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) adrenocorticotropic 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 adrenocorticotropic hormone is reduced by at least 25%.

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

401. The compound of any one of claims 393-398, wherein the level of adrenocorticotropic 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) adrenocorticotropic 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) adrenocorticotropic 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) adrenocorticotropic 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) adrenocorticotropic 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.

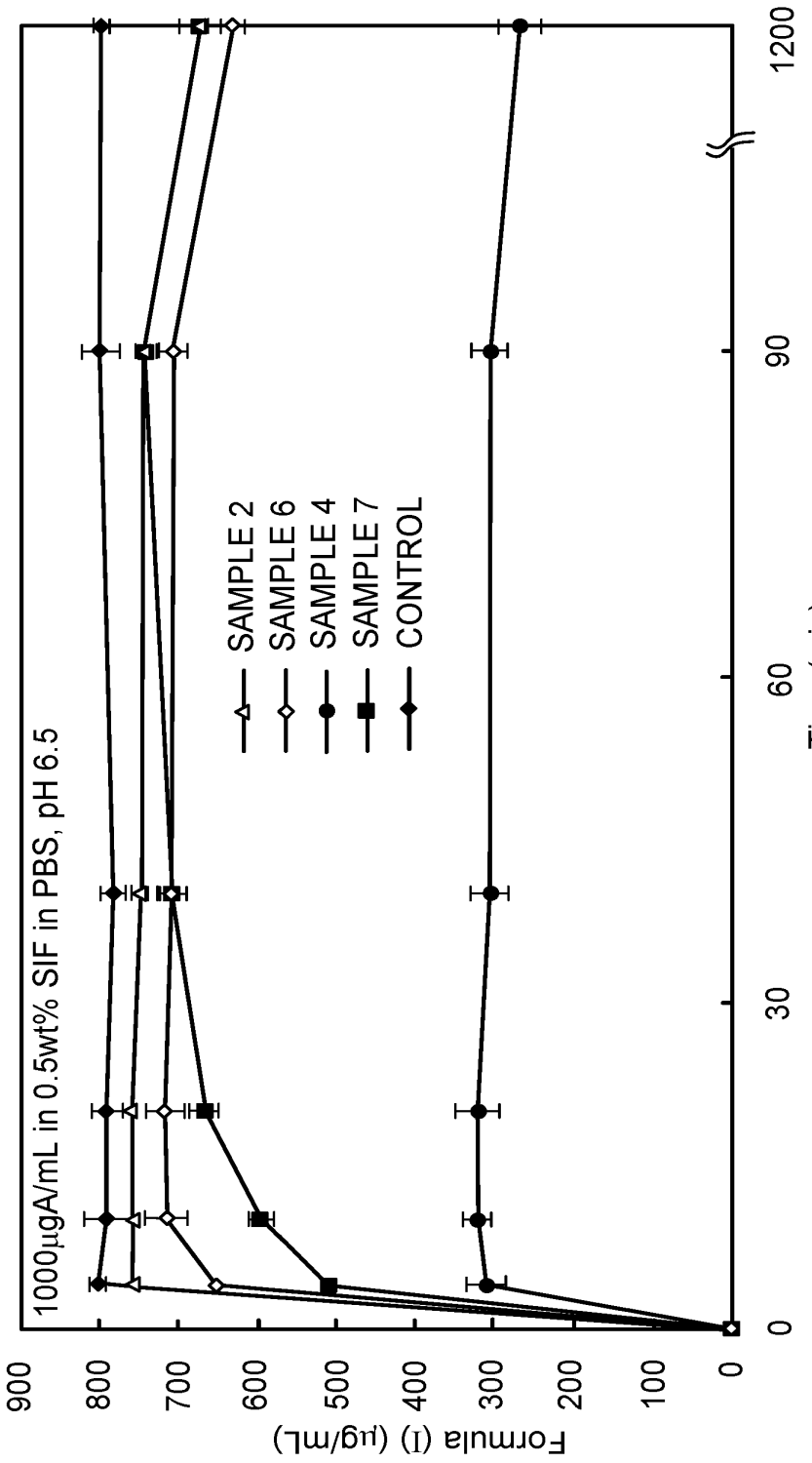

1000μgA/mL in 0.5wt% SIF in PBS, pH 6.5
SAMPLE 2
SAMPLE 6
SAMPLE 4
SAMPLE 7
CONTROL
Formula (I) (μg/mL)
Time (min)
0
100
200
300
400
500
600
700
800
900
0
30
60
90
1200

FIG. 1

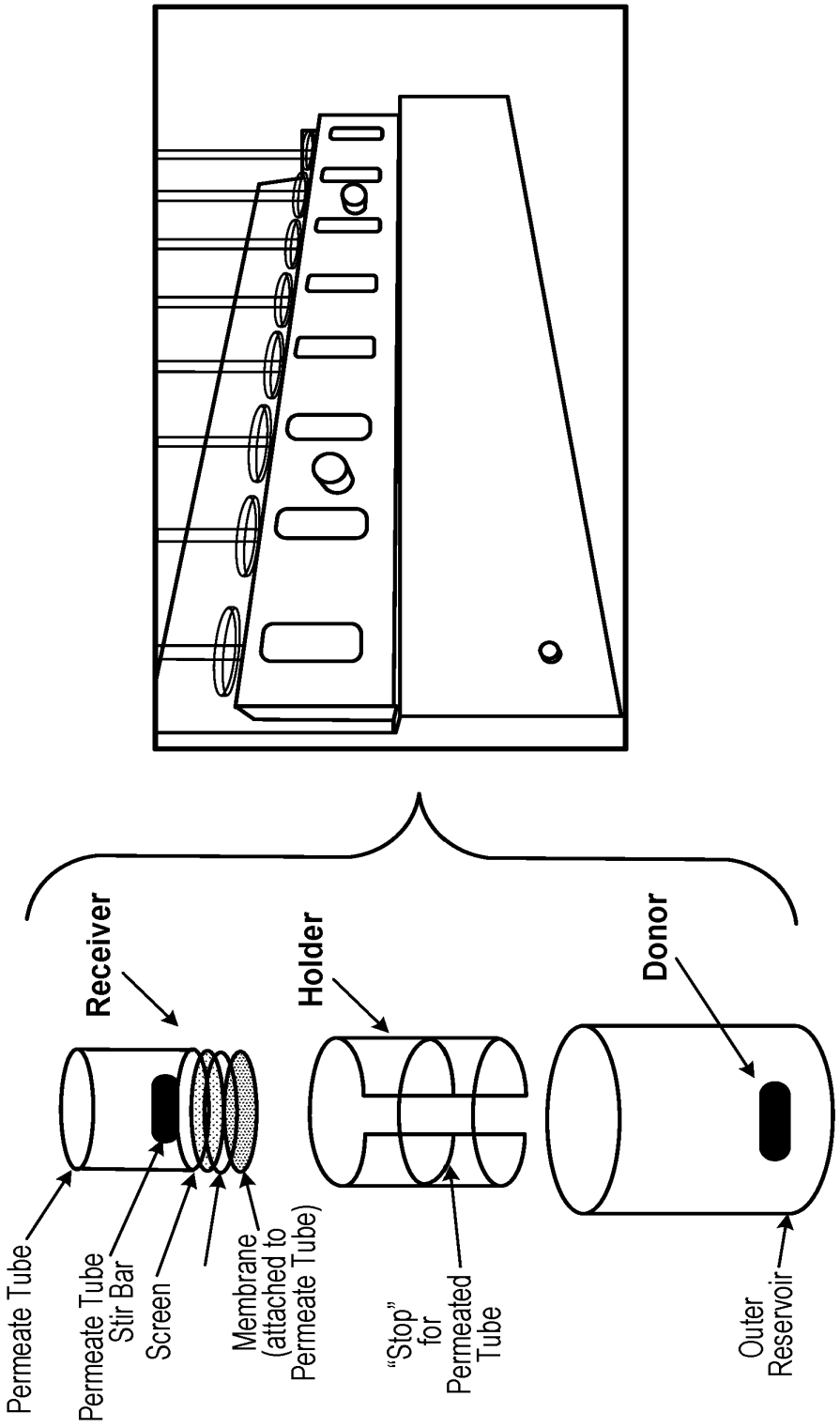

Receiver
Holder
Donor
Permeate Tube
Permeate Tube Stir Bar
Screen
Membrane (attached to Permeate Tube)
"Stop" for Permeated Tube
Outer Reservoir

FIG. 2

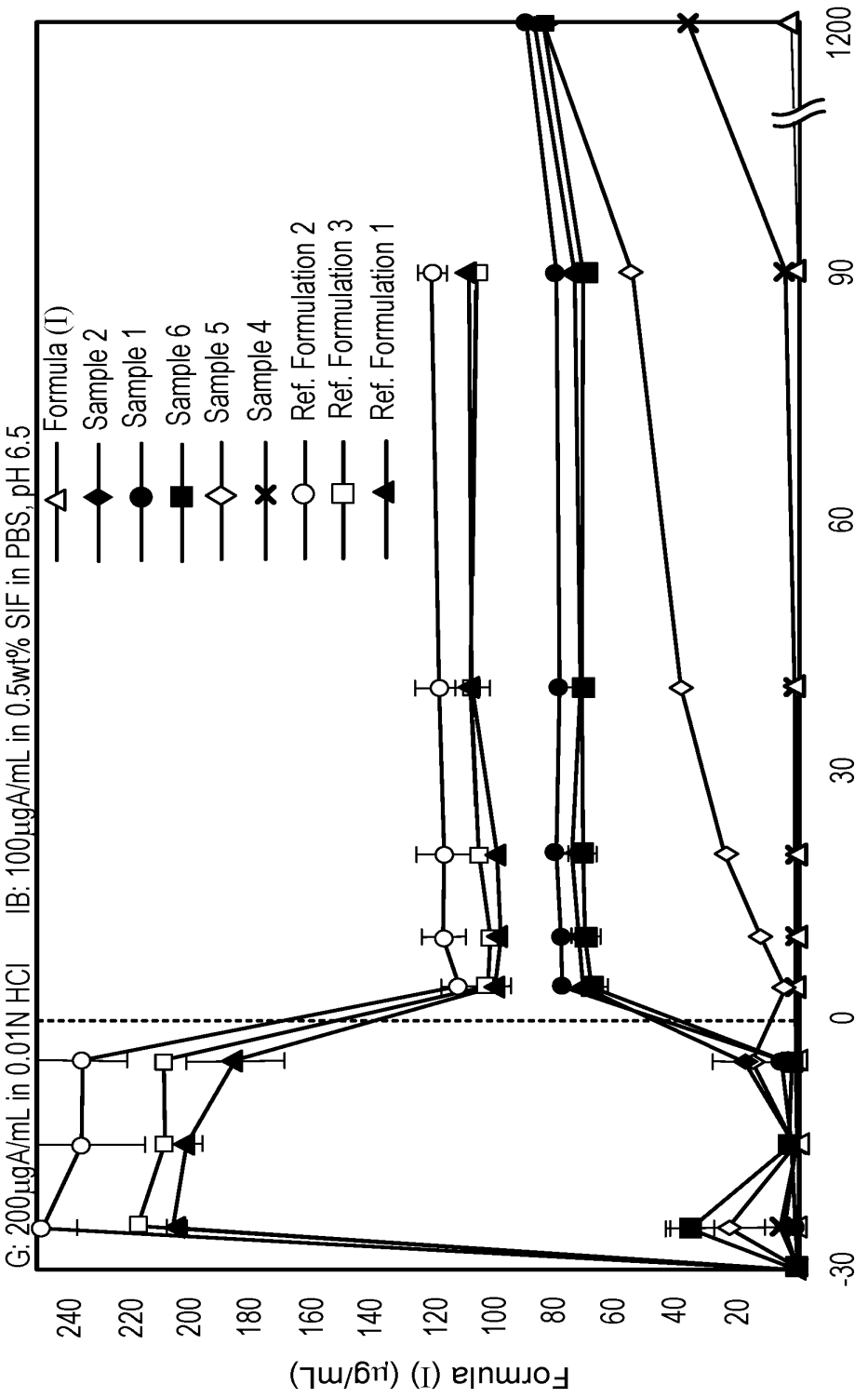

G: 200µgA/mL in 0.01N HCl IB: 100µgA/mL in 0.5wt% SIF in PBS, pH 6.5
Formula (I)
Sample 2
Sample 1
Sample 6
Sample 5
Sample 4
Ref. Formulation 2
Ref. Formulation 3
Ref. Formulation 1
Formula (I) (µg/mL)
240
220
200
180
160
140
120
100
80
60
40
20
-30
0
30
60
90
1200
Time (min)

FIG. 3

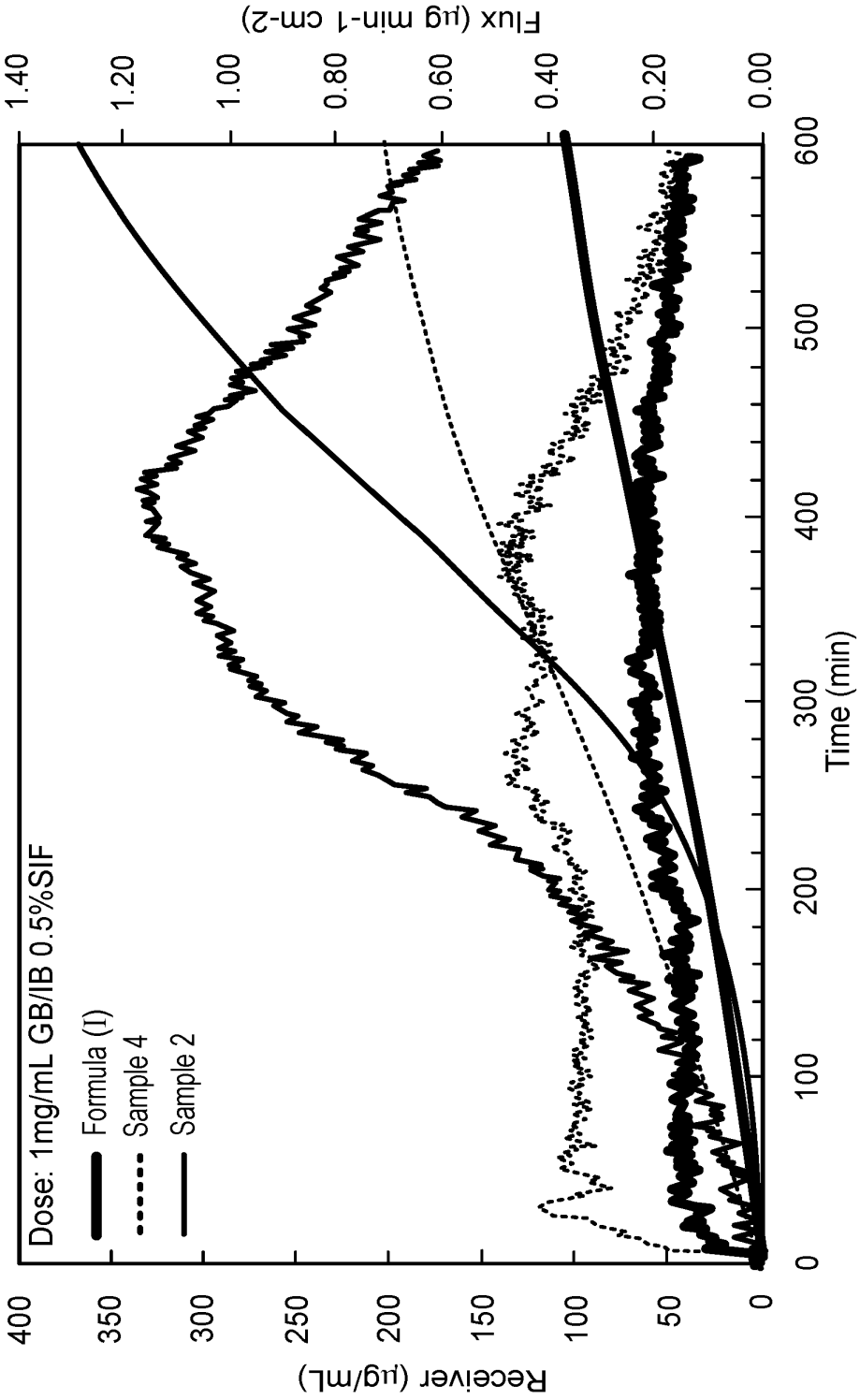

Dose: 1mg/mL GB/IB 0.5%SIF
Formula (I)
Sample 4
Sample 2
Receiver (µg/mL)
Flux (µg min-1 cm-2)
Time (min)
0
50
100
150
200
250
300
350
400
0.00
0.20
0.40
0.60
0.80
1.00
1.20
1.40
0
100
200
300
400
500
600

FIG. 4

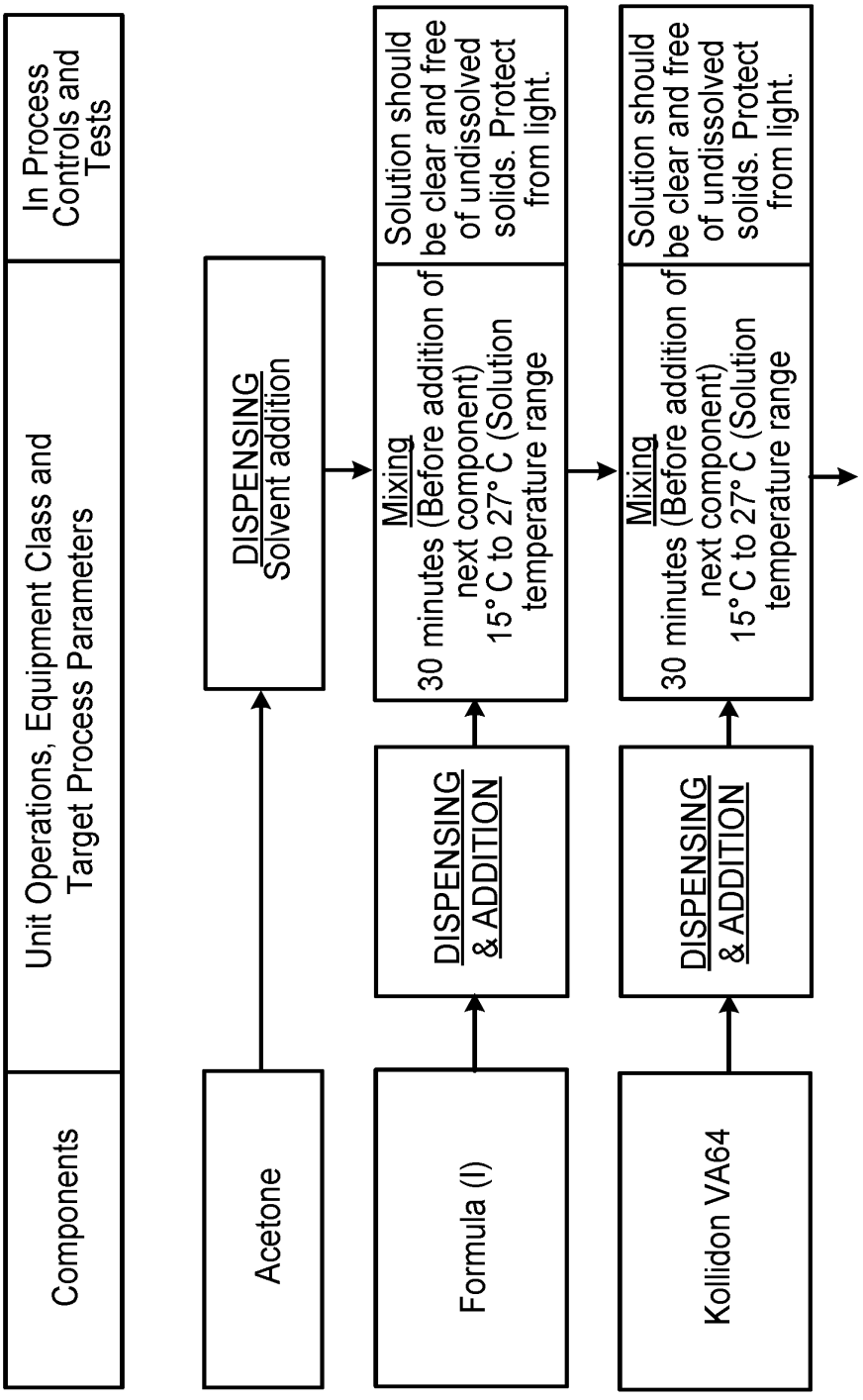

Components
Unit Operations, Equipment Class and Target Process Parameters
In Process Controls and Tests
Acetone
DISPENSING
Solvent addition
Formula (I)
DISPENSING & ADDITION
Mixing
30 minutes (Before addition of next component)
15° C to 27° C (Solution temperature range
Solution should be clear and free of undissolved solids. Protect from light.
Kollidon VA64
DISPENSING & ADDITION
Mixing
30 minutes (Before addition of next component)
15° C to 27° C (Solution temperature range
Solution should be clear and free of undissolved solids. Protect from light.

FIG. 5

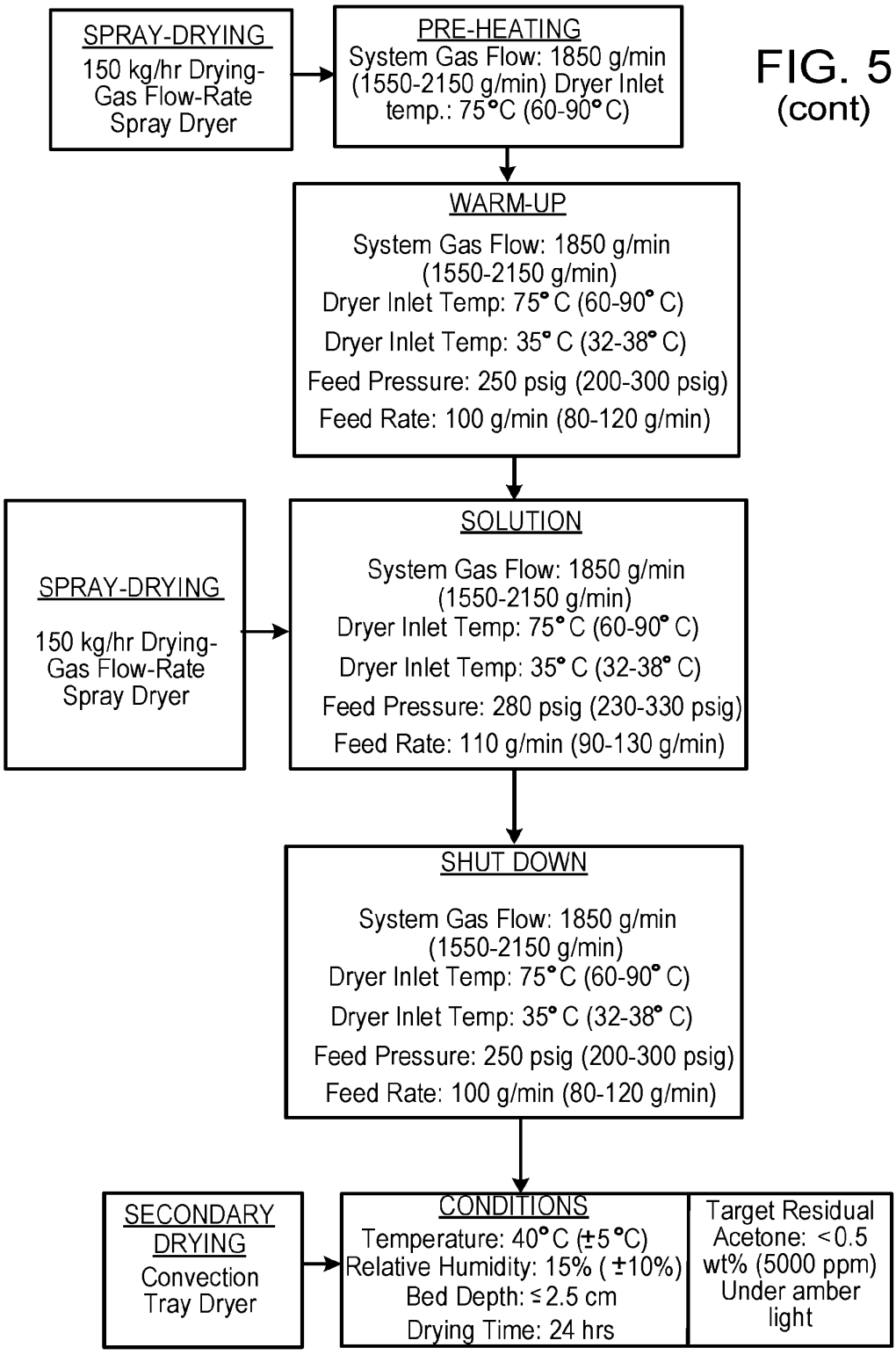

SPRAY-DRYING
150 kg/hr Drying-Gas Flow-Rate Spray Dryer
PRE-HEATING
System Gas Flow: 1850 g/min (1550-2150 g/min) Dryer Inlet temp.: 75°C (60-90° C)
WARM-UP
System Gas Flow: 1850 g/min (1550-2150 g/min)
Dryer Inlet Temp: 75° C (60-90° C)
Dryer Inlet Temp: 35° C (32-38° C)
Feed Pressure: 250 psig (200-300 psig)
Feed Rate: 100 g/min (80-120 g/min)
SPRAY-DRYING
150 kg/hr Drying-Gas Flow-Rate Spray Dryer
SOLUTION
System Gas Flow: 1850 g/min (1550-2150 g/min)
Dryer Inlet Temp: 75° C (60-90° C)
Dryer Inlet Temp: 35° C (32-38° C)
Feed Pressure: 280 psig (230-330 psig)
Feed Rate: 110 g/min (90-130 g/min)
SHUT DOWN
System Gas Flow: 1850 g/min (1550-2150 g/min)
Dryer Inlet Temp: 75° C (60-90° C)
Dryer Inlet Temp: 35° C (32-38° C)
Feed Pressure: 250 psig (200-300 psig)
Feed Rate: 100 g/min (80-120 g/min)
SECONDARY DRYING
Convection Tray Dryer
CONDITIONS
Temperature: 40° C (±5 °C)
Relative Humidity: 15% (±10%)
Bed Depth: ≤ 2.5 cm
Drying Time: 24 hrs
Target Residual Acetone: <0.5 wt% (5000 ppm) Under amber light

FIG. 5
(cont)

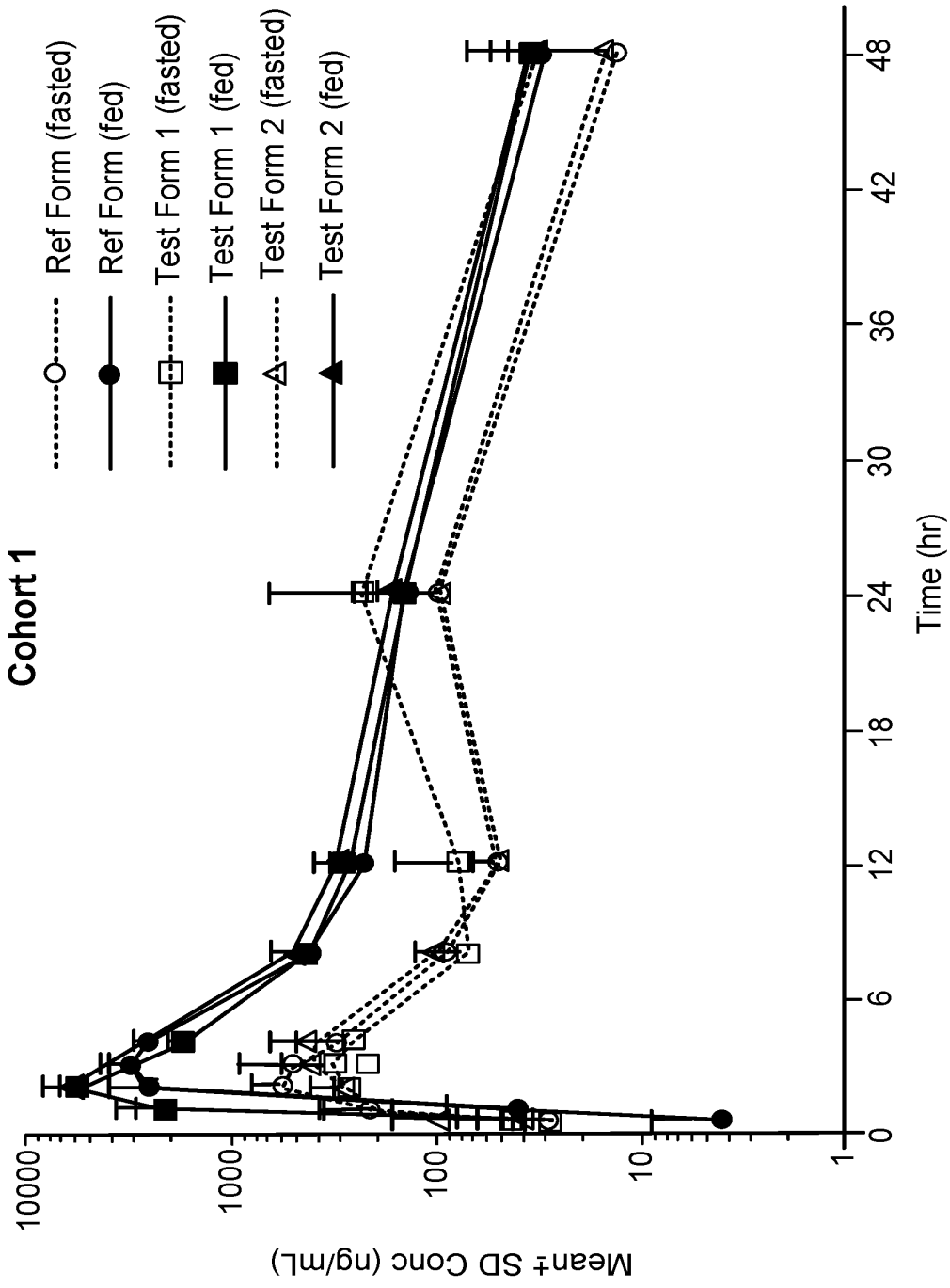

Cohort 1
Ref Form (fasted)
Ref Form (fed)
Test Form 1 (fasted)
Test Form 1 (fed)
Test Form 2 (fasted)
Test Form 2 (fed)
Mean± SD Conc (ng/mL)
10000
1000
100
10
1
0
6
12
18
24
30
36
42
48
Time (hr)

