bicarbonate. In some embodiments, the disintegrant is croscarmellose sodium.

[0364] In some embodiments, the filler is a glidant. Glidants can be used to improve the flowability of a powder or granules or both. Glidants include, but are not limited to, silicone dioxide, such as colloidal silicon dioxide or hydrated silicon dioxide, magnesium silicate, magnesium aluminometasilicate, talc, starch, calcium silicate, light anhydrous silicic acid, and silicon dioxide aerogels.

[0365] In some embodiments, the pharmaceutical composition comprises a glidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 5 w/w% of the glidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 1 w/w% of the glidant. In some embodiments, the pharmaceutical composition comprises about 0.67 w/w% of the glidant. In some embodiments, the glidant is selected from calcium silicate, silicon dioxide, and talc. In some embodiments, the glidant is calcium silicate.

[0366] In some embodiments, the filler is a surfactant, wetting agent, solubilizer, or combination thereof. Examples include, but are not limited to, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., Tween®), polyoxyethylene stearates, sodium dodecylsulfate, tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type, also known as superinone or triton). Other examples

include, but are not limited to, poloxamers such as Pluronic® F68, F127, and F108, which are block copolymers of ethylene oxide and propylene oxide, and polyxamines such as Tetronic® 908 (also known as Poloxamine® 908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (available from BASF), dextran, lecithin, dialkylesters of sodium sulfosuccinic acid, such as Aerosol® OT, which is a dioctyl ester of sodium sulfosuccinic acid (available from American Cyanamid), Duponol® P, which is a sodium lauryl sulfate (available from DuPont), Triton® X-200, which is an alkyl aryl polyether sulfonate (available from Rohm and Haas), Tween® 20 and Tween® 80, which are polyoxyethylene sorbitan fatty acid esters (available from ICI Specialty Chemicals), Carbowax™ 3550 and 934, which are polyethylene glycols (available from Union Carbide), Crodesta™ F-110, which is a mixture of sucrose stearate and sucrose distearate, and Crodesta™ SL-40 (both available from Croda Inc.), and SA90HCO, which has the chemical formula $C_{18}H_{37}-CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$.

[0367] In some embodiments, the pharmaceutical composition comprises a filler. In some embodiments, the pharmaceutical composition comprises about 30 w/w% to about 99 w/w% of the filler. In some embodiments, the pharmaceutical composition comprises about 50 w/w% to about 90 w/w% of the filler. In some embodiments, the pharmaceutical composition comprises about 75.5 w/w% of the filler. In some embodiments, the filler is selected from mannitol, microcrystalline cellulose, lactose, starch, isomalt, silicified microcrystalline cellulose, Dicalcium Phosphate, maltodextrin, and a combination thereof. In some embodiments, the filler is a combination of mannitol and microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 30 w/w% to about 80 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 50 w/w% to about 60 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 56 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 1 w/w% to about 50 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 10 w/w% to about 30 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 20 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose.

[0368] In some embodiments, the pharmaceutical composition includes a lubricant. Lubricants are agents added to pharmaceutical formulations to reduce friction during processing and prevent ingredients from clumping together. Exemplary lubricants include, but are not limited to, talc, starch, magnesium stearate, calcium stearate, sodium stearate, zinc stearate, stearic acid, vegetable stearin, adipic acid, waxy fatty acids, such as glyceryl behenate, a hydrogenated vegetable oil, a mineral oil, a polyethylene glycol, lycopodium, sodium lauryl sulfate, magnesium lauryl sulfate, glyceryl palmitostearate, sodium benzoate, sodium chloride, sterotex, glycerol monostearate, sodium stearyl fumarate, colloidal silicon dioxide, sodium benzoate, sodium oleate, and sodium acetate. Other lubricants known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

[0369] In some embodiments, the pharmaceutical composition comprises a lubricant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 10 w/w% of the lubricant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 1 w/w% of the lubricant. In some embodiments, the pharmaceutical composition comprises about 0.5 w/w% of the lubricant. In some embodiments, the pharmaceutical lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid sodium lauryl sulfate, sodium oleate, glyceryl behenate, and talc. In some embodiments, the lubricant is sodium stearyl fumarate.

[0370] In some embodiments, the pharmaceutical composition comprises:

- (a) the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;
- (b) a glidant;
- (c) a filler; and
- (d) a disintegrant.

[0371] In some embodiments, the pharmaceutical composition comprises:

- (a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;
- (b) about 0.1 w/w% to about 1 w/w% of a glidant;
- (c) about 50 w/w% to about 90 w/w% of a filler; and
- (d) about 5 w/w% to about 0.2 w/w% of a disintegrant.

[0372] In some embodiments, the pharmaceutical composition comprises:

- (a) about 13 w/w% of the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;

- (b) about 0.67 w/w% of a glidant;
- (c) about 75.5 w/w% of a filler; and
- (d) about 10 w/w% of a disintegrant.

5 **[0373]** In some embodiments, the pharmaceutical composition comprises:

- (a) the spray-dried dispersion of Example 3;
- (b) calcium silicate;
- (c) a combination of mannitol and microcrystalline cellulose; and
- (d) croscarmellose sodium.

[0374] In some embodiments, the pharmaceutical composition comprises:

- (a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of Example 3;
- (b) about 0.1 w/w% to about 1 w/w% of calcium silicate;
- (c) about 50 w/w% to about 60 w/w% of mannitol and about 10 w/w% to about 30 w/w% of microcrystalline cellulose; and
- (d) about 5 w/w% to about 0.2 w/w% of croscarmellose sodium.

20 **[0375]** In some embodiments, the pharmaceutical composition comprises:

- (a) about 13 w/w% of the spray-dried dispersion of Example 3;
- (b) about 0.67 w/w% of calcium silicate;
- (c) about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose; and
- (d) about 10 w/w% of croscarmellose sodium.

[0376] Additional excipients can be included in the pharmaceutical formulations of the present disclosure. Further examples of excipients include, but are not limited to, pigments, colorants, flavoring agents, preservatives, and sweeteners. Flavors and colors can be added to improve the taste or appearance of a formulation. Examples of preservatives used in pharmaceutical compositions are aromatic alcohols, such as benzyl or phenol alcohol, antioxidants such as vitamin A, vitamin E, vitamin C, and selenium, amino acids such as cysteine and methionine, citric acid and sodium citrate, or synthetic preservatives such as methyl paraben and propyl paraben. Sweeteners can be added to make the ingredients more palatable, especially in chewable tablets or liquids like syrups.

[0377] Also provided are methods for preparing a pharmaceutical composition, such as a pharmaceutical composition of the present disclosure. In some embodiments, the method includes combining the spray-dried dispersion described herein with one or more pharmaceutically acceptable excipients, e.g., a pharmaceutically acceptable excipient described herein.

[0378] In some embodiments, the method for preparing the pharmaceutical composition comprises:

- (a) blending the spray-dried dispersion described herein, with a glidant;
- (b) further blending the blend of step (a) with a filler and a disintegrant;
- (c) screening the blend of step (b) to break up aggregates and assist with blend uniformity;
- (d) further blending the intragranular blend of step (c);
- (e) compaction of the intragranular blend of step (d) via roller compaction to form granules; and
- (f) milling of ribbon from roller compaction into granules of step (e).

[0379] In some embodiments, the spray-dried dispersion is the spray-dried dispersion described in Example 3.

[0380] The pharmaceutical compositions of the present disclosure are formulated for oral administration. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media can be employed. For solid oral preparations such as, for example, powders, capsules, caplets, gelcaps, and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

[0381] Oral pharmaceutical dosage forms can be solid, gel, or liquid. In some embodiments, the dosage form is a solid dosage form. In some embodiments, the solid dosage form is a pill, tablet, capsule, caplet, gelcaps, granules, powder, sachet, melting strip, or melting film. In some embodiments, the solid dosage form is coated. In some embodiments, the

coating is an enteric coating, a sugar coating, or a film coating. In some embodiments, the solid dosage form is a coated particle, coated tablet, enterocoated tablet, or enterocoated capsule. In some embodiments, the solid dosage form is a pill or tablet. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric coated, sugar coated or film coated. In some embodiments, the pharmaceutical composition is formulated as a capsule. In some

[0382] The pharmaceutical compositions of the present disclosure can contain, per dosage unit, e.g., tablet, capsule, powder, and the like, an amount of the active ingredient necessary to deliver an effective dose as described above.

[0383] In some embodiments, the pharmaceutical compositions of the present disclosure are formulated in unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg in the unit dosage form. For example, about 5 mg to about 175 mg, about 5 mg to about 150 mg, about 5 mg to about 125 mg, about 5 mg to about 100 mg, about 5 mg to about 75 mg, about 5 mg to about 50 mg, about 5 mg to about 25 mg, about 25 mg to about 200 mg, about 25 mg to about 175 mg, about 25 mg to about 150 mg, about 25 mg to about 125 mg, about 25 mg to about 100 mg, about 25 mg to about 75 mg, about 25 mg to about 50 mg, about 50 mg to about 200 mg, about 50 mg to about 175 mg, about 50 mg to about 150 mg, about 50 mg to about 125 mg, about 50 mg to about 100 mg, about 50 mg to about 75 mg, about 75 mg to about 200 mg, about 75 mg to about 175 mg, about 75 mg to about 150 mg, about 75 mg to about 125 mg, about 75 mg to about 100 mg, about 100 mg to about 200 mg, about 100 mg to about 175 mg, about 100 mg to about 150 mg, about 100 mg to about 125 mg, about 125 mg to about 200 mg, about 125 mg to about 175 mg, about 125 mg to about 150 mg, about 150 mg to about 200 mg, about 150 mg to about 175 mg, or about 175 mg to about 200 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg to about 125 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg, about 10 mg, about 25 mg, about 35 mg, about 50 mg, about 65 mg, about 75 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, or about 200 mg in the unit dosage form, or within a range defined by any of the preceding values. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 5 mg to 250 mg in the unit dosage form. For example, 5 mg to 175 mg, 5 mg to 150 mg, 5 mg to 125 mg, 5 mg to 100 mg, 5 mg to 75 mg, 5 mg to 50 mg, 5 mg to 25 mg, 25 mg to 200 mg, 25 mg to 175 mg, 25 mg to 150 mg, 25 mg to 125 mg, 25 mg to 100 mg, 25 mg to 75 mg, 25 mg to 50 mg, 50 mg to 200 mg, 50 mg to 175 mg, 50 mg to 150 mg, 50 mg to 125 mg, 50 mg to 100 mg, 50 mg to 75 mg, 75 mg to 200 mg, 75 mg to 175 mg, 75 mg to 150 mg, 75 mg to 125 mg, 75 mg to 100 mg, 100 mg to 200 mg, 100 mg to 175 mg, 100 mg to 150 mg, 100 mg to 125 mg, 125 mg to 200 mg, 125 mg to 175 mg, 125 mg to 150 mg, 150 mg to 200 mg, 150 mg to 175 mg, or 175 mg to 200 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 25 mg to 125 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 75 mg to 150 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 5 mg, 10 mg, 25 mg, 35 mg, 50 mg, 65 mg, 75 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg in the unit dosage form, or within a range defined by any of the preceding values. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 50 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 100 mg in the unit dosage form. In some embodiments, the pharmaceutical compositions of the present disclosure are formulated as a tablet. In some embodiments, the tablet is coated. In some

[0384] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 25 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 75 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 100 mg, based on the weight of the

free base.

[0385] In some embodiments, the pharmaceutical composition is administered in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

[0386] In some embodiments, the pharmaceutical composition comprises about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

[0387] The daily dosage of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a pharmaceutical composition as described in the present disclosure can be varied over a wide range from about 1.0 mg to about 10,000 mg per adult human per day, or higher, or any range therein. For oral administration, the compositions can be provided in the form of tablets containing, for example, about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2.5 mg, about 5.0 mg, about 10.0 mg, about 15.0 mg, about 25.0 mg, about 50.0 mg, about 75.0 mg, about 100 mg, about 150 mg, about 200 mg, about 250 or about 500 milligrams of the compound of Formula (I), or pharmaceutically acceptable salt thereof, for the symptomatic adjustment of the dosage to the subject to be treated. In some embodiments, an effective amount of the compound of Formula (I), or pharmaceutically acceptable salt thereof, can be supplied at a dosage level of from about 0.1 mg/kg to about 1000 mg/kg of body weight per day, or any range therein, for example, the range can be from about 0.5 mg/kg to about 500 mg/kg, about 1.0 mg/kg to about 250 mg/kg, about 0.1 mg/kg to about 100 mg/kg, about 0.1 mg/kg to about 50.0 mg/kg of body weight per day, about 0.1 mg/kg to about 15.0 mg/kg of body weight per day, about 0.5 mg/kg to about 7.5 mg/kg of body weight per day, or any amount to range therein. In some embodiments, an effective amount of the compound of Formula (I), or pharmaceutically acceptable salt thereof, can be supplied at a dosage level of from 0.1 mg/kg to 1000 mg/kg of body weight per day, or any range therein, for example, the range can be from 0.5 mg/kg to 500 mg/kg, 1.0 mg/kg to 250 mg/kg, 0.1 mg/kg to 100 mg/kg, 0.1 mg/kg to 50.0 mg/kg of body weight per day, 0.1 mg/kg to 15.0 mg/kg of body weight per day, 0.5 mg/kg to 7.5 mg/kg of body weight per day, or any amount to range therein. A pharmaceutical composition as provided herein can be administered on a regimen of 1 to 4 times per day or in a single daily dose.

[0388] In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 25 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 50 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 75 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 100 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 150 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 200 mg, based on the weight of the free base.

[0389] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 25 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 75 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 100 mg, based on the weight of the free base.

[0390] In some embodiments, the daily dose of the pharmaceutical composition is about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

[0391] In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

[0392] In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

[0393] In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof, twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

[0394] Factors associated with the particular subject being treated, including subject age, weight, diet, and time of administration, can result in the need to adjust dosages. In some embodiments, the subject is a human adult. In some embodiments, the subject is a pediatric subject.

[0395] One skilled in the art will recognize that both *in vivo* and *in vitro* trials using suitable, known, and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder. One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy subjects and/or those suffering from a given disorder, can be completed according to methods well known in the clinical and medical arts. For example, determining proper dosages for pediatric subjects can be determined using known methods, including weight, age, and models such as Simcyp® Pediatric Simulation modeling (CERTARA, Princeton, N.J.) which can be used to establish a pharmacokinetic approach for dosing that takes into account subject age, ontogeny of the clearance pathways that a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and body surface area (BSA).

[0396] In some embodiments, the pharmaceutical compositions of the present disclosure are stable for at least 3 months. In some embodiments, the pharmaceutical compositions are stable for at least 6 months. In some embodiments, the pharmaceutical compositions are stable for at least 9 months. In some embodiments, the pharmaceutical compositions are stable for at least 12 months. For example, the compositions do not exhibit a change (e.g., greater than 5%) in appearance, pH, percent impurities, activity (as measured by *in vitro* assays), or osmolality over time, e.g., at least 3 months, 6 months, 9 months, or at least 12 months as compared to the original composition after manufacturing. In some embodiments, the pharmaceutical compositions do not exhibit a significant change, as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in one or more of appearance, pH, percent impurities, activity (as measured by *in vitro* assays), or osmolality over time, e.g., at least 12 months as compared to the original pharmaceutical composition after manufacturing.

Kits

[0397] Also provided are kits. Typically, a kit includes one or more pharmaceutical compositions as described herein, e.g., a pharmaceutical composition containing, e.g., a spray-dried dispersion as described in Examples 1-4, or the formulation described in Example 9. In certain embodiments, a kit can include one or more delivery systems, e.g., for delivering or administering the pharmaceutical composition as provided herein, and directions for use of the kit (e.g., instructions for treating a subject). In some embodiments, the kit can include a pharmaceutical composition as described herein and a label that indicates that the contents are to be administered to a subject with congenital adrenal hyperplasia. The actual dose of the compound of Formula (I), or pharmaceutically acceptable salt thereof, provided herein depends on the specific formulation, the weight of the patient, and on the condition to be treated.

EXAMPLES

Example 1: Spray-dried dispersion formulations containing the compound of Formula

(I) and various polymers

Spray-dried dispersion formulations

[0398] A series of spray-dried dispersion (SDD) formulations containing the compound of Formula (I) and a polymer were prepared. The SDD formulations included: (1) 10% compound of Formula (I)/90% hydroxypropylmethylcellulose acetate succinate-L (HPMCAS-L); (2) 25% compound of Formula (I)/75% HPMCAS-L; (3) 40% compound of Formula (I)/60% HPMCAS-L; (4) 25% compound of Formula (I)/75% polyvinyl pyrrolidone vinyl acetate 64 (PVP/VA 64); (5) 25% compound of Formula (I)/60% Cabosil (fumed silica)/15% HPMCAS-L; (6) 25% compound of Formula (I)/75% HPMCAS-M; and (7) 25% compound of Formula (I)/75% methyl methacrylate copolymer (1:1) (Eudragit® L100).

[0399] The PVP/VA polymer was a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate with a ratio of 60:40 by weight 1-vinyl-2-pyrrolidone:vinyl acetate with an average molecular weight of 45,000-70,000 (copovidone, sold as Kollidon® VA 64, BASF, Florham Park, NJ). The HPMCAS was a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose that was either grade L (HPMCAS-L), with an acetyl content of 5-9%, a succinoyl content of 14-18%, a methoxyl content of 20-24%, and a hydroxypropoxy content of 5-9% (sold by Shin-Etsu, Japan); or grade M (HPMCAS-M), with an acetyl content of 7-11%, a succinoyl content of 10-14%, a methoxyl content of 21-25%, and a hydroxypropoxy content of 5-9% (sold by Shin-Etsu, Japan).

Dissolution performance

[0400] Dissolution performance of several of the SDD formulations described above was tested (see FIG. 1). 1000 µg/mL of each SDD was tested in 0.5 wt% simulated intestinal fluid (SIF) in PBS, pH 6.5. Samples were tested at 5, 10, 20, 45, 90, and 1200 minutes. A lipid formulation containing 10% of the compound of Formula (I) was used as a control. The results are shown in Table 4, below.

Table 4. Dissolution data of various SDDs

Sample	C _{max90} (µg/mL)	AUC ₉₀ (min*µg/mL)	C _{mix90} (µg/mL)	Ultra ₉₀ (µg/mL)	C ₁₂₀₀ (µg/mL)	Ultra ₁₂₀₀ (µg/mL)
2	762	66,080	743	210	671	166
4	322	27,330	306	109*	268	199
6	718	62,240	708	202	632	217
7	742	60,600	742	113*	674	194
Control	802	69,580	800	253	799	270
*Large variability between replicates, high value discarded						

Non-sink dissolution

[0401] A membrane flux assay was performed (see, e.g., Stewart et al., Mol. Pharm. (2017) 14:2032-2046) and non-sink dissolution data was collected for several of the SDD formulations described above and compared to the compound

of Formula (I) and several reference formulations, including a semi-solid lipidic formulation (Reference Formulation 1) and two self-emulsifying drug delivery system (SEDDS) formulations (Reference Formulations 2 and 3). The components of the Reference Formulations are shown in Table 5, below, and include, in addition to the compound of Formula (I), caprylic/capric triglyceride (Labrafac® Lipophile, Gattefossé, France); propylene glycol dicaprate/dicaprate (Labrafac® PG, Gattefossé, France); oleoyl polyoxyl-6 glycerides (Labrafil® M 1944 CS, Gattefossé, France); polysorbate 20; polyoxyl castor oil (Kolliphor® RH 40, BASF, Germany); polyoxyl 15 hydroxystearate (Kolliphor® HS 15, BASF, Germany); lauroyl polyoxyl-32 glycerides (Gelucire® 44/14, Gattefossé, France); d- α -tocopheryl polyethylene glycol 1000 succinate (TPGS); and diethylene glycol monoethyl ether (Transcutol®, Gattefossé, France).

Table 5. Reference formulations (capsules)

Formulation (mg/caps)	Ref. Formulation 1	Ref. Formulation 2	Ref. Formulation 3
Formula (I)	50.0	50.0	50.0
Labrafac® Lipophile	196.0	100.0	100.0
Labrafac® PG	102.0	-	-
Labrafil® M 1944 CS	-	135.0	46.0
Polysorbate 20	-	-	89.9
Kolliphor® RH 40	-	-	100.0
Kolliphor® HS 15	-	165.0	-
Gelucire® 44/14	95.0	-	-
TPGS	57.0	-	65.0
Transcutol®	-	50.0	50.0
Total	500.0	500.0	500.0

[0402] The assay measured the flux across simulated gastric and intestinal walls via UV spectroscopy (μ Diss Profiler™, Pion Inc., Billerica, MA). Briefly, the assay was performed as follows. A vertical membrane flux cell consisting of a donor compartment and a receiver compartment, and separated by an Accurel PP 1E (55% porous, 100 μ m thickness) polypropylene membrane (3M, Maplewood, MN) (FIG. 2), was impregnated with 50 μ L of Pion GIT-0 lipid solution consisting of 20% w/w phospholipid dissolved into dodecane (Pion Inc., Billerica, MA) and attached to the receiver vessel. Both the donor and receiver compartments were agitated by magnetic stirring. The receiver compartment contained a plastic spacer and grating to elevate the stir bar above the membrane. Samples were introduced to the donor vessel by pre-weighing directly into the donor vessel and subsequently adding dissolution medium. Once the dissolution medium was added to the donor vessel, the receiver vessel was inserted into the donor vessel and suspended vertically 5 mm above the donor compartment by a plastic sleeve. For this assay, the simulated gastric (feed) media was 0.1 N HCl, pH 2 and included 200 μ g/mL of each SDD, and the simulated intestinal (receiver) media was 0.5 wt% SIF in PBS, pH 6.5 and included 100 μ g/mL of each SDD. The temperature for the assay was maintained at 44.5°C. UV probes (10 mm path length) connected to a Rainbow UV spectrometer (Pion Inc.) system were used to determine the apparent drug concentration in the receiver vessels. Samples of the donor compartment were removed with a disposable pipet for centrifugation followed by HPLC and DLS analysis of the supernatant. The results are shown in FIG. 3 and Table 6, below.

Table 6. Non-sink dissolution data

Sample	C _{maxGB} (μ g/mL)	C _{max90 IB} (μ g/mL)	AUC _{4-90IB} (min* μ g/mL)	C ₉₀ (μ g/mL)	Ultra ₉₀ (μ g/mL)	C ₁₂₀₀ (μ g/mL)
Formula (I)	0	1	10	0	0	3
1	6	80	6,800	80	79	90
2	17	74	6,240	73	73	86
4	6	4	200	4	5	36
5	23	55	3,180	55	54	83
6	35	71	6,070	71	77	83

(continued)

Sample	C _{maxGB} (μg/mL)	C _{max90 IB} (μg/mL)	AUC _{4-90IB} (min*μg/mL)	C ₉₀ (μg/mL)	Ultra ₉₀ (μg/mL)	C ₁₂₀₀ (μg/mL)
Ref. Formulation 1	205	109	9,050	109	-	-
Ref. Formulation 2	249	120	10,160	120	-	-
Ref. Formulation 3	218	107	9,100	107	-	-

[0403] The membrane flux of 1 mg/mL gastric barrier/intestinal barrier (GB/IB) 0.5 wt% SIF doses of the compound of Formula (I) and spray-dried dispersions (2) 25% compound of Formula (I)/75% HPMCAS-L and (4) 25% compound of Formula (I)/75% PVP/VA 64 were also determined. The results are shown in FIG. 4 as receiver concentration vs. time and flux vs. time (smoothed derivative of receiver concentration x volume/surface area).

Example 2: Characterization of a spray-dried dispersion containing 25% of the compound of Formula (I) and 75% of a polyvinyl pyrrolidone vinyl acetate (PVP/VA) polymer

SDD stability screening

[0404] Several of the SDDs described in Example 1 were tested for chemical and physical stability. Wet SDD stability studies were performed, with samples stored at both 5°C and 25°C. Measurements were taken after 1 week and 2 weeks of storage. The results are shown in Table 7 below. The column with a retention time of 32.36 min correlates with the compound of Formula (I).

Table 7. Wet SDD stability data

Retention time (min)					11.04	16.79	17.26	30.94	32.26			
Relative retention time					0.34	0.52	0.53	0.96	1.00			
	Storage temp	Timepoint								Total impurities	Potency (mgA/g)	Std Dev
Ref. Std.								0.37	99.63	0.37		
Formula (I)								0.26	99.74	0.26		
Sample 1		initial				0.13	0.16	0.25	99.46	0.54	100	1.3
	5°C	1 week				0.03	0.03	0.26	99.69	0.31	99	0.0
		2 weeks					0.12	0.16	0.28	99.45	0.55	99
	25°C	1 week				0.03	0.04	0.26	99.67	0.33	99	0.3
2 weeks						0.21	0.27	0.28	99.24	0.76	98	0.8
Sample 2		initial			<LOQ	0.07	0.08	0.26	99.59	0.41	247	0.3
	5°C	1 week			<LOQ	0.02	0.03	0.26	99.70	0.30	248	1.3
		2 weeks				<LOQ	0.22	0.27	0.27	99.24	0.76	246
	25°C	1 week			<LOQ	0.02	0.03	0.26	99.69	0.31	248	0.9
2 weeks					<LOQ	0.23	0.28	0.26	99.23	0.77	246	1.4
LOQ = limit of quantification												

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[0405] Solution stability studies were also performed, with samples stored at both 5°C and 25°C. Measurements were taken after 1 week and 2 weeks of storage. The results are shown in Table 8 below. The column with a retention time of 32.36 min correlates with the compound of Formula (I).

Table 8. SDD solution stability data

Retention time (min)			31.51	32.26	
Relative retention time			0.97	1.00	
	Storage temp	Timepoint			Total impurities
Ref. Std.			0.74	99.26	0.74
Formula (I)			0.26	99.74	0.26
Sample 1		initial	0.33	99.67	0.33
	5°C	2 weeks	0.29	99.71	0.29
	25°C	2 weeks	0.38	99.62	0.38
Sample 2		initial	0.25	99.75	0.25
	5°C	2 weeks	0.26	99.74	0.26
	25°C	2 weeks	0.33	99.67	0.33

[0406] Stability studies were also performed for the SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64, with samples stored at both 5°C (closed with desiccant), 25°C (60% RH, closed with desiccant), and 30°C (65% RH, closed with desiccant). Measurements were taken after storage for 1 month, 2 months, 3 months, 6 months, and 12 months. No change in purity was observed after 12 months of storage. The results are shown in Table 9 below. The column with a retention time of 30.2 min correlates with the compound of Formula (I).

Table 9. SDD stability data

Retention time (min)			28.7	30.2		
Relative retention time			0.95	1.00		
	Storage conditions	Timepoint			Total impurities	Potency (mgA/g)
Crystalline Formula (I)			0.26	99.74	0.26	1001

(continued)

	Storage conditions	Timepoint			Total impurities	Potency (mgA/g)
Sample 4 (25% Formula (I):75% PVP/VA 64)	5°C (closed w/ desiccant)	initial	0.26	99.74	0.26	245
		1 month	0.25	99.75	0.25	247
		2 months	0.25	99.75	0.25	244
		3 months	0.26	99.74	0.26	246
		6 months	0.25	99.75	0.25	245
		12 months	0.25	99.75	0.25	248
	25°C/60% RH (closed with desiccant)	1 month	0.25	99.75	0.25	245
		2 months	0.25	99.75	0.25	247
		3 months	0.25	99.75	0.25	246
		6 months	0.25	99.75	0.25	242
		12 months	0.25	99.75	0.25	245
	30°C/65% RH (closed with desiccant)	1 month	0.25	99.75	0.25	249
		2 months	0.25	99.75	0.25	242
		3 months	0.25	99.75	0.25	246
		6 months	0.25	99.73	0.25	243
		12 months	0.25	99.75	0.25	242

[0407] While Samples 1 and 2 showed degradation after about 2 weeks of storage, the SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64 (Sample 4) was found to be both chemically and physically stable and was further screened and characterized as described below.

25% Formula (I)/75% PVP/VA 64 SDD process parameter screening manufacture Round 1

[0408] The 25% Formula (I)/75% PVP/VA 64 SDD was prepared on a Pharmaceutical Spray Dryer with 100 kg/hr drying gas capacity (PSD-1). The manufacturing summary is shown in Table 10, below.

Table 10. Manufacturing summary of process parameters

Formulation	25% Formula (I):75% PVP/VA 64
Solids Loading (wt%)	10
Batch Size (kg)	1.5
Solvent	Acetone
Atomizer (Pressure Swirl)	SK 80-16
Solution Flow-rate (g/min)	160
Atomization Pressure (psig)	480
Inlet Temperature (°C)	94
Outlet Temperature (°C)	40
Calculated Outlet Acetone Saturation (% RS)	6.2
Dry Yield (%)	73

[0409] Based on the 73% yield observed in the first round of process screening, three sprays were performed to investigate the effect of reducing solution throughput and outlet temperature on product yield. All sprays were conducted

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at a reduced flow-rate of 110 g/min. The outlet temperature was varied at 40°C (Lot A), 35°C (Lot B), and 30°C (Lot C). The outlet temperature was decreased while maintaining a low outlet acetone saturation to increase the difference between the chamber outlet temperature and the wet SDD T_g , thus improving product yields. The spray dryer chamber and outlet ductwork were cleaned between all manufactures. A manufacturing summary is shown in Table 11.

Table 11. Manufacturing summary for process parameters (1.5 kg batch size)

Description	Low Flow-Rate	Low Flow-Rate/Low Outlet Temperature	Low Flow-Rate/Lower Outlet Temperature
Lot	A	B	C
Solids Loading (wt%)	10	10	10
Batch Size (kg)	1.5	1.5	1.5
Solvent	Acetone	Acetone	Acetone
Atomizer (Pressure Swirl)	Steinen A75	Steinen A75	Steinen A75
Solution Flow-Rate (g/min)	110	110	110
Atomization Pressure (psig)	275	285	285
Inlet Temperature (°C)	79	72	63
Outlet Temperature (°C)	40	35	30
Calculated Outlet Acetone Saturation (% RS)	4.3	5.2	6.4
Calculated wet SDD T_g (°C)	72	71	69
Dry Yield (%)	55	80	43

[0410] The conditions used for Lot B were found to give the highest yield. One additional spray was then performed at the same processing conditions as Lot B while increasing the batch size from 1.5 kg to 3.5 kg to evaluate process consistency and to determine if product yield would continue to improve over time. The averaged process conditions for this lot are shown in Table 12.

Table 12. Manufacturing summary of process parameters (1.5 kg and 3.5 kg batch sizes)

Description	Low Flow-Rate/Low Outlet Temperature	Low Flow-Rate/Low Outlet Temperature/Larger Batch Size
Lot	B	D
Solids Loading (wt%)	10	10
Batch Size (kg)	1.5	3.5
Solvent	Acetone	Acetone
Atomizer (Pressure Swirl)	Steinen A75	Steinen A75
Solution Flow-Rate (g/min)	110	110
Atomization Pressure (psig)	285	285
Inlet Temperature (°C)	72	72
Outlet Temperature (°C)	35	35
Calculated Outlet Acetone Saturation (% RS)	5.2	5.2
Calculated wet SDD T_g (°C)	71	71
Dry Yield (%)	80	84

[0411] The 1.5 kg batch size (Lot D) was sprayed with an 84% yield compared to the 80% yield of the 3.5 kg batch (Lot B).

25% Formula (I)/75% PVP/VA 64 SDD process parameter screening characterisation

[0412] The 25% Formula (I)/75% PVP/VA 64 SDDs manufactured to evaluate processing parameters were characterized for powder properties, performance, and physical and chemical properties. Testing included particle size distribution by Malvern, determination of bulk and tapped density, microcentrifuge dissolution, modulated differential scanning calorimetry (mDSC), powder x-ray diffraction (PXRD), scanning electron microscope (SEM), and assay and related substances. The results did not show any significant differences between the lots.

[0413] The particle size distribution (PSD) and tabulated powder properties data of the 25% Formula (I)/75% PVP/VA 64 SDDs are shown in Table 13. All 25% Formula (I)/75% PVP/VA 64 SDDs were observed to have a very similar PSD with a D_{50} of approximately 16 μm . All 25% Formula (I)/75% PVP/VA 64 SDDs were observed to have low bulk and tapped densities.

Table 13. Powder properties of process parameter screening PVP/VA-64 SDDs

Sample	Lot	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)	$D_{(3,2)}$ (μm)	$D_{(4,3)}$ (μm)	Span	Bulk density (g/mL)	Tapped density (g/mL)
40°C Outlet	A	5	15	34	8	17	1.93	0.12	0.25
35°C Outlet	B	5	16	36	9	19	1.97	0.11	0.23
30°C Outlet	C	5	15	32	7	17	1.86	0.12	0.27
35°C Outlet, 3.5 kg batch	D	5	16	38	9	19	1.98	0.12	0.24

[0414] The 3.5 kg batch size lot was analyzed and compared to process parameter Lot A. Dissolution performance was similar for each of these lots. Dissolution was rapid to C_{max} and high free drug was sustained through 90 minutes. These data are shown in Table 14.

Table 14. Dissolution performance of Lot A (1.5 kg batch size) vs. Lot D (3.5 kg batch size)

Sample	$C_{\text{max}90}$ ($\mu\text{g/mL}$)	AUC_{90} ($\text{min} \cdot \mu\text{g/mL}$)	C_{90} ($\mu\text{g/mL}$)	Ultra_{90} ($\mu\text{g/mL}$)
Lot A	447	37,740	437	319
Lot D	437	37,120	433	301

[0415] The 25% Formula (I)/75% PVP/VA 64 SDDs were also evaluated by DSC, PXRD, and SEM. The DSC thermograms showed a single T_g at 84°C, indicating homogeneous dispersions. PXRD diffractograms showed no evidence of crystals in the SDDs. SEM images showed inflated sphere morphology with some broken particles and some very small particles.

[0416] Additional testing on Lot B was carried out, which included assessing the chemical/physical stability of both spray solution and SDD prior to secondary drying (wet SDD) to establish maximum in-process hold times. Residual acetone concentration as a function of secondary drying time in a convection tray dryer was also evaluated to nominate tray drying conditions to ensure the SDD is dried below International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for acetone.

[0417] Residual acetone content as a function of drying time was assessed by drying wet SDD in a tray dryer and collecting samples over a 24-hour period. Wet SDD was dried at 40°C/15% relative humidity (RH) and was observed to dry below ICH acetone guidelines (0.5 wt%, 5000 ppm) by four hours.

[0418] Spray solution hold time was determined by making up a representative solution that contained 2.5 wt% compound of Formula (I), 7.5 wt% PVP/VA 64, and 90 wt% acetone. These solutions were analyzed initially for related substances, and then aged at 5°C and 25°C. Aliquots were taken and analyzed for related substances periodically for 14 days. Results showed no change in impurity profile at either condition through 14 days.

[0419] Wet SDD was analyzed for impurities after storage at 5°C and 25°C for 1 and 2 weeks and compared to the impurity profiles of the ingoing compound of Formula (I) and the SDD that was secondarily dried immediately after spray drying. The impurity profiles were similar to that of the initial dried sample and the ingoing compound of Formula (I) through 2 weeks of storage.

[0420] The wet SDD stability samples were characterized for physical stability by DSC, PXRD, and SEM. DSC thermograms showed a single T_g at 81°C, indicative of a homogeneous dispersion with no phase separation. The PXRD diffractograms did not show any evidence of crystals after storage at either condition. SEM images showed a typical morphology of mostly inflated spheres with some broken particles.

Example 3: Preparation of a 1000 g batch of a spray-dried dispersion containing 25% of the compound of Formula (I) and 75% PVP/VA 64

[0421] A 1000 g batch of the spray-dried dispersion containing 25% of the compound of Formula (I) and 75% PVP/VA 64 was prepared as described in Example 2 for the 1.5 kg and 3.5 kg batches. Briefly, acetone (90% (w/w) of the total mixture) was added to the mixing tank followed by the addition of 250.0 g of the compound of Formula (I) (2.5% (w/w) of the total mixture). The mixture was mixed for 30 minutes in the dark at a temperature range of 15°C to 27°C. At the end of the mixing period, the solution was clear and free of undissolved solids. The PVP/VA 64 (750.0 g, 7.5% (w/w) of the total mixture) was then added and the mixture was stirred for an additional 30 minutes in the dark at a temperature range of 15°C to 27°C. At the end of the mixing period, the solution was clear and free of undissolved solids.

[0422] The solution was pumped and atomized in a drying chamber. The spray-dried dispersions were prepared in a Pharmaceutical Spray Dryer with 100 kg/hr drying gas capacity (PSD-1). The inlet temperature was set at 75°C (varied between 60°C-90°C). The outlet temperature was set at 35°C (varied between 32°C-38°C). The feed pressure was set at 280 psig (varied between 230-330 psig). The feed rate was set at 110 g/min (varied between 90-130 g/min). The spray dried powder was then dried in a convection tray dryer with a bed depth of ≤ 2.5 cm at 40°C ($\pm 5^\circ\text{C}$) and 15% relative humidity ($\pm 10\%$) for 24 hours under amber light. The residual acetone after drying was < 0.5 wt% (5000 ppm). FIG. 5 is a flow diagram of the manufacturing process.

Example 4: Preparation of spray-dried dispersion formulations of the compound of Formula (I) for clinical use

[0423] The spray-dried dispersion (SDD) containing 25% compound of Formula (I) and 75% PVP/VA 64, prepared as described above, was formulated as a suspension or a capsule for clinical use.

Suspension preparation

[0424] A suspension that contained 50 mg of the SDD was prepared as follows. A 30 mL amber dosing bottle was tared on a balance. 200.0 mg SDD (50 mgA) $\pm 5\%$ was then weighed into the dosing bottle. Using a 10-mL syringe, 5.0 mL of water (purified, USP) was added to the dosing bottle and the bottle was capped and shaken moderately for 30 seconds. The SDD suspension was stored in an amber vial at 2-8°C prior to use, and dosed within 24 hours of preparation.

Capsule preparation

[0425] An empty hard gelatin capsule, size 0 (Capsugel, Morristown, NJ), was placed on a balance and the weight was recorded. 200.0 mg SDD (50 mgA) $\pm 5\%$ was then weighed onto weigh paper or an equivalent. All contents were transferred to the capsule using a ProFunnel device for Size 0 capsules. The filled capsule was placed on the balance and the weight was recorded. The weight of the empty capsule was subtracted from the filled weight, ensuring that the weight of the SDD within the capsule was 200.0 mg SDD $\pm 5\%$, or from 190.0 mg to 210.0 mg. The capsule was securely closed with the head, assuring it clicked into place. The capsules were stored in an amber vial at 2-8°C prior to use, and were dosed within 24 hours of preparation.

Example 5: Dog relative bioavailability and food effect study

[0426] Four spray-dried dispersions (SDDs), formulated in 0.25% methylcellulose as a suspension, were prepared: (1) 25% compound of Formula (I)/75% HPMCAS-L; (2) 10% compound of Formula (I)/90% HPMCAS-L; (3) 25% compound of Formula (I)/75% methyl methacrylate copolymer (1:1) (Eudragit® L100); and (4) 25% compound of Formula (I)/75% PVP/VA 64. A clinical capsule formulation was prepared as a reference formulation (Reference Formulation 1 from Table 5, above).

[0427] Dogs (two cohorts, six dogs in each) were dosed in six sessions, including fasted state sessions and fed sessions (high fat diet), with 50 mg dose of one of the SDDs or reference per dog in a 3-way crossover design. Each session had a 3-day washout in between. All formulations were well tolerated. The study design is shown in Table 15, below.

Table 15. Study design

Cohort 1	Session 1 (Fasted)	Session 2 (Fed)	Session 3 (Fasted)	Session 4 (Fed)	Session 5 (Fasted)	Session 6 (Fed)
Dog 1001	Reference	Reference	SDD 1	SDD 1	SDD 2	SDD 2
Dog 1002	Reference	Reference	SDD 1	SDD 1	SDD 2	SDD 2
Dog 2001	SDD 1	SDD 1	SDD 2	SDD 2	Reference	Reference
Dog 2002	SDD 1	SDD 1	SDD 2	SDD 2	Reference	Reference
Dog 3001	SDD 2	SDD 2	Reference	Reference	SDD 1	SDD 1
Dog 3002	SDD 2	SDD 2	Reference	Reference	SDD 1	SDD 1
Cohort 2	Session 1 (Fasted)	Session 2 (Fed)	Session 3 (Fasted)	Session 4 (Fed)	Session 5 (Fasted)	Session 6 (Fed)
Dog 4001	Reference	Reference	SDD 3	SDD 3	SDD 4	SDD 4
Dog 4002	Reference	Reference	SDD 3	SDD 3	SDD 4	SDD 4
Dog 5001	SDD 3	SDD 3	SDD 4	SDD 4	Reference	Reference
Dog 5002	SDD 3	SDD 3	SDD 4	SDD 4	Reference	Reference
Dog 6001	SDD 4	SDD 4	Reference	Reference	SDD 3	SDD 3
Dog 6002	SDD 4	SDD 4	Reference	Reference	SDD 3	SDD 3

[0428] The area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), the apparent terminal half-life ($t_{1/2}$), and the time to achieve maximum plasma concentration (t_{max}) were calculated. Results are shown in Table 16, below, and in FIGS. 6A and 6B.

Table 16. Pharmacokinetic results

Cohort	Form	Fasted [Mean (%CV)]		Fed [Mean (%CV)]		Ratio of Fed/Fasted [Mean (%CV)]	
		C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	C_{max}	AUC
1 (N=4) *	Ref	652 (55.5)	5170 (69.4)	3650 (19.5)	20100 (22)	6.9 (48)	5.5 (69.2)
	SDD 1	524 (62.7)	2870 (62.9)	5760 (25.6)	22800 (14.6)	15.4 (66.9)	8 (89.6)
	SDD 2	487 (45.7)	3950 (26.4)	4220 (27.4)	18100 (26.8)	16.5 (40.7)	6.3 (34.6)

(continued)

Cohort	Form	Fasted [Mean (%CV)]		Fed [Mean (%CV)]		Ratio of Fed/Fasted [Mean (%CV)]	
		C _{max} (ng/mL)	AUC _{inf} (hr*ng/mL)	C _{max} (ng/mL)	AUC _{inf} (hr*ng/mL)	C _{max}	AUC
2 (N=6)	Ref	854 (40.2)	5520 (59.1)	4220 (27.4)	18100 (26.8)	5.8 (46.5)	4.1 (49.2)
	SDD 3	453 (28.3)	2830 (21.6)	5320 (13.5)	23800 (26.1)	12.6 (30.3)	8.6 (22.2)
	SDD 4	353 (20.1)	1840 (21.9)	3060 (20.7)	17200 (20.5)	8.9 (29.3)	8.4 (46.1)
*Animals 2001 and 2002 were excluded from summary statistics due to emesis in all 3 fed sessions, which resulted in notably lower exposures							

[0429] The results showed that $t_{1/2}$ and t_{max} were similar among the formulations, and comparable between the fed and fasted states. Under the fed state with a high fat meal, exposures increased and inter-animal variability decreased. The food effect was more notable with the spray-dried dispersion formulations, especially for peak exposure (C_{max}).

[0430] Compared to the reference form, SDD 4 (25% compound of Formula (I)/75% PVP/VA 64) appeared to have lower inter-animal variability, lower exposures under the fasted state, and slightly lower C_{max} but relatively comparable AUC in the fed state.

Example 6: Phase 1 study to evaluate the pharmacokinetics, effect of food on pharmacokinetics, and safety of the compound of Formula (I) in healthy adult subjects

[0431] The present study was designed to evaluate the pharmacokinetics (PK) of the compound of Formula (I) as well as to evaluate the effect of a fed condition on the PK of the compound of Formula (I). The 50 mg dose was chosen for this study because it was within the tested dose range in completed Phase 1 and Phase 2 trials and was well tolerated in those studies. The objectives of the study were: to evaluate the PK of the compound of Formula (I) 50 mg in healthy adult subjects; to evaluate the effect of food on the PK of the compound of Formula (I) 50 mg; and to evaluate the safety and tolerability of the compound of Formula (I) 50 mg.

Study Design

[0432] This was a Phase 1, open-label, randomized, 2-period crossover study of the PK and the effect of food on the PK of the compound of Formula (I) in 16 healthy male and female adult subjects, 18 to 55 years of age.

[0433] After providing informed consent, subjects were screened for eligibility to participate in the study up to 28 days prior to Day 1 of treatment period 1. Eligible subjects were admitted to the clinical unit on Day -1 and randomized to 1 of the 2 treatment sequences (16 subjects [8 males and 8 females]; see Table 17, below). On Day 1 of each treatment period, subjects received a single dose of the compound of Formula (I) 50 mg under fasted or fed conditions. There were 21 days between doses.

Table 17. Treatment sequences

Treatment sequence	Treatment period 1	Treatment period 2
1	Formula (I) - fasted	Formula (I) - fed
2	Formula (I) - fed	Formula (I) - fasted

[0434] Subjects were required to fast for at least 4 hours before check-in on Day -1. In the fasted condition, subjects were required to fast overnight for at least 10 hours prior to dosing and continued to fast for an additional 4 hours after dosing. In the fed condition, subjects were required to fast overnight for at least 10 hours and then ingest a liquid dietary supplement with study drug (liquid dietary supplement was consumed within 30 minutes) and not consume any other food for 4 hours after dosing. During both treatment periods, water was not permitted for 1 hour before dosing until 2 hours after dosing except for the water/liquid dietary supplement provided for study drug dosing. Vanilla-flavored Ensure Plus® was used as the liquid dietary supplement.

[0435] On Day 1 of each treatment period, subjects were dosed with the compound of Formula (I) 50 mg. Blood samples were collected for PK analysis over a period of 36 hours during the in-house stay. Subjects remained in the

unit on the day of dosing and were discharged on Day 2 of each treatment period, following completion of all required procedures. On the mornings of Days 8 and 15 of each treatment period, subjects returned to the clinical unit on an outpatient basis for PK blood sample collection and safety assessments. On Day 21 of treatment period 1, subjects arrived at the site and had Day 21 assessments completed in the evening, and they stayed overnight at the site and began Day 1 of treatment period 2 the following day. A final follow-up study visit was conducted on Day 22 of treatment period 2 (21 + 2 days after treatment period 2 dosing) or upon early termination.

[0436] During each treatment period, blood samples for PK analysis were collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

[0437] Safety assessments (including clinical safety laboratory tests, vital sign measurements, physical examinations, and electrocardiograms (ECGs)) were conducted at scheduled times throughout the study. Adverse events (AEs) and the use of concomitant medications were monitored throughout the study. FIG. 7 illustrates the study design.

Test product, dose and mode of administration

[0438] The compound of Formula (I) was supplied as an encapsulated, lipidic semi-solid containing 50 mg of the compound of Formula (I) as free base equivalent for oral administration. Subjects swallowed a single capsule with approximately 240 mL of water in the fasted condition. Subjects swallowed a single capsule with a liquid dietary supplement (Ensure Plus® [237 mL container]) with up to an additional 120 mL of water in the fed condition.

Duration of treatment

[0439] The duration of study participation for each adult subject was approximately 10 weeks, including up to 28 days of screening, 2 days of dosing separated by 21 days, and a final follow-up study visit 21 days after receiving the last dose of study drug during treatment period 2.

Criteria for Evaluation

Pharmacokinetics

[0440] The following plasma PK parameters were calculated for the compound of Formula (I):

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0-t_{last}}$)
- Area under the plasma concentration versus time curve from 0 to 24 hours (AUC_{0-24})
- Area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0-\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{1/2}$)
- Apparent terminal rate constant (λ_z)
- Apparent mean residence time (MRT)
- Molar AUC ratio of the hydroxylated metabolite of the compound of Formula (I) to the parent drug the compound of Formula (I)

[0441] The following plasma PK parameters were calculated only for the compound of Formula (I):

- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (V_z/F)

Safety

[0442] Safety was monitored throughout the study and included the following assessments:

- Adverse events (AEs)
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiograms (ECGs)

Statistical Methods

[0443] Pharmacokinetic parameters were calculated using noncompartmental methods and summarized by condition (fed or fasted) using descriptive statistics. Two-sided 90% confidence intervals were calculated for the ratio under the fed condition vs. under the fasted condition for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} for the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I).

[0444] Safety data were summarized with descriptive statistics.

Pharmacokinetics

Pharmacokinetic assessments

[0445] PK plasma samples for analyses of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) were collected at the following times during each treatment period:

- Day 1: within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, and 16 hours after dosing.
- Day 2: approximately 24 and 36 hours after dosing.
- Day 8: approximately 168 hours after dosing.
- Day 15: approximately 336 hours after dosing.
- Approximately 504 hours after dosing (for treatment period 1, this sample was collected in the morning at least 30 minutes prior to the predose sample on Day 1 of treatment period 2).
- Final study visit for subjects who terminate early: 1 sample.

[0446] Blood samples on Day 1 were collected within 5 minutes of the scheduled sampling times (other than the predose sample). Blood samples on Days 2, 8, and 15 were collected within 2 hours of the scheduled sampling time. The 504 hour blood sample for treatment period 2 had a $\pm$ 2-day window. A PK sample was to be collected from subjects who terminated early. The exact time of sampling in hour and minutes was recorded.

Bioanalytical methods

[0447] Plasma samples were analyzed for the compound of Formula (I) and for its hydroxylated metabolite by in Ventiv Health, Princeton NJ, in compliance with Good Laboratory Practice (GLP) and relevant Standard Operating Procedures (SOPs).

[0448] The concentrations of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) were quantified in plasma samples according to validated methods using tandem mass spectrometry in positive ion mode. This method was validated for the analysis of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) in 25.0 μ L dipotassium ethylenediaminetetraacetic acid (K_2 -EDTA) human plasma samples over concentration ranges of 5.00 to 2500 ng/mL and 0.500 and 250 ng/mL, respectively. All analytical results were within acceptable limits. Incurred sample reanalysis (ISR) was successfully conducted in this study for both analytes.

Results

Pharmacokinetic results

[0449] Eight male and eight female subjects were enrolled. The mean age was 37.1 years (range, 21 to 55 years). The majority of subjects were White (93.8%) and of Hispanic ethnicity (81.3%). The mean weight at screening was 160.28 lbs (range, 102.0 to 222.2 lbs) and mean BMI was 25.50 kg/m² (range, 20.7 to 30.5 kg/m²). The randomization was well balanced with respect to demographics and baseline characteristics.

[0450] All 16 subjects were included in the safety analysis set. No subjects were excluded from the safety analysis set and no subject had his or her PK data excluded from analysis.

[0451] The mean plasma concentration versus time profiles for the compound of Formula (I) under fasted and fed conditions are presented in FIGS. 8A and 8B, respectively. The compound of Formula (I) was slowly absorbed after oral administration in both fasted and fed conditions. Mean plasma concentrations were lower in the fasted than in the fed condition.

[0452] PK parameters for the compound of Formula (I) after treatment with the compound of Formula (I) under fasted and fed conditions are summarized in Table 18, below, where AUC_{0-24} =area under the plasma concentration vs. time curve from 0 to 24 hours, $AUC_{0-t_{bu}}$ =AUC from 0 hours to last measurable concentration, $AUC_{0-\infty}$ =AUC from 0 hours

extrapolated to infinity, CL/F=apparent systemic clearance after oral administration, CV=coefficient of variation, C_{max} =maximum plasma concentration, CV(%)=coefficient of variation, max=maximum, min=minimum, MRT=apparent mean residence time, PK=pharmacokinetic, SD=standard deviation, $t_{1/2}$ =apparent terminal half-life, T_{lag} =delay time between time of dosing and time of appearance of measurable test article, t_{max} =time to maximum plasma concentration, VZ/F=apparent volume of distribution during the terminal phase after oral administration.

[0453] The PK data for t_{max} , T_{lag} , $t_{1/2}$, MRT, and Vz/F were rounded to 2 significant figures and all other parameters (AUC_{0-24} , $AUC_{0-tlast}$, $AUC_{0-\infty}$, C_{max} , and CL/F) were rounded to 3 significant figures. The last significant figure was rounded up if the digit to the right of it was ≥ 5 , and was rounded down if the digit to the right of it was ≤ 4 .

Table 18. Summary of Formula (I) PK parameters (safety analysis set)

Parameter Statistic	Fasted Formula (I) (50 mg) (N=16)	Fed Formula (I) (50 mg) (N=15)
AUC_{0-24} (ng×hr/mL) Mean (SD) Geometric CV%	5590 (2230) 32.7	9950 (2540) 26.2
$AUC_{0-tlast}$ (ng×hr/mL) Mean (SD) Geometric CV%	8020 (5110) 53.6	16200 (5450) 39.7
$AUC_{0-\infty}$ (ng×hr/mL) Mean (SD) Geometric CV%	9440 (2990) [n=7] 39.7	17800 (4990) [n=12] 28.1
C_{max} (ng/mL) Mean (SD) Geometric CV%	731 (301) 36.6	1550 (392) 24.2
t_{max} (hours) Median (min, max)	6.0 (3.0, 6.0)	5.0 (3.0, 6.0)
T_{lag} (hours) Mean (SD)	0.63 (0.22)	0.94 (0.37)
$t_{1/2}$ (hours) Mean (SD) Geometric CV%	33 (17) [n=7] 99	42 (6.8) [n=12] 15
MRT (hours) Mean (SD) Geometric CV%	28 (11) [n=7] 49	30 (5.0) [n=12] 16
CL/F (L/hr) Mean (SD) Geometric CV%	6.0 (2.7) [n=7] 40	3.0 (0.82) [n=12] 28
VZ/F (L) Mean (SD) Geometric CV%	240 (120) [n=7] 67	180 (57) [n=12] 30

[0454] As seen in Table 18, above, administration of the compound of Formula (I) 50 mg under fed compared with fasted conditions resulted in a higher mean C_{max} of the compound of Formula (I) (approximately 2-fold higher; 1550 vs. 731 ng/mL), a longer $t_{1/2}$ (42 vs. 33 hours), a slightly shorter median t_{max} (5.0 vs. 6.0 hours), and a higher mean $AUC_{0-\infty}$ (approximately 2-fold higher; 17800 vs. 9440 ngxh/mL). The compound of Formula (I) geometric mean ratios for C_{max} and $AUC_{0-tlast}$ for fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approximately 2-fold greater when administered with food. The upper and lower 90% confidence interval (CI) bounds for both C_{max} (187.4% and 255.1%, respectively) and $AUC_{0-tlast}$ (182.9% and 253.1%, respectively) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure.

[0455] Frequency distribution of T_{lag} and t_{max} values are presented in Table 19 and Table 20, respectively. Spaghetti plots for the compound of Formula (I) $AUC_{0-tlast}$, $AUC_{0-\infty}$ and C_{max} are shown in FIGS. 9A, 9B, and 9C, respectively.

Table 19. Frequency distribution of plasma Formula (I) T_{lag} values by treatment (safety analysis set)

T_{lag} (hr)	Statistic	Fasted (Formula (I) 50 mg) (N=16)	Fed (Formula (I) 50 mg) (N=15)
0.50	n (%)	11 (68.8%)	3 (20.0%)
0.53	n (%)	1 (6.3%)	0 (0.0%)
0.55	n (%)	0 (0.0%)	1 (6.7%)
1.00	n (%)	4 (25.0%)	8 (53.3%)
1.02	n (%)	0 (0.0%)	1 (6.7%)
1.03	n (%)	0 (0.0%)	1 (6.7%)
2.00	n (%)	0 (0.0%)	1 (6.7%)

Table 20. Frequency distribution of plasma Formula (I) T_{max} values by treatment (safety analysis set)

T_{max} (hr)	Statistic	Fasted (Formula (I) 50 mg) (N=16)	Fed (Formula (I) 50 mg) (N=15)
3.00	n (%)	1 (6.3%)	2 (13.3%)
4.02	n (%)	1 (6.3%)	0 (0.0%)
5.00	n (%)	4 (25.0%)	8 (53.3%)
5.03	n (%)	0 (0.0%)	1 (6.7%)
5.05	n (%)	0 (0.0%)	1 (6.7%)
6.00	n (%)	10 (62.5%)	2 (13.3%)
6.02	n (%)	0 (0.0%)	1 (6.7%)

[0456] The compound of Formula (I) was slowly absorbed after oral administration in the fasted and fed conditions. In the fasted condition, the mean compound of Formula (I) C_{max} was approximately 53% lower than in the fed condition (731 vs. 1550 ng/mL). Due to a prolonged elimination phase, $t_{1/2}$ values and therefore, $AUC_{0-\infty}$ values could not be determined for some the compound of Formula (I) concentration-time profiles. Mean $AUC_{0-\infty}$ was approximately 47% lower in the fasted condition than in the fed condition (9440 vs. 17800 ngxh/mL) for those subjects for whom $AUC_{0-\infty}$ could be determined. Mean $AUC_{0-tlast}$ was approximately 50% lower in the fasted condition than in the fed condition (8020 vs. 16200 ngxh/mL). Median t_{max} was slightly longer in the fasted condition than in the fed condition (6.0 vs. 5.0 hours) and mean $t_{1/2}$ was shorter in the fasted condition than in the fed condition (33 vs. 42 hours) for those subjects for whom a $t_{1/2}$ could be determined. Variability in the compound of Formula (I) PK (geometric CV%) for AUC, C_{max} , $t_{1/2}$, and MRT was lower in the fed condition compared with the fasted condition.

[0457] The geometric mean ratios and associated 90% CIs for $AUC_{0-tlast}$ and C_{max} for the compound of Formula (I) after treatment with the compound of Formula (I) for the fed vs. fasted condition are provided in Table 21, below, where $AUC_{0-tlast}$ = AUC from 0 hours to last measurable concentration, C_{max} = maximum plasma concentration, and PK = pharmacokinetic.

Table 21. Formula (I) geometric mean ratios for PK exposure parameters under fed vs. fasted conditions (safety analysis set)

Parameter	Ratio ^a (%) (Fed vs. Fasted Condition)	90% Confidence Interval ^b
$AUC_{0-tlast}$ (ngxh/mL)	215.2	182.9, 253.1
C_{max} (ng/mL)	218.6	187.4, 255.1
^a Ratio of geometric least-squares means was based on a mixed model using log-transformed (base 10) data. ^b The 90% confidence interval for geometric mean ratio was based on least-squares means using log-transformed (base 10) data.		

[0458] The compound of Formula (I) geometric mean ratios for C_{max} and $AUC_{0-tlast}$ for the fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approximately 2-fold greater when administered with food. The upper and lower 90% CI bounds for both C_{max} (187.4%, 255.1%) and $AUC_{0-tlast}$ (182.9%, 253.1%) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure. Due to the missing $AUC_{0-\infty}$ values, the food effect on overall exposure was not assessed using $AUC_{0-\infty}$ values.

Conclusion

[0459] Administration of the compound of Formula (I) 50 mg under fed compared with fasted conditions resulted in a higher mean C_{max} of the compound of Formula (I) (approximately 2-fold higher; 1550 vs. 731 ng/mL), a longer $t_{1/2}$ (42 vs. 33 hours), a slightly shorter median t_{max} (5.0 vs. 6.0 hours), and a higher mean $AUC_{0-\infty}$ (approximately 2-fold higher; 17800 vs. 9440 ngxh/mL). The compound of Formula (I) geometric mean ratios for C_{max} and $AUC_{0-tlast}$ for fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approx-

imately 2-fold greater when administered with food. The upper and lower 90% CI bounds for both $C_{\max}$ (187.4%, 255.1%) and $AUC_{0-\text{last}}$ (182.9%, 253.1%) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure. Similar results were observed with the hydroxylated metabolite of the compound of Formula (I). Overall, these results indicate that the compound of Formula (I) 50 mg was well tolerated in healthy subjects when administered under fasted or fed conditions and that the total AUC and $C_{\max}$ were increased when the compound of Formula (I) was taken with food.

Example 7: Phase 1 study to evaluate the relative bioavailability, effect of food on pharmacokinetics, and safety of formulations of the compound of Formula (I) in healthy adult subjects

[0460] A Phase 1 study to compare the relative bioavailability of a 50 mg dose of different formulations of the compound of Formula (I) as well as to evaluate the effect of fasting and fed conditions on the pharmacokinetics (PK) of the compound of Formula (I) was designed. The 50 mg dose was chosen for this study because it is within the tested dose range in completed Phase 1 and Phase 2 trials and was well tolerated in those studies. The objectives of the study are: to evaluate the PK and compare the relative bioavailability of the compound of Formula (I) 50 mg formulations in healthy adult subjects; to evaluate the effect of food on the PK of the compound of Formula (I) 50 mg formulations; and to evaluate the safety and tolerability of the compound of Formula (I) 50 mg formulations.

Study Design

[0461] This is a Phase 1, open-label, randomized, three-period crossover study of the relative bioavailability and the effect of food on the PK of the compound of Formula (I) 50 mg in healthy adult subjects. During treatment period 1 and treatment period 2, subjects will receive a single dose of the compound of Formula (I) 50 mg administered as an encapsulated, lipidic semi-solid (reference) and 1 of 2 different spray-dried dispersion (SDD) test formulations (suspension or capsule) under fed conditions, and during treatment period, three subjects will receive the same SDD test formulation under fasted conditions.

[0462] A total of 36 healthy adult subjects will be randomized to 1 of 4 treatment sequences (9 subjects per sequence; approximately equal distribution of males and females per sequence; see Table 22, below). There will be 21 days between each dose.

Table 22. Treatment sequences

Treatment sequence	Treatment period 1 (Fed)	Treatment period 2 (Fed)	Treatment period 3 (Fasted)
1	Reference	SDD suspension	SDD suspension
2	SDD suspension	Reference	SDD suspension
3	Reference	SDD capsule	SDD capsule
4	SDD capsule	Reference	SDD capsule

[0463] After providing informed consent, subjects will be screened for eligibility to participate in the study. Screening will begin up to 28 days prior to Day 1 of treatment period 1. Eligible subjects will be admitted to the clinical unit on Day -1, and randomized to 1 of the 4 treatment sequences on Day 1 of treatment period 1. During treatment periods 1 and 2, subjects will fast overnight for at least 10 hours and then ingest a liquid dietary supplement (vanilla-flavored Ensure Plus®, 237 mL container) with the study drug and not consume any other food for 4 hours after dosing. During treatment period 3, subjects will fast overnight for at least 10 hours prior to dosing and continue to fast for an additional 4 hours after dosing. During all treatment periods, water will not be permitted for 1 hour before dosing until 2 hours after dosing except for the water/liquid dietary supplement provided for study drug dosing.

[0464] On Day 1 of each treatment period, subjects will be dosed with the compound of Formula (I) 50 mg and have blood samples collected for PK analysis. Subjects will complete a taste satisfaction questionnaire after study drug ingestion on Day 1 of treatment period 3 (only for subjects who receive the SDD suspension under the fasted condition). Subjects will remain in the unit on the day of dosing and will be discharged on Day 2 of each treatment period, following completion of all required procedures, including collection of the 36-hour PK sample. On the mornings of Days 8 and 15 of each treatment period, subjects will return to the clinical unit on an outpatient basis for PK blood sample collection and safety assessments. On Day 21 of treatment period 1 and treatment period 2, subjects will arrive at the site and have Day 21 assessments completed, and they will stay overnight at the site and begin Day 1 of treatment period 2 or treatment period 3 the following day. A final follow-up study visit will be conducted on Day 22 of treatment period 3 (21 ± 2 days after treatment period 3 dosing) or upon early termination.

[0465] Blood samples for PK analysis and safety assessments will be collected/conducted at scheduled times throughout the study. The study design schematic is shown in FIG. 10.

Duration of treatment

[0466] The expected duration of study participation for each healthy adult subject will be approximately 13 weeks, including up to 28 days of screening, 3 doses each separated by 21 days, and a final follow-up study visit 21 days after receiving the last dose of study drug during treatment period 3.

Test product, dose, and mode of administration

[0467] The compound of Formula (I) will be supplied as two different test formulations for oral administration: as powder in bottles for constitution into a suspension (20 mL) and as powder-filled capsules. The compound of Formula (I) test formulations will contain 50 mg of the compound of Formula (I) as free base equivalent. Subjects must swallow the study drug with a liquid dietary supplement (Ensure Plus® [237 mL container]) with an additional 100 mL of water (SDD capsule formulation) or with an additional 80 mL of water (SDD suspension formulation) during treatment period 1 or 2. Subjects must swallow the study drug with 330 mL of water (SDD capsule formulation) or 310 mL of water (SDD suspension formulation) during treatment period 3.

Reference therapy, dose, and mode of administration

[0468] The compound of Formula (I) reference formulation (encapsulated, lipidic semi-solid formulation) will be supplied as capsules for oral administration. The compound of Formula (I) reference capsules will contain 50 mg of the compound of Formula (I) as free base equivalent. Subjects must swallow a single capsule with a liquid dietary supplement (Ensure Plus [237 mL container]) with an additional 100 mL of water during treatment period 1 or 2.

Criteria for Evaluation

Pharmacokinetics

[0469] Blood samples for assessment of plasma concentrations of the compound of Formula (I) and metabolites will be collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

[0470] The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to the time of the last measurable concentration ($AUC_{0-t_{last}}$)
- Area under the plasma concentration curve extrapolated from 0 hours to infinity ($AUC_{0-\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{1/2}$)
- Apparent terminal rate constant (λ_z)
- Apparent mean residence time (MRT)
- Molar AUC ratio of primary metabolite(s) to the parent drug the compound of Formula (I)

[0471] The following plasma PK parameters will be calculated only for the compound of Formula (I):

- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (V_z/F)

Other assessment

[0472] A taste satisfaction questionnaire will be administered.

Safety assessments

[0473] Safety will be monitored throughout the study and will include the following assessments:

- AEs
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiogram (ECG)

Statistical methods

[0474] Pharmacokinetic parameters will be calculated using noncompartmental methods and summarized by formulation using descriptive statistics. Two-sided 90% confidence intervals will be calculated for the ratio of each test formulation (SDD suspension and SDD capsule) vs. the reference formulation for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} for the compound of Formula (I) and metabolites under fed conditions. Further, two-sided 90% confidence intervals will be calculated for the ratio of each test formulation under fasted conditions vs. under fed conditions for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} for the compound of Formula (I) and metabolites.

[0475] Safety and taste satisfaction questionnaire data will be summarized with descriptive statistics.

Results

Pharmacokinetic results

[0476] Pharmacokinetic results are shown in Tables 23-26, below.

Table 23: Summary of Plasma Pharmacokinetic Parameters (Safety Analysis Set - SDD Suspension Group)

		Compound of Formula (I) Plasma Concentration	
Parameter (units) Statistic	Reference Capsule (Fed) (N=18)	SDD Suspension (Fed) (N=18)	SDD Suspension (Fasted) (N=18)
AUC _{0-tlast} (ng×hr/mL)			
Mean (SD)	16600 (7880)	5980 (3960)	737 (417)
Geom CV(%)	46.8	72.8	68.7
AUC _{0-∞} (ng×hr/mL)			
Mean	17400 (8010)	6500 (4180)	893 (480)
Geom CV(%)	45.4	71.7	60.1
C _{max} (ng/mL)			
Mean (SD)	1480 (506)	672 (323)	72.3 (44.9)
Geom CV(%)	32.1	57.9	57.5
t _{max} (hr)			
Median (min, max)	5.0 (3.0, 6.0)	5.0 (5.0, 10)	7.0 (5.0, 12)
T _{lag} (hr)			
Mean (SD)	1.0 (0.31)	0.85 (0.29)	1.2 (0.65)
t _½ (hr)			
Mean (SD)	50 (20)	19 (6.1)	9.0 (0.46)
Geom CV(%)	140	93	23
MRT (hr)			
Mean (SD)	36 (43)	23 (24)	17 (2.9)
Geom CV(%)	84	62	18
CL/F (L/hr)			

(continued)

Parameter (units) Statistic	Reference Capsule (Fed) (N=18)	Compound of Formula (I) Plasma Concentration	
		SDD Suspension (Fed) (N=18)	SDD Suspension (Fasted) (N=18)
Mean (SD)	3.4 (1.4)	11 (8.0)	80 (54)
Geom CV(%)	45	72	63
V_z/F (L)			
Mean (SD)	180 (260)	210 (140)	970 (560)
Geom CV(%)	93	77	53
T_{last} (hr)			
Mean (SD)	170 (140)	77 (110)	31 (7.6)
Geom CV(%)	120	92	30

Table 24: Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by formulation and fed vs fasted (Safety Analysis Set - SDD Suspension Group)

Analyte Parameter (units)	Treatment Comparison	Ratio (%)	90% CI
Compound of Formula (I)			
AUC _{0-tlast} (ngxh/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	32.2	(26.4%, 39.4%)
AUC _{0-∞}	SDD Suspension (Fed) vs. Reference Capsule (Fed)	33.5	(27.7%, 40.6%)
C _{max} (ng/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	42.2	(34.8%, 51.2%)
AUC _{0-tlast} (ngxh/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	4.4	(3.4%, 5.7%)
AUC _{0-∞}	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	5.0	(3.8%, 6.5%)
C _{max} (ng/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	4.5	(3.8%, 5.4%)

Table 25: Summary of Plasma Pharmacokinetic Parameters (Safety Analysis Set - SDD Capsule Group)

Parameter (units) Statistic	Reference Capsule (Fed) (N=18)	Compound of Formula (I) Plasma Concentration	
		SDD Capsule (Fed) (N=18)	SDD Capsule (Fasted) (N=17)
AUC_{0-tlast} (ngxh/mL)			
Mean (SD)	19500 (7960)	9470 (4670)	1840 (1650)
Geom CV (%)	50.4	48.0	78.7
AUC_{0-∞} (ngxh/mL)			
Mean	20100 (7850)	10000 (4610)	2120 (1830)
Geom CV (%)	47.1	44.9	73.7

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(continued)

Parameter (units) Statistic	Reference Capsule (Fed) (N=18)	Compound of Formula (I) Plasma Concentration	
		SDD Capsule (Fed) (N=18)	SDD Capsule (Fasted) (N=17)
C_{max} (ng/mL)			
Mean (SD)	1770 (494)	1110 (449)	143 (110)
Geom CV (%)	25.7	44.5	74.1
t_{max} (hr)			
Median (min,max)	5.0 (5.0, 8.0)	5.0 (3.0, 6.0)	7.0 (6.0, 12)
T_{lag} (hr)			
Mean (SD)	1.0 (0.38)	1.3 (0.49)	1.2 (0.88)
t_{1/2} (hr)			
Mean (SD)	35 (18)	26 (20)	14 (11)
Geom CV (%)	69	98	49
MRT (hr)			
Mean (SD)	28 (12)	25 (14)	21 (9.2)
Geom CV (%)	45	55	31
CL/F (L/hr)			
Mean (SD)	3.0 (1.5)	5.9 (2.4)	36 (18)
Geom CV (%)	47	45	74
Vz/F (L)			
Mean (SD)	130 (61)	190 (140)	630 (380)
Geom CV (%)	47	75	72
T_{last} (hr)			
Mean (SD)	170 (96)	100 (89) 44 (32)	
Geom CV (%)	91	100	39

Table 26: Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by formulation and fed vs fasted (Safety Analysis Set - SDD Suspension Group)

Analyte Parameter (units)	Treatment Comparison	Ratio (%)	90% CI
Compound of Formula (I)			
AUC _{0-tlast}	SDD Capsule (Fed) vs. Reference Capsule (Fed)	48.2	(41.4%, 56.1%)
AUC _{0-∞} (ngxh/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	49.7	(43.1%, 57.2%)

(continued)

Analyte Parameter (units)	Treatment Comparison	Ratio (%)	90% CI
Compound of Formula (I)			
$C_{\max}$ (ng/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	59.8	(51.7%, 69.2%)
$AUC_{0-t_{\text{last}}}$ (ngxh/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	8.0	(5.7%, 11.2%)
$AUC_{0-\infty}$ (ngxh/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	9.0	(6.6%, 12.4%)
$C_{\max}$ (ng/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	6.7	(4.9%, 9.2%)

Example 8: Phase 2 study of the compound of Formula (I) in adult subjects with congenital adrenal hyperplasia

[0477] A Phase 2 study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of the compound of Formula (I) in adult subjects with classic congenital adrenal hyperplasia (CAH) was designed. The objectives of the study are: to assess the safety and tolerability of two ascending doses of the compound of Formula (I) in adult subjects with CAH; to evaluate the effect of repeated doses of the compound of Formula (I) on endogenous levels of PD biomarkers in adult subjects with CAH; and to evaluate plasma exposures following repeated doses of the compound of Formula (I) administered nightly.

[0478] The lower dose strength selected for this study, the compound of Formula (I) 50 mg, was well tolerated in both single and repeat-dose safety and PK studies in healthy volunteers. Doses up to 100 mg were also well tolerated in both single-dose and repeat-dose Phase 1 studies in healthy volunteers, and importantly, in a large Phase 2 study in non-elderly female and male subjects with major depressive disorder receiving the compound of Formula (I) during an 8-week, double-blind treatment period. Furthermore, the anticipated steady state exposures with the selected the compound of Formula (I) doses, using the predicted $C_{\max}$ and AUC, are within the acceptable safety margins defined by the nonclinical toxicology studies that have been conducted to date.

Study Design

[0479] A Phase 2, open-label, multiple-dose, dose-escalation study to assess the safety, tolerability, PK, and PD of the compound of Formula (I) in approximately 30 adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH was designed. The study will include a sequential-cohort design with four compound of Formula (I) dose cohorts: 50 mg and 100 mg, with each dose administered for 14 consecutive days:

- Cohort 1: compound of Formula (I) 50 mg once daily with a bottle of vanilla-flavored Ensure Plus® (~237 mL) at approximately 2200 hours.
- Cohort 2: compound of Formula (I) 100 mg once daily with a bottle of vanilla-flavored Ensure Plus® (~237 mL) at approximately 2200 hours.
- Cohort 3: compound of Formula (I) 100 mg once daily with the evening meal at approximately 1900 hours.
- Cohort 4: compound of Formula (I) 100 mg twice daily with breakfast at approximately 0700 hours and with the evening meal at approximately 1900 hours.

[0480] There will be an approximate 2-week period to evaluate safety and tolerability data before proceeding from Cohort 1 to Cohort 2. Subjects who previously completed the current study in Cohort 1 or Cohort 2 may reenroll to participate in Cohorts 3 or 4 (in addition to new subjects). Table 27 below depicts the dose cohorts, doses, and number of subjects per cohort.

Table 27. Dose cohorts, doses, and number of subjects

Cohort	Compound of Formula (I) Dose	Approximate Dosing Time(s)	Number of Subjects
1	50 mg	2200 hours	8-10
2	100 mg	2200 hours	8-10

(continued)

Cohort	Compound of Formula (I) Dose	Approximate Dosing Time(s)	Number of Subjects
3	100 mg	1900 hours	8-10
4	100 mg	0700 and 1900 hours	Up to 8

[0481] Subjects will be screened for eligibility to participate in the study for up to approximately 3 weeks (Days -28 to -8). Subjects who reenroll and have had a stable medication regimen for CAH since their last visit in this study do not have to undergo screening; those who reenroll and have had a change to their medication regimen for CAH must undergo a second screening visit. During screening, subjects will provide a single blood sample in the morning between 0700 and 1000 hours (prior to first morning dose of hydrocortisone) to determine their 17-hydroxyprogesterone (17-OHP) levels for study entry.

[0482] Eligible subjects who have a screening 17-OHP level $\geq 1,000$ ng/dL will be admitted to the study center for 1 night and have baseline serial PD samples collected over a 24-hour period beginning in the evening of Day -7. Baseline serial PD samples will be collected at approximately 2145, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, and 2200 hours. The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

[0483] Subjects within each dose cohort will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for CYP21A2 genotyping. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. Study drug (the compound of Formula (I) 50 or 100 mg) will be administered at approximately 2200 hours for Cohorts 1 and 2 and at approximately 1845, 2000, 2100, 2200, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1800, 1900, and 2200 hours for Cohorts 3 and 4. The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

[0484] Subjects in Cohorts 1 and 2 will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for cytochrome P450 (CYP) 21A2 genotyping. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. Study drug (compound of Formula(I) 50 mg or 100 mg) will be administered at approximately 2200 hours. The subjects' usual morning dose of concurrent steroidal treatments will be administered after the 12-hour post-dose PK/PD samples are collected (at approximately 1000 hours) on Day 2 and after the 16-hour post-dose PK/PD samples are collected (at approximately 1400 hours) on Day 15. Subjects will be discharged from the study center the evening on Days 2 and 15 following completion of all study-related procedures for those days. Prior to this discharge on Day 2, study drug will be administered at the study center at approximately 2200 hours. Study drug will then be selfadministered nightly at home at approximately 2200 hours on Days 3 to 13. Subjects will take their usual morning dose of concurrent steroidal treatments at approximately 1000 hours on Days 3 to 14. On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center.

[0485] Subjects in Cohorts 3 and 4 will have a blood sample collected on Day 1 for CYP21A2 genotyping (only for subjects who have not previously participated in Cohorts 1 or 2). Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. For Cohort 3, study drug (compound of Formula(I) 100 mg) will be administered at home on Days 1 to 13 at approximately 1900 hours with each subject's evening meal. For Cohort 4, study drug compound of Formula(I) 100 mg) will be administered at home on Days 2 to 14 at approximately 0700 hours with each subject's breakfast and on Days 1 to 13 at approximately 1900 hours with each subjects' evening meal. For both cohorts, the Day 14 evening dose will be administered at the study site. Subjects will take their usual morning dose of concurrent steroidal treatments at approximately 1000 hours on Days 1 to 14. On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center. Subjects will be admitted to the study center on Day 14 (last day of dosing). On Day 14, subjects will receive study drug in the study center at approximately 1900 hours with a standard (moderate fat/moderate calorie) evening meal. The subjects' usual morning dose of concurrent steroidal treatments will be administered after PK/PD samples are collected at approximately 1400 hours on Day 15. Subjects will be discharged from the study center the evening on Day 15 following completion of all study-related procedures.

[0486] For all cohorts, follow-up visits on Days 21, 28, and 35 will be conducted at the study center or the subject's home by a qualified home healthcare provider (based on the subject's preference). A final study visit will be conducted at the study site approximately 5 weeks after the last dose of study drug (on Day 49 or early termination). There will be a visit window of - 8 hours for Day 7, -8 hours/+3 days for Days 21, 28, and 35, and +7 days for the final study visit. Safety, tolerability, PK, and PD will be assessed at scheduled times throughout the study. The study design schematic is shown in FIG. 11.

Dose escalation procedure

[0487] Cohort 1 will consist of approximately 8 to 10 subjects who will receive a daily dose of the compound of Formula (I) 50 mg at approximately 2200 hours for 14 days (subjects will receive study drug at the site on Days 1, 2, and 14, and self-administer study drug at home on Days 3 to 13). Following the completion of Day 15 assessments for all subjects in the Cohort 1, a medical monitor will review the accumulated safety and tolerability results to ensure there are no safety concerns with proceeding to the 100 mg dose (Cohorts 2 and 3), and to determine if a maximum tolerated dose (MTD) has been reached. If the MTD is reached, no dose escalation will occur. There will be an approximate 2-week period between Cohorts 1 and 2 to accommodate this safety review. A similar procedure will be used prior to proceeding to the 100 mg twice daily dose (Cohort 4).

[0488] If the medical monitor determines that it is safe to proceed to the compound of Formula (I) 100 mg, subjects in Cohort 2 will be administered the compound of Formula (I) 100 mg daily for 14 days. Dosing for Cohorts 3 and 4 may begin simultaneously with Cohort 2.

[0489] During the 14-day dosing period for any cohort, dosing may be postponed or halted if one or more subjects experience a severe or serious adverse event (AE), or if the type, frequency, or severity of AEs becomes unacceptable. If dosing is postponed, the medical monitor will review all available safety, tolerability, and PK data before allowing any further subjects to receive study drug.

Study Population

[0490] Approximately 30 adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH, who meet all protocol eligibility criteria, will be enrolled. Subjects who previously completed the current study in Cohort 1 or Cohort 2 may reenroll to participate in Cohorts 3 or 4 (in addition to new subjects).

Duration of treatment

[0491] The expected duration of study participation for each subject is approximately 11 weeks, including up to approximately 3 weeks for screening, a 24-hour PD baseline period (approximately 7 days prior to the first day of dosing), 14 days of dosing, and a follow-up period of approximately 5 weeks. The total duration of the study will be an additional 8 to 11 weeks for subjects who reenroll.

Test product, dose, and mode of administration

[0492] The compound of Formula (I) will be supplied as capsules containing 50 mg of the compound of Formula (I) free base for oral administration (see, e.g., Reference 1 formulation as described in Example 9). Doses of the compound of Formula (I) are 50 mg and 100 mg, administered in oral capsule form. Each dose of study drug for Cohorts 1 and 2 is to be administered with a bottle of vanilla-flavored Ensure Plus® (~237 mL). Each dose of study drug for Cohort 3 is to be administered with each subject's evening meal at approximately 1900 hours. Each dose of study drug for Cohort 4 is to be administered with each subject's breakfast at approximately 1900 hours (i.e., a total daily dose of 200 mg).

Criteria for EvaluationCohorts 1 and 2

[0493] Blood samples to evaluate 24-hour PD baseline will be collected on Days -7 to -6 at approximately 2145, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, and 2200 hours. Blood samples to evaluate PK and PD parameters of the compound of Formula (I) will be collected on Days 1 to 2 and Days 14 to 15 at: 15 minutes pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours post-dose; Day 7 (at approximately 24 hours post-dose); Days 21, 28, and 35 (at approximately 168, 336, and 504 hours post-dose); and at the final study visit (Day 49 or early termination).

Cohorts 3 and 4

[0494] Blood samples to evaluate 24-hour PD baseline will be collected on Days -7 to -6 at approximately 1845, 2000, 2100, 2200, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1800, 1900, and 2200 hours. Blood samples to evaluate PK and PD parameters of the compound of Formula (I) will be collected on Days 14 to 15 at the following times (for Cohort 4, all times are relative to evening dosing unless otherwise indicated): 15 minutes predose and at 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 17, 19, 23, 24, and 27 hours postdose; Day 7 (at 24 hours postdose for Cohort 3 or at 12

hours post morning dose but prior to the evening dose for Cohort 4); Days 21, 28, and 35 (at approximately 168, 336, and 504 hours postdose); and at the final study visit (Day 49 or early termination).

Pharmacokinetics

[0495] The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0-t_{last}}$)
- Area under the plasma concentration versus time curve from 0 to 24 hours (AUC_{0-24})
- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Terminal half-life ($t_{1/2}$)
- Apparent terminal rate constant (λ_z)
- Apparent mean residence time (MRT)

[0496] Additional PK parameters for Day 14 only:

- Average plasma concentration at steady state (C_{avg})
- Percent fluctuation at steady state (% fluctuation)
- Accumulation index at steady state
- Apparent systemic clearance after oral administration (CL/F) (the compound of Formula (I) only)

Pharmacodynamics

[0497] Primary: Morning 17-OHP (serum; ng/dL) from the 0600, 0800, and 1000 hour samples (8-, 10-, and 12-hour post-dose samples from Cohorts 1 and 2 and 11-, 13-, and 15-hour postdose samples from Cohorts 3 and 4.

[0498] Secondary: 17-OHP at all other times, androstenedione (serum; ng/dL), testosterone (serum; ng/dL), cortisol (serum; μ g/dL), and adrenocorticotrophic hormone (plasma ACTH; pg/mL).

Safety

[0499] Safety and tolerability will be monitored throughout the study and will include the following assessments:

- Adverse events
- Clinical laboratory tests - clinical chemistry (including creatine kinase, myoglobin, total and conjugated bilirubin), hematology, coagulation (prothrombin time, aPTT, d-dimer, fibrinogen), and urinalysis (including quantitative myoglobin, casts and crystals)
- Vital signs
- Physical examinations (including musculoskeletal exam)
- 12-lead electrocardiograms (ECGs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Brief Psychiatric Rating Scale (BPRS)

Statistical methods

[0500] Safety, PK, and PD variables will be summarized within each dose cohort (the compound of Formula (I) 50 mg and 100 mg) using descriptive statistics. Summaries of PD measures will include both observed values and changes from pre-dose.

Results

Pharmacokinetic results

[0501] Eight subjects (four female and four male) were enrolled in this study and completed Cohort 1. Age, sex, and BMI information for the study participants is shown in Table 28, below.

Table 28. Cohort 1 Subjects

Subject ID	Age (years)	Sex (Male/Female)	BMI (kg/m ²)
001	37	Female	24.9
002	25	Female	32.0
003	49	Male	37.2
004	36	Male	25.0
005	27	Female	25.5
006	19	Male	21.7
007	25	Male	27.5
008	31	Female	34.4

[0502] The subjects received a daily dose of the compound of Formula (I) at 50 mg at approximately 2200 hours (~10 p.m. or bedtime) for 14 days. Arithmetic mean values for ACTH (FIG. 12A) and 17-OHP (FIG. 12B) for all 8 Cohort 1 subjects were plotted at each timepoint for Pre-treatment Baseline, Day 1, and Day 14. Both ACTH and 17OHP concentration profiles at day 1 and day 14 show clear reductions from the baseline mean profiles. Cohort 1 mean PK parameters of T_{max} , C_{max} , and AUC_{24} for the compound of Formula (I) are shown in Table 29 below. These PK parameters are consistent with observations from Phase 1 studies in healthy volunteers.

Table 29. Cohort 1 Mean PK parameters of T_{max} , C_{max} , and AUC_{24}

	Day 1			Day 14		
	T_{max}	C_{max}	AUC_{24}	T_{max}	C_{max}	AUC_{24}
Mean	5.4	1305	10,292	4.4	1349	14,297
CV%	30	25	24	32	15	24

[0503] Additional measurements of cohort 1 and cohort 2 mean PK parameters of T_{max} , C_{max} , and AUC_{24} for the compound of Formula (I) on Day 1 of dosing are shown in Table 30 below.

Table 30: Mean PK parameters of T_{max} , C_{max} , and AUC_{24} on Day 1 of dosing

	Cohort 1 50 mg- Ensure			Cohort 2 100 mg-Ensure		
Day 1	T_{max}^* (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)
G.Mean	6	1,270	10,411	4	2,370	24,725
CV%	-	25	24	-	21	42
N	8	8	8	8	4	4
*Median						

[0504] Additional measurements of cohort 1, cohort 2 and cohort 3 mean PK parameters of T_{max} , C_{max} , and AUC_{24} for the compound of Formula (I) on Day 14 of dosing are shown in Table 31 below.

Table 31: Mean PK parameters of T_{max} , C_{max} , and AUC_{24} on Day 14 of dosing

	Cohort 1 50 mg- Ensure			Cohort 2 100 mg-Ensure			Cohort 3 100 mg w/evening Meal		
Day 14	T_{max}^* (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)
G. Mean	4	1,335	14,070	4	3,379	35,416	3	3,650	34,706

(continued)

	Cohort 1 50 mg- Ensure			Cohort 2 100 mg-Ensure			Cohort 3 100 mg w/evening Meal		
Day 14	Tmax* (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)	Tmax (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)	Tmax (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)
CV%		15	24		31	7		2	15
N	8	8	8	6	6	6	8	8	8
*Median									

[0505] Arithmetic mean values for androstenedione (FIG. 13A) and testosterone (FIG. 13B) for all 8 Cohort 1 subjects were plotted at each timepoint for Pre-treatment Baseline, day 1, and day 14. The androstenedione concentration profile on Day 1 and Day 14 shows a clear reduction from the baseline mean profile.

[0506] When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of ACTH show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 14A). Arithmetic mean values across all three timepoints show $\geq 50\%$ reductions from baseline at Day 1 and Day 14 (FIG. 14B).

[0507] When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of 17-OHP show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 15A). Arithmetic mean values across all three timepoints show $\geq 40\%$ reductions from baseline at Day 1 and Day 14 (FIG 15B).

[0508] When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of androstenedione show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 16A). Arithmetic mean values across all three timepoints show $\geq 30\%$ reductions from baseline at Day 1 and Day 14 (FIG. 16B).

[0509] A summary of reduction in 17-OHP and androstenedione in cohort 1 is shown in Table 32. Further, the androstenedione levels of three subjects was normalized by the treatment for the three subjects with Subject ID Nos. 001, 002, and 006).

Table 32. Cohort 1 Summary of Reduction in 17-OHP and Androstenedione at each timepoint in the morning window (6 a.m. to 10 a.m.)

Subject ID	Sex/Age	Dosing Day	17-OHP % change from baseline			Androstenedione % change from baseline		
			6 AM	8 AM	10 AM	6 AM	8 AM	10 AM
001	F/37	D1	-61.4	14.7	-24.1	-42.0	2.0	-19.5
		D14	-90.3	-67.2	-37.2	-84.6	-58.6	-55.1
002	F/25	D1	-96.0	-95.5	45.4	-68.0	-66.7	-21.7
		D14	-37.7	-58.6	-24.9	-34.2	-47.8	-38.7
003	M/49	D1	-11.8	-46.6	-34.0	-13.4	-47.1	-22.7
		D14	-24.5	-5.2	-22.9	-7.5	-10.8	-16.0
004	M/36	D1	-13.7	17.1	10.1	4.5	15.9	3.0
		D14	-53.6	-46.8	-35.8	-13.8	-15.2	-21.2
005	F/27	D1	-24.4	-83.6	-52.2	-35.6	-50.3	-33.5
		D14	-78.8	-95.1	-86.3	26.7	-13.7	-10.9
006	M/19	D1D14	-5.1	-1.1	-97.8	-10.0	-18.5	-78.9
		D14	-25.4	-20.4	-98.3	-67.8	-62.7	-92.1
007	M/25	D1	-50.0	-28.0	-27.4	-24.8	-30.0	-15.8
		D14	14.9	4.0	-7.1	-4.8	-36.8	-30.2
008	F/31	D1	-64.5	-80.7	-92.8	-12.2	7.0	-9.3
		D14	-59.0	-65.2	-89.1	74.5	99.4	59.2

Table 33. Cohort 1 Summary of PK parameters of T_{max} , C_{max} , and AUC_{24} for each subject at days 1 and 14

Day 1	Day 1			Day 14		
Subject ID	T_{max} (h)	AUC_{24} C_{max} (ng/ml) (h*ng/ml)		T_{max} (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)
001	6	1830	14,487	6	1570	20,863
002	6	1210	11,829	4	1610	15,494
003	6	1060	11,068	3	1310	15,599
004	4	1670	9,669	3	1160	10,180
005	8	961	9,266	6	1550	15,130
006	4	1030	6,574	3	1090	10,288
007	6	1550	8,239	6	1170	12,880
008	3	1130	11,209	4	1330	13,944
Mean	5.4	1305	10,292	4.4	1349	14,297
CV%	30	25	24	32	15	24
N	8	8	8	8	8	8

[0510] After 14 days of once-daily compound of Formula (I) administration, a majority of participants in Cohorts 1-3 showed reduced serum concentrations of adrenal androgens and precursors. Mean changes from baseline ($\pm$ standard deviation) in Cohort 1 were as follows: 17-OHP, -2341.0 ± 1535.0 ng/dL; androstenedione, -98.4 ± 98.7 ng/dL; and ACTH, -157.0 ± 194.9 pg/mL. Mean reductions were larger in Cohort 2 (17-OHP, -4406.0 ± 5516.1 ; androstenedione, -362.8 ± 354.0 ; ACTH, -180.9 ± 155.2) and Cohort 3 (17-OHP, -4760.1 ± 4018.2 ; androstenedione, -210.9 ± 188.6 ; ACTH, -358.9 ± 177.6), suggesting a possible dose response. FIGs. 17A-17C, 18A-18C, and 19A-19C depict results from Cohorts 1, 2, and 3, respectively.

Summary

[0511] The results from this ongoing Phase II open-label study demonstrated a reduction of at least 50 percent from baseline in 17-hydroxyprogesterone (17-OHP) and adrenocorticotrophic hormone (ACTH) levels in more than 50 percent of CAH patients in cohort 1 treated with the compound of Formula (I) for 14 days (i.e., 6 of 8 patients in cohort 1 had a reduction of $\geq 50\%$ from baseline levels of 17-OHP during at least one morning window timepoint, see, e.g., Table 32). Meaningful reductions were also observed in other biomarkers, including androstenedione (i.e., 4 of these patients also had a reduction of $\geq 50\%$ from baseline levels of androstenedione during at least one morning window timepoint, see, e.g., Table 32). The greater reductions in biomarkers in cohorts 2 and 3, treated with double the dose of the compound of Formula (I) compared with cohort 1, suggest a possible dose response. Further, the compound of Formula (I) was well-tolerated with a relatively small number of mild adverse events (AEs) reported (e.g., headache, ovulation pain, fatigue, localized infection (toe), dizziness, nausea, URI, contusion with the most common being headache). No clinically significant findings from routine labs, vital signs, or electrocardiograms were found.

Example 9: Reference Formulation 1 of the compound of Formula (I)

[0512] Tables 34A and 34B show Reference formulation 1 of the compound of Formula (I) as used in the clinical studies described in Examples 6 and 8, above. An example manufacturing process is shown in FIG. 20. Another example manufacturing process is shown in FIG. 21.

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Table 34A:

Component	Quality Standard	Function	50 mg Capsule	
			Weight mg/un it)	% (w/w)
Compound of Formula (I), free base	In-house	Active Ingredient	50.0	10.0
Medium-Chain Triglycerides Labrafac TM Lipophile WL1349)	NF	Oily Phase Vehicle	196.0	39.2
Propylene Glycol Dicaprylate/Dicaprate, (LabrafacTM PG)	NF	Emulsifying Agent	102.0	20.4
Lauroyl Polyoxyl-32 Glycerides (Gelucire® 44/14)	NF	Nonionic Surfactant & Solubilizing Agent	95.0	19.0
Vitamin E Polyethylene Glycol Succinate (Kolliphor® TPGS)	USP/NF	Solubilizing Agent	57.0	11.4
Total Emulsion Weight			500.0	100.0
Gelatin Capsule Shell. Size #00, Swedish Orange cap/body; (Coni-Snap®)	Non -Pharmacopoeial	Capsule Shell	--	
Gelatin Powder, 220 Bloom	USP	Capsule shell banding agent	--	--
Purified Water	USP	Capsule shell banding solvent	--	--

Table 34B:

Component	Quality Standard	Function	50 mg Capsule	
			Weight (mg/un it)	% (w/w)
Compound of Formula (I), free base	In-house	Active Ingredient	50.0	10.0
Medium-Chain Triglycerides (caprylic:capric acid 60:40; Miglyol 812N)	Ph. Eur./NF	Vehicle	195.85	39.2
Propylene Glycol Dicaprylocaprate, (LabrafacTM PG)	Ph. Eur.	Vehicle	102.15	20.4
Lauroyl macrogolglycerides type 1500-Lauroyl polyoxyglycerides type 1500 (Gelucire® 44/14)	Ph. Eur./NF	Surfactant	95.0	19.0
Vitamin E Polyethylene Glycol Succinate, 260 mg/g d-alpha tocopherol (Vitamin E/TPGS 260)	NF	Surfactant	57.0	11.4
Total Emulsion Weight			500.0	100.0
Orange opaque hard capsule, size 0, composed of gelatin, titanium dioxide and red ferric oxide (Swedish Orange ®)	Non Pharmacopoeial	Capsule Shell	--	--
Ethanol (96%) and Purified Water	USP	Capsule shell banding solvent	--	--

Example 10: Study Evaluating Effect of Ensure Plus, Ensure Pudding, Milk and High Fat Meal on Reference Capsule**Study design**

[0513] This is a Phase 1, open-label, randomized, four-period crossover study to evaluate the effect of food with different levels of fat and caloric content on the PK, safety, and tolerability of the compound of Formula (I) in healthy adult subjects.

[0514] A total of 16 healthy adult subjects (8 males and 8 females) will be randomly assigned to 1 of 4 treatment sequences (4 subjects per sequence [2 males and 2 females per sequence]; see Table 35 below). During each treatment period, subjects will receive a single dose of the compound of Formula (I) 100 mg administered with the appropriate meal, according to the randomization scheme. There will be a washout of at least 21 days between each dose.

Table 35:

Treatment Sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4
1	Reference meal	Test meal 1	Test meal 2	Test meal 3
2	Test meal 1	Test meal 3	Reference meal	Test meal 2
3	Test meal 2	Reference meal	Test meal 3	Test meal 1
4	Test meal 3	Test meal 2	Test meal 1	Reference meal
Reference meal: vanilla-flavored Ensure Plus® Test meal 1: Low fat, low caloric content meal 1 Test meal 2: Low fat, low caloric content meal 2 Test meal 3: standard high fat, high caloric content meal				

[0515] After providing informed consent, subjects will be screened for eligibility to participate in the study. Screening will begin up to 28 days before Day 1 of treatment period 1. Eligible subjects will be admitted to the clinical unit on Day -1 and randomized to 1 of the 4 treatment sequences on Day 1 of treatment period 1. During each treatment period, subjects will fast overnight for at least 10 hours until the start of the assigned meal, according to the randomization scheme, and ingest the study drug at approximately 0800 hours. Subjects must complete the entire meal within the specified time period and should not consume any other food for 4 hours after dosing. For all treatment periods, water will not be permitted for 1 hour before dosing until 2 hours after dosing except for the water provided with study drug dosing and planned meals.

[0516] On Day 1 of each treatment period, subjects will be dosed with the compound of Formula (I) 100 mg. Blood samples will be collected for PK analysis over a period of 36 hours during the in-house stay. During each treatment period, subjects will remain in the clinic on the day of dosing and will be discharged on Day 2 after completing all required procedures. On the mornings of Days 8 and 15 of each treatment period, subjects will return for an outpatient visit to the clinic for PK blood sample collection and safety assessments. On Day 21 of treatment periods 1 to 3, subjects will arrive at the site and have Day 21 assessments completed and they will stay overnight at the site and begin Day 1 of the subsequent treatment period the following day. A final follow-up study visit will be conducted on Day 22 of treatment period 4 (21 ± 2 days after treatment period 4 dosing) or upon early termination.

[0517] Blood samples for PK d/conducted at scheduled times throughout the study.

Study population

[0518] Sixteen healthy adult subjects (8 males and 8 females) between 18 and 55 years of age, inclusive, who meet all protocol eligibility criteria, will be enrolled.

Duration of treatment

[0519] The expected duration of study participation for each healthy adult subject will be approximately 16 weeks, including up to 28 days of screening, 4 days of dosing with at least 21 days between consecutive doses, and a final follow-up study visit 21 days (± 2 days) after receiving the last dose of study drug during treatment period 4.

Test product, dose, and mode of administration

[0520] The compound of Formula (I) will be supplied as capsules for oral administration (encapsulated, lipidic semi-solid formulation, e.g., Example 9). The compound of Formula (I) capsules will contain 50 mg of the compound of Formula (I) as free base equivalent. During each treatment period, subjects will receive two 50 mg capsules (100 mg) of the study drug along with a meal and water as defined by the randomization scheme. The food, water, and study drug administration are as follows:

Reference meal: Two capsules of study drug will be administered approximately 5 minutes after the start of a liquid dietary supplement (i.e., Ensure Plus® [237 mL container]) and an additional 120 mL of water for study drug dosing.

Test meal 1: Two capsules of study drug will be administered approximately 5 minutes after the start of a low fat, low caloric meal 1 with 120 mL of water for study drug dosing.

Test meal 2: Two capsules of study drug will be administered approximately 5 minutes after the start of a low fat, low caloric meal 2 with 120 mL of water for study drug dosing.

Test meal 3: Two capsules of study drug will be administered approximately 30 minutes after the start of a high fat, high caloric meal with 120 mL of water for study drug dosing.

CRITERIA FOR EVALUATION**Pharmacokinetics**

[0521] Blood samples for assessment of plasma concentrations of the compound of Formula (I) and metabolites will be collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

[0522] The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0-t_{last}}$)
- Area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0-\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{1/2}$)
- Apparent terminal rate constant (λ_z)
- Apparent mean residence time (MRT)
- Molar AUC ratio of primary metabolite(s) to the parent drug compound of Formula (I). The following plasma PK parameters will be calculated only for the compound of Formula (I):
- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (V_z/F)

Safety Assessments

[0523] Safety will be monitored throughout the study and will include the following assessments:

- Adverse events (AEs)
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiograms (ECGs)

Statistical methods

[0524] Pharmacokinetic parameters will be calculated using noncompartmental methods and summarized by meal type (test meal/reference meal) using descriptive statistics. Two-sided 90% confidence intervals will be calculated for the ratio of each test meal versus the reference meal for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} for the compound of Formula (I)

and metabolites.

[0525] Safety data will be summarized with descriptive statistics.

Results

Pharmacokinetic results

[0526] Pharmacokinetic results are shown in Table 36 below.

Table 36: Summary of Plasma Pharmacokinetic Parameters

Parameter (units) Statistic	Ensure Plus (Fed) (N=18)	Compound of Formula (I) Plasma Concentration		High Fat Meal (Fed) (N=17)	
		Ensure Pudding (Fed) (N=18)	Whole Milk (Fed) (N=17)		
AUC_{0-tlast} (ng×hr/mL)					
Mean (SD)	36703 (17400)	34077 (11597)	35561 (15866)	55487 (23242)	
Geom CV(%)	58	39.7	44.6	41.9	
AUC_{0-∞} (ng×hr/mL)					
Mean		45386 (19648)	40037 (9515)	46737 (17395)	63755 (19139)
Geom CV(%)		43.3	23.8	38.8	31
C_{max} (ng/mL)					
Mean (SD)		3090 (1070)	3038 (984)	2835 (1005)	4336 (1938)
Geom CV(%)		39.7	34.9	34.5	53.6
t_{max} (hr)					
Median (min, max)		5.0 (2.0, 10.0)	5.0 (4.0, 6.0)	5.0 (4.0, 7.0)	5.0 (4.0, 7.0)
T_{lag} (hr)					
Mean (SD)		0.38 (0.46)	0.20 (0.25)	0.16 (0.31)	0.29 (0.37)
t_½ (hr)					
Mean (SD)		361 (263)	373 (196)	373 (143)	326 (120)
Geom CV(%)		61.1	48.6	37.1	33.8
CL/F (L/hr)					
Mean (SD)		2.49 (0.956)	2.636 (0.659)	2.427 (0.975)	1.706 (0.526)
Geom CV(%)		41.2	24.8	38.8	31.1
Vz/F (L)					
Mean (SD)		1254 (906)	1414 (720)	1308 (627)	816 (378)
Geom CV(%)		72.7	58.4	61.3	54.9

Example 11: Spray-dried Dispersion Granule Formulation of the Compound of Formula (I) (SDD-G)

[0527] Table 37 shows a granule formulation of the compound of Formula (I) using a SDD prepared according to Example 3, above. An example manufacturing process is shown in FIG. 22A and FIG. 22B.

Table 37:

Component	Quality Standard	Function	50 mg Sachet		Batch Weight (g)
			Weight (mg/unit)	% (w/w)	
Example 3, SDD	In-house	Drug Substance	200.0	13.33	40
Calcium Silicate (ZEOPHARM 250)	NF	Glidant	10.0	0.67	2
Mannitol (Pearlitol 200SD)	NF / EP / JP	Filler	832.5	55.5	166.5
Microcrystalline Cellulose (Avicel PH-102)	NF / EP / JP	Filler	300.0	20.0	60
Croscarmellose Sodium (Ac-Di-Sol®) SD711	NF / EP / JP	Disintegrant	150.0	10.0	30
Sodium Stearyl Fumarate	NF / EP / JP	Lubricant	7.5	0.5	1.5
Total			1500	100.0	300

Example 12: Liquid Formulation 1 of the Compound of Formula (I)

[0528] Table 38 shows liquid formulation 1 of the Compound of Formula (I) free base. An example manufacturing process is shown in FIG. 23.

Table 38:

Component	Quality Standard	Function	50 mg/mL Oral Solution		Batch Weight (g)
			Weight (mg/mL)	% (w/v)	
Compound of Formula (I) FB	In-house	Drug Substance	50.0	5	20.03
Saccharin	NF / EP	Sweetener	1.5	0.15	0.61
Butylated hydroxytoluene	NF / EP	Anti-oxidant	1.7	0.17	0.69
FONA orange flavor	NF	Flavor	1.0	0.1	0.41
Labrafac Lipophile WL1349	NF / EP	Liquid Vehicle	to 1 mL	94.58	358.87
Total			1 mL	100.0	380.6

Example 13: Liquid Formulation 2 of the Compound of Formula (I)

[0529] Table 39 shows liquid formulation 2 of the Compound of Formula (I) free base. An example manufacturing process is shown in FIG. 24.

Table 39:

Component	Quality Standard	Function	50 mg/mL Oral Solution		Batch Weight (g)
			Weight (mg/mL)	% (w/v)	
Compound of Formula (I) FB	In-house	Drug Substance	50.0	5	20.17
Saccharin	NF / EP	Sweetener	1.5	0.15	0.61

(continued)

Component	Quality Standard	Function	50 mg/mL Oral Solution		Batch Weight (g)
			Weight (mg/mL)	% (w/v)	
Butylated hydroxytoluene	NF / EP	Anti-oxidant	1.7	0.17	0.68
LABRAFIL M 1944 CS	NF / EP	Surfactant	200.0	20	80.16
FONA orange flavor	NF	Flavor	1.0	0.1	0.40
Labrafac Lipophile WL1349	NF / EP	Liquid Vehicle	to 1 mL	74.58	278.68
Total			1 mL	100.0	380.7

Example 14: A Phase I, Open-Label Study to Evaluate the Pharmacokinetics, Relative Bioavailability, Effect of Food, Safety and Tolerability of Different Compound of Formula (I) Prototype Formulations in Healthy Adult Subjects.

Methodology

[0530] This is a single center, open-label, randomized, single dose 4-period crossover study in healthy adult subjects designed to investigate the pharmacokinetic (PK) and safety of up to 4 compound of Formula (I) liquid lipidic prototype formulations (compound of Formula (I) Oral Solution, Prototype Formulations, 50 mg/mL), a compound of Formula (I) spray dried dispersion formulation (compound of Formula (I) Granule for Sprinkle, 25 - 50 mg) and compound of Formula (I), 50 mg Capsules (Reference). It is planned to enroll 36 subjects to be allocated as 3 cohorts of 12 subjects per cohort, with 6 sub-cohorts of 6 subjects per sub-cohort. In each of these 6 sub-cohorts, 6 subjects will be assigned to one of 3 sub-cohorts where a single oral dose of Investigational Medicinal Product (IMP) is administered in 4 dosing periods (Periods 1 to 4) in multiple fed or fasted states or to one of 3 sub-cohorts where a single oral dose of IMP is administered in 2 dosing periods (Periods 1 and 2) only in the fed state. Within each sub-cohort, subjects will also be randomized before administration of the first dose of IMP in Period 1 to one of the following treatment sequences (Table 40):

Table 40:

Sub-Cohort	Sequence	Number of Subjects	Total Number of Periods Dosed	Regimen			
				Period 1	Period 2	Period 3	Period 4
1A	ABEF	3	4	Regimen A	Regimen B	Regimen E	Regimen F
	BAEF	3	4	Regimen B	Regimen A	Regimen E	Regimen F
1B	AB	3	2	Regimen A	Regimen B	N/A	N/A
	BA	3	2	Regimen B	Regimen A	N/A	N/A
2A	ADEF	3	4	Regimen A	Regimen D	Regimen E	Regimen F
	DAEF	3	4	Regimen D	Regimen A	Regimen E	Regimen F
2B	AD	3	2	Regimen A	Regimen D	N/A	N/A
	DA	3	2	Regimen D	Regimen A	N/A	N/A

(continued)

Sub-Cohort	Sequence	Number of Subjects	Total Number of Periods Dosed	Regimen			
				Period 1	Period 2	Period 3	Period 4
3A	ACEF	3	4	Regimen A	Regimen C	Regimen E	Regimen F
	CAEF	3	4	Regimen C	Regimen A	Regimen E	Regimen F
3B	AC	3	2	Regimen A	Regimen C	N/A	N/A
	CA	3	2	Regimen C	Regimen A	N/A	N/A

[0531] At informed consent, subjects will agree either to participate in 2 study periods or 4 study periods. Once placed into a sub-cohort, the order in which subjects receive the study treatments will be randomized based on the schedule above.

[0532] Subjects will receive up to 4 regimens in up to 4 periods in an order according to the randomization schedule within each sub-cohort.

[0533] The effect of different prandial states on the PK of the compound of Formula (I) may be explored in Periods 3 and 4 by administering in the fasted state or after an alternative meal (e.g. high fat, standard or light breakfast, etc.).

[0534] The proposed regimens are presented in Table 41 below:

Table 41:

Regimen	Investigational Medicinal Product	Dose	Route of Administration	Prandial State
A	Compound of Formula (I), 50 mg Capsules (Reference)	50 mg	Oral	Fed (Ensure Plus)
B	Compound of Formula (I) Oral Solution, Prototype Formulation 1, 50 mg/mL	50 mg	Oral	Fed (Ensure Plus)
C	Compound of Formula (I) Oral Solution, Prototype Formulation 2, 50 mg/mL	50 mg	Oral	Fed (Ensure Plus)
D	Compound of Formula (I) Granule for Sprinkle, 25 - 50 mg	50 mg	Oral	Fed (Ensure Plus)
E	Compound of Formula (I) Oral Solution, Prototype Formulation 1	100 mg	Oral	Fed (Ensure Plus)
F	Compound of Formula (I) Oral Solution, Granule for Sprinkle	50 mg	Oral	Fed (alternative meal)

Study Design:

[0535] Subjects will be screened for eligibility to participate in the study up to 28 days before the first dose of IMP in Period 1. Each study period will follow the same study design. Subjects will be admitted to the clinical unit on the evening prior to IMP administration (Day -1). For Periods 1 and 2 (Regimen A and one of either Regimens B, C or D), all subjects will receive the compound of Formula (I) formulations in the morning according to the randomization schedule in the fed state with a liquid dietary supplement (Ensure Plus). For Periods 3 and 4 (Regimens E and F), subjects will receive the compound of Formula (I) formulations in the morning according to the randomization schedule in the fed state with a liquid dietary supplement or an alternate prandial state (fasted or alternative meal). IMP administration will be performed on Day 1 with an appropriate interval between subjects based on logistical requirements (approximately 10 min). Meals will be standardized for each treatment regimen across periods.

[0536] Subjects will remain in the clinical unit until 36 h post-dose when they will be discharged. Subjects will return to the clinical unit at 168 h (7 days) and 336 h (14 days) postdose for a PK blood sample and safety assessments. The

minimum washout between IMP dosing occasions will be 14 days between Periods 1 and 2 and 21 days or more to accommodate interim data reviews between Periods 2 and 3 and between Periods 3 and 4.

[0537] There will be a follow-up phone call 18 to 24 days post-final visit to ensure the ongoing wellbeing of subjects.

[0538] Following the completion of Period 2 for all cohorts, there will be an interim data review during which the PK and safety data will be reviewed, plus any relevant emerging Chemistry, Manufacturing and Control (CMC) stability study information, to determine the formulation, dose level and prandial state in which to administer the IMP in Period 3 (Regimen E). There will be a similar interim review following completion of Period 3 (administration of Regimen E) to determine the formulation, dose level and prandial state in which to administer the IMP in Period 4 (Regimen F). The criteria for the interim decisions will be based on available compound of Formula (I) PK data: e.g., C_{max} , T_{max} , AUC(0-36), F_{rel} and safety data.

Number of Subjects Planned:

[0539] It is planned to enroll 36 healthy male and female (non-pregnant, non-lactating) subjects in 6 sub-cohorts of 6 subjects per sub-cohort. These sub-cohorts will be combined in sets of 2 to create 3 cohorts of $n = 12$ for Periods 1 and 2 to target data in 10 evaluable subjects in each cohort for the primary objectives per formulation variant. A total of 18 subjects, 6 from each of Sub-Cohorts 1A, 2A and 3A participating in Periods 1 and 2, will additionally participate in Periods 3 and 4 with a target of a minimum of 6 evaluable subjects. A subject will be considered evaluable for a particular regimen if they have received an IMP and has completed sufficient planned PK assessments up to 336 h (14 days) after dosing for that regimen to allow for the assessment of study endpoints. A subject will be considered evaluable for a particular comparison (e.g., food effect, relative bioavailability) if they have received both IMPs under comparison and have sufficient PK data up to 14 days after each regimen to allow for assessment of study endpoints.

[0540] Subjects withdrawn due to an IMP-related adverse event (AE) will not be replaced. Subjects who are withdrawn for other reasons may be replaced as required by agreement between the principal investigator (PI) and sponsor to ensure sufficient numbers of evaluable subjects at the end of each study period. Replacement subjects may be required to be dosed with specific formulations from the previous regimens in order to obtain the minimum number of evaluable subjects required for interim decisions and to obtain data in any other regimen that is required to fulfil the study objective comparisons, with the exception that any previously dosed IMP that has been considered sub-optimal will not be dosed. Up to 8 replacement subjects in total may be enrolled into the study. The maximum number of subjects that may be dosed is 44 in total.

[0541] If a subject withdraws from Sub-Cohort 1A, 2A or 3A after Period 2, it is acceptable to replace them with a subject from Sub-Cohort 1B, 2B or 3B provided the subject signs an updated consent form agreeing to participate in four treatment periods. At the discretion of the investigator, such a subject may not be required to undergo repeat screening procedures.

Duration of Study:

[0542] For subjects enrolled to receive single dose administration on 4 separate occasions in Periods 1 to 4 (Sub-Cohorts 1A, 2A and 3A), the estimated time from screening until the follow-up phone call is approximately 15 to 16 weeks.

[0543] For subjects enrolled to receive single dose administration on 2 separate occasions in Periods 1 to 2 only (Sub-Cohorts 1B, 2B and 3B), the estimated time from screening until the follow-up phone call is approximately 8 to 9 weeks.

Pharmacokinetic Assessments:

[0544] The plasma concentration data for a compound of Formula (I) will be analyzed for final reporting by Quotient Sciences and for interim reviews by Neurocrine Biosciences, Inc. (NBI), using Phoenix WinNonlin v8.0 or a more recent version (Certara USA, Inc., USA). NBI will be responsible for PK analysis for interim review.

[0545] PK analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the following PK parameters (Table 42) where possible and appropriate:

Table 42:

T_{lag}	Time prior to the first measurable (nonzero) concentration
T_{max}	Time to maximum plasma concentration
C_{max}	Maximum plasma concentration
$AUC_{0-tilast}$	Area under the plasma concentration versus time curve (AUC) from 0 h to last measurable concentration

(continued)

	AUC _{0-inf}	AUC from 0 h extrapolated to infinity
5	AUC _{extrap}	Percentage of AUC _{0-inf} extrapolated beyond the last measurable concentration
	Lambda-z	Slope of the apparent terminal phase
	T _{1/2}	Apparent terminal half-life
	CL/F ^a	Apparent systemic clearance after oral administration
10	Vd/F ^a	Apparent volume of distribution based on the area after a single oral administration
	MRT	Mean residence time
	MPR AUC _{0-tlast}	Metabolite to parent ratio based on AUC _{0-tlast}
15	MPR AUC _{0-inf}	Metabolite to parent ratio based on AUC _{0-inf}

Taste Assessments:

[0546] Taste will be assessed for each IMP formulation and vehicle (e.g., Ensure Plus, soft food) using a questionnaire designed for this purpose and adapted for this specific study as required.

[0547] The questionnaire will ask subjects to rate the acceptability of smell, sweetness, bitterness, flavor, mouth feel, and aftertaste on a 6-point scale, and overall experience on a 5-point scale for each IMP formulation independently of any previous formulations.

Statistical Methodology:

[0548] Descriptive summaries for all safety data, PK assessments and taste questionnaire data will be provided. No hypothesis testing will be performed for the safety or taste questionnaire data.

Periods 1 and 2 - for Each Cohort Separately**Relative Bioavailability**

[0549] Statistical modelling will be performed on the natural log-transformed compound of Formula (I) PK parameters (AUC(0-tlast), AUC(0-inf) and Cmax) to assess relative bioavailability (Frel) using a mixed effects model with terms for regimen, period and sequence as fixed effects and subject within sequence as a random effect. Ratios of geometric means (GMRs) and 90% confidence interval (CI) for the relevant comparison of interest, i.e., between each of the prototype formulations (compound of Formula (I) Oral Solution, Prototype Formulation 1, 50 mg/mL, e.g., Example 12; compound of Formula (I) Oral Solution, Prototype Formulation 2, 50 mg/mL, e.g., Example 13; and compound of Formula (I) Granule for Sprinkle, 25 - 50 mg, e.g. Example 11 [Regimens B, C and D, respectively]) and compound of Formula (I), 50 mg Capsules, e.g., Example 9 (Reference; Regimen A) will be presented.

All Periods (Periods 1 to 4)**Food Effect**

[0550] Statistical modelling will be performed on the compound of Formula (I) PK parameters AUC(0-tlast), AUC(0-inf) and Cmax to assess for the effects of food, if relevant. The natural log-transformed PK parameters will be analyzed for bioavailability using a mixed effects model with terms for prandial state (and meal type if applicable) as a fixed effect and subject as a random effect. Ratios of geometric means and 90% CI for the relevant comparisons of interest will be presented where the ratio is defined as fasted/fed or test meal/reference meal (if applicable).

Relative Bioavailability

[0551] Statistical modelling will be performed on the natural log-transformed compound of Formula (I) PK parameters (AUC(0-tlast), AUC(0-inf) and Cmax) to assess relative bioavailability using a mixed effects model with terms for regimen as a fixed effect and subject as a random effect. Ratios of geometric means and 90% CI for the relevant comparison of interest i.e., between each of the prototype formulations (Regimens E and F, IMPs to be determined by interim reviews

following completion of Periods 2 and 3) and compound of Formula (I), 50 mg Capsules (Reference; Regimen A) will be presented.

Results

[0552] Preliminary PK data is summarized in Table 43 below:

Table 43: Preliminary Data from Periods 1 and 2

	A- Reference	B-Oral Solution 1	C-Oral Solution 2	D- SDD Granule
N	35	12	12	12
Tmax * (h)	5 (2,6)	6 (5,7)	5 (5,7)	5 (5,7)
Cmax (ng/ml)	1361 (33)	790 (31)	1082 (46)	1075 (35)
AUC36 (h*ng/ml)	9452 (30)	5556 (34)	7582 (37)	6691 (41)
*Geometric Mean /CV% for AUC and Cmax; Median for Tmax				

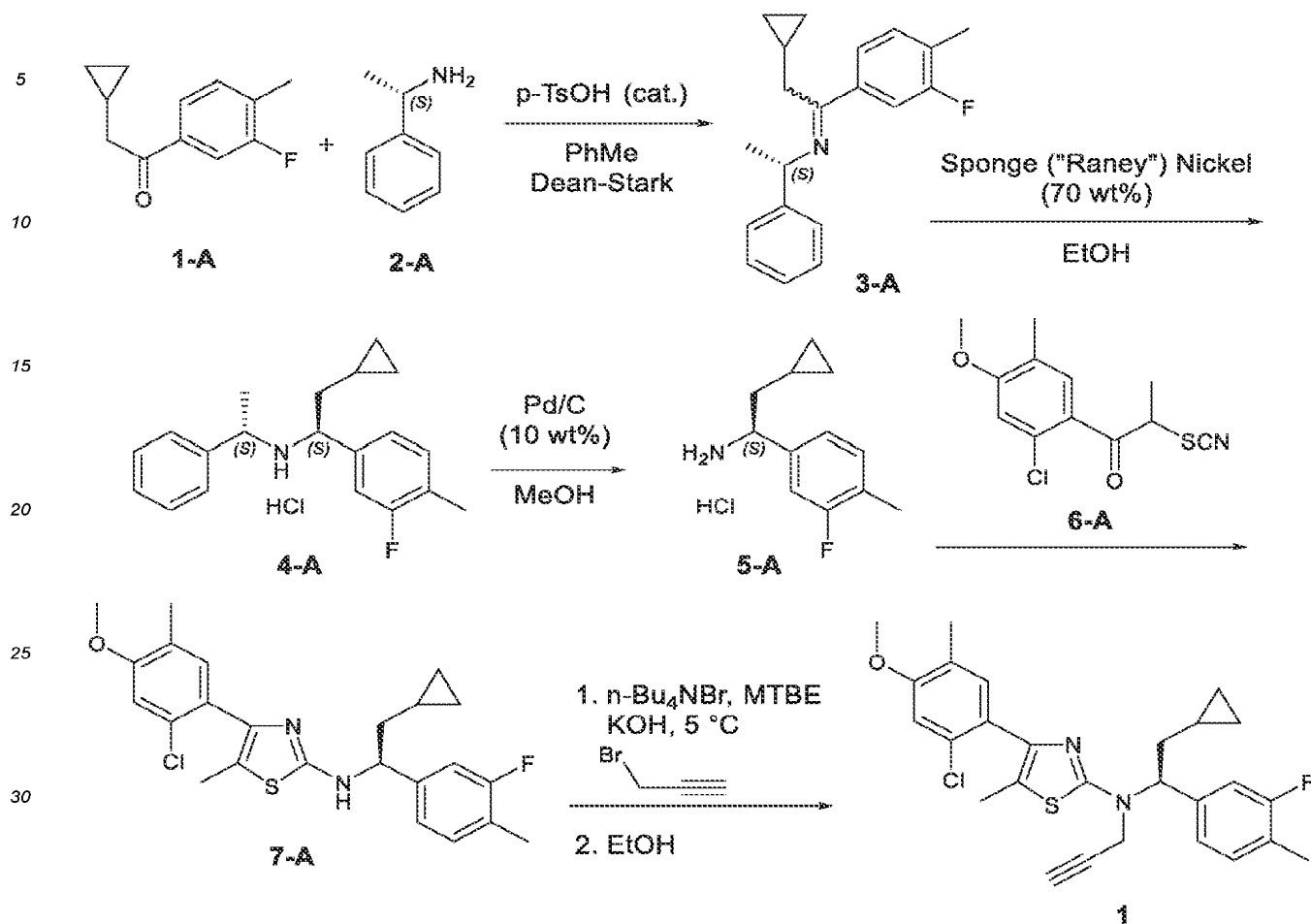
Example 15. Compound of Formula (I) Crystalline Free Base Form I

Example 15A

Scheme 1: Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I), Form I)

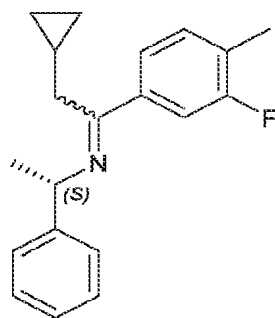
[0553]

Scheme 1



Step 1: Preparation of (S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-N-(1-phenylethyl)ethan-1-imine (Compound 3-A)

[0554]



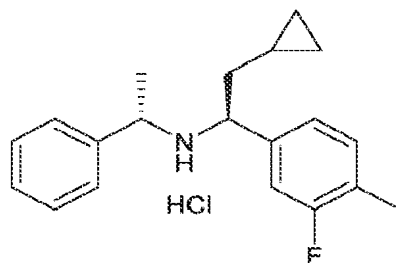
Compound 3-A

[0555] A mixture of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (1-A, 150.7 kg, 1 eq., as a 27.6% w/w solution in toluene, Example 15C), (S)-(-)-1-Phenylethylamine (2-A, 112.9 kg, 1.19 eq.), and *p*-toluenesulfonic acid (7.4 kg, 0.05 eq.) is refluxed at 110 - 120 °C for 23 - 25 h in a reactor set up in a Dean-Stark configuration. The solvent is then removed at 125 - 135 °C under atmospheric pressure until distillation halts and a portion of toluene (275 kg, 2.24 w/w) is added to afford a suspension. The suspension is refluxed at 110 - 120 °C for 23 - 25 h. The mixture is cooled to

22 °C and washed twice with aqueous NH₄Cl (10%, 301.2 kg, 0.72 eq.) and once with aqueous NaHCO₃ (5%, 301.2 kg, 0.23 eq., check pH 8 - 9). The solvent is removed at 125 - 135 °C and atmospheric pressure to a target volume of 256 L, the mixture is filtered over celite, the cake is washed with toluene (25 kg). The resulting mixture containing compound 3-A is used directly in the next step without isolation. The yield is determined by correcting for the LOD and GC-FID purity of the sample (208.4 kg, 90.0% corrected, 0.89% Compound 2-A). EI-MS: 294.1 [M-H]⁺, 190.1 [M-C₆H₅CH(CH₃)]⁺, 105.1 [C₆H₅CH(CH₃)]⁺.

Step 2: Preparation of (S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-N-((S)-1-phenylethyl)ethan-1-amine hydrochloride (Compound 4-A)

[0556]



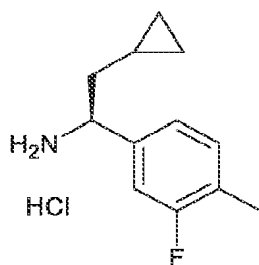
Compound 4-A

[0557] Sponge nickel catalyst (144 kg, 0.70 w/w, shipped as a 50% w/w suspension in water) is added to a hydrogenation reactor, equipped with a dip tube capable of removing material from the top of the mass inside, minimizing the amount of water introduced. The supernatant is discarded, ethanol (329.3 kg, 1.58 w/w, anhydrous) is added, the suspension is stirred and then allowed to settle. This process is repeated four more times and the Karl Fisher (KF) of the supernatant is checked ($\leq 1\%$ H₂O w/w). Compound 3-A (208.4 kg, 1 eq., as a 62.6% solution in toluene) is added to the mixture in the hydrogenation reactor and ethanol (387.6 kg, 1.86 w/w) is used to rinse the addition flask into the hydrogenation reactor. The hydrogenation reactor is pressurized/depressurized twice with nitrogen (2 bar) and twice with hydrogen (5 bar) then pressurized with hydrogen (9.8 - 10.2 bar) and heated to 33 - 37 °C and stirred for 17 - 19 h. The system is depressurized/pressurized three times with nitrogen (1 bar) and the suspension is filtered and washed with three times with ethanol (493.8 kg, 2.37 w/w). HCl (concentrated, 83.4 kg, 1.07 eq.) is added and the mixture stirred 25 - 35 min at 20

[0558] - 24 °C. The mixture is concentrated by distillation at 78 - 80 °C and atmospheric pressure to remove water with a distillate target volume of 1167 L (5.6 L/kg, Compound 3-A) and the KF of the solution is checked ($\leq 1.5\%$ H₂O w/w). The mixture is stirred at 48 - 52 °C for 55 - 65 min, then 68 - 72 °C for 55 - 65 min, then cooled to 20 - 24 °C at a rate of 12 °C/h and stirred for 25 - 35 min, then cooled to 0 - 4 °C at a rate of 10 °C/h and stirred for 55 - 65 min. The suspension is filtered, the cake is washed twice with precooled ethanol (329.2 kg, 1.58 w/w, 0 °C), and the collected solid is dried at 40 °C to afford compound 4-A (156.5 kg, 66.4% uncorrected). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm -0.33 - -0.06 (m, 2 H) 0.11 - 0.31 (m, 3 H) 1.57 (d, *J*=6.57 Hz, 3 H) 1.95 (br t, *J*=7.07 Hz, 2 H) 2.26 (d, *J*=1.26 Hz, 3 H) 3.68 (br d, *J*=7.83 Hz, 1 H) 3.92 (br t, *J*=6.44 Hz, 1H) 6.98 (dd, *J*=7.71, 1.14 Hz, 1H) 7.28 - 7.36 (m, 2 H) 7.37 - 7.50 (m, 5 H). ESI-MS: 298.2 m/z [M+H]⁺.

Step 3: Preparation of (S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-amine hydrochloride (Compound 5-A)

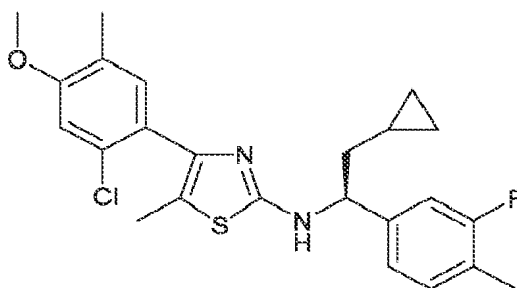
[0559]



Compound 5-A

[0560] Compound 4-A (156.5 kg, 1.00 eq.) and Pd/C (7.8 kg, 10% Pd basis) are added to an inerted hydrogenation reactor. The reactor is then pressurized/depressurized twice with nitrogen (2 bar) and then methanol (494.5 kg, 3.16 w/w) is added. The reactor is depressurized/pressurized three times with nitrogen (2 bar) then three times with hydrogen (5 bar), pressurized with hydrogen (9.8 - 10.2 bar), heated to 58 - 62 °C and stirred for 7 - 9 h. The reaction mixture is cooled to 20 - 24 °C. The reactor is depressurized/pressurized three times with nitrogen (1 bar) and the suspension is filtered and washed three times with methanol (492.9 kg, 3.15 w/w). The solution is concentrated at 63 - 67 °C and atmospheric pressure to a distillate target volume of 1408 L (9.0 L/kg Compound 4-A). *n*-Heptane (1173.8 kg, 7.5 w/w) is added and the mixture is refluxed at 65 - 80 °C and atmospheric pressure in Dean-Stark configuration to remove methanol. The suspension is cooled to 31 - 35 °C and filtered, the cake washed with *n*-heptane (147.1 kg, 0.94 w/w), and the solid dried at 40 °C (101.0 kg, 93.8% uncorrected, 99.2% ee). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm -0.12 - 0.14 (m, 2 H) 0.26 - 0.42 (m, 2 H) 0.44 - 0.55 (m, 1 H) 1.70 - 1.83 (m, 2 H) 2.23 (d, *J*=1.52 Hz, 3 H) 4.24 (t, *J*=7.33 Hz, 1 H) 7.22 - 7.29 (m, 1 H) 7.29 - 7.36 (m, 1 H) 7.40 (dd, *J*=10.99, 1.39 Hz, 1 H). ESI-MS: 194.2 [M+H]⁺, 177.0 [M-NH₂]⁺.

Step 4: Preparation of (*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methylthiazol-2-amine (Compound 7-A)



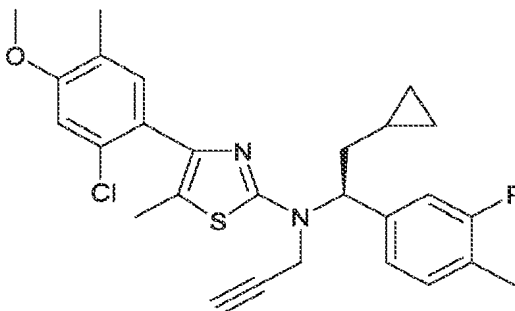
Compound 7-A

[0562] A mixture of *n*-heptane (146 kg), water (142 kg), Compound 5-A (57.4 kg), and aqueous sodium hydroxide (30% w/w, 41.0 kg) was stirred together. The layers were partitioned, and the aqueous layer removed. The organic layer was washed with water (170 kg) and the layers partitioned. The organic layer was set aside using *n*-heptane (40 kg) to rinse and *n*-heptane (145 kg) and 1-(2-chloro-4-methoxy-5-methylphenyl)-2-thiocyanatopropan-1-one (6-A, 66.1 kg) were added to the reactor and heated to 85 °C. The previously set aside organic layer containing the free base of Compound 5-A was added at 84 - 85 °C to the reactor and rinsed with *n*-heptane (20 kg). The resulting mixture was stirred for 2 h at 83 °C. Subsequently, the solvent was switched to methanol by four put-and-take additions/vacuum distillations of methanol (180 kg) at 55 °C with the target volume being 287 L remaining in the reactor. The suspension was cooled to 5 °C and water (570 kg) was added over 4 h at 5 - 10 °C, with the first 60 kg added very slowly. The suspension was aged 2 h at °C and then isolated by filtration and washed with a mixture of methanol/water (91/115 kg) and then a mixture of methanol/water (134/57 kg). The yellow solid was dried at 25 °C and 1 mbar for 17 h then 40 °C and 1 mbar for 22 h to afford Compound 7-A (97.4 kg, 87.5% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm -0.01 - 0.14 (m, 2 H) 0.29 - 0.42 (m, 2 H) 0.61 - 0.73 (m, 1 H) 1.47 (dt, *J*=13.83, 6.85 Hz, 1 H) 1.76 (dt, *J*=13.89, 7.20 Hz, 1 H) 2.00 (s, 3 H) 2.11 (s, 3 H) 2.19 (d, *J*=1.01 Hz, 3 H) 3.82 (s, 3 H) 4.54 (q, *J*=7.58 Hz, 1 H) 7.00 (s, 1 H) 7.06 (d, *J*=0.76 Hz,

¹H) 7.08 - 7.14 (m, 2 H) 7.18 - 7.23 (m, 1 H) 7.89 (d, *J*=8.08 Hz, 1 H). ESI-MS: 445.3 *m/z* [M+H]⁺.

Step 5: Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I))

[0563]



Compound of Formula (I)

[0564] A mixture of MTBE (279 kg), tetra-*n*-butylammonium bromide (10.5 kg), and Compound 7-A (95.4 kg) were heated at 60 °C external temperature for 30 min and then cooled to 0 °C. Aqueous potassium hydroxide (52.4% w/w, 364 kg) and propargyl bromide (39.4 kg as an 80% w/w solution in toluene, 1.19 eq.) were added at 0 - 5 °C and the biphasic mixture aged 14.5 h at 4 - 6 °C with vigorous stirring. Subsequently, water (191 kg) was added and the aqueous layer was discharged. The organic layer was washed twice with water (382 kg) and once with aqueous acetic acid (5.26% w/w, 190 kg) at 20 °C. The mixture is polish filtered, rinsed with ethanol (11 kg) and then the solvent switched to ethanol by 3 put-and-take additions/vacuum distillations of ethanol (300 kg) at 25 - 30 °C for the first cycle and then 35 - 40 °C with the target volume of each cycle being 250 L remaining in the reactor. Ethanol (164 kg) was added and the mixture heated at 60 °C external for 0.5 h before it was cooled to 25 °C in 1 h and seeded with authentic compound of Formula (I) (0.340 kg) which may be prepared as described below in Example 15B. The suspension was aged for 5 h, cooled to 0 °C in 2 h, aged 12 h, filtered, and washed twice with ethanol (24 kg each) precooled to 0 °C. The white solid was dried at 40 °C and 1 mbar for 19 h to yield 80.15 kg of the compound of Formula (I), Form I (77.2% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.14 (qt, *J*=8.59, 4.42 Hz, 2 H) 0.29 - 0.48 (m, 2 H) 0.61 - 0.82 (m, 1 H) 1.89 (dt, *J*=14.08, 6.98 Hz, 1 H), 2.07 (br d, *J*=7.83 Hz, 1 H) 2.10 (s, 3 H) 2.14 (s, 3 H) 2.20 (d, *J*=1.01 Hz, 3 H) 3.11 (t, *J*=2.27 Hz, 1 H) 3.83 (s, 3 H) 3.94 - 4.22 (m, 2 H) 5.26 (t, *J*=7.58 Hz, 1 H) 7.05 (s, 1 H) 7.10 ~ 7.36 (m, 4 H). ESI-MS: 483.2 *m/z* [M+H]⁺.

[0565] The crystallinity of the crystalline free base Compound of Formula (I), Form I was confirmed by XRPD (Figure 25, Table 44) and further supported by DSC (Figure 26), indicating the crystalline compound having an onset of melt at about 84.4 °C (71.9 J/g). TGA of the crystalline free base exhibited about 0.6% of weight loss due to solvent/H₂O.

Table 44. XRPD Peak Data for the Compound of Formula (I) Crystalline Free Base Form I

2-Theta (°)	Height (cps)
5.901(15)	1221(101)
10.367(11)	1280(103)
11.762(13)	1377(107)
12.582(11)	1591(115)
13.802(2)	7326(247)
14.1541(16)	20179(410)
15.173(14)	449(61)
15.854(7)	2906(156)
16.746(5)	5113(206)
18.366(7)	1171(99)

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(continued)

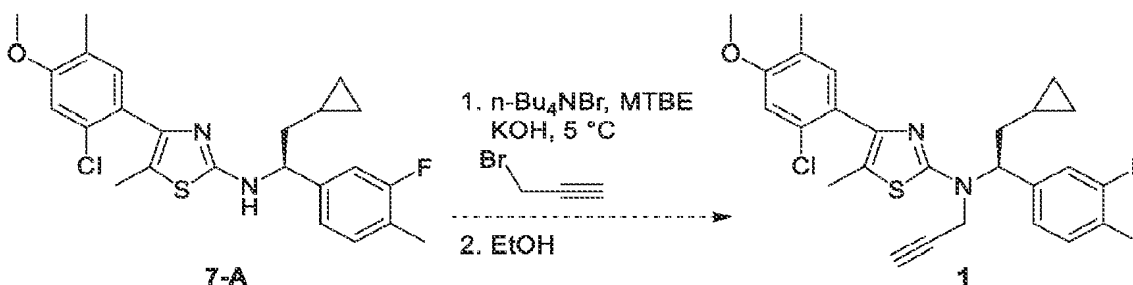
	2-Theta (°)	Height (cps)
5	19.586(2)	27789(481)
	20.100(4)	10759(299)
	20.794(4)	5441(213)
	21.730(5)	7125(244)
10	22.239(7)	10370(294)
	23.056(11)	3482(170)
	23.714(7)	2300(138)
15	24.115(7)	8402(265)
	25.666(4)	26173(467)
	26.296(6)	1505(112)
	26.752(4)	9919(288)
20	27.264(7)	1016(92)
	27.874(7)	2092(132)
	28.623(3)	10560(297)
25	29.546(6)	5811(220)
	30.025(3)	2248(137)
	30.737(10)	1333(105)
	31.017(19)	1406(108)
30	31.588(10)	2292(138)
	31.809(8)	2212(136)
	32.126(13)	593(70)
35	33.200(16)	839(84)
		996(158)
	33.914(13)	1156(98)
40	34.276(16)	1008(92)
	34.564(12)	1056(94)
	35.397(18)	816(82)
	36.073(10)	1928(127)
45	36.67(3)	562(68)
	37.347(9)	1553(114)
	37.776(12)	1573(114)
	39.070(7)	1890(125)
50	39.743(15)	1042(93)
	40.643(9)	2808(153)
	41.106(8)	1107(96)
55	41.984(11)	2686(150)
	42.376(16)	986(91)
	42.901(16)	492(64)

(continued)

2-Theta (°)	Height (cps)
43.543(10)	4744(199)
44.419(16)	2810(153)

Example 15B

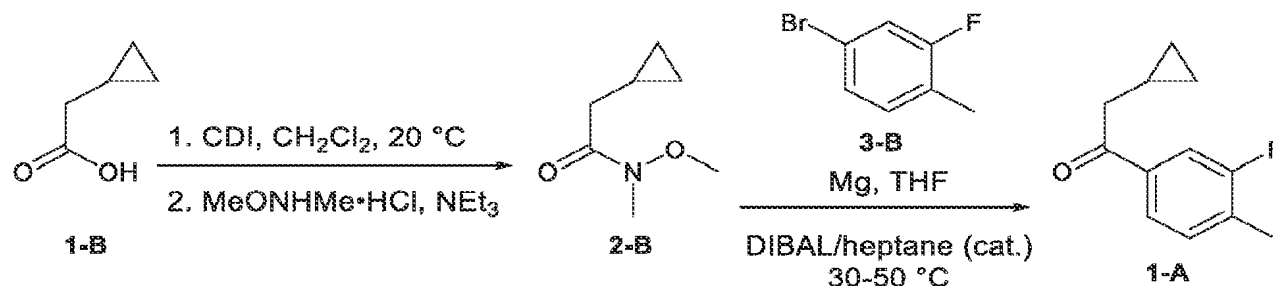
Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I), seed batch)

[0566]

[0567] A mixture of MTBE, *tetra*-*n*-butylammonium bromide, and Compound 7-A cooled to 0 °C is treated with aqueous potassium hydroxide and propargyl bromide maintaining the temperature at 0 - 5 °C. The resulting biphasic mixture is aged 23 h at 4 - 6 °C. Subsequently, water and MTBE are added and the aqueous layer is discharged. The organic layer is washed twice with water and once with aqueous acetic acid at 20 °C. Ethanol is added and then the solvent switched to ethanol by 3 put-and-take additions/vacuum distillations of ethanol at 35 - 40 °C with a target volume of each cycle remaining in the vessel, except for the third cycle where the mixture is concentrated to dryness. Ethanol is added to the vessel and the mixture heated at 60 °C external for 0.5 h before it is cooled to 20 °C in 1 h and aged 18 h affording a suspension. The suspension is cooled to 0 °C, aged 6 h, filtered, and washed twice with ethanol pre-cooled to 0 °C to afford a solid. The solid is dried at 40 °C under vacuum to afford the compound of Formula (I).

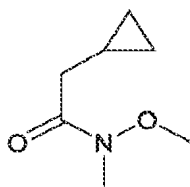
Example 15C

Scheme 2: Preparation of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (Compound 1-A)

[0568]**Scheme 2**

Step 1: Preparation of 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (Compound 2-B)

[0569]

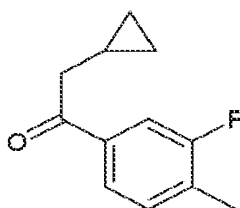


Compound 2-B

[0570] A suspension of 1,1'-Carbonyldiimidazole (152.6 kg, 1.01 eq.) in DCM (682 kg, 513 L, 7.3 w/w relative to 2-cyclopropylacetic acid) was treated with a solution of 2-cyclopropylacetic acid (1-B, 93.6 kg, 1 eq.) in DCM (248 kg, 186 L, 2.65 w/w) over at least 1 h, keeping the temperature $\leq 25^\circ\text{C}$ and compensating for significant effervescence. The resulting mixture is stirred for 15 min at 22°C and then *N,O*-dimethylhydroxylamine-HCl (93.3 kg, 1.03 eq.) is added in portions, keeping the temperature $\leq 30^\circ\text{C}$. Subsequently, triethylamine (46.4 kg, 0.49 eq.) is added to the stirring mixture at $20 - 25^\circ\text{C}$. The resulting mixture is stirred at 22°C at least 1 h. The mixture is washed once with KHSO_4 solution (0.24 M, 357.1 kg, 0.09 eq.), once with KHSO_4 solution (0.40 M, 365.4 kg, 0.15 eq.), once with KHSO_4 solution (0.80 M, 384.5 kg, 0.30 eq.), and once with NaHCO_3 solution (0.60 M, 393.1 kg, 0.24 eq.). Residual DCM is removed by three put-and-takes of THF (166.6 kg, 1.78 w/w) and vacuum distillation ($50 - 60^\circ\text{C}$, to minimum volume/until distillation stops). THF (333.2 kg, 3.56 w/w) is added and the yield is determined by correcting for the LOD and GC-FID purity of the sample (131.5 kg, 98.2% corrected). $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : - 0.01 - 0.03 (m, 2H) 0.32 - 0.36 (m, 2H) 0.81 - 0.90 (br m, 1H) 2.18 (d, $J=6.80$ Hz, 2H) 2.97 (s, 3 H) 3.53 (s, 3H). ESI-MS: 144.0 $[\text{M}+\text{H}]^+$.

Step 2: Preparation of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (Compound 1-A)

[0571]



Compound 1-A

[0572] Mg (turnings, 28.6 kg, 1.37 eq.) are suspended in THF (244.7 kg, 2.0 w/w) and DIBAL-H (1 M in n-heptane, 18.9 kg, 0.03 eq.) is added dropwise at 30°C . The resulting mixture is stirred at 30°C for at least 10 min and then 4-bromo-2-fluoro-1-methylbenzene (3-B, neat, 21.1 kg, 0.13 eq.) is added over at least 30 min at $30 - 50^\circ\text{C}$. Subsequently, the mixture is treated with a solution of 4-bromo-2-fluoro-1-methylbenzene (3-B, 191.6 kg, 1.18 eq.) in THF (414.5 kg, 3.37 w/w) at $30 - 50^\circ\text{C}$ over 3 h or less. The mixture is stirred at 30°C for at least 1 h. Subsequently, the mixture is treated with 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (2-B, 123.0 kg, 1 eq., 25.9% w/w solution in THF) over at least 1 h at $15 - 25^\circ\text{C}$. The resulting mixture is stirred at $20 - 25^\circ\text{C}$ for at least 1 h. The stirring mixture is then treated with aqueous HCl (3 M, 10.3% w/w, 668.9 kg, 2.24 eq.) at $10 - 25^\circ\text{C}$ and the resulting mixture is stirred at least 2 h (check pH 3.0 - 3.5). The layers are separated, and the aqueous layer is combined with heptane (290.3 kg, 2.36 w/w). The layers are separated, and the organic layer is washed once with NaHCO_3 solution (0.63 M, 211.6 kg, 0.15 eq.) and once with NaCl solution (2.57 M, 213.0 kg, 0.55 eq.). The residual solvents are removed by vacuum distillation at $58 - 62^\circ\text{C}$ until distillation stops and then one put-and-take of toluene (275.5 kg, 2.24 w/w) at $107 - 117^\circ\text{C}$ until distillation stops. Toluene (275.5 kg, 2.24 w/w) is added and the yield is determined by correcting for the LOD and GC-FID purity of the sample (150.7 kg, 91.3% corrected). $^1\text{H NMR}$ (400 MHz, DMSO-d_6) δ ppm 0.07 - 0.21 (m, 2 H) 0.40 - 0.54 (m, 2 H) 1.02 (ttt, $J=8.16, 8.16, 6.68, 6.68, 4.86, 4.86$ Hz, 1 H) 2.30 (d, $J=1.77$ Hz, 3 H) 2.91 (d, $J=6.57$ Hz, 2 H) 7.44 (t, $J=7.83$ Hz, 1 H) 7.57 - 7.78 (m, 2 H). ESI-MS: 193.1 $[\text{M}+\text{H}]^+$.

Example 16: Compound of Formula (I) Crystalline Tosylate Salt Form 1

[0573] Approximately 20 mg of the Compound of Formula (I) was weighed into a vial. Using a positive displacement

pipette, 250 μ L of solvent (IPA) was added to the vial along with a stir bar. The vial was placed in an aluminum block on a Reacti-Therm mixer and heated to 60 °C for ~1 hour. A molar equivalent of para-toluenesulfonic acid was added to the vial (20 μ L of a 2M solution in water) and allowed to stir. The sample was slow cooled back to room temperature along with mild Nitrogen gas for evaporation. Precipitate was collected, left to dry overnight, and then analyzed by XRPD, DSC, and TGA.

[0574] The crystallinity of the crystalline tosylate form 1 was confirmed by XRPD (Figure 27, Table 45) and further supported by DSC (Figure 28), indicating the crystalline compound having an onset of melt at about 156 °C (22.2 J/g). TGA of the crystalline compound is provided in Figure 28, and exhibited about 0.5% of weight loss due to solvent/H₂O.

Table 45. XRPD Peak Data for the Compound of Formula (I) Crystalline Tosylate Form 1

2-Theta (°)	Height (cps)
8.112(9)	957(89)
9.124(2)	12296(320)
9.471(2)	4519(194)
10.525(3)	8507(266)
11.316(3)	10211(292)
13.182(5)	6158(227)
13.494(6)	1598(115)
14.249(9)	2197(135)
15.208(9)	1746(121)
15.711(7)	1437(109)
16.252(5)	5723(218)
16.692(3)	3848(179)
17.540(4)	1578(115)
19.031(6)	6774(238)
19.265(4)	6491(233)
19.499(10)	3152(162)
20.401(3)	8581(267)
20.656(4)	3040(159)
21.142(3)	11498(310)
21.703(6)	4979(204)
21.870(11)	5331(211)
22.277(5)	3701(176)
22.769(3)	10159(291)
23.297(3)	14954(353)
23.532(4)	3597(173)
23.810(3)	9590(283)
24.73(2)	2325(139)
25.47(4)	1704(119)
26.087(5)	2413(142)
26.71(3)	422(59)
27.210(6)	1648(117)
27.593(5)	2825(153)

(continued)

2-Theta (°)	Height (cps)
28.472(4)	6417(231)
29.51(3)	1423(109)
29.98(3)	849(84)
30.63(6)	1262(103)
30.77(3)	1121(97)
31.577(3)	5563(215)
32.74(4)	874(85)
33.73(4)	1111(96)
34.415(13)	2054(131)
34.799(11)	706(77)
35.139(15)	1320(105)
35.682(16)	1028(93)
38.39(4)	751(79)
39.743(17)	1790(122)
40.219(16)	762(80)
41.23(3)	925(88)
43.16(3)	1540(113)
44.288(12)	1142(98)

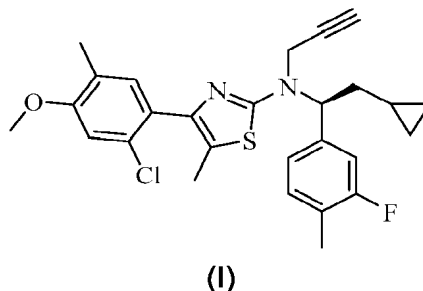
OTHER EMBODIMENTS

[0575] It is to be understood that the foregoing description is intended to illustrate and not limit the scope of the disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

[0576] The following numbered paragraphs set out preferred features and preferred combinations of features of the present invention:

1. A pharmaceutical composition comprising:

(a) a compound of Formula (I):



or a pharmaceutically acceptable salt thereof; and

(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

2. The pharmaceutical composition of paragraph 1, comprising about 1 wt% to about 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

3. The pharmaceutical composition of paragraph 1, comprising about 5 wt% to about 15 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

4. The pharmaceutical composition of paragraph 1, comprising about 10 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

5. The pharmaceutical composition of any one of paragraphs 1-4, comprising an oily phase vehicle.

6. The pharmaceutical composition of any one of paragraphs 1-5, comprising about 1 wt% to about 50 wt% of the oily phase vehicle.

7. The pharmaceutical composition of any one of paragraphs 1-5, comprising about 20 wt% to about 50 wt% of the oily phase vehicle.

8. The pharmaceutical composition of any one of paragraphs 1-5, comprising about 35 wt% to about 45 wt% of the oily phase vehicle.

9. The pharmaceutical composition of any one of paragraphs 1-5, comprising about 39 wt% of the oily phase vehicle.

10. The pharmaceutical composition of any one of paragraphs 1-9, wherein the oily phase vehicle is selected from medium-chain triglycerides, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

11. The pharmaceutical composition of any one of paragraphs 1-10, wherein the oily phase vehicle is medium-chain triglycerides.

12. The pharmaceutical composition of any one of paragraphs 10-11, wherein the medium-chain triglycerides are Labrafac TM Lipophile WL1349.

13. The pharmaceutical composition of any one of paragraphs 10-11, wherein the medium-chain triglycerides are Miglyol 812N.

14. The pharmaceutical composition of any one of paragraphs 1-13, comprising an emulsifying agent.

15. The pharmaceutical composition of any one of paragraphs 1-14, comprising about 5 wt% to about 50 wt% of the emulsifying agent.

16. The pharmaceutical composition of any one of paragraphs 1-14, comprising about 10 wt% to about 30 wt% of the emulsifying agent.

17. The pharmaceutical composition of any one of paragraphs 1-14, comprising about 15 wt% to about 25 wt% of the emulsifying agent.

18. The pharmaceutical composition of any one of paragraphs 1-14, comprising about 20 wt% of the emulsifying agent.

19. The pharmaceutical composition of any one of paragraphs 1-18, wherein the emulsifying agent is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

20. The pharmaceutical composition of any one of paragraphs 1-19, wherein the emulsifying agent is propylene glycol dicaprylate/dicaprate.

21. The pharmaceutical composition of any one of paragraphs 19-20, wherein the propylene glycol dicaprylate/dicaprate is Labrafac TM PG.

22. The pharmaceutical composition of any one of paragraphs 1-21, comprising a nonionic surfactant.

23. The pharmaceutical composition of any one of paragraphs 1-22, comprising about 5 wt% to about 50 wt% of the nonionic surfactant.

24. The pharmaceutical composition of any one of paragraphs 1-22, comprising about 10 wt% to about 30 wt% of the nonionic surfactant.

25. The pharmaceutical composition of any one of paragraphs 1-22, comprising about 15 wt% to about 25 wt% of the nonionic surfactant.

26. The pharmaceutical composition of any one of paragraphs 1-22, comprising about 19 wt% of the nonionic surfactant.

27. The pharmaceutical composition of any one of paragraphs 1-26, wherein the nonionic surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, Gelucire, lauroyl polyoxyl-32 glycerides, Poloxamer, PEG-32 stearate, and PEG-32 hydrogenated palm glycerides.

28. The pharmaceutical composition of any one of paragraphs 1-27, wherein the nonionic surfactant is lauroyl polyoxyl-32 glycerides.

29. The pharmaceutical composition of any one of paragraphs 27-28, wherein the lauroyl polyoxyl-32 glycerides are Gelucire® 44/14.

30. The pharmaceutical composition of any one of paragraphs 1-29, comprising a solubilizing agent.

31. The pharmaceutical composition of any one of paragraphs 1-30, comprising about 1 wt% to about 50 wt% of the solubilizing agent.

32. The pharmaceutical composition of any one of paragraphs 1-30, comprising about 1 wt% to about 20 wt% of the solubilizing agent.

33. The pharmaceutical composition of any one of paragraphs 1-30, comprising about 5 wt% to about 15 wt% of the solubilizing agent.

34. The pharmaceutical composition of any one of paragraphs 1-30, comprising about 11 wt% of the solubilizing agent.

35. The pharmaceutical composition of any one of paragraphs 1-34, wherein the solubilizing agent is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, and Poloxamer.

36. The pharmaceutical composition of any one of paragraphs 1-35, wherein the solubilizing agent is vitamin E polyethylene glycol succinate.

37. The pharmaceutical composition of any one of paragraphs 35-36, wherein the vitamin E polyethylene glycol succinate is Kolliphor® TPGS.

38. The pharmaceutical composition of any one of paragraphs 35-36, wherein the vitamin E polyethylene glycol succinate is Vitamin E/TPGS 260.

39. The pharmaceutical composition of paragraph 1, comprising:

- (a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
- (b) an oily phase vehicle;
- (c) an emulsifying agent;
- (d) a nonionic surfactant; and
- (e) a solubilizing agent.

40. The pharmaceutical composition of paragraph 1, comprising:

- (a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 35 wt% to about 45 wt% of an oily phase vehicle;
- (c) about 15 wt% to about 25 wt% of an emulsifying agent;
- (d) about 15 wt% to about 25 wt% of a nonionic surfactant; and
- (e) about 5 wt% to about 15 wt% of a solubilizing agent.

41. The pharmaceutical composition of paragraph 1, comprising:

- (a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 39 wt% of an oily phase vehicle;
- (c) about 20 wt% of an emulsifying agent;
- (d) about 19 wt% of a nonionic surfactant; and
- (e) about 11 wt% of a solubilizing agent.

42. The pharmaceutical composition of paragraph 1, comprising:

- (a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
- (b) a medium-chain triglycerides component;
- (c) a propylene glycol dicaprylate/dicaprate component;
- (d) a lauroyl polyoxyl-32 glycerides component; and
- (e) a vitamin E polyethylene glycol succinate component.

43. The pharmaceutical composition of paragraph 1, comprising:

- (a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
- (b) about 35 wt% to about 45 wt% of medium-chain triglycerides;
- (c) about 15 wt% to about 25 wt% of propylene glycol dicaprylate/dicaprate;
- (d) about 15 wt% to about 25 wt% of lauroyl polyoxyl-32 glycerides; and
- (e) about 5 wt% to about 15 wt% of vitamin E polyethylene glycol succinate.

44. The pharmaceutical composition of paragraph 1, comprising:

- (a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
- (b) about 39 wt% of medium-chain triglycerides;
- (c) about 20 wt% of propylene glycol dicaprylate/dicaprate;
- (d) about 19 wt% of lauroyl polyoxyl-32 glycerides; and
- (e) about 11 wt% of vitamin E polyethylene glycol succinate.

45. The pharmaceutical composition of any one of paragraphs 1-44, wherein the compound of Formula (I), or pharmaceutically acceptable salt thereof, is in crystalline form.

46. The pharmaceutical composition of any one of paragraphs 1-45, comprising the compound of Formula (I) as a free base.

47. The pharmaceutical composition of paragraph 45, wherein the crystalline form comprises Form I of the compound of Formula (I).

48. The pharmaceutical composition of any one of paragraphs 1-47, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to

about 200 mg, based on the weight of the free base.

49. The pharmaceutical composition of paragraph 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg, based on the weight of the free base.

50. The pharmaceutical composition of paragraph 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg, based on the weight of the free base.

51. The pharmaceutical composition of paragraph 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg, based on the weight of the free base.

52. The pharmaceutical composition of paragraph 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg, based on the weight of the free base.

53. The pharmaceutical composition of any one of paragraphs 1-52, that is in the form of a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film.

54. The pharmaceutical composition of any one of paragraphs 48-53, wherein the pharmaceutical composition is in tablet form.

55. The pharmaceutical composition of any one of paragraphs 48-53, wherein the pharmaceutical composition is in capsule form.

56. The pharmaceutical composition of any one of paragraphs 48-55, wherein the dosage form is coated.

57. A method for preparing the pharmaceutical composition of any one of paragraphs 1-56, comprising:

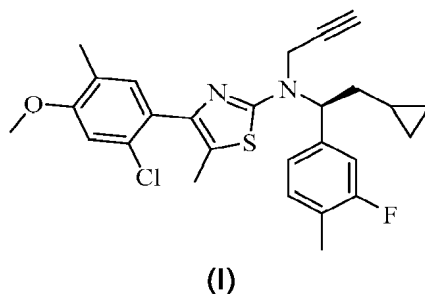
- (a) heating a mixture of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent;
- (b) mixing the mixture of step (a) until a homogeneous mixture is achieved; and
- (c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the homogeneous mixture of step (b) until the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dissolved, forming a composition.

58. The method of paragraph 57, further comprising:

- (d) encapsulating the composition of step (c) in a capsule shell to form a capsule; and
- (e) banding the capsule of step (d) in a mixture of banding agent and banding solvent.

59. A pharmaceutical composition in oral solution dosage form comprising:

- (a) a compound of Formula (I):



- or a pharmaceutically acceptable salt thereof;
- (b) one or more of a sweetener, an anti-oxidant, and a flavor; and
- (c) a liquid vehicle.

60. The pharmaceutical composition of paragraph 59, comprising about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

61. The pharmaceutical composition of paragraph 59, comprising about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

62. The pharmaceutical composition of paragraph 59, comprising about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

63. The pharmaceutical composition of any one of paragraphs 59-62, comprising a sweetener.

64. The pharmaceutical composition of any one of paragraphs 59-63, comprising about 0.01 w/v% to about 1.5 w/v% of the sweetener.

65. The pharmaceutical composition of any one of paragraphs 59-63, comprising about 0.1 w/v% to about 0.5 w/v% of the sweetener.

66. The pharmaceutical composition of any one of paragraphs 59-63, comprising about 0.15 w/v% of the sweetener.

67. The pharmaceutical composition of any one of paragraphs 59-66, wherein the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and advantame.

68. The pharmaceutical composition of any one of paragraphs 59-67, wherein the sweetener is saccharin.

69. The pharmaceutical composition of any one of paragraphs 59-68, comprising an anti-oxidant.

70. The pharmaceutical composition of any one of paragraphs 59-69, comprising about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant.

71. The pharmaceutical composition of any one of paragraphs 59-69, comprising about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant.

72. The pharmaceutical composition of any one of paragraphs 59-69, comprising about 0.17 w/v% of the anti-oxidant.

73. The pharmaceutical composition of any one of paragraphs 59-72, wherein the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TP GS, butylated hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid.

74. The pharmaceutical composition of any one of paragraphs 59-73, wherein the anti-oxidant is butylated hydroxytoluene.

75. The pharmaceutical composition of any one of paragraphs 59-74, comprising a flavor.

76. The pharmaceutical composition of any one of paragraphs 59-75, comprising about 0.01 w/v% to about 0.5 w/v% of the flavor.

77. The pharmaceutical composition of any one of paragraphs 59-75, comprising about 0.05 w/v% to about 0.2 w/v% of the flavor.

78. The pharmaceutical composition of any one of paragraphs 59-75, comprising about 0.10 w/v% of the flavor.

79. The pharmaceutical composition of any one of paragraphs 59-78, wherein the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetraome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor.

80. The pharmaceutical composition of any one of paragraphs 59-79, wherein the flavor is FONA orange flavor.

81. The pharmaceutical composition of any one of paragraphs 59-80, comprising about 50 w/v% to about 99.9 w/v%

of the liquid vehicle.

82. The pharmaceutical composition of any one of paragraphs 59-80, comprising about 92 w/v% to about 97 w/v% of the liquid vehicle.

83. The pharmaceutical composition of any one of paragraphs 59-80, comprising about 94.6 w/v% of the liquid vehicle.

84. The pharmaceutical composition of any one of paragraphs 59-83, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcitol.

85. The pharmaceutical composition of any one of paragraphs 59-84, wherein the liquid vehicle is medium-chain triglycerides.

86. The pharmaceutical composition of any one of paragraphs 84-85, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.

87. The pharmaceutical composition of any one of paragraphs 59-86, further comprising a surfactant.

88. The pharmaceutical composition of paragraph 87, comprising about 1 w/v% to about 50 w/v% of the surfactant.

89. The pharmaceutical composition of paragraph 87, comprising about 10 w/v% to about 30 w/v% of the surfactant.

90. The pharmaceutical composition of paragraph 87, comprising about 20 w/v% of the surfactant.

91. The pharmaceutical composition of any one of paragraphs 87-90, wherein the surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, sodium lauryl sulfate, Poloxamer, corn oil PEG-6 esters, and hydrogenated palm/palm kernel oil PEG-6 esters.

92. The pharmaceutical composition of any one of paragraphs 87-91, wherein the surfactant is oleoyl polyoxyl-6 glycerides.

93. The pharmaceutical composition of any one of paragraphs 91-92, wherein the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS.

94. The pharmaceutical composition of any one of paragraphs 59-93, comprising about 70 w/v% to about 80 w/v% of the liquid vehicle.

95. The pharmaceutical composition of any one of paragraphs 59-93, comprising about 75 w/v% of the liquid vehicle.

96. The pharmaceutical composition of any one of paragraphs 59-95, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcitol.

97. The pharmaceutical composition of any one of paragraphs 59-96, wherein the liquid vehicle is medium-chain triglycerides.

98. The pharmaceutical composition of any one of paragraphs 95-96, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.

99. The pharmaceutical composition of paragraph 59, comprising:

- (a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
- (b) a sweetener;
- (c) an anti-oxidant;
- (d) a flavor; and

(e) a liquid vehicle.

100. The pharmaceutical composition of paragraph 99, further comprising a surfactant.

101. The pharmaceutical composition of paragraph 59, comprising:

- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
- (c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
- (d) about 0.05 w/v% to about 0.2 w/v% of a flavor; and
- (e) about 92 w/v% to about 97 w/v% of a liquid vehicle.

102. The pharmaceutical composition of paragraph 59, comprising:

- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.15 w/v% of a sweetener;
- (c) about 0.17 w/v% of an anti-oxidant;
- (d) about 0.1 w/v% of a flavor; and
- (e) about 94.6 w/v% of a liquid vehicle.

103. The pharmaceutical composition of paragraph 59, comprising:

- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
- (c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
- (d) about 0.05 w/v% to about 0.2 w/v% of a flavor;
- (e) about 15 w/v% to about 25 w/v% of a surfactant; and
- (f) about 70 w/v% to about 80 w/v% of a liquid vehicle.

104. The pharmaceutical composition of paragraph 59, comprising:

- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.15 w/v% of a sweetener;
- (c) about 0.17 w/v% of an anti-oxidant;
- (d) about 0.1 w/v% of a flavor;
- (e) about 20 w/v% of a surfactant; and
- (f) about 75 w/v% of a liquid vehicle.

105. The pharmaceutical composition of paragraph 59, comprising:

- (a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
- (b) saccharin;
- (c) butylated hydroxytoluene;
- (d) FONA orange flavor; and
- (e) medium-chain triglycerides.

106. The pharmaceutical composition of paragraph 105, further comprising oleoyl polyoxyl-6 glycerides.

107. The pharmaceutical composition of paragraph 106, comprising:

- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
- (c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
- (d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor; and
- (e) about 92 w/v% to about 97 w/v% of medium-chain triglycerides.

108. The pharmaceutical composition of paragraph 59, comprising:

- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.15 w/v% of saccharin;
- (c) about 0.17 w/v% of butylated hydroxytoluene;
- (d) about 0.1 w/v% of FONA orange flavor; and
- (e) about 94.6 w/v% of medium-chain triglycerides.

109. The pharmaceutical composition of paragraph 59, comprising:

- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
- (c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
- (d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor;
- (e) about 15 w/v% to about 25 w/v% of oleoyl polyoxyl-6 glycerides; and
- (f) about 70 w/v% to about 80 w/v% of medium-chain triglycerides.

110. The pharmaceutical composition of paragraph 59, comprising:

- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.15 w/v% of saccharin;
- (c) about 0.17 w/v% of butylated hydroxytoluene;
- (d) about 0.1 w/v% of FONA orange flavor;
- (e) about 20 w/v% of oleoyl polyoxyl-6 glycerides; and
- (f) about 75 w/v% of medium-chain triglycerides.

111. The pharmaceutical composition of any one of paragraphs 59-110, comprising the compound of Formula (I) as a free base.

112. The pharmaceutical composition of any one of paragraphs 59-111, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg/mL to about 200 mg/mL, based on the weight of the free base.

113. The pharmaceutical composition of paragraph 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg/mL to about 150 mg/mL, based on the weight of the free base.

114. The pharmaceutical composition of paragraph 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg/mL, based on the weight of the free base.

115. The pharmaceutical composition of paragraph 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg/mL, based on the weight of the free base.

116. The pharmaceutical composition of any one of paragraphs 1-56, having a viscosity between about 15 to about

40 centipoise at about 45 °C.

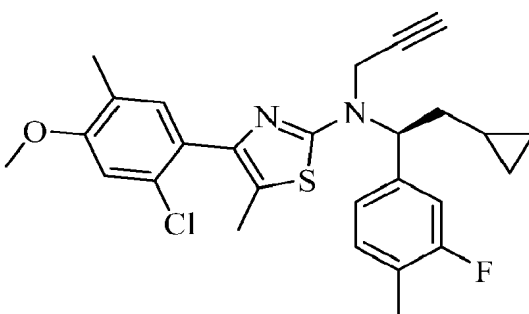
117. A method for preparing the pharmaceutical composition of any one of paragraphs 59-116, comprising:

- (a) mixing a liquid vehicle with a sweetener;
- (b) mixing the mixture of step (a) with an anti-oxidant and a flavor;
- (c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the mixture of step (b); and
- (d) mixing the mixture of step (c) with an additional portion of the liquid vehicle.

118. The method of paragraph 117, wherein step (a) comprises mixing a liquid vehicle with a sweetener and a surfactant.

119. A spray-dried dispersion comprising:

a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and
a polymer selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer;
wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:1 to about 1:9.

120. The spray-dried dispersion of paragraph 119, wherein the neutral polymer is selected from hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

121. The spray-dried dispersion of paragraph 119, wherein the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer.

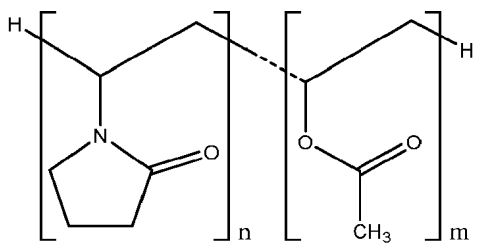
122. The spray-dried dispersion of paragraph 119, wherein the pyrrolidone polymer is selected from polyvinyl pyrrolidone (PVP) and a polyvinyl pyrrolidone vinyl acetate (PVP/VA).

123. The spray-dried dispersion of paragraph 122, wherein the pyrrolidone polymer is PVP/VA.

124. The spray-dried dispersion of paragraph 123, wherein the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 40:60 to about 60:40 by weight.

125. The spray-dried dispersion of paragraph 124, wherein the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight.

126. The spray-dried dispersion of any one of paragraphs 122-125, wherein the copolymer has the structure:



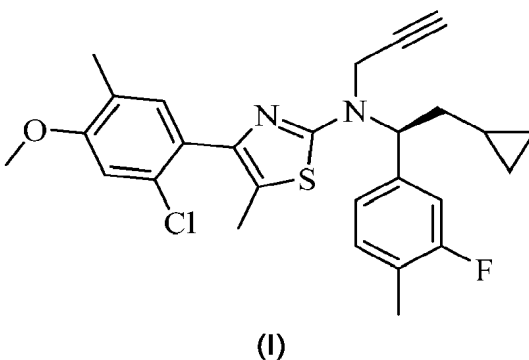
wherein the value of n is about 1 to about 2 times the value of m .

127. The spray-dried dispersion of paragraph 126, wherein the copolymer is copovidone, wherein the value of n is about 1.16 times the value of m .

128. The spray-dried dispersion of paragraph 126, wherein the copolymer is copovidone having an average molecular weight of about 45,000 to about 70,000.

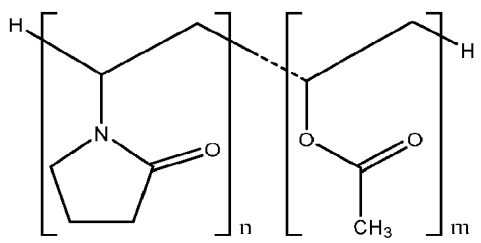
129. A spray-dried dispersion comprising:

a compound having the structure of Formula (I):



or a pharmaceutically acceptable salt thereof; and

a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



wherein the value of n is about 1 to about 2 times the value of m and the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight; and
wherein the weight ratio of the compound of Formula (I) to the copolymer is from about 1:1 to about 1:9.

130. The spray-dried dispersion of any one of paragraphs 119-129, wherein the compound of Formula (I) and the polymer together form homogeneous particles.

131. The spray-dried dispersion of any one of paragraphs 119-130, wherein the particles have a particle size distribution D_{50} of about 5 μm to about 100 μm .

132. The spray-dried dispersion of any one of paragraphs 119-131, wherein the particles have a particle size distribution D_{50} of about 10 μm to about 50 μm .

133. The spray-dried dispersion of any one of paragraphs 119-132, wherein the particles have a particle size distribution D_{50} of about 15 μm to about 30 μm .

134. The spray-dried dispersion of any one of paragraphs 119-133, wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:1.5 to about 1:9.

135. The spray-dried dispersion of any one of paragraphs 119-134, wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:2.5 to about 1:4.

136. The spray-dried dispersion of any one of paragraphs 119-135, wherein the weight ratio of the compound of Formula (I) to the polymer is about 1:3.

137. The spray-dried dispersion of any one of paragraphs 119-136, wherein the particles have a residual solvent content less than about 2 wt %.

138. The spray-dried dispersion of any one of paragraphs 119-137, wherein the particles have a residual solvent content less than about 1 wt %.

139. The spray-dried dispersion of any one of paragraphs 119-138, wherein the particles have a residual solvent content of about 0.5 wt % or less.

140. The spray-dried dispersion of any one of paragraphs 119-139, wherein the compound of Formula (I) in the dispersion is substantially amorphous.

141. A pharmaceutical composition comprising the spray-dried dispersion of any one of paragraphs 119-140 and one or more pharmaceutically acceptable excipients.

142. The pharmaceutical composition of paragraph 141, wherein the spray-dried dispersion is present in an amount of about 20% to about 90% w/w of the composition.

143. The pharmaceutical composition of paragraph 142, wherein the spray-dried dispersion is present in an amount of about 40% to about 80% w/w of the composition.

144. The pharmaceutical composition of paragraph 141, wherein the spray-dried dispersion is present in an amount of about 1% to about 20% w/w of the composition.

145. The pharmaceutical composition of paragraph 144, wherein the spray-dried dispersion is present in an amount of about 13% w/w of the composition.

146. The pharmaceutical composition of any one of paragraphs 141-145, wherein the pharmaceutical excipients are selected from the group consisting of a filler, a lubricant, and combinations thereof.

147. The pharmaceutical composition of paragraph 146, wherein the filler is selected from the group consisting of a binder, a diluent, a disintegrant, a glidant, a surfactant, and combinations thereof.

148. The pharmaceutical composition of any one of paragraphs 141-147 formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg.

149. The pharmaceutical composition of paragraph 148, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg.

150. The pharmaceutical composition of paragraph 149, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg.

151. The pharmaceutical composition of paragraph 149, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg.

152. The pharmaceutical composition of any one of paragraphs 141-151, wherein the pharmaceutical excipients are selected from the group consisting of a glidant, a filler, a disintegrant, a lubricant, and a combination thereof.

153. The pharmaceutical composition of any one of paragraphs 141-152, comprising a glidant.

154. The pharmaceutical composition of any one of paragraphs 152-153, comprising about 0.1 w/w% to about 5 w/w% of the glidant.

155. The pharmaceutical composition of any one of paragraphs 152-153, comprising about 0.1 w/w% to about 1 w/w% of the glidant.

156. The pharmaceutical composition of any one of paragraphs 152-153, comprising about 0.67 w/w% of the glidant.

157. The pharmaceutical composition of any one of paragraphs 152-156, wherein the glidant is selected from calcium silicate, silicon dioxide, and talc.

158. The pharmaceutical composition of any one of paragraphs 152-157, wherein the glidant is calcium silicate.

159. The pharmaceutical composition of any one of paragraphs 141-158, comprising a filler.

160. The pharmaceutical composition of any one of paragraphs 152-159, comprising about 30 w/w% to about 99 w/w% of the filler.

161. The pharmaceutical composition of any one of paragraphs 152-159, comprising about 50 w/w% to about 90 w/w% of the filler.

162. The pharmaceutical composition of any one of paragraphs 152-159, comprising about 75.5 w/w% of the filler.

163. The pharmaceutical composition of any one of paragraphs 152-162, wherein the filler is selected from mannitol, microcrystalline cellulose, lactose, starch, isomalt, silicified microcrystalline cellulose, Dicalcium Phosphate, maltodextrin, and a combination thereof.

164. The pharmaceutical composition of any one of paragraphs 152-163, wherein the filler is a combination of mannitol and microcrystalline cellulose.

165. The pharmaceutical composition of any one of paragraphs 163-164, comprising about 30 w/w% to about 80 w/w% of mannitol.

166. The pharmaceutical composition of any one of paragraphs 163-164, comprising about 50 w/w% to about 60 w/w% of mannitol.

167. The pharmaceutical composition of any one of paragraphs 163-164, comprising about 56 w/w% of mannitol.

168. The pharmaceutical composition of any one of paragraphs 163-167, comprising about 1 w/w% to about 50 w/w% of microcrystalline cellulose.

169. The pharmaceutical composition of any one of paragraphs 163-167, comprising about 10 w/w% to about 30 w/w% of microcrystalline cellulose.

170. The pharmaceutical composition of any one of paragraphs 163-167, comprising about 20 w/w% of microcrystalline cellulose.

171. The pharmaceutical composition of any one of paragraphs 163-167, comprising about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose.

172. The pharmaceutical composition of any one of paragraphs 141-171, comprising a disintegrant.

173. The pharmaceutical composition of any one of paragraphs 152-172, comprising about 1 w/w% to about 30 w/w% of the disintegrant.

174. The pharmaceutical composition of any one of paragraphs 152-172, comprising about 5 w/w% to about 15 w/w% of the disintegrant.

175. The pharmaceutical composition of any one of paragraphs 152-172, comprising about 10 w/w% of the disintegrant.

176. The pharmaceutical composition of any one of paragraphs 152-175, wherein the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, and sodium bicarbonate.

177. The pharmaceutical composition of any one of paragraphs 152-176, wherein the disintegrant is croscarmellose sodium.

178. The pharmaceutical composition of any one of paragraphs 141-177, comprising a lubricant.

179. The pharmaceutical composition of any one of paragraphs 152-178, comprising about 0.1 w/w% to about 10 w/w% of the lubricant.

180. The pharmaceutical composition of any one of paragraphs 152-178, comprising about 0.1 w/w% to about 1 w/w% of the lubricant.

181. The pharmaceutical composition of any one of paragraphs 152-178, comprising about 0.5 w/w% of the lubricant.

182. The pharmaceutical composition of any one of paragraphs 152-181, wherein the lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid, sodium lauryl sulfate, sodium oleate, glyceryl behenate, and talc.

183. The pharmaceutical composition of any one of paragraphs 152-182, wherein the lubricant is sodium stearyl fumarate.

184. The pharmaceutical composition of any one of paragraphs 141-183, comprising:

- (a) the spray-dried dispersion of any one of paragraphs 119-140;
- (b) a glidant;
- (c) a filler; and
- (d) a disintegrant.

185. The pharmaceutical composition of any one of paragraphs 141-183, comprising:

- (a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of any one of paragraphs 119-140;
- (b) about 0.1 w/w% to about 1 w/w% of a glidant;
- (c) about 50 w/w% to about 90 w/w% of a filler; and
- (d) about 5 w/w% to about 0.2 w/w% of a disintegrant.