FIG. 6A

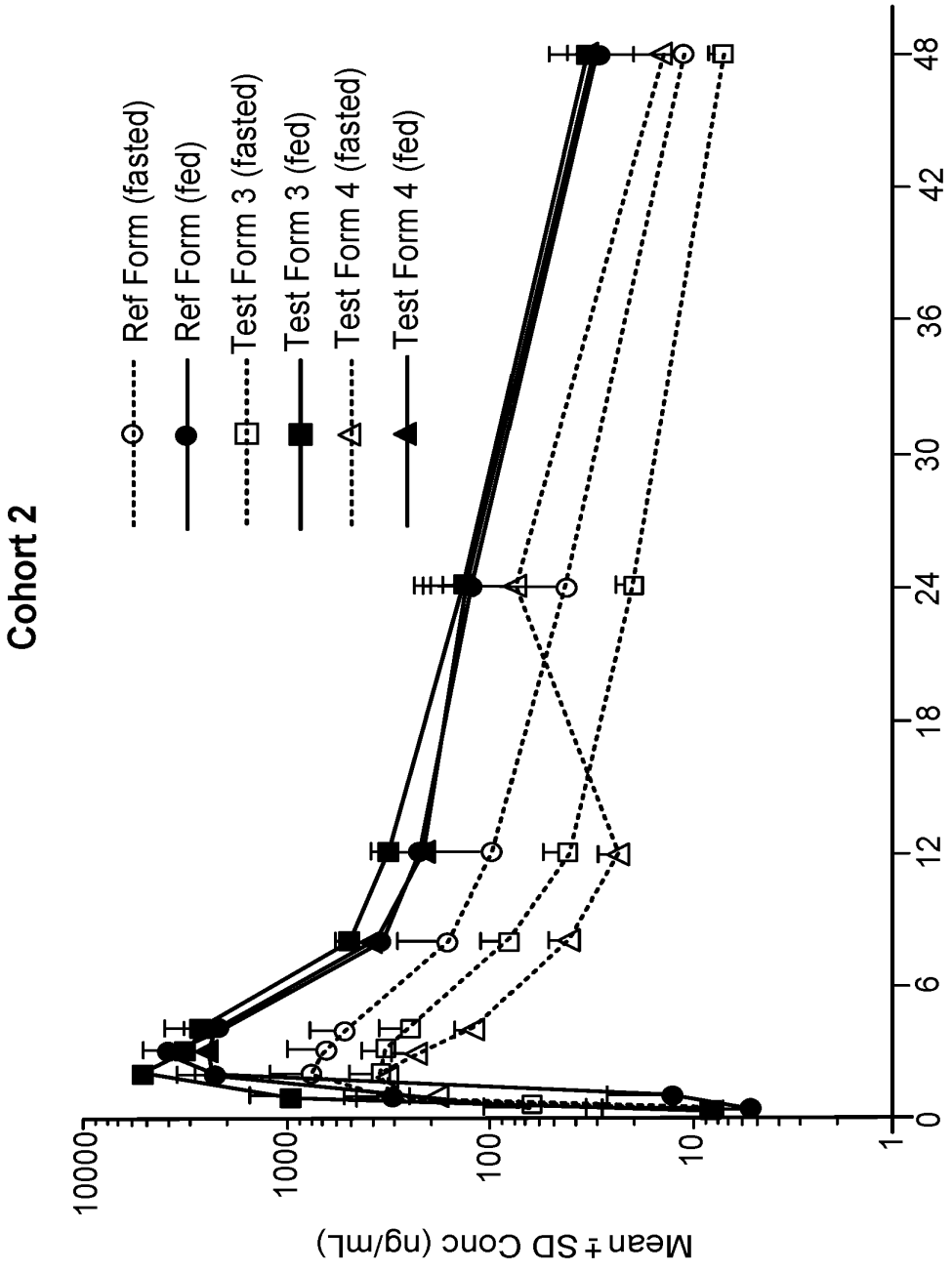

Cohort 2
Ref Form (fasted)
Ref Form (fed)
Test Form 3 (fasted)
Test Form 3 (fed)
Test Form 4 (fasted)
Test Form 4 (fed)
Mean ± SD Conc (ng/mL)
10000
1000
100
10
1
0
6
12
18
24
30
36
42
48
Time (hr)

FIG. 6B

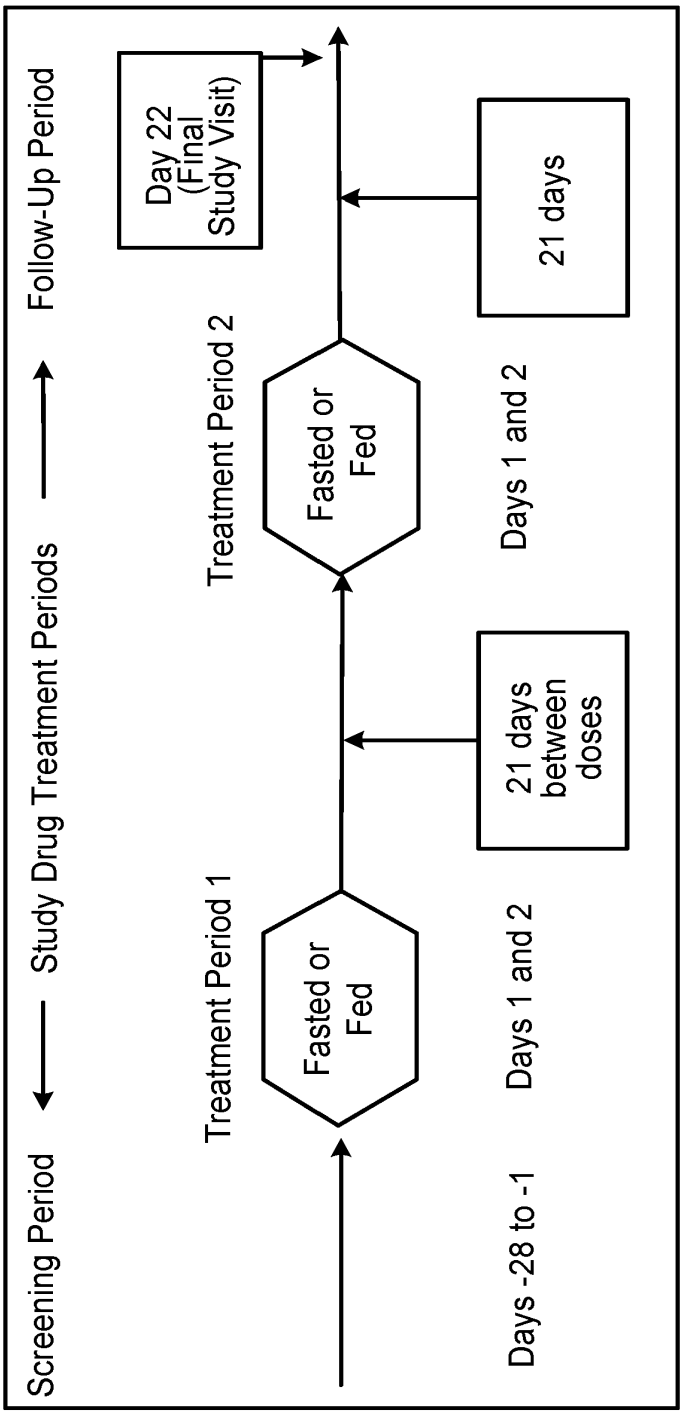

Screening Period
Study Drug Treatment Periods
Follow-Up Period
Days -28 to -1
Treatment Period 1
Fasted or Fed
Days 1 and 2
21 days between doses
Treatment Period 2
Fasted or Fed
Days 1 and 2
21 days
Day 22 (Final Study Visit)

FIG. 7

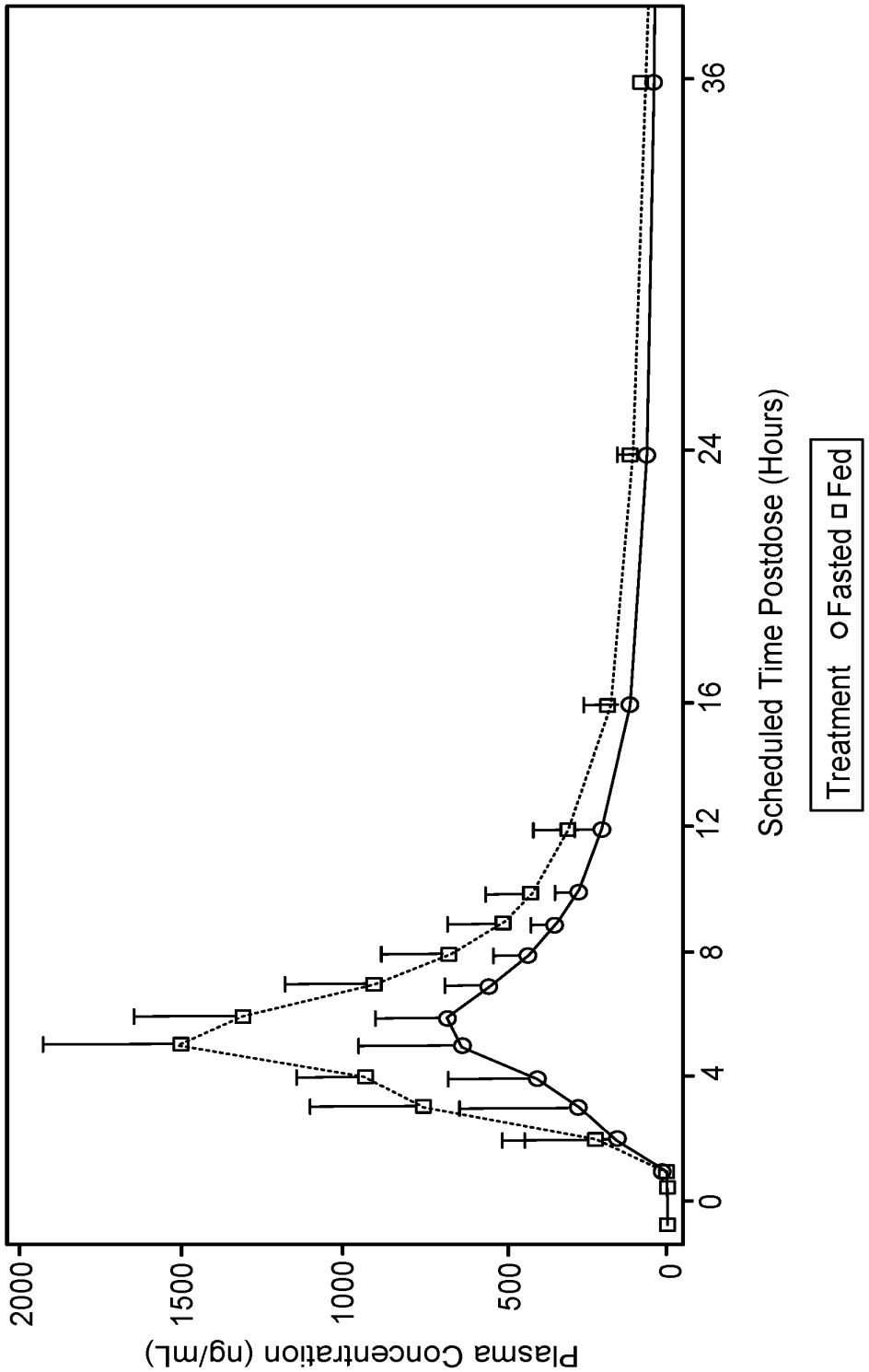

Plasma Concentration (ng/mL)
2000
1500
1000
500
0
0
4
8
12
16
24
36
Scheduled Time Postdose (Hours)
Treatment Fasted Fed

FIG. 8A

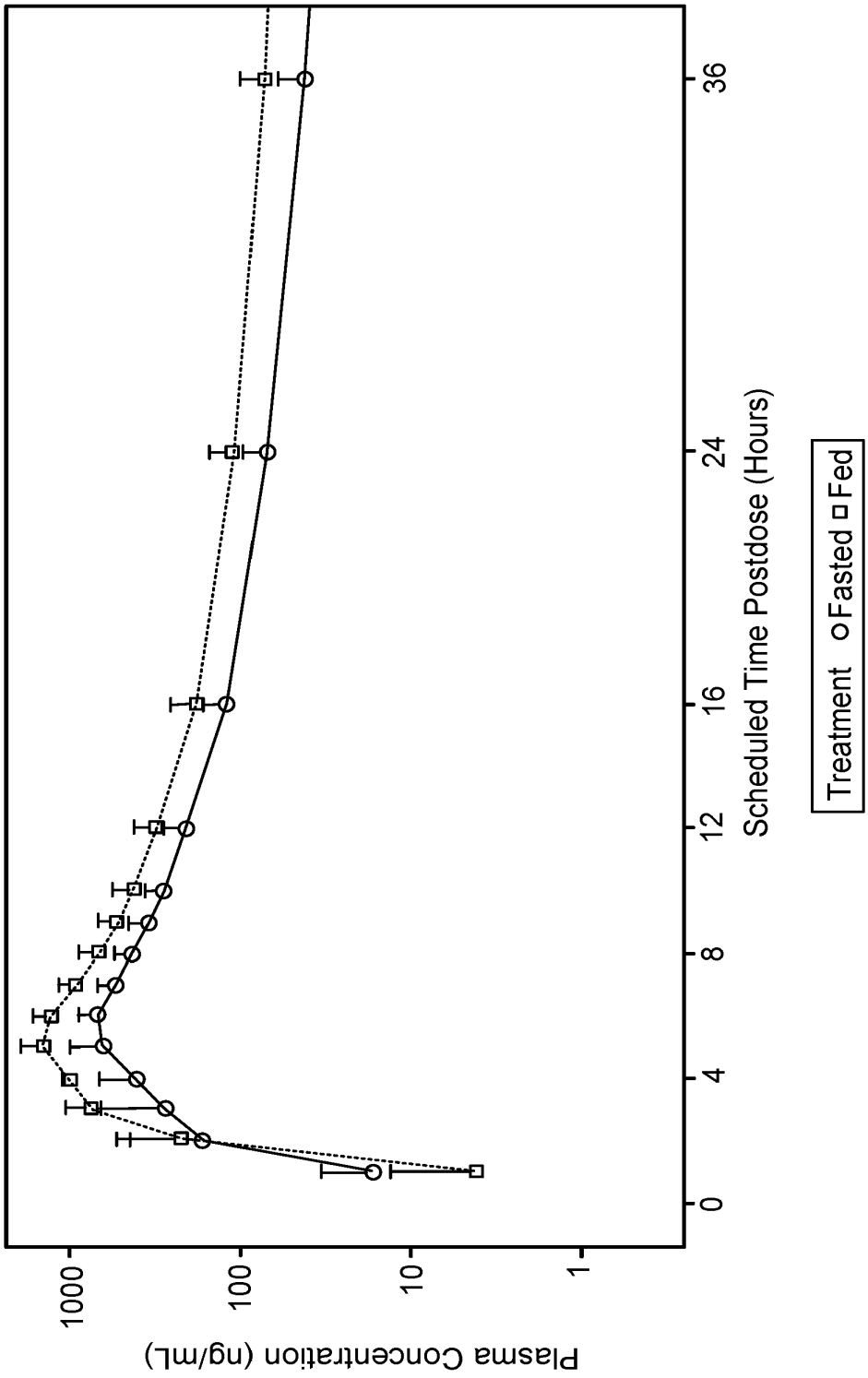

Plasma Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
24
36
Scheduled Time Postdose (Hours)
Treatment Fasted Fed

FIG. 8B

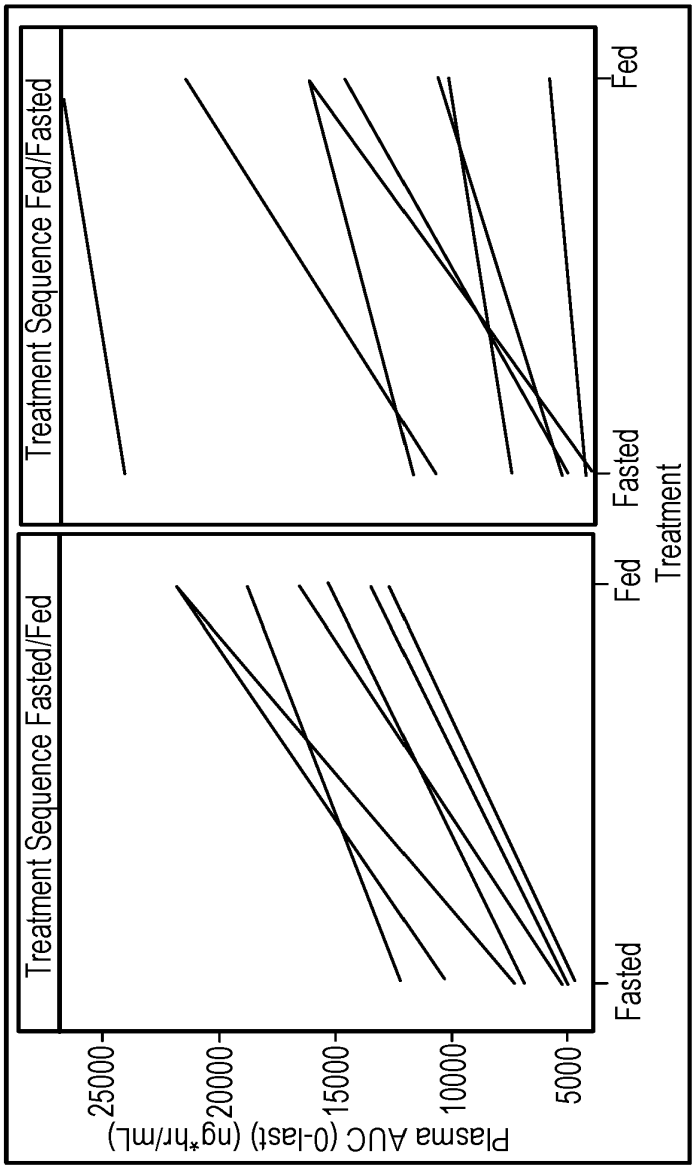

Treatment Sequence Fasted/Fed
Treatment Sequence Fed/Fasted
Plasma AUC (0-last) (ng*hr/mL)
25000
20000
15000
10000
5000
Fasted
Fed
Fed
Fasted
Treatment

FIG. 9A

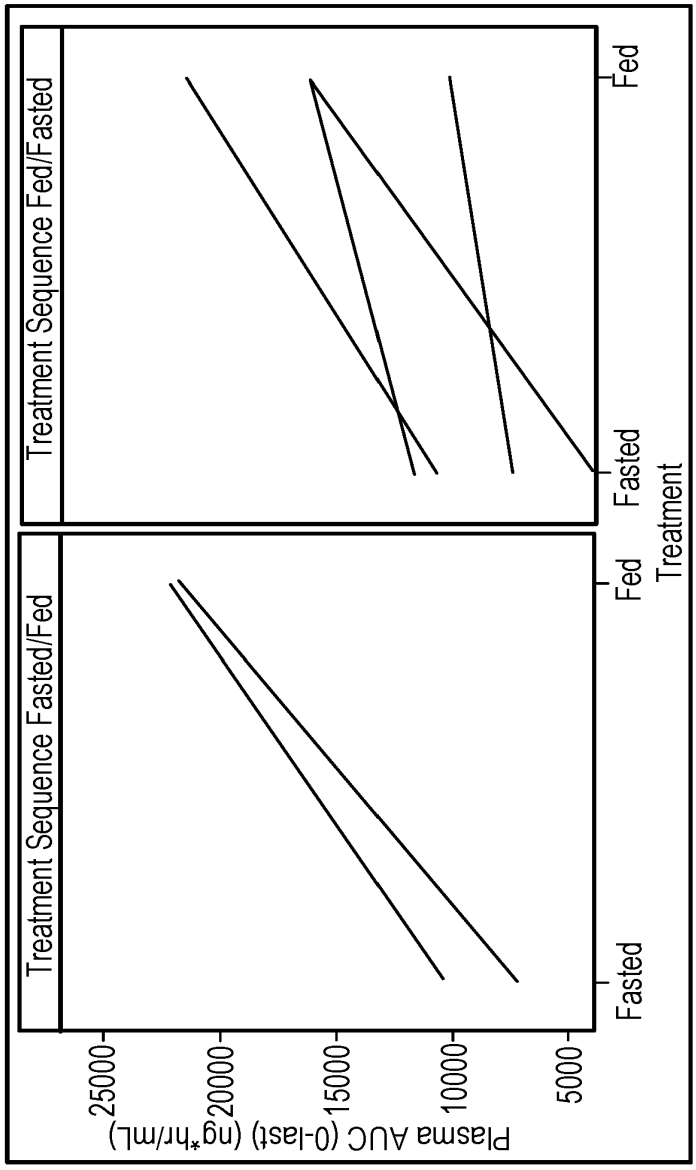

Treatment Sequence Fasted/Fed
Treatment Sequence Fed/Fasted
Plasma AUC (0-last) (ng*hr/mL)
25000
20000
15000
10000
5000
Fasted
Fed
Fed
Fasted
Treatment

FIG. 9B

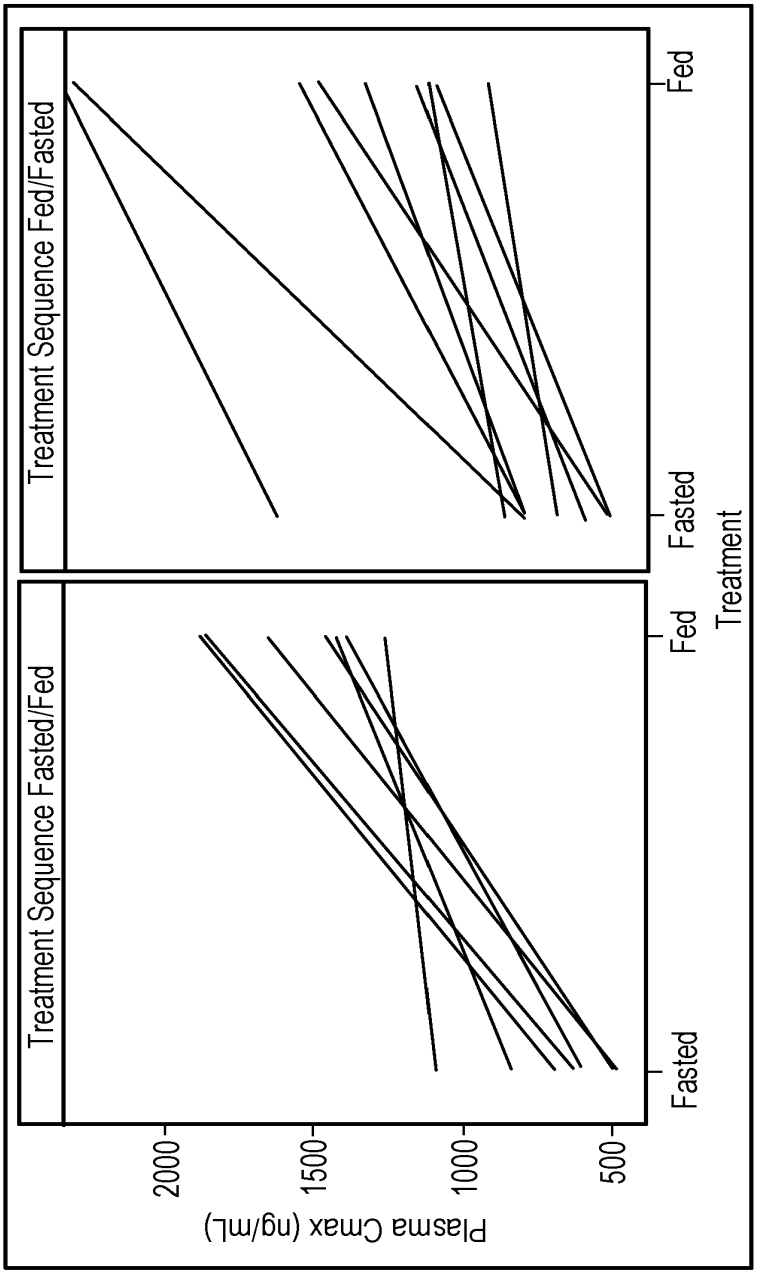
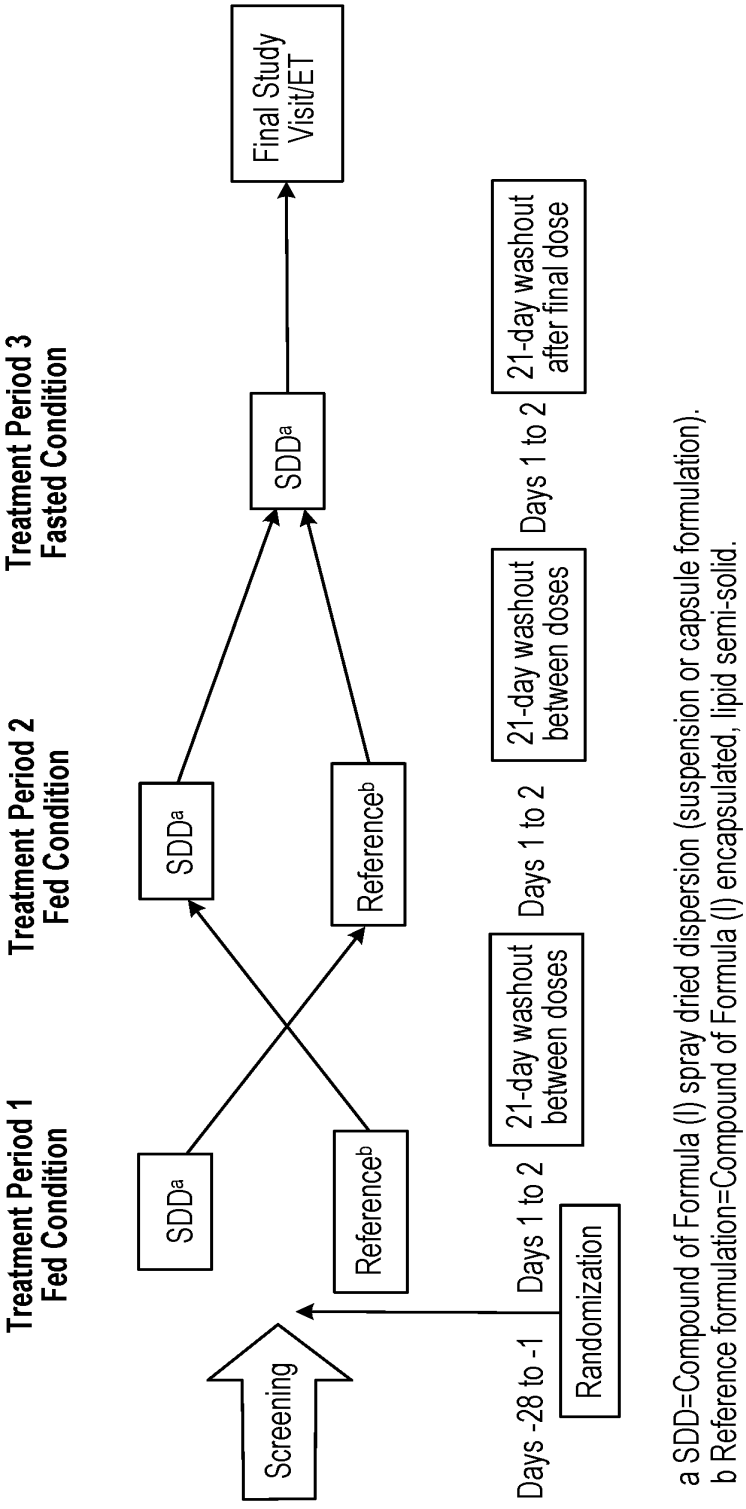

Treatment Sequence Fasted/Fed
Treatment Sequence Fed/Fasted
Plasma Cmax (ng/mL)
2000
1500
1000
500
Fasted
Fed
Fed
Fasted
Treatment

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

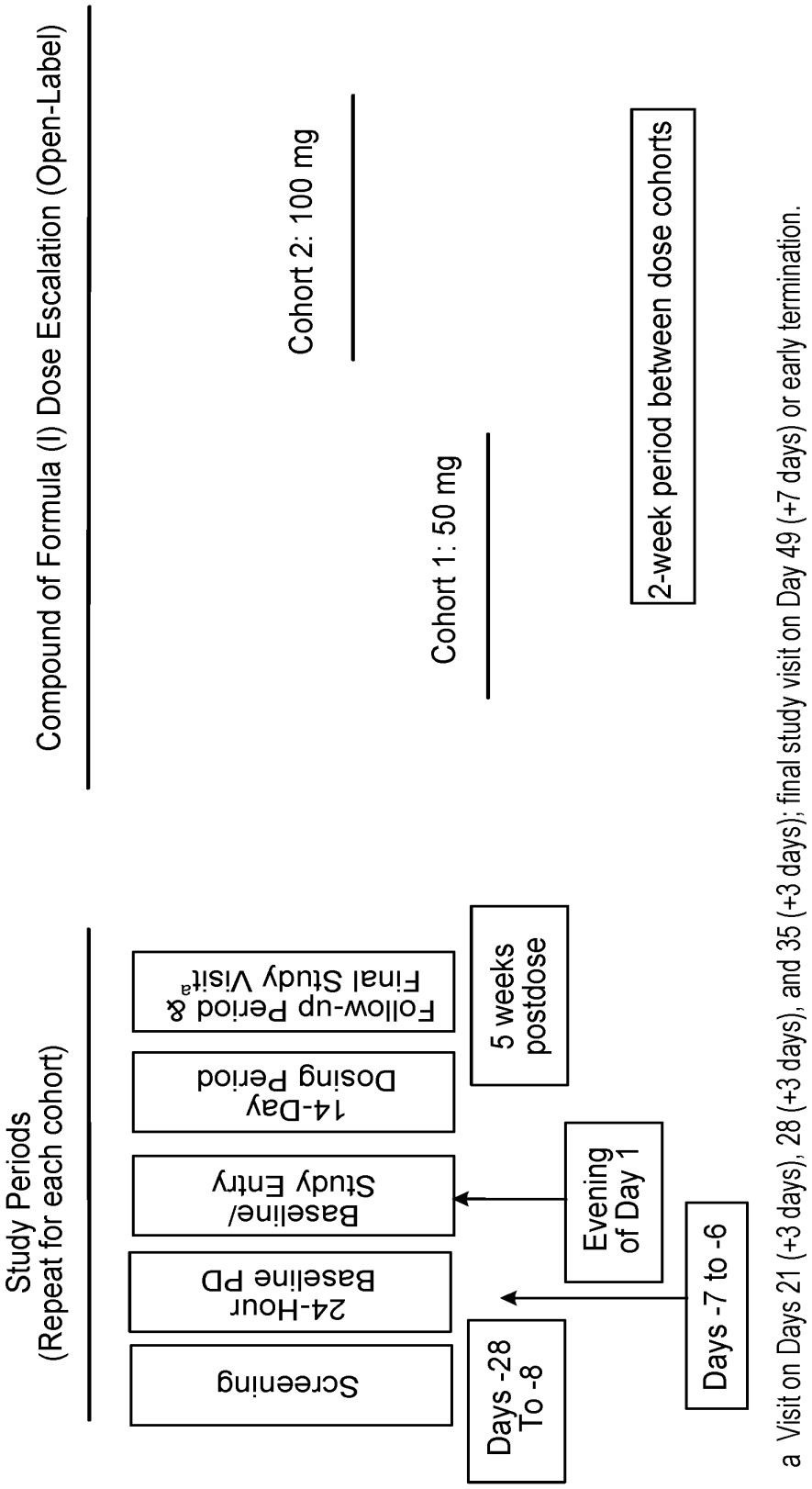


FIG. 11

a Visit on Days 21 (+3 days), 28 (+3 days), and 35 (+3 days); final study visit on Day 49 (+7 days) or early termination.
PD = pharmacodynamic.

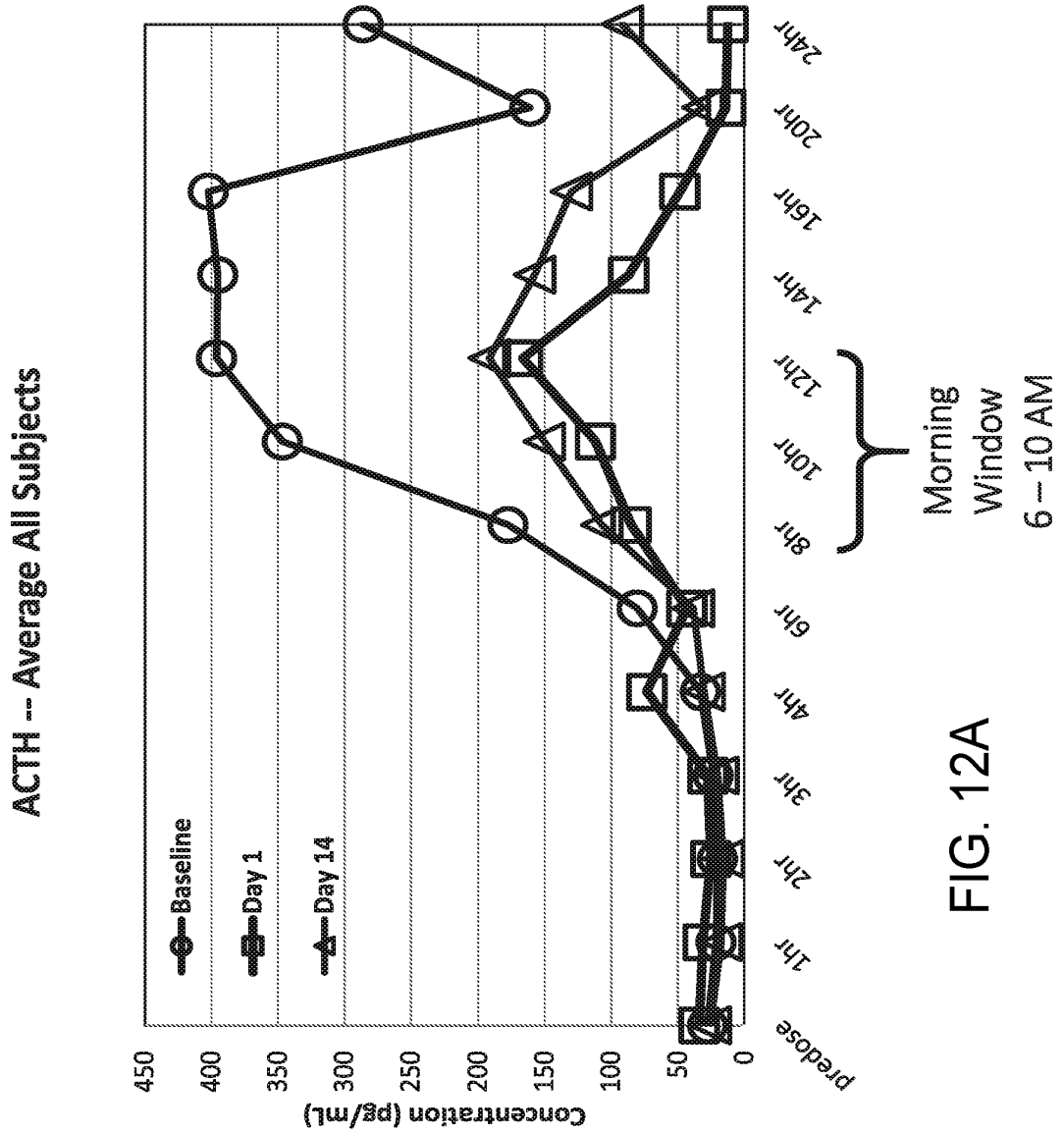

ACTH -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
450
400
350
300
250
200
150
100
50
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 12A

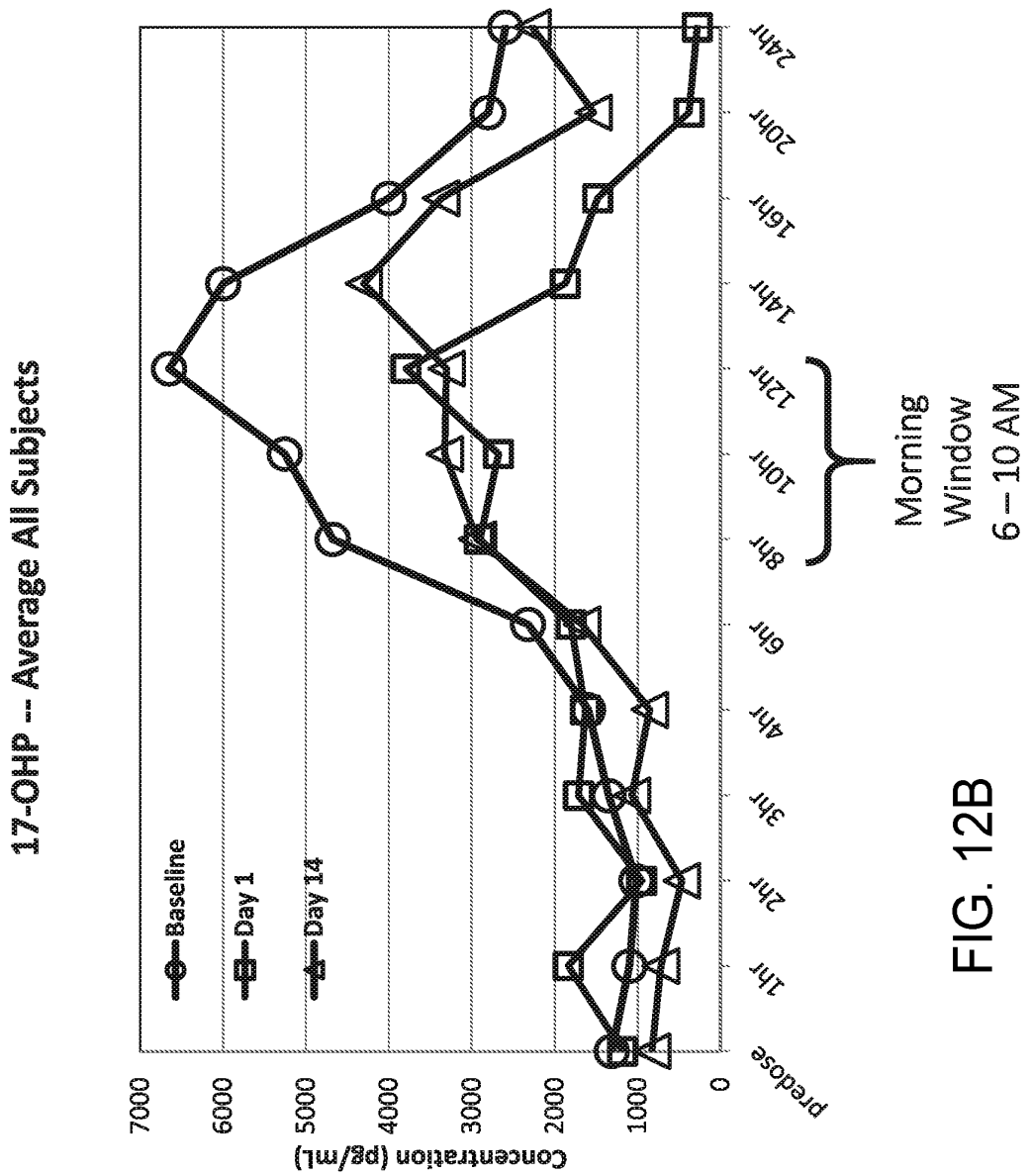

17-OHP -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 12B

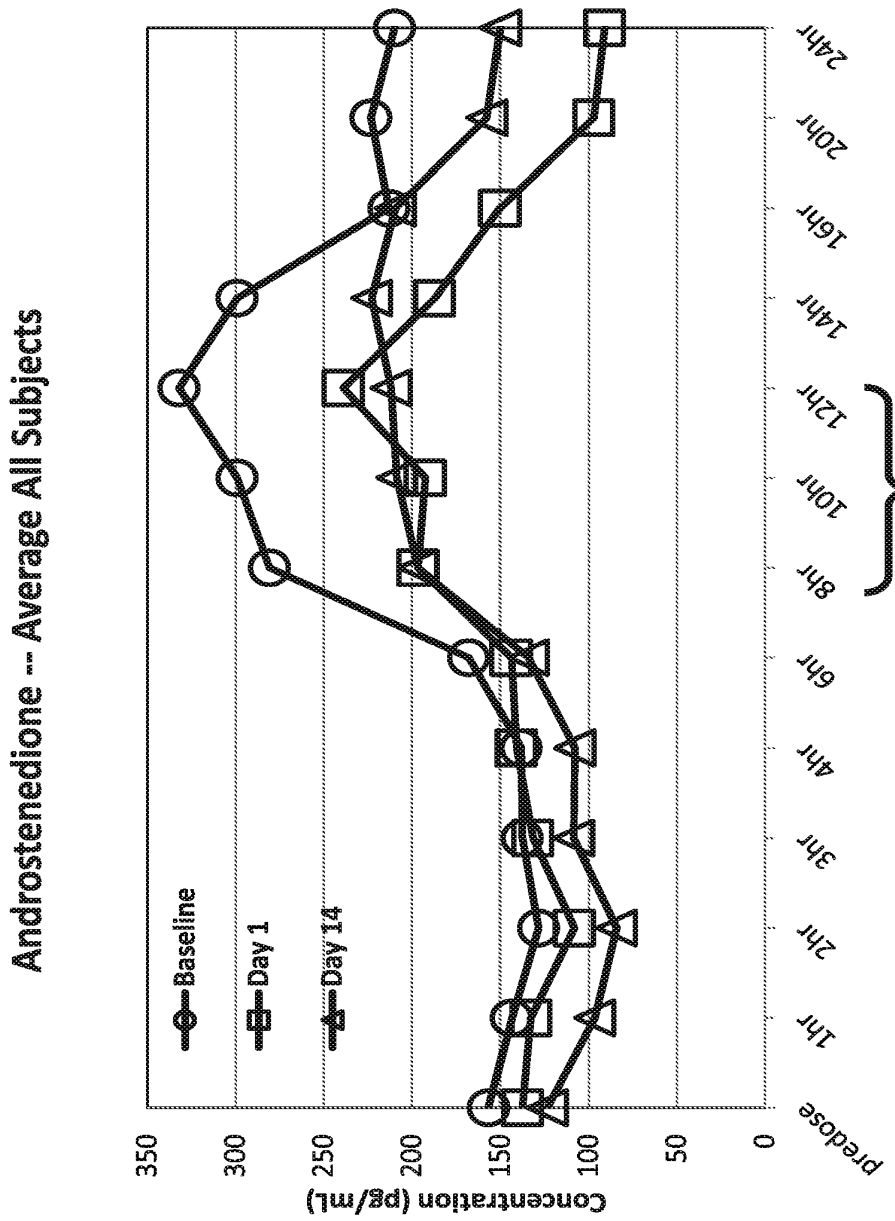

Androstenedione -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
350
300
250
200
150
100
50
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 13A

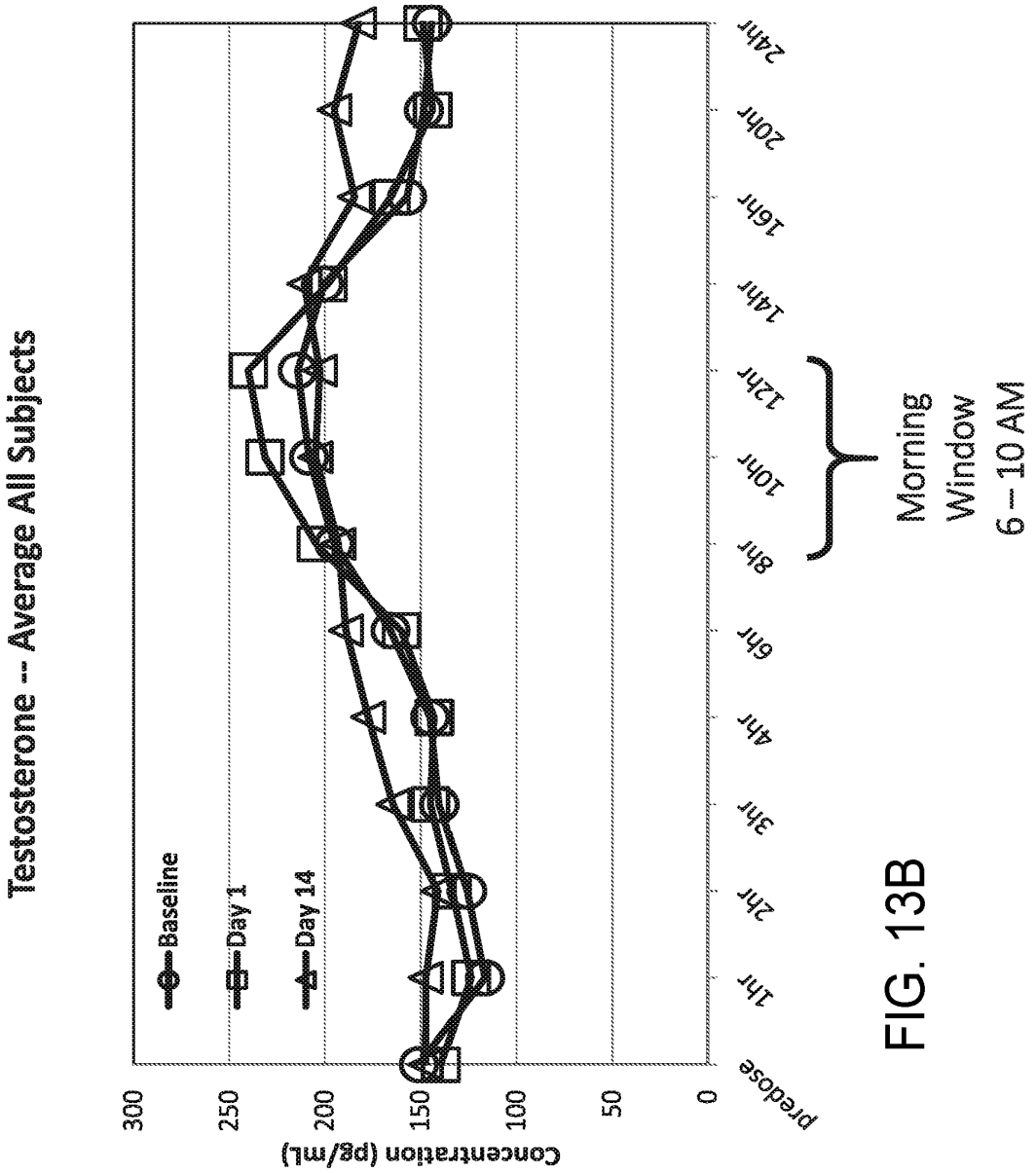

Testosterone -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
300
250
200
150
100
50
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 13B

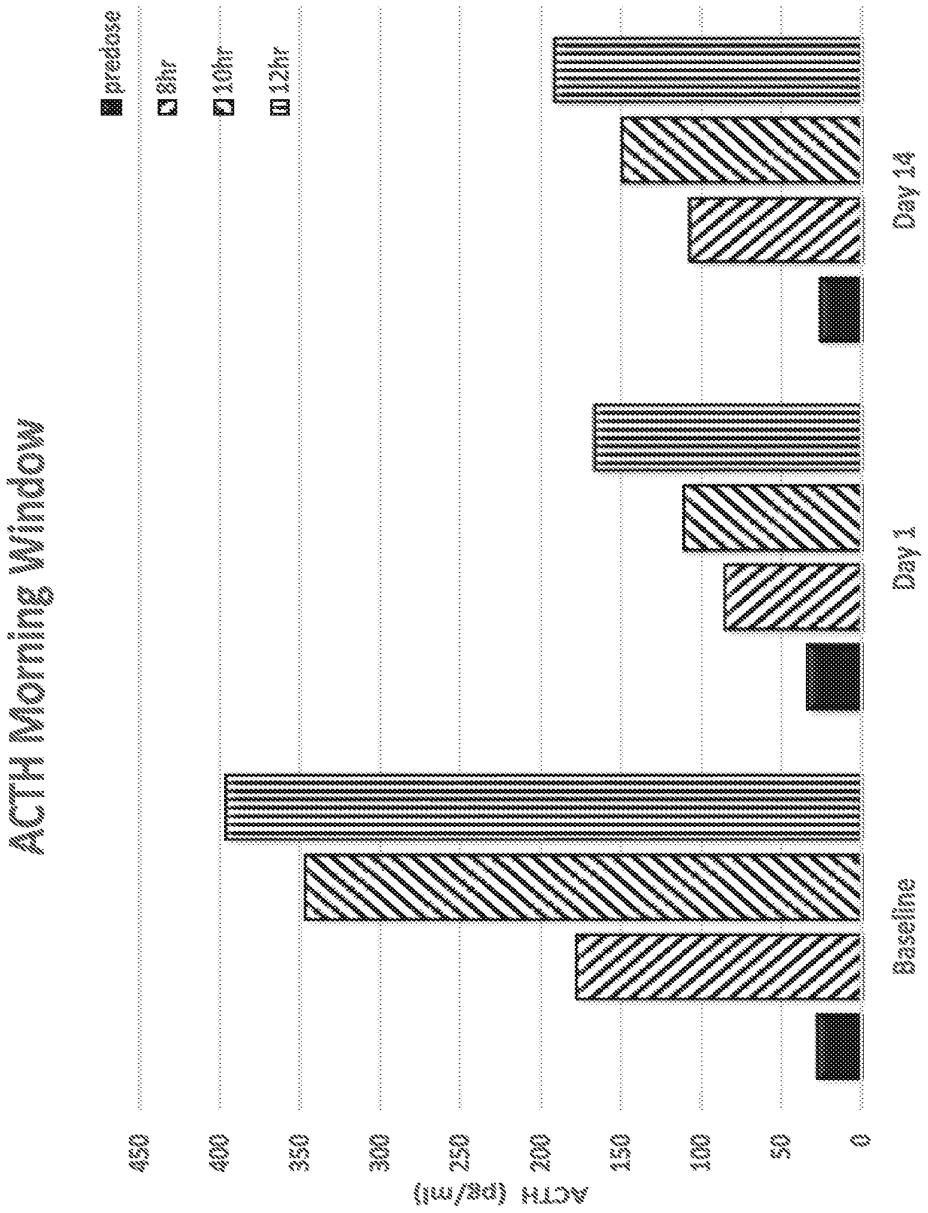

ACTH Morning Window
predose
8hr
10hr
12hr
ACTH (pg/ml)
450
400
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 14A

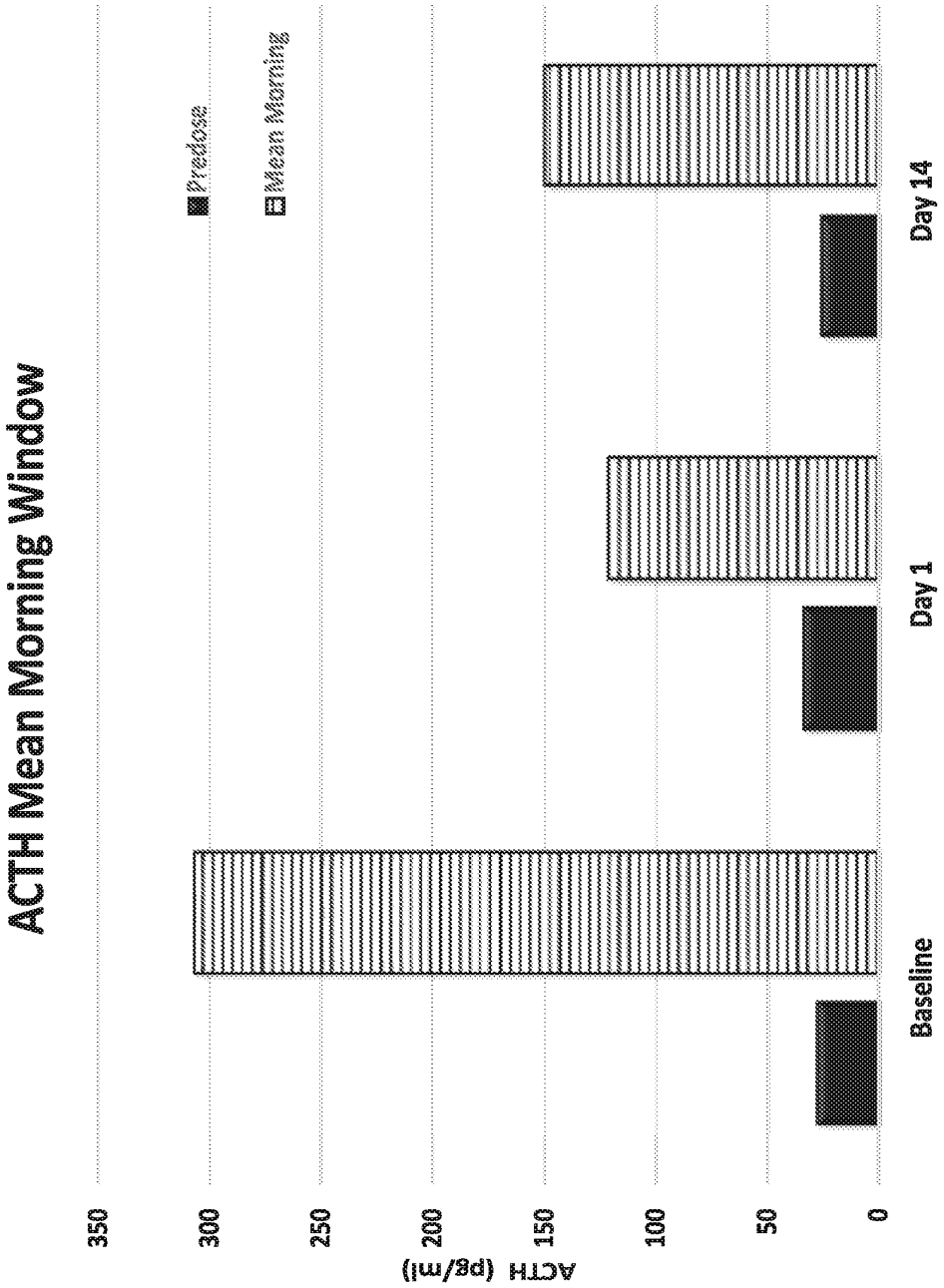

ACTH Mean Morning Window
Predose
Mean Morning
ACTH (pg/ml)
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 14B

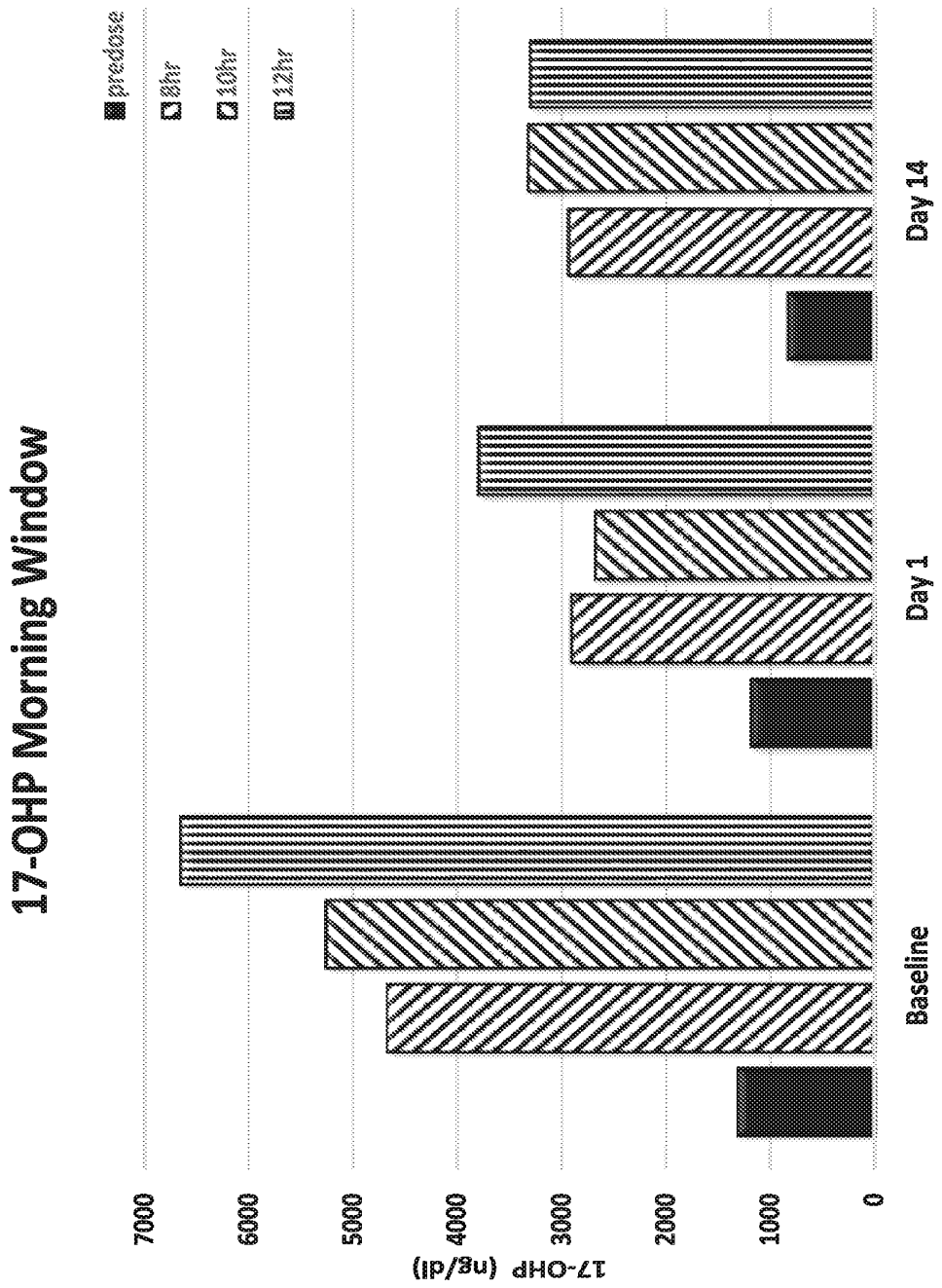

17-OHP Morning Window
predose
2hr
10hr
12hr
17-OHP (ng/dl)
7000
6000
5000
4000
3000
2000
1000
0
Baseline
Day 1
Day 14