186. The pharmaceutical composition of any one of paragraphs 141-183, comprising:

- (a) about 13 w/w% of the spray-dried dispersion of any one of paragraphs 119-140;
- (b) about 0.67 w/w% of a glidant;
- (c) about 75.5 w/w% of a filler; and
- (d) about 10 w/w% of a disintegrant.

187. The pharmaceutical composition of any one of paragraphs 141-183, comprising:

- (a) the spray-dried dispersion of Example 3;

- (b) calcium silicate;
- (c) a combination of mannitol and microcrystalline cellulose; and
- (d) croscarmellose sodium.

5 188. The pharmaceutical composition of paragraph 187, comprising:

- (a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of Example 3;
- (b) about 0.1 w/w% to about 1 w/w% of calcium silicate;
- 10 (c) about 50 w/w% to about 60 w/w% of mannitol and about 10 w/w% to about 30 w/w% of microcrystalline cellulose; and
- (d) about 5 w/w% to about 0.2 w/w% of croscarmellose sodium.

189. The pharmaceutical composition of paragraph 188, comprising:

- 15 (a) about 13 w/w% of the spray-dried dispersion of Example 3;
- (b) about 0.67 w/w% of calcium silicate;
- (c) about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose; and
- (d) about 10 w/w% of croscarmellose sodium.

20 190. The pharmaceutical composition of any one of paragraphs 141-189 that is formulated as a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film.

25 191. The pharmaceutical composition of paragraph 190, wherein the pharmaceutical composition is in tablet form.

192. The pharmaceutical composition of paragraph 190, wherein the pharmaceutical composition is in capsule form.

193. The pharmaceutical composition of paragraph 190, wherein the pharmaceutical composition is in sachet form.

30 194. The pharmaceutical composition of paragraph 190, wherein the pharmaceutical composition is in granule form.

195. The pharmaceutical composition of any one of paragraphs 190-192, wherein the pharmaceutical composition is coated.

35 196. A method for preparing the spray-dried dispersion of any one of paragraphs 119-140, comprising:

- dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and
- 40 spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer.

197. The method of paragraph 196, comprising removing the organic solvent after formation of the spray-dried dispersion by drying the spray-dried dispersion.

45 198. The method of paragraph 197, wherein the spray-dried dispersion is dried with a convection tray dryer.

199. The method of any one of paragraphs 196-198, wherein the organic solvent is acetone.

50 200. The method of any one of paragraphs 196-199, wherein the spray dryer inlet temperature is about 60°C to about 80°C.

201. The method of paragraph 200, wherein the spray dryer inlet temperature is about 72°C.

55 202. The method of any one of paragraphs 196-201, wherein the spray dryer outlet temperature is about 25°C to about 45°C.

203. The method of paragraph 202, wherein the spray dryer outlet temperature is about 35°C.

204. The method of any one of paragraphs 196-203, wherein the homogeneous particles comprise a bulk density of less than about 0.2 g/mL.

205. The method of paragraph 204, wherein the homogeneous particles comprise a bulk density of less than about 0.15 g/mL.

206. The method of any one of paragraphs 196-205, wherein the homogeneous particles comprise a tapped density of less than about 0.3 g/mL.

207. The method of paragraph 206, wherein the homogeneous particles comprise a tapped density of less than about 0.25 g/mL.

208. A method for preparing a pharmaceutical composition, comprising combining the spray-dried dispersion of any one of paragraphs 119-140 with one or more pharmaceutically acceptable excipients.

209. The method of paragraph 208, comprising:

- (a) blending the spray-dried dispersion of any one of paragraphs 119-140, with a glidant;
- (b) further blending the blend of step (a) with a filler and a disintegrant;
- (c) screening the blend of step (b) to break up aggregates and assist with blend uniformity;
- (d) further blending the intragranular blend of step (c);
- (e) compaction of the intragranular blend of step (d) via roller compaction to form granules; and
- (f) milling of ribbon from roller compaction into granules of step (e).

210. A method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the spray-dried dispersion of any one of paragraphs 119-140 or the pharmaceutical composition of any one of paragraphs 141-195.

211. The method of paragraph 210, wherein the spray-dried dispersion or the pharmaceutical composition is administered to the subject in a fed state.

212. The method of paragraph 210 or paragraph 211, wherein the spray-dried dispersion or the pharmaceutical composition is administered to the subject with a nutritional composition.

213. The method of paragraph 212, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

214. The method of paragraph 212 or paragraph 213, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

215. The method of any one of paragraphs 212-214, wherein the nutritional composition is administered within 30 minutes of administration of the spray-dried dispersion or the pharmaceutical composition.

216. The method of any one of paragraphs 211-215, wherein administering the spray-dried dispersion or the pharmaceutical composition exhibits a positive food effect.

217. The method of paragraph 216, wherein the positive food effect is measured in terms of C_{max} , AUC, or combinations thereof when comparing oral administration of the spray-dried dispersion or pharmaceutical composition in the fed and fasting states.

218. The method of any one of paragraphs 211-217, wherein the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10.

219. The method of any one of paragraphs 211-217, wherein the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10.

220. The method of any one of paragraphs 210-219, wherein the subject is a pediatric subject.

221. A method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, comprising orally administering to the subject the pharmaceutical composition of any one of paragraphs 141-195, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

222. The method of paragraph 221, wherein the subject is a pediatric subject.

223. A method of improving oral bioavailability of a compound of Formula (I) in a subject, comprising orally administering to the subject the pharmaceutical composition of any one of paragraphs 141-195, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

224. The method of paragraph 223, wherein the subject is a pediatric subject.

225. The spray-dried dispersion of any one of paragraphs 119-140, wherein the spray-dried dispersion is formulated for oral administration and exhibits a positive food effect when administered orally.

226. The spray-dried dispersion of paragraph 225, wherein the spray-dried dispersion has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10.

227. The spray-dried dispersion of paragraph 225, wherein the spray-dried dispersion has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 5 to about 10.

228. A crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

229. The salt of paragraph 228, having Form 1 of the Compound of Formula (I).

230. The salt of paragraph 228 or paragraph 229, having an X-ray powder diffraction pattern as substantially shown in Figure 27.

231. The salt of any one of paragraphs 228-230, having a DSC thermogram substantially as depicted in Figure 28.

232. The salt of any one of paragraphs 228-231, having a thermogravimetric analysis (TGA) thermogram substantially as depicted in Figure 28.

233. The salt of any one of paragraphs 228-232, having at least one X-ray powder diffraction (XRPD) peak, in terms of 2-theta ($\pm$ 0.2 degrees), selected 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

234. The salt of any one of paragraphs 228-232, having at least two X-ray powder diffraction (XRPD) peaks, in terms of 2-theta ($\pm$ 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

235. The salt of any one of paragraphs 228-232, having at least three X-ray powder diffraction (XRPD) peaks, in terms of 2-theta ($\pm$ 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

236. The salt of any one of paragraphs 228-232, having at least four X-ray powder diffraction (XRPD) peaks, in terms of 2-theta ($\pm$ 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

237. The salt of any one of paragraphs 228-232, having characteristic X-ray powder diffraction (XRPD) peaks, in terms of 2-theta ($\pm$ 0.2 degrees), at 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

238. The salt of any one of paragraphs 228-237, having an endothermic peak having an onset of melt at about 156 °C (22.2 J/g) in a differential scanning calorimetry (DSC) thermogram.

239. A method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone

(ACTH); and (c) androstenedione in the subject.

240. The method of paragraph 239, wherein the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

241. The method of paragraph 240, wherein the circadian release occurs between the hours of 2 a.m. and 10 a.m.

242. The method of any one of paragraphs 239-241, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

243. The method of any one of paragraphs 239-242, wherein the level of 17-hydroxyprogesterone is reduced by at least 25%.

244. The method of any one of paragraphs 239-242, wherein the level of 17-hydroxyprogesterone is reduced by at least 50%.

245. The method of any one of paragraphs 239-244, wherein the level of adrenocorticotrophic hormone is reduced by at least 25%.

246. The method of any one of paragraphs 239-244, wherein the level of adrenocorticotrophic hormone is reduced by at least 40%.

247. The method of any one of paragraphs 239-244, wherein the level of adrenocorticotrophic hormone is reduced by at least 50%.

248. The method of any one of paragraphs 239-247, wherein the level of androstenedione is reduced by at least 25%.

249. The method of any one of paragraphs 239-247, wherein the level of androstenedione is reduced by at least 30%.

250. The method of any one of paragraphs 239-247, wherein the level of androstenedione is reduced by at least 50%.

251. The method of any one of paragraphs 239-250, wherein the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

252. The method of any one of paragraphs 239-251, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

253. The method of any one of paragraphs 239-252, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

254. A method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of androstenedione in the subject.

255. The method of paragraph 254, wherein the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

256. The method of paragraph 254 or 255, wherein the androstenedione is reduced by at least 25%.

257. The method of paragraph 254 or 255, wherein the androstenedione is reduced by at least 30%.

258. The method of paragraph 254 or 255, wherein the androstenedione is reduced by at least 50%.

259. A method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

260. The method of paragraph 259, wherein the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

261. A method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

262. The method of paragraph 261, wherein the corticosteroid is a glucocorticoid.

263. A method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof,

wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatopropsis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

264. The method of any one of paragraphs 259-263, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

265. The method of any one of paragraphs 259-264, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

266. The method of any one of paragraphs 259-264, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

267. The method of any one of paragraphs 259-266, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

268. The method of any one of paragraphs 259-267, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-

2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

269. The method of any one of paragraphs 259-268, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

270. A method of treating congenital adrenal hyperplasia in a subject comprising

- (i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
- (ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
- (iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

271. The method of paragraph 270, further comprising (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i).

272. The method of paragraph 271, further comprising (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

273. The method of paragraph 271 or 272, wherein steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window.

274. The method of any one of paragraphs 271-273, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m.

275. The method of any one of paragraphs 271-273, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

276. The method of any one of paragraphs 271-275, wherein steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

277. The method of any one of paragraphs 271-275, wherein steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

278. The method of any one of paragraphs 270-277, wherein step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

279. The method of any one of paragraphs 270-278, wherein step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

280. The method of any one of paragraphs 270-279, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

281. The method of any one of paragraphs 270-279, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

282. The method of any one of paragraphs 270-281, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

283. A method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, where in the subject is in a fed state.

284. The method of paragraph 283, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition.

285. The method of paragraph 284, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

286. The method of paragraph 284 or 285, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

287. The method of any one of paragraphs 284-286, wherein the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

288. A pharmaceutical composition of any one of paragraphs 1-56, 59-116 or 141-195 for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

289. The pharmaceutical composition for use according to paragraph 288, wherein the subject is in a fed state.

290. The pharmaceutical composition for use according to paragraph 288 or paragraph 289, wherein the subject is administered the pharmaceutical composition with a nutritional composition.

291. The pharmaceutical composition for use according to paragraph 290, wherein the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than about 30%.

292. The pharmaceutical composition for use according to paragraph 290, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

293. The pharmaceutical composition for use according to any one of paragraphs 290-292, wherein the nutritional composition is administered in an amount of about 6 to about 12 fluid ounces.

294. The pharmaceutical composition for use according to any one of paragraphs 290-293, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

295. The pharmaceutical composition for use according to any one of paragraphs 290-294, wherein the nutritional composition is administered within 30 minutes of administration of the pharmaceutical composition.

296. The pharmaceutical composition for use according to any one of paragraphs 289-295, wherein administering the pharmaceutical composition exhibits a positive food effect.

297. The pharmaceutical composition for use according to paragraph 296, wherein the positive food effect is meas-

ured in terms of $C_{\max}$, AUC, or a combination thereof of a compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states.

298. The pharmaceutical composition for use according to any one of paragraphs 289-297, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

299. The pharmaceutical composition for use according to any one of paragraphs 289-297, wherein the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

300. The pharmaceutical composition for use according to any one of paragraphs 289-297, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

301. The pharmaceutical composition for use according to any one of paragraphs 289-297, wherein the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

302. The pharmaceutical composition for use according to any one of paragraphs 288-301, wherein the subject is a pediatric subject.

303. The pharmaceutical composition for use according to any one of paragraphs 289-295, wherein the pharmaceutical composition exhibits a positive food effect when administered orally.

304. The pharmaceutical composition for use according to paragraph 303, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4 or about 5 to about 10.

305. The pharmaceutical composition for use according to paragraph 303, wherein the compound of Formula (I) has a ratio of the $C_{\max}$ in the fed state to the $C_{\max}$ in the fasted state of about 1 to about 4 or about 5 to about 10.

306. The pharmaceutical composition for use according to paragraph 303, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1.5 to about 3.

307. The pharmaceutical composition for use according to paragraph 303, wherein the compound of Formula (I) has a ratio of the $C_{\max}$ in the fed state to the $C_{\max}$ in the fasted state of about 1.5 to about 3.

308. The pharmaceutical composition for use according to any one of paragraphs 288-307, wherein the pharmaceutical composition is administered to the subject with a meal.

309. The pharmaceutical composition for use according to paragraph 308, wherein the meal is a high fat meal.

310. The pharmaceutical composition for use according to paragraph 308, wherein the meal is a low fat meal.

311. The pharmaceutical composition for use according to any one of paragraphs 308-310, wherein the pharmaceutical composition is administered within about 5 minutes after the start of the meal.

312. The pharmaceutical composition for use according to any one of paragraphs 308-311, wherein the meal is an evening meal.

313. The pharmaceutical composition for use according to any one of paragraphs 308-311, wherein the meal is a morning meal.

314. The pharmaceutical composition for use according to any one of paragraphs 308-313, wherein administering the pharmaceutical composition exhibits a positive food effect.

315. The pharmaceutical composition for use according to paragraph 314, wherein the positive food effect is measured in terms of $C_{\max}$, AUC, or combinations thereof of the compound of Formula (I) when comparing oral admin-

istration of the pharmaceutical composition in the fed and fasting states.

316. The pharmaceutical composition for use according to any one of paragraphs 308-315, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

317. The pharmaceutical composition for use according to any one of paragraphs 308-316, wherein the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

318. The pharmaceutical composition for use according to any one of paragraphs 308-315, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

319. The pharmaceutical composition for use according to any one of paragraphs 308-315 or 318, wherein the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

320. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the pharmaceutical composition comprises about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

321. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the pharmaceutical composition comprises about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

322. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the pharmaceutical composition comprises about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

323. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the pharmaceutical composition comprises about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

324. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

325. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

326. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

327. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

328. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

329. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

330. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

5 331. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

10 332. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

15 333. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

334. The pharmaceutical composition for use according to any one of paragraphs 288-333, wherein the subject is concurrently receiving a dose of a glucocorticoid.

20 335. The pharmaceutical composition for use according to paragraph 334, wherein the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate.

25 336. The pharmaceutical composition for use according to paragraph 334 or 335, wherein the glucocorticoid is cortisol (hydrocortisone).

337. The pharmaceutical composition for use according to paragraph 334 or 335, wherein the glucocorticoid is cortisone.

30 338. The pharmaceutical composition for use according to paragraph 334 or 335, wherein the glucocorticoid is prednisone.

339. The pharmaceutical composition for use according to any one of paragraphs 334-338, wherein the glucocorticoid dose is measured in hydrocortisone equivalents.

35 340. The pharmaceutical composition for use according to any one of paragraphs 334-339, wherein the glucocorticoid dose is measured as a multiple of the upper limit of normal of physiologic dosing in hydrocortisone equivalents.

40 341. The pharmaceutical composition for use according to any one of paragraphs 334-340, wherein the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the pharmaceutical composition.

45 342. The pharmaceutical composition for use according to any one of paragraphs 334-340, wherein the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m²/day as measured after a time period of administration of the pharmaceutical composition.

343. The pharmaceutical composition for use according to any one of paragraphs 334-340, wherein the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m²/day as measured after a time period of administration of the pharmaceutical composition.

50 344. The pharmaceutical composition for use according to any one of paragraphs 334-340, wherein the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m²/day as measured after a time period of administration of the pharmaceutical composition.

55 345. The pharmaceutical composition for use according to any one of paragraphs 334-344, wherein the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition

358. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the pharmaceutical composition.

5 359. The pharmaceutical composition for use according to any one of paragraphs 288-358, wherein the level of adrenocorticotrophic hormone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotrophic hormone is relative to the level of adrenocorticotrophic hormone prior to administration of the pharmaceutical composition.

10 360. The pharmaceutical composition for use according to any one of paragraphs 288-358, wherein the level of adrenocorticotrophic hormone is reduced by at least about 40% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotrophic hormone is relative to the level of adrenocorticotrophic hormone prior to administration of the pharmaceutical composition.

15 361. The pharmaceutical composition for use according to any one of paragraphs 288-358, wherein the level of adrenocorticotrophic hormone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotrophic hormone is relative to the level of adrenocorticotrophic hormone prior to administration of the pharmaceutical composition.

20 362. The pharmaceutical composition for use according to any one of paragraphs 288-358, wherein the level of adrenocorticotrophic hormone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

25 363. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of adrenocorticotrophic hormone is within normal limits after a time period of administration of the pharmaceutical composition.

30 364. The pharmaceutical composition for use according to any one of paragraphs 288-363, wherein the level of androstenedione is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

35 365. The pharmaceutical composition for use according to any one of paragraphs 288-363, wherein the level of androstenedione is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

40 366. The pharmaceutical composition for use according to any one of paragraphs 288-363, wherein the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

45 367. The pharmaceutical composition for use according to any one of paragraphs 288-363, wherein the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

368. The pharmaceutical composition for use according to any one of paragraphs 288-363, wherein the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

50 369. The pharmaceutical composition for use according to any one of paragraphs 288-368, wherein the level of testosterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

55 370. The pharmaceutical composition for use according to any one of paragraphs 288-368, wherein the level of testosterone is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

371. The pharmaceutical composition for use according to any one of paragraphs 288-368, wherein the level of testosterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

372. The pharmaceutical composition for use according to any one of paragraphs 288-368, wherein the level of testosterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

373. The pharmaceutical composition for use according to any one of paragraphs 288-368, wherein the level of testosterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

374. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% and the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the pharmaceutical composition.

375. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal and the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

376. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

377. The pharmaceutical composition for use according to any one of paragraphs 334-376, wherein the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the pharmaceutical composition, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the pharmaceutical composition.

378. The pharmaceutical composition for use according to paragraph 377, wherein one or more symptoms of glucocorticoid burden selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicality, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the pharmaceutical composition, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the pharmaceutical composition.

379. The pharmaceutical composition for use according to any one of paragraphs 341-378, wherein the time period of administration is at least about 4 weeks.

380. The pharmaceutical composition for use according to any one of paragraphs 341-378, wherein the time period of administration is at least about 24 weeks.

381. The pharmaceutical composition for use according to any one of paragraphs 341-378, wherein the time period of administration is at least about one year.

382. The pharmaceutical composition for use according to any one of paragraphs 288-381, wherein the subject is a pediatric subject.

383. The pharmaceutical composition for use according to paragraph 382, wherein the pediatric subject is less than or equal to six years old.

384. The pharmaceutical composition for use according to paragraph 382, wherein the pediatric subject is greater than six years old and less than eleven years old.

385. The pharmaceutical composition for use according to paragraph 382, wherein the pediatric subject is greater than ten years old and less than fifteen years old.

386. The pharmaceutical composition for use according to paragraph 382, wherein the pediatric subject is greater than fourteen years old and less than nineteen years old.

387. The pharmaceutical composition for use according to any one of paragraphs 288-381, wherein the subject is an adult subject.

388. The pharmaceutical composition for use according to any one of paragraphs 387, wherein the adult subject is over eighteen years old.

389. The pharmaceutical composition for use according to any one of paragraphs 288-388, wherein the subject is female.

390. The pharmaceutical composition for use according to any one of paragraphs 288-388, wherein the subject is male.

391. The pharmaceutical composition for use according to any one of paragraphs 288-390, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a hydrochloric acid salt or p-toluenesulfonic acid salt.

392. The pharmaceutical composition for use according to any one of paragraphs 288-390, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a p-toluenesulfonic acid salt of any one of paragraphs 228-238.

393. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or a pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in the subject.

394. The compound of paragraph 393, wherein the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

395. The compound of paragraph 394, wherein the circadian release occurs between the hours of 2 a.m. and 10 a.m.

396. The compound of any one of paragraphs 393-395, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

397. The compound of any one of paragraphs 393-396, wherein the level of 17-hydroxyprogesterone is reduced by at least 25%.

398. The compound of any one of paragraphs 393-396, wherein the level of 17-hydroxyprogesterone is reduced by at least 50%.

399. The compound of any one of paragraphs 393-398, wherein the level of adrenocorticotrophic hormone is reduced by at least 25%.

400. The compound of any one of paragraphs 393-398, wherein the level of adrenocorticotrophic hormone is reduced by at least 40%.

401. The compound of any one of paragraphs 393-398, wherein the level of adrenocorticotrophic hormone is reduced by at least 50%.

402. The compound of any one of paragraphs 393-401, wherein the level of androstenedione is reduced by at least 25%.

403. The compound of any one of paragraphs 393-401, wherein the level of androstenedione is reduced by at least 30%.

404. The compound of any one of paragraphs 393-401, wherein the level of androstenedione is reduced by at least 50%.

405. The compound of any one of paragraphs 393-401, wherein the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

406. The compound of any one of paragraphs 393-405, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

407. The compound of any one of paragraphs 393-406, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

408. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound is administered in an amount sufficient to reduce the level of androstenedione in the subject.

409. The compound of paragraph 408, wherein the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

410. The compound of paragraph 408 or 409, wherein the level of androstenedione is reduced by at least 25%.

411. The compound of paragraph 408 or 409, wherein the level of androstenedione is reduced by at least 30%.

412. The compound of paragraph 408 or 409, wherein the level of androstenedione is reduced by at least 50%.

413. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

414. The compound of paragraph 413, wherein the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

415. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

416. The compound of paragraph 415, wherein the corticosteroid is a glucocorticoid.

417. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital

adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

418. The compound of any one of paragraphs 413-417, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

419. The compound of any one of paragraphs 413-418, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

420. The compound of any one of paragraphs 413-417, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

421. The compound of any one of paragraphs 413-420, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

422. The compound of any one of paragraphs 413-421, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

423. The compound of any one of paragraphs 413-422, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

424. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject comprising

- (i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
- (ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
- (iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

425. The compound of paragraph 424, further comprising (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i).

426. The compound of paragraph 425, further comprising (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

427. The compound of paragraph 425 or 426, wherein steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window.

428. The compound of any one of paragraphs 425-427, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m.

429. The compound of any one of paragraphs 425-427, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

430. The compound of any one of paragraphs 425-429, wherein steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

431. The compound of any one of paragraphs 425-429, wherein steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotrophic hormone (ACTH); and (c) androstenedione.

432. The compound of any one of paragraphs 424-431, wherein step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

433. The compound of any one of paragraphs 424-432, wherein step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

434. The compound of any one of paragraphs 424-433, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

435. The compound of any one of paragraphs 424-433, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

436. The compound of any one of paragraphs 424-435, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

437. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof for use in a method of treating congenital adrenal hyperplasia (CAH), in a subject, wherein the subject is in a fed state.

438. The compound of paragraph 437, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition.

439. The compound of paragraph 438, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

440. The compound of paragraph 438 or 439, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

441. The compound of any one of paragraphs 438-440, wherein the nutritional composition is administered within

30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

442. The compound of any one of paragraphs 437-441, wherein administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, exhibits a positive food effect.

443. The compound of paragraph 442, wherein the positive food effect is measured in terms of C_{max} , AUC, or combinations thereof when comparing oral administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the fed and fasting states.

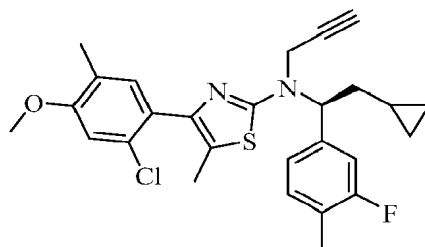
444. The compound of any one of paragraphs 437-443, wherein the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10.

445. The compound of any one of paragraphs 437-443, wherein the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10.

Claims

1. A pharmaceutical composition in oral solution dosage form comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

(b) one or more of a sweetener, an anti-oxidant, and a flavor; and

(c) a liquid vehicle, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

2. The pharmaceutical composition of claim 1, comprising about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

3. The pharmaceutical composition of claim 1, comprising about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

4. The pharmaceutical composition of claim 1, comprising about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

5. The pharmaceutical composition of any one of claims 1-4, comprising a sweetener.

6. The pharmaceutical composition of any one of claims 1-5, comprising about 0.01 w/v% to about 1.5 w/v% of the sweetener.

7. The pharmaceutical composition of any one of claims 1-5, comprising about 0.1 w/v% to about 0.5 w/v% of the

sweetener.

8. The pharmaceutical composition of any one of claims 1-5, comprising about 0.15 w/v% of the sweetener.
- 5 9. The pharmaceutical composition of any one of claims 1-8, wherein the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and advantame.
- 10 11. The pharmaceutical composition of any one of claims 1-10, comprising an anti-oxidant.
12. The pharmaceutical composition of any one of claims 1-11, comprising about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant.
- 15 13. The pharmaceutical composition of any one of claims 1-11, comprising about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant.
14. The pharmaceutical composition of any one of claims 1-11, comprising about 0.17 w/v% of the anti-oxidant.
- 20 15. The pharmaceutical composition of any one of claims 1-14, wherein the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TPGS, butylated hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid.
- 25 16. The pharmaceutical composition of any one of claims 1-15, wherein the anti-oxidant is butylated hydroxytoluene.
17. The pharmaceutical composition of any one of claims 1-16, comprising a flavor.
- 30 18. The pharmaceutical composition of any one of claims 1-17, comprising about 0.01 w/v% to about 0.5 w/v% of the flavor.
19. The pharmaceutical composition of any one of claims 1-17, comprising about 0.05 w/v% to about 0.2 w/v% of the flavor.
- 35 20. The pharmaceutical composition of any one of claims 1-17, comprising about 0.10 w/v% of the flavor.
21. The pharmaceutical composition of any one of claims 1-20, wherein the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetarome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor.
- 40 22. The pharmaceutical composition of any one of claims 1-21, wherein the flavor is FONA orange flavor.
23. The pharmaceutical composition of any one of claims 1-22, comprising about 50 w/v% to about 99.9 w/v% of the liquid vehicle.
- 45 24. The pharmaceutical composition of any one of claims 1-22, comprising about 90 w/v% to about 99 w/v% of the liquid vehicle.
25. The pharmaceutical composition of any one of claims 1-22, comprising about 92 w/v% to about 97 w/v% of the liquid vehicle.
- 50 26. The pharmaceutical composition of any one of claims 1-22, comprising about 94.6 w/v% of the liquid vehicle.
27. The pharmaceutical composition of any one of claims 1-22, comprising about 70 w/v% to about 80 w/v% of the liquid vehicle.
- 55 28. The pharmaceutical composition of any one of claims 1-22, comprising about 75 w/v% of the liquid vehicle.
29. The pharmaceutical composition of any one of claims 1-28, wherein the liquid vehicle is medium-chain triglycerides.

30. The pharmaceutical composition of claim 29, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.
31. The pharmaceutical composition of any one of claims 1-30, further comprising a surfactant.
- 5 32. The pharmaceutical composition of claim 31, comprising about 1 w/v% to about 50 w/v% of the surfactant.
33. The pharmaceutical composition of claim 31, comprising about 10 w/v% to about 30 w/v% of the surfactant.
- 10 34. The pharmaceutical composition of claim 31, comprising about 20 w/v% of the surfactant.
35. The pharmaceutical composition of any one of claims 31-34, wherein the surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, sodium lauryl sulfate, Poloxamer, corn oil PEG-6 esters, and hydrogenated palm/palm kernel oil PEG-6 esters.
- 15 36. The pharmaceutical composition of any one of claims 31-35, wherein the surfactant is oleoyl polyoxyl-6 glycerides.
37. The pharmaceutical composition of any one of claims 35-36, wherein the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS.
- 20 38. The pharmaceutical composition of any one of claims 1-37, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcitol.
- 25 39. The pharmaceutical composition of any one of claims 1-38, wherein the liquid vehicle is medium-chain triglycerides.
40. The pharmaceutical composition of any one of claims 1-38, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.
- 30 41. The pharmaceutical composition of claim 1, comprising:
- (a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
 - (b) a sweetener;
 - 35 (c) an anti-oxidant;
 - (d) a flavor; and
 - (e) a liquid vehicle.
42. The pharmaceutical composition of claim 41, further comprising a surfactant.
- 40 43. The pharmaceutical composition of claim 1, comprising:
- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
 - 45 (b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
 - (c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
 - (d) about 0.05 w/v% to about 0.2 w/v% of a flavor; and
 - (e) about 92 w/v% to about 97 w/v% of a liquid vehicle.
- 50 44. The pharmaceutical composition of claim 1, comprising:
- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
 - 55 (b) about 0.15 w/v% of a sweetener;
 - (c) about 0.17 w/v% of an anti-oxidant;
 - (d) about 0.1 w/v% of a flavor; and

(e) about 94.6 w/v% of a liquid vehicle.

45. The pharmaceutical composition of claim 1, comprising:

- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
- (c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
- (d) about 0.05 w/v% to about 0.2 w/v% of a flavor;
- (e) about 15 w/v% to about 25 w/v% of a surfactant; and
- (f) about 70 w/v% to about 80 w/v% of a liquid vehicle.

46. The pharmaceutical composition of claim 1, comprising:

- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.15 w/v% of a sweetener;
- (c) about 0.17 w/v% of an anti-oxidant;
- (d) about 0.1 w/v% of a flavor;
- (e) about 20 w/v% of a surfactant; and
- (f) about 75 w/v% of a liquid vehicle.

47. The pharmaceutical composition of claim 1, comprising:

- (a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
- (b) saccharin;
- (c) butylated hydroxytoluene;
- (d) FONA orange flavor; and
- (e) medium-chain triglycerides.

48. The pharmaceutical composition of claim 47, further comprising oleoyl polyoxyl-6 glycerides.

49. The pharmaceutical composition of claim 48, comprising:

- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
- (c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
- (d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor; and
- (e) about 92 w/v% to about 97 w/v% of medium-chain triglycerides.

50. The pharmaceutical composition of claim 1, comprising:

- (a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
- (b) about 0.15 w/v% of saccharin;
- (c) about 0.17 w/v% of butylated hydroxytoluene;
- (d) about 0.1 w/v% of FONA orange flavor; and
- (e) about 94.6 w/v% of medium-chain triglycerides.

51. The pharmaceutical composition of claim 1, comprising:

- (a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-

4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;

(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;

(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor;

(e) about 15 w/v% to about 25 w/v% of oleoyl polyoxyl-6 glycerides; and

(f) about 70 w/v% to about 80 w/v% of medium-chain triglycerides.

52. The pharmaceutical composition of claim 1, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of saccharin;

(c) about 0.17 w/v% of butylated hydroxytoluene;

(d) about 0.1 w/v% of FONA orange flavor;

(e) about 20 w/v% of oleoyl polyoxyl-6 glycerides; and

(f) about 75 w/v% of medium-chain triglycerides.

53. The pharmaceutical composition of claim 51 or 52, wherein:

the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS; and

the medium-chain triglycerides is Labrafac TM Lipophile WL1349.

54. The pharmaceutical composition of any one of claims 1-53, comprising the compound of Formula (I) as a free base.

55. The pharmaceutical composition of any one of claims 1-54, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg/mL to about 200 mg/mL, based on the weight of the free base.

56. The pharmaceutical composition of claim 55, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg/mL to about 150 mg/mL, based on the weight of the free base.

57. The pharmaceutical composition of claim 55, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg/mL, based on the weight of the free base.

58. The pharmaceutical composition of claim 55, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg/mL, based on the weight of the free base.

59. The pharmaceutical composition of any one of claims 1-58, having a viscosity between about 1 to about 50 centipoise at about 25 °C.

60. A method for preparing the pharmaceutical composition of any one of claims 1-59, comprising:

(a) mixing a liquid vehicle with a sweetener;

(b) mixing the mixture of step (a) with an anti-oxidant and a flavor;

(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the mixture of step (b); and

(d) mixing the mixture of step (c) with an additional portion of the liquid vehicle.

61. The method of claim 60, wherein step (a) comprises mixing a liquid vehicle with a sweetener and a surfactant.

62. A pharmaceutical composition of any one of claims 1-59 for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

63. The pharmaceutical composition for use according to claim 62, wherein the subject is in a fed state.

64. The pharmaceutical composition for use according to claim 62 or 63, wherein the subject is administered the phar-

maceutical composition with a nutritional composition.

- 5 **65.** The pharmaceutical composition for use according to claim 64, wherein the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than about 30%.
- 66.** The pharmaceutical composition for use according to claim 64, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.
- 10 **67.** The pharmaceutical composition for use according to any one of claims 64-66, wherein the nutritional composition is administered in an amount of about 6 to about 12 fluid ounces.
- 68.** The pharmaceutical composition for use according to any one of claims 64-67, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.
- 15 **69.** The pharmaceutical composition for use according to any one of claims 64-68, wherein the nutritional composition is administered within 30 minutes of administration of the pharmaceutical composition.
- 70.** The pharmaceutical composition for use according to any one of claims 63-69, wherein administering the pharmaceutical composition exhibits a positive food effect.
- 20 **71.** The pharmaceutical composition for use according to claim 70, wherein the positive food effect is measured in terms of $C_{\max}$, AUC, or a combination thereof of a compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states.
- 25 **72.** The pharmaceutical composition for use according to any one of claims 63-71, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.
- 30 **73.** The pharmaceutical composition for use according to any one of claims 63-71, wherein the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.
- 35 **74.** The pharmaceutical composition for use according to any one of claims 63-71, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.
- 40 **75.** The pharmaceutical composition for use according to any one of claims 63-71, wherein the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 1.5 to about 3.
- 45 **76.** The pharmaceutical composition for use according to any one of claims 62-75, wherein the subject is a human subject.
- 77.** The pharmaceutical composition for use according to any one of claims 63-69, wherein the pharmaceutical composition exhibits a positive food effect when administered orally.
- 78.** The pharmaceutical composition for use according to claim 77, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4 or about 5 to about 10.
- 50 **79.** The pharmaceutical composition for use according to claim 77, wherein the compound of Formula (I) has a ratio of the $C_{\max}$ in the fed state to the $C_{\max}$ in the fasted state of about 1 to about 4 or about 5 to about 10.
- 80.** The pharmaceutical composition for use according to claim 77, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1.5 to about 3.
- 55 **81.** The pharmaceutical composition for use according to claim 77, wherein the compound of Formula (I) has a ratio of the $C_{\max}$ in the fed state to the $C_{\max}$ in the fasted state of about 1.5 to about 3.

82. The pharmaceutical composition for use according to any one of claims 62-81, wherein the pharmaceutical composition is administered to the subject with a meal.
83. The pharmaceutical composition for use according to claim 82, wherein the meal is a high fat meal.
84. The pharmaceutical composition for use according to claim 82, wherein the meal is a low fat meal.
85. The pharmaceutical composition for use according to any one of claims 82-84, wherein the pharmaceutical composition is administered within about 5 minutes after the start of the meal.
86. The pharmaceutical composition for use according to any one of claims 82-85, wherein the meal is an evening meal.
87. The pharmaceutical composition for use according to any one of claims 82-85, wherein the meal is a morning meal.
88. The pharmaceutical composition for use according to any one of claims 82-87, wherein administering the pharmaceutical composition exhibits a positive food effect.
89. The pharmaceutical composition for use according to claim 88, wherein the positive food effect is measured in terms of $C_{\max}$, AUC, or combinations thereof of the compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states.
90. The pharmaceutical composition for use according to any one of claims 82-89, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.
91. The pharmaceutical composition for use according to any one of claims 82-90, wherein the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.
92. The pharmaceutical composition for use according to any one of claims 82-89, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.
93. The pharmaceutical composition for use according to any one of claims 82-89 and 92, wherein the ratio of the $C_{\max}$ of the compound of Formula (I) in the fed state to the $C_{\max}$ of the compound of Formula (I) in the fasted state is about 1.5 to about 3.
94. The pharmaceutical composition for use according to any one of claims 62-93, wherein the pharmaceutical composition comprises about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.
95. The pharmaceutical composition for use according to any one of claims 62-93, wherein the pharmaceutical composition comprises about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.
96. The pharmaceutical composition for use according to any one of claims 62-93, wherein the pharmaceutical composition comprises about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.
97. The pharmaceutical composition for use according to any one of claims 62-93, wherein the pharmaceutical composition comprises about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.
98. The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.
99. The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises

administering a daily dose of the pharmaceutical composition comprising about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

5 **100.**The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

10 **101.**The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

15 **102.**The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

103.The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

20 **104.**The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

25 **105.**The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

30 **106.**The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

35 **107.**The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

108.The pharmaceutical composition for use according to any one of claims 62-107, wherein the subject is concurrently receiving a dose of a glucocorticoid.

40 **109.**The pharmaceutical composition for use according to claim 108, wherein the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate.

45 **110.**The pharmaceutical composition for use according to claim 108 or 109, wherein the glucocorticoid is cortisol (hydrocortisone).

111.The pharmaceutical composition for use according to claim 108 or 109, wherein the glucocorticoid is cortisone.

112.The pharmaceutical composition for use according to claim 108 or 109, wherein the glucocorticoid is prednisone.

50 **113.**The pharmaceutical composition for use according to any one of claims 108-112, wherein the glucocorticoid dose is measured in hydrocortisone equivalents.

55 **114.**The pharmaceutical composition for use according to any one of claims 108-113, wherein the glucocorticoid dose is measured as a multiple of the upper limit of normal of physiologic dosing in hydrocortisone equivalents.

115.The pharmaceutical composition for use according to any one of claims 108-114, wherein the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the pharmaceutical composition.

- [illegible]

of the subject is reduced by greater than about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

- 5 **129.**The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition.
- 10 **130.**The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition.
- 15 **131.**The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.
- 20 **132.**The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the pharmaceutical composition.
- 25 **133.**The pharmaceutical composition for use according to any one of claims 62-132, wherein the level of adrenocorticotrophic hormone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotrophic hormone is relative to the level of adrenocorticotrophic hormone prior to administration of the pharmaceutical composition.
- 30 **134.**The pharmaceutical composition for use according to any one of claims 62-132, wherein the level of adrenocorticotrophic hormone is reduced by at least about 40% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotrophic hormone is relative to the level of adrenocorticotrophic hormone prior to administration of the pharmaceutical composition.
- 35 **135.**The pharmaceutical composition for use according to any one of claims 62-132, wherein the level of adrenocorticotrophic hormone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotrophic hormone is relative to the level of adrenocorticotrophic hormone prior to administration of the pharmaceutical composition.
- 40 **136.**The pharmaceutical composition for use according to any one of claims 62-132, wherein the level of adrenocorticotrophic hormone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.
- 45 **137.**The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of adrenocorticotrophic hormone is within normal limits after a time period of administration of the pharmaceutical composition.
- 50 **138.**The pharmaceutical composition for use according to any one of claims 62-137, wherein the level of androstenedione is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.
- 55 **139.**The pharmaceutical composition for use according to any one of claims 62-137, wherein the level of androstenedione is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.
- 60 **140.**The pharmaceutical composition for use according to any one of claims 62-137, wherein the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

141.The pharmaceutical composition for use according to any one of claims 62-137, wherein the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

142.The pharmaceutical composition for use according to any one of claims 62-137, wherein the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

143.The pharmaceutical composition for use according to any one of claims 62-142, wherein the level of testosterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

144.The pharmaceutical composition for use according to any one of claims 62-142, wherein the level of testosterone is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

145.The pharmaceutical composition for use according to any one of claims 62-142, wherein the level of testosterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

146.The pharmaceutical composition for use according to any one of claims 62-142, wherein the level of testosterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

147.The pharmaceutical composition for use according to any one of claims 62-142, wherein the level of testosterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

148.The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% and the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the pharmaceutical composition.

149.The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal and the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

150.The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

151.The pharmaceutical composition for use according to any one of claims 108-150, wherein the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the pharmaceutical composition, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the pharmaceutical composition.

152.The pharmaceutical composition for use according to claim 151, wherein one or more symptoms of glucocorticoid burden selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicality, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the pharmaceutical composition, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the pharmaceutical composition.

153.The pharmaceutical composition for use according to any one of claims 115-152, wherein the time period of administration is at least about 4 weeks.

154.The pharmaceutical composition for use according to any one of claims 115-152, wherein the time period of administration is at least about 24 weeks.

155.The pharmaceutical composition for use according to any one of claims 115-152, wherein the time period of administration is at least about one year.

156.The pharmaceutical composition for use according to any one of claims 62-155, wherein the subject is a pediatric subject.

157.The pharmaceutical composition for use according to claim 156, wherein the pediatric subject is less than or equal to six years old.

158.The pharmaceutical composition for use according to claim 156, wherein the pediatric subject is greater than six years old and less than eleven years old.

159.The pharmaceutical composition for use according to claim 156, wherein the pediatric subject is greater than ten years old and less than fifteen years old.

160.The pharmaceutical composition for use according to claim 156, wherein the pediatric subject is greater than fourteen years old and less than nineteen years old.

161.The pharmaceutical composition for use according to any one of claims 62-155, wherein the subject is an adult subject.

162.The pharmaceutical composition for use according to any one of claims 161, wherein the adult subject is over eighteen years old.

163.The pharmaceutical composition for use according to any one of claims 62-162, wherein the subject is female.

164.The pharmaceutical composition for use according to any one of claims 62-162, wherein the subject is male.

165.The pharmaceutical composition for use according to any one of claims 62-164, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a hydrochloric acid salt or p-toluenesulfonic acid salt.

166.The pharmaceutical composition for use according to any one of claims 62-164, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a p-toluenesulfonic acid crystalline salt.

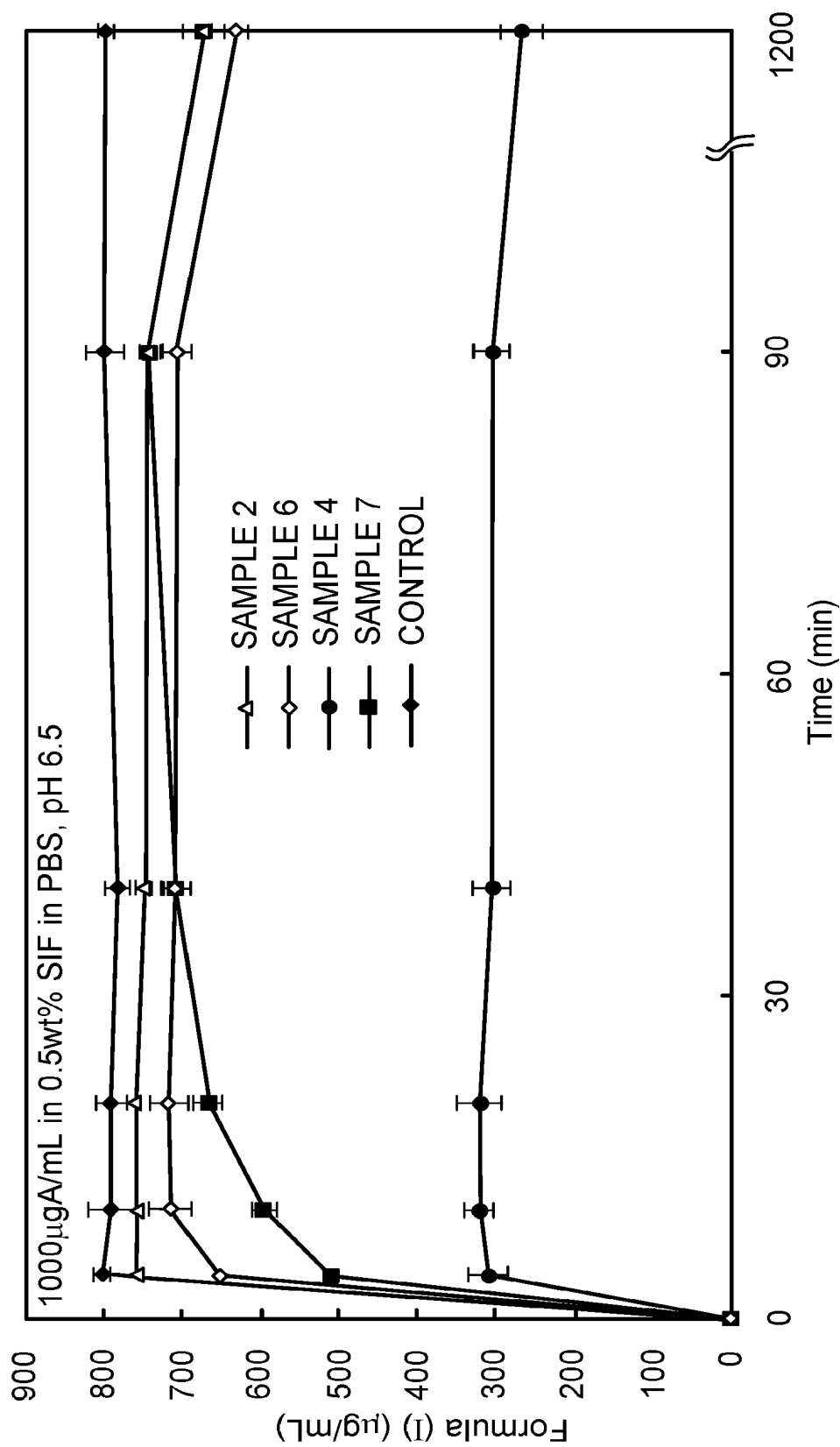


FIG. 1

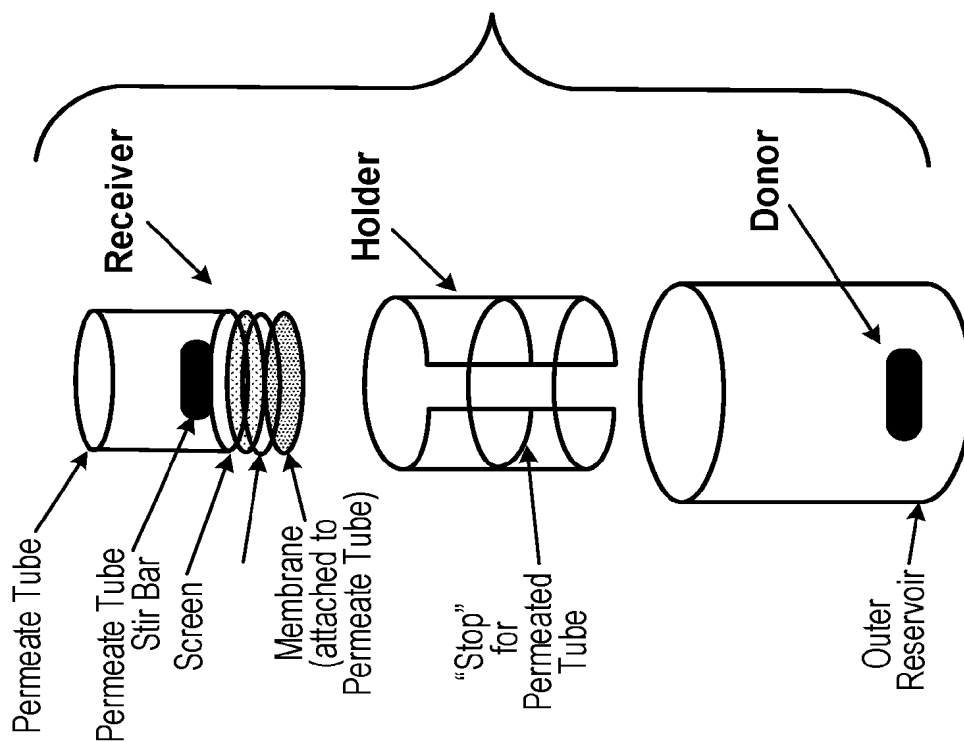
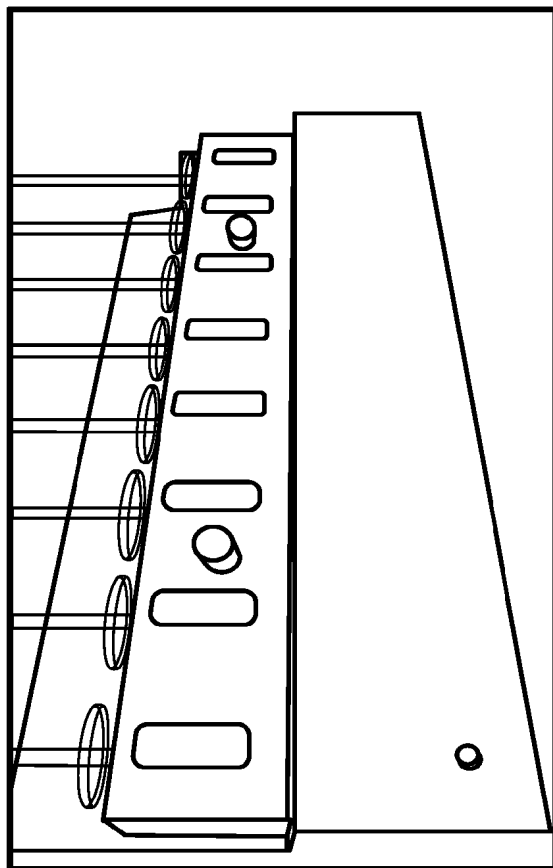


FIG. 2

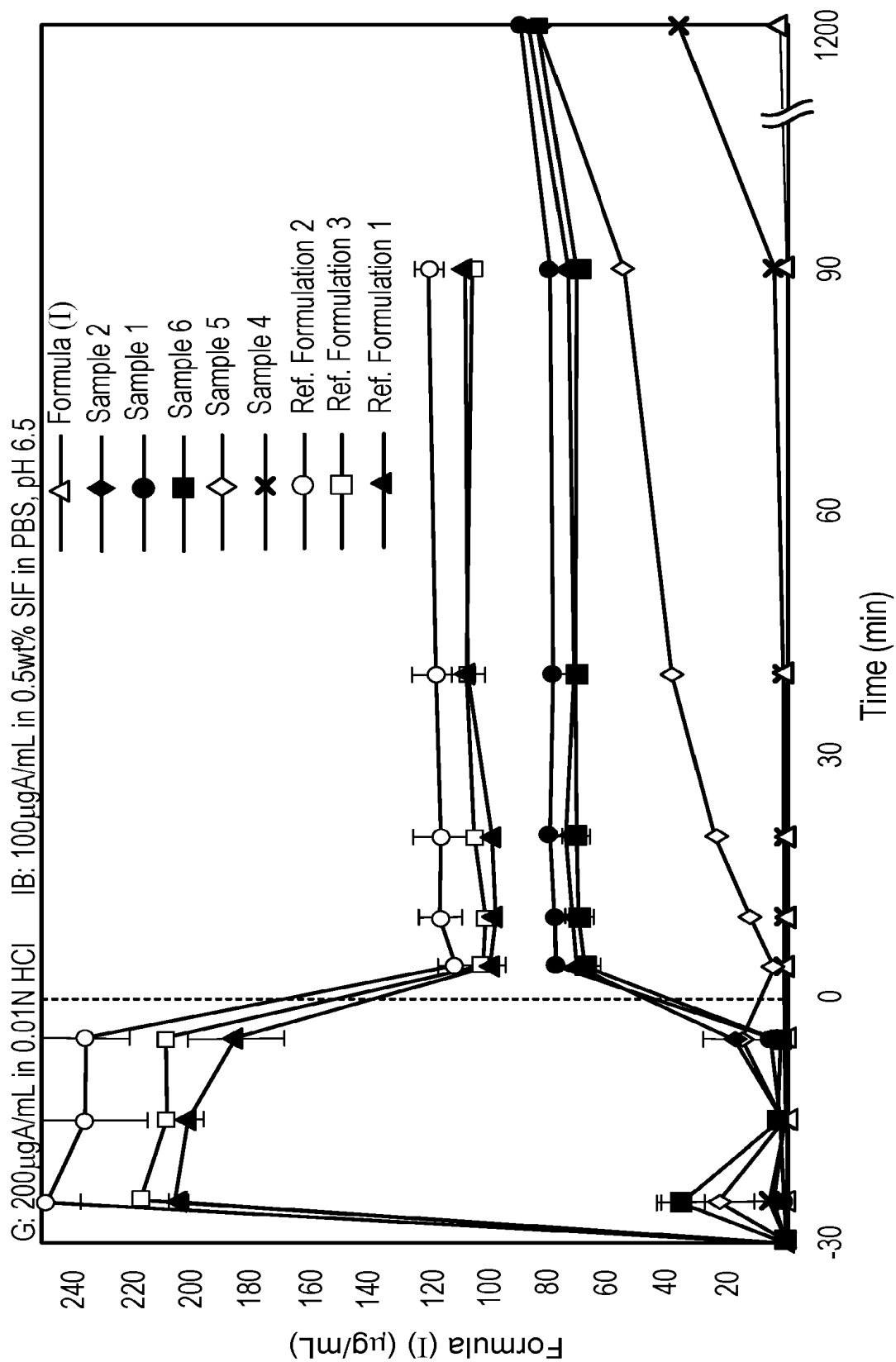


FIG. 3

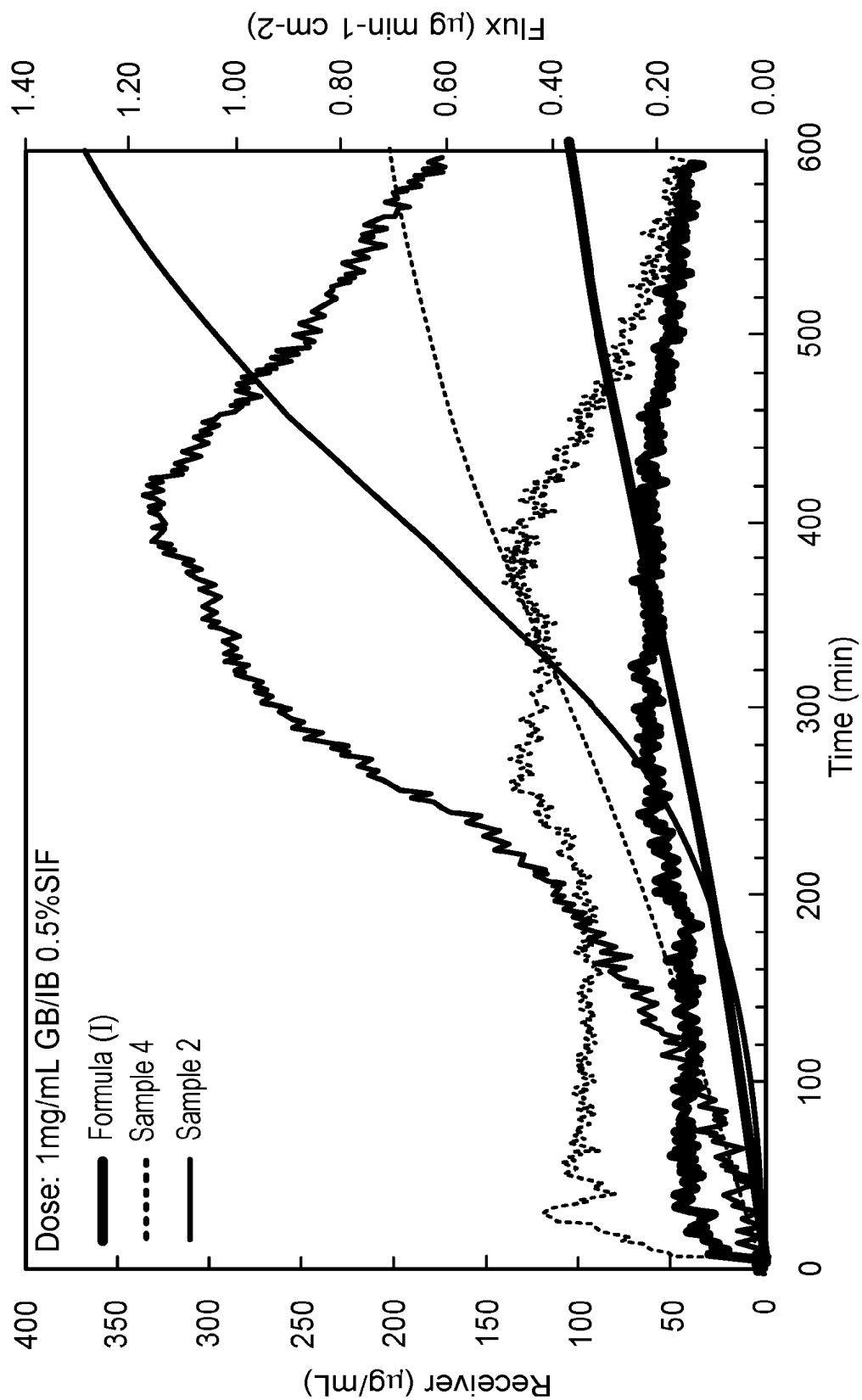


FIG. 4

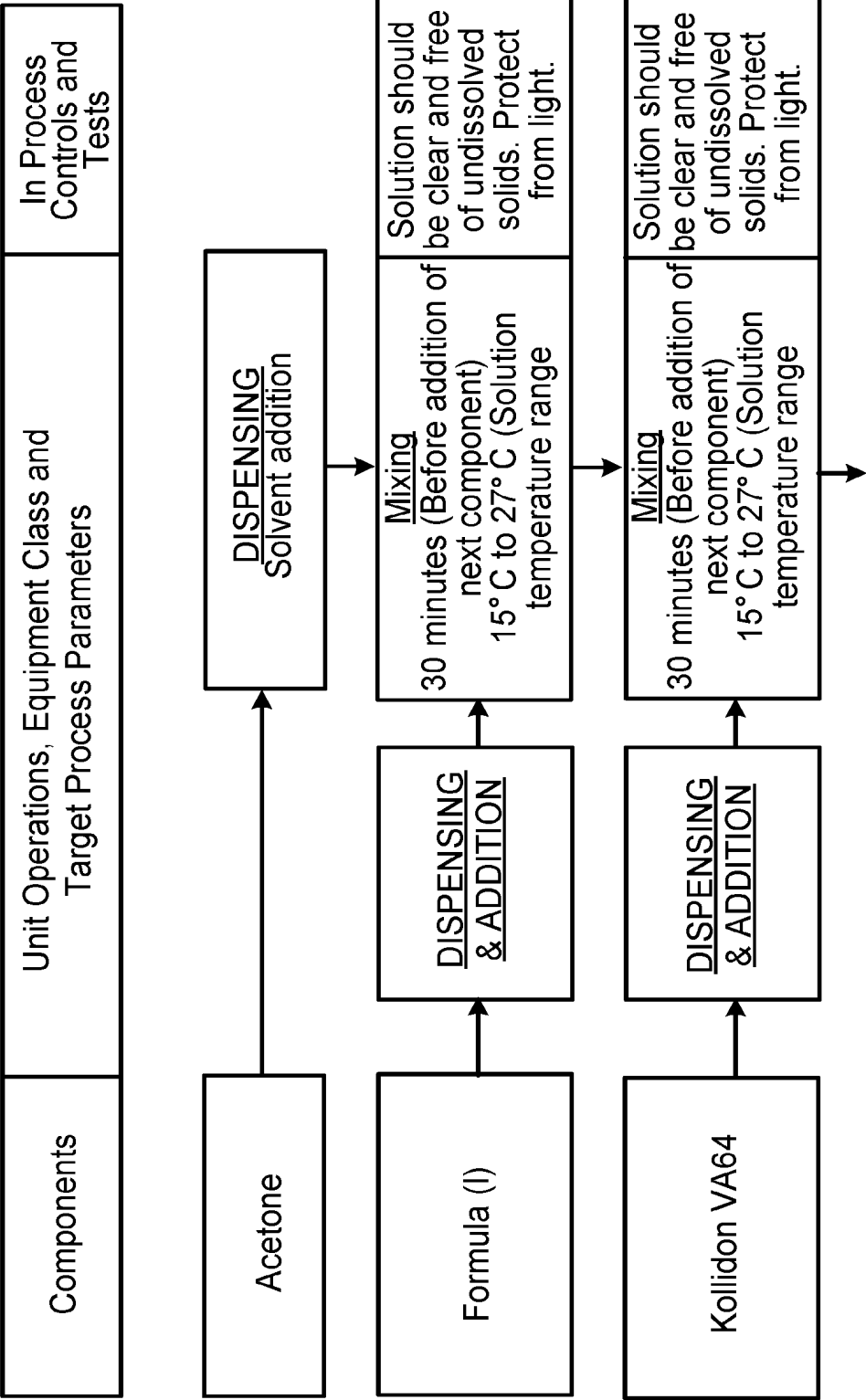
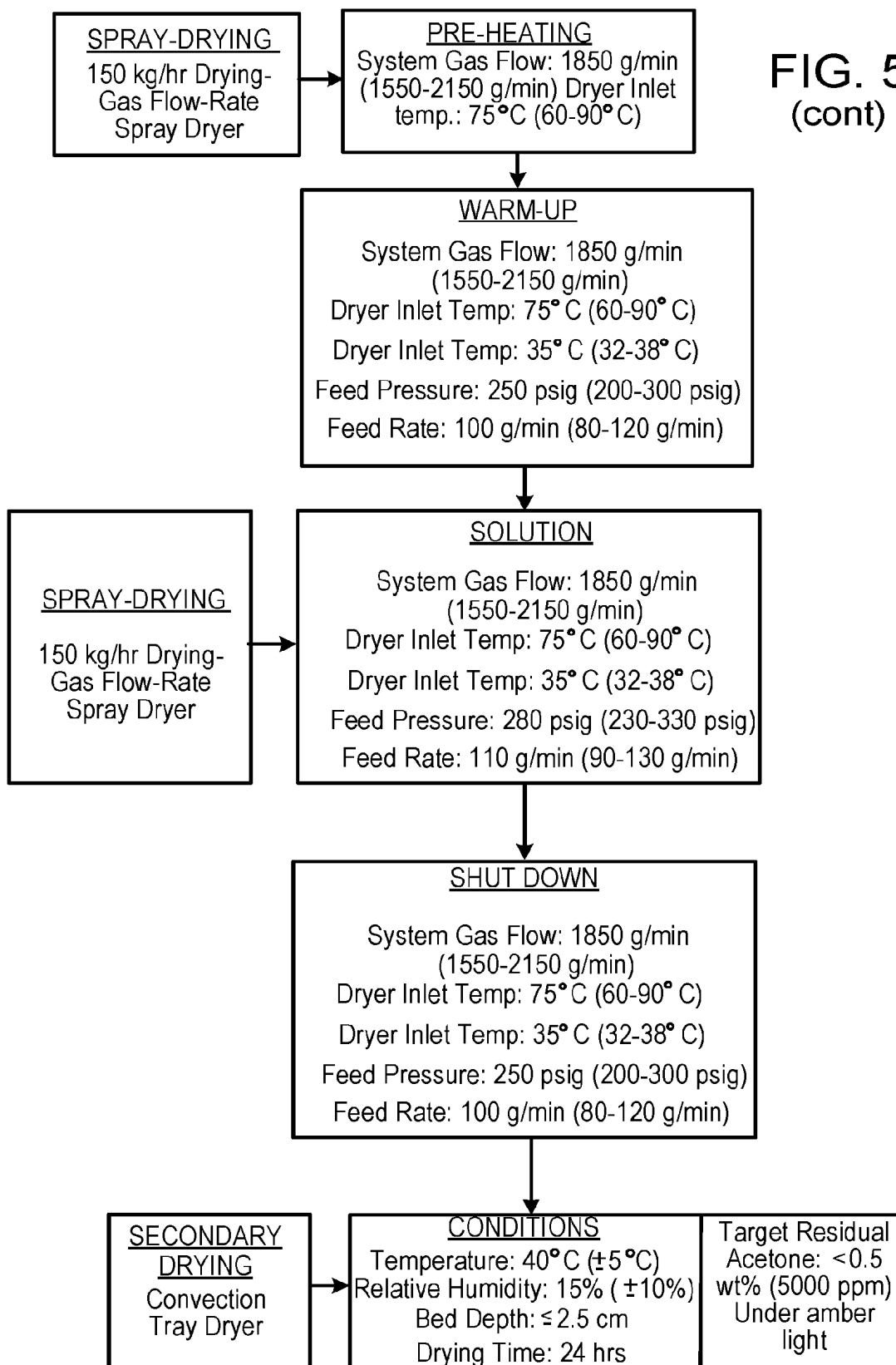


FIG. 5

FIG. 5
(cont)

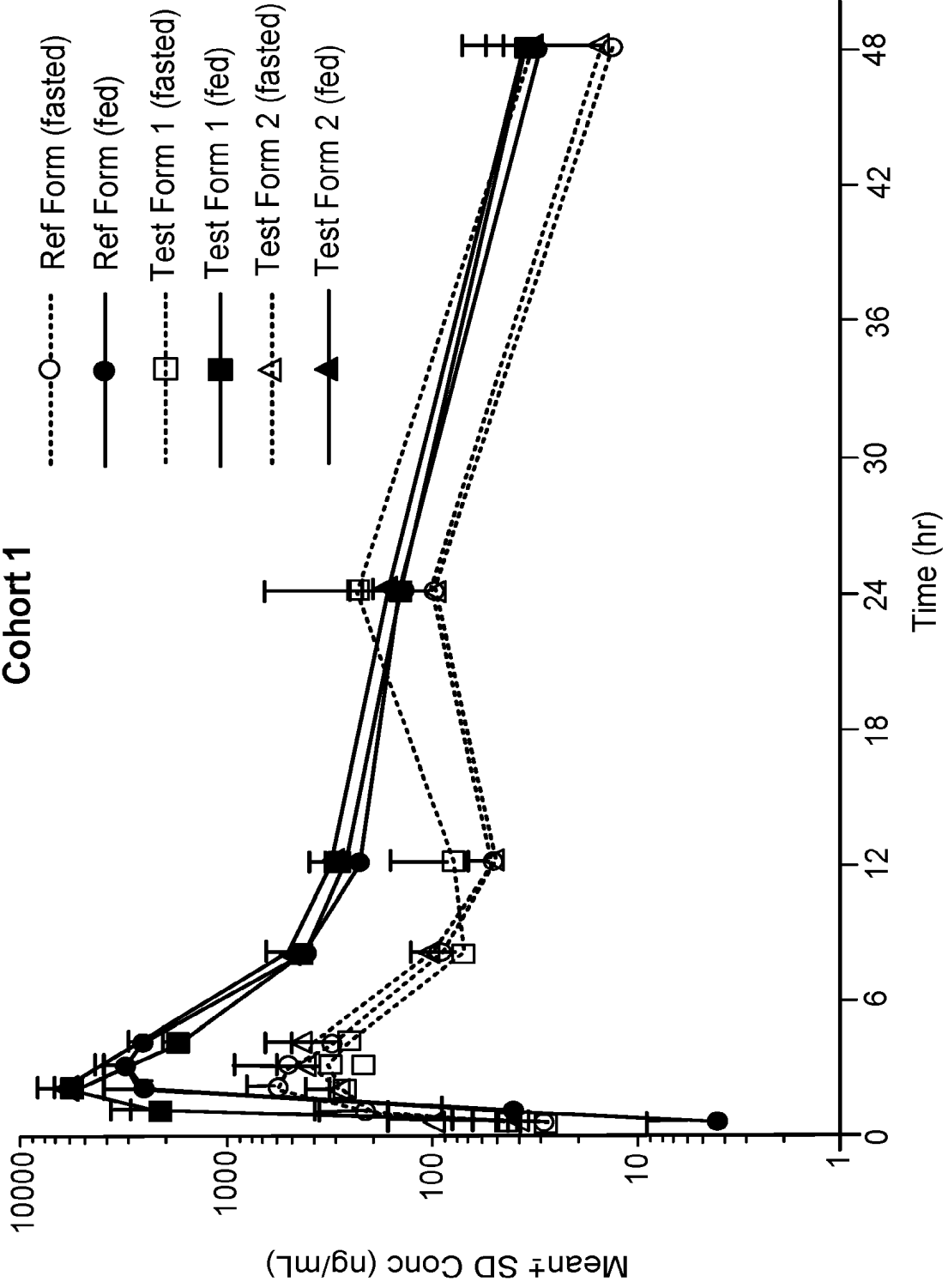


FIG. 6A

Cohort 2

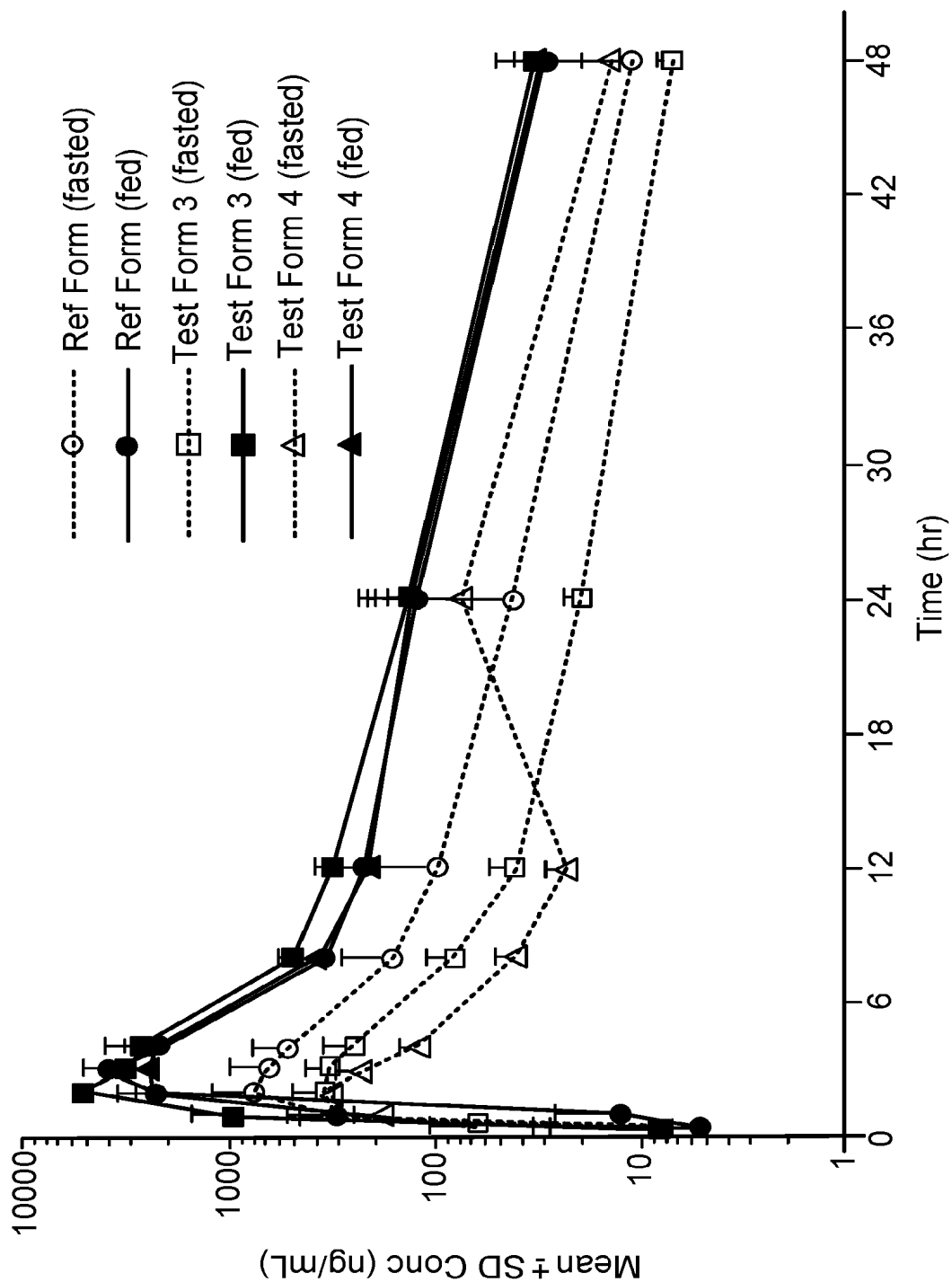


FIG. 6B

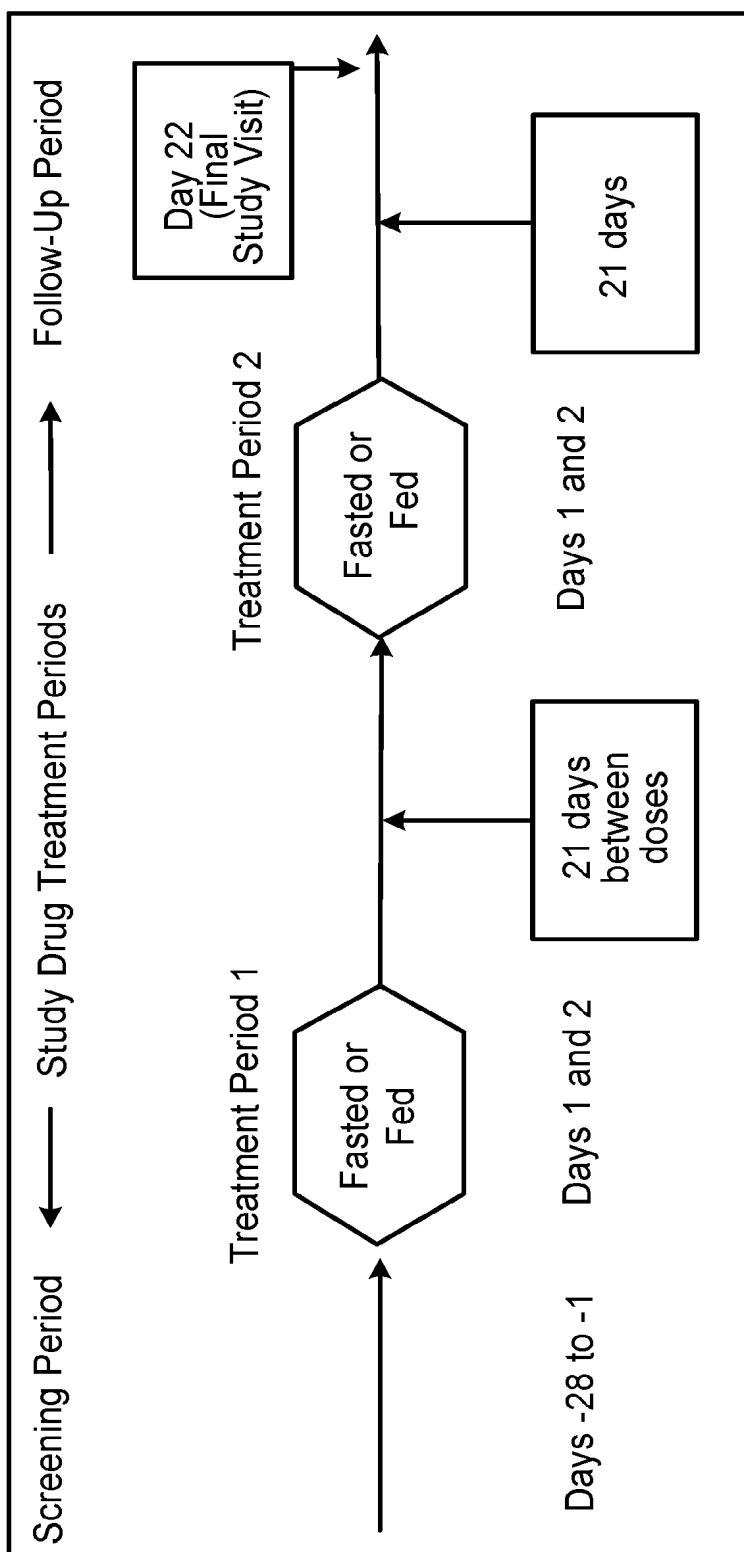


FIG. 7

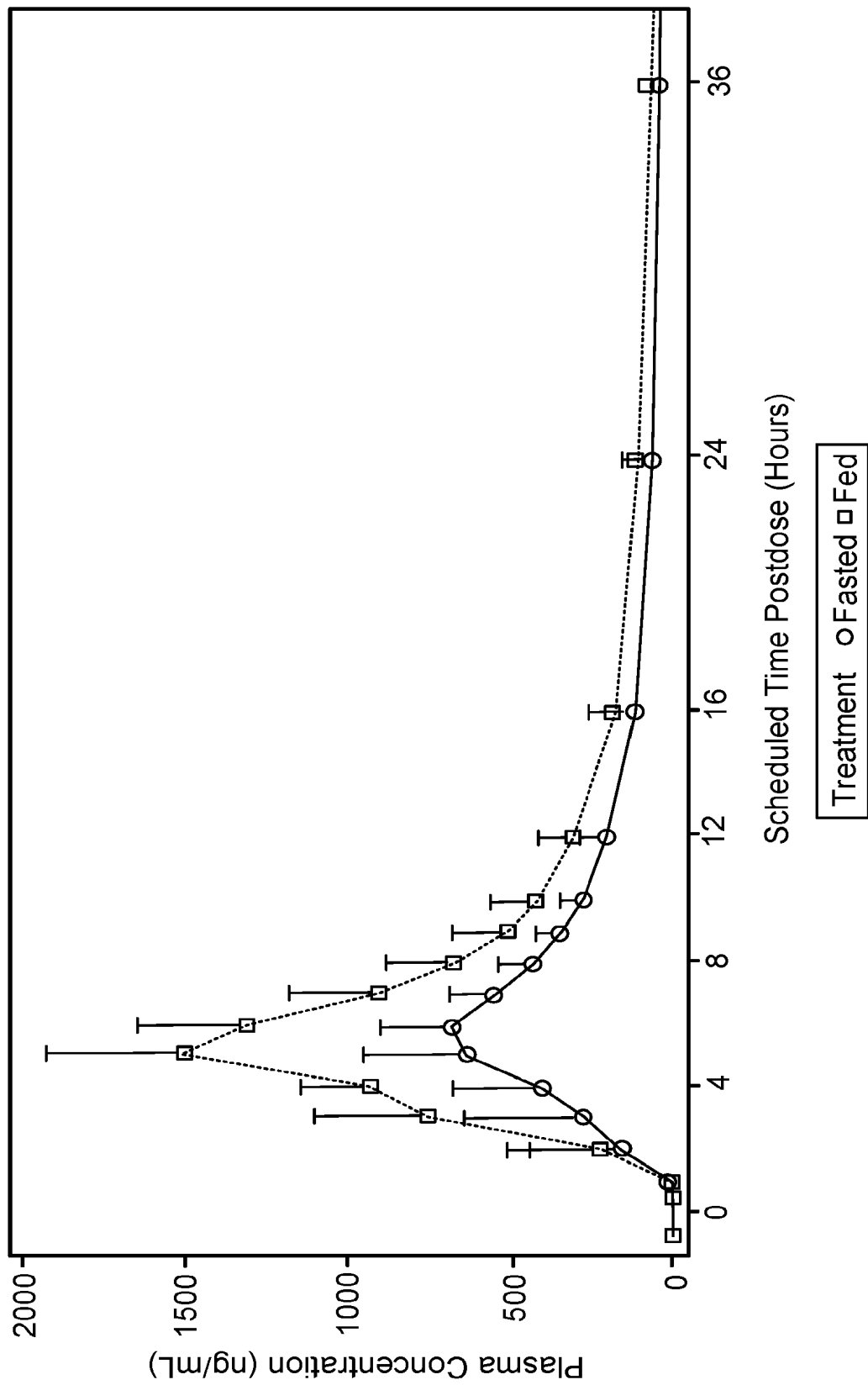


FIG. 8A

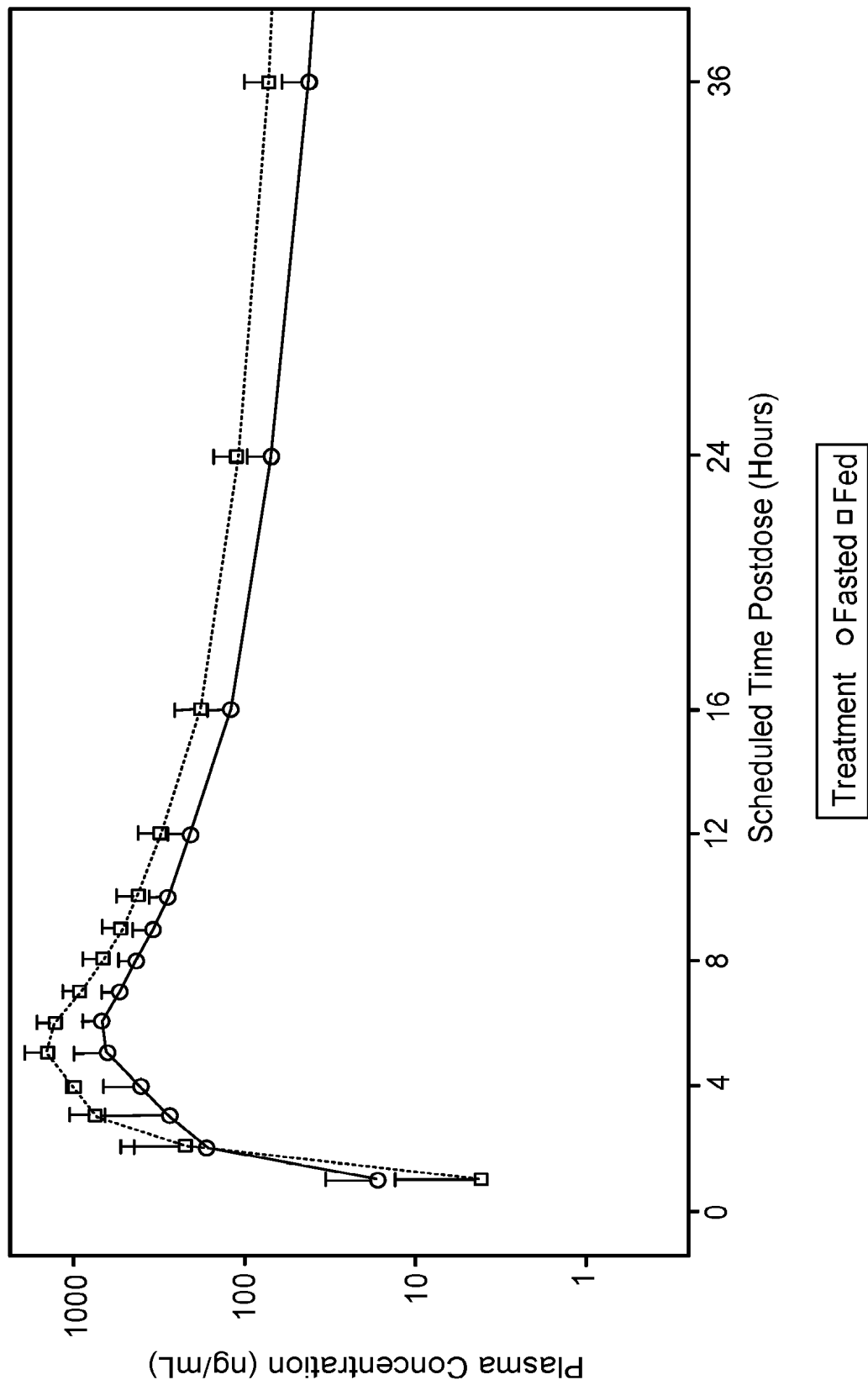


FIG. 8B

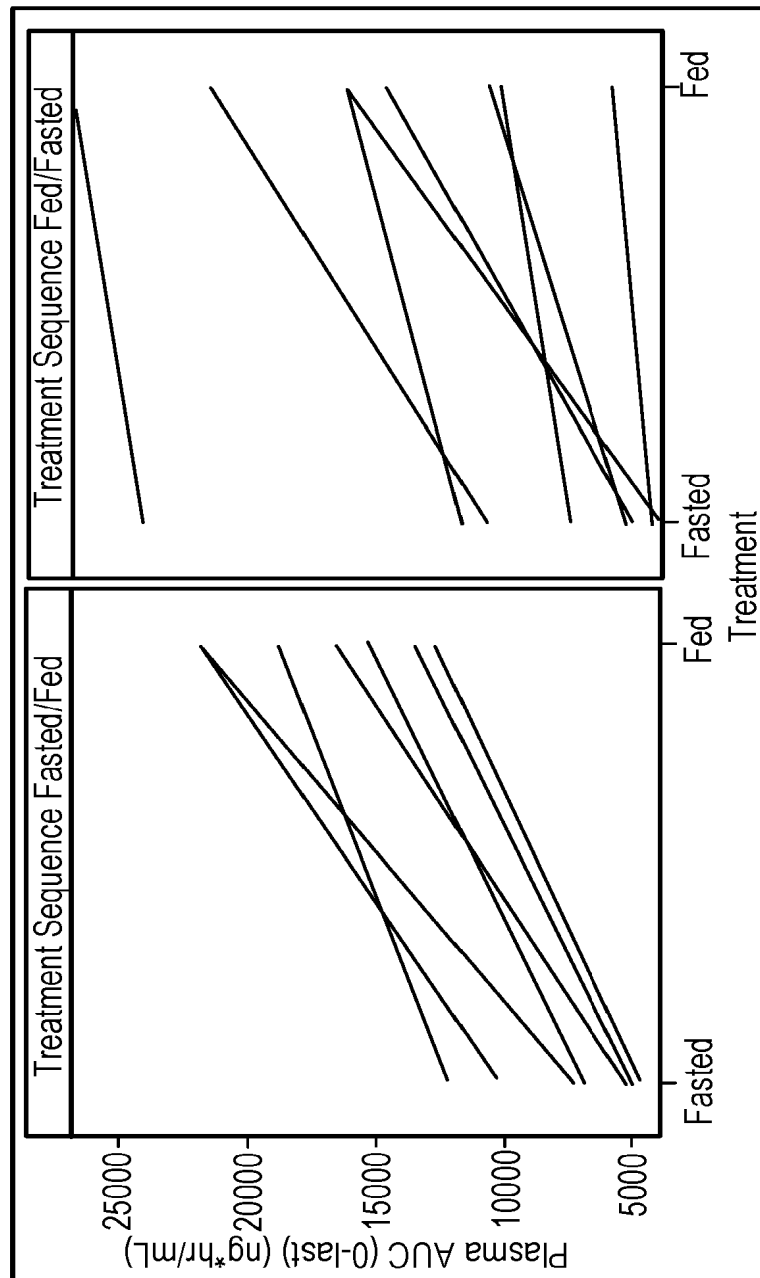


FIG. 9A

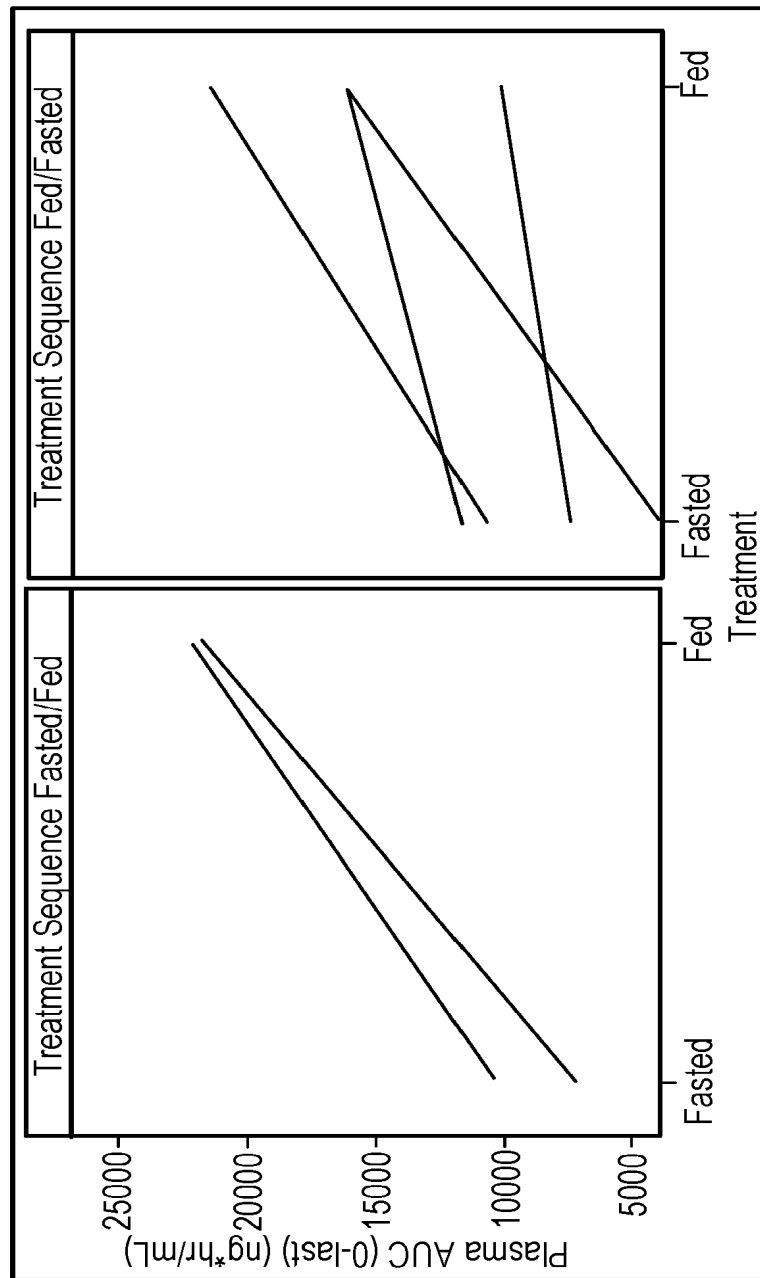


FIG. 9B

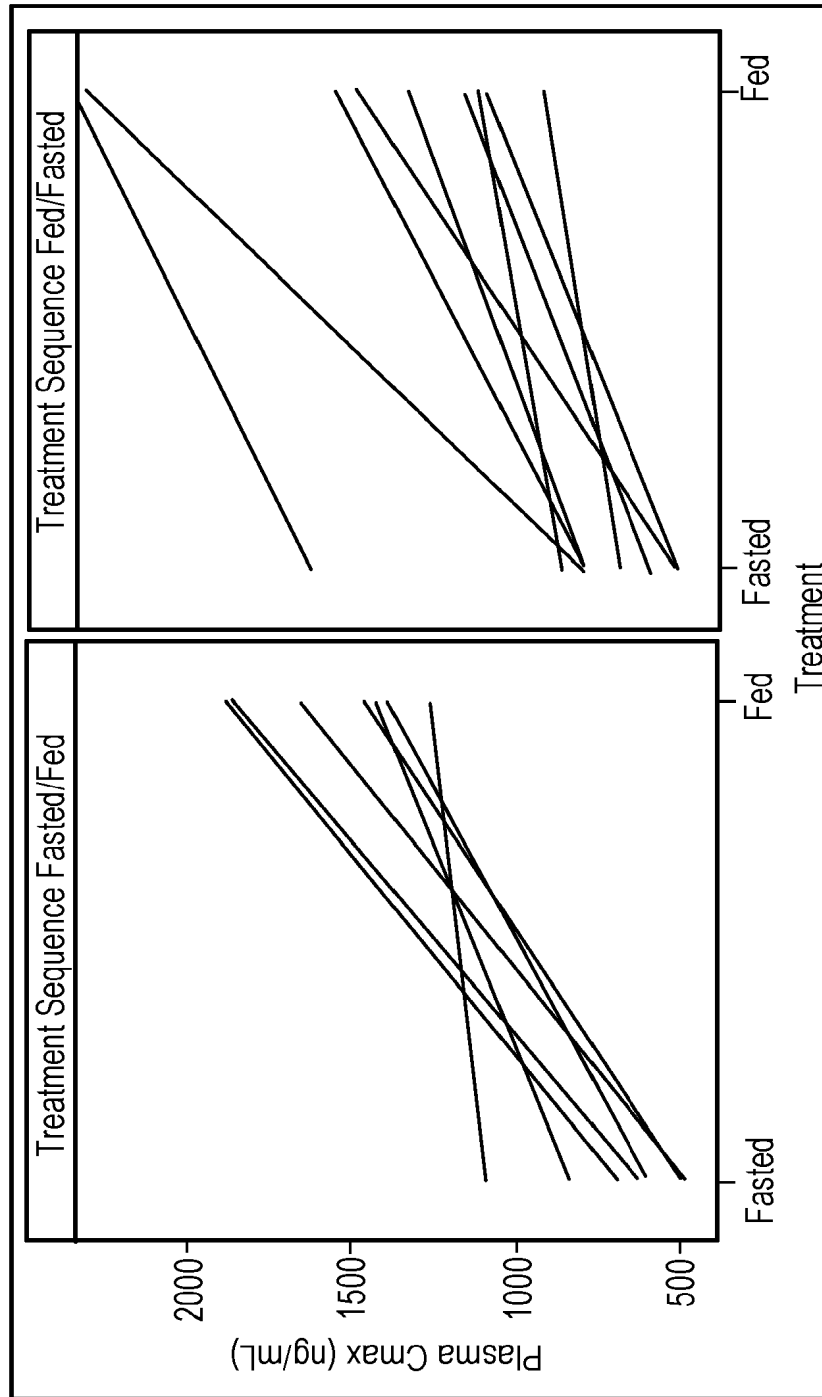
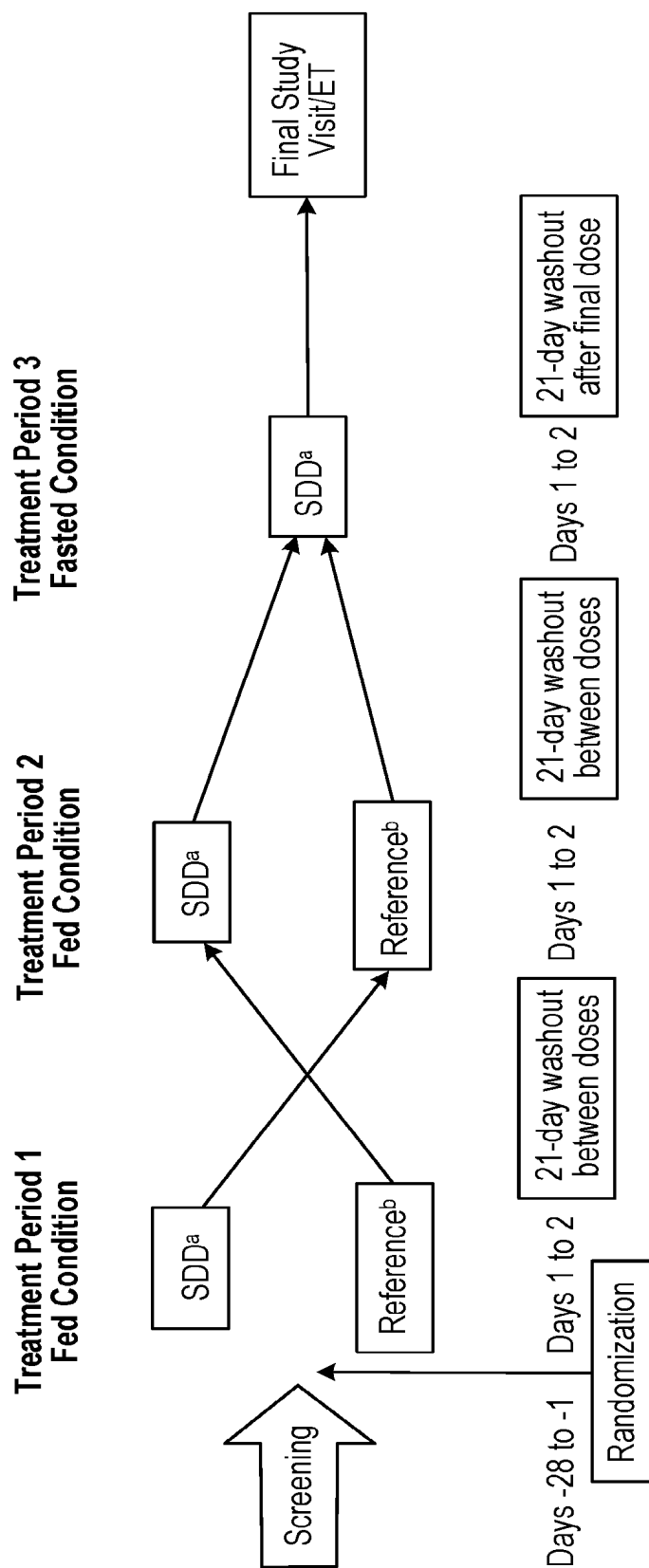


FIG. 9C



a SDD=Compound of Formula (I) spray dried dispersion (suspension or capsule formulation).

b Reference formulation=Compound of Formula (I) encapsulated, lipid semi-solid.

FIG. 10

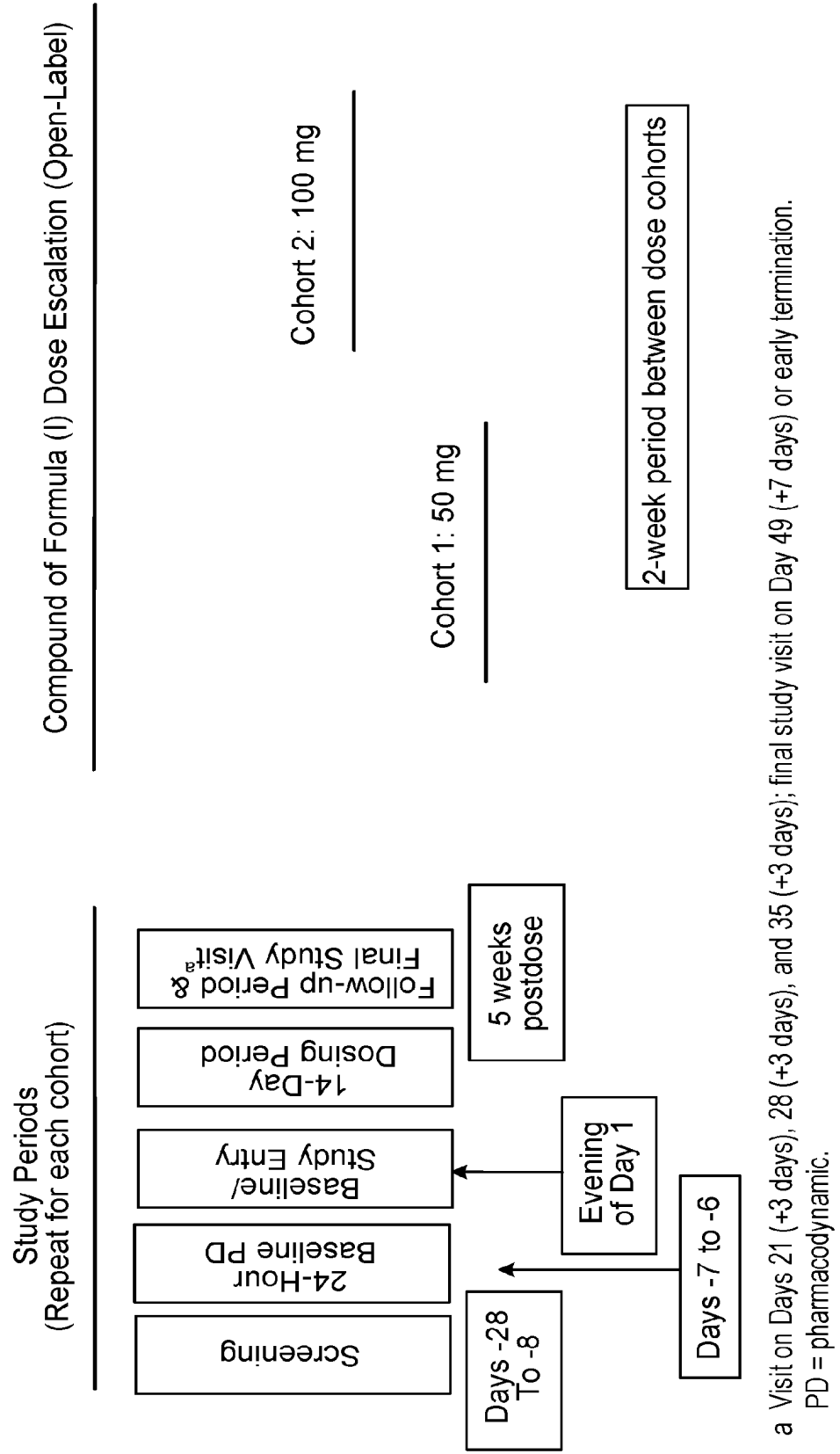


FIG. 11

ACTH -- Average All Subjects

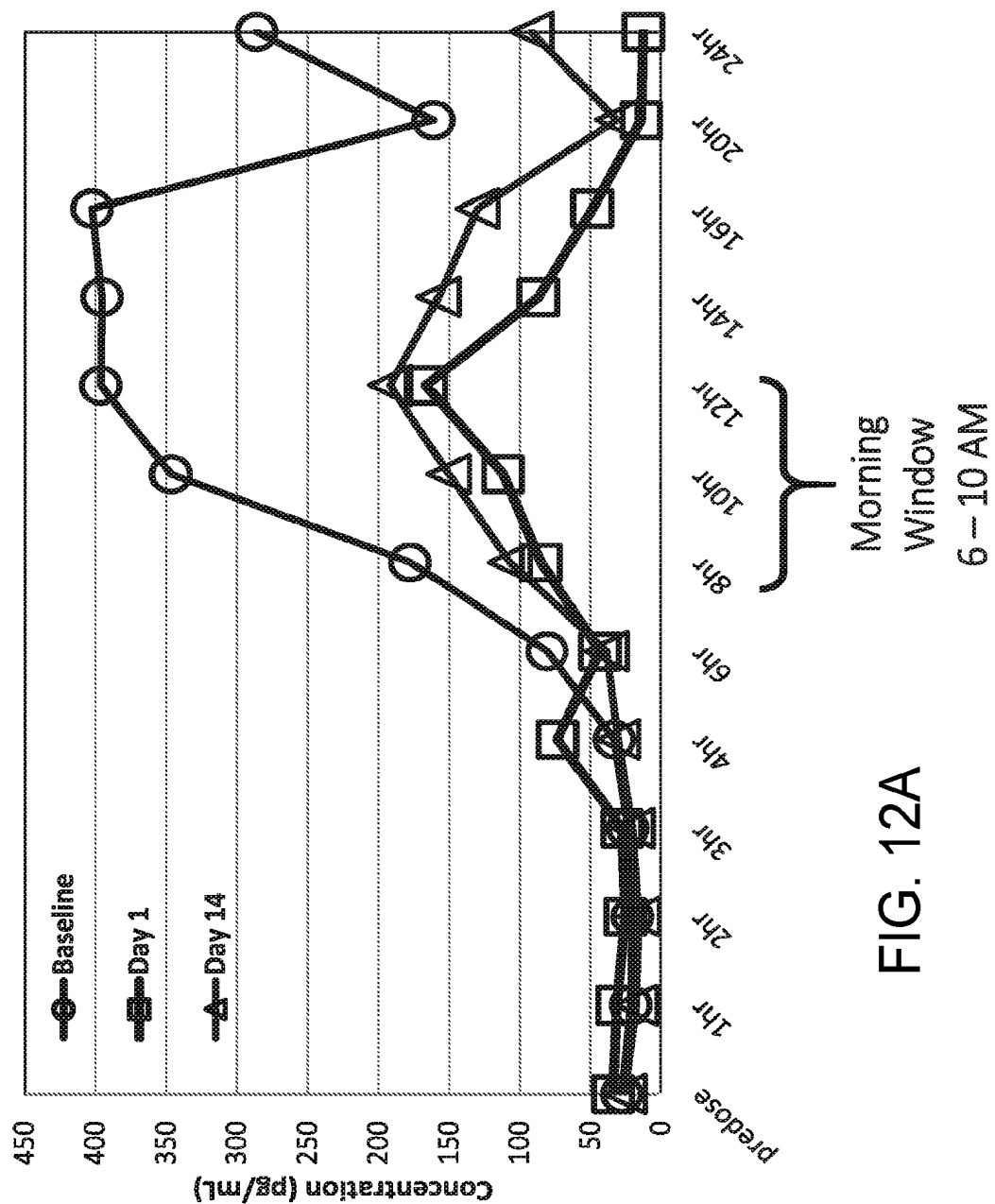


FIG. 12A

17-OHP -- Average All Subjects

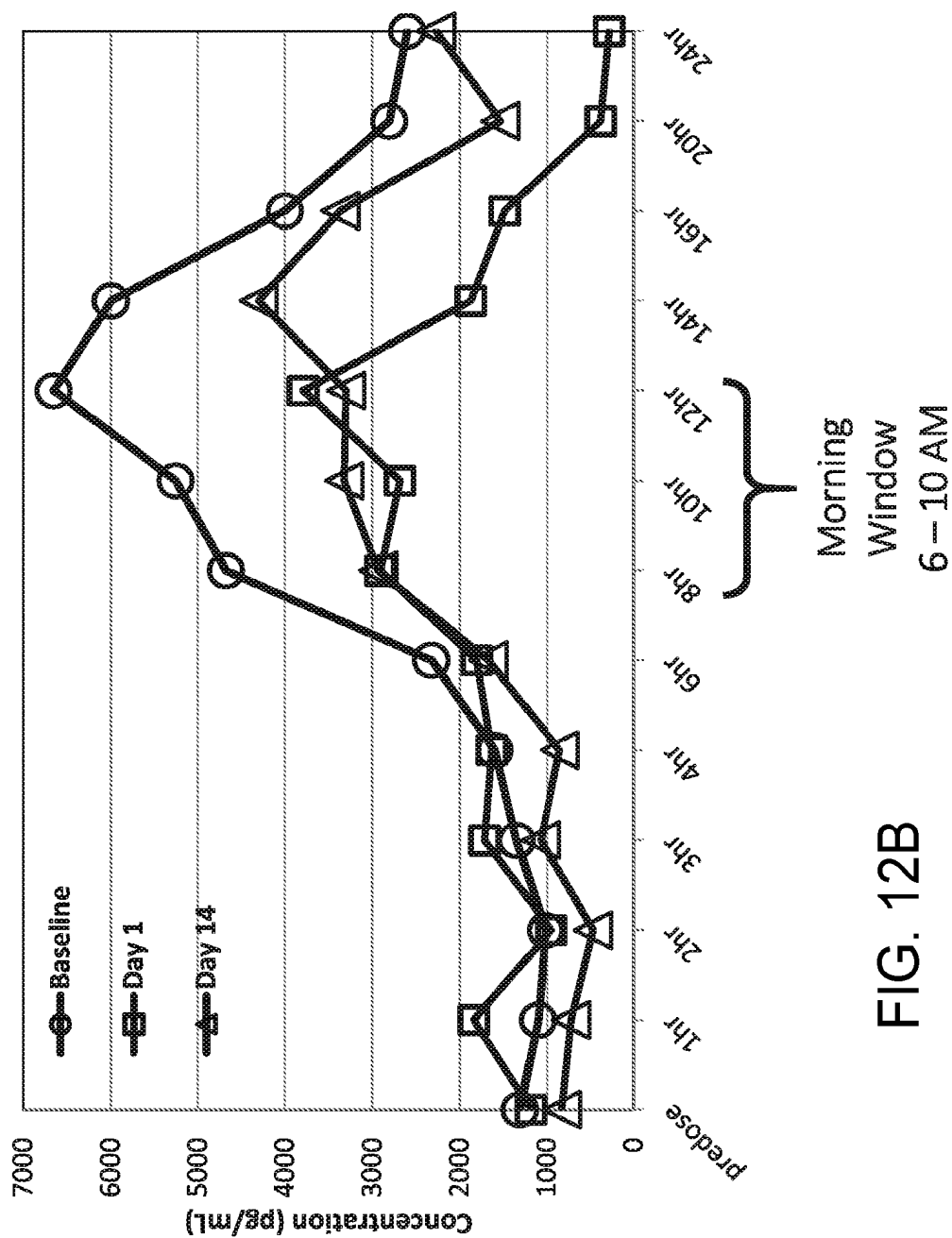


FIG. 12B

Androstenedione -- Average All Subjects

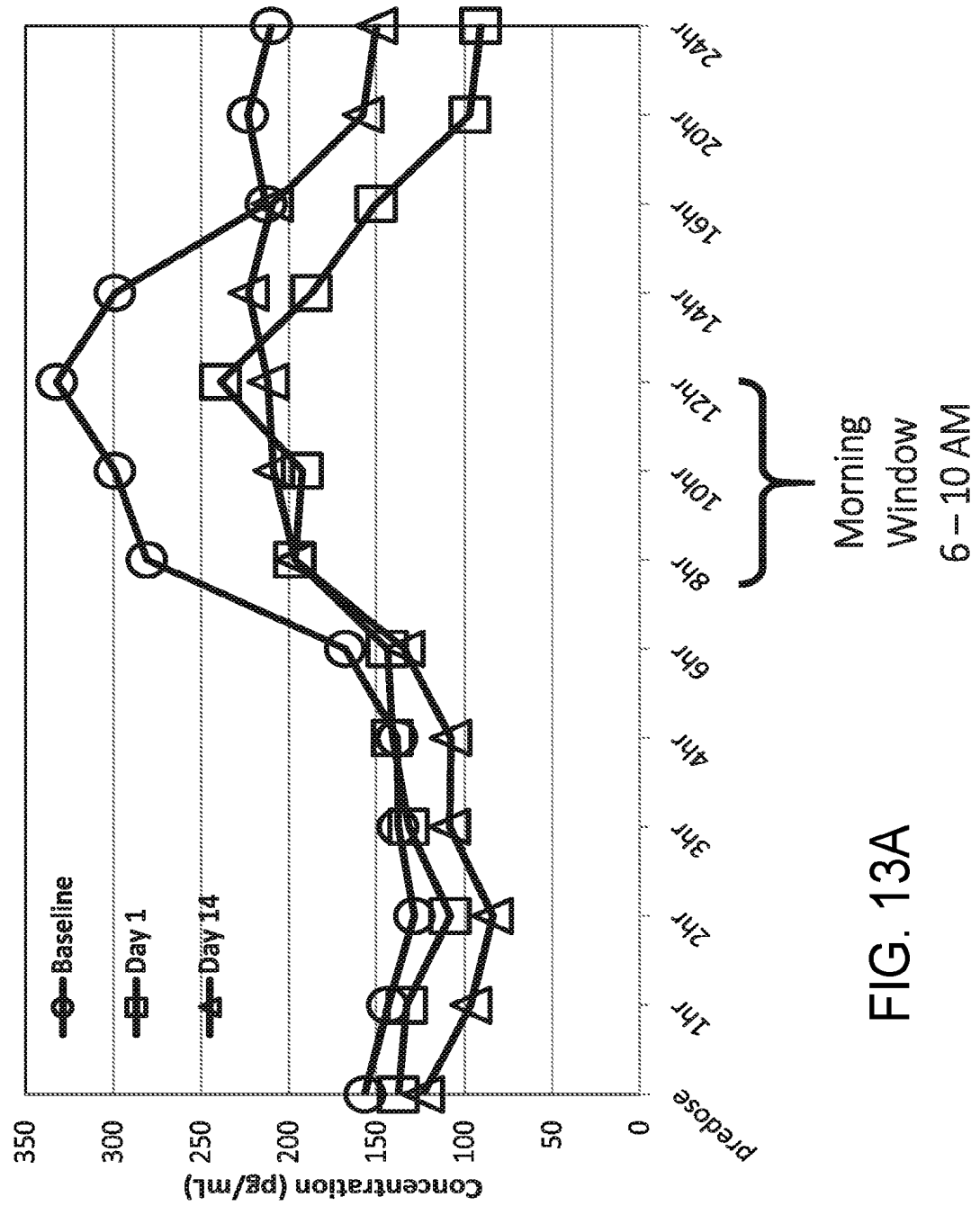


FIG. 13A

Testosterone -- Average All Subjects

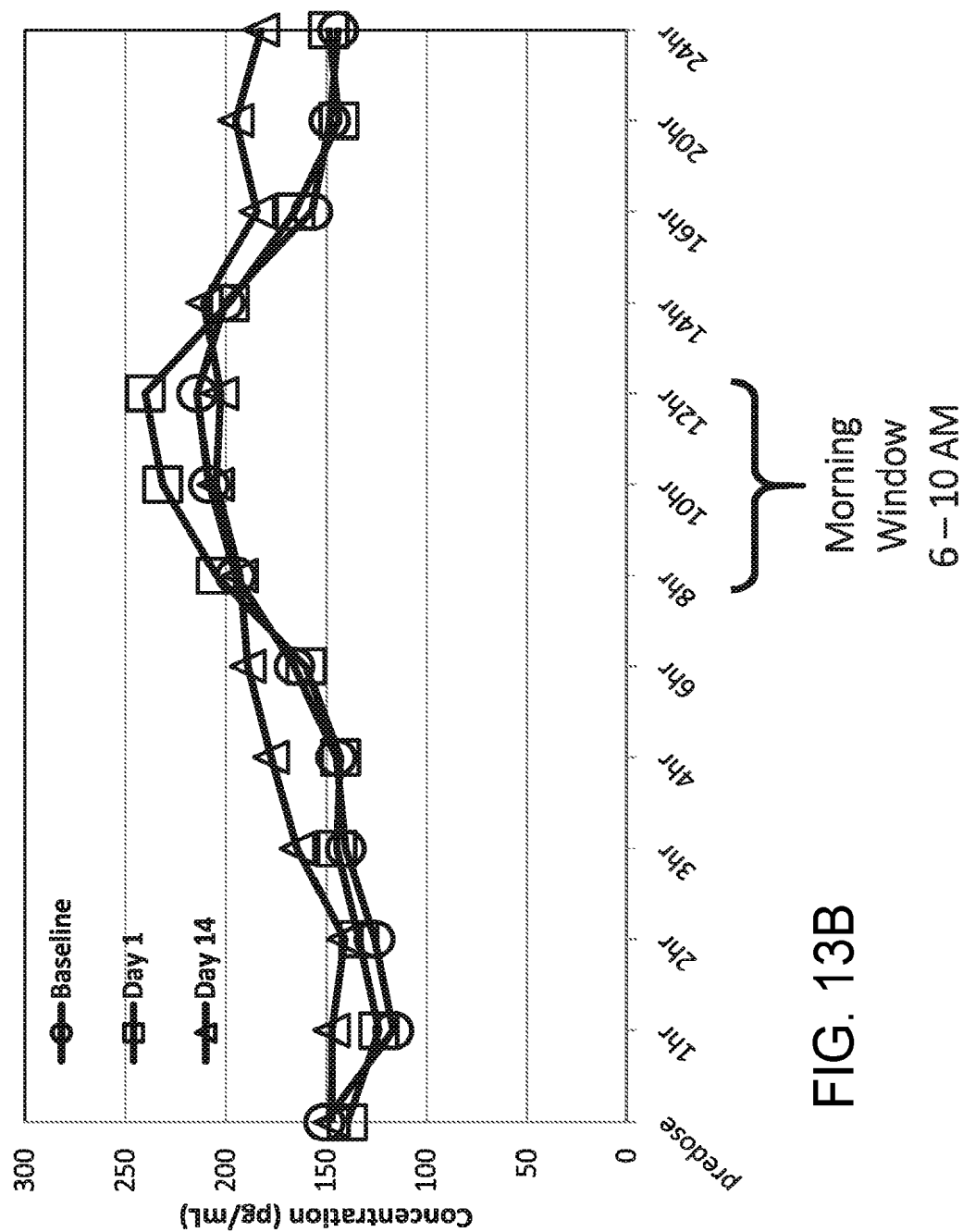


FIG. 13B

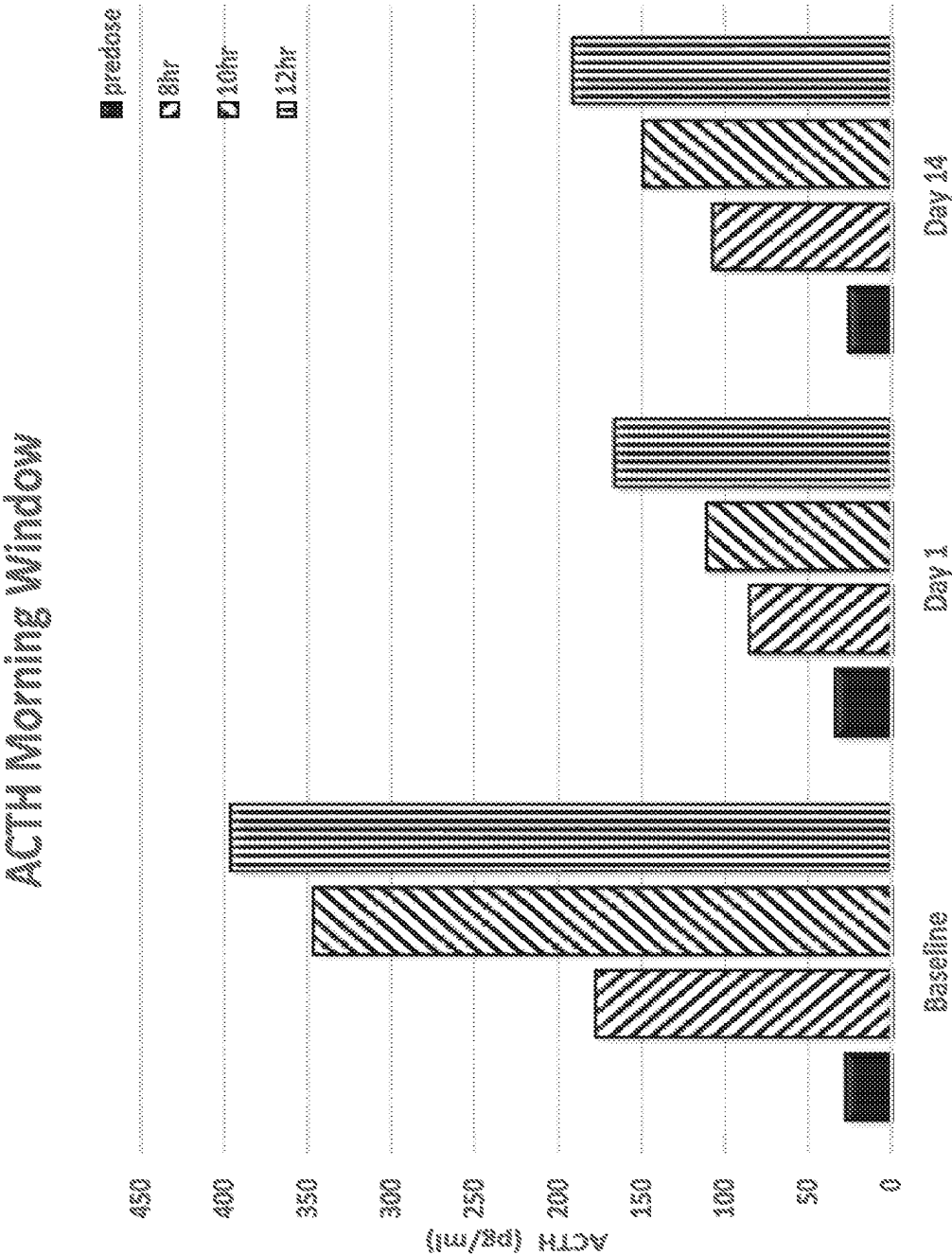


FIG. 14A

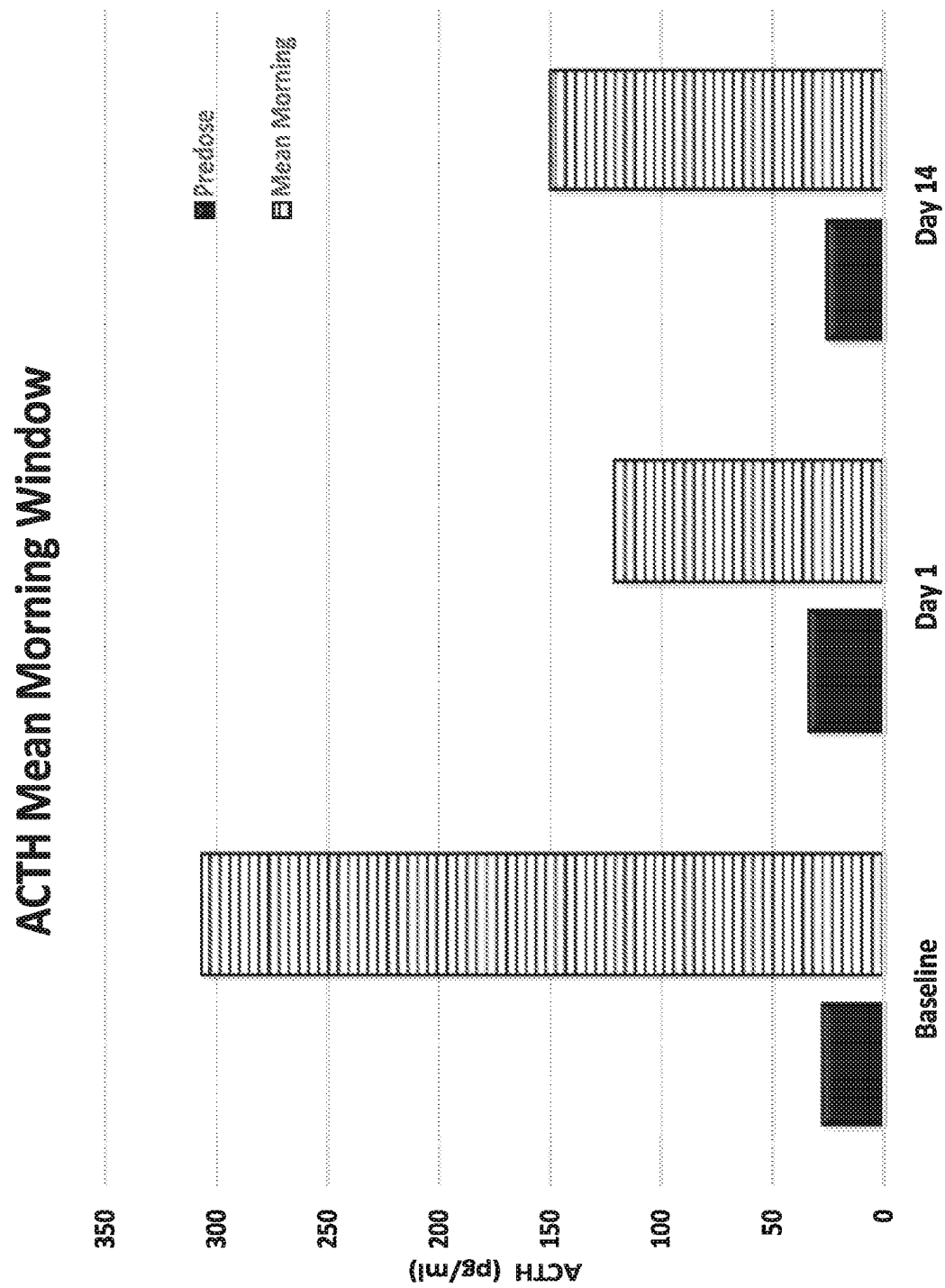


FIG. 14B

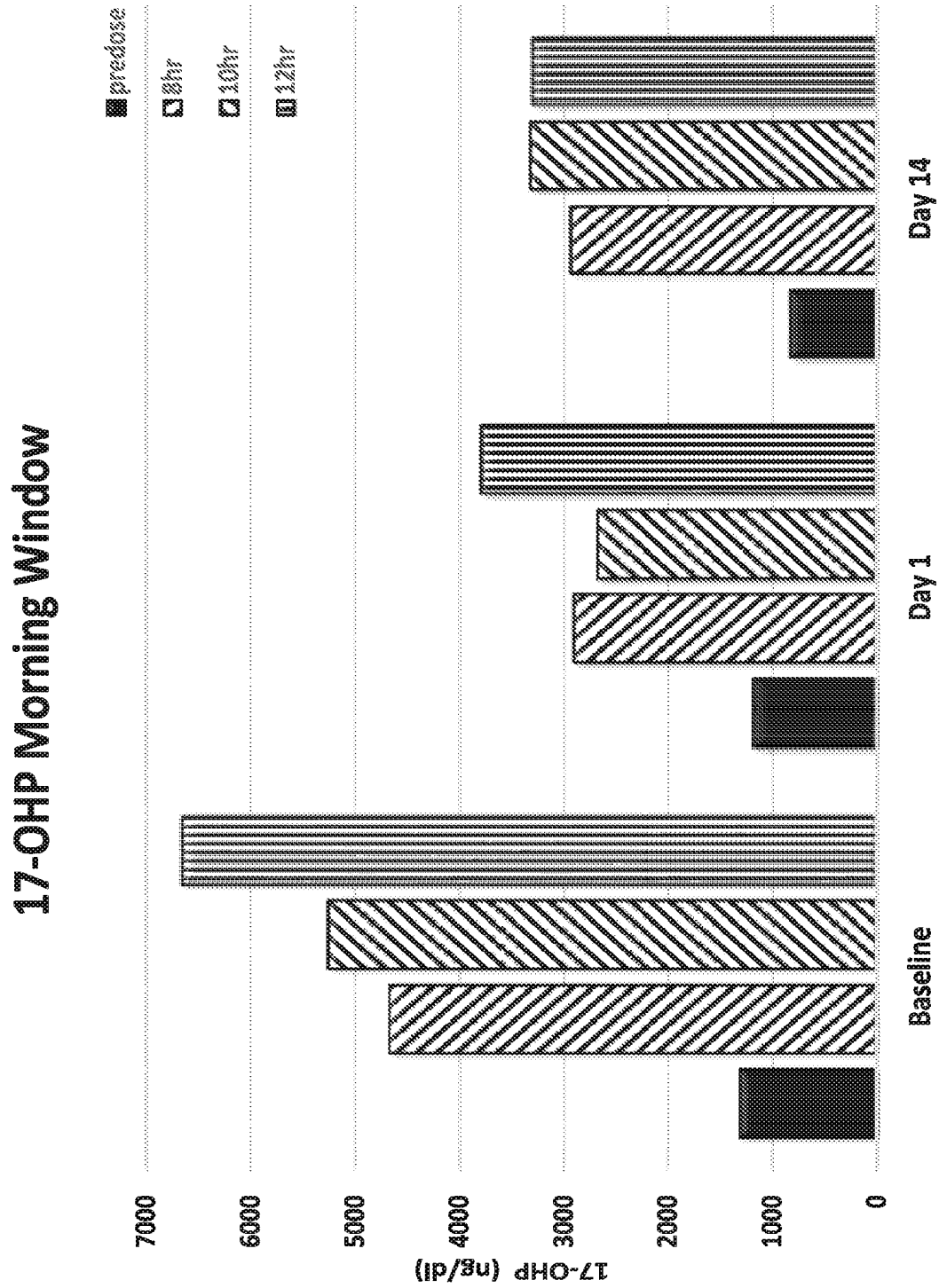


FIG. 15A

17-OHP Mean Morning Window

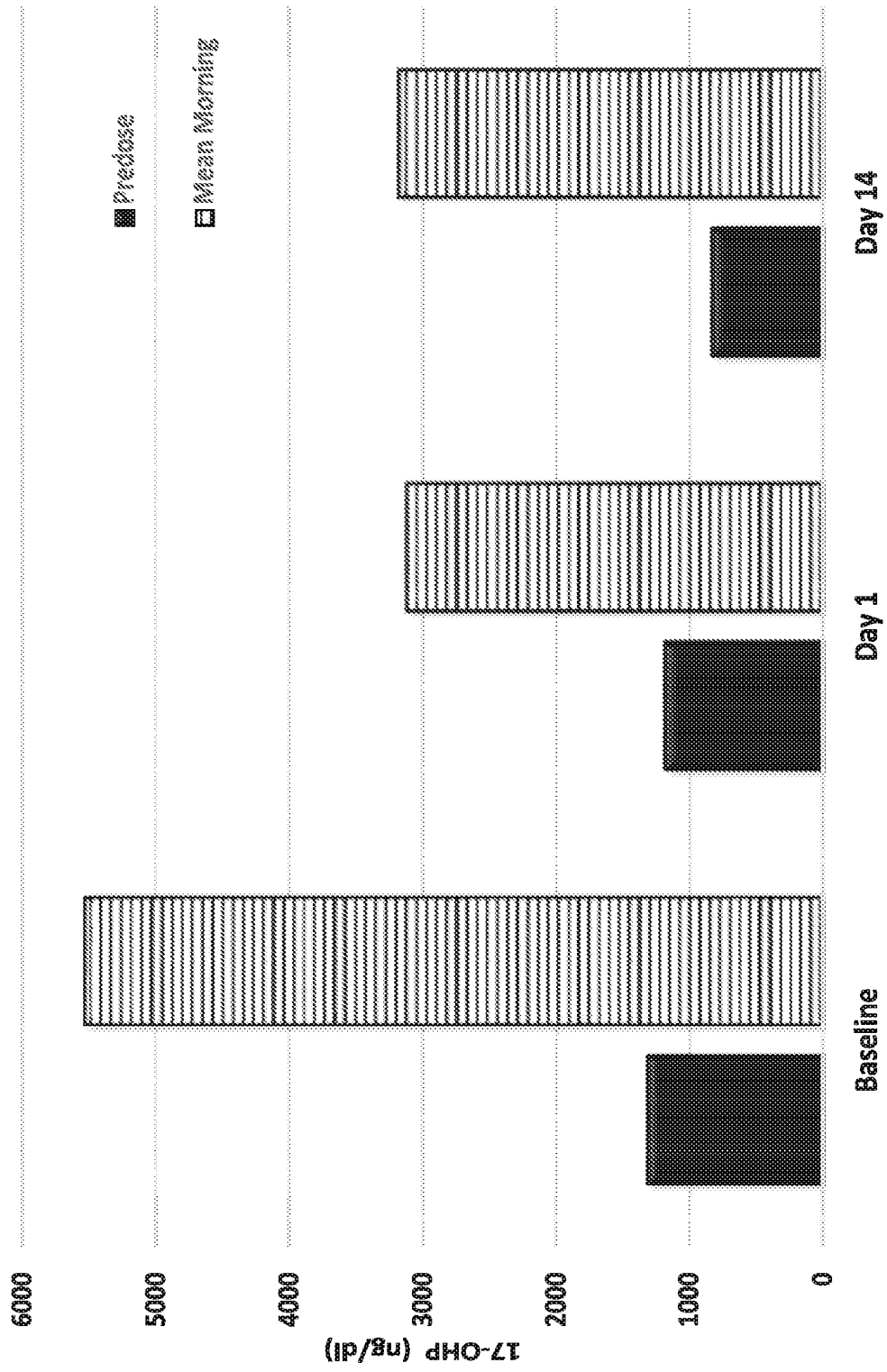


FIG. 15B

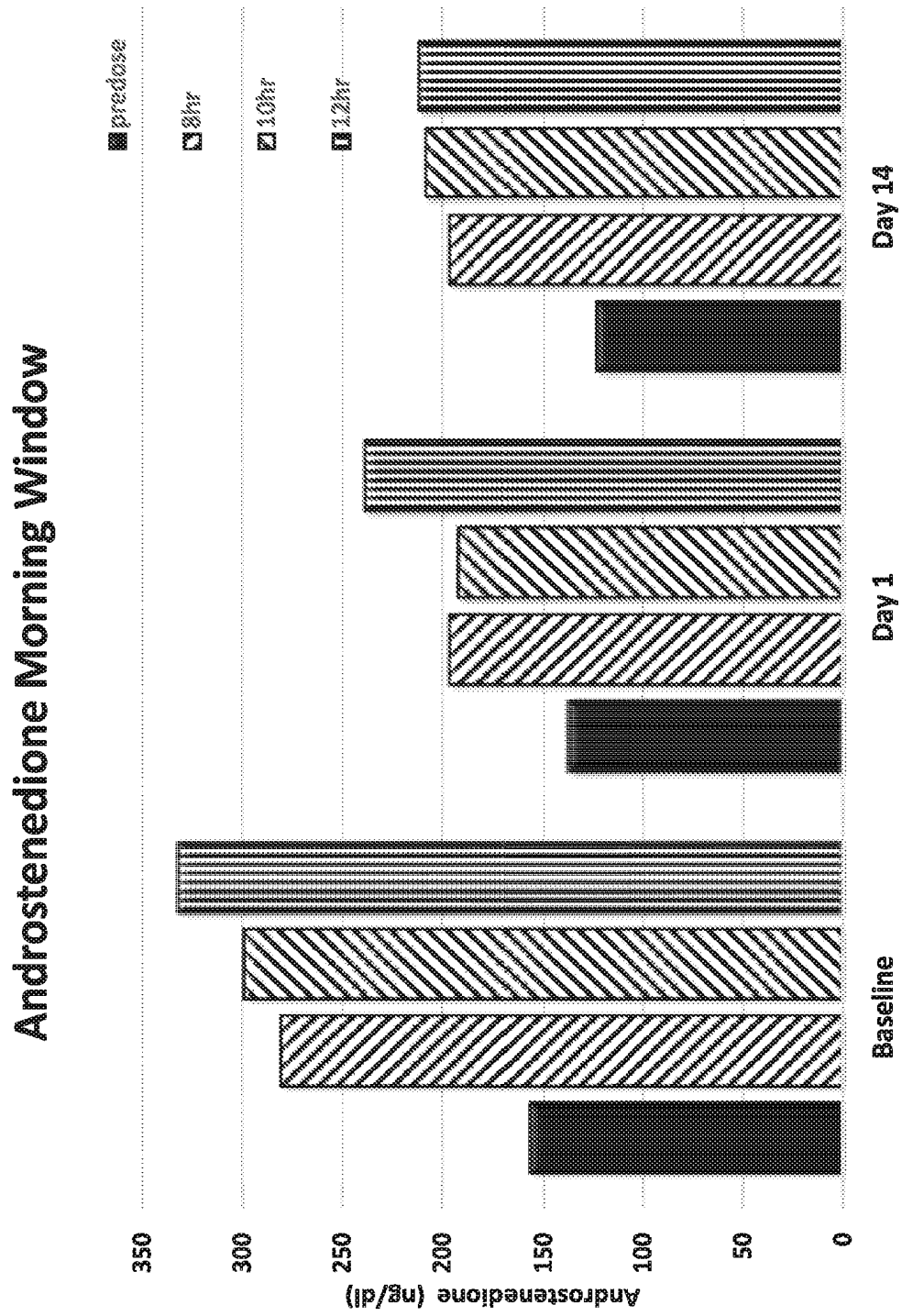


FIG. 16A

Androstenedione Mean Morning Window

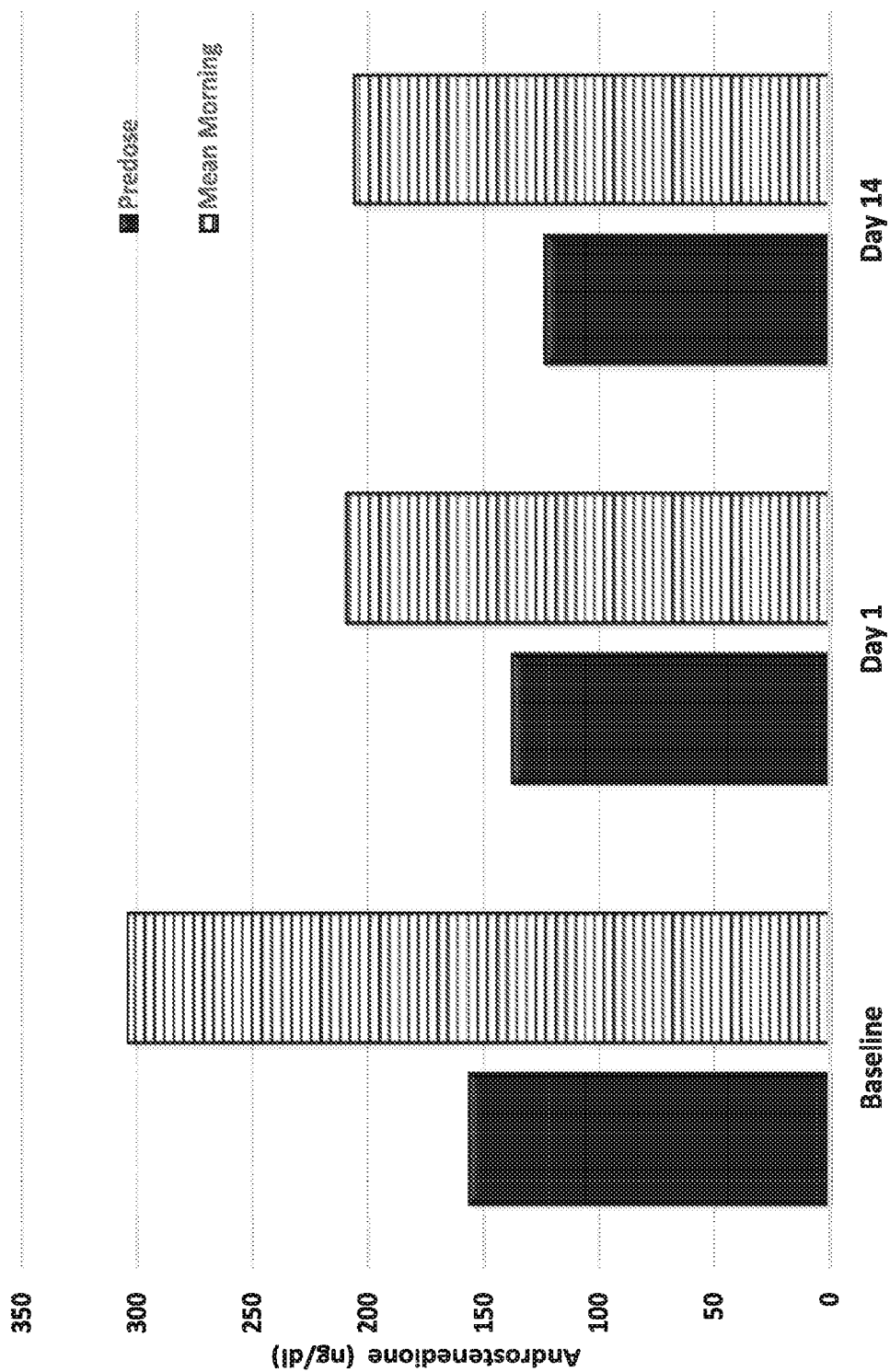


FIG. 16B

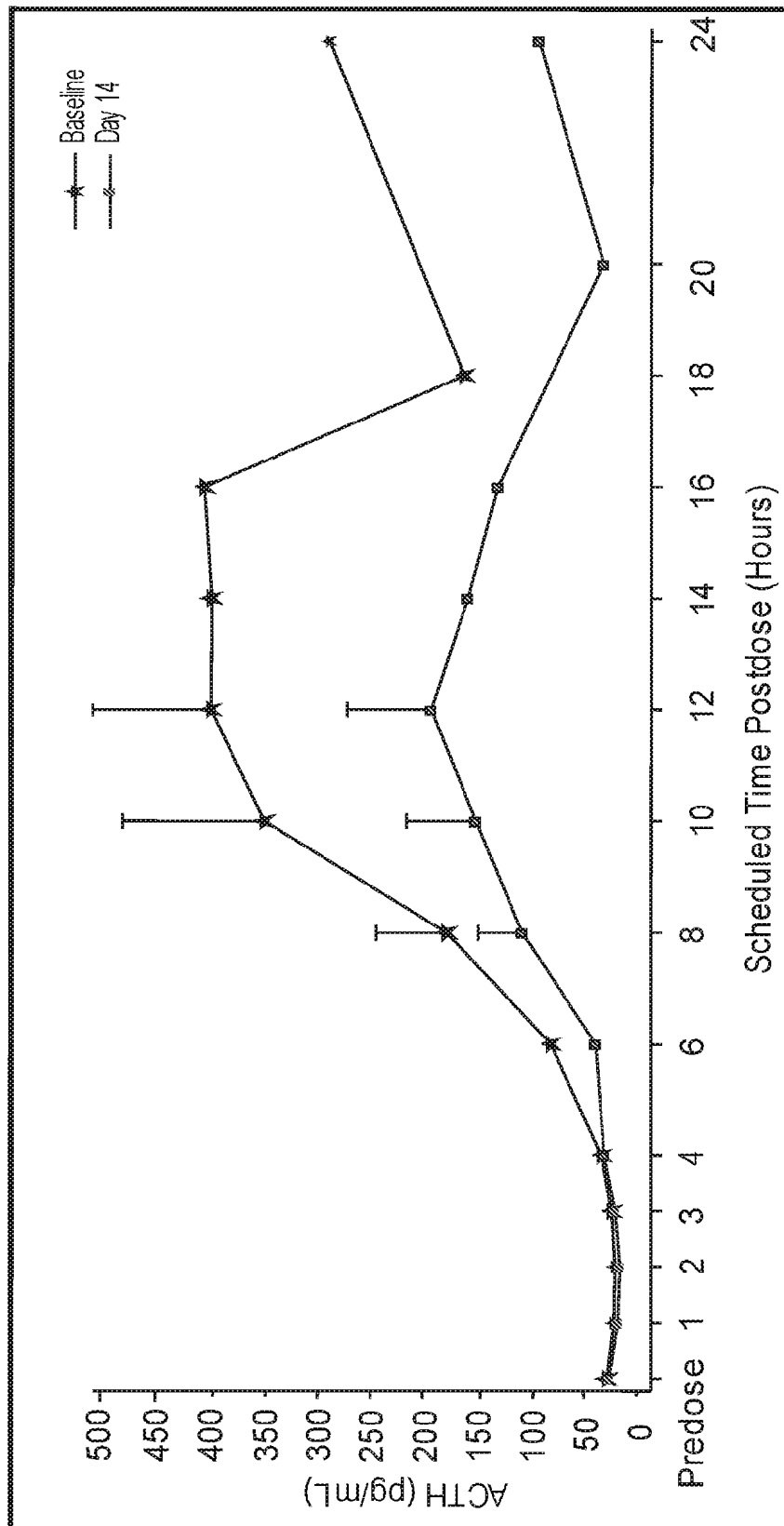


FIG. 17A

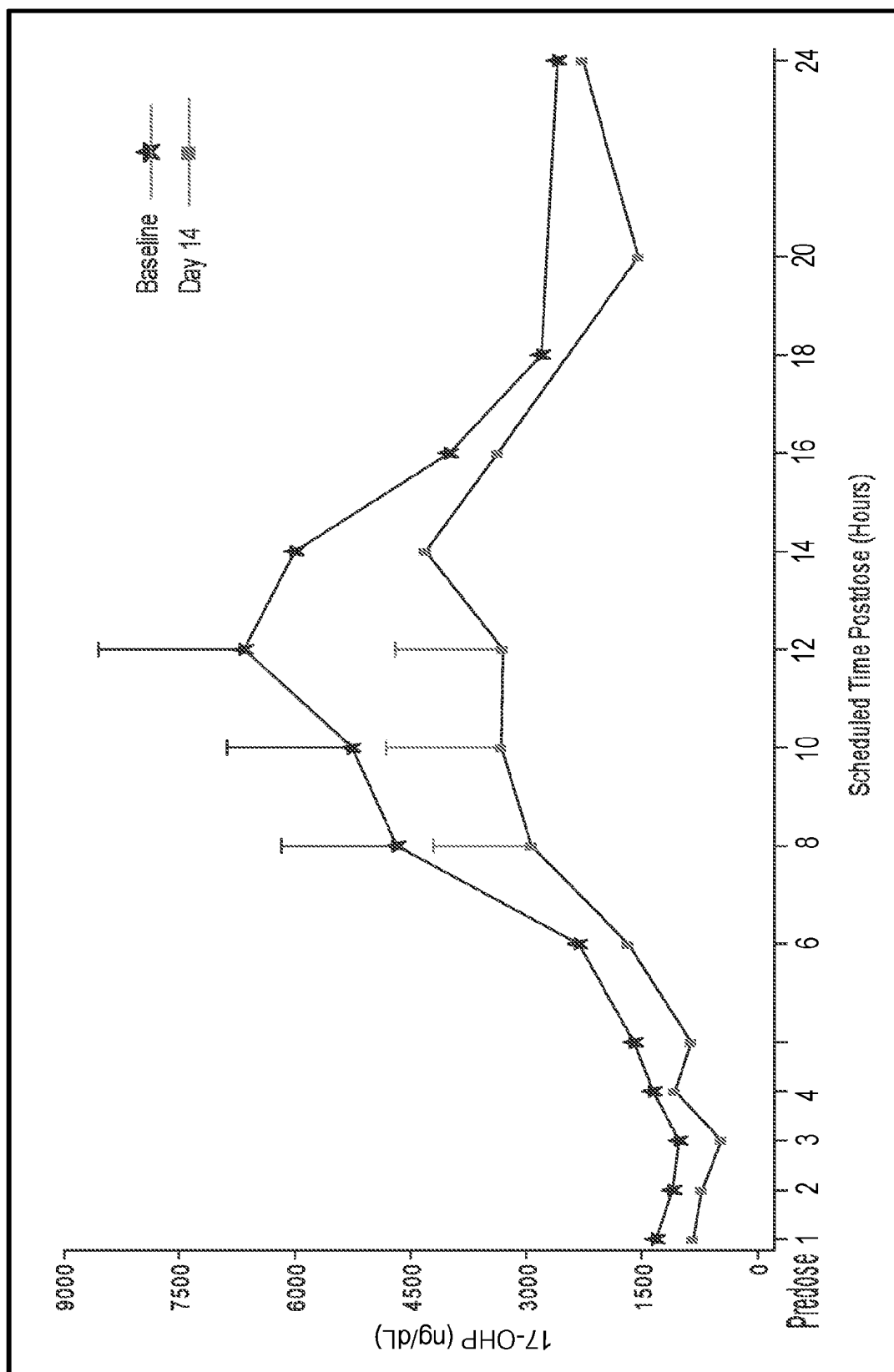


FIG. 17B

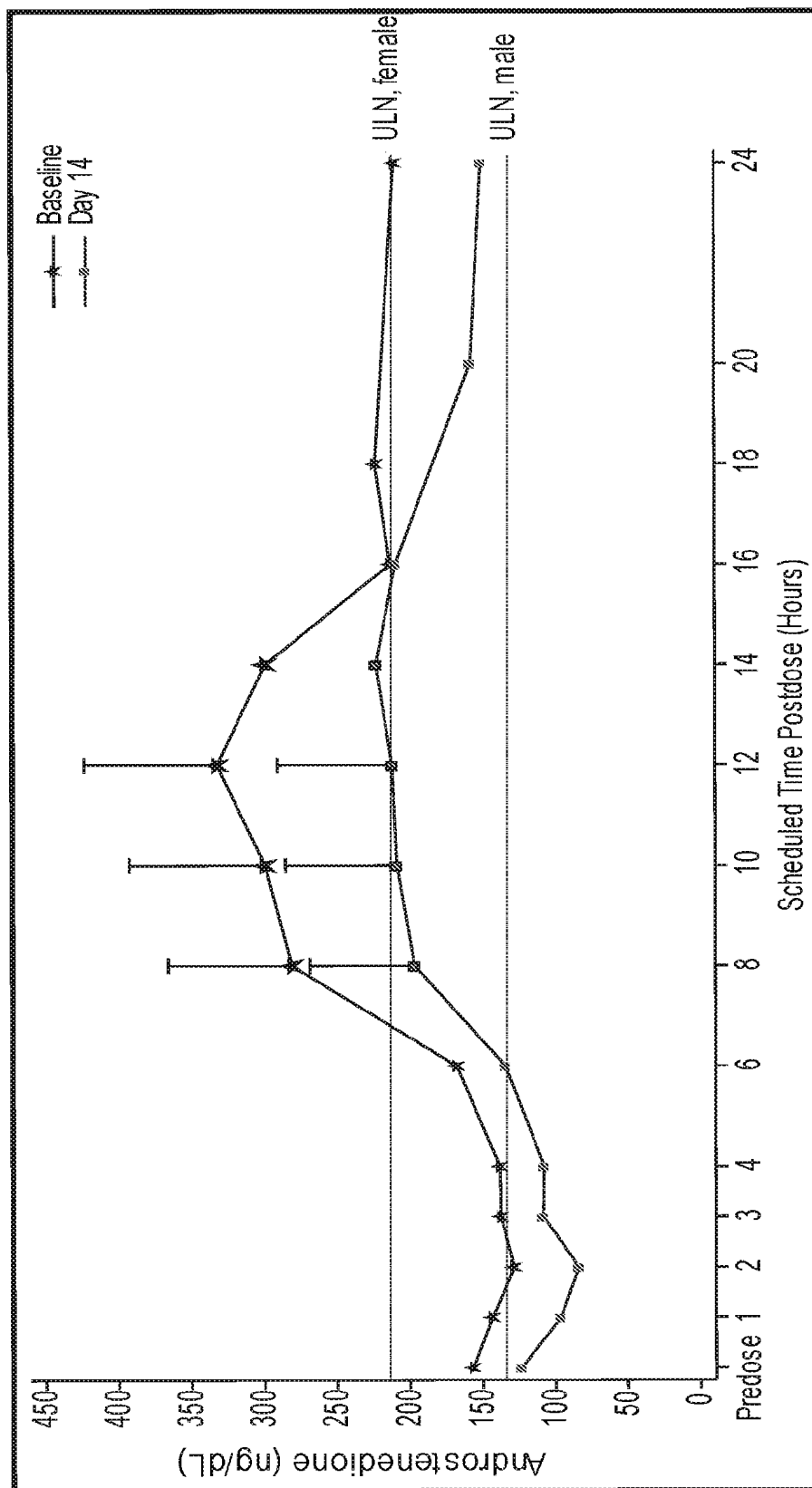


FIG. 17C

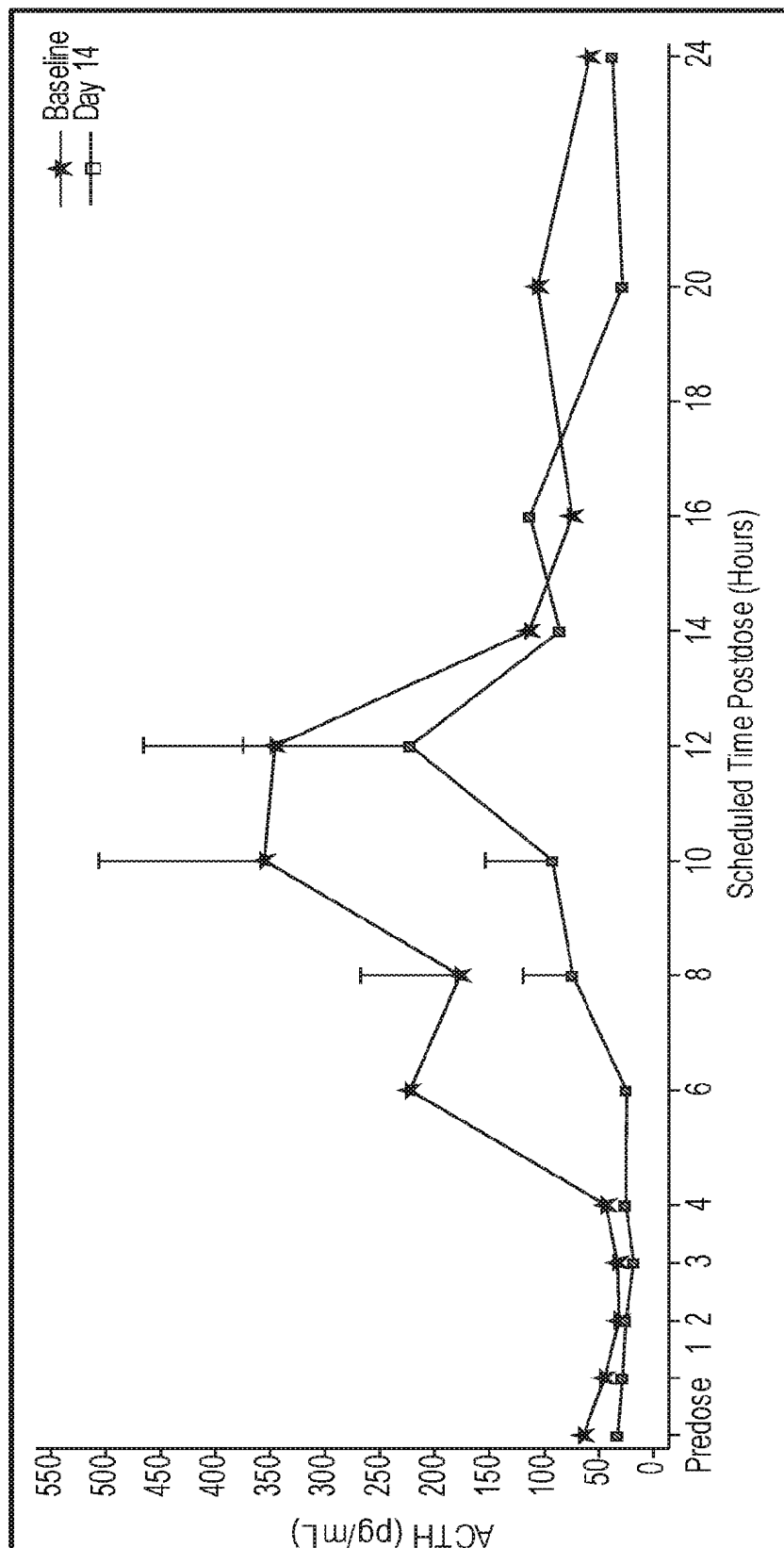


FIG. 18A

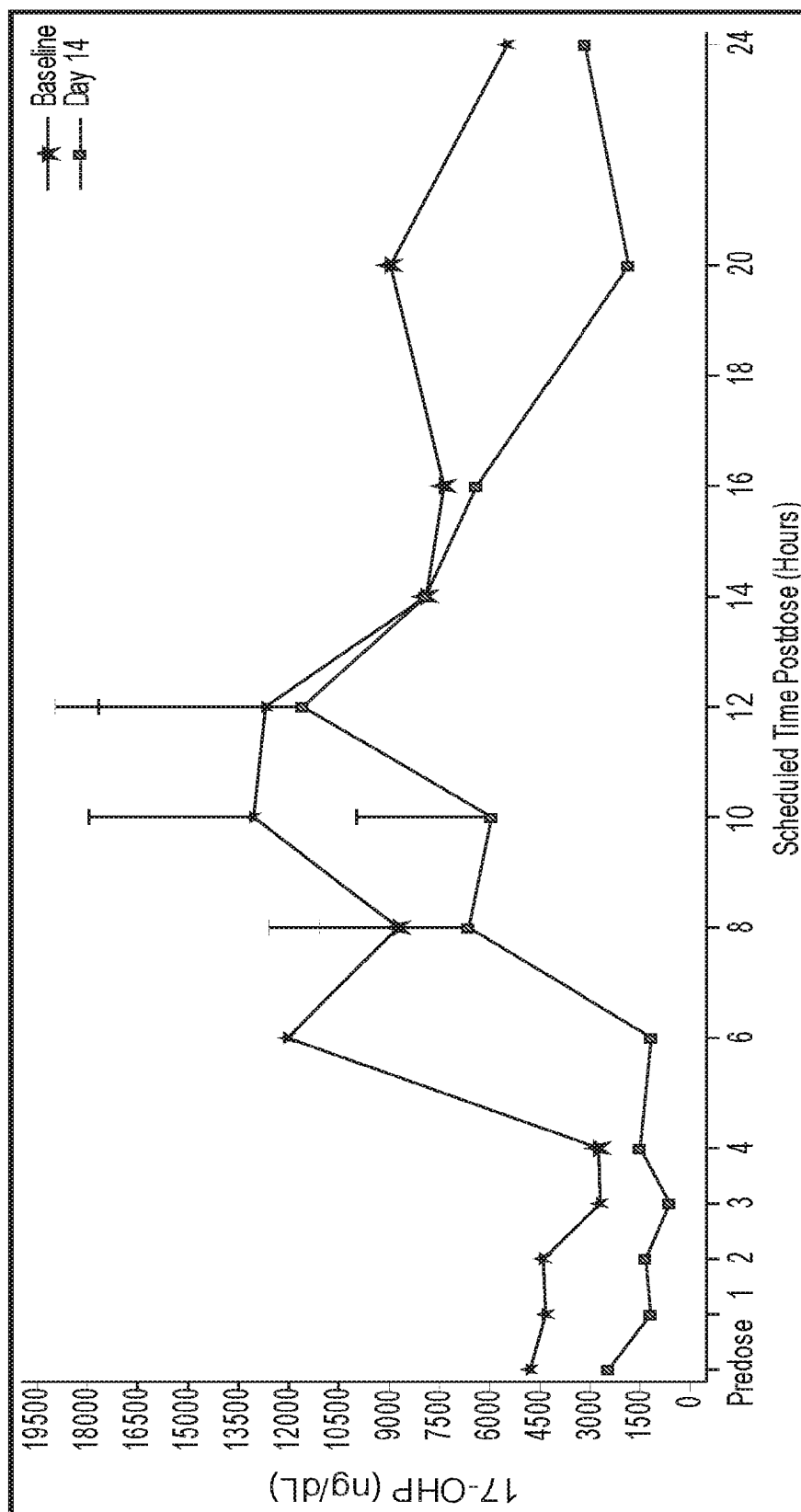


FIG. 18B

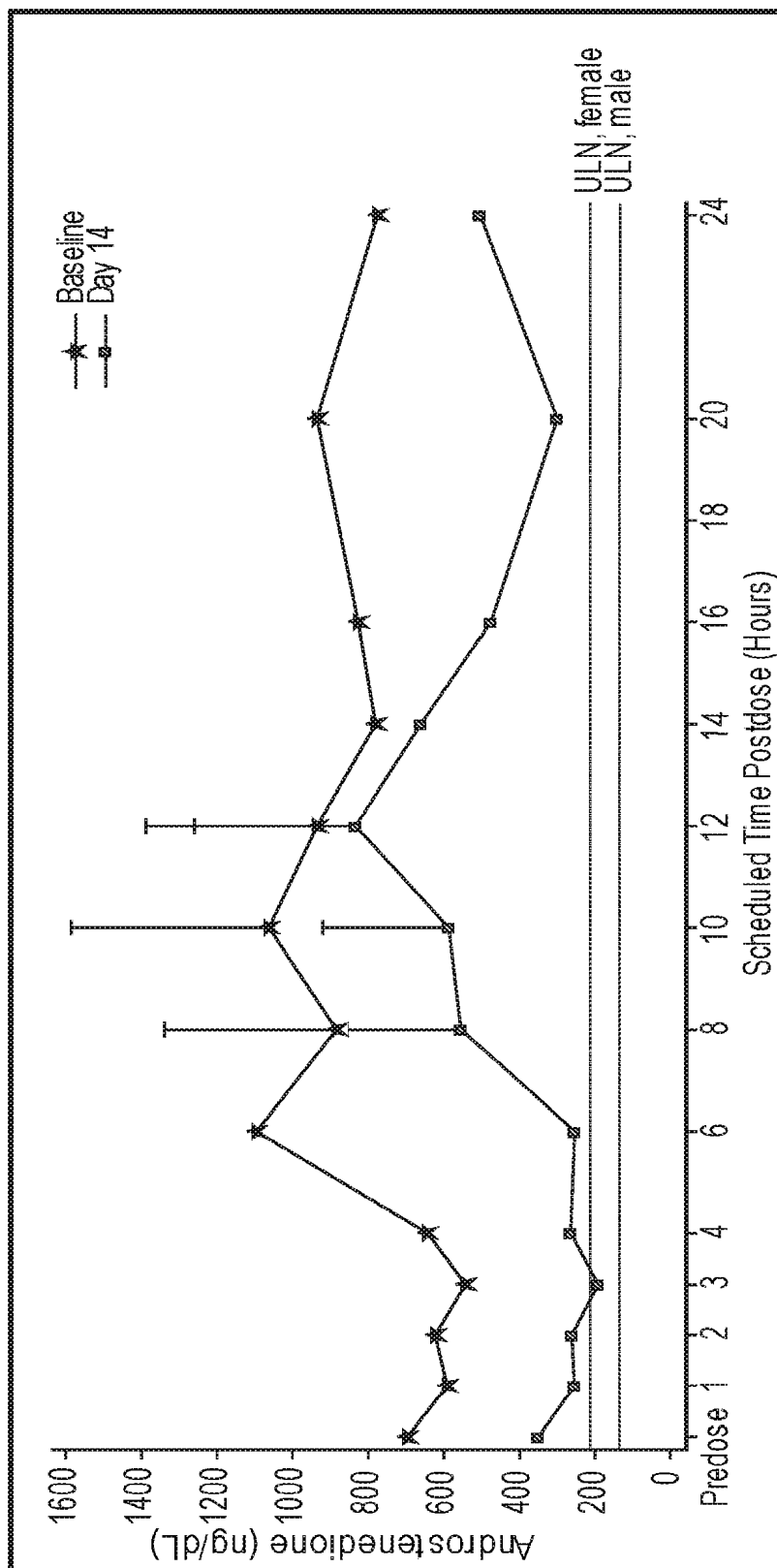


FIG. 18C

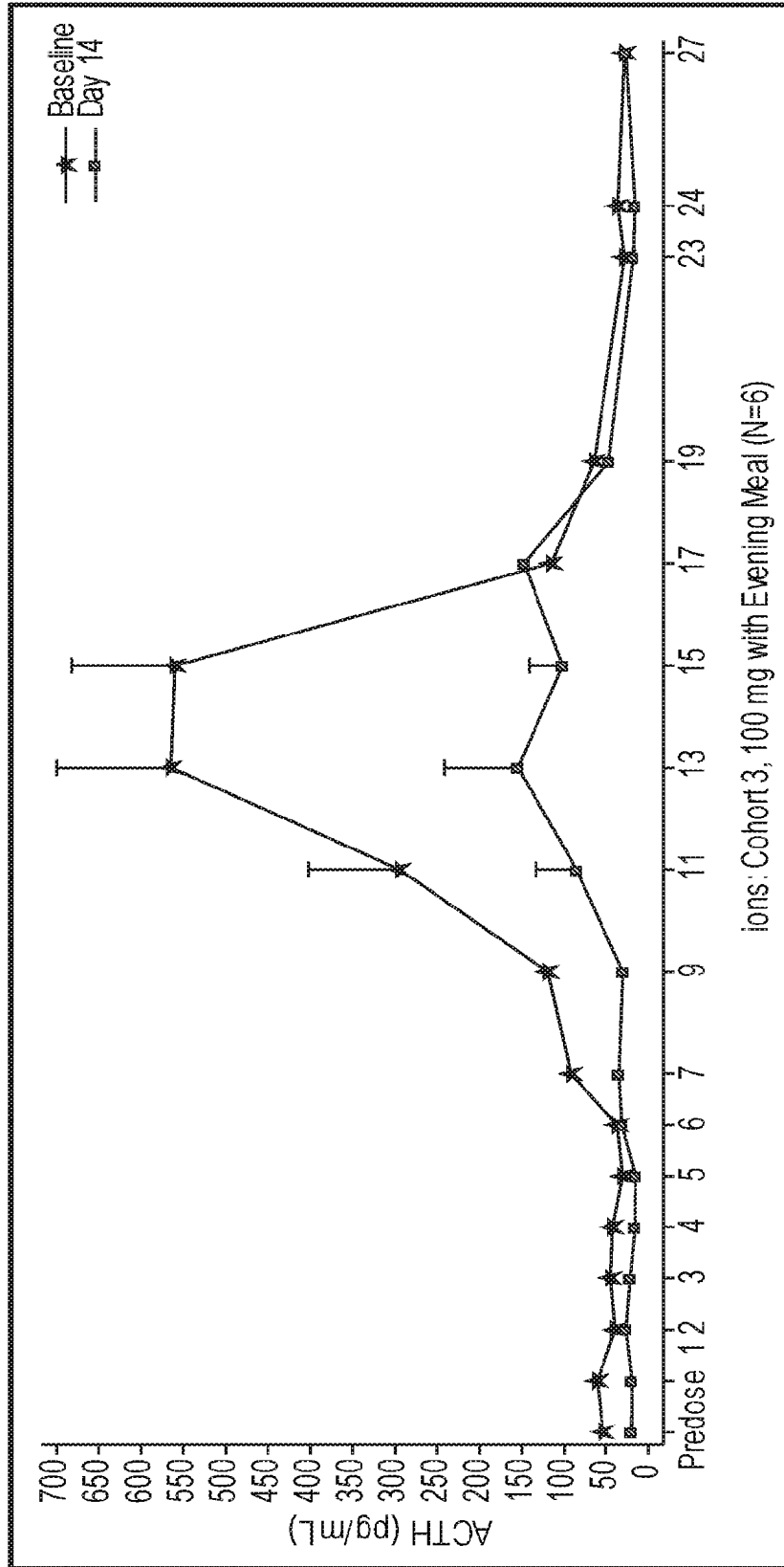


FIG. 19A

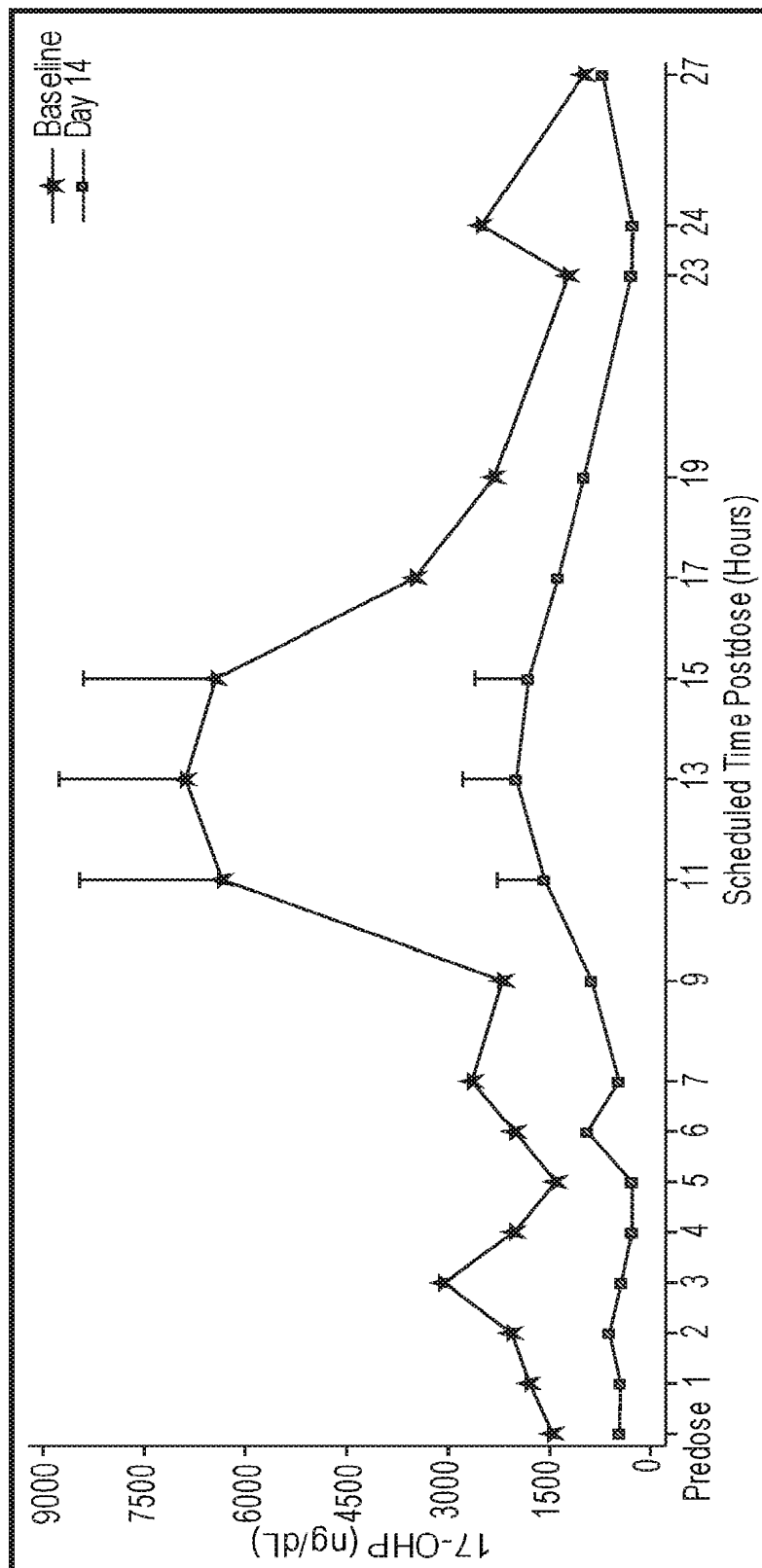


FIG. 19B

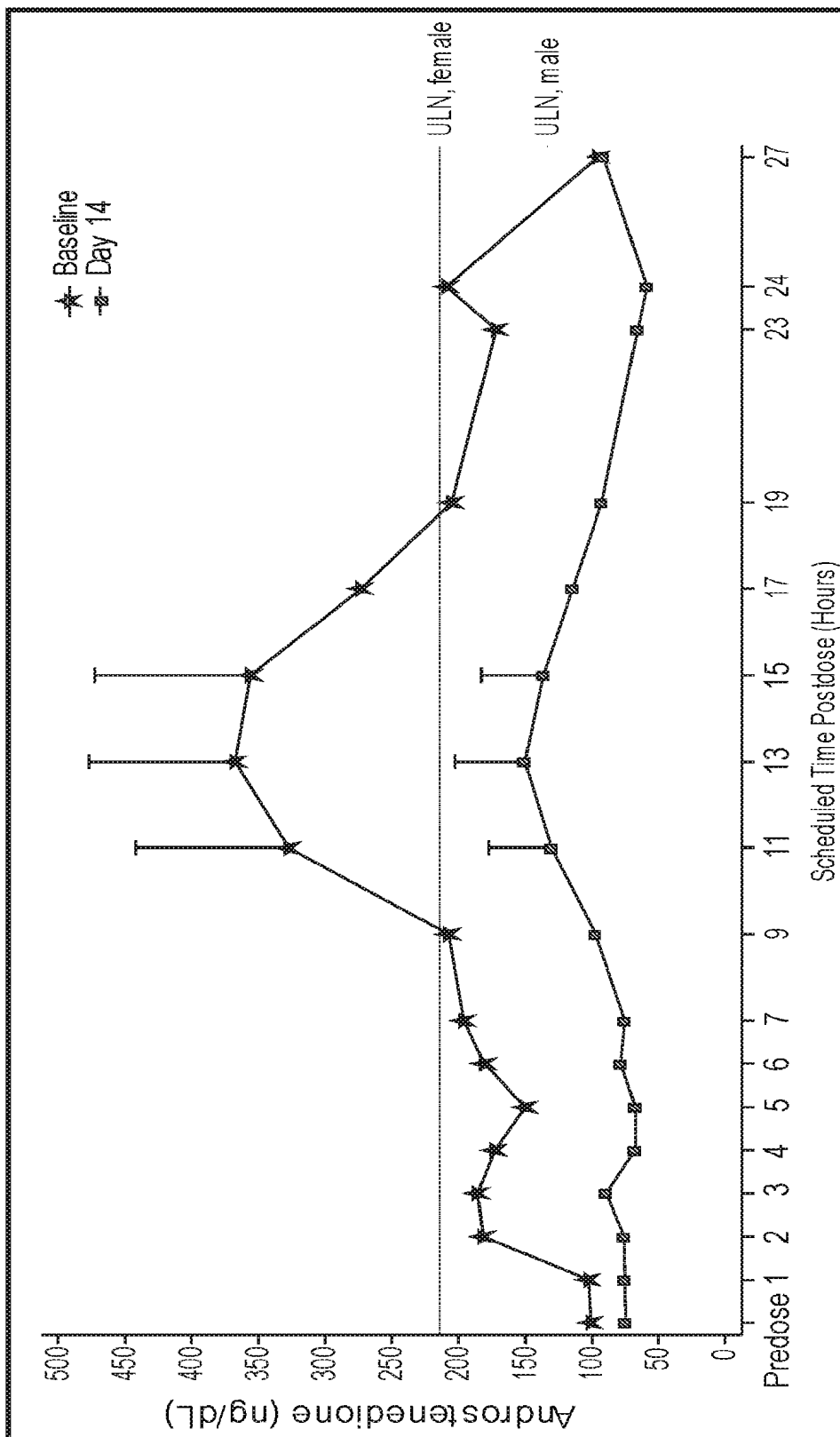


FIG. 19C

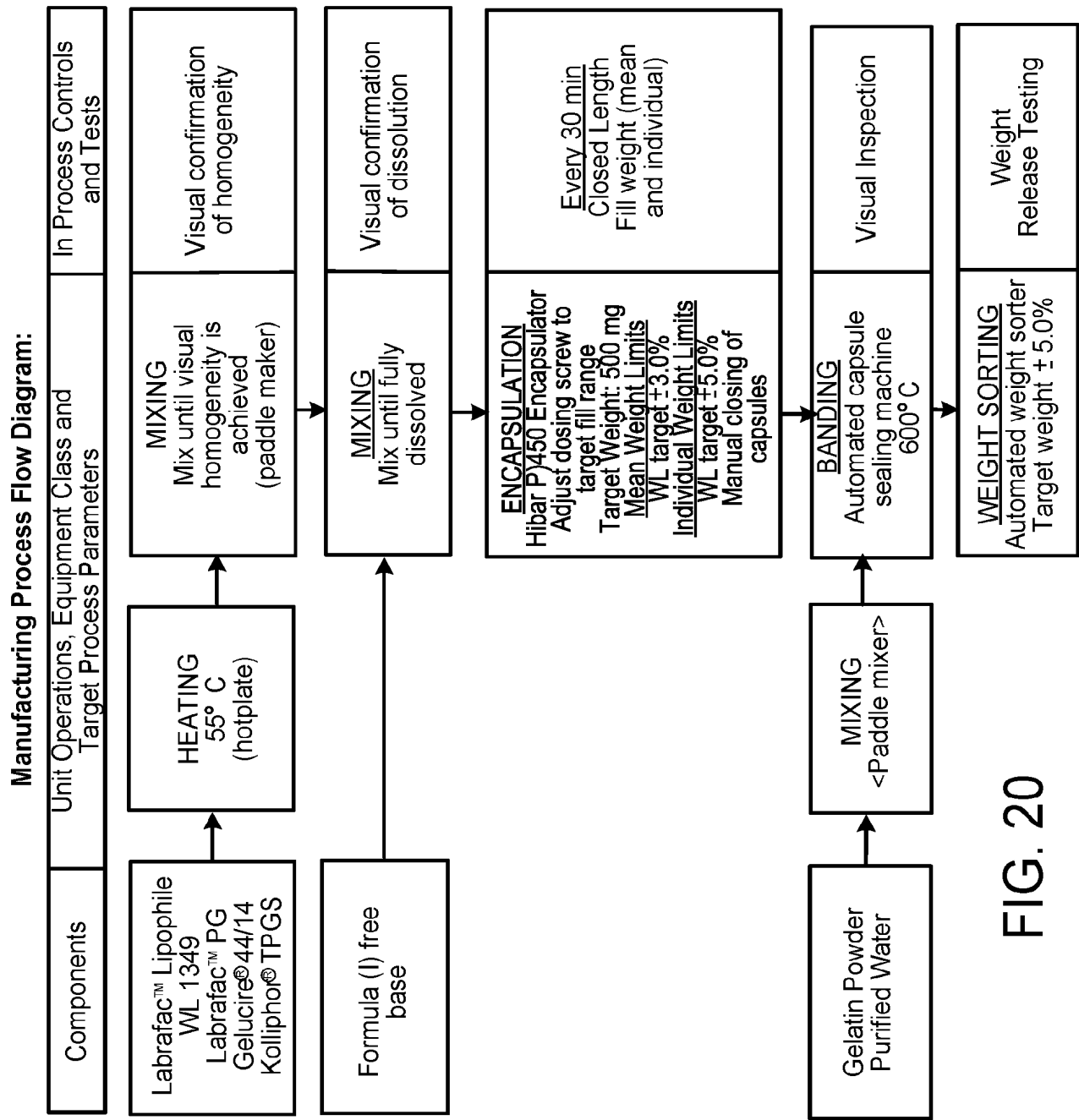
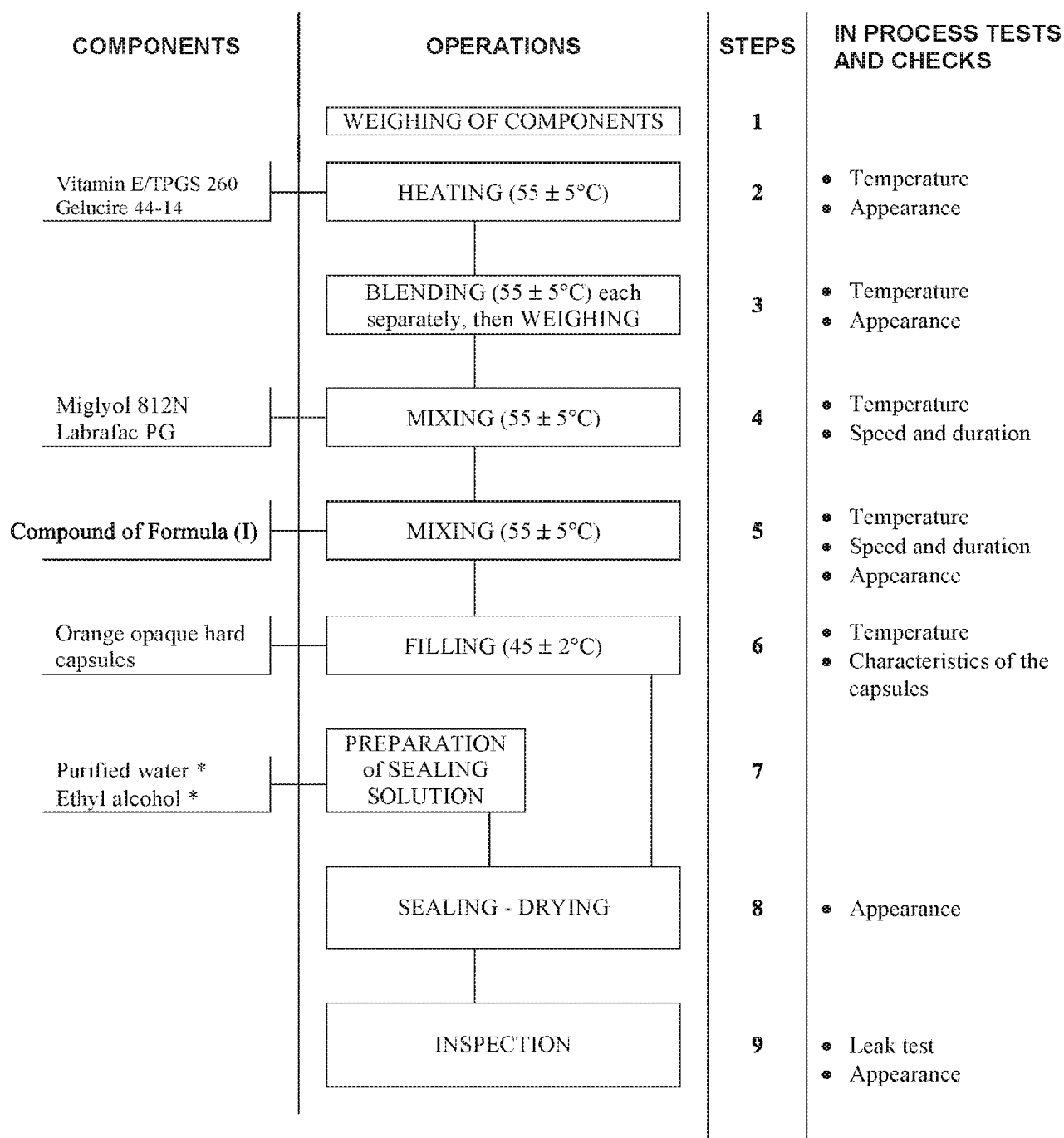