FIG. 15A

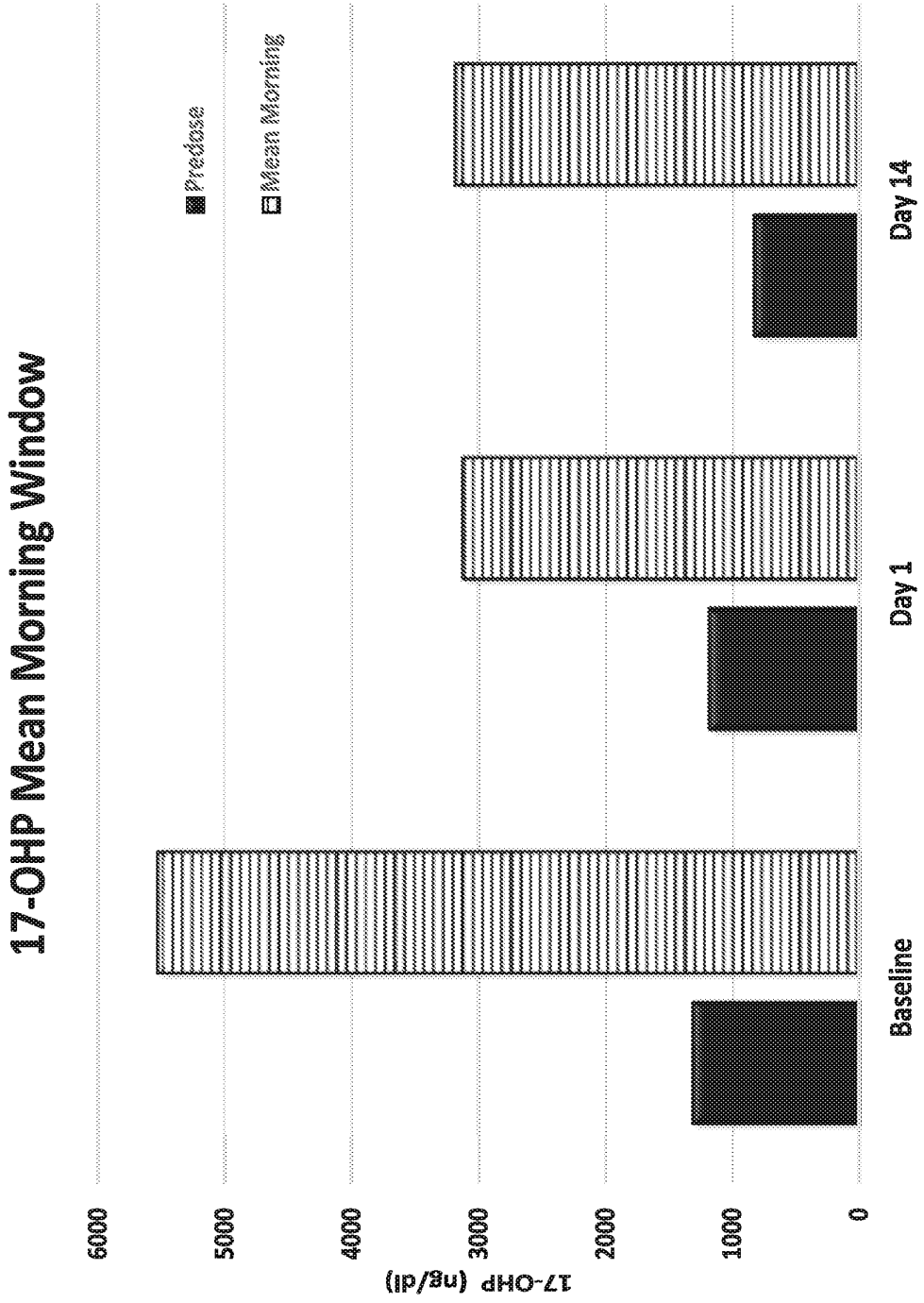

17-OHP Mean Morning Window
Predose
Mean Morning
17-OHP (ng/dl)
6000
5000
4000
3000
2000
1000
0
Baseline
Day 1
Day 14

FIG. 15B

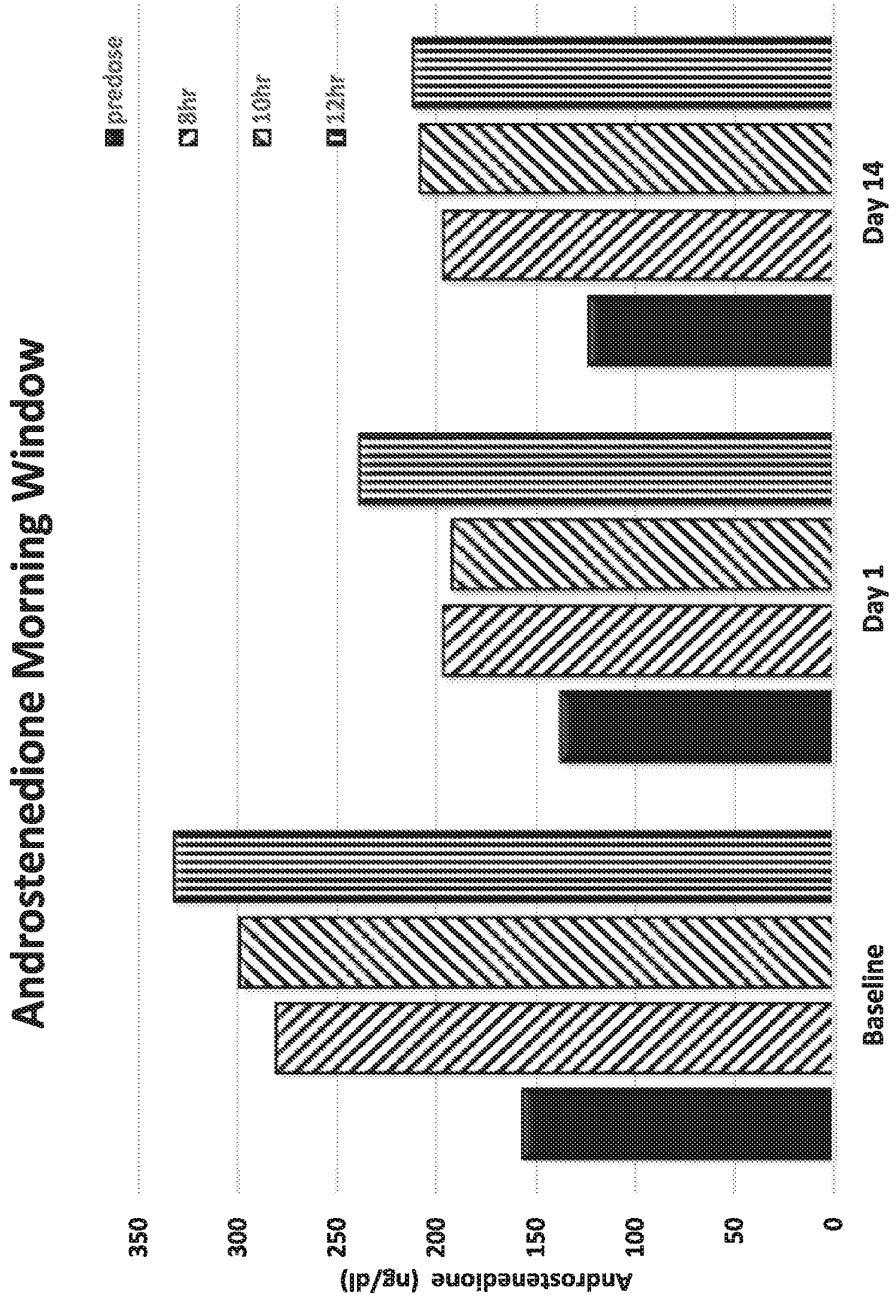

predose
8hr
10hr
12hr
Androstenedione Morning Window
Day 14
Day 1
Baseline
350
300
250
200
150
100
50
0
Androstenedione (ng/dl)

FIG. 16A

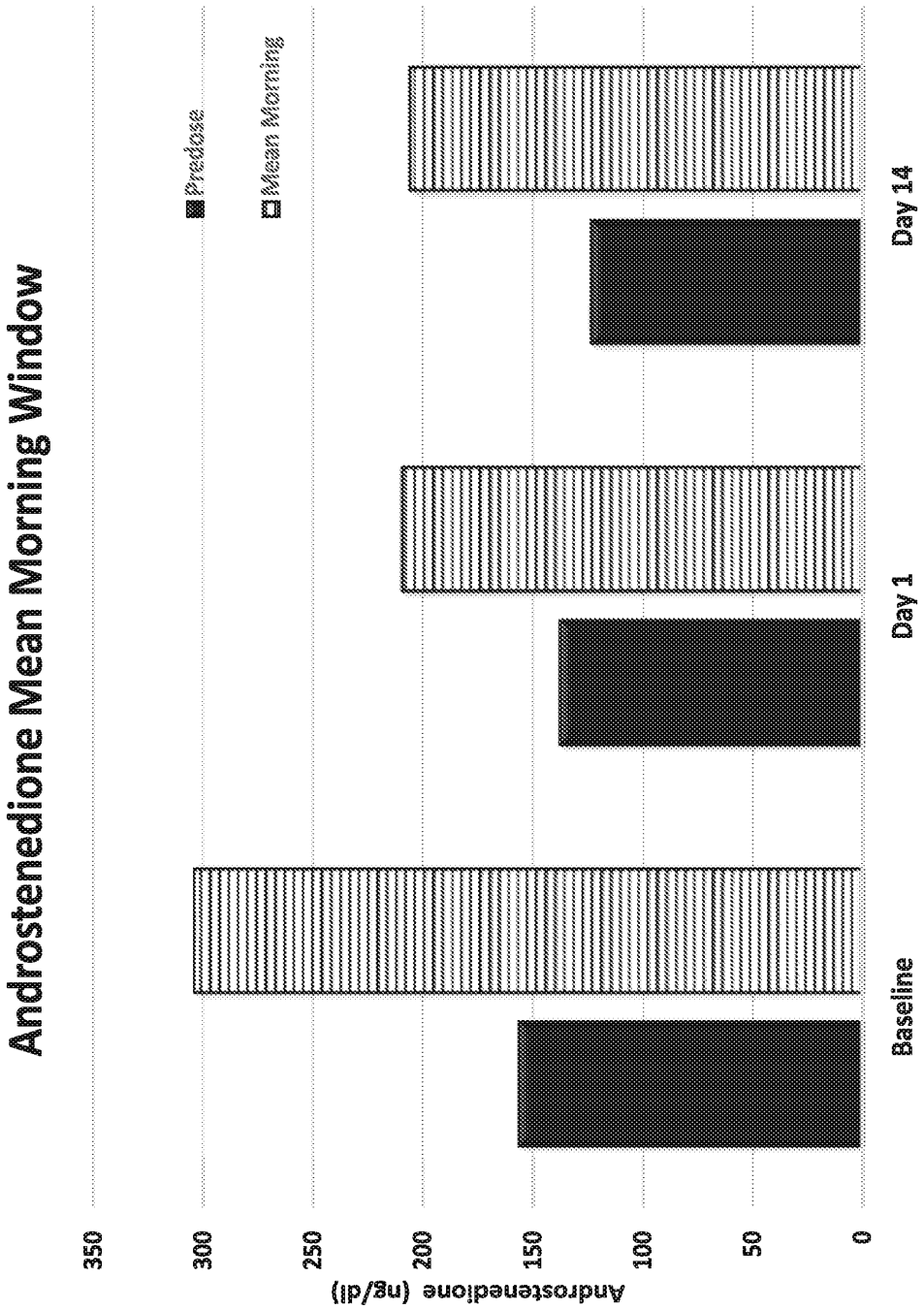

Androstenedione Mean Morning Window
Predose
Mean Morning
Androstenedione (ng/dl)
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 16B

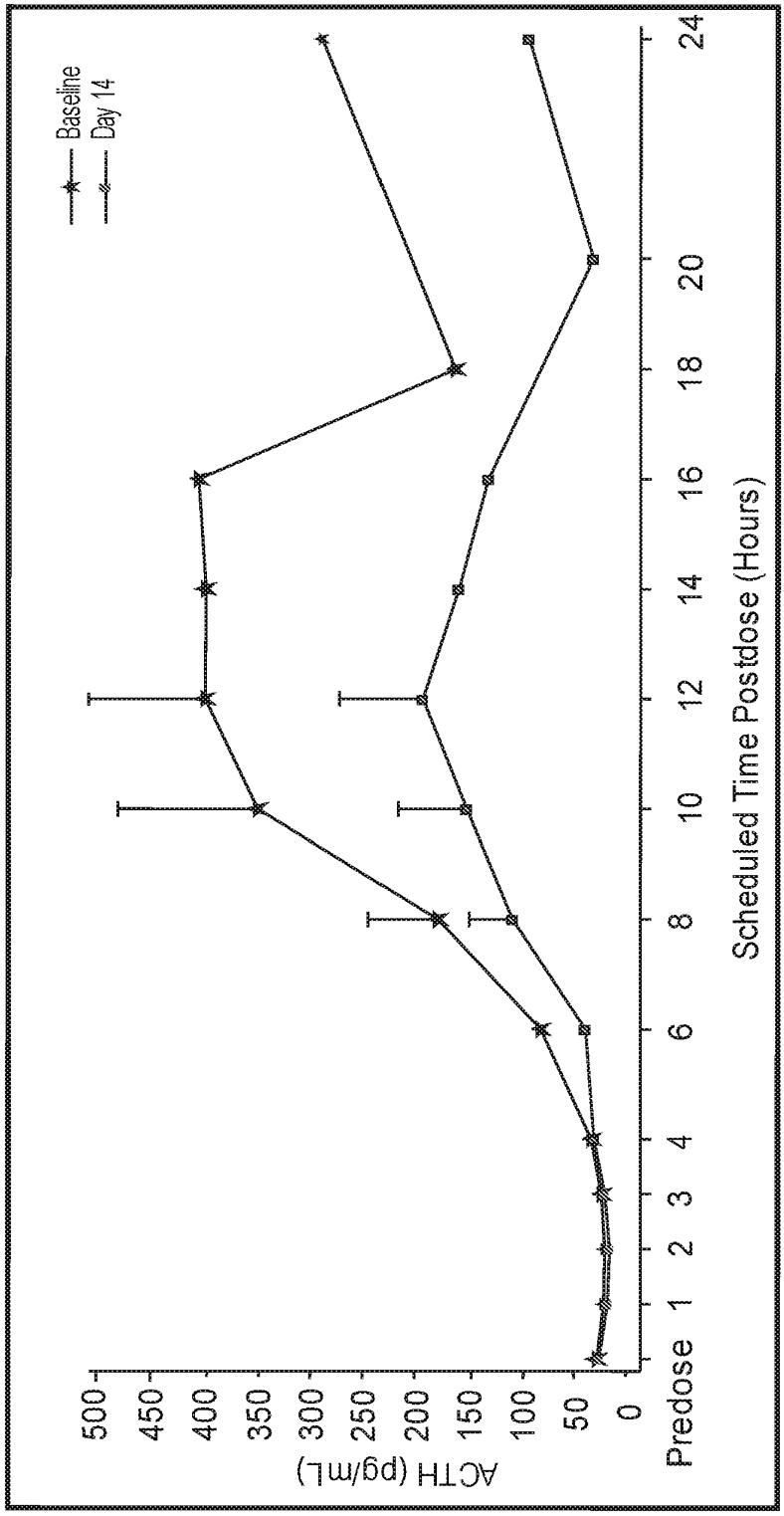

Baseline
Day 14
ACTH (pg/mL)
500
450
400
350
300
250
200
150
100
50
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 17A

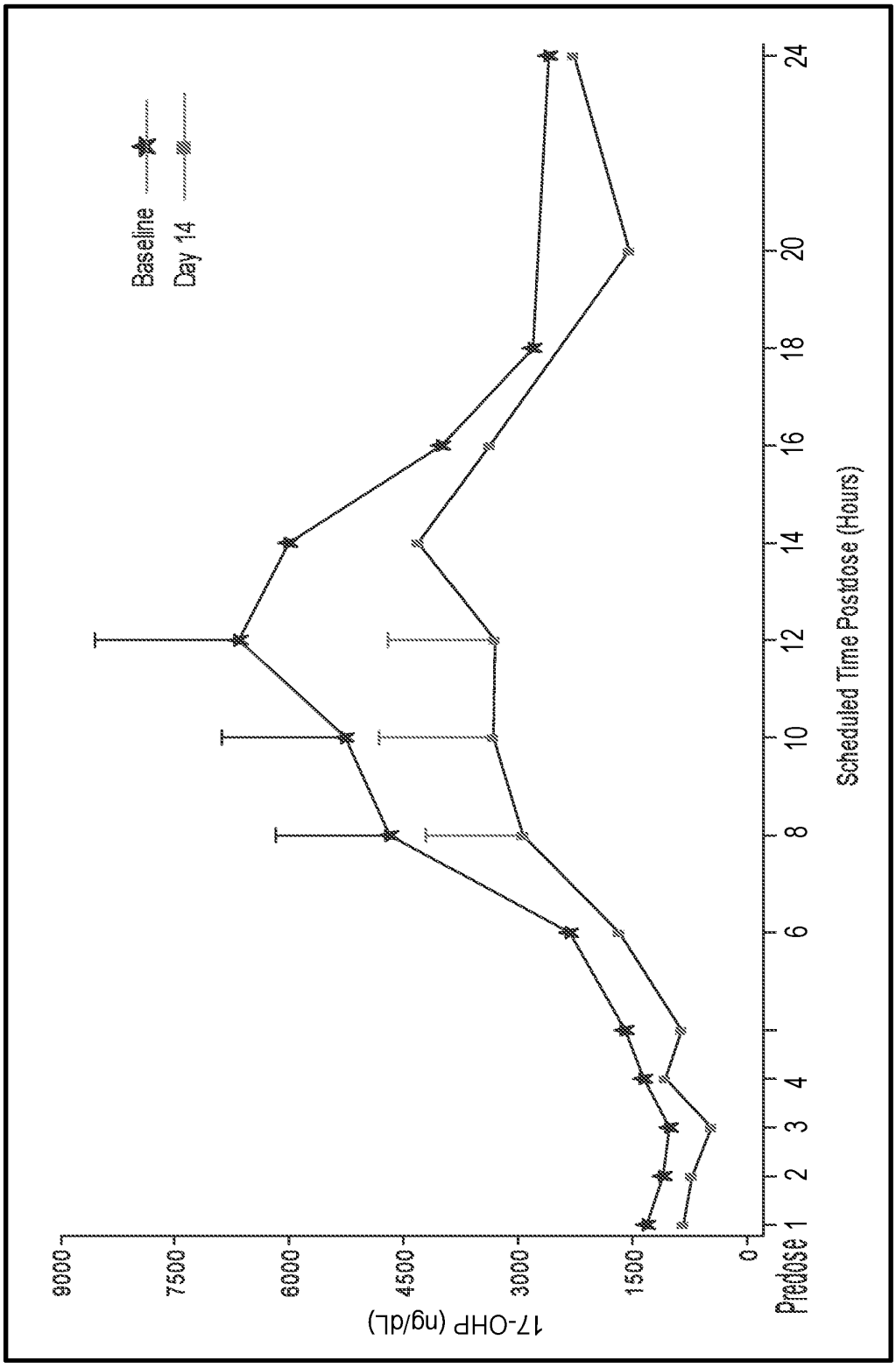

Baseline
Day 14
17-OHP (ng/dL)
9000
7500
6000
4500
3000
1500
0
Predose 1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 17B

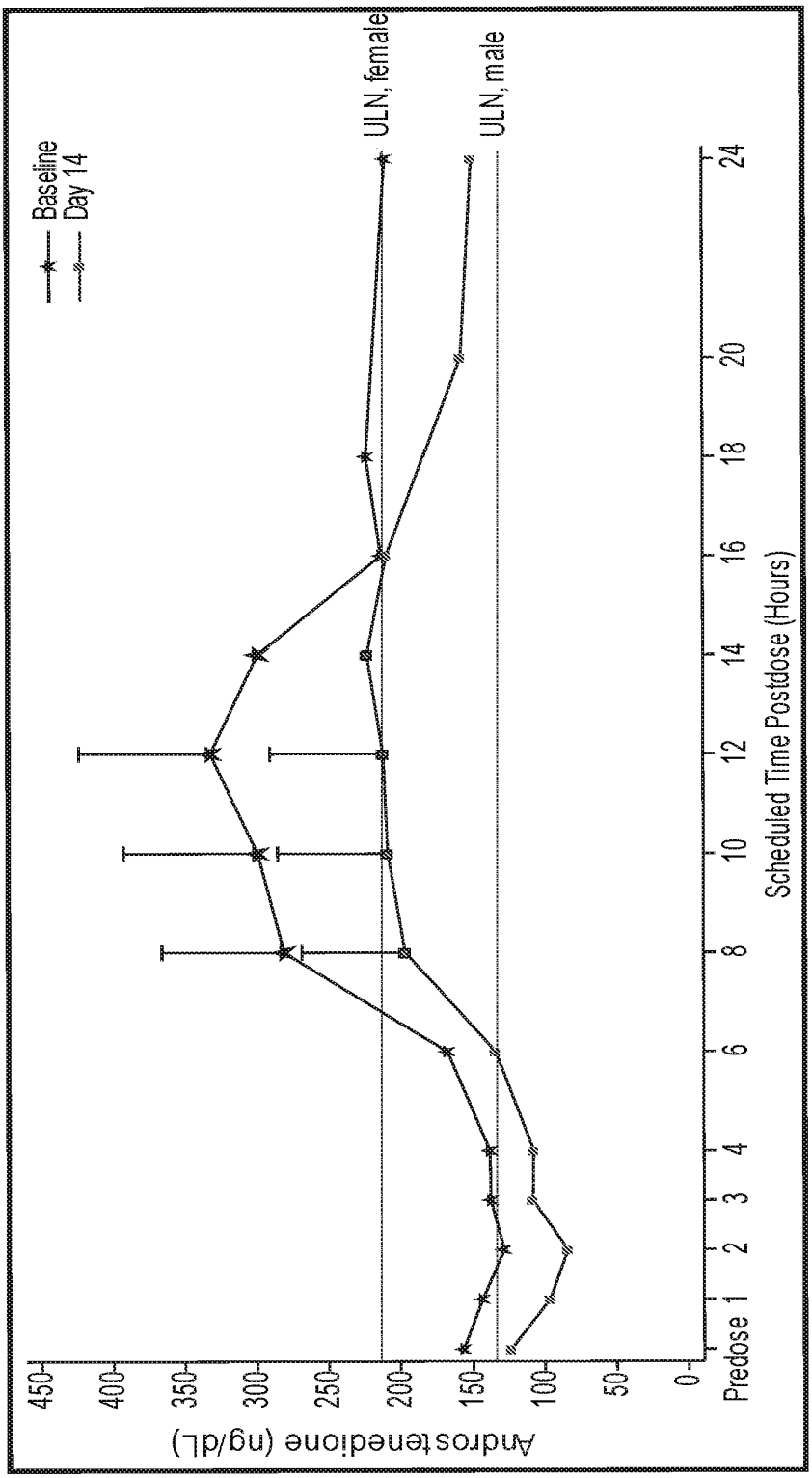

Androstenedione (ng/dL)
450
400
350
300
250
200
150
100
50
0
Predose 1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)
ULN, female
ULN, male
Baseline
Day 14

FIG. 17C

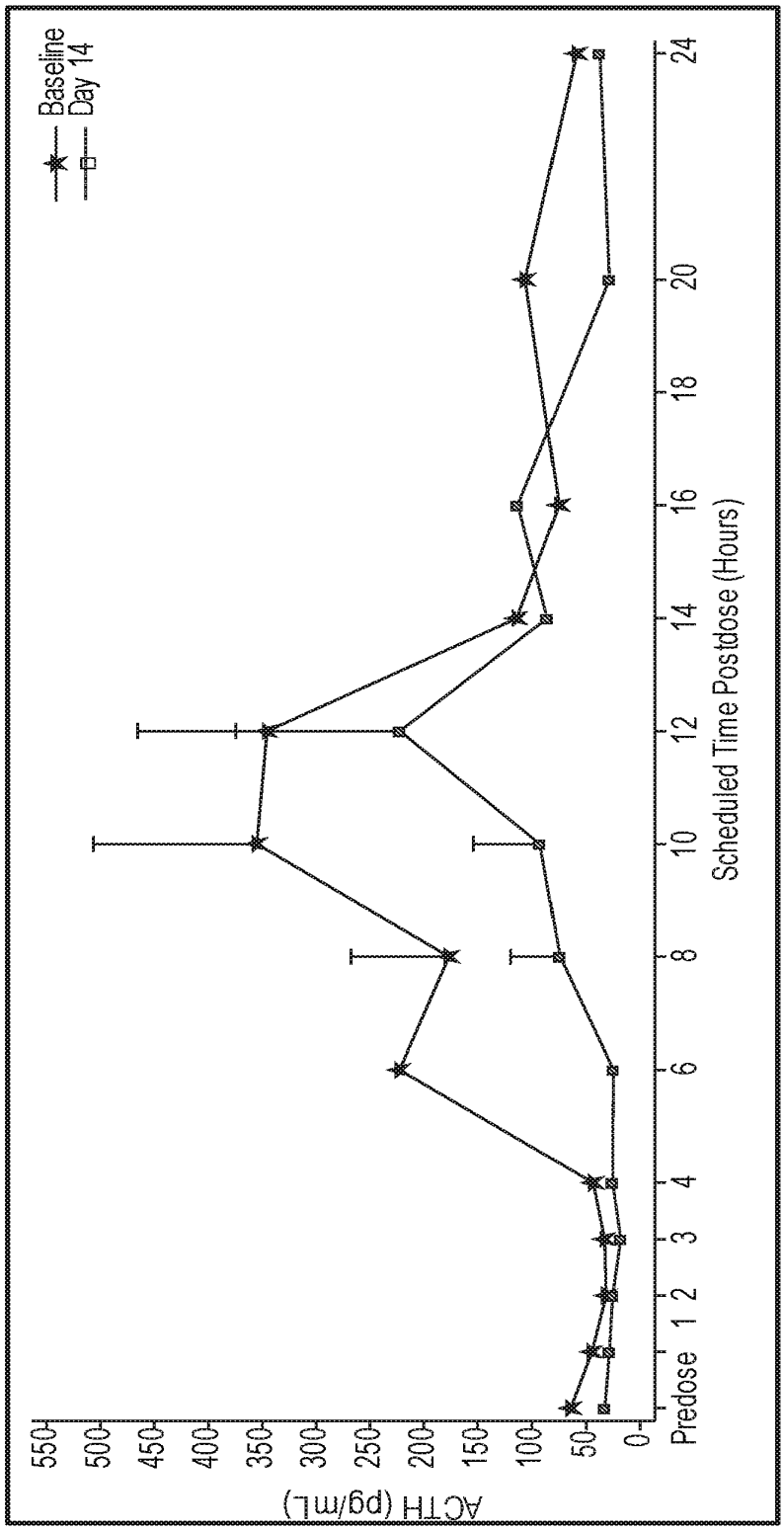

Baseline
Day 14
ACTH (pg/mL)
550
500
450
400
350
300
250
200
150
100
50
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 18A

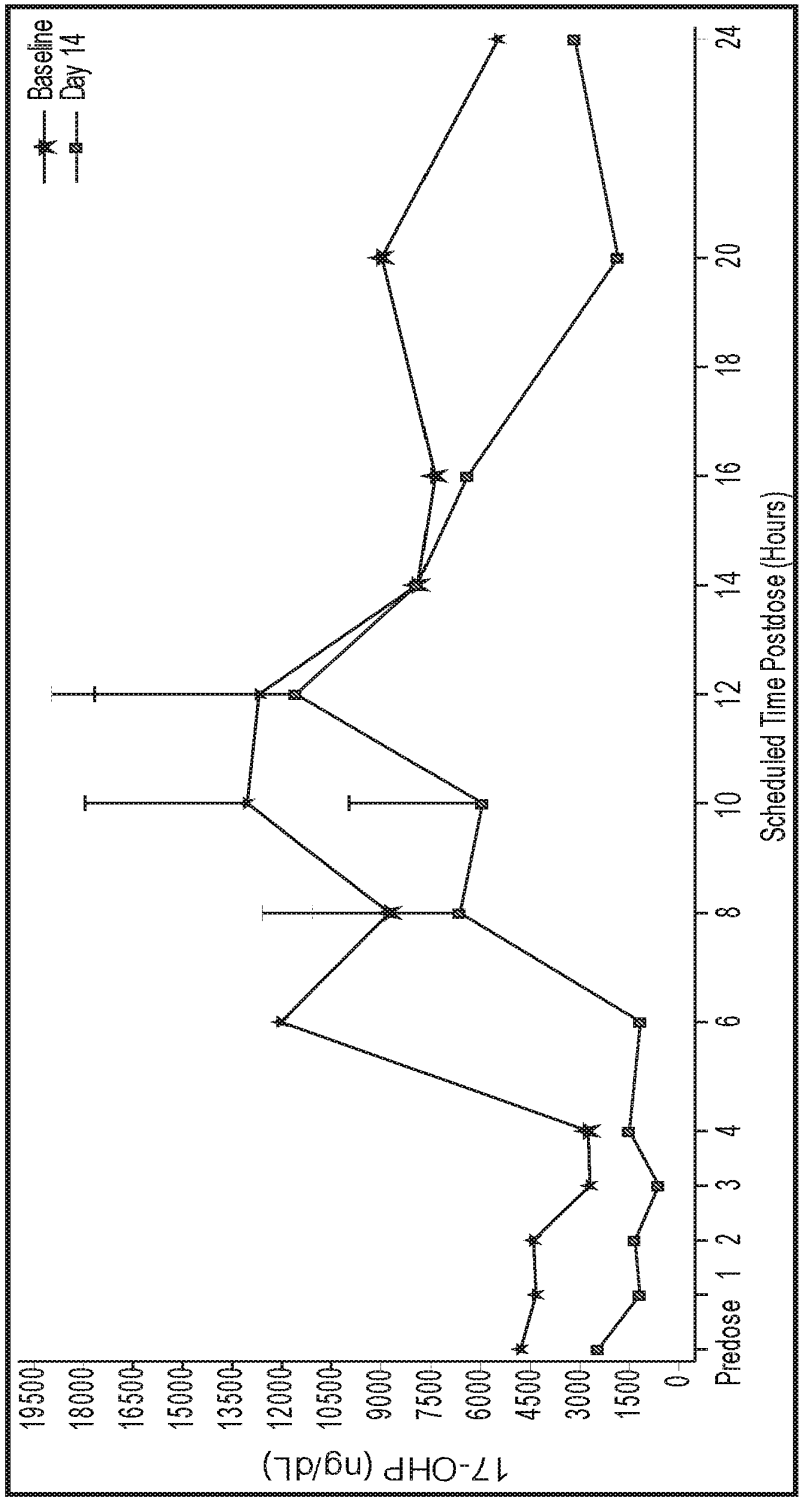

Baseline
Day 14
17-OHP (ng/dL)
19500
18000
16500
15000
13500
12000
10500
9000
7500
6000
4500
3000
1500
0
Predose 1 2 3 4 6 8 10 12 14 16 18 20 24
Scheduled Time Postdose (Hours)