FIG. 20



* Can be contained in hydro-alcoholic solution ready for manufacturing use

FIG. 21

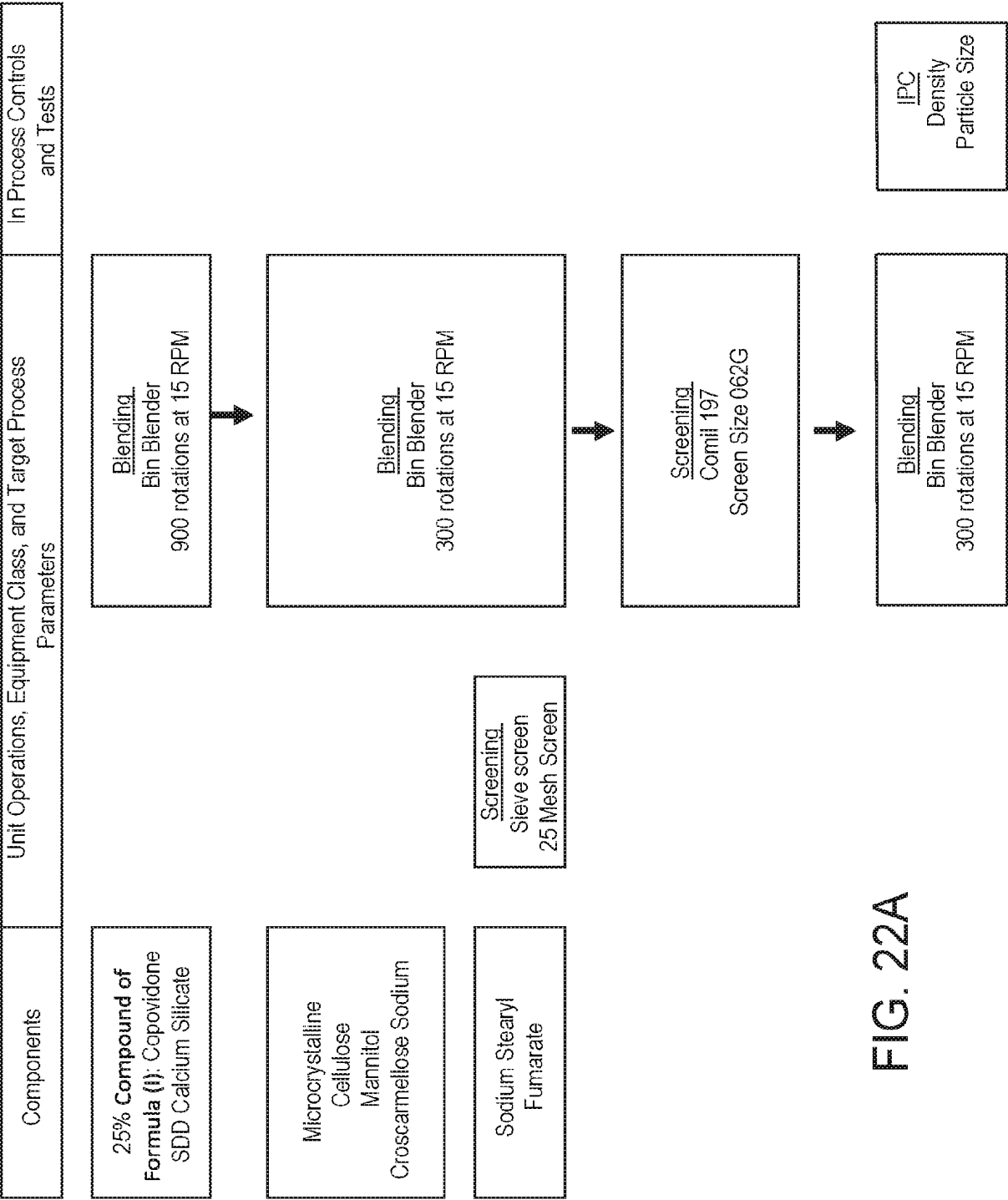


FIG. 22A

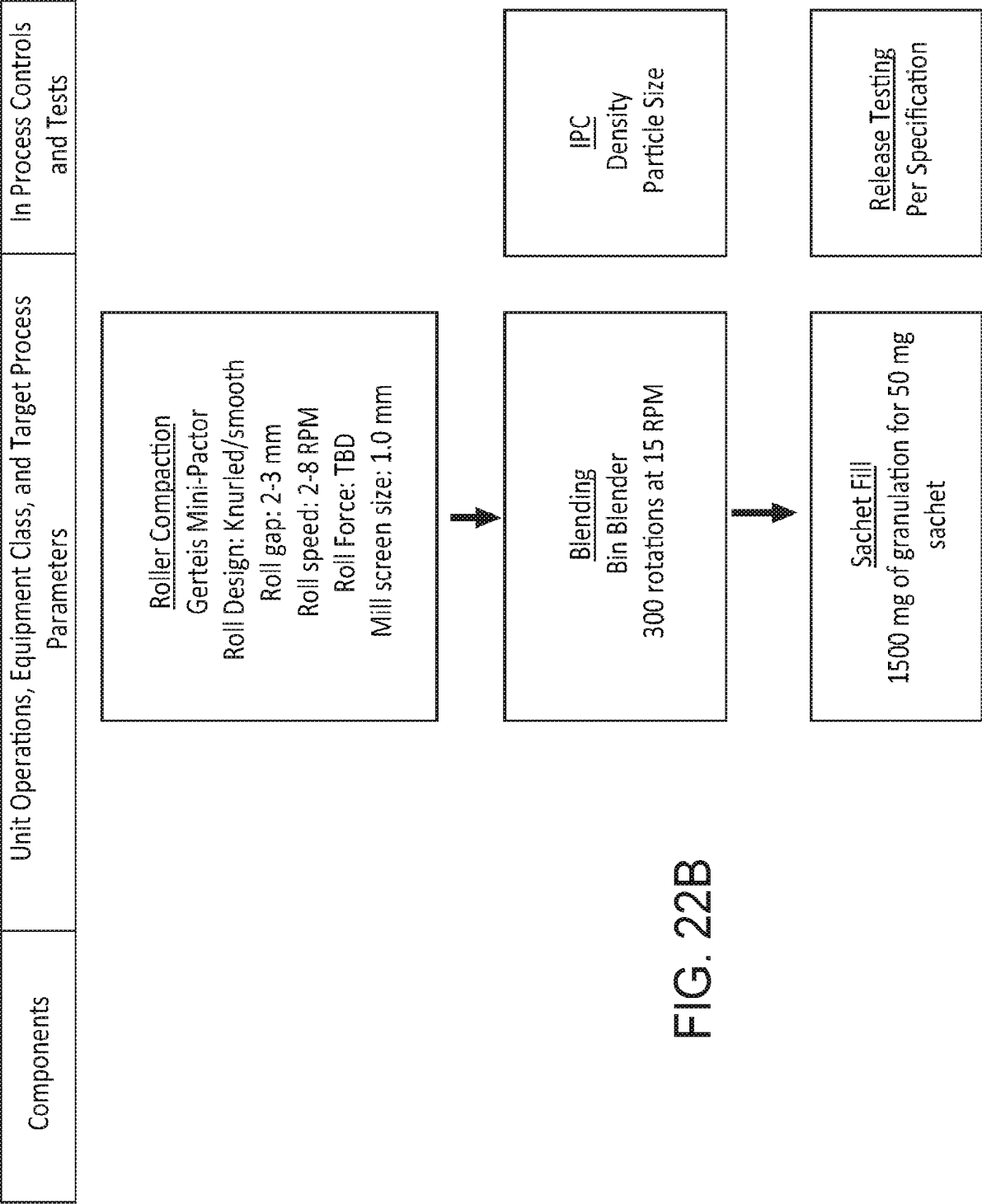


FIG. 22B

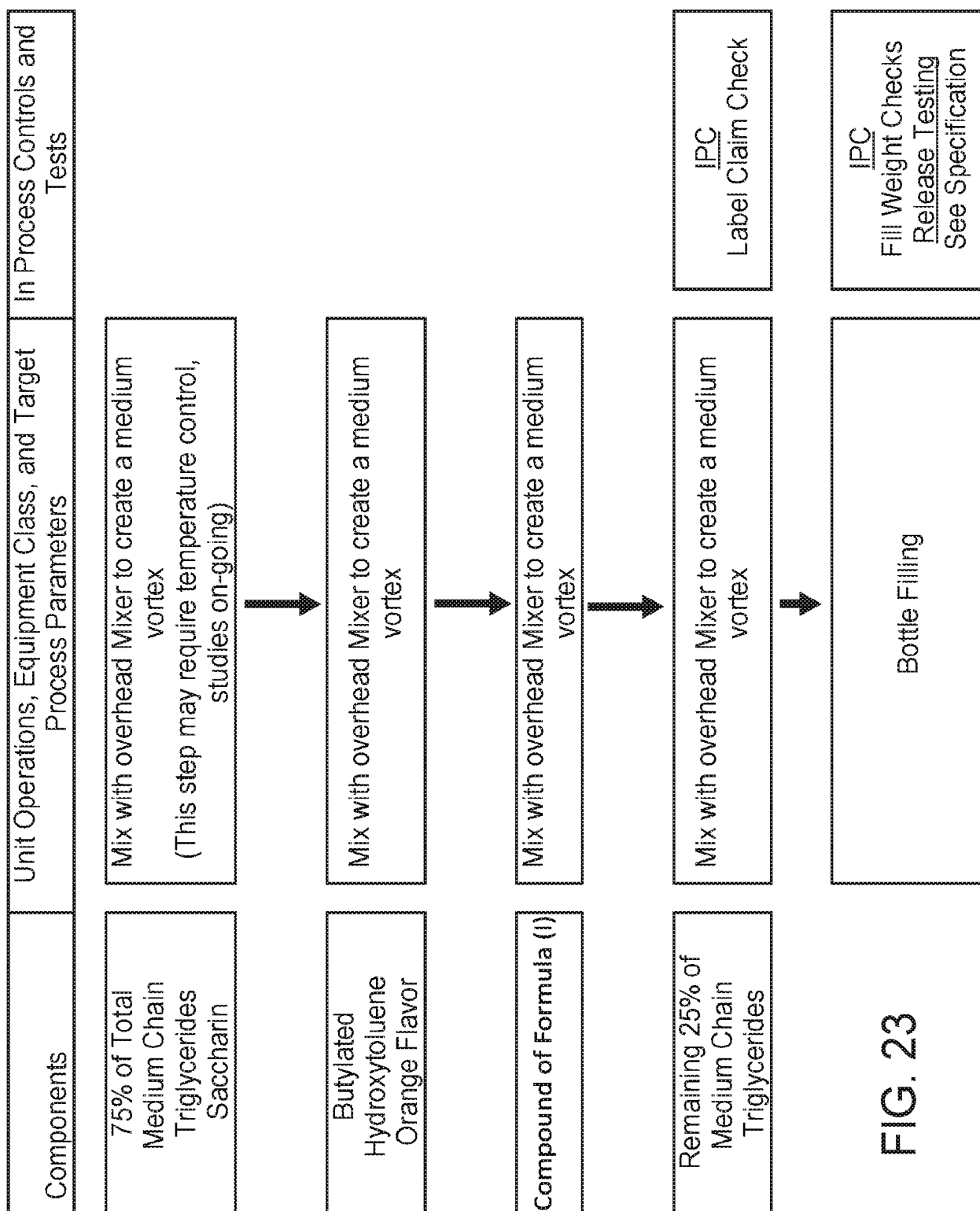


FIG. 23

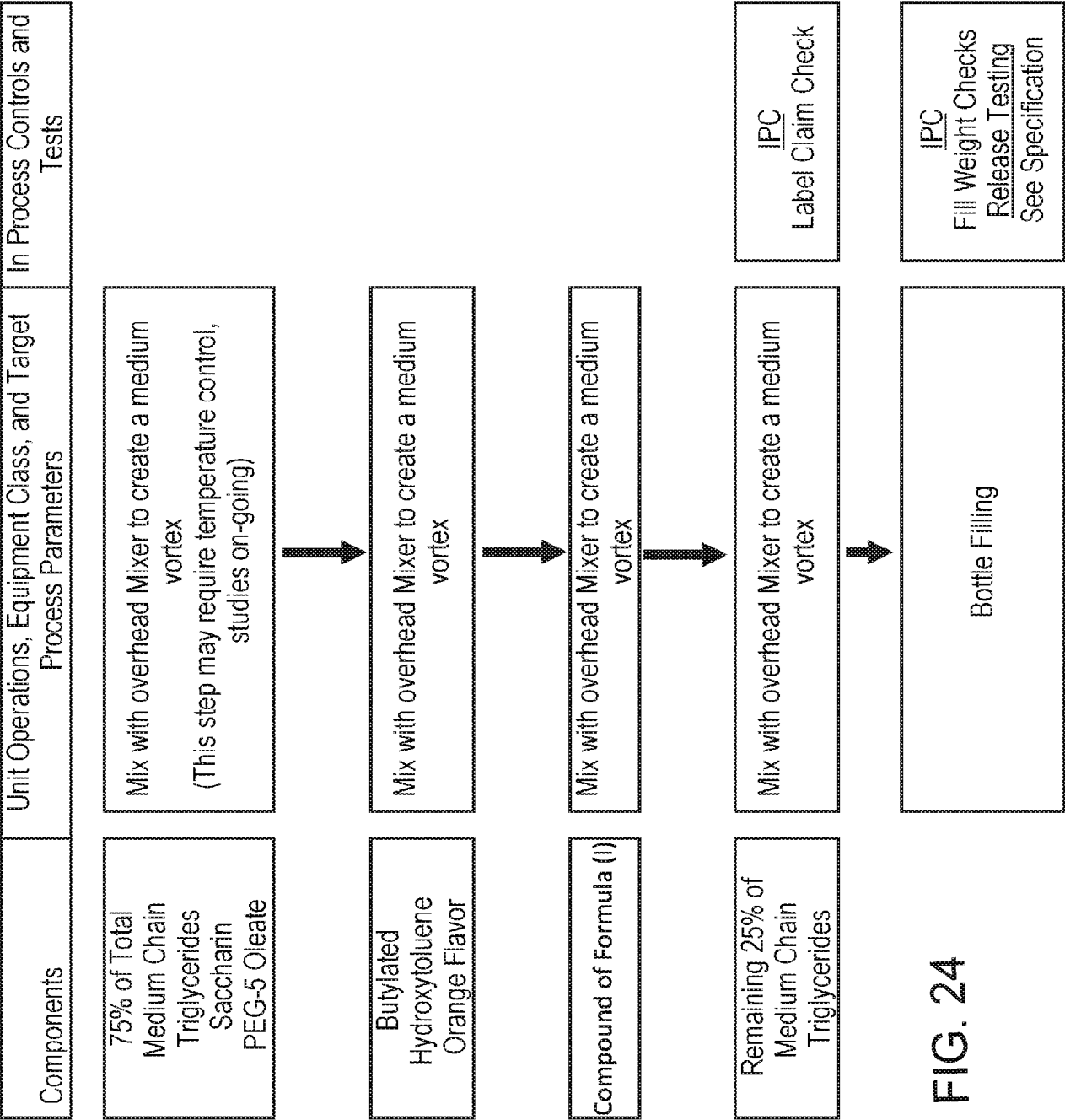


FIG. 24

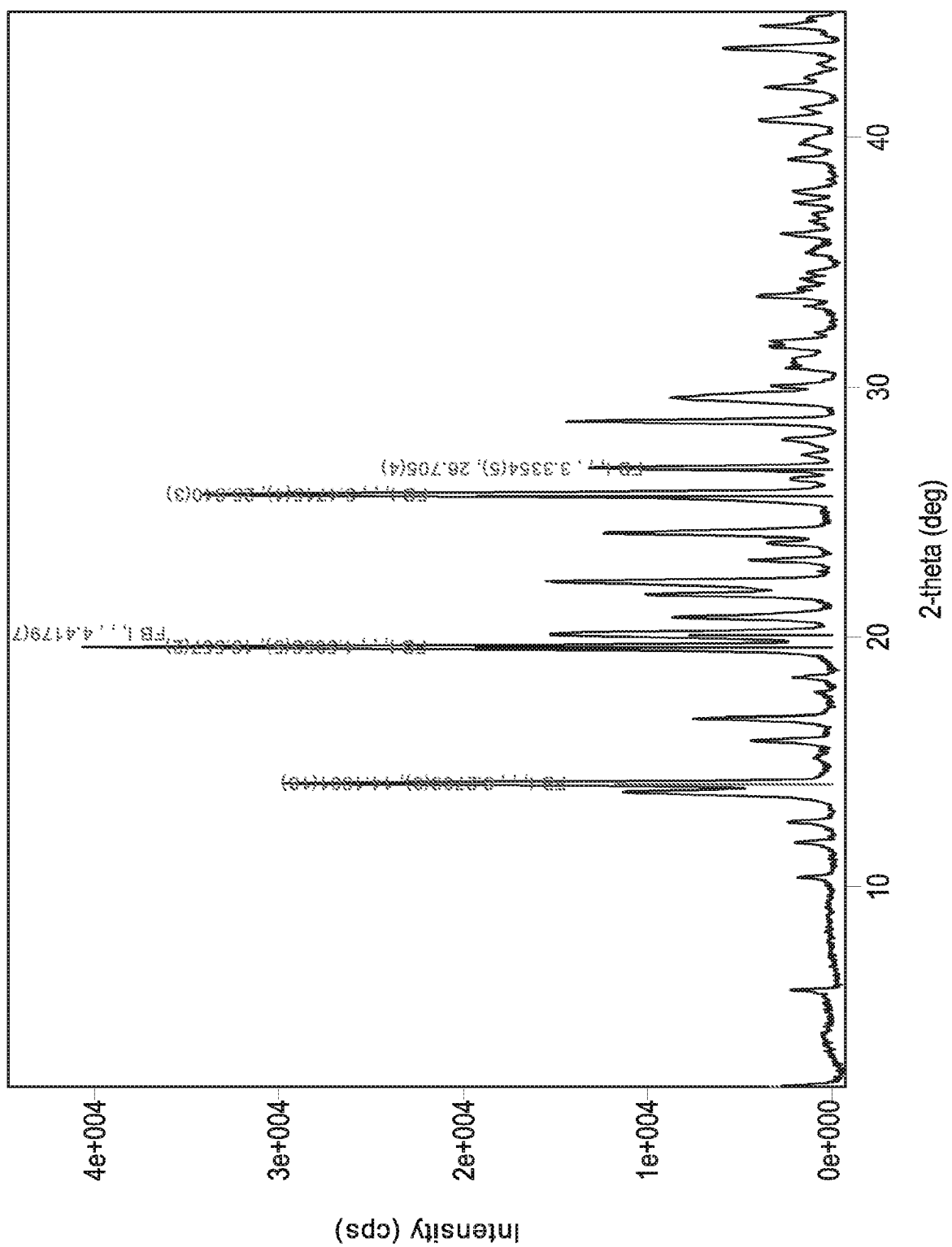


FIG. 25

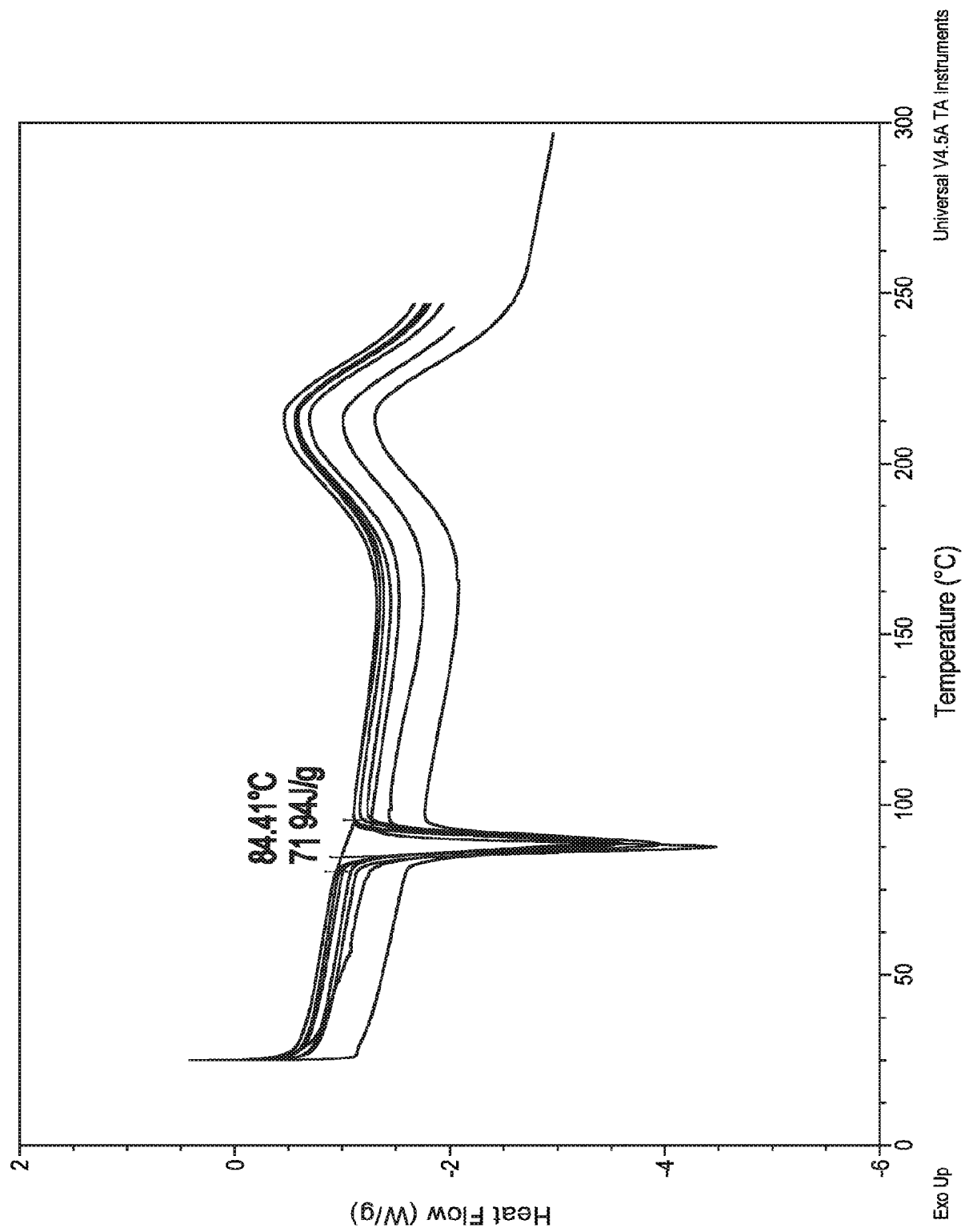


FIG. 26

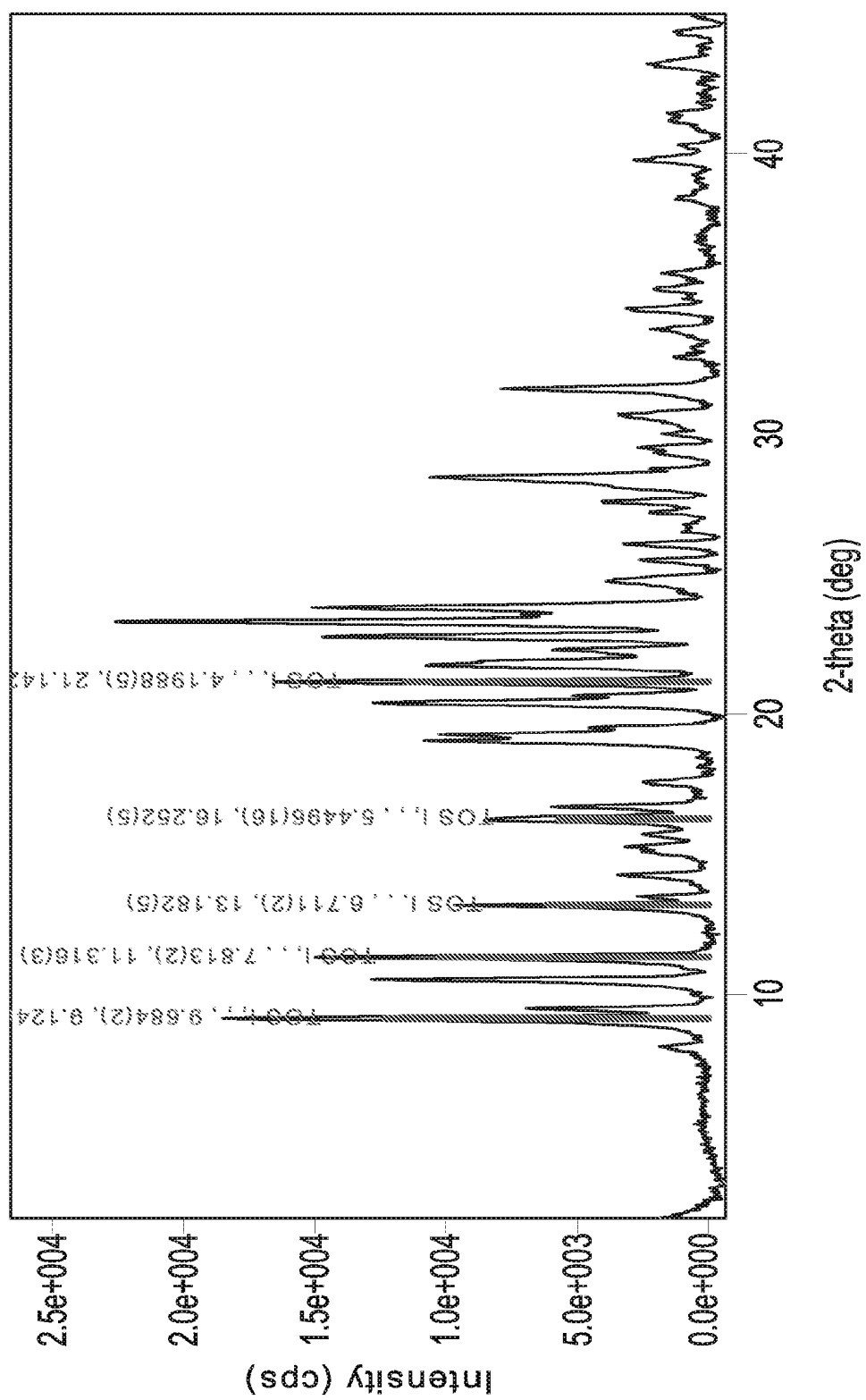


FIG. 27

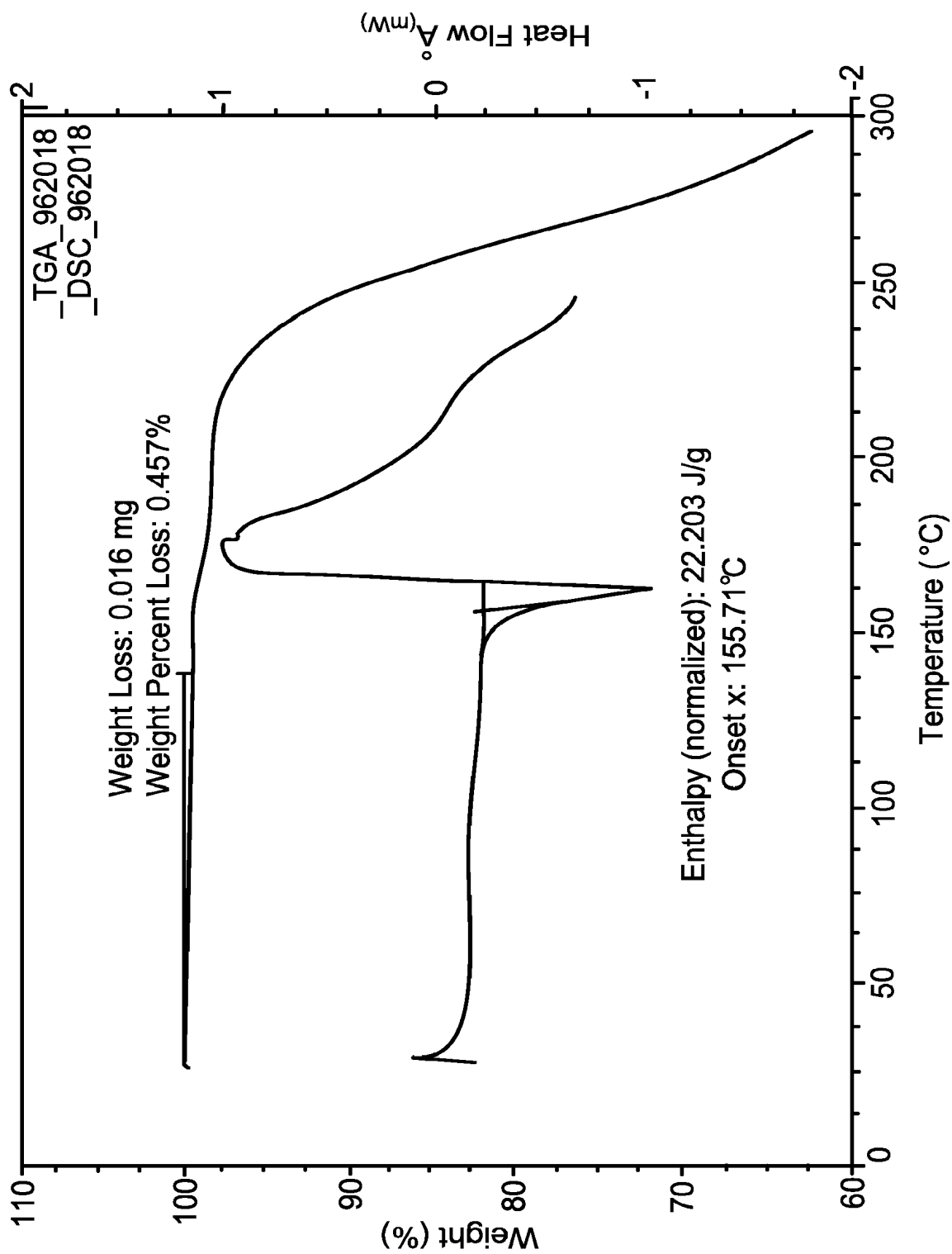


FIG. 28



EUROPEAN SEARCH REPORT

Application Number

EP 21 21 3854

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	WO 2015/112642 A1 (NEUROCRINE BIOSCIENCES INC [US]) 30 July 2015 (2015-07-30) * SSR-125543; page 14 * * claims 1-21 *	1-166	INV. A61K9/00 A61K31/395 A61K31/426 A61K31/573 A61P5/00
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A	WO 2018/219804 A1 (BAYER PHARMA AG [DE]) 6 December 2018 (2018-12-06) * the whole document *	1-166	
1 The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (IPC) A61K
Place of search Munich		Date of completion of the search 14 March 2022	Examiner Schüle, Stefanie
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

EPO FORM 1503 03.82 (PC4C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO.

EP 21 21 3854

5 This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

14-03-2022

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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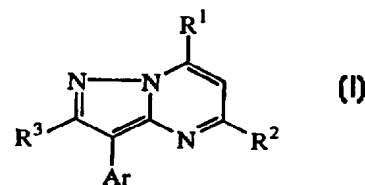
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP97/00459 (22) International Filing Date: 30 January 1997 (30.01.97) (30) Priority Data: 60/011,279 7 February 1996 (07.02.96) US 60/027,688 8 October 1996 (08.10.96) US (71) Applicants (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). NEUROCRINE BIOSCIENCES INC. [US/US]; 3050 Science Park Road, San Diego, CA 92121-1102 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CHEN, Chen [CN/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). WEBB, Thomas, R. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). McCARTHY, James, R. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). MORAN, Terence, J. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). WILCOXEN, Keith, M. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US).			(74) Agent: WANTE, Dirk; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE). (81) Designated States: AL, AM, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.

(54) Title: PYRAZOLOPYRIMIDINES AS CRF RECEPTOR ANTAGONISTS

(57) Abstract

This invention concerns compounds of formula (I), including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein R¹ is NR⁴R⁵ or OR⁵; R² is C₁₋₆alkyl, C₁₋₆alkyloxy or C₁₋₆alkylthio; R³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfoxy or C₁₋₆alkylthio; R⁴ is hydrogen, C₁₋₆alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, C₃₋₆cycloalkyl, C₃₋₆alkenyl, hydroxyC₁₋₆alkyl, C₁₋₆alkylcarbonyloxyC₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl; R⁵ is C₁₋₆alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, Ar¹CH₂, C₁₋₆alkyloxyC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₃₋₆alkenyl, thienylmethyl, furanylmethyl, C₁₋₆alkylthioC₁₋₆alkyl, morpholinyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylC₁₋₆alkyl, C₁₋₆alkyl substituted with imidazolyl; or a radical of the formula -Alk-O-CO-Ar¹; or R⁴ and R⁵ taken together with the nitrogen atom to which they are attached may form an optionally substituted pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group; having CRF receptor antagonistic properties; pharmaceutical compositions containing such compounds as active ingredients; methods of treating disorders related to hypersecretion of CRF such as depression, anxiety, substance abuse, by administering an effective amount of a compound of formula (I).



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PYRAZOLOPYRIMIDINES AS CRF RECEPTOR ANTAGONISTS

Background of the invention

- 5 This invention relates to pyrazolopyrimidines which possess CRF receptor antagonistic properties, to pharmaceutical compositions containing these compounds as active ingredient, and the use thereof in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.
- 10 The first corticotropin-releasing factor (CRF) was isolated from ovine hypothalmi and identified as a 41-amino acid peptide (Vale et al., *Science* 213:1394-1397, 1981). Subsequently, sequences of human and rat CRF were isolated and determined to be identical, but different from ovine CRF in 7 of the 41 amino acid residues (Rivier et al., *Proc. Natl. Acad. Sci. USA* 80:4851, 1983; Shibahara et al., *EMBO J.* 2:775, 1983).
- 15 CRF has been found to produce profound alterations in endocrine, nervous and immune system functions. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotrophic hormone ("ACTH"), β -endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (Vale et al., *Science* 213:1394-1397, 1981). Briefly, CRF is believed to initiate its biological
- 20 effects by binding to a plasma membrane receptor which has been found to be distributed throughout the brain (DeSouza et al., *Science* 221:1449-1451, 1984), pituitary (DeSouza et al., *Methods Enzymol.* 124:560, 1986; Wynn et al., *Biochem. Biophys. Res. Comm.* 110:602-608, 1983), adrenals (Udelsman et al., *Nature* 319:147-150, 1986) and spleen (Webster, E.L., and E.B. DeSouza, *Endocrinology* 122:609-617, 1988). The CRF receptor is coupled to a GTP-binding protein (Perrin et al., *Endocrinology* 118: 1171- 1179, 1986) which mediates CRF-stimulated increase in
- 25 intracellular production of cAMP (Bilezikjian, L.M., and W.W. Vale, *Endocrinology* 113:657-662, 1983).
- 30 In addition to its role in stimulating the production of ACTH and POMC, CRF is also believed to coordinate many of the endocrine autonomic, and behavioral responses to stress, and may be involved in the pathophysiology of affective disorders. Moreover, CRF is believed to be a key intermediary in communication between the immune, central nervous, endocrine and cardiovascular systems (Crofford et al., *J. Clin. Invest.* 90:2555-2564, 1992; Sapolsky et al., *Science* 238:522-524, 1987; Tilders et al., *Regul. Peptides* 5:77-84, 1982). Overall, CRF appears to be one of the pivotal central nervous
- 35 system neurotransmitters and plays a crucial role in integrating the body's overall response to stress.

Administration of CRF directly to the brain elicits behavioral, physiological, and endocrine responses identical to those observed for an animal exposed to a stressful environment. For example, intracerebroventricular injection of CRF results in behavioral activation (Sutton et al., *Nature* 297:331, 1982), persistent activation of the electroencephalogram (Ehlers et al., *Brain Res.* 2/8332, 1983), stimulation of the sympathoadrenomedullary pathway (Brown et al., *Endocrinology* 110:928, 1982), an increase of heart rate and blood pressure (Fisher et al., *Endocrinology* 110:2222, 1982), an increase in oxygen consumption (Brown et al., *Life Sciences* 30:207, 1982), alteration of gastrointestinal activity (Williams et al., *Am. J. Physiol.* 253:G582, 1987), suppression of food consumption (Levine et al., *Neuropharmacology* 22:337, 1983), modification of sexual behavior (Sirinathsinghji et al., *Nature* 305:232, 1983), and immune function compromise (Irwin et al., *Am. J. Physiol.* 255:R744, 1988). Furthermore, clinical data suggest that CRF may be hypersecreted in the brain in depression, anxiety-related disorders, and anorexia nervosa. (DeSouza, *Ann. Reports in Med. Chem.* 25:215-223, 1990).

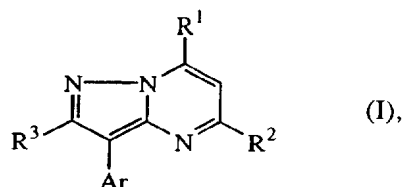
Accordingly, clinical data suggest that CRF receptor antagonists may represent novel antidepressant and/or anxiolytic drugs that may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF.

CRF receptor antagonists have been reported in for example, U.S. Patent No. 5,063,245 disclosing substituted 4-thio-5-oxo-3-pyrazoline derivatives and Australian Patent No. AU-A-41399/93, disclosing substituted 2-aminothiazole derivatives. WO-92/18504 and JP-32/04877 disclose pyrazolo[1,5-a]pyrimidines as antiinflammatory agents. Also, WO-94/13676, WO-94/13677 and WO-95/33750 disclose pyrrolopyrimidines, pyrazolo[3,4-d]pyrimidines and substituted purines as CRF receptor antagonists. Arylpyrazolo[1,5-a]pyrimidines have been described as xanthine oxidase inhibitors (Robins et al., *J. Heterocyclic Chem.* 22:601-634, 1985). JP-42/011,753 discloses 7-methylamino-pyrazolo[1,5-a]pyrimidine derivatives useful as sedative and antiphlogistic agents. And JP-61/057,587 discloses pyrazolo[1,5-a]pyrimidine derivatives useful as antiulcer agents.

Due to the physiological significance of CRF, the development of further biologically active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF receptor remains a desirable goal. Such CRF receptor antagonists would be useful in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.

Description of the invention

This invention concerns CRF antagonistic compounds of formula (I)



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including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

R^1 is NR^4R^5 or OR^5 ;

R^2 is C_{1-6} alkyl, C_{1-6} alkyloxy or C_{1-6} alkylthio;

10 R^3 is hydrogen, C_{1-6} alkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfoxy or C_{1-6} alkylthio;

R^4 is hydrogen, C_{1-6} alkyl, mono- or di(C_{3-6} cycloalkyl)methyl, C_{3-6} cycloalkyl, C_{3-6} alkenyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyloxy C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl;

15 R^5 is C_{1-8} alkyl, mono- or di(C_{3-6} cycloalkyl)methyl, Ar^1CH_2 , C_{1-6} alkyloxy C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{3-6} alkenyl, thienylmethyl, furanylmethyl, C_{1-6} alkylthio C_{1-6} alkyl, morpholinyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, di(C_{1-6} alkyl)amino, C_{1-6} alkylcarbonyl C_{1-6} alkyl, C_{1-6} alkyl substituted with imidazolyl; or a radical of formula $-Alk-O-CO-Ar^1$;

20 or R^4 and R^5 taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl; and

25 Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C_{1-6} alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6} alkyloxy, benzyloxy, C_{1-6} alkylthio, nitro, amino and mono- or di(C_{1-6} alkyl)amino; pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents independently selected from halo, C_{1-6} alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6} alkyloxy, benzyloxy, C_{1-6} alkylthio, nitro, amino, mono- or di(C_{1-6} alkyl)amino and piperidinyl; and wherein said substituted phenyl may optionally be further substituted with one or more halogens;

30 Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6} alkyl, C_{1-6} alkyloxy, di(C_{1-6} alkyl)amino C_{1-6} alkyl, trifluoromethyl and C_{1-6} alkyl substituted with morpholinyl; or pyridinyl; and Alk is C_{1-6} alkanediyl.

In a further aspect the invention concerns novel compounds of formula (I) as defined above, with the proviso that 5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo[1,5-a]-pyrimidine and 2,5-dimethyl-7-(methylamino)-3-phenyl-pyrazolo[1,5-a]pyrimidine are not included

The proviso is intended to exclude compounds disclosed in JP-61/057,587 and JP-42/011,753.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C₁₋₆alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof; C₁₋₂alkyl defines straight saturated hydrocarbon radicals having from 1 to 2 carbon atoms such as methyl and ethyl; C₂₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 2 to 4 carbon atoms such as ethyl, propyl, butyl, 1-methylethyl and the like; C₃₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 3 to 4 carbon atoms such as propyl, butyl, 1-methylethyl and the like; C₁₋₆alkyl includes C₁₋₂alkyl and C₃₋₄alkyl radicals as defined hereinbefore and the higher homologs thereof having from 5 to 6 carbon atoms such as, pentyl, the pentyl isomers, hexyl and the hexyl isomers; C₁₋₈alkyl includes C₁₋₆alkyl and the higher homologues thereof having from 7 to 8 carbon atoms such as, for example, heptyl, octyl and the like; C₃₋₆alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, and the like; and where said C₃₋₆alkenyl is linked to a nitrogen or oxygen, the carbon atom making the link preferably is saturated. C₃₋₆cycloalkyl comprises cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. HydroxyC₁₋₆alkyl refers to C₁₋₆alkyl substituted with a hydroxyl-group. Homopiperidinyl refers to a 7 membered saturated ring containing one nitrogen atom.

Depending on the nature of some of the substituents, the compounds of formula (I) may contain one or more asymmetric centers which may be designated with the generally used R and S nomenclature.

- The compounds of the present invention contain basic nitrogen atoms and, as such, can be present as the free base or in the form of acid addition salts, both being part of this invention. Acid addition salts may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids.
- Particular groups of compounds within the invention are those compounds of formula (I) wherein one or more of the following restrictions apply :
- a) R^1 is NR^4R^5 wherein R^4 is hydrogen, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyloxy C_{1-6} alkyl or C_{3-6} alkenyl; in particular C_{2-4} alkyl, hydroxy C_{1-2} alkyl, C_{3-4} alkenyl or C_{1-2} alkylcarbonyloxy C_{2-4} alkyl; and R^5 is C_{1-8} alkyl, C_{3-6} alkenyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, phenylmethyl or C_{3-6} cycloalkylmethyl; in particular C_{2-4} alkyl, C_{3-4} alkenyl, hydroxy C_{2-4} alkyl or cyclopropylmethyl;
 - b) R^1 is OR^5 wherein R^5 is C_{1-6} alkyl; in particular C_{2-4} alkyl;
 - c) R^2 is C_{1-6} alkyl; in particular C_{1-2} alkyl;
 - d) R^3 is hydrogen, C_{1-6} alkyl or C_{1-6} alkylthio; in particular hydrogen, C_{1-2} alkyl or C_{1-2} alkylthio;
 - e) Ar is a phenyl substituted with 1, 2 or 3 substituents each independently selected from C_{1-6} alkyl, C_{1-6} alkyloxy or halo; wherein the phenyl moiety is preferably substituted in the 3-, 4-, 6-, 2,4- or 2,4,6-positions; or Ar is a pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, amino, nitro, trifluoromethyl, mono- or di(C_{1-6} alkyl)amino, piperidinyl or C_{1-6} alkyl; wherein the pyridinyl moiety preferably is connected via the 2- or 3-position to the remainder of the molecule.
- Another particular group of compounds are those compounds of formula (I) wherein R^1 is NR^4R^5 and R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl.
- Preferred compounds are those compounds of formula (I) wherein R^1 is NR^4R^5 and R^4 is C_{3-4} alkyl or allyl, preferably propyl; R^5 is C_{2-4} alkyl, allyl or cyclopropylmethyl, preferably propyl; R^2 is methyl; R^3 is hydrogen, methyl or methylthio, preferably

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propyl; and Ar is a phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, methyl or methoxy; and Ar in particular is pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, methyl or dimethylamino.

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More preferably Ar is 3-pyridinyl substituted in the 4- and/or 6-position with methyl or dimethylamino.

Most preferred are those compounds selected from

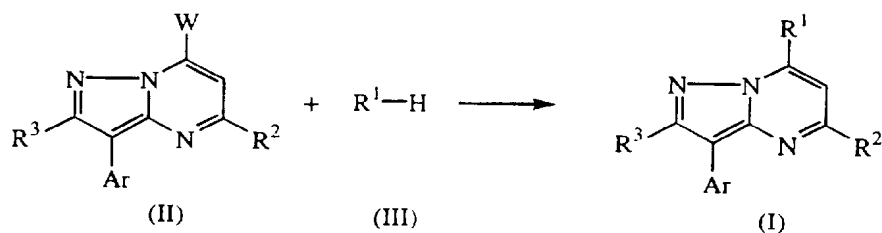
- 10 3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-propyl-*N*-cyclopropanemethylamino)-pyrazolo[2,3-*a*]pyrimidine;
3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-allyl-*N*-cyclopropanemethylamino)-pyrazolo[2,3-*a*]pyrimidine;
2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(*N,N*-diallylamino)-
15 pyrazolo[2,3-*a*]pyrimidine;
2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-butyl-*N*-cyclopropanemethylamino)pyrazolo[2,3-*a*]pyrimidine;
2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-propyl-*N*-cyclopropanemethylamino)pyrazolo[2,3-*a*]pyrimidine;
20 2-methyl-3-(4-chlorophenyl)-5-methyl-7-(*N,N*-dipropylamino)-pyrazolo[2,3-*a*]pyrimidine;
3-[6-(dimethylamino)-3-pyridinyl]-2,5-dimethyl-*N,N*-dipropylpyrazolo[2,3-*a*]pyrimidin-7-amine; or
3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-*N,N*-dipropyl-
25 pyrazolo[2,3-*a*]pyrimidine-7-amine; or
3-(2,4-dimethoxyphenyl)-2,5-dimethyl-7-(*N*-propyl-*N*-methoxyethylamino)-pyrazolo[2,3-*a*]pyrimidine;
the stereoisomeric forms and the pharmaceutically acceptable acid addition salts thereof.

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The compounds of the present invention can generally be prepared by alkylating a pyrazolopyrimidine of formula (II) with an intermediate of formula (III). In intermediate (II), W is an appropriate leaving group such as halo, e.g. chloro, bromo, or a sulfonyloxy group, e.g. a mesyloxy or a tosyloxy group.

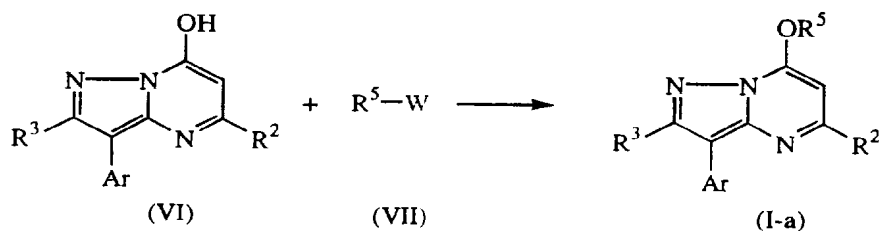
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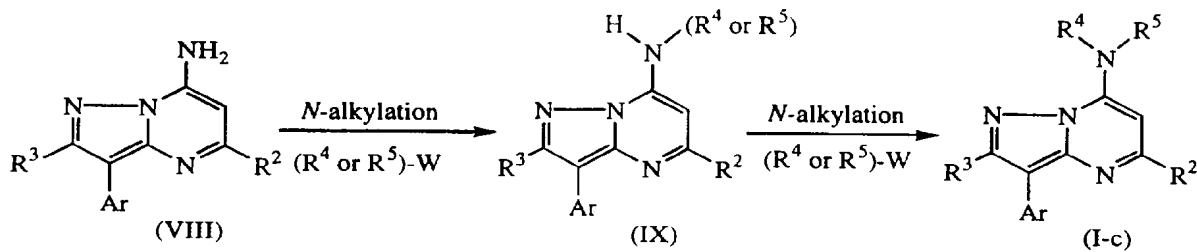
The above reaction is typically conducted in a suitable solvent, e.g. an aprotic solvent such as DMF or acetonitrile, an ether, e.g. tetrahydrofuran, preferably at an elevated temperature and, when the intermediates of formula (III) are volatile amines, in a sealed reaction vial.

Also, compounds of formula (I) wherein R^1 is OR^5 , said compounds being represented by formula (I-a), may be prepared by *O*-alkylating an intermediate of formula (VI) with an intermediate of formula (VII), wherein W is as defined above.



Said reaction for preparing compounds of formula (I-a) can be performed in a reaction-inert solvent such as, for example, *N,N*-dimethylformamide, and in the presence of a suitable base such as, for example, sodium hydride, preferably at a temperature ranging between room temperature and reflux temperature.

The compounds of formula (I) wherein R^1 is NR^4R^5 , represented by formula (I-c), can be prepared from either compounds of formula (VIII) or (IX) by suitable *N*-alkylation reactions as depicted herebelow, wherein W is as previously defined. These *N*-alkylations are conducted in a reaction-inert solvent such as, for example, an ether e.g. tetrahydrofuran and preferably in the presence of a strong base, e.g. NaH.



In certain instances, this reaction can give rise to side products wherein R^2 is alkylated by $(R^4 \text{ or } R^5)\text{-W}$, in particular where R^2 is methyl and R^4 or R^5 is C_{1-6} alkyl.

5 As outlined below, compounds of formula (I) may be converted into each other following art-known transformation procedures.

10 The compounds of formula (I) wherein R^3 is C_{1-6} alkylthio can be converted into compounds of formula (I) wherein R^3 is C_{1-6} alkylsulfonyl or C_{1-6} alkylsulfoxy by an oxidation reaction, e.g. treatment with a peroxide such as 3-chloroperbenzoic acid in a reaction-inert solvent, e.g. dichloromethane. By controlling the amount of oxidant and other reaction parameters, either compounds of formula (I) wherein R^3 is C_{1-6} alkylsulfonyl or C_{1-6} alkylsulfoxy can be obtained, or a mixture of both, which subsequently can be separated by conventional methods, e.g. column chromatography.

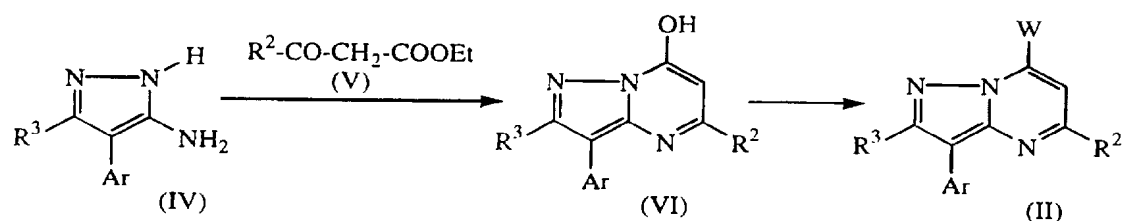
15 The compounds of formula (I) may also be converted into each other via art-known reactions or functional group transformations. For instance, compounds of formula (I) bearing a hydroxy C_{1-6} alkyl group may be converted into compounds of formula (I) bearing a C_{1-6} alkylcarbonyloxy C_{1-6} alkyl group, e.g. by treatment with an acid anhydride in an reaction-inert solvent such as, e.g. dichloromethane, and optionally in
20 the presence of a base such as, e.g. pyridine.

Compounds of formula (I) bearing a nitro group may be converted to compounds of formula (I) bearing an amino group and subsequently to compounds of formula (I) having a mono- or di(C_{1-6} alkyl)amino group. Also, the amino group may be converted
25 using a diazotization reaction to a halo.

Further, the Ar group of compounds of formula (I) can be halogenated using a halogenating agent such as, e.g. chlorine or bromine, in a suitable solvent, e.g. acetic acid, and optionally the reaction may be performed at a temperature ranging between
30 room temperature and the reflux temperature of the reaction mixture.

Intermediates of formula (II) can be prepared according to the procedure as described in Robins et al., *J. Heterocyclic Chem.* 22:601-634, 1985.

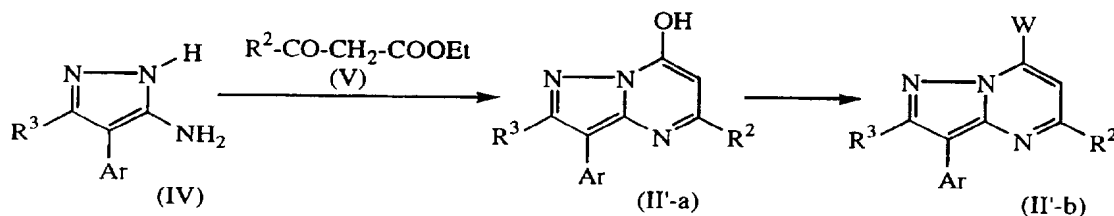
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Aminopyrazole derivatives (IV) are reacted with a β-keto ester (V), preferably under reflux conditions and in a suitable reaction-inert solvent such as an ether, e.g. THF, yielding hydroxypyrazolopyrimidines (VI) which are converted into intermediates of formula (II) by converting the hydroxy group of intermediate (VI) into leaving group W, e.g. by treating (VI) with methanesulfonyloxy chloride or a halogenating reagent such as, e.g. POCl₃.

Intermediates of formula (VIII) are prepared by treating intermediates of formula (II) with ammonia.

In an embodiment, this invention also provides for intermediates of formula (II'), wherein W' represents hydroxy, halo, mesyloxy or tosyloxy; with the proviso that Ar is other than phenyl.



Said intermediates of formula (II') may be prepared according to procedures used to prepare intermediates of formula (II), thereby thereby yielding compounds of formula (II'-a), defined as compounds of formula (II') wherein W' is hydroxy; and optionally converting compounds of formula (II'-a) into compounds of formula (II'-b), defined as compounds of formula (II') wherein W' is other than hydroxy.

Stereoisomers may be prepared by separation of the end products of formula (I) following art-known procedures, e.g. by treatment with an optically active acid and separating the thus-formed diastereoisomeric salts by selective crystallization or column chromatography. Or, stereoisomers may be prepared by using stereoisomeric starting materials in any of the above reaction schemes or in the preparation of intermediates described hereinafter.

The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention are capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of structure (I) may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (*J. Neuroscience* 7:88, 1987) and Battaglia et al. (*Synapse* 1:572, 1987). As mentioned above, suitable CRF antagonists include compounds which demonstrate CRF receptor affinity. CRF receptor affinity may be determined by binding studies that measure the ability of a compound to inhibit the binding of a radiolabeled CRF (e.g. [¹²⁵I]tyrosine CFR) to receptor (e.g., receptors prepared from rat cerebral cortex membranes). The radioligand binding assay described by DeSouza et al. (*supra*, 1987) provides an assay for determining a compound's affinity for the CRF receptor. Such activity is typically calculated from the IC₅₀ as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the receptor, and is reported as a "K_i" value calculated by the following equation :

$$K_i = \frac{IC_{50}}{1 + L / K_D}$$

where L = radioligand and K_D = affinity of radioligand for receptor (Cheng and Prusoff, *Biochem. Pharmacol.* 22:3099, 1973).

In addition to inhibiting CRF receptor binding, a compound's CRF receptor antagonist activity may be established by the ability of the compound to antagonize an activity associated with CRF. For example, CRF is known to stimulate various biochemical processes, including adenylate cyclase activity. Therefore, compounds may be evaluated as CRF antagonists by their ability to antagonize CRF-stimulated adenylate cyclase activity by, for example, measuring cAMP levels. The CRF-stimulated adenylate cyclase activity assay described by Battaglia et al. (*supra*, 1987) provides an assay for determining a compound's ability to antagonize CRF activity. Accordingly, CRF receptor antagonist activity may be determined by assay techniques which generally include an initial binding assay (such as disclosed by DeSouza (*supra*, 1987)) followed by a cAMP screening protocol (such as disclosed by Battaglia (*supra*, 1987)). With reference to CRF receptor binding affinities, CRF receptor antagonists of this invention have a K_i of less than 10 μM. In a preferred embodiment of this invention, a

CRF receptor antagonist has a K_i of less than 1 μM , and more preferably less than 0.25 μM (*i.e.*, 250 nM).

The CRF receptor antagonists of the present invention demonstrate activity at the CRF receptor site, and may be used as therapeutic agents for the treatment of a wide range of disorders or illnesses including endocrine, psychiatric, and neurologic disorders or illnesses. More specifically, the CRF receptor antagonists of the present invention may be useful in treating physiological conditions or disorders arising from the hypersecretion of CRF. Because CRF is believed to be a pivotal neurotransmitter that activates and coordinates the endocrine, behavioral and automatic responses to stress, the CRF receptor antagonists of the present invention can be used to treat neuropsychiatric disorders. Neuropsychiatric disorders which may be treatable by the CRF receptor antagonists of this invention include affective disorders such as depression; anxiety-related disorders such as generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, cardiovascular abnormalities such as unstable angina and reactive hypertension; and feeding disorders such as anorexia nervosa, bulimia, and irritable bowel syndrome. CRF antagonists may also be useful in treating stress-induced immune suppression associated with various diseases states, as well as stroke. Other uses of the CRF antagonists of this invention include treatment of inflammatory conditions (such as rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and G.I. motility), Cushing's disease, infantile spasms, epilepsy and other seizures in both infants and adults, and various substance abuse and withdrawal (including alcoholism).

In another embodiment of the invention, pharmaceutical compositions containing one or more CRF receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a CRF receptor antagonist of the present invention (*i.e.*, a compound of structure (I)) and a pharmaceutically acceptable carrier and/or diluent. The CRF receptor antagonist is present in the composition in an amount which is effective to treat a particular disorder, that is, in an amount sufficient to achieve CRF receptor antagonist activity, and preferably with acceptable toxicity to the patient. Preferably, the pharmaceutical compositions of the present invention may include a CRF receptor antagonist in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more preferably from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a CRF receptor antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the CRF receptor antagonist in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, USA, 1990.

In another embodiment, the present invention provides a method for treating a variety of disorders or illnesses, including endocrine, psychiatric and neurologic disorders or illnesses. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the disorder or illness. Such methods include systemic administration of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of CRF receptor antagonists include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions which may contain, in addition to the CRF receptor antagonist, buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

As mentioned above, administration of a compound of the present invention can be used to treat a wide variety of disorders or illnesses. In particular, the compounds of the present invention may be administered to a warm-blooded animal for the treatment of depression, anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, unstable angina, reactive hypertension, anorexia nervosa, bulimia, irritable bowel syndrome, stress-induced immune suppression, stroke, inflammation, Cushing's disease, infantile spasms, epilepsy, and substance abuse or withdrawal.

Hence, this invention provides the use of compounds of formula (I) for the manufacture of a medicine for treating physiological conditions or disorders arising from the hypersecretion of corticotropin-releasing factor (CRF); and in a further embodiment the use of novel compounds of formula (I) as a medicine is provided.

The following examples are provided for purposes of illustration, not limitation.

Experimental part

Hereinafter "THF" means tetrahydrofuran and "DCM" means dichloromethane.

A. Preparation of the intermediates.

Example A.1

a) 3-Amino-4-(2,4-dichlorophenyl)pyrazole and ethyl acetoacetate (2 equivalents) were dissolved in dioxane and heated under reflux overnight. The mixture was concentrated *in vacuo* and diluted with ethyl acetate. An off-white solid formed after 2 days standing was collected by vacuum filtration, yielding 3-(2,4-dichlorophenyl)-5-methyl-7-hydroxypyrazolo[2,3-a]pyrimidine (intermediate 1).

b) Intermediate 1 (300 mg) was mixed with POCl₃ (1.5 ml) and heated to reflux for 1 hour. The resultant purple solution was carefully transferred into ice-water. The product was extracted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over MgSO₄ and concentrated *in vacuo* to give 3-(2,4-dichlorophenyl)-5-methyl-7-chloropyrazolo[2,3-a]pyrimidine (intermediate 2) as a brown solid (260 mg, 82%).

Example A.2

a) To a stirred solution of sodium hydride (60%, 25 mmol) in THF (10 ml) 6-(dimethylamino)-3-pyridineacetonitrile was added dropwise (10 mmol) in THF (10 ml). The solution was allowed to stir for 10 minutes before ethyl acetate (30 mmol) was added slowly. The resulting suspension was stirred at room temperature for another hour. The reaction mixture was concentrated under vacuum and dissolved in ethyl acetate/methanol (1:1) and filtered through silica. The filtrate was concentrated, yielding (intermediate 7).

b) A mixture of intermediate 7 and hydrazine hydrobromide (100 mmol) was dissolved in ethanol/water (9:1, total 100 ml) and refluxed for 1 hour. The reaction mixture was concentrated and the residue was partitioned between ethyl acetate and sodium bicarbonate solution. The combined extracts were dried over sodium sulfate, filtered and concentrated to dryness. The residue was dissolved in 1,4-dioxane (200 ml) and

refluxed for 16 hours in the presence of ethyl acetoacetate. The reaction mixture was cooled and an off-white solid precipitated out. Diethyl ether was added to aid in crystallization and the precipitate was filtered off and dried, yielding 3-[2-(dimethyl-

5 (intermediate 8).

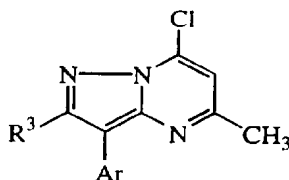
c) Intermediate 8 was dissolved in POCl_3 (2 ml) and refluxed for 2 hours. The reaction mixture was cooled and poured onto ice. The solution was made basic ($\text{pH} = 9$) by addition of solid sodium carbonate and extracted with diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated, yielding 3-[6-

10 (dimethylamino)-3-pyridinyl]-2,5-dimethyl-7-chloro-pyrazolo[2,3-a]pyrimidine (intermediate 9).

Table 1 lists the intermediates that were prepared according to one of the above Examples.

15

Table 1 :



Interm. No.	Ex. No.	R ³	Ar
2	A.1	H	2,4-dichlorophenyl
3	A.1	CH ₃ S	2,4-dichlorophenyl
4	A.1	CH ₃	2,4-dichlorophenyl
5	A.1	H	4-chlorophenyl
6	A.1	H	2,6-dichlorophenyl
13	A.1	CH ₃	4-chlorophenyl
14	A.1	CH ₃	3-methoxyphenyl
15	A.1	CH ₃	4-methoxyphenyl
16	A.1	CH ₃	2,4-dimethoxyphenyl
17	A.1	CH ₃ CH ₂	3,4-dimethoxyphenyl
18	A.1	H	2,4,6-trimethoxyphenyl
9	A.2	CH ₃	6-dimethylamino-3-pyridinyl
10	A.2	CH ₃	6-dimethylamino-4-methyl-3-pyridinyl
11	A.2	CH ₃	6-methyl-5-nitro-2-pyridinyl
12	A.2	CH ₃	5-chloro-2-pyridinyl

Interm. No.	Ex. No.	R ³	Ar
19	A.1	CH ₃	6-methyl-3-pyridinyl
20	A.1	CH ₃	3-methyl-5-nitro-2-pyridinyl

B. Preparation of the final products.

Example B.1

- 5 A mixture of intermediate 2 (21 mg) and *N*-propyl-*N*-cyclopropanemethylamine (75 mg) was heated in a sealed reaction vial at 100°C overnight. Chromatography on a preparative TLC plate with 1:5 ethyl acetate-hexanes gave 3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-propyl-*N*-cyclopropanemethylamino)-pyrazolo[2,3-*a*]pyrimidine (compound 17) (17.4 mg) and 3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-cyclopropanemethylamino)-pyrazolo[2,3-*a*]pyrimidine (compound 8) (1 mg).
- 10 In a similar way, starting from intermediate 2 and (*S*)-(-)-leucinol respectively (*R*)-(+)-leucinol, (*S*)-2[[3-(2,4-dichlorophenyl)-5-methyl-7-pyrazolo[2,3-*a*]pyrimidinyl]amino]-4-methyl-1-pentanol (compound 11) and its *R*-analog (compound 12) were prepared.

15 Example B.2

- A solution of intermediate 10 (8 g) and di-*n*-propylamine (13 g) in acetonitrile (50 ml) was heated at reflux for 3 hours. The mixture was filtrated through a short silica gel plug with ethyl acetate and the filtrate was concentrated *in vacuo* to provide a light yellow solid which was recrystallized from ether-hexanes, yielding 8.9 g (93%) of 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-*N,N*-dipropylpyrazolo[2,3-*a*]pyrimidin-7-amine (compound 53).
- 20 Compound 53 was also converted to its hydrochloric acid addition salt by dissolving compound 53 (8.1 g) in a mixture of diethyl ether (150 ml) and DCM (50 ml) and treating said mixture with HCl in diethyl ether (1 M, 21.3 ml) dropwise with stirring.
- 25 The resulting off-white solid was collected by filtration, yielding 8.7 g (98%) of 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-*N,N*-dipropylpyrazolo[2,3-*a*]pyrimidin-7-amine monohydrochloride.

Example B.3

- Intermediate 3 (15 mg) was dissolved in ethanol (0.5 ml) and stirred in the presence of sodium ethoxide (12 mg) for 1 hour. Chromatography on silica gel gave 3-(2,4-dichlorophenyl)-7-(ethoxy)-5-methyl-2-methylthio-pyrazolo[2,3-*a*]pyrimidine (compound 50).
- 30

Example B.4

A solution of compound 6 (14 mg) in THF (3 ml) was treated with sodium hydride (60 mg, excess) at room temperature for 5 minutes, followed by iodopropane (0.3 ml). The reaction was stirred at room temperature overnight and quenched with methanol (0.5 ml). The resultant mixture was loaded onto a preparative TLC plate and developed with 1:5 ethyl acetate-hexanes to give 3-(2,4-dichlorophenyl)-5-methyl-7-[*N*-(3-methoxypropyl)-*N*-propylamino]-pyrazolo[2,3-*a*]pyrimidine (compound 45) (5.7 mg) as a colorless oil, 3-(2,4-dichlorophenyl)-5-butyl-7-[*N*-(3-methoxypropyl)-*N*-propylamino]-pyrazolo[2,3-*a*]pyrimidine (compound 46) (4 mg) and 3-(2,4-dichlorophenyl)-5-butyl-7-[3-methoxy-propylamino]-pyrazolo[2,3-*a*]pyrimidine (compound 47) (3.5 mg).

Example B.5

Compound 26 (8 mg) was dissolved in DCM (1 ml) and treated with acetic anhydride (0.1 ml) and pyridine (0.1 ml). The mixture was stirred at room temperature overnight and concentrated in vacuo. The residue was diluted with ethyl acetate and filtrated through a short silica gel column. Concentration of the filtrate gave 3-(2,4-dichlorophenyl)-5-methyl-7-[*N*-(2-acetoxyethyl)-*N*-benzylamino]-pyrazolo[2,3-*a*]pyrimidine (compound 27) (8.6 mg) as a colorless oil.

Example B.6

A solution of compound 40 (20 mg) in DCM (3 ml) was treated with 3-chloroperbenzoic acid (19 mg). The solution was stirred at room temperature for 1 hour. Chromatography on a silica gel plate with ethyl acetate-hexanes (1:1) yielded compound 43 and compound 44.

Example B.7

A mixture of compound 55, palladium on activated carbon (100 mg) in dry ethanol (100 ml) was put on the hydrogenation unit and hydrogenation was carried out at 2.7 10^5 Pa (40 psi) for 2 hours. The reaction mixture was filtered and concentrated. The residue was dissolved in diethyl ether and concentrated, yielding 1.49 g of 3-(5-amino-3-methyl-2-pyridinyl)-2,5-dimethyl-*N,N*-dipropyl-pyrazolo[2,3-*a*]pyrimidine-7-amine (compound 56).

Example B.8

To a stirring solution of compound 56 (1.39 g) and aqueous formaldehyde (6.4 g) in ACN (20 ml) was added sodium cyanoborohydride (743 mg) at 0°C. Glacial acetic

-17-

- acid (1 ml) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over sodium sulfate, filtered, concentrated to dryness and purified by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 150:10:1). The desired fraction was isolated, yielding 1.30 g of 3-[5-(dimethylamino)-3-methyl-2-pyridinyl]-2,5-dimethyl-*N,N*-dipropyl-pyrazolo[2,3-*a*]pyrimidine-7-amine (compound 57).

Example B.9

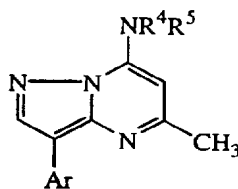
- To a solution of compound 56 (100 mg) in a mixture of concentrated HCl (1 ml) and water (1 ml), cooled in an ice bath, was added a solution of sodium nitrite (21 mg) in water (1 ml). The solution was added to a mixture of copper(I)chloride (281 mg) in concentrated HCl with stirring in an ice bath. A solid separated and the mixture was heated to 60°C and a clear solution was obtained. The reaction mixture was basified with NaOH, extracted with ethyl acetate, washed with brine and concentrated. Purification by preparative TLC yielded 16 mg of compound 98.

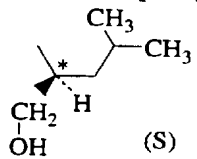
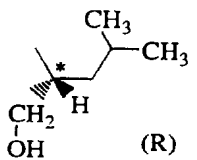
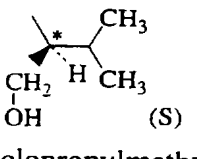
Example B.10

- Compound 56 (100 mg) was added to a solution of fluoroboric acid (48% wt in water, 2 ml), cooled in an ice bath, followed by addition of a solution of sodium nitrite (20 mg) in water (1 ml). The temperature was kept under 10°C. The solid was collected by filtration, dried and partitioned between an aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was washed with brine, concentrated and the residue was purified by preparative TLC yielding 20 mg of compound 100.

Tables 2 to 5 list the compounds that were prepared according to one of the above Examples and tables 6 and 7 list the analytical data for these compounds.

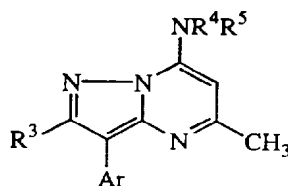
Table 2 :



Co. No.	Ex. No.	R ⁴	R ⁵	Ar
1	B.1	hydrogen	n-propyl	2,4-dichlorophenyl
2	B.1	hydrogen	2-methylpropyl	2,4-dichlorophenyl
3	B.1	hydrogen	1,1-dimethylethyl	2,4-dichlorophenyl
4	B.1	hydrogen	3-hydroxypropyl	2,4-dichlorophenyl
5	B.1	hydrogen	3-pentyl	2,4-dichlorophenyl
6	B.1	hydrogen	CH ₃ O(CH ₂) ₃ -	2,4-dichlorophenyl
7	B.1	hydrogen	(CH ₃) ₂ CHO(CH ₂) ₃ -	2,4-dichlorophenyl
8	B.1	hydrogen	cyclopropylmethyl	2,4-dichlorophenyl
9	B.1	hydrogen	3-methyl-2-butyl	2,4-dichlorophenyl
10	B.1	hydrogen	4-methyl-2-pentyl	2,4-dichlorophenyl
11	B.1	hydrogen		2,4-dichlorophenyl
12	B.1	hydrogen		2,4-dichlorophenyl
13	B.1	hydrogen		2,4-dichlorophenyl
14	B.3	methyl	cyclopropylmethyl	2,4-dichlorophenyl
15	B.1	ethyl	n-butyl	2,4-dichlorophenyl
16	B.2	n-propyl	n-propyl	2,4-dichlorophenyl
17	B.1	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
18	B.1	n-propyl	HOCH ₂ CH ₂ -	2,4-dichlorophenyl
19	B.1	n-propyl	CH ₃ O(CH ₂) ₂ -	2,4-dichlorophenyl
20	B.2	n-propyl	n-propyl	4-chlorophenyl
21	B.1	n-propyl	cyclopropyl	2,6-dichlorophenyl
22	B.1	n-propyl	CH ₃ O(CH ₂) ₂	2,6-dichlorophenyl
23	B.4	n-butyl	cyclopropylmethyl	2,4-dichlorophenyl
24	B.1	2-methylpropyl	cyclopropylmethyl	2,4-dichlorophenyl
25	B.1	3-methyl-2-butyl	cyclopropylmethyl	2,4-dichlorophenyl

Co. No.	Ex. No.	R ⁴	R ⁵	Ar
26	B.1	HOCH ₂ CH ₂ -	phenylmethyl	2,4-dichlorophenyl
27	B.5	CH ₃ COO(CH ₂) ₂ -	phenylmethyl	2,4-dichlorophenyl
28	B.5	CH ₃ COO(CH ₂) ₂ -	n-propyl	2,4-dichlorophenyl
29	B.4	allyl	cyclopropylmethyl	2,4-dichlorophenyl
45	B.4	n-propyl	CH ₃ O(CH ₂) ₃	2,4-dichlorophenyl
58	B.1	CH ₃ O(CH ₂) ₂ -	CH ₃ O(CH ₂) ₂ -	2,4-dichlorophenyl
59	B.1	hydrogen	CH ₃ OCH ₂ CH(CH ₃)-	2,4-dichlorophenyl
60	B.1	hydrogen	1-hydroxy-2-hexyl	2,4-dichlorophenyl
61	B.1	hydrogen	1-hydroxy-2-pentyl	2,4-dichlorophenyl
62	B.2	n-propyl	n-propyl	6-dimethylamino- 2,4-dimethyl-3-pyridinyl
63	B.1	ethyl	n-butyl	6-dimethylamino- 2,4-dimethyl-3-pyridinyl
64	B.1	n-propyl	cyclopropylmethyl	6-dimethylamino- 2,4-dimethyl-3-pyridinyl
65	B.1	n-propyl	cyclopropylmethyl	6-methyl-3-pyridinyl
66	B.1	n-butyl	n-butyl	6-methyl-3-pyridinyl
67	B.1	n-propyl	cyclopropylmethyl	2,4-dimethoxyphenyl
68	B.2	n-propyl	n-propyl	2,4,6-trimethoxyphenyl
69	B.1	n-propyl	CH ₃ O(CH ₂) ₂ -	2,4,6-trimethoxyphenyl
70	B.1	n-propyl	cyclopropylmethyl	2,4,6-trimethoxyphenyl
71	B.1	ethyl	n-butyl	2,4,6-trimethoxyphenyl
72	B.1	ethyl	ethyl	2,4,6-trimethoxyphenyl

Table 3 :



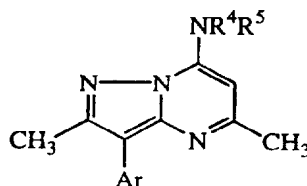
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Co. No.	Ex. No.	R ³	R ⁴	R ⁵	Ar
30	B.1	CH ₃ S	hydrogen	n-propyl	2,4-dichlorophenyl
31	B.1	CH ₃ S	hydrogen	2-propyl	2,4-dichlorophenyl

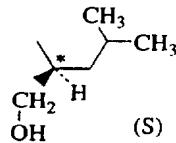
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Co. No.	Ex. No.	R ³	R ⁴	R ⁵	Ar
32	B.1	CH ₃ S	hydrogen	3-heptyl	2,4-dichlorophenyl
34	B.1	CH ₃ S	hydrogen	2-methoxyphenylmethyl	2,4-dichlorophenyl
35	B.1	CH ₃ S	methyl	methyl	2,4-dichlorophenyl
36	B.1	CH ₃ S	ethyl	ethyl	2,4-dichlorophenyl
37	B.2	CH ₃ S	n-propyl	n-propyl	2,4-dichlorophenyl
38	B.1	CH ₃ S	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
39	B.1	CH ₃ S	2-propyl	2-propyl	2,4-dichlorophenyl
40	B.1	CH ₃ S	n-butyl	n-butyl	2,4-dichlorophenyl
41	B.1	CH ₃ S	n-butyl	cyclopropylmethyl	2,4-dichlorophenyl
42	B.1	CH ₃ S	allyl	allyl	2,4-dichlorophenyl
43	B.6	CH ₃ SO	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
44	B.6	CH ₃ SO ₂	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
73	B.2	CH ₃ CH ₂	n-propyl	n-propyl	3,4-dimethoxyphenyl

Table 4 :



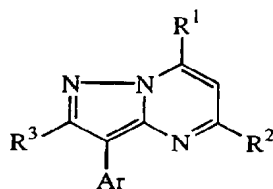
Co. No.	Ex. No.	R ⁴	R ⁵	Ar
48	B.2	n-propyl	n-propyl	4-chlorophenyl
49	B.1	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
51	B.1	n-propyl	CH ₃ O(CH ₂) ₂ -	2,4-dimethoxyphenyl
52	B.2	n-propyl	n-propyl	6-dimethylamino-3-pyridinyl
53	B.2	n-propyl	n-propyl	6-dimethylamino-4-methyl-3-pyridinyl
54	B.2	n-propyl	n-propyl	5-chloro-2-pyridinyl
55	B.2	n-propyl	n-propyl	3-methyl-5-nitro-2-pyridinyl
56	B.7	n-propyl	n-propyl	5-amino-3-methyl-2-pyridinyl
57	B.8	n-propyl	n-propyl	5-dimethylamino-3-methyl-2-pyridinyl
74	B.1	CH ₃ O(CH ₂) ₂ -	CH ₃ O(CH ₂) ₂ -	4-chlorophenyl
75	B.1	HOCH ₂ CH ₂ -	phenylmethyl	4-chlorophenyl

Co. No.	Ex. No.	R ⁴	R ⁵	Ar
76	B.1	hydrogen	1-hydroxy-2-hexyl	4-chlorophenyl
77	B.1	hydrogen	1-hydroxy-2-pentyl	4-chlorophenyl
78	B.1	hydrogen	CH ₃ S(CH ₂) ₂ -	4-chlorophenyl
79	B.1	hydrogen	 (S)	4-chlorophenyl
80	B.1	hydrogen	1-hydroxy-2-hexyl	6-dimethylamino-4-methyl-3-pyridinyl
81	B.1	ethyl	n-butyl	6-dimethylamino-4-methyl-3-pyridinyl
82	B.1	n-propyl	cyclopropylmethyl	6-dimethylamino-4-methyl-3-pyridinyl
83	B.1	n-propyl	phenylmethyl	6-dimethylamino-4-methyl-3-pyridinyl
84	B.1	allyl	allyl	6-dimethylamino-4-methyl-3-pyridinyl
85	B.1	n-butyl	n-butyl	6-dimethylamino-4-methyl-3-pyridinyl
86	B.1	hydrogen	3-pentyl	6-dimethylamino-4-methyl-3-pyridinyl
87	B.1	hydrogen	2-propyl	6-dimethylamino-4-methyl-3-pyridinyl
88	B.1	hydrogen	4-methyl-2-pentyl	6-dimethylamino-4-methyl-3-pyridinyl
89	B.1	methyl	n-butyl	6-dimethylamino-4-methyl-3-pyridinyl
90	B.2	n-propyl	n-propyl	6-dimethylamino-2-methyl-3-pyridinyl
91	B.1	n-propyl	cyclopropylmethyl	6-dimethylamino-2-methyl-3-pyridinyl
92	B.1	ethyl	n-butyl	6-dimethylamino-2-methyl-3-pyridinyl
93	B.1	n-butyl	n-butyl	6-dimethylamino-2-methyl-3-pyridinyl
94	B.1	n-propyl	n-propyl	4,6-dimethyl-3-pyridinyl
95	B.1	n-propyl	cyclopropylmethyl	4,6-dimethyl-3-pyridinyl
96	B.2	n-propyl	n-propyl	6-dimethylamino-2,4-dimethyl-3-pyridinyl
97	B.1	n-propyl	cyclopropylmethyl	6-dimethylamino-2,4-dimethyl-3-pyridinyl

Co. No.	Ex. No.	R ⁴	R ⁵	Ar
98	B.9	n-propyl	n-propyl	5-chloro-3-methyl-2-pyridinyl
99	B.9	n-propyl	n-propyl	5-iodo-3-methyl-2-pyridinyl
100	B.10	n-propyl	n-propyl	5-fluoro-3-methyl-2-pyridinyl
101	B.2	n-propyl	n-propyl	3-chloro-5-trifluoromethyl-2-pyridinyl
102	B.1	CH ₃ O(CH ₂) ₂ -	CH ₃ O(CH ₂) ₂ -	3-chloro-5-trifluoromethyl-2-pyridinyl
103	B.2	n-propyl	n-propyl	3,5-dichloro-2-pyridinyl
104	B.1	n-propyl	CH ₃ O(CH ₂) ₂ -	3,5-dichloro-2-pyridinyl
105	B.1	n-propyl	cyclopropylmethyl	3,5-dichloro-2-pyridinyl
106	B.2	n-propyl	n-propyl	3-methyl-5-methoxy-2-pyridinyl
107	B.8	n-propyl	n-propyl	5-diethylamino-3-methyl-2-pyridinyl
33	B.8	n-propyl	n-propyl	6-diethylamino-4-methyl-3-pyridinyl
108	B.8	n-propyl	n-propyl	5-N-piperidinyl-3-methyl-2-pyridinyl
109	B.2	n-propyl	n-propyl	5-methyl-3-nitro-2-pyridinyl
110	B.2	n-propyl	n-propyl	3-amino-5-methyl-2-pyridinyl
111	B.9	n-propyl	n-propyl	3-chloro-5-methyl-2-pyridinyl
112	B.2	n-propyl	n-propyl	3-methylamino-5-methyl-2-pyridinyl
113	B.2	n-propyl	n-propyl	3-dimethylamino-5-methyl-2-pyridinyl
114	B.2	n-propyl	n-propyl	2-methyl-5-pyridinyl
115	B.1	n-propyl	cyclopropylmethyl	4-isopropylphenyl
116	B.2	n-propyl	n-propyl	3,4-dimethoxyphenyl
117	B.1	n-propyl	CH ₃ O(CH ₂) ₂ -	3,4-dimethoxyphenyl
118	B.1	n-propyl	cyclopropyl	2,4-dimethoxyphenyl
119	B.1	hydrogen	CH ₃ O(CH ₂) ₂ -	2,4-dimethoxyphenyl
120	B.1	n-propyl	HO(CH ₂) ₂ -	2,4-dimethoxyphenyl
121	B.8	n-propyl	n-propyl	5-methylamino-3-methyl-2-pyridinyl
122	B.2	n-propyl	n-propyl	2,4-dimethoxyphenyl
123	B.1	ethyl	n-butyl	2,4-dimethoxyphenyl
124	B.1	n-propyl	2-hydroxypropyl	2,4-dimethoxyphenyl
125	B.2	n-propyl	n-propyl	4-methoxyphenyl
126	B.2	n-propyl	n-propyl	3-methoxyphenyl
127	B.1	n-propyl	cyclopropylmethyl	3-methoxyphenyl

Co. No.	Ex. No.	R ⁴ and R ⁵ taken together	Ar
128	B.1		4-chlorophenyl
129	B.1		4-chlorophenyl
130	B.1		6-dimethylamino-4-methyl-3-pyridinyl
131	B.1		6-dimethylamino-4-methyl-3-pyridinyl

Table 5 :



Co. No.	Ex. No.	R ¹	R ²	R ³	Ar
46	B.4		n-C ₄ H ₉	H	2,4-dichlorophenyl
47	B.4		n-C ₄ H ₉	H	2,4-dichlorophenyl
50	B.3	CH ₃ CH ₂ O-	CH ₃	CH ₃ -S-	2,4-dichlorophenyl

5

Table 6 : Analytical data

Co. No.	¹ H NMR data (CDCl ₃)	MS M + 1
1	δ 0.45 (m,2H), 0.78 (m,2H), 1.20 (m,1H), 2.84 (s,3H), 3.40 (d,2H), 5.98 (s,1H), 7.41 (dd,1H), 7.52 (d,1H), 7.76 (d,1H), 8.32 (s,1H)	335
2	δ 0.88 (d,3H), 1.05 (d,3H), 1.74 (m,1H), 2.52 (s,3H), 3.20 (t,2H), 5.87 (s,1H), 6.40 (t,1H), 7.30 (dd,1H), 7.47 (d,1H), 7.99 (d,1H), 8.42 (s,1H)	349

Co. No.	^1H NMR data (CDCl_3)	MS M + 1
3	δ 1.57 (s,9H), 2.54 (s,3H), 6.05 (s,1H), 6.48 (s,1H), 7.31 (d,1H), 7.47 (s,1H), 7.99 (d,1H), 8.39 (s,1H)	349
4	δ 1.97 (m,2H), 2.43 (s,3H), 3.62 (m,2H), 3.75 (t,3H), 4.00 (brs, 1H), 6.18 (s,1H), 7.39 (dd,1H), 7.52 (d,1H), 8.19 (d,1H), 8.43 (s,1H)	351
5	δ 1.03 (t,6H), 1.60-1.85 (m,4H), 2.56 (s,3H), 3.49 (m,1H), 5.92 (s,1H), 6.19 (d,1H), 7.35 (dd,1H), 7.50 (dd,1H), 8.01 (d,1H), 8.44 (s,1H)	363
6	δ 2.02 (m,2H), 2.51 (s,3H), 3.40 (s,3H), 3.51 (m,4H), 5.91 (s,1H), 6.71 (t,1H), 7.31 (dd,1H), 7.47 (d,1H), 7.99 (d,1H), 8.42 (s,1H)	365
7	δ 1.23 (d,6H), 2.00 (m,2H), 2.52 (s,1H), 3.51 (dd,2H), 3.59 (m,2H), 5.90 (s,1H), 6.92 (t,1H), 7.31 (dd, 1H), 7.46 (d,1H), 8.00 (d,1H), 8.41 (s,1H)	393
8	δ 0.35 (m,2H), 0.68 (m,2H), 1.25 (m,1H), 2.52 (s,3H), 3.23 (dd,2H), 5.88 (s,1H), 6.40 (t,1H), 7.32 (d,1H), 7.48 (s,1H), 7.99 (s,1H), 8.43 (s,1H)	347
9	δ 1.03 (d,3H), 1.06 (d,3H), 1.31 (d,3H), 1.95 (m,1H), 2.52 (s,3H), 3.54 (m,1H), 5.88 (s,1H), 6.23 (d,1H), 7.32 (d,1H), 7.47 (s,1H), 7.98 (d,1H), 8.41 (s,1H)	363
10	δ 0.95 (d,3H), 0.97 (d,3H), 1.40-1.80 (m,3H), 2.53 (s,3H), 3.76 (m,1H), 5.89 (s,1H), 6.12 (d,1H), 7.32 (d,1H), 7.47 (s,1H), 7.97 (d,1H), 8.40 (s,1H)	377
11	δ 0.94 (d,3H), 0.99 (d,3H), 1.53 (m,1H), 1.76 (m,1H), 2.50 (s,3H), 2.93 (brs,1H), 3.48 (m,1H), 3.76 (m,1H), 5.97 (s,1H), 6.22 (d,1H), 7.35 (dd, 1H), 7.51 (d,1H), 7.95 (d,1H), 8.36 (s,	393
12	δ 0.92 (d,3H), 0.97 (d,3H), 1.52 (m,2H), 1.72 (m,1H), 2.47 (s,3H), 3.02 (brs,1H), 3.42 (m,1H), 3.72 (m,2H), 5.94 (s,1H), 6.20 (d,1H), 7.33 (d,1H), 7.49 (s,1H), 7.92 (d,1H), 8.33 (s,	393
13	δ 0.99 (d,6H), 1.98 (m,1H), 2.44 (s,3H), 3.22 (brs, 1H), 3.46 (m,2H), 3.73 (m,1H), 5.88 (s,1H), 6.31 (d,1H), 7.32 (d,1H), 7.48 (s,1H), 7.92 (d,1H), 8.32 (s, 1H)	379
14	δ 0.21 (m,2H), 0.54 (m,2H), 1.10 (m,1H), 2.53 (s,3H), 3.28 (s,3H), 3.91 (d,2H), 5.99 (s,1H), 7.32 (d,1H), 7.48 (s,1H), 7.97 (d,1H), 8.43 (s,1H)	379

Co. No.	¹ H NMR data (CDCl ₃)	MS M + 1
15	δ 0.96 (t,3H), 1.31 (t,3H), 1.38 (m,2H), 1.71 (m,2H), 2.49 (s,3H), 3.74 (t,2H), 3.65 (q,2H), 5.90 (s,1H), 7.30 (dd,1H), 7.46 (d,1H), 7.97 (d,1H), 8.40 (s,1H)	377
16	δ 0.96 (t,6H), 1.73 (m,4H), 2.49 (s,3H), 3.73 (t,4H), 5.88 (s,1H), 7.33 (dd,1H), 7.46 (d,1H), 7.98 (d,1H), 8.40 (s,1H)	377
17	δ 0.26 (m,2H), 0.58 (m,2H), 0.98 (t,3H), 1.18 (m,1H), 1.76 (m,2H), 2.53 (s,3H), 3.76 (d,2H), 3.81 (t,2H), 6.02 (s,1H), 7.34 (dd,1H), 7.49 (dd,1H), 8.44 (s,1H)	389
18	δ 1.04 (t,3H), 1.77 (m,2H), 2.53 (s,3H), 3.47 (t,2H), 3.98 (m,2H), 4.06 (m,2H), 5.52 (brs, 1H), 6.03 (s,1H), 7.33 (d,1H), 7.48 (s,1H), 7.93 (d, 1H), 8.39 (s, 1H)	379
19	δ 0.98 (t,3H), 1.76 (m,2H), 2.50 (s,3H), 3.35 (s,3H), 3.67 (t,2H), 3.72 (m,2H), 4.14 (m,2H), 5.95 (s,3H), 7.29 (d,1H), 7.47 (s,1H), 7.97 (d,1H), 8.39 (s,1H)	393
20	δ 0.96 (t,6H), 1.73 (m,4H), 2.55 (s,3H), 3.74 (t,4H), 5.90 (s,1H), 7.40 (d,2H), 8.04 (d,2H), 8.25 (s,1H)	343
21	δ 0.26 (m,2H), 0.51 (m,2H), 0.92 (t,3H), 1.10 (m,1H), 1.69 (m,2H), 2.72 (s,3H), 3.41 (d,2H), 3.47 (t,2H), 6.17 (s,1H), 7.18 (t,1H), 7.43 (d,2H), 7.99 (s,1H)	389
22	δ 0.93 (t,3H), 1.67 (m,2H), 2.71 (s,3H), 3.32 (s,3H), 3.44 (t,2H), 3.61 (m,2H), 3.68 (m,2H), 6.16 (s,1H), 7.17 (t,1H), 7.41 (d,2H), 7.99 (s,1H)	393
23	δ 0.24 (m,2H), 0.55 (m,2H), 0.95 (t,3H), 1.38 (m,2H), 1.69 (m,2H), 2.51 (s,3H), 3.74 (d,2H), 3.82 (t,2H), 6.00 (s,1H), 7.31 (dd,1H), 7.48 (dd,1H), 7.98 (d,1H), 8.42 (s,1H)	403
24	δ 0.28 (m,2H), 0.50 (m,2H), 0.94 (d,6H), 1.10 (m,1H), 2.05 (m,1H), 2.52 (s,3H), 3.62 (d,2H), 3.82 (d,2H), 6.03 (s,1H), 7.32 (d,1H), 7.47 (s,1H), 7.99 (d,1H), 8.43 (s,1H)	403
25	δ 0.17 (m,2H), 0.47 (m,2H), 0.97 (t,6H), 1.05 (m,1H), 1.67 (m,4H), 2.52 (s,3H), 2.43 (d,2H), 4.71 (m,1H), 6.13 (s,1H), 7.32 (dd,1H), 7.47 (d,1H), 8.02 (d,1H), 8.43 (s,1H)	417
26	δ 2.41 (s,3H), 4.01 (m,2H), 4.15 (m,2H), 4.79 (s,2H), 5.62 (brs, 1H), 6.02 (s,1H), 7.35 (m,6H), 7.48 (s,1H), 7.91 (d,1H), 8.41 (s,1H)	427
27	δ 1.91 (s,3H), 2.47 (s,3H), 4.20 (t,2H), 4.43 (t,2H), 4.96 (s,2H), 6.03 (s,1H), 7.34 (m,6H), 7.49 (s,1H), 7.94 (d,1H), 8.44 (s,1H)	469

28	δ 0.98 (t,3H), 1.74 (m,2H), 1.93 (s,3H), 2.49 (s,3H), 3.59 (m,2H), 4.84 (m,2H), 4.39 (m,2H), 5.95 (s,1H), 7.30 (dd,1H), 7.46 (d,1H), 7.92 (d,1H), 8.38 (s,1H)	421
29	δ 0.28 (m,2H), 0.60 (m,2H), 1.20 (m,1H), 2.51 (s,3H), 3.70 (d,2H), 4.50 (d,2H), 5.29 (d,1H), 5.30 (d,1H), 5.96 (m,1H), 6.05 (s,1H), 7.32 (dd,1H), 7.48 (d,1H), 7.96 (d,1H), 8.44 (s,1H)	387
30	δ 1.07 (t,3H), 1.80 (m,2H), 2.46 (s,3H), 2.55 (s,3H), 3.36 (dt,2H), 5.82 (s,1H), 6.29 (t,1H), 7.29 (d,1H), 7.38 (d,1H), 7.51 (s,1H)	381
31	δ 1.41 (d,6H), 2.46 (s,3H), 2.55 (s,3H), 3.85 (m,1H), 5.82 (s,1H), 6.08 (d,1H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	381
32	δ 0.92 (t,3H), 1.01 (t,3H), 1.25-1.80 (m,8H), 2.45 (s,3H), 2.54 (s,3H), 3.48 (m,1H), 5.79 (s,1H), 6.02 (d,1H), 7.27 (d,1H), 7.39 (d,1H), 7.50 (s,1H)	437
33	δ 0.96 (t,3H), 1.20 (t,6H), 1.74 (m, 4H), 2.15 (s,3H), 2.34 (s,3H), 2.41 (s, 3H), 3.56 (t,4H), 3.79 (t,4H), 5.77 (s,1H), 6.41 (s,1H), 7.54 (s,1H)	-
34	δ 2.45 (s,3H), 2.56 (s,3H), 3.93 (s,3H), 4.60 (d,2H), 5.90 (s,1H), 6.70 (t,1H), 6.99 (t,2H), 7.27-7.41 (m,4H), 7.52 (s,1H)	459
35	δ 2.44 (s,3H), 2.60 (s,3H), 3.35 (s,6H), 5.00 (brs,1H), 5.84 (s,1H), 7.29 (d,1H), 7.38 (d,1H), 7.51 (s,1H)	367
36	δ 1.36 (s,6H), 2.42 (s,3H), 2.59 (s,3H), 3.80 (m,4H), 5.80 (s,1H), 7.29 (d,1H), 7.38 (d,1H), 7.51 (s,1H)	395
37	δ 0.98 (t,6H), 1.78 (m,4H), 2.40 (s,3H), 2.59 (s,3H), 3.69 (m,4H), 5.74 (s,1H), 7.28 (d,1H), 7.48 (d,1H)	423
38	δ 0.30 (m,2H), 0.62 (m,2H), 0.99 (t,3H), 1.20 (m,1H), 1.81 (m,2H), 2.49 (s,3H), 2.59 (s,3H), 3.65-3.90 (m,4H), 5.87 (s,1H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	435
39	δ 1.05 (d,3H), 1.38 (d,3H), 2.45 (s,3H), 2.56 (s,3H), 3.40 (m,1H), 5.80 (s,1H), 7.30 (d,1H), 7.37 (d,1H), 7.51 (s,1H)	423
40	δ 0.98 (t,6H), 1.40 (m,4H), 1.75 (m,4H), 2.42 (s,3H), 2.59 (s,3H), 3.71 (m,4H), 5.76 (s,1H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	451
41	δ 0.29 (m,2H), 0.61 (m,2H), 0.93 (t,3H), 1.20-1.56 (m,3H), 1.75 (m,2H), 2.43 (s,3H), 2.59 (s,3H), 3.65-3.90 (m,4H), 5.88 (s,1H), 7.30 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	449
42	δ 2.42 (s,3H), 2.59 (s,3H), 4.34 (d,4H), 5.30 (m,4H), 5.87 (s,1H), 6.05 (m,2H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	419

Co. No.	¹ H NMR data (CDCl ₃)	MS M + 1
43	δ 0.31 (m,2H), 0.62 (m,2H), 1.00 (t,3H), 1.23 (m,1H), 1.81 (m,1H), 2.49 (s,3H), 3.05 (brs,3H), 3.42-3.95 (m,4H), 6.04 (s,1H), 7.33 (d,1H), 7.50 (s,1H), 7.51 (d,1H)	451
44	δ 0.13 (m,2H), 0.48 (m,2H), 0.90 (t,3H), 1.05 (m,1H), 1.60 (m,2H), 2.64 (s,3H), 3.05 (brs,3H), 3.48 (d,2H), 3.71 (m,2H), 6.04 (s,1H), 7.37 (d,1H), 7.54 (s,1H), 7.60 (d,1H)	485 (+H ₂ O)
45	δ 0.95 (t,3H), 1.42 (m,2H), 1.98 (m,2H), 2.49 (s,3H), 3.33 (s,3H), 3.56 (m,2H), 3.75 (m,2H), 5.93 (m,1H), 7.31 (d,1H), 7.46 (s,1H), 7.96 (d,1H), 8.40 (s,1H)	407
46	δ 0.91 (t,3H), 0.95 (t,3H), 1.35-2.05 (m,8H), 2.70 (t,2H), 3.33 (s,3H), 3.40 (m,6H), 5.92 (s,1H), 7.30 (d,1H), 7.46 (s,1H), 8.02 (d,1H), 8.41 (s,1H)	449
47	δ 0.87 (t,3H), 1.25 (m,2H), 1.70 (m,2H), 2.04 (m,2H), 2.68 (m,2H), 3.41 (s,3H), 3.56 (m,4H), 5.86 (s,1H), 6.60 (t,1H), 7.31 (d,1H), 7.46 (s,1H), 8.14 (d,1H), 8.50 (s,1H)	407
48	δ 0.95 (t,6H), 1.71 (m,4H), 2.47 (s,3H), 2.55 (s,3H), 3.71 (t,4H), 5.82 (s,1H), 7.39 (d,2H), 7.70 (d,2H)	357
49	δ 0.24 (m,2H), 0.54 (m,2H), 0.96 (t,3H), 1.12 (m,1H), 1.74 (m,2H), 2.35 (s,3H), 2.44 (s,3H), 3.73 (d,2H), 3.76 (t,2H), 5.93 (s,1H), 7.29 (d,1H), 7.35 (d,1H), 7.51 (s,1H)	403
50	δ 1.64 (t,3H), 2.52 (s,3H), 2.60 (s,3H), 4.56 (q,2H), 6.02 (s,3H), 7.30 (d,1H), 7.37 (d,1H), 7.51 (s,1H)	368
52	δ 0.9 (t, 6H), 1.68 (m, 4H), 2.13 (s, 3H), 2.30 (s, 3H), 2.37 (s, 3H), 3.05 (s, 6H), 3.65 (m, 4H), 5.74 (s, 1H), 6.44 (s, 1H), 8.01 (s, 1H)	M ⁺ = 366
53	δ 0.9 (t, 6H), 1.70 (m, 4H), 2.35 (s, 3H), 2.45 (s, 3H), 3.05 (s, 6H), 3.65 (m, 4H), 5.74 (s, 1H), 6.44 (s, 1H), 8.01 (s, 1H)	M ⁺ = 380
54	δ 0.95 (t, 6H), 1.73 (m, 4H), 2.52 (s, 3H), 2.76 (s, 3H), 3.73 (t, 4H), 5.85 (s, 1H), 7.68 (dd, 1H), 8.45 (d, 1H), 8.57 (d, 1H)	-
55	δ 0.96 (t, 6H), 1.70 - 1.78 (m, 4H), 2.44 (s, 3H), 2.47 (s, 3H), 2.50 (s, 3H), 3.73 (t, 4H), 5.48 (s, 1H), 8.36 (d, 1H), 9.32 (d, 1H)	383
56	δ 0.93 (t, 6H), 1.66 - 1.73 (m, 4H), 2.19 (s, 3H), 2.36 (s, 3H), 2.42 (s, 3H), 3.71 (t, 4H), 5.79 (s, 1H), 6.39 (d, 1H), 8.05 (d, 1H)	353
57	δ 0.96 (t, 6H), 1.62 - 1.70 (m, 4H), 2.2 (s, 3H), 2.36 (s, 3H), 2.40 (s, 3H), 2.96 (s, 6H), 3.68 (t, 4H), 5.76 (s, 1H), 6.91 (d, 1H), 8.08 (d,1H)	381

Table 7 : Analytical data

Co. No.	Mass spectral data	Co. No.	Mass spectral data
58	409 [M ⁺]	95	364 [MH ⁺]
59	365 [M ⁺]	96	395 [MH ⁺]
60	394 [MH ⁺]	97	407 [MH ⁺]
61	380 [MH ⁺]	98	372 [MH ⁺] (Cl ³⁵)
62	381 [MH ⁺]	99	464 [MH ⁺]
63	381 [MH ⁺]	100	356 [MH ⁺]
64	393 [MH ⁺]	101	426 [MH ⁺] (Cl ³⁵)
65	350 [MH ⁺]	102	458 [MH ⁺] (Cl ³⁵)
66	366 [MH ⁺]	103	392 [MH ⁺] (Cl ³⁵)
67	381 [MH ⁺]	104	408 [MH ⁺] (Cl ³⁵)
68	399 [MH ⁺]	105	404 [MH ⁺] (Cl ³⁵)
69	415 [MH ⁺]	106	368 [MH ⁺]
70	411 [MH ⁺]	107	409 [MH ⁺]
71	399 [MH ⁺]	108	421 [MH ⁺]
72	371 [MH ⁺]	109	383 [MH ⁺]
73	397 [MH ⁺]	110	353 [MH ⁺]
74	388 [M ⁺]	111	372 [MH ⁺] (Cl ³⁵)
75	407 [MH ⁺]	112	366 [MH ⁺]
76	373 [MH ⁺]	113	381 [MH ⁺]
77	359 [MH ⁺]	114	338 [MH ⁺]
78	346 [M ⁺]	115	377 [MH ⁺]
79	373 [MH ⁺]	116	383 [MH ⁺]
80	397 [MH ⁺]	117	399 [MH ⁺]
81	381 [MH ⁺]	118	395 [MH ⁺]
82	393 [MH ⁺]	119	415 [MH ⁺]
83	429 [MH ⁺]	120	385 [MH ⁺]
84	377 [MH ⁺]	121	367 [MH ⁺]
85	409 [MH ⁺]	122	383 [MH ⁺]
86	367 [MH ⁺]	123	383 [MH ⁺]
87	339 [MH ⁺]	124	399 [MH ⁺]
88	381 [MH ⁺]	125	338 [MH ⁺]
89	367 [MH ⁺]	126	353 [MH ⁺]
90	381 [MH ⁺]	127	365 [MH ⁺]
91	393 [MH ⁺]	128	370 [M ⁺]

Co. No.	Mass spectral data	Co. No.	Mass spectral data
92	381 [MH ⁺]	129	368 [M ⁺]
93	409 [MH ⁺]	130	393 [MH ⁺]
94	352 [MH ⁺]	131	379 [MH ⁺]

C. Pharmacological examples

Example C.1

REPRESENTATIVE COMPOUNDS HAVING CRF RECEPTOR BINDING

5 ACTIVITY

Compounds were evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by DeSouza et al. (*J. Neurosci.* 7:88-100, 1987). By utilizing various radiolabeled CRF ligands, the assay may be used
10 to evaluate the binding activity of the compounds of the present invention with any CRF receptor subtype. Briefly, the binding assay involves the displacement of a radiolabeled CRF ligand from the CRF receptor.

More specifically, the binding assay was performed in 1.5 ml Eppendorf tubes using approximately 1×10^6 cells per tube stably transfected with human CRF receptors.
15 Each tube received about 0.1 ml of assay buffer (*e.g.*, Dulbecco's phosphate buffered saline, 10 mM magnesium chloride, 20 μ M bacitracin) with or without unlabeled sauvagine, urotensin I or CRF (final concentration, 1 μ M) to determine nonspecific binding, 0.1 ml of [¹²⁵I] tyrosine - ovine CRF (final concentration ~200 pM or approximately the K_D as determined by Scatchard analysis) and 0.1 ml of a membrane
20 suspension of cells containing the CRF receptor. The mixture was incubated for 2 hours at 22°C followed by the separation of the bound and free radioligand by centrifugation. Following two washes of the pellets, the tubes were cut just above the pellet and monitored in a gamma counter for radioactivity at approximately 80% efficiency. All radioligand binding data was analyzed using a non-linear least-square
25 curve-fitting program.

Binding activity corresponds to the concentration (nM) of the compound necessary to displace 50% of the radiolabeled ligand from the receptor. The following compounds have a $K_i \leq 250$ nM : 5, 10, 12, 15 - 17, 19, 23, 24, 26, 27, 29, 31 - 33, 36 - 43, 48, 49, 51 - 54 and 57 - 130 as listed in Tables 2 - 5. Compounds 17, 29, 38, 41, 42, 48, 49, 51
30 - 54, 57, 58, 70, 71, 81 - 85, 90 - 92, 101, 103 - 105, 115, 118, 121 - 123 and 125 were found to show the best score in this test.

Example C.2CRF STIMULATED ADENYLATE CYCLASE ACTIVITY

The compounds of the present invention may also be evaluated by various functional testing. For example, the compounds of the present invention may be screened for
5 CRF-stimulated adenylate cyclase activity. An assay for the determination of CRF-stimulated adenylate cyclase activity may be performed as generally described by Battaglia et al. (*Synapse* 1:572, 1987), with modifications to adapt the assay to whole cell preparations.

More specifically, the standard assay mixture may contain the following in a final
10 volume of 0.5 ml: 2 mM L-glutamine, 20 mM HEPES, and 1 mM IMBX in DMEM buffer. In stimulation studies, whole cells with the transfected CRF receptors are plated in 24-well plates and incubated for 1 hour at 37°C with various concentrations of CRF-related and unrelated peptides in order to establish the pharmacological rank-order profile of the particular receptor subtype. Following the incubation, the medium is
15 aspirated, the wells rinsed once gently with fresh medium, and the medium aspirated. To determine the amount of intracellular cAMP, 300 µl of a solution of 95% ethanol and 20 mM aqueous hydrochloric acid is added to each well and the resulting suspensions are incubated at -20°C for 16 to 18 hours. The solution is removed into 1.5 ml Eppendorf tubes and the wells washed with an additional 200 µl of ethanol/aqueous
20 hydrochloric acid and pooled with the first fraction. The samples are lyophilized and then resuspended with 500 µl sodium acetate buffer. The measurement of cAMP in the samples is performed using a single antibody kit. For the functional assessment of the compounds, a single concentration of CRF or related peptides causing 80% stimulation of cAMP production is incubated along with various concentrations of competing
25 compounds (10^{-12} to 10^{-6} M).

Example C.3

The plus-maze and defensive withdrawal paradigms are correlated measures of
exploratory activity sensitive to anxiogenic and anxiolytic effects of experimental
30 treatments. These animal models are employed to examine anxiolytic and anti-stress actions of compounds of the present invention.

Example C.3-a : The Elevated Plus-Maze Paradigm

This test predicts how animals respond to an approach-avoidance situation involving a
35 bright lighted space versus a dark "safe" area. Both spaces are elevated off the ground and constitute two runways intersecting in the form of plus sign. This type of

- approach-avoidance situation is a classical test of "emotionality" and reactivity and is very sensitive to treatments that produce disinhibition (such as sedative/hypnotic drugs) and stress. No motivational constraints are necessary and the animal is free to remain in the dark or venture out on the open arms. The plus-maze apparatus has four arms (10 x 50 cm) at right angles to each other and is elevated from the floor (50 cm). Two of the arms are enclosed with walls (40 cm high) and two arms have no walls (open arms). Subjects are placed individually onto the center of the maze and allowed free access to all four arms for 5 minutes. Subjects are observed through a window in the door and via an on-line display of the rat's location on a computer monitor. Time spent in each arm is recorded automatically by photocell beams and a computer program. The maze is wiped clean with a damp cloth between each trial. The measure of anxiogenic-like behavior in this task is a decrease in time spent on open arms while the measure of anti-stress efficacy is a complementary increase in time spent on open arms.
- 15 Validation of the Plus-Maze Using CRF Peptides :
Central administration of CRF and exposure to any of several experimental stressors suppresses exploration in the elevated plus maze model of anxiety. When measuring the behavioral response to social defeat, central administration of the alpha-helical CRF (9-41) antagonist either post-stress [25 µg ICV] or pre-stress [1 µg ICV] reverses the anxiogenic effect of social defeat. This anti-stress action of the CRF antagonist is also exerted following intracerebral administration into the central nucleus of amygdala [250 ng IC].
- 25 Rats were administered the test compounds orally one hour prior to the five minute test. Some groups were placed in a water-filled pool for ninety seconds immediately prior to placement on the Plus-Maze (Stress group) while control subjects were removed directly from the home cage (Non-Stress group). In the non-treated animal group a significant reduction of the percentage of the average time spent in the open arms was observed (from about 36 to about 16 %). Upon administration of 2.5 or 20 mg/kg of compound 53, the % time in the open arms returned to a level equal, within the error range, to the untreated group.

Example C.3-b : The defensive Withdrawal Paradigm

- 35 Testing takes place in a plexiglas open field (106 x 92 x 77 cm) containing a cylindrical galvanized steel chamber measuring 17.1 cm deep and 10.2 cm in diameter. The chamber is open at one end and is located along the wall of the open field aligned

lengthwise and 15.0 cm away from a corner of the open field. The open end faces the corner. The open field is illuminated by fluorescent ceiling lighting. For testing, the animals are introduced into the unfamiliar test environment by placing them into the small chamber. Tests take 5 minutes in duration and the apparatus is cleaned with a mild acetic acid solution after each test. The test compound is administered orally one hour before the 5 minutes test. The behavior of the animals is monitored and recorded by video camera. The latency to leave the chamber will be measured and defined as the placement of all four paws in the open field. Also measured is the number of passages made between the chamber and the open field and the average length of time in the chamber per entry. The measure of anxiolytic efficacy is a decrease in mean time spent within the enclosed chamber. Compound 53 reduced the mean time in the chamber from about 80 seconds to about 20 to 40 seconds when administered at doses of 0.63, 2.5 and 20 mg/kg p.o. to rats.

15 Validation of Defensive Withdrawal using CRF peptides

When injected ICV, both alpha-helical CFR (9-41) and CRF modify behavior in the defensive withdrawal paradigm. In particular, ICV administration of CRF in animals previously familiarized with the apparatus increases both the latency to emerge from the small chamber and mean time spent in the chamber over the fifteen minute session.

20 Similarly, infusion of CRF into the locus ceruleus produced similar changes in defensive withdrawal behavior suggesting that the interaction of CRF with noradrenergic neurons is involved in defensive withdrawal behavior in rats. Conversely, ICV administration of alpha-helical CRF (9-14) or d-Phe CRF (12-41), competitive CRF receptor antagonists, reverses the CRF-like effect of a restraint stressor in familiar environment condition and significantly decreases latency to emerge and mean time in chamber measures in animals unfamiliar with the apparatus.

D. Composition examples

The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic or topical administration to warm-blooded animals in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable acid or base addition salt or a stereochemically isomeric form thereof.

Example D.1 : Oral solutions

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate are dissolved in 4 l of boiling purified water. In 3 l of this solution are dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution is
5 combined with the remaining part of the former solution and 12 l of 1,2,3-propanetriol and 3 l of sorbitol 70% solution are added thereto. 40 g of sodium saccharin are dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence are added. The latter solution is combined with the former, water is added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml).
10 The resulting solution is filled in suitable containers.

Example D.2 : Capsules

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate are vigorously stirred together. The
15 resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I..

Example D.3 : Film-coated tabletsPreparation of tablet core

20 A mixture of 100 g of the A.I., 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there are added 100 g microcrystalline cellulose and 15 g hydrogenated vegetable oil. The whole is mixed well and compressed into tablets,
25 giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl cellulose in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol is
30 molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating
35 apparatus.

Example D.4 : Injectable solution

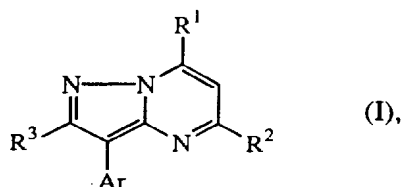
1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I. The solution
5 was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg/ml of A.I. The solution was sterilized by filtration and filled in sterile containers.

Example D.5 : Suppositories

10 3 Grams A.I. was dissolved in a solution of 3 grams 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 Grams surfactant and 300 grams triglycerides were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37 to 38°C to form 100 suppositories each containing 30 mg/ml of the A.I.

Claims

1. A compound of formula



- 5 including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein
- R^1 is NR^4R^5 or OR^5 ;
- R^2 is C_{1-6} alkyl, C_{1-6} alkyloxy or C_{1-6} alkylthio;
- R^3 is hydrogen, C_{1-6} alkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfoxy or C_{1-6} alkylthio;
- 10 R^4 is hydrogen, C_{1-6} alkyl, mono- or di(C_{3-6} cycloalkyl)methyl, C_{3-6} cycloalkyl, C_{3-6} alkenyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyloxy C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl;
- R^5 is C_{1-8} alkyl, mono- or di(C_{3-6} cycloalkyl)methyl, Ar^1CH_2 , C_{3-6} alkenyl, C_{1-6} alkyloxy C_{1-6} alkyl, hydroxy C_{1-6} alkyl, thienylmethyl, furanylmethyl,
- 15 C_{1-6} alkylthio C_{1-6} alkyl, morpholinyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, di(C_{1-6} alkyl)amino, C_{1-6} alkylcarbonyl C_{1-6} alkyl, C_{1-6} alkyl substituted with imidazolyl; or a radical of formula $-Alk-O-CO-Ar^1$;
- or R^4 and R^5 taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group,
- 20 optionally substituted with C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl; and
- Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C_{1-6} alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6} alkyloxy, benzyloxy, C_{1-6} alkylthio, nitro, amino and mono- or di(C_{1-6} alkyl)amino; pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents independently
- 25 selected from halo, C_{1-6} alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6} alkyloxy, benzyloxy, C_{1-6} alkylthio, nitro, amino, mono- or di(C_{1-6} alkyl)amino and piperidinyl; and wherein said substituted phenyl may optionally be further substituted with one or more halogens;
- Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently
- 30 selected from halo, C_{1-6} alkyl, C_{1-6} alkyloxy, di(C_{1-6} alkyl)amino C_{1-6} alkyl, trifluoromethyl and C_{1-6} alkyl substituted with morpholinyl; or pyridinyl; and
- Alk is C_{1-6} alkanediyl;

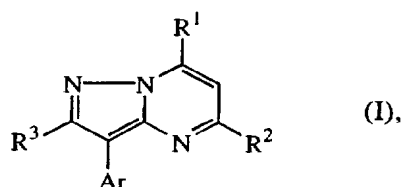
with the proviso that 5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo[1,5-a]-pyrimidine and 2,5-dimethyl-7-(methylamino)-3-phenyl-pyrazolo[1,5-a]pyrimidine are not included.

- 5 2. A compound according to claim 1 wherein R^1 is OR^5 and R^5 is C_{1-6} alkyl; or R^1 is NR^4R^5 and R^4 is hydrogen, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyloxy- C_{1-6} alkyl or C_{3-6} alkenyl, R^5 is C_{1-8} alkyl, C_{3-6} alkenyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, phenylmethyl or C_{3-6} cycloalkylmethyl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a
10 pyrrolidiny, piperidiny, homopiperidiny or morpholiny group, optionally substituted with C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl; R^2 is C_{1-6} alkyl; R^3 is hydrogen, C_{1-6} alkyl or C_{1-6} alkylthio; and Ar is a phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6} alkyl or C_{1-6} alkyloxy; or Ar is a pyridiny substituted with 1, 2 or 3 substituents each independently selected
15 from halo, amino, nitro, trifluoromethyl, mono- or di(C_{1-6} alkyl)amino, piperidiny or C_{1-6} alkyl.
3. A compound according to any of claims 1 to 2 wherein R^1 is NR^4R^5 and R^4 is C_{2-4} alkyl, hydroxy C_{1-2} alkyl, C_{3-4} alkenyl or C_{1-2} alkylcarbonyloxy C_{2-4} alkyl; R^5 is
20 C_{2-4} alkyl, C_{3-4} alkenyl, hydroxy C_{2-4} alkyl or cyclopropylmethyl; R^2 is C_{1-2} alkyl; R^3 is hydrogen, C_{1-2} alkyl or C_{1-2} alkylthio.
4. A compound according to any of claims 1 to 3 wherein R^1 is NR^4R^5 and R^4 is C_{3-4} alkyl or allyl; R^5 is C_{2-4} alkyl, allyl or cyclopropylmethyl; R^2 is methyl; R^3 is
25 methyl; and Ar is phenyl substituted in the 3-, 4-, 6-, 2,4- or 2,4,6-positions with halo, C_{1-6} alkyl or C_{1-6} alkyloxy.
5. A compound according to any of claims 1 to 3 wherein R^1 is NR^4R^5 and R^4 is C_{3-4} alkyl or allyl; R^5 is C_{3-4} alkyl, allyl or cyclopropylmethyl; R^2 is methyl; R^3 is
30 methyl; and Ar is 3-pyridiny substituted on the 4- and/or 6-position with methyl or dimethylamino.
6. A compound according to claim 1 wherein the compound is
35 3-[6-(dimethylamino)-3-pyridiny]-2,5-dimethyl-*N,N*-dipropylpyrazolo[2,3-a]pyrimidin-7-amine, or
3-[6-(dimethylamino)-4-methyl-3-pyridiny]-2,5-dimethyl-*N,N*-dipropylpyrazolo[2,3-a]pyrimidin-7-amine;

-37-

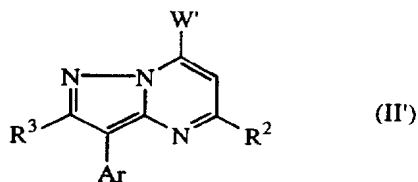
the stereochemically isomeric forms, or the pharmaceutically acceptable acid addition salts thereof.

7. A composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 6.
8. A process for preparing a composition as claimed in claim 7 characterized in that a therapeutically effective amount of a compound as claimed in any one of claims 1 to 6 is intimately mixed with a pharmaceutically acceptable carrier.
9. A compound according to any one of claims 1 to 6 for use as a medicine.
10. The use of compounds of formula

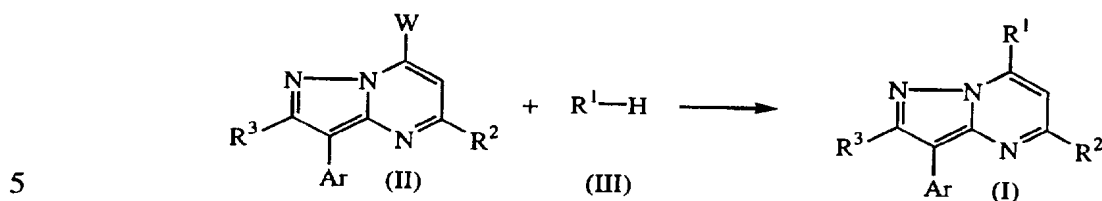


including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein R^1 , R^2 , R^3 and Ar are as defined in claim 1, including the compounds 5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo[1,5-a]pyrimidine and 2,5-dimethyl-7-(methylamino)-3-phenyl-pyrazolo[1,5-a]pyrimidine, for the manufacture of a medicament for treating physiological conditions or disorders arising from the hypersecretion of corticotropin-releasing factor (CRF).

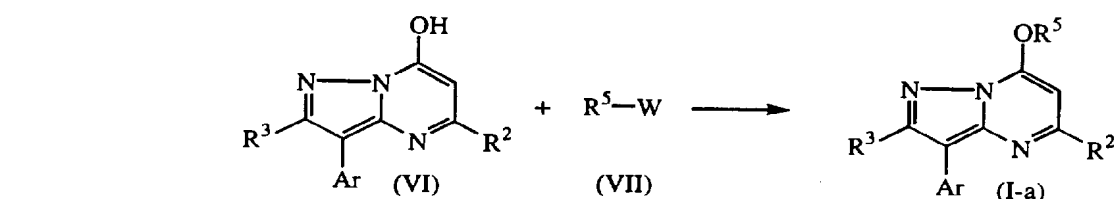
11. A compound of formula (II') wherein the radicals R^2 , R^3 and Ar are as defined in any of claims 1 to 5 and radical W' is hydroxy, halo, mesyloxy or tosyloxy; a stereoisomeric form or an acid addition salt form thereof, with the proviso that compounds wherein Ar is unsubstituted phenyl are not included.



12. A process of preparing a compound as claimed in claim 1, characterized by
a) reacting an intermediate of formula (II) with an intermediate of formula (III) in a
reaction-inert solvent,



- 10 b) *O*-alkylating an intermediate of formula (VI) with an intermediate of formula (VII) in a reaction-inert solvent and in the presence of a suitable base, yielding compounds of formula (I-a), defined as compounds of formula (I) wherein R¹ is OR⁵,

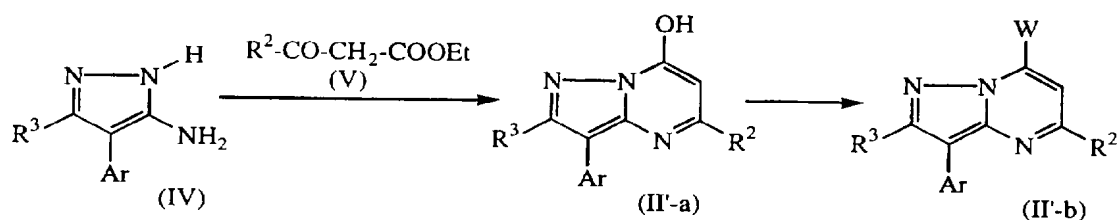


15 wherein in the above reaction schemes the radicals R¹, R², R³, R⁵ and Ar are as defined in claim 1 and W is an appropriate leaving group;

or, if desired, converting compounds of formula (I) into each other following art-known transformation reactions; and further, if desired, converting the compounds of formula (I), into an acid addition salt by treatment with an acid, or conversely, converting the acid addition salt form into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

13. A process of preparing a compound of formula (II') as claimed in claim 10
characterized by
 25 reacting an intermediate of formula (IV) with a β -keto ester (V) in a reaction-inert
 solvent, thereby yielding compounds of formula (II'-a), defined as compounds of
 formula (II') wherein W' is hydroxy;

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and optionally converting compounds of formula (II'-a) into compounds of formula (II'-b), defined as compounds of formula (II') wherein W' is other than hydroxy;

5 wherein in the above reaction schemes the radicals R², R³ and Ar are as defined in claim 1 and W' is hydroxy, halo, mesyloxy or tosyloxy;

or, if desired, converting compounds of formula (II') into each other following art-known transformation reactions; and further, if desired, converting the compounds of formula (II'), into an acid addition salt by treatment with an acid, or conversely, converting the acid addition salt form into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 97/00459

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 61 057 587 A (SHIONOGI AND CO., LTD., JAPAN) 1986 cited in the application & CHEMICAL ABSTRACTS, vol. 105, no. 25, 22 December 1986 Columbus, Ohio, US; abstract no. 226617e, see abstract	1
X	JP 42 011 753 A (SHIONOGI AND CO., LTD.) 1967 cited in the application see the whole document & CHEMICAL ABSTRACTS, vol. 67, no. 23, 4 December 1967 Columbus, Ohio, US; abstract no. 108663r, see abstract	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

15 May 1997

Date of mailing of the international search report

29. 05. 97

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De Jong, B

INTERNATIONAL SEARCH REPORT

Intern. al Application No

PCT/EP 97/00459

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. MED. CHEM. (1976), 19(4), 512-16 CODEN: JMCMAR, 1976, XP002030876 NOVINSON, THOMAS ET AL: "Novel heterocyclic nitrofurfural hydrazones. In vivo antitrypanosomal activity" see page 516, compounds 7a, 7b ---	11
X	J. MED. CHEM. (1981), 24(5), 610-13 CODEN: JMCMAR;ISSN: 0022-2623, 1981, XP002030877 SENGA, KEITARO ET AL: "Synthesis and antischistosomal activity of certain pyrazolo[1,5-a]pyrimidines" see Table II, no. 33,35 ---	11
A	WO 94 13677 A (PFIZER ;CHEN YUHPYNG LIANG (US)) 23 June 1994 cited in the application see claims -----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/EP 97/00459

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 61057587 A	24-03-86	NONE	
JP 42011753 A		NONE	
WO 9413677 A	23-06-94	AU 5728194 A	04-07-94
		CA 2150709 A	23-06-94
		CN 1094048 A,B	26-10-94
		CZ 9501586 A	15-11-95
		EP 0674642 A	04-10-95
		FI 935675 A	18-06-94
		HU 70426 A	30-10-95
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		PL 309359 A	02-10-95
		ZA 9309405 A	15-06-95



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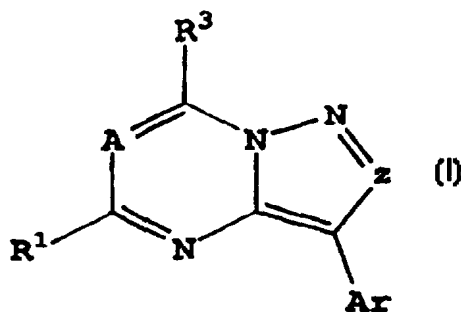
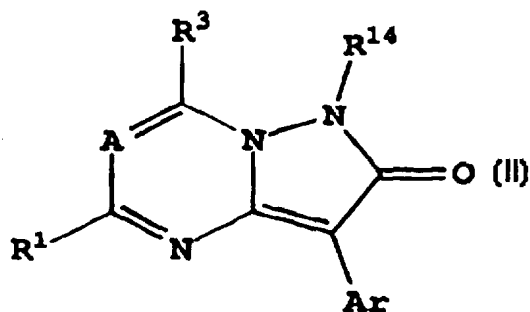
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(54) Title: AZOLO TRIAZINES AND PYRIMIDINES

**(57) Abstract**

Corticotropin releasing factor (CRF) antagonists of formula (I) or (II) and their use in treating anxiety, depression, and other psychiatric, neurological disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

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TITLE

AZOLO TRIAZINES AND PYRIMIDINES

5 FIELD OF THE INVENTION

 This invention relates a treatment of
psychiatric disorders and neurological diseases
including major depression, anxiety-related
10 disorders, post-traumatic stress disorder,
supranuclear palsy and feeding disorders as well as
treatment of immunological, cardiovascular or heart-
related diseases and colonic hypersensitivity
associated with psychopathological disturbance and
15 stress, by administration of certain [1,5-a]-
pyrazolo-1,3,5-triazines, [1,5-a]-1,2,3-triazolo-
1,3,5-triazines, [1,5-a]-pyrazolo-pyrimidines and
[1,5-a]-1,2,3-triazolo-pyrimidines.

20 BACKGROUND OF THE INVENTION

 Corticotropin releasing factor (herein referred
to as CRF), a 41 amino acid peptide, is the primary
physiological regulator of proopiomelanocortin(POMC)
-derived peptide secretion from the anterior
25 pituitary gland [J. Rivier et al., *Proc. Nat. Acad.*
Sci. (USA) 80:4851 (1983); W. Vale et al., *Science*
213:1394 (1981)]. In addition to its endocrine role
at the pituitary gland, immunohistochemical
localization of CRF has demonstrated that the hormone
30 has a broad extrahypothalamic distribution in the
central nervous system and produces a wide spectrum
of autonomic, electrophysiological and behavioral
effects consistent with a neurotransmitter or
neuromodulator role in brain [W. Vale et al., *Rec.*
35 *Prog. Horm. Res.* 39:245 (1983); G.F. Koob, *Persp.*
Behav. Med. 2:39 (1985); E.B. De Souza et al., *J.*

Neurosci. 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (1989); J.E. Morley, *Life Sci.* 41:527 (1987)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (1988)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (1984); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R.D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol Psychiatry* 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (1984); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the

hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)].

There is preliminary evidence that tricyclic
5 antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

There has also been a role postulated for CRF in
10 the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety
15 models [D.R. Britton et al., *Life Sci.* 31:363 (1982); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (1986)]. Preliminary studies using the putative CRF receptor antagonist α -helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the
20 antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (1987), *Brain Research Reviews* 15:71 (1990)]. Neurochemical, endocrine and receptor binding studies
25 have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et
30 al., *Psychopharmacology* 86:170 (1985); K.T. Britton et al., *Psychopharmacology* 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which
35 was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-

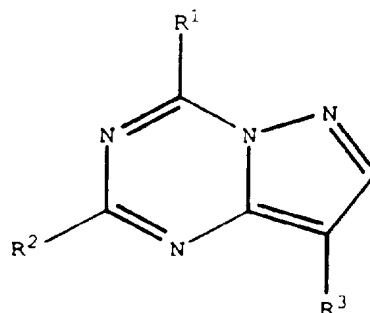
dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (1988)].

5 The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular
10 interest is that preliminary studies examining the effects of a CRF receptor antagonist (α -helical CRF₉₋₄₁) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to
15 the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

Several publications describe corticotropin
20 releasing factor antagonist compounds and their use to treat psychiatric disorders and neurological diseases. Examples of such publications include DuPont Merck PCT application US94/11050 , Pfizer WO 95/33750, Pfizer WO 95/34563, Pfizer WO 95/33727 and
25 Pfizer EP 0778 277 A1.

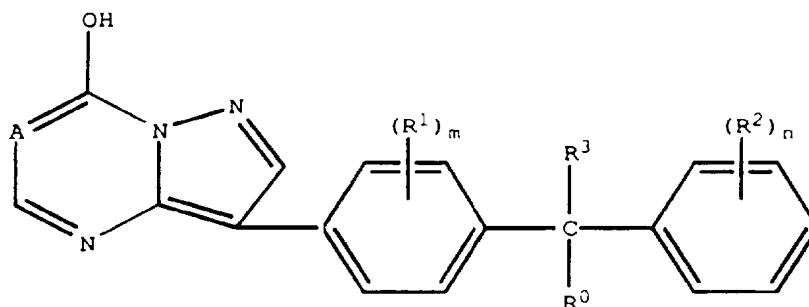
Insofar as is known, [1,5-a]-pyrazolo-1,3,5-triazines, [1,5-a]-1,2,3-triazolo-1,3,5-triazines, [1,5-a]-pyrazolo-pyrimidines and [1,5-a]-1,2,3-triazolo-pyrimidines, have not been previously
30 reported as corticotropin releasing factor antagonist compounds useful in the treatment of psychiatric disorders and neurological diseases. However, there have been publications which teach some of these compounds for other uses.

35 For instance, EP 0 269 859 (Ostuka, 1988) discloses pyrazolotriazine compounds of the formula



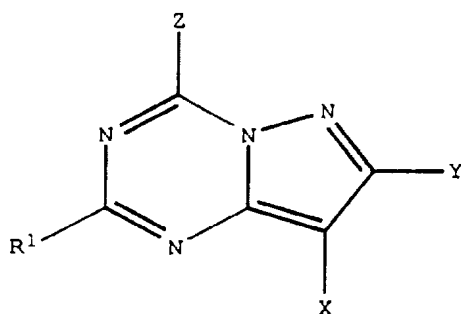
5 where R¹ is OH or alkanoyl, R² is H, OH, or SH, and R³ is an unsaturated heterocyclic group, naphthyl or substituted phenyl, and states that the compounds have xanthine oxidase inhibitory activity and are useful for treatment of gout.

10 EP 0 594 149 (Ostuka, 1994) discloses pyrazolotriazine and pyrazolopyrimidine compounds of the formula



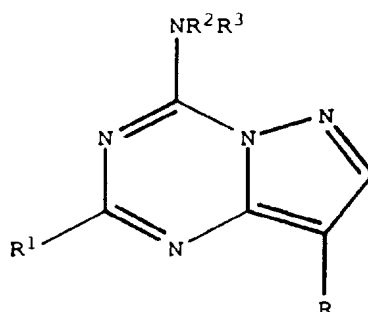
15 where A is CH or N, R⁰ and R³ are H or alkyl, and R¹ and R² are H, alkyl, alkoxyl, alkylthio, nitro, etc., and states that the compounds inhibit androgen and are useful in treatment of benign prostatic hypertrophy and
20 prostatic carcinoma.

US 3,910,907 (ICI, 1975) discloses pyrazolotriazines of the formula:



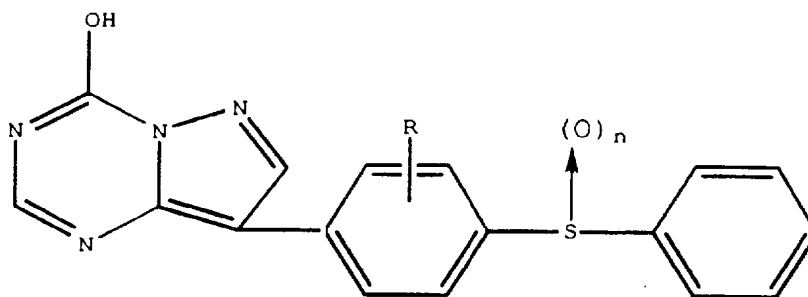
- where R¹ is CH₃, C₂H₅ or C₆H₅, X is H, C₆H₅, m-CH₃C₆H₄, CN, COOEt, Cl, I or Br, Y is H, C₆H₅, o-CH₃C₆H₄, or p-CH₃C₆H₄, and Z is OH, H, CH₃, C₂H₅, C₆H₅, n-C₃H₇, i-C₃H₇, SH, SCH₃, NHC₄H₉, or N(C₂H₅)₂, and states that the compounds are c-AMP phosphodiesterase inhibitors useful as bronchodilators.

- 10 US 3,995,039 discloses pyrazolotriazines of the formula:



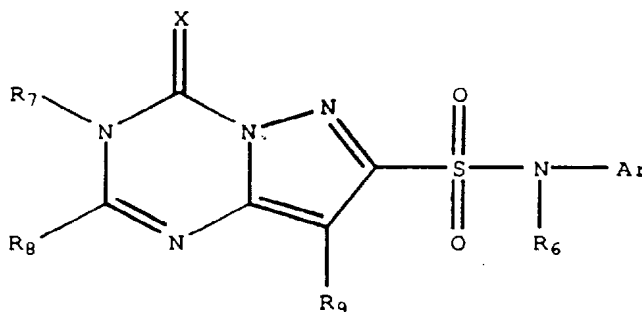
- 15 where R¹ is H or alkyl, R² is H or alkyl, R³ is H, alkyl, alkanoyl, carbamoyl, or lower alkylcarbamoyl, and R is pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

- 20 US 5,137,887 discloses pyrazolotriazines of the formula



where R is lower alkoxy, and teaches that the compounds
are xanthine oxidase inhibitors and are useful for
5 treatment of gout.

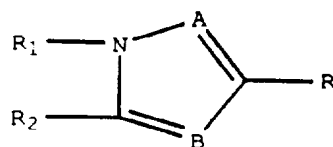
US 4,892,576 discloses pyrazolotriazines of the
formula



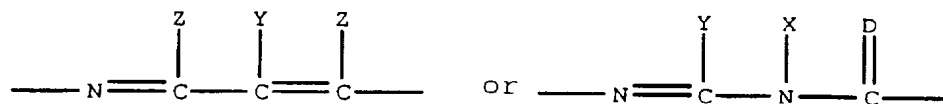
10

where X is O or S, Ar is a phenyl, naphthyl, pyridyl or
thienyl group, R₆-R₈ are H, alkyl, etc., and R₉ is H,
alkyl, phenyl, etc. The patent states that the
15 compounds are useful as herbicides and plant growth
regulants.

US 5,484,760 and WO 92/10098 discloses
herbicidal compositions containing, among other things,
20 a herbicidal compound of the formula

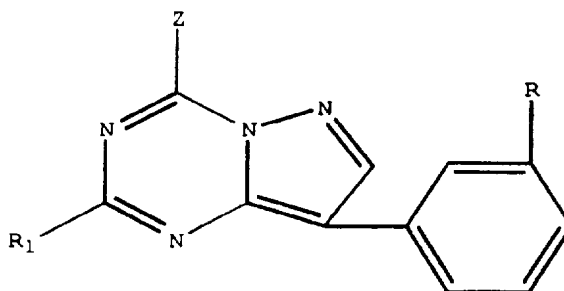


where A can be N, B can be CR₃, R₃ can be phenyl or substituted phenyl, etc., R is -N(R₄)SO₂R₅ or -SO₂N(R₆)R₇ and R₁ and R₂ can be taken together to form



where X, Y and Z are H, alkyl, acyl, etc. and D is O or S.

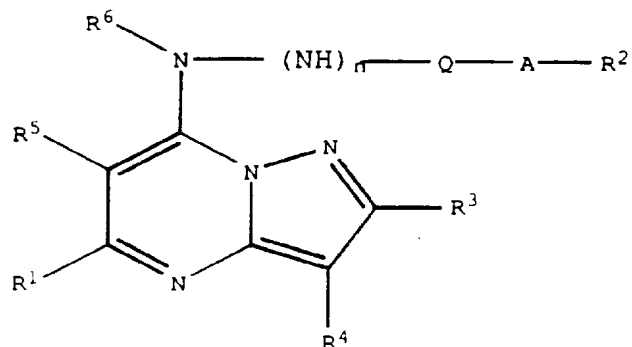
US 3,910,907 and Senga et al., J. Med. Chem., 1982, 25, 243-249, disclose triazolotriazines cAMP phosphodiesterase inhibitors of the formula



where Z is H, OH, CH₃, C₂H₅, C₆H₅, n-C₃H₇, iso-C₃H₇, SH, SCH₃, NH(n-C₄H₉), or N(C₂H₅)₂, R is H or CH₃, and R₁ is CH₃ or C₂H₅. The reference lists eight therapeutic areas where inhibitors of cAMP phosphodiesterase could have utility: asthma, diabetes mellitus, female fertility control, male infertility, psoriasis, thrombosis, anxiety, and hypertension.

WO95/35298 (Otsuka, 1995) discloses pyrazolopyrimidines and states that they are useful as analgesics. The compounds are represented by the formula

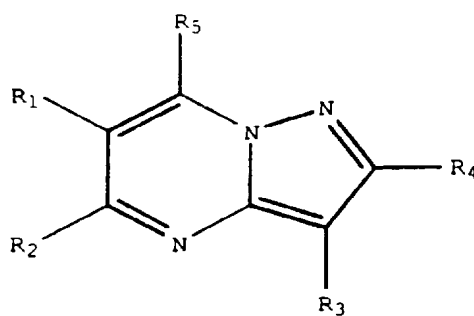
5



where Q is carbonyl or sulfonyl, n is 0 or 1, A is a single bond, alkylene or alkenylene, R¹ is H, alkyl, etc., R² is naphthyl, cycloalkyl, heteroaryl, substituted phenyl or phenoxy, R³ is H, alkyl or phenyl, R⁴ is H, alkyl, alkoxycarbonyl, phenylalkyl, optionally phenylthio-substituted phenyl, or halogen, R⁵ and R⁶ are H or alkyl.

15

EP 0 591 528 (Otsuka, 1991) discloses anti-inflammatory use of pyrazolopyrimidines represented by the formula

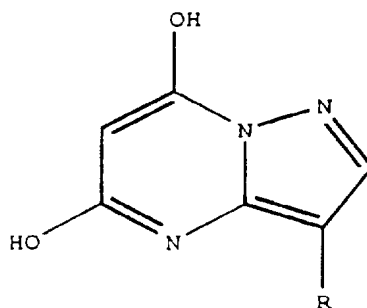


20

where R₁, R₂, R₃ and R₄ are H, carboxyl, alkoxycarbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, R₅

is SR_6 or NR_7R_8 , R_6 is pyridyl or optionally substituted phenyl, and R_7 and R_8 are H or optionally substituted phenyl.

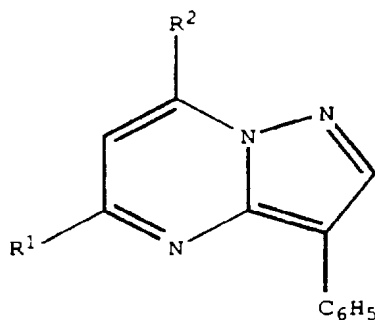
- 5 Springer et al, J. Med. Chem., 1976, vol. 19, no. 2, 291-296 and Springer U.S. patents 4021,556 and 3,920,652 disclose pyrazolopyrimidines of the formula



10

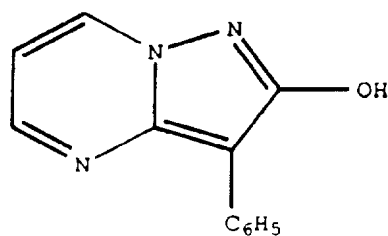
where R can be phenyl, substituted phenyl or pyridyl, and their use to treat gout, based on their ability to inhibit xanthine oxidase.

- 15 Joshi et al., J. Prakt. Chemie, 321, 2, 1979, 341-344, discloses compounds of the formula

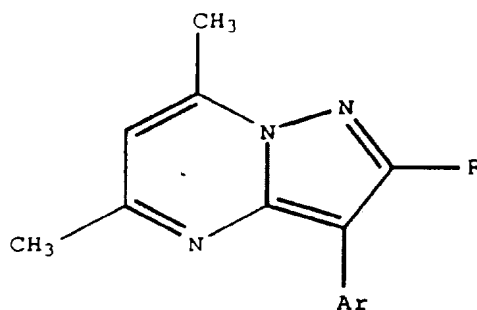


- 20 where R^1 is CF_3 , C_2F_5 , or C_6H_4F , and R^2 is CH_3 , C_2H_5 , CF_3 , or C_6H_4F .

Maquestiau et al., Bull. Soc. Belg., vol.101,
no. 2, 1992, pages 131-136 discloses a pyrazolo[1,5-
a]pyrimidine of the formula



Ibrahim et al., Arch. Pharm. (weinheim) 320,
487-491 (1987) discloses pyrazolo[1,5-a]pyrimidines of
the formula



where R is NH₂ or OH and Ar is 4-phenyl-3-cyano-2-
aminopyrid-2-yl.

15

Other references which disclose
azolopyrimidines included EP 0 511 528 (Otsuka, 1992), US
4,997,940 (Dow, 1991), EP 0 374 448 (Nissan, 1990), US
4,621,556 (ICN,1997), EP 0 531 901 (Fujisawa, 1993), US
20 4,567,263 (BASF, 1986), EP 0 662 477 (Isagro, 1995), DE
4 243 279 (Bayer, 1994), US 5,397,774 (Upjohn, 1995), EP
0 521 622 (Upjohn, 1993), WO 94/109017 (Upjohn, 1994),
J. Med. Chem., 24, 610-613 (1981), and J. Het. Chem.,
22, 601 (1985).

25

SUMMARY OF THE INVENTION

In accordance with one aspect, the present invention provides novel compounds, pharmaceutical compositions and methods which may be used in the treatment of affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder, fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthymia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress;

stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g.,
5 cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress
10 induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction
15 related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin,
20 benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in a mammal.

The present invention provides novel compounds
25 which bind to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compounds of the present invention are useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related
30 disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and
35 stress in a mammal.

According to another aspect, the present invention provides novel compounds of Formulae (1) and (2) (described below) which are useful as antagonists of the corticotropin releasing factor.

5 The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such compounds

10 of Formulae (1) and (2), and methods of using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect of the invention, the compounds provided by this invention (and especially labelled compounds of this invention) are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

20

DETAILED DESCRIPTION OF INVENTION

[1] The present invention comprises a method of treating affective disorder, anxiety, depression,

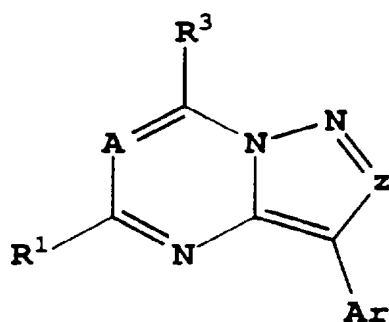
25 headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms,

30 inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic

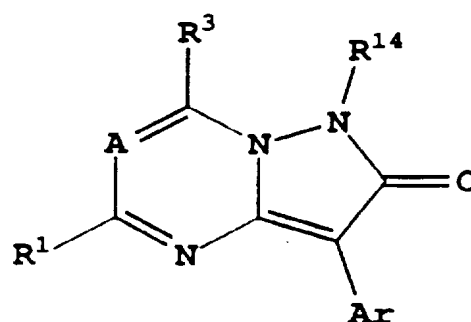
35 lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by

antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of

5 Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or

10 mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

A is N or CR;

15

Z is N or CR²;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-

20 dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R⁴ groups and each Ar is

25 attached to an unsaturated carbon atom;

R is independently selected at each occurrence from
H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl, halo,
CN, C₁-C₄ haloalkyl;

5

R¹ is independently selected at each occurrence from
H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
halo, CN, C₁-C₄ haloalkyl, C₁-C₁₂ hydroxyalkyl,
C₂-C₁₂ alkoxyalkyl, C₂-C₁₀ cyanoalkyl, C₃-C₆
cycloalkyl, C₄-C₁₀ cycloalkylalkyl, NR⁹R¹⁰, C₁-
C₄ alkyl-NR⁹R¹⁰, NR⁹COR¹⁰, OR¹¹, SH or S(O)_nR¹²;

10

R² is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl,
C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀
cycloalkylalkyl, C₁-C₄ hydroxyalkyl, halo, CN,
-NR⁶R⁷, NR⁹COR¹⁰, -NR⁶S(O)_nR⁷, S(O)_nNR⁶R⁷, C₁-
C₄ haloalkyl, -OR⁷, SH or -S(O)_nR¹²;

15

R³ is selected from:

20 -H, OR⁷, SH, S(O)_nR¹³, COR⁷, CO₂R⁷,
OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂, NR⁸CONR⁶R⁷,
NR⁸CO₂R¹³, NR⁶R⁷, NR^{6a}R^{7a}, N(OR⁷)R⁶,
CONR⁶R⁷, aryl, heteroaryl and heterocyclyl,
or

25 -C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, C₄-
C₁₂ cycloalkylalkyl or C₆-C₁₀
cycloalkenylalkyl, each optionally
substituted with 1 to 3 substituents

30 independently selected at each occurrence
from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³,
NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
35 heteroaryl and heterocyclyl;

- R^4 is independently selected at each occurrence from:
 C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, NO₂,
 5 halo, CN, C₁-C₄ haloalkyl, NR⁶R⁷, NR⁸COR⁷,
 NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO(NOR⁹)R⁷, CO₂R⁷,
 or S(O)_nR⁷, where each such C₁-C₁₀ alkyl, C₂-
 C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl
 and C₄-C₁₂ cycloalkylalkyl are optionally
 10 substituted with 1 to 3 substituents
 independently selected at each occurrence from
 C₁-C₄ alkyl, NO₂, halo, CN, NR⁶R⁷, NR⁸COR⁷,
 NR⁸CO₂R⁷, COR⁷ OR⁷, CONR⁶R⁷, CO₂R⁷, CO(NOR⁹)R⁷,
 or S(O)_nR⁷;
 15
 R^6 and R^7 , R^{6a} and R^{7a} are independently selected at
 each occurrence from:
 -H,
 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 20 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 25 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 30 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);
 35

alternatively, NR^6R^7 and $\text{NR}^{6a}\text{R}^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 $\text{C}_1\text{-C}_4$ alkyl groups;

5

R^8 is independently selected at each occurrence from H or $\text{C}_1\text{-C}_4$ alkyl;

10 R^9 and R^{10} are independently selected at each occurrence from H, $\text{C}_1\text{-C}_4$ alkyl, or $\text{C}_3\text{-C}_6$ cycloalkyl;

R^{11} is selected from H, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl, or $\text{C}_3\text{-C}_6$ cycloalkyl;

15

R^{12} is $\text{C}_1\text{-C}_4$ alkyl or $\text{C}_1\text{-C}_4$ haloalkyl;

20 R^{13} is selected from $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_2\text{-C}_8$ alkoxyalkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_4\text{-C}_{12}$ cycloalkylalkyl, aryl, aryl($\text{C}_1\text{-C}_4$ alkyl)-, heteroaryl or heteroaryl($\text{C}_1\text{-C}_4$ alkyl)-;

25 R^{14} is selected from $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_{10}$ alkenyl, $\text{C}_3\text{-C}_{10}$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, or $\text{C}_4\text{-C}_{12}$ cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, halo, $\text{C}_1\text{-C}_4$ haloalkyl, cyano, OR^{15} , SH, $\text{S(O)}_n\text{R}^{15}$, COR^{15} , CO_2R^{15} , OC(O)R^{15} , $\text{NR}^8\text{COR}^{15}$, $\text{N(COR}^{15})_2$, $\text{NR}^8\text{CONR}^{16}\text{R}^{15}$, $\text{NR}^8\text{CO}_2\text{R}^{15}$, $\text{NR}^{16}\text{R}^{15}$, $\text{CONR}^{16}\text{R}^{15}$, and $\text{C}_1\text{-C}_6$ alkylthio, $\text{C}_1\text{-C}_6$ alkylsulfinyl and $\text{C}_1\text{-C}_6$ alkylsulfonyl;

30

35 R^{15} and R^{16} are independently selected at each occurrence from H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_{10}$

cycloalkyl, C₄-C₁₆ cycloalkylalkyl, except that for S(O)_nR¹⁵, R¹⁵ cannot be H;

aryl is phenyl or naphthyl, each optionally
 5 substituted with 1 to 5 substituents
 independently selected at
 each occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano,
 OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵,
 10 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵,
 NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

heteroaryl is pyridyl, pyrimidinyl, triazinyl,
 furanyl, pyranal, quinolinyl, isoquinolinyl,
 15 thienyl, imidazolyl, thiazolyl, indolyl,
 pyrrolyl, oxazolyl, benzofuranyl, benzothienyl,
 benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-
 dihydrobenzothienyl or 2,3-dihydrobenzofuranyl,
 each being optionally substituted with 1 to 5
 20 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹⁵, -COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and
 25 CONR¹⁶R¹⁵;

heterocyclyl is saturated or partially saturated
 heteroaryl, optionally substituted with 1 to 5
 substituents independently selected at each
 30 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁵R¹⁶, and
 CONR¹⁶R¹⁵;

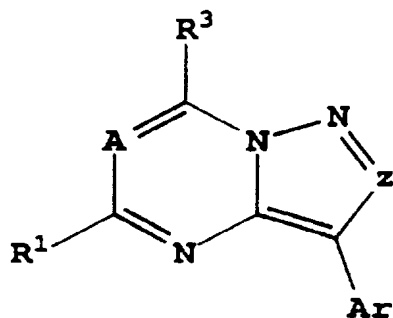
35

n is independently at each occurrence 0, 1 or 2,

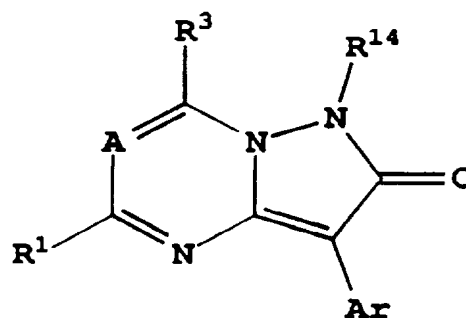
[2] Preferred methods of the present invention are methods in wherein in the compound of Formulae (1) or
 5 (2), Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

[3] Further preferred methods of the above invention
 10 are methods wherein, in the compound of Formulae (1) or (2), A is N, Z is CR^2 , Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3 , and R^3 is $NR^{6a}R^{7a}$.

15 [4] The present invention comprises compounds of Formulae (1) or (2):



(1)



(2)

20

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms
 25 thereof wherein:

A is N or CR;

Z is N or CR²;

Ar is selected from phenyl, naphthyl, pyridyl,
 5 pyrimidinyl, triazinyl, furanyl, thienyl,
 benzothienyl, benzofuranyl, 2,3-
 dihydrobenzofuranyl, 2,3-dihydrobenzothienyl,
 indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-
 benzopyranyl, tetralinyl, each Ar optionally
 10 substituted with 1 to 5 R⁴ groups and each Ar is
 attached to an unsaturated carbon atom;

R is independently selected at each occurrence from
 H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
 15 C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl, halo,
 CN, C₁-C₄ haloalkyl;

R¹ is independently selected at each occurrence from
 H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
 20 halo, CN, C₁-C₄ haloalkyl, C₁-C₁₂ hydroxyalkyl,
 C₂-C₁₂ alkoxyalkyl, C₂-C₁₀ cyanoalkyl, C₃-C₆
 cycloalkyl, C₄-C₁₀ cycloalkylalkyl, NR⁹R¹⁰, C₁-
 C₄ alkyl-NR⁹R¹⁰, NR⁹COR¹⁰, OR¹¹, SH or S(O)_nR¹²;

25 R² is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl,
 C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀
 cycloalkylalkyl, C₁-C₄ hydroxyalkyl, halo, CN,
 -NR⁶R⁷, NR⁹COR¹⁰, -NR⁶S(O)_nR⁷, S(O)_nNR⁶R⁷, C₁-
 C₄ haloalkyl, -OR⁷, SH or -S(O)_nR¹²;

30 R³ is selected from:
 -H, OR⁷, SH, S(O)_nR¹³, COR⁷, CO₂R⁷,
 OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂, NR⁸CONR⁶R⁷,
 NR⁸CO₂R¹³, NR⁶R⁷, NR^{6a}R^{7a}, N(OR⁷)R⁶,
 35 CONR⁶R⁷, aryl, heteroaryl and
 heterocyclyl, or

-C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, C₄-
 C₁₂ cycloalkylalkyl or C₆-C₁₀
 cycloalkenylalkyl, each optionally
 5 substituted with 1 to 3 substituents
 independently selected at each occurrence
 from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
 C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³,
 10 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl and heterocyclyl;

R⁴ is independently selected at each occurrence from:
 15 C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, NO₂,
 halo, CN, C₁-C₄ haloalkyl, NR⁶R⁷, NR⁸COR⁷,
 NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO(NOR⁹)R⁷, CO₂R⁷,
 or S(O)_nR⁷, where each such C₁-C₁₀ alkyl, C₂-
 20 C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl
 and C₄-C₁₂ cycloalkylalkyl are optionally
 substituted with 1 to 3 substituents
 independently selected at each occurrence from
 C₁-C₄ alkyl, NO₂, halo, CN, NR⁶R⁷, NR⁸COR⁷,
 25 NR⁸CO₂R⁷, COR⁷ OR⁷, CONR⁶R⁷, CO₂R⁷, CO(NOR⁹)R⁷,
 or S(O)_nR⁷;

R⁶ and R⁷, R^{6a} and R^{7a} are independently selected at
 each occurrence from:
 30 -H,
 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 35 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3

- substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
5 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl, -aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or
10 heterocyclyl(C₁-C₄ alkyl), alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently piperidine, pyrrolidine, piperazine; N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C₁-C₄ alkyl groups;
15 R⁸ is independently selected at each occurrence from H or C₁-C₄ alkyl;
R⁹ and R¹⁰ are independently selected at each
20 occurrence from H, C₁-C₄ alkyl, or C₃-C₆ cycloalkyl;
R¹¹ is selected from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;
25 R¹² is C₁-C₄ alkyl or C₁-C₄ haloalkyl;
R¹³ is selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-,
30 heteroaryl or heteroaryl(C₁-C₄ alkyl)-;
R¹⁴ is selected from C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₃-C₈ cycloalkyl, or C₄-C₁₂ cycloalkylalkyl, each optionally substituted
35 with 1 to 3 substituents independently selected

at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵,
5 NR¹⁶R¹⁵, CONR¹⁶R¹⁵, and C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl and C₁-C₆ alkylsulfonyl;

R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀
10 cycloalkyl, C₄-C₁₆ cycloalkylalkyl, except that for S(O)_nR¹⁵, R¹⁵ cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents
15 independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵,
20 NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl,
25 pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each
30 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, -COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

35

heterocyclyl is saturated or partially saturated
heteroaryl, optionally substituted with 1 to 5
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
5 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁵R¹⁶, and
CONR¹⁶R¹⁵;

10 n is independently at each occurrence 0, 1 or 2,

with the provisos that:

- 15 (1) when A is N, Z is CR², R² is H, R³ is -OR⁷ or
-OCOR¹³, and R⁷ is H, then R¹ is not H, OH or
SH;
- 20 (2) when A is N, Z is CR², R¹ is CH₃ or C₂H₅, R² is H,
and R³ is OH, H, CH₃, C₂H₅, C₆H₅, n-C₃H₇, i-C₃H₇,
SH, SCH₃, NHC₄H₉, or N(C₂H₅)₂, then Ar is not
phenyl or m-CH₃-phenyl;
- 25 (3) when A is N, Z is CR², R² is H, and Ar is
pyridyl, pyrimidinyl or pyrazinyl, and R³ is
NR^{6a}R^{7a}, then R^{6a} and R^{7a} are not H or alkyl;
- (4) when A is N, Z is CR², and R² is SO₂NR⁶R⁷, then R³
is not OH or SH;
- 30 (5) when A is CR and Z is CR², then R² is not -NR⁶SO₂R⁷
or -SO₂NR⁶R⁷;
- (6) when A is N, Z is CR² and R² is -NR⁶SO₂R⁷ or
- SO₂NR⁶R⁷, then R³ is not OH or SH;
- 35 (7) when A is N, Z is CR², R¹ is methyl or ethyl, R²
is H, and R³ is H, OH, CH₃, C₂H₅, C₆H₅, n-C₃H₇,

iso-C₃H₇, SH, SCH₃, NH(n-C₄H₉), or N(C₂H₅)₂, then Ar is not unsubstituted phenyl or m-methylphenyl;

- 5 (8) when A is CR, Z is CR², R² is H, phenyl or alkyl, R³ is NR⁸COR⁷ and Ar is phenyl or phenyl substituted with phenylthio, then R⁷ is not aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl);
- 10 (9) when A is CR, Z is CR², R² is H or alkyl, Ar is phenyl, and R³ is SR¹³ or NR^{6a}R^{7a}, then R¹³ is not aryl or heteroaryl and R^{6a} and R^{7a} are not H or aryl; or
- 15 (10) when A is CH, Z is CR², R¹ is OR¹¹, R² is H, R³ is OR⁷, and R⁷ and R¹¹ are both H, then Ar is not phenyl, p-Br-phenyl, p-Cl-phenyl, p-NHCOCH₃-phenyl, p-CH₃-phenyl, pyridyl or naphthyl;
- 20 (11) when A is CH, Z is CR², R² is H, Ar is unsubstituted phenyl, and R³ is CH₃, C₂H₅, CF₃ or C₆H₄F, then R₁ is not CF₃ or C₂F₅;
- 25 (12) when A is CR, R is H, Z is CR², R² is OH, and R¹ and R³ are H, then Ar is not phenyl;
- (13) when A is CR, R is H, Z is CR², R² is OH or NH₂, R¹ and R³ are CH₃, then Ar is not 4-phenyl-3-cyano-2-aminopyrid-2-yl.

30

- [5] Preferred compounds of the above invention are compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof with the additional provisos that: (1) when A is N, R¹ is H, C₁-C₄ alkyl, halo, CN, C₁-C₁₂ hydroxyalkyl, C₁-C₄

alkoxyalkyl or $\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$, R^3 is $\text{NR}^{6a}\text{R}^{7a}$ and R^{6a} is unsubstituted $\text{C}_1\text{-C}_4$ alkyl, then R^{7a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or $\text{C}_3\text{-C}_6$ cycloalkyl; and (2) A is N, R^1 is H, $\text{C}_1\text{-C}_4$ alkyl, halo, CN, $\text{C}_1\text{-C}_{12}$ hydroxyalkyl, $\text{C}_1\text{-C}_4$ alkoxyalkyl or $\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$, R^3 is $\text{NR}^{6a}\text{R}^{7a}$ and R^{7a} is unsubstituted $\text{C}_1\text{-C}_4$ alkyl, then R^{6a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or $\text{C}_3\text{-C}_6$ cycloalkyl.

[6] Preferred compounds of the above invention also include compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

[7]. Preferred compounds of the above invention also include compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N, Z is CR^2 , Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3 , and R^3 is $\text{NR}^{6a}\text{R}^{7a}$.

[11] More preferred compounds of the above invention are compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N.

[12] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[13] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

[14] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is NR^6aR^7a or OR^7 .

[15] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is NR^6aR^7a or OR^7 .

[16] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR^2 .

[17] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.

10 [18] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR^{6a}R^{7a} or OR⁷.

[19] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,
-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
25 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, 35 heteroaryl or heterocyclyl,

-aryl, aryl(C₁-C₄ alkyl)-, heteroaryl, heteroaryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-; and

R^{7a} is independently selected at each occurrence from:

- 5 -H,
 -C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
10 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
15 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
20 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);

- alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently
piperidine, pyrrolidine, piperazine, N-
25 methylpiperazine, morpholine or thiomorpholine, each
 optionally substituted with 1-3 C₁-C₄ alkyl groups.

- [20] More preferred compounds of the above invention
also include compounds and isomers thereof,
30 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein R^{6a}
 and R^{7a} are identical and are selected from:
 -C₁-C₄ alkyl or C₃-C₆ cycloalkyl, each optionally
35 substituted with 1 to 3 substituents
 independently selected at each occurrence from

C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, -COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 5 aryl, heteroaryl or heterocyclyl, and
 -aryl or heteroaryl.

[21] More preferred compounds of the above invention also include compounds and isomers thereof,
 10 stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,
 15 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each
 20 optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 25 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 30 heterocyclyl(C₁-C₄ alkyl);

R^{7a} is selected from:

-C₁-C₄ alkyl and each such C₁-C₄ alkyl is substituted with 1-3 substituents independently selected at each occurrence from
 35 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,

CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl.

5 [22] More preferred compounds of the above invention
also include compounds and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein

10 one of R^{6a} and R^{7a} is selected from:

-C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
optionally substituted with 1-3 substituents
independently selected at each occurrence from
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
15 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl,
-aryl,
20 -heteroaryl or
-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
alkyl.

25 [23] More preferred compounds of the above invention
also include compounds and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein
30 R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,
each such C₁-C₁₀ alkyl optionally substituted with
1 to 3 substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³,
35 COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,

$R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[24] More preferred compounds of the above invention
 5 also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar
 10 is optionally substituted with 1 to 4 R^4 substituents, and R^3 is NR^6aR^7a or OR^7 .

[25] More preferred compounds of the above invention also include compounds and isomers thereof,
 15 stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,
 20 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each
 25 optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR^{15} , SH, $S(O)_nR^{13}$, COR^{15} , CO_2R^{15} ,
 30 $OC(O)R^{13}$, NR^8COR^{15} , $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl)-, heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 35 heterocyclyl(C₁-C₄ alkyl);

- R^{7a} is independently selected at each occurrence from:
- H,
 - C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl, -aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl),
- alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C₁-C₄ alkyl groups.
- [26] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:
- C₁-C₄ alkyl or C₃-C₆ cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, -COR¹⁵,

CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl, and
-aryl or heteroaryl.

5

[27] More preferred compounds of the above invention
also include compounds and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
10 acceptable salt or pro-drug forms thereof wherein R^{6a}
and R^{7a} are identical and are

-C₁-C₄ alkyl, each such C₁-C₄ alkyl
optionally substituted with 1 to 3
substituents independently selected at each
15 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
S(O)_nR¹³, -COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵,
N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵,
CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

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[28] More preferred compounds of the above invention
also include compounds and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
25 acceptable salt or pro-drug forms thereof wherein
R^{6a} is selected from:

-H,
-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
30 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
substituents independently selected at each
35 occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,

cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 5 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);

R^{7a} is:

-C₁-C₄ alkyl and each such C₁-C₄ alkyl is
 10 substituted with 1-3 substituents
 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 15 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl.

[29] More preferred compounds of the above invention
 also include compounds and isomers thereof,
 20 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein one of
 R^{6a} and R^{7a} is selected from:

-C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
 25 optionally substituted with 1-3 substituents
 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 30 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl,
 -aryl,
 -heteroaryl or
 -heterocyclyl,
 35 and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
 alkyl.

[30] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, each such C₁-C₁₀ alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

[31] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

- Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents,
- R³ is NR^{6a}R^{7a} or OR⁷ and
- R¹ and R² are independently selected from H, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl.

[32] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 5 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 10 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl)-, heteroaryl, heteroaryl(C₁-
 15 C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄
 alkyl);
 R^{7a} is independently selected at each occurrence from:
 -H,
 -C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 20 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 25 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 30 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl),
 35

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1 - C_4 alkyl groups.

5

[33] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

10

- C_1 - C_4 alkyl or C_3 - C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo, C_1 - C_4 haloalkyl, cyano, OR^{15} , SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15} , $OC(O)R^{13}$, NR^8COR^{15} , $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and

15

20

-aryl or heteroaryl.

[34] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

25

- C_1 - C_4 alkyl, each such C_1 - C_4 alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo, C_1 - C_4 haloalkyl, cyano, OR^{15} , SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15} , $OC(O)R^{13}$, NR^8COR^{15} , $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

30

35

[35] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,
-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl,
-aryl, aryl(C₁-C₄ alkyl), heteroaryl,
heteroaryl(C₁-C₄ alkyl), heterocyclyl or
heterocyclyl(C₁-C₄ alkyl);

R^{7a} is:

-C₁-C₄ alkyl and each such C₁-C₄ alkyl is
substituted with 1-3 substituents
independently selected at each occurrence from
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl.

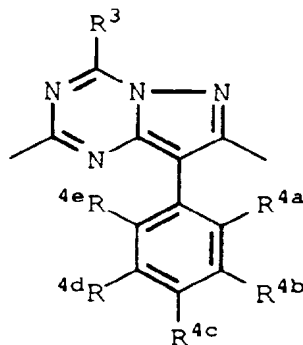
[36] More preferred compounds of the above invention also include compounds and isomers thereof,

stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

- 5 -C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
10 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl,
 -aryl,
 -heteroaryl or
15 -heterocyclyl,
and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄ alkyl.

- [37] More preferred compounds of the above invention
20 also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,
25 each such C₁-C₁₀ alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
30 R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

- [38] Specifically preferred compounds of the above invention are compounds of Formula (50)
35



FORMULA (50)

- 5 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, selected from the group consisting of:
- 10 a compound of Formula (50) wherein R³ is -NHCH(n-Pr)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R³ is -N(Et)(n-Bu), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R³ is -(n-Pr)(CH₂cPr), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R³ is -N(CH₂CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R³ is -NHCH(Et)(n-Bu), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R³ is -NHCH(Et)(CH₂OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 H;
- a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-N(Me)(Ph)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(n-Pr)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 20 H;
- a compound of Formula (50) wherein R^3 is $-NHCH(Et)(n-Pr)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 H;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 H;
- a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 40 H;
- a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-OEt$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 45 H;

- a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(CH_2CN)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-OCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-N(n-Pr)(CH_2cPr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2N(Me)_2)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(cPr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-N(n-Bu)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 40 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 45

- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 15 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2CH_2OMe)(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 20 a compound of Formula (50) wherein R^3 is morpholino, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NH(c-Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is CN, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 45 a compound of Formula (50) wherein R^3 is $-NCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

- 5 a compound of Formula (50) wherein R^3 is
-NHCH(CH₂OMe)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c}
is Br, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is -NHCH(CH₂OMe)₂,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e}
is H;
- 15 a compound of Formula (50) wherein R^3 is -N(CH₂CH₂OMe)₂,
 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e}
is H;
- 20 a compound of Formula (50) wherein R^3 is -NHCH(Et)₂, R^{4a}
is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is
H;
- 25 a compound of Formula (50) wherein a compound of Formula
(50) wherein R^3 is -N(Et)₂, R^{4a} is Me, R^{4b} is H,
 R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is -NHCH(CH₂OMe)₂,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is
H;
- 35 a compound of Formula (50) wherein R^3 is
-NHCH(Et)(CH₂OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me,
 R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is -N(c-
Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d}
is Me and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is -N(c-
Pr)(CH₂CH₂CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d}
is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is (S)-
NHCH(CH₂OMe)(CH₂CH₂OMe), R^{4a} is Cl, R^{4b} is H, R^{4c}
is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is
-NHCH(CH₂OMe)(CH₂CH₂OMe), R^{4a} is Cl, R^{4b} is H, R^{4c}
is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is -NHCH(Et)₂, R^{4a}
is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is -N(CH₂CH₂OMe)₂,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is
H;
- 15 a compound of Formula (50) wherein R^3 is
-NH(CH₂OMe)(CH₂-iPr), R^{4a} is Me, R^{4b} is H, R^{4c} is
Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is -N(CH₂CH₂OMe)₂,
 R^{4a} is Me, R^{4b} is H, R^{4c} is H, R^{4d} is H and R^{4e} is
H;
- 25 a compound of Formula (50) wherein R^3 is -N(CH₂CH₂OMe)₂,
 R^{4a} is Me, R^{4b} is H, R^{4c} is NMe₂, R^{4d} is H and R^{4e}
is H;
- a compound of Formula (50) wherein R^3 is
-NHCH(CH₂OMe)(n-Pr), R^{4a} is Me, R^{4b} is H, R^{4c} is
30 Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is
-NHCH(CH₂OEt)(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me,
35 R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is
-NHCH(CH₂OMe)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c}
is NMe₂, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is -N(Et)₂, R^{4a} is
Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is -NHCH(Et)₂, R^{4a}
45 is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_2 , R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is (S)- $NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is (S)- $NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-NH(Et)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 45

- a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)(CH_2CH_2OH)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-N(CH_2c-Pr)(n-Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is CN, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OH)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and
- 5 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H.
- 10 [39] More specifically preferred is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and
- 15 pharmaceutically acceptable salt or pro-drug forms thereof.
- [40] More specifically preferred is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine and
- 20 isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.
- 25 [41] More preferred are compounds of the above invention are compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms
- 30 thereof wherein A is CR.
- [42] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of
- 35 stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[43] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.

[44] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR⁶Ar^{7a} or OR⁷.

[45] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents, and R³ is NR⁶Ar^{7a} or OR⁷.

[46] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR².

[47] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is

phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.

5 [48] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR^{6a}R^{7a} or OR⁷.

10

[49] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically
15 acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents, and R³ is NR^{6a}R^{7a} or OR⁷.

20 [50] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein
25 R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, and each such C₁-C₁₀ alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵,
30 SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

[51] More preferred compounds of the above invention
35 also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl,

and each Ar is optionally substituted with 1

5 to 4 R⁴ substituents,

-R³ is NR^{6a}R^{7a} or OR⁷ and

-R¹ and R² are independently selected from H, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl.

10

[52] More preferred compounds of the above invention also include compounds and isomers thereof,

stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically

15 acceptable salt or pro-drug forms thereof wherein

R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,

and each such C₁-C₁₀ alkyl is optionally

substituted with 1 to 3 substituents independently

selected at each occurrence from C₁-C₆ alkyl, C₃-

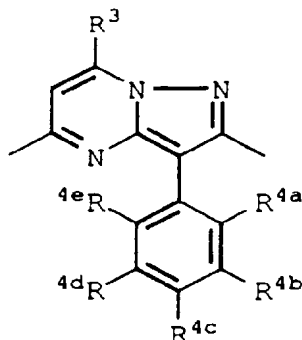
20 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵,

SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵,

N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵,

CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

25 [53] Specifically preferred compounds of the above invention are compounds of Formula (51)



FORMULA (51)

- 5 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof selected from the group consisting of:
- 10 a compound of Formula (51) wherein R³ is -NHCH(n-Pr)₂, R⁴ᵃ is Me, R⁴ᵇ is H, R⁴ᶜ is Me, R⁴ᵈ is H and R⁴ᵉ is H;
- 15 a compound of Formula (51) wherein R³ is -NHCH(CH₂OMe)₂, R⁴ᵃ is Me, R⁴ᵇ is H, R⁴ᶜ is Me, R⁴ᵈ is H and R⁴ᵉ is H;
- 20 a compound of Formula (51) wherein R³ is -N(CH₂CH₂OMe)₂, R⁴ᵃ is Me, R⁴ᵇ is H, R⁴ᶜ is Me, R⁴ᵈ is H and R⁴ᵉ is H;
- 25 a compound of Formula (51) wherein R³ is -N(c-Pr)(CH₂CH₂CN), R⁴ᵃ is Me, R⁴ᵇ is H, R⁴ᶜ is Me, R⁴ᵈ is H and R⁴ᵉ is H;
- 30 a compound of Formula (51) wherein R³ is -NHCH(CH₂OMe)₂, R⁴ᵃ is Cl, R⁴ᵇ is H, R⁴ᶜ is Me, R⁴ᵈ is H and R⁴ᵉ is H;

- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(n-Bu)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is (S)
 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is
 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NH(Et)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is (S) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is (S) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

- 5 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (51) wherein R^3 is $-NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NEt_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 and
- a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H.
- 20

[54] More specifically preferred is 7-(3-pentylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

25

[55] More specifically preferred is 7-(Diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

30

[56] More specifically preferred is 7-(N-(3-cyanopropyl)-N-propylamino)-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and

35

40

pharmaceutically acceptable salt or pro-drug forms thereof.

The present invention also provides
5 pharmaceutical compositions comprising compounds of Formulae (1) and (2) and a pharmaceutically acceptable carrier.