FIG. 18B

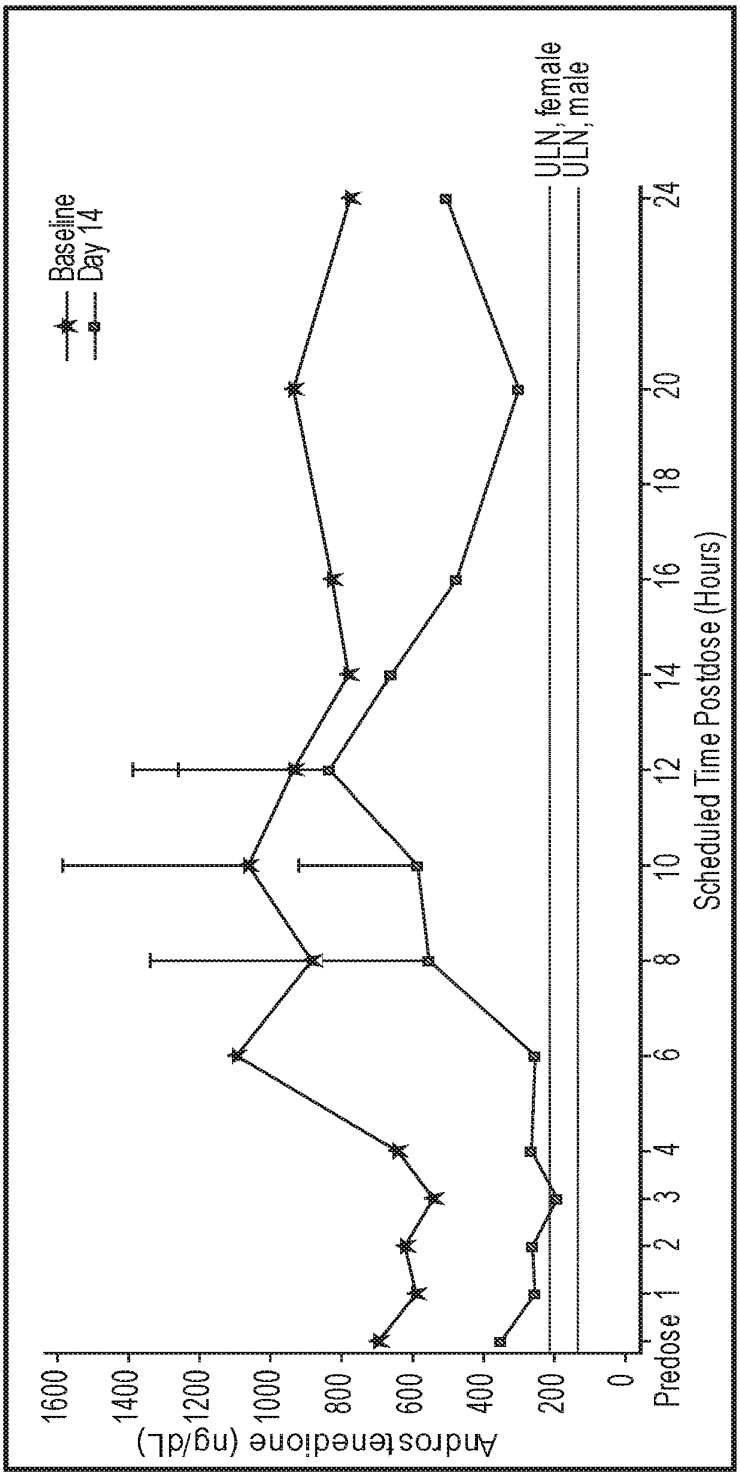

Androstenedione (ng/dL)
1600
1400
1200
1000
800
600
400
200
0
Predose 1 2 3 4 6 8 10 12 14 16 18 20 24
Scheduled Time Postdose (Hours)
Baseline
Day 14
ULN, female
ULN, male

FIG. 18C

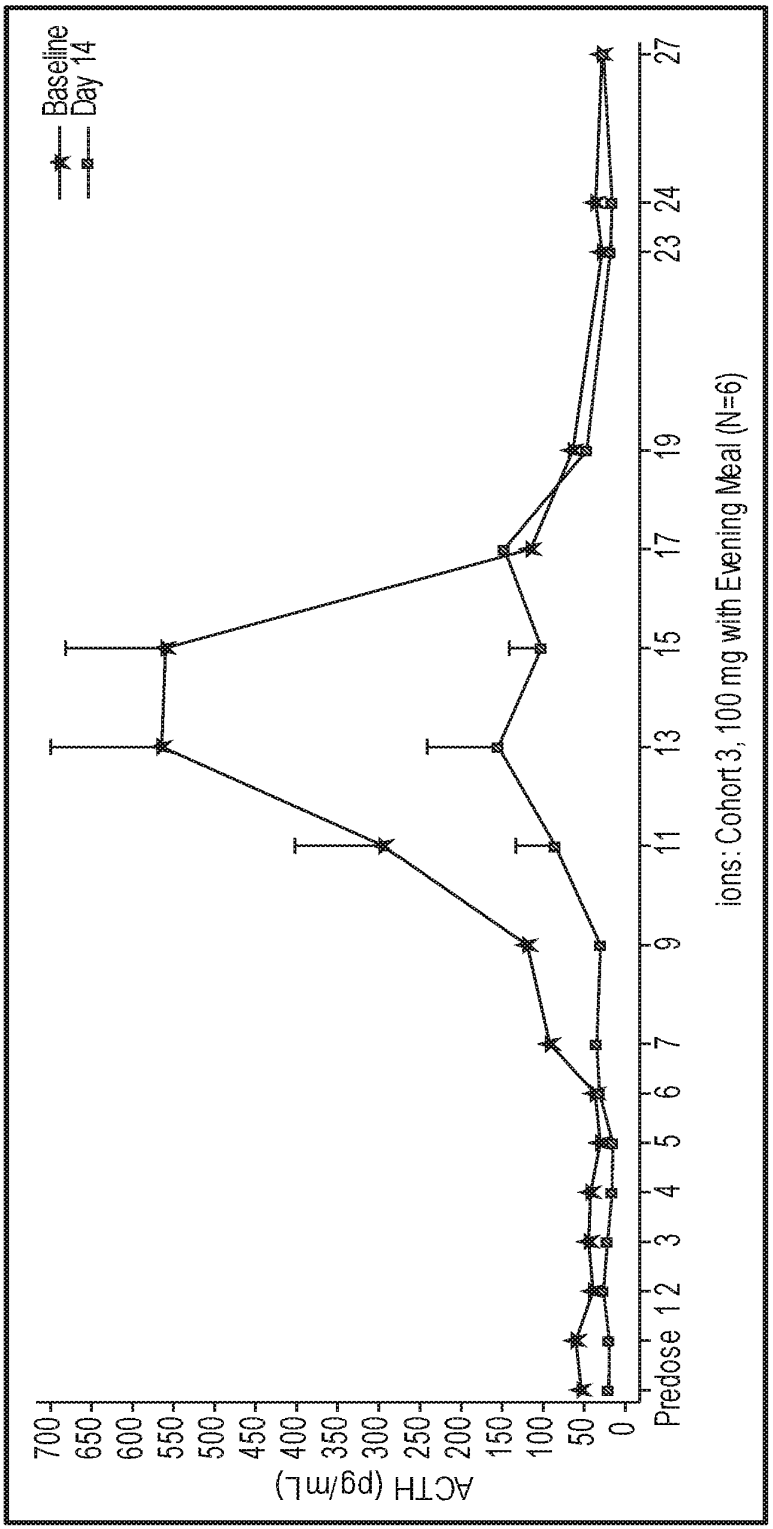

Baseline
Day 14
ACTH (pg/mL)
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
Predose 1 2 3 4 5 6 7 9 11 13 15 17 19 23 24 27
ions: Cohort 3, 100 mg with Evening Meal (N=6)

FIG. 19A

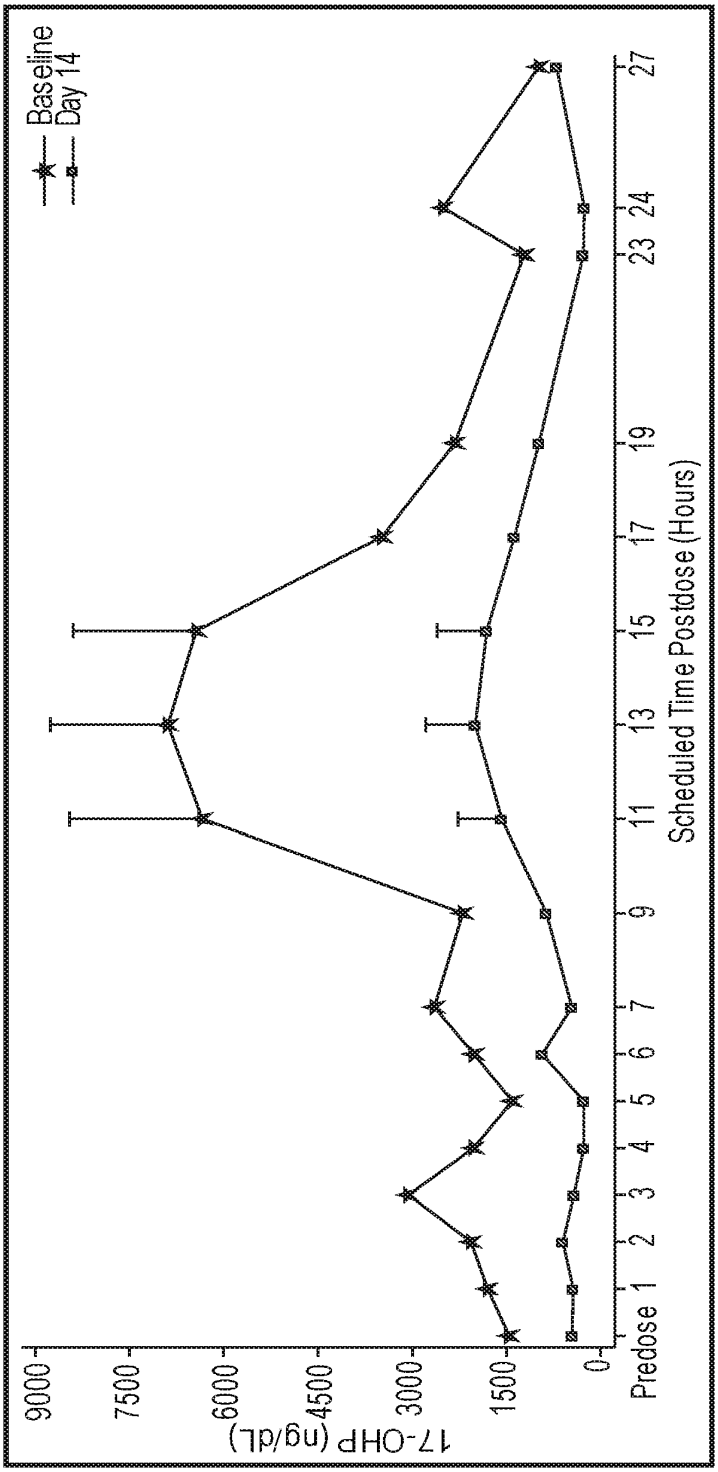

Baseline
Day 14
17-OHP (ng/dL)
9000
7500
6000
4500
3000
1500
0
Predose 1 2 3 4 5 6 7 9 11 13 15 17 19 23 24 27
Scheduled Time Postdose (Hours)

FIG. 19B

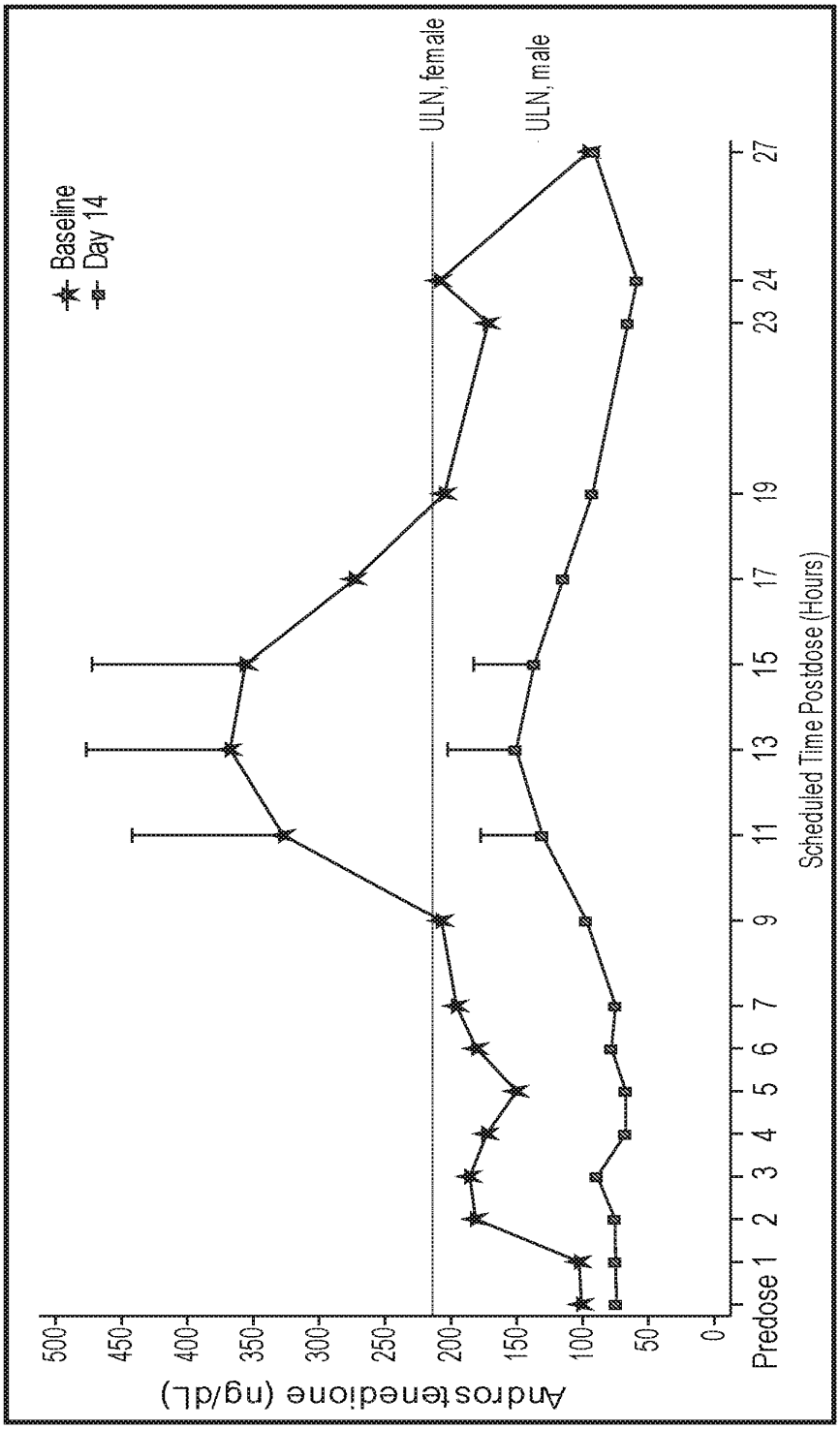

Baseline
Day 14
ULN, female
ULN, male
Androstenedione (ng/dL)
500
450
400
350
300
250
200
150
100
50
0
Predose 1 2 3 4 5 6 7 9 11 13 15 17 19 23 24 27
Scheduled Time Postdose (Hours)

FIG. 19C

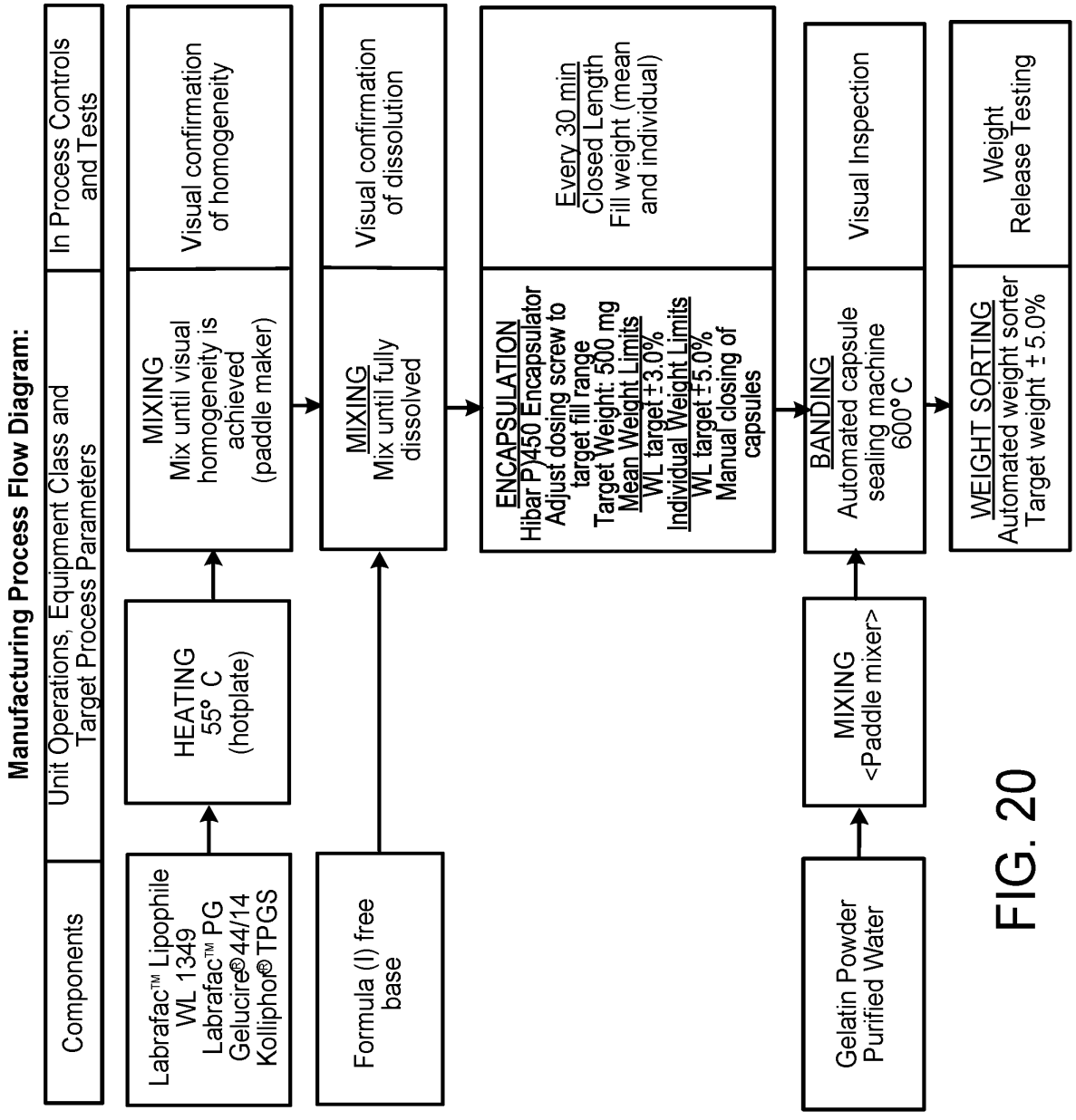
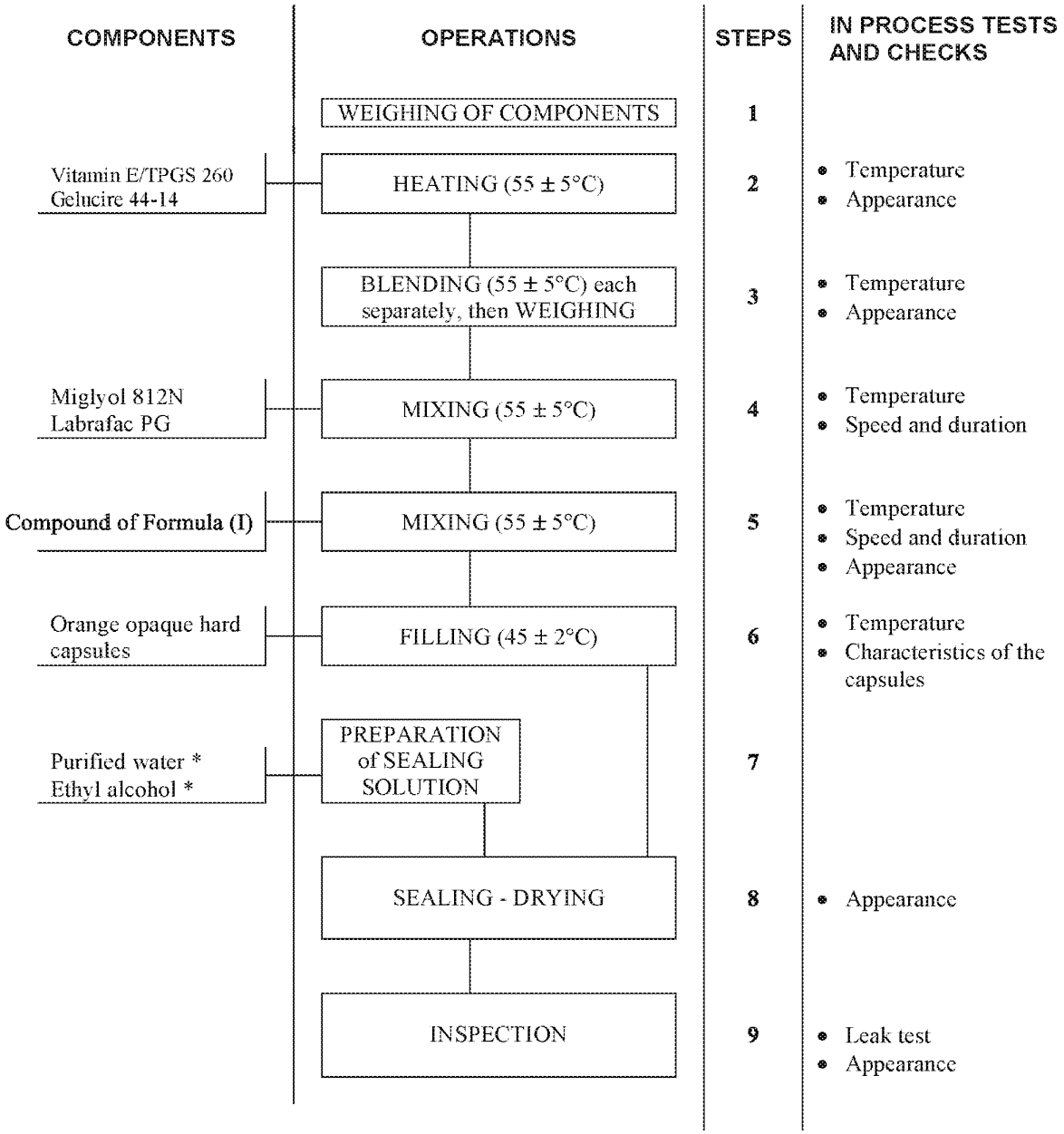

Manufacturing Process Flow Diagram:
Components
Unit Operations, Equipment Class and Target Process Parameters
In Process Controls and Tests
Labrafac™ Lipophile WL 1349
Labrafac™ PG
Gelucire® 44/14
Kolliphor® TPGS
HEATING
55° C
(hotplate)
MIXING
Mix until visual homogeneity is achieved
(paddle maker)
Visual confirmation of homogeneity
Formula (I) free base
MIXING
Mix until fully dissolved
Visual confirmation of dissolution
ENCAPSULATION
Hibar P/450 Encapsulator
Adjust dosing screw to target fill range
Target Weight: 500 mg
Mean Weight Limits
WL target ±3.0%
Individual Weight Limits
WL target ±5.0%
Manual closing of capsules
Every 30 min
Closed Length
Fill weight (mean and individual)
Gelatin Powder
Purified Water
MIXING
<Paddle mixer>
BANDING
Automated capsule sealing machine
600° C
Visual Inspection
WEIGHT SORTING
Automated weight sorter
Target weight ± 5.0%
Weight
Release Testing

FIG. 20



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

FIG. 21

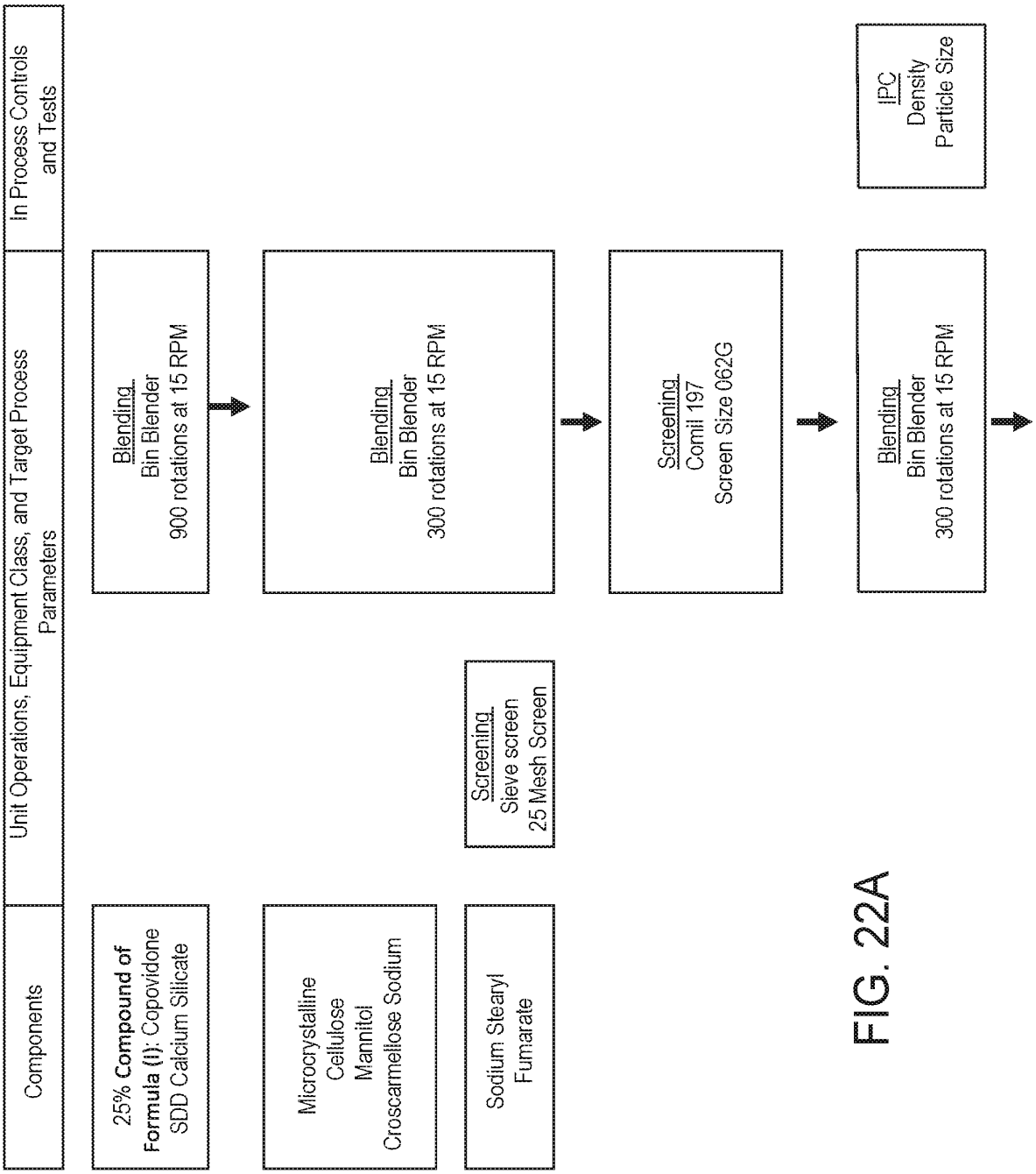

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
25% Compound of Formula (I): Copovidone SDD Calcium Silicate
Blending
Bin Blender
900 rotations at 15 RPM
Microcrystalline Cellulose Mannitol Croscarmellose Sodium
Blending
Bin Blender
300 rotations at 15 RPM
Sodium Stearyl Fumarate
Screening
Sieve screen
25 Mesh Screen
Screening
Comil 197
Screen Size 062G
Blending
Bin Blender
300 rotations at 15 RPM
IPC
Density
Particle Size