Many compounds of this invention have one or more
10 asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all
15 such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from
20 optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

25 The term "alkyl" includes both branched and straight-chain alkyl having the specified number of carbon atoms. Commonly used abbreviations have the following meanings: Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl. The prefix "n" means a straight
30 chain alkyl. The prefix "c" means a cycloalkyl. The prefix "(S)" means the S enantiomer and the prefix "(R)" means the R enantiomer. Alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-
35 carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the

like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-, bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "appropriate amino acid protecting group" means any group known in the art of organic synthesis for the protection of amine or carboxylic acid groups. Such amine protecting groups include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis,

Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentylloxycarbonyl and adamantylloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of Formulae (1) and (2). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing

Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

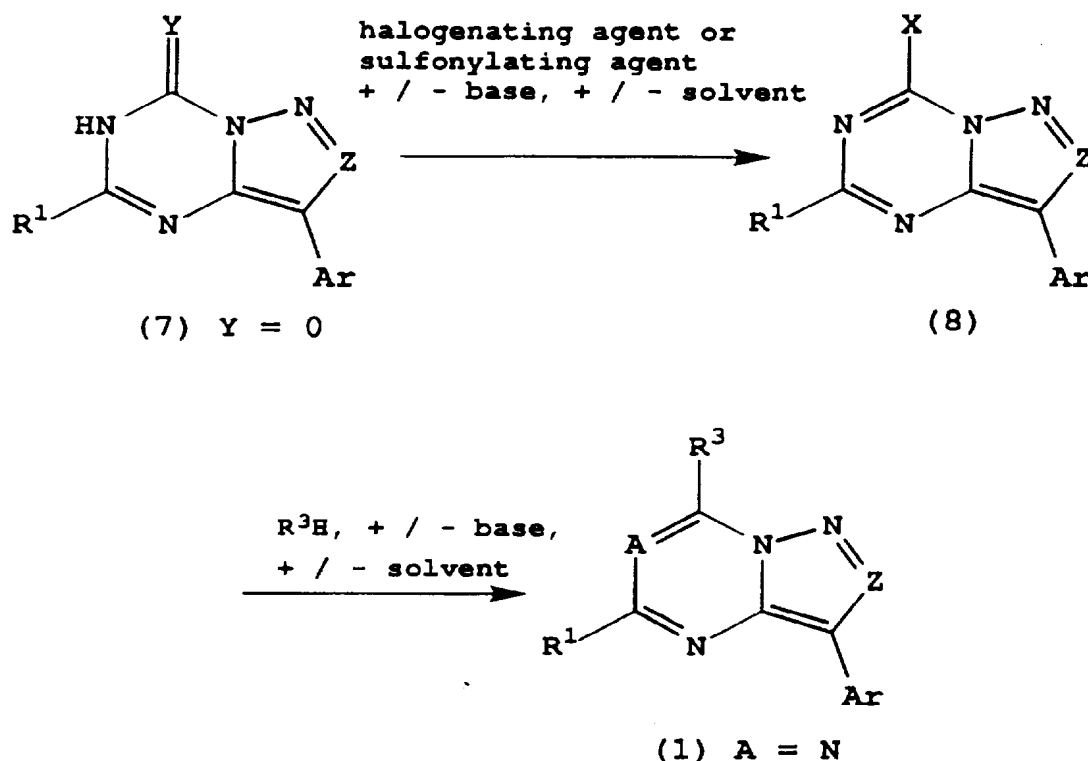
"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) or (II) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) and (II) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formulas (I) and (II); and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

Syntheses

Some compounds of Formula (1) may be prepared from intermediate compounds of Formula (7), using the procedures outlined in Scheme 1:

SCHEME 1



- Compounds of Formula (7) (where Y is O) may be treated with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (8) (where X is halogen, alkanesulfonyloxy, arylsulfonyloxy or haloalkane-sulfonyloxy). Halogenating agents include, but are not limited to, SOCl_2 , POCl_3 , PCl_3 , PCl_5 , POBr_3 , PBr_3 or PBr_5 . Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (such as methanesulfonyl chloride or methanesulfonic acid anhydride), arylsulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride) or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, alkali metal

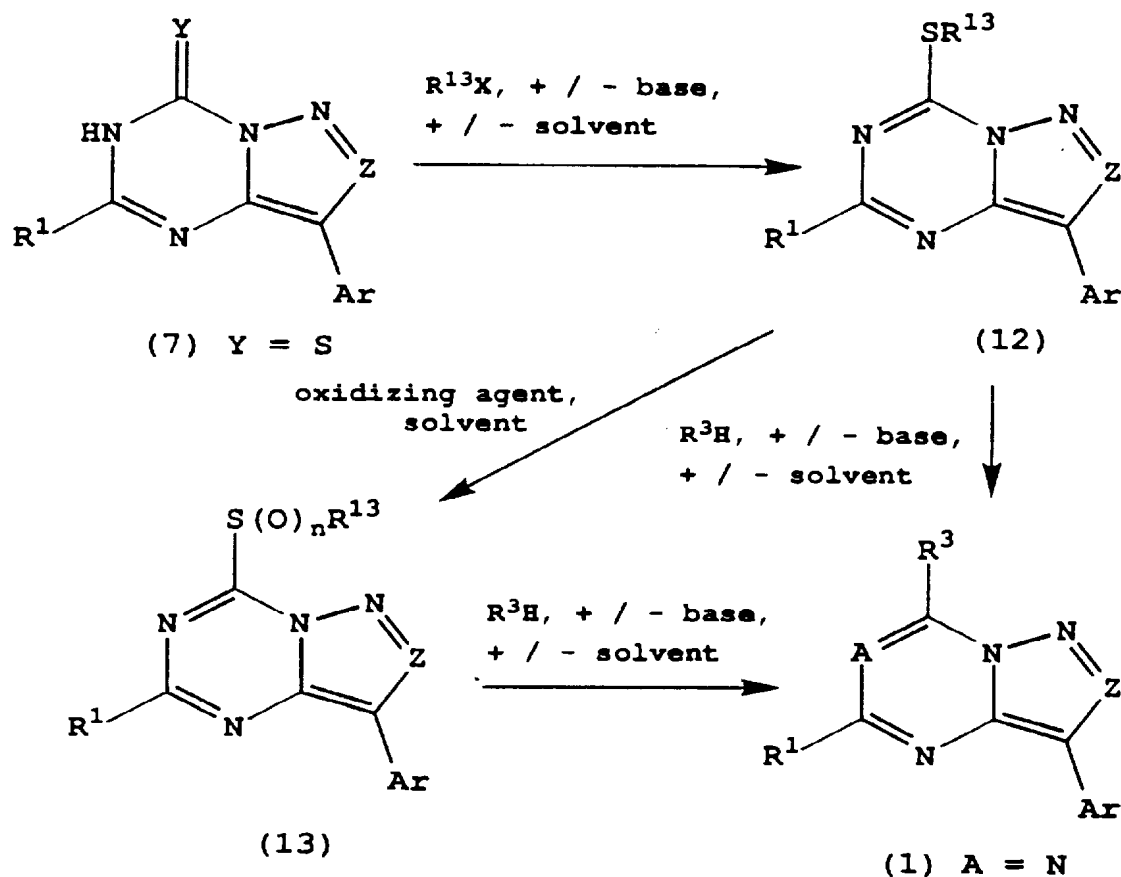
hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

Compounds of Formula (8) may be reacted with compounds of Formula R^3H (where R^3 is defined as above except R^3 is not SH, COR^7 , CO_2R^7 , aryl or heteroaryl) in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80 to 250°C to generate compounds of Formula (1). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably

N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

Scheme 2 delineates the procedures for converting intermediate compounds of Formula (7) (where Y is S) to some compounds of Formula (1).

SCHEME 2



- Compounds of Formula (7) (where Y is S) may be treated with an alkylating agent $R^{13}X$ (where R^{13} is defined as above, except R^{13} is not aryl or heteroaryl) in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C . Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium

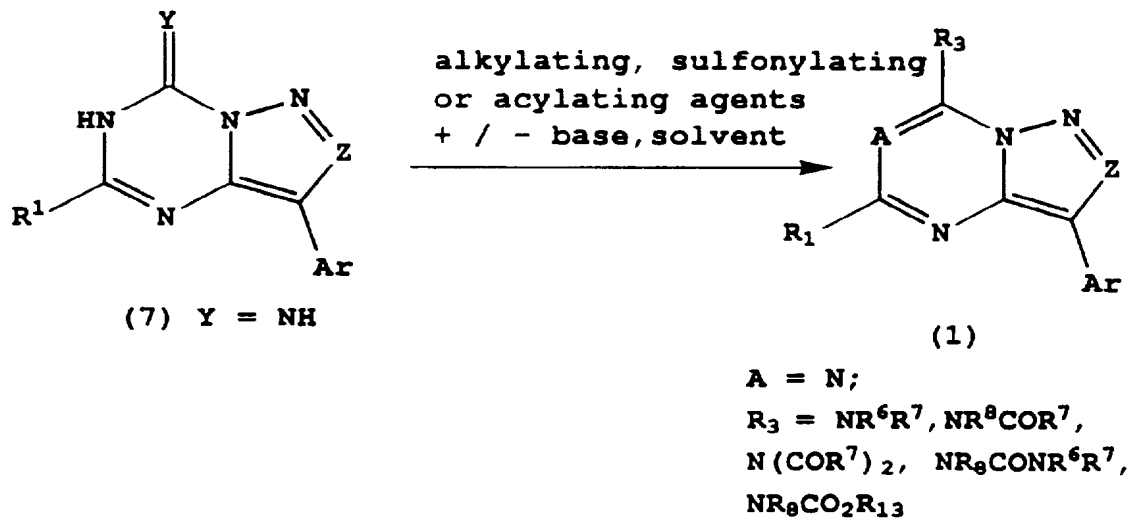
bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 100°C.

Compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may then be reacted with compounds of Formula R^3H to give compounds of Formula (1), using the same conditions and reagents as were used for the conversion of compounds of Formula (8) to compounds of Formula (1) as outlined for Scheme 1 above. Alternatively, compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may be oxidized to compounds of Formula (13) (Formula (1) where R^3 is $S(O)_nR^{13}$, n is 1,2) by treatment with an oxidizing agent in the presence of an inert solvent at temperatures ranging from -80°C to 250°C. Oxidizing agents include, but are not limited to, hydrogen peroxide, alkane or aryl peracids (preferably peracetic acid or m-chloro-perbenzoic acid), dioxirane, oxone, or sodium periodate. Inert solvents may include, but are not limited to, alkanones (3 to 10 carbons, preferably acetone), water, alkyl alcohols (1 to 6 carbons), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens

(preferably dichloromethane) or combinations thereof. The choices of oxidant and solvent are known to those skilled in the art (cf. Uemura, S., Oxidation of Sulfur, Selenium and Tellurium, in Comprehensive Organic
 5 Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 7, 762-769). Preferred reaction temperatures range from -20°C to 100°C. Compounds of Formula (13) (Formula (1) where R^3 is $S(O)_nR^{13}$, n is 1,2) may then be reacted with compounds of Formula R^3H to
 10 give compounds of Formula (1), using the same conditions and reagents as were used for the conversion of compounds of Formula (8) to compounds of Formula (1) as outlined for Scheme (1) above.

Compounds of Formula (1), where R^3 may be $-NR^8COR^7$,
 15 $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$, may be prepared from compounds of Formula (7), where Y is NH, by the procedures depicted in Scheme 3.

SCHEME 3.



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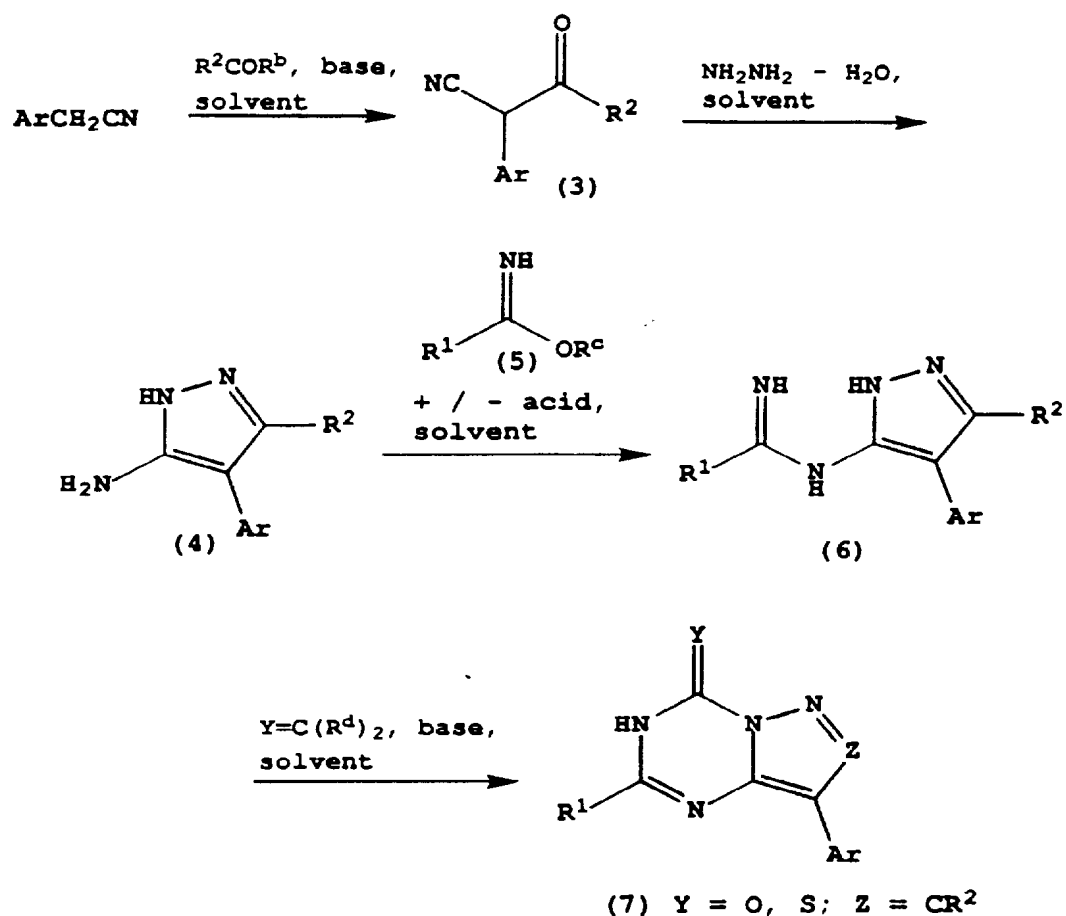
Reaction of compounds of Formula (7), where Y is NH, with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with

combinations thereof, in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -80°C to 250°C may afford compounds of Formula (1), where R³ may be -NR⁸COR⁷, -N(COR⁷)₂,
5 -NR⁸CONR⁶R⁷, -NR⁸CO₂R¹³, -NR⁶R⁷, -NR⁸SO₂R⁷. Alkylating agents may include, but are not limited to, C₁-C₁₀ alkyl-halides, -tosylates, -mesylates or -triflates; C₁-C₁₀ haloalkyl(1 - 10 halogens)-halides, -tosylates, -mesylates or -triflates; C₂-C₈ alkoxyalkyl-halides,
10 -tosylates, -mesylates or -triflates; C₃-C₆ cycloalkyl-halides, -tosylates, -mesylates or -triflates; C₄-C₁₂ cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; aryl(C₁-C₄ alkyl)-halides, -tosylates, -mesylates or -triflates; heteroaryl(C₁-C₄ alkyl)-
15 halides, -tosylates, -mesylates or -triflates; or heterocyclyl(C₁-C₄ alkyl)-halides, -tosylates, -mesylates or -triflates. Acylating agents may include, but are not limited to, C₁-C₁₀ alkanoyl halides or anhydrides, C₁-C₁₀ haloalkanoyl halides or anhydrides
20 with 1 - 10 halogens, C₂-C₈ alkoxyalkanoyl halides or anhydrides, C₃-C₆ cycloalkanoyl halides or anhydrides, C₄-C₁₂ cycloalkylalkanoyl halides or anhydrides, aroyl halides or anhydrides, aryl(C₁-C₄) alkanoyl halides or anhydrides, heteroaroyl halides or anhydrides,
25 heteroaryl(C₁-C₄) alkanoyl halides or anhydrides, heterocyclylcarboxylic acid halides or anhydrides or heterocyclyl(C₁-C₄) alkanoyl halides or anhydrides. Sulfonylating agents include, but are not limited to, C₁-C₁₀ alkylsulfonyl halides or anhydrides, C₁-C₁₀
30 haloalkylsulfonyl halides or anhydrides with 1 - 10 halogens, C₂-C₈ alkoxyalkylsulfonyl halides or anhydrides, C₃-C₆ cycloalkylsulfonyl halides or anhydrides, C₄-C₁₂ cycloalkylalkylsulfonyl halides or anhydrides, arylsulfonyl halides or anhydrides, aryl(C₁-
35 C₄ alkyl)-, heteroarylsulfonyl halides or anhydrides, heteroaryl(C₁-C₄ alkyl)sulfonyl halides or anhydrides,

heterocyclylsulfonyl halides or anhydrides or heterocyclyl(C₁-C₄ alkyl)sulfonyl halides or anhydrides. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal
5 alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium
10 bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6
15 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides
20 (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Scheme 4 delineates procedures, which may be
25 employed to prepare intermediate compounds of Formula (7), where Y is O, S and Z is CR².

SCHEME 4



- Compounds of the formula ArCH₂CN are reacted with compounds of the formula R²COR^b, where R² is defined
- 5 above and R^b is halogen, cyano, lower alkoxy (1 to 6 carbons) or lower alkanoyloxy (1 to 6 carbons), in the presence of a base in an inert solvent at reaction temperatures ranging from -78°C to 200°C to afford compounds of Formula (3). Bases may include, but are
- 10 not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal

dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Compounds of Formula (3) may be treated with hydrazine-hydrate in the presence of an inert solvent at temperatures ranging from 0°C to 200°C, preferably 70°C to 150°C, to produce compounds of Formula (4). Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Compounds of Formula (4) may be reacted with compounds of Formula (5) (where R^c is alkyl (1-6 carbons)) in the presence or absence of an acid in the presence of an inert solvent at temperatures ranging from 0°C to 200°C to produce compounds of Formula (6). Acids may include, but are

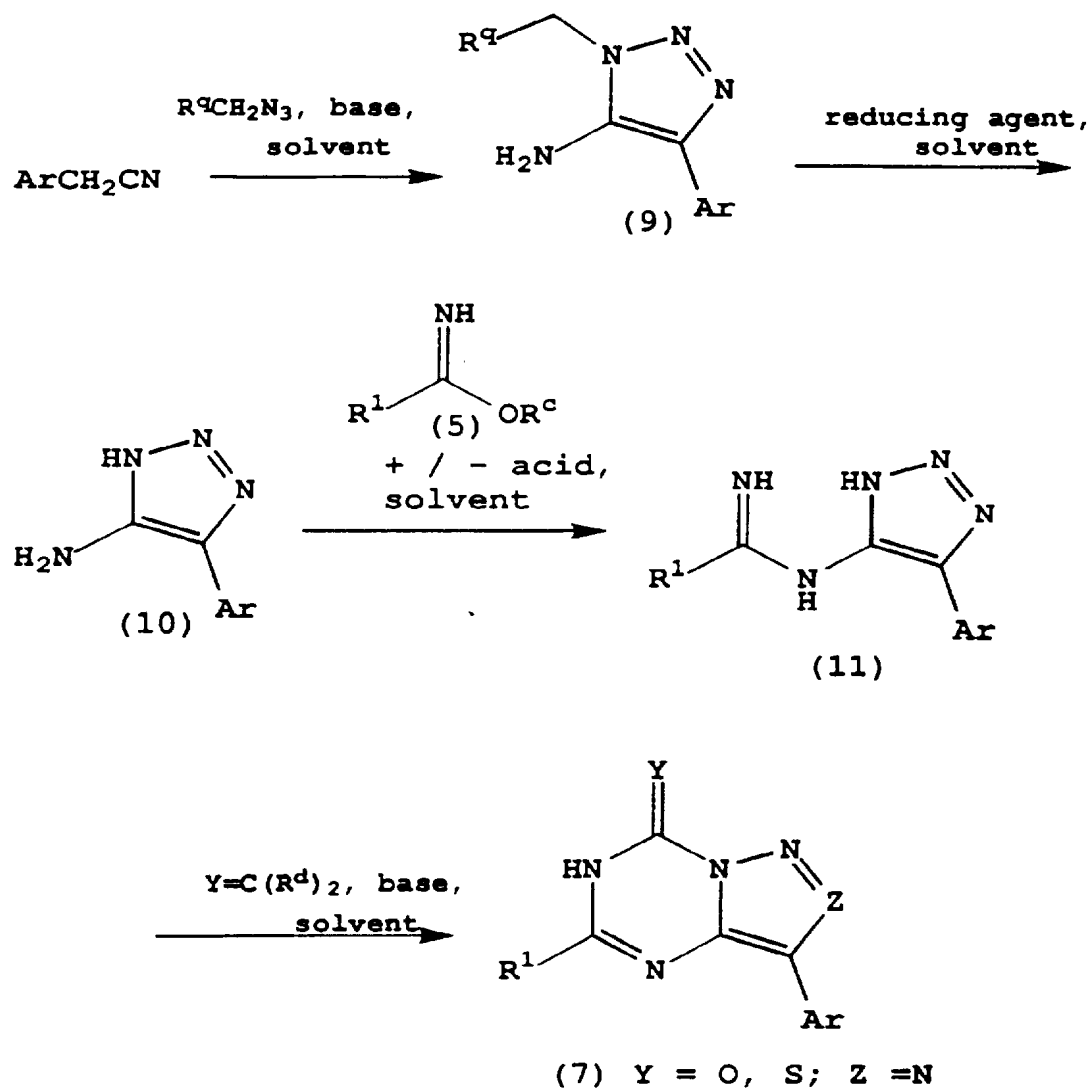
not limited to alkanolic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or
5 benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Inert solvents may include, but are not limited to, water,
10 alkanenitriles (1 to 6 carbons, preferably acetonitrile), halocarbons of 1 to 6 carbons and 1 to 6 halogens (preferably dichloromethane or chloroform), alkyl alcohols of 1 to 10 carbons (preferably ethanol), dialkyl ethers (4 to 12 carbons, preferably diethyl
15 ether or di-isopropylether) or cyclic ethers such as dioxan or tetrahydrofuran. Preferred temperatures range from ambient temperature to 100°C.

Compounds of Formula (6) may be converted to intermediate compounds of Formula (7) by treatment with
20 compounds $C=Y(R^d)_2$ (where Y is O or S and R^d is halogen (preferably chlorine), alkoxy (1 to 4 carbons) or alkylthio (1 to 4 carbons)) in the presence or absence of a base in an inert solvent at reaction temperatures from -50°C to 200°C. Bases may include, but are not
25 limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkali metal carbonates, alkali metal hydroxides, trialkyl amines (preferably N,N-di-
30 isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably
35 acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably

dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred temperatures are 0°C to 150°C.

Intermediate compounds of Formula (7), where Z is N, may be synthesized according the methods outlined in Scheme 5.

SCHEME 5



Compounds of ArCH_2CN are reacted with compounds of Formula $\text{R}^q\text{CH}_2\text{N}_3$ (where R^q is a phenyl group optionally substituted by H, alkyl (1 to 6 carbons) or alkoxy (1 to 6 carbons)) in the presence or absence of a base in an inert solvent at temperatures ranging from 0°C to 200°C to generate compounds of Formula (9). Bases may include, but are not limited to, alkali metal hydrides

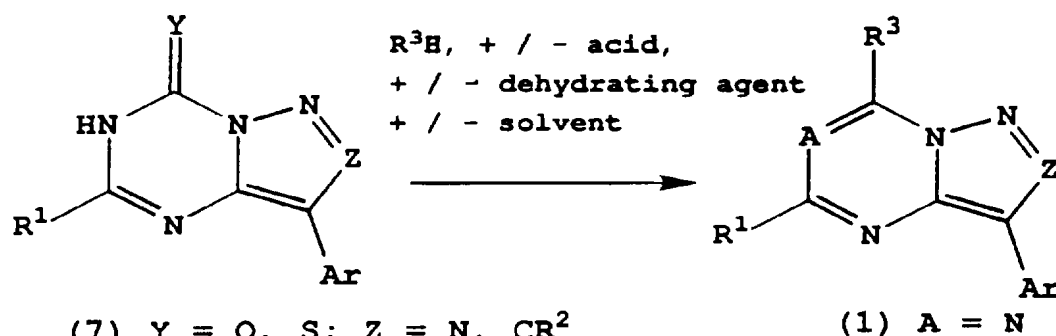
- (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide, sodium ethoxide or potassium t-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine).
- 10 Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably
- 15 tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons
- 20 (preferably benzene or toluene). Preferred reaction temperatures range from ambient temperature to 100°C.

- Compounds of Formula (9) may be treated with a reducing agent in an inert solvent at -100°C to 100°C to afford products of Formula (10). Reducing agents
- 25 include, but are not limited to, (a) hydrogen gas in combination with noble metal catalysts such as Pd-on-carbon, PtO₂, Pt-on-carbon, Rh-on-alumina or Raney nickel, (b) alkali metals (preferably sodium) in combination with liquid ammonia or (c) ceric ammonium
- 30 nitrate. Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably
- 35 tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides

(preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). The preferred reaction temperatures are -50°C to 60°C. Compounds of Formula (9) are then converted to compounds of Formula (7) (where Z is N) via intermediates of Formula (11) using the reagents and reaction conditions outlined in Scheme 4 for the conversion of compounds of Formula (4) to compounds of Formula (7) (where Z is CR²).

Compounds of Formula (1) may also be prepared from compounds of Formula (7) (where Y is O, S and Z is defined above) as outlined in Scheme 6:

SCHEME 6

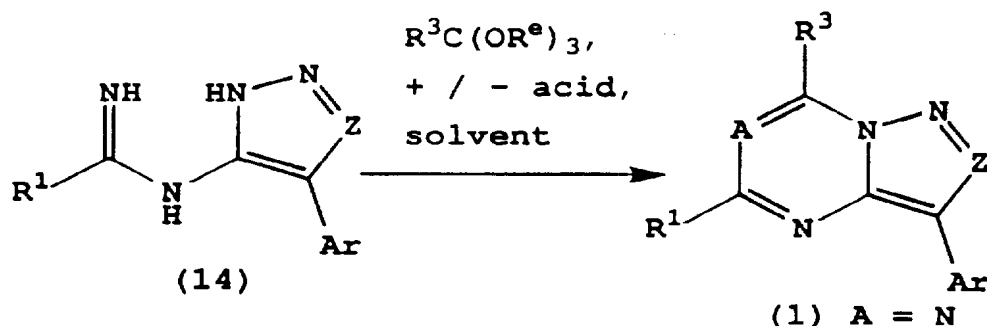


Compounds of Formula (7) may be reacted with compounds of Formula R³H in the presence of a dehydrating agent in an inert solvent at reaction temperatures ranging from 0°C to 250°C. Dehydrating agents include, but are not limited to, P₂O₅, molecular sieves or inorganic or organic acids. Acids may include, but are not limited to alkanolic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Inert solvents may include, but are not limited to,

alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably glyme or diglyme), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or halocarbons of 1 to 10 carbons and 1 to 10 halogens (preferably chloroform). Preferred reaction temperatures range from ambient temperature to 150°C.

Some compounds of Formula (1) (where A is N) may also be prepared by the methods shown in Scheme 7:

SCHEME 7

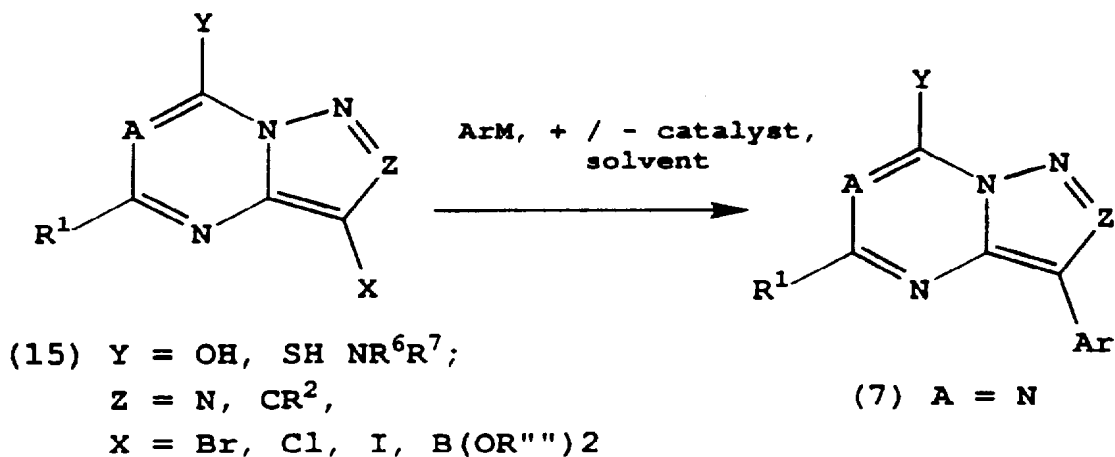


Intermediate compounds of Formula (14), where Z is defined above, may be reacted with compounds of Formula R³C(ORᵉ)₃, where Rᵉ may be alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or

catalytic amounts of such acids may be used. Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 50°C to 150°C.

Intermediate compounds of Formula (7) may also be synthesized by the reactions displayed in Scheme 8.

SCHEME 8



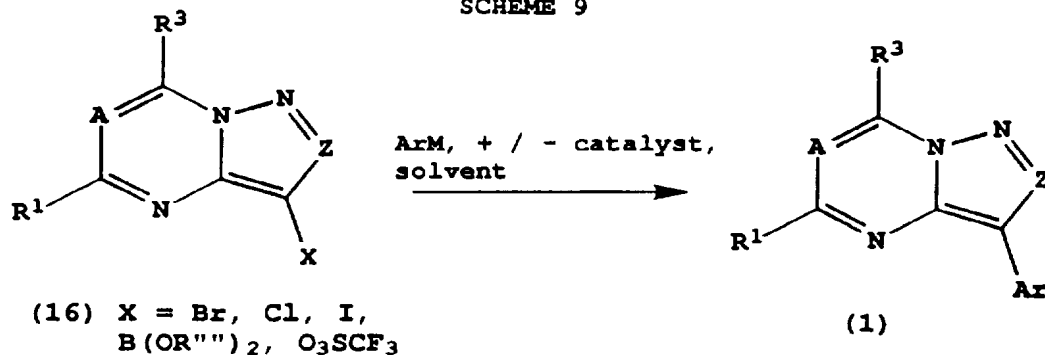
Compounds of Formula (15), (where Y is OH, SH, NR⁶R⁷; Z is defined above, X is Br, Cl, I, O₃SCF₃ or B(OR^{'''})₂ and R^{'''} is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, CeCl₂, CeBr₂ or copper halides) in the presence or absence of an

organometallic catalyst in the presence or absence of a base in an inert solvents at temperatures ranging from -100°C to 200°C. Those skilled in the art will recognize that the reagents ArM may be generated in situ. Organometallic catalysts include, but are not limited to, palladium phosphine complexes (such as Pd(PPh₃)₄), palladium halides or alkanoates (such as PdCl₂(PPh₃)₂ or Pd(OAc)₂) or nickel complexes (such as NiCl₂(PPh₃)₂). Bases may include, but are not limited to, alkali metal carbonates or trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or water. Preferred reaction temperatures range from -80°C to 100°C.

The choices of M and X are known to those skilled in the art (cf. Imamoto, T., Organocerium Reagents in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 1, 231-250; Knochel, P., Organozinc, Organocadmium and Organomercury Reagents in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 1, 211-230; Knight, D.W., Coupling Reactions between sp² Carbon Centers, in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 3, 481-520).

Compounds of Formula (1) may also be prepared using the methods shown in Scheme 9.

SCHEME 9



Compounds of Formula (16), where A, Z, R¹ and R³ are defined above and X is Br, Cl, I, O₃SCF₃ or B(OR''')₂ and

5 R''' is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, CeCl₂, CeBr₂ or copper halides) in the presence or absence of an organometallic catalyst in the presence or absence of a

10 base in an inert solvents at temperatures ranging from -100°C to 200°C. Those skilled in the art will recognize that the reagents ArM may be generated in situ (see the above references in Comprehensive Organic Synthesis). Organometallic catalysts include, but are

15 not limited to, palladium phosphine complexes (such as Pd(PPh₃)₄), palladium halides or alkanoates (such as PdCl₂(PPh₃)₂ or Pd(OAc)₂) or nickel complexes (such as NiCl₂(PPh₃)₂). Bases may include, but are not limited to, alkali metal carbonates or trialkyl amines

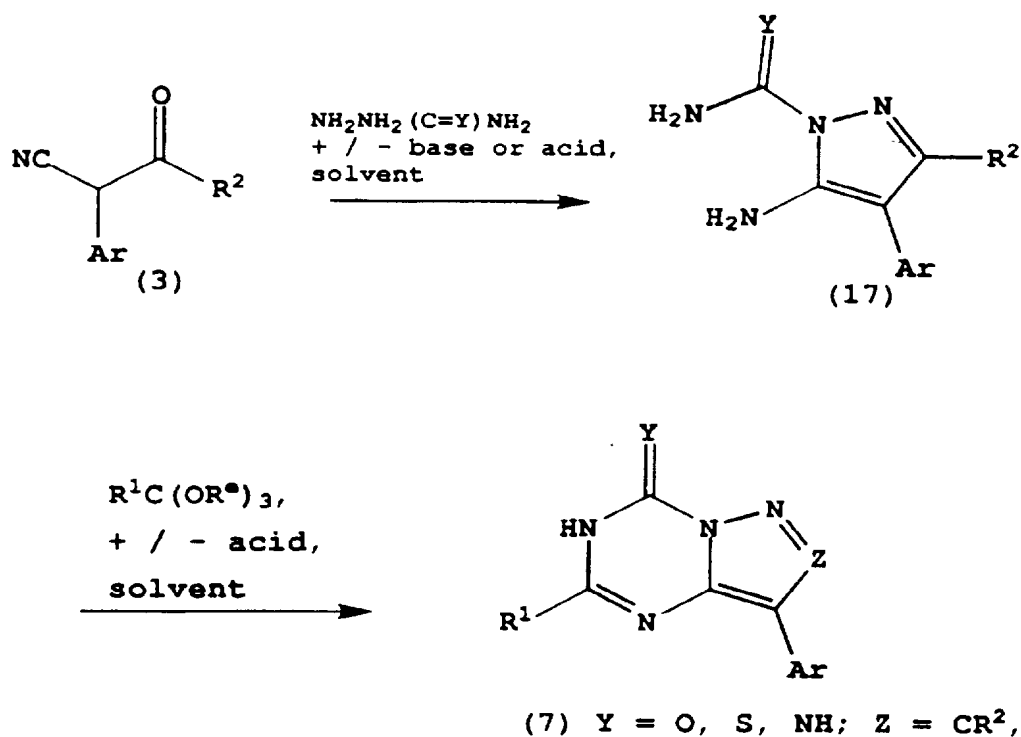
20 (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably

25 dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably

benzene or toluene) or water. Preferred reaction temperatures range from -80°C to 100°C .

Intermediate compounds of Formula (7) (where Y is O, S, NH, Z is CR^2 and R^1 , R^2 and Ar are defined as above) may be prepared as illustrated in Scheme 10.

SCHEME 10



Compounds of Formula (3) may be reacted with compounds of Formula $\text{H}_2\text{NNH}(\text{C}=\text{Y})\text{NH}_2$, where Y is O, S or NH, in the presence or absence of a base or acid in an inert solvent at temperatures from 0°C to 250°C to produce compounds of Formula (17). Acids may include, but are not limited to alkanolic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts

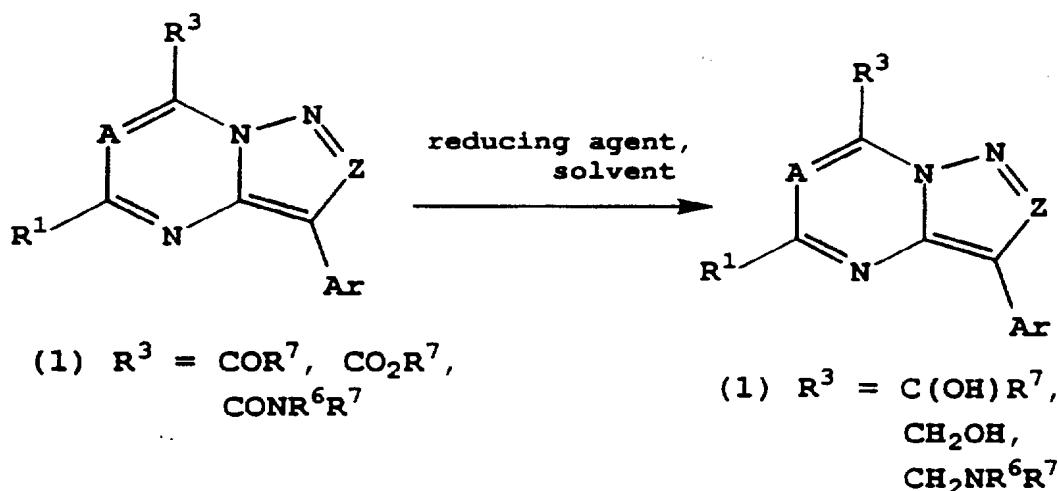
of such acids may be used. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane).

Preferred reaction temperatures range from 0°C to 150°C. Compounds of Formula (17) may then be reacted with compounds of Formula $R^3C(OR^e)_3$, where R^e may be alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may include, but are not limited to alkanolic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably

- acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane).
- Preferred reaction temperatures range from 50°C to 150°C.

In Scheme 11, the procedures which may be used to convert compounds of Formula (1), where R^3 is COR^7 , CO_2R^7 , NR^8COR^7 and $CONR^6R^7$, to other compounds of Formula (1), where R^3 is $CH(OH)R^7$, CH_2OH , $NR^8CH_2R^7$ and $CH_2NR^6R^7$ by treatment with a reducing agent in an inert solvent at temperatures ranging from -80°C to 250°C.

SCHEME 11

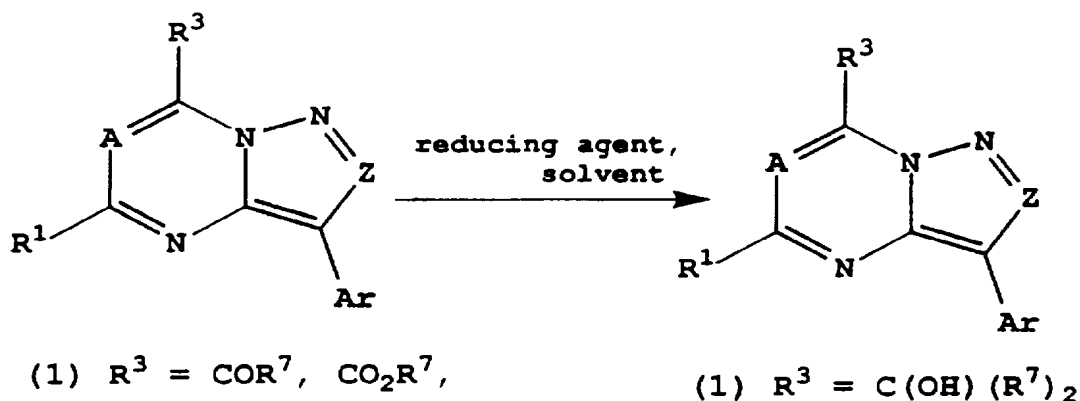


- Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane, dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxo)aluminum hydrides, or dialkyl aluminum

hydrides (such as di-isobutylaluminum hydride). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

In Scheme 12, the procedures are shown which may be used to convert compounds of Formula (1), where R^3 is COR^7 or CO_2R^7 , to other compounds of Formula (1), where R^3 is $C(OH)(R^7)_2$ by treatment with a reagent of Formula R^7M in an inert solvent at temperatures ranging from -80°C to 250°C.

SCHEME 12



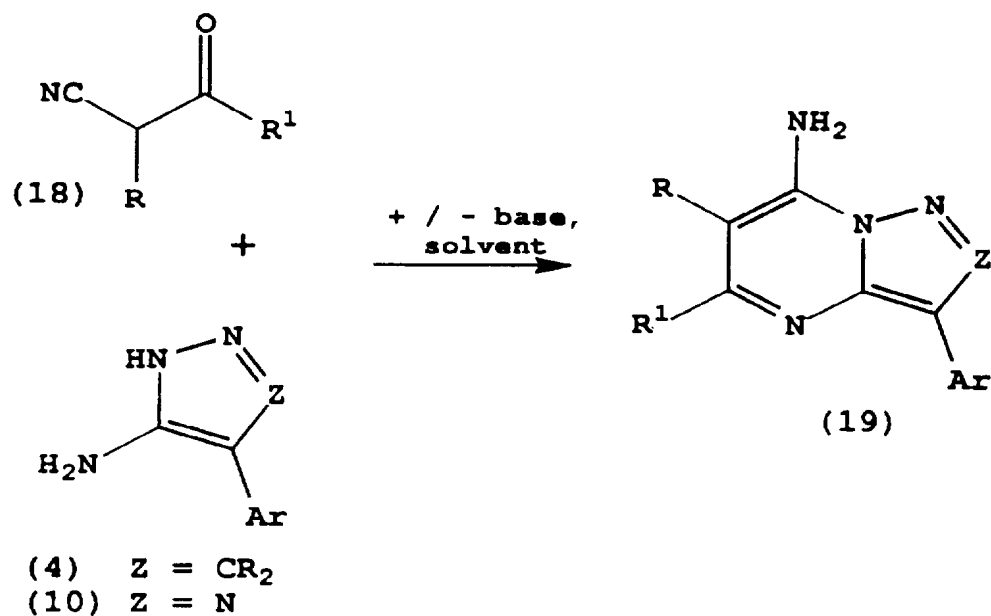
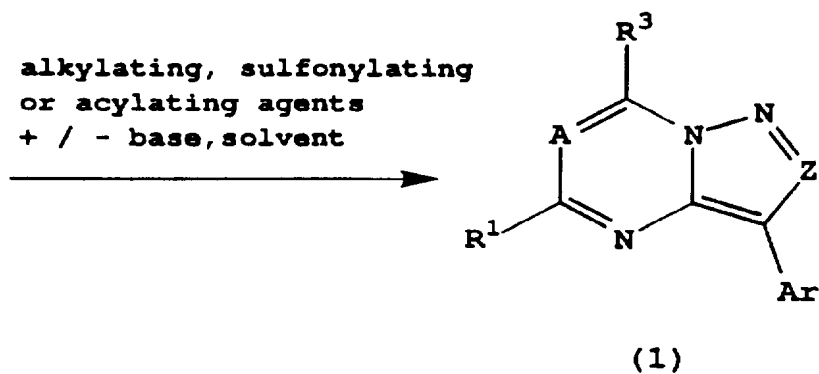
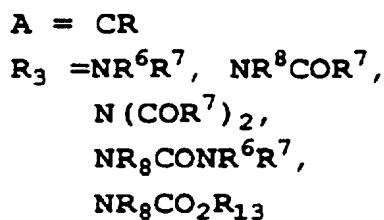
15

M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, CeCl₂, CeBr₂ or copper halides. Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

Compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$, may be synthesized as depicted in Scheme 13.

25

SCHEME 13



Reaction of compounds of Formula (18), where R and R¹
 5 are defined above, with compounds of Formula (4) or (10)
 in the presence or absence of base in an inert solvent
 may produce compounds of Formula (19) at temperatures

ranging from -50°C to 250°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Compounds of Formula (19) may then be reacted with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with combinations thereof, in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -80°C to 250°C may afford compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$. Alkylating agents may include, but are not limited to, C_1 - C_{10} alkyl -halides, -tosylates, -mesylates or -triflates; C_1 - C_{10} haloalkyl(1-10 halogens)-halides, -tosylates, -mesylates or -triflates; C_2 - C_8 alkoxyalkyl-halides, -tosylates, -mesylates or -triflates; C_3 - C_6 cycloalkyl-halides, -tosylates, -mesylates or -triflates; C_4 -

C₁₂ cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; aryl(C₁-C₄ alkyl)-halides, -tosylates, -mesylates or -triflates; heteroaryl(C₁-C₄ alkyl)-halides, -tosylates, -mesylates or -triflates; or

5 heterocyclyl(C₁-C₄ alkyl)-halides, -tosylates, -mesylates or -triflates. Acylating agents may include, but are not limited to, C₁-C₁₀ alkanoyl halides or anhydrides, C₁-C₁₀ haloalkanoyl halides or anhydrides with 1 - 10 halogens, C₂-C₈ alkoxyalkanoyl halides or

10 anhydrides, C₃-C₆ cycloalkanoyl halides or anhydrides, C₄-C₁₂ cycloalkylalkanoyl halides or anhydrides, aroyl halides or anhydrides, aryl(C₁-C₄) alkanoyl halides or anhydrides, heteroaroyl halides or anhydrides, heteroaryl(C₁-C₄) alkanoyl halides or anhydrides,

15 heterocyclylcarboxylic acid halides or anhydrides or heterocyclyl(C₁-C₄) alkanoyl halides or anhydrides. Sulfonylating agents include, but are not limited to, C₁-C₁₀ alkylsulfonyl halides or anhydrides, C₁-C₁₀ haloalkylsulfonyl halides or anhydrides with 1 - 10

20 halogens, C₂-C₈ alkoxyalkylsulfonyl halides or anhydrides, C₃-C₆ cycloalkylsulfonyl halides or anhydrides, C₄-C₁₂ cycloalkylalkylsulfonyl halides or anhydrides, arylsulfonyl halides or anhydrides, aryl(C₁-C₄ alkyl)-, heteroarylsulfonyl halides or anhydrides,

25 heteroaryl(C₁-C₄ alkyl)sulfonyl halides or anhydrides, heterocyclylsulfonyl halides or anhydrides or heterocyclyl(C₁-C₄ alkyl)sulfonyl halides or anhydrides. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal

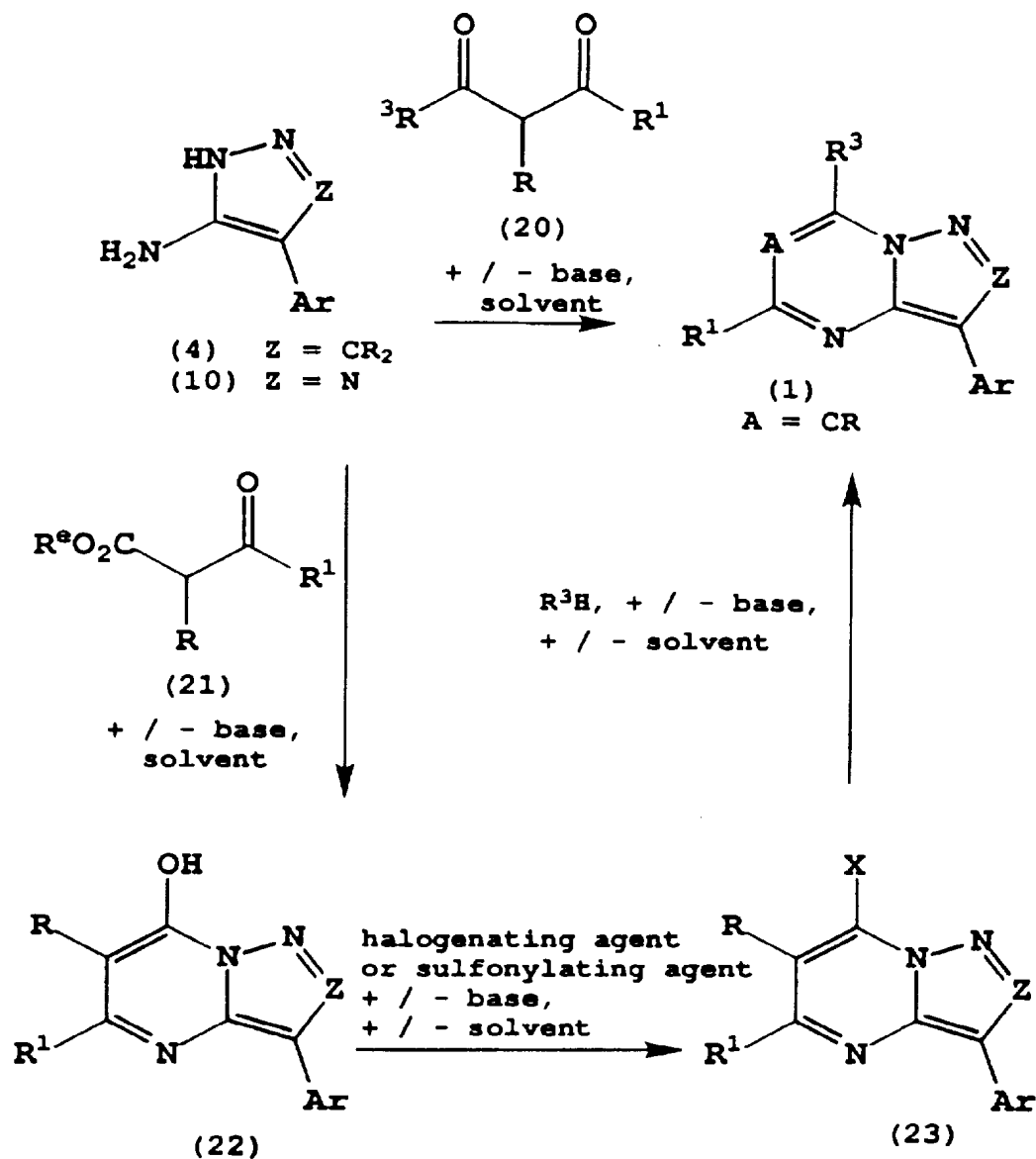
30 alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium

35 bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably

pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Compounds of Formula (1), where A is CR and R is defined above, may be synthesized by the methods depicted in Scheme 14.

SCHEME 14



Compounds of Formula (4) or (10) may be treated with compounds of Formula (20), where R^1 and R^3 are defined above in the presence or absence of base in an inert solvent at temperatures ranging from $0^\circ C$ to $250^\circ C$ to give compounds of Formula (1), where A is CR and R is defined above. Bases may include, but are not limited

to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C. Alternatively, compounds of Formula (1) where A is CR and R is defined above, may be synthesized through intermediates (22) and (23).

Compounds of Formula (4) or (10) may be treated with compounds of Formula (21), where R¹ is defined above and R^e is alkyl (1 - 6 carbons), in the presence or absence of base in an inert solvent at temperatures ranging from 0°C to 250°C to give compounds of Formula (1), where A is CR and R is defined above. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium

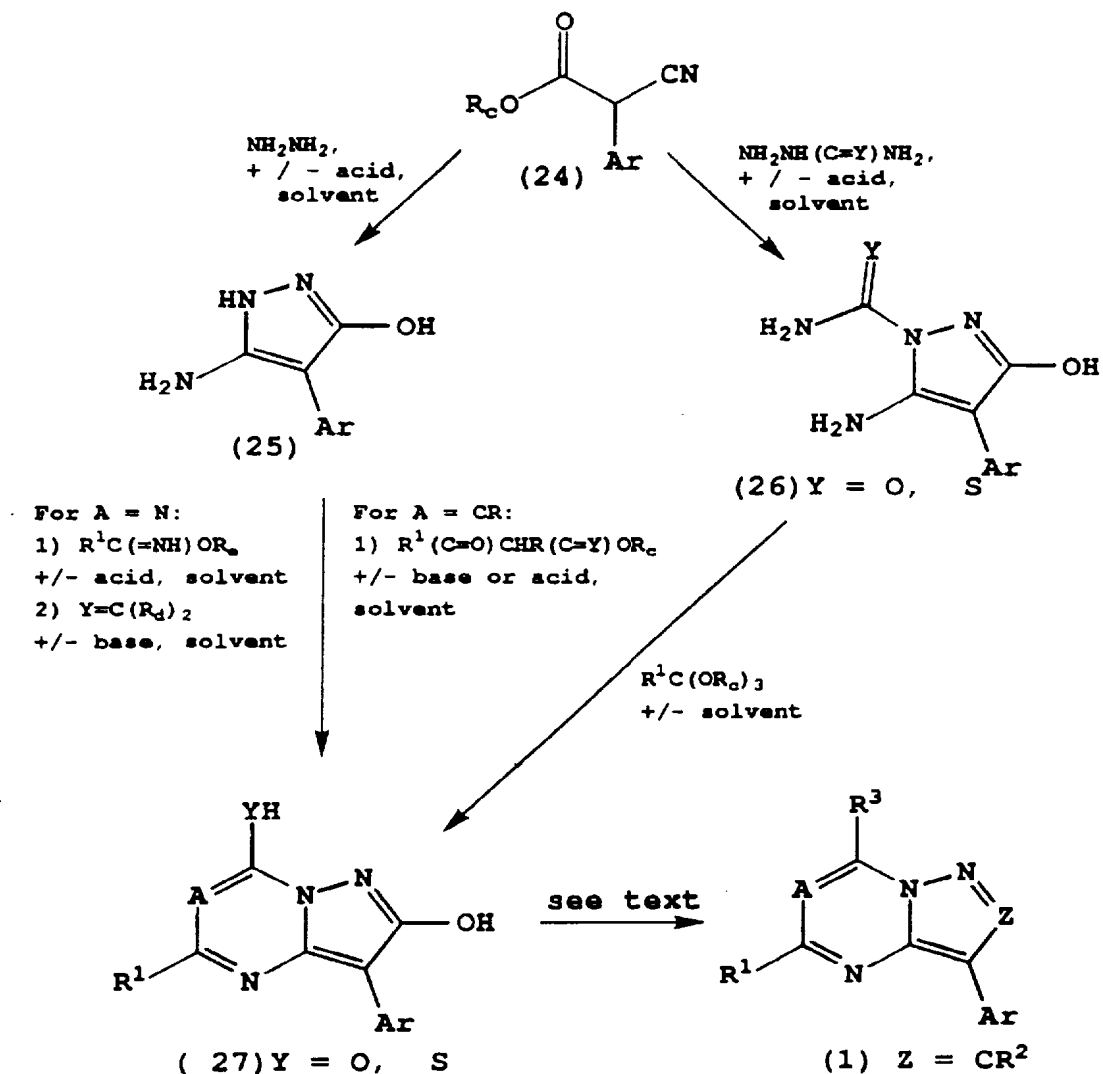
bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C. Compounds of Formula (22) may be treated with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (23) (where X is halogen, alkanesulfonyloxy, arylsulfonyloxy or haloalkanesulfonyloxy). Halogenating agents include, but are not limited to, SOCl₂, POCl₃, PCl₃, PCl₅, POBr₃, PBr₃ or PBr₅. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (such as methanesulfonyl chloride or methanesulfonic acid anhydride), arylsulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride) or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably

N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably
5 acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-
10 methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to
15 100°C.

Compounds of Formula (23) may be reacted with compounds of Formula R^3H (where R^3 is defined as above except R^3 is not SH, COR^7 , CO_2R^7 , aryl or heteroaryl) in the presence or absence of a base in the presence or
20 absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to generate compounds of Formula (1). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably
25 sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal
bis(trialkylsilyl)amides (preferably sodium
30 bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1
35 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably

- tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.
- 10 Some compounds of Formula (1) may also be prepared using the methods shown in Scheme 15.

SCHEME 15



- A compound of Formula (24) (R_c is a lower alkyl group and Ar is defined as above) may be reacted with
- 5 hydrazine in the presence or absence of an inert solvent to afford an intermediate of Formula (25), where Ar is defined as above. The conditions employed are similar to those used for the preparation of intermediate of Formula (4) from compound of Formula (3) in Scheme 4.
- 10 Compounds of Formula (25), where A is N, may be reacted with reagents of the formula $\text{R}^1\text{C}(=\text{NH})\text{OR}_c$, where R^1 is

defined above and R_e is a lower alkyl group) in the presence or absence of an acid in an inert solvent, followed by reaction with a compound of formula $YisC(R_d)2$ (where Y is O or S and R^d is halogen preferably chlorine), alkoxy (1 to 4 carbons) or alkylthio (1 to 4 carbons)) in the presence or absence of a base in an inert solvent to give compounds of Formula (27) (where A is N and Y is O, S). The conditions for these transformations are the same as those employed for the conversions of compound of Formula (4) to compound of Formula (7) in Scheme 4.

Alternatively, compounds of Formula (25), where A is CR, may be reacted with compounds of the formula $R^1(C=O)CHR(C=Y)OR_c$ (where R^1 and R are defined as above and R_c is a lower alkyl group) to give a compound of Formula (27) (where A is CR) using conditions similar to those employed for the conversion of compounds of Formula (21) to compounds of Formula (22) in Scheme 14. Intermediates of Formula (27) (where Y is O) may be treated with halogenating agents or sulfonylating agents in the presence or absence of a base in an inert solvent, followed by reaction with R^3H or R^2H in the presence or absence of a base in an inert solvent to give compounds of Formula (1) (where Z is CR^2).

It will be recognized by those skilled in the art that various combinations of halogenating agents, sulfonylating agents, R^3H or R^2H may be used in different orders of reaction sequences in Scheme 15 to afford compounds of Formula (1). For example, in some cases, it may be desirable to react compounds with stoichiometric amounts of halogenating agents or sulfonylating agents, react with R^2H (or R^3H), then repeat the reaction with halogenating agents or sulfonylating agents and react with R^3H (or R^2H) to give compounds of Formula (1). The reaction conditions and reagents used for these conversions are similar to the

ones employed for the conversion of intermediate compounds of Formulae (22) to (23) to (1) in Scheme 14 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8) to (1) in Scheme 1

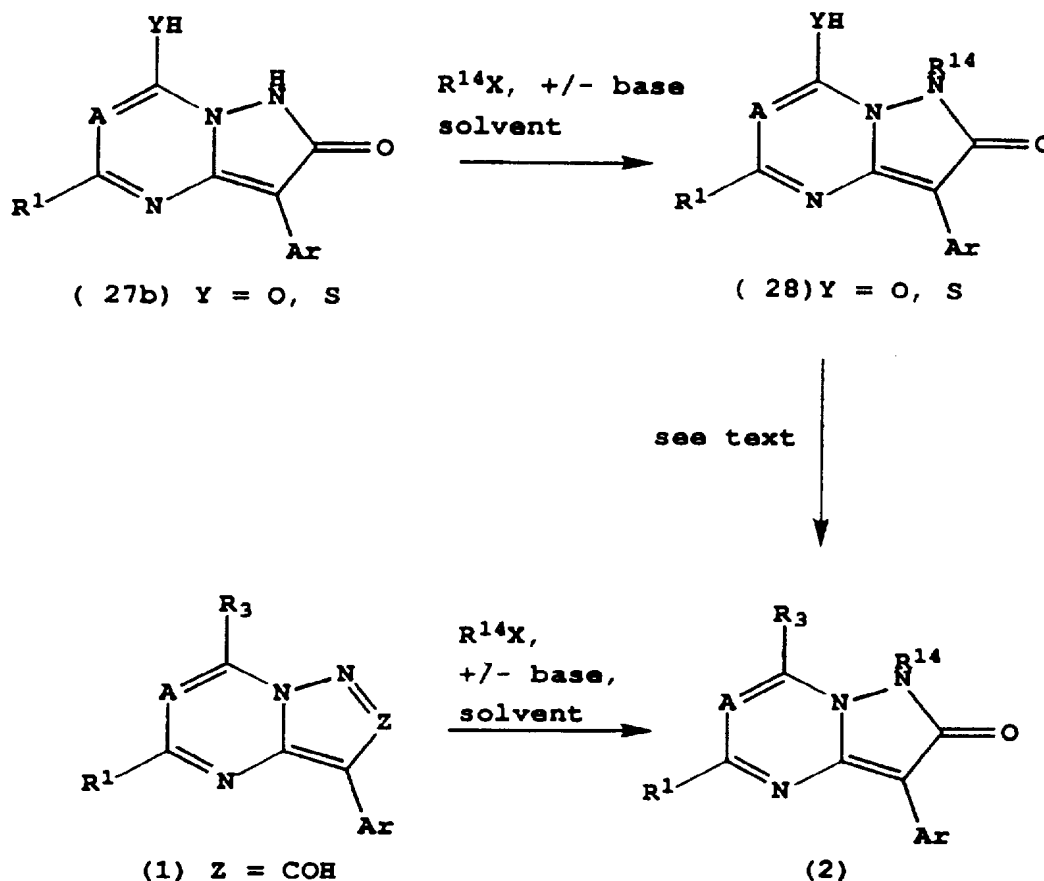
5 (where A is N).

Alternatively, compounds of Formula (27) (where Y is S) may be converted to compounds of Formula (1) in Scheme 15. Intermediate compounds of Formula (27) may be alkylated with a compound R^fX (where R^f is lower
10 alkyl and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in an inert solvent, (then optionally oxidized with an oxidizing agent in an inert solvent) and then reacted with R^3H in the presence or absence of a base in an inert solvent to give a compound
15 of Formula (1). The conditions and reagents employed are similar to those used in the conversion of intermediate compounds of Formulae (7) to (12) (or to (13)) to compounds of Formula (1) in Scheme 2.

Compounds of Formula (1) may be prepared from
20 compounds of Formula (24), using an alternate route as depicted in Scheme 15. Compounds of Formula (24) may be converted to compounds of Formula (27) via reaction with compounds of formula $NH_2NH(C=NH)NH_2$ in the presence or absence of an acid in an inert solvent, followed by
25 reaction with compounds $R^1C(OR_C)_3$ (where R_C is lower alkyl and R^1 is defined as above), using the conditions employed for the conversion of compounds of Formulae (3) to (17) to (7) in Scheme 10.

Some compounds of Formula (2) may be prepared by
30 the methods illustrated in Scheme 16.

SCHEME 16



Compounds of Formula (27b) may be treated with various
 alkylating agents R^{14}X (where R^{14} is defined above and X
 5 is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy)
 in the presence or absence of a base in an inert solvent
 to afford structures of Formula (28). Compounds of
 Formula (28) (Y is O) may then be converted to compounds
 of Formula (2) by treatment with halogenating agents or
 10 sulfonylating agents in the presence or absence of a
 base in an inert solvent, followed by reaction with R^3H
 in the presence or absence of a base in an inert solvent
 to give compounds of Formula (2). The reaction
 conditions used for these conversions are similar to the

ones employed for the conversion of intermediate compounds (22) to (23) to (1) in Scheme 14 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8) to (1) in Scheme 1 (where A is N).

- 5 Alternatively, compounds of Formula (28) (Y is S) may be alkylated with a compound R^fX (where R^f is lower alkyl and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in an inert solvent, (then optionally oxidized with an oxidizing agent in an inert solvent) and then reacted with R^3H in the presence or
10 absence of a base in an inert solvent to give a compound of Formula (1). The conditions and reagents employed are similar to those used in the conversion of intermediate compounds of Formulae (7) to (12) (or to
15 (13)) to compounds of Formula (1) in Scheme 2.

Compounds of Formula (1), where Z is COH, may be converted to compounds of Formula (2) as illustrated in Scheme 16. Treatment with various alkylating agents $R^{14}X$ (where R^{14} is defined above and X is halogen,
20 alkanesulfonyloxy or haloalkanesulfonyloxy) in the presence or absence of a base in an inert solvent to afford structures (2). It will be recognized by one skilled in the art that the methods used in Scheme 16 may also be used to prepare compounds of Formula (1)
25 where Z is COR^7 .

For Scheme 16, the terms "base" and "inert solvent" may have the meanings given below. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1
30 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably
35 N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents

may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

15

EXAMPLES

Analytical data were recorded for the compounds described below using the following general procedures. Proton NMR spectra were recorded on an IBM-Bruker FT-NMR (300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethylsilane standard in deuteriochloroform or deuterodimethylsulfoxide as specified below. Mass spectra (MS) or high resolution mass spectra (HRMS) were recorded on a Finnegan MAT 8230 spectrometer (using chemi-ionization (CI) with NH_3 as the carrier gas or gas chromatography (GC) as specified below) or a Hewlett Packard 5988A model spectrometer. Melting points were recorded on a Buchi Model 510 melting point apparatus and are uncorrected. Boiling points are uncorrected. All pH determinations during workup were made with indicator paper.

Reagents were purchased from commercial sources and, where necessary, purified prior to use according to the general procedures outlined by D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., (New York: Pergamon Press, 1988). Chromatography was

performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight.

5

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to
10 illustrate and not to limit the invention.

EXAMPLE 1

Preparation of

15 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]
-pyrazolo-[1,3,5]-triazin-4(3H)-one
(Formula 7, where Y is O, R₁ is CH₃, Z is C-CH₃,
Ar is 2,4-dimethylphenyl)

20 A. 1-Cyano-1-(2,4-dimethylphenyl)propan-2-one

Sodium pellets (9.8g, 0.43 mol) were added portionwise to a solution of 2,4-dimethylphenylacetonitrile (48 g, 0.33 mol) in ethyl acetate (150 mL) at ambient temperature. The reaction
25 mixture was heated to reflux temperature and stirred for 16 hours. The resulting suspension was cooled to room temperature and filtered. The collected precipitate was washed with copious amounts of ether and then air-dried. The solid was dissolved in water and a 1N HCl solution
30 was added until the pH = 5-6. The mixture was extracted with ethyl acetate (3 X 200 mL); the combined organic layers were dried over MgSO₄ and filtered. Solvent was removed *in vacuo* to afford a white solid (45.7g, 74%
yield): NMR (CDCl₃, 300 MHz):; CI-MS: 188 (M + H).

35

B. 5-Amino-4-(2,4-dimethylphenyl)-3-methylpyrazole

A mixture of 1-cyano-1-(2,4-dimethylphenyl)propan-2-one (43.8g, 0.23 mol), hydrazine-hydrate (22 mL, 0.46 mol), glacial acetic acid (45 mL, 0.78 mol) and toluene (500 mL) were stirred at reflux temperature for 18 hours in an apparatus fitted with a Dean-Stark trap. The reaction mixture was cooled to ambient temperature and solvent was removed in vacuo. The residue was dissolved in 6N HCl and the resulting solution was extracted with ether three times. A concentrated ammonium hydroxide solution was added to the aqueous layer until pH = 11. The resulting semi-solution was extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and filtered. Solvent was removed in vacuo to give a pale brown viscous oil (34.6g, 75% yield): NMR (CDCl₃, 300 MHz): 7.10 (s, 1H), 7.05 (d, 2H, J=1), 2.37 (s, 3H), 2.10 (s, 3H); CI-MS: 202 (M + H).

C. 5-Acetamidino-4-(2,4-dimethylphenyl)-3-methylpyrazole, acetic acid salt

Ethyl acetamidate hydrochloride (60g, 0.48 mol) was added quickly to a rapidly stirred mixture of potassium carbonate (69.5g, 0.50 mol), dichloromethane (120 mL) and water (350 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 X 120 mL). The combined organic layers were dried over MgSO₄ and filtered. Solvent was removed by simple distillation and the pot residue, a clear pale yellow liquid, (35.0 g) was used without further purification.

Glacial acetic acid (9.7 mL, 0.17 mol) was added to a stirred mixture of 5-amino-4-(2,4-dimethylphenyl)-3-methylpyrazole (34g, 0.17 mol), ethyl acetamidate (22g, 0.25 mol) and acetonitrile (500 mL). The resulting reaction mixture was stirred at room temperature for 3 days; at the end of which time, it was concentrated in vacuo to about one-third of its original volume. The resulting suspension was filtered and the collected

solid was washed with copious amounts of ether. The white solid was dried *in vacuo* (31.4g, 61% yield): NMR (DMSO- d_6 , 300 MHz): 7.00 (s, 1H), 6.90 (dd, 2H, $J=7, 1$), 2.28 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.81 (s, 3H); CI-MS: 243 (M + H).

D. 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-[1,3,5]-triazin-4(3H)-one

Sodium pellets (23g, 1 mol) were added portionwise to ethanol (500 mL) with vigorous stirring. After all the sodium reacted, 5-acetamidino-4-(2,4-dimethylphenyl)-3-methylpyrazole, acetic acid salt (31.2g, 0.1 mol) and diethyl carbonate (97 mL, 0.8 mol) were added. The resulting reaction mixture was heated to reflux temperature and stirred for 18 hours. The mixture was cooled to room temperature and solvent was removed *in vacuo*. The residue was dissolved in water and a 1N HCl solution was added slowly until pH = 5-6. The aqueous layer was extracted with ethyl acetate three times; the combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a pale tan solid (26g, 98% yield): NMR ($CDCl_3$, 300 MHz): 7.15 (s, 1H), 7.09 (s, 2H), 2.45 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H); CI-MS: 269 (M + H).

25

EXAMPLE 2

Preparation of

5-methyl-3-(2,4,6-trimethylphenyl)[1,5-a]-[1,2,3]-triazolo-[1,3,5]-triazin-7(6H)-one
(Formula 7, where Y is O, R_1 is CH_3 , Z is N, Ar is 2,4,6-trimethylphenyl)

30

A. 1-Phenylmethyl-4-(2,4,6-trimethylphenyl)-5-aminotriazole

35

A mixture of 2,4,6-trimethylbenzyl cyanide (1.0g, 6.3 mmol), benzyl azide (0.92g, 6.9 mmol) and potassium

t-butoxide (0.78g, 6.9 mmol) in tetrahydrofuran (10mL) was stirred at ambient temperature for 2.5 days. The resulting suspension was diluted with water and extracted three times with ethyl acetate. The combined
5 organic layers were dried over MgSO_4 and filtered. Solvent was removed in vacuo to give a brown oil. Trituration with ether and filtration afforded a yellow solid (1.12g, 61% yield): NMR (CDCl_3 , 300 MHz): 7.60-7.30 (m, 5H), 7.30-7.20 (m, 2H), 5.50 (s, 2H), 3.18 (br s,
10 2H), 2.30 (s, 3H), 2.10 (s, 6H); CI-MS: 293 (M + H).

B. 4-(2,4,6-Trimethylphenyl)-5-aminotriazole

Sodium (500 mg, 22 mmol) was added with stirring to a mixture of liquid ammonia (30 mL) and 1-phenylmethyl-
15 4-(2,4,6-trimethylphenyl)-5-aminotriazole (1.1g, 3.8 mmol). The reaction mixture was stirred until a dark green color persisted. An ammonium chloride solution (mL) was added and the mixture was stirred while warming to ambient temperature over 16 hours. The residue was
20 treated with a 1M HCl solution and filtered. The aqueous layer was basified with a concentrated ammonium hydroxide solution (pH = 9) and then extracted with ethyl acetate three times. The combined organic layers were dried over MgSO_4 and filtered. Solvent was removed
25 in vacuo to give a yellow solid (520 mg), which was homogeneous by thin layer chromatography (ethyl acetate):
NMR (CDCl_3 , 300 MHz): 6.97 (s, 2H), 3.68-3.50 (br.s, 2H), 2.32 (s, 3H), 2.10 (s, 6H); CI-MS: 203 (M + H).

30

C. 4-(2,4,6-Trimethylphenyl)-5-acetamidinotriazole, acetic acid salt

A mixture of 4-(2,4,6-trimethylphenyl)-5-aminotriazole (400 mg, 1.98 mmol), ethyl acetamidate (
35 261 mg, 3 mmol) and glacial acetic acid (0.1 mL, 1.98 mmol) in acetonitrile (6 mL) was stirred at ambient

temperature for 4 hours. The resulting suspension was filtered and the collected solid was washed with copious amounts of ether. Drying *in vacuo* afforded a white solid (490 mg, 82% yield): NMR (DMSO- d_6 , 300 MHz): 7.90-

5 7.70 (br s, 0.5H), 7.50-7.20 (br. s, 0.5H), 6.90 (s, 2H), 6.90 (s, 2H), 3.50-3.10 (br s, 3H), 2.30-2.20 (br s, 3H), 2.05 (d, 1H, $J = 7$), 1.96 (s, 6H), 1.87 (s, 6H); CI-MS: 244 (M + H).

10 D. 5-methyl-3-(2,4,6-trimethylphenyl)[1,5-a]-[1,2,3]-triazolo-[1,3,5]-triazin-7(4H)-one

Sodium (368 mg, 16.2 mmol) was added with stirring to ethanol (10 mL) at room temperature. After the sodium had reacted, 4-(2,4,6-trimethylphenyl)-5-
 15 acetamidino-triazole, acetic acid salt (490 mg, 1.6 mmol) and diethyl carbonate (1.6 mL, 13 mmol) were added. The reaction mixture was stirred at reflux temperature for 5 hours, then cooled to room temperature. The reaction mixture was diluted with
 20 water; a 1N HCl solution was added until pH = 5-6 and three extractions with ethyl acetate were performed. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a yellow residue. Trituration with ether and filtration afforded
 25 a yellow solid (300 mg, 69% yield): NMR ($CDCl_3$, 300 MHz): 6.98 (s, 2H), 2.55 (s, 3H), 2.35 (s, 3H), 2.10 (s, 6H); CI-MS: 270 (M + H).

EXAMPLE 3

30 Preparation of 4-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine
 (Formula 1, where R^3 is $CH(CHCO_2CH_3)_2$, R_1 is CH_3 , Z is C- CH_3 , Ar is 2,4-dimethylphenyl)

35

A. 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolotriazine

A mixture of 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38g, 4.5 mmol), N,N-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) was stirred at reflux temperature for 48 hours. The excess phosphorus oxychloride was removed *in vacuo*. The residue was poured onto ice-water, stirred briefly and extracted quickly with ethyl acetate three times. The combined organic layers were washed with ice water, then dried over MgSO₄ and filtered. Solvent was removed *in vacuo* to give a brown oil. Flash column chromatography (ethyl acetate:hexanes::1:4) gave one fraction (R_f = 0.5). Solvent was removed *in vacuo* to afford a yellow oil (1.0g, 68% yield): NMR (CDCl₃, 300 MHz): 7.55 (d, 1H, J = 1), 7.38 (dd, 1H, J = 7, 1), 7.30 (d, 1H, J = 7), 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

20

B. 4-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine

Sodium hydride (60% in oil, 80 mg, 2 mmol) was washed with hexanes twice, decanted after each washing and taken up in anhydrous tetrahydrofuran (THF, 1 mL). A solution of diethyl malonate (0.32g, 2 mmol) in THF (2 mL) was added dropwise over 5 min, during which time vigorous gas evolution ensued. A solution of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolotriazine (0.5g, 1.75 mmol) in THF (2 mL) was added and the reaction mixture was then stirred under a nitrogen atmosphere for 48 hours. The resulting suspension was poured onto water and extracted three times with ethyl acetate. The combined organic layers were washed once with brine, dried over MgSO₄ and filtered. Solvent was removed *in vacuo* to give a brown

35

oil. Column chromatography (ethyl acetate:hexanes::1:9) afforded, after removal of solvent *in vacuo*, a pale yellow solid ($R_f = 0.2$, 250 mg, 35% yield): mp 50-52°C; NMR ($CDCl_3$, 300 MHz): 12.35 (br.s, 1H, 7.15-7.00 (m, 3H), 4.40 (q, 2H, $J = 7$), 4.30 (q, 2H, $J = 7$), 2.4, 2.35, 2.3, 2.2, 2.1 (5 s, 12H), 1.4 (t, 3H, $J = 7$), 1.35-1.25 (m, 3H); CI-HRMS: Calcd: 411.2032, Found: 411.2023.

10

EXAMPLE 6

Preparation of 4-(1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine

15 (Formula 1, where R^3 is $NHCH(CH_2OCH_3)_2$, R_1 is CH_3 , Z is $C-CH_3$, Ar is 2,4-dichlorophenyl)

A. 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolotriazine

20 A mixture of 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38g, 4.5 mmol), *N,N*-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) was stirred at reflux temperature for 48 hours. The excess
25 phosphorus oxychloride was removed *in vacuo*. The residue was poured onto ice-water, stirred briefly and extracted quickly with ethyl acetate three times. The combined organic layers were washed with ice water, then dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a brown oil. Flash column chromatography (ethyl acetate:hexanes::1:4) gave one fraction ($R_f =$
30 0.5) Solvent was removed *in vacuo* to afford a yellow oil (1.0g, 68% yield): NMR ($CDCl_3$, 300 MHz): 7.55 (d, 1H, $J = 1$), 7.38 (dd, 1H, $J = 7, 1$), 7.30 (d, 1H, $J = 7$),
35 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 ($M + H$).

B. 4-(1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine

A mixture of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine (Part A, 570 mg, 1.74 mmol), 1,3-dimethoxypropyl-2-aminopropane (25mg, 2.08 mmol) and ethanol (10 mL) was stirred at ambient temperature for 18 hours. The reaction mixture was poured onto water (25 mL) and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO_4 and filtered. Solvent was removed *in vacuo*. Column chromatography ($\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}::50:1$) afforded one fraction. Removal of solvent *in vacuo* gave a solid (250 mg, 35% yield): mp 118-120°C; NMR (CDCl_3 , 300 MHz): 7.50 (s, 1H), 7.28 (dd, 2H, $J = 8, 1$), 6.75 (d, 1H, $J = 8$), 4.70-4.58 (m, 1H), 3.70-3.55 (m, 4H), 3.43 (s, 6H), 2.50 (s, 3H), 2.35 (s, 3H); CI-HRMS: Calcd: 409.1072, Found: 409.1085; Analysis Calcd. for $\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{N}_5\text{O}_2$: C, 52.69, H, 5.17, N, 17.07, Cl, 17.28; Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17.50.

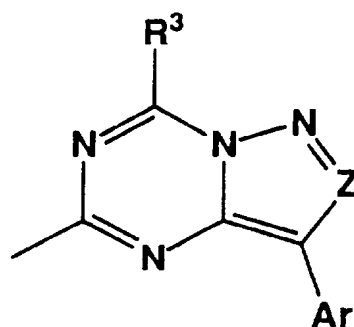
Using the above procedures and modifications known to one skilled in the art of organic synthesis, the following additional examples of Tables 1-4 may be prepared.

The examples delineated in TABLE 1 may be prepared by the methods outlined in Examples 1, 2, 3 or 6.

Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is

Example.

TABLE 1



5	Ex.	Z	R ₃	Ar	mp (°C)
	6 ^a	C-Me	NHCH(CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	118-120
	7 ^b	C-Me	NHCHPr ₂	2,4-Cl ₂ -Ph	114-116
	8 ^c	C-Me	NEtBu	2,4-Cl ₂ -Ph	oil
	9 ^d	C-Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Cl ₂ -Ph	oil
10	10 ^e	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	oil
	11 ^f	C-Me	NH-3-heptyl	2,4-Cl ₂ -Ph	90-92
	12 ^g	C-Me	NHCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph	179-181
	13 ^h	C-Me	NEt ₂	2,4-Cl ₂ -Ph	133-134
	14 ⁱ	C-Me	NHCH(CH ₂ OEt) ₂	2,4-Cl ₂ -Ph	oil
15	15 ^j	C-Me	NH-3-pentyl	2,4-Cl ₂ -Ph	139-140
	16 ^k	C-Me	NMePh	2,4-Cl ₂ -Ph	60-62
	17 ^l	C-Me	NPr ₂	2,4-Cl ₂ -Ph	oil
	18 ^m	C-Me	NH-3-hexyl	2,4-Cl ₂ -Ph	130-132
	19	C-Me	morpholino	2,4-Cl ₂ -Ph	
20	20	C-Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Cl ₂ -Ph	
	21	C-Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Cl ₂ -Ph	
	22	C-Me	NH-4-tetrahydropyranyl	2,4-Cl ₂ -Ph	
	23	C-Me	NH-cyclopentyl	2,4-Cl ₂ -Ph	
	24	C-Me	1,2,3,4-tetrahydro-	2,4-Cl ₂ -Ph	
25			isoquinolinyl		
	25	C-Me	CH ₂ -(1,2,3,4-tetrahydro-	2,4-Cl ₂ -Ph	
			isoquinolinyl)		
	26 ⁿ	C-Me	OEt	2,4-Cl ₂ -Ph	141-143
	27	C-Me	OCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph	

	28	C-Me	OCH ₂ Ph	2,4-Cl ₂ -Ph	
	29	C-Me	O-3-pentyl	2,4-Cl ₂ -Ph	
	30	C-Me	SEt	2,4-Cl ₂ -Ph	
	31	C-Me	S(O)Et	2,4-Cl ₂ -Ph	
5	32	C-Me	SO ₂ Et	2,4-Cl ₂ -Ph	
	33	C-Me	CH(CO ₂ Et) ₂	2,4-Cl ₂ -Ph	
	34	C-Me	C(Et)(CO ₂ Et) ₂	2,4-Cl ₂ -Ph	
	35	C-Me	CH(Et)CH ₂ OH	2,4-Cl ₂ -Ph	
	36	C-Me	CH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph	
10	37	C-Me	CONMe ₂	2,4-Cl ₂ -Ph	
	38	C-Me	COCH ₃	2,4-Cl ₂ -Ph	
	39	C-Me	CH(OH)CH ₃	2,4-Cl ₂ -Ph	
	40	C-Me	C(OH)Ph-3-pyridyl	2,4-Cl ₂ -Ph	
	41	C-Me	Ph	2,4-Cl ₂ -Ph	
15	42	C-Me	2-CF ₃ -Ph	2,4-Cl ₂ -Ph	
	43	C-Me	2-Ph-Ph	2,4-Cl ₂ -Ph	
	44	C-Me	3-pentyl	2,4-Cl ₂ -Ph	
	45	C-Me	cyclobutyl	2,4-Cl ₂ -Ph	
	46	C-Me	3-pyridyl	2,4-Cl ₂ -Ph	
20	47	C-Me	CH(Et)CH ₂ CONMe ₂	2,4-Cl ₂ -Ph	
	48	C-Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4-Cl ₂ -Ph	
	49 ^o	C-Me	NHCH(CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph	125-127
	50	C-Me	NHCHPr ₂	2,4,6-Me ₃ -Ph	
	51	C-Me	NEtBu	2,4,6-Me ₃ -Ph	
25	52	C-Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4,6-Me ₃ -Ph	
	53 ^{ae}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph	123-124
	54	C-Me	NH-3-heptyl	2,4,6-Me ₃ -Ph	
	55 ^{ac}	C-Me	NHCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph	145-146
	56 ^{ah}	C-Me	NEt ₂	2,4,6-Me ₃ -Ph	88-90
30	57 ^{ai}	C-Me	NHCH(CH ₂ OEt) ₂	2,4,6-Me ₃ -Ph	132-134
	58 ^{ad}	C-Me	NH-3-pentyl	2,4,6-Me ₃ -Ph	134-135
	59	C-Me	NMePh	2,4,6-Me ₃ -Ph	
	60	C-Me	NPr ₂	2,4,6-Me ₃ -Ph	
	61	C-Me	NH-3-hexyl	2,4,6-Me ₃ -Ph	
35	62	C-Me	morpholino	2,4,6-Me ₃ -Ph	
	63	C-Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4,6-Me ₃ -Ph	

	64	C-Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4,6-Me ₃ -Ph	
	65	C-Me	NH-4-tetrahydropyranyl	2,4,6-Me ₃ -Ph	
	66	C-Me	NH-cyclopentyl	2,4,6-Me ₃ -Ph	
	67	C-Me	1,2,3,4-tetrahydro-	2,4,6-Me ₃ -Ph	
5			isoquinolinyl		
	68	C-Me	CH ₂ -(1,2,3,4-tetrahydro-	2,4,6-Me ₃ -Ph	
			isoquinolinyl)		
	69	C-Me	OEt	2,4,6-Me ₃ -Ph	
	70	C-Me	OCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph	
10	71	C-Me	OCH ₂ Ph	2,4,6-Me ₃ -Ph	
	72	C-Me	O-3-pentyl	2,4,6-Me ₃ -Ph	
	73	C-Me	SEt	2,4,6-Me ₃ -Ph	
	74	C-Me	S(O)Et	2,4,6-Me ₃ -Ph	
	75	C-Me	SO ₂ Et	2,4,6-Me ₃ -Ph	
15	76	C-Me	CH(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph	
	77	C-Me	C(Et)(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph	
	78	C-Me	CH(Et)CH ₂ OH	2,4,6-Me ₃ -Ph	
	79	C-Me	CH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph	
	80	C-Me	CONMe ₂	2,4,6-Me ₃ -Ph	
20	81	C-Me	COCH ₃	2,4,6-Me ₃ -Ph	
	82	C-Me	CH(OH)CH ₃	2,4,6-Me ₃ -Ph	
	83	C-Me	C(OH)Ph-3-pyridyl	2,4,6-Me ₃ -Ph	
	84	C-Me	Ph	2,4,6-Me ₃ -Ph	
	85	C-Me	2-CF ₃ -Ph	2,4,6-Me ₃ -Ph	
25	86	C-Me	2-Ph-Ph	2,4,6-Me ₃ -Ph	
	87	C-Me	3-pentyl	2,4,6-Me ₃ -Ph	
	88	C-Me	cyclobutyl	2,4,6-Me ₃ -Ph	
	89	C-Me	3-pyridyl	2,4,6-Me ₃ -Ph	
	90	C-Me	CH(Et)CH ₂ CONMe ₂	2,4,6-Me ₃ -Ph	
30	91	C-Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4,6-Me ₃ -Ph	
	92 ^P	C-Me	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph	44-45
	93 ^Q	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph	oil
	94 ^R	C-Me	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph	102-104
	95 ^S	C-Me	NH-3-pentyl	2,4-Me ₂ -Ph	102-104
35	96 ^t	C-Me	NEt ₂	2,4-Me ₂ -Ph	oil
	97 ^u	C-Me	N(CH ₂ CN) ₂	2,4-Me ₂ -Ph	148-150

	98 ^v	C-Me	NHCH(Me)CH ₂ OMe	2,4-Me ₂ -Ph	102-104
	99 ^w	C-Me	OCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph	oil
	100 ^x	C-Me	NPr-c-C ₃ H ₅	2,4-Me ₂ -Ph	oil
	101 ^y	C-Me	NHCH(Me)CH ₂ NMe ₂	2,4-Me ₂ -Ph	47-48
5	102 ^z	C-Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	117-118
	103 ^{aa}	C-Me	N(Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	oil
	104 ^{ab}	C-Me	N(Bu)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	oil
	105	C-Me	NHCHPr ₂	2,4-Me ₂ -Ph	
	106	C-Me	NEtBu	2,4-Me ₂ -Ph	
10	107	C-Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Me ₂ -Ph	
	108	C-Me	NH-3-heptyl	2,4-Me ₂ -Ph	
	109	C-Me	NEt ₂	2,4-Me ₂ -Ph	
	110	C-Me	NHCH(CH ₂ OEt) ₂	2,4-Me ₂ -Ph	
	111	C-Me	NH-3-pentyl	2,4-Me ₂ -Ph	
15	112	C-Me	NMePh	2,4-Me ₂ -Ph	
	113	C-Me	NPr ₂	2,4-Me ₂ -Ph	
	114	C-Me	NH-3-hexyl	2,4-Me ₂ -Ph	
	115	C-Me	morpholino	2,4-Me ₂ -Ph	
	116	C-Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Me ₂ -Ph	
20	117	C-Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Me ₂ -Ph	
	118	C-Me	NH-4-tetrahydropyranyl	2,4-Me ₂ -Ph	
	119	C-Me	NH-cyclopentyl	2,4-Me ₂ -Ph	
	120	C-Me	1,2,3,4-tetrahydro- isoquinolinyl	2,4-Me ₂ -Ph	
25	121	C-Me	CH ₂ -(1,2,3,4-tetrahydro- isoquinolinyl)	2,4-Me ₂ -Ph	
	122	C-Me	OEt	2,4-Me ₂ -Ph	
	123	C-Me	OCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph	
	124	C-Me	OCH ₂ Ph	2,4-Me ₂ -Ph	
30	125	C-Me	O-3-pentyl	2,4-Me ₂ -Ph	
	126	C-Me	SEt	2,4-Me ₂ -Ph	
	127	C-Me	S(O)Et	2,4-Me ₂ -Ph	
	128	C-Me	SO ₂ Et	2,4-Me ₂ -Ph	
	3	C-Me	CH(CO ₂ Et) ₂	2,4-Me ₂ -Ph	50-52
35	129	C-Me	C(Et)(CO ₂ Et) ₂	2,4-Me ₂ -Ph	

	130	C-Me	CH(Et)CH ₂ OH	2,4-Me ₂ -Ph	
	131	C-Me	CH(Et)CH ₂ OMe	2,4-Me ₂ -Ph	
	132	C-Me	CH(Et)CH ₂ OEt	2,4-Me ₂ -Ph	
	133	C-Me	CONMe ₂	2,4-Me ₂ -Ph	
5	134	C-Me	COCH ₃	2,4-Me ₂ -Ph	
	135	C-Me	CH(OH)CH ₃	2,4-Me ₂ -Ph	
	136	C-Me	C(OH)Ph-3-pyridyl	2,4-Me ₂ -Ph	
	137	C-Me	Ph	2,4-Me ₂ -Ph	
	138	C-Me	2-CF ₃ -Ph	2,4-Me ₂ -Ph	
10	139	C-Me	2-Ph-Ph	2,4-Me ₂ -Ph	
	140	C-Me	3-pentyl	2,4-Me ₂ -Ph	
	141	C-Me	cyclobutyl	2,4-Me ₂ -Ph	
	142	C-Me	3-pyridyl	2,4-Me ₂ -Ph	
	143	C-Me	CH(Et)CH ₂ CONMe ₂	2,4-Me ₂ -Ph	
15	144	C-Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4-Me ₂ -Ph	
	145 ^{bc}	C-Me	NHCH(CH ₂ OMe) ₂	2-Me-4-MeO-Ph	45-46
	146 ^{bd}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-MeO-Ph	oil
	147 ^{be}	C-Me	NHCH(Et)CH ₂ OMe	2-Me-4-MeO-Ph	86-88
	148 ^{bf}	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-MeO-Ph	oil
20	149	C-Me	OCH(Et)CH ₂ OMe	2-Me-4-MeO-Ph	
	150 ^{af}	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-MeO-Ph	88-90
	151 ^{al}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-MeO-Ph	oil
	152 ^{ag}	C-Me	NHCH(Et)CH ₂ OMe	2-Br-4-MeO-Ph	95-97
	153	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-MeO-Ph	
25	154	C-Me	OCH(Et)CH ₂ OMe	2-Br-4-MeO-Ph	
	155	C-Me	NHCH(CH ₂ OMe) ₂	2-Me-4-NMe ₂ -Ph	
	156	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-NMe ₂ -Ph	oil
	157	C-Me	NHCH(Et)CH ₂ OMe	2-Me-4-NMe ₂ -Ph	
	158	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-NMe ₂ -Ph	
30	159	C-Me	OCH(Et)CH ₂ OMe	2-Me-4-NMe ₂ -Ph	
	160	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-NMe ₂ -Ph	
	161	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-NMe ₂ -Ph	
	162	C-Me	NHCH(Et)CH ₂ OMe	2-Br-4-NMe ₂ -Ph	
	163	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-NMe ₂ -Ph	
35	164	C-Me	OCH(Et)CH ₂ OMe	2-Br-4-NMe ₂ -Ph	
	165	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-i-Pr-Ph	

	166	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-i-Pr-Ph	
	167	C-Me	NHCH(Et)CH ₂ OMe	2-Br-4-i-Pr-Ph	
	168	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-i-Pr-Ph	
	169	C-Me	OCH(Et)CH ₂ OMe	2-Br-4-i-Pr-Ph	
5	170	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-Me-Ph	
	171	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-Me-Ph	
	172	C-Me	NHCH(Et)CH ₂ OMe	2-Br-4-Me-Ph	
	173	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-Me-Ph	
	174	C-Me	OCH(Et)CH ₂ OMe	2-Br-4-Me-Ph	
10	175 ^{ar}	C-Me	NHCH(CH ₂ OMe) ₂	2-Me-4-Br-Ph	108-109
	176	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-Br-Ph	
	177	C-Me	NHCH(Et)CH ₂ OMe	2-Me-4-Br-Ph	
	178	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-Br-Ph	
	179	C-Me	OCH(Et)CH ₂ OMe	2-Me-4-Br-Ph	
15	180	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,6-Me ₂ -Ph	
	181	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-Me ₂ -Ph	
	182	C-Me	NHCH(CH ₂ OMe) ₂	4-Br-2,6-(Me) ₂ -Ph	
	183	C-Me	N(CH ₂ CH ₂ OMe) ₂	4-Br-2,6-(Me) ₂ -Ph	
	184	C-Me	NHCH(CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph	
20	185	C-Me	N(CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph	
	186	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-CF ₃ -Ph	
	187	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-CF ₃ -Ph	
	188	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4,6-(MeO) ₂ -Ph	
	189	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4,6-(MeO) ₂ -Ph	
25	190	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ -Ph	
	191	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ -Ph	
	192	C-Me	NHCH(CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph	
	193	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph	
	194	C-Me	NHCH(CH ₂ OMe) ₂	4-(COMe)-2-Br-Ph	
30	195	C-Me	N(CH ₂ CH ₂ OMe) ₂	4-(COMe)-2-Br-Ph	
	196	C-Me	NHCH(CH ₂ OMe) ₂	2,4,6-Me ₃ -pyrid-3-yl	
	197	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -pyrid-3-yl	
	198	C-Me	NHCH(CH ₂ OMe) ₂	2,4-(Br) ₂ -Ph	
	199	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-(Br) ₂ -Ph	
35	200	C-Me	NHCH(CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph	
	201	C-Me	N(CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph	

	202	C-Me	NHCH (CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	203	C-Me	N (CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	204	C-Me	NHCH (CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
	205	C-Me	N (CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
5	206	C-Me	NHCH (CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SO ₂ Me-Ph
	207	C-Me	N (CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SO ₂ Me-Ph
	208	C-Me	NHCH (CH ₂ OMe) ₂	2-I-4-i-Pr-Ph
	209	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-I-4-i-Pr-Ph
	210	C-Me	NHCH (CH ₂ OMe) ₂	2-Br-4-N (Me) ₂ -6-MeO-Ph
10	211	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-Br-4-N (Me) ₂ -6-MeO-Ph
	212	C-Me	NHCH (CH ₂ OMe) ₂	2,4-[SMe] ₂ -Ph
	213	C-Me	N (CH ₂ CH ₂ OMe) ₂	2,4-[SMe] ₂ -Ph
	214	C-Me	NHCH (CH ₂ OMe) ₂	2,4-[SO ₂ Me] ₂ -Ph
	215	C-Me	N (CH ₂ CH ₂ OMe) ₂	2,4-[SO ₂ Me] ₂ -Ph
15	216	C-Me	NHCH (CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	217	C-Me	N (CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	218	C-Me	NHCH (CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	219	C-Me	N (CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	220	C-Me	NHCH (CH ₂ OMe) ₂	2-N (Me) ₂ -4-Me-Ph
20	221	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-N (Me) ₂ -4-Me-Ph
	222	C-Me	NHCH (CH ₂ OMe) ₂	2-MeS-4,6-(Me) ₂ -Ph
	223	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-MeS-4,6-(Me) ₂ -Ph
	224	C-Me	NHCH (CH ₂ OMe) ₂	2-(CH ₃ CO)-4,6-(Me) ₂ -Ph
	225	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-(CH ₃ CO)-4,6-(Me) ₂ -Ph
25	226	H	NHCH (CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	227	H	NHCH (CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	228	CF ₃	N (CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	229	CF ₃	N (CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	230	N	NHCH (CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph
30	231	N	NHCHPr ₂	2,4,6-Me ₃ -Ph
	232	N	NEtBu	2,4,6-Me ₃ -Ph
	233	N	NPr (CH ₂ -c-C ₃ H ₅)	2,4,6-Me ₃ -Ph
	234	N	N (CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph
	235	N	NH-3-heptyl	2,4,6-Me ₃ -Ph
35	236	N	NHCH (Et) CH ₂ OMe	2,4,6-Me ₃ -Ph
	237	N	NEt ₂	2,4,6-Me ₃ -Ph

	238	N	NHCH(CH ₂ OEt) ₂	2,4,6-Me ₃ -Ph
	239	N	NH-3-pentyl	2,4,6-Me ₃ -Ph
	240	N	NMePh	2,4,6-Me ₃ -Ph
	241	N	NPr ₂	2,4,6-Me ₃ -Ph
5	242	N	NH-3-hexyl	2,4,6-Me ₃ -Ph
	243	N	morpholino	2,4,6-Me ₃ -Ph
	244	N	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4,6-Me ₃ -Ph
	245	N	NHCH(CH ₂ Ph)CH ₂ OMe	2,4,6-Me ₃ -Ph
	246	N	NH-4-tetrahydropyranyl	2,4,6-Me ₃ -Ph
10	247	N	NH-cyclopentyl	2,4,6-Me ₃ -Ph
	248	N	1,2,3,4-tetrahydro- isoquinolinyl	2,4,6-Me ₃ -Ph
	249	N	CH ₂ -(1,2,3,4-tetrahydro- isoquinolinyl)	2,4,6-Me ₃ -Ph
15	250	N	OEt	2,4,6-Me ₃ -Ph
	251	N	OCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	252	N	OCH ₂ Ph	2,4,6-Me ₃ -Ph
	253	N	O-3-pentyl	2,4,6-Me ₃ -Ph
	254	N	SEt	2,4,6-Me ₃ -Ph
20	255	N	S(O)Et	2,4,6-Me ₃ -Ph
	256	N	SO ₂ Et	2,4,6-Me ₃ -Ph
	257	N	CH(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph
	258	N	C(Et)(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph
	259	N	CH(Et)CH ₂ OH	2,4,6-Me ₃ -Ph
25	260	N	CH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	261	N	CONMe ₂	2,4,6-Me ₃ -Ph
	262	N	COCH ₃	2,4,6-Me ₃ -Ph
	263	N	CH(OH)CH ₃	2,4,6-Me ₃ -Ph
	264	N	C(OH)Ph-3-pyridyl	2,4,6-Me ₃ -Ph
30	265	N	Ph	2,4,6-Me ₃ -Ph
	266	N	2-CF ₃ -Ph	2,4,6-Me ₃ -Ph
	267	N	2-Ph-Ph	2,4,6-Me ₃ -Ph
	268	N	3-pentyl	2,4,6-Me ₃ -Ph
	269	N	cyclobutyl	2,4,6-Me ₃ -Ph
35	270	N	3-pyridyl	2,4,6-Me ₃ -Ph
	271	N	CH(Et)CH ₂ CONMe ₂	2,4,6-Me ₃ -Ph

	272	N	CH(Et)CH ₂ CH ₂ NMe ₂	2,4,6-Me ₃ -Ph
	273	N	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	274	N	NHCHPr ₂	2,4-Me ₂ -Ph
	275	N	NEtBu	2,4-Me ₂ -Ph
5	276	N	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Me ₂ -Ph
	277	N	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	278	N	NH-3-heptyl	2,4-Me ₂ -Ph
	279	N	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	280	N	NEt ₂	2,4-Me ₂ -Ph
10	281	N	NHCH(CH ₂ OEt) ₂	2,4-Me ₂ -Ph
	282	N	NH-3-pentyl	2,4-Me ₂ -Ph
	283	N	NMePh	2,4-Me ₂ -Ph
	284	N	NPr ₂	2,4-Me ₂ -Ph
	285	N	NH-3-hexyl	2,4-Me ₂ -Ph
15	286	N	morpholino	2,4-Me ₂ -Ph
	287	N	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Me ₂ -Ph
	288	N	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Me ₂ -Ph
	289	N	NH-4-tetrahydropyranyl	2,4-Me ₂ -Ph
	290	N	NH-cyclopentyl	2,4-Me ₂ -Ph
20	291	N	1,2,3,4-tetrahydro- isoquinolinyl	2,4-Me ₂ -Ph
	292	N	CH ₂ -(1,2,3,4-tetrahydro- isoquinolinyl)	2,4-Me ₂ -Ph
	293	N	OEt	2,4-Me ₂ -Ph
25	294	N	OCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	295	N	OCH ₂ Ph	2,4-Me ₂ -Ph
	296	N	O-3-pentyl	2,4-Me ₂ -Ph
	297	N	SEt	2,4-Me ₂ -Ph
	298	N	S(O)Et	2,4-Me ₂ -Ph
30	299	N	SO ₂ Et	2,4-Me ₂ -Ph
	300	N	CH(CO ₂ Et) ₂	2,4-Me ₂ -Ph
	301	N	C(Et)(CO ₂ Et) ₂	2,4-Me ₂ -Ph
	302	N	CH(Et)CH ₂ OH	2,4-Me ₂ -Ph
	303	N	CH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
35	304	N	CONMe ₂	2,4-Me ₂ -Ph
	305	N	COCH ₃	2,4-Me ₂ -Ph

	306	N	CH(OH)CH ₃	2,4-Me ₂ -Ph	
	307	N	C(OH)Ph-3-pyridyl	2,4-Me ₂ -Ph	
	308	N	Ph	2,4-Me ₂ -Ph	
	309	N	2-CF ₃ -Ph	2,4-Me ₂ -Ph	
5	310	N	2-Ph-Ph	2,4-Me ₂ -Ph	
	311	N	3-pentyl	2,4-Me ₂ -Ph	
	312	N	cyclobutyl	2,4-Me ₂ -Ph	
	313	N	3-pyridyl	2,4-Me ₂ -Ph	
	314	N	CH(Et)CH ₂ CONMe ₂	2,4-Me ₂ -Ph	
10	315	N	CH(Et)CH ₂ CH ₂ NMe ₂	2,4-Me ₂ -Ph	
	316 ^{an}	C-Me	NEt ₂	2-Br-4-MeO-Ph	oil
	317 ^{am}	C-Me	NH-3-pentyl	2-Br-4-MeO-Ph	oil
	318 ^{aj}	C-Me	NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2,4,6-Me ₃ -Ph	101-103
	319 ^{ao}	C-Me	NH(c-C ₃ H ₅)	2,4-Me ₂ -Ph	oil
15	320 ^{ak}	C-Me	morpholino	2,4,6-Me ₃ -Ph	139-141
	321 ^{ap}	C-Me	NHCH(CH ₂ OMe) ₂	2-CN-4-Me-Ph	152-153
	322 ^{aq}	C-Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4,6-Me ₃ -Ph	149-151
	324 ^{as}	C-Me	NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Me-4-Br-Ph	115-117
	325 ^{at}	C-Me	NHCH(CH ₂ OMe) ₂	2,5-Me ₂ -4-MeO-Ph	55-57
20	326 ^{au}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,5-Me ₂ -4-MeO-Ph	72
	327 ^{av}	C-Me	NH-3-pentyl	2,5-Me ₂ -4-MeO-Ph	45-47
	328 ^{aw}	C-Me	NEt ₂	2,5-Me ₂ -4-MeO-Ph	oil
	329 ^{ax}	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MePh	80-81
	330 ^{ay}	C-Me	NCH(Et)CH ₂ OMe	2-Cl-4-MePh	77-79
25	331 ^{az}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MePh	oil
	332 ^{ba}	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Cl-4-MePh	139-140
	333 ^{bb}	C-Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,5-Me ₂ -4-MeOPh	120-122
	334 ^{bg}	C-Me	NEt ₂	2-Me-4-MeOPh	oil
	335 ^{bh}	C-Me	OEt	2-Me-4-MeOPh	oil
30	336 ^{bi}	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Me-4-MeOPh	oil
	337 ^{bj}	C-Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2-Me-4-MeOPh	129
	338 ^{bk}	C-Me	NHCH(CH ₂ CH ₂ OEt) ₂	2-Me-4-MeOPh	amorph.
	339	C-Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4-Cl ₂ -Ph	109-110
	340	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2,4-Cl ₂ -Ph	93-94
35	341	C-Me	NH-3-pentyl	2-Me-4-BrPh	118-119
	342	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-BrPh	oil

	343	C-Me	NHCH(CH ₂ -iPr)CH ₂ OMe	2,4-Me ₂ -Ph	oil
	344	C-Me	NHCH(Pr)CH ₂ OMe	2,4-Me ₂ -Ph	94-95
	345	C-Me	NHCH(Et)CH ₂ OEt	2,4-Me ₂ -Ph	76-77
	346	C-Me	NHCH(CH ₂ OMe)CH ₂ CH ₂ OMe	2-Me-4-Me ₂ NPh	oil
5	347	C-Me	NEt ₂	2-Me-4-ClPh	oil
	348	C-Me	NH-3-pentyl	2-Me-4-ClPh	122-124
	349	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-ClPh	oil
	350	C-Me	NHCH(CH ₂ OMe) ₂	2-Me-4-ClPh	122-123
	351	C-Me	NEt ₂	2-Me-4-ClPh	oil
10	352	C-Me	NEt ₂	2-Cl-4-MePh	oil
	353	C-Me	NH-3-pentyl	2-Cl-4-MePh	120-121
	354	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MeOPh	
	355 ^{bl}	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MeOPh	oil
	356 ^{bm}	C-Me	NHCH(Et)CH ₂ OMe	2-Cl-4-MeOPh	108-110
15	357 ^{bn}	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4-MeOPh	127-129
	358 ^{bo}	C-Me	NEt ₂	2-Cl-4-MeOPh	oil
	359 ^{bp}	C-Me	NH-3-pentyl	2-Cl-4-MeOPh	77-79
	360	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh	
	361	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh	
20	362	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4-MeOPh	
	363	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4-MeOPh	
	364	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh	
	365	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh	
	366	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph	
25	367	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph	
	368	C-Me	NHCH(Et)CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph	
	369	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4,5-(MeO) ₂ Ph	
	370	C-Me	NEt ₂	2-Cl-4,5-(MeO) ₂ Ph	
	371	C-Me	NH-3-pentyl	2-Cl-4,5-(MeO) ₂ Ph	
30	372	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph	
	373	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph	
	374 ^{bq}	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph	137-138
	375	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph	
	376 ^{br}	C-Me	NHCH(Et)CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph	147-148
35	377	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Br-4,5-(MeO) ₂ Ph	
	378 ^{bs}	C-Me	NEt ₂	2-Br-4,5-(MeO) ₂ Ph	52-58

	379	C-Me	NH-3-pentyl	2-Br-4, 5-(MeO) ₂ Ph
	380	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4, 5-(MeO) ₂ Ph
	381	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4, 5-(MeO) ₂ Ph
	382	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4, 6-(MeO) ₂ Ph
5	383	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4, 6-(MeO) ₂ Ph
	384	C-Me	NHCH(Et)CH ₂ OMe	2-Cl-4, 6-(MeO) ₂ Ph
	385	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4, 6-(MeO) ₂ Ph
	386	C-Me	NEt ₂	2-Cl-4, 6-(MeO) ₂ Ph
	387	C-Me	NH-3-pentyl	2-Cl-4, 6-(MeO) ₂ Ph
10	388	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4, 6-(MeO) ₂ Ph
	389	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4, 6-(MeO) ₂ Ph
	390	C-Me	NHCH(CH ₂ OMe) ₂	2-Me-4, 6-(MeO) ₂ Ph
	391	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4, 6-(MeO) ₂ Ph
	392	C-Me	NHCH(Et)CH ₂ OMe	2-Me-4, 6-(MeO) ₂ Ph
15	393	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Me-4, 6-(MeO) ₂ Ph
	395	C-Me	NEt ₂	2-Me-4, 6-(MeO) ₂ Ph
	396	C-Me	NH-3-pentyl	2-Me-4, 6-(MeO) ₂ Ph
	397	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4, 6-(MeO) ₂ Ph
	398	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4, 6-(MeO) ₂ Ph
20	399	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Br-4, 6-(MeO) ₂ Ph
	400	C-Me	NEt ₂	2-Br-4, 6-(MeO) ₂ Ph
	401	C-Me	NH-3-pentyl	2-Br-4, 6-(MeO) ₂ Ph
	402	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4, 6-(MeO) ₂ Ph
	403	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4, 6-(MeO) ₂ Ph
25	404	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	405	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	406	C-Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
	407	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	408	C-Me	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh
30	409	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh
	410	C-Me	NEt ₂	2-MeO-4-MePh
	411	C-Me	NH-3-pentyl	2-MeO-4-MePh
	412	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	413	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh
35	414	C-Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
	415	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh

	416	C-Me	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh	
	417	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh	
	418	C-Me	NEt ₂	2-MeO-4-MePh	
	419	C-Me	NH-3-pentyl	2-MeO-4-MePh	
5	420	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh	
	421	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh	
	423 ^{bt}	C-Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-ClPh	oil
	424	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-ClPh	
	425	C-Me	NHCH(Et)CH ₂ OMe	2-MeO-4-ClPh	
10	426	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-ClPh	
	427	C-Me	NEt ₂	2-MeO-4-ClPh	
	428	C-Me	NH-3-pentyl	2-MeO-4-ClPh	
	429	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-ClPh	
	430	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-ClPh	

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NOTES FOR TABLE 1:

- a) Analysis Calcd: C, 52.69, H, 5.17, N, 17.07, Cl, 17.28; Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17.50.
- 20 b) CI-HRMS: Calcd: 406.1565, Found: 405.1573 (M + H); Analysis Calcd: C: 59.11; H: 6.20; N: 17.23; Cl: 17.45; Found: C: 59.93; H: 6.34; N: 16.50; Cl: 16.95; NMR (CDCl₃, 300 MHz): 0.95 (t, J = 8, 4H), 1.30-1.40 (m, 4H), 1.50-1.75 (m, 4H), 2.35 (s, 3H), 2.48 (s, 3H), 4.30-4.45 (m, 1H), 6.15 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (s, 1H)
- 25 c) CI-HRMS: Calcd: 392.1409, Found: 392.1388 (M + H); NMR (CDCl₃, 300 MHz): 1.00 (t, J = 8, 3H), 1.35 (t, J = 8, 3H), 1.41 (q, J = 8, 2H), 1.65-1.85 (m, 2H), 2.30 (s, 3H), 2.40 (s, 3H), 3.85-4.20 (m, 4H), 7.30 (s, 2H), 7.50 (s, 1H).
- 30 d) CI-HRMS: Calcd: 404.1409, Found: 404.1408 (M + H); NMR (CDCl₃, 300 MHz): 0.35-0.45 (m, 2H), 0.52-0.62 (m, 2H), 0.98 (t, J = 8, 3H), 1.70-1.90 (m, 2H),
- 35

- 2.30 (s, 3H), 2.40 (s, 3H), 3.85-4.02 (m, 2H),
4.02-4.20 (m, 2H), 7.30 (s, 2H), 7.50 (s, 1H).
- 5 e) CI-HRMS: Calcd: 424.1307, Found: 424.1307 (M + H);
NMR (CDCl₃, 300 MHz): 2.28 (s, 3H), 2.40 (s, 3H),
3.40 (s, 6H), 3.75 (t, J = 8, 4H), 4.20-4.45 (m,
4H), 7.30 (s, 2H), 7.50 (s, 1H).
- 10 f) CI-HRMS: Calcd: 406.1565, Found: 406.1578 (M + H);
NMR (CDCl₃, 300 MHz): 0.90 (t, J = 8, 3H), 1.00 (t,
J = 8, 3H), 1.28-1.45 (m, 4H), 1.50-1.80 (m, 4H),
2.35 (s, 3H), 2.50 (s, 3H), 4.20-4.35 (m, 1H),
6.10-6.23 (m, 1H), 7.30 (s, 2H), 7.50 (s, 1H).
- 15 g) CI-HRMS: Calcd: 394.1201, Found: 394.1209 (M + H);
NMR (CDCl₃, 300 MHz): 1.02 (t, J = 8, 3H), 1.65-
1.90 (m, 2H), 2.35 (s, 3H), 2.48 (s, 3H), 3.40 (s,
3H), 3.50-3.60 (m, 2H), 4.35-4.45 (brs, 1H), 6.50-
6.60 (m, 1H), 7.30 (s, 2H), 7.50 (s, 1H).
- 20 h) CI-HRMS: Calcd: 364.1096, Found: 364.1093 (M + H);
Analysis: Calcd: C: 56.05; H: 5.27; N: 19.23; Cl:
19.46; Found: C: 55.96; H: 5.24; N: 18.93; Cl:
19.25;
NMR (CDCl₃, 300 MHz): 1.35 (t, J = 8, 6H), 2.30 (s,
3H), 2.40 (s, 3H), 3.95-4.15 (m, 4H), 7.30 (s, 2H),
7.50 (d, J = 1, 1H).
- 25 i) CI-HRMS: Calcd: 438.1464, Found: 438.1454 (M + H);
NMR (CDCl₃, 300 MHz): 1.22 (t, J = 8, 6H), 2.35 (s,
3H), 2.47 (s, 3H), 3.39 (q, J = 8, 4H), 3.65 (dd, J
= 8, 1, 2H), 3.73 (dd, J = 8, 1, 2H), 4.55-4.65 (m,
1H), 6.75 (d, J = 8, 1H), 7.30 (d, J = 1, 2H), 7.50
(s, 1H).
- 30 j) CI-HRMS: Calcd: 378.1252, Found: 378.1249 (M + H);
Analysis: Calcd: C: 57.15; H: 5.61; N: 18.51; Cl:
18.74; Found: C: 57.56; H: 5.65; N: 18.35; Cl:
18.45;
NMR (CDCl₃, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-
35 1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.35 (s, 3H), 2.50

- (s, 3H), 4.15-4.25 (m, 1H), 6.18 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (s, 1H).
- 5 k) CI-HRMS: Calcd: 398.0939, Found: 398.0922 (M + H); Analysis: Calcd: C: 60.31; H: 4.30; N: 17.58; Cl: 17.80; Found: C: 60.29; H: 4.59; N: 17.09; Cl: 17.57; NMR (CDCl₃, 300 MHz): 2.05 (s, 3H), 2.50 (s, 3H), 3.78 (s, 3H), 7.20-7.45 (m, 7H), 7.50 (d, J = 1, 1H).
- 10 l) CI-HRMS: Calcd: 392.1409, Found: 392.1391 (M + H); NMR (CDCl₃, 300 MHz): 0.98 (t, J = 8, 6H), 1.70-1.85 (m, 4H), 2.30 (s, 3H), 2.40 (s, 3H), 3.80-4.10 (m, 4H), 7.30 (s, 2H), 7.50 (d, J = 1, 1H).
- 15 m) CI-HRMS: Calcd: 392.1409, Found: 392.1415 (M + H); Analysis: Calcd: C: 58.17; H: 5.92; N: 17.85; Cl: 18.07; Found: C: 58.41; H: 5.85; N: 18.10; Cl: 17.75; NMR (CDCl₃, 300 MHz): 0.90-1.05 (m, 6H), 1.35-1.55 (m, 2H), 1.55-1.85 (m, 4H), 2.35 (s, 3H), 2.48 (s, 3H), 4.20-4.35 (m, 1H), 6.15 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (d, J = 1, 1H).
- 20 n) CI-HRMS: Calcd: 337.0623, Found: 337.0689 (M + H); Analysis: Calcd: C: 53.43; H: 4.18; N: 16.62; Cl: 21.03, Found: C: 53.56; H: 4.33; N: 16.56; Cl: 20.75; NMR (CDCl₃, 300 MHz): 1.60 (t, J = 8, 3H), 2.40 (s, 3H), 2.55 (s, 3H), 4.80 (q, J = 8, 2H), 7.30 (d, J = 8, 1H), 7.35 (dd, J = 8, 1, 1H), 7.55 (d, J = 1, 1H).
- 25 o) CI-HRMS: Calcd: 383.2321, Found: 383.2309 (M + H); NMR (CDCl₃, 300 MHz): 2.00 (s, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.45 (s, 3H), 3.45 (s, 6H), 3.61 (dd, J = 8, 8, 2H), 3.70 (dd, J = 8, 8, 2H), 4.60-4.70 (m, 1H), 6.70 (d, J = 8, 1H), 6.94 (s, 2H).
- 30 p) CI-HRMS: Calcd: 370.2243, Found: 370.2246 (M + H);
- 35

- Analysis: Calcd: C: 65.02; H: 7.38; N: 18.96;
Found: C: 65.22; H: 7.39; N: 18.71;
NMR (CDCl₃, 300 MHz): 2.18 (s, 3H), 2.30 (s, 3H),
2.45 (s, 3H), 3.45 (s, 6H), 3.60 (dd, J = 8, 8,
5 2H), 3.69 (dd, J = 8, 8, 2H), 4.60-4.70 (m, 1H),
6.70 (d, J = 8, 1H), 7.05 (d, J = 8, 1H), 7.07 (d,
J = 8, 1H), 7.10 (s, 1H).
- q) CI-HRMS: Calcd: 384.2400, Found: 384.2393 (M + H);
NMR (CDCl₃, 300 MHz): 2.16 (s, 3H), 2.25 (s, 3H),
10 2.35 (s, 3H), 2.39 (s, 3H), 3.40 (s, 6H), 3.77 (t,
J = 8, 4H), 4.20-4.45 (m, 4H), 7.02 (d, J = 8, 1H)
7.05 (s, 1H), 7.10 (d, J = 7, 1H).
- r) CI-HRMS: Calcd: 354.2294, Found: 354.2271 (M + H);
Analysis: Calcd: C: 67.96; H: 7.71; N: 19.81;
15 Found: C: 67.56; H: 7.37; N: 19.60;
NMR (CDCl₃, 300 MHz): 1.03 (t, J = 8, 3H), 1.65-
1.88 (m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 2.35 (s,
3H), 2.45 (s, 3H), 3.40 (s, 3H), 3.50-3.62 (m, 2H),
4.30-4.45 (m, 1H), 6.51 (d, J = 8, 1H), 7.04 (d, J
20 = 8, 1H), 7.10 (d, J = 8, 1H), 7.12 (s, 1H).
- s) CI-HRMS: Calcd: 338.2345, Found: 338.2332 (M + H);
Analysis: Calcd: C: 71.18; H: 8.06; N: 20.75;
Found: C: 71.43; H: 7.80; N: 20.70;
NMR (CDCl₃, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-
25 1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.19 (s, 3H), 2.30
(s, 3H), 2.35 (s, 3H), 2.46 (s, 3H), 4.15-4.26 (m,
1H), 6.17 (d, J = 8, 1H), 7.06 (d, J = 8, 1H), 7.10
(d, J = 1, 1H), 7.13 (s, 1H).
- t) CI-HRMS: Calcd: 324.2188, Found: 324.2188 (M + H);
NMR (CDCl₃, 300 MHz): 1.25 (t, J = 8, 6H), 2.16 (s,
30 3H), 2.28 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H),
3.95-4.20 (m, 4H), 7.05 (dd, J = 8, 1, 1H), 7.07
(s, 1H), 7.10 (d, J = 1, 1H)
- u) CI-HRMS: Calcd: 346.1780, Found: 346.1785 (M + H);
35 Analysis: Calcd: C: 66.07; H: 5.54; N: 28.39;
Found: C: 66.07; H: 5.60; N: 27.81;

- NMR (CDCl₃, 300 MHz): 2.15 (s, 3H), 2.32 (s, 3H)
2.17 (s, 3H), 2.52 (s, 3H), 5.25-5.35 (m, 4H), 7.08
(s, 2H), 7.15 (s, 1H).
- 5 v) CI-HRMS: Calcd: 340.2137, Found: 340.2137 (M + H);
Analysis: Calcd: C: 67.23; H: 7.42; N: 20.63;
Found: C: 67.11; H: 7.39; N: 20.26;
NMR (CDCl₃, 300 MHz): 1.40 (d, J = 8, 3H), 2.16 (s,
3H), 2.32 (s, 3H), 2.35 (s, 3H), 2.47 (s, 3H), 3.42
(s, 3H), 3.50-3.60 (m, 2H), 4.50-4.15 (m, 1H), 6.56
10 (d, J = 8, 1H), 7.00-7.15 (m, 3H).
- w) CI-HRMS: Calcd: 355.2134, Found: 355.2134 (M + H);
NMR (CDCl₃, 300 MHz): 1.05 (t, J = 8, 3H), 1.85-
2.00 (m, 2H), 2.17 (s, 3H), 2.36 (s, 6H), 2.50 (s,
3H), 3.41 (s, 3H), 3.45 (dd, J = 8, 3, 1H), 3.82
15 (dd, J = 8, 1, 1H), 5.70-5.80 (m, 1H), 7.00-7.20
(m, 3H).
- x) CI-HRMS: Calcd: 364.2501, Found: 364.2501 (M + H);
NMR (CDCl₃, 300 MHz): 0.35-0.43 (m, 2H), 0.50-0.60
(m, 2H), 0.98 (t, J = 8, 3H), 1.20-1.30 (m, 1H),
20 1.72-1.90 (m, 2H), 2.18 (s, 3H) 2.28 (s, 3H), 2.35
(s, 3H), 2.40 (s, 3H), 3.88-4.03 (m, 2H), 4.03-4.20
(m, 2H), 7.00-7.15 (m, 3H).
- y) CI-HRMS: Calcd: 353.2454, Found: 353.2454 (M + H);
Analysis: Calcd: C: 68.15; H: 8.02; N: 23.84;
25 Found: C: 67.43; H: 7.81; N: 23.45;
NMR (CDCl₃, 300 MHz): 1.38 (d, J = 8, 3H), 2.18 (s,
3H), 2.30-2.40 (m, 12H), 2.47 (s, 3H), 2.60-2.75
(m, 2H), 4.30-4.50 (m, 1H), 6.60-6.70 (m, 1H),
7.00-7.15 (m, 3H).
- 30 z) CI-HRMS: Calcd: 361.2140, Found: 361.2128 (M + H);
NMR (CDCl₃, 300 MHz): 0.75-0.83 (m, 2H), 1.00-1.10
(m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H),
2.47 (s, 3H), 2.85 (t, J = 8, 2H), 3.30-3.40 (m,
1H), 4.40-4.55 (m, 2H), 7.00-7.18 (m, 3H).
- 35 aa) CI-HRMS: Calcd: 363.2297, Found: 363.2311 (M + H);

- 5 NMR (CDCl₃, 300 MHz): 1.01 (t, 3H, J=8), 1.75-1.90 (m, 2H), 2.15 (s, 3H), 2.19 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 2.40 (s, 3H), 2.98 (t, 2H, J = 8), 3.97-4.15 (m, 2H), 4.15-4.30 (m, 2H), 7.03 (d, 1H, 1H), 7.08 (d, 1H, J = 8), 7.10 (s, 1H).
- ab) CI-HRMS: Calcd: 363.2297, Found: 363.2295 (M + H); NMR (CDCl₃, 300 MHz): 1.01 (t, 3H, J = 8), 1.35-1.55 (m, 2H), 1.75-1.90 (m, 2H), 2.15 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 2.46 (s, 3H), 4.10-4.30 (m, 10 2H), 4.95-5.10 (br s, 2H), 7.05 (d, 1H, J = 8), 7.10 (d, 1H, J = 8), 7.15 (s, 1H).
- ac) CI-HRMS: Calcd: 368.2450, Found: 368.2436; Analysis: Calcd: C, 68.62, H, 7.95, N, 19.06; Found: C, 68.73, H, 7.97, N, 19.09; NMR (CDCl₃, 300 15 MHz): 1.05 (t, J = 8, 3H), 1.70-1.90 (m, 2H), 2.01 (d, J = 3, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.46, 2.465 (s, s, 3H), 3.42, 3.48 (s, s, 3H), 3.53-3.63 (m, 2H), 4.35-4.45 (m, 1H), 6.73 (d, J = 8, 1H), 6.97 (s, 2H).
- 20 (ad) CI- HRMS: Calcd: 352.2501, Found: 352.2500 (M + H): Analysis: Calcd: C: 71.76; H: 8.33; N: 19.92, Found: C: 71.55; H: 8.15; N: 19.28; NMR (CDCl₃, 300 MHz): 1.01 (t, J = 8, 6H), 1.58 -1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.02 (s, 6H), 2.19 (s, 3H), 2.45 (s, 3H), 4.12-4.28 (m, 1H), 6.18 25 (d, J = 8, 1H), 6.95 (s, 2H).
- (ae) CI- HRMS: Calcd: 398.2556, Found: 398.2551 (M + H); Analysis: Calcd: C: 66.47; H: 7.86; N: 17.62, Found: C: 66.74; H: 7.79; N: 17.70; NMR (CDCl₃, 300 MHz): 2.00 (s, 6H), 2.12 (s, 3H), 2.30 (s, 3H), 2.37 (s, 3H), 3.40 (s, 6H), 3.78 (t, J = 8, 4H), 4.25-4.40 (m, 4H), 6.93 (s, 2H). 30
- (af) CI-HRMS: Calcd: 450.1141, Found: 450.1133 (M + H); Analysis: Calcd: C: 50.67; H: 5.37; N: 15.55; Br: 17.74; Found: C: 52.36; H: 5.84; N: 14.90; Br: 17.44; 35

- 5 NMR (CDCl₃, 300 MHz): 2.32 (s, 3H), 2.57 (s, 3H),
3.42 (s, 6H), 3.60 (q, J = 8, 2H), 3.69 (q, J = 8,
2H), 3.82 (s, 3H), 4.60-4.70 (m, 1H), 6.73 (d, J =
8, 1H), 6.93 (dd, J = 8, 1, 1H), 7.22 (d, J = 8,
1H).
- ag) CI-HRMS: Calcd: 434.1192, Found: 434.1169 (M + H);
Analysis: Calcd: C: 52.54; H: 5.58; N: 16.12; Br:
18.40; Found: C: 52.57; H: 5.60; N: 15.98; Br:
18.22;
- 10 NMR (CDCl₃, 300 MHz): 1.00-1.07 (m, 3H), 1.65-1.85
(m, 2H), 2.35 (s, 3H), 2.46, 2.47 (s, s, 3H), 3.40,
3.45 (s, s, 3H), 3.83 (s, 3H), 4.35-4.45 (m, 1H),
6.55 (d, J = 8, 1H), 6.92 (dd, J = 8, 1, 1H), 7.20-
7.30 (m, 2H).
- 15 ah) CI-HRMS: Calcd: 337.2266, Found: 337.2251 (M + H);
Analysis: Calcd: C: 70.18; H: 8.06; N: 20.75;
Found: C: 70.69; H: 7.66; N: 20.34;
NMR (CDCl₃, 300 MHz): 1.35 (t, J = 8, 6H), 2.01 (s,
6H), 2.15 (s, 3H), 2.30 (s, 3H), 2.38 (s, 3H), 4.07
20 (q, J = 8, 4H), 6.93 (s, 2H).
- ai) CI-HRMS: Calcd: 412.2713, Found: 412.2687 (M + H);
Analysis: Calcd: C: 67.13; H: 8.08; N: 17.02;
Found : C: 67.22; H: 7.85; N: 17.13;
NMR (CDCl₃, 300 MHz): 1.24 (t, J = 8, 6H), 2.00 (s,
25 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.43 (s, 3H), 3.60
(q, J = 8, 4H), 3.66 (dd, J = 8, 3, 2H), 3.75 (dd,
J = 8, 3, 2H), 4.55-4.65 (m, 1H), 6.75 (d, J = 8,
1H), 6.95 (s, 2H).
- aj) CI-HRMS: Calcd: 398.2556, Found: 398.2545 (M + H);
30 Analysis: Calcd: C: 66.47; H: 7.86; N: 17.62;
Found: C: 66.87; H: 7.62; N: 17.75;
NMR (CDCl₃, 300 MHz): 1.95-2.10 (m, 8H), 2.20 (s,
3H), 2.32 (s, 3H), 2.44 (s, 3H), 3.38 (s, 3H), 3.42
(s, 3H), 3.50-3.70 (m, 4H), 4.58-4.70 (m, 1H), 6.87
35 (d, J = 8, 1H), 6.95 (s, 2H).
- ak) CI-HRMS: Calcd: 338.1981, Found: 338.1971 (M + H);

- Analysis: Calcd: C: 67.63; H: 6.87; N: 20.06;
Found: C: 67.67; H: 6.82; N: 20.31;
NMR (CDCl₃, 300 MHz): 2.15 (s, 3H), 2.29 (s, 3H),
2.35 (s, 3H), 2.43 (s, 3H), 3.90 (t, J = 8, 4H),
4.35-4.45 (m, 4H), 7.00-7.15 (m, 3H).
- 5 al) CI-HRMS: Calcd: 464.1297, Found: 464.1297 (M + H);
NMR (CDCl₃, 300 MHz): 2.28 (s, 3H), 2.40 (s, 3H),
3.40 (s, 6H), 3.75 (t, J = 8, 4H), 3.83 (s, 3H),
4.20-4.50 (m, 4H), 6.93 (dd, J = 8, 1, 1H), 7.20
10 (s, 1H), 7.24 (d, J = 1, 1H).
- am) CI-HRMS: Calcd: 418.1242, Found: 418.1223 (M + H);
NMR (CDCl₃, 300 MHz): 1.00 (t, d, J = 8, 1, 6H),
1.55-1.75 (m, 4H), 2.34 (s, 3H), 2.49 (s, 3H), 2.84
15 (s, 3H), 4.15-4.27 (m, 1H), 6.19 (d, J = 8, 1H),
6.93 (dd, J = 8, 1, 1H), 7.21-7.30 (m, 2H).
- an) CI-HRMS: Calcd: 404.1086, Found: 404.1079 (M + H);
NMR (CDCl₃, 300 MHz): 1.35 (t, J = 8, 6H), 2.28 (s,
3H), 2.40 (s, 3H), 3.83 (s, 3H), 3.90-4.08 (m, 2H),
4.08-4.20 (m, 2H), 6.92 (dd, J = 8, 1, 1H), 7.20-
20 7.25 (m, 2H).
- ao) CI-HRMS: Calcd: 308.1875, Found: 308.1872 (M + H);
NMR (CDCl₃, 300 MHz): 0.75-0.80 (m, 2H), 0.93-1.00
(m, 2H), 2.16 (s, 3H), 2.28 (s, 3H), 2.35 (s, 3H),
2.53 (s, 3H), 3.00-3.10 (m, 1H), 6.50-6.55 (m, 1H),
25 7.00-7.15 (m, 3H).
- ap) CI-HRMS: Calcd: 397.1988, Found: 397.1984 (M + H);
NMR (CDCl₃, 300 MHz): 2.43 (s, 3H), 2.50 (s, 3H),
3.43 (s, 3H), 3.61 (dd, J = 8, 8, 2H), 3.69 (dd, J =
8, 8, 2H), 3.88 (s, 3H), 4.58-4.70 (m, 1H), 6.75
30 (d, J = 8, 1H), 7.20 (dd, J = 8, 1, 1H), 7.25 (d, J
= 1, 1H), 7.40 (s, 1H).
- aq) CI-HRMS: Calcd: 375.2297, Found: 375.2286 (M + H);
Analysis: Calcd: C: 70.56; H: 7.01; N: 22.44;
Found: C: 70.49; H: 6.99; N: 22.45;
35 NMR (CDCl₃, 300 MHz): 0.79-0.85 (m, 2H), 1.00-1.05
(m, 1H), 2.00 (s, 6H), 2.19 (s, 3H), 2.32 (s, 3H),

- 2.44 (s, 3H), 2.84 (t, J = 8, 2H), 3.30-3.40 (m, 1H), 4.50 (t, J = 8, 2H), 6.95 (s, 2H).
- ar) CI-HRMS: Calcd: 434.1192, Found: 434.1189 (M + H);
Analysis: Calcd: C: 52.54; H: 5.58; N: 16.12; Br: 18.40; Found: C: 52.75; H: 5.59; N: 16.09; Br: 18.67;
NMR (CDCl₃, 300 MHz): 2.19 (s, 3H), 2.30 (s, 3H), 2.47 (s, 3H), 3.43 (s, 6H), 3.60 (dd, J = 8, 8, 2H), 3.70 (dd, J = 8, 8, 2H), 4.58-4.70 (m, 1H), 6.71 (d, J = 8, 1H), 7.08 (d, J = 8, 1H), 7.37 (dd, J = 8, 1, 1H), 7.45 (d, J = 1, 1H).
- as) CI-HRMS: Calcd: 448.1348, Found: 448.1332 (M + H);
Analysis: Calcd: C: 53.58; H: 5.85; N: 16.62; Br: 17.82; Found: C: 53.68; H: 5.74; N: 15.52; Br: 13.03;
NMR (CDCl₃, 300 MHz): 1.95-2.10 (m, 2H), 2.20 (s, 3H), 2.30 (s, 3H), 2.47 (s, 3H), 3.38 (s, 3H), 3.41 (s, 3H), 3.50-3.67 (m, 4H), 4.55-4.70 (m, 1H), 6.89 (d, J = 8, 1H), 7.05 (d, J = 8, 1H), 7.35 (dd, J = 8, 1, 1H), 7.47 (d, J = 1, 1H).
- at) CI-HRMS: Calcd: 400.2349, Found: 400.2348 (M + H);
Analysis: Calcd: C: 63.14; H: 7.32; N: 17.53; Found: C: 63.40; H: 7.08; N: 17.14;
NMR (CDCl₃, 300 MHz): 2.16 (s, 3H), 2.20 (s, 3H), 2.30 (s, 3H), 2.46 (s, 3H), 3.42 (s, 6H), 3.60 (q, J = 8, 2H), 3.70 (q, J = 8, 2H), 3.85 (s, 3H), 4.59-4.70 (m, 1H), 6.70 (d, J = 8, 1H), 6.76 (s, 1H), 6.96 (s, 1H).
- au) CI-HRMS: Calcd: 414.2505, Found: 414.2493 (M + H);
NMR (CDCl₃, 300 MHz): 2.15 (s, 3H), 2.19 (s, 3H), 2.25 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.76 (t, J = 8, 4H), 3.84 (s, 3H), 4.20-4.45 (m, 4H), 6.77 (s, 1H), 6.93 (s, 1H).
- av) CI-HRMS: Calcd: 368.2450, Found: 368.2447 (M + H);
NMR (CDCl₃, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-1.85 (m, 4H), 2.19 (s, 3H), 2.20 (s, 3H), 2.30 (s,

- 3H), 2.47 (s, 3H), 3.88 (s, 3H), 4.10-4.30 (m, 1H), 6.15 (d, J = 8, 1H), 6.78 (s, 1H), 6.98 (s, 1H).
- aw) CI-HRMS: Calcd: 353.2216, Found: 353.2197 (M + H);
NMR (CDCl₃, 300 MHz): 1.35 (t, J = 8, 6H), 2.17 (s,
5 3H), 2.19 (s, 3H), 2.28 (s, 3H), 2.40 (s, 3H), 3.85 (s, 3H), 3.90-4.20 (m, 4H), 6.78 (s, 1H), 6.95 (s, 1H).
- ax) CI-HRMS: Calcd: 390.1697, Found: 390.1688 (M + H);
Analysis: Calcd: C: 58.53; H: 6.20; N: 17.96; Cl: 9.09;
10 Found: C: 58.95; H: 6.28; N: 17.73; Cl: 9.15;
NMR (CDCl₃, 300 MHz): 2.35 (s, 3H), 2.37 (s, 3H), 2.48 (s, 3H), 3.42 (s, 6H), 3.60 (dd, J = 8, 8, 2H) 3.68 (dd, J = 8, 8, 2H), 4.59-4.72 (m, 1H), 6.72 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.23 (d, J = 15 8, 1H), 7.32 (s, 1H).
- ay) CI-HRMS: Calcd: 374.1748, Found: 374.1735 (M + H);
Analysis: Calcd: C: 61.04; H: 6.47; N: 18.73; Cl: 9.48;
Found: C: 61.47; H: 6.54; N: 18.23; Cl: 9.61;
NMR (CDCl₃, 300 MHz): 1.01 (t, J = 8, 3H), 1.62-
20 1.88 (m, 4H), 2.35 (s, 3H), 2.37 (s, 3H), 2.48 (d, J = 1, 3H), 3.40, 3.45 (s, s, 3H), 3.50-3.64 (m, 2H), 4.38-4.47 (m, 1H), 6.53 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.07 (d, J = 8, 1H), 7.12 (s, 1H).
- az) CI-HRMS: Calcd: 404.1853, Found: 404.1839 (M + H);
25 NMR (CDCl₃, 300 MHz): 2.29 (s, 3H), 2.38 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.76 (t, J = 8, 4H), 4.20-4.45 (m, 4H), 7.11 (d, J = 8, 1H), 7.22 (d, J = 8, 1H), 7.31 (s, 1H).
- ba) CI-HRMS: Calcd: 404.1853, Found: 404.1859 (M + H);
30 Analysis: C: 59.47; H: 6.50; N: 17.34; Cl: 8.79;
Found: C: 59.73; H: 6.46; N: 17.10; Cl: 8.73;
NMR (CDCl₃, 300 MHz): 1.95-2.08 (m, 2H), 2.35 (s,
3H), 2.38 (s, 3H), 2.46 (s, 3H), 3.38 (s, 3H), 3.41 (s, 3H), 3.50-3.65 (m, 4H), 4.56-4.70 (m, 1H), 6.85
35 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.45 (d, J = 8, 1H), 7.32 (s, 1H).

- bb) CI-HRMS: Calcd: 391.2246, Found: 391.2258 (M + H);
Analysis: C: 67.67; H: 6.71; N: 21.52; Found: C:
67.93; H: 6.70; N: 21.48;
NMR (CDCl₃, 300 MHz): 0.76-0.84 (m, 2H), 0.84-0.91
5 (m, 2H), 1.00-1.08 (m, 2H), 2.15 (s, 3H), 2.20 (s,
3H), 2.29 (s, 3H), 2.45 (s, 3H), 2.85 (t, J = 8,
2H), 3.28-3.30 (m, 1H), 3.85 (s, 3H), 6.78 (s, 1H),
6.95 (s, 1H).
- bc) CI-HRMS: Calcd: 386.2192, Found: 386.2181 (M + H);
10 Analysis: C: 62.32; H: 7.06; N: 18.17; Found: C:
62.48; H: 6.83; N: 18.15;
NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.9 (d,
1H, J = 1), 6.8 (dd, 1H, J = 8,1), 6.7 (br.d, 1H,
J = 8), 4.7-4.6 (m, 1H), 3.85 (s, 3H), 3.70-3.55
15 (m, 4H), 3.45 (s, 6H), 2.5 (s, 3H), 2.3 (s, 3H),
2.15 (s, 3H).
- bd) CI-HRMS: Calcd: 400.2349, Found: 400.2336 (M + H);
NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 7), 6.85 (d,
1H, J = 1), 6.75 (dd, 1H, J = 7,1), 4.45-4.25
20 (br.s, 4H), 3.75 (t, 4H, J = 7), 3.4 (s, 6H), 2.4
(s, 3H), 2.25 (s, 3H), 2.15 (s, 3H).
- be) CI-HRMS: Calcd: 370.2243, Found: 370.2247 (M + H);
Analysis: C: 65.02; H: 7.38; N: 18.96; Found: C:
65.28; H: 7.27; N: 18.71;
25 NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d,
1H, J = 1), 6.8 (dd, 1H, J = 8,1), 6.5 (br. d, 1H,
J = 1), 4.5-4.3 (m, 1H), 3.85 (s, 3H), 3.65-3.5 (m,
2H), 3.4 (s, 2H), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s,
3H), 1.9-1.7 (m, 2H), 1.05 (t, 3H, J = 7).
- 30 bf) CI-HRMS: Calcd: 379.2246, Found: 379.2248 (M + H);
NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d,
1H, J = 1), 6.8 (dd, 1H, J = 8,1), 4.3-4.0 (m, 4H),
3.85 (s, 3H), 3.0 (t, 2H, J = 7), 2.45 (s, 3H), 2.3
(s, 3H), 2.2 (s, 3H), 1.9-1.8 (m, 2H), 1.0 (t, 3H,
35 J = 7).
- bg) CI-HRMS: Calcd: 340.2137, Found: 340.2122 (M + H);

- NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.75 (dd, 1H, J = 8, 1), 4.2-4.0 (br.m, 4H), 3.85 (s, 3H), 2.4 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.35 (t, 6H, J = 7).
- 5 bh) CI-HRMS: Calcd: 313.1665, Found: 313.6664 (M + H).
 bi) CI-HRMS: Calcd: 400.2349, Found: 400.2346 (M + H);
 NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 7), 6.9-6.75 (m, 3H), 4.7-4.55 (m, 1H), 3.8 (s, 3H), 3.7-3.5 (m, 4H), 3.45 (s, 3H), 3.35 (s, 3H), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 2.1-1.95 (m, 2H).
- 10 bj) CI-HRMS: Calcd: 377.2090, Found: 377.2092 (M + H);
 Analysis: C: 67.00; H: 6.44; N: 22.32; Found: C: 67.35; H: 6.44; N: 22.23;
 NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.8 (dd, 1H, J = 8, 1), 4.55-4.4 (m, 2H), 3.85 (s, 3H), 3.4-3.3 (m, 1H), 2.85 (t, 2H, J = 7), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.1-1.0 (m, 2H), 0.85-0.75 (m, 2H).
- 15 bk) CI-HRMS: Calcd: 413.2427, Found: 413.2416 (M + H);
 20 NMR (CDCl₃, 300Hz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.75 (dd, 1H, J = 8, 1), 4.6 (m, 1H), 3.85 (s, 3H), 3.75-3.6 (m, 4H), 3.6 (q, 4H, J = 7), 2.5 (s, 3H), 2.3 s, 3H), 2.2 (s, 3H), 1.25 (t, 6H, J = 7).
- 25 bl) CI-HRMS: Calcd: 420.1802, Found: 420.1825 (M + H);
 bm) CI-HRMS: Calcd: 390.1697, Found: 390.1707 (M + H);
 bn) CI-HRMS: Calcd: 397.1465, Found: 397.1462 (M + H);
 bo) CI-HRMS: Calcd: 360.1513, Found: 360.1514 (M + H);
 bp) CI-HRMS: Calcd: 374.1748, Found: 374.1737 (M + H);
- 30 bq) CI-HRMS: Calcd: 479.1155, Found: 479.1154 (M + H);
 br) CI-HRMS: Calcd: 463.1219, Found: 463.1211 (M + H);
 Analysis Calcd: C: 51.96, H: 5.23, N: 15.15, Br: 17.28; Found: C: 52.29, H: 5.62, N: 14.79, Br: 17.47
- 35 bs) CI-HRMS: Calcd: 433.1113, Found: 433.1114 (M, ⁷⁹Br);
 bt) NH₃-CI MS: Calcd: 406, Found: 406 (M + H)+;

NMR (CDCl₃, 300 MHz) : δ 7.28 (d, J=10Hz, 1H), 7.03 (d, J=8Hz, 1H), 6.96 (s, 1H), 6.7 (d, J=9, 1H), 4.63 (m, 1H), 3.79 (s, 3H), 3.6 (m, 4H), 3.42 (s, 6H), 2.47 (s, 3H), 2.32 (s, 3H).

5

EXAMPLE 431

Preparation of 2,4,7-dimethyl-8-(4-methoxy-2-methylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine (Formula 1, where R³ is CH₃, R₁ is CH₃, Z is C-CH₃, Ar is 2,4-dimethylphenyl)

5-Acetamidino-4-(4-methoxy-2-methylphenyl)-3-methylpyrazole, acetic acid salt (602 mg, 2 mmol) was mixed with a saturated NaHCO₃ solution (10 mL). The aqueous mixture was extracted with EtOAc three times. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The residue was taken up in toluene (10 mL) and trimethyl orthoacetate (0.36 g, 3 mmol) was added to the suspension. The reaction mixture was heated to reflux temperature under a nitrogen atmosphere and stirred for 16 hours. After being cooled to ambient temperature, the reaction mixture was concentrated in vacuo to give an oily solid. Column chromatography (CHCl₃:MeOH::9:1) afforded, after removal of solvent in vacuo, a yellow viscous oil (R_f = 0.6, 210 mg, 37% yield): NMR (CDCl₃, 300 MHz): 7.15 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.85 (dd, 1H, J = 8, 1), 3.85 (s, 3H), 2.95 (s, 3H), 2.65 (s, 3H), 2.4 (s, 3H), 2.15 (s, 3H); CI-HRMS: Calcd: 283.1559, Found: 283.1554 (M + H).

35

EXAMPLE 432

7-hydroxy-5-methyl-3-(2-chloro-
4-methylphenyl)pyrazolo[1,5-a]pyrimidine
(Formula 1 where A is CH, R1 is Me, R3 is OH,
5 Z is C-Me, Ar is 2-chloro-4-methylphenyl)

5-Amino-4-(2-chloro-4-methylphenyl)-3-
methylpyrazole (1.86 g, 8.4 mmol) was dissolved in
glacial acetic acid (30 mL) with stirring. Ethyl
10 acetoacetate (1.18 mL, 9.2 mmol) was then added dropwise
to the resulting solution. The reaction mixture was
then heated to reflux temperature and stirred for 16
hours, then cooled to room temperature. Ether (100 mL)
was added and the resulting precipitate was collected by
15 filtration. Drying in vacuo afforded a white solid (
1.0 g, 42% yield): NMR (CDCl₃, 300Hz): 8.70 (br.s 1H),
7.29 (s, 1H), 7.21-7.09 (m, 2H), 5.62 (s, 1H), 2.35
(s, 6H), 2.29 (s, 3H); CI-MS: 288 (M+H).

20

EXAMPLE 433

7-chloro-5-methyl-3-(2-chloro-
4-methylphenyl)pyrazolo[1,5-a]pyrimidine
(Formula 1 where A is CH, R1 is Me, R3 is Cl,
25 Z is C-Me, Ar is 2-chloro-4-methylphenyl)

A mixture of 7-hydroxy-5-methyl-3-(2-chloro-4-
methylphenyl)-pyrazolo[1,5-a]pyrimidine (1.0 g, 3.5
mmol), phosphorus oxychloride (2.7 g, 1.64 mL, 17.4
30 mmol), N,N-diethylaniline (0.63 g, 0.7 mL, 4.2 mmol) and
toluene (20 mL) was stirred at reflux temperature for 3
hours, then it was cooled to ambient temperature. The
volatiles were removed in vacuo. Flash chromatography
(EtOAc:hexane::1:2) on the residue gave 7-chloro-5-
35 methyl-3-(2-chloro-4-methylphenyl)-pyrazolo[1,5-
a]pyrimidine (900 mg, 84% yield) as a yellow oil: NMR

(CDCl₃, 300Hz): 7.35 (s, 1H), 7.28-7.26 (m, 1H), 71.6 (d, 1H, J = 7), 6.80 (s, 1H), 2.55 (s, 3H), 2.45 (s, 3H), 2.40 (s, 3H); CI- MS: 306 (M+H).

5

EXAMPLE 434

7-(pentyl-3-amino)-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine
(Formula 1 where A is CH, R₁ is Me, R₃ is pentyl-3-amino, Z is C-Me, Ar is 2-chloro-4-methylphenyl)

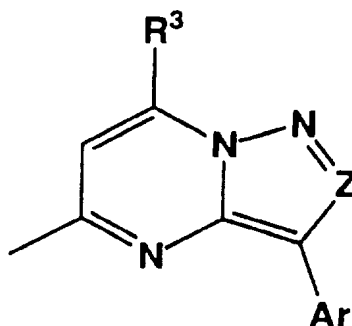
A solution of 3-pentylamine (394mg, 6.5 mmol) and 7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine (200 mg, 0.65 mmol) in dimethylsulfoxide (DMSO, 10 mL) was stirred at 150°C for 2 hours; then it was cooled to ambient temperature. The reaction mixture was then poured onto water (100 mL) and mixed. Three extractions with dichloromethane, washing the combined organic layers with brine, drying over MgSO₄, filtration and removal of solvent in vacuo produced a yellow solid. Flash chromatography (EtOAc:hexanes::1:4) afforded a white solid (140 mg, 60% yield): mp 139-141°C; NMR (CDCl₃, 300Hz): 7.32 (s, 1H), 7.27 (d, 1H, J = 8), 7.12 (d, 1H, J = 7), 6.02 (d, 1H, J = 9), 5.78 (s, 1H), 3.50-3.39 (m, 1H), 2.45 (s, 3H), 2.36 (s, 6H), 1.82-1.60 (m, 4H), 1.01 (t, 6H, J = 8); Analysis Calcd for C₂₀H₂₅ClN₄: C, 67.31, H, 7.06, N, 15.70, Cl: 9.93; Found: C, 67.32, H, 6.95, N, 15.50, Cl, 9.93.

30

The examples delineated in TABLE 2 may be prepared by the methods outlined in Examples 1A, 1B, 432, 433, 434. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example, EtOAc is ethyl acetate.

35

TABLE 2



5	Ex.	Z	R ₃	Ar	mp (°C)
	435 ^b	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	71-73
	436 ^c	C-Me	N(Bu)Et	2,4-Cl ₂ -Ph	86-87
	437 ^d	C-Me	NHCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph	110-111
	438 ^e	C-Me	N(Pr)CH ₂ CH ₂ CN	2,4-Cl ₂ -Ph	83-85
10	439 ^f	C-Me	NH-3-pentyl	2,4-Cl ₂ -Ph	175-176
	440 ^g	C-Me	NHCH(CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	107
	441 ^h	C-Me	NHCH(Et) ₂	2,4-Me ₂ -Ph	oil
	442 ⁱ	C-Me	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph	103-105
	443 ^j	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph	87-89
15	444 ^k	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	133(dec)
	445 ^l	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl,4-MePh	77-78
	446 ^m	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl,4-MePh	131-133
	447 ⁿ	C-Me	NHCH(Et) ₂	2-Cl,4-MePh	139-141
	448 ^o	C-Me	NEt ₂	2,4-Me ₂ -Ph	92-94
20	449 ^p	C-Me	N(Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	143-144
	450 ^q	C-Me	N(Bu)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	115-117
	451 ^r	C-Me	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph	oil
	452 ^s	C-Me	NHCH(Et) ₂	2-Me,4-MeOPh	104-106
	453 ^t	C-Me	NHCH(CH ₂ OMe) ₂	2-Me,4-MeOPh	115-116
25	454 ^u	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me,4-MeOPh	oil
	455 ^v	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe)-(CH ₂ OMe)	2-Me,4-MeOPh	oil
	456 ^w	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe)-(CH ₂ OMe)	2,4-Me ₂ -Ph	oil

	457 ^x	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me, 4-ClPh	oil
	458 ^y	C-Me	NHEt	2, 4-Me ₂ -Ph	oil
	459 ^z	C-Me	NHCH(Et) ₂	2-Me, 4-ClPh	94-96
	460 ^{aa}	C-Me	NHCH(CH ₂ OMe) ₂	2-Me, 4-ClPh	113-114
5	461 ^{ab}	C-Me	N(Ac)Et	2, 4-Me ₂ -Ph	oil
	462 ^{ac}	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe) - (CH ₂ OMe)	2-Me, 4-ClPh	oil
	463 ^{ad}	C-Me	N(Pr)CH ₂ CH ₂ CN	2-Me, 4-MeOPh	118-119
	464 ^{ae}	C-Me	NEt ₂	2-Me, 4-MeOPh	97-99
10	465 ^{af}	C-Me	(S)-NHCH(CH ₂ CH ₂ OMe) - (CH ₂ OMe)	2-Cl, 4-MePh	101-103
	466 ^{ag}	C-Me	NEt ₂	2-Cl, 4-MePh	129-130
	467 ^{ah}	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Me, 4-MeOPh	177-178
	468 ^{ai}	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl, 4-MePh	162-163
15	469 ^{aj}	C-Me	NHCH(Et)CH ₂ OMe	2-Me, 4-MeOPh	oil
	470 ^{ak}	C-Me	NHCH(Et)CH ₂ OMe	2-Cl, 4-MePh	111-113
	471	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MeOPh	
	472	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MeOPh	
	473	C-Me	NHCH(Et)CH ₂ OMe	2-Cl-4-MeOPh	
20	474	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4-MeOPh	
	475	C-Me	NEt ₂	2-Cl-4-MeOPh	
	476	C-Me	NH-3-pentyl	2-Cl-4-MeOPh	
	477	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh	
	478	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh	
25	479	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4-MeOPh	
	480	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4-MeOPh	
	481	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh	
	482	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh	
	483	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-4, 5-(MeO) ₂ Ph	
30	484	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4, 5-(MeO) ₂ Ph	
	485	C-Me	NHCH(Et)CH ₂ OMe	2-Cl-4, 5-(MeO) ₂ Ph	
	486	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4, 5-(MeO) ₂ Ph	
	487	C-Me	NEt ₂	2-Cl-4, 5-(MeO) ₂ Ph	99-101
	488	C-Me	NH-3-pentyl	2-Cl-4, 5-(MeO) ₂ Ph	169-170
35	489	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4, 5-(MeO) ₂ Ph	

	490	C-Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Cl-4, 5- (MeO) ₂ Ph	
	491	C-Me	NHCH (CH ₂ OMe) ₂	2-Br-4, 5- (MeO) ₂ Ph	90-93
	492	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-Br-4, 5- (MeO) ₂ Ph	110
	493	C-Me	NHCH (Et) CH ₂ OMe	2-Br-4, 5- (MeO) ₂ Ph	
5	494	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2-Br-4, 5- (MeO) ₂ Ph	
	495	C-Me	NEt ₂	2-Br-4, 5- (MeO) ₂ Ph	
	496	C-Me	NH-3-pentyl	2-Br-4, 5- (MeO) ₂ Ph	
	497	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Br-4, 5- (MeO) ₂ Ph	
	498	C-Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Br-4, 5- (MeO) ₂ Ph	
10	499	C-Me	NHCH (CH ₂ OMe) ₂	2-Cl-4, 6- (MeO) ₂ Ph	
	500	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-Cl-4, 6- (MeO) ₂ Ph	
	501	C-Me	NHCH (Et) CH ₂ OMe	2-Cl-4, 6- (MeO) ₂ Ph	
	502	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2-Cl-4, 6- (MeO) ₂ Ph	
	503	C-Me	NEt ₂	2-Cl-4, 6- (MeO) ₂ Ph	
15	504	C-Me	NH-3-pentyl	2-Cl-4, 6- (MeO) ₂ Ph	
	505	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Cl-4, 6- (MeO) ₂ Ph	
	506	C-Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Cl-4, 6- (MeO) ₂ Ph	
	507	C-Me	NHCH (CH ₂ OMe) ₂	2-Me-4, 6- (MeO) ₂ Ph	
	508	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-Me-4, 6- (MeO) ₂ Ph	
20	509	C-Me	NHCH (Et) CH ₂ OMe	2-Me-4, 6- (MeO) ₂ Ph	
	510	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2-Me-4, 6- (MeO) ₂ Ph	
	511	C-Me	NEt ₂	2-Me-4, 6- (MeO) ₂ Ph	
	512	C-Me	NH-3-pentyl	2-Me-4, 6- (MeO) ₂ Ph	
	513	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Me-4, 6- (MeO) ₂ Ph	
25	514	C-Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Me-4, 6- (MeO) ₂ Ph	
	515	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2-Br-4, 6- (MeO) ₂ Ph	
	516	C-Me	NEt ₂	2-Br-4, 6- (MeO) ₂ Ph	
	517	C-Me	NH-3-pentyl	2-Br-4, 6- (MeO) ₂ Ph	
	518	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Br-4, 6- (MeO) ₂ Ph	
30	519	C-Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Br-4, 6- (MeO) ₂ Ph	
	520	C-Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Me-4-MeOPh	
	521	C-Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Me-4-MeOPh	
	522	C-Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-MePh	
	523	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh	
35	524	C-Me	NHCH (Et) CH ₂ OMe	2-MeO-4-MePh	
	525	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2-MeO-4-MePh	

	526	C-Me	NEt ₂	2-MeO-4-MePh
	527	C-Me	NH-3-pentyl	2-MeO-4-MePh
	528	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	529	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh
5	530	C-Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-MePh
	531	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	532	C-Me	NHCH(Et)CH ₂ OMe	2-MeO-4-MePh
	533	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-MePh
	534	C-Me	NEt ₂	2-MeO-4-MePh
10	535	C-Me	NH-3-pentyl	2-MeO-4-MePh
	536	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	537	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-MePh
	538	C-Me	NHCH(CH ₂ OMe) ₂	2-MeO-4-ClPh
	539	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-MeO-4-ClPh
15	540	C-Me	NHCH(Et)CH ₂ OMe	2-MeO-4-ClPh
	541	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-MeO-4-ClPh
	542	C-Me	NEt ₂	2-MeO-4-ClPh
	543	C-Me	NH-3-pentyl	2-MeO-4-ClPh
	544	C-Me	NHCH(Et)CH ₂ CH ₂ OMe	2-MeO-4-ClPh
20	545	C-Me	NHCH(Me)CH ₂ CH ₂ OMe	2-MeO-4-ClPh

NOTES FOR TABLE 2:

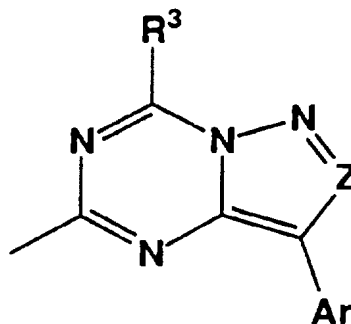
- b) CI-HRMS: Calcd: 423.1355; Found: 423.1337 (M + H).
- 25 c) Analysis: Calcd: C, 61.38, H, 6.18, N, 14.32;
Found: C, 61.54, H, 6.12, N, 14.37.
- d) Analysis: Calcd: C: 58.02, H, 5.65, N, 14.24;
Found: C, 58.11, H, 5.52, N, 14.26.
- e) Analysis: Calcd: C, 59.71, H, 5.26, N, 14.85;
30 Found: C, 59.94, H, 5.09, N, 17.23.
- f) Analysis: Calcd: C, 60.48, H, 5.89, N, 14.85,
Found: C, 60.62, H, 5.88, N, 14.82.
- h) CI-HRMS: Calcd: 337.2388; Found: 337.2392 (M + H).
- i) Analysis: Calcd: C, 68.45, H, 7.669, N, 15.21,
35 Found: C, 68.35, H, 7.49 N, 14.91.

- j) Analysis: Calcd: C, 69.08, H, 7.915, N, 14.65,
Found: C, 68.85, H, 7.83, N, 14.54.
- k) Analysis: Calcd: C, 73.51, H, 7.01, N, 19.48,
Found: C, 71.57, H, 7.15, N, 19.12.
- 5 l) CI-HRMS: Calcd: 403.1899; Found: 403.1901 (M + H).
m) Analysis: Calcd: C, 61.77, H, 6.49, N, 14.41, Cl,
9.13; Found: C, 61.90, H, 6.66, N, 13.62, Cl, 9.25.
n) Analysis: Calcd: C, 67.31, H, 7.06, N, 15.70, Cl,
9.93; Found: C, 67.32, H, 6.95, N, 15.50, Cl, 9.93.
- 10 o) Analysis: Calcd: C, 74.50, H, 8.14, N, 17.38,
Found: C, 74.43, H, 7.59, N, 17.16.
p) Analysis: Calcd: C, 73.10, H, 7.54, N, 19.37,
Found: C, 73.18, H, 7.59, N, 18.81.
q) Analysis: Calcd: C, 73.57, H, 7.78, N, 18.65,
15 Found: C, 73.55, H, 7.79, N, 18.64.
r) CI-HRMS: Calcd: 353.2333; Found: 353.2341 (M + H).
s) Analysis: Calcd: C, 71.56, H, 8.02, N, 15.90,
Found: C, 71.45, H, 7.99, N, 15.88.
t) Analysis: Calcd: C, 65.60, H, 7.34, N, 14.57,
20 Found: C, 65.42, H, 7.24, N, 14.37.
u) CI-HRMS: Calcd: 399.2398; Found: 399.2396 (M + H).
v) CI-HRMS: Calcd: 399.2398; Found: 399.2396 (M + H).
w) CI-HRMS: Calcd: 383.2450; Found: 383.2447 (M + H).
x) CI-HRMS: Calcd: 403.1887; Found: 403.1901 (M + H).
25 y) CI-HRMS: Calcd: 295.1919; Found: 295.1923 (M + H).
z) Analysis: Calcd: C, 67.31, H, 7.06, N, 15.70,
Found: C, 67.12, H, 6.86, N, 15.53.
aa) Analysis: Calcd: C, 61.77, H, 6.49, N, 14.41, Cl,
9.13; Found: C, 62.06, H, 6.37, N, 14.25, Cl, 9.12.
- 30 ab) CI-HRMS: Calcd: 337.2017; Found: 337.2028 (M + H).
ac) CI-HRMS: Calcd: 403.1893; Found: 403.1901 (M + H).
ad) Analysis: Calcd: C, 70.00, H, 7.22, N, 18.55,
Found: C, 70.05, H, 7.22, N, 18.36.
ae) Analysis: Calcd: C, 70.98, H, 7.74, N, 16.55,
35 Found: C, 71.15, H, 7.46, N, 16.56.

- ag) Analysis: Calcd: C, 66.59, H, 6.76, N, 16.34,
Found: C, 66.69, H, 6.82, N, 16.20.
- ah) Analysis: Calcd: C, 70.38, H, 6.71, N, 18.65,
Found: C, 70.35, H, 6.82, N, 18.83.
- 5 ai) Analysis: Calcd: C, 66.39, H, 5.85, N, 18.44, Cl,
9.33;
Found: C, 66.29, H, 5.51, N, 18.36, Cl, 9.31.
- aj) CI-HRMS: Calcd: 369.2278; Found: 369.2291 (M + H).
- ak) Analysis: Calcd: C, 64.42, H, 6.77, N, 15.02,
10 Found: C, 64.59, H, 6.51, N, 14.81.

The examples delineated in TABLE 3 may be prepared by
the methods outlined in Examples 1, 2, 3 or 6. Commonly
15 used abbreviations are: Ph is phenyl, Pr is propyl, Me
is methyl, Et is ethyl, Bu is butyl, Ex is Example.

TABLE 3



Ex.	Z	R ₃	Ar	mp (°C)
546 ^a	C-Me	NHCH(Et) ₂	2-Me-4-Me ₂ N-Ph	164-166
25 547 ^b	C-Me	S-NHCH(CH ₂ CH ₂ OMe) -CH ₂ OMe	2,4-Me ₂ -Ph	oil
548 ^c	C-Me	S-NHCH(CH ₂ CH ₂ OMe) -CH ₂ OMe	2-Me-4-Cl-Ph	oil
549 ^d	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Me-4-Cl-Ph	115-116

	550 ^e	C-Me	NHCH(Et)CH ₂ CN	2-Me-4-Cl-Ph	131-132
	551 ^f	C-Me	N(Et) ₂	2,3-Me ₂ -4-OMe-Ph	oil
	552 ^g	C-Me	N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ OH	2,4-Cl ₂ -Ph	oil
	553 ^h	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,3-Me ₂ -4-OMe-Ph	oil
5	554 ⁱ	C-Me	NHCH(Et) ₂	2,3-Me ₂ -4-OMePh	123-124
	555 ^j	C-Me	N(CH ₂ -c-Pr)Pr	2-Me-4-Cl-Ph	oil
	556 ^k	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2,3-Me ₂ -4-OMePh	158-160
	557	C-Me	N(c-Pr)Et	2-Cl-4-OMePh	
	558	C-Me	N(c-Pr)Me	2-Cl-4-OMePh	
10	559	C-Me	N(c-Pr)Pr	2-Cl-4-OMePh	
	560	C-Me	N(c-Pr)Bu	2-Cl-4-OMePh	
	561 ^l	C-Me	N(Et) ₂	2-Cl-4-CN-Ph	115-117
	562	C-Me	N(c-Pr) ₂	2-Cl-4-OMe	127-129
	563 ^m	C-Me	NHCH(CH ₂ OH) ₂	2,4-Cl ₂ -Ph	128-129
15	564	C-Me	N(c-Pr)Et	2-Br-4,5-(MeO) ₂ Ph	
	565	C-Me	N(c-Pr)Me	2-Br-4,5-(MeO) ₂ Ph	
	566	C-Me	NH-c-Pr	2-Me-4-MeOPh	126-128
	567	C-Me	NHCH(Et)CH ₂ OH	2-Me-4-MeOPh	60-62
	568	C-Me	NMe ₂	2-Br-4,5-(MeO) ₂ Ph	
20	569	C-Me	NHCH(Et) ₂	2-Me-4-MeOPh	103-105
	570	C-Me	N(c-Pr)Et	2-Me-4-MeOPh	173-174
	571	C-Me	NH-2-pentyl	2,4-Cl ₂ -Ph	118-120
	572	C-Me	NHCH(Et)CH ₂ CN	2,4-Cl ₂ -Ph	141-142
	573	C-Me	NHCH(Pr)CH ₂ OMe	2,4-Cl ₂ -Ph	87-88
25	574	C-Me	NHCH(CH ₂ -iPr)CH ₂ OMe	2,4-Cl ₂ -Ph	amorphous
	575	C-Me	NH-2-butyl	2,4-Me ₂ -Ph	oil
	576	C-Me	NH-2-pentyl	2,4-Me ₂ -Ph	oil
	577	C-Me	NH-2-hexyl	2,4-Me ₂ -Ph	oil
	578	C-Me	NHCH(i-Pr)Me	2,4-Me ₂ -Ph	oil
30	579	C-Me	NHCH(Me)CH ₂ -iPr	2,4-Me ₂ -Ph	oil
	580	C-Me	NHCH(Me)-c-C ₆ H ₁₁	2,4-Me ₂ -Ph	oil
	581	C-Me	NH-2-indanyl	2,4-Me ₂ -Ph	oil
	582	C-Me	NH-1-indanyl	2,4-Me ₂ -Ph	oil
	583	C-Me	NHCH(Me)Ph	2,4-Me ₂ -Ph	oil
35	584	C-Me	NHCH(Me)CH ₂ -(4-ClPh)	2,4-Me ₂ -Ph	oil

	585	C-Me	NHCH (Me) CH ₂ COCH ₃	2,4-Me ₂ -Ph	oil
	586	C-Me	NHCH (Ph) CH ₂ Ph	2,4-Me ₂ -Ph	oil
	587	C-Me	NHCH (Me) (CH ₂) ₃ NEt ₂	2,4-Me ₂ -Ph	oil
	588	C-Me	NH- (2-Ph-c-C ₃ H ₄)	2,4-Me ₂ -Ph	oil
5	589	C-Me	NHCH (Et) CH ₂ CN	2,4-Me ₂ -Ph	119-120
	590	C-Me	NH-3-hexyl	2,4-Me ₂ -Ph	oil
	591 ⁿ	C-Me	NEt ₂	2-MeO-4-ClPh	oil
	592 ^o	C-Me	NHCH (Et) ₂	2-MeO-4-ClPh	oil
	593 ^p	C-Me	NHCH (Et) CH ₂ OMe	2-MeO-4-ClPh	oil
10	594	C-Me	NMe ₂	2-MeO-4-ClPh	oil
	595 ^q	C-Me	NHCH (Et) ₂	2-OMe-4-MePh	oil
	596 ^r	C-Me	NEt ₂	2-OMe-4-MePh	oil
	597 ^s	C-c-Pr	NHCH (CH ₂ OMe) ₂	2,4-Cl ₂ -Ph	oil
	598	C-Me	N (c-Pr) Et	2,4-Me ₂ -Ph	
15	599	C-Me	N (c-Pr) Et	2,4-Cl ₂ -Ph	
	600	C-Me	N (c-Pr) Et	2,4,6-Me ₃ -Ph	
	601	C-Me	N (c-Pr) Et	2-Me-4-Cl-Ph	
	602	C-Me	N (c-Pr) Et	2-Cl-4-Me-Ph	
	603	C-Me	NHCH (c-Pr) ₂	2,4-Cl ₂ -Ph	
20	604	C-Me	NHCH (c-Pr) ₂	2,4-Me ₂ -Ph	
	605	C-Me	NHCH (c-Pr) ₂	2-Me-4-Cl-Ph	
	606	C-Me	NHCH (c-Pr) ₂	2-Cl-4-Me-Ph	
	607	C-Me	NHCH (c-Pr) ₂	2-Me-4-OMe-Ph	
	608	C-Me	NHCH (c-Pr) ₂	2-Cl-4-OMe-Ph	
25	609	C-Me	NHCH (CH ₂ OMe) ₂	2-Cl-5-F-OMePh	
	610	C-Me	NEt ₂	2-Cl-5-F-OMePh	
	611	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2-Cl-5-F-OMePh	
	612	C-Me	NHCH (Et) ₂	2-Cl-5-F-OMePh	
	613	C-Me	N (CH ₂ CH ₂ OMe) ₂	2-Cl-5-F-OMePh	
30	614	C-Me	NEt ₂	2,6-Me ₂ -pyrid-3-yl	
	615	C-Me	N (c-Pr) CH ₂ CH ₂ CN	2,6-Me ₂ -pyrid-3-yl	
	616	C-Me	NHCH (Et) ₂	2,6-Me ₂ -pyrid-3-yl	
	617	C-Me	N (CH ₂ CH ₂ OMe) ₂	2,6-Me ₂ -pyrid-3-yl	
	618	C-OH	NHCH (CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
35	619	C-OH	NEt ₂	2,4-Me ₂ -Ph	
	620	C-OH	N (c-Pr) CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	

	621	C-OH	NHCH(Et) ₂	2,4-Me ₂ -Ph
	623	C-OH	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	624	C-NEt ₂	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	625	C-NEt ₂	NEt ₂	2,4-Me ₂ -Ph
5	626	C-NEt ₂	N(c-Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	627	C-NEt ₂	NHCH(Et) ₂	2,4-Me ₂ -Ph
	628	C-NEt ₂	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	629	C-Me	NHCH(Et) ₂	2-Me-4-CN-Ph
	630	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-CN-Ph

10

Notes for Table 3:

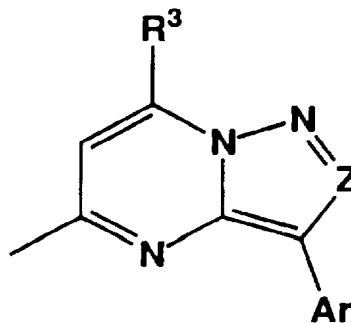
- a) CI-HRMS: Calcd:367.2610, Found: 367.2607 (M + H);
- b) CI-HRMS: Calcd:384.2400, Found: 384.2393 (M + H);
- 15 c) CI-HRMS: Calcd:404.1853, Found: 404.1844 (M + H);
- d) CI-HRMS: Calcd:381.1594, Found: 381.1596 (M + H);
Analysis: Calcd: C: 63.07, H, 5.57, N, 22.07, Cl, 9.32;
Found: C: 63.40, H, 5.55, N, 21.96, Cl: 9.15
- 20 e) CI-HRMS: Calcd:369.1594, Found: 369.1576 (M + H);
- f) CI-HRMS: Calcd:354.2216, Found: 354.2211 (M + H);
- g) CI-HRMS: Calcd:410.1072, Found: 410.1075 (M + H);
- h) CI-HRMS: Calcd:414.2427, Found: 414.2427 (M + H);
- i) CI-HRMS: Calcd:368.2372, Found: 368.2372 (M + H);
- 25 j) CI-HRMS: Calcd:384.1955, Found: 384.1947 (M + H);
- k) CI-HRMS: Calcd:391.2168, Found: 391.2160 (M + H);
- l) CI-HRMS: Calcd:335.1984, Found: 335.1961 (M + H);
- m) CI-HRMS: Calcd:382.0759, Found: 382.0765 (M + H);
- n) NH₃-CI MS: Calcd: 360, Found: 360 (M + H)+
- 30 o) NH₃-CI MS: Calcd: 374, Found: 374 (M + H)+;
NMR (CDCl₃, 300 MHz) : δ 7.29 (d, J=8.4Hz, 1H), 7.04 (dd, J=1.8,8Hz, 1H), 6.96 (d, J=1.8Hz, 1H), 6.15 (d, J=10, 1H), 4.19 (m, 1H), 3.81 (s, 3H), 2.47 (s, 3H), 2.32 (s, 3H), 1.65 (m, 4H), 0.99 (t, J=7.32Hz, 6H)
- 35 p) NH₃-CI MS: Calcd: 390, Found: 390 (M + H)+;

NMR (CDCl₃, 300 MHz) : δ 7.28 (d, J=8Hz, 1H), 7.03 (d, J=8Hz, 1H), 6.96 (s, 1H), 6.52 (d, J=9Hz, 1H), 4.36 (m, 1H), 3.8 (s, 3H), 3.55 (m, 2H), 3.39 (s, 3H), 2.47 (s, 3H), 2.32 (s, 3H), 1.76 (m, 2H), 1.01 (t, J=7.32Hz, 3H).

- q) CI-HRMS: Calcd: 354.2294, Found: 354.2279 (M + H)⁺
 r) CI-HRMS: Calcd: 340.2137, Found: 340.2138 (M + H)⁺
 s) CI-HRMS: Calcd: 436.1307, Found: 436.1296 (M + H)⁺

The examples delineated in TABLE 4 may be prepared by the methods outlined in Examples 1A, 1B, 432, 433, 434. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example, EtOAc is ethyl acetate.

TABLE 4

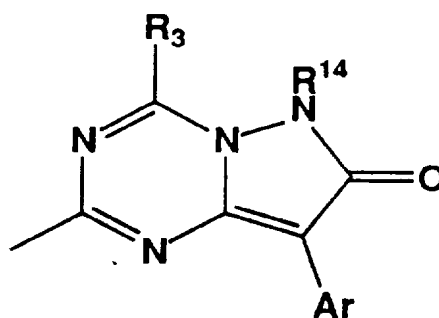


Ex.	Z	R ₃	Ar	mp (°C)
631	C-Me	NHCH(Et) ₂	2-Br-4,5-(MeO) ₂ Ph	160-161
632	C-Me	NHCH(Et) ₂	2-Br-4-MeOPh	110-111
633	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-MeOPh	74-76
634	C-Me	NHCH(CH ₂ OMe) ₂	2-Br-4-MeOPh	128-130

	635	C-Me	N(Et) ₂	2-Me-4-ClPh	113-114
	636	C-Me	N(c-Pr)Et	2,4-Cl ₂ Ph	
	637	C-Me	N(c-Pr)Et	2,4-Me ₂ Ph	
	638	C-Me	N(c-Pr)Et	2,4,6-Me ₃ Ph	
5	639	C-Me	N(c-Pr)Et	2-Me-4-MeOPh	
	640	C-Me	N(c-Pr)Et	2-Cl-4-MeOPh	
	641	C-Me	N(c-Pr)Et	2-Cl-4-MePh	
	642	C-Me	N(c-Pr)Et	2-Me-4-ClPh	
	643	C-Me	NHCH(c-Pr) ₂	2,4-Cl ₂ -Ph	
10	644	C-Me	NHCH(c-Pr) ₂	2,4-Me ₂ -Ph	
	645	C-Me	NHCH(c-Pr) ₂	2-Me-4-Cl-Ph	
	646	C-Me	NHCH(c-Pr) ₂	2-Cl-4-Me-Ph	
	647	C-Me	NHCH(c-Pr) ₂	2-Me-4-OMe-Ph	
	648	C-Me	NHCH(c-Pr) ₂	2-Cl-4-OMe-Ph	
15	649	C-Me	NHCH(CH ₂ OMe) ₂	2-Cl-5-F-OMePh	
	650	C-Me	NEt ₂	2-Cl-5-F-OMePh	
	651	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-5-F-OMePh	
	652	C-Me	NHCH(Et) ₂	2-Cl-5-F-OMePh	
	653	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-5-F-OMePh	
20	654	C-Me	NEt ₂	2,6-Me ₂ -pyrid-3-yl	
	655	C-Me	N(c-Pr)CH ₂ CH ₂ CN	2,6-Me ₂ -pyrid-3-yl	
	656	C-Me	NHCH(Et) ₂	2,6-Me ₂ -pyrid-3-yl	
	657	C-Me	N(CH ₂ CH ₂ OMe) ₂	2,6-Me ₂ -pyrid-3-yl	
	658	C-OH	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
25	659	C-OH	NEt ₂	2,4-Me ₂ -Ph	
	660	C-OH	N(c-Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	
	661	C-OH	NHCH(Et) ₂	2,4-Me ₂ -Ph	
	662	C-OH	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
	663	C-NEt ₂	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
30	664	C-NEt ₂	NEt ₂	2,4-Me ₂ -Ph	
	665	C-NEt ₂	N(c-Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph	
	666	C-NEt ₂	NHCH(Et) ₂	2,4-Me ₂ -Ph	
	667	C-NEt ₂	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph	
	668	C-Me	NHCH(Et) ₂	2-Me-4-CN-Ph	
35	669	C-Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-CN-Ph	

The examples in Tables 5 or 6 may be prepared by the methods illustrated in Examples 1A, 1B, 2, 3, 6, 431, 432, 433, 434 or by appropriate combinations thereof. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example.