FIG. 22A

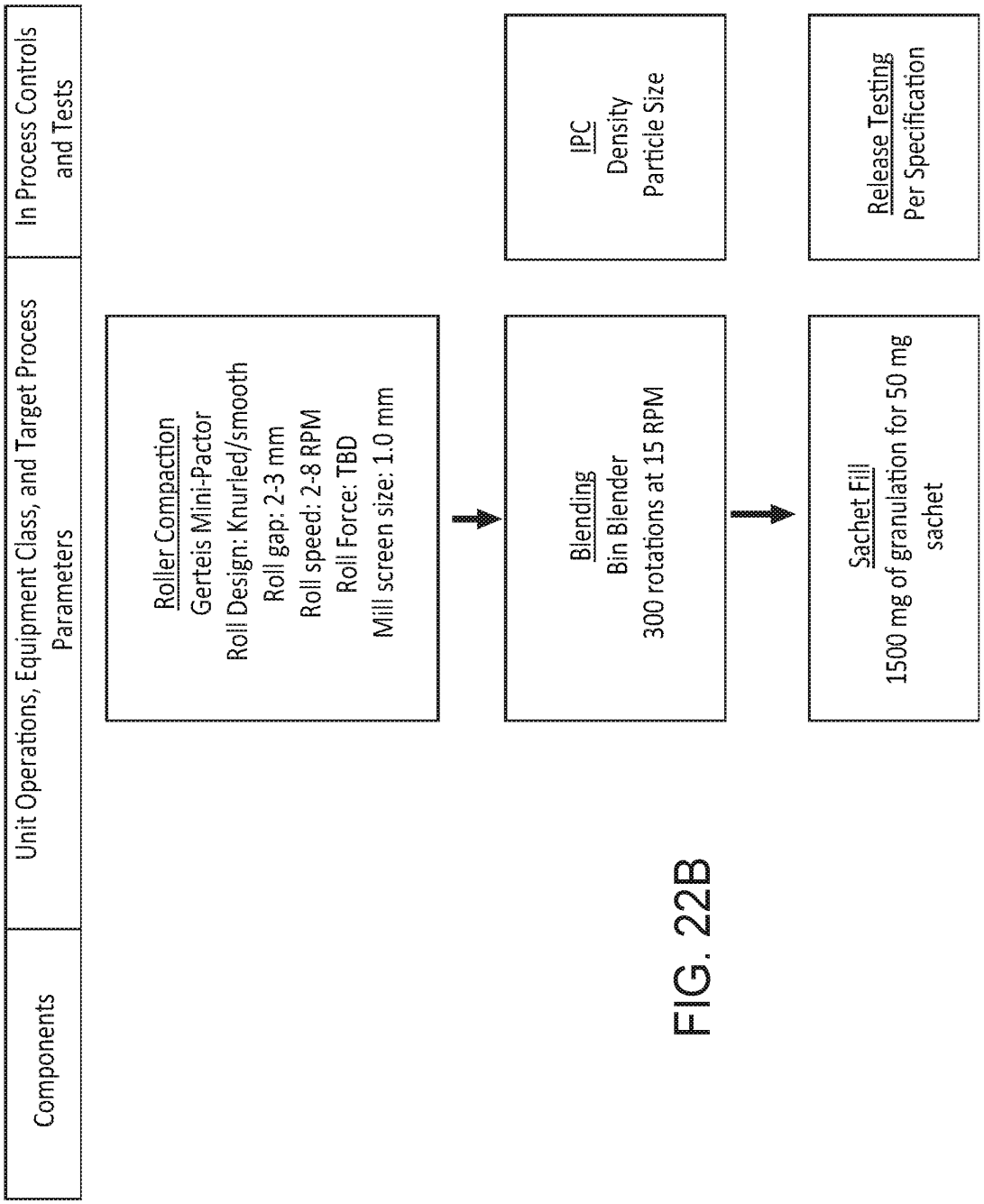

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
Roller Compaction
Gerteis Mini-Pactor
Roll Design: Knurled/smooth
Roll gap: 2-3 mm
Roll speed: 2-8 RPM
Roll Force: TBD
Mill screen size: 1.0 mm
Blending
Bin Blender
300 rotations at 15 RPM
IPC
Density
Particle Size
Sachet Fill
1500 mg of granulation for 50 mg sachet
Release Testing
Per Specification

FIG. 22B

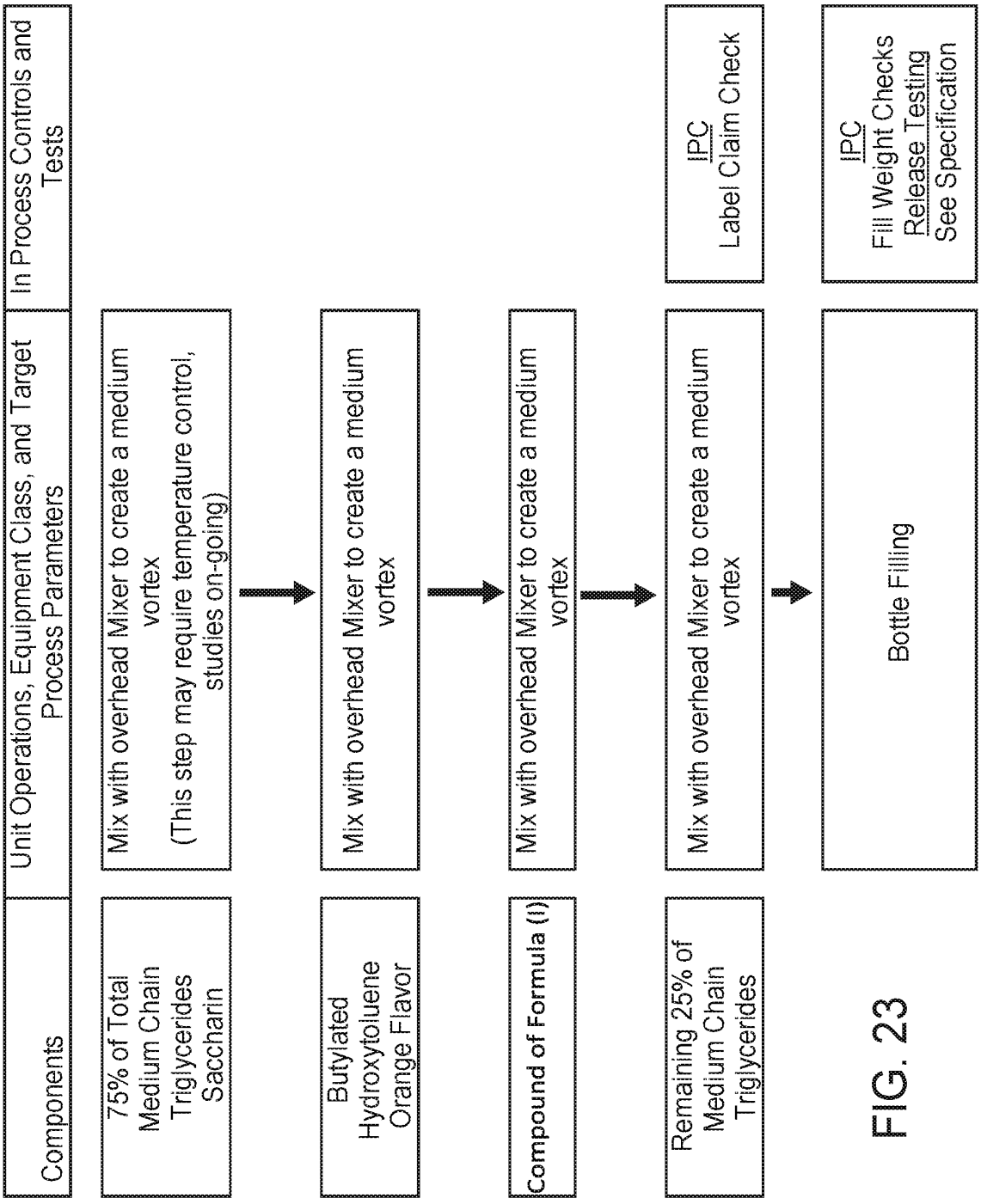

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
75% of Total Medium Chain Triglycerides Saccharin
Mix with overhead Mixer to create a medium vortex (This step may require temperature control, studies on-going)
Butylated Hydroxytoluene Orange Flavor
Mix with overhead Mixer to create a medium vortex
Compound of Formula (I)
Mix with overhead Mixer to create a medium vortex
Remaining 25% of Medium Chain Triglycerides
Mix with overhead Mixer to create a medium vortex
Bottle Filling
IPC Label Claim Check
IPC Fill Weight Checks Release Testing See Specification

FIG. 23

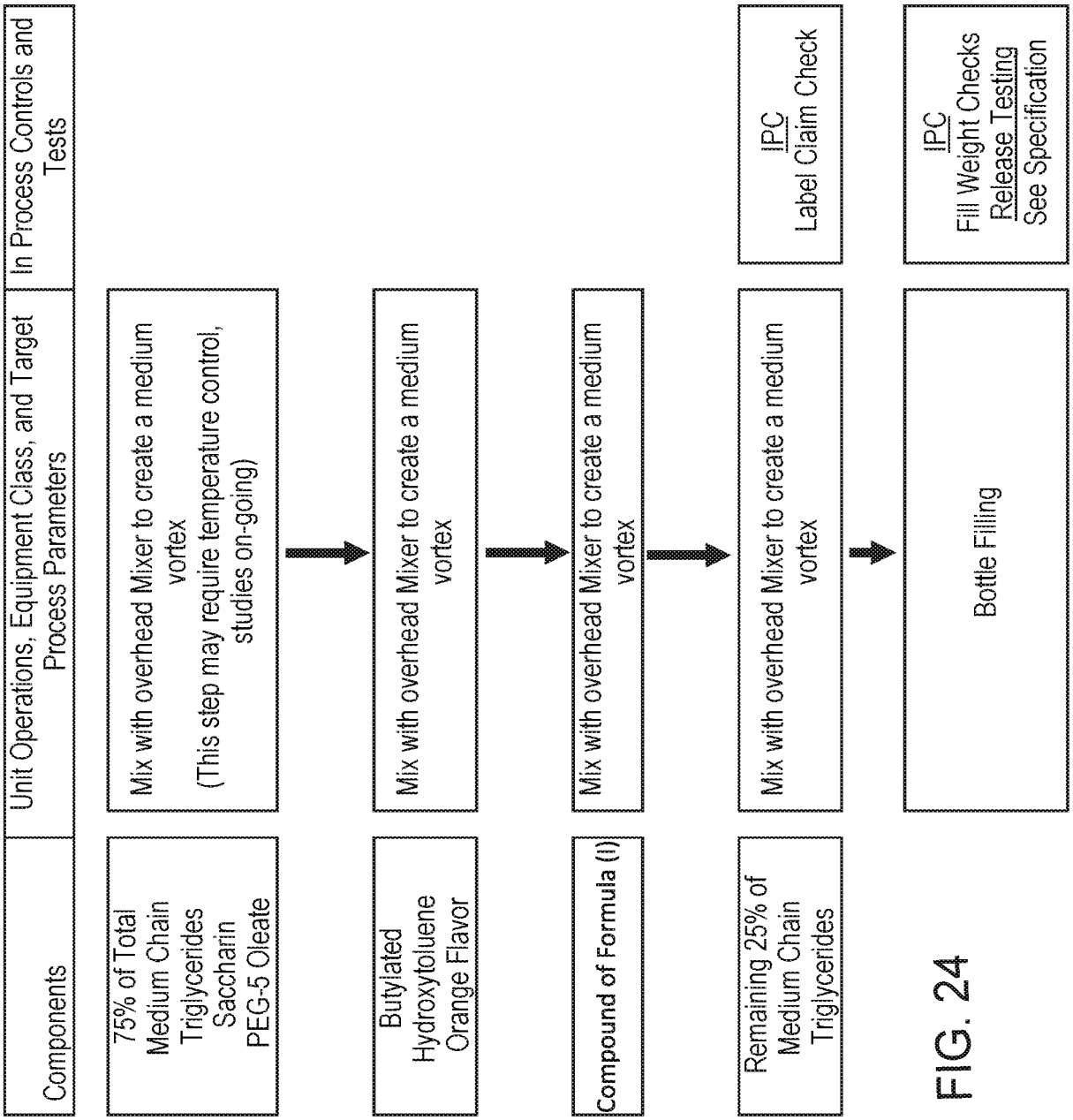

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
75% of Total Medium Chain Triglycerides Saccharin PEG-5 Oleate
Mix with overhead Mixer to create a medium vortex (This step may require temperature control, studies on-going)
Butylated Hydroxytoluene Orange Flavor
Mix with overhead Mixer to create a medium vortex
Compound of Formula (I)
Mix with overhead Mixer to create a medium vortex
Remaining 25% of Medium Chain Triglycerides
Mix with overhead Mixer to create a medium vortex
IPC
Label Claim Check
Bottle Filling
IPC
Fill Weight Checks
Release Testing
See Specification

FIG. 24

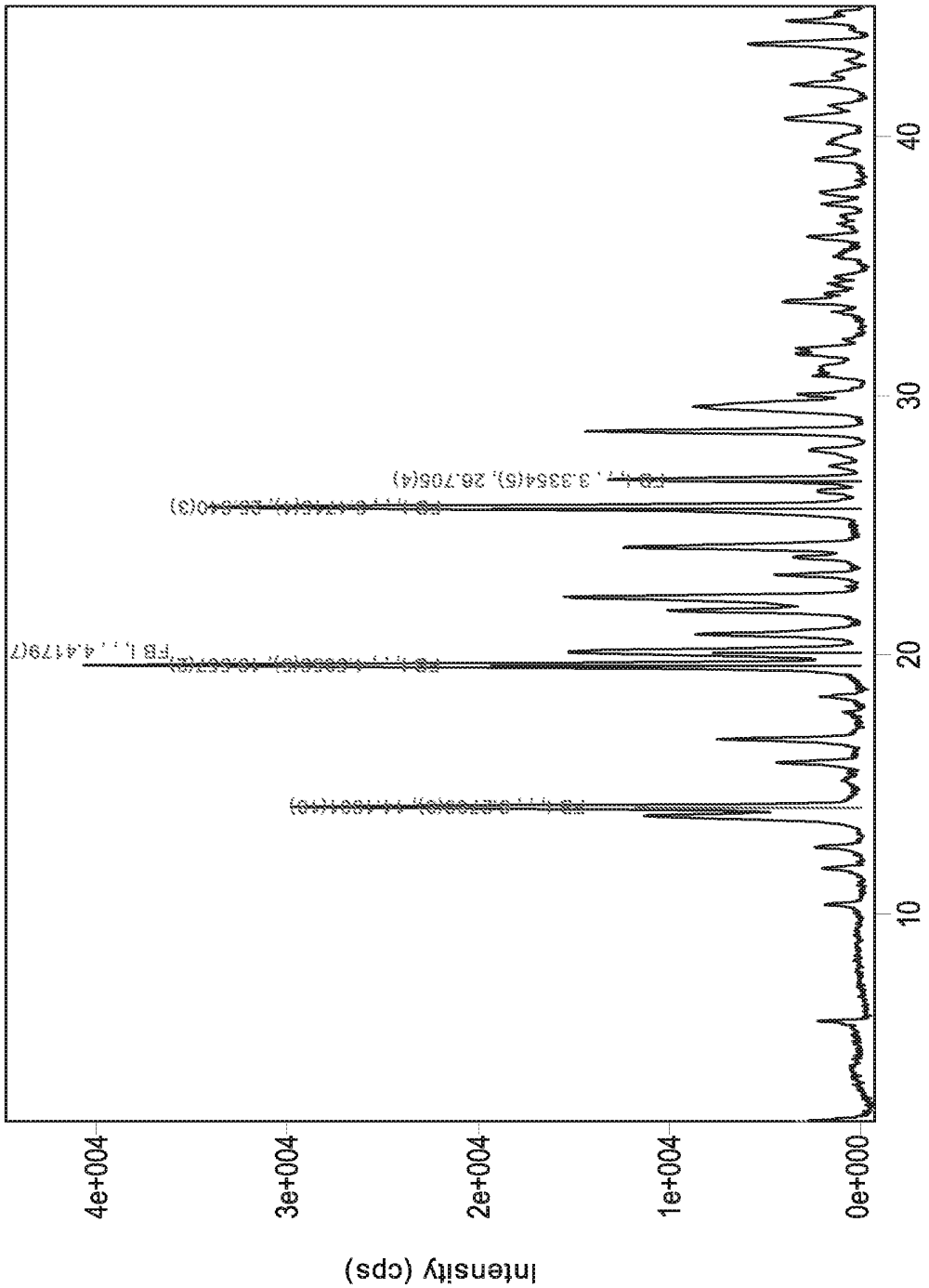

Intensity (cps)
0e+000
1e+004
2e+004
3e+004
4e+004
10
20
30
40
2-theta (deg)

FIG. 25

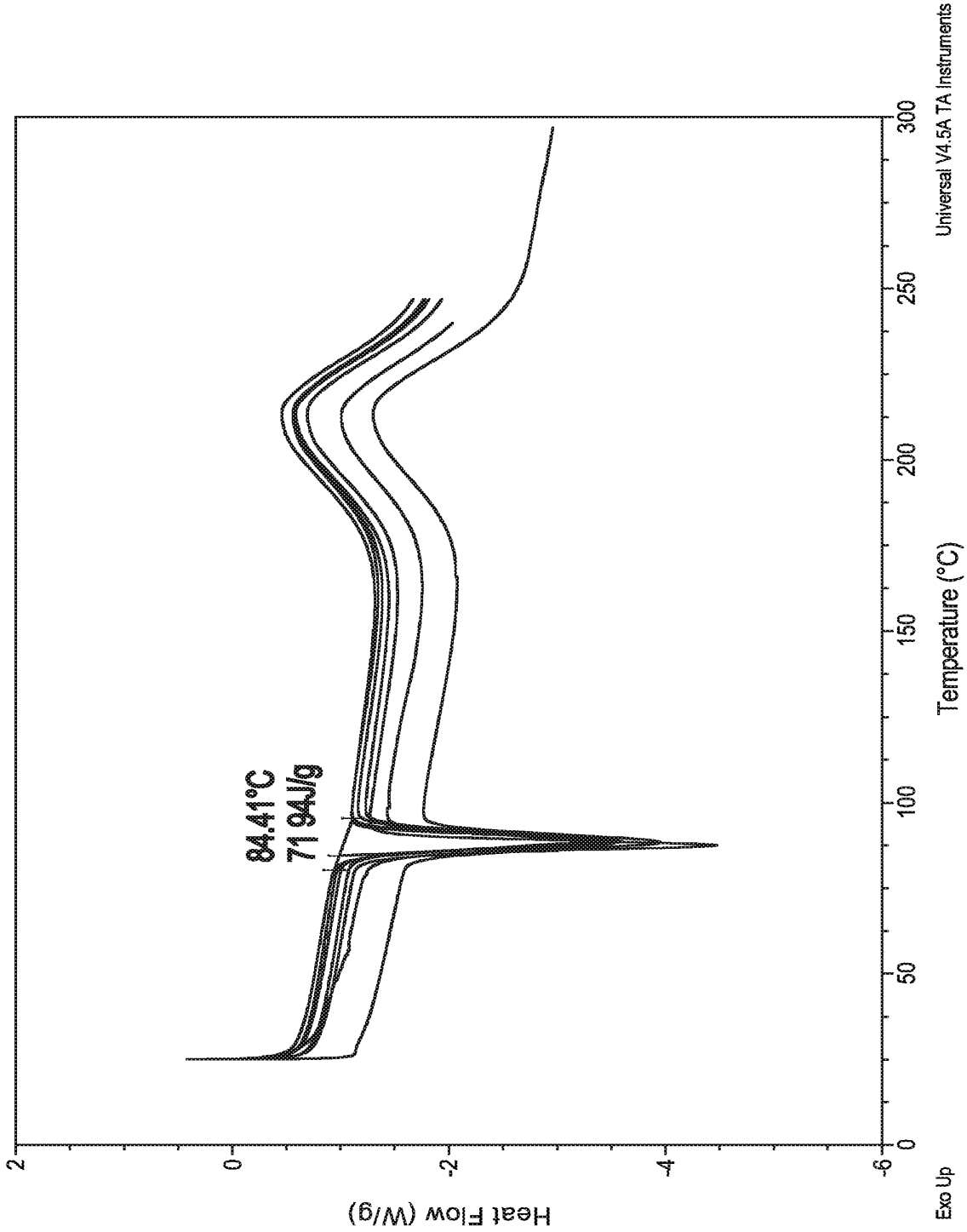

84.41°C
71.94J/g
Heat Flow (W/g)
Exo Up
Temperature (°C)
Universal V4.5A TA Instruments
2
0
-2
-4
-6
0
50
100
150
200
250
300

FIG. 26

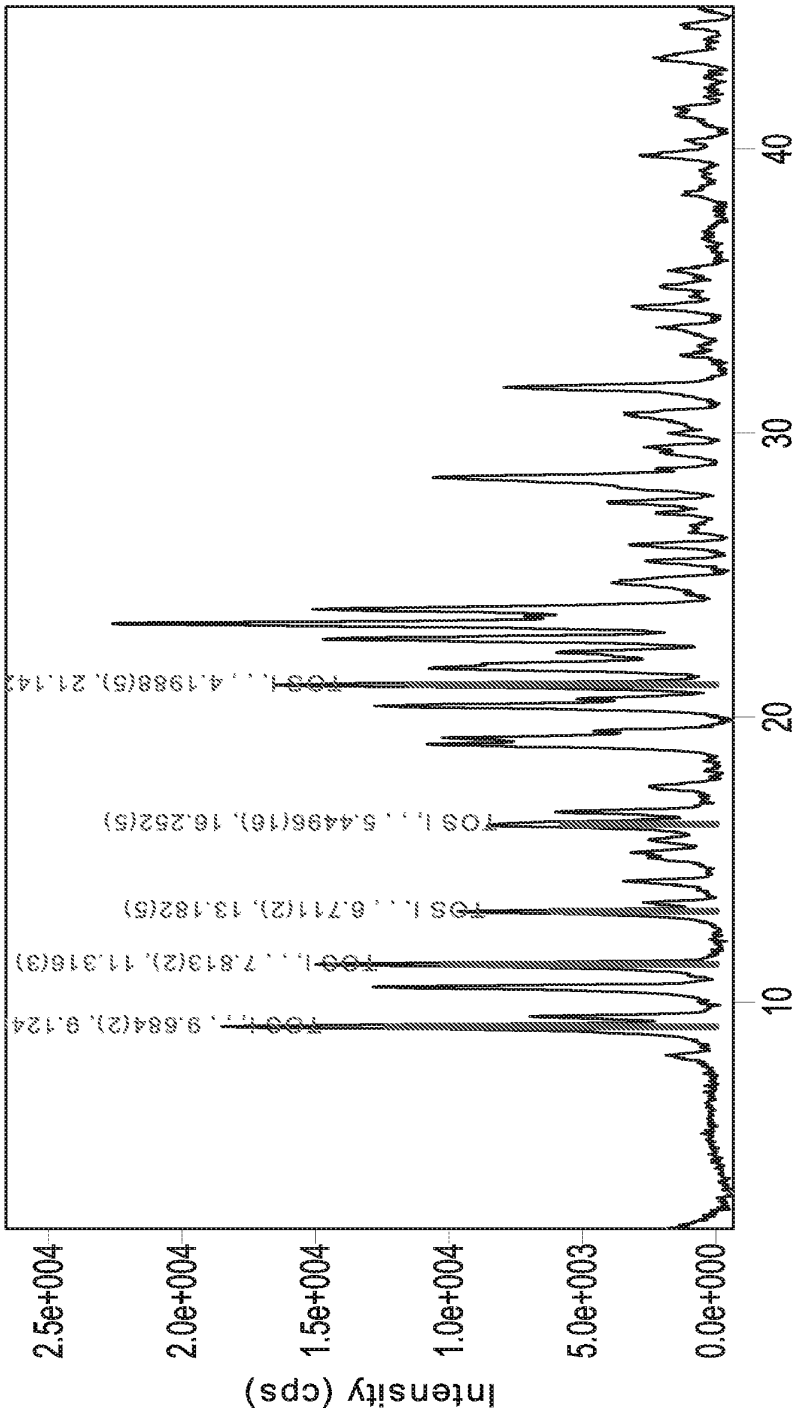

Intensity (cps)
2.5e+004
2.0e+004
1.5e+004
1.0e+004
5.0e+003
0.0e+000
10
20
30
40
2-theta (deg)

FIG. 27

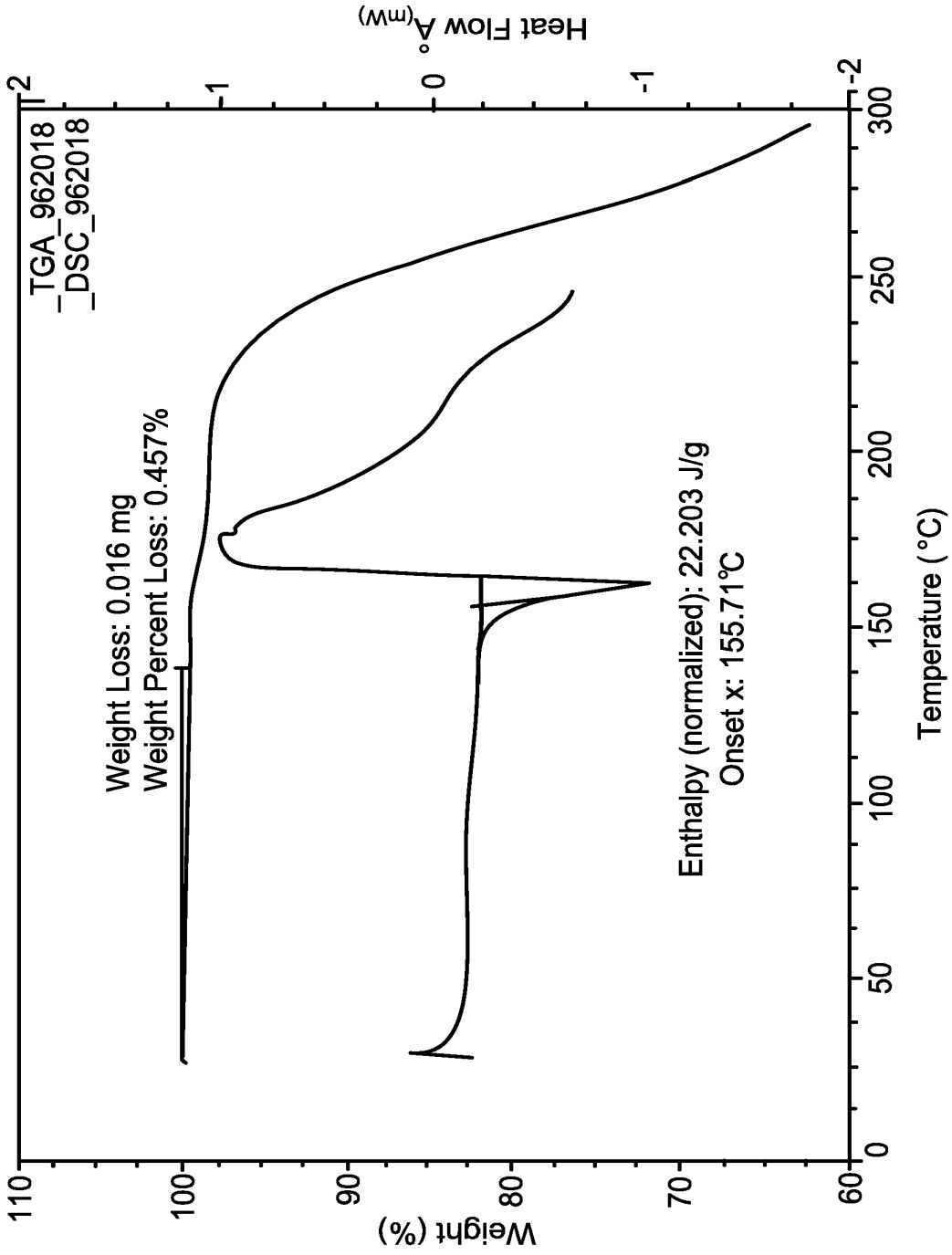

_TGA_962018
_DSC_962018
Weight Loss: 0.016 mg
Weight Percent Loss: 0.457%
Enthalpy (normalized): 22.203 J/g
Onset x: 155.71°C
Weight (%)
Heat Flow A (mW)
Temperature (°C)
110
100
90
80
70
60
2
1
0
-1
-2
0
50
100
150
200
250
300

FIG. 28

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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International Bureau

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28 September 2006 (28.09.2006)

PCT

(10) International Publication Number
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A61K 31/5025 (2006.01)

(21) International Application Number:
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(22) International Filing Date: 20 March 2006 (20.03.2006)

(25) Filing Language: English

(26) Publication Language: English

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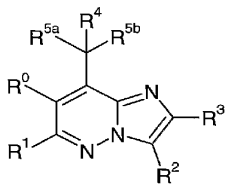
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(54) Title: IMIDAZOPYRIDAZINE COMPOUNDS



(I)

(57) Abstract: The present invention relates to novel substituted imidazo[1,2-b]pyridazine compounds of Formula (I): pharmaceutical compositions thereof, and the use such compounds as corticotropin releasing factor 1 (CRF1) receptor antagonists in the treatment of psychiatric disorders and neurological diseases.