Table 5



Ex.	R ₁₄	R ₃	Ar
670	Me	NHCH(CH ₂ OMe) ₂	2,4-Cl ₂ -Ph
671	Me	NHCHPr ₂	2,4-Cl ₂ -Ph
672	Me	NEtBu	2,4-Cl ₂ -Ph
20 673	Me	NPr(CH ₂ -C-C ₃ H ₅)	2,4-Cl ₂ -Ph
674	Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Cl ₂ -Ph
675	Me	NH-3-heptyl	2,4-Cl ₂ -Ph
676	Me	NHCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph
677	Me	NEt ₂	2,4-Cl ₂ -Ph
25 678	Me	NHCH(CH ₂ OEt) ₂	2,4-Cl ₂ -Ph
679	Me	NH-3-pentyl	2,4-Cl ₂ -Ph
680	Me	NMePh	2,4-Cl ₂ -Ph
681	Me	NPr ₂	2,4-Cl ₂ -Ph
682	Me	NH-3-hexyl	2,4-Cl ₂ -Ph
30 683	Me	morpholino	2,4-Cl ₂ -Ph

	684	Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Cl ₂ -Ph
	685	Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Cl ₂ -Ph
	686	Me	NH-4-tetrahydropyranyl	2,4-Cl ₂ -Ph
	687	Me	NH-cyclopentyl	2,4-Cl ₂ -Ph
5	688	Me	OEt	2,4-Cl ₂ -Ph
	689	Me	OCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph
	690	Me	OCH ₂ Ph	2,4-Cl ₂ -Ph
	691	Me	O-3-pentyl	2,4-Cl ₂ -Ph
	692	Me	SEt	2,4-Cl ₂ -Ph
10	693	Me	S(O)Et	2,4-Cl ₂ -Ph
	694	Me	SO ₂ Et	2,4-Cl ₂ -Ph
	695	Me	Ph	2,4-Cl ₂ -Ph
	696	Me	2-CF ₃ -Ph	2,4-Cl ₂ -Ph
	697	Me	2-Ph-Ph	2,4-Cl ₂ -Ph
15	698	Me	3-pentyl	2,4-Cl ₂ -Ph
	699	Me	cyclobutyl	2,4-Cl ₂ -Ph
	700	Me	3-pyridyl	2,4-Cl ₂ -Ph
	701	Me	CH(Et)CH ₂ CONMe ₂	2,4-Cl ₂ -Ph
	702	Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4-Cl ₂ -Ph
20	703	Me	NHCH(CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph
	704	Me	NHCHPr ₂	2,4,6-Me ₃ -Ph
	705	Me	NEtBu	2,4,6-Me ₃ -Ph
	706	Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4,6-Me ₃ -Ph
	707	Me	N(CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph
25	708	Me	NH-3-heptyl	2,4,6-Me ₃ -Ph
	709	Me	NHCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	710	Me	NEt ₂	2,4,6-Me ₃ -Ph
	711	Me	NHCH(CH ₂ OEt) ₂	2,4,6-Me ₃ -Ph
	712	Me	NH-3-pentyl	2,4,6-Me ₃ -Ph
30	713	Me	NMePh	2,4,6-Me ₃ -Ph
	714	Me	NPr ₂	2,4,6-Me ₃ -Ph
	715	Me	NH-3-hexyl	2,4,6-Me ₃ -Ph
	716	Me	morpholino	2,4,6-Me ₃ -Ph
	717	Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4,6-Me ₃ -Ph
35	718	Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4,6-Me ₃ -Ph
	719	Me	NH-4-tetrahydropyranyl	2,4,6-Me ₃ -Ph

	720	Me	NH-cyclopentyl	2,4,6-Me ₃ -Ph
	721	Me	OEt	2,4,6-Me ₃ -Ph
	722	Me	OCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	723	Me	OCH ₂ Ph	2,4,6-Me ₃ -Ph
5	724	Me	O-3-pentyl	2,4,6-Me ₃ -Ph
	725	Me	SEt	2,4,6-Me ₃ -Ph
	726	Me	S(O)Et	2,4,6-Me ₃ -Ph
	727	Me	SO ₂ Et	2,4,6-Me ₃ -Ph
	728	Me	CH(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph
10	729	Me	C(Et)(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph
	730	Me	CH(Et)CH ₂ OH	2,4,6-Me ₃ -Ph
	731	Me	CH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	732	Me	CONMe ₂	2,4,6-Me ₃ -Ph
	733	Me	COCH ₃	2,4,6-Me ₃ -Ph
15	734	Me	CH(OH)CH ₃	2,4,6-Me ₃ -Ph
	735	Me	C(OH)Ph-3-pyridyl	2,4,6-Me ₃ -Ph
	736	Me	Ph	2,4,6-Me ₃ -Ph
	737	Me	2-Ph-Ph	2,4,6-Me ₃ -Ph
	738	Me	3-pentyl	2,4,6-Me ₃ -Ph
20	739	Me	cyclobutyl	2,4,6-Me ₃ -Ph
	740	Me	3-pyridyl	2,4,6-Me ₃ -Ph
	741	Me	CH(Et)CH ₂ CONMe ₂	2,4,6-Me ₃ -Ph
	742	Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4,6-Me ₃ -Ph
	743	Me	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph
25	744	Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	745	Me	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	746	Me	NH-3-pentyl	2,4-Me ₂ -Ph
	747	Me	NEt ₂	2,4-Me ₂ -Ph
	748	Me	N(CH ₂ CN) ₂	2,4-Me ₂ -Ph
30	749	Me	NHCH(Me)CH ₂ OMe	2,4-Me ₂ -Ph
	750	Me	OCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	751	Me	NPr-c-C ₃ H ₅	2,4-Me ₂ -Ph
	752	Me	NHCH(Me)CH ₂ NMe ₂	2,4-Me ₂ -Ph
	753	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
35	754	Me	N(Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	755	Me	N(Bu)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph

	756	Me	NHCHPr ₂	2,4-Me ₂ -Ph
	757	Me	NEtBu	2,4-Me ₂ -Ph
	758	Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Me ₂ -Ph
	759	Me	NH-3-heptyl	2,4-Me ₂ -Ph
5	760	Me	NEt ₂	2,4-Me ₂ -Ph
	761	Me	NHCH(CH ₂ OEt) ₂	2,4-Me ₂ -Ph
	762	Me	NH-3-pentyl	2,4-Me ₂ -Ph
	763	Me	NMePh	2,4-Me ₂ -Ph
	764	Me	NPr ₂	2,4-Me ₂ -Ph
10	765	Me	NH-3-hexyl	2,4-Me ₂ -Ph
	766	Me	morpholino	2,4-Me ₂ -Ph
	767	Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Me ₂ -Ph
	768	Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Me ₂ -Ph
	769	Me	NH-4-tetrahydropyranyl	2,4-Me ₂ -Ph
15	770	Me	NH-cyclopentyl	2,4-Me ₂ -Ph
	771	Me	NHCH(CH ₂ OMe) ₂	2-Me-4-MeO-Ph
	772	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-MeO-Ph
	773	Me	NHCH(Et)CH ₂ OMe	2-Me-4-MeO-Ph
	774	Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-MeO-Ph
20	775	Me	OCH(Et)CH ₂ OMe	2-Me-4-MeO-Ph
	776	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-MeO-Ph
	777	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-MeO-Ph
	778	Me	NHCH(Et)CH ₂ OMe	2-Br-4-MeO-Ph
	779	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-MeO-Ph
25	780	Me	OCH(Et)CH ₂ OMe	2-Br-4-MeO-Ph
	781	Me	NHCH(CH ₂ OMe) ₂	2-Me-4-NMe ₂ -Ph
	782	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-NMe ₂ -Ph
	783	Me	NHCH(Et)CH ₂ OMe	2-Me-4-NMe ₂ -Ph
	784	Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-NMe ₂ -Ph
30	785	Me	OCH(Et)CH ₂ OMe	2-Me-4-NMe ₂ -Ph
	786	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-NMe ₂ -Ph
	787	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-NMe ₂ -Ph
	788	Me	NHCH(Et)CH ₂ OMe	2-Br-4-NMe ₂ -Ph
	789	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-NMe ₂ -Ph
35	790	Me	OCH(Et)CH ₂ OMe	2-Br-4-NMe ₂ -Ph
	791	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-i-Pr-Ph

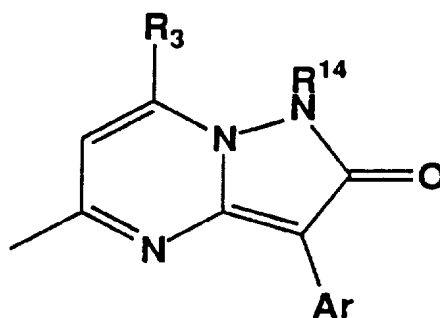
	792	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-i-Pr-Ph
	793	Me	$NHCH(Et)CH_2OMe$	2-Br-4-i-Pr-Ph
	794	Me	$N(Pr)CH_2CH_2CN$	2-Br-4-i-Pr-Ph
	795	Me	$OCH(Et)CH_2OMe$	2-Br-4-i-Pr-Ph
5	796	Me	$NHCH(CH_2OMe)_2$	2-Br-4-Me-Ph
	797	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-Me-Ph
	798	Me	$NHCH(Et)CH_2OMe$	2-Br-4-Me-Ph
	799	Me	$N(Pr)CH_2CH_2CN$	2-Br-4-Me-Ph
	800	Me	$OCH(Et)CH_2OMe$	2-Br-4-Me-Ph
10	801	Me	$NHCH(CH_2OMe)_2$	2-Me-4-Br-Ph
	802	Me	$N(CH_2CH_2OMe)_2$	2-Me-4-Br-Ph
	803	Me	$NHCH(Et)CH_2OMe$	2-Me-4-Br-Ph
	804	Me	$N(Pr)CH_2CH_2CN$	2-Me-4-Br-Ph
	805	Me	$OCH(Et)CH_2OMe$	2-Me-4-Br-Ph
15	806	Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-Me ₂ -Ph
	807	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-Me ₂ -Ph
	808	Me	$NHCH(CH_2OMe)_2$	4-Br-2,6-(Me) ₂ -Ph
	809	Me	$N(CH_2CH_2OMe)_2$	4-Br-2,6-(Me) ₂ -Ph
	810	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
20	811	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
	812	Me	$NHCH(CH_2OMe)_2$	2-Br-4-CF ₃ -Ph
	813	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-CF ₃ -Ph
	814	Me	$NHCH(CH_2OMe)_2$	2-Br-4,6-(MeO) ₂ -Ph
	815	Me	$N(CH_2CH_2OMe)_2$	2-Br-4,6-(MeO) ₂ -Ph
25	816	Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-(MeO) ₂ -Ph
	817	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-(MeO) ₂ -Ph
	818	Me	$NHCH(CH_2OMe)_2$	2,6-(Me) ₂ -4-SMe-Ph
	819	Me	$N(CH_2CH_2OMe)_2$	2,6-(Me) ₂ -4-SMe-Ph
	820	Me	$NHCH(CH_2OMe)_2$	4-(COMe)-2-Br-Ph
30	821	Me	$N(CH_2CH_2OMe)_2$	4-(COMe)-2-Br-Ph
	822	Me	$NHCH(CH_2OMe)_2$	2,4,6-Me ₃ -pyrid-3-yl
	823	Me	$N(CH_2CH_2OMe)_2$	2,4,6-Me ₃ -pyrid-3-yl
	824	Me	$NHCH(CH_2OMe)_2$	2,4-(Br) ₂ -Ph
	825	Me	$N(CH_2CH_2OMe)_2$	2,4-(Br) ₂ -Ph
35	826	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
	827	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph

	828	Me	NHCH (CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	829	Me	N (CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	830	Me	NHCH (CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
	831	Me	N (CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
5	832	Me	NHCH (CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SO ₂ Me-Ph
	833	Me	N (CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SO ₂ Me-Ph
	834	Me	NHCH (CH ₂ OMe) ₂	2-I-4-i-Pr-Ph
	835	Me	N (CH ₂ CH ₂ OMe) ₂	2-I-4-i-Pr-Ph
	836	Me	NHCH (CH ₂ OMe) ₂	2-Br-4-N(Me) ₂ -6-MeO-Ph
10	837	Me	N (CH ₂ CH ₂ OMe) ₂	2-Br-4-N(Me) ₂ -6-MeO-Ph
	838	Me	NEt ₂	2-Br-4-MeO-Ph
	839	Me	NH-3-pentyl	2-Br-4-MeO-Ph
	840	Me	NHCH (CH ₂ OMe) ₂	2-CN-4-Me-Ph
	841	Me	N (c-C ₃ H ₅) CH ₂ CH ₂ CN	2,4,6-Me ₃ -Ph
15	842	Me	NHCH (CH ₂ CH ₂ OMe) CH ₂ OMe	2-Me-4-Br-Ph
	843	Me	NHCH (CH ₂ OMe) ₂	2,5-Me ₂ -4-MeO-Ph
	844	Me	N (CH ₂ CH ₂ OMe) ₂	2,5-Me ₂ -4-MeO-Ph
	845	Me	NH-3-pentyl	2,5-Me ₂ -4-MeO-Ph
	846	Me	NEt ₂	2,5-Me ₂ -4-MeO-Ph
20	847	Me	NHCH (CH ₂ OMe) ₂	2-Cl-4-MePh
	848	Me	NCH (Et) CH ₂ OMe	2-Cl-4-MePh
	849	Me	N (CH ₂ CH ₂ OMe) ₂	2-Cl-4-MePh
	850	Me	(S)-NHCH (CH ₂ CH ₂ OMe) CH ₂ OMe	2-Cl-4-MePh
	851	Me	N (c-C ₃ H ₅) CH ₂ CH ₂ CN	2,5-Me ₂ -4-MeOPh
25	852	Me	NEt ₂	2-Me-4-MeOPh
	853	Me	OEt	2-Me-4-MeOPh
	854	Me	(S)-NHCH (CH ₂ CH ₂ OMe) CH ₂ OMe	2-Me-4-MeOPh
	855	Me	N (c-C ₃ H ₅) CH ₂ CH ₂ CN	2-Me-4-MeOPh
	856	Me	NHCH (CH ₂ CH ₂ OEt) ₂	2-Me-4-MeOPh
30	857	Me	N (c-C ₃ H ₅) CH ₂ CH ₂ CN	2,4-Cl ₂ -Ph
	858	Me	NEt ₂	2-Me-4-ClPh
	859	Me	NH-3-pentyl	2-Me-4-ClPh
	860	Me	N (CH ₂ CH ₂ OMe) ₂	2-Me-4-ClPh
	861	Me	NHCH (CH ₂ OMe) ₂	2-Me-4-ClPh
35	862	Me	NEt ₂	2-Me-4-ClPh
	863	Me	NEt ₂	2-Cl-4-MePh

	864	Me	NH-3-pentyl	2-Cl-4-MePh
	865	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MeOPh
	866	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4-MeOPh
	867	Me	NHCH(Et)CH ₂ OMe	2-Cl-4-MeOPh
5	868	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4-MeOPh
	869	Me	NEt ₂	2-Cl-4-MeOPh
	870	Me	NH-3-pentyl	2-Cl-4-MeOPh
	871	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh
	872	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh
10	873	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Br-4-MeOPh
	874	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Br-4-MeOPh
	875	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	876	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	877	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph
15	878	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph
	879	Me	NHCH(Et)CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	880	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4,5-(MeO) ₂ Ph
	881	Me	NEt ₂	2-Cl-4,5-(MeO) ₂ Ph
	882	Me	NH-3-pentyl	2-Cl-4,5-(MeO) ₂ Ph
20	883	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	884	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	885	Me	NHCH(CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph
	886	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph
	887	Me	NHCH(Et)CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph
25	888	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Br-4,5-(MeO) ₂ Ph
	889	Me	NEt ₂	2-Br-4,5-(MeO) ₂ Ph
	890	Me	NH-3-pentyl	2-Br-4,5-(MeO) ₂ Ph
	891	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
	892	Me	N(CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
30	893	Me	NEt ₂	2-Cl-4,6-(MeO) ₂ Ph
	894	Me	NH-3-pentyl	2-Cl-4,6-(MeO) ₂ Ph
	895	Me	NHCH(CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
	896	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
	897	Me	NHCH(Et)CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
35	898	Me	NEt ₂	2-Me-4,6-(MeO) ₂ Ph
	899	Me	NH-3-pentyl	2-Me-4,6-(MeO) ₂ Ph

	900	Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	901	Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	902	Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-MePh
	903	Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
5	904	Me	NHCH (Et) CH ₂ OMe	2-MeO-4-MePh
	905	Me	N (c-Pr) CH ₂ CH ₂ CN	2-MeO-4-MePh
	906	Me	NEt ₂	2-MeO-4-MePh
	907	Me	NH-3-pentyl	2-MeO-4-MePh
	908	Me	NHCH (Et) CH ₂ CH ₂ OMe	2-MeO-4-MePh
10	909	Me	NHCH (Me) CH ₂ CH ₂ OMe	2-MeO-4-MePh
	910	Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-MePh
	911	Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	912	Me	NHCH (Et) CH ₂ OMe	2-MeO-4-MePh
	913	Me	N (c-Pr) CH ₂ CH ₂ CN	2-MeO-4-MePh
15	914	Me	NEt ₂	2-MeO-4-MePh
	915	Me	NH-3-pentyl	2-MeO-4-MePh
	916	Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-ClPh
	917	Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-ClPh
	918	Me	NHCH (Et) CH ₂ OMe	2-MeO-4-ClPh
20	919	Me	NEt ₂	2-MeO-4-ClPh
	920	Me	NH-3-pentyl	2-MeO-4-ClPh

Table 6



5	Ex.	R ₁₄	R ₃	Ar
	921	Me	NHCH(CH ₂ OMe) ₂	2,4-Cl ₂ -Ph
	922	Me	NHCHPr ₂	2,4-Cl ₂ -Ph
	923	Me	NEtBu	2,4-Cl ₂ -Ph
10	924	Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Cl ₂ -Ph
	925	Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Cl ₂ -Ph
	926	Me	NH-3-heptyl	2,4-Cl ₂ -Ph
	927	Me	NHCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph
	928	Me	NEt ₂	2,4-Cl ₂ -Ph
15	929	Me	NHCH(CH ₂ OEt) ₂	2,4-Cl ₂ -Ph
	930	Me	NH-3-pentyl	2,4-Cl ₂ -Ph
	931	Me	NMePh	2,4-Cl ₂ -Ph
	932	Me	NPr ₂	2,4-Cl ₂ -Ph
	933	Me	NH-3-hexyl	2,4-Cl ₂ -Ph
20	934	Me	morpholino	2,4-Cl ₂ -Ph
	935	Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Cl ₂ -Ph
	936	Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Cl ₂ -Ph
	937	Me	NH-4-tetrahydropyranyl	2,4-Cl ₂ -Ph
	938	Me	NH-cyclopentyl	2,4-Cl ₂ -Ph
25	939	Me	OEt	2,4-Cl ₂ -Ph
	940	Me	OCH(Et)CH ₂ OMe	2,4-Cl ₂ -Ph
	941	Me	OCH ₂ Ph	2,4-Cl ₂ -Ph
	942	Me	O-3-pentyl	2,4-Cl ₂ -Ph
	943	Me	SEt	2,4-Cl ₂ -Ph

	944	Me	S(O)Et	2,4-Cl ₂ -Ph
	945	Me	SO ₂ Et	2,4-Cl ₂ -Ph
	946	Me	Ph	2,4-Cl ₂ -Ph
	947	Me	2-CF ₃ -Ph	2,4-Cl ₂ -Ph
5	948	Me	2-Ph-Ph	2,4-Cl ₂ -Ph
	949	Me	3-pentyl	2,4-Cl ₂ -Ph
	950	Me	cyclobutyl	2,4-Cl ₂ -Ph
	951	Me	3-pyridyl	2,4-Cl ₂ -Ph
	952	Me	CH(Et)CH ₂ CONMe ₂	2,4-Cl ₂ -Ph
10	953	Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4-Cl ₂ -Ph
	954	Me	NHCH(CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph
	955	Me	NHCHPr ₂	2,4,6-Me ₃ -Ph
	956	Me	NEtBu	2,4,6-Me ₃ -Ph
	957	Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4,6-Me ₃ -Ph
15	958	Me	N(CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -Ph
	959	Me	NH-3-heptyl	2,4,6-Me ₃ -Ph
	960	Me	NHCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	961	Me	NEt ₂	2,4,6-Me ₃ -Ph
	962	Me	NHCH(CH ₂ OEt) ₂	2,4,6-Me ₃ -Ph
20	963	Me	NH-3-pentyl	2,4,6-Me ₃ -Ph
	964	Me	NMePh	2,4,6-Me ₃ -Ph
	965	Me	NPr ₂	2,4,6-Me ₃ -Ph
	966	Me	NH-3-hexyl	2,4,6-Me ₃ -Ph
	967	Me	morpholino	2,4,6-Me ₃ -Ph
25	968	Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4,6-Me ₃ -Ph
	969	Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4,6-Me ₃ -Ph
	970	Me	NH-4-tetrahydropyranyl	2,4,6-Me ₃ -Ph
	971	Me	NH-cyclopentyl	2,4,6-Me ₃ -Ph
	972	Me	OEt	2,4,6-Me ₃ -Ph
30	973	Me	OCH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	974	Me	OCH ₂ Ph	2,4,6-Me ₃ -Ph
	975	Me	O-3-pentyl	2,4,6-Me ₃ -Ph
	976	Me	SEt	2,4,6-Me ₃ -Ph
	977	Me	S(O)Et	2,4,6-Me ₃ -Ph
35	978	Me	SO ₂ Et	2,4,6-Me ₃ -Ph
	979	Me	CH(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph

	980	Me	C(Et)(CO ₂ Et) ₂	2,4,6-Me ₃ -Ph
	981	Me	CH(Et)CH ₂ OH	2,4,6-Me ₃ -Ph
	982	Me	CH(Et)CH ₂ OMe	2,4,6-Me ₃ -Ph
	983	Me	CONMe ₂	2,4,6-Me ₃ -Ph
5	984	Me	COCH ₃	2,4,6-Me ₃ -Ph
	985	Me	CH(OH)CH ₃	2,4,6-Me ₃ -Ph
	986	Me	C(OH)Ph-3-pyridyl	2,4,6-Me ₃ -Ph
	987	Me	Ph	2,4,6-Me ₃ -Ph
	988	Me	2-Ph-Ph	2,4,6-Me ₃ -Ph
10	989	Me	3-pentyl	2,4,6-Me ₃ -Ph
	990	Me	cyclobutyl	2,4,6-Me ₃ -Ph
	991	Me	3-pyridyl	2,4,6-Me ₃ -Ph
	992	Me	CH(Et)CH ₂ CONMe ₂	2,4,6-Me ₃ -Ph
	993	Me	CH(Et)CH ₂ CH ₂ NMe ₂	2,4,6-Me ₃ -Ph
15	994	Me	NHCH(CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	995	Me	N(CH ₂ CH ₂ OMe) ₂	2,4-Me ₂ -Ph
	996	Me	NHCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	997	Me	NH-3-pentyl	2,4-Me ₂ -Ph
	998	Me	NEt ₂	2,4-Me ₂ -Ph
20	999	Me	N(CH ₂ CN) ₂	2,4-Me ₂ -Ph
	1000	Me	NHCH(Me)CH ₂ OMe	2,4-Me ₂ -Ph
	1001	Me	OCH(Et)CH ₂ OMe	2,4-Me ₂ -Ph
	1002	Me	NPr-c-C ₃ H ₅	2,4-Me ₂ -Ph
	1003	Me	NHCH(Me)CH ₂ NMe ₂	2,4-Me ₂ -Ph
25	1004	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	1005	Me	N(Pr)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	1006	Me	N(Bu)CH ₂ CH ₂ CN	2,4-Me ₂ -Ph
	1007	Me	NHCHPr ₂	2,4-Me ₂ -Ph
	1008	Me	NEtBu	2,4-Me ₂ -Ph
30	1009	Me	NPr(CH ₂ -c-C ₃ H ₅)	2,4-Me ₂ -Ph
	1010	Me	NH-3-heptyl	2,4-Me ₂ -Ph
	1011	Me	NEt ₂	2,4-Me ₂ -Ph
	1012	Me	NHCH(CH ₂ OEt) ₂	2,4-Me ₂ -Ph
	1013	Me	NH-3-pentyl	2,4-Me ₂ -Ph
35	1014	Me	NMePh	2,4-Me ₂ -Ph
	1015	Me	NPr ₂	2,4-Me ₂ -Ph

	1016	Me	NH-3-hexyl	2,4-Me ₂ -Ph
	1017	Me	morpholino	2,4-Me ₂ -Ph
	1018	Me	N(CH ₂ Ph)CH ₂ CH ₂ OMe	2,4-Me ₂ -Ph
	1019	Me	NHCH(CH ₂ Ph)CH ₂ OMe	2,4-Me ₂ -Ph
5	1020	Me	NH-4-tetrahydropyranyl	2,4-Me ₂ -Ph
	1021	Me	NH-cyclopentyl	2,4-Me ₂ -Ph
	1022	Me	NHCH(CH ₂ OMe) ₂	2-Me-4-MeO-Ph
	1023	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-MeO-Ph
	1024	Me	NHCH(Et)CH ₂ OMe	2-Me-4-MeO-Ph
10	1025	Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-MeO-Ph
	1026	Me	OCH(Et)CH ₂ OMe	2-Me-4-MeO-Ph
	1027	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-MeO-Ph
	1028	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-MeO-Ph
	1029	Me	NHCH(Et)CH ₂ OMe	2-Br-4-MeO-Ph
15	1030	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-MeO-Ph
	1031	Me	OCH(Et)CH ₂ OMe	2-Br-4-MeO-Ph
	1032	Me	NHCH(CH ₂ OMe) ₂	2-Me-4-NMe ₂ -Ph
	1033	Me	N(CH ₂ CH ₂ OMe) ₂	2-Me-4-NMe ₂ -Ph
	1034	Me	NHCH(Et)CH ₂ OMe	2-Me-4-NMe ₂ -Ph
20	1035	Me	N(Pr)CH ₂ CH ₂ CN	2-Me-4-NMe ₂ -Ph
	1036	Me	OCH(Et)CH ₂ OMe	2-Me-4-NMe ₂ -Ph
	1037	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-NMe ₂ -Ph
	1038	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-NMe ₂ -Ph
	1039	Me	NHCH(Et)CH ₂ OMe	2-Br-4-NMe ₂ -Ph
25	1040	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-NMe ₂ -Ph
	1041	Me	OCH(Et)CH ₂ OMe	2-Br-4-NMe ₂ -Ph
	1042	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-i-Pr-Ph
	1043	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-i-Pr-Ph
	1044	Me	NHCH(Et)CH ₂ OMe	2-Br-4-i-Pr-Ph
30	1045	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-i-Pr-Ph
	1046	Me	OCH(Et)CH ₂ OMe	2-Br-4-i-Pr-Ph
	1047	Me	NHCH(CH ₂ OMe) ₂	2-Br-4-Me-Ph
	1048	Me	N(CH ₂ CH ₂ OMe) ₂	2-Br-4-Me-Ph
	1049	Me	NHCH(Et)CH ₂ OMe	2-Br-4-Me-Ph
35	1050	Me	N(Pr)CH ₂ CH ₂ CN	2-Br-4-Me-Ph
	1051	Me	OCH(Et)CH ₂ OMe	2-Br-4-Me-Ph

	1052	Me	NHCH (CH ₂ OMe) ₂	2-Me-4-Br-Ph
	1053	Me	N (CH ₂ CH ₂ OMe) ₂	2-Me-4-Br-Ph
	1054	Me	NHCH (Et) CH ₂ OMe	2-Me-4-Br-Ph
	1055	Me	N (Pr) CH ₂ CH ₂ CN	2-Me-4-Br-Ph
5	1056	Me	OCH (Et) CH ₂ OMe	2-Me-4-Br-Ph
	1057	Me	NHCH (CH ₂ OMe) ₂	2-Cl-4,6-Me ₂ -Ph
	1058	Me	N (CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-Me ₂ -Ph
	1059	Me	NHCH (CH ₂ OMe) ₂	4-Br-2,6-(Me) ₂ -Ph
	1060	Me	N (CH ₂ CH ₂ OMe) ₂	4-Br-2,6-(Me) ₂ -Ph
10	1061	Me	NHCH (CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	1062	Me	N (CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	1063	Me	NHCH (CH ₂ OMe) ₂	2-Br-4-CF ₃ -Ph
	1064	Me	N (CH ₂ CH ₂ OMe) ₂	2-Br-4-CF ₃ -Ph
	1065	Me	NHCH (CH ₂ OMe) ₂	2-Br-4,6-(MeO) ₂ -Ph
15	1066	Me	N (CH ₂ CH ₂ OMe) ₂	2-Br-4,6-(MeO) ₂ -Ph
	1067	Me	NHCH (CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ -Ph
	1068	Me	N (CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ -Ph
	1069	Me	NHCH (CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
	1070	Me	N (CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
20	1071	Me	NHCH (CH ₂ OMe) ₂	4-(COMe)-2-Br-Ph
	1072	Me	N (CH ₂ CH ₂ OMe) ₂	4-(COMe)-2-Br-Ph
	1073	Me	NHCH (CH ₂ OMe) ₂	2,4,6-Me ₃ -pyrid-3-yl
	1074	Me	N (CH ₂ CH ₂ OMe) ₂	2,4,6-Me ₃ -pyrid-3-yl
	1075	Me	NHCH (CH ₂ OMe) ₂	2,4-(Br) ₂ -Ph
25	1076	Me	N (CH ₂ CH ₂ OMe) ₂	2,4-(Br) ₂ -Ph
	1077	Me	NHCH (CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	1078	Me	N (CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SMe-Ph
	1079	Me	NHCH (CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
	1080	Me	N (CH ₂ CH ₂ OMe) ₂	4-i-Pr-2-SO ₂ Me-Ph
30	1081	Me	NHCH (CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
	1082	Me	N (CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SMe-Ph
	1083	Me	NHCH (CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SO ₂ Me-Ph
	1084	Me	N (CH ₂ CH ₂ OMe) ₂	2,6-(Me) ₂ -4-SO ₂ Me-Ph
	1085	Me	NHCH (CH ₂ OMe) ₂	2-I-4-i-Pr-Ph
35	1086	Me	N (CH ₂ CH ₂ OMe) ₂	2-I-4-i-Pr-Ph
	1087	Me	NHCH (CH ₂ OMe) ₂	2-Br-4-N(Me) ₂ -6-MeO-Ph

	1088	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-N(Me) ₂ -6-MeO-Ph
	1089	Me	NEt ₂	2-Br-4-MeO-Ph
	1090	Me	NH-3-pentyl	2-Br-4-MeO-Ph
	1091	Me	NHCH(CH ₂ OMe) ₂	2-CN-4-Me-Ph
5	1092	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4,6-Me ₃ -Ph
	1093	Me	NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Me-4-Br-Ph
	1094	Me	NHCH(CH ₂ OMe) ₂	2,5-Me ₂ -4-MeO-Ph
	1095	Me	$N(CH_2CH_2OMe)_2$	2,5-Me ₂ -4-MeO-Ph
	1096	Me	NH-3-pentyl	2,5-Me ₂ -4-MeO-Ph
10	1097	Me	NEt ₂	2,5-Me ₂ -4-MeO-Ph
	1098	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MePh
	1099	Me	NCH(Et)CH ₂ OMe	2-Cl-4-MePh
	1100	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4-MePh
	1101	Me	(S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Cl-4-MePh
15	1102	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,5-Me ₂ -4-MeOPh
	1103	Me	NEt ₂	2-Me-4-MeOPh
	1104	Me	OEt	2-Me-4-MeOPh
	1105	Me	(S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe	2-Me-4-MeOPh
	1106	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2-Me-4-MeOPh
20	1107	Me	NHCH(CH ₂ CH ₂ OEt) ₂	2-Me-4-MeOPh
	1108	Me	N(c-C ₃ H ₅)CH ₂ CH ₂ CN	2,4-Cl ₂ -Ph
	1109	Me	NEt ₂	2-Me-4-ClPh
	1110	Me	NH-3-pentyl	2-Me-4-ClPh
	1111	Me	$N(CH_2CH_2OMe)_2$	2-Me-4-ClPh
25	1112	Me	NHCH(CH ₂ OMe) ₂	2-Me-4-ClPh
	1113	Me	NEt ₂	2-Me-4-ClPh
	1114	Me	NEt ₂	2-Cl-4-MePh
	1115	Me	NH-3-pentyl	2-Cl-4-MePh
	1116	Me	NHCH(CH ₂ OMe) ₂	2-Cl-4-MeOPh
30	1117	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4-MeOPh
	1118	Me	NHCH(Et)CH ₂ OMe	2-Cl-4-MeOPh
	1119	Me	N(c-Pr)CH ₂ CH ₂ CN	2-Cl-4-MeOPh
	1120	Me	NEt ₂	2-Cl-4-MeOPh
	1121	Me	NH-3-pentyl	2-Cl-4-MeOPh
35	1123	Me	NHCH(Et)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh
	1124	Me	NHCH(Me)CH ₂ CH ₂ OMe	2-Cl-4-MeOPh

	1125	Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Br-4-MeOPh
	1126	Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Br-4-MeOPh
	1127	Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	1128	Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Me-4-MeOPh
5	1129	Me	NHCH (CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph
	1130	Me	N (CH ₂ CH ₂ OMe) ₂	2-Cl-4,5-(MeO) ₂ Ph
	1131	Me	NHCH (Et) CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	1132	Me	N (c-Pr) CH ₂ CH ₂ CN	2-Cl-4,5-(MeO) ₂ Ph
	1133	Me	NEt ₂	2-Cl-4,5-(MeO) ₂ Ph
10	1134	Me	NH-3-pentyl	2-Cl-4,5-(MeO) ₂ Ph
	1135	Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	1136	Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Cl-4,5-(MeO) ₂ Ph
	1137	Me	NHCH (CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph
	1138	Me	N (CH ₂ CH ₂ OMe) ₂	2-Br-4,5-(MeO) ₂ Ph
15	1139	Me	NHCH (Et) CH ₂ OMe	2-Br-4,5-(MeO) ₂ Ph
	1140	Me	N (c-Pr) CH ₂ CH ₂ CN	2-Br-4,5-(MeO) ₂ Ph
	1141	Me	NEt ₂	2-Br-4,5-(MeO) ₂ Ph
	1142	Me	NH-3-pentyl	2-Br-4,5-(MeO) ₂ Ph
	1143	Me	NHCH (CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
20	1144	Me	N (CH ₂ CH ₂ OMe) ₂	2-Cl-4,6-(MeO) ₂ Ph
	1145	Me	NEt ₂	2-Cl-4,6-(MeO) ₂ Ph
	1146	Me	NH-3-pentyl	2-Cl-4,6-(MeO) ₂ Ph
	1147	Me	NHCH (CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
	1148	Me	N (CH ₂ CH ₂ OMe) ₂	2-Me-4,6-(MeO) ₂ Ph
25	1149	Me	NHCH (Et) CH ₂ OMe	2-Me-4,6-(MeO) ₂ Ph
	1150	Me	NEt ₂	2-Me-4,6-(MeO) ₂ Ph
	1151	Me	NH-3-pentyl	2-Me-4,6-(MeO) ₂ Ph
	1152	Me	NHCH (Et) CH ₂ CH ₂ OMe	2-Me-4-MeOPh
	1153	Me	NHCH (Me) CH ₂ CH ₂ OMe	2-Me-4-MeOPh
30	1154	Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-MePh
	1155	Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	1156	Me	NHCH (Et) CH ₂ OMe	2-MeO-4-MePh
	1157	Me	N (c-Pr) CH ₂ CH ₂ CN	2-MeO-4-MePh
	1158	Me	NEt ₂	2-MeO-4-MePh
35	1159	Me	NH-3-pentyl	2-MeO-4-MePh
	1160	Me	NHCH (Et) CH ₂ CH ₂ OMe	2-MeO-4-MePh

	1161	Me	NHCH (Me) CH ₂ CH ₂ OMe	2-MeO-4-MePh
	1162	Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-MePh
	1163	Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-MePh
	1164	Me	NHCH (Et) CH ₂ OMe	2-MeO-4-MePh
5	1165	Me	N (c-Pr) CH ₂ CH ₂ CN	2-MeO-4-MePh
	1166	Me	NEt ₂	2-MeO-4-MePh
	1167	Me	NH-3-pentyl	2-MeO-4-MePh
	1168	Me	NHCH (CH ₂ OMe) ₂	2-MeO-4-ClPh
	1169	Me	N (CH ₂ CH ₂ OMe) ₂	2-MeO-4-ClPh
10	1170	Me	NHCH (Et) CH ₂ OMe	2-MeO-4-ClPh
	1171	Me	NEt ₂	2-MeO-4-ClPh
	1172	Me	NH-3-pentyl	2-MeO-4-ClPh

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Utility

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CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

The following is a description of the
25 isolation of cell membranes containing cloned human CRF-
R1 receptors for use in the standard binding assay as
well as a description of the assay itself.

Messenger RNA was isolated from human hippocampus.
The mRNA was reverse transcribed using oligo (dt) 12-18
30 and the coding region was amplified by PCR from start to
stop codons. The resulting PCR fragment was cloned into
the EcoRV site of pGEMV, from whence the insert was
reclaimed using XhoI + XbaI and cloned into the XhoI +
XbaI sites of vector pm3ar (which contains a CMV
35 promoter, the SV40 't' splice and early poly A signals,
an Epstein-Barr viral origin of replication, and a

hygromycin selectable marker). The resulting expression vector, called phchCRFR was transfected in 293EBNA cells and cells retaining the episome were selected in the presence of 400 μ M hygromycin. Cells surviving 4 weeks of selection in hygromycin were pooled, adapted to growth in suspension and used to generate membranes for the binding assay described below. Individual aliquots containing approximately 1×10^8 of the suspended cells were then centrifuged to form a pellet and frozen.

For the binding assay a frozen pellet described above containing 293EBNA cells transfected with hCRFR1 receptors is homogenized in 10 ml of ice cold tissue buffer (50 mM HEPES buffer pH 7.0, containing 10 mM $MgCl_2$, 2 mM EGTA, 1 μ g/ml aprotinin, 1 μ g/ml leupeptin and 1 μ g/ml pepstatin). The homogenate is centrifuged at 40,000 x g for 12 min and the resulting pellet rehomogenized in 10 ml of tissue buffer. After another centrifugation at 40,000 x g for 12 min, the pellet is resuspended to a protein concentration of 360 μ g/ml to be used in the assay.

Binding assays are performed in 96 well plates; each well having a 300 μ l capacity. To each well is added 50 μ l of test drug dilutions (final concentration of drugs range from 10^{-10} - 10^{-5} M), 100 μ l of ^{125}I -ovine-CRF (^{125}I -o-CRF) (final concentration 150 pM) and 150 μ l of the cell homogenate described above. Plates are then allowed to incubate at room temperature for 2 hours before filtering the incubate over GF/F filters (presoaked with 0.3% polyethyleneimine) using an appropriate cell harvester. Filters are rinsed 2 times with ice cold assay buffer before removing individual filters and assessing them for radioactivity on a gamma counter.

Curves of the inhibition of ^{125}I -o-CRF binding to cell membranes at various dilutions of test drug are analyzed by the iterative curve fitting program LIGAND

[P.J. Munson and D. Rodbard, *Anal. Biochem.* 107:220 (1980), which provides K_i values for inhibition which are then used to assess biological activity.

5 A compound is considered to be active if it has a K_i value of less than about 10000 nM for the inhibition of CRF.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

10 Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. *Synapse* 1:572 (1987). Briefly, assays are carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37°
15 C), 10 mM MgCl₂, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10⁻⁹ to 10⁻⁶m) and 0.8
20 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/³²P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In
25 order to monitor the recovery of cAMP, 1 µl of [³H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [³²P]cAMP from [³²P]ATP is performed by sequential elution over Dowex and alumina columns.

30

In vivo Biological Assay

The *in vivo* activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within
35 the art. Illustrative of these tests include the

Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (1990).
5 Compounds may be tested in any species of rodent or small mammal.

Compounds of this invention have utility in the
10 treatment of imbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

Compounds of this invention can be administered
15 to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as
20 individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard
25 pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight,
30 and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a
35 dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10

mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for

parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances.

- 5 Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain
10 preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

- 15 Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

- 20 A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

25

Soft Gelatin Capsules

- A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive
30 displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

- 35 A large number of tablets are prepared by conventional procedures so that the dosage unit was

100 mg active ingredient, 0.2 mg of colloidal silicon
dioxide, 5 mg of magnesium stearate, 275 mg of
microcrystalline cellulose, 11 mg of starch, and 98.8
mg lactose. Appropriate coatings may be applied to
5 increase palatability or delayed adsorption.

The compounds of this invention may also be used
as reagents or standards in the biochemical study of
neurological function, dysfunction, and disease.

10

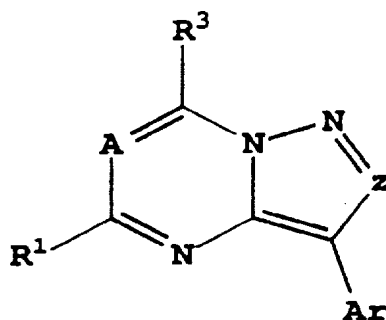
Although the present invention has been
described and exemplified in terms of certain
preferred embodiments, other embodiments will be
apparent to those skilled in the art. The invention
15 is, therefore, not limited to the particular
embodiments described and exemplified, but is capable
of modification or variation without departing from
the spirit of the invention, the full scope of which
is delineated by the appended claims.

20

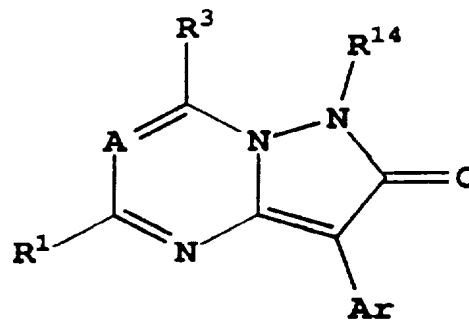
CLAIMS

WHAT IS CLAIMED IS:

- 5 1. A method of treating affective disorder,
anxiety, depression, headache, irritable bowel
syndrome, post-traumatic stress disorder,
supranuclear palsy, immune suppression, Alzheimer's
disease, gastrointestinal diseases, anorexia nervosa
10 or other feeding disorder, drug addiction, drug or
alcohol withdrawal symptoms, inflammatory diseases,
cardiovascular or heart-related diseases, fertility
problems, human immunodeficiency virus infections,
hemorrhagic stress, obesity, infertility, head and
15 spinal cord traumas, epilepsy, stroke, ulcers,
amyotrophic lateral sclerosis, hypoglycemia or a
disorder the treatment of which can be effected or
facilitated by antagonizing CRF, including but not
limited to disorders induced or facilitated by CRF,
20 in mammals comprising administering to the mammal a
therapeutically effective amount of a compound of
Formulae (1) or (2):



(1)



(2)

25

and isomers thereof, stereoisomeric forms thereof, or
mixtures of stereoisomeric forms thereof, and

pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

A is N or CR;

5

Z is N or CR²;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R⁴ groups and each Ar is attached to an unsaturated carbon atom;

15

R is independently selected at each occurrence from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl, halo, CN, C₁-C₄ haloalkyl;

20

R¹ is independently selected at each occurrence from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, CN, C₁-C₄ haloalkyl, C₁-C₁₂ hydroxyalkyl, C₂-C₁₂ alkoxyalkyl, C₂-C₁₀ cyanoalkyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl, NR⁹R¹⁰, C₁-C₄ alkyl-NR⁹R¹⁰, NR⁹COR¹⁰, OR¹¹, SH or S(O)_nR¹²;

25

R² is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl, C₁-C₄ hydroxyalkyl, halo, CN, -NR⁶R⁷, NR⁹COR¹⁰, -NR⁶S(O)_nR⁷, S(O)_nNR⁶R⁷, C₁-C₄ haloalkyl, -OR⁷, SH or -S(O)_nR¹²;

30

35 R³ is selected from:

- H, OR⁷, SH, S(O)_nR¹³, COR⁷, CO₂R⁷,
 OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂, NR⁸CONR⁶R⁷,
 NR⁸CO₂R¹³, NR⁶R⁷, NR^{6a}R^{7a}, N(OR⁷)R⁶,
 CONR⁶R⁷, aryl, heteroaryl and heterocyclyl,
 5 or
 -C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, C₄-
 C₁₂ cycloalkylalkyl or C₆-C₁₀
 cycloalkenylalkyl, each optionally
 10 substituted with 1 to 3 substituents
 independently selected at each occurrence
 from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
 C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³,
 15 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl and heterocyclyl;
- R⁴ is independently selected at each occurrence from:
 20 C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, NO₂,
 halo, CN, C₁-C₄ haloalkyl, NR⁶R⁷, NR⁸COR⁷,
 NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO(NOR⁹)R⁷, CO₂R⁷,
 or S(O)_nR⁷, where each such C₁-C₁₀ alkyl, C₂-
 25 C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl
 and C₄-C₁₂ cycloalkylalkyl are optionally
 substituted with 1 to 3 substituents
 independently selected at each occurrence from
 C₁-C₄ alkyl, NO₂, halo, CN, NR⁶R⁷, NR⁸COR⁷,
 30 NR⁸CO₂R⁷, COR⁷ OR⁷, CONR⁶R⁷, CO₂R⁷, CO(NOR⁹)R⁷,
 or S(O)_nR⁷;

- R⁶ and R⁷, R^{6a} and R^{7a} are independently selected at
 each occurrence from:
 35 -H,

- 5 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 10 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 15 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);

- alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently
 piperidine, pyrrolidine, piperazine, N-
 20 methylpiperazine, morpholine or thiomorpholine, each
 optionally substituted with 1-3 C₁-C₄ alkyl groups;

- R⁸ is independently selected at each occurrence from
 H or C₁-C₄ alkyl;

- 25 R⁹ and R¹⁰ are independently selected at each
 occurrence from H, C₁-C₄ alkyl, or C₃-C₆
 cycloalkyl;

- 30 R¹¹ is selected from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl,
 or C₃-C₆ cycloalkyl;

R¹² is C₁-C₄ alkyl or C₁-C₄ haloalkyl;

- 35 R¹³ is selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl,
 C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-

C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heteroaryl or heteroaryl(C₁-C₄ alkyl)-;

- 5 R¹⁴ is selected from C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₃-C₈ cycloalkyl, or C₄-C₁₂ cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, and C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl and C₁-C₆ alkylsulfonyl;
- 10
- 15 R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₄-C₁₆ cycloalkylalkyl, except that for S(O)_nR¹⁵, R¹⁵ cannot be H;
- 20 aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;
- 25
- heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranal, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5
- 30
- 35

substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, -COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
5 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

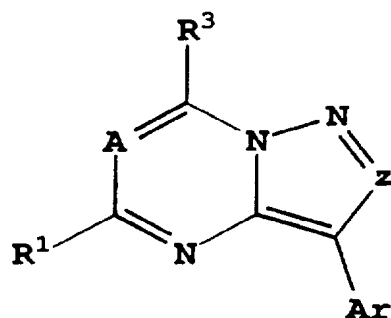
heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5
10 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁵R¹⁶, and
15 CONR¹⁶R¹⁵;

n is independently at each occurrence 0, 1 or 2,

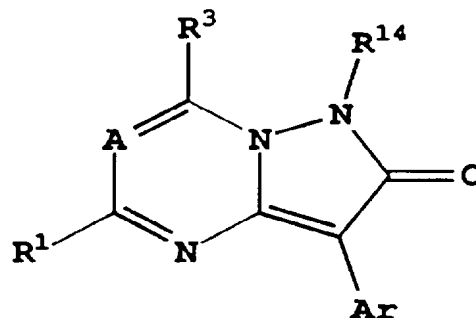
2. A method of claim 1 wherein, in the compound of
20 Formulae (1) or (2), Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R⁴ substituents.

3. A method of claim 1 wherein, in the compound of
25 Formulae (1) or (2), A is N, Z is CR², Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R¹ and R² are CH₃, and R³ is NR^{6a}R^{7a}.

4. A compound of Formulae (1) or (2):
30



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and
 5 pharmaceutically acceptable salt or pro-drug forms thereof wherein:

A is N or CR;

10 Z is N or CR²;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-
 15 dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R⁴ groups and each Ar is attached to an unsaturated carbon atom;

20

R is independently selected at each occurrence from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl, halo, CN, C₁-C₄ haloalkyl;

25

R¹ is independently selected at each occurrence from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,

halo, CN, C₁-C₄ haloalkyl, C₁-C₁₂ hydroxyalkyl,
 C₂-C₁₂ alkoxyalkyl, C₂-C₁₀ cyanoalkyl, C₃-C₆
 cycloalkyl, C₄-C₁₀ cycloalkylalkyl, NR⁹R¹⁰, C₁-
 C₄ alkyl-NR⁹R¹⁰, NR⁹COR¹⁰, OR¹¹, SH or S(O)_nR¹²;

5

R² is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl,
 C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀
 cycloalkylalkyl, C₁-C₄ hydroxyalkyl, halo, CN,
 -NR⁶R⁷, NR⁹COR¹⁰, -NR⁶S(O)_nR⁷, S(O)_nNR⁶R⁷, C₁-
 C₄ haloalkyl, -OR⁷, SH or -S(O)_nR¹²;

10

R³ is selected from:

-H, OR⁷, SH, S(O)_nR¹³, COR⁷, CO₂R⁷,
 OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂, NR⁸CONR⁶R⁷,
 NR⁸CO₂R¹³, NR⁶R⁷, NR^{6a}R^{7a}, N(OR⁷)R⁶,
 CONR⁶R⁷, aryl, heteroaryl and
 heterocyclyl, or

15

-C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, C₄-
 C₁₂ cycloalkylalkyl or C₆-C₁₀
 cycloalkenylalkyl, each optionally
 substituted with 1 to 3 substituents
 independently selected at each occurrence
 from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
 C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³,
 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl and heterocyclyl;

20

25

30

R⁴ is independently selected at each occurrence from:

C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, NO₂,
 halo, CN, C₁-C₄ haloalkyl, NR⁶R⁷, NR⁸COR⁷,
 NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO(NOR⁹)R⁷, CO₂R⁷,

35

- or $S(O)_nR^7$, where each such C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl are optionally substituted with 1 to 3 substituents
- 5 independently selected at each occurrence from C₁-C₄ alkyl, NO₂, halo, CN, NR⁶R⁷, NR⁸COR⁷, NR⁸CO₂R⁷, COR⁷ OR⁷, CONR⁶R⁷, CO₂R⁷, CO(NOR⁹)R⁷, or $S(O)_nR^7$;
- 10 R⁶ and R⁷, R^{6a} and R^{7a} are independently selected at each occurrence from:
- H,
- C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
- 15 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, $S(O)_nR^{13}$, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
- 20 heteroaryl or heterocyclyl,
- aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl),
- alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently
- 30 piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C₁-C₄ alkyl groups;
- R⁸ is independently selected at each occurrence from
- 35 H or C₁-C₄ alkyl;

- R⁹ and R¹⁰ are independently selected at each occurrence from H, C₁-C₄ alkyl, or C₃-C₆ cycloalkyl;
- 5 R¹¹ is selected from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;
- R¹² is C₁-C₄ alkyl or C₁-C₄ haloalkyl;
- 10 R¹³ is selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heteroaryl or heteroaryl(C₁-C₄ alkyl)-;
- 15 R¹⁴ is selected from C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₃-C₈ cycloalkyl, or C₄-C₁₂ cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, and C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl and C₁-C₆ alkylsulfonyl;
- 20 R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₄-C₁₆ cycloalkylalkyl, except that for S(O)_nR¹⁵, R¹⁵ cannot be H;
- 30 aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano,
- 35

OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵,
 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵,
 NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

5 heteroaryl is pyridyl, pyrimidinyl, triazinyl,
 furanyl, pyranyl, quinolinyl, isoquinolinyl,
 thienyl, imidazolyl, thiazolyl, indolyl,
 pyrrolyl, oxazolyl, benzofuranyl, benzothienyl,
 benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-
 10 dihydrobenzothienyl or 2,3-dihydrobenzofuranyl,
 each being optionally substituted with 1 to 5
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 15 S(O)_nR¹⁵, -COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and
 CONR¹⁶R¹⁵;

heterocyclyl is saturated or partially saturated
 20 heteroaryl, optionally substituted with 1 to 5
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
 25 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁵R¹⁶, and
 CONR¹⁶R¹⁵;

n is independently at each occurrence 0, 1 or 2,

30 with the provisos that:

- (1) when A is N, Z is CR², R² is H, R³ is -OR⁷ or
 -OCOR¹³, and R⁷ is H, then R¹ is not H, OH or
 SH;

35

- 5 (2) when A is N, Z is CR², R¹ is CH₃ or C₂H₅, R² is H, and R³ is OH, H, CH₃, C₂H₅, C₆H₅, n-C₃H₇, i-C₃H₇, SH, SCH₃, NHC₄H₉, or N(C₂H₅)₂, then Ar is not phenyl or m-CH₃-phenyl;
- (3) when A is N, Z is CR², R² is H, and Ar is pyridyl, pyrimidinyl or pyrazinyl, and R³ is NR^{6a}R^{7a}, then R^{6a} and R^{7a} are not H or alkyl;
- 10 (4) when A is N, Z is CR², and R² is SO₂NR⁶R⁷, then R³ is not OH or SH;
- (5) when A is CR and Z is CR², then R² is not-NR⁶SO₂R⁷ or -SO₂NR⁶R⁷;
- 15 (6) when A is N, Z is CR² and R² is -NR⁶SO₂R⁷ or -SO₂NR⁶R⁷, then R³ is not OH or SH;
- (7) when A is N, Z is CR², R¹ is methyl or ethyl, R² is H, and R³ is H, OH, CH₃, C₂H₅, C₆H₅, n-C₃H₇, iso-C₃H₇, SH, SCH₃, NH(n-C₄H₉), or N(C₂H₅)₂, then Ar is not unsubstituted phenyl or m-methylphenyl;
- 20 (8) when A is CR, Z is CR², R² is H, phenyl or alkyl, R³ is NR⁸COR⁷ and Ar is phenyl or phenyl substituted with phenylthio, then R⁷ is not aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl);
- 25 (9) when A is CR, Z is CR², R² is H or alkyl, Ar is phenyl, and R³ is SR¹³ or NR^{6a}R^{7a}, then R¹³ is not aryl or heteroaryl and R^{6a} and R^{7a} are not H or aryl; or
- 30 (10) when A is CH, Z is CR², R¹ is OR¹¹, R² is H, R³ is OR⁷, and R⁷ and R¹¹ are both H, then Ar is not
- 35

phenyl, p-Br-phenyl, p-Cl-phenyl, p-NHCOCH₃-phenyl, p-CH₃-phenyl, pyridyl or naphthyl;

5 (11) when A is CH, Z is CR², R² is H, Ar is unsubstituted phenyl, and R³ is CH₃, C₂H₅, CF₃ or C₆H₄F, then R₁ is not CF₃ or C₂F₅;

(12) when A is CR, R is H, Z is CR², R² is OH, and R¹ and R³ are H, then Ar is not phenyl;

10

(13) when A is CR, R is H, Z is CR², R² is OH or NH₂, R¹ and R³ are CH₃, then Ar is not 4-phenyl-3-cyano-2-aminopyrid-2-yl.

15 5. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof with the additional provisos that: (1) when A is N, R¹ is H,
20 C₁-C₄ alkyl, halo, CN, C₁-C₁₂ hydroxyalkyl, C₁-C₄ alkoxyalkyl or SO₂(C₁-C₄ alkyl), R³ is NR^{6a}R^{7a} and R^{6a} is unsubstituted C₁-C₄ alkyl, then R^{7a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl,
25 benzothiazolyl, indolyl or C₃-C₆ cycloalkyl; and (2) A is N, R¹ is H, C₁-C₄ alkyl, halo, CN, C₁-C₁₂ hydroxyalkyl, C₁-C₄ alkoxyalkyl or SO₂(C₁-C₄ alkyl), R³ is NR^{6a}R^{7a} and R^{7a} is unsubstituted C₁-C₄ alkyl, then R^{6a} is not phenyl, naphthyl, thienyl,
30 benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or C₃-C₆ cycloalkyl.

6. A compound of claim 4 and isomers thereof,
35 stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically

acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R⁴ substituents.

5 7. A compound of claim 6 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N, Z is CR², Ar is 2,4-dichlorophenyl, 2,4-
10 dimethylphenyl or 2,4,6-trimethylphenyl, R¹ and R² are CH₃, and R³ is NR^{6a}R^{7a}.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutical-
15 ly effective amount of a compound of claim 4.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutical-
20 ly effective amount of a compound of claim 6.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutical-
ly effective amount of a compound of claim 7.

25 11. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N.

30 12. A compound of Formula (2) of claim 11 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

35

13. A compound of claim 12 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is
5 phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.
14. A compound of claim 12 and isomers thereof, stereoisomeric forms thereof, or mixtures of
10 stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR⁶aR⁷a or OR⁷.
15. A compound of claim 12 and isomers thereof, stereoisomeric forms thereof, or mixtures of
15 stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents,
20 and R³ is NR⁶aR⁷a or OR⁷.
16. A compound of Formula (1) of claim 11 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically
25 acceptable salt or pro-drug forms thereof wherein Z is CR².
17. A compound of claim 16 and isomers thereof, stereoisomeric forms thereof, or mixtures of
30 stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.
- 35 18. A compound of claim 16 and isomers thereof, stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR^{6a}R^{7a} or OR⁷.

- 5 19. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

- 10 -H,
 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 15 or C₆-C₁₄ cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 20 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl)-, heteroaryl,
 25 heteroaryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-; and

R^{7a} is independently selected at each occurrence from:

- H,
 -C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 30 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each optionally substituted with 1 to 3
 35 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-

- C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
- 5 heteroaryl or heterocyclyl, -aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl);
- 10 alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C₁-C₄ alkyl groups.
- 15 20. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:
- 20 -C₁-C₄ alkyl or C₃-C₆ cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, -COR¹⁵,
- 25 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl, and -aryl or heteroaryl.
- 30 21. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:
- 35 -H,

- C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);
 R^{7a} is selected from:
 -C₁-C₄ alkyl and each such C₁-C₄ alkyl is
 substituted with 1-3 substituents
 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl.

22. A compound of claim 18 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein
 one of R^{6a} and R^{7a} is selected from:
 -C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
 optionally substituted with 1-3 substituents
 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,

CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl,

-aryl,

5 -heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
 alkyl.

- 10 23. A compound of claim 18 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein
 R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,
 15 each such C₁-C₁₀ alkyl optionally substituted with
 1 to 3 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³,
 COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 20 R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl.

24. A compound of claim 16 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 25 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein Ar is
 phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar
 is optionally substituted with 1 to 4 R⁴ substituents,
 and R³ is NR^{6a}R^{7a} or OR⁷.

- 30 25. A compound of claim 24 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein
 35 R^{6a} is independently selected from:

-H,

-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 5 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 10 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl)-, heteroaryl,
 15 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);

R^{7a} is independently selected at each occurrence from:

-H,
 -C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 20 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 25 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 30 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl),

35

alternatively, NR^6R^7 and $\text{NR}^{6a}\text{R}^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 $\text{C}_1\text{-C}_4$ alkyl groups.

5

26. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

10

$\text{-C}_1\text{-C}_4$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, halo, $\text{C}_1\text{-C}_4$ haloalkyl, cyano, OR^{15} , SH , $\text{S(O)}_n\text{R}^{13}$, -COR^{15} , CO_2R^{15} , OC(O)R^{13} , $\text{NR}^8\text{COR}^{15}$, $\text{N(COR}^{15})_2$, $\text{NR}^8\text{CONR}^{16}\text{R}^{15}$, $\text{NR}^8\text{CO}_2\text{R}^{13}$, $\text{NR}^{16}\text{R}^{15}$, $\text{CONR}^{16}\text{R}^{15}$, aryl, heteroaryl or heterocyclyl, and -aryl or heteroaryl.

15

20

27. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

25

$\text{-C}_1\text{-C}_4$ alkyl, each such $\text{C}_1\text{-C}_4$ alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, halo, $\text{C}_1\text{-C}_4$ haloalkyl, cyano, OR^{15} , SH , $\text{S(O)}_n\text{R}^{13}$, -COR^{15} , CO_2R^{15} , OC(O)R^{13} , $\text{NR}^8\text{COR}^{15}$, $\text{N(COR}^{15})_2$, $\text{NR}^8\text{CONR}^{16}\text{R}^{15}$, $\text{NR}^8\text{CO}_2\text{R}^{13}$, $\text{NR}^{16}\text{R}^{15}$, $\text{CONR}^{16}\text{R}^{15}$, aryl, heteroaryl or heterocyclyl.

30

28. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

5 R^{6a} is selected from:

- H,
- C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
10 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-
15 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl,
20 -aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl);

R^{7a} is:

- C₁-C₄ alkyl and each such C₁-C₄ alkyl is
25 substituted with 1-3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
30 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

29. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of
35 stereoisomeric forms thereof, and pharmaceutically

acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

- C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
optionally substituted with 1-3 substituents
independently selected at each occurrence from
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl,
-aryl,
-heteroaryl or
-heterocyclyl,
and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
alkyl.

30. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, each such C₁-C₁₀ alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

31. A compound of claim 16 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein
-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl,
and each Ar is optionally substituted with 1 to 4 R⁴ substituents,

-R³ is NR^{6a}R^{7a} or OR⁷ and
-R¹ and R² are independently selected from H, C₁-C₄
alkyl, C₃-C₆ cycloalkyl, C₄-C₁₀
cycloalkylalkyl.

5

32. A compound of claim 31 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein

10 R^{6a} is independently selected from:

-H,

-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
15 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-
20 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl,

25 -aryl, aryl(C₁-C₄ alkyl)-, heteroaryl,
heteroaryl(C₁-C₄ alkyl), heterocyclyl or
heterocyclyl(C₁-C₄ alkyl);R^{7a} is independently selected at each occurrence from:

-H,

30 -C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
35 optionally substituted with 1 to 3
substituents independently selected at each

- occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl, -aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl),
- alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C₁-C₄ alkyl groups.
33. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:
- C₁-C₄ alkyl or C₃-C₆ cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, -COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl, and -aryl or heteroaryl.
34. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

- C₁-C₄ alkyl, each such C₁-C₄ alkyl
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 5 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹³, -COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵,
 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵,
 CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.
- 10 35. A compound of claim 31 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein
 R^{6a} is selected from:
- 15 -H,
 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 20 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 25 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 30 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);
- R^{7a} is:
- C₁-C₄ alkyl and each such C₁-C₄ alkyl is
 substituted with 1-3 substituents
 35 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄

haloalkyl, cyano, OR¹⁵, SH, S(O)nR¹³, COR¹⁵,
 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl.

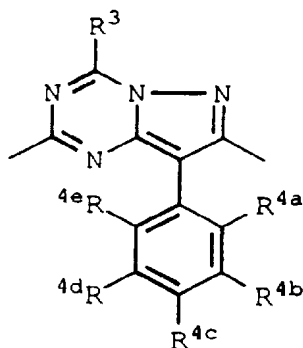
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36. A compound of claim 31 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein one of
 10 R^{6a} and R^{7a} is selected from:

-C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
 optionally substituted with 1-3 substituents
 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 15 haloalkyl, cyano, OR¹⁵, SH, S(O)nR¹³, COR¹⁵,
 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl,
 -aryl,
 20 -heteroaryl or
 -heterocyclyl,
 and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
 alkyl.

25 37. A compound of claim 31 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein
 R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,
 30 each such C₁-C₁₀ alkyl optionally substituted with
 1 to 3 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)nR¹³,
 COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 35 R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl.

38. A compound of claim 31 of Formula (50)



FORMULA (50)

5

10 and isomers thereof, stereoisomeric forms thereof, or
mixtures of stereoisomeric forms thereof, and
pharmaceutically acceptable salt or pro-drug forms
thereof, selected from the group consisting of:

15 a compound of Formula (50) wherein R³ is -NHCH(n-Pr)₂,
R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is
H;

20 a compound of Formula (50) wherein R³ is -N(Et)(n-Bu),
R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is
H;

25 a compound of Formula (50) wherein R³ is -(n-
Pr)(CH₂cPr), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is
H and R^{4e} is H;

a compound of Formula (50) wherein R³ is -N(CH₂CH₂OMe)₂,
R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is
H;

30 a compound of Formula (50) wherein R³ is -NHCH(Et)(n-
Bu), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and
R^{4e} is H;

- a compound of Formula (50) wherein R^3 is
-NHCH(Et)(CH₂OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,
 R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is -NHCH(CH₂OMe)₂,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is
H;
- 10 a compound of Formula (50) wherein R^3 is -N(Et)₂, R^{4a} is
Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is -NHCH(CH₂OEt)₂,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is
H;
- 15 a compound of Formula (50) wherein R^3 is -NHCH(Et)₂, R^{4a}
is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is -N(Me)(Ph), R^{4a}
is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is -N(n-Pr)₂, R^{4a}
is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is -NHCH(Et)(n-
Pr), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and
 R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is -NHCH(CH₂OMe)₂,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is
Me;
- a compound of Formula (50) wherein R^3 is -NHCH(CH₂OMe)₂,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is
H;
- 35
- 40 a compound of Formula (50) wherein R^3 is -N(CH₂CH₂OMe)₂,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is
H;
- a compound of Formula (50) wherein R^3 is
-NHCH(Et)(CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me,
 R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is -NHCH(Et)₂, R^{4a}
is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-OEt$, R^{4a} is Cl , R^{4b} is H , R^{4c} is Cl , R^{4d} is H and R^{4e} is H ;
- 5 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CN)_2$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 10 a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2OMe)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 15 a compound of Formula (50) wherein R^3 is $-OCH(Et)(CH_2OMe)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 20 a compound of Formula (50) wherein R^3 is $-N(n-Pr)(CH_2cPr)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2N(Me)_2)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 25 a compound of Formula (50) wherein R^3 is $-N(cPr)(CH_2CH_2CN)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 30 a compound of Formula (50) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 35 a compound of Formula (50) wherein R^3 is $-N(n-Bu)(CH_2CN)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 40 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is Me ;
- 45 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is Me ;

- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 5 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 20 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2CH_2OMe)(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 25 a compound of Formula (50) wherein R^3 is morpholino, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NH(c-Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is CN, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

- 5 a compound of Formula (50) wherein R^3 is $-NCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 20 a compound of Formula (50) wherein a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 45

- a compound of Formula (50) wherein R^3 is $-N(c\text{-Pr})(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $(S)\text{-NHCH}(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $\text{-NHCH}(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $\text{-NHCH}(\text{Et})_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $\text{-N}(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $\text{-NH}(CH_2OMe)(CH_2\text{-iPr})$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $\text{-N}(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is H, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $\text{-N}(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_2 , R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $\text{-NHCH}(CH_2OMe)(n\text{-Pr})$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $\text{-NHCH}(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_2 , R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is $\text{-N}(\text{Et})_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe₂, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is (S)- $NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is (S)- $NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-NH(Et)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)(CH_2CH_2OH)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-N(CH_2c-Pr)(n-Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is CN, R^{4d} is H and R^{4e} is H;
- 45

- a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OH)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and
- 10 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H
- 15 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and
- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H.
- 20
39. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein
- 25 said compound is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.
40. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein
- 30 said compound is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-
- 35 pyrazolo-1,3,5-triazine.
41. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically

acceptable salt or pro-drug forms thereof wherein A is CR.

42. A compound of Formula (2) of claim 41 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

43. A compound of claim 42 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.

44. A compound of claim 42 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR^{6a}R^{7a} or OR⁷.

45. A compound of claim 42 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents, and R³ is NR^{6a}R^{7a} or OR⁷.

46. A compound of Formula (1) of claim 41 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR².

47. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.
48. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR^{6a}R^{7a} or OR⁷.
49. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents, and R³ is NR^{6a}R^{7a} or OR⁷.
50. A compound of claim 49 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, and each such C₁-C₁₀ alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.
51. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

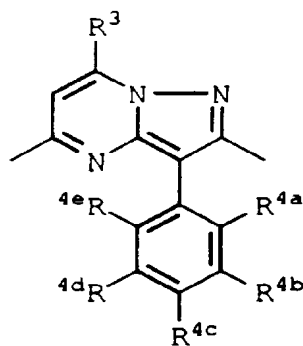
-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents,

-R³ is NR^{6a}R^{7a} or OR⁷ and

-R¹ and R² are independently selected from H, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl.

52. A compound of claim 51 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, and each such C₁-C₁₀ alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

53. A compound of claim 51 of Formula (51)



FORMULA (51)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof selected from the group consisting of:

- 10 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-N(n-Bu)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

- a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$,
10 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is (S)
 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is
 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NH(Et)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is (S)
 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is
40 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 45

- a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is (S)
 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is
 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 45

- a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-NEt_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 45 and

a compound of Formula (51) wherein R^3 is
-N(Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
 R^{4d} is H and R^{4e} is H.

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54. A compound of claim 51 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof, wherein
10 said compound is 7-(3-pentylamino)-2,5-dimethyl-3-(2-
methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine.

55. A compound of claim 51 and and isomers thereof,
stereoisomeric forms thereof, or mixtures of
15 stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof, wherein
said compound is 7-(Diethylamino)-2,5-dimethyl-3-(2-
methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine.

20 56. A compound of claim 51 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof, wherein
said compound is 7-(N-(3-cyanopropyl)-N-propylamino)-
25 2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-
pyrazolopyrimidine.

57. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and a therapeutical-
30 ly effective amount of a compound of claim 4.

58. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and a therapeutical-
ly effective amount of a compound of claim 24.

35

59. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 38.

60. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 39.

61. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 40.

62. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 53.

63. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 54.

64. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 55.

65. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 56.

66. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility

problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 4.

67. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 24.

68. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or

alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 38.

69. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 39.

70. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's

disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 40.

71. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 53.

72. A method of treating affective disorder, anxiety, depression, headache, irritable bowel

syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 54.

73. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 55.

74. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 56.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/13072

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D487/04 A61K31/505 //(C07D487/04,239:00,231:00),
(C07D487/04,251:00,231:00),(C07D487/04,249:00,239:00),
(C07D487/04,251:00,249:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 591 528 A (OTSUKA PHARMA CO LTD) 13 April 1994 cited in the application see the whole document ---	1-76
X	EP 0 531 901 A (FUJISAWA PHARMACEUTICAL CO) 17 March 1993 cited in the application see the whole document --- -/-	1-76

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

25 November 1997

Date of mailing of the international search report

23. 12. 97

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Inter. Jnal Application No
PCT/US 97/13072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 68, no. 25, 17 June 1968 Columbus, Ohio, US; abstract no. 114635v, TAKAMIZAWA: "7-Haloacylaminopyrazolo(1,5-a)pyrimidines " XP002048048 & JP-A-6716314 see abstract	1-76
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E	WO 97 29109 A (JANSSEN PHARMACEUTICA NV ;NEUROCRINE BIOSCIENCES INC (US); CHEN CH) 14 August 1997 see the whole document -----	1-76

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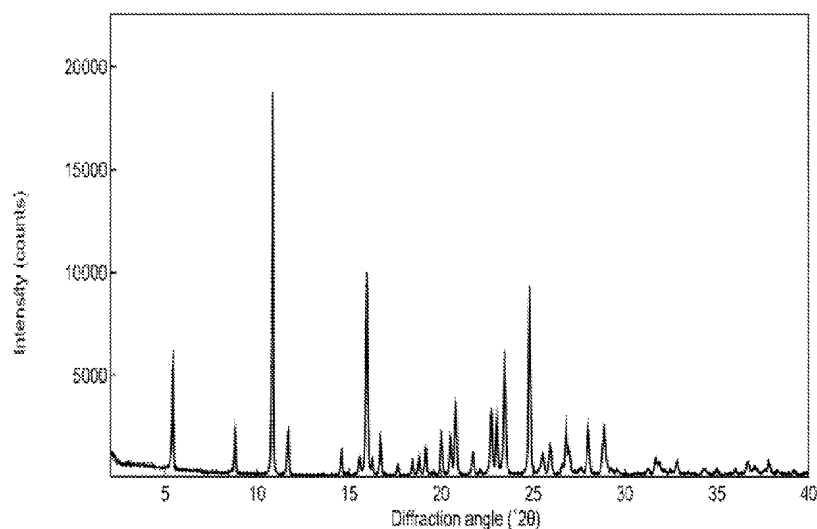
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(54) Title: CRYSTALLINE COMPOSITION OF TILDACERFONT AND METHODS OF USE AND PREPARATION THEREOF

FIG. 1



(57) Abstract: Described herein are crystalline composition, methods of making such crystalline composition, pharmaceutical compositions and medicaments comprising such crystalline composition, and methods of using such crystalline composition in the treatment of conditions, diseases, or disorders that would benefit from modulation of Corticotropin-releasing hormone receptor 1 (CRF1).

LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI,
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CRYSTALLINE COMPOSITION OF TILDACERFONT AND METHODS OF USE AND PREPARATION THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/281,462 filed November 19, 2021 and U.S. Provisional Application No. 63/340,874 filed May 11, 2022, each of which is incorporated herein by reference in its entirety.

INCORPORATION BY REFERENCE

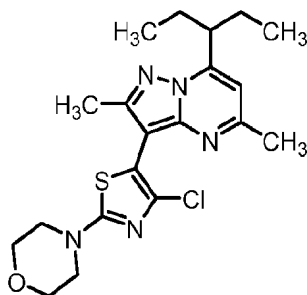
[0002] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BACKGROUND

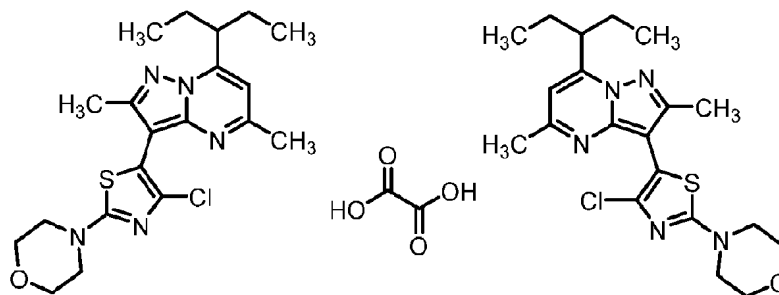
[0003] Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

SUMMARY

[0004] In a first aspect, the present disclosure provides a crystalline composition comprising Compound I:



[0005] In some embodiments, the crystalline composition comprising Compound 1 comprises a crystalline composition comprising Formula I:



Formula I.

[0006] In some embodiments, the crystals of the crystalline composition comprising Compound I (e.g., comprising Formula I) have unit cell parameters at $T = 150^\circ\text{K}$ of: $a = 34.003(4) \text{ \AA}$, $b = 6.5843(13) \text{ \AA}$, $c = 21.062(5) \text{ \AA}$; $\beta = 108.703(12)^\circ$, $V = 4466.5(15) \text{ \AA}^3$ and a monoclinic $C2/c$ space group.

[0007] In some embodiments, the crystals of the crystalline composition comprising Compound I (e.g., comprising Formula I) is characterized by:

- (a) an X-ray powder diffraction pattern comprising peaks at $10.84 \pm 0.2^\circ$ 2θ , $15.96 \pm 0.2^\circ$ 2θ , $23.44 \pm 0.2^\circ$ 2θ , and $24.80 \pm 0.2^\circ$ 2θ , and as measured by X-ray powder diffraction using an X-ray wavelength of $0.71073 \text{ \AA}$;
- (b) an X-ray powder diffraction pattern substantially the same as shown in FIG. 1;
- (c) a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160°C to 170°C ;
- (d) a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164°C and a peak of about 166°C ;
- (e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2;
- (f) a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25°C to about 200°C ;
- (g) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3; or
- (h) combinations thereof.

[0008] In some embodiments, the crystals of the crystalline composition comprising Compound I (e.g., comprising Formula I) is characterized by (a), (c), (d), and (f).

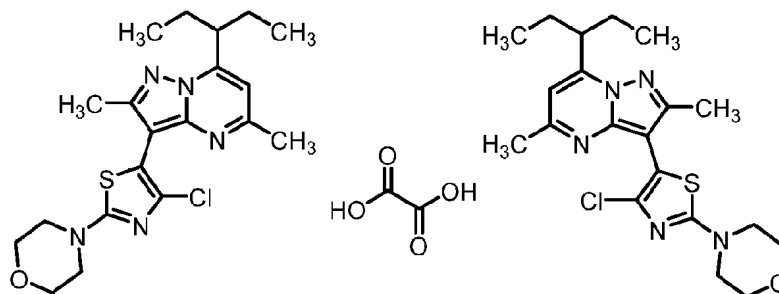
[0009] In some embodiments, the composition comprising a CRF1 antagonist (e.g., a crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by an X-ray powder diffraction pattern comprising one or more peaks at $10.84 \pm 0.2^\circ$ 2- θ , $15.96 \pm 0.2^\circ$ 2- θ , $23.44 \pm 0.2^\circ$ 2- θ , and $24.80 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the CRF1 antagonist (e.g., crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by an X-ray powder diffraction pattern comprising peaks at $10.84 \pm 0.2^\circ$ 2- θ , $15.96 \pm 0.2^\circ$ 2- θ , $23.44 \pm 0.2^\circ$ 2- θ , and $24.80 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least one peak selected from $5.44 \pm 0.2^\circ$ 2- θ , $20.78 \pm 0.2^\circ$ 2- θ , $22.74 \pm 0.2^\circ$ 2- θ , $23.04 \pm 0.2^\circ$ 2- θ , $26.80 \pm 0.2^\circ$ 2- θ , and $28.86 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least five peaks selected from $8.82 \pm 0.2^\circ$ 2- θ , $11.70 \pm 0.2^\circ$ 2- θ , $14.60 \pm 0.2^\circ$ 2- θ , $15.56 \pm 0.2^\circ$ 2- θ , $16.70 \pm 0.2^\circ$ 2- θ , $18.82 \pm 0.2^\circ$ 2- θ , $19.18 \pm 0.2^\circ$ 2- θ , $20.02 \pm 0.2^\circ$ 2- θ , $20.50 \pm 0.2^\circ$ 2- θ , $21.72 \pm 0.2^\circ$ 2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the crystalline composition is characterized by an X-ray powder diffraction pattern substantially the same as shown in FIG. 1.

[0010] In some embodiments, the crystalline composition comprising a CRF1 antagonist (e.g., crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C. In some embodiments, the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising an endotherm with an onset from about 160 °C to about 170 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising an endotherm with an onset from about 150 °C to about 170 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising an endotherm with an onset from about 160 °C to about 180 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising an endotherm with an onset at about 160 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising a peak of about 166 °C. In some embodiments, the crystalline composition is

characterized by a DSC thermogram comprising a peak from about 166 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 166 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 160 °C to about 170 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 150 °C to about 170 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 160 °C to about 180 °C. In some embodiments, the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2.

[0011] In some embodiments, the crystalline composition comprising a CRFI antagonist (e.g., crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition is characterized by a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3. In some embodiments, the crystalline composition is characterized by a TGA thermogram comprising a loss in mass of more than 10% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition is characterized by a TGA thermogram comprising a loss in mass of less than about 15% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition is characterized by a TGA thermogram comprising a loss in mass of less than about 20% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition is characterized by a dynamic vapor sorption (DVS) trace substantially the same as shown in FIG. 4.

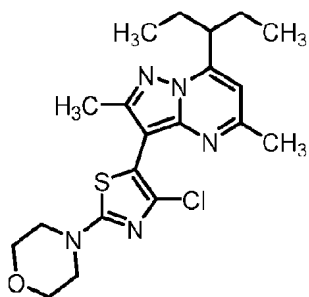
[0012] In some aspects, the present disclosure provides a pharmaceutical composition comprising crystalline composition comprising Formula I:



Formula I,

and at least one pharmaceutically acceptable carrier or excipient.

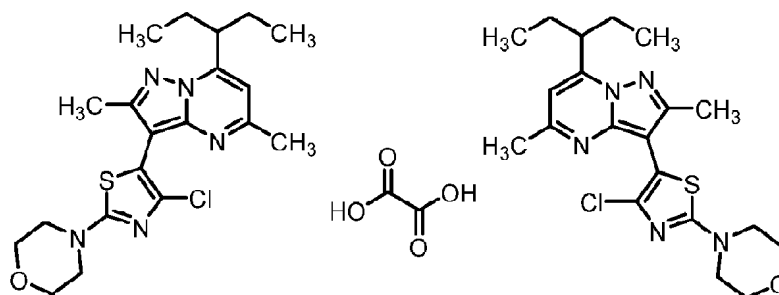
[0013] In some aspects, the present disclosure provides a pharmaceutical composition comprising Compound 1:



Compound 1

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutical composition comprising Compound 1 is a crystalline pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises crystalline Compound 1.

[0014] In another aspect, the present disclosure provides a method of preparing a crystalline composition comprising Compound 1 (e.g., comprising Formula I):



Formula I,

wherein the method comprises:

- a) dissolving 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (Compound 1) and oxalic acid in a solvent;
- (b) heating the solution or slurry from step (a); and
- (c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0015] In some embodiments of the method of preparing the crystalline composition comprising Compound I (e.g., comprising Formula I), the solvent in step (a) comprises acetone, heptane, water, 2-butanol, ethyl acetate, 2-propanol, methyl tert-butyl ether, ethanol, methyl ethyl ketone, 1-pentanol, or a combination thereof. In some embodiments, the solvent in step (a) is heptane. In some embodiments, the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone. In some embodiments, the solvent in step (a) is a mixture of heptane and methyl ethyl ketone. In some embodiments, step (b) is heated at about 50 °C.

[0016] In another aspect, the present disclosure provides a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the subject has congenital adrenal hyperplasia (CAH).

[0017] In another aspect, the present disclosure provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, a pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the CAH is a classic CAH. In some embodiments, the CAH is a non-classical CAH.

[0018] In another aspect, the present disclosure provides a method of improving (e.g., lessening the severity and/or frequency) hyperandrogenic symptoms in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism, amenorrhea, and alopecia.

[0019] In another aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein.

[0020] In another aspect, the present disclosure provides a method of improving (e.g., lessening the severity and/or frequency) metabolic symptoms in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the metabolic symptoms are

selected from the group consisting of body weight, BMI, fat mass, waist circumference, blood pressure and glycemic control. Metabolic symptoms may be evaluated using an assessment, such as, for example, fasting lipid panel, homeostatic model assessment of insulin resistance [HOMA-IR] based on fasting glucose and insulin levels, glycated hemoglobin [HbA1c], glucose tolerance test.

[0021] In another aspect, the present disclosure provides a method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein.

[0022] In another aspect, the present disclosure provides a method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein.

[0023] In another aspect, the present disclosure provides a method of treating endometriosis or improving the symptoms of endometriosis in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition improves the symptom of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition reduces the symptoms of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition prevents or lowers the perception of pain experienced by the subject (e.g., as measured on a pain scale). In some embodiments, the administration of the crystalline composition or the pharmaceutical composition eliminates the perception of pain experienced by the subject.

[0024] In various embodiments of the methods as described herein, the crystalline composition or the pharmaceutical composition is administered at a dose from about 5

mg/day to about 1000 mg/day. In some embodiments, the crystalline composition or the pharmaceutical composition is administered in a fed state. A fed state may mean that the subject has eaten within a 30-minute period before of receiving the crystalline composition or the pharmaceutical compositions. In some embodiments, the crystalline composition or the pharmaceutical composition is administered in a fasted state. A fasted state may mean that the subject has not eaten within a 30-minute period before of receiving the crystalline composition or the pharmaceutical compositions. In some embodiments, the crystalline composition or the pharmaceutical composition is administered at least once per day. In some embodiments, the crystalline composition or the pharmaceutical composition is administered once a day. In some embodiments, the crystalline composition or the pharmaceutical composition is administered twice a day.

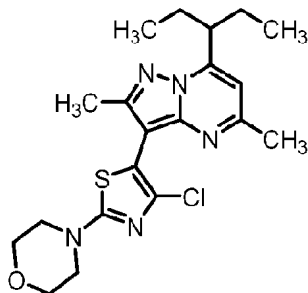
[0025] In various embodiments of the methods as described herein, the method further comprises administering to the subject an additional therapeutic agent. In some embodiments, the additional therapeutic agent is glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen agent. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone. In some embodiments, the additional therapeutic agent is a different CRF1 antagonist.

[0026] In various embodiments of the methods as described herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the crystalline composition as described herein, or the pharmaceutical composition comprising the crystalline composition as described herein. In some embodiments, the additional therapy is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the crystalline composition as described herein, the pharmaceutical composition comprising the crystalline composition as described herein, or the pharmaceutical composition comprising Compound 1 as described herein.

[0027] In various embodiments of the methods, the subject is from about 9 years of age to about 18 years of age. In some embodiments, the subject is from about 8 years of age to about 55 years of age.

[0028] In additional aspects, provided herein is a pharmaceutical composition comprising a CRF1 antagonist, wherein the composition is characterized by an X-ray powder diffraction

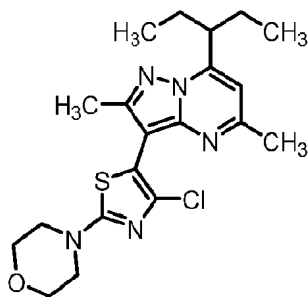
pattern comprising a peak selected from any one or more of $10.84 \pm 0.2^\circ$ 2- θ , $15.96 \pm 0.2^\circ$ 2- θ , $23.44 \pm 0.2^\circ$ 2- θ , and $24.80 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the composition is characterized by X-ray powder diffraction pattern comprising peaks at $10.84 \pm 0.2^\circ$ 2- θ , $15.96 \pm 0.2^\circ$ 2- θ , $23.44 \pm 0.2^\circ$ 2- θ , and $24.80 \pm 0.2^\circ$ 2- θ . In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $5.44 \pm 0.2^\circ$ 2- θ , $20.78 \pm 0.2^\circ$ 2- θ , $22.74 \pm 0.2^\circ$ 2- θ , $23.04 \pm 0.2^\circ$ 2- θ , $26.80 \pm 0.2^\circ$ 2- θ , and $28.86 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least five peaks selected from $8.82 \pm 0.2^\circ$ 2- θ , $11.70 \pm 0.2^\circ$ 2- θ , $14.60 \pm 0.2^\circ$ 2- θ , $15.56 \pm 0.2^\circ$ 2- θ , $16.70 \pm 0.2^\circ$ 2- θ , $18.82 \pm 0.2^\circ$ 2- θ , $19.18 \pm 0.2^\circ$ 2- θ , $20.02 \pm 0.2^\circ$ 2- θ , $20.50 \pm 0.2^\circ$ 2- θ , $21.72 \pm 0.2^\circ$ 2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the CRF1 antagonist comprises Compound 1:



Compound 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is a crystalline pharmaceutical composition. In some embodiments, the crystalline pharmaceutical composition further comprises oxalic acid. In some embodiments, the crystalline pharmaceutical composition comprises Compound 1 and oxalic acid in a molar ratio of about 2:1.

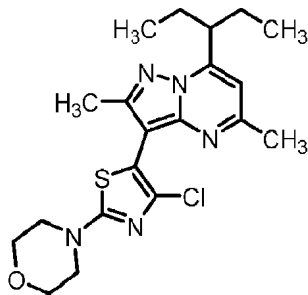
[0029] In additional aspects, provided herein is a pharmaceutical composition comprising a CRF1 antagonist, wherein the pharmaceutical composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C. In some embodiments, the pharmaceutical composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset

of about 164 °C and a peak of about 166 °C. In some embodiments, the pharmaceutical composition is characterized by a melting point of about 166 °C. In some embodiments, the CRF1 antagonist comprises Compound 1:



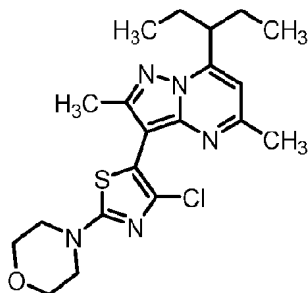
[0030] Compound 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is a crystalline pharmaceutical composition. In some embodiments, the crystalline pharmaceutical composition further comprises oxalic acid. In some embodiments, the crystalline pharmaceutical composition comprises Compound 1 and oxalic acid in a molar ratio of about 2:1. In some embodiments, the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C.

[0031] In additional aspects, provided herein is method of preparing a crystalline composition comprising Compound 1:



Compound 1, wherein the method comprises: (a) dissolving Compound 1 and an acid in a solvent; (b) heating the solution or slurry from step (a); and (c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Compound 1. In some embodiments, the acid comprises oxalic acid. In some embodiments, the solvent in step (a) is heptane. In some embodiments, the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone. In some embodiments, the solvent in step (a) is a mixture of heptane and methyl ethyl ketone. In some embodiments, step (b) is heated at about 50 °C.

[0032] In additional aspects, further provided herein is a pharmaceutical composition comprising Compound 1:



Compound 1, or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is present in an amount of 25% w/w; and a diluent in about 5% to about 70%. In some embodiments, Compound 1 is in an amount of about 50 mg to about 200 mg. In some embodiments, Compound 1 is in an amount of about 50 mg. In some embodiments, wherein the diluent is selected from the group consisting of calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose monohydrate, and a combination thereof. In some embodiments, the diluent is lactose monohydrate. In some embodiments, the lactose monohydrate is about 20% to about 45% by weight of the pharmaceutical composition. In some embodiments, the lactose monohydrate is about 20% to about 40.25% by weight of the pharmaceutical composition. In some embodiments, the lactose monohydrate is in an amount that is about 16.1, 40.25, 80.5, or 322 mg. In some embodiments, the diluent is microcrystalline cellulose. In some embodiments, the pharmaceutical composition further comprises a second diluent, wherein the second diluent comprises microcrystalline cellulose. In some embodiments, the microcrystalline cellulose is about 25% by weight of the pharmaceutical composition. In some embodiments, the microcrystalline cellulose is in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition further comprises a binder, wherein the binder is selected from the group consisting of corn starch and potato starch, gelatin, sucrose hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC), and a combination thereof. In some embodiments, the binder comprises HPC. In some embodiments, the HPC is about 3% by weight of the solid dosage form. In some embodiments, the pharmaceutical composition further comprises a surfactant, wherein the surfactant is selected from the group consisting of sodium lauryl sulfate, tetradecyl trimethyl ammonium bromide with dodecyl, hexadecyl compound, benzalkonium chloride, cetylpyridinium chloride, alkylsulphate, alkylethoxylate sulphate, soap, carboxylate ion, sulfate

ion, sulfonate ion, polyoxyethylene derivative, polyoxypropylene derivative, polyol derivative, polyol ester, polyoxyethylene ester, poloxamers, glycol, glycerol ester, sorbitan derivative, and polyethylene glycol, and a combination thereof. In some embodiments, the surfactant comprises sodium lauryl sulfate. In some embodiments, the sodium lauryl sulfate is about 0.75% by weight of the solid dosage form. In some embodiments, the sodium lauryl sulfate is in an amount that is about 1.5 mg. In some embodiments, the pharmaceutical composition further comprises a disintegrant, wherein the disintegrant is selected from the group consisting of starch, alginic acid, ac-di-sol, croscarmellose sodium, sodium starch glycolate, and crospovidone, and a combination thereof. In some embodiments, the disintegrant comprises croscarmellose sodium.

[0033] In some embodiments, the pharmaceutical composition further comprises a glidant, wherein the glidant comprises colloidal silicon dioxide. In some embodiments, the colloidal silicon dioxide is about 1% by weight of the solid dosage form. In some embodiments, the colloidal silicon dioxide is in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition further comprises a lubricant, wherein the lubricant is selected from the group consisting of talc, stearic acid, magnesium stearate, sodium stearyl fumarate, and a combination thereof. In some embodiments, the pharmaceutical formulation is in a solid dosage form. In some embodiments, the solid dosage form is a tablet. In some embodiments, the solid dosage form is a granules form. In some embodiments, said granules form is packaged in a capsule. In some embodiments, said granules form is packaged in a sachet.

[0034] In additional aspects, provided herein is a pharmaceutical formulation, comprising: (a) about 10 mg to about 300 mg of 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5- α) pyrimidine (Compound 1), or a pharmaceutically acceptable salt or solvate thereof; (b) a first diluent in about 40% to about 45% by weight, wherein the first diluent comprises lactose monohydrate; (c) a second diluent in about 25% by weight, wherein the second diluent comprises microcrystalline cellulose; (d) about 1% to about 6% by weight of hydroxypropyl cellulose; (e) about 0.5% to about 5% by weight of sodium lauryl sulfate; and (f) about 4% by weight of croscarmellose sodium.

DESCRIPTION OF THE DRAWINGS

[0035] The novel features of the present disclosure are set forth with particularity in the appended claims. An understanding of the features and advantages of the present disclosure may be obtained by reference to the following detailed description that sets forth illustrative

embodiments, in which the principles of the present disclosure are utilized, and the accompanying drawings of which:

[0036] FIG. 1 shows the X-ray powder diffraction (XRPD) pattern for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0037] FIG. 2 shows the differential scanning calorimetry (DSC) thermogram for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0038] FIG. 3 shows the thermogravimetric analysis (TGA) thermogram for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0039] FIG. 4 shows the dynamic vapor sorption (DVS) trace for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0040] FIG. 5 shows the infrared (IR) spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0041] FIG. 6 shows the proton nuclear magnetic resonance (^1H NMR) spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0042] FIG. 7 shows the Raman spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

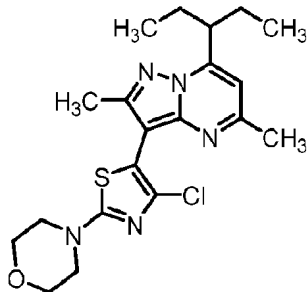
DETAILED DESCRIPTION

[0043] 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (Compound 1) is a potent antagonist of Corticotropin-releasing hormone receptor 1 (CRF1). CRF1 antagonists may be useful in the treatment of various diseases, conditions, and disorders for which abnormal CRF1 activity plays a role.

[0044] Crystalline forms of a small molecule drug candidate, such as a CRF1 antagonist, may have different physical properties, including melting point, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure, and density. These properties may have an effect on the ability to process or manufacture a drug substance and the drug product. Moreover, differences in these properties can and often lead to different pharmacokinetics profiles for different polymorphic forms of a drug. Polymorphism may affect the quality, safety, and/or efficacy of a drug product, such as a CRF1 antagonist. Thus, there still remains a need for crystalline compositions of CRF1 antagonist. The present disclosure addresses this need and provides related advantages as well.

Compound 1

[0045] As described herein, Compound 1 refers to 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine, which has the chemical structure as shown below:



Compound 1.

[0046] Compound 1 is a CRF1 modulator. CRF1 modulator, such as a CRF1 antagonist or inhibitor, are useful in the treatment of various conditions and disorders that are mediated by CRF1 activities.

[0047] In some embodiments, the present disclosure provides a crystalline composition comprising Compound 1. In some embodiments, the crystalline composition comprises Compound 1 and a weak acid (e.g., oxalic acid) (e.g., in a molar ratio of 2:1). In some embodiments, the crystalline composition comprises Compound 1 and an acid in a molar ratio of 2:1. In some embodiments, the crystalline composition comprises Compound 1 and an acid in a molar ratio of 1:1.

[0048] As used herein, “crystalline,” “crystalline form,” “polymorph,” “Form,” and “form” may be used interchangeably herein, and are meant to include all crystalline and amorphous forms of the compound, including, for example, co-crystals, polymorphs, pseudopolymorphs, salts, solvates, hydrates, unsolvated polymorphs (including anhydrides), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to. Compounds of the present disclosure include crystalline and amorphous forms of those compounds, including, for example, polymorphs, co-crystals, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrides), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

[0049] As used herein, “co-crystal” may be used to describe crystalline compositions comprising multi-component crystals based on hydrogen bonding interactions of hydrogen ions to form salt forms. In some embodiments, the crystalline composition as described

herein are co-crystals comprising an acid (e.g., a weak acid (e.g., oxalic acid)) and Compound 1.

Definitions

[0050] A “pharmaceutically acceptable carrier” refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative, such as those known in the art, for example, described in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

[0051] As used herein, “treating” and like terms refer to reducing the severity and/or frequency of symptoms, eliminating symptoms and/or the underlying cause of said symptoms, reducing the frequency or likelihood of symptoms and/or their underlying cause, delaying, preventing and/or slowing the progression of diseases and/or disorders and improving or remediating damage caused, directly or indirectly, by the diseases and/or disorders.

[0052] As used herein, “delaying development of a disease” or the like, means to defer, hinder, slow, retard, stabilize, and/or postpone development of the disease (such as cancer) or a sign or symptom of the disease. This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease. For example, a late stage cancer, such as development of metastasis, may be delayed.

[0053] As used herein, an “effective dosage” or “effective amount” of drug, compound, or pharmaceutical composition is an amount sufficient to effect beneficial or desired results. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, delaying development of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. In the case of cancer or tumor, an effective amount of the drug may have the effect in reducing the number of cancer cells;

reducing the tumor size; inhibiting (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibiting, to some extent, tumor growth; and/or relieving to some extent one or more of the symptoms associated with the disorder. An effective dosage can be administered in one or more administrations. For purposes of this invention, an effective dosage of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective dosage of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an “effective dosage” may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

[0054] As defined herein, the term “inhibition”, “inhibit”, “inhibiting” and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. Inhibition may refer to reduction of a disease or symptoms of disease. Inhibition may refer to a reduction in the activity of a particular protein or nucleic acid target. The protein may be deoxycytidine kinase. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein.

[0055] The term “modulator” refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule.

[0056] The term “modulate” is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. “Modulation” refers to the process of changing or varying one or more properties. For example, a modulator of a target protein changes by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. A modulator of a disease decreases a symptom, cause, or characteristic of the targeted disease.

[0057] “Selective” or “selectivity” or the like of a compound refers to the compound’s ability to discriminate between molecular targets.

[0058] “Specific”, “specifically”, “specificity”, or the like of a compound refers to the compound’s ability to cause a particular action, such as inhibition, to a particular molecular target with minimal or no action to other proteins in the cell.

[0059] “Pharmaceutically acceptable excipient” and “pharmaceutically acceptable carrier” refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer’s solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0060] The term “preparation” is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0061] As used herein, the term “administering” means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc.

[0062] By “co-administer” it is meant that a compound described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies, for example, an anticancer agent as described herein. The compounds described

herein can be administered alone or can be co-administered to the patient. Co-administration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. anticancer agents).

[0063] Co-administration includes administering one active agent (e.g. Compound 1 described herein) within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent (e.g. anti-cancer agents). Also contemplated herein, are embodiments, where co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. Co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In some embodiments, the active and/or adjunctive agents are linked or conjugated to one another. In some embodiments, the compounds described herein are combined with treatments for cancer such as chemotherapy or radiation therapy.

[0064] The term “associated” or “associated with” in the context of a substance or substance activity or function associated with a disease means that the disease is caused by (in whole or in part), a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function, or a side-effect of the compound (e.g. toxicity) is caused by (in whole or in part) the substance or substance activity or function.

[0065] “Patient,” “subject,” “patient in need thereof,” and “subject in need thereof” are herein used interchangeably and refer to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human. A “cancer-patient” is a patient suffering from, or prone to developing cancer.

[0066] Unless clearly indicated otherwise, the term “individual” as used herein refers to a mammal, including but not limited to, bovine, horse, feline, rabbit, canine, rodent, or primate (e.g., human). In some embodiments, an individual is a human. In some embodiments, an individual is a non-human primate such as chimpanzees and other apes and monkey species. In some embodiments, an individual is a farm animal such as cattle, horses, sheep, goats and swine; pets such as rabbits, dogs and cats; laboratory animals including rodents, such as rats,

mice, and guinea pigs; and the like. In some embodiments, the invention find use in both human medicine and in the veterinary context.

[0067] “Disease” or “condition” refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. In some embodiments, the disease as used herein refers to cancer.

[0068] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly indicates otherwise.

[0069] The term “about” when used in reference to numerical ranges, cut-offs, or specific values is used to indicate that the recited values may vary by up to as much as 10% from the listed value. As many of the numerical values used herein are experimentally determined, it should be understood by those skilled in the art that such determinations can, and often times will, vary among different experiments. The values used herein should not be considered unduly limiting by virtue of this inherent variation. Thus, the term “about” is used to encompass variations of $\pm 10\%$ or less, variations of $\pm 5\%$ or less, variations of $\pm 1\%$ or less, variations of $\pm 0.5\%$ or less, or variations of $\pm 0.1\%$ or less from the specified value.

[0070] It is understood that aspect and variations of the invention described herein include “consisting” and/or “consisting essentially of” aspects and variations.

Crystalline Composition Comprising Compound I (e.g., Comprising Formula I)

[0071] The crystalline composition prepared according to the methods of the present disclosure may be characterized by any methodology comprising the art. For example, the crystalline composition comprising Compound 1 ((e.g., comprising Formula I) e.g., prepared comprising the methods of the present disclosure)) may be characterized by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and/or spectroscopy (e.g., Raman, solid state nuclear magnetic resonance (ssNMR), proton nuclear magnetic resonance (^1H NMR), and infrared (IR)). In some embodiments, crystallinity of the solid form is determined by X-Ray Powder Diffraction (XPRD).

[0072] Formula 1 may represent a composition comprising two molecules of Compound 1 and one molecules of oxalic acid. As such, Formula I may represent a molar ratio of Compound 1 to oxalic acid in a ratio of about 2:1.

[0073] XRPD: Crystalline composition according to the present disclosure may be characterized by XRPD (e.g., crystalline composition(s) comprising the present disclosure can also be identified by its characteristic XRPD peaks, such as show in FIG. 1). The relative intensities of XRPD peaks may vary, depending upon the particle size, the sample

preparation technique, the sample mounting procedure and the particular instrument employed. Moreover, instrument variation and other factors may affect the 2- θ values. Therefore, the XRPD peak assignments may vary, for example by plus or minus about 0.2 degrees.

[0074] DSC: Crystalline composition according to the present disclosure can also be identified by its characteristic DSC thermograms such as shown in FIG. 2. For DSC, it is known that the temperatures observed may depend upon the rate of temperature change as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein relating to DSC thermograms may vary, for example by plus or minus about 4°C.

[0075] TGA: Crystalline composition according to the present disclosure may also give rise to thermal behavior different from that of the amorphous material or other crystalline forms. Thermal behavior may be measured in the laboratory by thermogravimetric analysis (TGA) which may be used to distinguish some crystalline forms from others. In one aspect, the crystalline composition as described herein may be characterized by thermogravimetric analysis.

[0076] DVS: Crystalline composition comprising the present disclosure may also give rise to vapors sorption behavior different from that of the amorphous material or other crystalline forms. The vapor sorption behavior may be measured in the laboratory by dynamic vapor sorption (DVS) which may be used to distinguish some crystalline forms from others. In one aspect, the crystalline composition as described herein may be characterized by dynamic vapor sorption.

[0077] The crystalline composition comprising Compound 1 (e.g. comprising Formula I) may be useful in the production of medicinal preparations and can be obtained by means of a crystallization process to produce crystalline and semi-crystalline forms or a solidification process to obtain the amorphous form. In some embodiments, the crystallization is carried out by either generating the desired compound (for example Compound 1) in a reaction mixture and isolating the desired crystalline composition from the reaction mixture, or by dissolving raw compound (e.g., Compound 1) in a solvent, optionally with heat, followed by crystallizing/solidifying the product by cooling (including active cooling) and/or by the addition of an antisolvent for a period of time. The crystallization or solidification may be followed by drying carried out under controlled conditions until the desired water content is reached in the end crystalline composition.

[0078] FIG. 1 shows the X-ray powder diffraction (XRPD) pattern for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0079] FIG. 2 shows the differential scanning calorimetry (DSC) thermogram for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0080] FIG. 3 shows the thermogravimetric analysis (TGA) thermogram for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

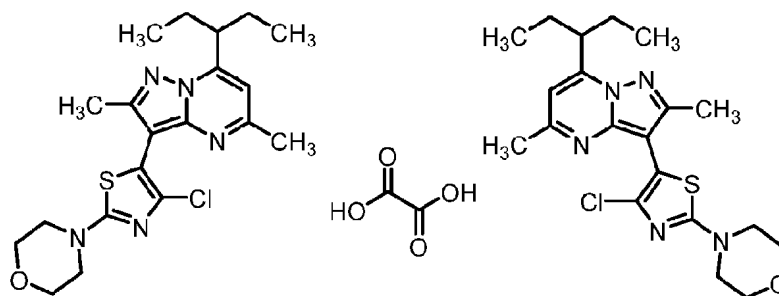
[0081] FIG. 4 shows the dynamic vapor sorption (DVS) trace for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0082] FIG. 5 shows the infrared (IR) spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0083] FIG. 6 shows the proton nuclear magnetic resonance (^1H NMR) spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0084] FIG. 7 shows the Raman spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0085] In some aspects, the present disclosure provides a crystalline composition comprising Compound 1. In some embodiments the crystalline composition comprising Compound 1 is a crystalline composition comprising Formula I:



Formula I.

[0086] In some embodiments, Formula I represents Compound 1 and oxalic acid in a molar ratio of 2:1.

[0087] In some embodiments, the crystals of the crystalline composition comprising Compound 1 (e.g., comprising Formula I) has unit cell parameters at $T = 150^\circ\text{K}$ of: $a = 34.003(4) \text{ \AA}$, $b = 6.5843(13) \text{ \AA}$, $c = 21.062(5) \text{ \AA}$; $\beta = 108.703(12)^\circ$, $V = 4466.5(15) \text{ \AA}^3$ and a monoclinic $C2/c$ space group.

[0088] In some embodiments, the crystals of a composition (e.g., a crystalline composition comprising Compound 1 (e.g., comprising Formula I)) is characterized by:

- (a) an X-ray powder diffraction pattern comprising peaks at $10.84 \pm 0.2^\circ$ 2- θ , $15.96 \pm 0.2^\circ$ 2- θ , $23.44 \pm 0.2^\circ$ 2- θ , and $24.80 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å;
- (b) an X-ray powder diffraction pattern substantially the same as shown in FIG. 1;
- (c) a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C;
- (d) a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C;
- (e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2;
- (f) a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C;
- (g) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3; or
- (h) combinations thereof.

[0089] In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., v Formula I)) is characterized by an X-ray powder diffraction pattern comprising any one or more peaks at $10.84 \pm 0.2^\circ$ 2- θ , $15.96 \pm 0.2^\circ$ 2- θ , $23.44 \pm 0.2^\circ$ 2- θ , and $24.80 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the XRPD pattern comprises at least one of the aforementioned peaks ($10.84 \pm 0.2^\circ$ 2- θ , $15.96 \pm 0.2^\circ$ 2- θ , $23.44 \pm 0.2^\circ$ 2- θ , and $24.80 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å). In some embodiments, the XRPD pattern comprises at least two of the aforementioned peaks. In some embodiments, the XRPD pattern comprises at least three of the aforementioned peaks. In some embodiments, the XRPD pattern comprises at least four of the aforementioned peaks. In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I)) is characterized by an X-ray powder diffraction pattern comprising peaks at $10.84 \pm 0.1^\circ$ 2- θ , $15.96 \pm 0.1^\circ$ 2- θ , $23.44 \pm 0.1^\circ$ 2- θ , and $24.80 \pm 0.1^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I)) is characterized by an X-ray powder diffraction pattern comprising peaks at about 10.84° 2- θ , about 15.96° 2- θ , about 23.44° 2- θ , and about 24.80° 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

[0090] In some embodiments, the X-ray powder diffraction (XRPD) pattern further comprising at least one peak selected from $5.44 \pm 0.2^\circ$ 2- θ , $20.78 \pm 0.2^\circ$ 2- θ , $22.74 \pm 0.2^\circ$ 2- θ , $23.04 \pm 0.2^\circ$ 2- θ , $26.80 \pm 0.2^\circ$ 2- θ , and $28.86 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least one peak selected from $5.44 \pm 0.1^\circ$ 2- θ , $20.78 \pm 0.1^\circ$ 2- θ , $22.74 \pm 0.1^\circ$ 2- θ , $23.04 \pm 0.1^\circ$ 2- θ , $26.80 \pm 0.1^\circ$ 2- θ , and $28.86 \pm 0.1^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least one peak selected from about 5.44° 2- θ , about 20.78° 2- θ , about 22.74° 2- θ , about 23.04° 2- θ , about 26.80° 2- θ , and about 28.86° 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

[0091] In some embodiments, the X-ray powder diffraction pattern further comprising at least one peak selected from $8.82 \pm 0.2^\circ$ 2- θ , $11.70 \pm 0.2^\circ$ 2- θ , $14.60 \pm 0.2^\circ$ 2- θ , $15.56 \pm 0.2^\circ$ 2- θ , $16.70 \pm 0.2^\circ$ 2- θ , $18.82 \pm 0.2^\circ$ 2- θ , $19.18 \pm 0.2^\circ$ 2- θ , $20.02 \pm 0.2^\circ$ 2- θ , $20.50 \pm 0.2^\circ$ 2- θ , $21.72 \pm 0.2^\circ$ 2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least two peaks selected from $8.82 \pm 0.2^\circ$ 2- θ , $11.70 \pm 0.2^\circ$ 2- θ , $14.60 \pm 0.2^\circ$ 2- θ , $15.56 \pm 0.2^\circ$ 2- θ , $16.70 \pm 0.2^\circ$ 2- θ , $18.82 \pm 0.2^\circ$ 2- θ , $19.18 \pm 0.2^\circ$ 2- θ , $20.02 \pm 0.2^\circ$ 2- θ , $20.50 \pm 0.2^\circ$ 2- θ , $21.72 \pm 0.2^\circ$ 2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least three peaks selected from $8.82 \pm 0.2^\circ$ 2- θ , $11.70 \pm 0.2^\circ$ 2- θ , $14.60 \pm 0.2^\circ$ 2- θ , $15.56 \pm 0.2^\circ$ 2- θ , $16.70 \pm 0.2^\circ$ 2- θ , $18.82 \pm 0.2^\circ$ 2- θ , $19.18 \pm 0.2^\circ$ 2- θ , $20.02 \pm 0.2^\circ$ 2- θ , $20.50 \pm 0.2^\circ$ 2- θ , $21.72 \pm 0.2^\circ$ 2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least four peaks selected from $8.82 \pm 0.2^\circ$ 2- θ , $11.70 \pm 0.2^\circ$ 2- θ , $14.60 \pm 0.2^\circ$ 2- θ , $15.56 \pm 0.2^\circ$ 2- θ , $16.70 \pm 0.2^\circ$ 2- θ , $18.82 \pm 0.2^\circ$ 2- θ , $19.18 \pm 0.2^\circ$ 2- θ , $20.02 \pm 0.2^\circ$ 2- θ , $20.50 \pm 0.2^\circ$ 2- θ , $21.72 \pm 0.2^\circ$ 2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least five peaks selected from $8.82 \pm 0.2^\circ$ 2- θ , $11.70 \pm 0.2^\circ$ 2- θ , $14.60 \pm 0.2^\circ$ 2- θ , $15.56 \pm 0.2^\circ$ 2- θ , $16.70 \pm 0.2^\circ$ 2- θ , $18.82 \pm 0.2^\circ$ 2- θ , $19.18 \pm 0.2^\circ$ 2- θ , $20.02 \pm 0.2^\circ$ 2- θ , $20.50 \pm 0.2^\circ$ 2- θ , $21.72 \pm 0.2^\circ$ 2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ .

2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least six peaks selected from $8.82 \pm 0.2^\circ$ 2- θ , $11.70 \pm 0.2^\circ$ 2- θ , $14.60 \pm 0.2^\circ$ 2- θ , $15.56 \pm 0.2^\circ$ 2- θ , $16.70 \pm 0.2^\circ$ 2- θ , $18.82 \pm 0.2^\circ$ 2- θ , $19.18 \pm 0.2^\circ$ 2- θ , $20.02 \pm 0.2^\circ$ 2- θ , $20.50 \pm 0.2^\circ$ 2- θ , $21.72 \pm 0.2^\circ$ 2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least seven peaks selected from $8.82 \pm 0.2^\circ$ 2- θ , $11.70 \pm 0.2^\circ$ 2- θ , $14.60 \pm 0.2^\circ$ 2- θ , $15.56 \pm 0.2^\circ$ 2- θ , $16.70 \pm 0.2^\circ$ 2- θ , $18.82 \pm 0.2^\circ$ 2- θ , $19.18 \pm 0.2^\circ$ 2- θ , $20.02 \pm 0.2^\circ$ 2- θ , $20.50 \pm 0.2^\circ$ 2- θ , $21.72 \pm 0.2^\circ$ 2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least eight peaks selected from $8.82 \pm 0.2^\circ$ 2- θ , $11.70 \pm 0.2^\circ$ 2- θ , $14.60 \pm 0.2^\circ$ 2- θ , $15.56 \pm 0.2^\circ$ 2- θ , $16.70 \pm 0.2^\circ$ 2- θ , $18.82 \pm 0.2^\circ$ 2- θ , $19.18 \pm 0.2^\circ$ 2- θ , $20.02 \pm 0.2^\circ$ 2- θ , $20.50 \pm 0.2^\circ$ 2- θ , $21.72 \pm 0.2^\circ$ 2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern comprises peaks selected from $8.82 \pm 0.1^\circ$ 2- θ , $11.70 \pm 0.1^\circ$ 2- θ , $14.60 \pm 0.1^\circ$ 2- θ , $15.56 \pm 0.1^\circ$ 2- θ , $16.70 \pm 0.1^\circ$ 2- θ , $18.82 \pm 0.1^\circ$ 2- θ , $19.18 \pm 0.1^\circ$ 2- θ , $20.02 \pm 0.1^\circ$ 2- θ , $20.50 \pm 0.1^\circ$ 2- θ , $21.72 \pm 0.1^\circ$ 2- θ , $25.52 \pm 0.1^\circ$ 2- θ , $25.92 \pm 0.1^\circ$ 2- θ , $26.94 \pm 0.1^\circ$ 2- θ , and $28.00 \pm 0.1^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern comprises peaks selected from 8.82° 2- θ , 11.70° 2- θ , 14.60° 2- θ , 15.56° 2- θ , 16.70° 2- θ , 18.82° 2- θ , 19.18° 2- θ , 20.02° 2- θ , 20.50° 2- θ , 21.72° 2- θ , 25.52° 2- θ , 25.92° 2- θ , 26.94° 2- θ , and 28.00° 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

[0092] In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I)) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C. In some embodiments, the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 166 °C. In some embodiments, the

crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2.

[0093] In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm at about 160 °C to about 170 °C, about 160 °C to about 169 °C, about 160 °C to about 168 °C, about 160 °C to about 167 °C, about 160 °C to about 166 °C, about 160 °C to about 165 °C, about 160 °C to about 164 °C, about 160 °C to about 163 °C, about 160 °C to about 162 °C, about 160 °C to about 161 °C, about 161 °C to about 170 °C, about 162 °C to about 170 °C, about 163 °C to about 170 °C, about 164 °C to about 170 °C, about 165 °C to about 170 °C, about 166 °C to about 170 °C, about 167 °C to about 170 °C, about 168 °C to about 170 °C, or about 169 °C to about 170 °C. In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm at about 162 °C to about 166 °C, for example at about 162 °C, about 163 °C, about 164 °C, 165 °C, or 166 °C. In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., (e.g., comprising Compound 1))) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm at about 164 °C. In some embodiments, the crystalline composition according for Formula I has a melting point of about 166 °C.

[0094] In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition decomposes above a temperature of about 50 °C, about 100 °C, about 150 °C, about 200 °C, about 250 °C, about 300 °C, about 350 °C, or about 400 °C. In some embodiments, the crystalline composition decomposes above a temperature of about 200 °C. In some embodiments, the crystalline composition decomposes above a temperature of about 250 °C. In some embodiments, the crystalline composition is characterized by a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3.

[0095] In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is characterized by a dynamic vapor sorption (DVS) trace substantially the same as shown in FIG. 4.

[0096] In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is anhydrous.

[0097] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is stable at room temperature. In some examples, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) can be stored at room temperature for an extended period of time without significant chemical degradation or change in the crystalline form. In some examples, crystalline composition comprising Compound 1 (e.g., comprising Formula I) can be stored at room temperature for a timer period of at least about 10 days, 30 days, 60 days, 90 days, 120 days, 150 days, or 180 days. In some examples, the crystalline composition can be stored at room temperature for a time period of more than about 180 days. In some examples, the crystalline composition can be stored at room temperature for a time period of 10-14 days, 10-18 days, 10-22 days, 10-26 days, 10-30 days, 10-40 days, 10-50 days, 10-60 days, 10-90 days, 10-120 days, 10-150 days, 10-180 days, 14-18 days, 14-22 days, 14-26 days, 14-30 days, 14-40 days, 14-50 days, 14-60 days, 14-90 days, 14-120 days, 14-150 days, 14-180 days, 18-22 days, 18-26 days, 18-30 days, 18-40 days, 18-50 days, 18-60 days, 18-90 days, 18-120 days, 18-150 days, 18-180 days, 22-26 days, 22-30 days, 22-40 days, 22-50 days, 22-60 days, 22-90 days, 22-120 days, 22-150 days, 22-180 days, 26-30 days, 26-40 days, 26-50 days, 26-60 days, 26-90 days, 26-120 days, 26-150 days, 26-180 days, 30-40 days, 30-50 days, 30-60 days, 30-90 days, 30-120 days, 30-150 days, 30-180 days, 40-50 days, 40-60 days, 40-90 days, 40-120 days, 40-150 days, 40-180 days, 50-60 days, 50-90 days, 50-120 days, 50-150 days, 50-180 days, 60-90 days, 60-120 days, 60-150 days, 60-180 days, 90-120 days, 90-150 days, or 90-180 days. In some examples, the crystalline composition can be stored at room temperature for a time period of at least 10 days, 14 days, 18 days, 22 days, 26 days, 30 days, 40 days, 50 days, 60 days, 90 days, 120 days, 150 days, or 180 days.

[0098] In some embodiments, the crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I)) is stable at room temperature or temperatures above the room temperature and/or at high relative humidity (RH) (e.g., accelerated aging conditions or long-term storage conditions). In some embodiments, the crystalline composition is stable for at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, at least twelve months, at least fourteen months, at least sixteen months, and at least eighteen months. In some examples, the crystalline composition can be stored at about 25 °C and at about 75%

RH for an extended period of time without significant chemical degradation or change in the crystalline form. In some examples, the crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I)) can be stored at about 25 °C and at about 75% RH for a time period of at least about 10 days, 30 days, 60 days, 90 days, 120 days, 150 days, or 180 days. In some examples, the crystalline composition can be stored at about 25 °C and at about 75% RH for a time period of 10-14 days, 10-18 days, 10-22 days, 10-26 days, 10-30 days, 10-40 days, 10-50 days, 10-60 days, 10-90 days, 10-120 days, 10-150 days, 10-180 days, 14-18 days, 14-22 days, 14-26 days, 14-30 days, 14-40 days, 14-50 days, 14-60 days, 14-90 days, 14-120 days, 14-150 days, 14-180 days, 18-22 days, 18-26 days, 18-30 days, 18-40 days, 18-50 days, 18-60 days, 18-90 days, 18-120 days, 18-150 days, 18-180 days, 22-26 days, 22-30 days, 22-40 days, 22-50 days, 22-60 days, 22-90 days, 22-120 days, 22-150 days, 22-180 days, 26-30 days, 26-40 days, 26-50 days, 26-60 days, 26-90 days, 26-120 days, 26-150 days, 26-180 days, 30-40 days, 30-50 days, 30-60 days, 30-90 days, 30-120 days, 30-150 days, 30-180 days, 40-50 days, 40-60 days, 40-90 days, 40-120 days, 40-150 days, 40-180 days, 50-60 days, 50-90 days, 50-120 days, 50-150 days, 50-180 days, 60-90 days, 60-120 days, 60-150 days, 60-180 days, 90-120 days, 90-150 days, or 90-180 days. In some examples, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) can be stored at about 25 °C for a time period of at least 10 days, 14 days, 18 days, 22 days, 26 days, 30 days, 40 days, 50 days, 60 days, 90 days, 120 days, 150 days, or 180 days.

[0099] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is thermodynamically stable.

[00100] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is highly bioavailable.

[00101] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is stable under accelerated storage conditions.

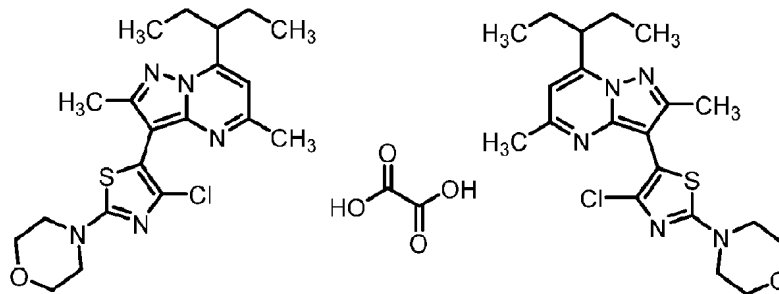
[00102] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is characterized by an infrared (IR) spectrum substantially the same as shown in FIG. 5.

[00103] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is characterized by a proton nuclear magnetic resonance (¹H NMR) spectrum substantially the same as shown in FIG. 6.

[00104] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is characterized by a Raman spectrum substantially the same as shown in FIG. 7.

Compositions and Formulations

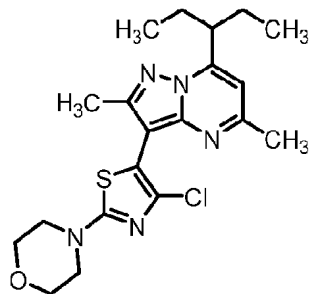
[00105] In some aspects, the present disclosure provides a pharmaceutical composition comprising a crystalline composition comprising Formula I:



Formula I,

and at least one pharmaceutically acceptable carrier or excipient.

[00106] In some aspects, the present disclosure provides a pharmaceutical composition comprising Compound 1:



Compound 1,

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutical composition is a crystalline pharmaceutical composition comprising Compound 1. In some embodiments, the crystalline pharmaceutical composition comprising Compound 1 comprises Formula I.

Dosage Form

[00107] In some embodiments, the pharmaceutical composition described herein is provided in unit dosage form. As used herein, a “unit dosage form” is a composition containing an amount of the crystalline composition comprising Compound 1 (e.g., comprising Formula I)

that is suitable for administration to a subject in a single dose. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded.

[00108] In some embodiments, the pharmaceutical compositions described herein are formulated as oral dosage forms. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules. In some embodiments, the pharmaceutical composition comprises one or more additional pharmaceutically acceptable excipients. See, e.g., Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005) for a list of pharmaceutically acceptable excipients.

Capsule

[00109] In some embodiments, the pharmaceutical composition comprising the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is formulated as a capsule. In some embodiments, the pharmaceutical composition is encapsulated in a hard gel capsule. In some embodiments, the pharmaceutical composition is encapsulated in a soft gel capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

[00110] In some embodiments, the pharmaceutical composition comprising Compound 1 is formulated as a capsule. In some embodiments, the pharmaceutical composition is encapsulated in a hard gel capsule. In some embodiments, the pharmaceutical composition is encapsulated in a soft gel capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

[00111] In some embodiments, the capsule is formed using materials which include, but are not limited to, natural or synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, or any combinations thereof. In some embodiments, the capsule is formed using preservatives, coloring and opacifying agents, flavorings and sweeteners, sugars, gastroresistant substances, or any combinations thereof. In some embodiments, the capsule is coated. In some embodiments, the coating covering the capsule includes, but is not limited to, immediate release coatings, protective coatings, enteric or delayed release coatings, sustained release coatings, barrier coatings, seal

coatings, or combinations thereof. In some embodiments, a capsule herein is hard or soft. In some embodiments, the capsule is seamless. In some embodiments, the capsule is broken such that the particulates are sprinkled on soft foods and swallowed without chewing. In some embodiments, the shape and size of the capsule also vary. Examples of capsule shapes include, but are not limited to, round, oval, tubular, oblong, twist off, or a non-standard shape. The size of the capsule may vary comprising the volume of the particulates. In some embodiments, the size of the capsule is adjusted based on the volume of the particulates and powders. Hard or soft gelatin capsules may be manufactured in accordance with conventional methods as a single body unit comprising the standard capsule shape. A single-body soft gelatin capsule typically may be provided, for example, in sizes from 3 to 22 minims (1 minims being equal to 0.0616 ml) and in shapes of oval, oblong or others. The gelatin capsule may also be manufactured in accordance with conventional methods, for example, as a two-piece hard gelatin capsule, sealed or unsealed, typically in standard shape and various standard sizes, conventionally designated as (000), (00), (0), (1), (2), (3), (4), and (5). The largest number corresponds to the smallest size. In some embodiments, the pharmaceutical composition described herein (e.g., capsule) is swallowed as a whole.

[00112] In some embodiments, the capsule comprises one or more pharmaceutically acceptable excipients.

[00113] In some embodiments, the capsule is free of additional excipients.

Tablet

[00114] In some embodiments, the pharmaceutical composition comprising the crystalline composition comprising Compound I (e.g., comprising Formula I) is formulated as a tablet.

[00115] In some embodiments, the pharmaceutical composition comprising Compound 1 is formulated as a tablet.

[00116] In some embodiments, the tablet size is less than about 1000 mg, less than about 800 mg, less than about 600 mg, less than about 400 mg or less than about 200 mg. In some embodiments, the tablet has a dose strength of more than about 50 mg, more than about 100 mg, more than about 150 mg, more than about 200 mg, or more than about 250 mg. In some embodiments, the tablet size is less than about 1000 mg for a dose strength of more than about 50 mg. In some embodiments, the tablet size is less than 800 mg for a dose strength of more than about 100 mg. In some embodiments, the tablet size is less than 600 mg for a dose strength of more than about 150 mg. In some embodiment, the tablet size is less than 400 mg for a dose strength of more than about 200 mg. In some embodiments, the tablet size is less

than 400 mg for a dose strength of 200 mg. In some embodiments, the tablet size is about 200 mg for a dose strength of about 50 mg.

[00117] In some embodiments, more than about 20% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 24 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 12 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 6 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 3 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 2 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than 70% of the tablet is dissolved in 60 minutes in conventional dissolution media.

[00118] In some embodiments, the tablet is produced at a commercial scale.

[00119] In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

[00120] In some embodiments, the tablet is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some embodiments, the coating material is in the form of a film coating, e.g., a glossy film, a pH independent film coating, an aqueous film coating, a dry powder film coating (e.g., complete

dry powder film coating), or any combination thereof. In some embodiments, the coating material is highly adhesive. In some embodiments, the coating material provides low level of water permeation. In some embodiments, the coating material provides oxygen barrier protection. In some embodiments, the coating material allows immediate disintegration for fast release of Compound 1. In some embodiments, the coating material is pigmented, clear, or white. In some embodiments, the coating is an enteric coating. Exemplary coating materials include, without limitation, polyvinylpyrrolidone, polyvinyl alcohol, an acrylate-methacrylic acid copolymer, a methacrylate-methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, cellulose acetate trimellitate, sodium alginate, zein, and any combinations thereof.

Oral dosage forms

[00121] In some embodiments, the pharmaceutical composition comprising Compound 1 or the crystalline composition comprising Formula I or is formulated as an oral dosage form. In some embodiments, the oral dosage form is selected from the group consisting of a tablet, a capsule, a buccal tablet, a sub-lingual table, an orally-disintegrating tablet, a thin film, a liquid solution, a liquid suspension, a syrup, a powder, and solid crystals. In some embodiment, the oral dosage form is selected from the group consisting of a tablet, a capsule, a buccal tablet, a sub-lingual table, an orally-disintegrating tablet, a thin film, a liquid solution, a liquid suspension, a syrup, a powder, solid crystals, minitabs, coated pellets and sachets.

[00122] Oral dosage forms may include capsules, tablets, pills, powders or granules. Such forms may include forms that dissolve or disintegrate quickly in the oral environment. Such forms may be prepared with coatings and shells. In some embodiments, these oral dosage forms are capable of controlled or sustained release.

Pharmaceutically Acceptable Excipients

[00123] In some embodiments, the pharmaceutical composition comprising Compound 1 (e.g., crystalline composition comprising Compound 1) or the crystalline composition comprising Formula I comprises a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is free of pharmaceutically acceptable excipients. The term “pharmaceutically acceptable excipient”, as used herein, means one or more compatible solid or encapsulating substances, which are suitable for administration to a

mammal. The term “compatible”, as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction, which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. In some embodiments, the pharmaceutically acceptable excipient is of sufficiently high purity and sufficiently low toxicity to render them suitable for administration preferably to an animal, preferably mammal, being treated.

[00124] Some examples of substances, which can serve as pharmaceutically acceptable excipients include:

- Amino acids such as alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, the amino acid is arginine. In some embodiments, the amino acid is L-arginine.
- Monosaccharides such as glucose (dextrose), arabinose, mannitol, fructose (levulose), and galactose.
- Cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose.
- Solid lubricants such as talc, stearic acid, magnesium stearate and sodium stearyl fumarate.
- Polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol.
- Emulsifiers such as the polysorbates.
- Wetting agents such as sodium lauryl sulfate, Tween®, Span , alkyl sulphates, and alkyl ethoxylate sulphates.
- Cationic surfactants such as cetrimide, benzalkonium chloride, and cetylpyridinium chloride.
- Diluents such as calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose.
- Binders such as starches (corn starch and potato starch), gelatin, sucrose hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC).
- Disintegrants such as starch, and alginic acid.
- Super-disintegrants such as ac-di-sol, croscarmellose sodium, sodium starch glycolate and crospovidone.

- Glidants such as silicon dioxide.
- Coloring agents such as the FD&C dyes.
- Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors.
- Preservatives such as benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate, phenylmercuric nitrate, parabens, and sodium benzoate.
- Tonicity adjustors such as sodium chloride, potassium chloride, mannitol, and glycerin.
- Antioxidants such as sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA.
- pH adjuster such as NaOH, sodium carbonate, sodium acetate, HCl, and citric acid.
- Cryoprotectants such as sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran.
- Surfactants such as sodium lauryl sulfate. For example, cationic surfactants such as cetrimide (including tetradecyl trimethyl ammonium bromide with dodecyl and hexadecyl compounds), benzalkonium chloride, and cetylpyridinium chloride. Some examples of anionic surfactants are alkylsulphates, alkylethoxylate sulphates, soaps, carboxylate ions, sulfate ions, and sulfonate ions. Some examples of non-ionic surfactants are polyoxyethylene derivatives, polyoxypropylene derivatives, polyol derivatives, polyol esters, polyoxyethylene esters, poloxamers, glycol, glycerol esters, sorbitan derivatives, polyethylene glycol (such as PEG-40, PEG-50, or PEG-55) and esters of fatty alcohols.
- Organic materials such as carbohydrates, modified carbohydrates, lactose (including α -lactose, monohydrate spray dried lactose or anhydrous lactose), starch, pregelatinized starch, sucrose, mannitol, sorbitol, cellulose (including powdered cellulose and microcrystalline cellulose).
- Inorganic materials such as calcium phosphates (including anhydrous dibasic calcium phosphate, dibasic calcium phosphate or tribasic calcium phosphate).
- Co-processed diluents.
- Compression aids.
- Anti-tacking agents such as silicon dioxide and talc.

[00125] In some embodiments, the pharmaceutical composition comprises the crystalline composition comprising Formula I.

[00126] In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprises Compound 1.

a diluent in about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 55% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 45% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 40% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 30% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 20% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% by weight of the dosage form.

[00129] In some embodiments, the pharmaceutical composition comprises a second diluent. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 95% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 90% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 85% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 80% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 70% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 65% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 55% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 45% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 40% by weight of the dosage

form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 30% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 20% by weight of the dosage form.

[00130] In some embodiments, the pharmaceutical composition comprises a second diluent in about 95% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 90% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 85% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 80% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 70% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 65% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 55% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 45% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 40% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 30% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 20% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% by weight of the dosage form.

[00131] In some embodiments, the diluent is selected from calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose. In some embodiments, the diluent is lactose monohydrate. In some embodiments, the diluent is microcrystalline cellulose. In some embodiments, the diluent is calcium carbonate. In some embodiments, the diluent is calcium phosphate. In some embodiments, the diluent is starch. In some embodiments, the diluent is pregelatinized starch. In some embodiments, the diluent is sodium carbonate. In some embodiments, the diluent is mannitol.

[00132] In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 9% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 8% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 7% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 2% by weight of the dosage form.

[00133] In some embodiments, the pharmaceutical composition comprises a binder in about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 9% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 8% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 7% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 2% by weight of the dosage form. In

some embodiments, the pharmaceutical composition comprises a binder in about 1% by weight of the dosage form.

[00134] In some embodiments, the binder is selected from starches (corn starch and potato starch), gelatin, sucrose hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC). In some embodiments, the binder is hydroxypropyl cellulose (HPC). In some embodiments, the binder is starch. In some embodiments, the binder is gelatin. In some embodiments, the binder is polyvinylpyrrolidone (PVP). In some embodiments, the binder is hydroxypropyl methyl cellulose (HPMC).

[00135] In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 4.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 4.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 3.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 3.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 2.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 2.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 1.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 1% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 0.8% by weight of the dosage form.

[00136] In some embodiments, the pharmaceutical composition comprises a surfactant in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 4.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 4.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 3.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 3.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 2.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 2.0% by weight of the dosage form. In some embodiments,

the pharmaceutical composition comprises a surfactant in about 1.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 1% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.1% by weight of the dosage form.

[00137] In some embodiments, the surfactant is selected from sodium lauryl sulfate, cetrimide, benzalkonium chloride, cetylpyridinium chloride, alkylsulphates, alkylethoxylate sulphates, soaps, carboxylate ions, sulfate ions, sulfonate ions, polyoxyethylene derivatives, polyoxypropylene derivatives, polyol derivatives, polyol esters, polyoxyethylene esters, poloxamers, glycol, glycerol esters, sorbitan derivatives, polyethylene glycol (such as PEG-40, PEG-50, or PEG-55) and esters of fatty alcohols. In some embodiments, the surfactant is sodium lauryl sulfate.

[00138] In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 9% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 8% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 7% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 1.5% by weight of the dosage form.

[00139] In some embodiments, the pharmaceutical composition comprises a disintegrant in about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 9% by weight of the dosage form. In some

embodiments, the pharmaceutical composition comprises a disintegrant in about 8% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 7% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% by weight of the dosage form.

[00140] In some embodiments, the disintegrant is selected from starch, alginic acid, ac-di-sol, croscarmellose sodium, sodium starch glycolate, and crospovidone. In some embodiments the disintegrant is croscarmellose sodium. In some embodiments the disintegrant is sodium starch glycolate. In some embodiments the disintegrant is crospovidone.

[00141] In some embodiments, the pharmaceutical composition comprises a glidant in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 1% to about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 1% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 1% to about 2% by weight of the dosage form.

[00142] In some embodiments, the pharmaceutical composition comprises a glidant in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 1% by weight of the dosage form.

[00143] In some embodiments the glidant is colloidal silicon dioxide.

[00144] In some embodiments, the pharmaceutical composition comprises a lubricant in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 1% to about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in

about 1% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 1% to about 2% by weight of the dosage form.

[00145] In some embodiments, the pharmaceutical composition comprises a lubricant in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 1% by weight of the dosage form.

[00146] In some embodiments the lubricant is selected from talc, stearic acid, magnesium stearate and sodium stearyl fumarate. In some embodiments, the lubricant is talc. In some embodiments, the lubricant is stearic acid. In some embodiments, the lubricant is magnesium stearate. In some embodiments, the lubricant is sodium stearyl fumarate.

[00147] In some embodiments, the pharmaceutical composition comprises a granulating agent. In some embodiments, the granulating agent is purified water.

[00148] In some embodiments, the pharmaceutical composition comprises a first diluent in about 10% to about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 10% to about 40% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 0.5% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 0.5% to about 5%.

[00149] In some embodiments, the pharmaceutical composition comprises a first diluent in about 35% to about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 15% to about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a

disintegrant in about 2% to about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 0.5% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 0.5% to about 3% by weight of the dosage form.

Amounts

[00150] In some embodiments, the pharmaceutical composition comprises between about 50 mg and about 200 mg. In some embodiments, the pharmaceutical composition comprises about 50 mg. In some embodiments, the pharmaceutical composition comprises about 200 mg. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 500 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 450 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 400 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 350 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 300 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 250 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 200 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 175 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 150 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 125 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 100 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 90 mg of the crystalline composition comprising

[illegible]

the pharmaceutical composition comprises between about 1 mg and about 2 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[00151] In some embodiments, the pharmaceutical composition comprises between about 500 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 450 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 400 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 350 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 300 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 250 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 200 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 150 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 100 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 90 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 80 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 70 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 60 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 50 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 40 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 30 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some

embodiments, the pharmaceutical composition comprises between about 20 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 10 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 5 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[00152] In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprising Compound 1 comprises between about 50 mg and about 200 mg of Compound 1. In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprising Compound 1 comprises about 50 of Compound 1. In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprising Compound 1 comprises about 100 of Compound 1. In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprising Compound 1 comprises about 200 of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 450 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 400 mg Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 350 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 300 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 250 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 200 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 175 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 150 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 125 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 100 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 90 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 80 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and

about 70 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 60 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 50 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 40 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 30 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 20 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 10 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 9 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 8 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 7 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 6 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 5 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 4 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 3 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 2 mg of Compound 1. **[00153]** In some embodiments, the pharmaceutical composition comprises about 500 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 450 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 400 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 350 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 90 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 80 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 70 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 50

mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 40 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 20 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 10 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 5 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 1 mg Compound 1.

[00154] In some embodiments, the pharmaceutical composition comprises Compound I in about 25 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in about 10 % to about 50 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in about 10 % to about 15 %, about 10 % to about 20 %, about 10 % to about 25 %, about 10 % to about 30 %, about 10 % to about 35 %, about 10 % to about 40 %, about 10 % to about 45 %, about 10 % to about 50 %, about 15 % to about 20 %, about 15 % to about 25 %, about 15 % to about 30 %, about 15 % to about 35 %, about 15 % to about 40 %, about 15 % to about 45 %, about 15 % to about 50 %, about 20 % to about 25 %, about 20 % to about 30 %, about 20 % to about 35 %, about 20 % to about 40 %, about 20 % to about 45 %, about 20 % to about 50 %, about 25 % to about 30 %, about 25 % to about 35 %, about 25 % to about 40 %, about 25 % to about 45 %, about 25 % to about 50 %, about 30 % to about 35 %, about 30 % to about 40 %, about 30 % to about 45 %, about 30 % to about 50 %, about 35 % to about 40 %, about 35 % to about 45 %, about 35 % to about 50 %, about 40 % to about 45 %, about 40 % to about 50 %, or about 45 % to about 50 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, or about 50 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in at least about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, or about 45 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in at most about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, or about 50 % w/w.

[00155] In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 500 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 450 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 400 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to

about 350 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 300 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 250 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 200 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 150 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 100 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 90 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 80 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 70 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 60 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 50 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 40 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 30 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 20 mg.

[00156] In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 300 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 200 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 20 mg. In some

embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 10 mg.

[00157] In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 300 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 200 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 10 mg.

[00158] In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 300 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 200 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 10 mg.

[00159] In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 100 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 90 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 80 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 70 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 60 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 50 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 40 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 30 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 20 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 10 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 5 mg.

[00160] In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises

a binder in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 4 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 3 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 1 mg.

[00161] In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 50 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 40 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 30 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 20 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 10 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 9 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 8 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 7 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 6 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 5 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 4 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 3 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 2 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 1.5 mg.

[00162] In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is

about 20 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 4 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 3 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 1.75 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 1.5 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 1.25 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 1 mg.

[00163] In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 100 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 90 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 80 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 70 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 60 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 50 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 40 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 30 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 20 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 10 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 9 mg. In some embodiments,

the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 8 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 7 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 6 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 5 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 4 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 3 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 2 mg.

[00164] In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 4 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 3 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 2 mg. In

some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 1 mg.

[00165] In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 50 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 45 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 40 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 35 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 30 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 25 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 20 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 15 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 10 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 5 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 2 mg.

[00166] In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 4 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 3 mg. In some

embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 1 mg.

[00167] In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 50 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 45 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 40 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 35 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 30 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 25 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 20 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 15 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 10 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 5 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 2 mg.

[00168] In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 4 mg. In some

embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 3 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 1 mg.

[00169] In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is between about 1 mg to about 200 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is between about 1 mg to about 200 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg to about 100 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg to about 50 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 100 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg to about 50 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg to about 50 mg by weight of the dosage form.

[00170] In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is between about 1 mg to about 100 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is between about 1 mg to about 100 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and 20 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg to about 10 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 20 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg to about 20 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg to about 20 mg by weight of the dosage form.

Particle size

[00171] In some embodiments, the pharmaceutical composition (e.g., comprising the crystalline composition comprising Compound 1 (e.g., comprising Formula I)) is in the form

[illegible]

microparticles of the crystalline composition have an average size from about 4 μm . In some embodiments, microparticles of the crystalline composition have an average size from about 3 μm . In some embodiments, microparticles of the crystalline composition have an average size from about 2 μm . In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm . In some embodiments, microparticles of the crystalline composition have an average size less than about 100 μm . In some embodiments, microparticles of the crystalline composition have an average size less than about 90 μm . In some embodiments, microparticles of the crystalline composition have an average size less than about 80 μm . In some embodiments, microparticles of the crystalline composition have an average size less than about 70 μm . In some embodiments, microparticles of the crystalline composition have an average size less than about 60 μm . In some embodiments, microparticles of the crystalline composition have an average size less than about 50 μm . In some embodiments, microparticles of the crystalline composition have an average size less than about 40 μm . In some embodiments, microparticles of the crystalline composition have an average size less than about 30 μm . In some embodiments, microparticles of the crystalline composition have an average size less than about 20 μm . In some embodiments, microparticles of the crystalline composition have an average size less than about 10 μm . In some embodiments, microparticles of the crystalline composition have an average size less than about 5 μm .

[00172] In some embodiments, the pharmaceutical composition comprises the crystalline composition comprising Compound 1 (e.g., comprising Formula I), wherein the crystalline composition has a D90 from about 1 μm to about 50 μm . In some embodiments, the crystalline composition has a D90 from about 1 μm to about 20 μm , from about 2 μm to about 19 μm , from about 3 μm to about 18 μm , from about 4 μm to about 17 μm , from about 5 μm to about 16 μm , from about 6 μm to about 15 μm , from about 7 μm to about 14 μm , from about 8 μm to about 13 μm , from about 9 μm to about 13 μm , or from about 8 μm to about 12 μm . In some embodiments, the pharmaceutical composition comprises the crystalline composition comprising Compound 1 (e.g., comprising Formula I), wherein the crystalline composition has a D90 of more than about 1 μm , more than about 2 μm , more than about 3 μm , more than about 4 μm , more than about 5 μm , more than about 6 μm , more than about 7 μm , more than about 8 μm , more than about 9 μm , more than about 10 μm , more than about 11 μm , more than about 12 μm , more than about 13 μm , more than about 14 μm , more than about 15 μm , more than about 16 μm , more than about 17 μm , more than about 18 μm , or more than about 19 μm . In some embodiments, the crystalline composition has a

D90 of less than about 20 μm , less than about 19 μm , less than about 18 μm , less than about 17 μm , less than about 16 μm , less than about 15 μm , less than about 14 μm , less than about 13 μm , less than about 12 μm , or less than about 11 μm .

[00173] In some embodiments, the pharmaceutical composition comprising Compound 1 is in the form of microparticles. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 100 μm . In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 90 μm . In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 80 μm . In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 70 μm . In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 60 μm . In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 50 μm . In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 40 μm . In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 30 μm . In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 20 μm . In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 10 μm . In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 5 μm . In some embodiments, microparticles of Compound 1 have an average size from about 100 μm . In some embodiments, microparticles of Compound 1 have an average size from about 90 μm . In some embodiments, microparticles of Compound 1 have an average size from about 80 μm . In some embodiments, microparticles of Compound 1 have an average size from about 70 μm . In some embodiments, microparticles of Compound 1 have an average size from about 60 μm . In some embodiments, microparticles of Compound 1 have an average size from about 50 μm . In some embodiments, microparticles of Compound 1 have an average size from about 40 μm . In some embodiments, microparticles of Compound 1 have an average size from about 30 μm . In some embodiments, microparticles of Compound 1 have an average size from about 20 μm . In some embodiments, microparticles of Compound 1 have an average size from about 10 μm . In some embodiments, microparticles of Compound 1 have an average size from about 9 μm . In some embodiments, microparticles of Compound 1 have an average size from about 8 μm . In some embodiments, microparticles of Compound 1 have an average size from about 7 μm . In some embodiments, microparticles of Compound 1 have an average size from about 6 μm . In some embodiments, microparticles of Compound 1 have an average size from about 5 μm . In some embodiments, microparticles of Compound 1 have an

average size from about 4 μm . In some embodiments, microparticles of Compound 1 have an average size from about 3 μm . In some embodiments, microparticles of Compound 1 have an average size from about 2 μm . In some embodiments, microparticles of Compound 1 have an average size from about 1 μm . In some embodiments, microparticles of Compound 1 have an average size less than about 100 μm . In some embodiments, microparticles of Compound 1 have an average size less than about 90 μm . In some embodiments, microparticles of Compound 1 have an average size less than about 80 μm . In some embodiments, microparticles of Compound 1 have an average size less than about 70 μm . In some embodiments, microparticles of Compound 1 have an average size less than about 60 μm . In some embodiments, microparticles of Compound 1 have an average size less than about 50 μm . In some embodiments, microparticles of Compound 1 have an average size less than about 40 μm . In some embodiments, microparticles of Compound 1 have an average size less than about 30 μm . In some embodiments, microparticles of Compound 1 have an average size less than about 20 μm . In some embodiments, microparticles of Compound 1 have an average size less than about 10 μm . In some embodiments, microparticles of Compound 1 have an average size less than about 5 μm .

[00174] In some embodiments, the pharmaceutical composition comprises Compound 1, wherein Compound 1 has a D90 from about 1 μm to about 50 μm . In some embodiments, Compound 1 has a D90 from about 1 μm to about 20 μm , from about 2 μm to about 19 μm , from about 3 μm to about 18 μm , from about 4 μm to about 17 μm , from about 5 μm to about 16 μm , from about 6 μm to about 15 μm , from about 7 μm to about 14 μm , from about 8 μm to about 13 μm , from about 9 μm to about 13 μm , or from about 8 μm to about 12 μm . In some embodiments, the pharmaceutical composition comprises Compound 1, wherein Compound 1 has a D90 of more than about 1 μm , more than about 2 μm , more than about 3 μm , more than about 4 μm , more than about 5 μm , more than about 6 μm , more than about 7 μm , more than about 8 μm , more than about 9 μm , more than about 10 μm , more than about 11 μm , more than about 12 μm , more than about 13 μm , more than about 14 μm , more than about 15 μm , more than about 16 μm , more than about 17 μm , more than about 18 μm , or more than about 19 μm . In some embodiments, Compound 1 has a D90 of less than about 20 μm , less than about 19 μm , less than about 18 μm , less than about 17 μm , less than about 16 μm , less than about 15 μm , less than about 14 μm , less than about 13 μm , less than about 12 μm , or less than about 11 μm .

Methods of Preparing the Crystalline Composition Comprising Compound I (e.g., Comprising Formula I)

[00175] Isolation and purification of the chemical entities and intermediates described herein can be performed, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples below. However, other equivalent separation or isolation procedures can also be used. Prior to crystallization, Compound 1 may be isolated in about 50% chemical purity, 55% chemical purity, 60% chemical purity, 65% chemical purity, 70% chemical purity, 75% chemical purity, 80% chemical purity, 90% chemical purity, 91% chemical purity, 92% purity, 93% chemical purity, 94% chemical purity, 95% chemical purity, 96% chemical purity, 97% chemical purity, 98% chemical purity, 99% chemical purity, about 98% chemical purity, or about 100% chemical purity.

[00176] In some embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) disclosed herein are obtained by crystallizing Compound 1 with a chemical purity of less than about 98%, less than about 97%, less than about 96%, less than about 95%, less than about 94%, less than about 93%, less than about 92%, less than about 91%, less than about 90%, less than about 89%, less than about 88%, less than about 87%, less than about 86%, less than about 85%, less than about 84%, less than about 83%, less than about 82%, less than about 81%, less than about 80%, less than about 78%, less than about 76%, less than about 74%, less than about 72%, or less than about 70%. In some embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is obtained by crystallizing Compound 1 with a chemical purity in the range of about 70% to about 99%, 80% to about 96%, about 85% to about 96%, about 90% to about 96%, about 80% to 98%, about 85% to about 98%, about 90% to about 98%, about 92% to about 98%, about 94% to 98%, or about 96% to about 98%.

Preparation of Crystalline Form I

[00177] In some aspects, the present disclosure provides a method of preparing a crystalline composition comprising Compound I (e.g., comprising Formula I), wherein the method comprises:

(a) dissolving 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (Compound 1) and an acid (e.g., oxalic acid) in a solvent;

(b) heating the solution or slurry from step (a); and

(c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Compound I (e.g., comprising Formula I).

[00178] In some embodiments, the solvent in step (a) comprises acetone, heptane, water, 2-butanol, ethyl acetate, 2-propanol, methyl tert-butyl ether, ethanol, methyl ethyl ketone, 1-pentanol, or a combination thereof. In some embodiments, the solvent in step (a) is heptane. In some embodiments, the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone. In some embodiments, the solvent in step (a) is a mixture of heptane and methyl ethyl ketone.

[00179] In some embodiments, step (b) is heated at about 50 °C. In some embodiments, step (b) is heated to at least about 50 °C.

[00180] In some embodiments, the concentration of the solution comprising Compound 1 obtained in step (a) is between about 20 mg/mL and about 300 mg/mL. In some embodiments, the concentration of the solution comprising Compound 1 obtained in step (a) is between about 40 mg/mL and about 250 mg/mL. In some embodiments, the concentration of the solution comprising Compound 1 obtained in step (a) is between about 100 mg/mL and about 200 mg/mL. In some embodiments, the concentration of the solution comprising Compound 1 obtained in step (a) is between 125 mg/mL and about 175 mg/mL.

[00181] In various embodiments, the method of preparing the crystalline composition comprising Compound I (e.g., comprising Formula I) involves recrystallization of Compound 1 from a binary, tertiary, or greater solvent system, collectively understood as a multi-solvent system. In some embodiments, the method of preparing the crystalline composition comprising Compound I (e.g., comprising Formula I) involves crystallization from a mono- or multi-solvent system, where the crystallization involves dissolving Compound 1 in the mono- or multi-solvent system at a temperature above ambient temperature. In some embodiments, the dissolving of Compound 1 in the mono- or multi-solvent system is performed at a temperature of about 0-90 °C, 5-90 °C, 10-90 °C, 15-90 °C, 20-90 °C, 25-90 °C, 30-90 °C, 35-90 °C, 40-90 °C, 45-90 °C, 50-90 °C, 55-90 °C, 60-90 °C, 65-90 °C, 70-90 °C, 75-90 °C, 80-90 °C, 85-90 °C, 0-80 °C, 5-80 °C, 10-80 °C, 20-80 °C, 30-80 °C, 40-80 °C, 50-80 °C, 60-80 °C, 70-80 °C, 0-70 °C, 5-70 °C, 10-70 °C, 15-70 °C, 20-70 °C, 30-70 °C, 40-70 °C, 50-70 °C, 60-70 °C, 0-60 °C, 10-60 °C, 20-60 °C, 30-60 °C, 40-60 °C, or 50-60 °C.

[00182] In various embodiments, the crystallization further involves actively heating the solution containing the dissolved Compound 1, for example to a temperature of about 40-100

°C, 40-90 °C, 40-80 °C, 40-70 °C, 40-60 °C, 40-50 °C, 50-100 °C, 50-90 °C, 50-80 °C, 50-70 °C, 50-60 °C, 60-100 °C, 60-90 °C, 60-80 °C, 60-70 °C, 70-100 °C, 70-90 °C, 70-80 °C, 80-100 °C, or 80-90 °C. In various embodiments, the solution containing the dissolved Compound 1 is maintained at the heated temperature for a period of time, for example for about 30 min, about 1 h, about 2 h, about 3 h, about 4 h, about 5 h, about 6 h, about 7 h, about 8 h, about 9 h, about 10 h, about 11 h, about 12 h, about 13 h, about 14 h, about 15 h, about 16 h, about 17 h, about 18 h, about 19 h, about 20 h, about 21 h, about 22 h, about 23 h, about 24 h or more.

[00183] In various embodiments, the crystallization further involves actively cooling the heated solution containing the dissolved Compound 1, for example to a temperature of about 0-40 °C, 0-30 °C, 0-20 °C, 0-10 °C, 10-40 °C, 10-30 °C, 10-20 °C, 20-40 °C, 20-30 °C, 20-10 °C, or 30 °C-40 °C. In some embodiments, the crystallization further involves actively cooling the heated solution containing the dissolved Compound 1 to a temperature of about 20-30 °C. In various embodiments, the solution containing the dissolved Compound 1 is further maintained at this lower temperature for a time period, for example for about 30 min, about 1 h, about 2 h, about 3 h, about 4 h, about 5 h, about 6 h, about 7 h, about 8 h, about 9 h, about 10 h, about 11 h, about 12 h, about 13 h, about 14 h, about 15 h, about 16 h, about 17 h, about 18 h, about 19 h, about 20 h, about 21 h, about 22 h, about 23 h, about 24 h or more.

[00184] In various embodiments, the steps of active heating followed by active cooling are repeated multiple times, for example at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10 times. In some embodiments, the steps of active heating followed by active cooling are repeated 2, 3, 4, 5, 6, 7, 8, 9, or 10 times.

[00185] In various embodiments, the crystallization further involves filtering the solution containing the obtained crystals of the crystalline composition comprising Compound I (e.g., comprising Formula I). In some embodiments, the crystallization optionally involves washing the obtained crystals by a solvent, for example by the recrystallization solvent one or more times. In some embodiments, the crystallization optionally involves drying the obtained crystals, for example under vacuum.

[00186] In some embodiments, the chemical purity of the crystalline composition comprising Compound I (e.g., comprising Formula I) is greater than 60%, 70%, 80%, 90%, 95%, or 99%. In some embodiments, the chemical purity of the crystalline composition comprising Compound I (e.g., comprising Formula I) is greater than about 90%. In some embodiments, the chemical purity of the crystalline composition comprising Compound I (e.g., comprising Formula I) is greater than about 95%. In some embodiments, the chemical purity of the

crystalline composition comprising Compound I (e.g., comprising Formula I) is greater than about 99%. The chemical purity of the crystalline composition comprising Compound I (e.g., comprising Formula I) may be measured by any available analytical technique, for example by HPLC analysis.

[00187] In various embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is dry. In various embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is non-solvated. In various embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is non-hydrated. In various embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is anhydrous.

Methods of Treatment

[00188] In another aspect, the present disclosure provides a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I as described herein, or a pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein. In some embodiments, the subject has congenital adrenal hyperplasia (CAH).

[00189] In another aspect, the present disclosure provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or a pharmaceutical composition comprising a crystalline composition comprising Formula I as described herein. In some embodiments, the CAH is classic CAH. In some embodiments, the CAH is non-classical CAH.

[00190] In another aspect, the present disclosure provides a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or a pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism, and alopecia.

[00191] In another aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or a pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein.

[00192] In another aspect, the present disclosure provides a method of improving metabolic symptoms in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein. In some embodiments, the metabolic symptoms are selected from the group consisting of body weight, BMI, fat mass, waist circumference, blood pressure and glycemic control.

[00193] In another aspect, the present disclosure provides a method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein.

[00194] In another aspect, the present disclosure provides a method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or the pharmaceutical composition comprising the crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein.

[00195] In another aspect, the present disclosure provides a method of treating endometriosis or improving the symptoms of endometriosis in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition improves the symptom of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the

pharmaceutical composition reduces the symptoms of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition prevents the symptom of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition eliminates the symptom of pain experienced by the subject.

[00196] In some embodiments, the methods described herein result in the reduction of a hormone level. Such hormones include deoxycorticosterone, 11-deoxycortisol, Cortisol, corticosterone, aldosterone, pregnenolone, hydroxy pregnenolone, progesterone, 17a-hydroxy progesterone (17-OHP), dehydroepiandrosterone, androstenediol, androstenedione, testosterone, dihydrotestosterone, estrone, estradiol, estriol, and adrenocorticotrophic hormone (ACTH). In some embodiments, the methods described herein result in the reduction of 17a-hydroxy progesterone (17-OHP). In some embodiments, the methods described herein result in the reduction of adrenocorticotrophic hormone (ACTH), also known as corticotropin.

[00197] In various embodiments of the methods as described herein, a composition comprising Compound I, or the crystalline composition or the pharmaceutical composition (e.g., comprising Compound 1) is administered at a dose from about 5 mg/day to about 1000 mg/day. In some embodiments, the crystalline composition or the pharmaceutical composition is administered in a fed state. In some embodiments, the crystalline composition or the pharmaceutical composition is administered in a fasted state. In some embodiments, the crystalline composition or the pharmaceutical composition is administered at least once per day.

[00198] In some embodiments of the methods described herein, the composition, or the crystalline composition or the pharmaceutical composition is administered at bedtime. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical composition described herein less than about 4 hours before sleep. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical composition described herein less than about 3 hours before sleep. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical composition described herein less than about 2 hours before sleep. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical compositions described herein less than about 1 hour before sleep. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical compositions described herein less than about 30 mins before sleep.

[00199] In some embodiments, the methods described herein include administration of the crystalline composition (e.g., comprising Compound 1) or the pharmaceutical compositions (e.g., comprising Compound 1) described herein at or before the expected circadian release of adrenocorticotrophic hormone (ACTH). In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical compositions described herein about 3-4 hours before the expected circadian release of adrenocorticotrophic hormone (ACTH).

[00200] In various embodiments of the methods as described herein, the method further comprises administering to the subject an additional therapeutic agent. In some embodiments, the additional therapeutic agent is glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen agent. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone. In some embodiments, the additional therapeutic agent is another CRF1 antagonist.

[00201] In various embodiments of the methods as described herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the crystalline composition as described herein, or the pharmaceutical composition comprising the crystalline composition as described herein. In some embodiments, the additional therapy is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the crystalline composition as described herein, or the pharmaceutical composition comprising the crystalline composition as described herein.

[00202] In various embodiments of the methods, the subject is from about 9 years of age to about 18 years of age. In some embodiments, the subject is from about 8 years of age to about 55 years of age.

[00203] In some aspects, described herein are crystalline compositions comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine ("crinecerfont"). In some embodiments, crinecerfont is a salt (e.g., hydrochloric acid salt, p-toluenesulfonic acid salt, etc.). Pharmaceutically acceptable acid addition salts of crinecerfont may be formed by combining a compound having a basic moiety with inorganic acids and organic acids. Inorganic acids which may be used to prepare salts of crinecerfont include, for example,

hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids which may be used to prepare salts of crinecerfont include, for example, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and the like.

Pharmaceutically acceptable base addition salts of crinecerfont may be formed by combining a compound having an acidic moiety with inorganic and organic bases. Inorganic bases which may be used to prepare salts of crinecerfont include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, manganese, aluminum hydroxides, carbonates, bicarbonates, phosphates, and the like. In some embodiments, the inorganic base salt is ammonium, potassium, sodium, calcium, and magnesium hydroxides, carbonates, bicarbonates, or phosphates. Organic bases from which may be used to prepare salts of crinecerfont include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Generally, such salts of crinecerfont may be prepared by reacting the free acid or base forms of these compounds with at least a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN). In some embodiments, they crystalline composition comprises crinecerfont and oxalic acid.

[00204] In some embodiments, the crystalline composition comprising crinecerfont comprises crinecerfont and an acid in a ratio of crinecerfont to acid of about 2:1, about 1:1, or about 1:2.

[00205] In some embodiments, the composition comprising crinecerfont is in a capsule (e.g., an immediate-release capsule or a capsule for opening (e.g., comprising crinecerfont granules)).

[00206] In some aspects, disclosed herein are methods of administering a composition (e.g., crystalline composition) comprising crinecerfont. In some embodiments, the method further comprises administering an additional therapeutic. In some embodiments, the additional therapeutic. In some embodiments, the additional therapeutic comprises hydrocortisone. In some embodiments, the hydrocortisone is an immediate-release hydrocortisone. In some embodiments, the hydrocortisone is in a capsule (e.g., a capsule for opening (e.g., hydrocortisone granules in a capsule)). In some embodiments, the hydrocortisone is an modified-release hydrocortisone. In some embodiments, the hydrocortisone is in a hard-capsule (e.g., a modified-release hard capsule).

ADDITIONAL EMBODIMENTS

[00207] The following embodiments are given for the purpose of illustrating various embodiments of the disclosure and are not meant to limit the present disclosure or any aspect thereof (e.g., element) in any fashion. The following embodiments may include additional elements disclosed herein. Changes therein and other uses which are encompassed within the spirit of the disclosure as defined by the scope of the claims will occur to those skilled in the art.

1. A pharmaceutical formulation, comprising:
 - (a) about 10 mg to about 300 mg of 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5- α) pyrimidine (Compound 1), or a pharmaceutically acceptable salt or solvate thereof;
 - (b) a first diluent in about 40% to about 45% by weight, wherein the first diluent comprises lactose monohydrate;
 - (c) a second diluent in about 25% by weight, wherein the second diluent comprises microcrystalline cellulose;
 - (d) about 1% to about 6% by weight of hydroxypropyl cellulose;
 - (e) about 0.5% to about 5% by weight of sodium lauryl sulfate; and
 - (f) about 4% by weight of croscarmellose sodium.
2. The pharmaceutical formulation of embodiment 1, further comprising a glidant, wherein the glidant comprises colloidal silicon dioxide.
3. The pharmaceutical formulation of embodiment 1, further comprising a lubricant, wherein the lubricant comprises magnesium stearate.
4. The pharmaceutical formulation of embodiment 3, wherein the magnesium stearate is about 1% by weight of the pharmaceutical formulation.
5. The pharmaceutical formulation of embodiment 3, wherein the magnesium stearate is in an amount that is about 2 mg.
6. The pharmaceutical formulation of embodiment 1, wherein Compound 1 or a pharmaceutically acceptable salt thereof is in an amount that is about 50 mg.
7. The pharmaceutical formulation of embodiment 1, wherein the lactose monohydrate is about 40.25% by weight of the pharmaceutical formulation.
8. The pharmaceutical formulation of embodiment 1, wherein the lactose monohydrate is in an amount that is about 80.50 mg.
9. The pharmaceutical formulation of embodiment 1, wherein the microcrystalline cellulose is in an amount that is about 50 mg.

10. The pharmaceutical formulation of embodiment 1, wherein the hydroxypropyl cellulose is about 3% by weight of the pharmaceutical formulation.
11. The pharmaceutical formulation of embodiment 1, wherein the hydroxypropyl cellulose is in an amount that is about 6 mg.
12. The pharmaceutical formulation of embodiment 1, wherein the sodium lauryl sulfate is about 0.75% by weight of the pharmaceutical formulation.
13. The pharmaceutical formulation of embodiment 1, wherein the sodium lauryl sulfate is in an amount that is about 1.50 mg.
14. The pharmaceutical formulation of embodiment 1, wherein the croscarmellose sodium is in an amount that is about 8 mg.
15. The pharmaceutical formulation of embodiment 2, wherein the colloidal silicon dioxide is about 1% by weight of the pharmaceutical formulation.
16. The pharmaceutical formulation of embodiment 2, wherein the colloidal silicon dioxide is in an amount that is about 2 mg.
17. The pharmaceutical formulation of embodiment 3, wherein the magnesium stearate is about 1% by weight of the pharmaceutical formulation.
18. The pharmaceutical formulation of embodiment 3, wherein the magnesium stearate is in an amount that is about 2 mg.
19. The pharmaceutical formulation of embodiment 1, wherein the pharmaceutical formulation is in a tablet form.
20. The pharmaceutical formulation of embodiment 1, wherein the pharmaceutical formulation is in a granule form.
21. The pharmaceutical formulation of embodiment 1, wherein the pharmaceutical formulation is in a capsule.
22. The pharmaceutical formulation of embodiment 1, wherein the pharmaceutical formulation is packaged in a sachet.

EXAMPLES

[00208] The following examples serve to further describe the manner of using the present disclosure. These examples are presented for illustrative purpose and should not serve to limit the true scope of the present disclosure.

[00209] In carrying out the procedures of the methods described herein, it is of course to be understood that references to particular buffers, media, reagents, cells, culture conditions, and the like are not intended to be limiting, but are to be read so as to include all related materials

that one of ordinary skill in the art would recognize as being of interest or value in the particular context in which that discussion is presented. For example, it is often possible to substitute on buffer system or culture medium for another and still achieve similar, if not identical, results. Those of skill in the art will have sufficient knowledge of such systems and methodologies so as to be able, without undue experimentation, to make such substitutions as will optimally serve their purposes in using the methods and procedures disclosed herein.

Example 1 – Preparation and Characterization of the Crystalline Composition Comprising Compound I (e.g., comprising Formula I)

Preparation of the Crystalline Composition Comprising Compound I (e.g., comprising Formula I)

[00210] A mixture of 185.0 mg (0.441 mmol) of 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (**Compound 1**), 45.0 mg (0.500 mmol) of oxalic acid, and 2.5 mL of diisopropyl ether was agitated. After one hour, an additional 1 mL of diisopropyl ether was added. After stirring overnight, the mixture was vacuum filtered and the resulting solid was dried to afford 170 mg (76%) of the crystalline composition comprising Compound I (e.g., comprising Formula I) as solid.

X-Ray Powder Diffraction

[00211] X-ray powder diffraction (XPRD) patterns were obtained on a Rigaku Smart-Lab X-ray diffraction system. A CuK source ($\lambda = 0.71073 \text{ \AA}$) operating minimally at 40 kV and 44 mA scans each sample between 2 and 40 degrees 2θ . The step size is $0.02^\circ 2\theta$.

[00212] The XRPD pattern obtained for the crystalline composition comprising Compound I (e.g., comprising Formula I) is summarized in Table 1 below and shown in **FIG. 1**.

Table 1 – XRPD Data of the Crystalline Composition Comprising Compound I (e.g., comprising Formula I)					
Peak #	Angle ($^\circ 2\theta$)	Intensity (%)	Peak #	Angle ($^\circ 2\theta$)	Intensity (%)
1	5.44	31	26	26.58	4
2	8.82	12	27	26.80	14
3	10.84	100	28	26.94	8
4	11.70	12	29	27.62	3
5	14.60	8	30	28.00	13

Table 1 – XRPD Data of the Crystalline Composition Comprising Compound I (e.g., comprising Formula I)					
6	15.56	6	31	28.86	14
7	15.96	52	32	29.54	3
8	16.28	5	33	31.26	3
9	16.70	10	34	31.66	5
10	17.66	4	35	31.88	4
11	18.44	5	36	32.16	3
12	18.82	6	37	32.48	2
13	19.18	8	38	32.86	5
14	19.60	2	39	33.46	2
15	20.02	11	40	34.36	2
16	20.50	11	41	35.02	3
17	20.78	20	42	35.44	1
18	21.72	7	43	35.98	2
19	22.12	2	44	36.72	4
20	22.74	18	45	37.04	3
21	23.04	16	46	37.80	5
22	23.44	31	47	38.28	2
23	24.80	48	48	38.90	2
24	25.52	6	49	39.20	2
25	25.92	9			

Differential Scanning Calorimetry (DSC)

[00213] Differential scanning calorimetry analysis was carried out on a TA Instruments Q2500 Discovery Series instrument. The instrument temperature calibration was performed using indium. The DSC cell was kept under a nitrogen purge of about 50 mL per minute during each analysis. The sample was placed in a standard, crimped, aluminum pan and was heated from approximately 25 °C to 350 °C at a rate of 10 °C per minute. The DSC trace of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 2**.

Thermogravimetric Analysis (TGA)

[00214] Thermogravimetry analyses were carried out using a TA Instruments Discovery TGA 5500 instrument that was cooled using a TA Instruments Refrigerated Cooling System (RCS) 90 chiller. The instrument balance was calibrated using class M weights and temperature calibration was performed by measurement of the Curie point of Alumel®. Sample was loaded onto a platinum sample pan and the pan was loaded into the TG instrument. The pan was heated from ambient temperature to 350 °C at a rate of 10 °C per minute. The instrument was controlled using TA Trios software. The TGA trace of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 3**.

Dynamic Vapor Sorption (DVS)

[00215] The DVS analysis was carried out on a TA Instruments Q5000 sorption analyzer. The instrument was calibrated with standard weights and a sodium bromide standard for humidity. For each analysis, a portion of the sample was weighed into a metal-coated, quartz pan. Each sample was analyzed at 25 °C with a maximum equilibration time of 60 minutes in 10% relative humidity (RH) steps from 5 to 95% RH (adsorption cycle) and from 95 to 5% RH (desorption cycle). Data collection was performed using Advantage for Q Series version 5.5.23. The percent weight change values were calculated using Microsoft Excel®. The DVS trace of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 4**.

Infrared (IR)

[00216] The IR spectrum was obtained using a Nicolet iS50 Model 60825 Fourier-transform (FT) IR spectrophotometer equipped with a deuterated triglycine sulfate (DTGS) detector, a potassium bromide (KBr) beamsplitter, and an electronically temperature controlled (ETC) Ever-Glo® IR source. The instrument was configured with a SMART iTR diamond attenuated total reflectance (ATR) sampling accessory. The single beam scan of the background (air) and sample were collected with 128 signal-averaged scans at a resolution of 2 cm⁻¹ over the spectral range 400-4000 cm⁻¹. The wavelength calibration was verified using a certified polystyrene standard. Data collection and processing was performed using Omnic 9.2 software. The IR spectrum of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 5**.

Proton Nuclear Magnetic Resonance (¹H NMR)

[00217] The ¹H NMR spectrum was acquired on a Bruker Avance 400 MHz spectrometer using TopSpin v3.2 software. The sample was dissolved in CD₃OD and the resulting solution was transferred into a 5-mm NMR tube for subsequent data acquisition. Data collection parameters are shown in Table 14. The spectrum was processed using the program MNova and referenced to the chemical shift of the residual protons in CD₃OD (3.31 ppm). The ¹H NMR spectrum of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 6**.

Raman

[00218] The Raman spectrum was acquired utilizing a Thermo Scientific model iS50 Fourier-transform (FT) IR spectrophotometer equipped with a Raman accessory. The system is equipped with an indium gallium arsenide (InGaAs) detector, a calcium fluoride (CaF₂) beamsplitter, and a 2.5 W laser operating at 1064 nm. The module was configured with a 180° reflective sampling accessory. A sample was prepared by loading particles onto a glass slide. Each FT-Raman spectrum was collected using 0.50 W laser power with 256 signal-averaged scans at a resolution of 4 cm⁻¹ over the spectral range 100-3700 cm⁻¹. The wavelength calibration was verified using a polystyrene. Data acquisition and processing were performed using Omnic 9.7 software. The Raman spectrum of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 7**.

Example 2 – Formulation Comprising Compound 1*General Manufacturing Procedure*

[00219] The relevant excipients were manually sieved and then dry mixed. A binder solution was added and the mixture subjected to wet granulation. The granules were then wet milled and dried. The resulting granules were dry milled and added to other relevant common granules and excipients. The mixture was then compressed into tablets to a target tablet weight.

[00220] A granulation was developed with a minimum amount and number of excipients. The granulation comprised of Compound 1 (“Tildacerfont”) with a surfactant and a binder and, in some cases, a super-disintegrant. After granulation was successful, other excipients were added to enable compression. These excipients included a compression aid, a lubricant, an anti-tacking agent, and a super-disintegrant.

[00221] Table 1 below summarizes formulations comprising Tildacerfont in both tablet and granules form.

Table 2 – Formulation Comprising Tildacerfont				
Material Description	Function	%w/w	mg/Tablet	Granules
			50 mg strength	50 mg strength
Intragranular				
Tildacerfont (SPN001)	Active ingredient	25.00	50.00	50.00
Lactose Monohydrate, USP/NF, Ph. Eur., JP. (Pharmatose 200M EU)	Diluent	40.25	80.50	80.50
Hydroxypropylcellulose USP/NF, Ph. Eur., JP (Klucel EXF)	Binder	3.00	6.00	6.00
Sodium Lauryl Sulfate, NF/ Ph. Eur./JP (Kolliphor SLS fine)	Surfactant	0.75	1.50	1.50
Microcrystalline Cellulose, NF, Ph.Eur., JP (Avicel PH101)	Diluent	20.00	40.00	40.00
Purified Water, USP, Ph. Eur	Granulating agent	QS*	-	-
Extragranular				
Microcrystalline Cellulose, NF, Ph.Eur., JP (Avicel PH101)	Diluent	5.00	10.00	10.00
Croscarmellose Sodium NF, Ph. Eur., JP (Ac-Di-Sol) SD-711	Disintegrant	4.00	8.00	8.00
Colloidal Silicon dioxide USP/NF, Ph. Eur., JP (Aerosil 200)	Glidant	1.00	2.00	2.00
Magnesium stearate, NF, Ph. Eur., JP (Hyqual 2257)	Lubricant	1.00	2.00	2.00
Total		100.00	200.00	200.00

Table 2 – Formulation Comprising Tildacerfont				
Film Coating				
Opadry II Yellow 85F42129	Film former	3.00	6.00	-
Purified Water, USP, Ph. Eur	Coating dispersion medium	QS*	-	-
Total		100.00	206.00	200.00

Example 3 – Stability of Crystalline Compositions Comprising Compound 1

[00222] To determine the stability of the crystalline compositions prepared comprising the methods described herein, crystalline compositions comprising Compound 1 and oxalic acid were formulated. Samples of the crystalline composition comprising Compound 1-oxalic acid co-crystal were packed in a transparent low-density polyethylene (LDPE) bag, and closed by twisting the bag and tying it with a strip seal. The transparent LDPE bag was then placed in a black LDPE bag that was twisted and tied with a strip seal. The bags were then placed in a high-density polyethylene container.

[00223] The samples were then subjected to accelerated aging conditions ($40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ relative humidity (RH)) or long-term storage conditions ($25 \pm 2^\circ\text{C}$ / $60 \pm 5\%$ RH). Sample stability measurements in each condition were measured at baseline (before exposure to accelerated aging conditions or long-term storage conditions), and one month, two months, and three months after exposure to said conditions. Sample stability measurements included a description of the sample's physical appearance (e.g., color and form), identification by Fourier-transform infrared spectroscopy (FT-IR), identification by X-ray powder diffraction (XRPD), water content (measured by Karl Fischer (KF) on a % weight/weight basis), identification of related substances (e.g., impurities), and high-performance liquid chromatography ((HPLC) measured on a % weight/weight on an anhydrous basis and solvent free basis).

[00224] **Table 3** summarizes the results of the measurements obtained from samples exposed to the accelerated aging conditions over the course of one to three months. **Table 4** summarizes the results of the study obtained from the samples exposed to the long-term storage conditions over the course of one to three months.

Table 3. Stability data under accelerated aging conditions.

Parameter	Specification	Baseline	1 Month	2 Months	3 Months
Description	Off-white to yellow color solid	Light yellow color solid	Light yellow color solid	Light yellow color solid	Light yellow color solid
Identification by FT-IR	IR spectrum of sample should be concordant with that of reference standard	IR spectrum of sample is concordant with that of reference standard	IR spectrum of sample is concordant with that of reference standard	IR spectrum of sample is concordant with that of reference standard	IR spectrum of sample is concordant with that of reference standard
Identification by XRPD	Diffraction pattern of the sample should be consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4 ±0.2°	Diffraction pattern of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4	Diffraction pattern of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.7, 15.9, 23.4	Diffraction pattern of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4	Diffraction pattern of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4
Water Content by KF (% w/w)	NMT 0.5	0.02	0.09	0.02	0.08
Related Substances by HPLC (% area) (see a.-d.)					

a. C07102401- F-Imp1	NMT 0.15	BDRL	BDRL	BDRL	BDRL
b. C07102401- F-Imp2	NMT 0.15	BDRL	BDRL	BDRL	BDRL
c. Any unspecified impurity	NMT 0.10	BDRL	BDRL	BDRL	BDRL
d. Total impurities	NMT 1.0	BDRL	BDRL	BDRL	BDRL
Assay of Compound 1 by HPLC (% w/w on anhydrous basis and solvent free basis)	NLT 98.0 and NMT 102.0	99.9	99.2	100.1	99.2

n/a: not applicable; NLT: not less than; NMT; not more than; BDRL: below disregard limit

[00225] The above data from **Table 3** indicates that the Compound 1-oxalic acid co-crystal is stable up to 3 months at accelerated aging conditions (40 ± 2 °C / 75 ± 5 % RH).

Table 4. Stability data under long-term storage conditions.

Parameter	Specificatio n	Baseline	1 Month	2 Months	3 Months
Description	Off-white to yellow color solid	Light yellow color solid	Light yellow color solid	Light yellow color solid	Light yellow color solid
Identificatio n by FT-IR	IR spectrum of sample should be	IR spectrum of sample is concordant	IR spectrum of sample is concordant	IR spectrum of sample is concordant	IR spectrum of sample is concordant

	concordant with that of reference standard	with that of reference standard	with that of reference standard	with that of reference standard	with that of reference standard
Identification by XRPD	Diffraction pattern of the sample should be consistent with characteristic 2- θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4 $\pm 0.2^\circ$	Diffraction pattern of the sample is consistent with characteristic 2- θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4	Diffraction pattern of the sample is consistent with characteristic 2- θ value of Form-I at 5.4, 8.8, 10.8, 11.7, 15.9, 23.4	Diffraction pattern of the sample is consistent with characteristic 2- θ value of Form-I at 5.4, 8.7, 10.8, 11.6, 15.9, 23.3	Diffraction pattern of the sample is consistent with characteristic 2- θ value of Form-I at 5.4, 8.7, 10.8, 11.6, 15.9, 23.4
Water Content by KF (% w/w)	NMT 0.5	0.02	0.10	0.03	0.05
Related Substances by HPLC (% area) (see a.-d.)					
a. C07102401-F-Imp1	NMT 0.15	BDRL	BDRL	BDRL	BDRL
b. C07102401-F-Imp2	NMT 0.15	BDRL	BDRL	BDRL	BDRL

c. Any unspecified impurity	NMT 0.10	BDRL	BDRL	BDRL	BDRL
d. Total impurities	NMT 1.0	BDRL	BDRL	BDRL	BDRL
Assay of Compound 1 by HPLC (% w/w on anhydrous basis and solvent free basis)	NLT 98.0 and NMT 102.0	99.9	99.2	100.1	99.2

n/a: not applicable; NLT: not less than; NMT; not more than; BDRL: below disregard limit

[00226] The above data from **Table 4** indicates that the Compound 1-oxalic acid co-crystal is stable up to 3 months at long-term storage conditions (25 ± 2 °C / 60 ± 5 % RH).

Example 4 – Stability of Crystalline Compositions Comprising Compound 1 for 6 Months

[00227] Samples of the crystalline composition comprising Compound 1-oxalic acid co-crystal prepared in Example 3 are subjected to accelerated aging conditions (40 ± 2 °C / 75 ± 5 % relative humidity (RH)) or long-term storage conditions (25 ± 2 °C / 60 ± 5 % RH).

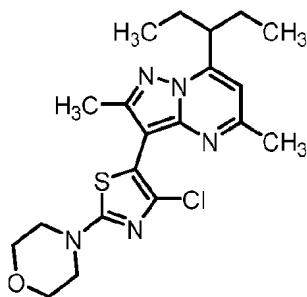
Sample stability measurements in each condition are measured at baseline (before exposure to accelerated aging conditions or long-term storage conditions), and four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, twelve months, fourteen months, sixteen months, and eighteen months after exposure to said conditions. Sample stability measurements include a description of the sample's physical appearance (e.g., color and form), identification by Fourier-transform infrared spectroscopy (FT-IR), identification by X-ray powder diffraction (XRPD), water content (measured by Karl Fischer (KF) on a % weight/weight basis), identification of related substances (e.g., impurities), and high-performance liquid chromatography ((HPLC) measured on a % weight/weight on an anhydrous basis and solvent free basis).

[00228] The samples of the crystalline composition comprising Compound 1-oxalic acid co-crystal will be stable at four months, five months, six months, seven months, eight months,

nine months, ten months, eleven months, twelve months, fourteen months, sixteen months, and eighteen months after exposure to said conditions, as demonstrated by sample stability measurements. Said sample stability measurements at four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, twelve months, fourteen months, sixteen months, and eighteen months after exposure to said conditions will be in accordance with the results listed in **Table 3** and **Table 4**.

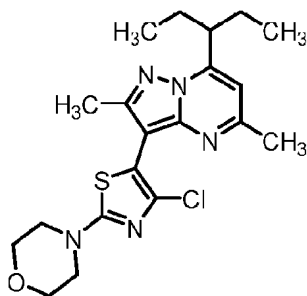
CLAIMS

1. A pharmaceutical composition comprising a CRF1 antagonist, wherein the composition is characterized by an X-ray powder diffraction pattern comprising a peak selected from any one or more of $10.84 \pm 0.2^\circ$ 2- θ , $15.96 \pm 0.2^\circ$ 2- θ , $23.44 \pm 0.2^\circ$ 2- θ , and $24.80 \pm 0.2^\circ$ 2- θ .
2. The pharmaceutical composition of claim 1, wherein the composition is measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.
3. The pharmaceutical composition of claim 1 or 2, wherein the X-ray powder diffraction pattern further comprising at least one peak selected from $5.44 \pm 0.2^\circ$ 2- θ , $20.78 \pm 0.2^\circ$ 2- θ , $22.74 \pm 0.2^\circ$ 2- θ , $23.04 \pm 0.2^\circ$ 2- θ , $26.80 \pm 0.2^\circ$ 2- θ , and $28.86 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.
4. The pharmaceutical composition of any one of claims 1 to 3, wherein the X-ray powder diffraction pattern further comprising at least five peaks selected from $8.82 \pm 0.2^\circ$ 2- θ , $11.70 \pm 0.2^\circ$ 2- θ , $14.60 \pm 0.2^\circ$ 2- θ , $15.56 \pm 0.2^\circ$ 2- θ , $16.70 \pm 0.2^\circ$ 2- θ , $18.82 \pm 0.2^\circ$ 2- θ , $19.18 \pm 0.2^\circ$ 2- θ , $20.02 \pm 0.2^\circ$ 2- θ , $20.50 \pm 0.2^\circ$ 2- θ , $21.72 \pm 0.2^\circ$ 2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.
5. The pharmaceutical composition of any one of claims 1 to 4, wherein the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C.
6. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram substantially similar to the one set forth in FIG. 2.
7. The pharmaceutical composition of any one of claims 1 to 6, wherein the CRF1 antagonist comprises Compound 1:



Compound 1

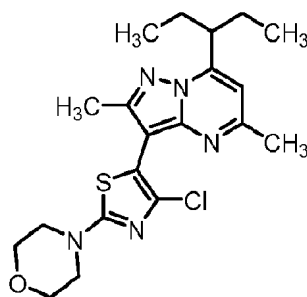
- or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.
8. The pharmaceutical composition of any one of claims 1 to 7, wherein the pharmaceutical composition is a crystalline pharmaceutical composition.
9. The pharmaceutical composition of claim 8, wherein the crystalline pharmaceutical composition further comprises oxalic acid.
10. The pharmaceutical composition of claim 9, wherein the crystalline pharmaceutical composition comprises Compound 1 and oxalic acid in a molar ratio of about 2:1.
11. A pharmaceutical composition comprising a CRF1 antagonist, wherein the pharmaceutical composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C.
12. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C.
13. The pharmaceutical composition of claim 11 or 12, wherein the pharmaceutical composition is characterized by a melting point of about 166 °C.
14. The pharmaceutical composition of any one of claims 11 to 13, wherein the CRF1 antagonist comprises Compound 1:



Compound 1

- or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.
15. The pharmaceutical composition of any one of claims 11 to 14, wherein the pharmaceutical composition is a crystalline pharmaceutical composition.
16. The pharmaceutical composition of claim 15, wherein the crystalline pharmaceutical composition further comprises oxalic acid.
17. The pharmaceutical composition of claim 16, wherein the crystalline pharmaceutical composition comprises Compound 1 and oxalic acid in a molar ratio of about 2:1.

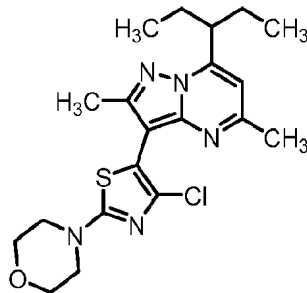
18. The pharmaceutical composition of any one of claims 11 to 17, wherein the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C.
19. A method of preparing a crystalline composition comprising Compound 1:



Compound 1,

wherein the method comprises:

- (a) dissolving Compound 1 and an acid in a solvent;
 - (b) heating the solution or slurry from step (a); and
 - (c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Compound 1.
20. The method of claim 19, wherein the acid comprises oxalic acid.
 21. The method of claim 19 or 20, wherein the solvent in step (a) is heptane.
 22. The method of claim 19 or 20, wherein the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone.
 23. The method of claim 19 or 20, wherein the solvent in step (a) is a mixture of heptane and methyl ethyl ketone.
 24. The method of any one of claims 19 to 23, wherein step (b) is heated at about 50 °C.
 25. A pharmaceutical composition comprising Compound 1:



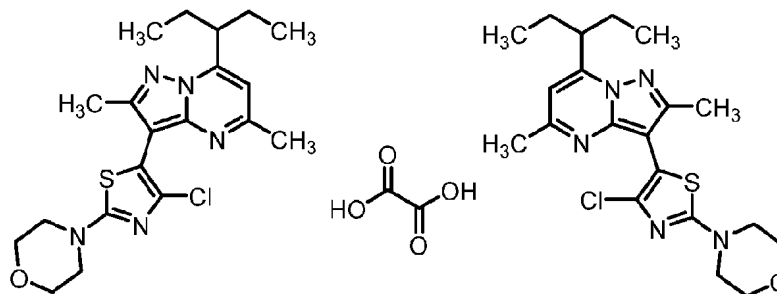
Compound 1, or a pharmaceutically acceptable salt or solvate thereof,

- wherein Compound 1 is present in an amount of 25% w/w; and
a diluent in about 5% to about 70%
26. The pharmaceutical composition of claim 25, wherein Compound 1 is in an amount of about 50 mg to about 200 mg.
 27. The pharmaceutical composition of claim 25, wherein Compound 1 is in an amount of about 50 mg.
 28. The pharmaceutical composition of claim 25, wherein the diluent is selected from the group consisting of calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose monohydrate, and a combination thereof.
 29. The pharmaceutical composition of claim 28, wherein the diluent is lactose monohydrate.
 30. The pharmaceutical composition of claim 29, wherein the lactose monohydrate is about 20% to about 45% by weight of the pharmaceutical composition.
 31. The pharmaceutical composition of claim 29, wherein the lactose monohydrate is about 20% to about 40.25% by weight of the pharmaceutical composition.
 32. The pharmaceutical composition of claim 31, wherein the lactose monohydrate is in an amount that is about 16.1, 40.25, 80.5, or 322 mg.
 33. The pharmaceutical composition of claim 28, wherein the diluent is microcrystalline cellulose.
 34. The pharmaceutical composition of claim 28, further comprising a second diluent, wherein the second diluent comprises microcrystalline cellulose
 35. The pharmaceutical composition of claim 33, wherein the microcrystalline cellulose is about 25% by weight of the pharmaceutical composition.
 36. The pharmaceutical composition of claim 35, wherein the microcrystalline cellulose is in an amount that is about 50 mg.
 37. The pharmaceutical composition of claim 25, further comprising a binder, wherein the binder is selected from the group consisting of corn starch and potato starch, gelatin, sucrose hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC), and a combination thereof.
 38. The pharmaceutical composition of claim 37, wherein the binder comprises HPC.
 39. The pharmaceutical composition of claim 38, wherein the HPC is about 3% by weight of the solid dosage form.

40. The pharmaceutical composition of claim 25, further comprising a surfactant, wherein the surfactant is selected from the group consisting of sodium lauryl sulfate, tetradecyl trimethyl ammonium bromide with dodecyl, hexadecyl compound, benzalkonium chloride, cetylpyridinium chloride, alkylsulphate, alkylethoxylate sulphate, soap, carxylate ion, sulfate ion, sulfonate ion, polyoxyethylene derivative, polyoxypropylene derivative, polyol derivative, polyol ester, polyoxyethylene ester, poloxamers, glycol, glycerol ester, sorbitan derivative, and polyethylene glycol, and a combination thereof.
41. The pharmaceutical composition of claim 40, wherein the surfactant comprises sodium lauryl sulfate.
42. The pharmaceutical composition of claim 41, wherein the sodium lauryl sulfate is about 0.75% by weight of the solid dosage form.
43. The pharmaceutical composition of claim 42, wherein the sodium lauryl sulfate is in an amount that is about 1.5 mg.
44. The pharmaceutical formulation of claim 25, further comprising a disintegrant, wherein the disintegrant is selected from the group consisting of starch, alginic acid, ac-di-sol, croscarmellose sodium, sodium starch glycolate, and crospovidone, and a combination thereof.
45. The pharmaceutical formulation of claim 44, wherein the disintegrant comprises croscarmellose sodium.
46. The pharmaceutical formulation of claim 25, further comprising a glidant, wherein the glidant comprises colloidal silicon dioxide.
47. The pharmaceutical formulation of claim 46, wherein the colloidal silicon dioxide is about 1% by weight of the solid dosage form.
48. The pharmaceutical formulation of claim 46, wherein the colloidal silicon dioxide is in an amount that is about 2 mg.
49. The pharmaceutical formulation of claim 25, further comprising a lubricant, wherein the lubricant is selected from the group consisting of talc, stearic acid, magnesium stearate, sodium stearyl fumarate, and a combination thereof.
50. The pharmaceutical formulation of claim 25, wherein the pharmaceutical formulation is in a solid dosage form.

51. The pharmaceutical formulation of claim 50, wherein the solid dosage form is a tablet.
52. The pharmaceutical formulation of claim 50, wherein the solid dosage form is a granules form.
53. The pharmaceutical formulation of claim 52, wherein said granules form is packaged in a capsule.
54. The pharmaceutical formulation of claim 52, wherein said granules form is packaged in a sachet.
55. A pharmaceutical formulation, comprising:
- (a) about 10 mg to about 300 mg of 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5- α) pyrimidine (Compound 1), or a pharmaceutically acceptable salt or solvate thereof;
 - (b) a first diluent in about 40% to about 45% by weight, wherein the first diluent comprises lactose monohydrate;
 - (c) a second diluent in about 25% by weight, wherein the second diluent comprises microcrystalline cellulose;
 - (d) about 1% to about 6% by weight of hydroxypropyl cellulose;
 - (e) about 0.5% to about 5% by weight of sodium lauryl sulfate; and
 - (f) about 4% by weight of croscarmellose sodium.

56. A crystalline composition comprising Formula I:

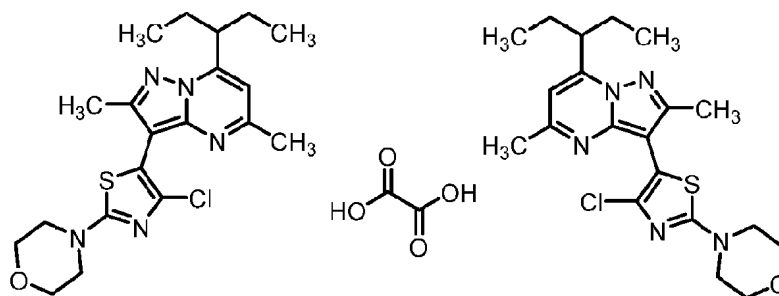


Formula I.

57. The crystalline composition of claim 56, wherein the crystals have unit cell parameters at $T = 150^\circ\text{K}$ of: $a = 34.003(4) \text{ \AA}$, $b = 6.5843(13) \text{ \AA}$, $c = 21.062(5) \text{ \AA}$; $\beta = 108.703(12)^\circ$, $V = 4466.5(15) \text{ \AA}^3$ and a monoclinic $C2/c$ space group.
58. The crystalline composition of claim 56, wherein the crystalline composition is characterized by:

- (a) an X-ray powder diffraction pattern comprising peaks at $10.84 \pm 0.2^\circ$ 2- θ , $15.96 \pm 0.2^\circ$ 2- θ , $23.44 \pm 0.2^\circ$ 2- θ , and $24.80 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å;
 - (b) an X-ray powder diffraction pattern substantially the same as shown in FIG. 1;
 - (c) a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C;
 - (d) a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C;
 - (e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2;
 - (f) a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C;
 - (g) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3; or
 - (h) combinations thereof.
59. The crystalline composition of any one of claim 56, wherein the crystalline composition is characterized by an X-ray powder diffraction pattern comprising peaks at $10.84 \pm 0.2^\circ$ 2- θ , $15.96 \pm 0.2^\circ$ 2- θ , $23.44 \pm 0.2^\circ$ 2- θ , and $24.80 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.
60. The crystalline composition of claim 59, wherein the X-ray powder diffraction pattern further comprising at least one peak selected from $5.44 \pm 0.2^\circ$ 2- θ , $20.78 \pm 0.2^\circ$ 2- θ , $22.74 \pm 0.2^\circ$ 2- θ , $23.04 \pm 0.2^\circ$ 2- θ , $26.80 \pm 0.2^\circ$ 2- θ , and $28.86 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.
61. The crystalline composition of claim 59, wherein the X-ray powder diffraction pattern further comprising at least five peaks selected from $8.82 \pm 0.2^\circ$ 2- θ , $11.70 \pm 0.2^\circ$ 2- θ , $14.60 \pm 0.2^\circ$ 2- θ , $15.56 \pm 0.2^\circ$ 2- θ , $16.70 \pm 0.2^\circ$ 2- θ , $18.82 \pm 0.2^\circ$ 2- θ , $19.18 \pm 0.2^\circ$ 2- θ , $20.02 \pm 0.2^\circ$ 2- θ , $20.50 \pm 0.2^\circ$ 2- θ , $21.72 \pm 0.2^\circ$ 2- θ , $25.52 \pm 0.2^\circ$ 2- θ , $25.92 \pm 0.2^\circ$ 2- θ , $26.94 \pm 0.2^\circ$ 2- θ , and $28.00 \pm 0.2^\circ$ 2- θ , and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.
62. The crystalline composition of any one of claims 56 to 61, wherein the crystalline composition is characterized by an X-ray powder diffraction pattern substantially the same as shown in FIG. 1.

63. The crystalline composition of any one of claims 56 to 62, wherein the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C.
64. The crystalline composition of any one of claims 56 to 62, wherein the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C.
65. The crystalline composition of any one of claims 56 to 64, wherein the crystalline composition is characterized by a melting point of about 166 °C.
66. The crystalline composition of any one of claims 56 to 65, wherein the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2.
67. The crystalline composition of any one of claims 56 to 66, wherein the crystalline composition is characterized by a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3.
68. The crystalline composition of any one of claims 56 to 67, wherein the crystalline composition is characterized by a dynamic vapor sorption (DVS) trace substantially the same as shown in FIG. 4.
69. A method of preparing a crystalline composition comprising Formula I:



Formula I,

wherein the method comprises:

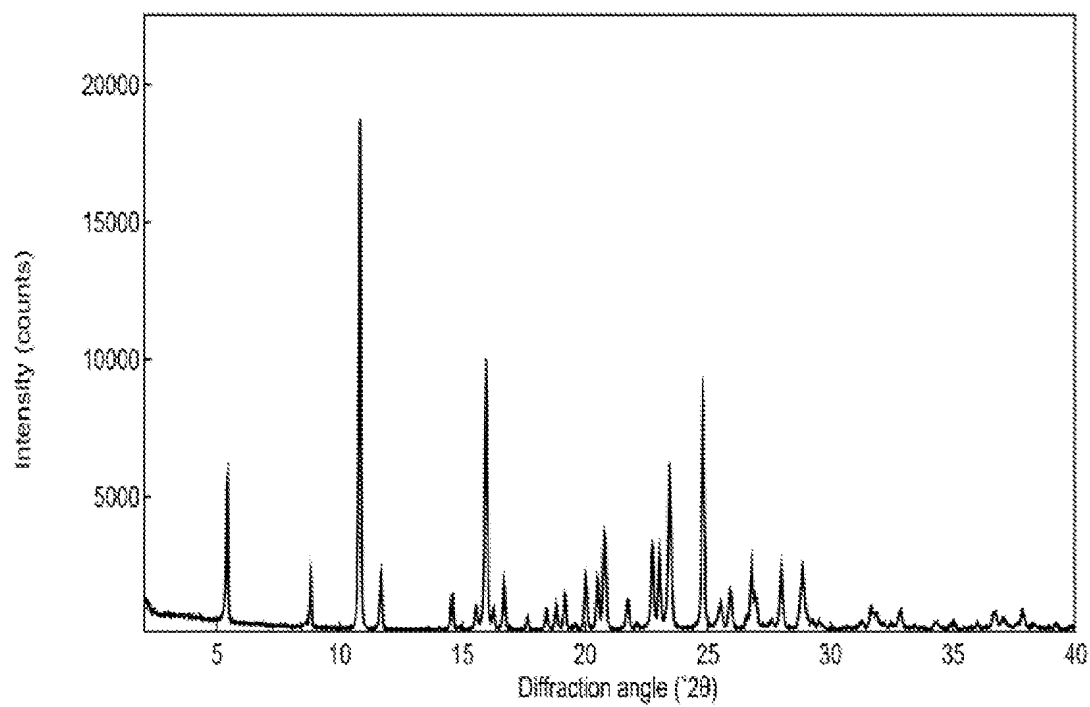
- (a) dissolving 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (Compound 1) and oxalic acid in a solvent;
- (b) heating the solution or slurry from step (a); and
- (c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Formula I.

70. The method of claim 69, wherein the solvent in step (a) comprises acetone, heptane, water, 2-butanol, ethyl acetate, 2-propanol, methyl tert-butyl ether, ethanol, methyl ethyl ketone, 1-pentanol, or a combination thereof.
71. The method of claim 70, wherein the solvent in step (a) is heptane.
72. The method of claim 70, wherein the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone.
73. The method of claim 70, wherein the solvent in step (a) is a mixture of heptane and methyl ethyl ketone.
74. The method of claim 69, wherein step (b) is heated at about 50 °C.
75. A method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof, comprising administering the subject the crystalline composition of any one of the preceding claims.
76. The method of claim 75, wherein the subject has congenital adrenal hyperplasia (CAH).
77. A method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
78. The method of claim 77, wherein the CAH is classic CAH.
79. The method of claim 77, wherein the CAH is non-classical CAH.
80. A method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
81. The method of claim 80, wherein the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism, and alopecia.
82. A method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
83. A method of improving metabolic symptoms in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
84. The method of claim 83, wherein the metabolic symptoms are selected from the group consisting of body weight, BMI, fat mass, waist circumference, blood pressure and glycemic control.
85. A method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a

- subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
86. A method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, administering to the subject the crystalline composition of any one of the preceding claims.
87. A method of treating endometriosis or improving the symptoms of endometriosis in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
88. The method of claim 87, wherein the administration of the crystalline composition or the pharmaceutical composition improves the symptom of pain experienced by the subject.
89. The method of claim 87, wherein the administration of the crystalline composition or the pharmaceutical composition reduces the symptom of pain experienced by the subject.
90. The method of claim 87, wherein the administration of the crystalline composition or the pharmaceutical composition prevents the symptom of pain experienced by the subject.
91. The method of claim 87, wherein the administration of the crystalline composition or the pharmaceutical composition eliminates the symptom of pain experienced by the subject.
92. The method of any one of claims 75 to 87, wherein the crystalline composition or the pharmaceutical composition is administered at a dose from about 5 mg/day to about 1000 mg/day.
93. The method of any one of claims 75 to 92, wherein the crystalline composition or the pharmaceutical composition is 75to in a fed state.
94. The method of any one of claims 75 to 92, wherein the crystalline composition or the pharmaceutical composition is administered in a fasted state.
95. The method of any one of claims 75 to 94, wherein the crystalline composition or the pharmaceutical composition is administered at least once per day.
96. The method of any one of claims 75 to 95, further comprising administering to the subject an additional therapeutic agent.
97. The method of anyone of the preceding claims, wherein the method further comprises administering an additional therapeutic agent, wherein the additional therapeutic agent is glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen agent.
98. The method of claim 97, wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone.
99. The method of claim 97, wherein the mineralocorticoid is fludrocortisone.

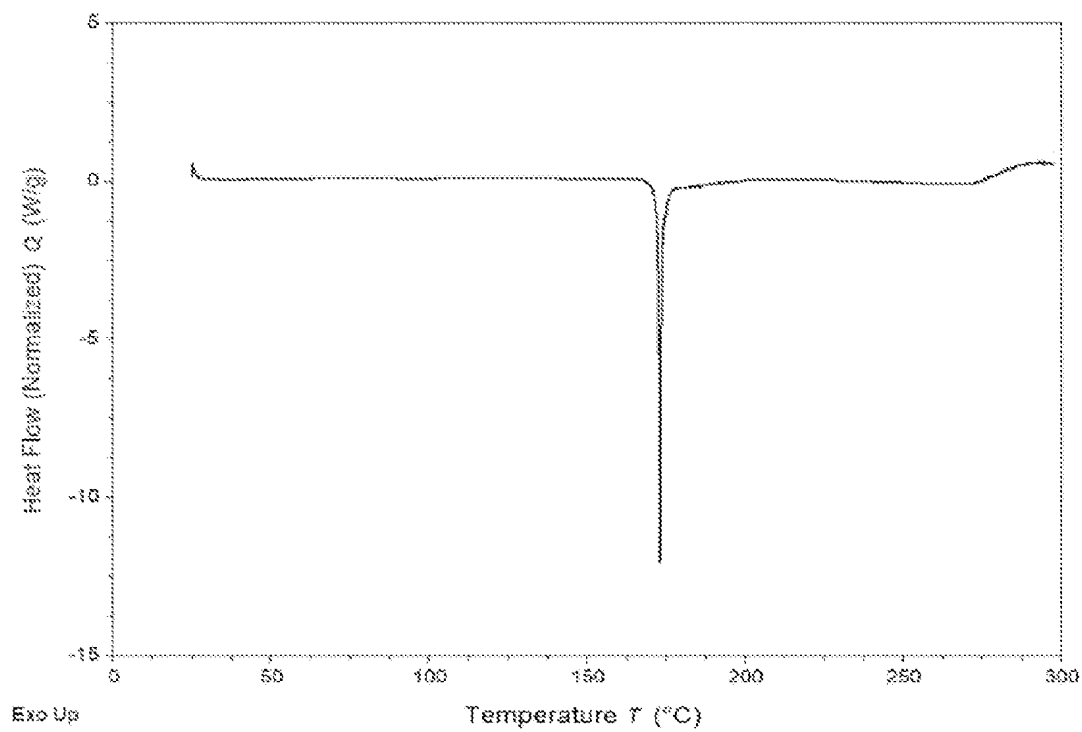
100. The method of claim 97, wherein the additional therapeutic agent is another CRF₁ antagonist.
101. The method of any one of claims 75 to 100, further comprising an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.
102. The method of claim 101, wherein the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the crystalline composition of any one of the preceding claims.
103. The method of any one of claims 75 to 97, wherein the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the crystalline composition of any one of the preceding claims.
104. The method of any one of the preceding claims, wherein the subject is from about 9 years of age to about 18 years of age.
105. The method of any one of the preceding claims, wherein the subject is from about 8 years of age to about 55 years of age.

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FIG. 1

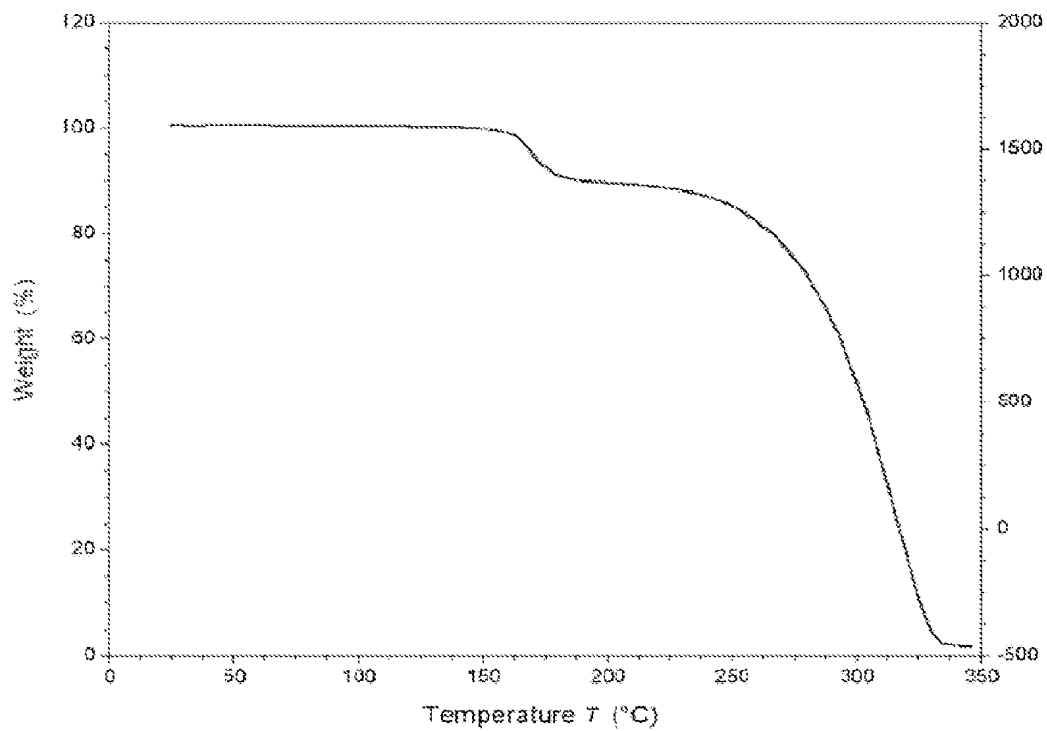
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FIG. 2



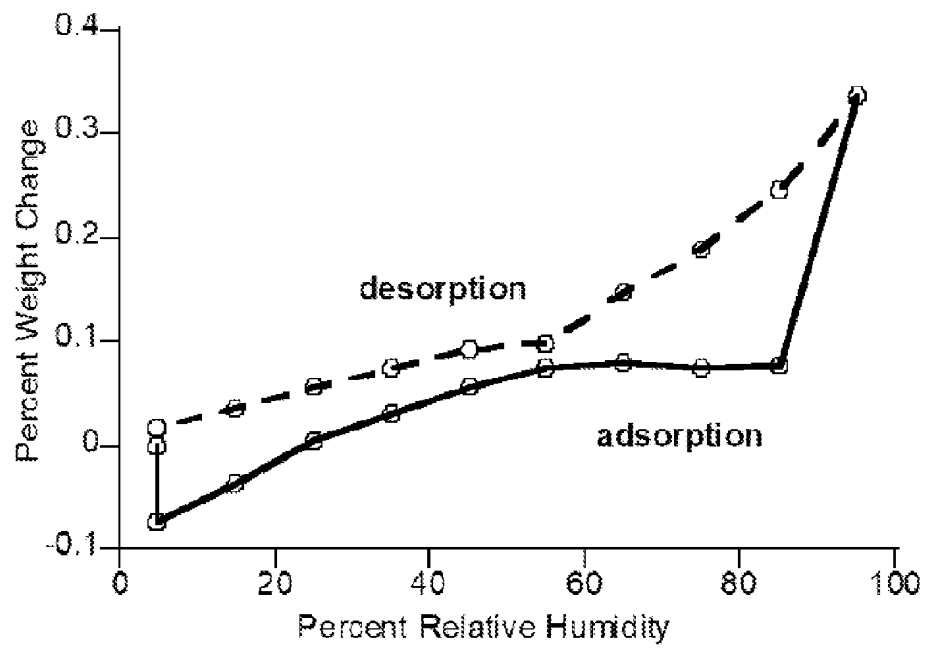
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FIG. 3



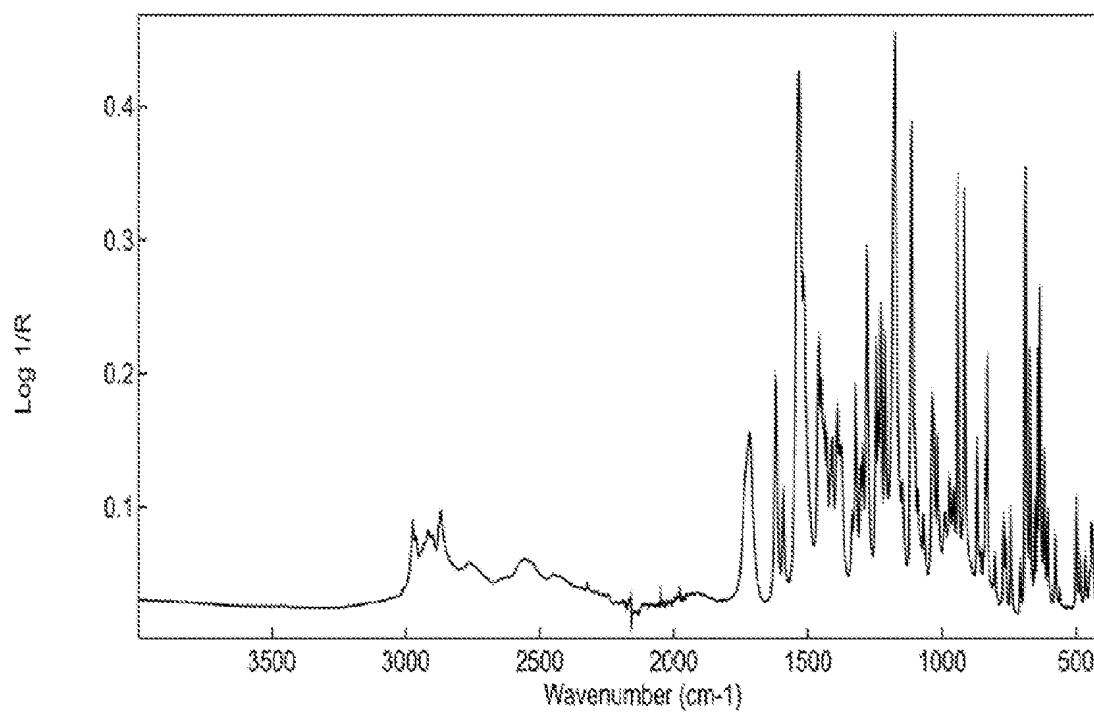
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FIG. 4



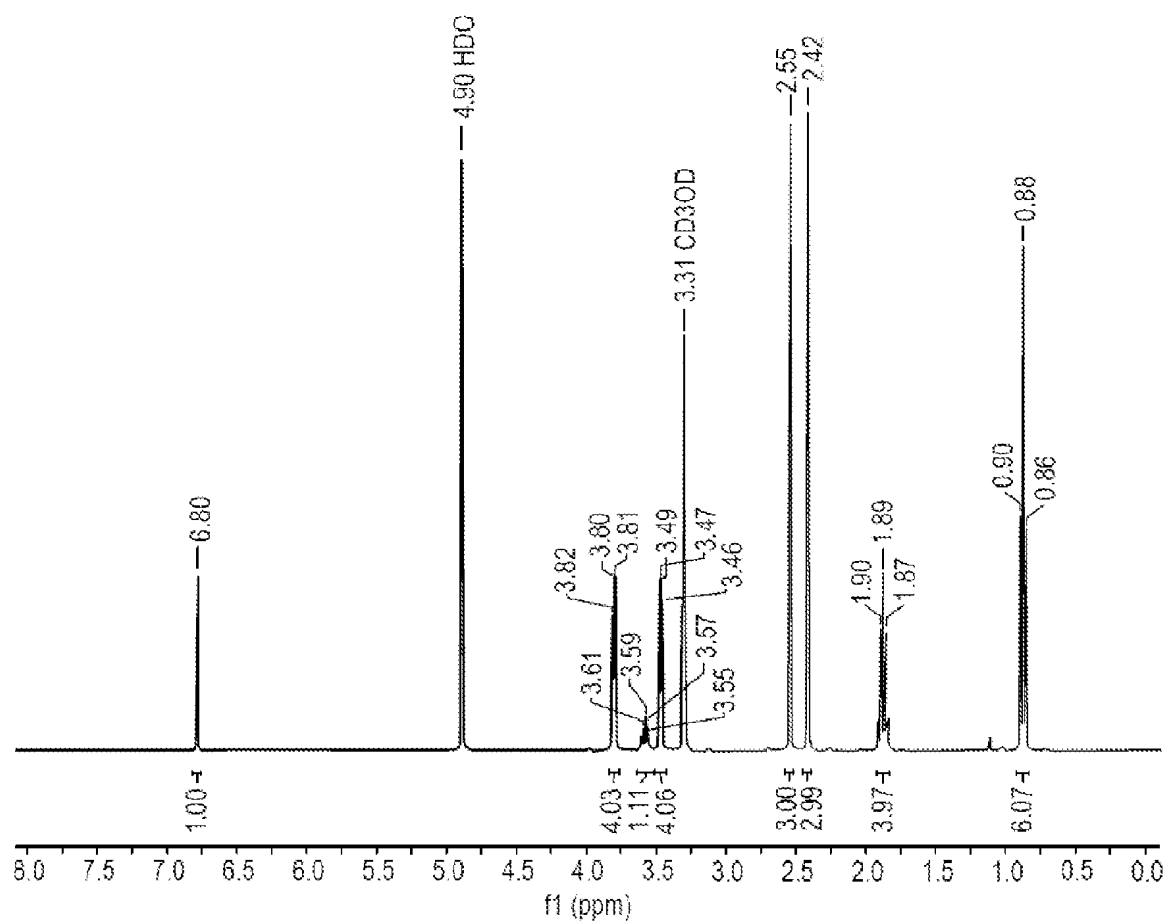
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FIG. 5



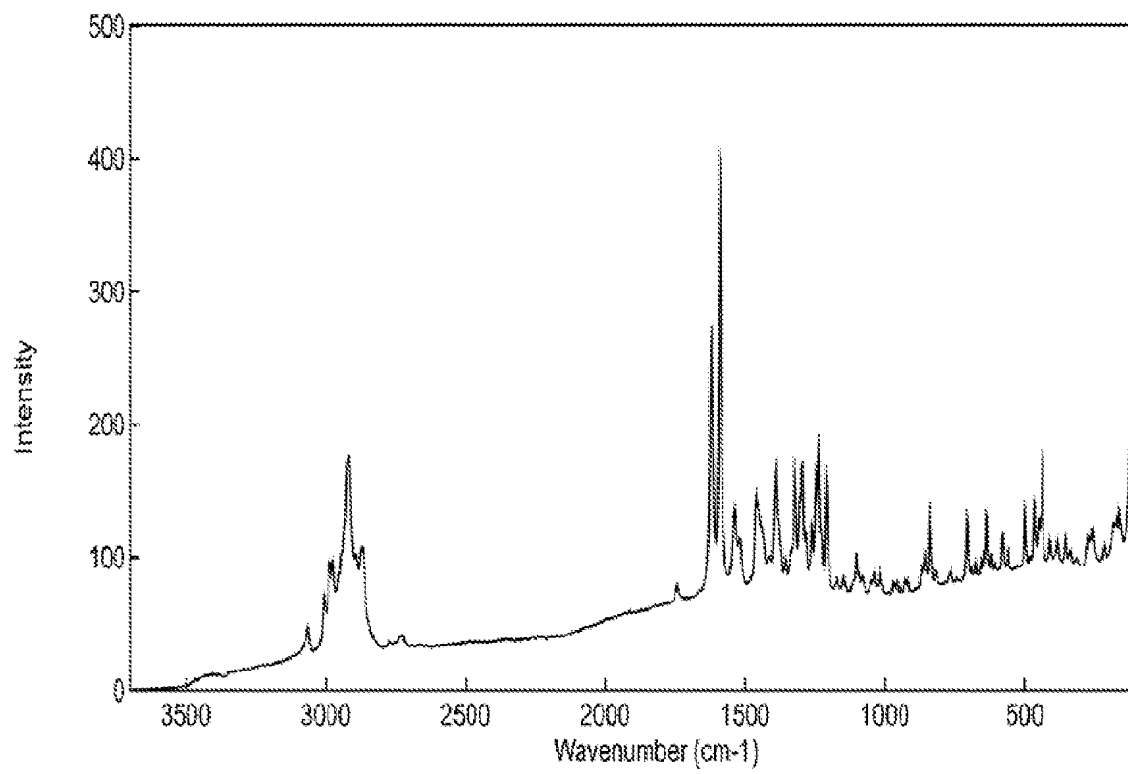
6/7

FIG. 6



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FIG. 7



Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER

**C07D 487/04 (2006.01) A61K 31/5377 (2006.01) A61K 47/12 (2006.01) A61K 9/00 (2006.01) A61P 5/38 (2006.01)
A61P 15/08 (2006.01) A61P 5/24 (2006.01)**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Google, EPOQUE and STN Search - PATENW, BIOSIS, CAPLUS, EMBASE, MEDLINE, REGISTRY; Keywords – tildacerfont, oxalic acid, corticotropin releasing factor, CRHRI, CRF1, congenital adrenal hyperplasia, CAH, and related terms

Applicant/Inventor Search - Espacenet, PubMed, AusPAT, Google Patents, IP Australia Internal Databases, REDDY, Dasharatha; RAJAGOPAL, Ashokraj; WANG, Lu; BARNES, Christopher; SPRUCE BIOSCIENCES, INC.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents:	
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
20 February 2023

Date of mailing of the international search report
20 February 2023

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/US2022/050436
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021016208 A1 (SPRUCE BIOSCIENCES, INC.) 28 January 2021 [0125]-[0126]; Examples 2-3	25-55 and 75-105
X	US 2020/0255436 A1 (Spruce Biosciences, Inc.) 13 August 2020 Abstract; [0019]; Example 10-12, Table 12 and 15-16	25-55 and 75-105
X	Sarafoglou K, Barnes CN, Huang M, Imel EA, Madu II, Merke DP, Moriarty D, Nakhle S, Newfield RS, Vogiatzi MG, Auchus RJ. Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies. J Clin Endocrinol Metab. 2021 Oct 21;106(11):c4666-c4679. doi: 10.1210/clinem/dgab438. Abstract	25-55 and 75-105
X	WO 2008/036579 A1 (ELI LILLY AND COMPANY) 27 March 2008 Abstract; Example 16	25-55 and 75-105

Form PCT/ISA/210 (fifth sheet) (July 2019)

3502

Supplemental Box**Continuation of: Box III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

- Claims 1-24 and 56-74 (in full), and claims 75-105 (in part) are directed to compositions comprising a salt crystal form of tildacerfont, wherein the feature of the salt crystal form of tildacerfont is specific to this group of claims
- Claims 25-55 (in full), and claims 75-105 (in part) are directed to compositions comprising tildacerfont available in any form, wherein the feature of tildacerfont is specific to this group of claims

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed inventions and which provides a technical relationship among them is tildacerfont

However it is considered that this feature is generic in this particular art. Therefore in this light this common feature cannot be a special technical feature. Hence there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a priori*.

International application No.

PCT/US2022/050436

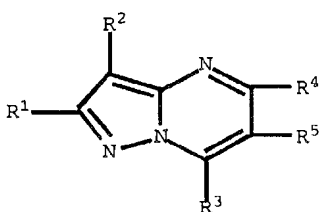
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		MX 2009003125 A	28 May 2009
		MY 146388 A	15 Aug 2012
		NZ 575572 A	28 Oct 2011
		PE 20081377 A1	18 Sep 2008
		RS 51545 B	30 Jun 2011
		TN 2009000095 A1	19 Aug 2010
		TW 200821312 A	16 May 2008
		TW I402269 B	21 Jul 2013
		US 2010222339 A1	02 Sep 2010
		US 8030304 B2	04 Oct 2011

End of Annex



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 487/04, A61K 31/519, A61P 25/00	A2	(11) International Publication Number: WO 00/59908 (43) International Publication Date: 12 October 2000 (12.10.00)
(21) International Application Number: PCT/US00/09111 (22) International Filing Date: 6 April 2000 (06.04.00) (30) Priority Data: 60/128,006 6 April 1999 (06.04.99) US (71) Applicant: DU PONT PHARMACEUTICALS COMPANY [US/US]; Chestnut Run Plaza, 974 Centre Road, Wilmington, DE 19807 (US). (72) Inventors: GILLIGAN, Paul, J.; 2629 Pennington Drive, Wilmington, DE 19810 (US). WILDE, Richard, G.; 205 Roseman Court, Newark, DE 19711 (US). (74) Agent: RUBIN, Kenneth, B.; Du Pont Pharmaceuticals Company, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).		(81) Designated States: AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, VN, ZA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: PYRAZOLOPYRIMIDINES AS CRF ANTAGONISTS <div style="text-align: center;">  (I) </div> (57) Abstract <p>The present invention relates to pyrazolopyrimidines according to formula (I) and stereoisomers, isomers and salts thereof wherein R¹-R⁵ are selected from certain alkyl, aryl and heteroaryl species as defined in the specification wherein all of the compounds are useful as CRF antagonists and are thus useful in the treatment of neurological disorders as well as a multitude of other CRF associated diseases or conditions.</p>		

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EE	Estonia						

TITLE

PYRAZOLOPYRIMIDINES AS CRF ANTAGONISTS

5

FIELD OF THE INVENTION

The present invention relates to novel compounds, compositions, and methods for the treatment of psychiatric disorders and neurological diseases, including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders, as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress. In particular, the present invention relates to novel pyrazolo[1,5-a]pyrimidines, pharmaceutical compositions containing such compounds and their use in treating psychiatric disorders, neurological diseases, immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin (POMC) - derived peptide secretion from the anterior pituitary gland [J. Rivier et al., Proc. Nat. Acad. Sci. (USA) 80:4851 (1983); W. Vale et al., Science 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., Rec. Prog. Horm. Res. 39:245 (1983); G.F. Koob, Persp. Behav. Med. 2:39 (1985); E.B. De

Souza et al., J. Neurosci. 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, Physiological Reviews 69:1 (1989); J.E. Morley, Life Sci. 41:527 (1987)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, Hosp. Practice 23:59 (1988)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., Science 226:1342 (1984); C.M. Banki et al., Am. J. Psychiatry 144:873 (1987); R.D. France et al., Biol. Psychiatry 28:86 (1988); M. Arato et al., Biol Psychiatry 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., Arch. Gen. Psychiatry 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., Am J. Psychiatry 141:619 (1984); F. Holsboer et al., Psychoneuroendocrinology 9:147 (1984); P.W. Gold et al., New Eng. J. Med. 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, Arch. Gen. Psychiatry 46:1047 (1989)]. There is preliminary evidence that tricyclic antidepressants

can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., Neuropsychopharmacology 2:53 (1989)].

It has also been postulated that CRF has a role in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., Life Sci. 31:363 (1982); C.W. Berridge and A.J. Dunn Regul. Peptides 16:83 (1986)]. Preliminary studies using the putative CRF receptor antagonist α -helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn Horm. Behav. 21:393 (1987), Brain Research Reviews 15:71 (1990)].

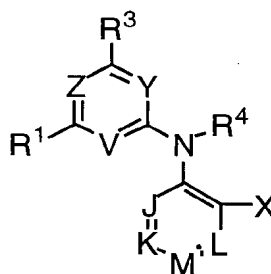
Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., Psychopharmacology 86:170 (1985); K.T. Britton et al., Psychopharmacology 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al., Psychopharmacology 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., Psychopharmacology 94:306 (1988)].

It has been further postulated that CRF has a role in immunological, cardiovascular or heart-related diseases such as hypertension, tachycardia and congestive heart failure, stroke, osteoporosis, premature birth, psychosocial dwarfism, stress-induced

fever, ulcer, diarrhea, post-operative ileus and colonic hypersensitivity associated with psychopathological disturbance and stress.

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (a-helical CRF9-41) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

DuPont Merck PCT application US94/11050 describes
20 corticotropin releasing factor antagonist compounds of
the formula:

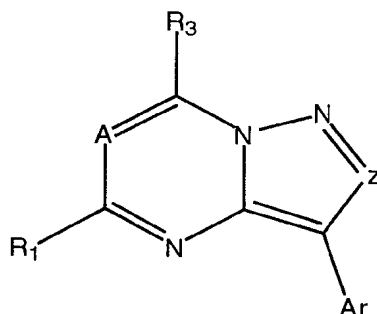


and their use to treat psychiatric disorders and neurological diseases. Included in the description are
25 fused pyridines and pyrimidines of the formula:

5

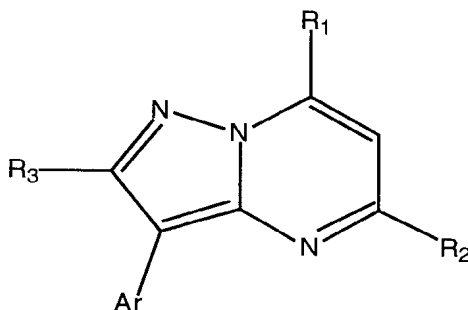
where: V is CR^{1a} or N; Z is CR² or N; A is CR³⁰ or N; and D is CR²⁸ or N.

WO 98/03510, published in January, 1998, also describes a series of CRF antagonist compounds having the
5 formula:



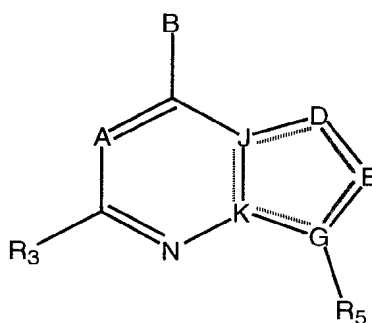
wherein z is N or CR² and A is N or CR.

WO 97/29109, published in August, 1997, similarly
10 describes certain CRF antagonist compounds having the formula:



wherein Ar is phenyl, pyridyl and substituted versions
15 thereof.

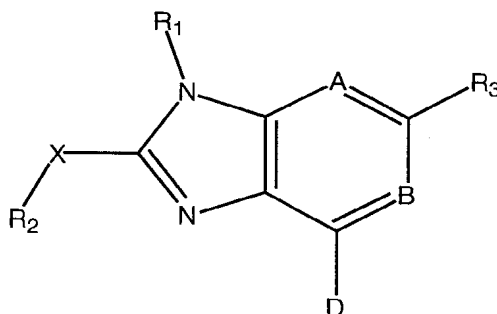
WO 98/08847, published March 5, 1998, discloses CRF antagonist compounds of the formula:



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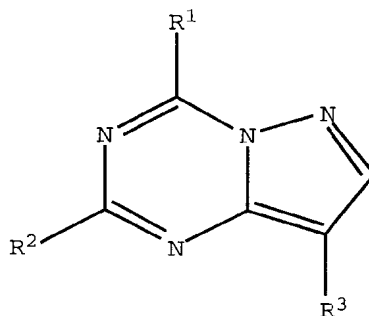
wherein B is selected from a variety of non-aryl groups and R⁵ is selected from certain groups such as phenyl or pyridyl or substituted versions thereof.

WO 99/01454, published on January 14, 1999,
5 discloses CRF antagonist compounds of the formula:



wherein D is an aryl or heteroaryl group and R¹ is selected from certain non-aryl or non-heteroaryl groups.

10 EP 0 269 859 (Ostuka, 1988) discloses pyrazolotriazine compounds of the formula



15 where R¹ is OH or alkanoyl, R² is H, OH, or SH, and R³ is an unsaturated heterocyclic group, naphthyl or substituted phenyl, and states that the compounds have xanthine oxidase inhibitory activity and are useful for treatment of gout.

20 EP 0 594 149 (Ostuka, 1994) discloses pyrazolotriazine and pyrazolopyrimidine compounds of the formula

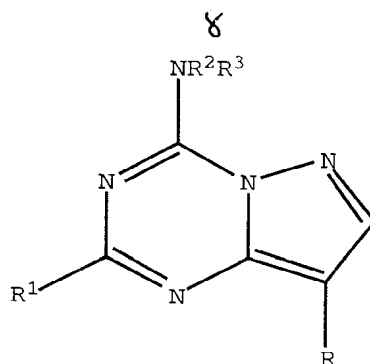
where A is CH or N, R⁰ and R³ are H or alkyl, and R¹ and R² are H, alkyl, alkoxy, alkylthio, nitro, etc., and
5 states that the compounds inhibit androgen and are useful in treatment of benign prostatic hypertrophy and prostatic carcinoma.

US 3,910,907 (ICI, 1975) discloses pyrazolotriazines of the formula:

10

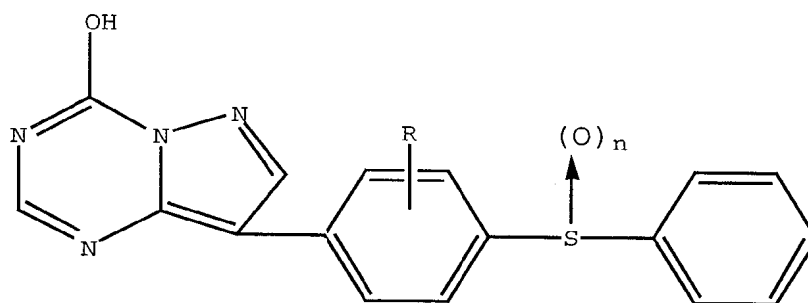
where R¹ is CH₃, C₂H₅ or C₆H₅, X is H, C₆H₅, m-CH₃C₆H₄, CN, COOEt, Cl, I or Br, Y is H, C₆H₅, o-CH₃C₆H₄, or p-CH₃C₆H₄,
15 and Z is OH, H, CH₃, C₂H₅, C₆H₅, n-C₃H₇, i-C₃H₇, SH, SCH₃, NHC₄H₉, or N(C₂H₅)₂, and states that the compounds are c-AMP phosphodiesterase inhibitors useful as bronchodilators.

US 3,995,039 discloses pyrazolotriazines of the
20 formula:



where R^1 is H or alkyl, R^2 is H or alkyl, R^3 is H, alkyl, alkanoyl, carbamoyl, or lower alkylcarbamoyl, and R is
 5 pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

US 5,137,887 discloses pyrazolotriazines of the formula



where R is lower alkoxy, and teaches that the compounds are xanthine oxidase inhibitors and are useful for treatment of gout.

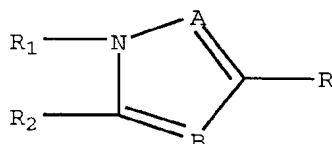
15 US 4,892,576 discloses pyrazolotriazines of the formula

20 where X is O or S, Ar is a phenyl, naphthyl, pyridyl or thienyl group, R_6 - R_8 are H, alkyl, etc., and R_9 is H,

9

alkyl, phenyl, etc. The patent states that the compounds are useful as herbicides and plant growth regulants.

US 5,484,760 and WO 92/10098 discloses herbicidal compositions containing, among other things, a herbicidal
5 compound of the formula



where A can be N, B can be CR₃, R₃ can be phenyl or
10 substituted phenyl, etc., R is -N(R₄)SO₂R₅ or -SO₂N(R₆)R₇ and R₁ and R₂ can be taken together to form

15 where X, Y and Z are H, alkyl, acyl, etc. and D is O or S.

US 3,910,907 and Senga et al., J. Med. Chem., 1982, 25, 243-249, disclose triazolotriazines cAMP phosphodiesterase inhibitors of the formula

20

where Z is H, OH, CH₃, C₂H₅, C₆H₅, n-C₃H₇, iso-C₃H₇, SH, SCH₃, NH(n-C₄H₉), or N(C₂H₅)₂, R is H or CH₃, and R₁ is CH₃
25 or C₂H₅. The reference lists eight therapeutic areas where inhibitors of cAMP phosphodiesterase could have utility: asthma, diabetes mellitus, female fertility control, male infertility, psoriasis, thrombosis, anxiety, and hypertension.

WO95/35298 (Otsuka, 1995) discloses pyrazolopyrimidines and states that they are useful as analgesics. The compounds are represented by the formula

5

where Q is carbonyl or sulfonyl, n is 0 or 1, A is a single bond, alkylene or alkenylene, R¹ is H, alkyl, etc., R² is naphthyl, cycloalkyl, heteroaryl, substituted
10 phenyl or phenoxy, R³ is H, alkyl or phenyl, R⁴ is H, alkyl, alkoxycarbonyl, phenylalkyl, optionally phenylthio-substituted phenyl, or halogen, R⁵ and R⁶ are H or alkyl.

EP 0 591 528 (Otsuka, 1991) discloses anti-
15 inflammatory use of pyrazolopyrimidines represented by the formula

20 where R₁, R₂, R₃ and R₄ are H, carboxyl, alkoxycarbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, R₅ is SR₆ or NR₇R₈, R₆ is pyridyl or optionally substituted phenyl, and R₇ and R₈ are H or optionally substituted phenyl.

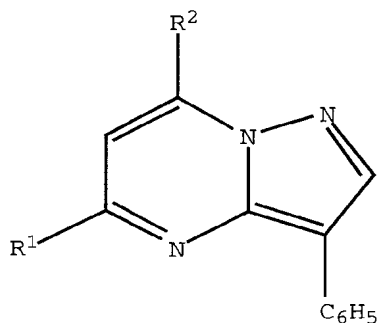
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Springer et al, J. Med. Chem., 1976, vol. 19, no. 2, 291-296 and Springer U.S. patents 4021,556 and 3,920,652 disclose pyrazolopyrimidines of the formula

5

where R can be phenyl, substituted phenyl or pyridyl, and their use to treat gout, based on their ability to inhibit xanthine oxidase.

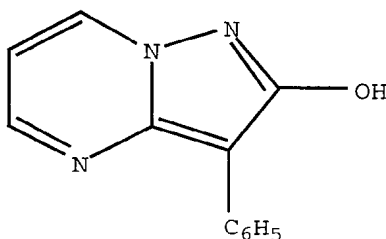
10 Joshi et al., J. Prakt. Chemie, 321, 2, 1979, 341-344, discloses compounds of the formula



15 where R¹ is CF₃, C₂F₅, or C₆H₄F, and R² is CH₃, C₂H₅, CF₃, or C₆H₄F.

Maquestiau et al., Bull. Soc. Belg., vol.101, no. 2, 1992, pages 131-136 discloses a pyrazolo[1,5-a]pyrimidine of the formula

20



12

Ibrahim et al., Arch. Pharm. (weinheim) 320, 487-491 (1987) discloses pyrazolo[1,5-a]pyrimidines of the formula

5

where R is NH₂ or OH and Ar is 4-phenyl-3-cyano-2-aminopyrid-2-yl.

Other references which disclose azolopyrimidines
10 included EP 0 511 528 (Otsuka, 1992), US 4,997,940 (Dow, 1991), EP 0 374 448 (Nissan, 1990), US 4,621,556 (ICN,1997), EP 0 531 901 (Fujisawa, 1993), US 4,567,263 (BASF, 1986), EP 0 662 477 (Isagro, 1995), DE 4 243 279 (Bayer, 1994), US 5,397,774 (Upjohn, 1995), EP 0 521 622
15 (Upjohn, 1993), WO 94/109017 (Upjohn, 1994), J. Med. Chem., 24, 610-613 (1981), and J. Het. Chem., 22, 601 (1985) or others as additionally described herein.

20

SUMMARY OF THE INVENTION

In accordance with one aspect, the present invention provides novel compounds which bind to corticotropin releasing factor receptors, thereby
25 altering the anxiogenic effects of CRF secretion. The compounds of the present invention are useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding
30 disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic

13

hypersensitivity associated with psychopathological disturbance and stress in mammals.

According to another aspect, the present invention
5 provides novel compounds of formula (I) (described
below) which are useful as antagonists of the
corticotropin releasing factor. The compounds of the
present invention exhibit activity as corticotropin
releasing factor antagonists and appear to suppress CRF
10 hypersecretion. The present invention also includes
pharmaceutical compositions containing such compounds
of formula (I), and methods of using such compounds for
the suppression of CRF hypersecretion, and/or for the
treatment of anxiogenic disorders.

15

According to yet another aspect, the present
invention provides novel compounds, pharmaceutical
compositions and methods which may be used in the
treatment of affective disorder, anxiety, depression,
20 irritable bowel syndrome, post-traumatic stress
disorder, supranuclear palsy, immune suppression,
Alzheimer's disease, gastrointestinal disease, anorexia
nervosa or other feeding disorder, drug or alcohol
withdrawal symptoms, drug addiction, inflammatory
25 disorder, fertility problems, disorders, the treatment
of which can be effected or facilitated by antagonizing
CRF, including but not limited to disorders induced or
facilitated by CRF, or a disorder selected from
inflammatory disorders such as rheumatoid arthritis and
30 osteoarthritis, pain, asthma, psoriasis and allergies;
generalized anxiety disorder; panic, phobias,
obsessive-compulsive disorder; post-traumatic stress
disorder; sleep disorders induced by stress; pain
perception such as fibromyalgia; mood disorders such as
35 depression, including major depression, single episode
depression, recurrent depression, child abuse induced
depression, and postpartum depression; dysthemia;
bipolar disorders; cyclothymia; fatigue syndrome;

stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as
5 ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa;
10 hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral
15 hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress
20 induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary
25 incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol
30 withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in mammals. The preferred uses include treatment of depression and anxiety.

The present invention also relates to the use of a compound of formula I and other compounds generically
35 and specifically disclosed herein in therapy.

According to a still further aspect of the invention, the compounds provided by this invention (and especially labelled compounds of this invention)

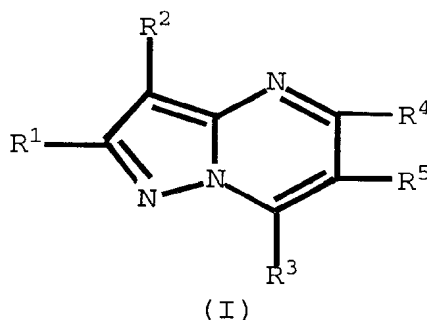
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are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

5

DETAILED DESCRIPTION OF INVENTION

[1] Thus, in a first embodiment, the present invention provides a novel compound of formula I:



or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from the group consisting of

- C₁₋₆ alkyl,
- 20 C₂₋₁₀ alkenyl,
- C₂₋₁₀ alkynyl,
- C₃₋₆ cycloalkyl,
- C₁₋₆ alkyloxy,
- C₁₋₆ alkylS(O)_n,
- 25 -NR^{1a}R^{1b} wherein R^{1a} and R^{1b} are independently selected from
 - H, C₁₋₄ alkyl, -C(O)C₁₋₄alkyl,
 - C(O)NR^{1a}R^{1b},
 - O-C(O)C₁₋₄alkyl,

16

-XR^{1c} wherein R^{1c} is selected from H or -C₁₋₄ alkylaryl;
X is selected from O or S(O)_n,

wherein R¹ is substituted with 0-6 substituents selected
5 from halogen, C₁₋₄ alkyl, C₁₋₆ alkyloxy, C₁₋₄ haloalkyl, -
NR^{1a}R^{1b}, -XR^{1c};

R² is selected from the group consisting of

- C₁₋₁₀ alkyl,
- 10 C₂₋₁₀ alkenyl,
- C₂₋₁₀ alkynyl,
- C₃₋₈ cycloalkyl,
- C₃₋₆ cycloalkyl C₁₋₆ alkyl,
- C₁₋₁₀ alkyloxy,
- 15 C₁₋₁₀ alkyloxyC₁₋₁₀ alkyl,
- C₁₋₄ alkoxy C₁₋₄ alkyl,
- SO₂-C₁₋₁₀alkyl
- SO₂R^{2a} wherein R^{2a} is aryl,
- SO₂R^{2b} wherein R^{2b} is heteroaryl,
- 20 -NR^{2c}R^{2d} wherein R^{2c} and R^{2d} are independently selected from
H, C₁₋₈ alkyl, S(O)_nC₁₋₄ alkyl, C(O)NR^{2c}R^{2d}, CO₂C₁₋₄alkyl,
C₃₋₈ cycloalkyl, C₁₋₆ alkyloxyC₁₋₆ alkyl, -C(O)C₁₋₄alkyl
or R^{2c} and R^{2d} may join to form a heterocyclic ring
having 0-3 heteroatoms selected from O, N or S,
- 25 - halogen,
- CN,
- C(O)L wherein L is selected from NR^{2c}R^{2d}, C₁₋₆ alkyl, H,
-OC₁₋₆ alkyl, O(CH₂)_mOC₁₋₆alkyl, O(CH₂)_mNR^{2c}R^{2d}, -OH,
- 30 aryl, heteroaryl or C(O)OC₁₋₆ alkyl, wherein m is 1-3,
or more particularly from,
-C(O)NR^{2c}R^{2d},
- C(O)R wherein R is C₁₋₆ alkyl,

- C(O)OC₁₋₄ alkyl,
- C(O)O(CH₂)₂OR wherein R is C₁₋₃ alkyl,
- C(O)O(CH₂)₂-NHR wherein R is C₁₋₃ alkyl,
- C(O)O(CH₂)₂-NR²,
- 5 -C(O)OH,
- C(O)H,
- C(O)Ph,
- C(O)R' wherein R' is aryl, heteroaryl or carboalkoxy;

10

n is 0, 1 or 2;

- R² is substituted with 0-3 substituents independently selected from R', R'', R''' wherein R', R'' and R''' are
- 15 independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ alkyloxyC₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ alkyloxy, hydroxy, or

- R² is substituted with 0-3 substituents independently
- 20 selected from:

halogen,

-CN,

-S(O)_nR^{2e} wherein R^{2e} is selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyloxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl;

25

-COR^{2f} wherein R^{2f} is selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyloxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl, and C₃₋₆ cycloalkylC₁₋₄ alkyl;

30

-CO₂R^{2f},

-NR^{2g}COR^{2f} wherein R^{2g} is selected from H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ cycloalkyl C₁₋₆ alkyl;

-N(COR^{2f})₂,

$-\text{NR}^{2g}\text{CONR}^{2f}\text{R}^{2h}$, wherein R^{2h} is selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy C_{1-4} alkyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl C_{1-6} alkyl;

5

$-\text{NR}^{2g}\text{CO}_2\text{R}^{2e}$,
 $-\text{CONR}^{2g}\text{R}^{2h}$,
 1-morpholinyl,
 1-piperidinyl,

10 1-piperazinyl,
 and

C_{3-8} cycloalkyl wherein 0-1 carbon atoms in the C_{4-8} cycloalkyl is replaced by a group selected from $-\text{O}-$, $-\text{S}(\text{O})_n-$, $-\text{NR}^{2g}-$, $-\text{NCO}_2\text{R}^{2e}$, $-\text{NCOR}^{2e}$,

15 and $-\text{NSO}_2\text{R}^{2e}$; and wherein N_4 in 1-piperazinyl is substituted with 0-1 substituents selected from R^{2g} , CO_2R^{2e} , COR^{2e} and SO_2R^{2e} ; or

20 the group R^{2i} , R^{2j} , R^{2k} , C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, Br, Cl, F, I, C_{1-4} haloalkyl, $-\text{OR}^{2g}$, $-\text{NR}^{2g}\text{R}^{2h}$, $-\text{C}_{1-6}$ alkyl OR^{2g} , and C_{3-8} cycloalkyl which is substituted with 0-1 R^{2i} and in which 0-1 carbons of C_{4-8} cycloalkyl is replaced by $-\text{O}-$, wherein

25 R^{2i} is selected from aryl wherein aryl includes phenyl, naphthyl, indanyl and indenyl, each R^{2i} being substituted with 0-1 OR^{2m} and 0-5 substituents independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, $-\text{CN}$,

30 nitro, $-\text{SH}$, $-\text{S}(\text{O})_n\text{R}^{2n}$, $-\text{COR}^{2m}$, $-\text{OC}(\text{O})\text{R}^{2n}$, $-\text{NR}^{2g}\text{COR}^{2m}$, $-\text{N}(\text{COR}^{2m})_2$, $-\text{NR}^{2g}\text{CONR}^{2o}\text{R}^{2p}$, $-\text{NR}^{2g}\text{CO}_2\text{R}^{2n}$, $-\text{NR}^{2o}\text{R}^{2p}$ and $-\text{CONR}^{2o}\text{R}^{2p}$;

R^{2j} is selected from heteroaryl wherein heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, OR^{2m} , -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heteroaryl being substituted on any nitrogen atom with 0-1 substituents selected from the group R^{2g} , CO_2R^{2e} , COR^{2e} and SO_2R^{2e} ;

R^{2k} is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for R^{2j} , each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group R^{2f} , CO_2R^{2e} , COR^{2e} and SO_2R^{2e} ;

wherein

R^{21} is H, C_{1-4} alkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl and C_{3-8} cycloalkyl;

R^{2m} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, C_{1-4} haloalkyl, $R^{2q}S(0)_n-C_{1-4}$ alkyl and $R^{2r}R^{2s}N-C_{2-4}$ alkyl;

5

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, and C_{1-4} haloalkyl;

R^{2o} and R^{2p} are independently selected at each occurrence
10 from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl and C_{1-4} haloalkyl;

R^{2q} is selected from C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, aryl,
15 aryl(C_{1-4} alkyl), heteroaryl and heteroaryl (C_{1-4} alkyl)- and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group C_{1-4} alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy C_{1-4} haloalkoxy, and dimethylamino;

20

$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein N_4 in 1-piperiazinyl is substituted with 0-1 substituents selected from the group R^{2t} , CO_2R^{2q} , COR^{2q} and SO_2R^{2q} ;

25

R^{2t} is selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl - C_{1-6} alkyl, aryl, aryl (C_{1-4} alkyl)-, heteroaryl and heteroaryl (C_{1-4} alkyl);

30

R^3 is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

21

- aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence from C₁₋₆ alkyl, C₃₋₆ cycloalkyl, methylenedioxy, C₁₋₄ alkyloxy-C₁₋₄ alkyloxy, -OR^{2m}, Br, Cl, F, I, C₁₋₄ haloalkyl, -CN, -NO₂, -SH, -S(O)_nR²ⁿ, -COR^{2m}, -CO₂R^{2m}, -OC(O)R²ⁿ, -NR^{2g}COR^{2m}, -N(COR^{2m})₂, -NR^{2g}CONR^{2o}R^{2p}, -NR^{2g}CO₂R^{2h}, -NR^{2o}R^{2p} and CONR^{2o}R^{2p} and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group C₁₋₃ alkyl, C₁₋₃ alkoxy, Br, Cl, F, I, -CN, dimethylamino, CF₃, C₂F₅, OCF₃, SO₂Me and acetyl;

- heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C₁₋₆ alkyl, C₃₋₆ cycloalkyl, Br, F, I, C₁₋₄ haloalkyl, -CN, NR^{2g}R^{2h}, nitro, -OR^{2m}, -SH, -S(O)_nR²ⁿ, COR^{2m}, -CO₂R^{2m}, -OC(O)R²ⁿ, -NR^{2g}COR^{2m}, -N(COR^{2m})₂, -NR^{2g}CONR^{2o}R^{2p} and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group R^{2g}, CO₂R^{3a}, COR^{3a} and SO₂R^{3a} wherein,

- R^{3a} is selected from the group C₁₋₆ alkyl, C₁₋₄ cycloalkyl-C₁₋₆ alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group

C₁₋₄ alkyl, Br, Cl, F, I, C₁₋₄ haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, and dimethylamino;

R⁴ and R⁵ are independently selected at each occurrence
 5 from H, Br, Cl, F, I, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, C₁₋₄ alkylamino, (C₁₋₄ alkyl)₂ amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of C₁₋₇
 10 alkyl, C₃₋₈ cycloalkyl, Br, Cl, F, I, -C(O)H, C₁₋₄ haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₆ alkylamino and (C₁₋₄ alkyl)₂ amino and wherein R⁴ and R⁵ non-phenyl groups may be substituted with 0-5
 15 substituents selected from OH, halogen, -C(O)H, -OC₁₋₆-alkyl and C₁₋₆ haloalkyl, C₁₋₆ alkyl, C₃₋₇ c-alkyl, C₁₋₆ alkyl(OH)_nCO₂R wherein R is H or C₁₋₆ alkyl, C₁₋₆ alkyl(OH)_n, wherein n is 0-3 or R⁴ and R⁵ may join together to form a C₃₋₆ alkylene chain; with the proviso that the compounds of
 20 Formula I with R¹, R², R³, R⁴ and R⁵ as specifically defined below are excluded:

- (a) a compound of formula I wherein R¹ is unsubstituted, unbranched (linear) C₁₋₃ alkyl and R² is -C(O)-Ph (EP O 129
 25 847 A2, US 4,521,422, US 4,654,347);
- (b) a compound of formula I, wherein R⁵ is H or C₁₋₃ alkyl and R³ is pyridyl, pyridyl-N-oxide, thien-3-yl or furan-3-yl or C₁₋₃ alkyl substituted versions thereof and R¹ is carboamoyl or unsubstituted, unbranched C₁₋₃ alkyl, R² is
 30 F, Cl, Br, formyl, carboxyl, CN, hydroxymethyl, unsubstituted, unbranched C₁₋₃ alkyl, -C(O)R, -C(O)OR, -CH₂OR, -C(O)O(CH₂)₂OR, -C(O)O(CH₂)₂NHR, or -C(O)O(CH₂)₂NR² wherein R is C₁₋₃ alkyl (US 4,281,000);

23

- (c) a compound of formula I, wherein R^1 is unsubstituted, unbranched C_{1-3} alkyl and R^2 is halogen, CN or $-C(O)R$ wherein R is H, C_{1-3} alkyl or C_{1-4} alkoxy, R^3 is Ph substituted with $NR^{2g}C(O)R^{2m}$ (US 4,626,538)
- 5 (d) a compound of formula I, R^2 is CN, halogen, CO_2R with R equal to C_{1-3} alkyl, unsubstituted, unbranched C_{1-3} alkyl, C_{1-3} haloalkyl or $CONH_2$ and R^1 is equal to OR, SR wherein R is C_{1-3} alkyl, C_{1-4} haloalkyl or C_{3-4} halocycloalkyl, and R^3 is phenyl or substituted phenyl (US
- 10 5,127,936);
- (e) a compound of formula I, wherein R^5 is H or C_{1-3} alkyl; R^3 is phenyl, ortho-trifluoromethylphenyl, meta-trifluorophenyl or meta-methoxyphenyl; R^1 is carbamoyl or unsubstituted C_{1-3} alkyl; R^2 is halogen, formyl, carboxyl,
- 15 cyano, hydroxymethyl, unsubstituted, unbranched C_{1-3} alkyl, $-C(O)R$, $-C(O)OR$, CH_2OR , $-C(O)O(CH_2)_2OR$, $-C(O)O(CH_2)_2NHR$ or $-C(O)O(CH_2)_2NR^2$ wherein R is C_{1-3} alkyl (US 4,178,449);
- (f) no entry
- 20 (g) in a compound of formula I, R^2 is CN, R^1 is methyl, R^4 and R^5 are H, R^3 is phenyl substituted with imidazo (or 2-methylimidazo) through the imidazo nitrogen atom (Registry Reference 20, 21);
- (h) in a compound of formula I, R^2 is CN, R^1 is SCH_3 , R^3
- 25 is para-chlorophenyl, R^4 is SCH_3 and R^5 is H (registry reference 25);
- (i) in a compound of formula I, R^2 is CN, R^1 is SCH_3 , R^3 is pyrid-4-yl, R^4 is SCH_3 and R^5 is H (Registry Reference 26);
- (j) in a compound of formula I, R^2 is CN, R^1 is SCH_3 , R^3 is
- 30 Ph, R^4 is SCH_3 and R^5 is H (Registry Reference 27);
- (k) in a compound of formula I, R^2 is $C(O)NH_2$, R^1 is SCH_3 , R^3 is pyrid-3-yl, R^4 is SCH_3 and R^5 is H (Registry Reference 28);

- (l) in a compound of formula I, R^2 is $C(O)NH_2$, R^1 is SCH_3 , R^3 is Ph, R^4 is SCH_3 (or Ph) and R^5 is H (Registry Reference 29, 31);
- (m) in a compound of formula I, R^2 is $C(O)OEt$, R^1 is SCH_3 ,
5 R^3 is Ph, R^4 is SCH_3 (or Ph) and R^5 is H (registry reference 30, 32);
- (n) in a compound of formula I, R^1 is $N(C(O)CH_3)_2$, R^2 is $CH_2Ph(p-Me, p-Cl)$, R^3 is Ph (p-ClPh), R^4 is SCH_3 and R^5 is H (Registry Reference 33, 34);
- 10 (o) in a compound of formula I, R^1 is $N(C(O)CH_3)_2$, R^2 is $CH_2Ph(p-OMe)$, R^3 is p-ClPh, R^4 is SCH_3 and R^5 is H (registry ref. 35);
- (p) in a compound of formula I, R^2 is CN, R^1 is CH_3 , R^3 is Ph, R^4 is H and R^5 is H (registry ref. 44);
- 15 (q) in a compound of formula I, R^2 is $C(O)NH_2$, R^1 is CH_3 , R^3 is Ph, R^4 is CH_3 and R^5 is H (reg. ref. 45);
- (s) in a compound of formula I, R^2 is $C(O)NH_2$, R^1 is CH_3 , R^3 is pyrid-4-yl, R^4 and R^5 are H (reg. ref. 46);
- (t) in a compound of formula I, R^2 is $C(O)NH_2$, R^1 is CH_3 , R^3
20 is m- CF_3Ph , R^4 and R^5 are H (reg. ref. 47);
- (u) in a compound of formula I, R^2 is CN, R^1 is CH_3 , R^3 is Ph, R^4 is CH_3 and R^5 is H (reg. ref. 48);
- (v) in a compound of formula I, R^2 is CN, R^1 is CH_3 , R^3 is pyrid-4-yl, R^4 and R^5 are H (reg. ref. 49);
- 25 (w) no entry
- (x) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)O-iPr$ (reg. ref. 75);
- (y) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is
30 p-F-Ph, R^4 is c-propyl and R^5 is $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)O-nPr$ (reg. ref. 76);

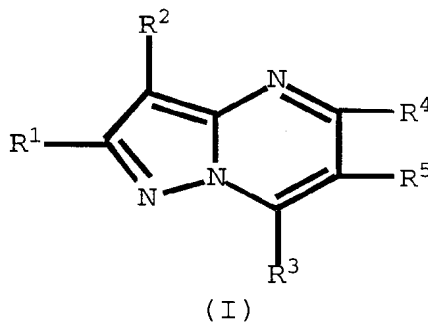
- (z) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)OMe$ (reg. ref. 77);
- (aa) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)OH$ (reg. ref. 78);
- (bb) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $-CH_2OH$ (reg. ref. 100);
- (cc) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $-C(O)H$ (reg. ref. 105);
- (dd) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $-CH=CH-C(O)H$ (reg. ref. 110);
- (ee) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)OEt$ (reg. ref. 115);
- (ff) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)O^-Na^+$ (reg. ref. 120);
- (gg) in a compound of formula I, R^2 is CN, R^1 is CF_3 , R^3 is m-Cl-Ph, R^4 is CH_3 and R^5 is H (reg. ref. 130);
- (hh) in a compound of formula I, R^2 is CN, R^1 is CF_3 , R^3 is m- CF_3 -Ph, R^4 is CH_3 and R^5 is H (reg. ref. 132);
- (ii) in a compound of formula I, R^2 is CN, R^1 is CF_3 , R^3 is Ph, R^4 is CH_3 and R^5 is H (reg. ref. 133);
- (jj)-(mm) no entry
- (nn) in a compound of formula I, R^2 is $-C(O)NH_2$, R^1 is Me, R^3 is Ph, R^4 is H and R^5 is Me (reg. ref. 140);
- (oo) in a compound of formula I, R^2 is CN, R^1 is Me, R^3 is Ph, R^4 is H and R^5 is Me (reg. ref. 141);
- (pp) in a compound of formula I, R^2 is CN, R^1 is Me, R^3 is o-Cl, m-Cl-Ph, R^4 is H and R^5 is H (reg. ref. 144);

- (qq) in a compound of formula I, R^2 is $C(O)NH_2$, R^1 is CH_3 , R^3 is Ph, R^4 and R^5 are H (reg. ref. 145);
- (rr) in a compound of formula I, R^2 is $C(O)NH_2$, R^1 is CH_3 , R^3 is 0-CL,m-Cl-Ph, R^4 and R^5 are H (reg. ref. 146);
- 5 (ss) in a compound of formula I, R^2 is $C(O)OMe$, R^1 is -
SCH₂-Ph, R^3 is Ph, R^4 is Me and R^5 is H (reg. ref. 147);
- (tt) in a compound of formula I, R^2 is $C(O)OMe$, R^1 is -
SCH₂-Ph, R^3 is Ph, R^4 is H and R^5 is H (reg. ref. 148);
- (uu) in a compound of formula I, R^2 is $C(O)Ph$, R^1 is Me, R^3
10 is pyrid-4-yl, R^4 and R^5 are H (reg. ref. 154);
- (vv) in a compound of formula I, R^2 is $C(O)Ph$, R^1 is Me, R^3
is m-CF₃-Ph, R^4 and R^5 are H (reg. ref. 155);
- (ww) in a compound of formula I, R^2 is $C(O)Ph$, R^1 is Me, R^3
is pyrid-3-yl, R^4 and R^5 are H (reg. ref. 156);
- 15 (xx) in a compound of formula I, R^2 is CN, R^1 is SCH₃, R^3
is Ph, R^4 is Ph and R^5 is H (reg. ref. 157);
- (yy) in a compound of formula I, R^2 is CN, R^1 is SCH₃, R^3
is Ph, R^4 is Ph and R^5 is H (reg. ref. 157);
- (zz) in a compound of formula I, R^2 is Cl, R^1 is Et, R^3 is
20 pyrid-3-yl, R^4 and R^5 are H (reg. ref. 163);
- (aaa) in a compound of formula I, R^2 is CO₂H, R^1 is Et, R^3
is pyrid-3-yl, R^4 and R^5 are H (reg. ref. 164);
- (bbb) in a compound of formula I, R^2 is CO₂H, R^1 is CH₃, R^3
is pyrid-3-yl, R^4 and R^5 are H and H Cl salt (reg. ref.
25 165);
- (ccc) in a compound of formula I, R^2 is $C(O)OEt$, R^1 is CH₃,
 R^3 is pyrid-3-yl, R^4 and R^5 are H (reg. ref. 166);
- (ddd) in a compound of formula I, R^2 is CN, R^1 is CH₃, R^3
is pyrid-3-yl, R^4 is H and R^5 is CH₃ (reg. ref. 167);
- 30 (eee) in a compound of formula I, R^2 is CN, R^1 is CH₃, R^3
is pyrid-3-yl, R^4 and R^5 are H (reg. ref. 168);
- (fff) in a compound of formula I, R^2 is $C(O)OEt$, R^1 is Et,
 R^3 is pyrid-3-yl, R^4 and R^5 are H (reg. ref. 169);

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- (ggg) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is pyrid-3-yl, R^4 and R^5 are H (reg. ref. 170);
- (hhh) in a compound of formula I, R^2 is CN, R^1 is CH_3 , R^3 is m- CF_3 -Ph, R^4 and R^5 are H (reg. ref. 172);
- 5 (iii) in a compound of formula I, R^2 is CN, R^1 is CH_2CN , R^3 is m- CF_3 -Ph, R^4 and R^5 are H (reg. ref. 173);
- (jjj) in a compound of formula I, R^2 is C(O)OMe, R^1 is Me, R^3 is m- CF_3 -Ph, R^4 and R^5 are H (reg. ref. 174);
- (kkk) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is
- 10 m-OMe-Ph, R^4 and R^5 are H (reg. ref. 175);
- (lll) in a compound of formula I, R^2 is C(O)OEt, R^1 is Et, R^3 is Ph, R^4 and R^5 are H (reg. ref. 176);
- (mmm) in a compound of formula I, R^2 is C(O)OEt, R^1 is Et, R^3 is m- CF_3 -Ph, R^4 and R^5 are H (reg. ref. 177);
- 15 (nnn) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is m- CF_3 -Ph, R^4 is H and R^5 is CH_3 (reg. ref. 178);
- (ooo) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is m- CF_3 , R^4 and R^5 are H (reg. ref. 179);
- (ppp) in a compound of formula I, R^2 is CN, R^1 is C(O)NH₂, R^3 is m- CF_3 -Ph, R^4 and R^5 are H (reg. ref. 180);
- 20 (qqq) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is Ph, R^4 and R^5 are H (reg. ref. 181).

- [1'] In a preferred embodiment, the present
- 25 invention provides a novel compound of formula I:



or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

- 5 R^1 is selected from the group consisting of
- C_{1-6} alkyl,
- C_{2-10} alkenyl,
- C_{2-10} alkynyl,
- 10 C_{3-6} cycloalkyl,
- C_{1-6} alkyloxy,
- C_{1-6} alkylS(O)_n,
- $-NR^{1a}R^{1b}$ wherein R^{1a} and R^{1b} are independently selected from
- H, C_{1-4} alkyl, $-C(O)C_{1-4}$ alkyl,
- 15 $-C(O)NR^{1a}R^{1b}$,
- $-O-C(O)C_{1-4}$ alkyl,
- $-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl;
- X is selected from O or S(O)_n,
- 20
- wherein R^1 is substituted with 0-6 substituents selected from halogen, C_{1-4} alkyl, C_{1-6} alkyloxy, C_{1-4} haloalkyl, $-NR^{1a}R^{1b}$, $-XR^{1c}$;
- 25 R^2 is selected from the group consisting of
- C_{1-10} alkyl excluding unsubstituted, unbranched C_{1-3} alkyl,
- C_{2-10} alkenyl,
- C_{2-10} alkynyl,
- C_{3-8} cycloalkyl,
- 30 C_{3-6} cycloalkyl C_{1-6} alkyl,
- C_{1-10} alkyloxy,
- C_{1-10} alkyloxy C_{1-10} alkyl,
- C_{1-4} alkoxy C_{1-4} alkyl,

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- SO₂-C₁₋₁₀alkyl
- SO₂R^{2a} wherein R^{2a} is aryl,
- SO₂R^{2b} wherein R^{2b} is heteroaryl,
- NR^{2c}R^{2d} wherein R^{2c} and R^{2d} are independently selected from
- 5 H, C₁₋₈ alkyl, S(O)_nC₁₋₄ alkyl, C(O)NR^{2c}R^{2d}, CO₂C₁₋₄alkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyloxyC₁₋₆ alkyl, -C(O)C₁₋₄alkyl or R^{2c} and R^{2d} may join to form a heterocyclic ring having 0-3 heteroatoms selected from O, N or S,
- 10 n is 0, 1 or 2;
- R² is substituted with 0-3 substituents independently selected from R', R'', R''' wherein R', R'' and R''' are
- 15 independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ alkyloxyC₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ alkyloxy, hydroxy, or
- R² is substituted with 0-3 substituents independently
- 20 selected from:
- CN,
- S(O)_nR^{2e} wherein R^{2e} is selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyloxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl;
- 25 -COR^{2f} wherein R^{2f} is selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyloxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl, and C₃₋₆ cycloalkylC₁₋₄ alkyl;
- CO₂R^{2f},
- 30 -NR^{2g}COR^{2f} wherein R^{2g} is selected from H, C₁₋₆ alkyl, C₃₋₇ c-alkyl, C₃₋₆ cycloalkyl C₁₋₆ alkyl;
- N(COR^{2f})₂,
- NR^{2g}CONR^{2f}R^{2h}, wherein R^{2h} is selected from H, C₁₋₆ alkyl,

30

C₁₋₄ haloalkyl, C₁₋₄ alkoxy C₁₋₄ alkyl,
C₃₋₆ cycloalkyl and C₃₋₆ cycloalkylC₁₋₆
alkyl;

- 5 -NR^{2g}CO₂R^{2e},
-CONR^{2g}R^{2h},
1-morpholinyl,
1-piperidinyl,
1-piperazinyl,
- 10 and
C₃₋₈ cycloalkyl wherein 0-1 carbon atoms in the C₄₋₈
cycloalkyl is replaced by a group selected from
-O-, -S(O)_n-, -NR^{2g}-, -NCO₂R^{2e}, -NCOR^{2e},
and -NSO₂R^{2e}; and wherein N₄ in
- 15 1-piperazinyl is substituted with 0-1
substituents selected from R^{2g}, CO₂R^{2e}, COR^{2e} and
SO₂R^{2e}; or
- the group R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈
- 20 alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g},
-NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl which is
substituted with 0-1 R^{2j} and in which 0-1 carbons of C₄₋₈
cycloalkyl is replaced by -O-, wherein
- 25 R^{2j} is selected from heteroaryl wherein heteroaryl
includes pyridyl, pyrimidinyl, triazinyl, furanyl,
quinolinyl, isoquinolinyl, thienyl, imidazolyl,
thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl,
benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl,
- 30 pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-
dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-
dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-
dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl

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- and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, OR^{2m} , -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, -
- 5 $OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, -
 $NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heteroaryl being substituted on any nitrogen atom with 0-1 substituents selected from the group R^{2g} , CO_2R^{2e} , COR^{2e} and SO_2R^{2e} ;
- 10 R^{2k} is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for R^{2j} , each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, $-OR^{2m}$,
- 15 $-SH$, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$,
 $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group R^{2f} , CO_2R^{2e} , COR^{2e} and SO_2R^{2e} ;
- 20 wherein
- R^{21} is H, C_{1-4} alkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl and C_{3-8} cycloalkyl;
- 25 R^{2m} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, C_{1-4} haloalkyl, $R^{2q}S(O)_n-C_{1-4}$ alkyl and $R^{2x}R^{2e}N-C_{2-4}$ alkyl;
- 30 R^{2n} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, and C_{1-4} haloalkyl;

R^{2o} and R^{2p} are independently selected at each occurrence from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl and C_{1-4} haloalkyl;

- 5 R^{2q} is selected from C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy-
 C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, aryl,
 aryl(C_{1-4} alkyl), heteroaryl and heteroaryl (C_{1-4} alkyl)-
 and benzyl, each benzyl being substituted on the aryl
 moiety with 0-1 substituents selected from the group C_{1-4}
 10 alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy C_{1-4}
 haloalkoxy, and dimethylamino;

- $R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-
 morpholinyl, 1-piperidinyl or 1-piperazinyl wherein N_4 in
 15 1-piperiazinyl is substituted with 0-1 substituents
 selected from the group R^{2t} , CO_2R^{2q} , COR^{2q} and SO_2R^{2q} ;

- R^{2t} is selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy
 - C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl - C_{1-6} alkyl,
 20 aryl, aryl (C_{1-4} alkyl)-, heteroaryl and heteroaryl (C_{1-4}
 alkyl);

- R^3 is selected from an aryl or heteroaryl group attached
 through an unsaturated carbon atom;

- 25 aryl is selected from phenyl, naphthyl, indanyl and
 indenyl, each aryl being substituted with 0-5
 substituents independently selected at each occurrence
 from C_{1-6} alkyl, C_{3-6} cycloalkyl, methylenedioxy, C_{1-4}
 30 alkyloxy- C_{1-4} alkyloxy, $-OR^{2m}$, Br, Cl, F, I, C_{1-4} haloalkyl,
 $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, -
 $NR^{2q}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2q}CONR^{2o}R^{2p}$, $-NR^{2q}CO_2R^{2n}$, $-NR^{2o}R^{2p}$ and
 $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being

substituted with 0-4 substituents selected from the group C_{1-3} alkyl, C_{1-3} alkoxy, Br, Cl, F, I, -CN, dimethylamino, CF_3 , C_2F_5 , OCF_3 , SO_2Me and acetyl;

- 5 heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-
- 10 dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted at 0-4 carbon atoms with a substituent independently selected at
- 15 each occurrence from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, F, I, C_{1-4} haloalkyl, -CN, $NR^{2g}R^{2h}$, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2n}$, COR^{2m} , $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2c}R^{2p}$ and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the
- 20 group R^{2g} , CO_2R^{3a} , COR^{3a} and SO_2R^{3a} wherein,

- R^{3a} is selected from the group C_{1-6} alkyl, C_{1-4} cycloalkyl- C_{1-6} alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group
- 25 C_{1-4} alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and dimethylamino;

- R^4 and R^5 are independently selected at each occurrence from H, Br, Cl, F, I, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-4} alkylamino, $(C_{1-4} \text{ alkyl})_2$ amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of C_{1-7}
- 30

alkyl, C₃₋₈ cycloalkyl, Br, Cl, F, I, -C(O)H, C₁₋₄
haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄
alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₆
alkylamino and (C₁₋₄ alkyl)₂ amino and wherein R⁴ and R⁵
5 non-phenyl groups may be substituted with 0-5
substituents selected from OH, halogen, -C(O)H, -OC₁₋₆-
alkyl and C₁₋₆ haloalkyl, C₁₋₆ alkyl, C₃₋₇ c-alkyl, C₁₋₆
alkyl(OH)_nCO₂R wherein R is H or C₁₋₆ alkyl, C₁₋₆ alkyl(OH)_n
, wherein n is 0-3 or R⁴ and R⁵ may join together to form a
10 C₃₋₆ alkylene chain.

[2] The present invention relates to a compound as
described directly above in [1] or [1'] wherein

15 R¹ is selected from C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆
alkoxy, C₁₋₆ alkylthio, -XR^{1c} wherein R¹ is substituted with
0-6 substituents selected from halogen, C₁₋₄ alkyl or C₁₋₄
haloalkyl;

R² is selected from substituted-C₁₋₁₀ alkyl, branched
20 C₃₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₈ cycloalkyl, C₃₋₆
cycloalkyl C₁₋₆ alkyl, -NR^{2c}R^{2d} wherein, in the case of
substituted-C₁₋₁₀ alkyl, 1-3 substituents are
independently selected from the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆
alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄
25 haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl
which is substituted with 0-1 R²ⁱ and in which 0-1 carbons
of C₄₋₈ cycloalkyl is replaced by -O- and wherein the R²
groups, other than substituted-C₁₋₁₀ alkyl, are substituted
with 0-3 substituents independently selected from the
30 group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br,
Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and
C₃₋₈ cycloalkyl which is substituted with 0-1 R²ⁱ and in
which 0-1 carbons of C₄₋₈ cycloalkyl is replaced by -O-.

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[3] The present invention also relates to a compound described in groups [1], [1'] or [2] wherein R³ is selected from an aryl group selected from phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

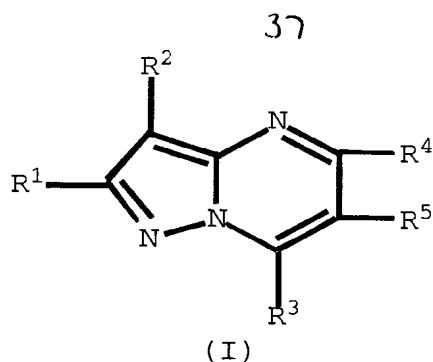
[4] The present invention relates to a compound described directly above in groups [1'] and [1]-[3] wherein R³ is substituted with 0-4 substituents independently selected from halogen, C₁₋₄ alkyloxy, C₁₋₆ alkyl or NR'R'' wherein R' and R'' are independently selected from H or C₁₋₆ alkyl.

[5] The present invention preferably relates to a compound as described directly above in groups [1'] and [1]-[4] wherein R³ is selected from 2,4-dichlorophenyl, 2-chloro-4-methoxyphenyl, 2,4,6-trimethylphenyl, 2,4,6-trimethoxyphenyl, 2-dimethylamino-4-methyl-pyridin-5-yl, 2,4-dichloro-5-fluorophenyl, 2-chloro-4-methoxy-5-fluorophenyl, 2-chloro-4,5-dimethoxyphenyl or 2-chloro-4,5-dimethoxyphenyl.

[6] The present invention also preferably relates to a compound as described in groups [1'] and [2]-[5] wherein R² is selected from C₁ alkyl of the formula -CR'R''R''' wherein R', R'' and R''' are independently selected from H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ alkyloxyC₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ alkyloxy, hydroxy, with the proviso that each of R', R'' and R''' cannot be H;

or R² is selected from NR^{2c}R^{2d} wherein R^{2c} and R^{2d} are independently selected from H or C₁₋₆ alkyl.

- [7] The present invention preferably relates to a compound according to groups [1'] and [1]-[6] wherein R^3 is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom wherein, aryl is phenyl, each phenyl being substituted with 0-5 substituents independently selected at each occurrence from C_{1-6} alkyl, C_{3-6} cycloalkyl, methylenedioxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, $-OR^{2m}$, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, $-NO_2$, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group C_{1-3} alkyl, C_{1-3} alkoxy, Br, Cl, F, I, -CN, dimethylamino, CF_3 , C_2F_5 , OCF_3 , SO_2Me and acetyl and wherein, heteroaryl is selected at each occurrence from pyridyl, each pyridyl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, F, I, C_{1-4} haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2n}$, COR^{2m} , $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each pyridyl being substituted at any nitrogen atom with 0-1 substituents selected from the group R^{2g} , CO_2R^{3a} , COR^{3a} and SO_2R^{3a} .
- [8] The present invention preferably relates to a compound of formula (I)



or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof, wherein

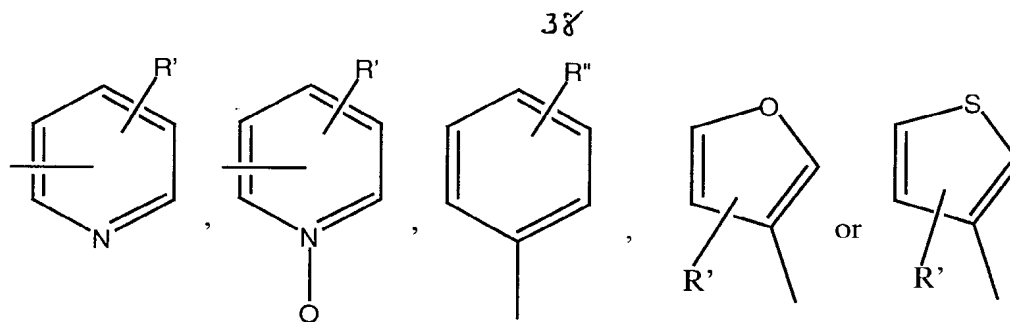
5 R^1 is selected from C_{1-6} alkyl, C_{1-6} alkyloxy, -SH or OH;

R^2 is selected from C_{1-4} alkyl which is unsubstituted or substituted with 1-4 substituents selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkylOR^{2g}, C_{2-6} alkenyl or OR^{2g}
 10 wherein R^{2g} is H or C_{1-6} alkyl;

R^3 is selected from an aryl or heteroaryl group bonded through an unsaturated carbon atom that is unsubstituted or substituted with 1-4 substituents selected from Cl, F, I, Br, -OH, CF₃, S(O)_nC₁₋₆ alkyl, -OC₁₋₆ alkyl, C_{1-6} alkyl or
 15 NR^{2g}R^{2h} wherein R^{2g} and R^{2h} are independently selected from H or C_{1-6} alkyl;

R^4 and R^5 are independently selected from H, C_{1-6} alkyl or
 20 C_{1-6} alkyloxy,

with the proviso that when R^1 and R^2 are unsubstituted, unbranched C_{1-3} alkyl, R^3 may not be



wherein R' is H or C₁₋₃ alkyl and R'' is H or o-
 5 trifluoromethyl, m-trifluoromethyl or m-methoxy (see
 4,281,000).

[9] The present invention also relates to a compound
 according to group [8] wherein R³ is substituted with 2-4
 10 substituents.

[10] The present invention also relates to a compound
 according to group [8] or [9] wherein R² is substituted
 with 1-4 substituents.

15

[11] The present invention also relates to a compound
 according to groups [8]-[10] having the formulae shown in
 Table 1.

20 [12] The present invention also relates to a method of
 antagonizing a CRF-1 receptor in mammals including humans
 wherein binding to the receptor causes and ultimately
 results in the treatment of affective disorder, anxiety,
 depression, headache, irritable bowel syndrome, post-
 25 traumatic stress disorder, supranuclear palsy, immune
 suppression, Alzheimer's disease, gastrointestinal
 diseases, anorexia nervosa or other feeding disorder,
 drug addiction, drug or alcohol withdrawal symptoms,

inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy,
 5 stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a
 10 therapeutically effective amount of a compound of Formula (I) wherein

R^1 is selected from the group consisting of

- C_{1-6} alkyl,
- 15 C_{2-10} alkenyl,
- C_{2-10} alkynyl,
- C_{3-6} cycloalkyl,
- C_{1-6} alkyloxy,
- C_{1-6} alkylS(O)_n,
- 20 $-NR^{1a}R^{1b}$ wherein R^{1a} and R^{1b} are independently selected from
 H, C_{1-4} alkyl, $-C(O)C_{1-4}$ alkyl,
 $-C(O)NR^{1a}R^{1b}$,
 $-O-C(O)C_{1-4}$ alkyl,
- 25 $-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl;
 X is selected from O or S(O)_n,

wherein R^1 is substituted with 0-6 substituents selected from halogen, C_{1-4} alkyl, C_{1-6} alkyloxy, C_{1-4} haloalkyl, -
 30 $NR^{1a}R^{1b}$, $-XR^{1c}$;

R^2 is selected from the group consisting of
 C_{1-10} alkyl,

40

- C_{2-10} alkenyl,
 C_{2-10} alkynyl,
 C_{3-8} cycloalkyl,
 C_{3-6} cycloalkyl C_{1-6} alkyl,
5 C_{1-10} alkyloxy,
 C_{1-10} alkyloxy C_{1-10} alkyl,
 C_{1-4} alkoxy C_{1-4} alkyl,
 $-SO_2-C_{1-10}$ alkyl
 $-SO_2R^{2a}$ wherein R^{2a} is aryl,
10 $-SO_2R^{2b}$ wherein R^{2b} is heteroaryl,
 $-NR^{2c}R^{2d}$ wherein R^{2c} and R^{2d} are independently selected from
 H , C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxy C_{1-6} alkyl,
 $-C(O)C_{1-4}$ alkyl or R^{2c} and R^{2d} may join to form a
heterocyclic ring having 0-3 heteroatoms selected
15 from O, N or S,

- halogen,
-CN,
 $-C(O)NR^{2c}R^{2d}$,
20 $-C(O)R$ wherein R is C_{1-6} alkyl,
 $-C(O)OC_{1-4}$ alkyl,
 $-C(O)O(CH_2)_2OR$ wherein R is C_{1-3} alkyl,
 $-C(O)O(CH_2)_2-NHR$ wherein R is C_{1-3} alkyl,
 $-C(O)O(CH_2)_2-NR^2$,
25 $-C(O)OH$,
 $-C(O)H$,
 $-C(O)Ph$,
 $-C(O)R'$ wherein R' is aryl, heteroaryl or carboalkoxy;
30
n is 0, 1 or 2;

R^2 is substituted with 0-3 substituents independently

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selected from R' , R'' , R''' wherein R' , R'' and R''' are independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy, or

5

R^2 is substituted with 0-3 substituents independently selected from

halogen,

-CN,

10 $-S(O)_n R^{2e}$ wherein R^{2e} is selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{3-6} cycloalkyl;

$-COR^{2f}$ wherein R^{2f} is selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{3-6}

15 cycloalkyl, and C_{3-6} cycloalkyl C_{1-4} alkyl;

$-CO_2 R^{2f}$,

$-NR^{2g} COR^{2f}$ wherein R^{2g} is selected from H, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl;

$-N(COR^{2f})_2$,

20 $-NR^{2g} CONR^{2f} R^{2h}$, wherein R^{2h} is selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy C_{1-4} alkyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl C_{1-6} alkyl;

$-NR^{2g} CO_2 R^{2e}$,

25 $-CONR^{2g} R^{2h}$,

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

30 C_{3-8} cycloalkyl wherein 0-1 carbon atoms in the C_{4-8} cycloalkyl is replaced by a group selected from

$-O-$, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2 R^{2e}$, $-NCOR^{2e}$,

and $-NSO_2 R^{2e}$; and wherein N_4 in

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- 1-piperazinyl is substituted with 0-1 substituents selected from R^{2g} , CO_2R^{2e} , COR^{2e} and SO_2R^{2e} ; or
- 5 the group R^{2i} , R^{2j} , R^{2k} , C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, Br, Cl, F, I, C_{1-4} haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkylOR^{2g}, and C_{3-8} cycloalkyl which is substituted with 0-1 R^{2i} and in which 0-1 carbons of C_{4-8} cycloalkyl is replaced by -O-, wherein
- 10 R^{2i} is selected from aryl wherein aryl includes phenyl, naphthyl, indanyl and indenyl, each R^{2i} being substituted with 0-1 OR^{2m} and 0-5 substituents independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN,
- 15 nitro, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2n}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$;
- R^{2j} is selected from heteroaryl wherein heteroaryl
- 20 includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-
- 25 dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected
- 30 from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, OR^{2m} , -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heteroaryl being substituted

on any nitrogen atom with 0-1 substituents selected from the group R^{2g} , CO_2R^{2e} , COR^{2e} and SO_2R^{2e} ;

R^{2k} is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for R^{2j} , each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group R^{2f} , CO_2R^{2e} , COR^{2e} and SO_2R^{2e} ;

wherein

R^{21} is H, C_{1-4} alkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl and C_{3-8} cycloalkyl;

R^{2m} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, C_{1-4} haloalkyl, $R^{2a}S(O)_n-C_{1-4}$ alkyl and $R^{2r}R^{2s}N-C_{2-4}$ alkyl;

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, and C_{1-4} haloalkyl;

R^{2o} and R^{2p} are independently selected at each occurrence from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl and C_{1-4} haloalkyl;

R^{2a} is selected from C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, aryl, aryl(C_{1-4} alkyl), heteroaryl and heteroaryl (C_{1-4} alkyl)-

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and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group C_{1-4} alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy C_{1-4} haloalkoxy, and dimethylamino;

5

$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein N_4 in 1-piperiazinyl is substituted with 0-1 substituents selected from the group R^{2t} , CO_2R^{2q} , COR^{2q} and SO_2R^{2q} ;

10

R^{2t} is selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl - C_{1-6} alkyl, aryl, aryl (C_{1-4} alkyl)-, heteroaryl and heteroaryl (C_{1-4} alkyl);

15

R^3 is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence from C_{1-6} alkyl, C_{3-6} cycloalkyl, methylenedioxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, $-OR^{2m}$, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, $-NO_2$, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, -
 25 $NR^{2q}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2q}CONR^{2o}R^{2p}$, $-NR^{2q}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group C_{1-3} alkyl, C_{1-3} alkoxy, Br, Cl, F, I, -CN, dimethylamino, CF_3 , C_2F_5 , OCF_3 , SO_2Me and acetyl;

30

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl,

- 45
- benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, F, I, C_{1-4} haloalkyl, -CN, $NR^{2g}R^{2h}$, nitro, $-OR^{2m}$, -SH, -S(O) $_nR^{2n}$, COR^{2m} , $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group R^{2g} , CO_2R^{3a} , COR^{3a} and SO_2R^{3a} wherein,
- 15 R^{3a} is selected from the group C_{1-6} alkyl, C_{1-4} cycloalkyl- C_{1-6} alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group C_{1-4} alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and dimethylamino;
- 20 R^4 and R^5 are independently selected at each occurrence from H, Br, Cl, F, I, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-4} alkylamino, (C₁₋₄ alkyl)₂ amino and phenyl, each phenyl is substituted
- 25 with 0-3 groups selected from the group consisting of C_{1-7} alkyl, C_{3-8} cycloalkyl, Br, Cl, F, I, -C(O)H, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-6} alkylamino and (C₁₋₄ alkyl)₂ amino and wherein R^4 and R^5
- 30 non-phenyl groups may be substituted with 0-5 substituents selected from OH, halogen, -C(O)H, $-OC_{1-6}-$ alkyl and C_{1-6} haloalkyl, C_{1-6} alkyl, C_{3-7} c-alkyl, C_{1-6}

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alkyl(OH)_nCO₂R wherein R is H or C₁₋₆ alkyl, C₁₋₆ alkyl(OH)_n, wherein n is 0-3 or R⁴ and R⁵ may join together to form a C₃₋₆ alkylene chain.

- 5 [13] The present invention also relates to a method as described directly above in group [12] wherein

R¹ is selected from C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, -XR^{1c} wherein R¹ is substituted with 0-6 substituents selected from halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl;

- 10 R² is selected from substituted-C₁₋₁₀ alkyl, branched C₃₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₈ cycloalkyl, C₃₋₆ cycloalkyl C₁₋₆ alkyl, -NR^{2c}R^{2d} wherein, in the case of substituted-C₁₋₁₀ alkyl, 1-3 substituents are
- 15 independently selected from the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl which is substituted with 0-1 R²ⁱ and in which 0-1 carbons of C₄₋₈ cycloalkyl is replaced by -O- and wherein the R²
- 20 groups, other than substituted-C₁₋₁₀ alkyl, are substituted with 0-3 substituents independently selected from the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl which is substituted with 0-1 R²ⁱ and in
- 25 which 0-1 carbons of C₄₋₈ cycloalkyl is replaced by -O-.

- [14] The present invention also relates to a method described directly above in [12] or [13] wherein R³ is selected from an aryl group selected from phenyl or
- 30 substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

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[15] The present invention relates to a method described directly above in groups [12]-[14] wherein R^3 is substituted with 0-4 substituents independently selected from halogen, C_{1-4} alkyloxy, C_{1-6} alkyl or $NR'R''$ wherein R' and R'' are independently selected from H or C_{1-6} alkyl.

[16] The present invention preferably relates to a method as described directly above in groups [12]-[15] wherein R^3 is selected from 2,4-dichlorophenyl, 2-chloro-4-methoxyphenyl, 2,4,6-trimethylphenyl, 2,4,6-trimethoxyphenyl, 2-dimethylamino-4-methyl-pyridin-5-yl, 2,4-dichloro-5-fluorophenyl, 2-chloro-4-methoxy-5-fluorophenyl, 2-chloro-4,5-dimethoxyphenyl or 2-chloro-4,5-dimethoxyphenyl.

15

[17] The present invention also preferably relates to a method as described in groups [13]-[15] wherein R^2 is selected from C_1 alkyl of the formula $-CR'R''R'''$ wherein R' , R'' and R''' are independently selected from H, C_{1-6} alkyl, C_{3-7} cycloalkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy, with the proviso that each of R', R'' and R''' cannot be H;

or R^2 is selected from $NR'R''$ wherein R' and R'' are independently selected from H or C_{1-6} alkyl.

[18] The present invention preferably relates to a method according to groups [13]-[17] wherein R^3 is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom wherein, aryl is phenyl, each phenyl being substituted with 0-5 substituents independently selected at each occurrence from C_{1-6} alkyl, C_{3-6} cycloalkyl, methylenedioxy, C_{1-4}

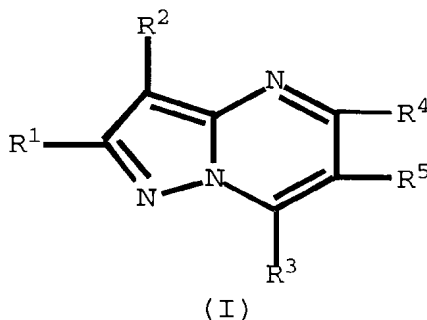
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alkyloxy-C₁₋₄ alkyloxy, -OR^{2m}, Br, Cl, F, I, C₁₋₄ haloalkyl, -CN, -NO₂, -SH, -S(O)_nR²ⁿ, -COR^{2m}, -CO₂R^{2m}, -OC(O)R²ⁿ, -NR^{2g}COR^{2m}, -N(COR^{2m})₂, -NR^{2g}CONR^{2o}R^{2p}, -NR^{2g}CO₂R^{2h}, -NR^{2o}R^{2p} and CONR^{2o}R^{2p} and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group C₁₋₃ alkyl, C₁₋₃ alkoxy, Br, Cl, F, I, -CN, dimethylamino, CF₃, C₂F₅, OCF₃, SO₂Me and acetyl and wherein, heteroaryl is selected at each occurrence from pyridyl, each pyridyl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C₁₋₆ alkyl, C₃₋₆ cycloalkyl, Br, F, I, C₁₋₄ haloalkyl, -CN, nitro, -OR^{2m}, -SH, -S(O)_nR²ⁿ, COR^{2m}, -CO₂R^{2m}, -OC(O)R²ⁿ, -NR^{2g}COR^{2m}, -N(COR^{2m})₂, -NR^{2g}CONR^{2o}R^{2p} and each pyridyl being substituted at any nitrogen atom with 0-1 substituents selected from the group R^{2g}, CO₂R^{3a}, COR^{3a} and SO₂R^{3a}.

[19] The present invention preferably relates to a method of antagonizing a CRF-1 receptor in mammals including humans wherein binding to the receptor causes and ultimately results in the treatment of affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders

49

induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of formula (I)



5

or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof, wherein

R^1 is selected from C_{1-6} alkyl, C_{1-6} alkyloxy, -SH or OH;

10

R^2 is selected from C_{1-4} alkyl which is unsubstituted or substituted with 1-4 substituents selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkylOR^{2g}, C_{2-6} alkenyl or OR^{2g} wherein R^{2g} is H or C_{1-6} alkyl;

15

R^3 is selected from an aryl or heteroaryl group bonded through an unsaturated carbon atom that is unsubstituted or substituted with 1-4 substituents selected from Cl, F, I, Br, -OH, CF₃, S(O)_nC₁₋₆ alkyl, -OC₁₋₆ alkyl, C_{1-6} alkyl or NR^{2g}R^{2h} wherein R^{2g} and R^{2h} are independently selected from H or C_{1-6} alkyl;

20

R^4 and R^5 are independently selected from H, C_{1-6} alkyl or C_{1-6} alkyloxy.

25

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[20] The present invention also relates to a method according to group [19] wherein R^3 is substituted with 2-4 substituents.

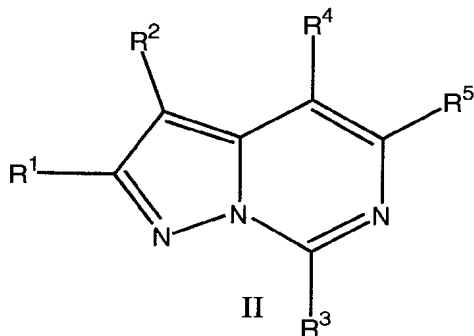
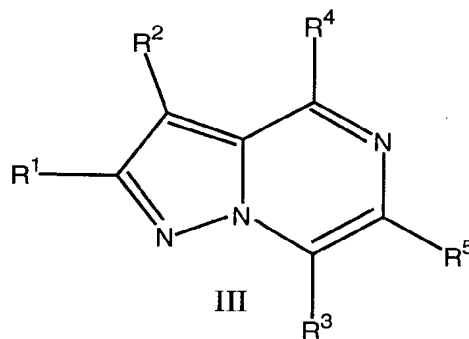
5 [21] The present invention also relates to a method according to group [19]-[20] wherein R^2 is substituted with 1-4 substituents.

[22] The present invention also relates to a method
10 according to group [19]-[21] using the formulae shown in Table 1.

[23] The present invention also provides pharmaceutical compositions comprising compounds of Formula (1) with
15 the variables as recited above in group [1] and [1'] with the proviso that the compounds excluded in proviso (d) in group [1] are included herein and a pharmaceutically acceptable carrier.

20 [24] The preferred pharmaceutical compositions include those compounds as shown in groups [1'] and [2]-[11] along with a pharmaceutically acceptable carrier.

[25] The present invention also relates to a compound
25 of the formulae shown below having the variables recited above in groups [1'] and [1]-[24]:



except that the provisos listed in group I are not
30 included for the compounds of formula II and III.

51

[26] The present invention further comprises a compound of formula II or III in combination with a pharmaceutically acceptable excipient to form a pharmaceutical composition.

[27] The present invention further relates to a method of treating CRF related disorders or conditions or use in therapy of compounds of formula II or III comprising administering a compound of formula II or III with the variables for R^1 - R^5 as shown above in groups [1'] and [1]-[24] to a patient in need of treatment thereof.

Many compounds of this invention have one or more asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

The term "alkyl", unless otherwise specified, includes both branched and straight-chain alkyl having the specified number of carbon atoms. "Alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any

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stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more
5 halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-, bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl,
10 cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided
15 that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are
20 permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious
25 therapeutic agent.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of formulas (I). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or
30 organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free
35 acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl

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acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formulas (I) and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety, depression, immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in a host.

The term "registry reference" refers to computer search generated sources of known chemical structures as identified by specific structure herein.

Compounds prepared according to the synthetic schemes and examples include, without limitation, those compounds specifically set forth in Table 1, hereinbelow, as well as the following:

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7-(2,4-dichloro-5-fluorophenyl)-2-ethyl-3-(2-pentyl)-
pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-6-methyl-3-(2-pentyl)-
pyrazolo[1,5-a]pyrimidine
7-(2-chloro-4-methoxyphenyl)-2-ethyl-3-(2-
pentyl)pyrazolo[1,5-a]pyrimidine
2-ethyl-3-(2-pentyl)-7-(2,4,6-trimethylphenyl)-
pyrazolo[1,5-a]pyrimidine
2-ethyl-3-(2-pentyl)-7-(2,4,6-trimethoxyphenyl)-
pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-
a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine-3-
carboxaldehyde
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxyethyl)-
pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-3-(1-ethoxyethyl)-2-ethyl-
pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-3-(1-ethoxyethyl)-2-
ethylpyrazolo[1,5-a]pyrimidine
2-ethyl-7-(2-methyl-4-methoxyphenyl)-3-(3-pentyl)-
pyrazolo[1,5-a]pyrimidine
2-ethyl-7-(2-methyl-4-methoxyphenyl)-3-(2-pentyl)-
pyrazolo[1,5-a]pyrimidine
7-(2,4-dimethylphenyl)-2-ethyl-3-(2-pentyl)-pyrazolo[1,5-
a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-5-methylthio-3-(2-pentyl)-
pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(6-methyl-5-hepten-2-yl)-
pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-4-pentyl)-
pyrazolo[1,5-a]pyrimidine
7-(4-difluoromethoxy-2-methyl)-2-ethyl-3-(3-

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pentyl)pyrazolo[1,5-a]pyrimidine
7-(4-difluoromethoxy-2-methyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-a]pyrimidine
7-(2-chloro-4-difluoromethoxyphenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine
7-(2-chloro-4-difluoromethoxyphenyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-a]pyrimidine
7-(2,4-dimethylphenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine
4-(7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidinyl)pentanoic acid
4-(7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidinyl)-N-methylpentanamide
3-(5-(benzoxazol-2-ylthio)-2-pentyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine
3-(5-(benzoxazolidinethione-3-yl)-2-pentyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-2-propyl)-pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-3-(1-ethoxy-2-propyl)-2-ethylpyrazolo[1,5-a]pyrimidine
3-(1-acetoxy-2-propyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine
3-(1-acetoxy-2-butyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-3-butyl)pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-methoxy-3-butyl)pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-6-methylpyrazolo[1,5-a]pyrimidine

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2-ethyl-3-(3-heptyl)-7-(2,4,6-trimethylphenyl)-
pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-pyrazolo[1,5-
a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-6-methyl-
pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethylphenyl)-
pyrazolo[1,5-a]pyrimidine

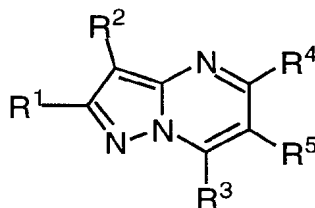
2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethoxyphenyl)-
pyrazolo[1,5-a]pyrimidine

Synthesis

5 Compounds of formula (I) can be prepared by the
following synthetic routes and schemes. Where a detailed
description is not provided, it is assumed that those
skilled in the art of organic synthesis will readily
understand the meaning.

10 Synthesis of compounds of formula (I) may be
prepared by the reaction shown in Scheme 1.

15 The embodiment of this invention concerning
compounds of Formula (I) with the structure



may be prepared according to the following methods:

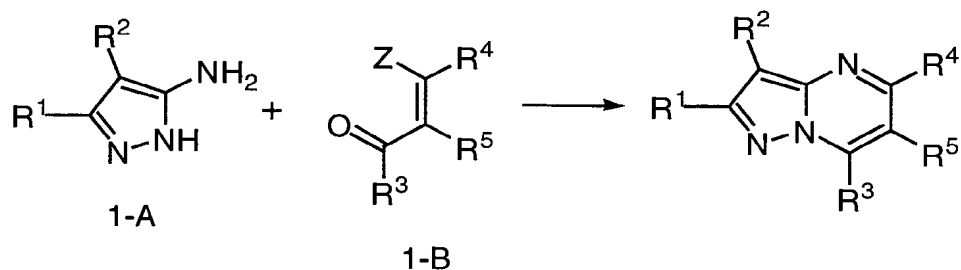
20 The pyrazolo[1,5-a]pyrimidine ring system is best
prepared by the condensation reaction of a 3-
aminopyrazole (1-A, Scheme 1A) with a compound of formula

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1-B. Here, Z is ethoxy or dimethylamino, and compound 1-B may be prepared by the reaction of a compound of formula $R^3C(=O)CH_2R^6$ with a reagent of formula $R^5C(Z)(OEt)_2$. These types of reactions are normally done by heating the two compounds (as a 1:1 mixture) without solvent, and distilling off the volatile components after the reaction is complete. The reaction between 1-A and 1-B is conveniently performed in a solvent such as acetic acid with heating; the acetic acid acts as both solvent and catalyst for the condensation.

Preparation of the pyrazoles can begin with the acylation of a nitrile compound 1-C (Scheme 1B). Normally, a strong base, such as lithium diisopropylamide, is used to deprotonate the nitrile, and the resulting anionic intermediate is treated with a carboxylic ester R^1CO_2Et or

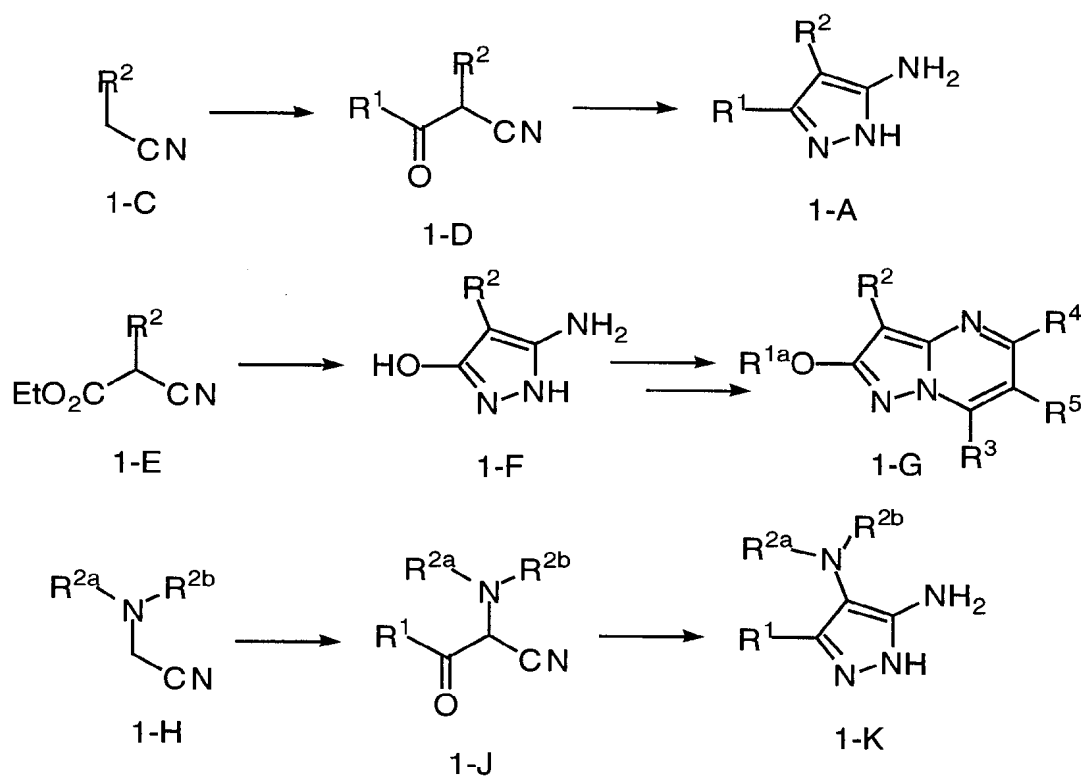
Scheme 1A



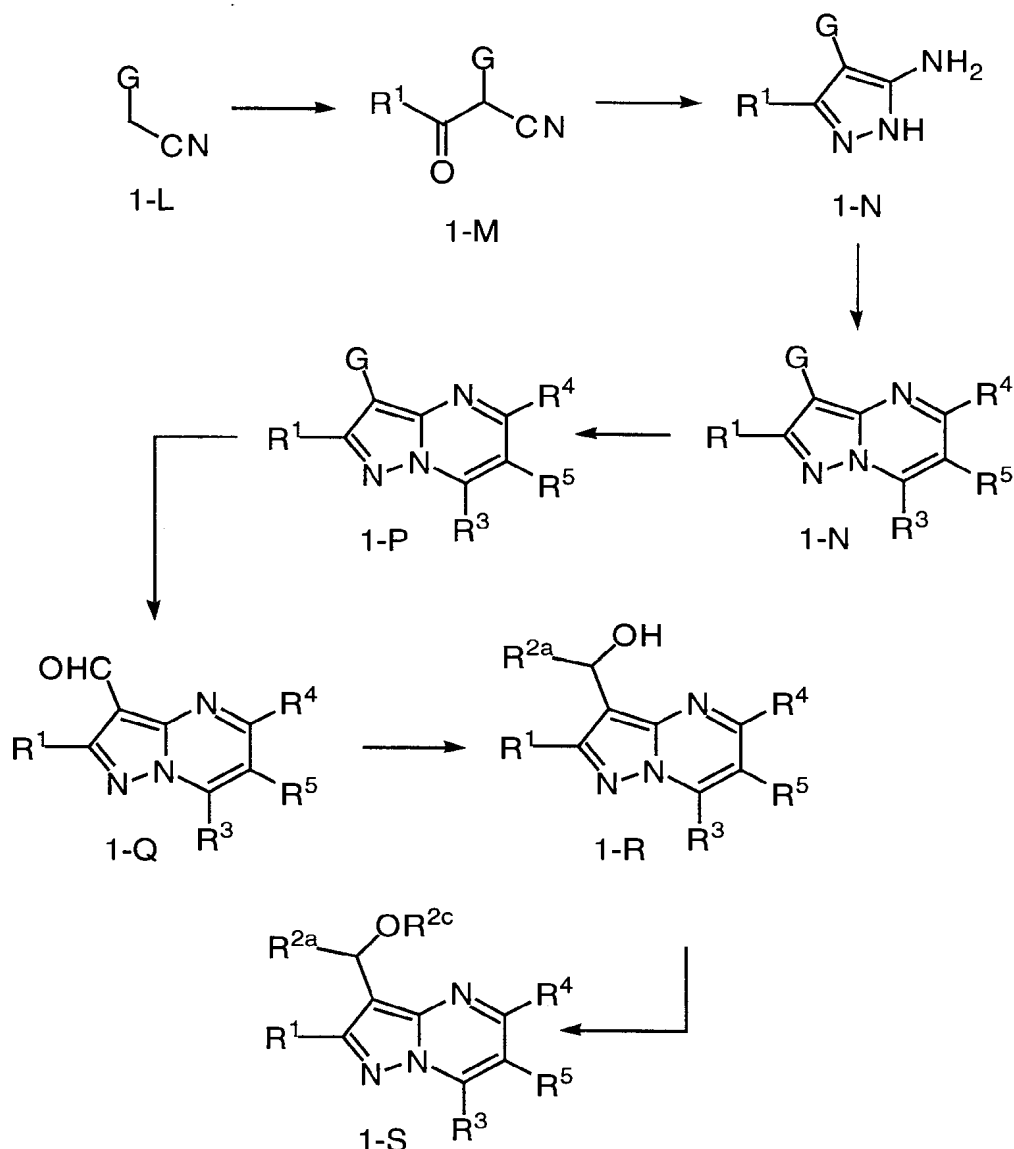
acid chloride R^1COCl to generate the ketonitrile 1-D. Condensation of this compound with hydrazine then gives the aminopyrazole. This reaction may be performed in refluxing alcoholic solvent with the optional presence of an acid catalyst, such as acetic acid. Heteroatomic versions of this route are possible. Aminopyrazoles with an R^1 group wherein $R^1 = R^{1a}O$ may be prepared by starting with cyanoacetic esters like 1-E, which react with hydrazine to afford 3-amino-5-hydroxypyrazole 1-F.

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Cyclization with reagent 1-B and O-alkylation with a reagent $R^{1a}X$, wherein X is a halide or pseudohalide group, gives compound 1-G. Finally, strong base treatment of aminonitrile 1-H, usually in the presence of a solvent mixture such as THF/HMPA, followed by acylation and ring-forming, gives diamine 1-K.

Scheme 1B

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Scheme 1C



Scheme 1C shows one application of a variation involving a group G (carboalkoxy or CN) which can serve as a functional handle for various R² substitutions. Since G is activating, the acylation of 1-L to give 1-M may not require as strong a base as is used for the transformation of 1-C to 1-D; a reagent such as an orthoester may also be used. Subsequent ring condensations to 1-N and then to 1-P proceed as described earlier. Then, the group G is converted to the R² group of

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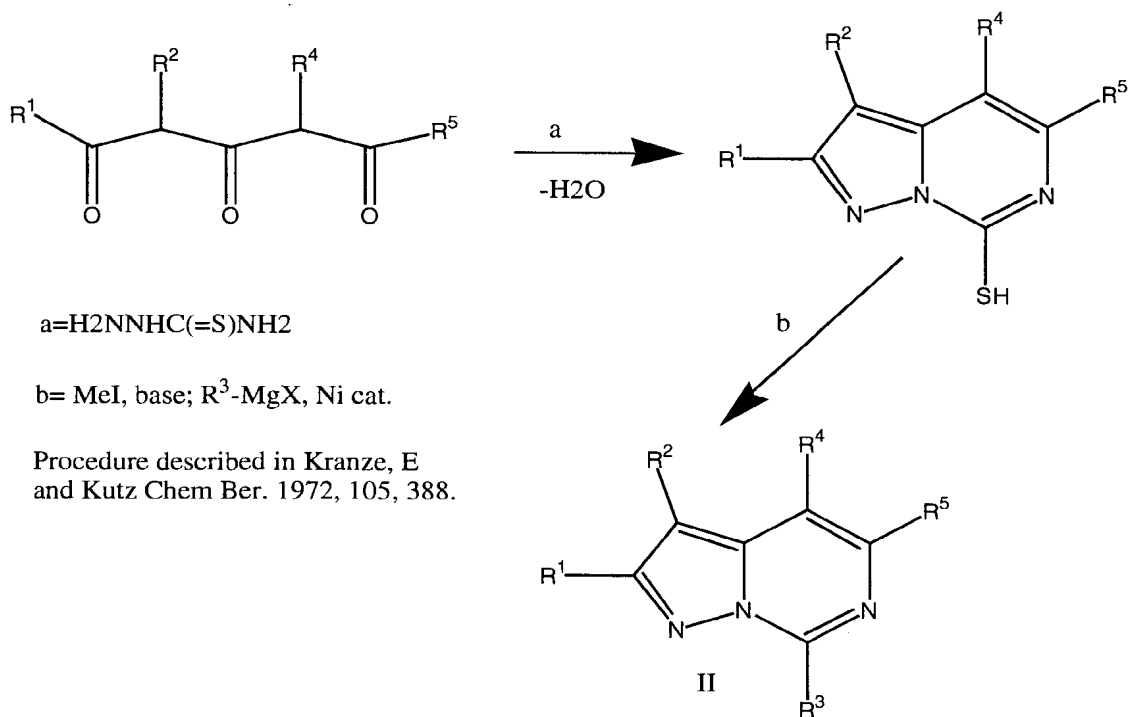
choice wherein R^2 and substituted versions thereof is as defined in the claims and as above in the specification; the following method is one example. Use of a reducing agent such as diisobutylaluminum hydride in a solvent
5 like toluene or dichloromethane at low temperatures can be used to obtain the aldehyde 1-Q. The aldehyde may be allowed to react with organometallic reagents such as the Grignard reagent $R^{2a}MgBr$ to afford the alcohol 1-R. The hydroxy group may then be O-alkylated (typically using a
10 reagent $R^{2c}X$ and a base such as sodium hydride in a polar aprotic solvent such as DMF) to give the compound 1-S. Other such manipulations of the G group should be familiar to those skilled in the art of organic synthesis.

15 Similarly, the remaining variables in the starting materials described above such as R^1 or R^3 are determined based upon the desired target moiety. Thus, varying the ketone 1-B with respect to the aryl or heteroaryl group R^3 permits synthesis of a compound of formula I having R^3 as
20 the desired heteroaryl or aryl group and substituted versions thereof as recited in the claims and above text and as further shown in the examples and table before the appended claims.

The synthesis of compounds of formula II or III may
25 be accomplished by the general schemes shown below in Scheme 2 and in Scheme 3.

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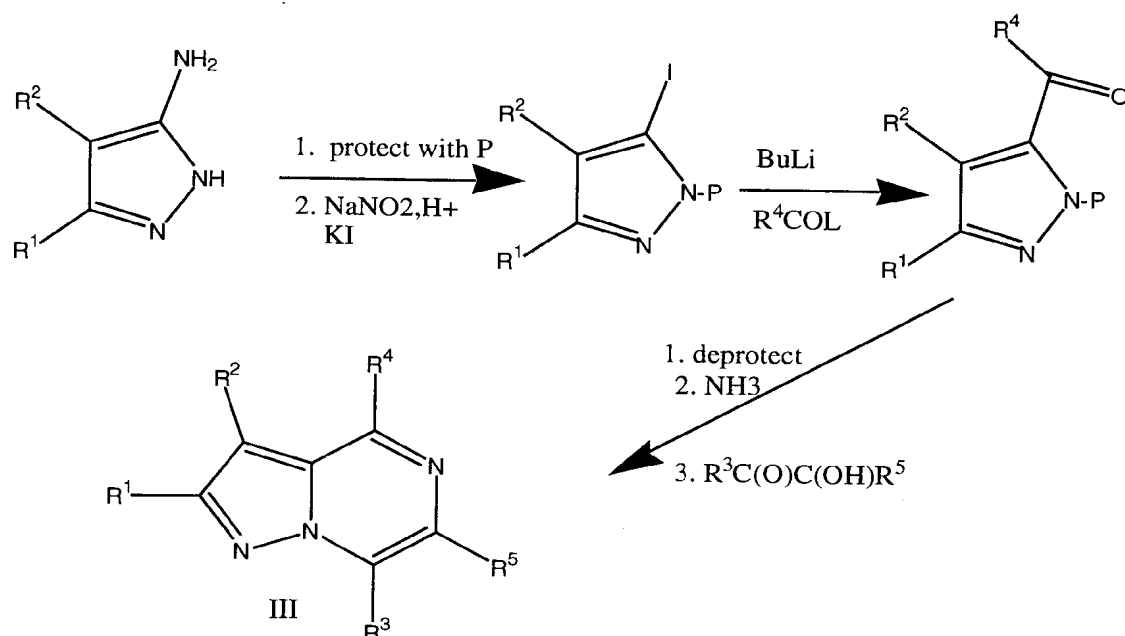
SCHEME 2



The variables for $\text{R}^1\text{-R}^5$ are selected from those variables
 as defined in any of the groups [1]-[24]. The compound
 of formula II is prepared by starting with the acyclic
 5 triketo intermediate shown above which is reacted with
 reagent a to form the bicyclic intermediate which is then
 treated with the grignard reagent b to form a compound of
 formula II.

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SCHEME 3



The variables for R¹-R⁵ in Scheme 3 are selected from those described in groups [1]-[24]. Compounds II and III
5 with the variables as defined above are useful as CRF antagonists.

10

Utility

CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

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Radioligand binding experiments

Compounds of the invention were tested for in vitro activity as CRF receptor antagonists. The tests described below demonstrated that the examples tested had K_is of 10,000 nM or less and are thus useful as CRF
20 receptor antagonists. Preferred antagonists have or will have a K_i of 1,000 nM or less. Radioligand binding experiments were performed with membranes from rat

frontal cortex to determine binding affinities (K_i 's) of test compounds for the rat CRH₁ receptor using a modified version of methods described earlier (see E.B. DeSouza, J. Neurosci, 7:88, 1987). Rat cortex was homogenized in
5 tissue buffer (containing 50 mM HEPES, 10 mM MgCl₂, 2 mM EGTA, and 1 µg/ml each of aprotonin, leupeptin, and pepstatin, pH 7.0 @ 23°C) using a Brinkman Polytron (PT-10, setting 6 for 10 sec). The homogenate was centrifuged at 48,000 X g for 12 min and the resulting pellet was
10 washed by two sequential re-suspension and centrifugation steps. The final pellet was suspended to tissue buffer to a working concentration of 0.1 mg/ml protein. Protein determinations were made using the bicinchoninic acid (BCA) assay (Pierce, Rockford, IL) with bovine serum
15 albumin as the standard.

All test compounds were prepared in assay buffer, which was identical to the tissue buffer except for the inclusion of 0.15 mM bacitracin and 0.1% w/v ovalbumin. Binding assay were conducted in disposable
20 polypropylene 96-well plates (Costar Corp., Cambridge, MA) and initiated by the addition of 100 µl membrane homogenate (containing 40-60 µg protein) to 200 µl of assay buffer containing radioligands (150 pM, final concentration, [¹²⁵I] tyr^o ovine CRH; New England
25 Nuclear, MA) and competing test compounds. Specific binding was determined in the presence of 10 µM α-helical CRH. Competition experiments were conducted using 12 concentrations of ligand (ranging from 1 X 10⁻¹¹ to 1 X 10⁻⁵ M). The reactions mixtures were incubated
30 to equilibrium for 2 hr at 23°C and terminated by rapid filtration using a cell harvester (Inotech Biosystems Inc., Lansing MI) over GFF glass-fibers (pre-soaked in 0.3 % v/v polyethyleneimine). Filters were rapidly washed 3X with 0.3 ml cold wash buffer (PBS, pH 7.0,
35 containing 0.01% Triton X-100), dried, and counted in a gamma counter at 80% efficiency.

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Binding affinities (K_i 's) of ligands for the CRH₁ receptor were calculated using the iterative nonlinear regression curve-fitting programs (LIGAND) of Munson and Rodbard (Anal. Biochem. 1980, 107, 220-239) or
5 Prism (GraphPad Prism, San Diego, CA). Data were best-fit by the one-site/state competition equation.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase
10 activity can be performed as described by G. Battaglia et al. Synapse 1:572 (1987). Briefly, assays are carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM MgCl₂, 0.4 mM EGTA, 0.1% BSA, 1 mM
15 isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10⁻⁹ to 10⁻⁶m) and 0.8 mg original wet weight tissue (approximately 40-60 mg
20 protein). Reactions are initiated by the addition of 1 mM ATP/³²P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 µl of [³H]cAMP
25 (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [³²P]cAMP from [³²P]ATP is performed by sequential elution over Dowex and alumina columns.

30 In vivo Biological Assay

The in vivo activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic
35 Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention

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have been outlined in C.W. Berridge and A.J. Dunn Brain Research Reviews 15:71 (1990).

5 Compounds may be tested in any species of rodent or small mammal.

Compounds of this invention have utility in the treatment of imbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

10 Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in
15 conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of
20 administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and
25 health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a dosage of the
30 active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

35 Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be

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present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and
5 powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active
10 ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release
15 products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective
20 disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

25 In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral
30 administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are
35 suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as

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benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a
5 standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

10 Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

15 Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive
20 displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

25 A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8
30 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The preferred indication and use of the compounds and compositions of the invention is in the treatment of depression or anxiety.

35 The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

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The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

Examples

The following specific synthetic example describes the procedures which, when applied to appropriately substituted substrates, may be employed in the synthesis of the compounds in Table 1.

Example 1

Preparation of 7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine

Part A. A mixture of 2-ethyl-1-bromobutane (10.0 mL, 71.4 mmol), potassium cyanide (14.0 g, 215 mmol) and aliquat 336 (10 drops) in 50 mL water was heated to reflux overnight with vigorous stirring. The mixture was cooled, and extracted with dichloromethane (2 x 50 mL). The extracts were combined, dried over magnesium sulfate, filtered and evaporated. The residual liquid was distilled bulb-to-bulb to afford pure product, 3-ethylpentanenitrile (5.50 g, 49.5 mmol, 69%). b.p. 40-45 °C (5 mm Hg). Spectral data: ¹H NMR (300 MHz, CDCl₃): δ 2.33 (2H, d, J = 5.8 Hz), 1.62-1.36 (5H, m), 0.92 (6H, t, J = 7.3 Hz). MS (H₂O-GC/MS): m/e 112 (100).

Part B. A solution of diisopropylamine (7.50 mL, 57.2 mmol) in THF (100 mL) was cooled to -78 °C, and treated

with n-butyllithium (34.0 mL of a 1.6 M solution in hexane). The solution was warmed briefly to 0 °C, and then recooled to -78 °C. The nitrile compound from Part A was then added by syringe, and the solution was allowed to stir for 1 hour. Then, ethyl propionate (6.50 mL, 56.7 mmol) was added by syringe, and the resulting mixture was allowed to stir and warm to ambient temperature for 12 hours. It was poured into 200 mL of satd. aq. NH_4Cl solution, and this was extracted with ethyl acetate (2 x 200 mL). The extracts were combined, dried over magnesium sulfate, filtered and evaporated. The residual oil was separated by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to afford the product, 4-cyano-5-ethyl-3-heptanone, as an oil 4.06 g, 24.3 mmol, 49%). TLC R_f 0.47 (20:80 ethyl acetate-hexane). Spectral data: ^1H NMR (300 MHz, CDCl_3): δ 3.49 (1H, d, J = 4.4 Hz), 2.74 (2H, q, J = 7.3 Hz), 2.08-1.98 (1H, m), 1.70-1.58 (1H, m), 1.50-1.20 (3H, m), 1.12 (3H, t, J = 7.3 Hz), 0.95 (3H, t, J = 7.3 Hz), 0.91 (3H, t, J = 7.3 Hz). MS (H_2O -GC/MS): m/e 167 (100).

Part C. A solution of the ketonitrile from Part B (4.06 g, 24.3 mmol), hydrazine hydrate (2.70 mL, 55.7 mmol) and acetic acid (5.00 mL, 83.7 mmol) in benzene (50 mL) was heated to reflux under a Dean-Stark trap with azeotropic distillation of water. After being heated for 12 hours, the mixture was cooled and poured into 100 mL 1 N aq. NaHCO_3 solution. This was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed in sequence with brine, combined, dried over sodium sulfate, filtered and evaporated to afford sufficiently-pure product, 3-amino-5-ethyl-4-(3-pentyl)pyrazole, as a viscous oil (2.48 g,

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13.7 mmol, 56%). Spectral data: ^1H NMR (300 MHz, CDCl_3): δ 3.48 (2H, br), 2.54 (2H, q, $J = 7.3$ Hz), 2.25-2.14 (1H, m), 1.71-1.49 (4H, m), 1.20 (3H, t, $J = 7.3$ Hz), 0.83 (6H, t, $J = 7.3$ Hz), 1H missing. MS (NH_3 -CI): m/e 183 (12), 182 (100).

Part D. A mixture of 2,4-dichloroacetophenone (10.0 g, 52.9 mmol) and dimethylformamide diethyl acetal (10.0 mL, 58.3 mmol) was heated to reflux for 12 hours, then cooled and evaporated under high vacuum. The residual oil was separated by column chromatography (silica gel, 1:1 ethyl acetate-hexane) to afford the product, 1-(2,4-dichlorobenzoyl)-2-(N,N-dimethylamino)ethene, as a viscous oil (12.11 g, 49.6 mmol, 94%). TLC R_f 0.05 (20:80 ethyl acetate-hexane). Spectral data: ^1H NMR (300 MHz, CDCl_3): δ 7.40 (1H, d, $J = 2.2$ Hz), 7.38-7.23 (3H, m), 5.33 (1H, d, $J = 12.4$ Hz), 3.11 (3H, br s), 2.89 (3H, br s). MS (NH_3 -CI): m/e 249 (1), 248 (10), 247 (8), 246 (64), 245 (16), 244 (100).

Part E. A solution of the product of Part C (2.25 g, 1.38 mmol) and that of Part D (0.337 g, 1.38 mmol) in acetic acid (5 mL) was heated to reflux for 10 hours, then cooled, and poured into water. This was neutralized by the addition of solid sodium bicarbonate until the evolution of CO_2 subsided. The resulting mixture was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed with brine (100 mL), combined, dried over sodium sulfate, filtered and evaporated. The resulting mixture of regioisomeric products (ca. 5:1 estimated by TLC visualization) were separated by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to afford the major regioisomer as the more TLC-mobile

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product, which was the title compound. TLC R_f 0.32 (10:90 ethyl acetate-hexane). Spectral data: ^1H NMR (300 MHz, CDCl_3): δ 8.38 (1H, d, $J = 4.1$ Hz), 7.58 (1H, d, $J = 2.0$ Hz), 7.55 (1H, d, $J = 8.2$ Hz), 7.41 (1H, dd, $J = 8.2, 2.0$ Hz), 6.65 (1H, d, $J = 4.1$ Hz), 2.79 (2H, q, $J = 7.7$ Hz), 2.78-2.68 (1H, m), 2.03-1.79 (4H, m), 1.25 (3H, t, $J = 7.7$ Hz), 0.83 (6H, t, $J = 7.3$ Hz). MS ($\text{NH}_3\text{-CI}$): m/e 367 (2), 366 (11), 365 (15), 364 (65), 363 (25), 362 (100). Analysis calc'd for $\text{C}_{19}\text{H}_{21}\text{Cl}_2\text{N}_3$: C, 62.99; H, 5.84; N, 11.60; found: C, 62.97; H, 5.74; N, 11.49.

Examples 2-30 were prepared and/or may be prepared in an analogous fashion.

Example 31Preparation of 7-(2,4-dichlorophenyl)-3-(N,N-diethylamino)-2-ethylpyrazolo[1,5-a]pyrimidine

- 5 Part A. A solution of diisopropylamine (10.0 mL, 76.3 mmol) in THF (60 mL) was cooled to -78 °C, and treated with n-butyllithium (50.0 mL of a 1.6 M solution in hexane). The solution was warmed briefly to 0 °C, and then recooled to
- 10 -78 °C. To this was added first, N,N'-dimethylpropyleneurea as cosolvent (15 mL), then, diethylaminoacetone (10.0 mL, 74.1 mmol), and the solution was allowed to stir for 1 hour. Then, ethyl propionate (10.0 mL, 87.2 mmol) was added by syringe, and
- 15 the resulting mixture was allowed to stir and warm to ambient temperature for 12 hours. It was poured into 200 mL of satd. aq. NH₄Cl solution, and this was extracted with ethyl acetate (2 x 200 mL). The extracts were combined, dried over magnesium sulfate, filtered and
- 20 evaporated. The residual oil was separated by column chromatography (silica gel, 20:80 ethyl acetate-hexane) to afford the product, 2-(N,N-diethylamino)-3-oxopentanenitrile, as an oil (5.31 g, 31.6 mmol, 43%).
- 25 Part B. A solution of the ketonitrile from Part A, hydrazine hydrate (3.00 mL, 61.9 mol) and acetic acid (6.00 mL, 104 mmol) in benzene (100 mL) was heated to reflux under a Dean-Stark trap with azeotropic removal of water for a period of 14 hours. Excess hydrazine (2 mL)
- 30 and excess acetic acid (5 mL) were then added, and refluxing was allowed to continue for 20 hours. The solution was cooled and poured into 200 mL 1 N aq. NaHCO₃ solution. This was extracted with ethyl acetate (2 x 200

- mL), and the extracts were washed in sequence with brine, combined, dried over sodium sulfate, filtered and evaporated. The residue was separated by column chromatography (silica gel, 30:70 ethyl acetate to remove unreacted starting material, then ethyl acetate) to afford the product, 3-amino-4-(N,N-diethylamino)-5-ethylpyrazole, as a viscous oil which darkens in air (750 mg, 4.41 mmol, 15%).
- 10 Part C. A solution of the diamine from Part B (300 mg, 1.76 mmol) and 1-(2,4-dichlorobenzoyl)-2-(N,N-dimethylamino)ethene (470 mg, 1.93 mmol) in acetic acid (5 mL) was heated to 100 °C for 10 hours, then cooled and poured into satd. aq. NaHCO₃ solution (100 mL). This mixture was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed with brine, combined, dried over sodium sulfate, filtered and evaporated. The residual oil was separated by column chromatography (silica gel, 20:80 ethyl acetate-hexane) to afford the title product as a red oil (411 mg, 1.13 mmol, 64%).
- 20 Spectral data: ¹H NMR (300 MHz, CDCl₃): δ 8.38 (1H, d, J = 4.0 Hz), 7.58 (1H, d, J = 1.8 Hz), 7.56 (1H, d, J = 8.4 Hz), 7.42 (1H, dd, J = 8.4, 1.8 Hz), 6.65 (1H, d, J = 4.0 Hz), 3.27 (4H, q, J = 7.3 Hz), 2.80 (2H, q, J = 7.3 Hz), 1.26 (3H, t, J = 7.3 Hz), 1.00 (6H, t, J = 7.3 Hz). MS (NH₃-CI): calculated for C₁₈H₂₁Cl₂N₄ 363.1143, measured 363.1146; m/e 367 (6), 366 (14), 365 (81), 364 (28), 363 (100).
- 25
- 30 Examples 32-45 were and/or may be prepared in an analogous manner.

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Preparation of 7-(2,4-dichlorophenyl)-2-hydroxy-6-methyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine (92) and 7-(2,4-dichlorophenyl)-2-methoxy-6-methyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine (51)

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Part A. A solution of triphenylphosphine (25.0 g, 95.3 mmol) in THF (200 mL) was cooled to -30 °C, and diethyl azodicarboxylate (15.0 mL, 95.2 mmol) was slowly added dropwise in conc. THF solution. After the addition was
10 complete, the mixture was treated with a THF solution of 3-pentanol (10.0 mL, 90.6 mmol) and ethyl cyanoacetate (10.0 mL, 92.1 mmol). The resulting mixture was allowed to stir and warm to ambient temperature for 12 hours, then was evaporated. The residual oil was separated by
15 column chromatography (10:90 ethyl acetate-hexane) to afford the product, ethyl 2-cyano-3-ethylpentanoate, as a viscous oil (3.41 g, 18.6 mmol, 21%). TLC R_f 0.43 (20:80 ethyl acetate-hexane). Spectral data: ^1H NMR (300 MHz, CDCl_3): δ 4.27 (2H, q, J = 7.0 Hz), 3.61 (1H, d, J = 4.4
20 Hz), 2.04-1.93 (1H, m), 1.70-1.35 (4H, m), 1.33 (3H, t, J = 7.0 Hz), 0.97 (3H, t, J = 7.3 Hz), 0.94 (3H, t, J = 7.3 Hz). MS (H_2O -GC/MS): m/e 185 (8), 184 (100).

Part B. A solution of the cyanoester from Part A and
25 hydrazine hydrate (2.00 mL, 41.2 mmol) in ethanol (30 mL) was heated to reflux for 10 hours. The solution was cooled, and poured into water. This was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed with brine, combined, dried over sodium sulfate, filtered
30 and evaporated. The resulting oil was sufficiently pure product, 3-amino-5-hydroxy-4-(3-pentyl)pyrazole (1.29 g, 7.62 mmol, 41%).

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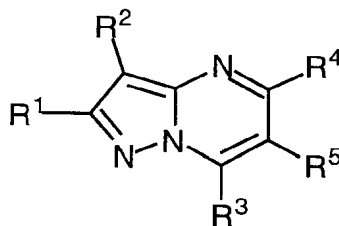
- Part C. A solution of the pyrazole compound from Part B (478 mg, 2.82 mmol) and 2-(2,4-dichlorobenzoyl)-1-(N,N-dimethylamino)-1-propene (729 mg, 2.82 mmol) in acetic acid (10 mL) was heated to reflux for 10 hours. The solution was cooled and poured into water (100 mL). This was neutralized by the addition of solid NaHCO₃, and the mixture was extracted with ethyl acetate (2 x 100 mL). The extracts were washed with brine, combined, dried over sodium sulfate, filtered and evaporated. The residue was separated by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to give the compound of Example 92 as a solid (210 mg, 0.576 mmol, 20%). m.p. 227-228 °C. TLC R_f 0.46 (20:80 ethyl acetate-hexane). Spectral data: ¹H NMR (300 MHz, CDCl₃): δ 10.53 (1H, br s), 8.27 (1H, s), 7.63 (1H, d, J = 2.2 Hz), 7.45 (1H, dd, J = 8.4, 2.2 Hz), 7.25 (1H, d, J = 8.4 Hz), 2.72-2.62 (1H, m), 2.02 (3H, s), 1.77-1.65 (4H, m), 0.82 (6H, t, J = 7.5 Hz). MS (ESI): m/e 366 (69), 364 (100).
- Part D. A solution of the compound of Example 92 (31 mg, 0.085 mmol) and Proton-Sponge™ (20 mg, 0.093 mmol) in acetonitrile (2 mL) was cooled to 0 °C, and treated with methyl methanetrifluorosulfonate (10 µL, 0.088 mmol). After stirring for 10 hours and warming to ambient temperature, the mixture was evaporated, and the residue was separated directly by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to give the compound of Example 51 as a viscous oil (7 mg, 0.019 mmol, 22%). TLC R_f 0.55 (20:80 ethyl acetate-hexane). Spectral data: ¹H NMR (300 MHz, CDCl₃): δ 8.27 (1H, s), 7.60 (1H, d, J = 2.2 Hz), 7.43 (1H, dd, J = 8.0, 2.0 Hz), 7.32 (1H, d, J = 8.0 Hz), 3.84 (3H, s), 2.80-2.70 (1H, m), 2.08 (3H, s), 1.86-1.70 (4H, m), 0.82 (6H, t, J = 7.4 Hz). MS (NH₃-CI): m/e

383 (2), 382 (12), 381 (14), 380 (65), 379 (25), 378
(100).

Examples 52-90 and 92 were and/or may be prepared
according to the procedures described above. The
5 additional examples prepared or readily prepared (93-281)
were (or may be) prepared according to the procedures
described above and shown in the general schemes and
described in the text. Table 1 shows the preferred
compounds.

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Table 1



<u>Ex</u> <u>No</u>	<u>R¹</u>	<u>R²</u>	<u>R⁴</u>	<u>R⁵</u>	<u>R³</u>	<u>m.p.</u> <u>°C</u>
1	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2,4-Cl ₂ -C ₆ H ₃	oil ^a
2	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	88- 89
3	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	oil ^b
4	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	166- 167
5	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
6	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	90- 91
7	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	CH ₃	2-Cl-4-CH ₃ O-C ₆ H ₃	-
8	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
9	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
10	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	CH ₃	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
11	C ₂ H ₅	(C ₂ H ₅) ₂ CH	CH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
12	C ₂ H ₅	(C ₂ H ₅) ₂ CH	CH ₃	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
13	C ₂ H ₅	(C ₂ H ₅) ₂ CH	CH ₃	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
14	C ₂ H ₅	(C ₂ H ₅) ₂ CH	CH ₃	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
15	C ₂ H ₅	(C ₂ H ₅) ₂ CH	CH ₃	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
16	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2,4-Cl ₂ -C ₆ H ₃	oil ^c
17	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
18	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	oil ^d
19	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-

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20	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
21	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	78- 79
22	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	CH ₃	2-Cl-4-CH ₃ O-C ₆ H ₃	-
23	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	CH ₃	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
24	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	CH ₃	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
25	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	CH ₃	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
26	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
27	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
28	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
29	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
30	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
31	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2,4-Cl ₂ -C ₆ H ₃	oil ^e
32	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	97- 98
33	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
34	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
35	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
36	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	-
37	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	CH ₃	2-Cl-4-CH ₃ O-C ₆ H ₃	-
38	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	CH ₃	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
39	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	CH ₃	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
40	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	CH ₃	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
41	C ₂ H ₅	(C ₂ H ₅) ₂ N	CH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
42	C ₂ H ₅	(C ₂ H ₅) ₂ N	CH ₃	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
43	C ₂ H ₅	(C ₂ H ₅) ₂ N	CH ₃	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
44	C ₂ H ₅	(C ₂ H ₅) ₂ N	CH ₃	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-

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45	C ₂ H ₅	(C ₂ H ₅) ₂ N	CH ₃	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
46	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
47	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
48	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
49	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
50	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
51	OCH ₃	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	oil ^f
52	OCH ₃	(C ₂ H ₅) ₂ CH	H	CH ₃	2-Cl-4-CH ₃ O-C ₆ H ₃	-
53	OCH ₃	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
54	OCH ₃	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
55	OCH ₃	(C ₂ H ₅) ₂ CH	H	CH ₃	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
56	OCH ₃	(C ₂ H ₅) ₂ CH	CH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
57	OCH ₃	(C ₂ H ₅) ₂ CH	CH ₃	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
58	OCH ₃	(C ₂ H ₅) ₂ CH	CH ₃	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
59	OCH ₃	(C ₂ H ₅) ₂ CH	CH ₃	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
60	OCH ₃	(C ₂ H ₅) ₂ CH	CH ₃	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
61	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
62	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
63	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
64	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
65	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
66	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	-
67	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	CH ₃	2-Cl-4-CH ₃ O-C ₆ H ₃	-
68	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	CH ₃	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
69	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	CH ₃	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
70	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	CH ₃	2-(CH ₃) ₂ N-4-CH ₃ -	-

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					pyridin-5-yl	
71	OCH ₃	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
72	OCH ₃	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
73	OCH ₃	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
74	OCH ₃	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
75	OCH ₃	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
76	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2,4-Cl ₂ -C ₆ H ₃	-
77	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
78	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
79	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
80	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
81	OCH ₃	(C ₂ H ₅) ₂ N	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	-
82	OCH ₃	(C ₂ H ₅) ₂ N	H	CH ₃	2-Cl-4-CH ₃ O-C ₆ H ₃	-
83	OCH ₃	(C ₂ H ₅) ₂ N	H	CH ₃	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
84	OCH ₃	(C ₂ H ₅) ₂ N	H	CH ₃	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
85	OCH ₃	(C ₂ H ₅) ₂ N	H	CH ₃	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
86	OCH ₃	(C ₂ H ₅) ₂ N	CH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
87	OCH ₃	(C ₂ H ₅) ₂ N	CH ₃	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
88	OCH ₃	(C ₂ H ₅) ₂ N	CH ₃	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
89	OCH ₃	(C ₂ H ₅) ₂ N	CH ₃	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
90	OCH ₃	(C ₂ H ₅) ₂ N	CH ₃	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
91	CH ₃	(C ₂ H ₅) ₂ CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
92	OH	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	227- 228
93	C ₂ H ₅	(C ₂ H ₅) ₂ CH	OCH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
94	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	OCH ₃	2,4-Cl ₂ -C ₆ H ₃	-
95	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
96	C ₂ H ₅	CH ₃ (c-C ₃ H ₅) CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-

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97	C ₂ H ₅	CH ₃ (c-C ₄ H ₇) CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
98	C ₂ H ₅	(c-C ₃ H ₅) ₂ CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
99	C ₂ H ₅	C ₂ H ₅ (c-C ₃ H ₅) CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
100	C ₂ H ₅	CH ₃ (c-C ₄ H ₇) CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
101	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2,4-Cl ₂ -C ₆ H ₃	-
102	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
103	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
104	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
105	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
106	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
107	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2-Cl-4-OCH ₃ -5-F	-
108	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2-Cl-4,5-(OCH ₃) ₂	-
109	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2,4-Cl ₂ -C ₆ H ₃	-
110	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
111	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
112	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
113	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
114	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
115	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2-Cl-4-OCH ₃ -5-F	-
116	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2-Cl-4,5-(OCH ₃) ₂	-
117	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃) C	H	H	2,4-Cl ₂ -C ₆ H ₃	-

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118	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
119	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
120	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
121	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
122	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
123	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2-Cl-4-OCH ₃ -5-F	-
124	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2-Cl-4,5-(OCH ₃) ₂	-
125	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2,4-Cl ₂ -C ₆ H ₃	-
126	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
127	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
128	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
129	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
130	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
131	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2-Cl-4-OCH ₃ -5-F	-
132	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2-Cl-4,5-(OCH ₃) ₂	-
133	C ₂ H ₅	(C ₂ H ₅) ₂ (OH)C	H	H	2,4-Cl ₂ -C ₆ H ₃	-
134	C ₂ H ₅	(C ₂ H ₅) ₂ (OH)C	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
135	C ₂ H ₅	(C ₂ H ₅) ₂ (OH)C	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
136	C ₂ H ₅	(C ₂ H ₅) ₂ (OH)C	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
137	C ₂ H ₅	(C ₂ H ₅) ₂ (OH)C	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
138	C ₂ H ₅	(C ₂ H ₅) ₂ (OH)C	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-

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139	C ₂ H ₅	(C ₂ H ₅) ₂ (OH) C	H	H	2-Cl-4-OCH ₃ -5-F	-
140	C ₂ H ₅	(C ₂ H ₅) ₂ (OH) C	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
141	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2, 4-Cl ₂ -C ₆ H ₃	-
142	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
143	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2, 4, 6- (CH ₃) ₃ -C ₆ H ₂	-
144	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2, 4, 6- (OCH ₃) ₃ - C ₆ H ₂	-
145	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2- (CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
146	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2, 4-Cl ₂ -5-F-C ₆ H ₂	-
147	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2-Cl-4-OCH ₃ -5-F	-
148	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
149	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2, 4-Cl ₂ -5-F-C ₆ H ₂	oil
150	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4-OCH ₃ -5-F	-
151	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
152	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	H	2, 4-Cl ₂ -5-F-C ₆ H ₂	-
153	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	H	2-Cl-4-OCH ₃ -5-F	-
154	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
155	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2, 4-Cl ₂ -5-F-C ₆ H ₂	oil ^g
156	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4-OCH ₃ -5-F	-
157	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
158	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2, 4-Cl ₂ -5-F-C ₆ H ₂	-
159	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-Cl-4-OCH ₃ -5-F	-
160	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
161	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
162	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2, 4, 6- (CH ₃) ₃ -C ₆ H ₂	-
163	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2, 4, 6- (OCH ₃) ₃ - C ₆ H ₂	-
164	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2- (CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
165	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2, 4-Cl ₂ -5-F-C ₆ H ₂	-
166	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2-Cl-4-OCH ₃ -5-F	-
167	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
168	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-CH ₃ -4-OCH ₃ -5-	-

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					F-C ₆ H ₂	
169	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-CH ₃ -4-OCH ₃ -5-	-
					F-C ₆ H ₂	
170	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-CH ₃ -4-OCH ₃ -5-	-
					F-C ₆ H ₂	
171	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-CH ₃ -4-OCH ₃ -5-	-
					F-C ₆ H ₂	
172	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-CH ₃ -4-OCH ₃ -5-	-
					F-C ₆ H ₂	
173	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2-CH ₃ -4-OCH ₃ -5-	-
					F-C ₆ H ₂	
174	C ₂ H ₅	C ₃ H ₇ (CH ₃)CH	H	H	2-CH ₃ -4-OCH ₃ -5-	-
					F-C ₆ H ₂	
175	OCH ₃	C ₃ H ₇ (CH ₃)CH	H	H	2-CH ₃ -4-OCH ₃ -5-	-
					F-C ₆ H ₂	
176	C ₂ H ₅	C ₂ H ₅ (OCH ₃)CH	H	H	2-CH ₃ -4-OCH ₃ -5-	-
					F-C ₆ H ₂	
177	OCH ₃	C ₂ H ₅ (OCH ₃)CH	H	H	2-CH ₃ -4-OCH ₃ -5-	-
					F-C ₆ H ₂	
178	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
179	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
180	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
181	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
182	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
183	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
184	C ₂ H ₅	C ₃ H ₇ (CH ₃)CH	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
185	OCH ₃	C ₃ H ₇ (CH ₃)CH	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
186	C ₂ H ₅	C ₂ H ₅ (OCH ₃)CH	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
187	OCH ₃	C ₂ H ₅ (OCH ₃)CH	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
188	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
189	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
190	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
191	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-

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192	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
193	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
194	C ₂ H ₅	C ₃ H ₇ (CH ₃)CH	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
195	OCH ₃	C ₃ H ₇ (CH ₃)CH	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
196	C ₂ H ₅	C ₂ H ₅ (OCH ₃)CH	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
197	OCH ₃	C ₂ H ₅ (OCH ₃)CH	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
198	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -C ₆ H ₃	oil ^h
199	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
200	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
201	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
202	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
203	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
204	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
205	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-OCH ₃ -5-F	-
206	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4,5-(OCH ₃) ₂	-
207	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -5- F-C ₆ H ₂	-
208	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
209	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
210	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -C ₆ H ₃	-
211	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
212	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
213	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
214	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
215	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-

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216	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
217	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-OCH ₃ -5-F	-
218	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4,5-(OCH ₃) ₂	-
219	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -5- F-C ₆ H ₂	-
220	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
221	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
222	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -C ₆ H ₃	-
223	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
224	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
225	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
226	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
227	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
228	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
229	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-OCH ₃ -5-F	-
230	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-Cl-4,5-(OCH ₃) ₂	-
231	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -5- F-C ₆ H ₂	-
232	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
233	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
234	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -C ₆ H ₃	-
235	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
236	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
237	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
238	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C	H	H	2-(CH ₃) ₂ N-4-CH ₃ -	-

		H			pyridin-5-yl	
239	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
240	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
241	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-OCH ₃ -5-F	-
242	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-Cl-4,5-(OCH ₃) ₂	-
243	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -5- F-C ₆ H ₂	-
244	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
245	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
246	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4-Cl ₂ -C ₆ H ₃	-
247	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
248	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
249	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
250	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
251	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
252	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
253	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-Cl-4-OCH ₃ -5-F	-
254	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-Cl-4,5-(OCH ₃) ₂	-
255	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-CH ₃ -4-OCH ₃ -5- F-C ₆ H ₂	-
256	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
257	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
258	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4-Cl ₂ -C ₆ H ₃	-
259	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
260	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-

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261	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
262	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
263	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
264	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
265	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-Cl-4-OCH ₃ -5-F	-
266	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-Cl-4,5-(OCH ₃) ₂	-
267	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-CH ₃ -4-OCH ₃ -5- F-C ₆ H ₂	-
268	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
269	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
270	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	oil ¹
271	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
272	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
273	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
274	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
275	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
276	C ₂ H ₅	C ₃ H ₇ (CH ₃)CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
277	OCH ₃	C ₃ H ₇ (CH ₃)CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
278	C ₂ H ₅	C ₂ H ₅ (OCH ₃)CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
279	OCH ₃	C ₂ H ₅ (OCH ₃)CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
280	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
281	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-

Key:

a) Spectral data for Example 1: ¹H NMR (300 MHz, CDCl₃): δ
5 8.38 (1H, d, J = 4.1 Hz), 7.58 (1H, d, J = 2.0 Hz), 7.55
(1H, d, J = 8.2 Hz), 7.41 (1H, dd, J = 8.2, 2.0 Hz), 6.65
(1H, d, J = 4.1 Hz), 2.79 (2H, q, J = 7.7 Hz), 2.78-2.68

δ

(1H, m), 2.03-1.79 (4H, m), 1.25 (3H, t, $J = 7.7$ Hz),
0.83 (6H, t, $J = 7.3$ Hz). MS ($\text{NH}_3\text{-CI}$): m/e 367 (2), 366
(11), 365 (15), 364 (65), 363 (25), 362 (100). Analysis
calc'd for $\text{C}_{19}\text{H}_{21}\text{Cl}_2\text{N}_3$: C, 62.99; H, 5.84; N, 11.60; found:
5 C, 62.97; H, 5.74; N, 11.49.

b) Spectral data for Example 3: ^1H NMR (300 MHz, CDCl_3): δ
8.36 (1H, d, $J = 5.0$ Hz), 7.00 (2H, s), 6.50 (1H, d, $J =$
5.0 Hz), 2.77 (2H, q, $J = 7.7$ Hz), 2.76-2.66 (1H, m),
2.36 (3H, s), 2.02 (6H, s), 2.00-1.80 (4H, m), 1.21 (3H,
10 t, $J = 7.7$ Hz), 0.83 (6H, t, $J = 7.5$ Hz). MS ($\text{NH}_3\text{-CI}$): m/e
338 (3), 337 (24), 336 (100). Analysis calc'd for $\text{C}_{22}\text{H}_{29}\text{N}_3$:
C, 78.76; H, 8.71; N, 12.53; found: C, 78.74; H, 8.74; N,
12.41.

c) Spectral data for Example 16: ^1H NMR (300 MHz, CDCl_3): δ
15 8.39 (1H, d, $J = 4.2$ Hz), 7.59 (1H, d, $J = 8.3$ Hz), 7.58
(1H, d, $J = 2.0$ Hz), 7.42 (1H, dd, $J = 8.3, 2.0$ Hz), 6.65
(1H, d, $J = 4.2$ Hz), 2.82-2.72 (1H, m), 2.79 (2H, q, $J =$
7.3 Hz), 2.00-1.77 (4H, m), 1.35-1.10 (4H, m), 1.25 (3H,
t, $J = 7.3$ Hz), 0.83 (3H, t, $J = 7.0$ Hz), 0.82 (3H, t, J
20 = 7.5 Hz). MS ($\text{NH}_3\text{-CI}$): m/e calculated for $\text{C}_{21}\text{H}_{26}\text{Cl}_2\text{N}_3$:
390.1504, found 390.1502; 395 (3), 394 (12), 393 (17),
392 (67), 391 (29), 390 (100).

d) Spectral data for Example 18: ^1H NMR (300 MHz, CDCl_3): δ
8.36 (1H, d, $J = 4.0$ Hz), 7.00 (2H, s), 6.50 (1H, d, $J =$
25 4.0 Hz), 2.82-2.73 (1H, m), 2.77 (2H, q, $J = 7.6$ Hz),
2.36 (3H, s), 2.02 (3H, s), 2.01 (3H, s), 2.00-1.78 (4H,
m), 1.38-1.09 (4H, m), 1.20 (3H, t, $J = 7.6$ Hz), 0.83
(3H, t, $J = 7.0$ Hz), 0.81 (3H, t, $J = 7.3$ Hz). MS ($\text{NH}_3\text{-}$
 CI): m/e calc'd for $\text{C}_{24}\text{H}_{34}\text{N}_3$: 364.2753, found 364.2754; 366
30 (4), 365 (27), 364 (100).

e) Spectral data for Example 31: ^1H NMR (300 MHz, CDCl_3): δ
8.38 (1H, d, $J = 4.0$ Hz), 7.58 (1H, d, $J = 1.8$ Hz), 7.56
(1H, d, $J = 8.4$ Hz), 7.42 (1H, dd, $J = 8.4, 1.8$ Hz), 6.65

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(1H, d, $J = 4.0$ Hz), 3.27 (4H, q, $J = 7.3$ Hz), 2.80 (2H, q, $J = 7.3$ Hz), 1.26 (3H, t, $J = 7.3$ Hz), 1.00 (6H, t, $J = 7.3$ Hz). MS ($\text{NH}_3\text{-CI}$): calculated for $\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{N}_4$: 363.1143, found 363.1146; m/e 367 (6), 366 (14), 365 (81), 364

5 (28), 363 (100).

f) Spectral data for Example 51: ^1H NMR (300 MHz, CDCl_3): δ 8.27 (1H, s), 7.60 (1H, d, $J = 2.2$ Hz), 7.43 (1H, dd, $J = 8.0, 2.0$ Hz), 7.32 (1H, d, $J = 8.0$ Hz), 3.84 (3H, s), 2.80-2.70 (1H, m), 2.08 (3H, s), 1.86-1.70 (4H, m), 0.82
10 (6H, t, $J = 7.4$ Hz). MS ($\text{NH}_3\text{-CI}$): m/e 383 (2), 382 (12), 381 (14), 380 (65), 379 (25), 378 (100).

g) Spectral data for Example 155: ^1H NMR (300 MHz, CDCl_3): δ 8.39 (1H, d, $J = 4.0$ Hz), 7.63 (1H, d, $J = 6.6$ Hz), 7.48 (1H, d, $J = 8.8$ Hz), 6.67 (1H, d, $J = 4.0$ Hz), 2.79
15 (2H, q, $J = 7.4$ Hz), 2.78-2.68 (1H, m), 2.03-1.79 (4H, m), 1.26 (3H, t, $J = 7.4$ Hz), 0.83 (6H, t, $J = 7.5$ Hz). MS ($\text{NH}_3\text{-CI}$): m/e 384 (11), 383 (16), 382 (79), 381 (20), 380 (100).

h) Spectral data for Example 198: ^1H NMR (300 MHz, CDCl_3):
20 δ 8.40 (1H, d, $J = 4.0$ Hz), 7.58 (1H, d, $J = 1.8$ Hz), 7.55 (1H, d, $J = 8.4$ Hz), 7.41 (1H, dd, $J = 8.4, 1.8$ Hz), 6.67 (1H, d, $J = 4.0$ Hz), 3.79 (2H, d, $J = 7.3$ Hz), 3.38 (3H, s), 3.37 (1H, m), 2.82 (2H, q, $J = 7.3$ Hz), 1.47 (3H, d, $J = 7.0$ Hz), 1.25 (3H, t, $J = 7.3$ Hz). Mass
25 Spectrum (AP-CI): m/e 364 (100), 366 (65), 368 (12.5).

High resolution mass spectrum: for $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{N}_3\text{O}$ m/e calculated: 364.0984, observed 364.0988.

i) Spectral data for Example 270: TLC R_f 0.19 (5:95 ethyl acetate-hexane). ^1H NMR (300 MHz, CDCl_3): δ 8.42 (1H, d, $J = 4.4$ Hz), 7.84 (1H, br s), 7.76 (1H, d, $J = 8.1$ Hz), 7.69 (1H, d, $J = 8.1$ Hz), 6.68 (1H, d, $J = 4.4$ Hz), 2.79
30 (2H, q, $J = 7.7$ Hz), 2.78-2.68 (1H, m), 2.02-1.80 (4H, m), 1.25 (3H, t, $J = 7.7$ Hz), 0.84 (6H, t, $J = 7.5$ Hz).

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MS (NH₃-CI): m/e 399 (7), 398 (33), 397 (25), 396 (100).

Analysis calc'd for C₂₀H₂₁ClF₃N₃: C, 60.68; H, 5.36; N, 10.62; found: C, 60.66; H, 5.15; N, 10.48.

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Additional Examples of Compounds Made According to the
Above-Described Synthetic Scheme and Examples

7-(2,4-dichloro-5-fluorophenyl)-2-ethyl-3-(2-pentyl)-
pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-6-methyl-3-(2-pentyl)-
pyrazolo[1,5-a]pyrimidine

7-(2-chloro-4-methoxyphenyl)-2-ethyl-3-(2-
pentyl)pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(2-pentyl)-7-(2,4,6-trimethylphenyl)-
pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(2-pentyl)-7-(2,4,6-trimethoxyphenyl)-
pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-
a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine-3-
carboxaldehyde

7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxyethyl)-
pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-3-(1-ethoxyethyl)-2-ethyl-
pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-3-(1-ethoxyethyl)-2-
ethylpyrazolo[1,5-a]pyrimidine

2-ethyl-7-(2-methyl-4-methoxyphenyl)-3-(3-pentyl)-
pyrazolo[1,5-a]pyrimidine

2-ethyl-7-(2-methyl-4-methoxyphenyl)-3-(2-pentyl)-
pyrazolo[1,5-a]pyrimidine

7-(2,4-dimethylphenyl)-2-ethyl-3-(2-pentyl)-pyrazolo[1,5-

a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-5-methylthio-3-(2-pentyl)-
pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(6-methyl-5-hepten-2-yl)-
pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-4-pentyl)-
pyrazolo[1,5-a]pyrimidine
7-(4-difluoromethoxy-2-methyl)-2-ethyl-3-(3-
pentyl)pyrazolo[1,5-a]pyrimidine
7-(4-difluoromethoxy-2-methyl)-2-ethyl-3-(2-
pentyl)pyrazolo[1,5-a]pyrimidine
7-(2-chloro-4-difluoromethoxyphenyl)-2-ethyl-3-(3-
pentyl)pyrazolo[1,5-a]pyrimidine
7-(2-chloro-4-difluoromethoxyphenyl)-2-ethyl-3-(2-
pentyl)pyrazolo[1,5-a]pyrimidine
7-(2,4-dimethylphenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-
a]pyrimidine
4-(7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-
a]pyrimidinyl)pentanoic acid
4-(7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-
a]pyrimidinyl)-N-methylpentanamide
3-(5-(benzoxazol-2-ylthio)-2-pentyl)-7-(2,4-
dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine
3-(5-(benzoxazolidinethione-3-yl)-2-pentyl)-7-(2,4-
dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-2-propyl)-
pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-3-(1-ethoxy-2-propyl)-2-ethyl-
pyrazolo[1,5-a]pyrimidine
3-(1-acetoxy-2-propyl)-7-(2,4-dichlorophenyl)-2-
ethylpyrazolo[1,5-a]pyrimidine
3-(1-acetoxy-2-butyl)-7-(2,4-dichlorophenyl)-2-
ethylpyrazolo[1,5-a]pyrimidine

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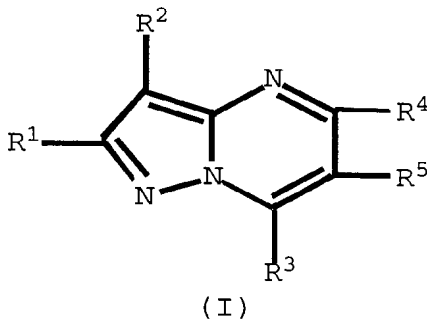
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-3-butyl)pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-methoxy-3-butyl)pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-6-methyl-pyrazolo[1,5-a]pyrimidine
2-ethyl-3-(3-heptyl)-7-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-6-methyl-pyrazolo[1,5-a]pyrimidine
2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine
2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine

Although the present invention has been described
5 and exemplified in terms of certain preferred
embodiments, other embodiments will be apparent to
those skilled in the art. The invention is, therefore,
not limited to the particular embodiments described and
exemplified, but is capable of modification or
10 variation without departing from the spirit of the
invention, the full scope of which is delineated by the
appended claims.