WO 2006/102194 A1

IMIDAZOPYRIDAZINE COMPOUNDS

Field of the Invention

This invention relates to novel substituted imidazo[1,2-b]pyridazine compounds, pharmaceutical compositions thereof, and the use of such compounds as corticotropin releasing factor 1 (CRF1) receptor antagonists in the treatment of psychiatric disorders and neurological diseases.

Background of the Invention

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 [J. Rivier et al., *Proc. Natl. 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 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 [J. E. Blalock, *Physiological Reviews* 69:1 (1989); J. E. Morley, *Life Sci.* 41:527 (1987)].

There is 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 a review, see: E. B. De Souze, *Hosp. Practice* 23:59 (1988)]. Furthermore, CRF is known to have a broad extrahypothalmic distribution in the CNS, contributing therein to a wide spectrum of autonomic behavioral and physiological effects [see, e.g., Vale et al., 1983; Koob, 1985; and E. B. De Souze et al., 1985]. For example,

CRF concentrations are significantly increased in the cerebral spinal fluid of patients afflicted with affective disorder or major depression [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)]. Moreover, excessive levels of CRF are known to produce anxiogenic effects in animal models [see, e.g., Britton et al., 1982; Berridge and Dunn, 1986 and 1987].

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 (intravenously 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 Engl. 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 also preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of receptors in the brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

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 both in 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 Ro 15-1788, 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 FG 7142 enhanced the actions of CRF [K. T. Britton et al., *Psychopharmacology* 94:396 (1988)]. Preliminary studies using the putative CRF receptor antagonist α-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrates 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)].

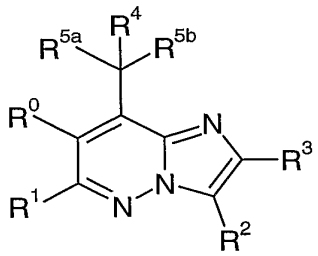
CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain [D. T. Chalmers et al., *TIPS* 17:166-72 (1996)] thereby suggesting potential functional diversity [S. C. Heinrichs et al., *Regul. Peptides* 71:15 (1997)]. For example, widely distributed brain CRF1 receptors 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/hypothalmic 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 an altogether 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 many cases, CRF2 agonism produces similar effects to those reported for CRF1 antagonists or CRF1 gene deletion [S. C. Heinrichs, *Trends in Pharmacological Sciences* 20(8):311-5 (1999)]. While CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well [C. Contoreggi et al., *Neuroendocrinology* 80(2):111-23 (2004)].

In view of the above, efficacious and selective antagonists of CRF1 are desired as potentially valuable therapeutic agents for the treatment of psychiatric disorders and neurological diseases. It is thus desirable to discover new CRF1 antagonists.

SUMMARY OF THE INVENTION

The compounds of the present invention include CRF1 receptor antagonists.

One embodiment of the present invention is a compound of Formula I:



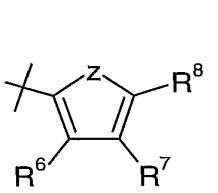
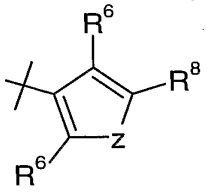
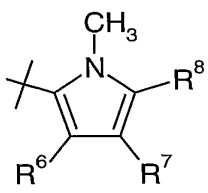
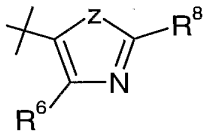
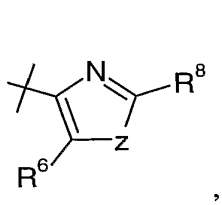
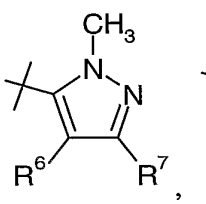
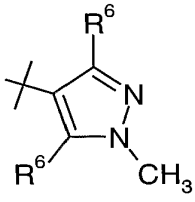
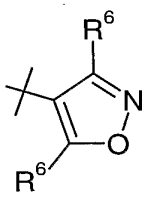
Formula I

wherein:

R^0 is hydrogen, halo, methyl or ethyl;

R^1 and R^3 are independently methyl, methoxy, or trifluoromethyl;

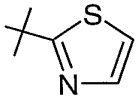
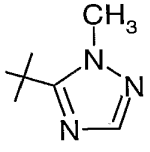
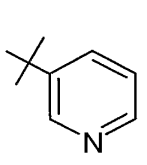
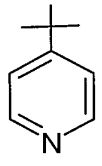
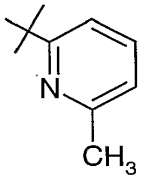
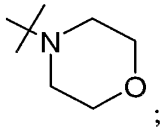
R^2 is selected from the group consisting of:


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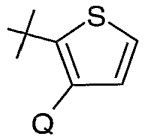
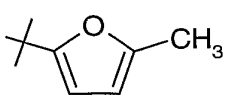
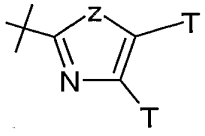
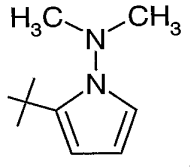
R^4 is hydrogen, halo, or hydroxy;

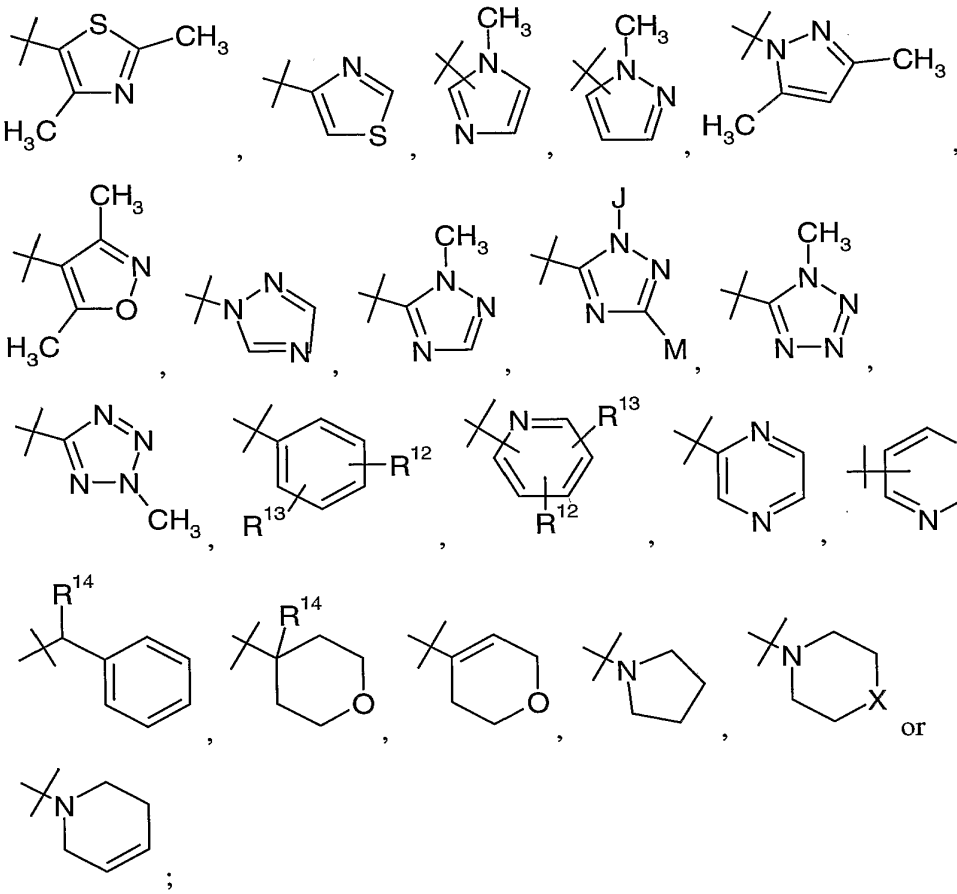
R^{5a} and R^{5b} are independently ethyl or n-propyl;

R^6 at each occurrence is independently hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, trifluoromethyl, methoxy, or phenyl;

R^7 is hydrogen, halo, methyl, methoxy, dimethylamino,

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, or

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R^8 is selected from the group consisting of hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, R^aR^bN-, carbamyl, $(C_1\text{-}C_2)$alkoxy$(C_1\text{-}C_2)$alkyl, R^{11}-C(O)-,


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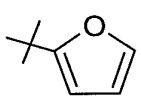
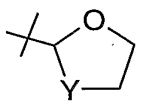


R^{11} is methoxy, methylamino, dimethylamino, or phenyl;

R^{12} is hydrogen, halo, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxy dimethylamino, acetyl, or methylsulfonyl;

R^{13} is hydrogen, methyl or halo;

R^{14} is hydrogen or hydroxy;

R^{15} is methylthio, cyclopropyl, phenyl,  or  ;

R^a is hydrogen, $(C_1\text{-}C_5)$alkyl, $(C_3\text{-}C_5)$cycloalkyl, methoxy$(C_2\text{-}C_4)$alkyl, acetyl, $(C_1\text{-}C_2)$alkylsulfonyl, (C_3)alkenyl, $R^{15}\text{-}(CH_2)n\text{-}$, or $(C_1\text{-}C_2)$alkyl substituted with cyano, formyl, vinyl, or ethynyl;

R^b is hydrogen or $(C_1\text{-}C_3)$alkyl;

X is $-CH_2-$, -CO-, -O-, -S- or $-SO_2-$;

Y is -CH_2- or -O-;

z is S or O;

n is 1 or 2;

Q is hydrogen or methyl;

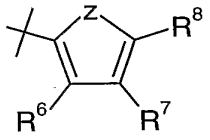
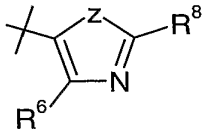
T is hydrogen or methyl;

J is methyl, trifluoroethyl, or tert-butyl; and

M is methyl or halo;

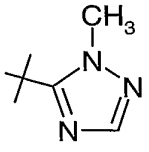
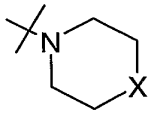
and pharmaceutically acceptable salts thereof.

Another embodiment of the present invention is a compound of Formula I wherein R^0 and R^4 are hydrogen, R^1 and R^3 are methyl, and R^{5a} and R^{5b} are ethyl.

Yet another embodiment of the present invention is a compound of Formula I wherein R^2 is selected from the group consisting of  or  where z is S.

A further embodiment of the present invention is a compound of Formula I wherein R^7 is hydrogen.

Another another embodiment of the present invention is a compound of Formula I wherein R^6 is halo or methyl.

Yet another embodiment of the present invention is a compound of Formula I wherein R^8 is  or  where X is O.

Another embodiment of the present invention is a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

Yet another embodiment of the present invention is a compound of Formula I, for use as a medicament.

A further embodiment of the present invention is use of a compound of Formula I for the manufacture of a medicament for treating anxiety, depression, major depressive disorder, alcohol withdrawal symptoms, or irritable bowel syndrome in a mammal. In another further embodiment, the mammal is a human.

DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Alkoxy" means an alkyl-O- group, wherein the alkyl group is as herein described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, and *n*-butoxy.

"Alkyl" means a saturated aliphatic hydrocarbon group, which may be straight or branched, having 1 to 5 carbon atoms in the chain.

"Alkenyl" means an unsaturated aliphatic hydrocarbon group, which may be straight or branched, having 2 to 4 carbon atoms in the chain.

"Cycloalkyl" means a monocyclic group, having 3 to 5 carbon atoms.

"Halo" means fluoro, chloro, bromo, or iodo.

"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. Exemplary acid addition salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, sulphamates, malonates, salicylates, propionates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinateslaurylsulphonate salts, and the like. See, for example S.M. Berge, et al.,

"Pharmaceutical Salts," J. Pharm. Sci., 66, 1-19 (1977). Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing. Company, Easton, Pa., 1985, p. 1418.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts thereof.

"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.

The terms "treatment," "treat," "treating," and the like, are meant to include both slowing or 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.

The symbol "——" in a molecular structure indicates the position of attachment for that particular substituent.

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. R^1, R^2, etc., are to be chosen in conformity with well- known principles of chemical structure connectivity.

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-.

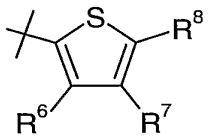
The present invention contemplates specific classes of compounds of Formula I. The following paragraphs describe such specific classes:

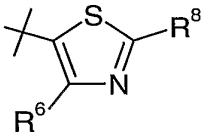
(a) R^0 is hydrogen;

(b) R^1 is methyl;

(c) R^3 is methyl;

(d) $R^1$and R^3 are methyl;

(e) R^2 is  ;

(f) R^2 is  ;

(g) R^4 is hydrogen;

(h) R^{5a} is ethyl;

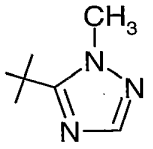
(i) R^{5b} is ethyl;

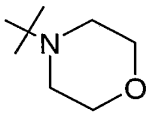
(j) R^{5a} and R^{5b} are ethyl;

(k) R^6 is halo;

(l) R^6 is methyl;

(m) R^7 is hydrogen;

(n) R^8 is  ;

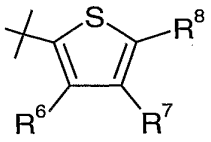
(o) R^8 is  .

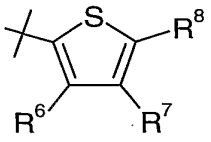
While all the compounds of Formula I are useful CRF1 receptor antagonists, the following paragraphs describe further specific classes:

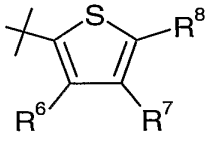
(a) Each of R^1 and R^3 is methyl and each of R^{5a} and R^{5b} is ethyl;

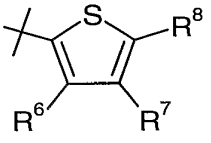
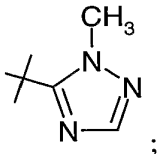
(b) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 is hydrogen;

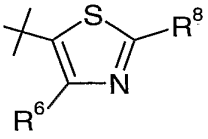
(c) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen;

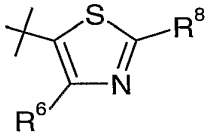
(d) R^2 is  and R^7 is hydrogen;

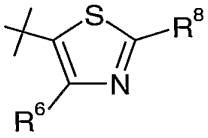
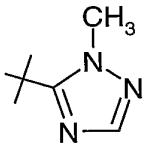
(e) R^2 is  , R^7 is hydrogen, and R^6 is halo;

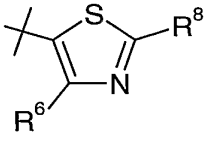
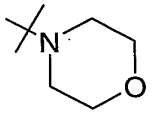
(f) R^2 is  , R^7 is hydrogen, and R^6 is methyl;

(g) R^2 is  , R^7 is hydrogen, and R^6 is halo or methyl, and R^8 is  ;

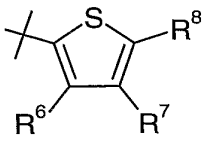
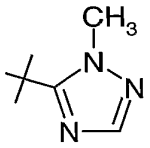
(h) R^2 is  and R^6 is halo;

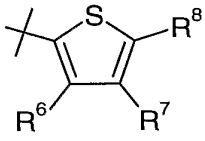
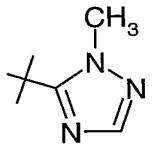
(i) R^2 is  and R^6 is methyl;

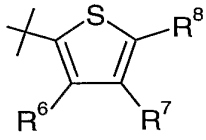
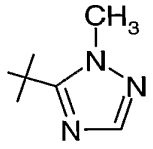
(j) R^2 is  , R^6 is halo or methyl, and R^8 is  ;

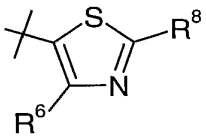
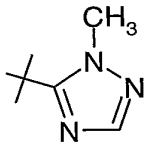
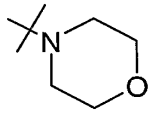
(k) R^2 is  , R^6 is halo or methyl, and R^8 is  .

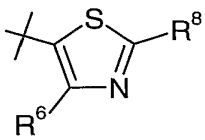
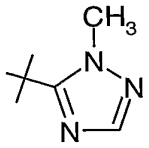
The following paragraphs describe even more specific classes of CRF1 receptor antagonists of the invention:

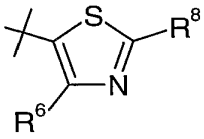
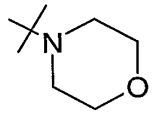
(a) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is halo or methyl, and R^8 is  ;

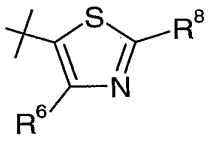
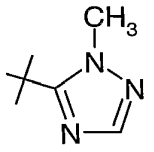
(b) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is halo, and R^8 is  ;

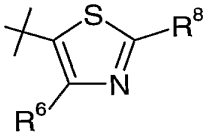
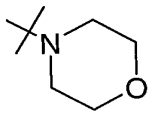
(c) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is methyl, and R^8 is  ;

(d) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is halo or methyl, and R^8 is  or  ;

(e) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is halo, and R^8 is  ;

(f) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is halo, and R^8 is  .

(g) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is methyl, and R^8 is  ;

(h) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is methyl, and R^8 is  .

Preferably compounds of the invention exhibit a Ki value for CRF1 binding of 1 micromolar or less, more preferably of 500 nanomolar or less. Even more preferably, compounds of the invention exhibit a Ki value for CRF1 binding of 250 nanomolar or less, with 100 nanomolar or less being even further preferred. With even greater preference, compounds of the invention exhibit a Ki value for CRF1 binding of 30 nanomolar or less, while 15 nanomolar or less is even more greatly preferred. Compounds of the invention exhibiting a Ki value for CRF1 binding of 5 nanomolar or less are most preferred.

The present invention also provides a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent, or excipient. A "pharmaceutically acceptable carrier, diluent, or excipient" is a medium generally accepted in the art for the delivery of biologically active agents to mammals, e.g., humans. Such carriers are generally formulated according to a number of factors well within the purview of those of ordinary skill in the art to determine and account for. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers and excipients include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi- solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, e.g., stabilization of the active agent, well known to those of ordinary skill in the art. Descriptions of suitable

pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources, e.g., Remington's Pharmaceutical Sciences, 17 th ed., Mack Publishing Company, Easton, Pa., 1985.

These compounds of formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Dosage forms suitable for administration generally contain from about 1 mg to about 300 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. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of formula I are antagonists at the CRF1 receptor and are useful in the treatment of anxiety disorders, depression, major depressive disorder, and stress related disorders. Anxiety disorders are a group of diseases, recognized in the art, that includes phobic disorders, anxiety states, post-traumatic stress disorder and atypical anxiety disorders [The Merck Manual of Diagnosis and Therapy, 16 th edition (1992)]. Emotional stress is often a precipitating factor in anxiety disorders, and such disorders generally respond to medications that lower response to stress. The compounds are also useful in smoking cessation programs. The method of treatment involves administration to a mammal (e.g. a human) an effective amount of a compound of the invention. In particular, therapeutically effective amounts of the compounds of this invention are amounts effective to antagonize, or lower, levels of corticotropin releasing factor (CRF) in a mammal (e.g. a human), thereby alleviating in the mammal's conditions characterized by abnormally high levels of CRF expression.

As such, the present invention provides a method for treating a condition which is treatable by reducing CRF1 receptor stimulation, comprising administering to the mammal (e.g. a human) in need thereof a compound of Formula I, or a pharmaceutically acceptable salt thereof, in an amount effective to antagonize CRF1 receptor stimulation.

The present invention also provides use of a compound of Formula I for the manufacture of a medicament for treating a condition which is treatable by reducing CRF1 receptor stimulation.

The present invention also provides a method of antagonizing CRF1 receptors in a warm-blooded animal, comprising administering to the animal a compound of the invention at amount effective to antagonize CRF1 receptors. The warm-blooded animal is preferably a mammal, and more preferably a human.

The present invention also provides a method of treating a disorder in a warm-blooded animal, which disorder manifests hypersecretion of CRF, or the treatment of which disorder can be effected or facilitated by antagonizing CRF1 receptors, comprising administering to the animal a therapeutically effective amount of a compound of the invention. The warm-blooded animal is preferably a mammal, and more preferably a human.

Compounds of Formula I, or a pharmaceutically acceptable salt thereof, are useful for treating various disorders and conditions in a mammal (e.g. human) including social anxiety disorder; panic disorder; obsessive-compulsive disorder; major depressive disorder; anxiety with co-morbid depressive illness; affective disorder; anxiety; depression; irritable bowel syndrome; post-traumatic stress disorder; supranuclear palsy; immune suppression; gastrointestinal disease; anorexia nervosa, bulimia, or other feeding disorder; drug or alcohol withdrawal symptoms; substance abuse disorder (e.g., nicotine, cocaine, ethanol, opiates, or other drugs); 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; 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; sleep disorders induced by stress; stress- related illnesses; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; chronic fatigue syndrome; stress- induced headache; headache; cancer; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, senile

dementia of the Alzheimer's type, and multiinfarct dementia; 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; obesity and the metabolic syndrome; infertility; premature birth; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and heart related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, stress induced infections in humans and animals, 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 incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependences on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia.

A compound of this invention can be administered to treat the above disorders or abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal (e.g. human), such as by oral or parenteral administration using appropriate dosage forms. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. It 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 pharmaceutical practice.

The therapeutically effective amounts of the compounds of the invention for treating the diseases or disorders described above in a warm-blooded animal can be determined in a variety of ways known to those of ordinary skill in the art, e.g., by administering various amounts of a particular agent to an animal afflicted with a particular condition and then determining the effect on the animal. Typically,

therapeutically effective amounts of a compound of this invention can be orally administered daily at a 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. It will be understood, however, that the specific dose levels for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease. Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most CNS disorders, a dosage regimen of four-times daily or less is preferred. For the treatment of stress and depression, a dosage regimen of one or two-times daily is particularly preferred.

It will be appreciated that all combinations of specific and preferred embodiments discussed above and the examples discussed below are contemplated as being encompassed by the present invention, provided such combinations do not comprise inconsistent groupings. In addition, all examples described herein are for illustrative purposes, and are not intended to narrow the scope of the invention in any way.

Compounds of the invention can generally be prepared using the synthetic routes illustrated in the Schemes below. Starting materials can be prepared by procedures described in these schemes or by procedures that would be well known to one of ordinary skill in organic chemistry. The variables used in the schemes are as defined below or as in the claims.

The skilled artisan will appreciate that the introduction of certain substituents will create asymmetry in the compounds of Formula I. The present invention contemplates all enantiomers and mixtures of enantiomers and stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, including racemates. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral phase gas chromatography, chiral-phase high performance liquid chromatography, or crystallizing the compound as a chiral salt complex. Enantiomers and stereoisomers can

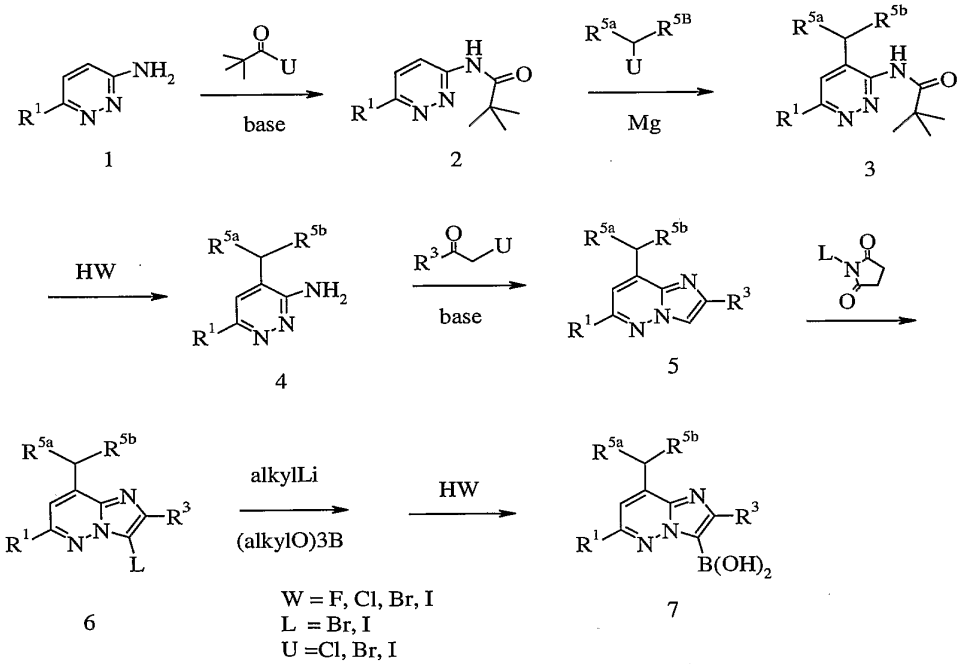
also be obtained from stereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

Pharmaceutically acceptable salts are contemplated to be within the scope of the present invention. The compounds of the present invention are bases and salts of such compounds may be formed with acids, for example, a salt with inorganic acid such as hydrochloric acid or a salt with organic acid such as trifluoroacetic acid.

The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. These schemes, therefore, are not limited by the compounds listed nor by any particular substituents employed for illustrative purposes.

Scheme I

Synthesis of Imidazo[1,2-b]pyridazine fragment



R^1, R^3, R^{5a}, and R^{5b} are defined supra.

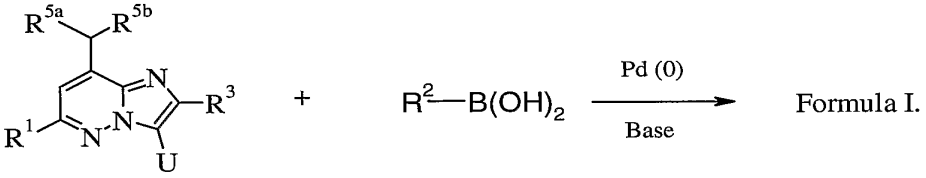
In Scheme I, a substituted 3-amino-pyridazine 1 is acylated with pivaloyl halide and a base, e.g., triethylamine in a polar aprotic solvent, e.g., methylene chloride at from

room temperature to the reflux to give amide 2. Amide 2 is treated with a Grignard reagent in diethylether or THF to give the 4-substituted amide 3. Amide 3 is hydrolyzed with aqueous HCl at from room temperature to 110 °C then neutralized to provide free amine 4. Amine 4 is treated with an alpha-halo ketone and base, e.g., sodium bicarbonate in 95% ethanol at from room temperature to 110 °C to give imidazopyridazine 5. Imidazopyridazine 5 is treated with a halogenating reagent e.g., N-iodo or N-bromosuccinimide in a polar aprotic solvent (e.g., acetonitrile) at from 0 °C to room temperature to give halide 6. Halide 6 undergoes halogen metal exchange with an alkyl lithium reagent, e.g., n-, sec-, or tert- butyllithium in diethylether or THF at from –78 °C to room temperature, followed by treatment with a trialkylborate, e.g., trimethylborate to give an intermediate boronic ester, which is hydrolyzed upon workup with aqueous HCl to provide boronic acid 7.

Scheme II

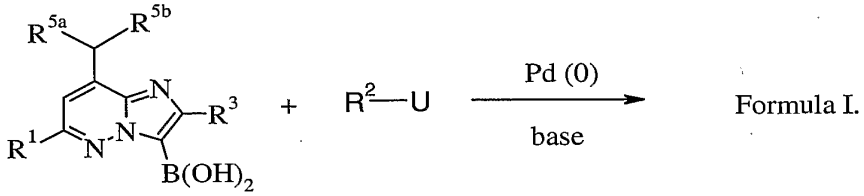
Synthesis of Compounds of Formula I by transition metal catalysis.

Equation 1.



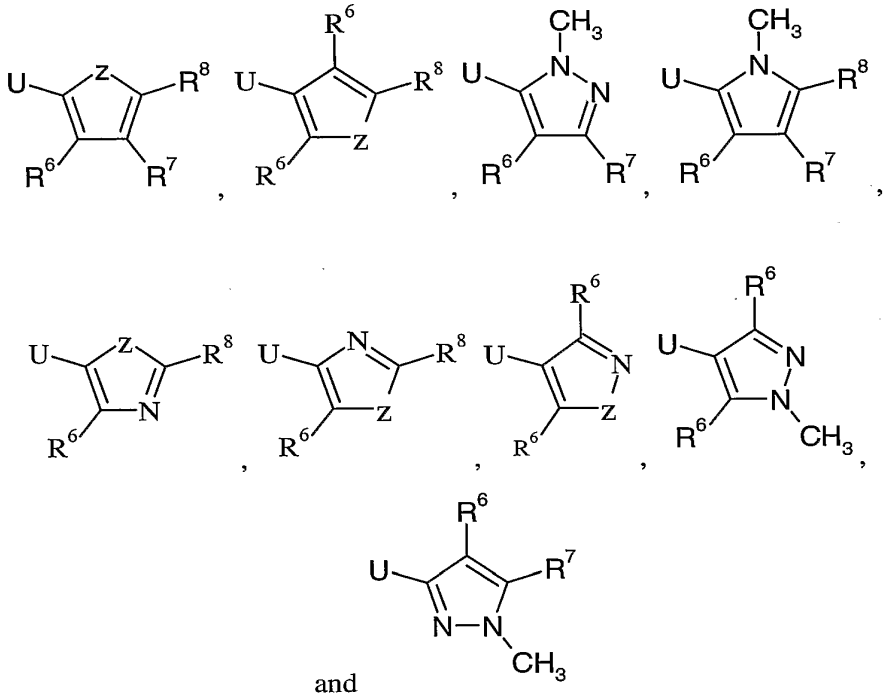
6 8

Equation 2.