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WHAT IS CLAIMED IS:

1. A compound of formula I:



5

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of

10 C_{1-6} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkyloxy,15 C_{1-6} alkylS(O)_n,

$-NR^{1a}R^{1b}$ wherein R^{1a} and R^{1b} are independently selected from

H, C_{1-4} alkyl, $-C(O)C_{1-4}$ alkyl,

$-C(O)NR^{1a}R^{1b}$,

$-O-C(O)C_{1-4}$ alkyl,

20 $-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl;

X is selected from O or S(O)_n,

wherein R^1 is substituted with 0-6 substituents selected from halogen, C_{1-4} alkyl, C_{1-6} alkyloxy, C_{1-4} haloalkyl, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

25

R^2 is selected from the group consisting of

 C_{1-10} alkyl, C_{2-10} alkenyl,

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- C_{2-10} alkynyl,
 C_{3-8} cycloalkyl,
 C_{3-6} cycloalkyl C_{1-6} alkyl,
 C_{1-10} alkyloxy,
5 C_{1-10} alkyloxy C_{1-10} alkyl,
 $-SO_2-C_{1-10}$ alkyl
 $-SO_2R^{2a}$ wherein R^{2a} is aryl,
 $-SO_2R^{2b}$ wherein R^{2b} is heteroaryl,
 $-NR^{2c}R^{2d}$ wherein R^{2c} and R^{2d} are independently selected from
10 H, C_{1-8} alkyl, $S(O)_n C_{1-4}$ alkyl, $C(O)NR^{2c}R^{2d}$, CO_2C_{1-4} alkyl,
 C_{3-8} cycloalkyl, C_{1-6} alkyloxy C_{1-6} alkyl, $-C(O)C_{1-4}$ alkyl
or R^{2c} and R^{2d} may join to form a heterocyclic ring
having 0-3 heteroatoms selected from O, N or S,

15 - halogen,
-CN,
 $-C(O)L$ wherein L is selected from $NR^{2c}R^{2d}$, C_{1-6} alkyl, H,
 $-OC_{1-6}$ alkyl, $O(CH_2)_m OC_{1-6}$ alkyl, $O(CH_2)_m NR^{2c}R^{2d}$, -OH, aryl,
heteroaryl or $C(O)OC_{1-6}$ alkyl wherein m is 1-3;
20

n is 0, 1 or 2;

 R^2 is substituted with 0-3 substituents independently
25 selected from R' , R'' , R''' wherein R' , R'' and R''' are
independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl,
hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6}
alkyloxy, hydroxy; or

30 R^2 is substituted with 0-3 substituents independently
selected from
halogen,
-CN,

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- S(O)_nR^{2e} wherein R^{2e} is selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyloxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl;
- 5 -COR^{2f} wherein R^{2f} is selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyloxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl, and C₃₋₆ cycloalkylC₁₋₄ alkyl;
- CO₂R^{2f},
- NR^{2g}COR^{2f} wherein R^{2g} is selected from H, C₁₋₆ alkyl, C₃₋₇ c-alkyl, C₃₋₆ cycloalkyl C₁₋₆ alkyl;
- 10 -N(COR^{2f})₂,
- NR^{2g}CONR^{2f}R^{2h}, wherein R^{2h} is selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl and C₃₋₆ cycloalkylC₁₋₆ alkyl;
- 15 -NR^{2g}CO₂R^{2e},
- CONR^{2g}R^{2h},
- 1-morpholinyl,
- 1-piperidinyl,
- 20 1-piperazinyl,
- and
- C₃₋₈ cycloalkyl wherein 0-1 carbon atoms in the C₄₋₈ cycloalkyl is replaced by a group selected from
- O-, -S(O)_n-, -NR^{2g}-, -NCO₂R^{2e}, -NCOR^{2e},
- 25 and -NSO₂R^{2e}; and wherein N₄ in
- 1-piperazinyl is substituted with 0-1 substituents selected from R^{2g}, CO₂R^{2e}, COR^{2e} and SO₂R^{2e}; or
- 30 the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl which is substituted with 0-1 R²¹ and in which 0-1 carbons of C₄₋₈

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- cycloalkyl is replaced by -O-, wherein R^{2i} is selected from aryl wherein aryl includes phenyl, naphthyl, indanyl and indenyl, each R^{2i} being substituted with 0-1 OR^{2m} and 0-5
- 5 substituents independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2n}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$;
- 10 R^{2j} is selected from heteroaryl wherein heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl,
- 15 benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl
- 20 and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, OR^{2m} , -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heteroaryl being substituted
- 25 on any nitrogen atom with 0-1 substituents selected from the group R^{2g} , CO_2R^{2e} , COR^{2e} and SO_2R^{2e} ;
- R^{2k} is heterocyclyl which is a saturated or partially
- 30 saturated heteroaryl as defined for R^{2j} , each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, $-OR^{2m}$,

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-SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$,
 $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each
heterocyclyl being substituted on any nitrogen atom with
0-1 substituents selected from the group R^{2f} , CO_2R^{2e} , COR^{2e}
5 and SO_2R^{2e} ;

wherein

R^{21} is H, C_{1-4} alkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl and C_{3-8}
10 cycloalkyl;

R^{2m} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl C_{1-6} alkyl, C_{1-2}
alkyloxy C_{1-2} alkyl, C_{1-4} haloalkyl, $R^{2q}S(O)_n-C_{1-4}$ alkyl
and $R^{2r}R^{2s}N-C_{2-4}$ alkyl;

15

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl-
 C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, and C_{1-4} haloalkyl;

R^{2o} and R^{2p} are independently selected at each occurrence
20 from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl
and C_{1-4} haloalkyl;

R^{2q} is selected from C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy-
 C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, aryl,
25 aryl(C_{1-4} alkyl), heteroaryl and heteroaryl (C_{1-4} alkyl)-
and benzyl, each benzyl being substituted on the aryl
moiety with 0-1 substituents selected from the group C_{1-4}
alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy C_{1-4}
haloalkoxy, and dimethylamino;

30

$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-
morpholinyl, 1-piperidinyl or 1-piperazinyl wherein N_4 in

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1-piperiazinyl is substituted with 0-1 substituents selected from the group R^{2t} , CO_2R^{2q} , COR^{2q} and SO_2R^{2q} ;

R^{2t} is selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy
5 $-C_{1-4}$ alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl - C_{1-6} alkyl, aryl, aryl (C_{1-4} alkyl)-, heteroaryl and heteroaryl (C_{1-4} alkyl);

R^3 is selected from an aryl or heteroaryl group attached
10 through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence
15 from C_{1-6} alkyl, C_{3-6} cycloalkyl, methylenedioxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, $-OR^{2m}$, Br, Cl, F, I, C_{1-4} haloalkyl, $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being
20 substituted with 0-4 substituents selected from the group C_{1-3} alkyl, C_{1-3} alkoxy, Br, Cl, F, I, $-CN$, dimethylamino, CF_3 , C_2F_5 , OCF_3 , SO_2Me and acetyl;

heteroaryl is selected from the group pyridyl, pyrimidyl,
25 triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted at 0-4 carbon atoms with a substituent independently selected at
30

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each occurrence from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, F, I, C_{1-4} haloalkyl, $-CN$, $NR^{2g}R^{2h}$, nitro, $-OR^{2m}$, $-SH$, $-S(O)_nR^{2n}$, COR^{2m} , $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each heteroaryl being substituted at any
 5 nitrogen atom with 0-1 substituents selected from the group R^{2g} , CO_2R^{3a} , COR^{3a} and SO_2R^{3a} wherein,

R^{3a} is selected from the group C_{1-6} alkyl, C_{1-4} cycloalkyl- C_{1-6} alkyl and benzyl, each benzyl being substituted on the
 10 aryl moiety with 0-1 substituents selected from the group C_{1-4} alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and dimethylamino;

R^4 and R^5 are independently selected at each occurrence
 15 from H, Br, Cl, F, I, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-4} alkylamino, $(C_{1-4} \text{ alkyl})_2$ amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of C_{1-7}
 20 alkyl, C_{3-8} cycloalkyl, Br, Cl, F, I, $-C(O)H$, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-6} alkylamino and $(C_{1-4} \text{ alkyl})_2$ amino and wherein R^4 and R^5 non-phenyl groups may be substituted with 0-5
 25 substituents selected from OH, halogen, $-C(O)H$, $-OC_{1-6}-$ alkyl and C_{1-6} haloalkyl, C_{1-6} alkyl, C_{3-7} c-alkyl, C_{1-6} alkyl(OH) $_n$ CO $_2$ R wherein R is H or C_{1-6} alkyl, C_{1-6} alkyl(OH) $_n$, wherein n is 0-3 or R^4 and R^5 may join together to form a C_{3-6} alkylene chain; with the proviso that the compounds of
 30 Formula I with R^1 , R^2 , R^3 , R^4 and R^5 as specifically defined below are excluded:

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- (a) a compound of formula I wherein R^1 is unsubstituted, unbranched (linear) C_{1-3} alkyl and R^2 is $-C(O)-Ph$;
- (b) a compound of formula I, wherein R^5 is H or C_{1-3} alkyl and R^3 is pyridyl, pyridyl-N-oxide, thien-3-yl or furan-3-yl or C_{1-3} alkyl substituted versions thereof and R^1 is carboamoyl or unsubstituted, unbranched C_{1-3} alkyl, R^2 is F, Cl, Br, formyl, carboxyl, CN, hydroxymethyl, unsubstituted, unbranched C_{1-3} alkyl, $-C(O)R$, $-C(O)OR$, $-CH_2OR$, $-C(O)O(CH_2)_2OR$, $-C(O)O(CH_2)_2NHR$, or $-C(O)O(CH_2)_2NR^2$ wherein R is C_{1-3} alkyl;
- (c) a compound of formula I, wherein R^1 is unsubstituted, unbranched C_{1-3} alkyl and R^2 is halogen, CN or $-C(O)R$ wherein R is H, C_{1-3} alkyl or C_{1-4} alkoxy, R^3 is Ph substituted with $NR^{2g}C(O)R^{2m}$;
- (d) a compound of formula I, R^2 is CN, halogen, CO_2R with R equal to C_{1-3} alkyl, unsubstituted, unbranched C_{1-3} alkyl, C_{1-3} haloalkyl or $CONH_2$ and R^1 is equal to OR, SR wherein R is C_{1-3} alkyl, C_{1-4} haloalkyl or C_{3-4} halocycloalkyl, and R^3 is phenyl or substituted phenyl;
- (e) a compound of formula I, wherein R^5 is H or C_{1-3} alkyl; R^3 is phenyl, ortho-trifluoromethylphenyl, meta-trifluorophenyl or meta-methoxyphenyl; R^1 is carbamoyl or unsubstituted, unbranched C_{1-3} alkyl; R^2 is halogen, formyl, carboxyl, cyano, hydroxymethyl, unsubstituted, unbranched C_{1-3} alkyl, $-C(O)R$, $-C(O)OR$, CH_2OR , $-C(O)O(CH_2)_2OR$, $-C(O)O(CH_2)_2NHR$ or $-C(O)O(CH_2)_2NR^2$ wherein R is C_{1-3} alkyl;
- (g) in a compound of formula I, R^2 is CN, R^1 is methyl, R^4 and R^5 are H, R^3 is phenyl substituted with imidazo (or 2-methylimidazo) through the imidazo nitrogen atom;
- (h) in a compound of formula I, R^2 is CN, R^1 is SCH_3 , R^3 is para-chlorophenyl, R^4 is SCH_3 and R^5 is H;

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- (i) in a compound of formula I, R^2 is CN, R^1 is SCH₃, R^3 is pyrid-4-yl, R^4 is SCH₃ and R^5 is H ;
- (j) in a compound of formula I, R^2 is CN, R^1 is SCH₃, R^3 is Ph, R^4 is SCH₃ and R^5 is H ;
- 5 (k) in a compound of formula I, R^2 is C(O)NH₂, R^1 is SCH₃, R^3 is pyrid-3-yl, R^4 is SCH₃ and R^5 is H ;
- (l) in a compound of formula I, R^2 is C(O)NH₂, R^1 is SCH₃, R^3 is Ph, R^4 is SCH₃ (or Ph) and R^5 is H ;
- (m) in a compound of formula I, R^2 is C(O)OEt, R^1 is SCH₃,
 10 R^3 is Ph, R^4 is SCH₃ (or Ph) and R^5 is H ;
- (n) in a compound of formula I, R^1 is N(C(O)CH₃)₂, R^2 is CH₂Ph(p-Me, p-Cl), R^3 is Ph (p-ClPh), R^4 is SCH₃ and R^5 is H;
- (o) in a compound of formula I, R^1 is N(C(O)CH₃)₂, R^2 is
 15 CH₂Ph(p-OMe), R^3 is p-ClPh, R^4 is SCH₃ and R^5 is H ;
- (p) in a compound of formula I, R^2 is CN, R^1 is CH₃, R^3 is Ph, R^4 is H and R^5 is H;
- (q) in a compound of formula I, R^2 is C(O)NH₂, R^1 is CH₃, R^3 is Ph, R^4 is CH₃ and R^5 is H;
- 20 (s) in a compound of formula I, R^2 is C(O)NH₂, R^1 is CH₃, R^3 is pyrid-4-yl, R^4 and R^5 are H;
- (t) in a compound of formula I, R^2 is C(O)NH₂, R^1 is CH₃, R^3 is m-CF₃Ph, R^4 and R^5 are H ;
- (u) in a compound of formula I, R^2 is CN, R^1 is CH₃, R^3 is
 25 Ph, R^4 is CH₃ and R^5 is H ;
- (v) in a compound of formula I, R^2 is CN, R^1 is CH₃, R^3 is pyrid-4-yl, R^4 and R^5 are H ;
- (x) in a compound of formula I, R^2 is CH₃, R^1 is CH₃, R^3 is p-F-Ph, R^4 is c-propyl and R^5 is CH=CH-
 30 CH(OH)CH₂CH(OH)CH₂C(O)O-iPr;
- (y) in a compound of formula I, R^2 is CH₃, R^1 is CH₃, R^3 is p-F-Ph, R^4 is c-propyl and R^5 is CH=CH-
 CH(OH)CH₂CH(OH)CH₂C(O)O-nPr;

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- (z) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $\text{CH}=\text{CH}-\text{CH}(\text{OH})\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{C}(\text{O})\text{OMe}$;
- 5 (aa) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $\text{CH}=\text{CH}-\text{CH}(\text{OH})\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{C}(\text{O})\text{OH}$;
- (bb) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $-\text{CH}_2\text{OH}$;
- 10 (cc) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $-\text{C}(\text{O})\text{H}$;
- (dd) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $-\text{CH}=\text{CH}-\text{C}(\text{O})\text{H}$;
- (ee) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $\text{CH}=\text{CH}-$
- 15 $\text{CH}(\text{OH})\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{C}(\text{O})\text{OEt}$;
- (ff) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $\text{CH}=\text{CH}-\text{CH}(\text{OH})\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{C}(\text{O})\text{O}^-\text{Na}^+$;
- (gg) in a compound of formula I, R^2 is CN, R^1 is CF_3 , R^3 is
- 20 m-Cl-Ph, R^4 is CH_3 and R^5 is H;
- (hh) in a compound of formula I, R^2 is CN, R^1 is CF_3 , R^3 is m- CF_3 -Ph, R^4 is CH_3 and R^5 is H;
- (ii) in a compound of formula I, R^2 is CN, R^1 is CF_3 , R^3 is Ph, R^4 is CH_3 and R^5 is H;
- 25 (nn) in a compound of formula I, R^2 is $-\text{C}(\text{O})\text{NH}_2$, R^1 is Me, R^3 is Ph, R^4 is H and R^5 is Me;
- (oo) in a compound of formula I, R^2 is CN, R^1 is Me, R^3 is Ph, R^4 is H and R^5 is Me;
- (pp) in a compound of formula I, R^2 is CN, R^1 is Me, R^3 is
- 30 o-Cl,m-Cl-Ph, R^4 is H and R^5 is H;
- (qq) in a compound of formula I, R^2 is $\text{C}(\text{O})\text{NH}_2$, R^1 is CH_3 , R^3 is Ph, R^4 and R^5 are H ;

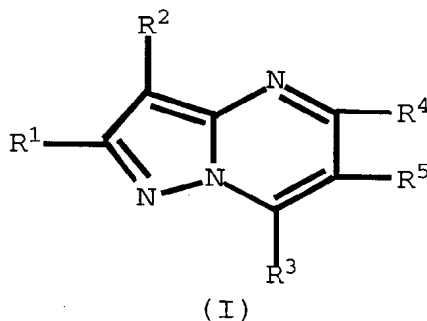
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- (rr) in a compound of formula I, R^2 is $C(O)NH_2$, R^1 is CH_3 , R^3 is $O-CL, m-Cl-Ph$, R^4 and R^5 are H ;
- (ss) in a compound of formula I, R^2 is $C(O)OMe$, R^1 is $-SCH_2-Ph$, R^3 is Ph, R^4 is Me and R^5 is H ;
- 5 (tt) in a compound of formula I, R^2 is $C(O)OMe$, R^1 is $-SCH_2-Ph$, R^3 is Ph, R^4 is H and R^5 is H ;
- (uu) in a compound of formula I, R^2 is $C(O)Ph$, R^1 is Me, R^3 is pyrid-4-yl, R^4 and R^5 are H ;
- (vv) in a compound of formula I, R^2 is $C(O)Ph$, R^1 is Me, R^3 is m- CF_3-Ph , R^4 and R^5 are H ;
- 10 (ww) in a compound of formula I, R^2 is $C(O)Ph$, R^1 is Me, R^3 is pyrid-3-yl, R^4 and R^5 are H
- (xx) in a compound of formula I, R^2 is CN, R^1 is SCH_3 , R^3 is Ph, R^4 is Ph and R^5 is H ;
- 15 (yy) in a compound of formula I, R^2 is CN, R^1 is SCH_3 , R^3 is Ph, R^4 is Ph and R^5 is H ;
- (zz) in a compound of formula I, R^2 is Cl, R^1 is Et, R^3 is pyrid-3-yl, R^4 and R^5 are H ;
- (aaa) in a compound of formula I, R^2 is CO_2H , R^1 is Et, R^3 is pyrid-3-yl, R^4 and R^5 are H ;
- 20 (bbb) in a compound of formula I, R^2 is CO_2H , R^1 is CH_3 , R^3 is pyrid-3-yl, R^4 and R^5 are H and H Cl salt ;
- (ccc) in a compound of formula I, R^2 is $C(O)OEt$, R^1 is CH_3 , R^3 is pyrid-3-yl, R^4 and R^5 are H ;
- 25 (ddd) in a compound of formula I, R^2 is CN, R^1 is CH_3 , R^3 is pyrid-3-yl, R^4 is H and R^5 is CH_3 ;
- (eee) in a compound of formula I, R^2 is CN, R^1 is CH_3 , R^3 is pyrid-3-yl, R^4 and R^5 are H ;
- (fff) in a compound of formula I, R^2 is $C(O)OEt$, R^1 is Et, R^3 is pyrid-3-yl, R^4 and R^5 are H ;
- 30 (ggg) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is pyrid-3-yl, R^4 and R^5 are H ;

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- (hhh) in a compound of formula I, R^2 is CN, R^1 is CH_3 , R^3 is m- CF_3 -Ph, R^4 and R^5 are H ;
- (iii) in a compound of formula I, R^2 is CN, R^1 is CH_2CN , R^3 is m- CF_3 -Ph, R^4 and R^5 are H ;
- 5 (jjj) in a compound of formula I, R^2 is C(O)OMe, R^1 is Me, R^3 is m- CF_3 -Ph, R^4 and R^5 are H ;
- (kkk) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is m-OMe-Ph, R^4 and R^5 are H ;
- (lll) in a compound of formula I, R^2 is C(O)OEt, R^1 is Et,
 10 R^3 is Ph, R^4 and R^5 are H ;
- (mmm) in a compound of formula I, R^2 is C(O)OEt, R^1 is Et, R^3 is m- CF_3 -Ph, R^4 and R^5 are H ;
- (nnn) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is m- CF_3 -Ph, R^4 is H and R^5 is CH_3 ;
- 15 (ooo) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is m- CF_3 , R^4 and R^5 are H ;
- (ppp) in a compound of formula I, R^2 is CN, R^1 is C(O)NH₂, R^3 is m- CF_3 -Ph, R^4 and R^5 are H ;
- (qqq) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is
 20 Ph, R^4 and R^5 are H.

2. A compound of formula I:



25

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

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- R^1 is selected from the group consisting of
- C_{1-6} alkyl,
 - C_{2-10} alkenyl,
 - 5 C_{2-10} alkynyl,
 - C_{3-6} cycloalkyl,
 - C_{1-6} alkyloxy,
 - C_{1-6} alkylS(O)_n,
 - $-NR^{1a}R^{1b}$ wherein R^{1a} and R^{1b} are independently selected from
 - 10 H , C_{1-4} alkyl, $-C(O)C_{1-4}$ alkyl,
 - $-C(O)NR^{1a}R^{1b}$,
 - $-O-C(O)C_{1-4}$ alkyl,
 - $-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl;
 - X is selected from O or $S(O)_n$,
 - 15 wherein R^1 is substituted with 0-6 substituents selected from halogen, C_{1-4} alkyl, C_{1-6} alkyloxy, C_{1-4} haloalkyl, $-NR^{1a}R^{1b}$, $-XR^{1c}$;
- R^2 is selected from the group consisting of
- 20 C_{1-10} alkyl excluding unsubstituted, unbranched C_{1-3} alkyl,
 - C_{2-10} alkenyl,
 - C_{2-10} alkynyl,
 - C_{3-8} cycloalkyl,
 - C_{3-6} cycloalkyl C_{1-6} alkyl,
 - 25 C_{1-10} alkyloxy,
 - C_{1-10} alkyloxy C_{1-10} alkyl,
 - C_{1-4} alkoxy C_{1-4} alkyl,
 - $-SO_2-C_{1-10}$ alkyl
 - $-SO_2R^{2a}$ wherein R^{2a} is aryl,
 - 30 $-SO_2R^{2b}$ wherein R^{2b} is heteroaryl,
 - $-NR^{2c}R^{2d}$ wherein R^{2c} and R^{2d} are independently selected from
 - H , C_{1-8} alkyl, $S(O)_nC_{1-4}$ alkyl, $C(O)NR^{2c}R^{2d}$, CO_2C_{1-4} alkyl,
 - C_{3-8} cycloalkyl, C_{1-6} alkyloxy C_{1-6} alkyl, $-C(O)C_{1-4}$ alkyl

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or R^{2c} and R^{2d} may join to form a heterocyclic ring having 0-3 heteroatoms selected from O, N or S,

n is 0, 1 or 2;

5

R^2 is substituted with 0-3 substituents independently selected from R' , R'' , R''' wherein R' , R'' and R''' are independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy, or

10

R^2 is substituted with 0-3 substituents independently selected from:

-CN,

15

$-S(O)_nR^{2e}$ wherein R^{2e} is selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{3-6} cycloalkyl;

$-COR^{2f}$ wherein R^{2f} is selected from H, C_{1-4} alkyl, C_{1-4}

haloalkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{3-6}

20

cycloalkyl, and C_{3-6} cycloalkyl C_{1-4} alkyl;

$-CO_2R^{2f}$,

$-NR^{2g}COR^{2f}$ wherein R^{2g} is selected from H, C_{1-6} alkyl, C_{3-7} c-alkyl, C_{3-6} cycloalkyl C_{1-6} alkyl;

25

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, wherein R^{2h} is selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy C_{1-4} alkyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl C_{1-6} alkyl;

30

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

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- 1-piperidinyl,
 1-piperazinyl,
 and
 C_{3-8} cycloalkyl wherein 0-1 carbon atoms in the C_{4-8}
 5 cycloalkyl is replaced by a group selected from
 $-O-$, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2R^{2e}$, $-NCOR^{2e}$,
 and $-NSO_2R^{2e}$; and wherein N_4 in
 1-piperazinyl is substituted with 0-1
 substituents selected from R^{2g} , CO_2R^{2e} , COR^{2e} and
 10 SO_2R^{2e} ; or
- the group R^{2j} , R^{2k} , C_{1-6} alkyl, C_{2-8}
 alkenyl, C_{2-8} alkynyl, Br, Cl, F, I, C_{1-4} haloalkyl, $-OR^{2g}$,
 $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkylOR^{2g}, and C_{3-8} cycloalkyl which is
 15 substituted with 0-1 R^{21} and in which 0-1 carbons of C_{4-8}
 cycloalkyl is replaced by $-O-$, wherein
- R^{2j} is selected from heteroaryl wherein heteroaryl
 includes pyridyl, pyrimidinyl, triazinyl, furanyl,
 20 quinolinyl, isoquinolinyl, thienyl, imidazolyl,
 thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl,
 benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl,
 pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-
 dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-
 25 dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-
 dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl
 and benzodioxane, each heteroaryl being substituted on 0-
 4 carbon atoms with a substituent independently selected
 from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4}
 30 haloalkyl, $-CN$, nitro, OR^{2m} , $-SH$, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-$
 $OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-$
 $NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heteroaryl being substituted

on any nitrogen atom with 0-1 substituents selected from the group R^{2g} , CO_2R^{2e} , COR^{2e} and SO_2R^{2e} ;

- R^{2k} is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for R^{2j} , each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group R^{2f} , CO_2R^{2e} , COR^{2e} and SO_2R^{2e} ;

- 15 wherein

R^{21} is H, C_{1-4} alkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl and C_{3-8} cycloalkyl;

- 20 R^{2m} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, C_{1-4} haloalkyl, $R^{2q}S(O)_n-C_{1-4}$ alkyl and $R^{2r}R^{2s}N-C_{2-4}$ alkyl;

- R^{2n} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, and C_{1-4} haloalkyl;

R^{2o} and R^{2p} are independently selected at each occurrence from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl and C_{1-4} haloalkyl;

- 30

R^{2q} is selected from C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy- C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, aryl, aryl(C_{1-4} alkyl), heteroaryl and heteroaryl (C_{1-4} alkyl)-

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and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group C_{1-4} alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy C_{1-4} haloalkoxy, and dimethylamino;

5

$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein N_4 in 1-piperiazinyl is substituted with 0-1 substituents selected from the group R^{2t} , CO_2R^{2q} , COR^{2q} and SO_2R^{2q} ;

10

R^{2t} is selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy $-C_{1-4}$ alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl - C_{1-6} alkyl, aryl, aryl (C_{1-4} alkyl)-, heteroaryl and heteroaryl (C_{1-4} alkyl);

15

R^3 is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence from C_{1-6} alkyl, C_{3-6} cycloalkyl, methylenedioxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, $-OR^{2m}$, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, $-NO_2$, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, -
 25 $NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group C_{1-3} alkyl, C_{1-3} alkoxy, Br, Cl, F, I, -CN, dimethylamino, CF_3 , C_2F_5 , OCF_3 , SO_2Me and acetyl;

30

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl,

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- benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, F, I, C_{1-4} haloalkyl, -CN, $NR^{2g}R^{2h}$, nitro, $-OR^{2m}$, -SH, -S(O) $_nR^{2n}$, COR^{2m} , $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, - $NR^{2g}CONR^{2o}R^{2p}$ and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group R^{2g} , CO_2R^{3a} , COR^{3a} and SO_2R^{3a} wherein,
- 15 R^{3a} is selected from the group C_{1-6} alkyl, C_{1-4} cycloalkyl- C_{1-6} alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group C_{1-4} alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and dimethylamino;
- 20 R^4 and R^5 are independently selected at each occurrence from H, Br, Cl, F, I, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-4} alkylamino, (C₁₋₄ alkyl)₂ amino and phenyl, each phenyl is substituted
- 25 with 0-3 groups selected from the group consisting of C_{1-7} alkyl, C_{3-8} cycloalkyl, Br, Cl, F, I, -C(O)H, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-6} alkylamino and (C₁₋₄ alkyl)₂ amino and wherein R^4 and R^5
- 30 non-phenyl groups may be substituted with 0-5 substituents selected from OH, halogen, -C(O)H, $-OC_{1-6}-$ alkyl and C_{1-6} haloalkyl, C_{1-6} alkyl, C_{3-7} c-alkyl, C_{1-6}

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alkyl(OH)_nCO₂R wherein R is H or C₁₋₆ alkyl, C₁₋₆ alkyl(OH)_n, wherein n is 0-3 or R⁴ and R⁵ may join together to form a C₃₋₆ alkylene chain.

5

3. The compound according to Claim 1 or 2 wherein

R¹ is selected from C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, -XR^{1c} wherein R¹ is substituted with
10 0-6 substituents selected from halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl;

R² is selected from substituted-C₁₋₁₀ alkyl, branched C₃₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₈ cycloalkyl, C₃₋₆
15 cycloalkyl C₁₋₆ alkyl, -NR^{2c}R^{2d} wherein, in the case of substituted-C₁₋₁₀ alkyl, 1-3 substituents are independently selected from the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl
20 which is substituted with 0-1 R²ⁱ and in which 0-1 carbons of C₄₋₈ cycloalkyl is replaced by -O- and wherein the R² groups, other than substituted-C₁₋₁₀ alkyl, are substituted with 0-3 substituents independently selected from the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br,
25 Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl which is substituted with 0-1 R²ⁱ and in which 0-1 carbons of C₄₋₈ cycloalkyl is replaced by -O-.

4. The compound according to Claims 1 or 2 or 3 wherein
30 R³ is selected from an aryl group selected from phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

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5. The compound according to Claims 1, 2, 3 or 4 wherein R^2 is selected from C_1 alkyl of the formula $-CR'R''$ wherein R' , R'' and R''' are independently selected from H, C_{1-6} alkyl, C_{3-7} cycloalkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy, with the proviso that each of R' , R'' and R''' cannot be H;

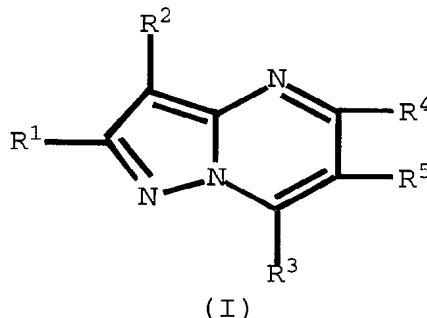
or R^2 is selected from $NR^{2c}R^{2d}$ wherein R^{2c} and R^{2d} are independently selected from H or C_{1-6} alkyl.

10

6. The compound according to Claims 1-5 wherein R^3 is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom wherein, aryl is phenyl, each phenyl being substituted with 0-5 substituents independently selected at each occurrence from C_{1-6} alkyl, C_{3-6} cycloalkyl, methylenedioxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, $-OR^{2m}$, Br, Cl, F, I, C_{1-4} haloalkyl, $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group C_{1-3} alkyl, C_{1-3} alkoxy, Br, Cl, F, I, $-CN$, dimethylamino, CF_3 , C_2F_5 , OCF_3 , SO_2Me and acetyl and wherein, heteroaryl is selected at each occurrence from pyridyl, each pyridyl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, F, I, C_{1-4} haloalkyl, $-CN$, nitro, $-OR^{2m}$, $-SH$, $-S(O)_nR^{2n}$, COR^{2m} , $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each pyridyl being substituted at any nitrogen atom with 0-1 substituents selected from the group R^{2g} , CO_2R^{3a} , COR^{3a} and SO_2R^{3a} .

7. A compound of formula (I)

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or a pharmaceutically acceptable salt, stereoisomer or
prodrug thereof, wherein

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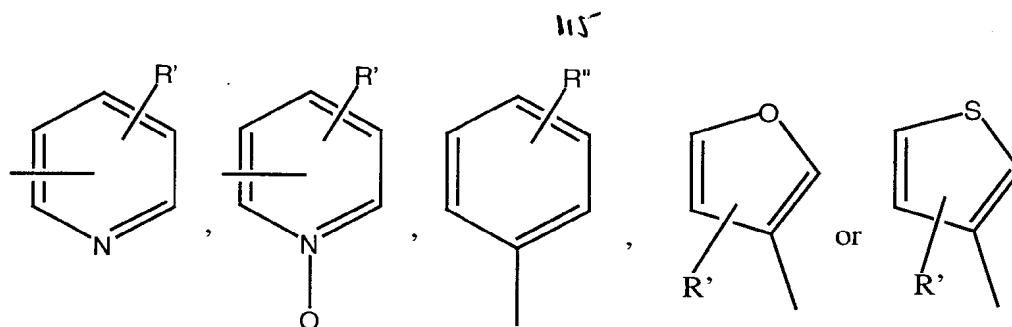
R^1 is selected from C_{1-6} alkyl, C_{1-6} alkyloxy, -SH or OH;

R^2 is selected from C_{1-4} alkyl which is unsubstituted or
substituted with 1-4 substituents selected from C_{1-6}

10 alkyl, C_{3-8} cycloalkyl, C_{1-6} alkylOR^{2g}, C_{2-6} alkenyl or OR^{2g}
wherein R^{2g} is H or C_{1-6} alkyl;

R^3 is selected from an aryl or heteroaryl group bonded
through an unsaturated carbon atom that is unsubstituted
15 or substituted with 1-4 substituents selected from Cl, F,
I, Br, -OH, CF₃, S(O)_nC₁₋₆ alkyl, -OC₁₋₆ alkyl, C_{1-6} alkyl or
NR^{2g}R^{2h} wherein R^{2g} and R^{2h} are independently selected from H
or C_{1-6} alkyl;

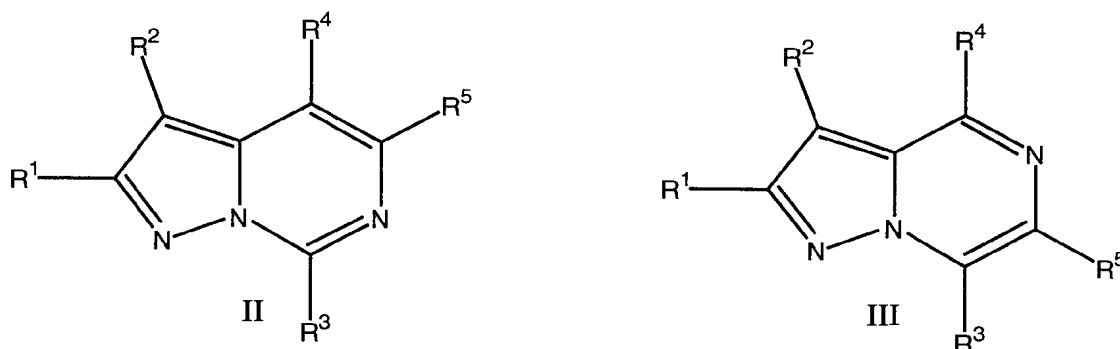
20 R^4 and R^5 are independently selected from H, C_{1-6} alkyl or
 C_{1-6} alkyloxy,
with the proviso that when R^1 and R^2 are unsubstituted,
unbranched C_{1-3} alkyl, R^3 may not be



wherein R' is H or C₁₋₃ alkyl and R'' is H or o-
 5 trifluoromethyl, m-trifluoromethyl or m-methoxy.

8. The compound according to Claims 1-7 wherein R³ is substituted with 2-4 substituents.

10 9. A compound of the formula:



or a pharmaceutically acceptable salt or isomer thereof
 15 wherein R¹-R⁵ and other variables are as defined in claims 1-8.

10. Use of a compound according to Claims 1-9 in therapy.

20

11. Use of a compound according to Claims 1-9 to antagonize a CRF-1 receptor in mammals including humans wherein binding to the receptor causes and ultimately

results in the treatment of affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of according to Claims 1-9.

12. A pharmaceutical composition comprising a compound according to Claims 1-9 and a pharmaceutically acceptable carrier with the proviso that, in a compound of formula I according to Claim 1, proviso (d) compounds are not excluded.

Bibliographic data

Title: CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR PREVENTING SUDDEN DEATH
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Inventor(s): FOSSA ANTHONY ANDREA|FOSSA ANTHONY ANDREA
Applicant(s): PFIZER PROD INC
Classification: A61K31/41AI; A61K31/437AI; A61K31/44AI; A61K31/4409AI; A61K31/4418AI; A61K31/455AI; A61K31/505AI; A61K31/506AI; A61K31/519AI; A61K31/52AI; A61K31/522AI; A61K45/00AI; A61P43/00AI; C07D213/69AI; C07D213/70AI; C07D213/74AI; C07D239/34AI; C07D239/47AI; C07D239/48AI; C07D239/50AI; C07D471/04AI; C07D473/34AI
Application number: JP20000100606 2000-04-03
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Abstract of JP2000302693A

PROBLEM TO BE SOLVED: To obtain a medicine having low side effect, effective for preventing the sudden death of animal and useful for the treatment of cardiac diseases, hypertension, osteoporosis, anxiety, diabetes, or the like, by including a therapeutically effective amount of a corticotropin releasing factor antagonist. **SOLUTION:** The objective medicine contains a therapeutically effective amount of a corticotropin releasing factor antagonist such as a compound (salt) expressed by formula I or II [the dotted line is optionally existing double bond; A is N or CR7 (R7 is H, a 1-4C alkyl, or the like); B is NR1R2, CR1R2R11 (R1 is H or a 1-6C alkyl; R2 is a 1-6C alkyl, an aryl, or the like; R11 is H, hydroxy, or the like), or the like; D is N, CR10 (R10 is H, a 1-6C alkyl, or the like), or the like; E is N, CR4 (R4 is H, a 1-6C alkyl, or the like), or the like; Z is NH, O, S, or the like; R3 is H, a halogen, a 1-6C alkyl, or the like; R5 is phenyl, naphthyl, or the like], e.g. 4-(1-ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethyl- benzyl)-pyrimidine. The daily administration rate of the compound is preferably 1.0-20 mg/kg body-weight.

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(54) 【発明の名称】 突然死予防のためのコルチコトロピン放出因子アンタゴニスト

(57) 【要約】

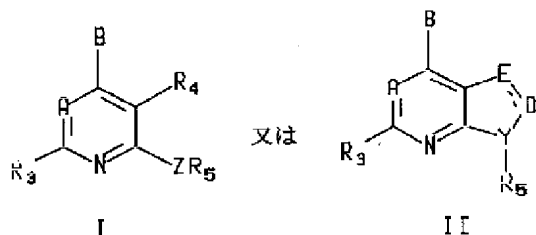
コルチコトロピン放出因子アンタゴニストの治療上有効量を動物に投与する。本発明の方法は、心臓疾患、高血圧、頻脈、うっ血性心不全、脳卒中、骨粗鬆症、早産、心理的萎縮、ストレス性発熱、潰瘍、下痢、術後腸閉塞、精神的不安及びストレスに関連する腸の過敏、糖尿病、神経性疾患、脳障害、ギランバレー症候群、小児突然死症候群、先天性過換気症候群又は尿毒症性神経障害の患者に特に有用である。

【特許請求の範囲】

【請求項1】 動物における突然死の予防のための、治療上有効量のコルチコトロピン放出因子アンタゴニストを含む、薬剤。

【請求項2】 コルチコトロピン放出因子アンタゴニストが、式I又はII：

【化1】



〔式中、点線は所望により存在する二重結合を表し、
 Al は $-CR_7$ 又は N であり、
 B は $-NR_{11}R_2$ 、 $-CR_{11}R_2R_{11}$ 、 $-C(=CR_{11}R_{12})R_2$ 、 $-NHC_{11}R_1R_2$ 、 $OC_{11}R_1R_2$ 、 $SC_{11}R_1R_2$ 、 $CR_{11}R_2OR_1$ 、 $C_{11}R_1R_2SR_1$ 、 $-C(S)R_2$ 、 $-NHN_{11}R_2$ 、 $-CR_2R_{11}NHR_1$ 又は $-C(O)R_2$ であり、 D は E と D とが二重結合で結合し、及び E が $-CR_4$ であるとき、 N 又は $-CR_{10}$ であり； E と D とが二重結合で結合し、及び E が N であるとき、 $-CR_{10}$ であり；又は E と D とが単結合で結合しているとき、 $-CR_8R_9$ 、 $-CHR_{10}$ 、 $-C=O$ 、 $-C=S$ 、 $-C=NH$ 又は $-C=NCH_3$ であり； E は E と D とが二重結合で結合しているとき、 $-CR_4$ 又は N であり；又は E と D とが単結合で結合しているとき、 $-CR_4R_6$ 又は $-NR_6$ であり； Y は N 又は $-CH$ であり； Z は NH 、 O 、 S 、 $N(C_1\sim C_2$ アルキル)又は $CR_{12}R_{13}$ であり、このとき R_{12} 及び R_{13} は各々独立に水素、トリフルオロメチル若しくはメチルであるか、又は R_{12} 及び R_{13} の一方がシアノ、他方が水素若しくはメチルであり； R_1 は水素又は $C_1\sim C_6$ アルキルであり、このとき前記 $C_1\sim C_6$ アルキルはヒドロキシ、シアノ、ニトロ、フルオロ、クロロ、ブロモ、ヨード、 CF_3 、 $C_1\sim C_4$ アルコキシ、 $O-CO-(C_1\sim C_4$ アルキル)、 $-O-CO-NH(C_1\sim C_4$ アルキル)、 $-O-CO-N(C_1\sim C_4$ アルキル)($C_1\sim C_2$ アルキル)、 $-NH(C_1\sim C_4$ アルキル)、 $-N(C_1\sim C_2$ アルキル)($C_1\sim C_4$ アルキル)、 $-S(C_1\sim C_4$ アルキル)、 $-N(C_1\sim C_4$ アルキル) $CO(C_1\sim C_4$ アルキル)、 $-NHCO(C_1\sim C_4$ アルキル)、 $CO_2(C_1\sim C_4$ アルキル)、 $CONH(C_1\sim C_4$ アルキル)、 $-CON(C_1\sim C_4$ アルキル)($C_1\sim C_2$ アルキル)、($C_1\sim C_4$ アルキル)スルフィニル、($C_1\sim C_4$ アルキル)スルホニル及び($C_1\sim C_4$ アルキル)スルファニルから独立して選択される2個以下の置換基で置換されていてもよく、このとき前述の R_1 基中の前記 $C_1\sim C_6$ アルキル、 $C_1\sim C_4$ アルコキシ及び $C_1\sim C_4$ アルキル部分は、1個の二重結合又は三重結合を含んでもよく； R_2 は $C_1\sim C_6$ アルキル、ヘテロアリール、アリール、ヘテロアリール($C_1\sim C_4$ アルキル)又はアリール($C_1\sim C_4$ アルキル)であり、このとき前記アリール及び前記(アリール) C_1

へ C_4 アルキルのアリール部分はフェニル及びナフチルから選択され、及び前記ヘテロアリール及び前記(ヘテロアリール) $C_1 \sim C_4$ アルキルのヘテロアリール部分はチエニル、ベンゾチエニル、ピリジル、チアゾリル、キノリル、ピラジニル、ピリミジル、イミダズリル、フラニル、ベンゾフラニル、ベンゾチアゾリル、イソチアゾリル、ベンズイソチアゾリル、ベンズイソキサゾリル、ベンズイミダズリル、インドリル及びベンゾキサゾリルから選択されるか；又は R_2 は $C_3 \sim C_8$ シクロアルキル又は($C_3 \sim C_8$ シクロアルキル) $C_1 \sim C_6$ アルキルであり、このとき少なくとも4個の環員を有する前記シクロアルキル及び少なくとも4個の環員を有する前記($C_3 \sim C_8$ シクロアルキル) $C_1 \sim C_6$ アルキルのシクロアルキル部分の環員炭素の1又は2個は、酸素若しくは硫黄によって、又は $-NR_{14}$ (このとき R_{14} は水素又は $C_1 \sim C_4$ アルキルである)によって置換されていてもよく；及び前述の R_2 基の各々は、クロロ、フルオロ及び $C_1 \sim C_4$ アルキルから独立して選択される3個以下の置換基によって、又はブロモ、ヨード、シアノ、ニトロ、 $C_1 \sim C_6$ アルコキシ、 $-O-CO-$ ($C_1 \sim C_4$ アルキル)、 $-O-CO-N$ ($C_1 \sim C_4$ アルキル)($C_1 \sim C_2$ アルキル)、 $-CO_2$ ($C_1 \sim C_4$ アルキル)、($C_1 \sim C_4$ アルキル)スルファニル、($C_1 \sim C_4$ アルキル)スルフィニル及び($C_1 \sim C_4$ アルキル)スルホニルから選択される1個の置換基によって置換されていてもよく、このとき前記 $C_1 \sim C_4$ アルキル及び前述の R_2 基の $C_1 \sim C_6$ アルキル部分は、1個の炭素-炭素二重結合又は三重結合を含んでもよく；又は前記 $-NR_1 R_2$ 及び前記 $-CR_1 R_2 R_{11}$ の R_1 及び R_2 は一緒に飽和若しくは部分飽和の5~8員環を形成し、このとき前記環は1又は2個の炭素-炭素二重結合を含んでもよく、及びこのとき環員炭素の1又は2個はO、S及びNから選択されるヘテロ原子により置き換えられていてもよく； R_3 は水素、 $C_1 \sim C_6$ アルキル、フルオロ、クロロ、ブロモ、ヨード、ヒドロキシ、アミノ、SH、 $-NH$ ($C_1 \sim C_4$ アルキル)、 N ($C_1 \sim C_4$ アルキル)($C_1 \sim C_2$ アルキル)、 $-CH_2OH$ 、 $-CH_2OCH_3$ 、 $-O$ ($C_1 \sim C_4$ アルキル)、($C_1 \sim C_4$ アルキル)スルファニル、($C_1 \sim C_4$ アルキル)スルホニル又は($C_1 \sim C_4$ アルキル)スルフィニルであり、このとき前記 $C_1 \sim C_6$ アルキル及び前述の R_3 基の $C_1 \sim C_4$ アルキル部分は1個の二重結合又は三重結合を含んでもよく、及びヒドロキシ、アミノ、 $C_1 \sim C_3$ アルコキシ、 $-NH$ ($C_1 \sim C_2$ アルキル)、 $-N$ ($C_1 \sim C_2$ アルキル) $_2$ 、 $-NHCOCH_3$ 、フルオロ、クロロ及び $C_1 \sim C_3$ チオアルキルから独立して選択される1~3個の置換基によって置換されていてもよく； R_4 は水素、 $C_1 \sim C_6$ アルキル、フルオロ、クロロ、ブロモ、ヨード、 $C_1 \sim C_6$ アルコキシ、ホルミル、トリフルオロメトキシ、 CH_2OCH_3 、 $CH_2OCCH_2CH_3$ 、 $-CH_2CH_2OCH_3$ 、 $-CH_2CF_3$ 、 CF_3 、アミノ、ニトロ、 $-NH$ ($C_1 \sim C_4$ アルキル)、 $-N(CH_3)_2$ 、 $-NHCOCH_3$ 、 $-NHCONHCH_3$ 、($C_1 \sim C_4$ アルキル)スルファニル、($C_1 \sim C_4$ アルキル)スルフィニル、($C_1 \sim C_4$ アルキル)

スルホニル、シアノ、ヒドロキシ、 $-\text{CO}$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $-\text{CHO}$ 又は $-\text{CO}_2$ ($\text{C}_1 \sim \text{C}_4$ アルキル) であり、このとき前述の R_4 基の前記 $\text{C}_1 \sim \text{C}_6$ アルキル、 $\text{C}_1 \sim \text{C}_6$ アルコキシ及び $\text{C}_1 \sim \text{C}_4$ アルキル部分は、1個の二重結合又は三重結合を含んでもよく、及びヒドロキシ、アミノ、 $-\text{NHCOCH}_3$ 、 NH ($\text{C}_1 \sim \text{C}_2$ アルキル)、 N ($\text{C}_1 \sim \text{C}_2$ アルキル)₂、 $-\text{CO}_2$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $-\text{CO}$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $\text{C}_1 \sim \text{C}_3$ アルコキシ、($\text{C}_1 \sim \text{C}_3$ アルキル) スルファニル、フルオロ、クロロ、シアノ及びニトロから選択される1個の置換基で置換されていてもよく； R_5 はフェニル、ナフチル、チエニル、ベンゾチエニル、ピリジル、キノリル、ピラジノリル、ピリミジル、イミダゾリル、フラニル、ベンゾフラニル、ベンゾチアゾリル、イソチアゾリル、ベンゾイソチアゾリル、チアゾリル、イソキサゾリル、ベンズイソキサゾリル、ベンズイミダゾリル、トリアゾリル、ピラゾリル、ピロリル、インドリル、アザインドリル、ベンズオキサゾリル、オキサゾリル、ピロジニル、チアゾリジニル、モルホリニル、ピリジニル、テトラゾリル又は3～8員シクロアルキル環又は9～12員ビシクロアルキル環システムであり、このとき前記シクロアルキル環及び前記ビシクロアルキル環システムは、1又は2個のO、S又は $-\text{N}-\text{G}$ (このときGは水素、 $\text{C}_1 \sim \text{C}_4$ アルキル、 $\text{C}_1 \sim \text{C}_4$ アルカノイル、フェニル又はベンジルである) であり、このとき前述の R_5 基の各々は、フルオロ、クロロ、 $\text{C}_1 \sim \text{C}_6$ アルキル、 $\text{C}_1 \sim \text{C}_6$ アルコキシ及びトリフルオロメチルから独立して選択される3個以下の置換基によって、又はブロモ、ヨード、シアノ、ニトロ、アミノ、 NH ($\text{C}_1 \sim \text{C}_4$ アルキル)、 N ($\text{C}_1 \sim \text{C}_4$ アルキル) ($\text{C}_1 \sim \text{C}_2$ アルキル)、 $-\text{CO}_2$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $-\text{CO}$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $-\text{SO}_2\text{NH}$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $-\text{SO}_2\text{N}$ ($\text{C}_1 \sim \text{C}_4$ アルキル) ($\text{C}_1 \sim \text{C}_2$ アルキル)、 $-\text{SO}_2\text{NH}_2$ 、 $-\text{NHSO}_2$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $-\text{S}$ ($\text{C}_1 \sim \text{C}_4$ アルキル) 及び $-\text{SO}_2$ ($\text{C}_1 \sim \text{C}_4$ アルキル) から選択される1個の置換基によって置換されていてもよく、このとき前述の R_5 基の前記 $\text{C}_1 \sim \text{C}_4$ アルキル及び $\text{C}_1 \sim \text{C}_6$ アルキル部分は、1個の二重結合又は三重結合を含んでもよく、及びフルオロ、クロロ、ヒドロキシ、アミノ、メチルアミノ、ジメチルアミノ及びアセチルから独立して選択される1又は2個の置換基によって置換されていてもよく； R_6 は水素又は $\text{C}_1 \sim \text{C}_6$ アルキルであり、このとき前記 $\text{C}_1 \sim \text{C}_6$ アルキルは1個のヒドロキシ、メトキシ、エトキシ又はフルオロ基により置換されていてもよく； R_7 は水素、 $\text{C}_1 \sim \text{C}_4$ アルキル、フルオロ、クロロ、ブロモ、ヨード、シアノ、ヒドロキシ、 $\text{C}_1 \sim \text{C}_4$ アルコキシ、 $-\text{CO}$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $-\text{CO}_2$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $-\text{OCF}_3$ 、 CF_3 、 CH_2OH 、 CH_2OCH_3 又は $\text{CH}_2\text{OCH}_2\text{CH}_3$ であり； R_8 及び R_9 は各々独立して水素、ヒドロキシ、メチル、エチル、メトキシ又はエトキシであるか；又は R_8 及び R_9 は一緒にオキソ (=O) 基を形成し； R_{10} は水素、 $\text{C}_1 \sim \text{C}_6$ アルキル、フルオロ、クロロ、ブロモ、ヨード、 $\text{C}_1 \sim \text{C}_6$ アル

コキシ、ホルミル、アミノ、 $-\text{NH}$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $-\text{N}$ ($\text{C}_1 \sim \text{C}_4$ アルキル) ($\text{C}_1 \sim \text{C}_2$ アルキル)、シアノ、カルボキシ、アミド又は $-\text{SO}_n$ ($\text{C}_1 \sim \text{C}_4$ アルキル) (このとき n は0、1又は2である) であり、このとき前述の R_{10} 基の前記 $\text{C}_1 \sim \text{C}_6$ アルキル及び $\text{C}_1 \sim \text{C}_4$ アルキル部分は1個のヒドロキシ、トリフルオロメチル、アミノ、カルボキシ、アミド、 $-\text{NHCO}$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $-\text{NH}$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $-\text{N}$ ($\text{C}_1 \sim \text{C}_4$ アルキル) ($\text{C}_1 \sim \text{C}_2$ アルキル)、 $-\text{CO}_2$ ($\text{C}_1 \sim \text{C}_4$ アルキル)、 $\text{C}_1 \sim \text{C}_3$ アルコキシ、 $\text{C}_1 \sim \text{C}_3$ チオアルキル、フルオロ、ブロモ、クロロ、ヨード、シアノ又はニトロによって置換されていてもよく；並びに R_{11} は水素、ヒドロキシ、フルオロ又はメトキシである] の化合物、又はその医薬として許容できる塩である、請求項1記載の薬剤。

【請求項3】 Bが $-\text{NR}_1\text{R}_2$ 、 $-\text{NHCHR}_1\text{R}_2$ 、 $-\text{CR}_1\text{R}_2\text{R}_{11}$ 、 $-\text{SCHR}_1\text{R}_2$ 又は $-\text{OCHR}_1\text{R}_2$ であり； R_1 が、1個のヒドロキシ、フルオロ又は $\text{C}_1 \sim \text{C}_2$ アルコキシ基で置換されていてもよく、及び1個の炭素-炭素二重結合又は二重結合を含んでもよい、 $\text{C}_1 \sim \text{C}_6$ アルキルであり； R_2 がベンジル又は1個の炭素-炭素二重結合又は三重結合を含んでもよい $\text{C}_1 \sim \text{C}_6$ アルキルであり、このとき前記 $\text{C}_1 \sim \text{C}_6$ アルキル及び前記ベンジルのフェニル部分がフルオロ、 $\text{C}_1 \sim \text{C}_2$ アルキル又は $\text{C}_1 \sim \text{C}_2$ アルコキシにより置換されていてもよく；並びに R_{11} が水素又はフルオロである、請求項2記載の薬剤。

【請求項4】 R_2 が (アリール) $\text{C}_1 \sim \text{C}_4$ アルキル又は (ヘテロアリール) $\text{C}_1 \sim \text{C}_4$ アルキルであり、このとき前記アリール部分がフェニル、フラニル又はベンゾフラニルであり、及び前記ヘテロアリール部分がチエニル、ベンゾチエニル、チアゾリル、ピリジル又はベンゾチアゾリルである、請求項2記載の薬剤。

【請求項5】 Bが NR_1R_2 又は CHR_1R_2 であり、このとき R_1 及び R_2 が N 又は CH と一緒になって5又は6員環を形成し、このとき前記環が硫黄、酸素、又はBが NR_1R_2 であるときはさらに窒素を有してもよい、請求項2記載の薬剤。

【請求項6】 Bが $-\text{NHCHR}_1\text{R}_2$ 又は $-\text{OCHR}_1\text{R}_2$ であり、このとき CHR_1R_2 部分が1個の酸素又は硫黄を含んでもよい5又は6員環である、請求項2記載の薬剤。

【請求項7】 R_3 がメチル、クロロ又はメトキシであり； R_4 がメチル、 CH_2OH 、シアノ、トリフルオロメトキシ、メトキシ、トリフルオロメチル、クロロ、 $-\text{CO}_2\text{CH}_3$ 、 $-\text{CH}_2\text{OCH}_3$ 、 $-\text{CH}_2\text{Cl}$ 、 $-\text{CH}_2\text{F}$ 、アミノ又はニトロであり； R_6 が水素、メチルスルフィニル、メチルスルファニル、メチルスルホニル又はエチルであり；並びに R_5 がフェニル又はピリジルであり、このとき前記フェニル又はピリジルがフルオロ、クロロ、ブロモ、ヨード、 $\text{C}_1 \sim \text{C}_4$ アルコキシ、トリフルオロメチル、 $\text{C}_1 \sim \text{C}_3$ ヒドロキシアルキル、 $-\text{CO}_2$ ($\text{C}_1 \sim \text{C}_2$ アルキル)、 $\text{C}_1 \sim \text{C}_2$ アルキルアミノ、 $-\text{CO}$ ($\text{C}_1 \sim \text{C}_4$ アルキル) 及び $\text{C}_1 \sim \text{C}_6$ アルキルから独立して選択される1個の置換基によって置換され、

このとき前記 $C_1 \sim C_6$ アルキル及び前記 $C_1 \sim C_4$ アルキルが、1個のヒドロキシ又はフルオロ基によって置換されていてもよく、及び1個の炭素-炭素二重結合又は三重結合を含んでもよい；請求項2記載の薬剤。

【請求項8】 式I又はIIの化合物が、以下から選択される、請求項2記載の薬剤：4-(1-エチルプロポキシ)-2,5-ジメチル-6-(2,4,6-トリメチルベンジル)-ピリミジン；2-(4-ブromo-2,6-ジメチルフェノキシ)-4-(1-エチルプロポキシ)-3,6-ジメチルピリジン；2-(4-エチル-2,6-ジメチルフェノキシ)-4-(1-エチルプロポキシ)-3,6-ジメチルピリジン；3-エチル-4-(1-エチルプロポキシ)-6-メチル-2-(2,4,6-トリメチルフェノキシ)-ピリジン；2-(2,6-ジメチル-4-プロピルフェノキシ)-4-(1-エチルプロポキシ)-3,6-ジメチルピリジン；4-(1-エチルプロポキシ)-2-(4-メトキシ-2,6-ジメチルフェノキシ)-3,6-ジメチルピリジン；2-(4-エトキシ-2,6-ジメチルフェノキシ)-4-(1-エチルプロポキシ)-3,6-ジメチルピリジン；2-(4-クロロ-2,6-ジメチルフェノキシ)-4-(1-エチルプロポキシ)-3,6-ジメチルピリジン；4-(1-メトキシメチルプロポキシ)-3,6-ジメチル-2-(2,4,6-トリメチルフェノキシ)-ピリジン；[3,6-ジメチル-2-(2,4,6-トリメチルフェノキシ)-ピリジン-4-イル]-ジエチルアミン；[3,6-ジメチル-2-(2,4,6-トリメチルフェノキシ)ピリジン-4-イル]エチルプロピルアミン；[2,5-ジメチル-6-(2,4,6-トリメチルフェノキシ)-ピリミジン-4-イル]-(1-エチルプロピル)アミン；ブチル-[3,6-ジメチル-2-(2,4,6-トリメチルフェノキシ)-ピリジン-4-イル]-エチルアミン；4-(1-エチルプロポキシ)-3,6-ジメチル-2-(2,4,6-トリメチルフェノキシ)-ピリジン；ブチル-[2-(4-クロロ-2,6-ジメチルフェノキシ)-3,6-ジメチルピリジン-4-イル]-エチルアミン；4-(1-エチルプロピルアミノ)-6-メチル-2-(2,4,6-トリメチルフェノキシ)-ニコチン酸メチルエステル；[3,6-ジメチル-2-(2,4,6-トリメチルフェニルスルファニル)-ピリジン-4-イル]-エチルプロピルアミン；[4-(1-エチルプロピルアミノ)-6-メチル-2-(2,4,6-トリメチルフェノキシ)-ピリジン-3-イル]-メタノール；[2-(4-クロロ-2,6-ジメチルフェノキシ)-3,6-ジメチルピリジン-4-イル]エチルプロピルアミン；1-(エチルプロピル)-[6-メチル-3-ニトロ-2-(2,4,6-トリメチルフェノキシ)-ピリジン-4-イル]-アミン；N4-(1-エチルプロピル)-6-メチル-3-ニトロ-N2-(2,4,6-トリメチル

-フェニル)-ピリジン-2,4-ジアミン；N4-(1-エチルプロピル)-6-メチル-2-(2,4,6-トリメチルフェノキシ)-ピリジン-3,4-ジアミン；N4-(1-エチルプロピル)-6-メチル-N2-(2,4,6-トリメチルフェニル)-ピリジン-2,3,4-トリアミン；[3,6-ジメチル-2-(2,4,6-トリメチルフェノキシ)-ピリジン-4-イル]-エチル-2,2-トリフルオロエチルアミン；[3-クロロメチル-6-メチル-2-(2,4,6-トリメチルフェノキシ)ピリジン-4-イル]-(1-エチルプロピル)アミン；[3,6-ジメチル-2-(2,4,6-トリメチルフェノキシ)ピリジン-4-イル]-(1-エチルプロピル)アミン；(1-エチルプロピル)-[2-メチル-5-ニトロ-6-(2,4,6-トリメチルピリジン-3-イルオキシ)-ピリミジン-4-イル]-アミン；(1-エチルプロピル)-[3-メトキシメチル-6-メチル-2-(2,4,6-トリメチルフェノキシ)ピリジン-4-イル]アミン；N-(1-エチルプロピル)-2-メチル-5-ニトロ-N-(2,4,6-トリメチルピリジン-3-イル)-ピリミジン-4,6-ジアミン；[2-(4-クロロ-2,6-ジメチルフェノキシ)-3,6-ジメチルピリジン-4-イル]-ジエチルアミン；4-(1-エチルプロポキシ)-3,6-ジメチル-2-(2,4,6-トリメチルフェノキシ)-ピリジン；ブチル-[2,5-ジメチル-7-(2,4,6-トリメチルフェニル)-6,7-ジヒドロ-5H-ピロロ[2,3-d]ピリミジン-4-イル]-エチルアミン；4-(ブチルエチルアミノ)-2,5-ジメチル-7-(2,4,6-トリメチルフェニル)-5,7-ジヒドロ-ピロロ[2,3-d]ピリミジン-6-オン；4-(1-エチルプロポキシ)-2,5-ジメチル-6-(2,4,6-トリメチルフェノキシ)-ピリミジン；N-ブチル-N-エチル-2,5-ジメチル-N-(2,4,6-トリメチルフェニル)ピリミジン-4,6-ジアミン；(1-エチルプロピル)-[5-メチル-3-(2,4,6-トリメチルフェニル)-3H-イミダゾ[4,5-b]ピリジン-7-イル]-アミン；[2,5-ジメチル-3-(2,4,6-トリメチルフェニル)-3H-イミダゾ[4,5-b]ピリジン-7-イル]-(1-エチルプロピル)アミン；N4-(1-エチルプロピル)-6,N3-ジメチル-2-(2,4,6-トリメチルフェノキシ)-ピリジン-3,4-ジアミン；N4-(1-エチルプロピル)-6,N3,N3-トリメチル-2-(2,4,6-トリメチルフェノキシ)-ピリジン-3,4-ジアミン；6-(1-エチルプロポキシ)-2-メチル-N4-(2,4,6-トリメチルフェニル)ピリミジン-4,5-ジアミン；[4-(1-エチルプロポキシ)-3,6-ジメチルピリジン-2-イル]-(2,4,6-トリメチルフェニル)アミン；及び6-(エチルプロピルアミノ)-2,7-ジメチル-9-(2,4,6-トリメチルフェニル)-7,9-

ジヒドロプリン-8-オン。

【請求項9】 化合物が、以下から選択される、請求項2記載の方法：ブチル-〔3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-b] ピリジン-4-イル〕 -エチルアミン；3, 6-ジメチル-4

(テトラヒドロフラン 3 イルオキシ) 1 (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-b] ピリジン；〔3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-b] ピリジン-4-イル〕 - (1-メトキシメチルプロピル) -アミン；4- (1-メトキシメチルプロポキシ) -3, 6-ジメチル 1 (2, 4, 6 トリメチルフェニル) 1H ピラゾロ [3, 4-b] ピリジン；(1-エチルプロピル) -〔3, 5, 6-トリメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-b] ピリジン-4-イル〕 -アミン；4- (1-エチルプロポキシ) -2, 5-ジメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-b] ピリジン；4 (1 エチルプロポキシ) -2, 5, 6-トリメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-b] ピリジン；4- (1-エチルプロポキシ) -2, 5-ジメチル-7- (2, 6-ジメチル-4-プロモフェニル) -7H-ピロロ [2, 3-b] ピリジン；3- { (4-メチル-ベンジル) -〔3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル〕 -アミノ} -プロパン-1-オール；ジエチル-〔6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) 1H ピラゾロ [3, 4 d] ピリミジン 4 イル〕 -アミン；2-〔ブチル-〔6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル〕 -アミノ} -エタノール；ジブチル-〔6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H ピラゾロ [3, 4 d] ピリミジン 4 イル〕 アミン；ブチル-エチル-〔6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル〕 -アミン；ブチル-エチル-〔6-メチル-3-メチルスルホニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4 d] ピリミジン 4 イル〕 アミン；ブチル シクロプロピルメチル-〔6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル〕 -アミン；ジ-1-プロピル-〔6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4 d] ピリミジン 4 イル〕 アミン；ジアリル-〔6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル〕 -アミン；ブチル-エチル-〔6-クロロ-3-メチルスルファニル-1- (2, 4, 6-トリ

クロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル〕 -アミン；ブチル-エチル-〔6-メトキシ-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル〕 -アミン；プロピル-エチル-〔3, 6-ジメチル 1 (2, 4, 6 トリメチルフェニル) 1H ピラゾロ [3, 4-d] ピリミジン-4-イル〕 -アミン；4- (1-エチルプロピル) -6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン；2-〔3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4 d] ピリミジン 4 イルアミン〕 ブタン 1-オール；〔3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル〕 - (1-メチルプロピル) アミン；4- (1-メトキシメチルプロポキシ) -3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4 d] ピリミジン；n ブチル エチル [2, 5-ジメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミン；ジ-n-プロピル-〔2, 5-ジメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミン；エチル-n-プロピル-〔2, 5-ジメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミン；ジエチル-2, 5-ジメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミン；n ブチル エチル [2, 5, 6 トリメチル 7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミン；2-〔N-n-ブチル-N-〔2, 5-ジメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミノ〕 -エタノール；4- (1-エチルプロピル) 2, 5, 6 トリメチル 7 (2, 4, 6 トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン；n-ブチル-エチル-〔2, 5-ジメチル-7- (2, 4-ジメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミン；2, 5-ジメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン 4 イル〕 (1 エチル プロピル) アミン；2 [7- (4-プロモ-2, 6-ジメチルフェニル) -2, 5-ジメチル-7H-ピロロ [2, 3-d] ピリミジン-4-イルアミノ] -ブタン-1-オール；2- (S) -〔7- (4-プロモ-2, 6-ジメチルフェニル) -2, 5-ジメチル-7H-ピロロ [2, 3-d] ピリミジン-4-イルアミノ〕 -ブタン 1 オール；4 (1 エチル プロポキシ) 2, 5, 6-トリメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン；4- (1-メトキシメチルプロポキシ) -2, 5, 6-トリメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3

—d] ピリミジン；4—(1-エチル—ブチル)—2, 5, 6—トリメチル—7—(2, 4, 6—トリメチルフェニル)—7H—ピロロ—[2, 3—d] ピリミジン；[7—(4—ブチル)—2, 6—ジメチル—フェニル)—2, 5—ジメチル—7H—ピロロ [2, 3—d] ピリミジン—4—イル]—(1—メトキシメチル プロピル) アミン；2 [7—(2—ブチル)—4, 6—ジメチル—フェニル)—2, 5—ジメチル—7H—ピロロ [2, 3—d] ピリミジン—4—イルアミノ]—ブタン—1—オール；2—[7—(4—エチル—2, 6—ジメチル—フェニル)—2, 5—ジメチル—7H—ピロロ [2, 3—d] ピリミジン—4—イルアミノ]—ブタン—1—オール；及び2—[7—(2—フルオロメチル—4, 6—ジメチルフェニル)—2, 5—ジメチル—7H—ピロロ [2, 3—d] ピリミジン—4—イルアミノ]—ブタン—1—オール。

【請求項10】 突然死のリスクが、動物における疾患状態の存在に関連し、このとき前記疾患状態が、心臓疾患、高血圧、頻脈、うっ血性心不全、脳卒中、骨粗鬆症、早産、心理的萎縮、ストレス性発熱、潰瘍、下痢、術後腸閉塞、精神的不安及びストレスに関連する腸の過敏、糖尿病、神経性疾患、脳障害、ギランバレー症候群、小児突然死症候群、先天性過換気症候群又は尿毒症性神経障害である、請求項1記載の薬剤。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、臨床上有効な量のコルチコトロピン放出因子 (CRF) アンタゴニストを投与することによる、特定の患者における突然死の発生を減じる方法に関する。CRFアンタゴニストは、QT分散 (dispersion) 及び心拍変動 (heart rate variability) を改善することによって、患者における突然死の発生を減じると考えられる。

【0002】

【従来技術】突然の予期しない死が、中程度の心疾患にかかっていた患者の50%、重篤な心疾患を経験している患者の25%に起こっている (Barrら、Lancet、343 (8893) : 327—29 (1994))。心室再分極 (ventricular repolarization) における局所変化は、不整脈の電気神経学的基質を示すものであるが、QTインターバル (分散) の内部誘導 (interlead) 変動によって検出される。QTインターバル分散は、急性心筋梗塞の後の心室不整脈 (ventricular tachyarrhythmias)、長期のQT症候群、慢性心疾患及び肥大性心筋症にかかった患者に見られる (例えば、Potratzら、Eur. Heart J.、14 : 254 (1993) ; Dayら、Br. Heart J.、63 : 342—44 (1990) ; 及びBujaら、Am. J. Cardiol.、72 : 973—976 (1993) を参照せよ。)。

【0003】本明細書に記載されたような式I及びIIの

化合物及びそれらの医薬として許容できる塩、並びにそのような化合物の塩の製造方法は、欧州特許出願EP0773 023A1、並びに、より詳細にはPCT国際特許出願PCT/IB95/00373 (公開番号W095/34563)、PCT/IB95/00439 (公開番号W095/33750)、PCT/US93/11333 (公開番号W094/13677) 及び PCT/US93/10715 (公開番号W094/13676) 中に開示されている。上記のこれらの欧州特許出願及びPCT国際特許出願の内容はすべて、引用により本明細書中に取り込まれる。

【0004】前述のPCT国際特許出願は、CRFにより引き起こされ又は促進される病気の治療における、また、不安、鬱、倦怠症候群 (fatigue syndrome)、胃腸疾患、頭痛、痛み、ガン、免疫機能不全、出血性ストレス (hemorrhagic stress)、薬物中毒、薬物及びアルコールの中断症状、不妊 (fertility problems)、ストレスに起因する精神病性挿入 (stress-induced psychotic episodes)、アルツハイマー病のような神経変性性疾患、クローン病、痙攣性結腸及び過敏結腸のような過敏腸症候群 (irritable bowel syndrome)、食欲不振 (anorexia nervosa) のような摂食疾患、関節炎のような炎症性疾患、喘息及びアレルギー等の治療における、式I及びIIの化合物の使用についても言及している。

【0005】本発明の方法において列記されている疾患の治療のために用いることのできる他のCRFアンタゴニストは、PCT国際特許出願PCT/IB95/00318 (国際公開番号W095/33727)、PCT/IB97/00918 (国際公開番号W098/05661)、PCT/IB97/00904 (国際公開番号W098/08846) 及びPCT/IB97/00922 (国際公開番号W098/08847)、PCT/EP98/02267 (国際公開番号W098/47874)、PCT/EP98/02268 (国際公開番号W098/47903)、PCT/US98/09861 (国際公開番号W098/51312)、PCT/US98/13840 (国際公開番号W099/01439)、PCT/US98/13913 (国際公開番号W099/01454) 並びに米国特許5,063,245、5,109,111、5,132,111、5,245,009、5,464,847、5,493,006、5,510,458、5,605,642、5,644,057、5,663,292、5,668,145、5,705,646及び5,712,303に記載されている。ここで引用したPCT国際特許出願及び米国特許は、それらの全体を本明細書に援用する。

【0006】CRFアンタゴニストの重要性は文献、例えば米国特許5,063,245に論じられている。この内容はすべて、引用により本明細書中に取り込まれる。CRFアンタゴニストによって示される異なる活性の最近のアウトラインを、M. J. Owensら、Pharm. Rev.、43 : 425—73 (1991) に見ることができる。この内容もすべて、引用により本明細書中に取り込まれる。

【0007】PCT国際特許出願PCT/US98/07831 (国際公開番号W098/47899) は、炎症性疾患の治療における置換ピロロピリジンの有効性を開示する。開示された化合物は、特定の炎症性サイトカイン、即ちTNF- α I及び

L-1 β の産生を阻害する。掲げられている炎症性サイトカインに関連した炎症性疾患の一つは、うっ血性心疾患である。しかしながら、QT分散又は心拍変動については言及されていない。

【0008】

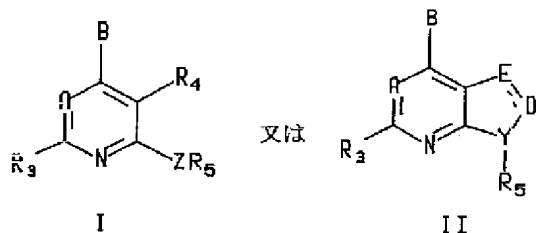
【課題を解決するための手段】本発明は、動物における突然死を予防する方法であって、前記動物、好ましくはヒトに、臨床上有効量のコルチコロトピン放出因子アンタゴニストを投与することを含む前記方法を提供する。

【0009】本発明の方法は、特定の患者、詳細には、心臓血管又は心臓に関連した疾患、例えば、高血圧(hypertension)、頻脈(tachycardia)、うっ血性心不全(congestive heart failure)等に苦しむ患者における突然死を予防する際に最も有用である。また、他の疾患、例えば、脳卒中(stroke)、骨粗鬆症(osteoporosis)、早産(premature birth)、心理的萎縮(psychosocial dwarfism)、ストレス性発熱(stress-induced fever)、潰瘍(ulcer)、下痢(diarrhea)、術後腸閉塞(post-operative ileus)、精神的不安及びストレスに関連する腸の過敏(colonic hypersensitivity associated with psychopathological disturbance and stress)等の患者においても同様に有用である。本発明の方法はまた、糖尿病患者における突然死を予防する際にも有用である。また、多くの神経疾患(neurological disorders)、例えば、脳障害(brain damage)、ギランバレー症候群(Guillain-Barre syndrome)、小児突然死症候群(sudden infant death syndrome)、先天性過換気症候群(congenital hypoventilation syndrome)又は尿毒症性神経障害(uremic neuropathy)等の患者においても同様に有用である。

【0010】好ましい実施態様において、本発明は式I又はIIの化合物を用いる。

【0011】

【化2】



【0012】式中、点線は所望により存在する二重結合を表し、Aは-CR₇又はNであり、Bは-NR₁R₂、-CR₁R₂R₁₁、-C(=CR₁R₂)R₂、-NHCR₁R₂R₂、-OCR₁R₂R₂、-SCR₁R₂R₂、-CR₁R₂OR₁、-CR₁R₂SR₁、-C(S)R₂、-NINR₁R₂、-CR₂R₁₁NHR₁又は-C(O)R₂であり；DはEとDとが二重結合で結合し、及びEが-CR₄であるとき、N又は-CR₁₀であり；EとDとが二重結合で結合し、及びEがNであるとき、-CR₁₀であり；又はEとDとが単結合で結合しているとき、-CR₈R₉、-CHR₁₀、-C=O、-

C=S、-C=NH又は-C=NCH₃であり；EはEとDとが二重結合で結合しているとき、-CR₄又はNであり；又はEとDとが単結合で結合しているとき、-CR₄R₆又は-NR₆であり；YはN又は-CHであり；ZはNH、O、S、-N(C₁~C₂アルキル)又は-CR₁₂R₁₃であり、このときR₁₂及びR₁₃は各々独立に水素、トリフルオロメチル若しくはメチルであるか、又はR₁₂及びR₁₃の一方がシアノ、他方が水素若しくはメチルであり；R₁は水素又はC₁~C₆アルキルであり、このとき前記C₁~C₆アルキルはヒドロキシ、シアノ、ニトロ、フルオロ、クロロ、プロモ、ヨード、CF₃、C₁~C₄アルコキシ、-O-CO-(C₁~C₄アルキル)、O-CO-NH(C₁~C₄アルキル)、O-CO-N(C₁~C₄アルキル)(C₁~C₂アルキル)、-NH(C₁~C₄アルキル)、-N(C₁~C₂アルキル)(C₁~C₄アルキル)、-S(C₁~C₄アルキル)、-N(C₁~C₄アルキル)CO(C₁~C₄アルキル)、-NHCO(C₁~C₄アルキル)、-CO₂(C₁~C₄アルキル)、-CONH(C₁~C₄アルキル)、

CON(C₁~C₄アルキル)(C₁~C₂アルキル)、(C₁~C₄アルキル)スルフィニル、(C₁~C₄アルキル)スルホニル及び(C₁~C₄アルキル)スルフェニルから独立して選択される2個以下の置換基で置換されていてもよく、このとき前述のR₁基中の前記C₁~C₆アルキル、C₁~C₄アルコキシ及びC₁~C₄アルキル部分は、1個の二重結合又は三重結合を含んでもよく；R₂はC₁~C₆アルキル、ヘテロアリール、アリール、ヘテロアリール(C₁~C₄アルキル)又はアリール(C₁~C₄アルキル)であり、このとき前記アリール及び前記(アリール)C₁~C₄アルキルのアリール部分はフェニル及びナフチルから選択され、及び前記ヘテロアリール及び前記(ヘテロアリール)C₁~C₄アルキルのヘテロアリール部分はチエニル、ベンゾチエニル、ピリジル、チアゾリル、キノリル、ピラジニル、ピリミジル、イミダゾリル、フラニル、ベンゾフラニル、ベンゾチアゾリル、イソチアゾリル、ベンズイソチアゾリル、ベンズイソキサゾリル、ベンズイミダゾリル、インドリル及びベンゾキサゾリルから選択されるか；又はR₂はC₃~C₈シクロアルキル又は(C₃~C₈シクロアルキル)C₁~C₆アルキルであり、このとき少なくとも4つの環員を有する前記シクロアルキル及び少なくとも4つの環員を有する前記(C₃~C₈シクロアルキル)C₁~C₆アルキルのシクロアルキル部分の環炭素の1又は2個は、酸素若しくは硫黄によって、又は-NR₁₄(このときR₁₄は水素又はC₁~C₄アルキルである)によって置換されていてもよく；及び前述のR₂基は、クロロ、フルオロ及びC₁~C₄アルキルから独立して選択される3個以下の置換基によって、又はプロモ、ヨード、シアノ、ニトロ、C₁~C₆アルコキシ、O-CO-(C₁~C₄アルキル)、O-CO-N(C₁~C₄アルキル)(C₁~C₂アルキル)、-CO₂(C₁~C₄アルキル)、(C₁~C₄アルキル)スルフェニル、(C₁~C₄アルキル)スルフィニル及び(C₁~C₄アルキル)スルホニルから選択される1個の置換基によって

置換されていてもよく、このとき前記 $C_1 \sim C_4$ アルキル及び前述の R_2 基の $C_1 \sim C_6$ アルキル部分は、1個の炭素-炭素二重結合又は三重結合を含んでもよく；又は前記 $-NR_1R_2$ 及び前記 $-CR_1R_2R_{11}$ の R_1 及び R_2 は、一緒になって飽和若しくは部分飽和の5~8員環を形成し、このとき前記環は1又は2個の炭素-炭素二重結合又は三重結合を含んでもよく、及びこのとき環員炭素の1又は2個は、O、S及びNから選択されるヘテロ原子により置き換えられていてもよく； R_3 は水素、 $C_1 \sim C_6$ アルキル、フルオロ、クロロ、ブロモ、ヨード、ヒドロキシ、アミノ、SH、 $-NH(C_1 \sim C_4$ アルキル)、 $-N(C_1 \sim C_4$ アルキル)($C_1 \sim C_2$ アルキル)、 CH_2OH 、 CH_2OCH_3 、 $O(C_1 \sim C_4$ アルキル)、($C_1 \sim C_4$ アルキル)スルファニル、($C_1 \sim C_4$ アルキル)スルホニル又は($C_1 \sim C_4$ アルキル)スルフィニルであり、このとき前記 $C_1 \sim C_6$ アルキル及び前述の R_3 基の $C_1 \sim C_4$ アルキル部分は1個の二重結合又は三重結合を含んでもよく、及びヒドロキシ、アミノ、 $C_1 \sim C_3$ アルコキシ、 $NH(C_1 \sim C_2$ アルキル)、 $N(C_1 \sim C_2$ アルキル) $_2$ 、 $-NHCOCH_3$ 、フルオロ、クロロ及び $C_1 \sim C_3$ チオアルキルから独立して選択される1~3個の置換基によって置換されていてもよく； R_4 は水素、 $C_1 \sim C_6$ アルキル、フルオロ、クロロ、ブロモ、ヨード、 $C_1 \sim C_6$ アルコキシ、ホルミル、トリフルオロメトキシ、 $-CH_2OCH_3$ 、 $-CH_2OCH_2CH_3$ 、 $-CH_2CH_2OCH_3$ 、 $-CH_2CF_3$ 、 CF_3 、アミノ、ニトロ、 $-NH(C_1 \sim C_4$ アルキル)、 $-N(CH_3)_2$ 、 $-NHCOC H_3$ 、 $-NHCONHCH_3$ 、($C_1 \sim C_4$ アルキル)スルファニル、($C_1 \sim C_4$ アルキル)スルフィニル、($C_1 \sim C_4$ アルキル)スルホニル、シアノ、ヒドロキシ、 $CO(C_1 \sim C_4$ アルキル)、 $-CHO$ 又は $-CO_2(C_1 \sim C_4$ アルキル)であり、このとき前述の R_4 基の前記 $C_1 \sim C_6$ アルキル、 $C_1 \sim C_6$ アルコキシ及び $C_1 \sim C_4$ アルキル部分は、1個の二重結合又は三重結合を含んでもよく、及びヒドロキシ、アミノ、 $-NHCOCH_3$ 、 $-NH(C_1 \sim C_2$ アルキル)、 $-N(C_1 \sim C_2$ アルキル) $_2$ 、 $CO_2(C_1 \sim C_4$ アルキル)、 $CO(C_1 \sim C_4$ アルキル)、 $C_1 \sim C_3$ アルコキシ、($C_1 \sim C_3$ アルキル)スルファニル、フルオロ、クロロ、シアノ及びニトロから選択される1個の置換基で置換されていてもよく； R_5 はフェニル、ナフチル、チエニル、ベンゾチエニル、ピリジル、キノリル、ピラジノリル、ピリミジル、イミダゾリル、フラニル、ベンゾフラニル、ベンゾチアゾリル、イソチアゾリル、ベンゾイソチアゾリル、チアゾリル、イソキサゾリル、ベンズイソキサゾリル、ベンズイミダゾリル、トリアゾリル、ピラゾリル、ピロリル、インドリル、アザインドリル、ベンズオキサゾリル、オキサゾリル、ピロジニル、チアゾリジニル、モルホリニル、ピリジニル、テトラゾリル又は3~8員シクロアルキル環若しくは9~12員ビシクロアルキル環システムであり、このとき前記シクロアルキル環及び前記ビシクロアルキル環システムは、1又は2個のO、S又は $-N-G$ (このときGは水素、 $C_1 \sim C_4$ アルキル、 $C_1 \sim C_4$ アルカノイル、フェニル又はベンジルである)であり、このとき前述の R_5 基の各々は、フルオロ、クロロ、 $C_1 \sim C_6$ アルキル、 $C_1 \sim C_6$ アルコキシ及びトリフルオロメチルから独立して選択される3個以下の置換基によって、又はブロモ、ヨード、シアノ、ニトロ、アミノ、 $-NH(C_1 \sim C_4$ アルキル)、 $-N(C_1 \sim C_4$ アルキル)($C_1 \sim C_2$ アルキル)、 $CO_2(C_1 \sim C_4$ アルキル)、 $-CO(C_1 \sim C_4$ アルキル)、 $-SO_2NH(C_1 \sim C_4$ アルキル)、 $-SO_2N(C_1 \sim C_4$ アルキル)($C_1 \sim C_2$ アルキル)、 $-SO_2NH_2$ 、 $-NHSO_2(C_1 \sim C_4$ アルキル)、 $-S(C_1 \sim C_4$ アルキル)及び $-SO_2(C_1 \sim C_4$ アルキル)から選択される1個の置換基によって置換されていてもよく、このとき前述の R_5 基の前記 $C_1 \sim C_4$ アルキル及び $C_1 \sim C_6$ アルキル部分は、1個の二重結合又は三重結合を含んでもよく、及びフルオロ、クロロ、ヒドロキシ、アミノ、メチルアミノ、ジメチルアミノ及びアセチルから独立して選択される1又は2個の置換基によって置換されていてもよく； R_6 は水素又は $C_1 \sim C_6$ アルキルであり、このとき前記 $C_1 \sim C_6$ アルキルは1個のヒドロキシ、メトキシ、エトキシ又はフルオロ基により置換されていてもよく； R_7 は水素、 $C_1 \sim C_4$ アルキル、フルオロ、クロロ、ブロモ、ヨード、シアノ、ヒドロキシ、 $C_1 \sim C_4$ アルコキシ、 $-CO(C_1 \sim C_4$ アルキル)、 $-CO_2(C_1 \sim C_4$ アルキル)、 $-OCF_3$ 、 CF_3 、 $-CH_2OH$ 、 $-CH_2OCH_3$ 又は $-CH_2OCH_2CH_3$ であり； R_8 及び R_9 は各々独立して水素、ヒドロキシ、メチル、エチル、メトキシ又はエトキシであるか；又は R_8 及び R_9 は一緒にオキソ(=O)基を形成し； R_{10} は水素、 $C_1 \sim C_6$ アルキル、フルオロ、クロロ、ブロモ、ヨード、 $C_1 \sim C_6$ アルコキシ、ホルミル、アミノ、 $NH(C_1 \sim C_4$ アルキル)、 $-N(C_1 \sim C_4$ アルキル)($C_1 \sim C_2$ アルキル)、シアノ、カルボキシ、アミド又は $-SO_n(C_1 \sim C_4$ アルキル)(このときnは0、1又は2である)であり、このとき前述の R_{10} 基の前記 $C_1 \sim C_6$ アルキル及び $C_1 \sim C_4$ アルキル部分は1個のヒドロキシ、トリフルオロメチル、アミノ、カルボキシ、アミド、 $NHCO(C_1 \sim C_4$ アルキル)、 $-NH(C_1 \sim C_4$ アルキル)、 $-N(C_1 \sim C_4$ アルキル)($C_1 \sim C_2$ アルキル)、 $-CO_2(C_1 \sim C_4$ アルキル)、 $C_1 \sim C_3$ アルコキシ、 $C_1 \sim C_3$ チオアルキル、フルオロ、ブロモ、クロロ、ヨード、シアノ又はニトロによって置換されていてもよく；並びに R_{11} は水素、ヒドロキシ、フルオロ又はメトキシである。

【0013】好ましくは、Bが $-NR_1R_2$ 、 $-NHCHR_1R_2$ 、 $-CR_1R_2R_{11}$ 、 $-SCHR_1R_2$ 又は $-OCHR_1R_2$ であり； R_1 が、1個のヒドロキシ、フルオロ又は $C_1 \sim C_2$ アルコキシ基で置換されていてもよく、及び1個の炭素-炭素二重結合又は三重結合を含んでもよい $C_1 \sim C_6$ アルキルであり； R_2 がベンジル又は1個の炭素-炭素二重結合又は三重結合を含んでもよい $C_1 \sim C_6$ アルキルであり、このとき前記 $C_1 \sim C_6$ アルキル及び前記ベンジルのフェニル部分がフルオロ、 $C_1 \sim C_2$ アルキル又は $C_1 \sim C_2$ アルコキシにより置換されていてもよく；並びに R_{11} が水素又はフルオロである。

【0013】好ましくは、Bが $-NR_1R_2$ 、 $-NHCHR_1R_2$ 、 $-CR_1R_2R_{11}$ 、 $-SCHR_1R_2$ 又は $-OCHR_1R_2$ であり； R_1 が、1個のヒドロキシ、フルオロ又は $C_1 \sim C_2$ アルコキシ基で置換されていてもよく、及び1個の炭素-炭素二重結合又は三重結合を含んでもよい $C_1 \sim C_6$ アルキルであり； R_2 がベンジル又は1個の炭素-炭素二重結合又は三重結合を含んでもよい $C_1 \sim C_6$ アルキルであり、このとき前記 $C_1 \sim C_6$ アルキル及び前記ベンジルのフェニル部分がフルオロ、 $C_1 \sim C_2$ アルキル又は $C_1 \sim C_2$ アルコキシにより置換されていてもよく；並びに R_{11} が水素又はフルオロである。

【0014】また好ましくは、 R_2 が(アリール) $C_1 \sim C_4$ アルキル又は(ヘテロアリール) $C_1 \sim C_4$ アルキルであり、このとき前記アリール部分がフェニル、フラニル又はベンゾフラニルであり、及び前記ヘテロアリール部分がチエニル、ベンゾチエニル、チアゾリル、ピリジル又はベンゾチアゾリルである。

【0015】また好ましくは、 B が NR_1R_2 又は CHR_1R_2 であり、このとき R_1 及び R_2 が N 又は CH と一緒になって5又は6員環を形成し、このとき前記環が硫黄、酸素、又は B が N R_1R_2 であるときはさらに窒素有してもよい。

【0016】また好ましくは、 B が $-NHCHR_1R_2$ 又は $-OCHR_1R_2$ であり、このとき CHR_1R_2 部分が1個の酸素又は硫黄を含んでもよい5又は6員環である。

【0017】また好ましくは、 R_3 がメチル、クロロ又はメトキシであり； R_4 がメチル、 $-CH_2OH$ 、シアノ、トリフルオロメトキシ、メトキシ、トリフルオロメチル、クロロ、 $-CO_2CH_3$ 、 $-CH_2OCH_3$ 、 $-CH_2Cl$ 、 $-CH_2F$ 、アミノ又はニトロであり； R_5 が水素、メチルスルフィニル、メチルスルファニル、メチルスルホニル又はエチルであり；並びに R_5 がフェニル又はピリジルであり、このとき前記フェニル又はピリジルがフルオロ、クロロ、ブロモ、ヨード、 $C_1 \sim C_4$ アルコキシ、トリフルオロメチル、 $C_1 \sim C_3$ ヒドロキシアルキル、 $-CO_2$ ($C_1 \sim C_2$ アルキル)、 $C_1 \sim C_2$ アルキルアミノ、 $-CO$ ($C_1 \sim C_4$ アルキル)及び $C_1 \sim C_6$ アルキルから独立して選択される1個の置換基によって置換され、このとき前記 $C_1 \sim C_6$ アルキル及び前記 $C_1 \sim C_4$ アルキルは1個のヒドロキシ又はフルオロ基によって置換されていてもよく、及び1個の炭素-炭素二重結合又は三重結合を含んでもよい。

【0018】式I又はIIの化合物は、以下の化合物を含む：4-(1-エチル-プロポキシ)-2,5-ジメチル-6-(2,4,6-トリメチル-ベンジル)-ピリミジン；2-(4-ブロモ-2,6-ジメチル-フェノキシ)-4-(1-エチル-プロポキシ)-3,6-ジメチル-ピリジン；2-(4-エチル-2,6-ジメチル-フェノキシ)-4-(1-エチル-プロポキシ)-3,6-ジメチル-ピリジン；3-エチル-4-(1-エチル-プロポキシ)-6-メチル-2-(2,4,6-トリメチル-フェノキシ)-ピリジン；2-(2,6-ジメチル-4-プロピル-フェノキシ)-4-(1-エチル-プロポキシ)-3,6-ジメチル-ピリジン；4-(1-エチル-プロポキシ)-2-(4-メトキシ-2,6-ジメチル-フェノキシ)-3,6-ジメチル-ピリジン；2-(4-エトキシ-2,6-ジメチル-フェノキシ)-4-(1-エチル-プロポキシ)-3,6-ジメチル-ピリジン；2-(4-クロロ-2,6-ジメチル-フェノキシ)-4-(1-エチル-プロポキシ)-3,6-ジメチル-ピリジン；4-(1-メトキシメチル-プロポキシ)-3,6-ジメチル-2-(2,4,6-トリメチル-フェノキシ)-ピリジン；[3,6-ジメチル-2-(2,4,6-トリメチル-フェノキシ)-ピリジン-4-

イル]-ジエチル-アミン；[3,6-ジメチル-2-(2,4,6-トリメチル-フェノキシ)-ピリジン-4-イル]-エチル-プロピル-アミン；[2,5-ジメチル-6-(2,4,6-トリメチル-フェノキシ)-ピリミジン-4-イル](1-エチル-プロピル)アミン；ブチル[3,6-ジメチル-2-(2,4,6-トリメチル-フェノキシ)-ピリジン-4-イル]-エチル-アミン；4-(1-エチル-プロポキシ)-3,6-ジメチル-2-(2,4,6-トリメチル-フェニルスルファニル)-ピリジン；ブチル[2-(4-クロロ-2,6-ジメチル-フェノキシ)-3,6-ジメチル-ピリジン-4-イル]-エチル-アミン；4-(1-エチル-プロピルアミノ)-6-メチル-2-(2,4,6-トリメチル-フェノキシ)-ニコチン酸メチルエステル；[3,6-ジメチル-2-(2,4,6-トリメチル-フェニルスルファニル)-ピリジン-4-イル]-エチル-プロピル-アミン；[4-(1-エチル-プロピルアミノ)-6-メチル-2-(2,4,6-トリメチル-フェノキシ)-ピリジン-3-イル]-メタノール；[2-(4-クロロ-2,6-ジメチル-フェノキシ)-3,6-ジメチル-ピリジン-4-イル]-エチル-プロピル-アミン；1-(エチル-プロピル)-[6-メチル-3-ニトロ-2-(2,4,6-トリメチル-フェノキシ)-ピリジン-4-イル]-アミン；N4-(1-エチル-プロピル)-6-メチル-3-ニトロ-N2-(2,4,6-トリメチル-フェニル)-ピリジン-2,4-ジアミン；N4-(1-エチル-プロピル)-6-メチル-2-(2,4,6-トリメチル-フェノキシ)-ピリジン-3,4-ジアミン；N4-(1-エチル-プロピル)-6-メチル-N2-(2,4,6-トリメチル-フェニル)-ピリジン-2,3,4-トリアミン；[3,6-ジメチル-2-(2,4,6-トリメチル-フェノキシ)-ピリジン-4-イル]-エチル-(2,2,2-トリフルオロ-エチル)-アミン；[3-クロロメチル-6-メチル-2-(2,4,6-トリメチル-フェノキシ)-ピリジン-4-イル]- (1-エチル-プロピル)-アミン；[3,6-ジメチル-2-(2,4,6-トリメチル-フェノキシ)-ピリジン-4-イル]- (1-エチル-プロピル)-アミン；(1-エチル-プロピル)-[2-メチル-5-ニトロ-6-(2,4,6-トリメチル-ピリジン-3-イルオキシ)-ピリミジン-4-イル]アミン；(1-エチル-プロピル)-[3-メトキシメチル-6-メチル-2-(2,4,6-トリメチル-フェノキシ)-ピリジン-4-イル]-アミン；N-(1-エチル-プロピル)-2-メチル-5-ニトロ-N-(2,4,6-トリメチル-ピリジン-3-イル)-ピリミジン-4,6-ジアミン；[2-(4-クロロ-2,6-ジメチル-フェノキシ)-3,6-ジメチル-ピリジン-4-イル]-ジエチル-アミン；4-(1-エチル-プロポキシ)-3,6-ジメチル-2-(2,4,6-トリメチル-フェノキシ)-ピリジン；ブチル[2,5-ジメチル-7-(2,4,6-トリメチル

フェニル) -6, 7-ジヒドロ-5H-ピロロ [2, 3-d] ピリミジン-4-イル] -エチル-アミン; 4- (ブチル-エチルアミノ) -2, 5-ジメチル-7- (2, 4, 6-トリメチルフェニル) -5, 7-ジヒドロ-ピロロ [2, 3-d] ピリミジン-6-オン; 4- (1-エチルプロボキシ)

2, 5 ジメチル 6 (2, 4, 6 トリメチルフェノキシ) -ピリミジン; N-ブチル-N-エチル-2, 5-ジメチル-N- (2, 4, 6-トリメチルフェニル) -ピリミジン-4, 6-ジアミン; (1-エチルプロピル) - [5-メチル-3- (2, 4, 6-トリメチルフェニル) -3H-イミダゾ [4, 5-b] ピリジン-7-イル] -アミン; [2, 5 ジメチル 3 (2, 4, 6 トリメチルフェニル) -3H-イミダゾ [4, 5-b] ピリジン-7-イル] - (1-エチルプロピル) -アミン; N4- (1-エチルプロピル) -6, N3-ジメチル-2- (2, 4, 6-トリメチルフェノキシ) -ピリジン-3, 4-ジアミン; N4- (1-エチルプロピル) -6, N3, N3-トリメチル-2 (2, 4, 6 トリメチルフェノキシ) ピリジン 3, 4-ジアミン; 6- (1-エチルプロボキシ) -2-メチル-N4- (2, 4, 6-トリメチルフェニル) -ピリミジン-4, 5-ジアミン; [4- (1-エチルプロボキシ) -3, 6-ジメチル-ピリジン-2-イル] - (2, 4, 6-トリメチルフェニル) -アミン; 及び6- (エチルプロピル-アミノ) -2, 7-ジメチル-9- (2, 4, 6-トリメチルフェニル) -7, 9-ジヒドロプリン-8-オン。

【0019】式I又はIIの化合物は、さらに以下の化合物を含む: ブチル [3, 6 ジメチル 1 (2, 4, 6 トリメチルフェニル) -1H-ピラゾロ [3, 4-b] ピリジン-4-イル] -エチルアミン; 3, 6-ジメチル-4- (テトラヒドロフラン-3-イルオキシ) -1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-b] ピリジン; [3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) 1H ピラゾロ [3, 4 b] ピリジン 4 イル] - (1-メトキシメチルプロピル) -アミン; 4- (1-メトキシメチルプロボキシ) -3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-b] ピリジン; (1-エチルプロピル) - [3, 5, 6-トリメチル-1- (2, 4, 6-トリメチルフェニル) 1H ピラゾロ [3, 4 b] ピリジン 4 イル] アミン; 4- (1-エチルプロボキシ) -2, 5-ジメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-b] ピリジン; 4- (1-エチルプロボキシ) -2, 5, 6-トリメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-b] ピリジン; 4- (1-エチルプロボキシ) 2, 5 ジメチル 7 (2, 6 ジメチル-4-プロモフェニル) -7H-ピロロ [2, 3-b] ピリジン; 3- { (4-メチルベンジル) - [3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル] -アミノ} -ブ

ロパン-1-オール; ジエチル [6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル] -アミン; 2- [ブチル [6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4 d] ピリミジン 4 イル] アミノ} エタノール; ジブチル [6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル] -アミン; ブチル-エチル [6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4 d] ピリミジン 4 イル] アミン; ブチル エチル [6-メチル-3-メチルスルホニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル] -アミン; ブチル-シクロプロピルメチル [6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4 d] ピリミジン 4 イル] アミン; ジ 1 プロピル [6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル] -アミン; ジアリル [6-メチル-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル] -アミン; ブチル-エチル [6-クロロ-3-メチルスルファニル-1- (2, 4, 6-トリクロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル] -アミン; ブチル-エチル [6-メトキシ-3-メチルスルファニル 1 (2, 4, 6 トリクロロフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル] -アミン; プロピル-エチル [3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル] -アミン; 4- (1-エチルプロピル) -6-メチル-3-メチルスルファニル-1 (2, 4, 6 トリメチルフェニル) 1H ピラゾロ [3, 4-d] ピリミジン; 2- [3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イルアミン] -ブタン-1-オール; [3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン-4-イル] (1-メチルプロピル) アミン; 4 (1-メトキシメチルプロボキシ) -3, 6-ジメチル-1- (2, 4, 6-トリメチルフェニル) -1H-ピラゾロ [3, 4-d] ピリミジン; n-ブチル-エチル [2, 5-ジメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミン; ジn-プロピル [2, 5 ジメチル 7 (2, 4, 6 トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミン; エチル-n-プロピル [2, 5-ジメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミン; ジエチル-2, 5-

ジメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミン; n-ブチル-エチル- [2, 5, 6-トリメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミン; 2-[N-n-ブチル-N- [2, 5 ジメチル 7 (2, 4, 6 トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] アミノ] -エタノール; 4- (1-エチル-プロピル) -2, 5, 6-トリメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン; n-ブチル-エチル- [2, 5-ジメチル-7- (2, 4-ジメチルフェニル) 7H ピロロ [2, 3 d] ピリミジン 4 イル] アミン; 2, 5-ジメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン-4-イル] - (1-エチル-プロピル) アミン; 2- [7- (4-ブプロモ-2, 6-ジメチルフェニル) -2, 5-ジメチル-7H-ピロロ [2, 3-d] ピリミジン-4-イルアミノ] -ブタン-1-オール; 2 (S) [7 (4 ブロモ 2, 6-ジメチルフェニル) -2, 5-ジメチル-7H-ピロロ [2, 3-d] ピリミジン-4-イルアミノ] -ブタン-1-オール; 4- (1-エチル-プロボキシ) -2, 5, 6-トリメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン; 4- (1-メトキシメチルプロボキシ) -2, 5, 6-トリメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3-d] ピリミジン; 4- (1-エチル-ブチル) -2, 5, 6-トリメチル-7- (2, 4, 6-トリメチルフェニル) -7H-ピロロ [2, 3 d] ピリミジン; [7 (4 ブロモ 2, 6-ジメチル-フェニル) -2, 5-ジメチル-7H-ピロロ [2, 3-d] ピリミジン-4-イル] - (1-メトキシメチル-プロピル) -アミン; 2- [7- (2-ブプロモ-4, 6-ジメチル-フェニル) -2, 5-ジメチル-7H-ピロロ [2, 3-d] ピリミジン-4-イルアミノ] -ブタン-1-オール; 2 [7 (4 エチル 2, 6 ジメチル フェニル) -2, 5-ジメチル-7H-ピロロ [2, 3-d] ピリミジン-4-イルアミノ] -ブタン-1-オール; 2- [7- (2-エチル-4, 6-ジメチルフェニル) -2, 5-ジメチル-7H-ピロロ [2, 3-d] ピリミジン-4-イルアミノ] -ブタン-1-オール; 及び2- [7- (2-フルオロメチル 4, 6 ジメチルフェニル) 2, 5 ジメチル-7H-ピロロ [2, 3-d] ピリミジン-4-イルアミノ] -ブタン-1-オール。

【0020】CRFアンタゴニストによる、心臓での副交感神経及び交感神経の電気的作用の正常化によるQT分散における改善は、致命的な心室不整脈の発生を減少させる結果になり、そして死亡率の低減の結果になると考えられる。同様に、CRFアンタゴニストは同じメカニズムを介して、心拍変動の改善により死亡率を低減すると考えられる。心拍変動は中間心拍の周囲の揺動 (fluctuations around the mean heart rate) であり、心臓

性呼吸のコントロール系 (cardiorespiratory control system) の相関として用いることができる。低い心拍の変動、即ち副交感神経又は交感神経の何れかの支配は、糖尿病、心疾患及び骨折後 (post-infarction) の患者における、並びに多くの神経障害 (例えば、脳障害、ギランバレー症候群、小児突然死症候群、先天性過換気症候群) 又は尿毒症性神経障害等における突然の心臓死に関係する (例えば、Malpasら、Diabetes, 39: 1177-1181 (1990); Wooら、J. Am. Coll. Cardiol., 23: 565-569 (1994); Biggerら、Circulation, 85: 164-171 (1992); 及びvan Ravenswaaij- ArtsらのAnnals of Internal Medicine, 118: 436-447 (1993)) を参照せよ。)

【0021】CRFアンタゴニストは、多くの疾患において、心臓及び呼吸器系への中樞神経の拍出 (neural outflow) のバランスをとることによって突然死の発生を減じる。リスクのある患者は、心電図QT分散及び心拍変動という手段で、容易かつ安価にモニターされて、そのような治療が有効であるかどうかを決定することができる。

【0022】疾患の状態に加えて、他の症状を緩和するために患者に投与されるある薬物は、QT分散及び/又は心拍変動を引き起こすか、又はそのような結果になりうる。このような薬物の例として、フェノチアジン及び非特異的抗精神病薬 (例えば、クロルプロマジン、レスピラドン)、クラスIA及びクラスIII不整脈薬 (例えば、キニジン及びソトロール)、並びに麻酔薬 (例えば、エンフルラン、イソフルラン) 等を挙げることができる。このような場合もまた、心臓における副交感神経及び交感神経の電気的作用を正常化し、患者のQT分散及び心拍変動を改善するために、CRFアンタゴニストを投与することが有効であると考えられる。

【0023】CRFアンタゴニストは単独で、特定の患者における突然死を減じる一方で、CRFアンタゴニストを他の薬物と組み合わせることも好ましいと考えられる。例えば、心臓及び/又は呼吸器系への神経の拍出のバランスをとることができる他の薬物は、CRFアンタゴニストの有効性を相互作用によって改善しうる。

【0024】本発明の方法において使用するための好ましい式I及びIIの化合物、並びにそれらの医薬として許容できる塩は、容易に製造することができる。式IIの化合物 (A、D、及びYはNであり、二重結合でEとDとが結合し、Eが-CR₄である) は、上記のPCT公開W094/13677に記載された1又はそれ以上の合成方法によって製造できる。式IIの化合物 (A及びYはNであり、二重結合でEとDとが結合し、Eが-CR₄であり、Dが-CR₁₀である) は、上記のPCT公開W094/13676に記載された1又はそれ以上の合成方法によって製造できる。式IIの化合物 (Aが-CR₇であり、二重結合でEとDとが結合し、Eが-CR₄であり、D及びNが-CR₁₀であり、YがNである) は、上記のPC

T公開W095/34563に記載された1又はそれ以上の合成方法によって製造できる。式IIの他の化合物及び式Iの化合物は、上記のPCT公開W095/33750に記載された1又はそれ以上の合成方法によって製造できる。好ましい化合物のあるものの製造に関する更なる有用な情報は、PCT/IB95/00437（公開番号W096/39388）中に与えられている。これは特定の中間体の生産を記載するものである。

【0025】式I又はIIの化合物の医薬として許容できる塩は、酸性又は塩基性の基の塩を含む。例えば、医薬として許容できる塩は、 R_1 置換基がカルボキシである場合のような酸性の基の、ナトリウム、カルシウム又はカリウム塩を含む。そのような塩は、一般的には式I又はIIの化合物の1を、適当な溶媒中で、1モル等量のNaOH又はKOHと組み合わせることにより製造される。アミノ基のような塩基性の基の医薬として許容できる酸付加塩は、式I又はIIの化合物の塩基形態のものと適当な酸を反応させることにより形成される。塩基性の基の医薬として許容できる塩は、塩酸塩、シュウ酸塩、硫酸塩、リン酸塩、リン酸水素塩、リン酸二水素塩、酢酸塩、コハク酸塩、クエン酸塩、酒石酸塩、乳酸塩、マンデル酸塩、メタンスルホン酸（メシラート；mesylate）塩及びp-トルエンスルホン酸（トシラート；tosylate）塩等を含む。1価の酸の塩（例えば、塩酸塩、シュウ酸塩、p-トルエンスルホン酸塩、酢酸塩）の場合、少なくとも1モル等量、そして通常はモル過剰の酸を用いる。しかし、そのような塩が、硫酸塩、ヘミコハク酸塩（hemisuccinate）、リン酸水素塩又はリン酸塩として所望される場合、一般的には適切かつ正確な化学等量の酸が用いられる。

【0026】フリーの塩基及び酸は、通常、所望の塩の沈殿が期待できる共溶媒中で組み合わせられ、そうでなければ濃縮するか又は非溶媒を添加することによって単離される。

【0027】本明細書において3～8員のシクロアルキル環、又は9～12員のビスシクロアルキル環システムに言及するときは、それらの各々は所望により1又は2個のO、S、又はN-Gを有してもよく、シクロアルキル環又はビスシクロアルキル環システムにおいては酸素及び硫黄原子が互いに結合しないことが理解される。シクロアルキル環が3員であるとき、1個のO、S又はN-Gを含んでもよい。例えば、O及びNHを有する6員のシクロアルキル環は、モルホリニルである。 R_2 又は R_5 がヘテロサイクリック基である場合、基は、1個の炭素原子を介して連結することができる。

【0028】上記の式I及びIIには、表される群類に含まれるすべての化合物のラセミ体及びすべての立体異性体（例えば、すべての幾何異性体、及びすべての光学異性体）が含まれることが意図されている。

【0029】本発明の方法においては、式I及びIIの化

合物、並びにそれらの医薬として許容できる塩は、単独で又は医薬として許容できるキャリアと組み合わせられて、単回又は複数回の何れかで投与される。好ましい医薬として許容できるキャリアは、不活性固体希釈剤又は充填剤、滅菌水性溶液、及び種々の有機溶媒を含む。そして、活性化合物及び医薬として許容できるキャリアとの組み合わせにより形成された医薬組成物は、種々の投与型、例えば、錠剤、粉末剤、トローチ剤（lozenge）、シロップ剤、注射用液剤等で容易に投与される。これらの医薬組成物は、適切であれば、芳香剤、結合剤、賦形剤等を含みうる。そして、経口投与の目的のためには、錠剤は、クエン酸ナトリウム、炭酸カルシウム及びリン酸カルシウムのような種々の賦形剤を含むことができ、でんぷん、アルギン酸及び特定の複合ケイ酸塩のような種々の崩壊剤と、ポリビニルピロリドン、ショ糖、ゼラチン及びアラビアゴムのような結合剤とを一緒に含んでもよい。加えて、ステアリン酸マグネシウム、ラウリル硫酸ナトリウム及びタルクのような滑剤は、錠剤化の目的のためにしばしば有用である。同一タイプの固体組成物はまた、軟質及び硬質ゼラチンカプセル中に充填物として用いることができる。これは、好ましくはラクトース（乳糖）及び高分子量のポリエチレングリコールを含む。水性懸濁剤又はエリキシル剤が経口投与のために求められるときは、水、エタノール、プロピレングリコール、グリセリン及びそれらの組み合わせのような希釈剤とともに、その剤の中の本質的な活性成分は、種々の甘味剤又は芳香剤、着色料又は染料及び、望ましければ、乳化剤又は懸濁化剤と組み合わせることができる。一般的には経口投与が好ましい。しかし、患者が嚥下することができないとき、又はそれ以外の理由で経口投与に支障があるときは、直腸、腸管外（parenteral）又は局所投与のような他の投与経路が適するであろう。

【0030】腸管外投与のためには、ゴマ油若しくは落花生油、水溶性プロピレングリコール又は滅菌水溶液中に溶解した活性成分の液剤を用いることができる。そのような液剤は、必要であれば緩衝化することが好ましく、また、そのような液体は最初に充分な塩類又はグルコース等で等張化する。このような特別の液剤は、静脈中、筋中、皮下又は腹腔内に投与するのに特に好ましい。用いられる滅菌水性溶媒は当業者に知られた標準的な技術によって得ることができる。

【0031】経皮的（例えば局所）投与の目的のためには、希釈され、滅菌された水性又は部分的に水性の液剤（通常約0.1%～5%濃度）、そうでなければ上記の腸管外投与用液剤と同様のものを用いることができる。

【0032】ある量の活性成分を有する種々の医薬組成物の製造方法は、当業者に知られており、又は本明細書の開示により明らかである。他には、例えば、Remington's Pharmaceutical Sciences、Mack Publishing社、Eaton, Pa.、第15版（1975）を参照せよ。

【 0 0 3 3 】本発明の方法において、式I及びIIの化合物並びにそれらの医薬として許容できる塩の効果的な投与量は、医者には一般的に知られているように、意図する投与経路及び他の要素（例えば、患者の年齢及び体重）に依存する。一般的には、一日あたりの投与量は、約0.1mg/kg～約50mg/kg（治療されるべき患者の体重）が好ましい。より好ましくは、一日あたりの投与量は、約1.0mg/kg～約20mg/kg（体重）である。この一日あたりの投与量は、単回又は分割投与により与えることができる。

【 0 0 3 4 】式I及びIIの化合物並びにそれらの医薬として許容できる塩の、CRFアンタゴニスト活性の検定方法は、Wynnら、Endocrinology、116：1653-1659（1985）及びGrigoriadisら、Peptides、10：179-188（1989）に記載されている。これらの方法は、試験されるされる化合物のCRF受容体に対する結合親和性（CRFアンタゴニストとして期待される活性に非常に関係がある）を測定するものである。IC₅₀値として表現される活性化合物の結合親和性は、概して、約0.2ナノモル濃度～約10マイクロモル濃度である。

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(54) Title: CRF RECEPTOR ANTAGONISTS, THEIR PREPARATIONS, THEIR PHARMACEUTICAL COMPOSITION AND
THEIR USES

(57) Abstract: CRF receptor antagonists are disclosed which have utility in the treatment of a variety of disorders, including the
treatment of disorders manifesting hypersecretion of CRF in a warm-blooded animals. CRF receptor antagonists which are labeled
with a positron emitting isotope for use in PET are also disclosed.



CRF RECEPTOR ANTAGONISTS, THEIR PREPARATION, THEIR PHARMACEUTICAL COMPOSITION AND THEIR USES

TECHNICAL FIELD

5 This invention relates generally to CRF receptor antagonists their preparation, their pharmaceutical composition and their uses. CRF receptor antagonists are disclosed which have utility in the treatment of a variety of disorders, including the treatment of disorders manifesting hypersecretion of CRF in a warm-blooded animals. CRF receptor antagonists which are labeled with a positron emitting isotope for use in
10 PET are also disclosed.

BACKGROUND OF THE INVENTION

 Positron Emission Tomography (PET) is a non-invasive imaging technology where a compound labeled with a positron-emitting isotope is administered to provide an in-situ image of the binding of the positron-emitting compound. The image
15 can be used to determine localization and quantification of specific areas where the labeled compound binds providing diagnostic and drug discovery applications. Positron emitting isotopes generally used for PET include ^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{76}Br and ^{124}I . The ^{13}N and ^{15}O isotopes have very short half lives limiting their usefulness. ^{76}Br and ^{124}I have half lives of 16.3 hours and 4.2 days respectively which would allow easy production of
20 labeled CRF antagonists but the addition of the large halogen group changes the activity of the compound and adds unwanted lipophilicity. ^{11}C has a relatively short 20.5 minute half life but ease of incorporating ^{11}C into a PET compound makes this a useful isotope. ^{18}F has a half life of 110 minutes which allows sufficient time for incorporation of the isotope into a tracer, purification and administration into a subject.

25 The incorporation of a positron emitting isotope into a Corticotropin-releasing factor (CRF) antagonist may allow for the use of PET imaging in determining the binding of labeled antagonists to CRF receptors. CRF is a 41 amino acid peptide which has been found to produce profound alterations in endocrine, nervous and immune

system function. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotrophic hormone ("ACTH"), β -endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (Vale et al., *Science* 213:1394-1397, 1981). The CRF receptor is coupled to a GTP-binding protein
5 (Perrin et al., *Endocrinology* 118:1171-1179, 1986) which mediates CRF-stimulated increase in intracellular production of cAMP (Bilezikjian, L.M., and W.W. Vale, *Endocrinology* 113:657-662, 1983). In addition to its role in stimulating the production of ACTH and POMC, CRF is also believed to coordinate many of the endocrine, autonomic, and behavioral responses to stress, and may be involved in the
10 pathophysiology of affective disorders. Moreover, CRF is believed to be a key intermediary in communication between the immune, central nervous, endocrine and cardiovascular systems (Crofford et al., *J. Clin. Invest.* 90:2555-2564, 1992; Sapolsky et al., *Science* 238:522-524, 1987; Tilders et al., *Regul. Peptides* 5:77-84, 1982). Overall, CRF appears to be one of the pivotal central nervous system neurotransmitters and plays
15 a crucial role in integrating the body's overall response to stress.

Administration of CRF directly to the brain elicits behavioral, physiological, and endocrine responses identical to those observed for an animal exposed to a stressful environment. For example, intracerebroventricular injection of CRF results in behavioral activation (Sutton et al., *Nature* 297:331, 1982), persistent activation of the
20 electroencephalogram (Ehlers et al., *Brain Res.* 278:332, 1983), stimulation of the sympathoadrenomedullary pathway (Brown et al., *Endocrinology* 110:928, 1982), an increase of heart rate and blood pressure (Fisher et al., *Endocrinology* 110:2222, 1982), an increase in oxygen consumption (Brown et al., *Life Sciences* 30:207, 1982), alteration of gastrointestinal activity (Williams et al., *Am. J. Physiol.* 253:G582, 1987), suppression
25 of food consumption (Levine et al., *Neuropharmacology* 22:337, 1983), modification of sexual behavior (Sirinathsinghji et al., *Nature* 305:232, 1983), and immune function compromise (Irwin et al., *Am. J. Physiol.* 255:R744, 1988). Furthermore, clinical data suggests that CRF may be hypersecreted in the brain in depression, anxiety-related disorders, and anorexia nervosa. (DeSouza, *Ann. Reports in Med. Chem.* 25:215-223,
30 1990). Accordingly, clinical data suggests that CRF receptor antagonists may represent

novel antidepressant and/or anxiolytic drugs that may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF.

The administration of CRF antagonist which has been labeled with a positron emitting isotope may permit the use of PET imaging to provide an in situ
 5 evaluation of the labeled antagonist's binding characteristics in the brain. The antagonist should possess several characteristics such as specific binding to CRF receptors, high brain penetration and the ability to be labeled with a positron emitting isotope as the ultimate step in the synthesis.

U.S. Patent Nos. 6,514,982, 6,531,475, 6,664,261 and PCT application
 10 WO98/03510 describe CRF antagonists for use in treating various CRF mediated diseases. The synthesis of certain pyrrolopyrimidines as PET ligands for the CRF receptor has also been described. (L. Martarello et al., *Nuclear Medicine and Biology*, **28** (2001) 187-195).

While significant strides have been made toward achieving CRF
 15 regulation through administration of CRF receptor antagonists, there remains a need in the art for effective small molecule CRF receptor antagonists. There is also a need for pharmaceutical compositions containing such CRF receptor antagonists, as well as methods relating to the use thereof to treat, for example, stress-related disorders. The use of CRF antagonists bearing a Positron emitting isotope as diagnostic and drug
 20 discovery tools is also addressed. The present invention fulfills these needs, and provides other related advantages.

SUMMARY OF THE INVENTION

In brief, this invention is generally directed to CRF receptor antagonists
 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-
 25 dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-
 a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(*S*)-
 methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-
 dimethoxyphenyl)-7-(*N*-ethyl-*N*-{2-fluoroethyl} amino)pyrazolo[2,3-a]pyrimidine and 6-
 (cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-(*S*)-ethyl-7,8-dihydro-4-methyl-6H-

1,3,6,8a-tetraazaacenaphthylene, including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof.

The CRF receptor antagonists of this invention may be radiolabeled and have utility as diagnostic agents, research agents and agents useful in drug development and evaluation. These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain procedures, compounds and/or compositions, and are hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to compounds useful as corticotropin-releasing factor (CRF) receptor antagonists and as PET ligands.

In a first embodiment, the CRF receptor antagonists of this invention are taken from 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(*S*)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-{2-fluoroethyl}amino)pyrazolo[2,3-a]pyrimidine and 6-(cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-(*S*)-ethyl-7,8-dihydro-4-methyl-6H-1,3,6,8a-tetraazaacenaphthylene.

In another embodiment, the CRF antagonist is labeled with a positron emitting isotope to allow for imaging of the antagonist by PET. The isotope is generally taken from ^{11}C and ^{18}F as these isotopes may generally be added as the last step of a synthesis, may be purified quickly and may be administered to a subject, generally in intravenous form.

The compounds of the present invention may generally be utilized as the free base. Alternatively, the compounds of this invention may be used in the form of acid addition salts. Acid addition salts of the free base amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic,

ascorbic, succinic, methanesulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Thus, the term "pharmaceutically acceptable salt" of structure (I) is intended to encompass any and all acceptable salt forms.

In general, the compounds of the present invention may be made according to the organic synthesis techniques known to those skilled in this field, as well as by the representative methods set forth in the Examples.

The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention are capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of the present invention may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (*J. Neuroscience* 7:88, 1987) and Battaglia et al. (*Synapse* 1:572, 1987). As mentioned above, suitable CRF antagonists include compounds which demonstrate CRF receptor affinity. CRF receptor affinity may be determined by binding studies that measure the ability of a compound to inhibit the binding of a radiolabeled CRF (e.g., [¹²⁵I]tyrosine-CRF) to its receptor (e.g., receptors prepared from rat cerebral cortex membranes). The radioligand binding assay described by DeSouza et al. (*supra*, 1987) provides an assay for determining a compound's affinity for the CRF receptor. Such activity is typically calculated from the IC₅₀ as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the receptor, and is reported as a "K_i" value calculated by the following equation:

$$K_i = \frac{IC_{50}}{1 + L / K_D}$$

where L = radioligand and K_D = affinity of radioligand for receptor (Cheng and Prusoff, *Biochem. Pharmacol.* 22:3099, 1973).

In addition to inhibiting CRF receptor binding, a compound's CRF receptor antagonist activity may be established by the ability of the compound to

antagonize an activity associated with CRF. For example, CRF is known to stimulate various biochemical processes, including adenylate cyclase activity. Therefore, compounds may be evaluated as CRF antagonists by their ability to antagonize CRF-stimulated adenylate cyclase activity by, for example, measuring cAMP levels. The
5 CRF-stimulated adenylate cyclase activity assay described by Battaglia et al. (*supra*, 1987) provides an assay for determining a compound's ability to antagonize CRF activity. Accordingly, CRF receptor antagonist activity may be determined by assay techniques which generally include an initial binding assay (such as disclosed by DeSouza (*supra*, 1987)) followed by a cAMP screening protocol (such as disclosed by Battaglia (*supra*,
10 1987)).

The CRF receptor antagonists of the present invention demonstrate activity at the CRF receptor site, and may be used as therapeutic agents for the treatment of a wide range of disorders or illnesses including endocrine, psychiatric, and neurological disorders or illnesses. More specifically, the CRF receptor antagonists of
15 the present invention may be useful in treating physiological conditions or disorders arising from the hypersecretion of CRF. Because CRF is believed to be a pivotal neurotransmitter that activates and coordinates the endocrine, behavioral and automatic responses to stress, the CRF receptor antagonists of the present invention can be used to treat neuropsychiatric disorders. Neuropsychiatric disorders which may be treatable by
20 the CRF receptor antagonists of this invention include affective disorders such as depression; anxiety-related disorders such as generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, cardiovascular abnormalities such as unstable angina and reactive hypertension; and feeding disorders such as anorexia nervosa, bulimia, and irritable bowel syndrome. CRF antagonists may also be useful in
25 treating stress-induced immune suppression associated with various diseases states, as well as stroke. Other uses of the CRF antagonists of this invention include treatment of inflammatory conditions (such as rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and G.I. motility), pain, Cushing's disease, infantile spasms, epilepsy and other seizures in both infants and adults, and various substance abuse and withdrawal
30 (including alcoholism).

Additional uses of the PET labeled CRF receptor antagonists of the present invention include use in clinical research and diagnosis of various disease states involving the CRF receptor. The labeled CRF receptor antagonists may also be useful in the study of pharmacology, drug pharmacokinetics, pharmacodynamics, biodistribution and metabolism (Victor Pike, *Drug Information Journal*, **31** (1997), 997-1013).

In another embodiment of the invention, pharmaceutical compositions containing one or more CRF receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a CRF receptor antagonist of the present invention (*i.e.*, a compound of structure (I)) and a pharmaceutically acceptable carrier and/or diluent. The CRF receptor antagonist is present in the composition in an amount which is effective to treat a particular disorder--that is, in an amount sufficient to achieve CRF receptor antagonist activity, and preferably with acceptable toxicity to the patient. Preferably, the pharmaceutical compositions of the present invention may include a CRF receptor antagonist in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more preferably from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a CRF receptor antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the CRF receptor antagonist in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, PA 1990.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (I) in

vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound.

In another embodiment, the present invention provides a method for
5 treating a variety of disorders or illnesses, including endocrine, psychiatric and neurological disorders or illnesses. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the disorder or illness. Such methods include systemic administration of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition. As
10 used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of CRF receptor antagonists include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other
15 pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions which may contain, in addition to the CRF receptor antagonist, buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

20 As mentioned above, administration of a compound of the present invention can be used to treat a wide variety of disorders or illnesses. In particular, the compounds of the present invention may be administered to a warm-blooded animal for the treatment of depression, anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, unstable angina, reactive hypertension, anorexia nervosa,
25 bulimia, irritable bowel syndrome, stress-induced immune suppression, stroke, inflammation, pain, Cushing's disease, infantile spasms, epilepsy, and substance abuse or withdrawal.

The following examples are provided for purposes of illustration, not limitation.

EXAMPLES

The CRF receptor antagonists of this invention may be prepared by the methods disclosed in Examples 1 to 4. Example 5 presents a method for determining the receptor binding affinity.

5 Analytical HPLC-MS (LC-MS)

HP 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (electrospray);

HPLC column: YMC ODS AQ, S-5, 5 μ , 2.0 x50 mm cartridge;

10 HPLC gradients: 1.5 mL/minute, from 10 % acetonitrile in water to 90 % acetonitrile in water in 2.5 minutes, maintaining 90 % for 1 minute.

Prep. HPLC-MS

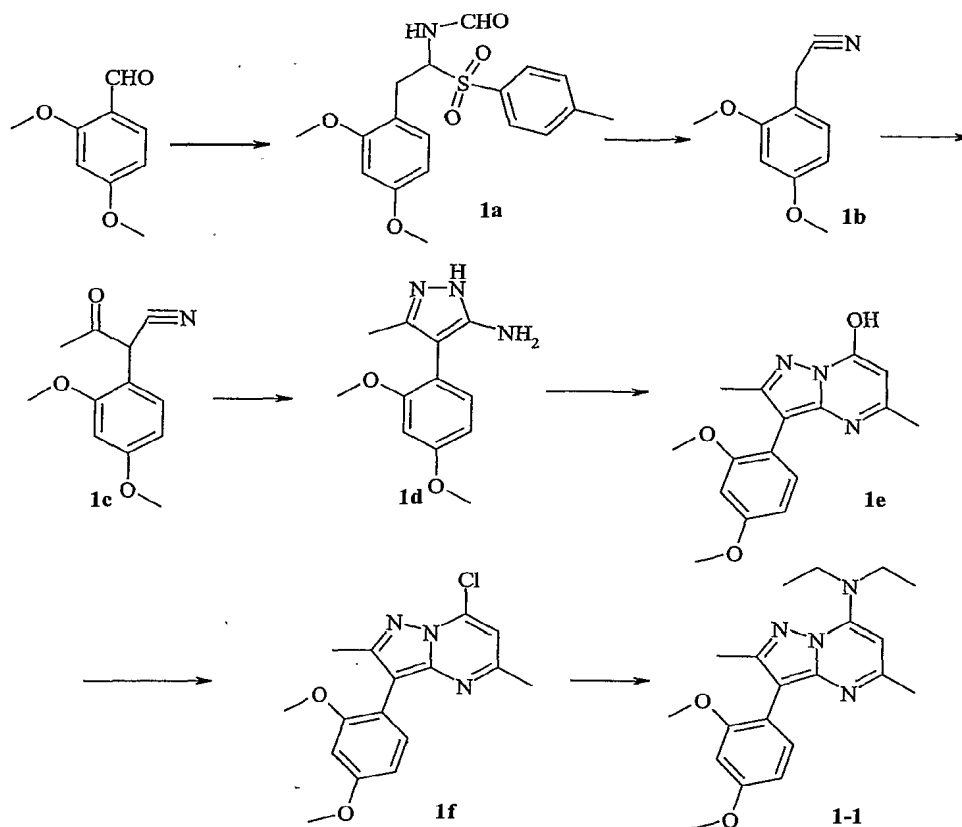
Gilson HPLC-MS equipped with Gilson 215 auto-sampler/fraction collector, an UV detector and a ThermoFinnigan AQA Single QUAD Mass detector (electrospray);

15 HPLC column: BHK ODS-O/B, 5 μ , 30x75 mm

HPLC gradients: 35 mL/minute, 10 % acetonitrile in water to 100 % acetonitrile in 7 minutes, maintaining 100 % acetonitrile for 3 minutes.

20

EXAMPLE 1

**Step 1A:**

- A suspension of potassium *t*-butoxide (7.3 g, 65 mmol, 1.4 eq) in 1,2-dimethoxyethane (DME, 40 mL) was chilled to -50°C under nitrogen. Tosylmethyl isocyanide (9.1 g, 46.5 mmol, 1 eq) in 40 mL DME was added dropwise while the temperature was kept below -50°C . 2,4-Dimethoxybenzaldehyde (7.7 g, 46.5 mmol, 1 eq) was added dropwise and the reaction mixture was stirred for 30 minutes to give compound **1a**. MeOH (100 mL) was added and the mixture was refluxed for 30 minutes.
- Most of the DME and MeOH were removed, the residue was resuspended in water (100 mL) and ethyl acetate (100 mL). Following neutralization with acetic acid, the organic layer was washed with brine and dried under sodium sulfate, concentrated and purified by silica gel column using 25% ethyl acetate in hexane to yield 5.5 g of **1b** as a white solid.

Step 1B:

To 2, 4-dimethoxyphenylacetonitrile **1b** (36.0 g, 204 mmol, 1 equiv.) in dry THF (300 mL) was added 12 g (510 mmol, 2.5 equiv) of 60% NaH portionwise. A few drops of EtOAc were added and the reaction was heated gently to initiate the reaction. The remaining EtOAc (150 mL) was then added dropwise. After 2 hours the reaction was poured into ice water and was washed with ether. The aqueous layer was acidified to pH = 6 and was extracted with EtOAc, dried over MgSO₄, filtered and concentrated in vacuo to give 44.2 g of **1c**.

10 Step 1C:

A mixture of **1c** (8.17 g, 37.3 mmol) and hydrazine monohydrobromide (15.3 g, 135.4 mmol) was refluxed in EtOH/H₂O (6:1) for 5 h. After evaporation of EtOH, the residue was extracted with EtOAc and water. The organic phase was dried and evaporated to dryness to give **1d**.

15 Step 1D:

A mixture of the compound **1d** (6.5 g, 27.9 mmol) was refluxed with ethyl acetoacetate (5.0 mL) in acetic acid (100 mL) for 3 h. After evaporation of AcOH, ethyl ether was added and **1e** (10.4 g) was obtained after filtration through a medium fritted funnel. In place of the acetic acid solvent, the reaction may be refluxed in dioxane (50 mL) overnight followed by addition of ether to precipitate the product.

Step 1E:

To a suspension of compound **1e** (1.9 g, 6.3 mmol) in acetonitrile was added POCl₃ (2.2 mL, 24.1 mmol). The suspension was heat to reflux for 5 h. The resulting orange solution was cooled to room temperature and poured onto ice-water. After extraction with EtOAc, compound **1f** was obtained by column chromatography purification (1.70 g, 85%).

Step 1F:

Compound **1f** (30 mg) and excess diethylamine in acetonitrile (0.8 mL) were heated at 160 °C with a microwave for 16 min. Purification with a Sciex2 prep LC-MS system

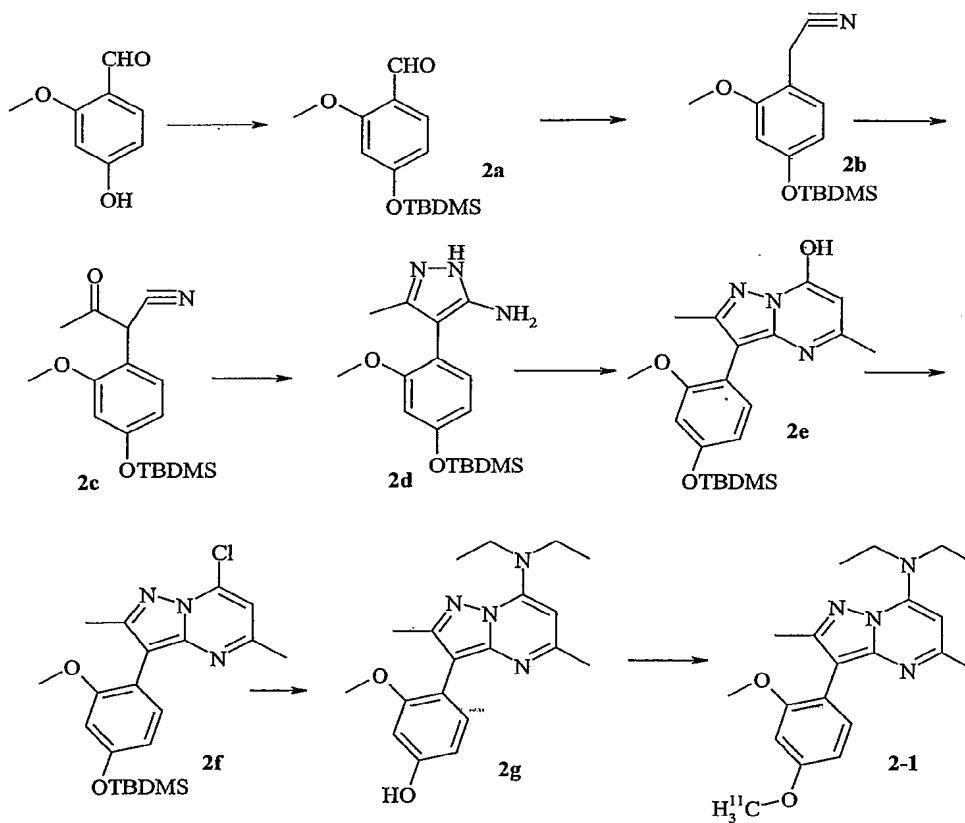
gave 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine 1-1. LCMS 355 (MH^+), FW = 354.45

Following the same general procedure the following compounds were also synthesized:

2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine. LCMS 385 (MH^+), FW = 384.48;

2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(*S*)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine. LCMS 396 (MH^+), FW = 396.49.

EXAMPLE 2



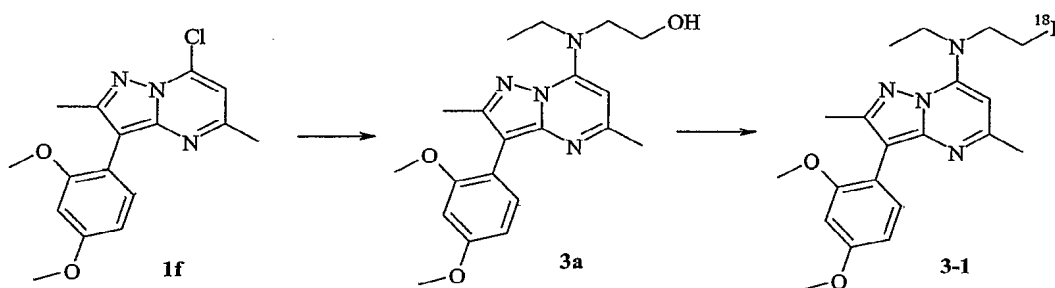
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Step 2A:

2-Hydroxy-4-methoxybenzaldehyde is protected by reaction with tert-butyldimethylsilyl chloride (TBDMSCl) and imidazole in DMF to give the tert-

butyldimethylsilyl ether **2a**. Using **2a** and following the procedure as outlined in steps 1A to 1E, compound **2f** is realized. **2f** and diethylamine following the procedure of Step 1F followed by deprotection of the tert-butyldimethylsilyl group with tetrabutylammonium fluoride or acid under standard conditions gives **2g**. Alkylation of the hydroxy group of **2g** with ^{11}C methyl iodide and sodium hydride in solvent such as DMF or acetonitrile gives **2-1**.

EXAMPLE 3



10 Step 3A:

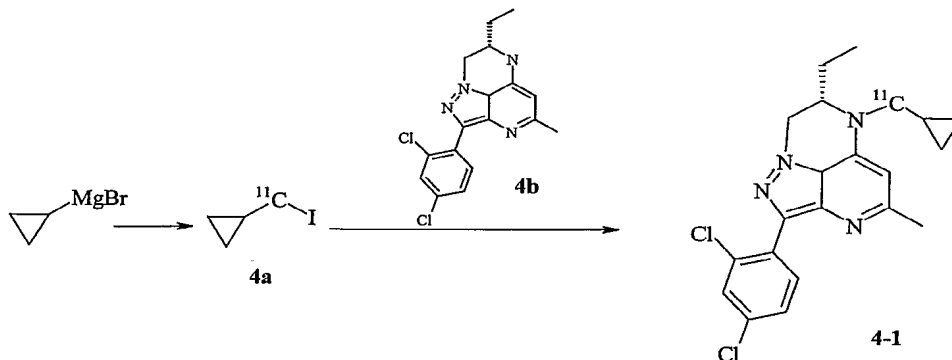
Compound **1f** and ethylaminoethanol following the procedure of Step 1F gives **3a**.

Step 3B:

Compound **3a** is converted to the sulfonate ester such as mesylate, tosylate or triflate followed by reaction with ^{18}F ion to give **3-1** (L. Martarello et al., Nuclear Medicine and Biology **28** (2001) 187-195). Compound **3a** and methanesulfonyl chloride in pyridine yields a mesylate which undergoes a nucleophilic substitution with K^{18}F to give **3-1** which is purified by HPLC.

EXAMPLE 4

6-(CYCLOPROPYLMETHYL)-2-(2,4-DICHLOROPHENYL)-7-(S)-ETHYL-7,8-DIHYDRO-4-METHYL-6H-1,3,6,8A-TETRAAZAACENAPHTHYLENE



5

Step 4A:

According to the general procedure of Ishiwata et al., *Appl. Radiat. Isot.*, 46, 10: 1009-1013, cyclopropyl-[¹¹C]-methyl iodide is prepared. [¹¹C]CO₂ is transferred into a solution of cyclopropyl magnesium bromide in THF at 0 – 5 °C, followed by immediate reduction with lithium aluminum hydride. Hydroiodic acid is added, the mixture is heated to give **4a** after purification.

Step 4B:

Compound **4b** (synthesized according to various procedures in U.S. Patent No. 6,531,475) is alkylated with compound **4a** using standard conditions such as sodium hydride, sodium methoxide or cesium carbonate in a solvent such as DMF followed by purification by HPLC to give **4-1**.

EXAMPLE 5

CRF RECEPTOR BINDING ACTIVITY

The compounds of this invention may be evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by

Grigoriadis et al. (*Mol. Pharmacol* vol50, pp679-686, 1996) and Hoare et al. (*Mol. Pharmacol* vol63 pp751-765, 2003.) By utilizing radiolabeled CRF ligands, the assay may be used to evaluate the binding activity of the compounds of the present invention with any CRF receptor subtype.

5 Briefly, the binding assay involves the displacement of a radiolabeled CRF ligand from the CRF receptor. More specifically, the binding assay is performed in 96-well assay plates using 1-10 μ g cell membranes from cells stably transfected with human CRF receptors. Each well receives about 0.05 ml assay buffer (*e.g.*, Dulbecco's phosphate buffered saline, 10 mM magnesium chloride, 2mM EGTA) containing
10 compound of interest or a reference ligand (for example, sauvagine, urocortin I or CRF), 0.05 ml of [¹²⁵I] tyrosine - sauvagine (final concentration ~150 pM or approximately the K_D as determined by Scatchard analysis) and 0.1 ml of a cell membrane suspension containing the CRF receptor. The mixture is incubated for 2 hours at 22 °C followed by separation of the bound and free radioligand by rapid filtration over glass fiber filters.
15 Following three washes, the filters are dried and radioactivity (Auger electrons from ¹²⁵I) is counted using a scintillation counter. All radioligand binding data may be analyzed using the non-linear least-squares curve-fitting programs Prism (GraphPad Software Inc) or XLfit (ID Business Solutions Ltd).

20

It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

25

CLAIMS

1. A compound taken from 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(*S*)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine, and 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-{2-fluoroethyl} amino)pyrazolo[2,3-a]pyrimidine.
2. A compound taken from 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(*S*)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-{2-fluoroethyl} amino)pyrazolo[2,3-a]pyrimidine and 6-(cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-(*S*)-ethyl-7,8-dihydro-4-methyl-6H-1,3,6,8a-tetraazaacenaphthylene for use as PET ligands.
3. A composition comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier or diluent.
4. A method for treating a disorder manifesting hypersecretion of CRF in a warm-blooded animal comprising administering to the animal an effective amount of the pharmaceutical composition of claim 3.
5. The method of claim 4 wherein the disorder is depression.
6. The method of claim 4 wherein the disorder is an anxiety-related disorder.
7. The method of claim 4 wherein the disorder is irritable bowel syndrome.
8. A composition comprising a compound of claim 2 in combination with a pharmaceutically acceptable carrier or diluent.



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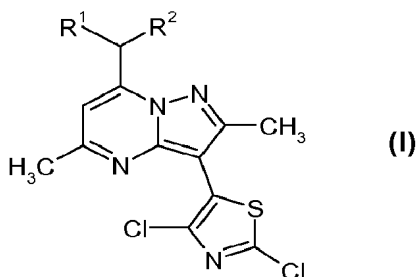
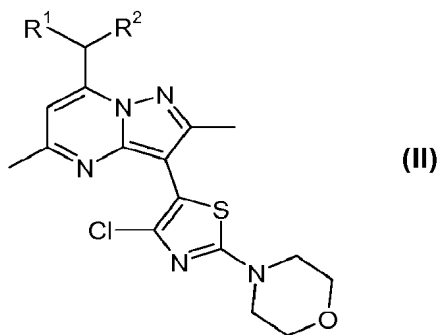
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(54) Title: THIAZOLYL-PYRAZOLOPYRIMIDINE COMPOUNDS AS SYNTHETIC INTERMEDIATES AND RELATED SYNTHETIC PROCESSES

(57) Abstract: The present invention relates to a synthetic intermediate of the formula (I) and its use in a synthetic process to make compounds of the formula (II).





GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

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THIAZOLYL-PYRAZOLOPYRIMIDINE COMPOUNDS AS SYNTHETIC
INTERMEDIATES AND RELATED SYNTHETIC PROCESSES

This invention relates to novel intermediates and processes in the synthesis of
5 thiazolyl-pyrazolopyrimidine compounds, which final compounds are useful as CRF-1
receptor antagonists for the treatment of certain psychiatric and neuroendocrine disorders.

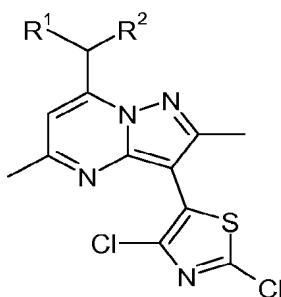
Corticotropin releasing factor (CRF) is a peptide hypothalamic hormone which
also has a broad spectrum of physiological effects consistent with a neurotransmitter or
neuromodulator role in the brain. CRF has been implicated in a wide range of psychiatric
10 disorders and neurological diseases including alcohol and substance abuse and associated
withdrawal symptoms, as well as depression and anxiety. CRF-1 receptor antagonists
have particularly been implicated for the treatment of alcohol dependency and depression.

Certain thiazolyl-pyrazolo[1,5-*a*]pyrimidines have been found to be particularly
useful as CRF-1 antagonists, as for example 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-
15 4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine and 7-(1-propyl-butyl)-3-(4-
chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine, as
described in WO 2008/036579. Recent advances in copper catalyzed arylation reactions
with different substrates have been described in J. Am. Chem. Soc., vol. 130, pg. 1128-
1129 (2008).

20 The present invention provides novel synthetic intermediates and synthetic
processes using said intermediates to make thiazolyl-pyrazolo[1,5-*a*]pyrimidine CRF-1
receptor antagonists more economically and in higher yields. Certain embodiments of the
presently claimed processes also avoid the use of mutagenic materials and
environmentally toxic catalysts, as compared to previously known synthetic methods, as
25 for example, those disclosed in WO 2008/036579.

In one aspect of the present invention, there is provided a compound of Formula I

2



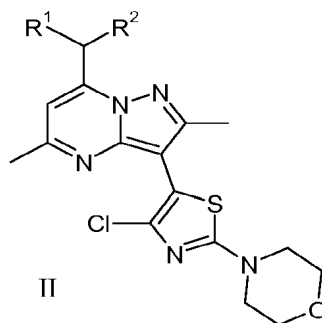
Formula I

wherein:

R^1 and R^2 are independently ethyl or *n*-propyl.

5 In one preferred embodiment, R^1 and R^2 are each ethyl. In a second preferred embodiment, R^1 and R^2 are each *n*-propyl.

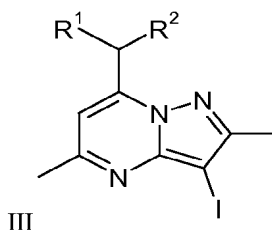
In another aspect of the present invention, there is provided a synthetic process for preparing a compound of the Formula II



II

10 wherein R^1 and R^2 are independently ethyl or *n*-propyl, comprising the steps of

i) reacting a compound of Formula III,



III

15 or a salt thereof, with 2,4-di-chlorothiazole, or a salt thereof, in the presence of a copper halide catalyst, a ligand selected from 1,10-phenanthroline and bipyridine,

and a base selected from K_3PO_4 and Cs_2CO_3 , to form a compound of Formula I (above); and

ii) reacting the compound of Formula I, with morpholine, or a salt thereof, in the presence of a suitable inorganic base.

5

In one preferred embodiment of this aspect of the invention, R^1 and R^2 are each ethyl. In a second preferred embodiment of this aspect of the invention, R^1 and R^2 are each *n*-propyl.

Suitable copper halide catalysts include CuI, CuBr, and CuCl. CuCl is preferred.

10

Use of a copper ligand facilitates the efficient catalysis by the copper ion. Both 1,10-phenanthroline and bipyridine are effective ligands in the present process. 1,10-phenanthroline is preferred. When bipyridine is used, higher mole percents of bipyridine and copper are needed for high yields, as for example from about 0.9 to about 1.1 equivalents, say about 1 equivalent bipyridine, and from about 0.5 to about 1.1 equivalents of the copper source, say about 1 equivalent of the copper source, with CuCl being preferred.

15

When 1,10-phenanthroline is used, it may be effectively used in catalytic amounts, and with catalytic amounts of the copper source, as for example from about 5-50 mole percent each (0.05-0.50 equivalents), with CuCl being the preferred copper source. In one embodiment, the 1,10-phenanthroline and the copper catalyst, say CuCl, are used at about 5-50 mole percent (0.05-0.50 equivalents). In another embodiment, the 1,10-phenanthroline and the copper catalyst, say CuCl, are used at about 10 ± 1 mole percent (0.10 equivalents). In yet another embodiment, the 1,10-phenanthroline and the copper catalyst, say CuCl, are used at about 30 ± 1 mole percent (0.30 equivalents).

20

The reaction of step i) is base driven and is sensitive to the base selected. The dichlorothiazole reagent is base and temperature labile and is susceptible to degradation if the selected base is too strong and/or the reaction temperature is too high, as for example with *t*-butoxy lithium or *t*-butoxy potassium and/or at temperatures higher than about 120° C. As such, suitable bases for step i) are K_3PO_4 and Cs_2CO_3 , with Cs_2CO_3 being preferred. Likewise, it is preferred that the reaction of step i) be run at a temperature of from about 80 to 120° C.

30

The reaction of step i) is less sensitive to the solvent selected with suitable solvents being aprotic solvents, as for example 1,4-dioxane, 2-MeTHF, DMAC, CPME, propanenitrile, 2-MeTHF/DMAC, *n*-BuOAc and DMF. The co-solvent system of 2-MeTHF/DMAC with proportions in the range of 70/30 to 80/20 being preferred, as for example 80/20 2-MeTHF/DMAC.

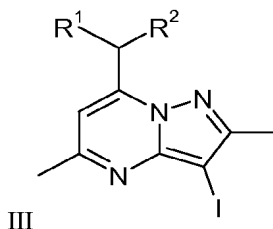
The reaction of step ii) is less sensitive to the inorganic base and solvent selected. Suitable bases include K₂CO₃, Cs₂CO₃, Na₂CO₃, K₃PO₄, NaOH, and the like. K₂CO₃ and K₃PO₄ are preferred with K₂CO₃ being particularly preferred.

Suitable solvents for the reaction of step ii) include most polar solvents, such as methanol, ethanol, *n*-propanol, 2-propanol, *n*-butanol, acetonitrile, 2-MeTHF, and morpholine. Morpholine is preferred in that it is an excellent solvent and a reactant in the reaction of step ii).

Preferred reaction temperatures for the reaction of step ii) are from about 60 - 120° C.

In one preferred embodiment of the present invention, the synthetic process comprises the steps of:

i) reacting a compound of Formula III,



or a salt thereof, wherein R¹ and R² are independently ethyl or *n*-propyl, with 2,4-di-chlorothiazole, or a salt thereof, in the presence of CuCl, 1,10-phenanthroline, and a base selected from K₃PO₄ and Cs₂CO₃, to form a compound of Formula I (above); and

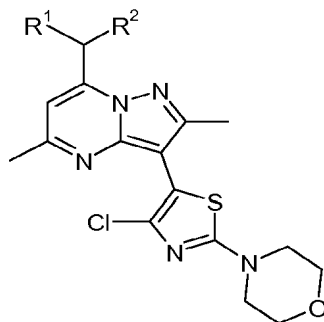
ii) reacting the compound of Formula I, with morpholine, or a salt thereof, in the presence of K₂CO₃.

It is further preferred in this embodiment of the process that the reaction of step i) use from about 5-50 mole percent, particularly about 30 mole percent, CuCl and from about 5-50 mole percent, particularly about 30 mole percent, 1,10-phenanthroline with 2-MeTHF/DMAC (particularly about 80/20 2-MeTHF/DMAC) as a solvent system and

5

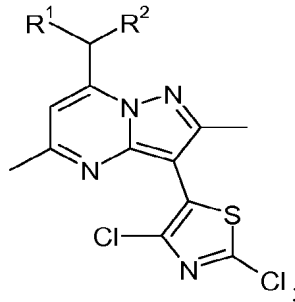
that the reaction be run at from about 80 to 120° C, and that the reaction of step ii) use morpholine as a solvent and K₂CO₃ as the base.

In a another aspect of the invention, there is provided a synthetic process for
5 preparing a compound of the formula



wherein R¹ and R² are independently ethyl or *n*-propyl,
comprising the steps of

i) reacting a compound of the formula

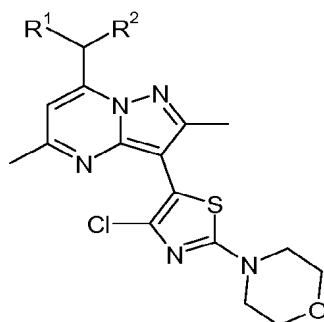


10

or a salt thereof, with an excess of morpholine or salt thereof, in the presence of a suitable solvent.

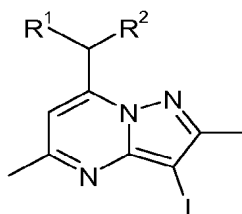
One embodiment of this aspect of the invention provides a synthetic process for preparing a compound of the formula

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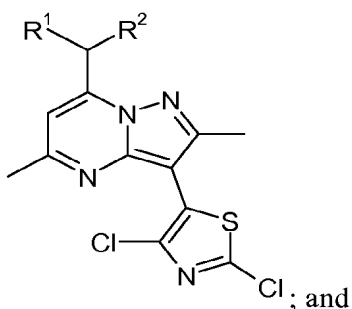
wherein R^1 and R^2 are independently ethyl or *n*-propyl,
comprising the steps of

i) reacting a compound of the formula



5

or a salt thereof, with 2,4-di-chlorothiazole, or a salt thereof, in the presence of a copper halide catalyst, a ligand selected from 1,10-phenanthroline and bipyridine, and a base selected from K_3PO_4 and Cs_2CO_3 , to form a compound of the formula



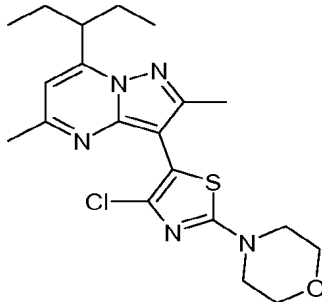
10 ii) reacting the product of step i), with an excess of morpholine, or a salt thereof,
in a suitable solvent.

In this aspect of the invention, various aprotic solvents may be suitable, but preferred solvents are 2-MeTHF and 2-propanol. In a preferred embodiment, 2-propanol
15 is used as solvent. It is surprisingly found that use of 2-propanol reduces reaction times about three fold over prior solvent systems tested. It is also surprisingly found that use of

2-propanol provides the desired amination product in high purity even in the presence of competing nucleophilic alcohol. Use of 2-propanol also further simplifies the work up of the final product by allowing crystallization directly from this solvent, thus avoiding a further solvent exchange prior to crystallization.

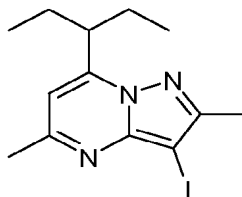
5 In this aspect of the invention, it has also been surprisingly found that morpholine can function as a suitable base for the amination reaction, thus eliminating the need for an additional base to drive the reaction. Additionally, yields are improved while maintaining quality of final product. Reduction of the amount of morpholine used is also of benefit in the final workup of the product. In one embodiment wherein 2-McTHF is used as the
 10 solvent, the reaction is run with between about 4.0 and about 6.0 equivalents, say about 5.35 equivalents, of morpholine, or salt thereof. In another embodiment wherein 2-propanol is used as the solvent, the reaction is run with between about 3.0 and about 4.0 equivalents, say about 3.3 equivalents, of morpholine, or salt thereof.

Thus in one embodiment of the invention, there is provided a synthetic process for
 15 preparing a compound of the formula



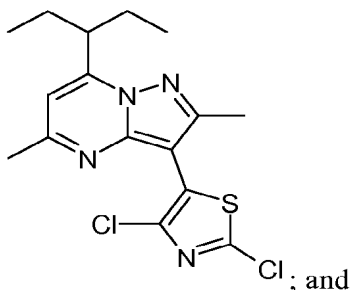
comprising the steps of

i) reacting a compound of the formula



20 or a salt thereof, with 2,4-di-chlorothiazole, or a salt thereof, in the presence of copper chloride, 1,10-phenanthroline, and Cs_2CO_3 , to form a compound of the formula

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ii) reacting the product of step i), with an excess of morpholine, or a salt thereof, in 2-propanol as a solvent.

5 Abbreviations use in this application are as follows:

CPME means cyclopentyl methyl ether.

DMAC means N,N-dimethylacetamide.

DMF means dimethylformamide.

EtOAc means ethylacetate.

10 2-MeTHF means 2-methyltetrahydrofuran.

2-MeTHF/DMAC system means 2-methyltetrahydrofuran and N,N-dimethylacetamide in a co-solvent system in proportions between about 70/30 and about 80/20.

n-BuOAc means *n*-butylacetate.

15 XRPD means X-ray powder diffraction.

DSC means differential scanning calorimetry.

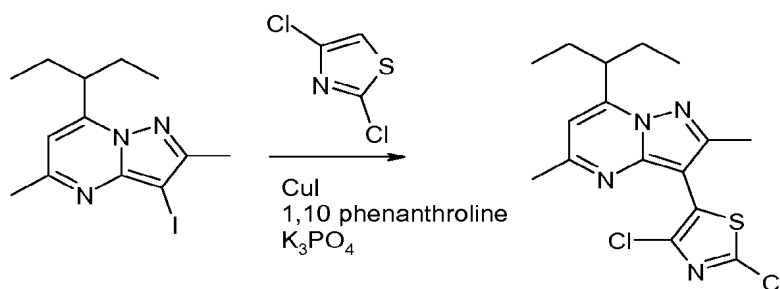
Further preferred embodiments for the synthetic process of the present invention are as described in the examples below.

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EXAMPLES

Example 1: 7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

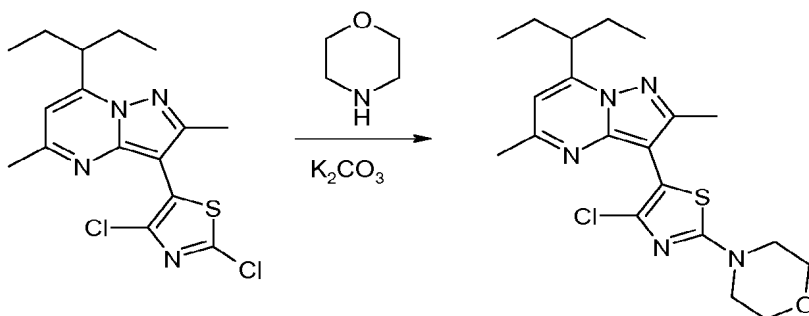
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Charge 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (1.03 g, 3.00 mmoles), K_3PO_4 (1.95 g, 9.00 mmoles), 2,4-dichlorothiazole (0.58 g, 3.75 mmoles), 1,10 phenanthroline (0.05 g, 0.30 mmoles) and anhydrous DMAC (5 mL) to a round
 5 bottom flask equipped with a magnetic stir bar, thermal couple and N_2 inlet. Degas the yellow heterogeneous reaction mixture with N_2 (gas) for 30 min. and then add CuI (0.06 g, 0.30 mmoles) in one portion followed by additional 30 min. degassing with N_2 (gas). Stir the reaction mixture at 120 °C for about 6 hr. Cool the reaction mixture to room temperature overnight, add toluene (10 mL) and stir for 1 hr. Purify the mixture through
 10 silica gel eluting with toluene (10ml). Extract with 1 M HCl (10 mL), water (10 mL), brine (10 mL) and concentrate under reduced pressure to give a yellow solid. Recrystallize the solid from methanol (5ml) to yield the title compound as a yellow crystalline solid. (0.78 g, 70% yield, >99% pure by LC) MS(ES) = 369 (M+1). ^1H NMR ($CDCl_3$) = 6.5 (1H, s); 3.6 (1H, m); 2.6 (3H, s); 2.5 (3H, s); 1.9 (4H, m); 0.9 (6H, t).

15

Example 2: 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine



20

Charge 7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (0.37 g, 1.00 mmoles), K_2CO_3 (0.28 g, 2.00 mmoles) and anhydrous morpholine (3 mL) to a round bottom flask equipped with a magnetic stir bar

and N₂ inlet. Stir the yellow mixture at 100 °C for about 4 hr., during which time the reaction becomes homogeneous. Cool the reaction mixture to room temperature, add H₂O (10 mL) and stir the heterogeneous reaction mixture overnight at room temperature. Collected the yellow solid by filtration, wash with H₂O and allowed to air dry overnight to give the crude title compound (391mg). Recrystallize from isopropyl alcohol (3 mL) to yield the title compound as a light yellow crystalline solid (380 mg, 90.6% yield, >99% by LC). MS(ES) = 420 (M+1). ¹H NMR (CDCl₃) = 6.45 (1H, s); 3.81 (m, 4H); 3.62 (1H, m); 3.50 (m, 4H); 2.6 (3H, s); 2.45 (3H, s); 1.85 (4H, m); 0.9 (6H, t).

10 Example 3:

The reactions of Example 1 are run with various other catalysts, ligands, bases and solvents, which are found to have the following effects on yield of 7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine. (See Tables 1 - 4).

15 Table 1: Evaluation of different ligands

Ligand	% Product
2,2'-bipyridine	72.7
1,10-phenanthroline	84.7
L-proline	23.7
2-acetylcyclohexanone	19.0

(Reactions are carried out in parallel reactors with 1.2 mmol 2,4-dichlorothiazole, 1 mmol 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine, 0.5 mmol CuI, 0.5 mmol ligand and 2.1 mmol Cs₂CO₃ in 4 mL DMAC. The reactions are degassed under N₂ for 30 min. and then heated at between 80 and 100°C overnight under N₂. Percent product is measured as the percent of total area under the HPLC curve for the product peak. Longer reaction times are shown in parenthesis)

25 Table 2: Evaluation of various solvents

Solvent	% Product
DMAC	82.4
10% H ₂ O in DMAC	1.6
DMAC (under air)	8.5
DMF	76.9
1-methyl-2-pyrrolidinone (NMP)	77.3
Dioxane	69.5
THF	66.9
Toluene	23.0

Ethylene glycol dimethyl ether (DME)	60.8
Dimethyl sulfoxide (DMSO)	76.7
Propanenitrile [CuCl catalyst]	99
Acetonitrile [CuCl catalyst]	8
2-MeTHF [48 hr, CuCl catalyst]	98
BuOAc [24 hr, CuCl catalyst]	98
CPME [127 hr, with CuCl catalyst]	87
2-MeTHF/DMAC (4:1) [14-24 hr, CuCl catalyst]	98 -100

(Reactions are carried out in parallel reactors with 1.2 mmol 2,4-dichlorothiazole
1 mmol 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine, 0.25
mmol CuI, 0.25 mmol 1,10-phenanthroline and 2.1 mmol Cs₂CO₃ in 3 mL
specified solvent. The reactions are degassed under N₂ for 30 minutes and then
heated at 100°C overnight under N₂. Percent product is measured as the percent of
total area under the HPLC curve for the product peak.)

Table 3: Evaluation of different copper sources

Copper Source	% Product
CuCl	81.3
CuBr	78.2
CuI	78.8

(Reactions are carried out in in parallel reactors with 1 mmol 2,4-dichlorothiazole
1 mmol 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine, 0.05
mmol CuX, 0.01 mmol 1,10-phenanthroline and 3 equivalents K₃PO₄ in 3 mL
DMAC. The reactions are degassed under N₂ for 30 minutes and then heated at
100°C overnight under N₂. Percent product is measured as the percent of total
area under the HPLC curve for the product peak.)

Table 4: Evaluation of various inorganic bases

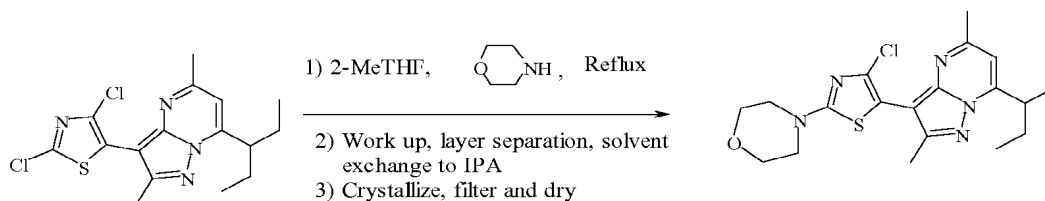
Base	% Product
Cs ₂ CO ₃	87.0
Cs ₂ CO ₃ (1.1 eq.)	71.0
K ₂ CO ₃	25.6
Na ₂ CO ₃	6.0
Li ₂ CO ₃	1.8
KOAc	5.3
K ₃ PO ₄	83.8

(Reactions are carried out in in parallel reactors with 1 mmol 2,4-dichlorothiazole
1 mmol 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine, 0.1
mmol CuI, 0.1 mmol 1,10-phenanthroline and 2.1 mmol base and degassed for 30
minutes prior to the addition of 3 mL DMAC. The reactions are degassed under
N₂ for 10 minutes and then heated at 100°C overnight under N₂. Percent product

is measured as the percent of total area under the HPLC curve for the product peak.)

Example 4. Use of morpholine both as a reactant and base in 2-MeTHF as solvent.

5



7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (15.2 g, 41.16 mmoles) is charged into a 250 mL 3-necked round bottomed flask, followed by addition of 2-MeTHF (61 mL, 4.0 volumes), the yellowish brown slurry is stirred at about 20 °C for 5 min. Then morpholine (19 g, 218.18 mmoles) is added over 2-5 minutes. Contents are heated to reflux and maintained at reflux for 12 hr. The slurry is cooled to 25 °C, followed by addition of 2-MeTHF (53 mL, 3.5 volumes) and water (38 mL 2.5 volumes). The reaction mixture is warmed to 40 °C, where upon a homogenous solution with two distinct layers formed. The layers are separated, the organic layer is filtered and concentrated to ~3 volumes at atmospheric pressure. Four volumes 2-propanol (61 mL) are added. The solution is concentrated to ~3 volumes followed by addition of 4 volumes 2-propanol (61 mL), re-concentrated to ~3 volumes, followed by addition of another 6 volumes 2-propanol (91 mL), and refluxed for 15 min. The clear solution is gradually cooled to 75 °C, seeded with 0.45 g 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine slurried in 2 mL 2-propanol, rinsed with an additional 2 mL 2-propanol and transferred to a crystallization flask. The slurry is cooled to between 0-5 °C, maintained for 1 hr, filtered and the product rinsed with 2-propanol (30 mL, 2 volumes). The solid is dried at 60 °C in a vacuum oven to afford 16.92 g 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine. Purity of product by HPLC assay is 100.00 %. XRPD and DSC data of product is consistent with reference sample. MS(ES) = 420 (M+1).

Example 5. Use of morpholine as both reactant and base in 2-propanol as solvent.

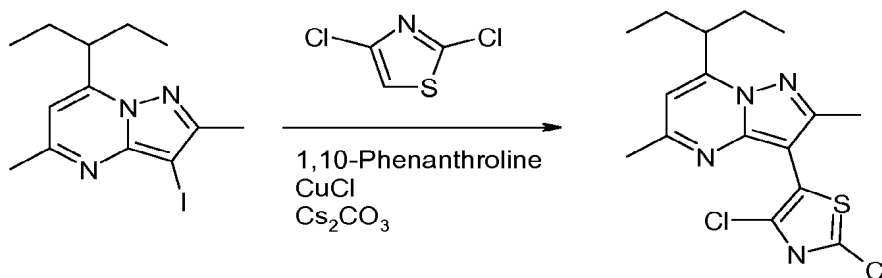
7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (11.64 mmoles) is charged into a 100 mL 3-necked round bottomed flask followed by addition of 2-propanol (16 mL, 3.72 volumes). The yellowish brown slurry is stirred at about 20 °C for 5 min. Then morpholine (3.3 g, 37.84 mmoles) is added over 2-5 minutes. Contents are refluxed for 6 hr. The slurry is cooled to 25 °C. 2-Propanol (32 mL, 7.44 volumes) and water (8.6 mL, 2.0 volumes) are added and the mixture warmed to 70-75 °C, filtered and concentrated to ~ 9 volumes at atmospheric pressure. The clear solution is gradually cooled to 55 °C, seeded with 0.06 g of crystalline 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine slurried in 0.5 mL 2-propanol, rinsed with additional 0.5 mL 2-propanol and added to crystallization flask. The slurry is cooled to 0-5 °C, maintained for 1 hr., filtered and the product rinsed with 2-propanol (9 mL, 2.1 volumes). Suctioned dried under vacuum at 60 °C to afford 4.6 g of dry 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (88.8 % yield, purity by HPLC assay is 99.88 %). MS(ES) = 420 (M+1).

Example 6: 7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (10 g, 29.17 mmoles), 2, 4-dichlorothiazole (5.2 g , 33.76 mmoles), cesium carbonate(19.9g, 61.07 mmoles) and 1,10-phenanthroline (1 g, 5.5 mmoles) are charged into a 250 mL 3-necked round bottomed flask, followed by 2-MeTHF (36 mL, 3.6 volumes). The reaction mixture is degassed with nitrogen and then evacuated. Cuprous chloride (0.57 g, 5.7 mmoles), DMAC (10 mL, 1 volume) and 2-MeTHF (4 mL, 0.4 volumes) are added in succession. The reaction mixture is degassed with nitrogen and then evacuated. The contents are refluxed for 20 hr. The reaction mixture is cooled to ~70 °C and 2-MeTHF (100 mL, 10 volumes) is added. The contents are filtered at ~70 °C and the residual cake is washed with 2-MeTHF (80 mL, 8 volumes) at about 65-72°C. The filtrate is transferred into a separatory funnel and extracted with water. The organic layer is separated and washed with dilute HCl. The resulting organic layer is treated with Darco G60, filtered hot (60°C). The filtrate is concentrated at atmospheric pressure to ~2.8

volumes. 25 mL 2-propanol is added, followed by re-concentration to ~2.8 volumes. An additional 25 mL 2-propanol is added, followed again by re-concentration to ~2.8 volumes. Finally, 48 mL 2-propanol is added. The contents are cooled to -7 °C, maintained at -7 °C for 1 hr., filtered and rinsed with 20 mL chilled 2-propanol. Product is suction dried and then vacuum dried at 60 °C to afford 9.41 g 7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (purity of product by HPLC assay is 95.88 %). MS(ES) = 369 (M+1).

Example 7. Synthesis of 7-(1-ethyl-propyl)-3-(2, 4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine using 1,4-Dioxane solvent and CuCl catalyst



Add dioxane (9.06X), Cs₂CO₃ (2.00X), 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (1.0 equivalent), 2,4-dichlorothiazole (0.54 equivalent) to a reactor under N₂. Purge the reactor with N₂ three times, degas with N₂ for 0.5~1 hr., and then add 1,10-phenanthroline (0.3 eq) and CuCl (0.3eq) under N₂, degassing with N₂ for 0.5~1 hr. Heat the reactor to 100 °C ~110 °C under N₂. Stir the mixture for 22~24 hr. at 100 °C ~110 °C. Cool to 10~20 °C and add water (10V) and CH₃OH (5V), stir the mixture for 1~1.5 hr. at 10~20 °C. Filter the suspension, resuspend the wet cake in water, stir for 1~1.5 hr. at 10~20 °C, and filter the suspension again. Charge the wet cake to n-heptane (16V) and EtOAc (2V) under N₂. Heat the reactor to 40 °C~50 °C under N₂.

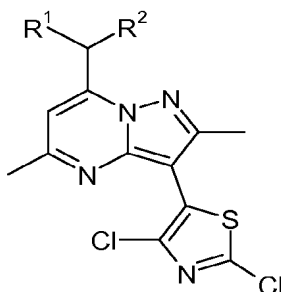
Active carbon (0.1X) is added at 40 °C~50 °C. The reactor is heated to 55 °C~65 °C under N₂ and stirred at 55 °C~65 °C for 1~1.5 hr. The suspension is filtered at 40~55 °C through diatomite (0.4 X). The cake is washed with n-heptane (2.5V). The filtrate is transferred to another reactor. EtOAc (10V) is added and the organic layer washed with 2 N HCl (10V) three times, followed by washing two times with water (10X, 10V). The organic layer is concentrated to 3~4V below 50 °C. The mixture is heated to

80~90 °C. The mixture is stirred at this temperature for 40~60 min. The mixture is cooled to 0~5°C, stirred for 1~1.5 hr. at 0~5°C and filtered. The cake is washed with n-heptane (1V) and vacuum dried at 45~50 °C for 8~10 hr. The crude product is dissolved in 2-propanol (7.5V) under N₂, and re-crystallized with 2-propanol. The cake is dried in a
5 vacuum oven at 45°C~50°C for 10-12 hr. (55~80% yield). ¹H NMR δ 6.537 (s, 1H) 3.591-3.659 (m, 1H, *J*=6.8Hz), 2.593 (s, 3H), 2.512 (s, 3H), 1.793-1.921(m, 4H), 0.885-0.903 (m, 6H).

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WE CLAIM:

1. A compound of the formula



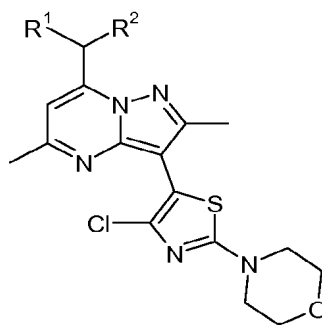
wherein:

- 5 R¹ and R² are independently ethyl or *n*-propyl;
or a salt thereof.

2. The compound according to claim 1, or a salt thereof, wherein R¹ and R²
are each ethyl.

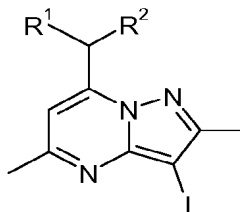
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3. A synthetic process for preparing a compound of the formula

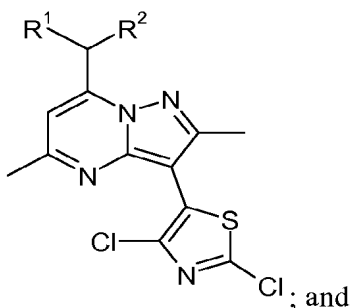


wherein R¹ and R² are independently ethyl or *n*-propyl,
comprising the steps of

- 15 i) reacting a compound of the formula



or a salt thereof, with 2,4-di-chlorothiazole, or a salt thereof, in the presence of a copper halide catalyst, a ligand selected from 1,10-phenanthroline and bipyridine, and a base selected from K_3PO_4 and Cs_2CO_3 , to form a compound of the formula



5 ii) reacting the product of step i), with morpholine, or a salt thereof, in the presence of a suitable inorganic base.

4. The process according to Claim 3 wherein R^1 and R^2 are each ethyl.

10 5. The process according to either Claim 3 or Claim 4 wherein the copper halide is CuCl

6. The process according to any one of Claims 3-5 wherein the ligand is 1,10-phenanthroline.

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7. The process according to any one of Claims 3-6 wherein the base in step i) is Cs_2CO_3 .

8. The process according to any one of Claims 3-7 wherein the base in step ii) is K_2CO_3 .

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9. The process according to claim 3 wherein R^1 and R^2 are each ethyl, the copper halide is CuCl, the ligand is 1,10-phenanthroline, the base in step i) is Cs_2CO_3 , and the base in step ii) is K_2CO_3 .

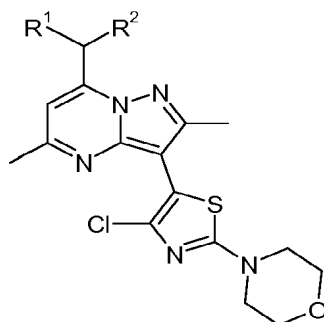
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10. The process according to Claim 9 wherein the solvent for step i) is 1, 4-Dioxane or 2-MeTHF/DMAC and the solvent for step ii) is morpholine, 2-MeTHF, or 2-propanol

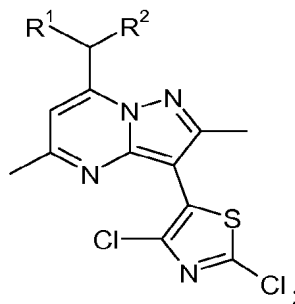
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11. A synthetic process for preparing a compound of the formula



wherein R¹ and R² are independently ethyl or *n*-propyl,
comprising the steps of

10 i) reacting a compound of the formula



or a salt thereof, with excess morpholine or salt thereof, in the presence of a suitable solvent.

15 12. The process of Claim 11 wherein the solvent is 2-methyl tetrahydrofuran.

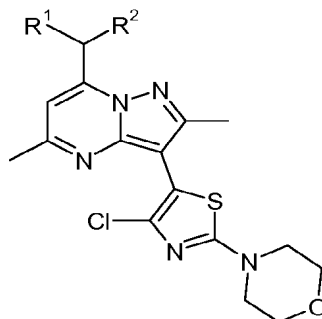
13. The process of Claim 11 wherein the solvent is 2-propanol.

14. The process of any one of Claims 11 – 13 wherein R¹ and R² are each ethyl.

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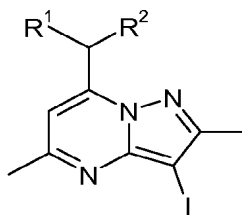
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15. A synthetic process for preparing a compound of the formula

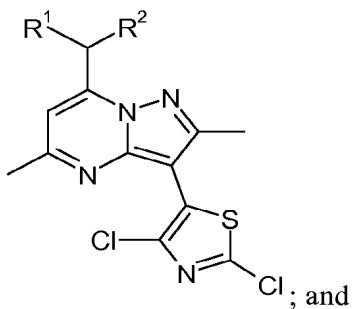


wherein R^1 and R^2 are independently ethyl or *n*-propyl,
comprising the steps of

5 i) reacting a compound of the formula



or a salt thereof, with 2,4-di-chlorothiazole, or a salt thereof, in the presence of a copper halide catalyst, a ligand selected from 1,10-phenanthroline and bipyridine, and a base selected from K_3PO_4 and Cs_2CO_3 , to form a compound of the formula



10

ii) reacting the product of step i), with an excess of morpholine, or a salt thereof, in in a suitable solvent.

16. The process of Claim 15 wherein the solvent is 2-methyl tetrahydrofuran.

15

17. The process of Claim 15 wherein the solvent is 2-propanol.

18. The process of any one of Claims 15 – 17 wherein R^1 and R^2 are each ethyl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/058722

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/036579 A1 (LILLY CO ELI [US]; CHEN ZHAOGEN [US]; HAMDOUCHI CHAFIQ HAMDOUCHI [US];) 27 March 2008 (2008-03-27) cited in the application Pages 30-32, 36-38 examples 4,14,16,16/alternate preparation,17	1-18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Date of the actual completion of the international search

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(54) Title: COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR THE TREATMENT OF ISCHEMIC MEDIATED CENTRAL NERVOUS SYSTEM DISORDERS OR INJURY

(57) Abstract: The present invention provides compositions and methods for the treatment of ischemic mediated central nervous system disorder or injury. More particularly, the invention provides a combination therapy for the treatment of a central nervous system ischemic mediated disorder or injury comprising the administration to a subject of a cyclooxygenase-2 selective inhibitor and a corticotropin releasing factor antagonist or a pharmaceutically acceptable salt or a prodrug thereof.

COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR THE TREATMENT OF ISCHEMIC MEDIATED CENTRAL NERVOUS SYSTEM DISORDERS OR INJURY

FIELD OF THE INVENTION

[0001] The present invention provides compositions and methods for the treatment of reduced blood flow to the central nervous system. More particularly, the invention is directed toward a combination therapy for the treatment or prevention of ischemic-mediated central nervous system disorders or injury, including ischemic stroke, comprising the administration to a subject of a cyclooxygenase-2 selective inhibitor in combination with a corticotropin releasing factor antagonist.

BACKGROUND OF THE INVENTION

[0002] The continued increase in the incidence of ischemic-mediated central nervous system damage, including ischemic stroke, provides compelling evidence that there is a continuing need for better treatment strategies. Stroke, for example, is consistently the second or the third leading cause of death annually and the leading producer of disability among adults in the United States and western countries. Moreover, roughly 10% of patients with stroke become heavily handicapped, often needing attendant care.

[0003] The pathology underlying ischemic-mediated central nervous system injury has been elucidated. Generally speaking, the normal amount of perfusion to brain gray matter is 60 to 70 mL/100 g of brain tissue/min. Death of central nervous system cells typically occurs only when the flow of blood falls below a certain level (approximately 8-10 mL/100 g of brain tissue/min), while at slightly higher levels the tissue remains alive but not able to function. For example, most strokes culminate in a core area of cell death (infarction) in which blood flow is so drastically reduced that the cells usually cannot recover. This threshold seems to occur when cerebral blood flow is 20 percent of normal or less. Without neuroprotective agents, nerve cells facing 80 to 100 percent ischemia will be irreversibly damaged within a few minutes. Surrounding the ischemic core is another area of tissue called the "ischemic penumbra" or "transitional zone" in which cerebral blood flow is between 20 and 50 percent of normal. Cells in this area are endangered, but not yet irreversibly damaged. Thus in the acute stroke, the affected central core brain tissue may die while the more peripheral tissues

remain alive for many years after the initial insult, depending on the amount of blood the brain tissue receives.

[0004] At the cellular level, if left untreated, brain or spinal cell injury and death progress in a stepwise manner rapidly within the core infarction, and over time within the ischemic penumbra. Without adequate blood supply, brain or spinal cells lose their ability to produce energy, particularly adenosine triphosphate (ATP). When this energy failure occurs, brain or spinal cells become damaged and will die if critical thresholds are reached. Immediate cell death within the ischemic core is typically necrotic, while cell death in the penumbra may be either necrotic or apoptotic. It is believed that there are an immense number of mechanisms at work causing brain or spinal cell damage and death following energy failure. Each of these mechanisms represents a potential route for intervention. One of the ways brain cells respond to energy failure is by elevating the concentration of intracellular calcium. Worsening this and driving the concentrations to dangerous levels is the process of excitotoxicity, in which brain cells release excessive amounts of glutamate, a neurotransmitter. This stimulates chemical and electrical activities in receptors on other brain cells, which leads to the degradation and destruction of vital cellular structures. Brain cells ultimately die as a result of the actions of calcium-activated proteases (enzymes which digest cell proteins), lipases (enzymes which digest cell membranes) and free radicals formed as a result of the ischemic cascade.

[0005] No drug therapy has yet been proven completely effective in preventing brain damage from cerebral ischemia. Interventions have been directed toward salvaging the ischemic penumbra and reducing its size. Restoration of blood flow is the first step toward rescuing the tissue within the penumbra. Therefore, timely recanalization of an occluded vessel to restore perfusion in both the penumbra and in the ischemic core is one treatment option employed. Partial recanalization also markedly reduces the size of the penumbra as well. Moreover, intravenous tissue plasminogen activator and other thrombolytic agents have been shown to have clinical benefit if they are administered within a few hours of symptom onset. Beyond this narrow time window, however, the likelihood of beneficial effects is reduced and hemorrhagic complications related to thrombolytic agents become excessive, seriously compromising their therapeutic value. Hypothermia decreases the size of the ischemic insult in both anecdotal clinical and laboratory reports. In addition, a wide variety of agents have been shown to reduce infarct volume in animal models. These agents

include pharmacologic interventions that involve thrombolysis, calcium channel blockade, and cell membrane receptor antagonism have been studied and have been found to be beneficial in animal cortical stroke models. But there is a continuing need for improved treatment regimens following ischemic-mediated central nervous system injury.

[0006] Corticotropin releasing factor ("CRF"), also referred to as corticotropin releasing hormone ("CRH"), is a 41 amino acid neuropeptide hormone. This peptide is the major physiologic regulator of the basal and stress-induced production and release of adrenocorticotrophic hormone ("ACTH"), β -endorphin, and other peptides from the pituitary via binding of CRF to its several receptors. ACTH release leads to the release of cortisol and other adrenal steroids. Important functions affected by the action of CRF include behavior, temperature regulation, food intake, reproduction, memory and learning, and can also induce seizures (Wong et al., *NeuroReport*, 6:13 (1995) 1785-1788). Increasing evidence exists to implicate the involvement of CRF in the pathogenesis of ischemic brain damage (Mackay et al., *J. Cerebral Blood Flow and Metabolism* (2001) 21:1208-1214; and DeVries et al. *Proc. Nat'l. Academy Science*, (2001) 98:11824-11828). CRF has also been implicated as being neurotoxic, being involved in neurodegeneration following cerebral ischemia (Lyons et al., *Brain Research*, 545 (1991) 339-342; Wong et al. (1995)). Additionally, several authors have noted that in humans, post-stroke concentrations of cortisol are predictive of stroke outcome, high cortisol concentrations being associated with increased morbidity and mortality (Feibel et al., *JAMA* (1977) 238: 1374-1376; Olsson, t., *J. Int. Med.* (1990) 228: 177-181).

[0007] Several recent studies have found that the administration of a corticotropin releasing factor antagonist reduces the extent of stroke-induced brain damage when administered to a subject shortly before or after the onset of the ischemic cascade. In one study, it was shown that a low dose of the corticotropin releasing factor antagonist α -helical CRF 9-41 in combination with a vehicle administered via injection either 30 minutes before or 10 minutes after a unilateral, permanent middle cerebral artery occlusion (MCAo) could markedly inhibit (by over 60%) the volume of the infarction (Strijbos, et al., *Brain Research*, 656 (1994) pp. 405-408). Corticotropin releasing factor antagonists, and in particular α -helical CRF, have also been found to demonstrate a neuroprotective effect in a dose-dependent manner (Lyons et al. (1991)). In addition, it appears that corticotropin releasing factor antagonists demonstrate an

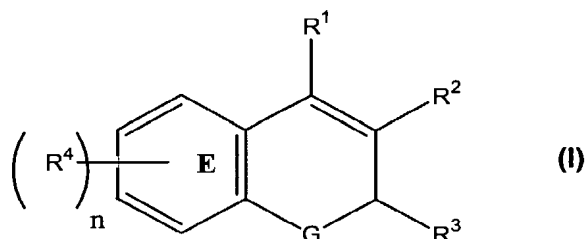
ability to inhibit neuronal damage induced by pharmacological activation of NMDA receptors , particularly in the striatum, indicating that NMDA receptor-mediated neurotoxicity is at least in part due to the release of endogenous corticotropin releasing factor (Strijbos et al. (1994)).

[0008] Moreover, several studies indicate that cyclooxygenase-2 is involved in the inflammatory component of the ischemic cascade. Cyclooxygenase-2 expression is known to be induced in the central nervous system following ischemic injury. In one study, it was shown that treatment with a cyclooxygenase-2 selective inhibitor reduced infarct volume in mice subjected to ischemic brain injury (Nagayama et al., (1999) J. Cereb. Blood Flow Metab.19(11):1213-19). A similar study showed that cyclooxygenase-2 deficient mice have a significant reduction in brain injury produced by occlusion of the middle cerebral artery when compared to mice that express cyclooxygenase-2 (Iadecola et al., (2001) PNAS 98:1294-1299). Another study demonstrated that treatment with cyclooxygenase-2 selective inhibitor results in improved behavioral deficits induced by reversible spinal ischemia in rabbits (Lapchak et al., (2001) Stroke 32(5):1220-1230).

SUMMARY OF THE INVENTION

[0009] Among the several aspects of the invention is provided a method for the treatment of ischemic mediated central nervous system disorders in a subject. The method comprises administering to the subject a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or a prodrug thereof in combination with a corticotropin releasing factor antagonist or a pharmaceutically acceptable salt or a prodrug thereof.

[0010] In one embodiment, the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or a prodrug thereof is a member of the chromene class of compounds. For example, the chromene compound may be a compound of the formula



[0011] wherein:

[0012] n is an integer which is 0, 1, 2, 3 or 4;

[0013] G is O, S or NR^a;

[0014] R^a is alkyl;

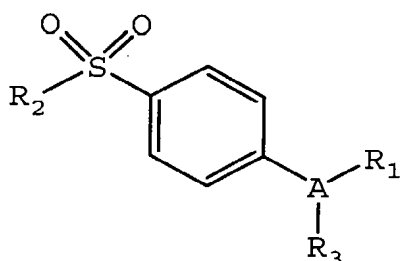
[0015] R¹ is H or aryl;

[0016] R² is carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl or alkoxy carbonyl;

[0017] R³ is haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro or alkylsulfonyl; and

[0018] each R⁴ is independently H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroaryl amino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, or alkylcarbonyl; or wherein R⁴ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0019] In another embodiment, the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or a prodrug thereof comprises a compound of the formula



[0020] wherein:

[0021] A is a partially unsaturated or unsaturated heterocyclyl ring or a partially unsaturated or unsaturated carbocyclic ring;

[0022] R¹ is heterocyclyl, cycloalkyl, cycloalkenyl or aryl, wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

[0023] R² is methyl or amino; and

[0024] R³ is H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxy carbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-aryl amino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-aryl amino, aminoalkyl, alkylaminoalkyl, N-aryl aminoalkyl, N-aralkyl aminoalkyl, N-alkyl-N-aralkyl aminoalkyl, N-alkyl-N-aryl aminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, or N-alkyl-N-arylaminosulfonyl.

[0025] In yet another embodiment, the corticotropin releasing factor antagonist is selected from the group consisting of α -helical CRF 9-41, antalarmin, CP-154,526, astressin, NBI 27914, and R121919.

[0026] Other aspects of the invention are described in more detail below.

ABBREVIATIONS AND DEFINITIONS

[0027] The term "acyl" is a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, and trifluoroacetyl.

[0028] The term "alkenyl" is a linear or branched radical having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl" also are radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

[0029] The terms "alkoxy" and "alkyloxy" are linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy.

[0030] The term "alkoxyalkyl" is an alkyl radical having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

[0031] The term "alkoxycarbonyl" is a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl portions having 1 to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

[0032] Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" is a linear, cyclic or branched radical having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

[0033] The term "alkylamino" is an amino group that has been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

[0034] The term "alkylaminoalkyl" is a radical having one or more alkyl radicals attached to an aminoalkyl radical.

[0035] The term "alkylaminocarbonyl" is an aminocarbonyl group that has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above.

[0036] The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl

radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl.

[0037] The term "alkylthio" is a radical containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio.

[0038] The term "alkylthioalkyl" is a radical containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl.

[0039] The term "alkylsulfinyl" is a radical containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent $-S(=O)-$ radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

[0040] The term "alkynyl" is a linear or branched radical having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

[0041] The term "aminoalkyl" is an alkyl radical substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like.

[0042] The term "aminocarbonyl" is an amide group of the formula $-C(=O)NH_2$.

[0043] The term "aralkoxy" is an aralkyl radical attached through an oxygen atom to other radicals.

[0044] The term "aralkoxyalkyl" is an aralkoxy radical attached through an oxygen atom to an alkyl radical.

[0045] The term "aralkyl" is an aryl-substituted alkyl radical such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl

may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

[0046] The term "aralkylamino" is an aralkyl radical attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" are amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl.

[0047] The term "aralkylthio" is an aralkyl radical attached to a sulfur atom.

[0048] The term "aralkylthioalkyl" is an aralkylthio radical attached through a sulfur atom to an alkyl radical.

[0049] The term "aroyl" is an aryl radical with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted.

[0050] The term "aryl", alone or in combination, is a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" includes aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

[0051] The term "arylamino" is an amino group, which has been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical.

[0052] The term "aryloxyalkyl" is a radical having an aryl radical attached to an alkyl radical through a divalent oxygen atom.

[0053] The term "arylthioalkyl" is a radical having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

[0054] The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", is $-(C=O)-$.

[0055] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", is $-CO_2H$.

[0056] The term "carboxyalkyl" is an alkyl radical substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which are lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl.

[0057] The term "corticotropin releasing factor" and "corticotropin releasing hormone" both refer to the same 41 amino acid polypeptide as described herein and are used interchangeably without consequence.

[0058] The term "corticotropin releasing factor antagonist" or alternatively "corticotropin releasing hormone antagonist" is any peptide or non-peptide substance that tends to nullify the action of corticotropin releasing factor or that binds to a cell receptor to which corticotropin releasing factor would otherwise be able to bind and does not elicit a biological response. Corticotropin releasing factor antagonists can include, for example, peptide and non-peptide antagonists, including the monocyclic five membered and six membered ring antagonists, and antagonists from the fused bicyclic, fused tricyclic, polycyclic, and acyclic systems. Specific examples of such corticotropin releasing factor antagonists include, for example, α -helical CRF 9-41, antalarmin, CP-154,526, astressin, NBI 27914, and R121919. Furthermore, a corticotropin releasing factor antagonist may bind any of the corticotropin releasing factor receptors, including, for example, CRF₁, CRF₂, and CRF-BP receptors.

[0059] The term "cycloalkenyl" is a partially unsaturated carbocyclic radical having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl, and cyclohexenyl.

[0060] The term "cycloalkyl" is a saturated carbocyclic radical having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0061] The term "cyclooxygenase-2 selective inhibitor" is a compound able to selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Typically, it includes compounds that have a cyclooxygenase-2 IC₅₀ of less than about 0.2 micro molar, and also have a selectivity ratio of cyclooxygenase-1 (COX-1) IC₅₀ to cyclooxygenase-2 (COX-2) IC₅₀ of at least about 5, more typically of at least about 50, and even more typically, of at least about 100. Moreover, the cyclooxygenase-2 selective inhibitors as

described herein have a cyclooxygenase-1 IC_{50} of greater than about 1 micro molar, and more preferably of greater than 10 micro molar. Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid used in the present method may inhibit enzyme activity through a variety of mechanisms. By the way of example, and without limitation, the inhibitors used in the methods described herein may block the enzyme activity directly by acting as a substrate for the enzyme.

[0062] The term "halo" is a halogen such as fluorine, chlorine, bromine or iodine.

[0063] The term "haloalkyl" is a radical wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically included are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" is a radical having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

[0064] The term "heteroaryl" is an unsaturated heterocyclyl radical. Examples of unsaturated heterocyclyl radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranlyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-

membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also includes radicals where heterocyclyl radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino.

[0065] The term "heterocyclyl" is a saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radical, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

[0066] The term "heterocyclylalkyl" is a saturated and partially unsaturated heterocyclyl-substituted alkyl radical, such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolyethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

[0067] The term "hydrido" is a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH₂-) radical.

[0068] The term "hydroxyalkyl" is a linear or branched alkyl radical having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

[0069] The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product; that is

the "pharmaceutically acceptable" material is relatively safe and/or non-toxic, though not necessarily providing a separable therapeutic benefit by itself. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiologically acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzyl ethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid, oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[0070] The term "prodrug" refers to a chemical compound that can be converted into a therapeutic compound by metabolic or simple chemical processes within the body of the subject. For example, a class of prodrugs of COX-2 inhibitors is described in US Patent No. 5,932,598, herein incorporated by reference.

[0071] The term "subject" for purposes of treatment includes any human or animal subject who is in need of treatment for an ischemic mediated central nervous system disorder or injury or who is at risk for developing an ischemic mediated central nervous system disorder or injury. The subject can be a domestic livestock species, a laboratory animal species, a zoo animal or a companion animal. In one embodiment, the subject is a mammal. In another embodiment, the mammal is a human being.

[0072] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, is a divalent radical $-\text{SO}_2-$. "Alkylsulfonyl" is an alkyl radical attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" are $\text{NH}_2\text{O}_2\text{S}-$.

[0073] The phrase "therapeutically-effective" is intended to qualify the amount of each agent (i.e. the amount of cyclooxygenase-2 selective inhibitor and the amount of corticotropin releasing factor antagonist) which will achieve the goal of improvement in disorder severity and the frequency of incidence over no treatment or treatment of each agent by itself.

[0074] The term "thrombotic event" or "thromboembolic event" includes, but is not limited to arterial thrombosis, including stent and graft thrombosis, cardiac thrombosis, coronary thrombosis, heart valve thrombosis, pulmonary thrombosis and venous thrombosis. Cardiac thrombosis is thrombosis in the heart. Pulmonary thrombosis is thrombosis in the lung. Arterial thrombosis is thrombosis in an artery. Coronary thrombosis is the development of an obstructive thrombus in a coronary artery, often causing sudden death or a myocardial infarction. Venous thrombosis is thrombosis in a vein. Heart valve thrombosis is a thrombosis on a heart valve. Stent thrombosis is thrombosis resulting from and/or located in the vicinity of a vascular stent. Graft thrombosis is thrombosis resulting from and/or located in the vicinity of an implanted graft, particularly a vascular graft. A thrombotic event as used herein is meant to embrace both a local thrombotic event and a distal thrombotic event occurring anywhere within the body (e.g., a thromboembolic event such as for example an embolic stroke).

[0075] The term "vaso-occlusive event" includes a partial occlusion (including a narrowing) or complete occlusion of a blood vessel, a stent or a vascular graft. A vaso-occlusive event intends to embrace thrombotic or thromboembolic events, and the vascular occlusion disorders or conditions to which they give rise. Thus, a vaso-occlusive event is intended to embrace all vascular occlusive disorders resulting in partial or total vessel occlusion from thrombotic or thromboembolic events.

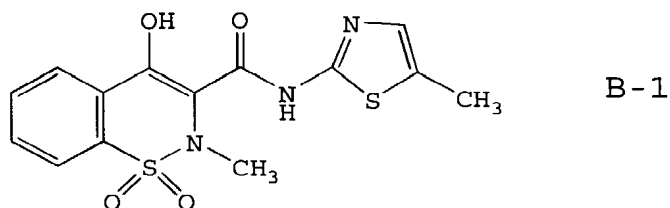
DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0076] The present invention provides a combination therapy comprising the administration to a subject of a therapeutically effective amount of a COX-2 selective inhibitor in combination with a therapeutically effective amount of a corticotropin releasing factor antagonist. The combination therapy is used to treat or prevent ischemic mediated central nervous system damage, such as damage to a central nervous system cell resulting from a decrease in blood flow to the cell or damage resulting from a traumatic injury to the cell. In addition, the combination therapy may

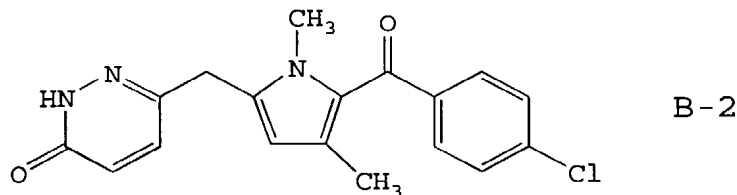
also be useful for the treatment of stroke or other vaso-occlusive events. When administered as part of a combination therapy, the COX-2 selective inhibitor together with the corticotropin releasing factor antagonist provide enhanced treatment options as compared to administration of the COX-2 selective inhibitor or the corticotropin releasing factor antagonist alone.

CYCLOOXYGENASE-2 SELECTIVE INHIBITORS

[0077] A number of suitable cyclooxygenase-2 selective inhibitors or isomers, pharmaceutically acceptable salts, esters, or prodrugs thereof, may be employed in the composition of the current invention. In one embodiment, the cyclooxygenase-2 selective inhibitor can be, for example, the cyclooxygenase-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having Formula B-1.



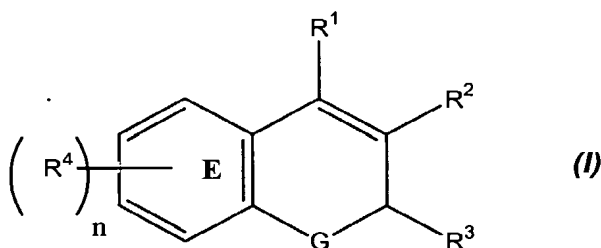
[0078] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is the cyclooxygenase-2 selective inhibitor, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having Formula B-2.



[0079] In still another embodiment the cyclooxygenase-2 selective inhibitor is a chromene compound that is a substituted benzopyran or a substituted benzopyran analog, and even more typically, selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, dihydronaphthalenes or a compound having

[0080] Formula I shown below and possessing, by way of example and not limitation, the structures disclosed in Table 1. Furthermore, benzopyran cyclooxygenase-2 selective inhibitors useful in the practice of the present methods are described in U.S. Patent No. 6,034,256 and 6,077,850 herein incorporated by reference in their entirety.

[0081] In another embodiment, the cyclooxygenase-2 selective inhibitor is a chromene compound represented by Formula I or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



[0082] wherein:

[0083] n is an integer which is 0, 1, 2, 3 or 4;

[0084] G is O, S or NR^a ;

[0085] R^a is alkyl;

[0086] R^1 is selected from the group consisting of H and aryl;

[0087] R^2 is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

[0088] R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

[0089] each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylaminosulfonyl, heteroarylalkylaminosulfonyl, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0090] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula (I) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0091] wherein:

[0092] n is an integer which is 0, 1, 2, 3 or 4;

[0093] G is O, S or NR^a;

[0094] R^a is alkyl;

[0095] R¹ is H;

[0096] R² is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

[0097] R³ is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

[0098] each R⁴ is independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R⁴ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0099] In a further embodiment, the cyclooxygenase-2 selective inhibitor may also be a compound of Formula (I), or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0100] wherein:

[0101] n is an integer which is 0, 1, 2, 3 or 4;

[0102] G is oxygen or sulfur;

[0103] R¹ is H;

[0104] R² is carboxyl, lower alkyl, lower aralkyl or lower alkoxycarbonyl;

[0105] R³ is lower haloalkyl, lower cycloalkyl or phenyl; and

[0106] each R⁴ is independently H, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower

alkylcarbonyl; or R⁴ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0107] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula (I) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0108] wherein:

[0109] n is an integer which is 0, 1, 2, 3 or 4;

[0110] G is oxygen or sulfur;

[0111] R¹ is H;

[0112] R² is carboxyl;

[0113] R³ is lower haloalkyl; and

[0114] each R⁴ is independently H, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or wherein R⁴ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0115] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula (I) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0116] wherein:

[0117] n is an integer which is 0, 1, 2, 3 or 4;

[0118] G is oxygen or sulfur;

[0119] R¹ is H;

[0120] R² is carboxyl;

[0121] R³ is fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, or trifluoromethyl; and

[0122] each R⁴ is independently H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropoxy, *tert*butyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-

methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl or phenyl; or wherein R⁴ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0123] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula (I) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0124] wherein:

[0125] n is an integer which is 0, 1, 2, 3 or 4;

[0126] G is oxygen or sulfur;

[0127] R¹ is H;

[0128] R² is carboxyl;

[0129] R³ is trifluoromethyl or pentafluoroethyl; and

[0130] each R⁴ is independently H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, or phenyl; or wherein R⁴ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0131] In yet another embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound having the structure of Formula (I) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0132] wherein:

[0133] n is 4;

[0134] G is O or S;

[0135] R¹ is H;

[0136] R² is CO₂H;

[0137] R³ is lower haloalkyl;

[0138] a first R⁴ corresponding to R⁹ is hydrido or halo;

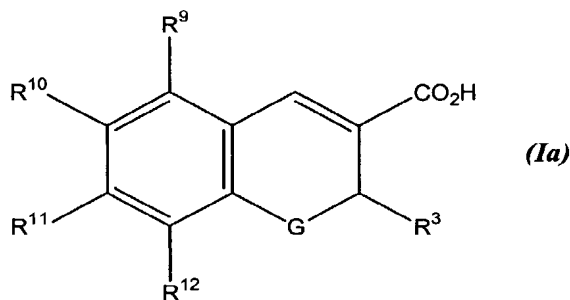
[0139] a second R⁴ corresponding to R¹⁰ is H, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-

membered nitrogen-containing heterocyclosulfonyl, or 6- membered nitrogen-containing heterocyclosulfonyl;

[0140] a third R^4 corresponding to R^{11} is H, lower alkyl, halo, lower alkoxy, or aryl; and

[0141] a fourth R^4 corresponding to R^{12} is H, halo, lower alkyl, lower alkoxy, or aryl;

[0142] wherein Formula (I) is represented by Formula (Ia):



[0143] The cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound of having the structure of Formula (Ia) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0144] wherein:

[0145] G is O or S;

[0146] R^3 is trifluoromethyl or pentafluoroethyl;

[0147] R^9 is H, chloro, or fluoro;

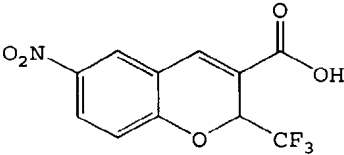
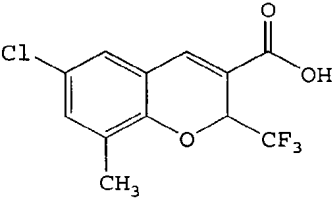
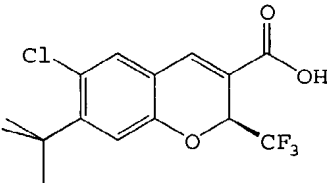
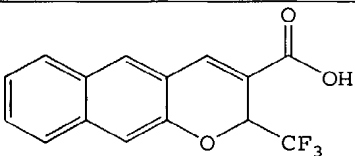
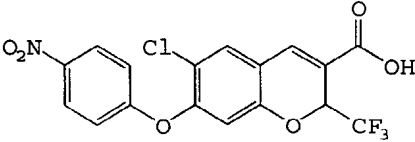
[0148] R^{10} is H, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, or morpholinosulfonyl;

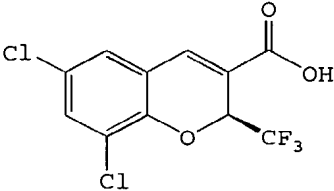
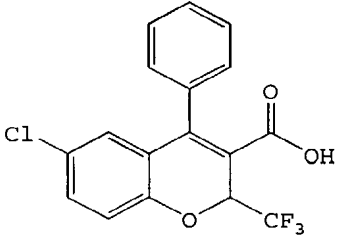
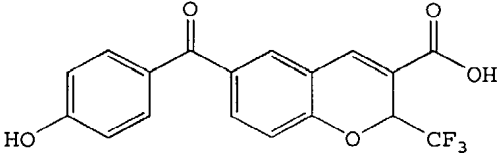
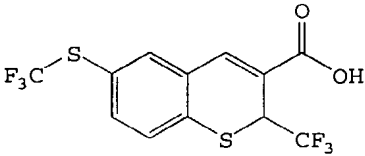
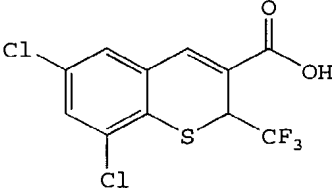
[0149] R^{11} is H, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, or phenyl; and

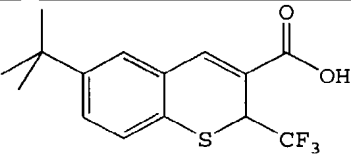
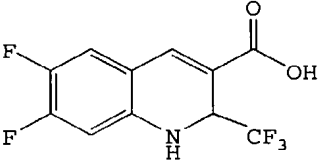
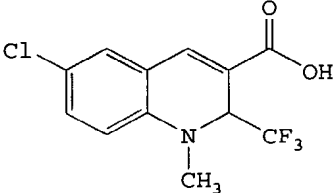
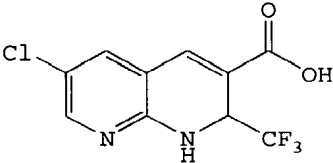
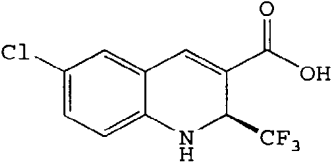
[0150] R^{12} is H, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, or phenyl.

[0151] Examples of exemplary chromene cyclooxygenase-2 selective inhibitors are depicted in Table 1 below.

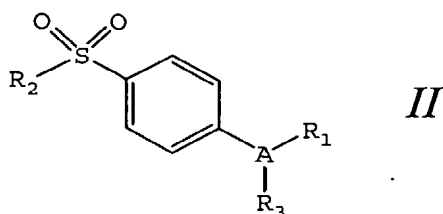
TABLE 1
EXAMPLES OF CHROMENE CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS
EMBODIMENTS

<u>Compound Number</u>	<u>Structural Formula</u>
B-3	 <p>6-Nitro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid</p>
B-4	 <p>6-Chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid</p>
B-5	 <p>(S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid</p>
B-6	 <p>2-Trifluoromethyl-2H-naphtho[2,3-b]pyran-3-carboxylic acid</p>
B-7	 <p>6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid</p>

<u>Compound Number</u>	<u>Structural Formula</u>
B-8	 <p data-bbox="719 493 1300 541">((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid</p>
B-9	 <p data-bbox="719 840 1352 888">6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid</p>
B-10	 <p data-bbox="719 1100 1333 1148">6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid</p>
B-11	 <p data-bbox="719 1388 1369 1436">2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid</p>
B-12	 <p data-bbox="719 1722 1274 1770">6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid</p>

<u>Compound Number</u>	<u>Structural Formula</u>
B-13	 <p>6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid</p>
B-14	 <p>6,7-Difluoro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid</p>
B-15	 <p>6-Chloro-1,2-dihydro-1-methyl-2-(trifluoromethyl)-3-quinolinecarboxylic acid</p>
B-16	 <p>6-Chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid</p>
B-17	 <p>((S)-6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid</p>

[0152] In a further embodiment, the cyclooxygenase-2 selective inhibitor is selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of Formula II or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,



[0153] wherein:

[0154] A is selected from the group consisting of a partially unsaturated or unsaturated heterocyclyl ring and a partially unsaturated or unsaturated carbocyclic ring;

[0155] R¹ is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

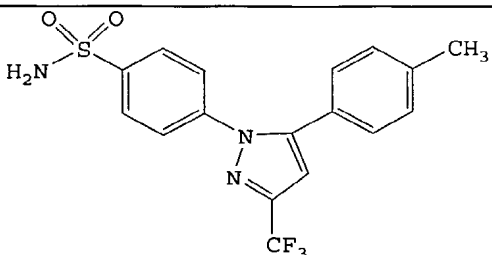
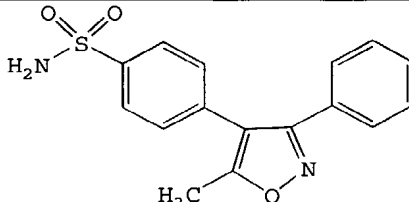
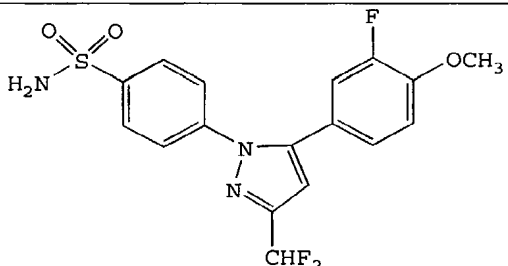
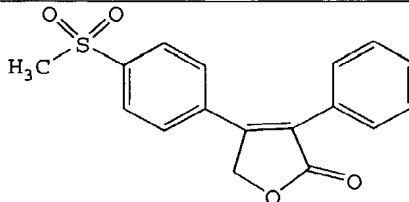
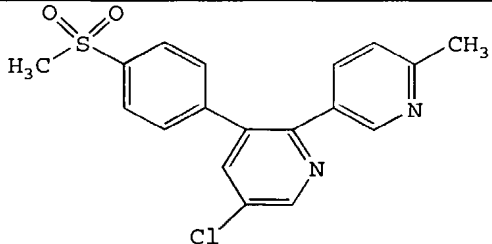
[0156] R² is selected from the group consisting of methyl and amino; and

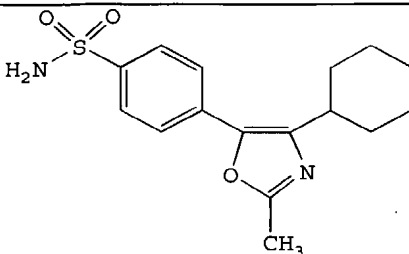
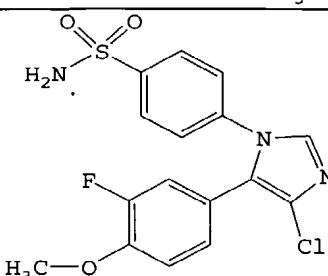
[0157] R³ is selected from the group consisting of H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-aryl amino, N-aralkyl amino, N-alkyl-N-aralkyl amino, N-alkyl-N-aryl amino, aminoalkyl, alkylaminoalkyl, N-aryl aminoalkyl, N-aralkyl aminoalkyl, N-alkyl-N-aralkyl aminoalkyl, N-alkyl-N-aryl aminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N- arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl.

[0158] In another embodiment, the cyclooxygenase-2 selective inhibitor represented by the above Formula II is selected from the group of compounds illustrated in Table 2, consisting of celecoxib (B-18; U.S. Patent No. 5,466,823; CAS No. 169590-42-5), valdecoxib (B-19; U.S. Patent No. 5,633,272; CAS No. 181695-72-7),

deracoxib (B-20; U.S. Patent No. 5,521,207; CAS No. 169590-41-4), rofecoxib (B-21; CAS No. 162011-90-7), etoricoxib (MK-663; B-22; PCT publication WO 98/03484), tilmacoxib (JTE-522; B-23; CAS No. 180200-68-4), and cimicoxib (UR-8880; B23a; CAS No. 265114-23-6).

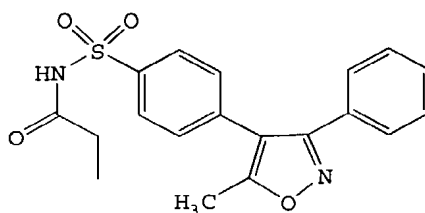
TABLE 2
EXAMPLES OF TRICYCLIC CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

<u>Compound Number</u>	<u>Structural Formula</u>
B-18	
B-19	
B-20	
B-21	
B-22	

<u>Compound Number</u>	<u>Structural Formula</u>
B-23	
B23a	

[0159] In still another embodiment, the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

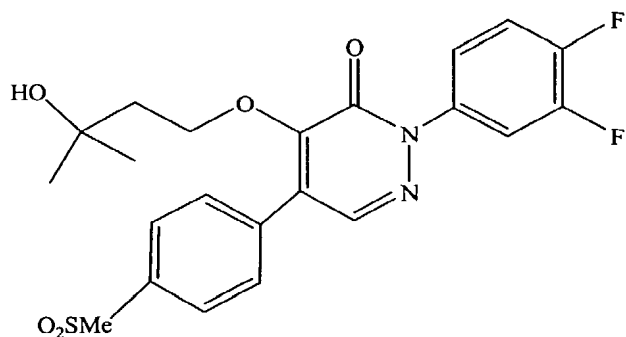
[0160] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is parecoxib (B-24, U.S. Patent No. 5,932,598, CAS No. 198470-84-7), which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, may be advantageously employed as a source of a cyclooxygenase inhibitor (US 5,932,598, herein incorporated by reference).



B-24

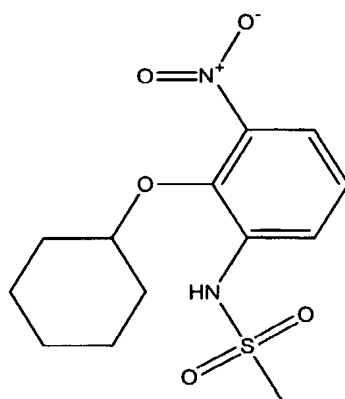
[0161] One form of parecoxib is sodium parecoxib.

[0162] In another embodiment of the invention, the compound having the formula B-25 or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having formula B-25 that has been previously described in International Publication number WO 00/24719 (which is herein incorporated by reference) is another tricyclic cyclooxygenase-2 selective inhibitor that may be advantageously employed.



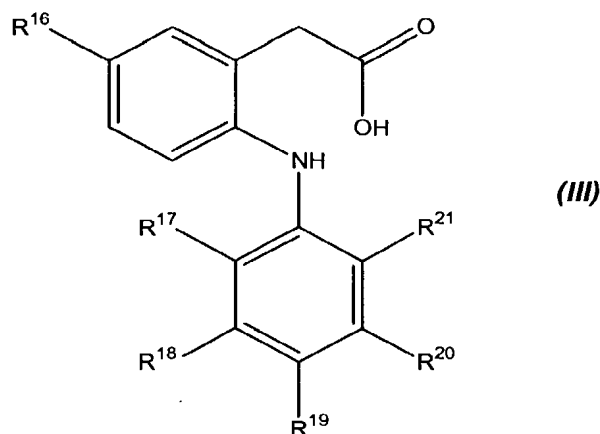
B-25

[0163] Another cyclooxygenase-2 selective inhibitor that is useful in connection with the method(s) of the present invention is N-(2-cyclohexyloxynitrophenyl)-methane sulfonamide (NS-398) having a structure shown below as B-26, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having formula B-26.



B-26

[0164] In yet a further embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula (III) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



[0165] wherein:

[0166] R^{16} is methyl or ethyl;

[0167] R^{17} is chloro or fluoro;

[0168] R^{18} is hydrogen or fluoro;

[0169] R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

[0170] R^{20} is hydrogen or fluoro; and

[0171] R^{21} is chloro, fluoro, trifluoromethyl or methyl, provided, however, that each of R^{17} , R^{18} , R^{20} and R^{21} is not fluoro when R^{16} is ethyl and R^{19} is H.

[0172] Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention is a compound that has the designation of COX 189 (lumiracoxib; B-211) and that has the structure shown in Formula (III) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

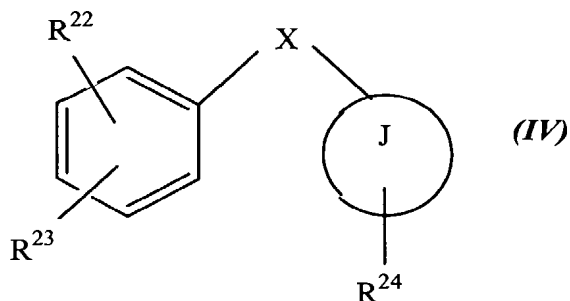
[0173] R^{16} is ethyl;

[0174] R^{17} and R^{19} are chloro;

[0175] R^{18} and R^{20} are hydrogen; and

[0176] R^{21} is methyl.

[0177] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is represented by Formula (IV) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



[0178] wherein:

[0179] X is O or S;

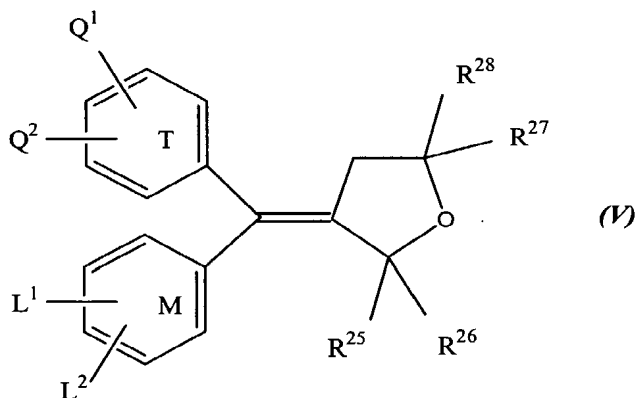
[0180] J is a carbocycle or a heterocycle;

[0181] R^{22} is NHSO_2CH_3 or F;

[0182] R^{23} is H, NO_2 , or F; and

[0183] R^{24} is H, NHSO_2CH_3 , or $(\text{SO}_2\text{CH}_3)\text{C}_6\text{H}_4$.

[0184] According to another embodiment, the cyclooxygenase-2 selective inhibitors used in the present method(s) have the structural Formula (V) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



[0185] wherein:

[0186] T and M are independently phenyl, naphthyl, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

[0187] R^{25} , R^{26} , R^{27} , and R^{28} are independently hydrogen, halogen, lower alkyl radical having from 1 to 6 carbon atoms, lower haloalkyl radical having from 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or

[0188] R^{25} and R^{26} , together with the carbon atom to which they are attached, form a carbonyl or a saturated hydrocarbon ring having from 3 to 7 carbon atoms; or

[0189] R^{27} and R^{28} , together with the carbon atom to which they are attached, form a carbonyl or a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

[0190] Q^1 , Q^2 , L^1 or L^2 are independently hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, trifluoromethyl, lower methoxy having from 1 to 6 carbon atoms, alkylsulfinyl or alkylsulfonyl; and

[0191] at least one of Q^1 , Q^2 , L^1 or L^2 is in the para position and is $-S(O)_n-R$, wherein n is 0, 1, or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms or a lower haloalkyl radical having from 1 to 6 carbon atoms, or an $-SO_2NH_2$; or Q^1 and Q^2 together form methylenedioxy; or L^1 and L^2 together form methylenedioxy.

[0192] In another embodiment, the compounds N-(2-cyclohexyloxynitrophenyl) methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide or isomers, pharmaceutically acceptable salts, esters, or prodrugs thereof having the structure of Formula (V) are employed as cyclooxygenase-2 selective inhibitors.

[0193] In a further embodiment, compounds that are useful for the cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof used in connection with the method(s) of the present invention, the structures for which are set forth in Table 3 below, include, but are not limited to:

[0194] 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-27);

[0195] 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-28);

[0196] 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-29);

[0197] 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-30);

[0198] 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid (B-31);

[0199] 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-32);

[0200] 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-33);

[0201] 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-34);

[0202] 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-35);

[0203] 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-36);

- [0204] 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-37);
- [0205] 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-38);
- [0206] 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-39);
- [0207] 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-40);
- [0208] 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-41);
- [0209] 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-42);
- [0210] 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-43);
- [0211] 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-44);
- [0212] 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-45);
- [0213] 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-46);
- [0214] 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-47);
- [0215] 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-48);
- [0216] 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-49);
- [0217] 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-50);
- [0218] 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-51);
- [0219] 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-52);
- [0220] 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-53);
- [0221] 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-54);

[0222] 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-55);

[0223] 6-[[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-56);

[0224] 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-57);

[0225] 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-58);

[0226] 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-59);

[0227] 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-60);

[0228] 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-61);

[0229] 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-62);

[0230] 8-chloro-6-[[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-63);

[0231] 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-64);

[0232] 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-65);

[0233] 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-66);

[0234] 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-67);

[0235] 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-68);

[0236] 6-[[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-69);

[0237] 6-[[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-70);

[0238] 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-71);

[0239] 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid (B-72);

[0240] 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-73);

[0241] 3-[(3-chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene]-dihydro-furan-2-one or BMS-347070 (B-74);

[0242] 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine (B-75);

[0243] 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone (B-76);

[0244] 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (B-77);

[0245] 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole (B-78);

[0246] 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-79);

[0247] 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-80);

[0248] 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl) benzenesulfonamide (B-81);

[0249] 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-82);

[0250] 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-83);

[0251] 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-84);

[0252] 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-85);

[0253] 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide (B-86);

[0254] 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-87);

[0255] 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-88);

- [0256] 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-89);
- [0257] 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-90);
- [0258] 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-91);
- [0259] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-92);
- [0260] 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-93);
- [0261] 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-94);
- [0262] 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl] benzenesulfonamide (B-95);
- [0263] 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-96);
- [0264] 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-97);
- [0265] 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-98);
- [0266] 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-99);
- [0267] 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl] benzenesulfonamide (B-100);
- [0268] 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-101);
- [0269] 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-102);
- [0270] 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-103);
- [0271] 5-ene (B-103);
- [0272] 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl] benzenesulfonamide (B-104);
- [0273] 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene (B-105);
- [0274] 6-ene (B-105);

[0275] 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl) phenyl]spiro [2.4]hept-5-ene (B-106);

[0276] 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl] benzenesulfonamide (B-107);

[0277] 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro [2.4]hept-5-ene (B-108);

[0278] 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl] spiro[2.4]hept-5-ene (B-109);

[0279] 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl] benzenesulfonamide (B-110);

[0280] 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonyl phenyl)thiazole (B-111);

[0281] 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonyl phenyl)thiazole (B-112);

[0282] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole (B-113);

[0283] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-114);

[0284] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole (B-115);

[0285] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole (B-116);

[0286] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino) thiazole (B-117);

[0287] 2-[(3,5-dichlorophenoxy)methyl]-4-(4-fluorophenyl)-5-[4-(methyl sulfonyl)phenyl]thiazole (B-118);

[0288] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-119);

[0289] 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene (B-120);

[0290] 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl] benzenesulfonamide (B-121);

[0291] 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene (B-122);

[0292] 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl] benzenesulfonamide (B-123);

[0293] 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-124);

[0294] 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-125);

[0295] 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile (B-126);

[0296] 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-127);

[0297] 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-128);

[0298] 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-129);

[0299] 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl] pyridine (B-130);

[0300] 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-

[0301] 2-yl]pyridine (B-131);

[0302] 2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-132);

[0303] 2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-133);

[0304] 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-134);

[0305] 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-135);

[0306] 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-136);

[0307] 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole (B-137);

[0308] 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole (B-138);

[0309] 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (B-139);

[0310] 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-140);

[0311] 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole (B-141);

[0312] 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-142);

[0313] 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-143);

[0314] 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-144);

[0315] 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-145);

[0316] 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-146);

[0317] 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl] benzene sulfonamide (B-147);

[0318] 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole (B-148);

[0319] 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl] benzenesulfonamide (B-149);

[0320] 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl] benzenesulfonamide (B-150);

[0321] 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl] benzenesulfonamide (B-151);

[0322] 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-152);

[0323] 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl] benzenesulfonamide (B-153);

[0324] N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide (B-154);

[0325] ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate (B-155);

[0326] 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole (B-156);

[0327] 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole (B-157);

[0328] 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-158);

[0329] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole (B-159);

[0330] 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole (B-160);

[0331] 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-161);

[0332] 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-162);

[0333] 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine (B-163);

[0334] 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-164);

[0335] 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide (B-165);

[0336] 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene (B-166);

[0337] 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole (B-167);

[0338] 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide (B-168);

[0339] 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-169);

[0340] 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-170);

[0341] 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide (B-171);

[0342] 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-172);

[0343] 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-173);

[0344] 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-174);

[0345] 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-175);

- [0346] 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-176);
- [0347] 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methyl sulfonyl)benzene (B-177);
- [0348] 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-178);
- [0349] 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzene sulfonamide (B-179);
- [0350] 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-180);
- [0351] 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzene sulfonamide (B-181);
- [0352] 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-182);
- [0353] 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-183);
- [0354] 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-184);
- [0355] 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-185);
- [0356] 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl] benzenesulfonamide (B-186);
- [0357] 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-187);
- [0358] 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl] benzenesulfonamide (B-188);
- [0359] 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide (B-189);
- [0360] ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate (B-190);
- [0361] 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl] acetic acid (B-191);
- [0362] 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] oxazole (B-192);
- [0363] 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole (B-193);

[0364] 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole (B-194);

[0365] 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl] benzenesulfonamide (B-195);

[0366] 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-196);

[0367] 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-197);

[0368] 5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone (B-198);

[0369] 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-199);

[0370] 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide (B-200);

[0371] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide (B-201);

[0372] 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-202);

[0373] 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-203);

[0374] 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-204);

[0375] 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-205);

[0376] 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-206);

[0377] 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-207);

[0378] [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl] benzenesulfonamide (B-208);

[0379] 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide (B-209);

[0380] 4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl] benzenesulfonamide (B-210);

[0381] [2-(2-chloro-6-fluoro-phenylamino)-5-methyl-phenyl]-acetic acid or COX 189 (lumiracoxib; B-211);

[0382] N-(4-Nitro-2-phenoxy-phenyl)-methanesulfonamide or nimesulide (B-212);

[0383] N-[6-(2,4-difluoro-phenoxy)-1-oxo-indan-5-yl]-methanesulfonamide or flosulide (B-213);

[0384] N-[6-(2,4-Difluoro-phenylsulfanyl)-1-oxo-1H-inden-5-yl]-methanesulfonamide, sodium salt (B-214);

[0385] N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide (B-215);

[0386] 3-(3,4-Difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl-5-(2,2,2-trifluoro-ethyl)-5H-furan-2-one (B-216);

[0387] (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4(5H)-thiazolone (B-217);

[0388] CS-502 (B-218);

[0389] LAS-34475 (B-219);

[0390] LAS-34555 (B-220);

[0391] S-33516 (B-221);

[0392] SD-8381 (B-222);

[0393] L-783003 (B-223);

[0394] N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide (B-224);

[0395] D-1367 (B-225);

[0396] L-748731 (B-226);

[0397] (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid (B-227);

[0398] CGP-28238 (B-228);

[0399] 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one or BF-389 (B-229);

[0400] GR-253035 (B-230);

[0401] 6-dioxo-9H-purin-8-yl-cinnamic acid (B-231);

[0402] S-2474 (B-232);

[0403] 4-[4-(methyl)-sulfonyl]phenyl]-3-phenyl-2(5H)-furanone;

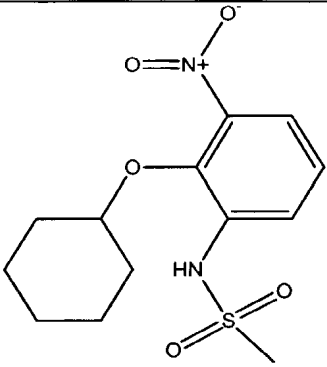
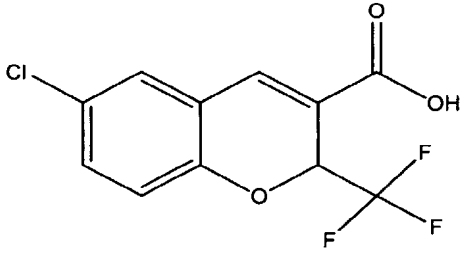
[0404] 4-(5-methyl-3-phenyl-4-isoxazolyl);

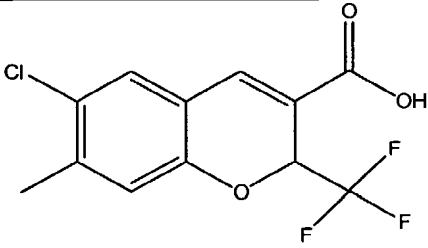
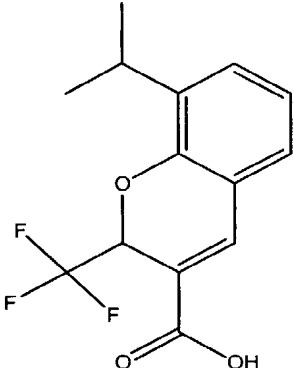
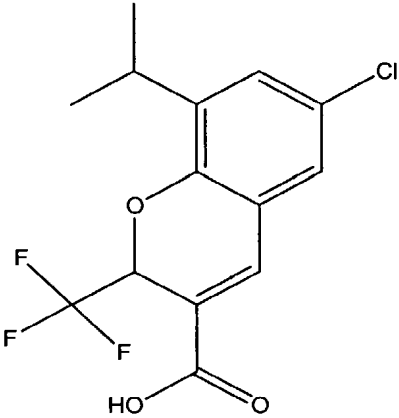
[0405] 2-(6-methylpyrid-3-yl)-3-(4-methylsulfonylphenyl)-5-chloropyridine;

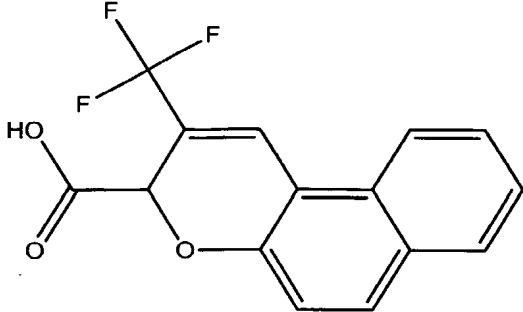
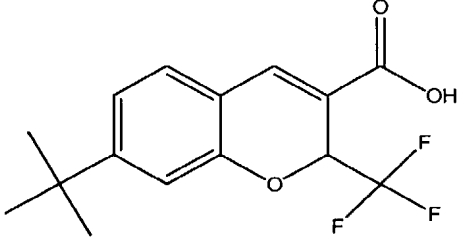
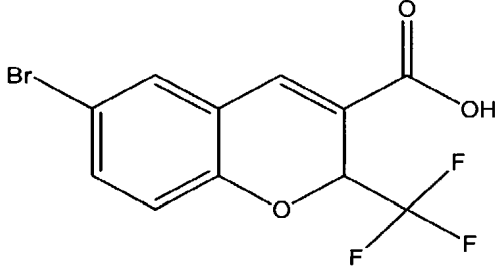
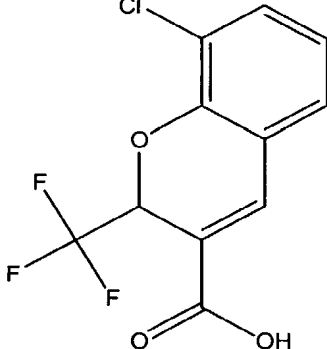
[0406] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl];

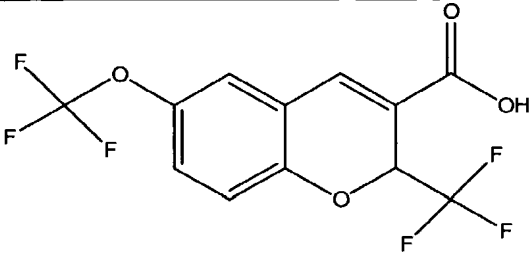
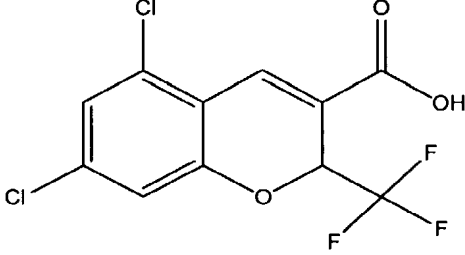
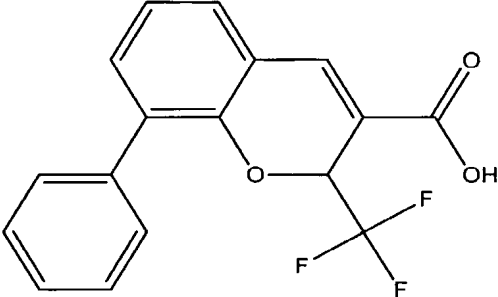
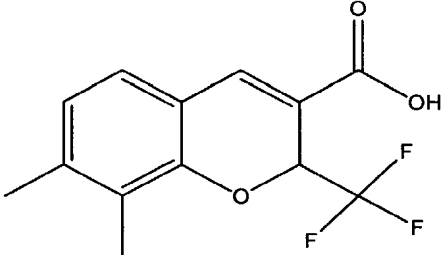
- [0407] N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl];
- [0408] 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl]-1H-pyrazol-
- [0409] 1-yl]benzenesulfonamide;
- [0410] (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;
- [0411] 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methyl sulfonyl)phenyl]-3(2H)-pyridzainone;
- [0412] 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid;
- [0413] 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0414] [2-(2,4-dichloro-6-ethyl-3,5-dimethyl-phenylamino)-5-propyl-phenyl]-acetic acid.

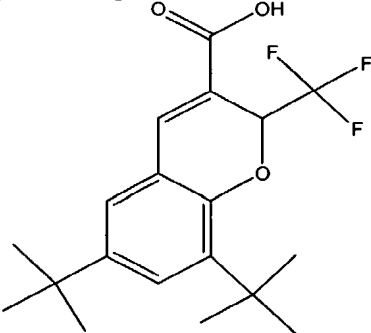
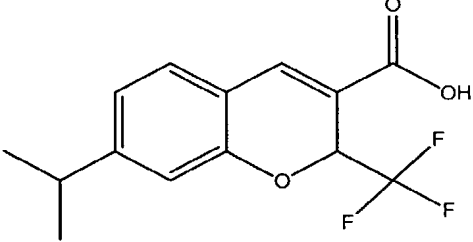
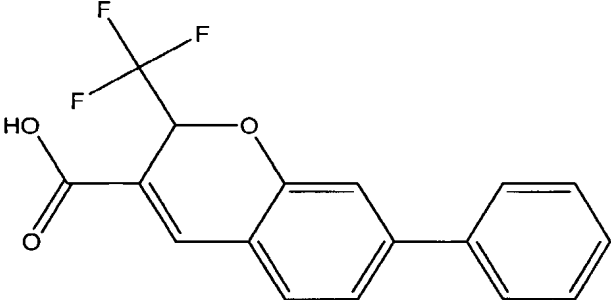
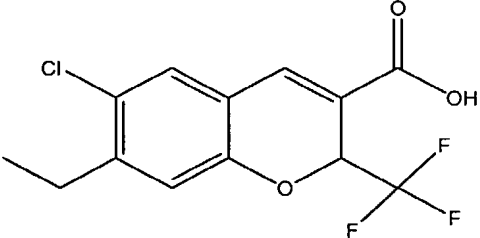
TABLE 3
EXAMPLES OF CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS
EMBODIMENTS

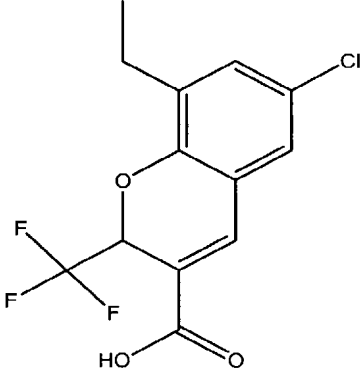
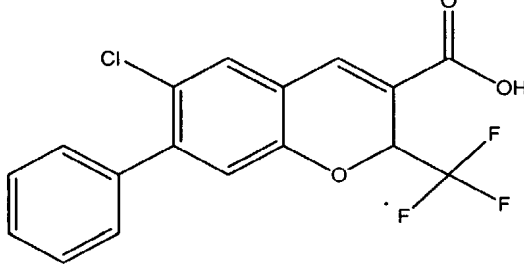
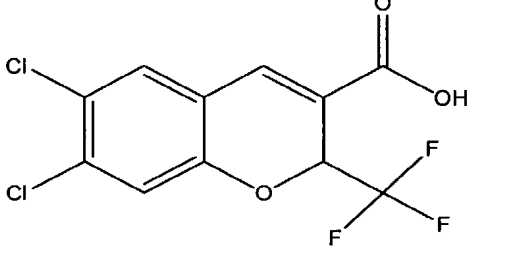
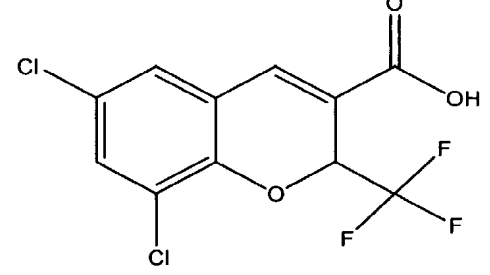
<u>Compound Number</u>	<u>Structural Formula</u>
B-26	 <p>N-(2-cyclohexyloxynitrophenyl) methane sulfonamide or NS-398;</p>
B-27	 <p>6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>

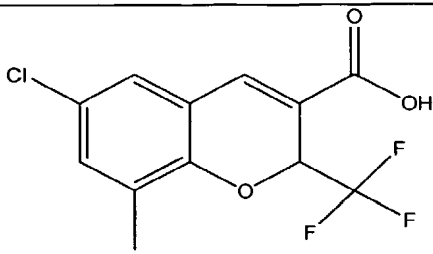
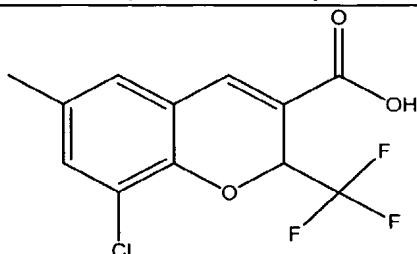
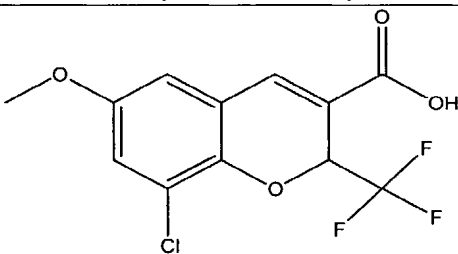
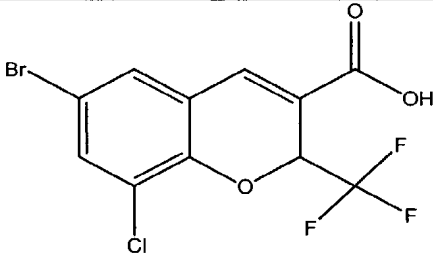
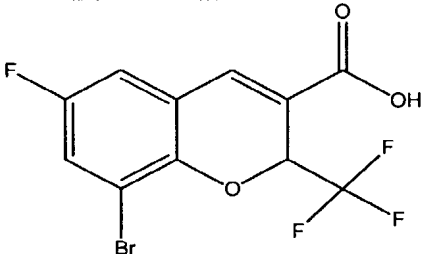
<u>Compound Number</u>	<u>Structural Formula</u>
B-28	 <p>6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-29	 <p>8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-30	 <p>6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>

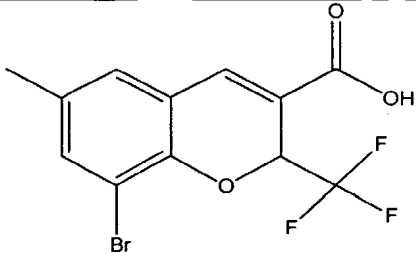
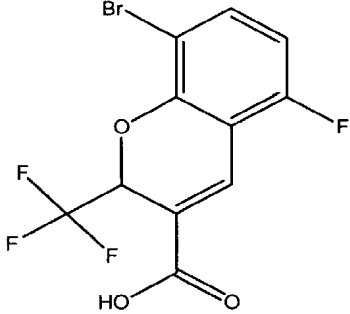
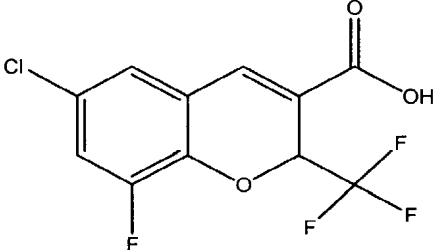
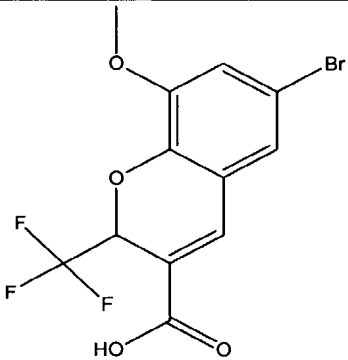
<u>Compound Number</u>	<u>Structural Formula</u>
B-31	 <p>2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid;</p>
B-32	 <p>7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-33	 <p>6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-34	 <p>8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>

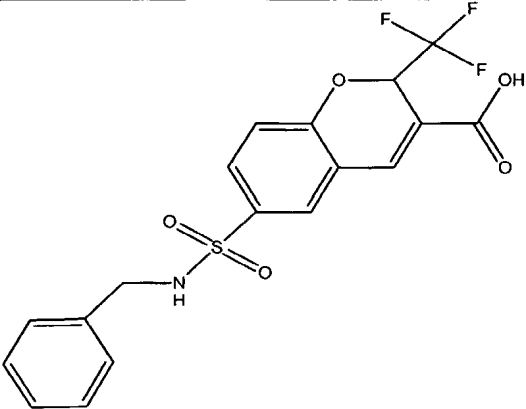
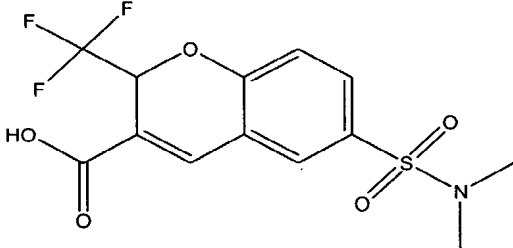
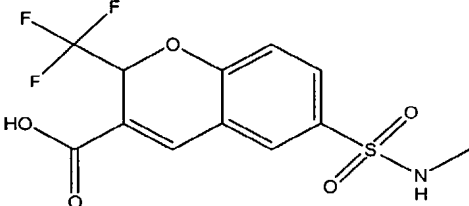
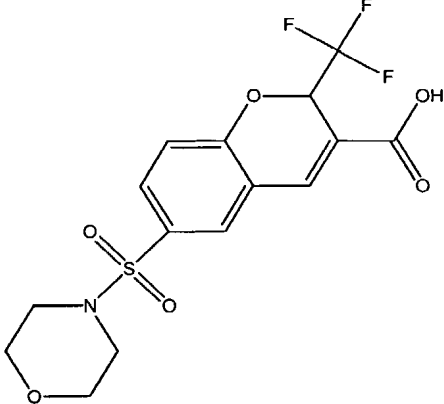
<u>Compound Number</u>	<u>Structural Formula</u>
B-35	 <p>6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-36	 <p>5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-37	 <p>8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-38	 <p>7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>

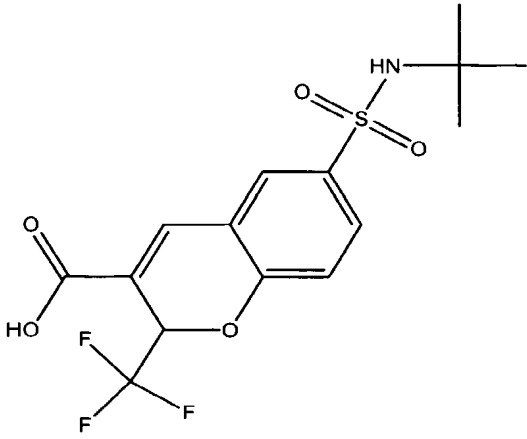
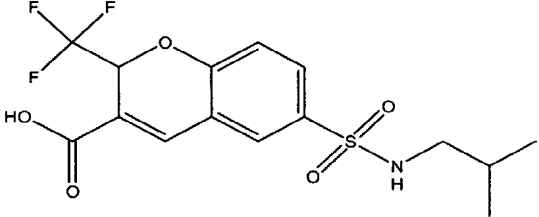
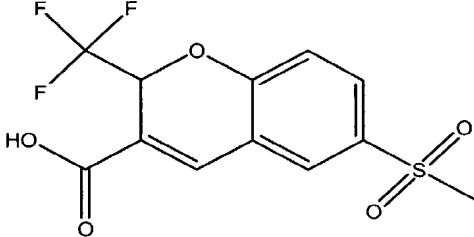
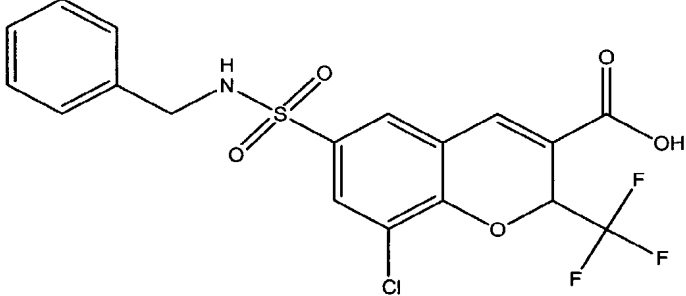
<u>Compound Number</u>	<u>Structural Formula</u>
B-39	 <p>6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-40	 <p>7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-41	 <p>7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-42	 <p>6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>

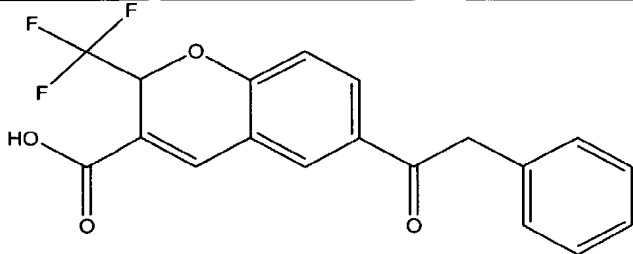
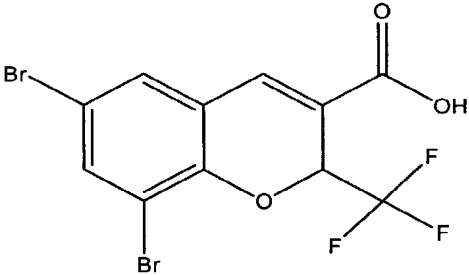
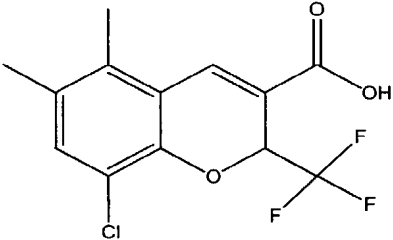
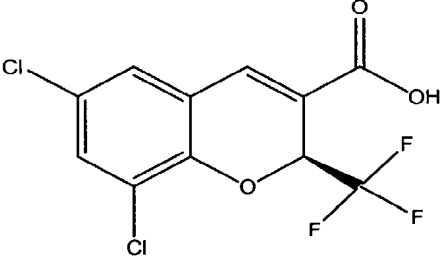
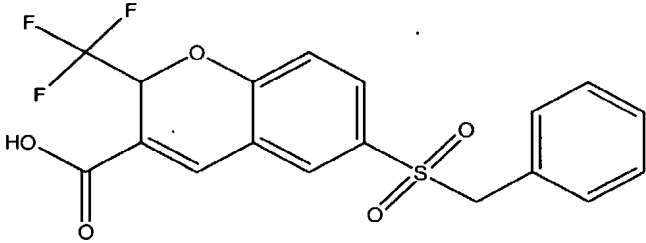
<u>Compound Number</u>	<u>Structural Formula</u>
B-43	 <p>6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-44	 <p>6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-45	 <p>6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-46	 <p>6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>

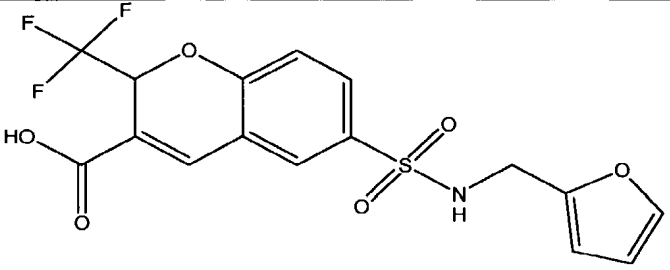
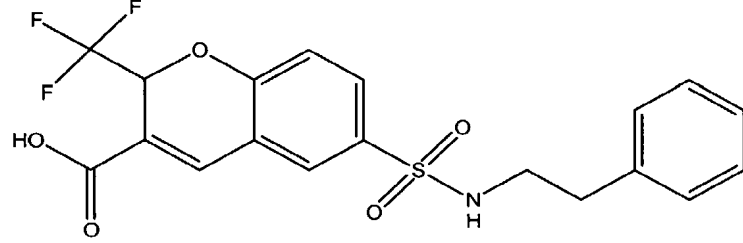
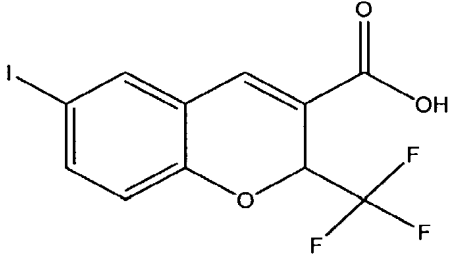
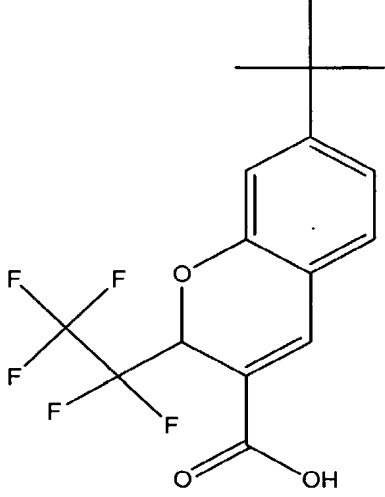
<u>Compound Number</u>	<u>Structural Formula</u>
B-47	 <p>6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-48	 <p>8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-49	 <p>8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-50	 <p>6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-51	 <p>8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>

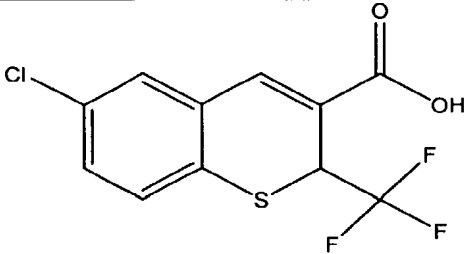
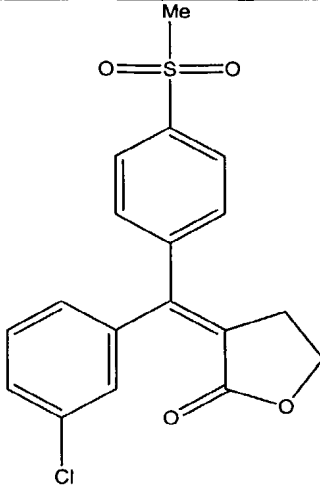
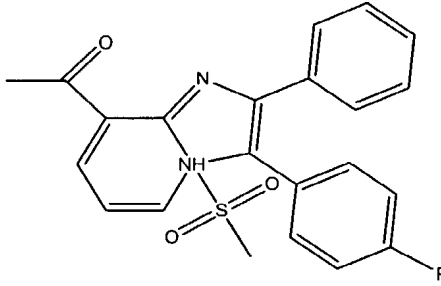
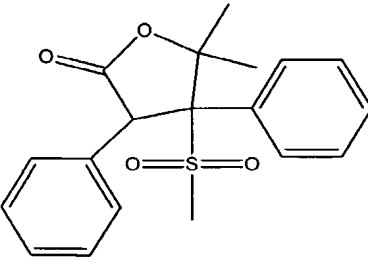
<u>Compound Number</u>	<u>Structural Formula</u>
B-52	 <p>8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-53	 <p>8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-54	 <p>6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-55	 <p>6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>

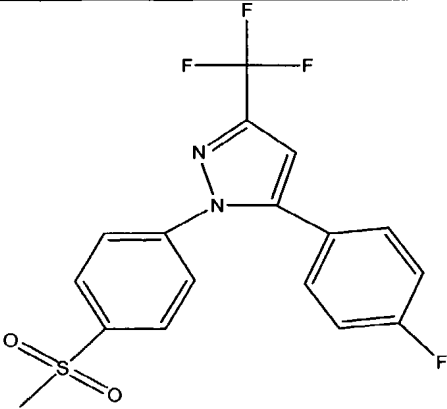
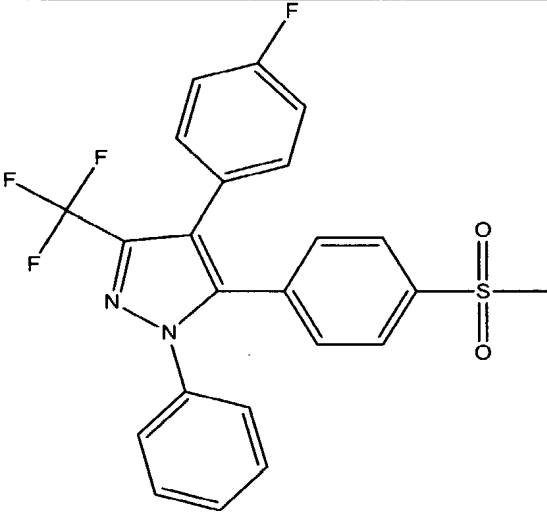
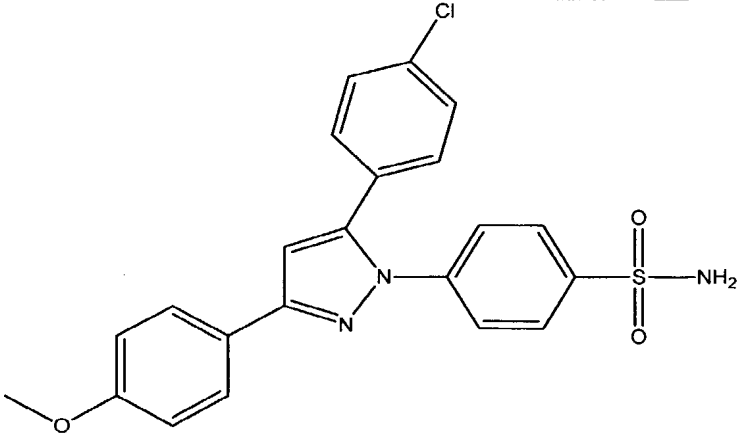
<u>Compound Number</u>	<u>Structural Formula</u>
B-56	 <p>6-[[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-57	 <p>6-[[[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-58	 <p>6-[[[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-59	 <p>6-[[[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>

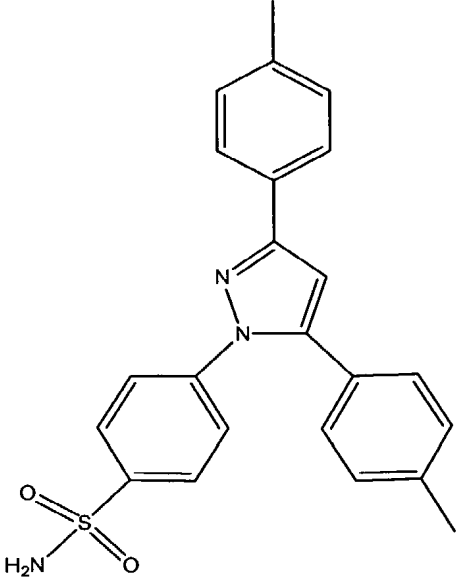
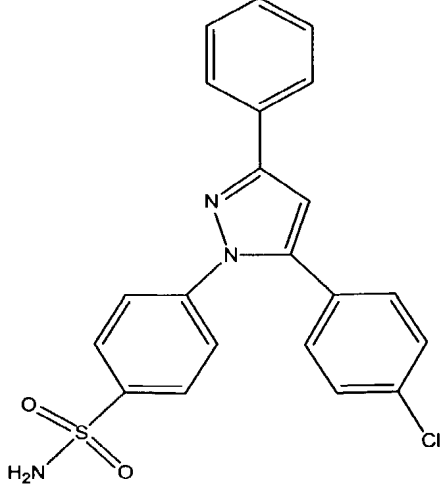
<u>Compound Number</u>	<u>Structural Formula</u>
B-60	 <p>6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-61	 <p>6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-62	 <p>6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-63	 <p>8-chloro-6-[[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>

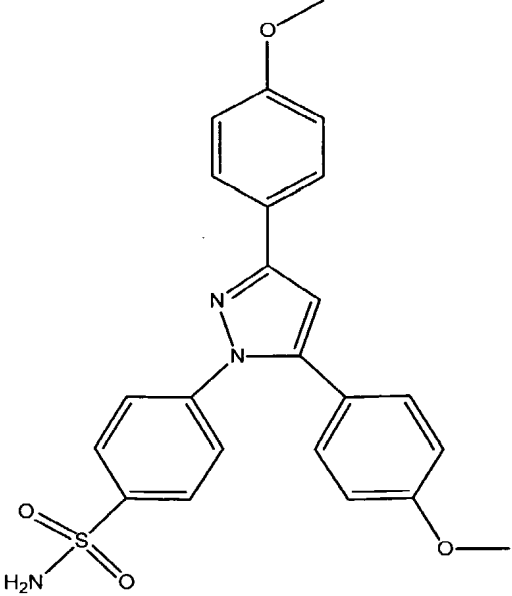
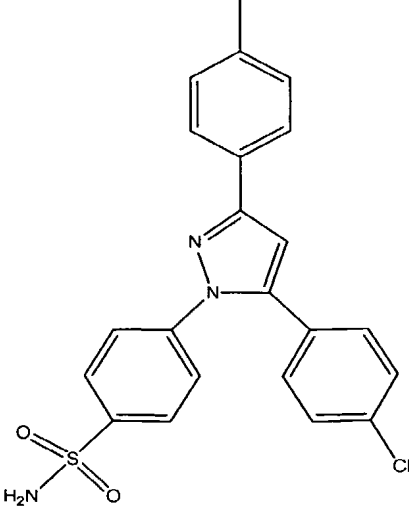
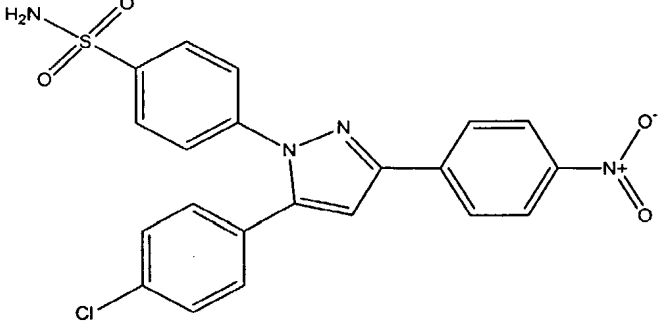
<u>Compound Number</u>	<u>Structural Formula</u>
B-64	 <p>6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-65	 <p>6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-66	 <p>8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-67	 <p>6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-68	 <p>6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>

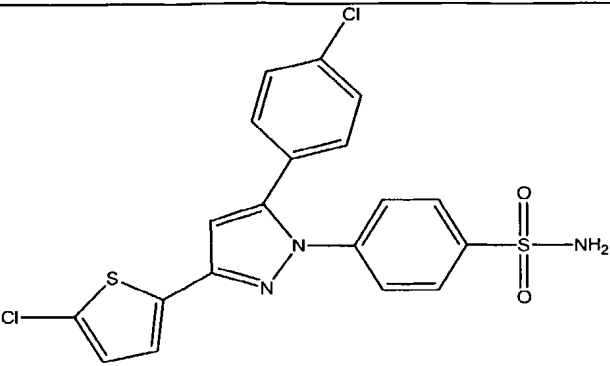
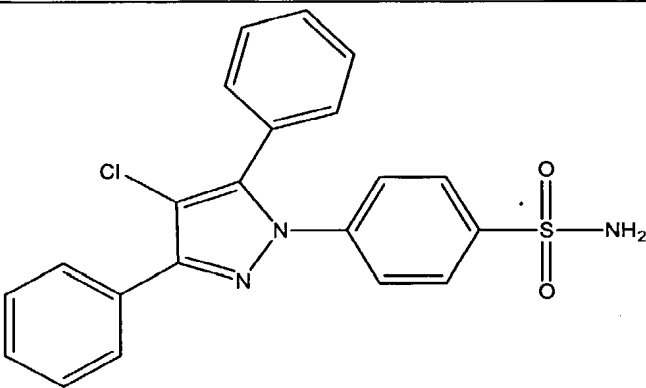
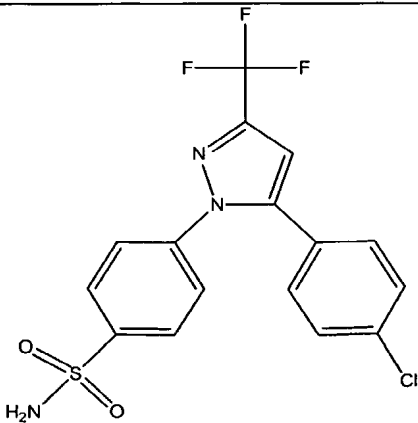
<u>Compound Number</u>	<u>Structural Formula</u>
B-69	 <p>6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-70	 <p>6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-71	 <p>6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-72	 <p>7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;</p>

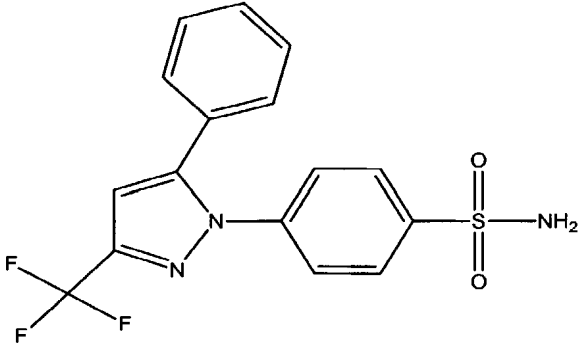
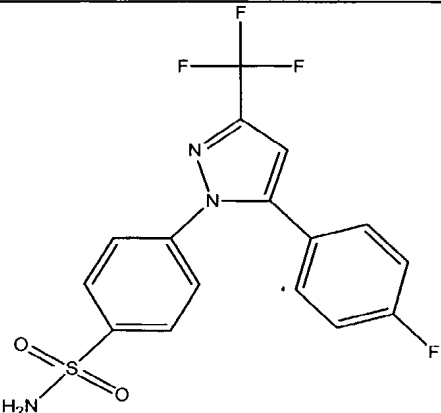
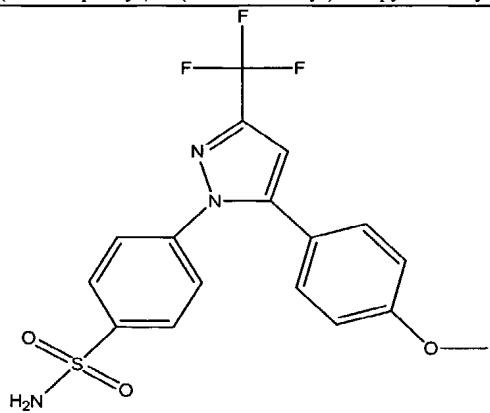
<u>Compound Number</u>	<u>Structural Formula</u>
B-73	 <p>6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;</p>
B-74	 <p>3-[(3-chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene]-dihydro-furan-2-one or BMS-347070;</p>
B-75	 <p>8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;</p>
B-76	 <p>5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;</p>

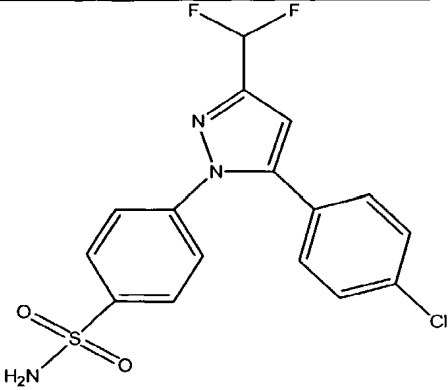
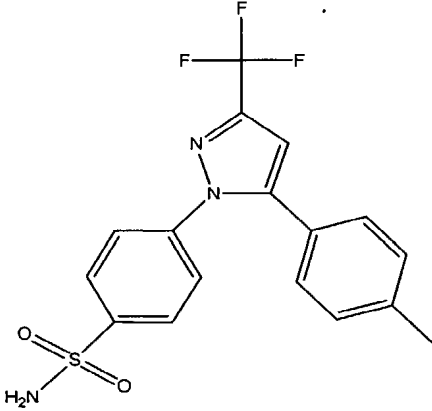
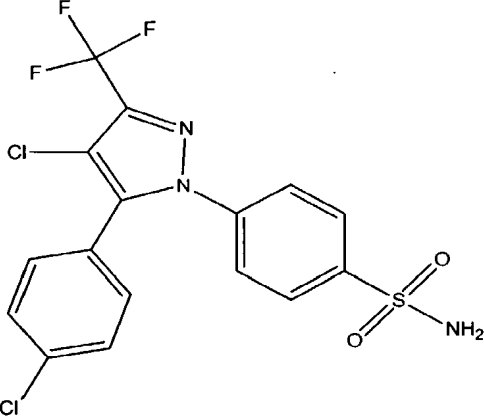
<u>Compound Number</u>	<u>Structural Formula</u>
B-77	 <p data-bbox="646 720 1398 747">5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;</p>
B-78	 <p data-bbox="646 1293 1170 1352">4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;</p>
B-79	 <p data-bbox="646 1845 1289 1904">4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;</p>

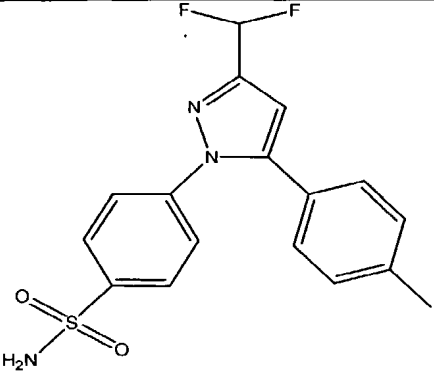
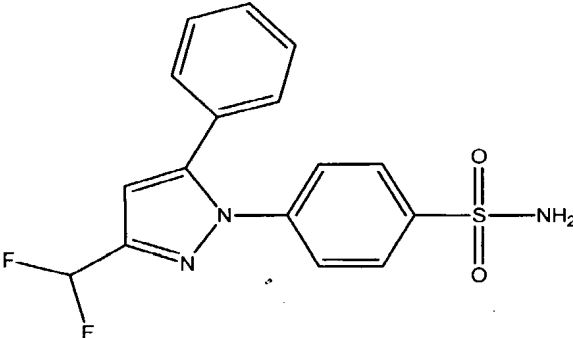
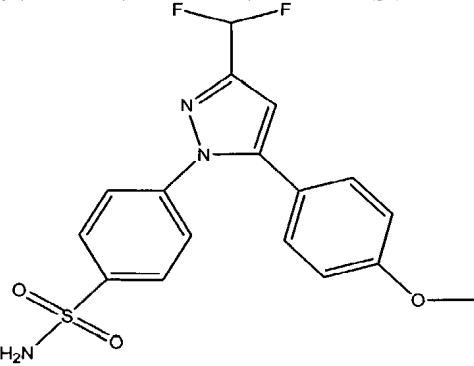
<u>Compound Number</u>	<u>Structural Formula</u>
B-80	 <p>4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;</p>
B-81	 <p>4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;</p>

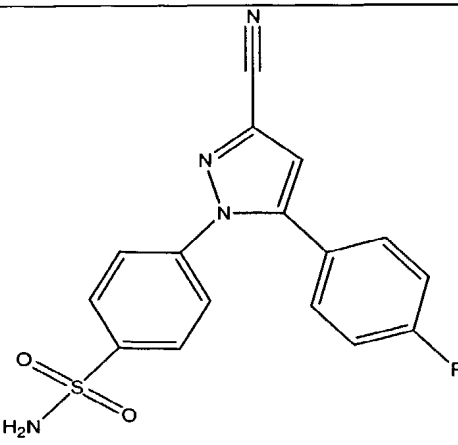
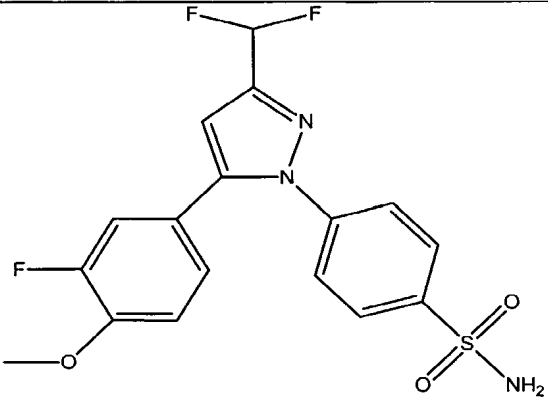
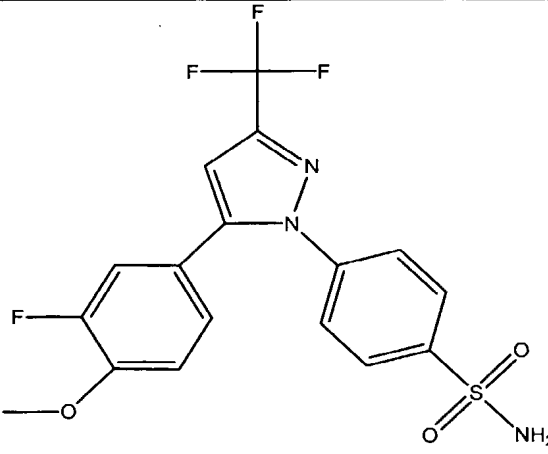
<u>Compound Number</u>	<u>Structural Formula</u>
B-82	 <p>4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;</p>
B-83	 <p>4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;</p>
B-84	 <p>4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;</p>

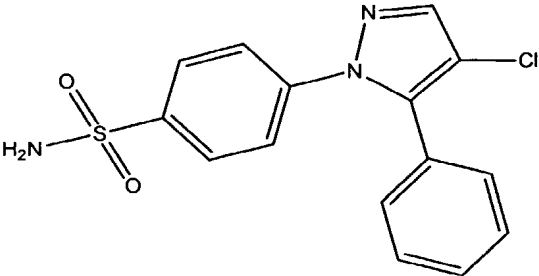
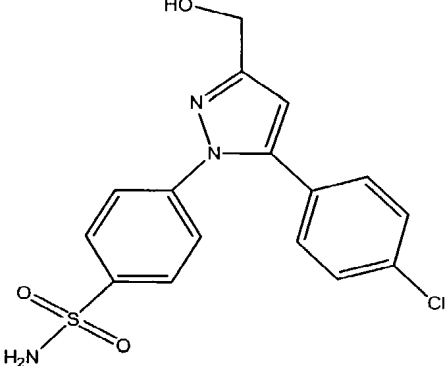
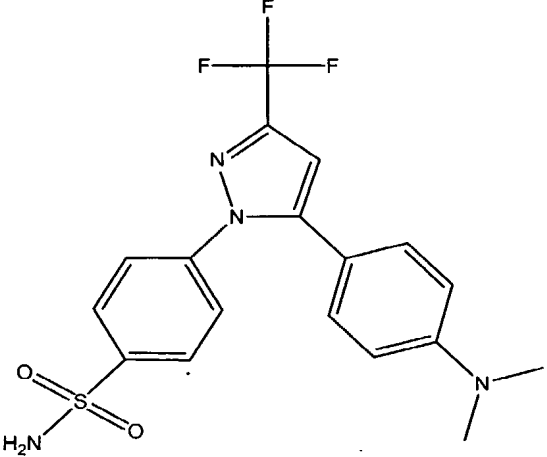
<u>Compound Number</u>	<u>Structural Formula</u>
B-85	 <p>4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;</p>
B-86	 <p>4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide;</p>
B-87	 <p>4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>

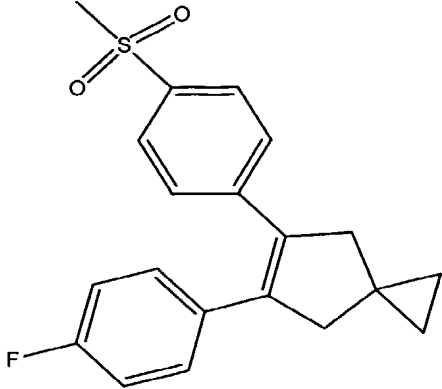
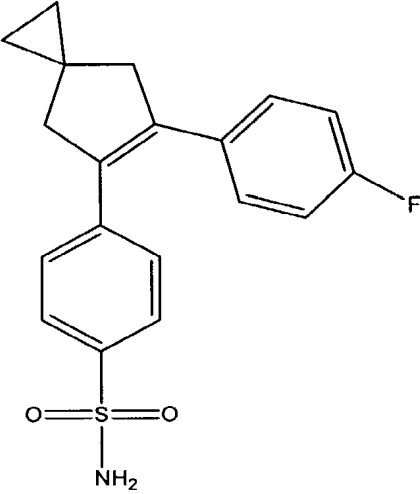
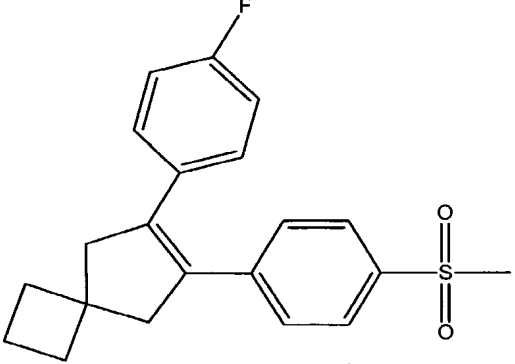
<u>Compound Number</u>	<u>Structural Formula</u>
B-88	 <p>4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>
B-89	 <p>4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>
B-90	 <p>4[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>

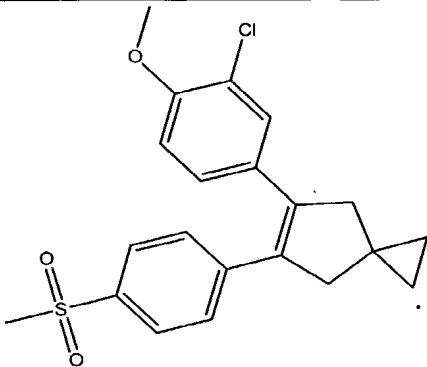
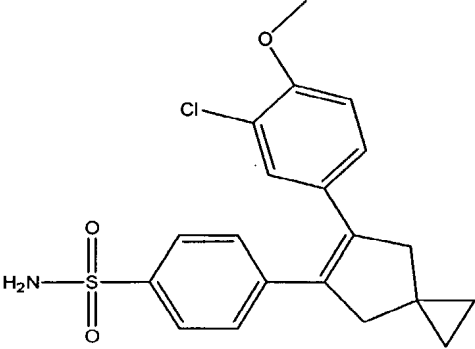
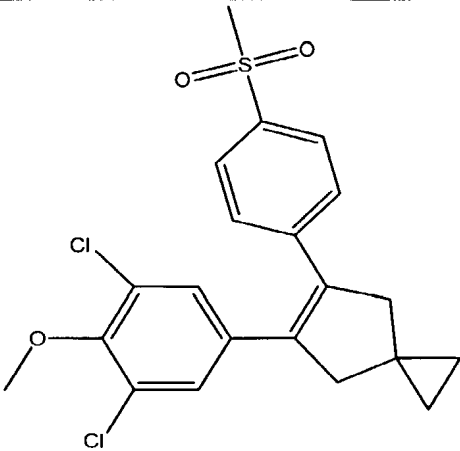
<u>Compound Number</u>	<u>Structural Formula</u>
B-91	 <p>Chemical structure of 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide. The structure features a central 1H-pyrazole ring. At position 3, there is a difluoromethyl group (-CF₂H). At position 5, there is a 4-chlorophenyl group. At position 1, there is a 4-sulfamoylphenyl group (-C₆H₄-SO₂NH₂).</p> <p>4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>
B-92	 <p>Chemical structure of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide. The structure features a central 1H-pyrazole ring. At position 3, there is a trifluoromethyl group (-CF₃). At position 5, there is a 4-methylphenyl group. At position 1, there is a 4-sulfamoylphenyl group (-C₆H₄-SO₂NH₂).</p> <p>4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>
B-93	 <p>Chemical structure of 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide. The structure features a central 1H-pyrazole ring. At position 3, there is a trifluoromethyl group (-CF₃). At position 5, there is a 4-chlorophenyl group. At position 4, there is a 4-chlorophenyl group. At position 1, there is a 4-sulfamoylphenyl group (-C₆H₄-SO₂NH₂).</p> <p>4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>

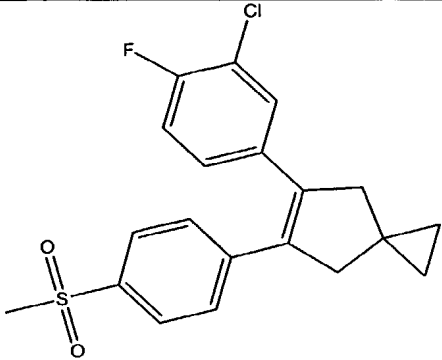
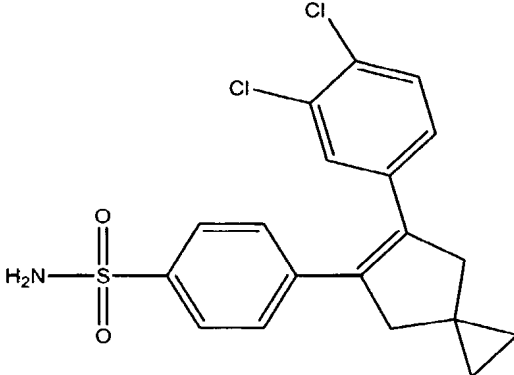
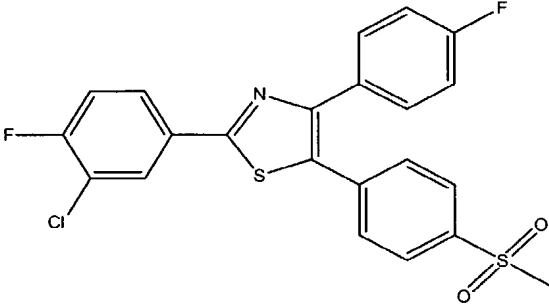
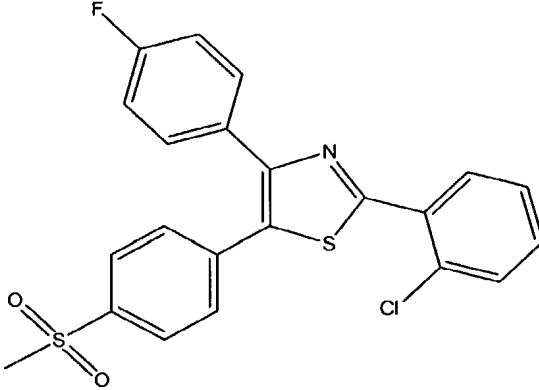
<u>Compound Number</u>	<u>Structural Formula</u>
B-94	 <p>4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>
B-95	 <p>4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;</p>
B-96	 <p>4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>

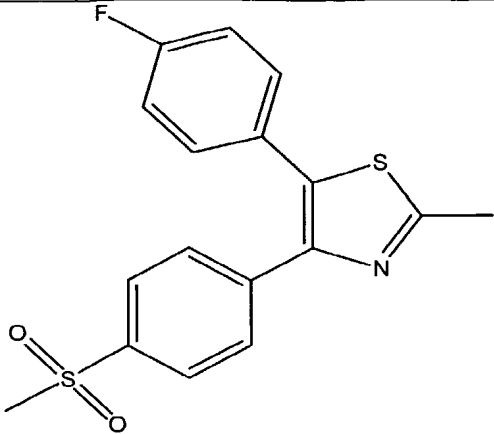
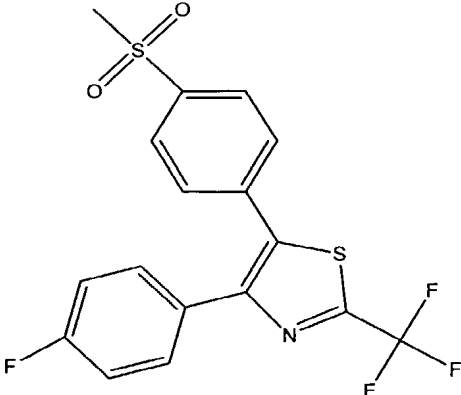
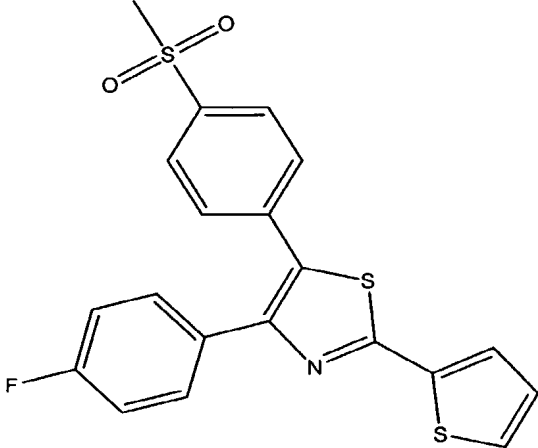
<u>Compound Number</u>	<u>Structural Formula</u>
B-97	 <p>4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>
B-98	 <p>4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide;</p>
B-99	 <p>4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;</p>

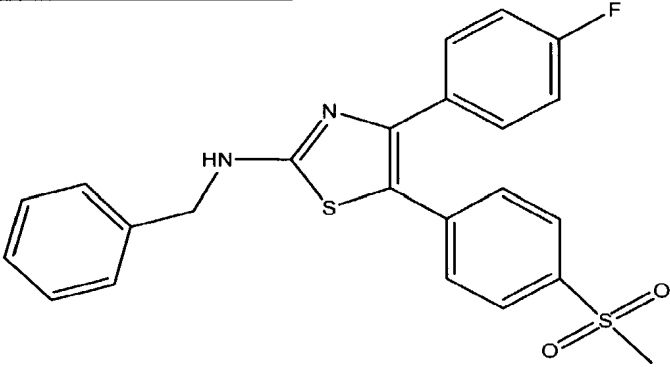
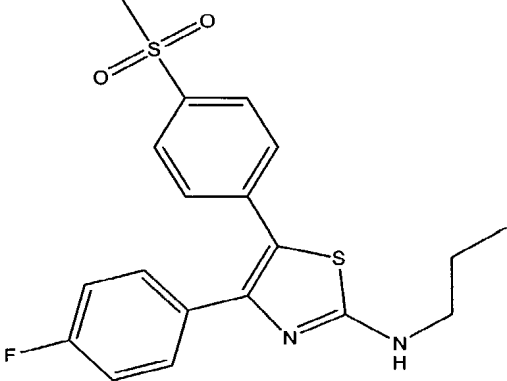
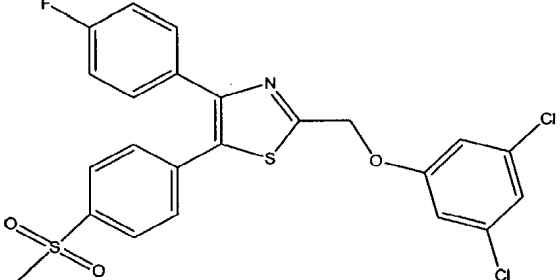
<u>Compound Number</u>	<u>Structural Formula</u>
B-100	 <p>4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;</p>
B-101	 <p>4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>
B-102	 <p>4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>

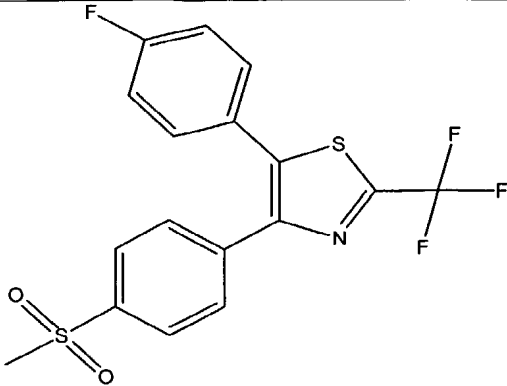
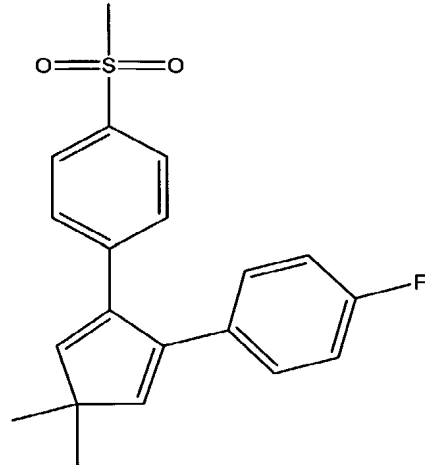
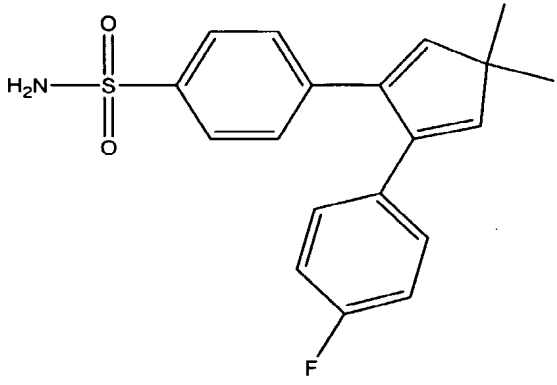
<u>Compound Number</u>	<u>Structural Formula</u>
B-103	 <p data-bbox="646 730 1393 762">5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;</p>
B-104	 <p data-bbox="646 1287 1393 1318">4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;</p>
B-105	 <p data-bbox="646 1755 1360 1787">6-(4-fluorophenyl)-7-[4-methylsulfonyl]phenyl]spiro[3.4]oct-6-ene;</p>

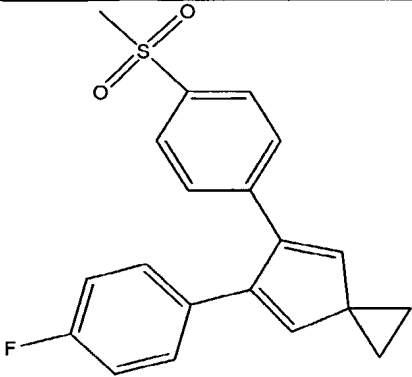
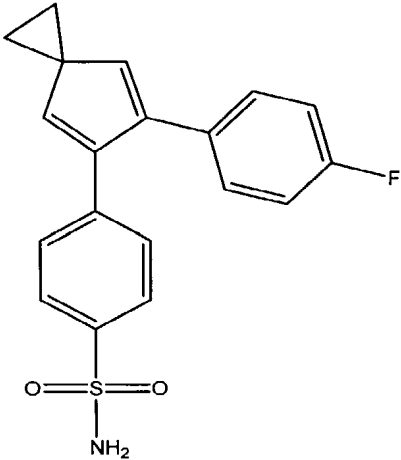
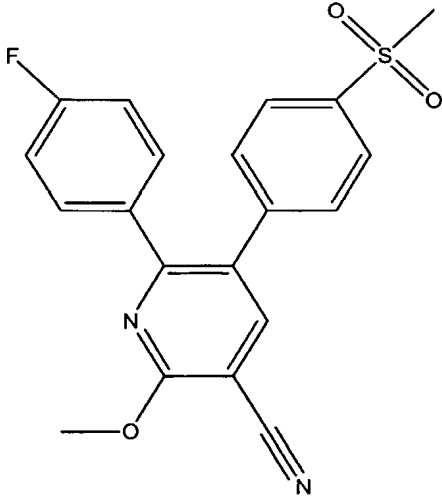
<u>Compound Number</u>	<u>Structural Formula</u>
B-106	 <p>5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;</p>
B-107	 <p>4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;</p>
B-108	 <p>5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;</p>

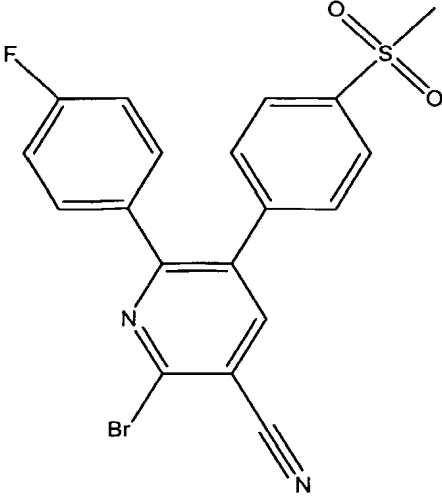
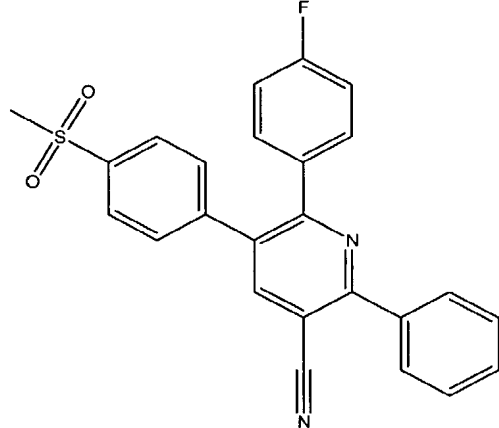
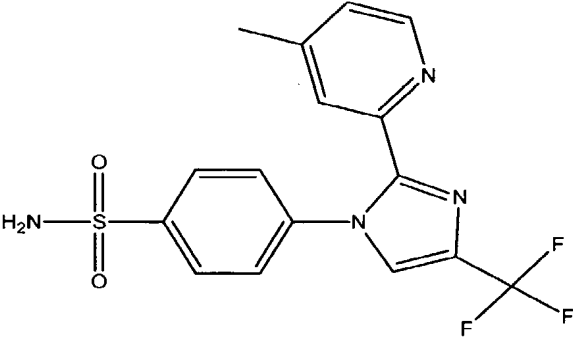
<u>Compound Number</u>	<u>Structural Formula</u>
B-109	 <p>5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;</p>
B-110	 <p>4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;</p>
B-111	 <p>2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;</p>
B-112	 <p>2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;</p>

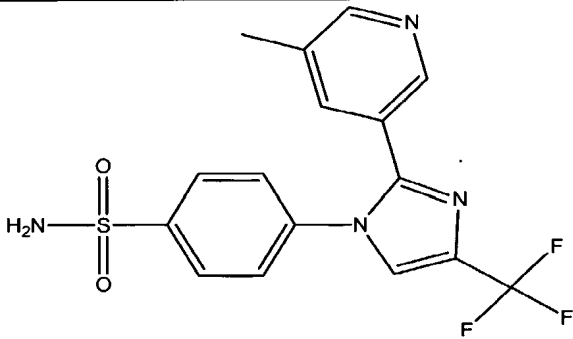
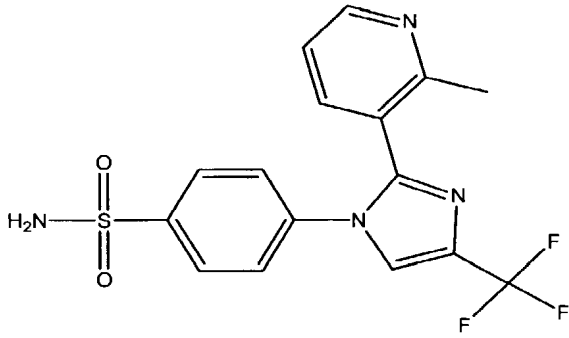
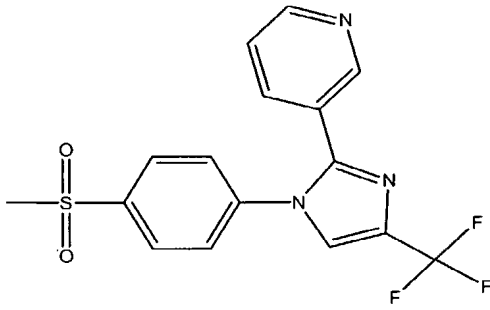
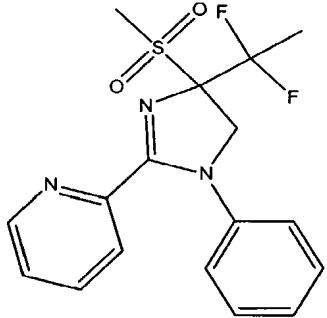
<u>Compound Number</u>	<u>Structural Formula</u>
B-113	 <p>5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;</p>
B-114	 <p>4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;</p>
B-115	 <p>4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;</p>

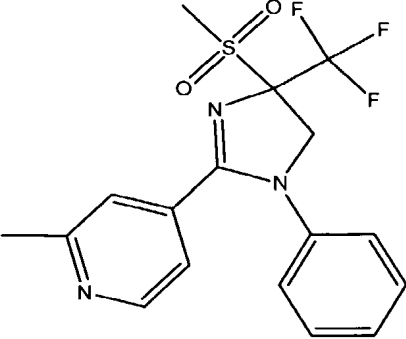
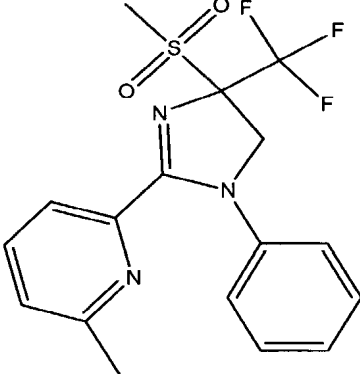
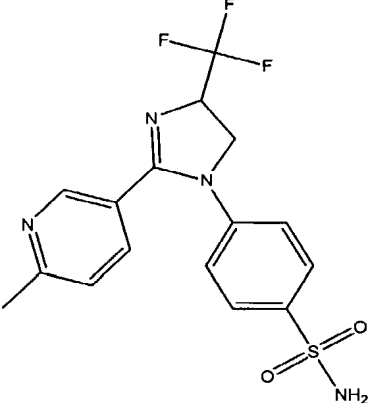
<u>Compound Number</u>	<u>Structural Formula</u>
B-116	 <p data-bbox="651 695 1398 726">4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;</p>
B-117	 <p data-bbox="651 1167 1398 1199">4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;</p>
B-118	 <p data-bbox="651 1545 1398 1577">2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;</p>

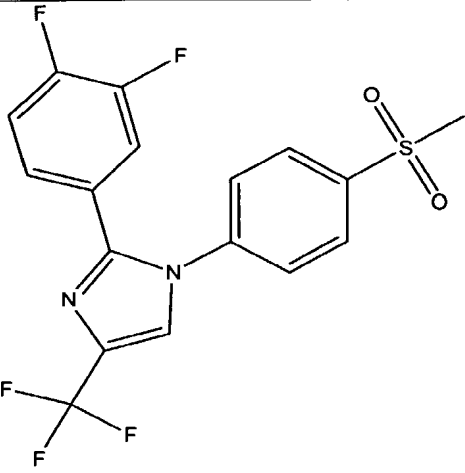
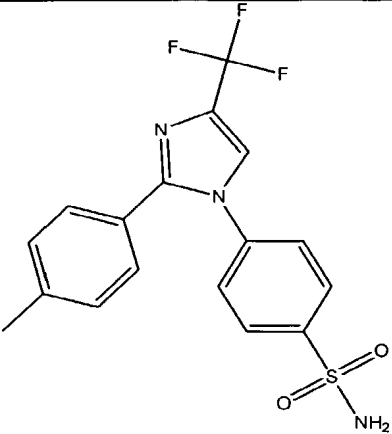
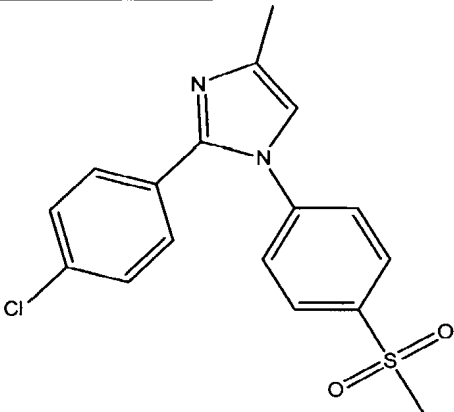
<u>Compound Number</u>	<u>Structural Formula</u>
B-119	 <p>5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;</p>
B-120	 <p>1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;</p>
B-121	 <p>4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;</p>

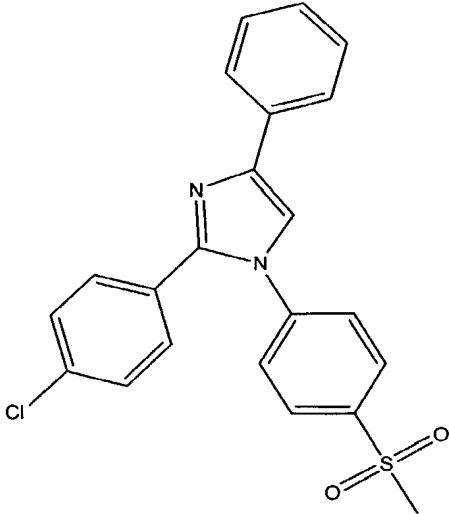
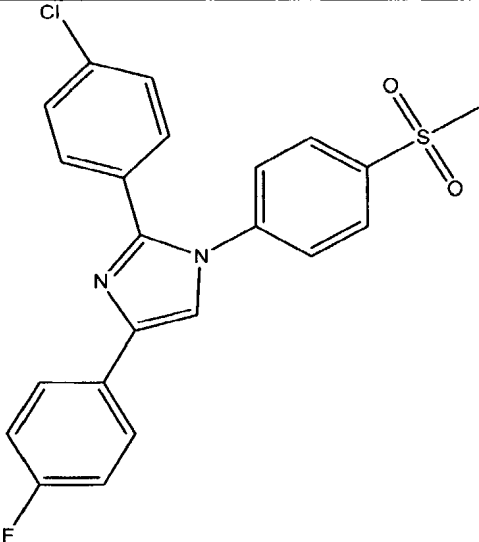
<u>Compound Number</u>	<u>Structural Formula</u>
B-122	 <p>5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;</p>
B-123	 <p>4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;</p>
B-124	 <p>6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]pyridine-3-carbonitrile;</p>

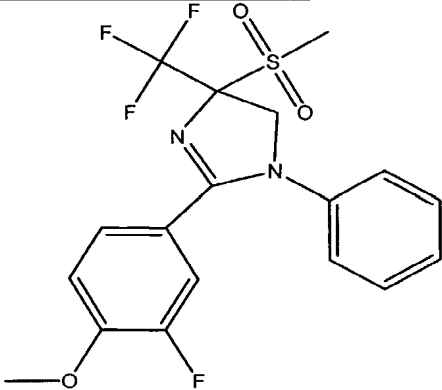
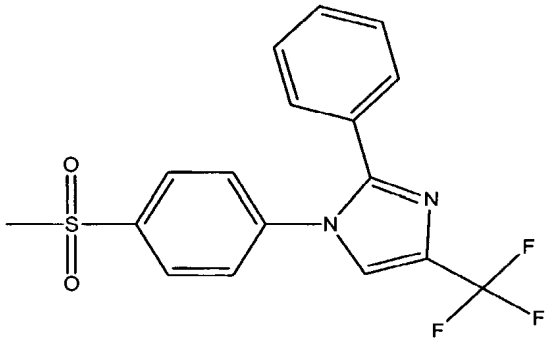
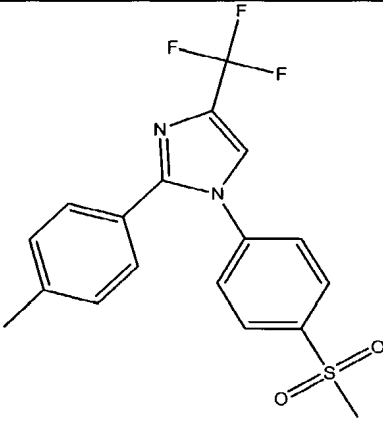
<u>Compound Number</u>	<u>Structural Formula</u>
B-125	 <p>2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;</p>
B-126	 <p>6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;</p>
B-127	 <p>4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;</p>

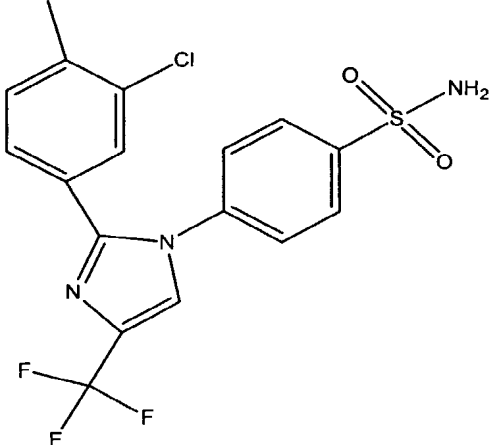
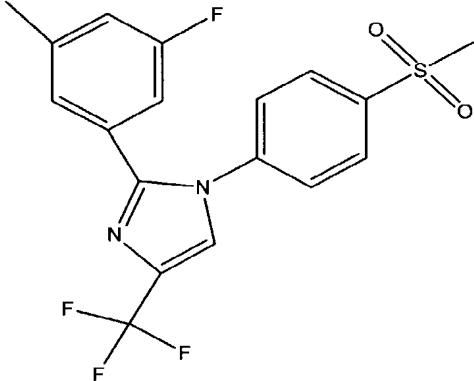
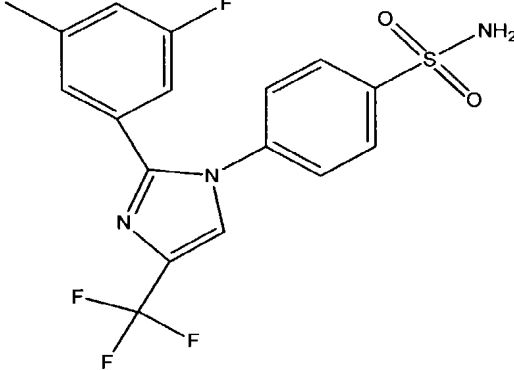
<u>Compound Number</u>	<u>Structural Formula</u>
B-128	 <p>4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;</p>
B-129	 <p>4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;</p>
B-130	 <p>3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;</p>
B-131	 <p>2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;</p>

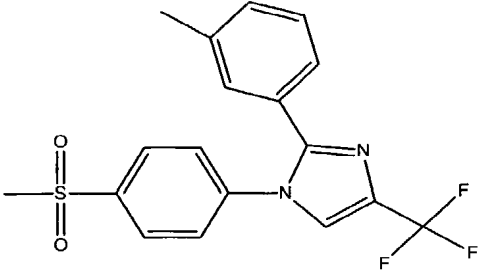
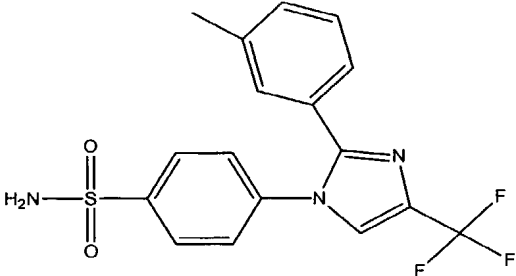
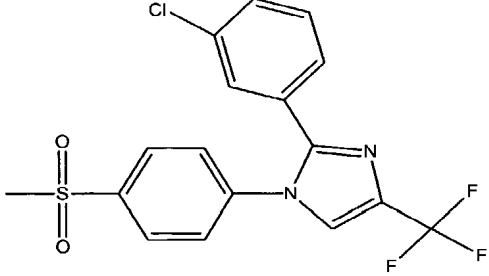
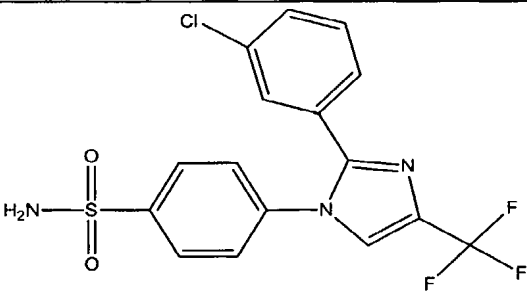
<u>Compound Number</u>	<u>Structural Formula</u>
B-132	 <p>2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)]-1H-imidazol-2-yl]pyridine;</p>
B-133	 <p>2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)]-1H-imidazol-2-yl]pyridine;</p>
B-134	 <p>4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;</p>

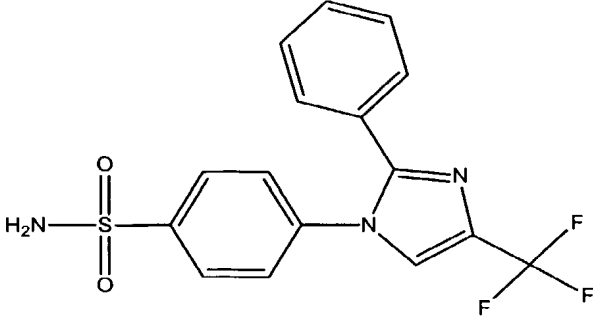
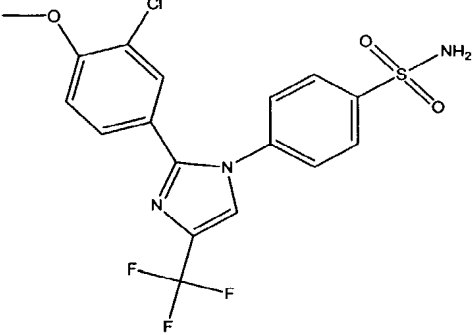
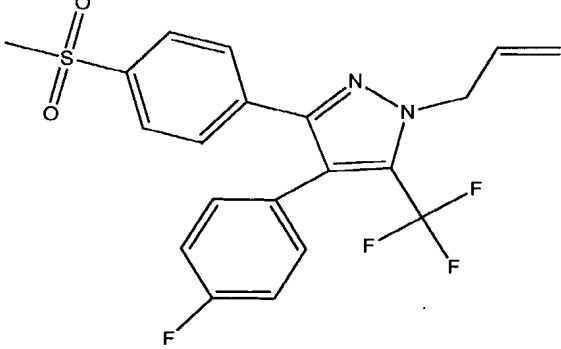
<u>Compound Number</u>	<u>Structural Formula</u>
B-135	 <p>2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;</p>
B-136	 <p>4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;</p>
B-137	 <p>2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;</p>

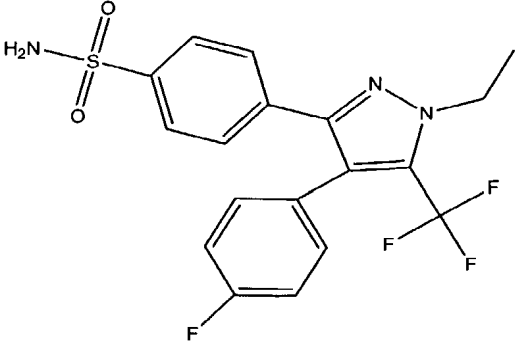
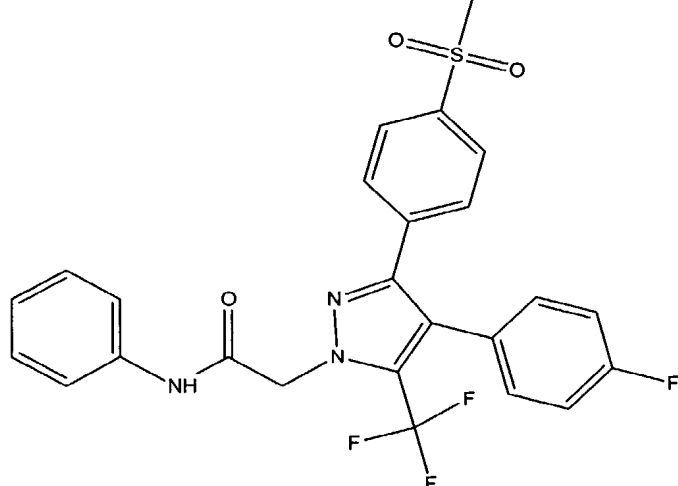
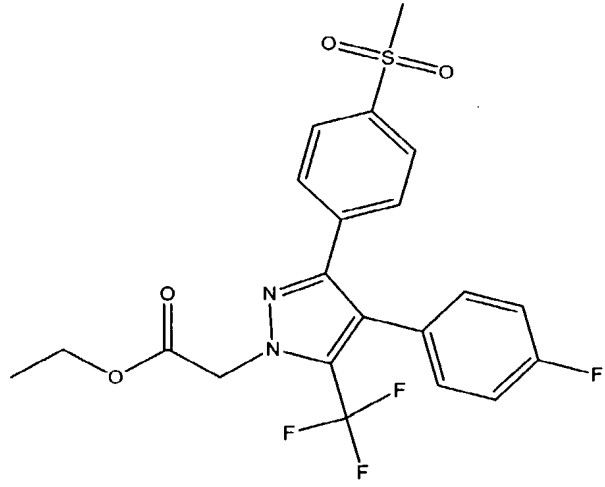
<u>Compound Number</u>	<u>Structural Formula</u>
B-138	 <p data-bbox="662 846 1408 873">2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;</p>
B-139	 <p data-bbox="662 1451 1372 1505">2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;</p>

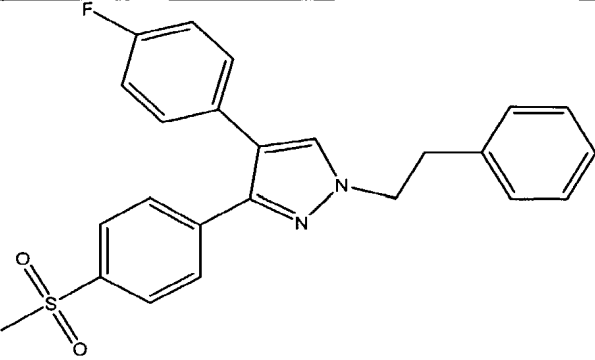
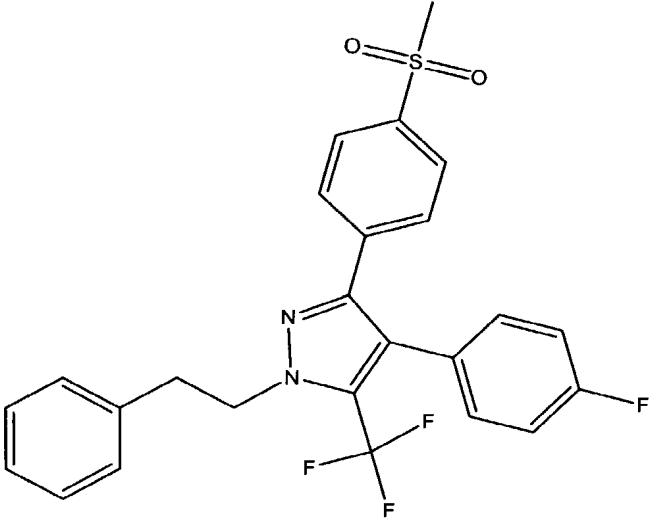
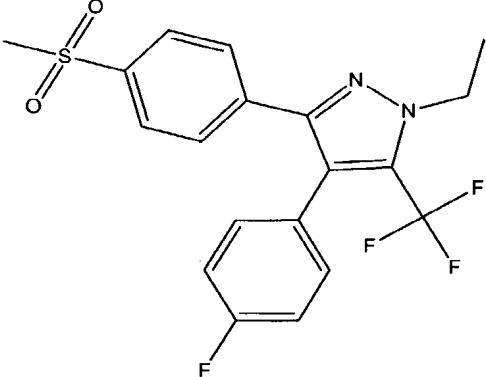
<u>Compound Number</u>	<u>Structural Formula</u>
B-140	 <p>2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;</p>
B-141	 <p>1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;</p>
B-142	 <p>2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;</p>

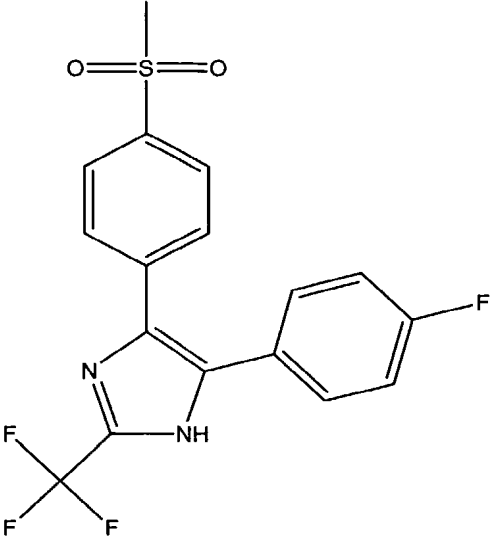
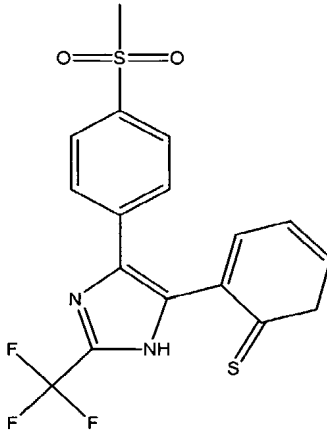
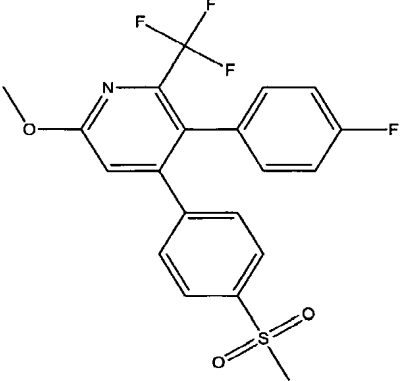
<u>Compound Number</u>	<u>Structural Formula</u>
B-143	 <p>4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;</p>
B-144	 <p>2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;</p>
B-145	 <p>4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazole-1-yl]benzenesulfonamide;</p>

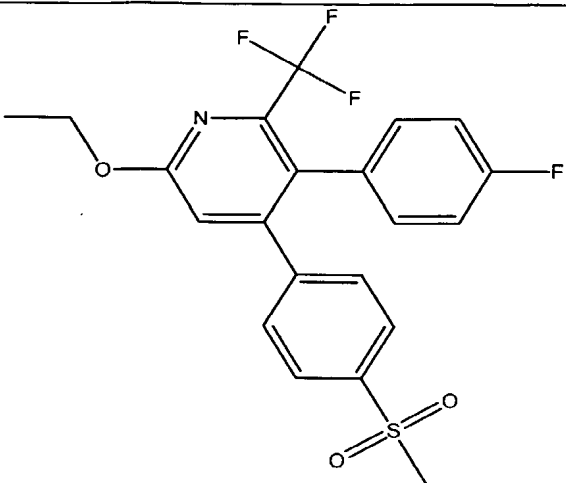
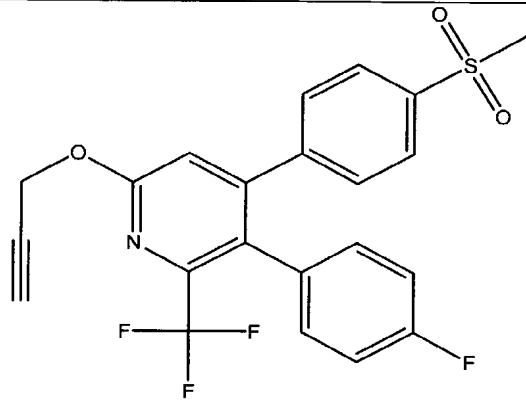
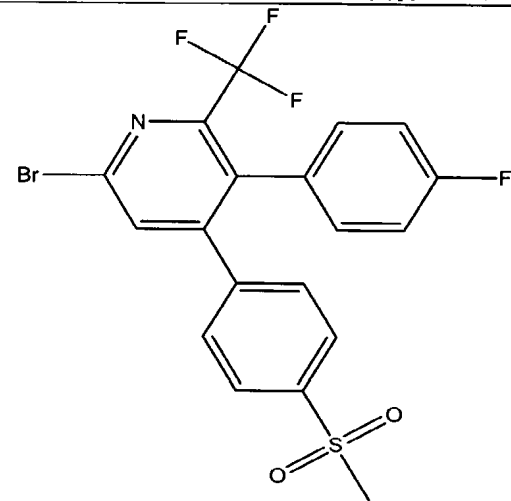
<u>Compound Number</u>	<u>Structural Formula</u>
B-146	 <p data-bbox="662 625 1409 653">2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;</p>
B-147	 <p data-bbox="678 972 1414 999">4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;</p>
B-148	 <p data-bbox="667 1331 1409 1358">1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole</p>
B-149	 <p data-bbox="667 1696 1419 1724">4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;</p>

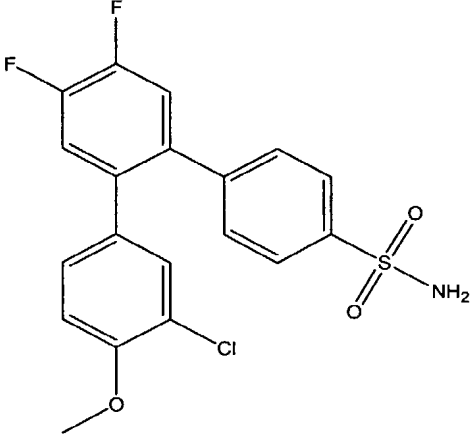
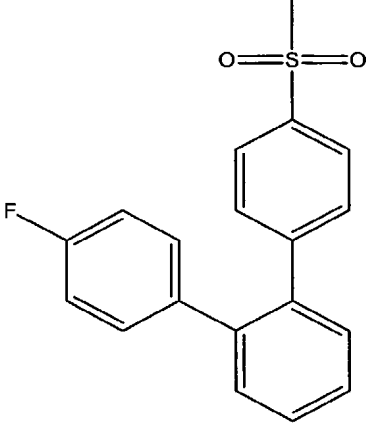
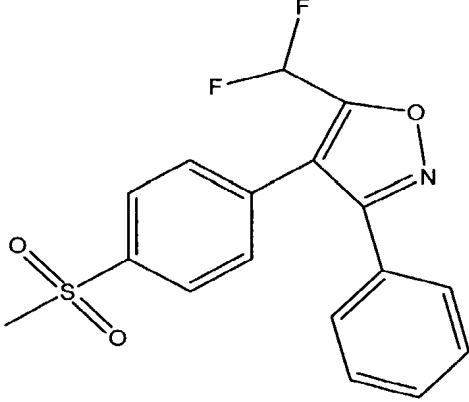
<u>Compound Number</u>	<u>Structural Formula</u>
B-150	 <p data-bbox="656 659 1398 688">4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;</p>
B-151	 <p data-bbox="649 1041 1398 1066">4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;</p>
B-152	 <p data-bbox="651 1476 1214 1526">1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;</p>

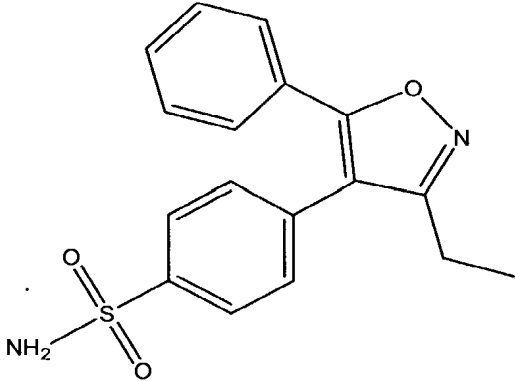
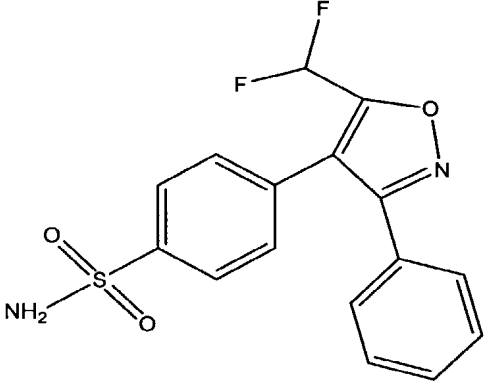
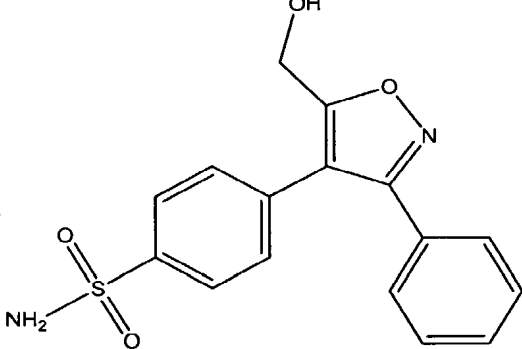
<u>Compound Number</u>	<u>Structural Formula</u>
B-153	 <p>4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl] benzenesulfonamide;</p>
B-154	 <p>N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;</p>
B-155	 <p>ethyl[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;</p>

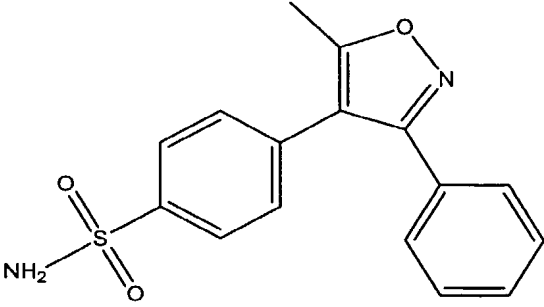
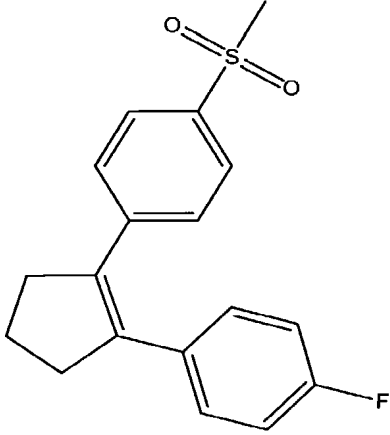
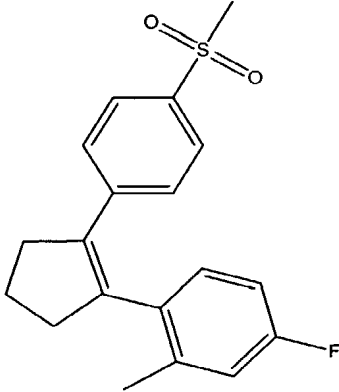
<u>Compound Number</u>	<u>Structural Formula</u>
B-156	 <p data-bbox="662 640 1409 667">4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;</p>
B-157	 <p data-bbox="662 1266 1177 1325">4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;</p>
B-158	 <p data-bbox="662 1738 1226 1793">1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;</p>

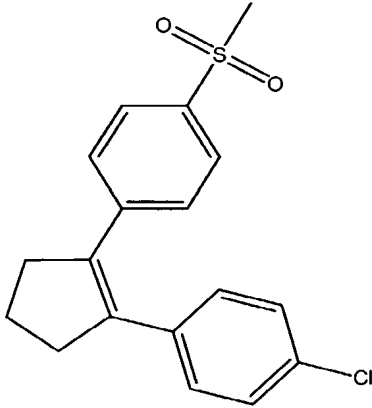
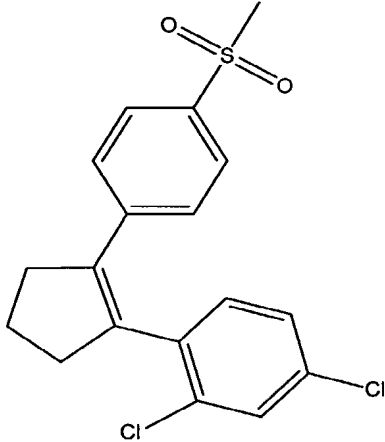
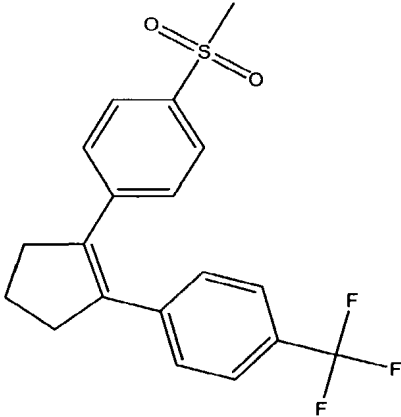
<u>Compound Number</u>	<u>Structural Formula</u>
B-159	 <p>5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;</p>
B-160	 <p>4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;</p>
B-161	 <p>5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;</p>

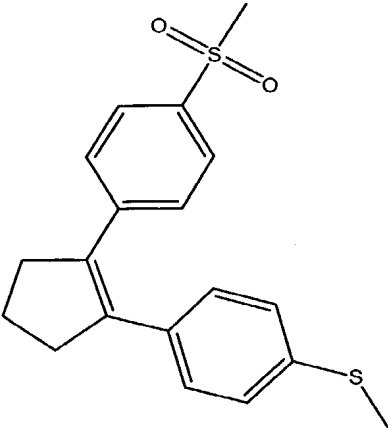
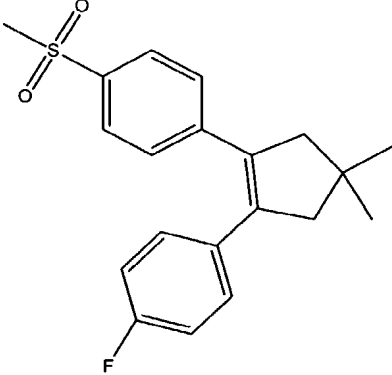
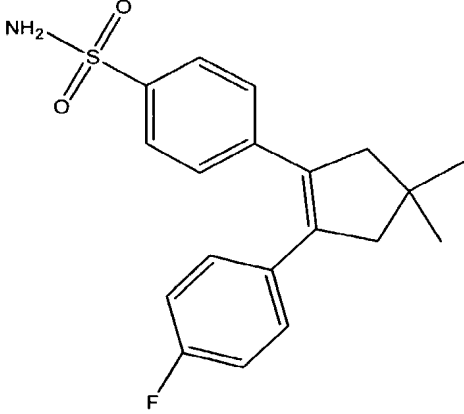
<u>Compound Number</u>	<u>Structural Formula</u>
B-162	 <p>2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;</p>
B-163	 <p>5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;</p>
B-164	 <p>2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;</p>

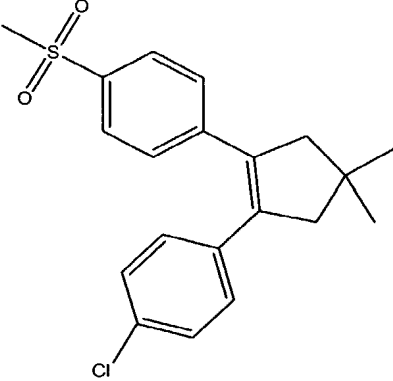
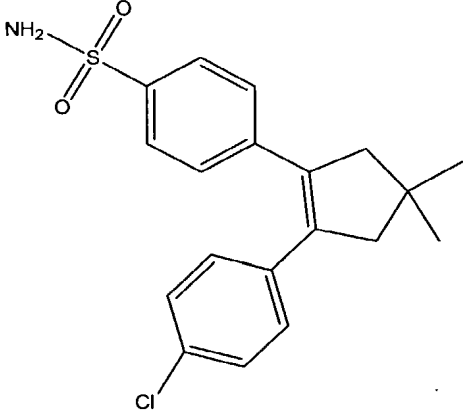
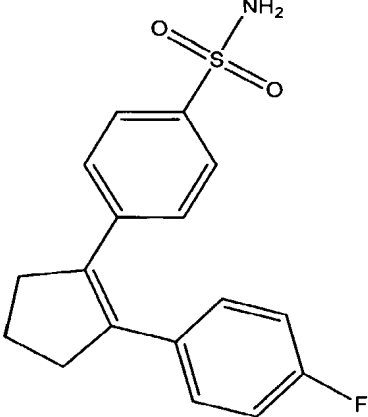
<u>Compound Number</u>	<u>Structural Formula</u>
B-165	 <p>4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;</p>
B-166	 <p>1-(4-fluorophenyl)-2-[4-methylsulfonyl]phenyl]benzene;</p>
B-167	 <p>5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;</p>

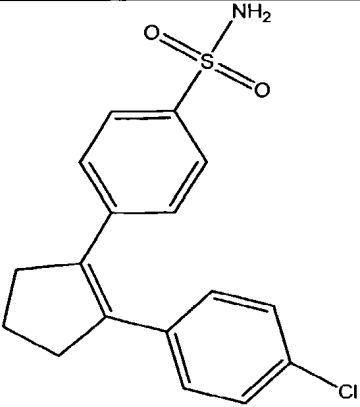
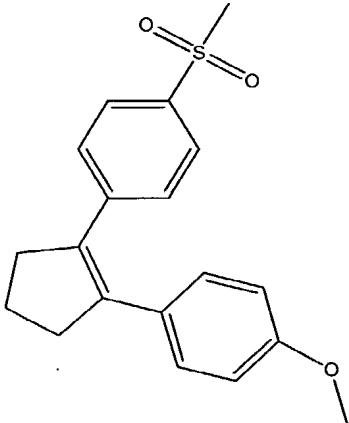
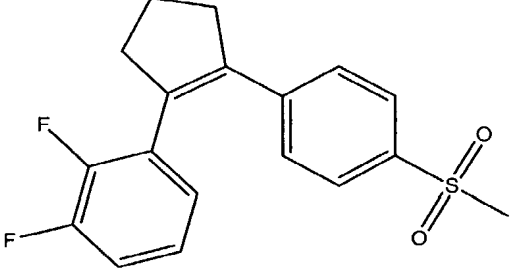
<u>Compound Number</u>	<u>Structural Formula</u>
B-168	 <p>4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;</p>
B-169	 <p>4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;</p>
B-170	 <p>4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;</p>

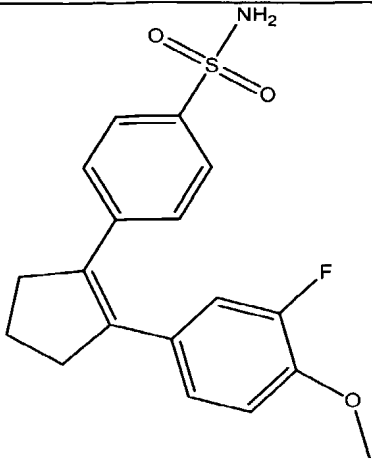
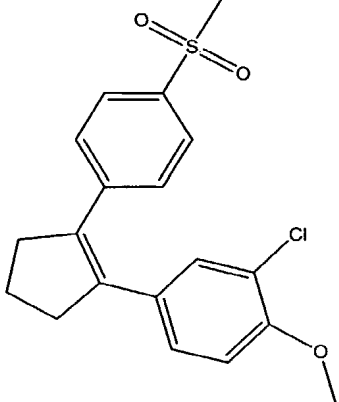
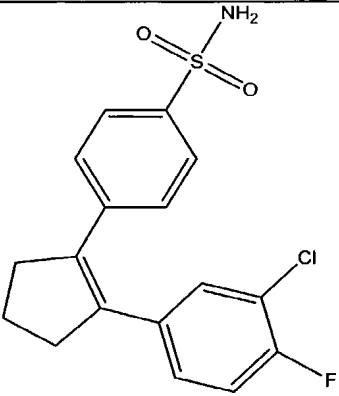
<u>Compound Number</u>	<u>Structural Formula</u>
B-171	 <p>4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;</p>
B-172	 <p>1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;</p>
B-173	 <p>1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;</p>

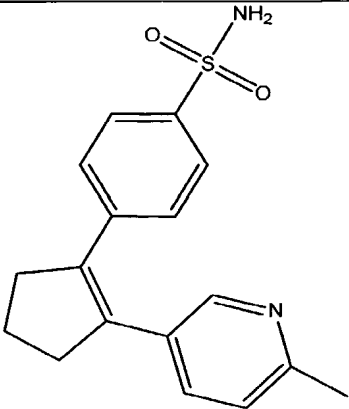
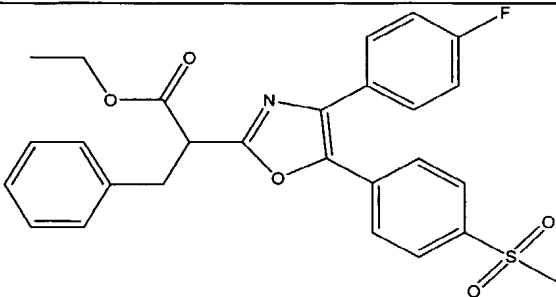
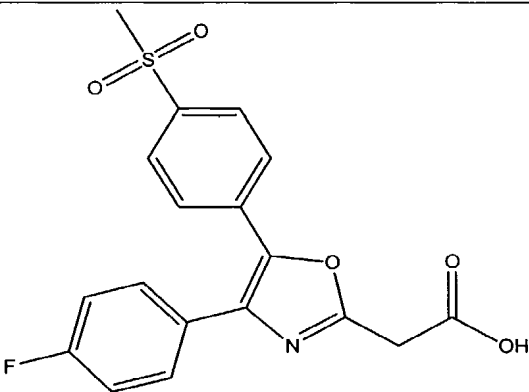
<u>Compound Number</u>	<u>Structural Formula</u>
B-174	 <p>1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;</p>
B-175	 <p>1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;</p>
B-176	 <p>1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;</p>

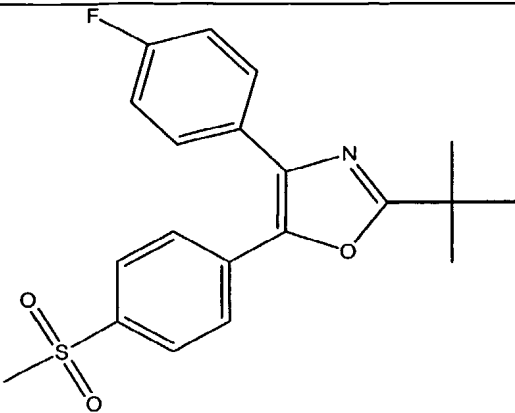
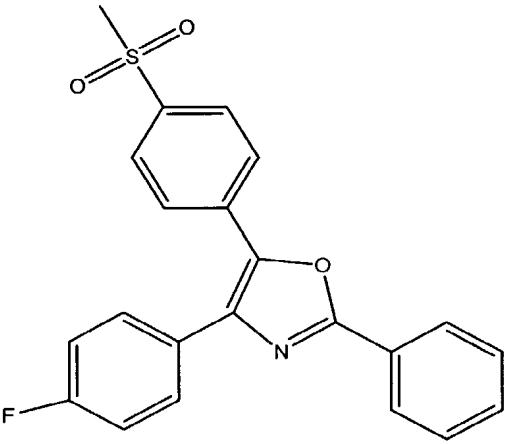
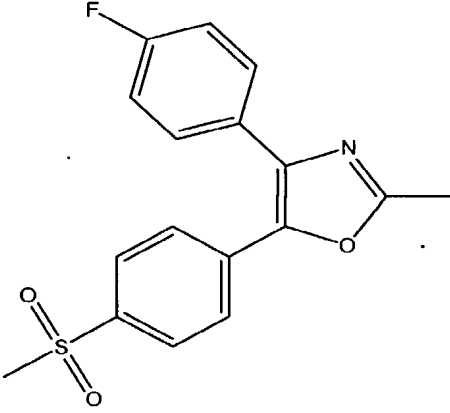
<u>Compound Number</u>	<u>Structural Formula</u>
B-177	 <p>1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;</p>
B-178	 <p>1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;</p>
B-179	 <p>4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;</p>

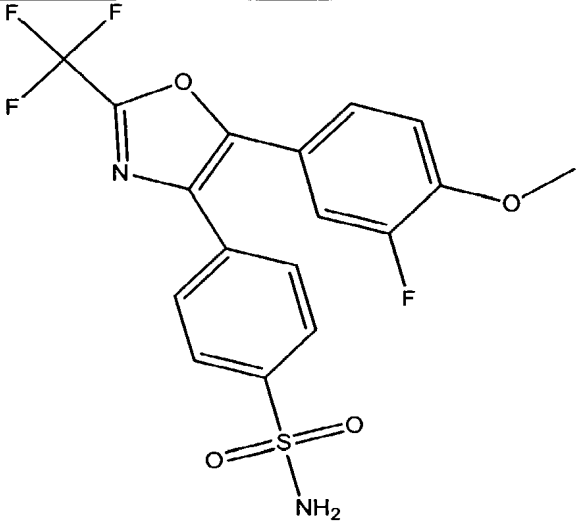
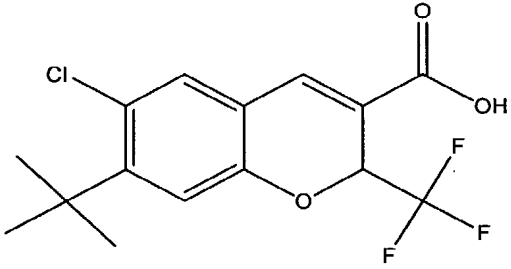
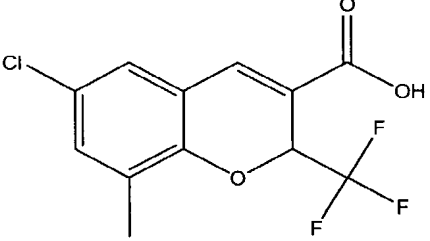
<u>Compound Number</u>	<u>Structural Formula</u>
B-180	 <p>1-[2-(3-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;</p>
B-181	 <p>4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;</p>
B-182	 <p>4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;</p>

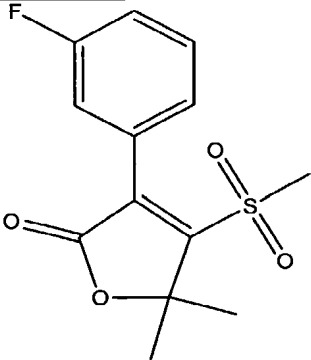
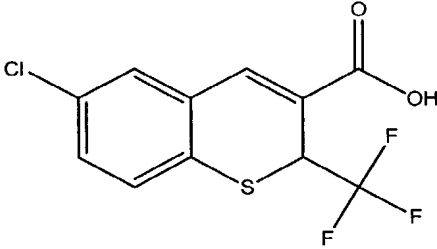
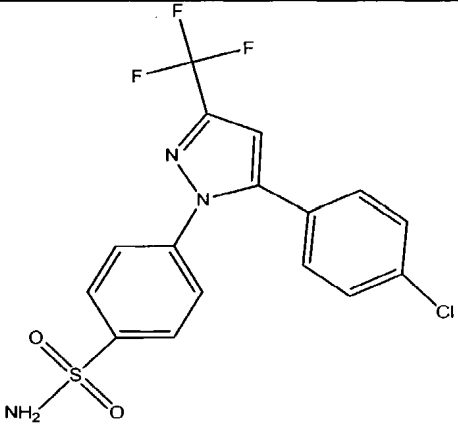
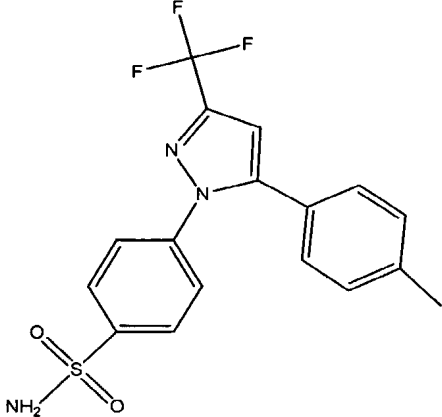
<u>Compound Number</u>	<u>Structural Formula</u>
B-183	 <p>4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;</p>
B-184	 <p>1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;</p>
B-185	 <p>1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;</p>

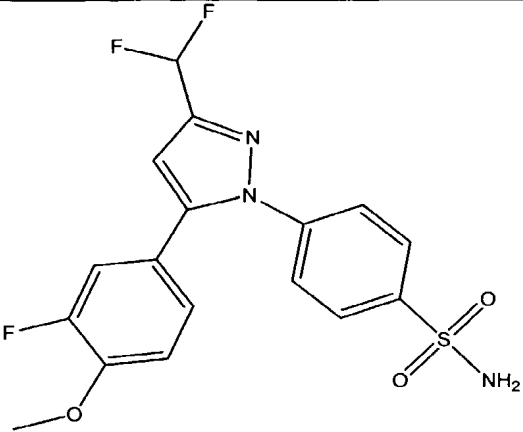
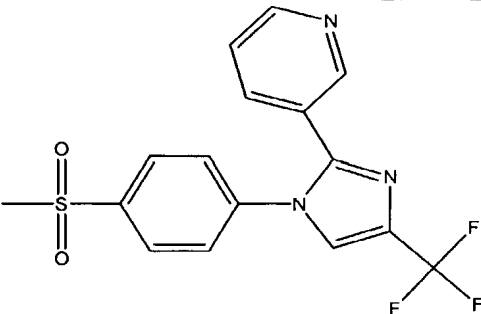
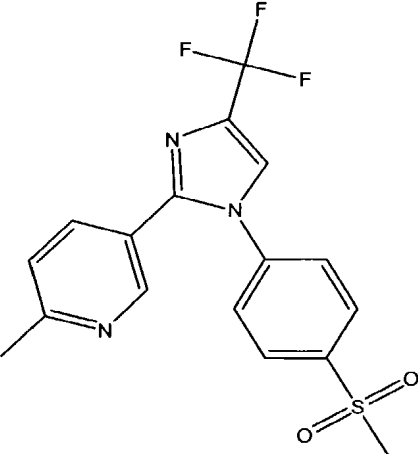
<u>Compound Number</u>	<u>Structural Formula</u>
B-186	 <p>4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;</p>
B-187	 <p>1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;</p>
B-188	 <p>4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;</p>

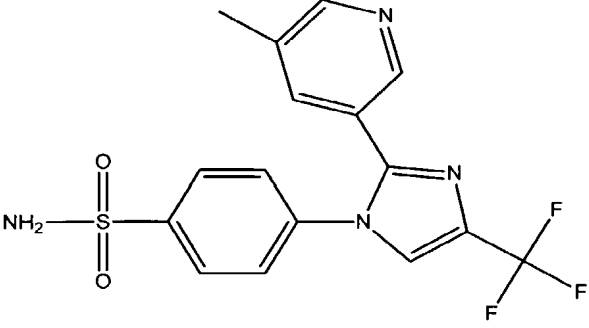
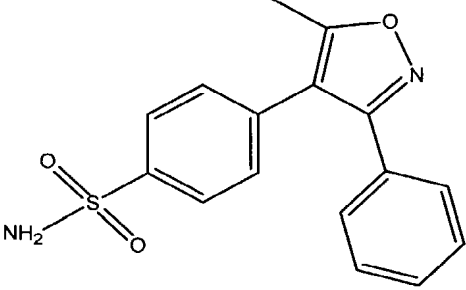
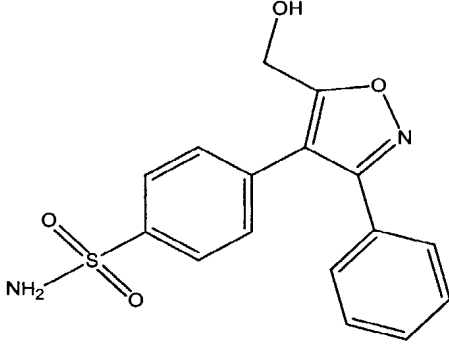
<u>Compound Number</u>	<u>Structural Formula</u>
B-189	 <p>4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;</p>
B-190	 <p>ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]-2-benzyl-acetate;</p>
B-191	 <p>2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;</p>

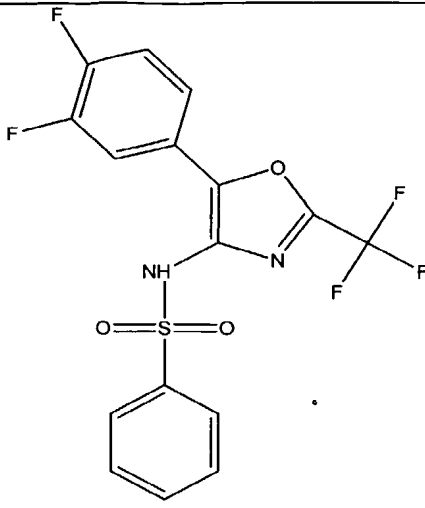
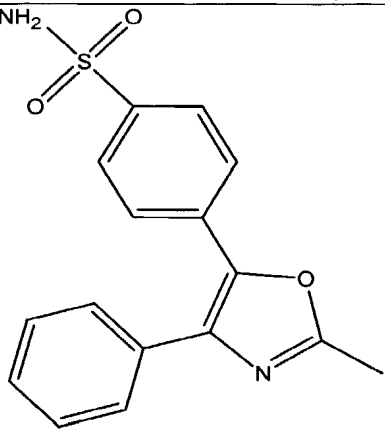
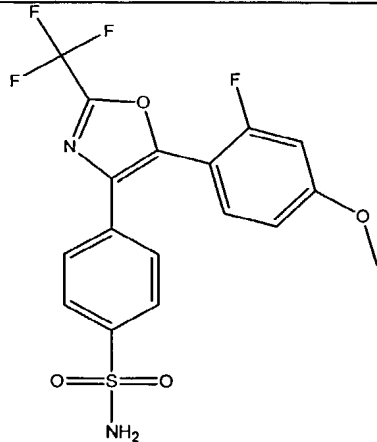
<u>Compound Number</u>	<u>Structural Formula</u>
B-192	 <p>2-(tert-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;</p>
B-193	 <p>4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;</p>
B-194	 <p>4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;</p>

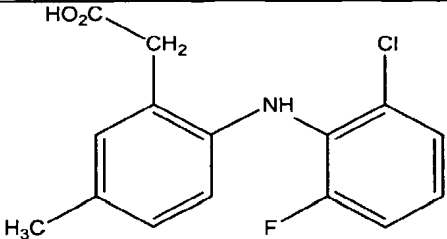
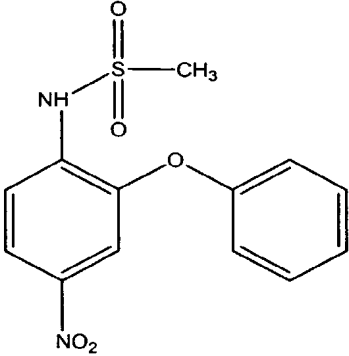
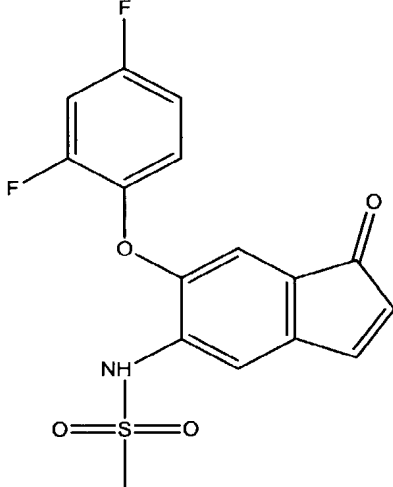
<u>Compound Number</u>	<u>Structural Formula</u>
B-195	 <p>4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;</p>
B-196	 <p>6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>
B-197	 <p>6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;</p>

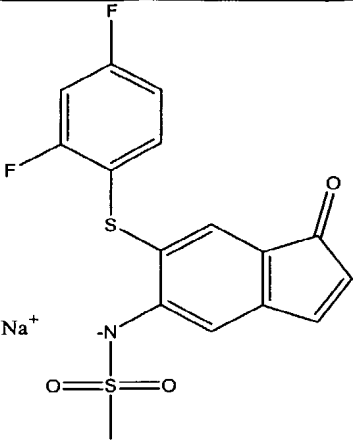
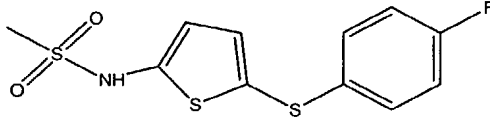
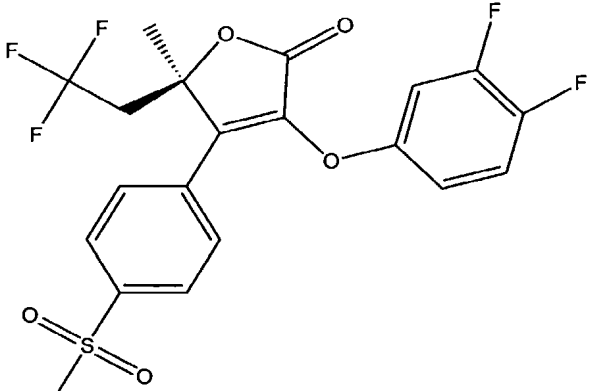
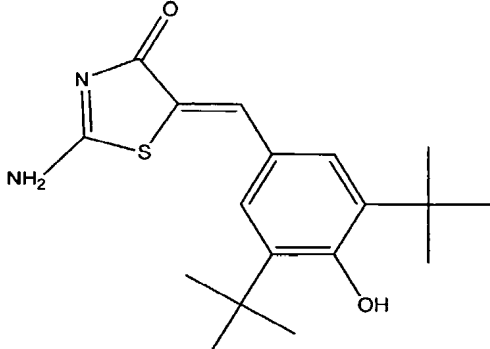
<u>Compound Number</u>	<u>Structural Formula</u>
B-198	 <p>5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone;</p>
B-199	 <p>6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;</p>
B-200	 <p>4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>
B-201	 <p>4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>

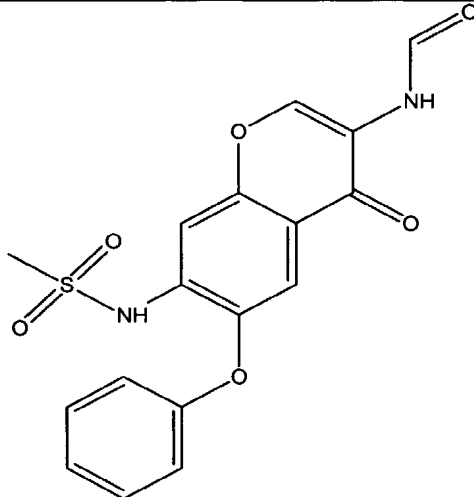
<u>Compound Number</u>	<u>Structural Formula</u>
B-202	 <p>4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;</p>
B-203	 <p>3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;</p>
B-204	 <p>2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;</p>

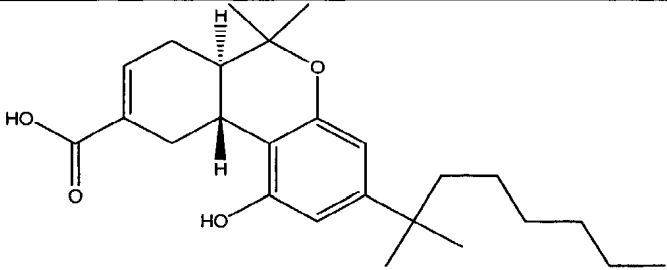
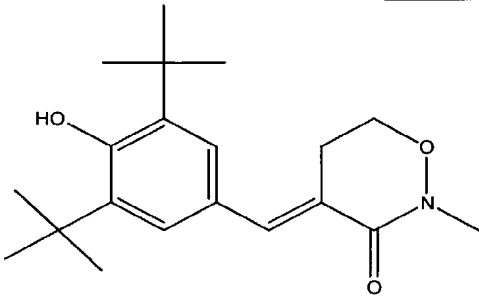
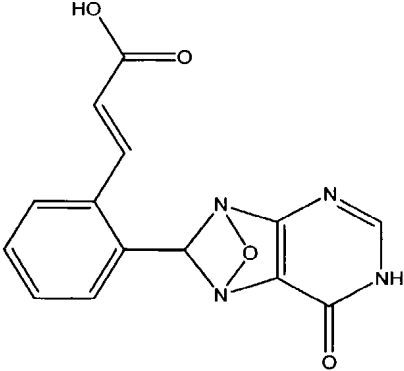
<u>Compound Number</u>	<u>Structural Formula</u>
B-205	 <p>4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;</p>
B-206	 <p>4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;</p>
B-207	 <p>4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;</p>

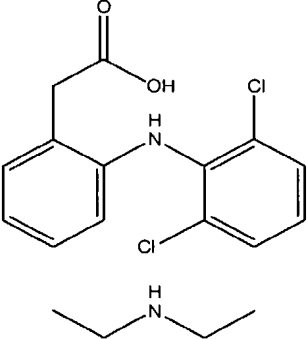
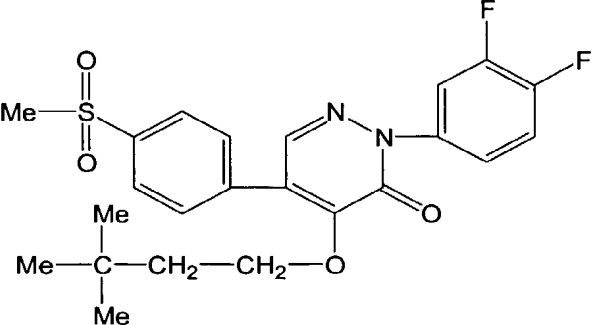
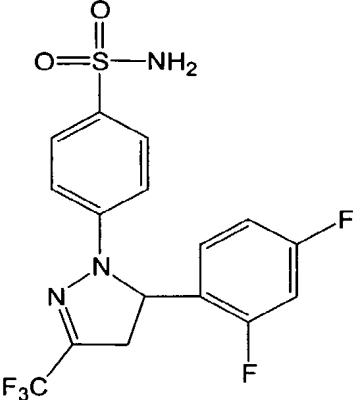
<u>Compound Number</u>	<u>Structural Formula</u>
B-208	 <p>[2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;</p>
B-209	 <p>4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide;</p>
B-210	 <p>4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;</p>

<u>Compound Number</u>	<u>Structural Formula</u>
B-211	 <chem>CC1=CC=C(C(=C1)NC2=CC=C(Cl)C=C2F)CC(=O)O</chem>
B-212	 <chem>CC(=O)S(=O)(=O)Nc1ccc(cc1Oc2ccccc2)[N+](=O)[O-]</chem> <i>N</i> -(4-nitro-2-phenoxy-phenyl)-methanesulfonamide
B-213	 <chem>CS(=O)(=O)Nc1ccc2c(c1)c(c3ccccc23=O)Oc4cc(F)cc(F)c4</chem> <i>N</i> -[6-(2,4-difluorophenoxy)-1-oxo-inden-5-yl]-methanesulfonamide

<u>Compound Number</u>	<u>Structural Formula</u>
B-214	 <p data-bbox="657 724 1404 766"><i>N</i>-[6-(2,4-difluoro-phenylsulfanyl)-1-oxo-1<i>H</i>-inden-5-yl]-methanesulfonamide, sodium salt</p>
B-215	 <p data-bbox="657 934 1266 955"><i>N</i>-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide</p>
B-216	 <p data-bbox="657 1407 1356 1459">3-(3,4-difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl-5-(2,2,2-trifluoro-ethyl)-5<i>H</i>-furan-2-one</p>
B-217	 <p data-bbox="657 1837 1404 1890">(5<i>Z</i>)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4(5<i>H</i>)-thiazolone</p>

<u>Compound Number</u>	<u>Structural Formula</u>
B-218	CS-502
B-219	LAS-34475
B-220	LAS-34555
B-221	S-33516
B-222	SD-8381
B-223	L-783003
B-224	<div><p>N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide</p></div>
B-225	D-1367
B-226	L-748731

<u>Compound Number</u>	<u>Structural Formula</u>
B-227	 <p>(6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid</p>
B-228	CGP-28238
B-229	 <p>4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one</p>
B-230	GR-253035
B-231	 <p>2-(6-dioxo-9H-purin-8-yl)cinnamic acid</p>
B-232	S-2474

<u>Compound Number</u>	<u>Structural Formula</u>
B-233	
B-234	
B-235	
B-236	