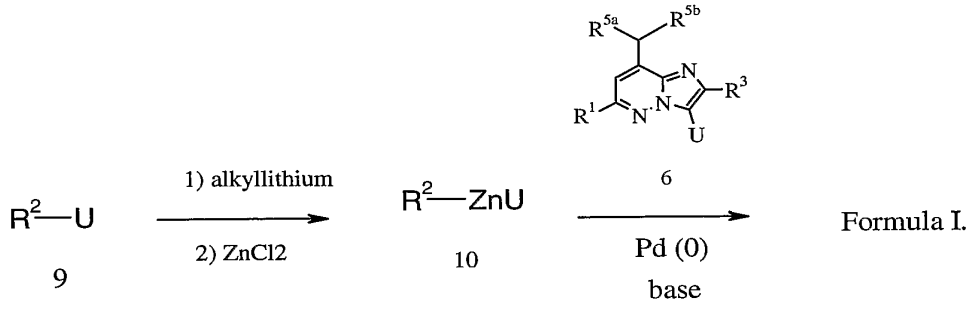
7 9

Where R^2-U is selected from the group consisting of:



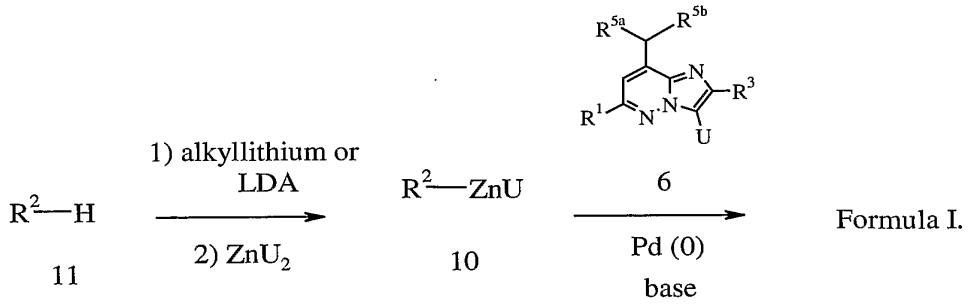
and

Equation 3.

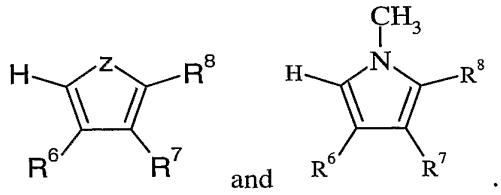


9 10 6

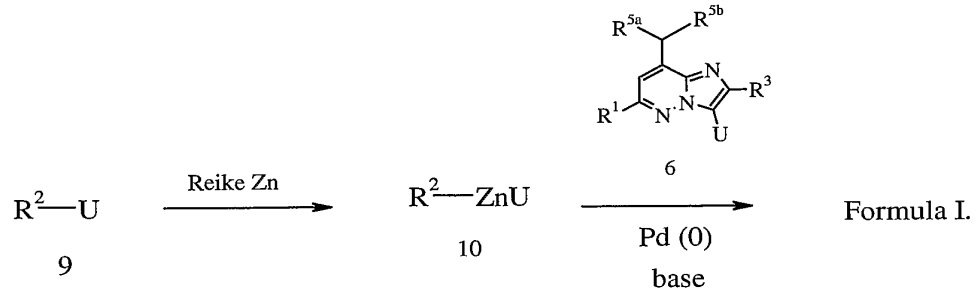
Equation 4.



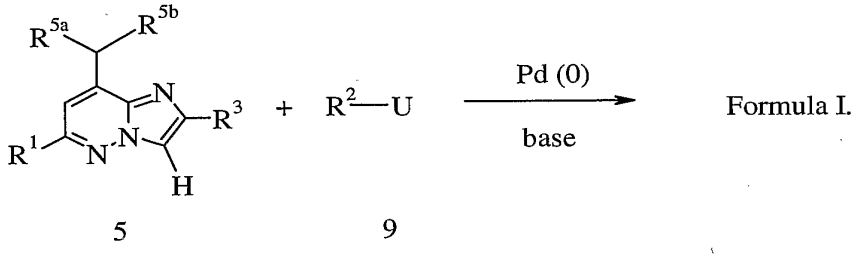
Where R^2-H is selected from the group consisting of:



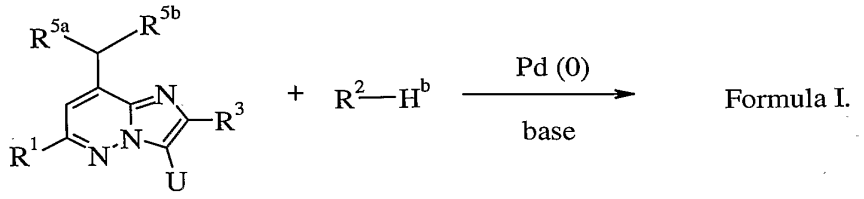
Equation 5.



Equation 6.

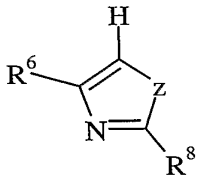


Equation 7.



6 12

Where R^2-H^b is selected from:



R^1, R^2, R^3, R^{5a}, R^{5b} R^6, R^7, R^8, U, and z are defined supra.

In Scheme II equation 1, halide 6 can be used in a coupling reaction with a 5-membered ring heterocyclic boronic acid 8 in the presence of palladium catalysis, e.g., tetrakis-triphenylphosphine palladium (0) in a lower alkanol (methanol or n- or i-propanol)/DME mixture at from 70-120 °C to give compounds of formula I.

Alternately in equation 2, boronic acid 7 can be used in a coupling reaction with a 5 membered ring heterocyclic halide 9 and palladium catalysis, e.g., tetrakis-triphenylphosphine palladium (0) in a lower alkanol (methanol or n- or i-propanol)/DME mixture at from 70-120 °C to give a compound of formula I.

In equation 3, 5-membered ring heterocyclic halides 9 may undergo halogen-lithium exchange with, e.g., n-, sec- or tert-butyl lithium in THF or ether at –65 °C, followed by lithium-zinc exchange with $ZnCl_2$ in either diethylether or THF at temperatures up to room temperature. The *in situ* organozinc reagent 10 may then undergo coupling with halide 6 in the presence of palladium, e.g., $PdCl_2$(dppf) in THF at from 70-120°C to give a compound of formula I.

In equation 4, a 5-membered heterocyclic ring with a ring proton may be lithiated by either an alkyllithium, e.g., n-, sec- or tert-butyl lithium or lithium diisopropyl amide in THF or ether at –65 °C to room temperature followed by lithium-zinc exchange with

anhydrous zinc halide in either diethylether or THF to give an organozinc reagent 10 that is used as in equation 3 above. One skilled in the art will also appreciate that commercially available organozinc reagents 10 can be used directly as an organozinc coupling partner.

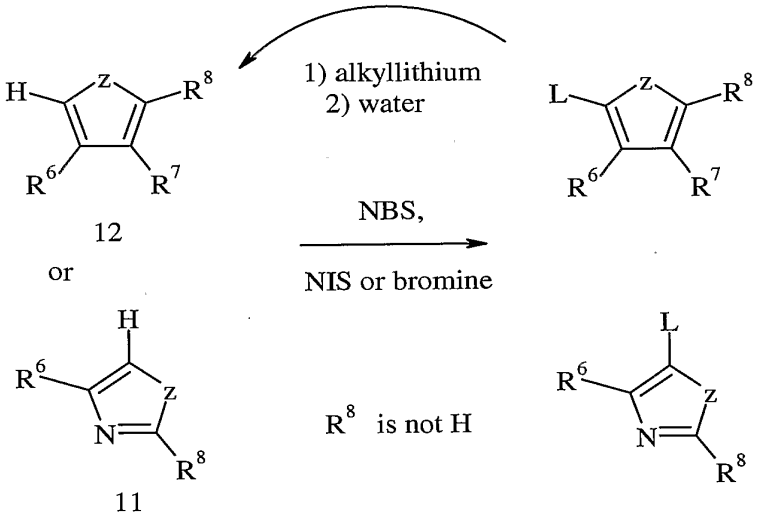
Furthermore from equation 5, it may be advantageous or convenient to use Reike Zn in THF to directly convert a 5-membered ring heterocyclic halide 9 to an organozinc reagent 10 for coupling with a halide 6.

In equation 6, a 5 membered heterocyclic halide 9 can be directly coupled with the imidazo[1,2-b]pyridazine intermediate 5 in the presence of palladium, e.g., $Pd_2(dba)_3$, $PdCl_2$, Palladium acetate/TDBPP, or tetrakis-triphenylphosphine palladium (0) in DMF, THF, or NMP solvent from 70-120°C to give a compound of formula I.

Alternately, from equation 7, the imidazo[1,2-b]pyridazine halide 6 may be directly coupled with a 5 membered heterocycle 11 in the presence of palladium, e.g., $Pd_2(dba)_3$, $PdCl_2$ or Palladium acetate/TDBPP in DMF, THF, or NMP solvent from 70-120 °C to give a compound of formula I.

Scheme III

Synthesis of Substituted 5 Membered Heterocyclic Halides



R^6, R^7, R^8, L, and z are defined supra.

Several 5 membered heterocyclic rings and/or their bromides and/or iodides useful as starting materials for the synthesis of compounds of Formula I are commercially available or may be prepared by methods well know to the skilled artisan. From Scheme III, they may also be prepared by halogenation, e.g., with bromine, NBS or NIS. Furthermore, some of the intermediates 11 and 12 may be prepared by lithium halogen exchange followed by water quench.

Compounds of Formula I as intermediates in the preparation of other compounds of Formula I include the addition of aryllithium reagents (generated by the methods of equations 3 and 4 in Scheme II) to carbonyl compounds, e.g., aldehydes, ketones, esters, and Weinreb amides. The resulting carbinols or carbonyl compounds are further elaborated by halogenation under acidic conditions and by a second aryllithium addition, respectively.

Abbreviations

TBDMSCl or TBDMSiCl – tert-butyl-dimethylsilyl chloride

MS (ES) – Electrospray Mass spectrum

THF – tetrahydrofuran

DMSO – Dimethylsulfoxide

DMF – Dimethylformamide

DCM, CH2Cl2 – dichloromethane

Dioxane – 1,4-dioxane

N2 – nitrogen gas

NIS – N-iodosuccinimide

NBS – N-bromosuccinimide

MeOH - methanol

EtOH – 95% ethanol

RBF, RB – round bottom flask

RBSN – round bottom single neck flask

SiO2 – silica gel

EtOAc, AcOEt – ethylacetate

GFF - glass microfiber filter

HPLC – high pressure liquid chromatography on silica gel

ISCO – ISCO brand low pressure liquid chromatography on silica gel

AcCl – acetyl chloride

LDA – lithium diisopropylamine

KOAc – Potassium Acetate

TBABr – Tetrabutyl ammonium bromide

NMP – N-Methylpyrrolidinone

TDBPP – Tris (2,4-di-*t*-butylphenyl) phosphite.

Pd_2dba_3 – Tris(dibenzylideneacetone)dipalladium

$PdCl_2$(dppf) – Dichloro(diphenylphosphinoferrocene)palladium

Tetrakis – tetrakis-(triphenylphosphine)-palladium

Dppf - 1,1'-bis(diphenylphosphino)ferrocene)

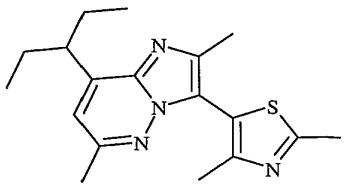
r.t., RT – room temperature

EXAMPLES

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 examples are provided to describe the invention in further detail. They are intended to illustrate and not to limit the invention in any way whatsoever. Examples 1-255 provide exemplary compounds and illustrate the preparation thereof. Examples A-D illustrate 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.

Example 1.

Preparation of 8-(1-ethyl-propyl)-3-(2,4-dimethyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 6-Methyl-pyridizin-3-ylamine.

3-Chloro-6-methylpyridazine (25.0g, 0.229 moles) is dissolve in 250 mL of NH_4OH and heated to 170 °C in a sealed container for 24 hours. The solvents are evaporated. The residue is triturated in methylene chloride, and a solid is filtered. This trituration procedure is repeated with the filtrate four times. The filtered solids are combined and dried in a vacuum oven overnight to obtain the title compound as an off-white solid 4.32 g (0.040 moles, 20%). ^{1}H-NMR (dmso-d6): δ 7.1 (d, J = 8.9 Hz, 1H); 6.67 (d, J = 8.9 Hz, 1H); 6.04 (s, br, 2H); 2.33 (s, 3H) ppm. ES+ = 110 (100%, M + 1).

B. 2,2-Dimethyl-N-(6-methyl-pyridazine-3-yl)-propionamide.

Method 1: To a dry flask is added 7.12 g (0.065 mole) of 6-methyl-pyridizin-3-ylamine in 170 ml dry methylene chloride. Next, 14.5 ml of triethylamine is added and the reaction is cooled to 0 °C. Pivaloyl chloride (2.7 ml, 1.2 eq) is carefully added, and the reaction mixture is stir 10 minutes, removed from the bath, and stirred 4 hours more. Dichloromethane (200 mL) is added, and the reaction mixture is washed 3 times with saturated aqueous sodium bicarbonate, then brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to an oil. The crude product is purified via silica gel chromatography using a hexane:ethyl acetate gradient giving the title compound as a white solid weighing 1.51 g (7.8 mmoles, 42.7%). ^{1}H-NMR (DMSO-d_6), δ 10.39 (s, 1H); 8.11 (d, J = 9.30 Hz, 1H); 7.51 (d, J = 9.29 Hz, 1H); 2.54 (s, 3H); 1.23 (s, 9H) ppm. ES^+ = 194 (M+1).

Method 2: To a dry pressure tube is added 200 mg (1.56 mol) of 3-chloro-5-methylpyridazine, 190 mg (1.87 mmol) of trimethylacetamide, 14.6 mg (0.023 mmol) of rac-2,2'-bis(diphenylphosphine)-1,1'-binaphthyl , tris(dibenzylideneacetone)-dipalladium (0) , 762.4 mg (2.34 mmol) of cesium carbonate and 1.5 ml dry tetrahydrofuran. The pressure tube is purged with nitrogen and sealed. The reaction is heated to 100 °C overnight. The reaction is then cooled, diluted with dichloromethane, and filtered through celite. Solvents are evaporated and the crude product is purified via silica gel chromatography using a ethyl acetate:hexane gradient to obtain 91 mg (0.47 mmol, 30%) as a white solid.

C. N-[4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-yl]-2,2-dimethyl-propionamide.

Activated magnesium powder (19.2 g, 0.792 moles) is added to a dry 3 L flask fitted with a condensor and a drop funnel. The entire apparatus is heated with a gun dry under vacuum and allowed to cool. Enough ether is added to cover the magnesium. 3-Bromopentane (100 g, 0.662 mmol) is added to the addition funnel in 175 ml of diethyl ether. A 1/3 of the bromopentane solution is added to the magnesium and the reaction mixture is stirred under nitrogen until bubbling occurs. Then, the rest is dripped in at such a rate that the bubbling continues gently. The reaction is stirred for 30 minutes after bubbling ceases. Next, 2,2-dimethyl-*N*-(6-methyl-pyridazine-3-yl)-propionamide (21.3 g, 0.110 mmol) dissolved in 225 ml of dry THF is added dropwise. The reaction mixture is stirred for 1 hour. Saturated sodium tartrate (1 L) is carefully added, and the reaction is stirred for 30 minutes. The reaction mixture is transferred to a larger flask, 2 L of ethyl acetate is added, and the reaction is stirred 1 hour more. The layers are separate and the aqueous layer is extracted several times with ethyl acetate. The organic extracts are combined, and the solvents are evaporated. The residue is taken up in 600 mL of dichloromethane, and iodine (28 g, 0.110 mol) is added. The reaction is stirred for 2 hours. The organic layer is washed once with aqueous solution of sodium sulfite and then with water. The organic layer is dried over sodium sulfate, filtered, and evaporated to red oil. The crude product is purified via silica gel chromatography using a hexanes:ethyl acetate gradient. The product fractions are combined and evaporated. The residue is triturated in ethyl acetate and a light tan solid is filtered to obtain 12.0 g (45.6 mmol, 41 %) of the title compound. ^{1}H-NMR (DMSO-d_6), δ 9.88 (s, 1H); 7.59 (s, 1H); 2.60 (s, 3H); 2.39-2.42 (m, 1H); 1.21-1.37 (m, 2H); 1.38-1.43(m, 2H); 1.23(s, 9H); 0.71 (t, J = 7.49 Hz, 6H) ppm. MS/ES$^+$ = 264.

D. 4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-ylamine.

N-[4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-yl]-2,2-dimethyl-propionamide (12.0 g, 45 mmol) is dissolved in 60 mL of concentrated hydrochloric acid. The reaction mixture is heated to 95 °C in a sealed flask for 2 hours. The reaction is worked up by pouring over ice and extracting with ethyl acetate three times. The organic layer is discarded, and the pH of the aqueous layer is adjusted using 2 N sodium hydroxide. The basic solution is extracted with ethyl acetate five times. The organic extracts are

combined, dried over magnesium sulfate, filtered, and evaporated to obtain 6.68 g (37 mmol, 81%) of the title compound as a brownish oil. ^{1}H-NMR (DMSO-d_6), δ 6.95 (s, 1H); 5.89 (s, br, 2H); 2.52-2.56 (m, 1H); 2.34 (s, 3H); 1.44-1.58 (m, 4H); 0.72 (t, J = 7.04 Hz, 6H) ppm. MS/ES$^+$ = 180 (100%, M+1).

E. 8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-ylamine (850 mg, 4.74 mmol), chloroacetone (0.415 ml, 5.22 mL) and 20 mL of ethanol are heated in the microwave at 110 °C for 35 minutes. Sodium bicarbonate (1.2 g, 14.2 mmol) is added, and the reaction mixture is heated in an oil bath at 100 °C overnight. The solvent is evaporate and the residue is taken up in ethyl acetate and washed three times with brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to a brown oil. The crude product is purified via silica gel chromatography using a hexane:ethyl acetate gradient. The title compound is an oil weighing 3.69 g (17.0 mmol, 84%). ^{1}H-NMR (DMSO-d_6), δ 7.34 (s, 1H); 6.84 (s, 1H); 2.85-3.10 (m, 1H); 2.43 (s, 3H); 2.32 (s, 3H); 1.70-1.80 (m, 4H); 0.712 (t, J = 7.49 Hz, 6H) ppm. MS/ES$^+$ = 219 (100%, M+2).

F. 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (5.1 g, 0.023 moles) and 50 mL of dry acetonitrile are added to a nitrogen purged flask and are cooled to 0 °C. *NIS* (5.54 g,0.025 moles) in 90 mL of dry acetonitrile is added. The bath is allowed to come to room temperature, and the reaction to stir overnight. The solvents are evaporated. The residue is taken up in ethyl acetate, washed two times with 50% aqueous solution of sodium thiosulfate and with brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to a residue again. The crude product is triturated in a small amount of acetonitrile, and a solid is filter off. The trituration is repeated several times to obtain the title compound as a light tan solid weighing 7.29 g (0.021 moles, 91%). ^{1}H-NMR (DMSO-d_6), δ 6.96 (s, 1H); 3.0-3.3 (m, 1H); 2.51 (s, 3H); 2.35 (s, 3H); 1.71-1.80 (m, 4H); 0.71 (t, J = 7.48 hz, 6H) ppm. MS/ES$^+$ = 344 (100%, M+1).

G. 8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine-3-yl boronic acid.

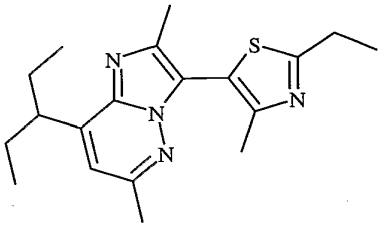
In an oven dried nitrogen purged 3 neck 50mL round bottom flask, 1.00g (2.91 mmol) of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine in 60mL of dry THF is cooled to -78°C. 4.12mL (7.00mmol) of 1.7 M tert-butyllithium in hexanes is added and reaction is stirred at -78 °C for 1 hour. 0.818mL (7.30mmol) of trimethyl borate is added and reaction is followed by MS and TLC (1:1 Hexane:EA) Indication of product is observed by mass spectrum. The reaction is allowed to stir for an additional hour, quenched with 1 N hydrochloric acid, and diluted with ethyl acetate. The organic layer is separated, and the aqueous layer is extracted three times with 100 mL of ethyl acetate. The extracts are combined, dried over $MgSO_4$, filtered, and concentrated. The reaction residue is triturated in hexanes and a solid is filter off. MS, ES^+ = 262.2 (M+1).

H. 8-(1-Ethyl-propyl)-3-(2,4-dimethyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a microwave pressure tube is added 0.340g (1.30mmol) of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine-3-yl boronic acid, 0.100g (0.521mmol) of 5-bromo-2,4-dimethylthiazole, 0.361g (0.313mmol) of Pd(PPh3)4, 0.650mL (1.30mmol) of 2 M aqueous Na2CO3, and 2mL 7:3:2 DME:H2O:EtOH, and the mixture is heated at 160 °C for 40min. Reaction is checked by MS which indicates product present. The reaction mixture is partitioned between 75mL of ethyl acetate and 75mL of water. The layers are separated and the aqueous is extracted 3X50mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using hexanes/ethyl acetate as a solvent system. The product containing fractions are combined to obtain 0.100g of the product, 58% yield. MS, ES+ = 329.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.974 (s, 1H); 3.085-3.052 (m, 1H); 2.665 (s, 3H); 2.438 (s, 3H); 2.290 (s, 3H); 2.147 (s, 3H); 1.849-1.727 (m, 4H); 0.776-0.738 (m, 6H) ppm.

Example 2.

Preparation of 8-(1-ethyl-propyl)-3-(2-ethyl-4-methyl-5- yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-2-ethyl-4-methylthiazole.

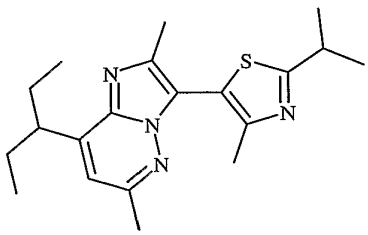
In an oven dried, N_2 purged, 50 mL round bottom flask, 1.00 g (7.86 mmol) of 2-ethyl-4-methylthiazole is reacted with 0.487 mL (9.43 mmol) of bromine in 7mL of acetic acid at room temperature. Reaction is checked by MS after 2 hours. The reaction mixture is partitioned between 50 mL H_2O and 25 mL of CH_2Cl_2. The layers are separated and the aqueous is extracted 3X25mL of CH_2Cl_2. The organics are combined and washed 1X25mL 1N $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated under vacuum to give 1.38g of the title compound, 85% yield. MS, ES+ = 206.0 (M+1); ^{1}H-NMR (DMSO-d6) = 2.940-2.810 (m, 2H); 2.253-2.251 (m, 3H); 1.225-1.222 (m, 3H) ppm.

B. 8-(1-Ethyl-propyl)-3-(2-ethyl-4-methyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-2-ethyl-4-methylthiazole produces the title product in 27% yield. MS, ES+ = 343.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.975 (s, 1H); 3.090-3.056 (m, 1H); 3.025-2.968 (m, 2H); 2.439 (s, 3H); 2.291 (s, 3H); 2.155 (s, 3H); 1.835-1.744 (m, 4H); 1.338-1.300 (m, 3H); 0.776-0.740 (m, 6H) ppm.

Example 3.

Preparation of 8-(1-ethyl-propyl)-3-(2-isopropyl-4-methyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-2-isopropyl-4-methylthiazole.

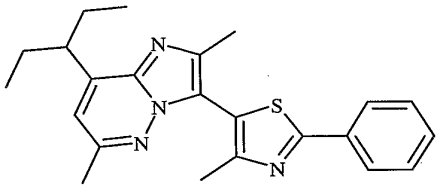
Using a procedure similar to Example 2A, 2-isopropyl-4-methylthiazole produces the title product in 90% yield. MS, ES+ = 220.0 (M+1); ^{1}H-NMR (DMSO-d6) = 3.210-3.175 (m, 1H); 2.257 (s, 3H); 1.264-1.248 (d, 6H) ppm.

B. 8-(1-Ethyl-propyl)-3-(2-isopropyl-4-methyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-2-isopropyl-4-methylthiazole produces the title product in 29% yield. MS, ES+ = 357.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.990 (s, 1H); 3.120-3.050 (m, 1H); 2.442 (s, 3H); 2.294 (s, 3H); 2.158 (s, 3H); 1.810-1.750 (m, 4H); 1.362-1.344 (d, 6H); 0.777-0.741 (m, 6H) ppm.

Example 4.

Preparation of 8-(1-ethyl-propyl)-3-(4-methyl-2-phenyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-4-methy-2-phenylthiazole.

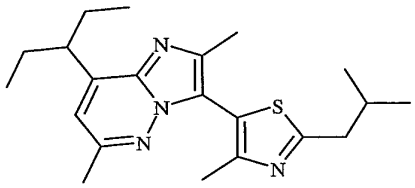
Using a procedure similar to Example 2A, 4-methyl-2-phenylthiazole produces the title product in 90% yield. MS, ES+ = 256.0 (M+1); ^{1}H-NMR (DMSO-d6) = 7.900-7.867 (m, 2H); 7.538-7.512 (m, 3H); 2.407 (s, 3H) ppm.

B. 8-(1-Ethyl-propyl)-3-(4-methyl-2-phenyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-4-methyl-2-phenylthiazole produces the title product in 24% yield. MS, ES+ = 391.3 (M+1); ^{1}H-NMR (DMSO-d6) = 8.005-7.995 (m, 2H); 7.538-7.534 (m, 3H); 7.010 (s, 1H); 3.185-3.095 (m, 1H); 2.496 (s, 3H); 2.394 (s, 3H); 2.316 (s, 3H); 1.895-1.785 (m, 4H); 0.826-0.788 (m, 6H) ppm.

Example 5.

Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2-methyl)propyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-4-methy-2-(2-methyl)propylthiazole.

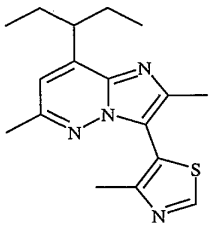
Using a procedure similar to Example 2A, 4-methyl-2-(2-methyl)propylthiazole produces the title product in 96% yield. MS, ES+ = 234.1 (M+1); ^{1}H-NMR (DMSO-d6) = 2.744 (m, 2H); 2.259 (s, 3H); 1.895-2.000 (m, 1H); 0.905-0.888 (m, 6H) ppm.

B. 8-(1-Ethyl-propyl)-3-(4-methyl-2-(2-methyl)propyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-4-methyl-2-(2-methyl)propylthiazole produces the title product in 7% yield. MS, ES+ = 371.3 (M+1); ^{1}H-NMR (DMSO-d6) = 7.013 (s, 1H); 3.109 (m, 1H); 2.892-2.875 (d, 2H); 2.517 (s, 3H); 2.513 (s, 3H); 2.476 (s, 3H); 2.107-2.073 (m, 1H); 1.868-1.780 (m, 4H); 1.018-1.002 (d, 6H); 0.813-0.775 (m, 6H) ppm.

Example 6.

Preparation of 8-(1-Ethyl-propyl)-3-[4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

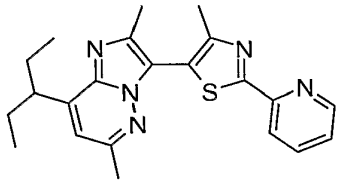


3.00 g of 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (8.74 mmol), 4.32 g of 4-methyl-2*H*-thiazole (43.6 mmol), 453 mg of triphenylphosphine (1.73 mmol) and 5.85 g of cesium carbonate (18.0 mmol) are placed into the sealed tube with

20 ml of DMF and N2 gas is bubbled in for 40 min. 39 mg of Pd2dba3 (0.43 mmol) is added and the tube is sealed and heated at 130°C overnight. The cooled reaction mixture is filtered and applied onto silica-gel column (Hexane → Hexane : AcOEt = 3: 1) to give 2.12 g of the title compound (77%).^{1}H-NMR (DMSO-d6) δ 9.215 (s, 1H); 6.993 (s, 1H); 3.079 (m, 1H); 2.480 (s, 3H); 2.439 (s, 3H); 2.302 (s, 3H); 1.824-1.751 (m, 4H); 0.780-0.743 (m, 6H) ppm. MS, ES+ = 315.2.

Example 7.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-2-yl-thiazol-5-yl)-imidazo[1,2-*b*]pyridazine.



A. 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

In an oven dried, N2 purged, 15mL round bottom flask, 0.028 g (0.089 mmol) of 8-(1-ethyl-propyl)-3-[4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine. in 1.5mL of dry CH_2Cl_2 is cooled to 0 C. 0.019 g (0.107 mmol) of NBS is added and reaction is stirred overnight allowing bath to come to room temperature. Reaction mixture is directly purified by chromatography using hexane/ethyl acetate as solvent system. The product containing fractions are combined to obtain 0.012 g, 34% yield. MS, ES+ = 395.1 (M+1); ^{1}H-NMR (DMSO-d6) = 7.070 (s, 1H); 3.10 (m, 1H); 2.49 (s, 3H); 2.36 (s, 3H); 2.25 (s, 3H); 1.85-1.78 (m, 4H); 0.81-0.77 (m, 6H) ppm.

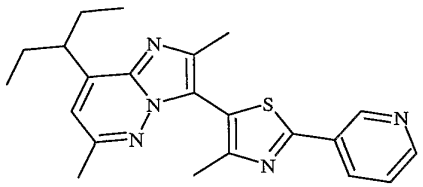
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-2-yl-thiazol-5-yl)-imidazo[1,2-*b*]pyridazine.

A mixture of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-*b*]pyridazine (380 mg, 0.96 mmol), 2-pyridinezinc bromide (0.5 M in THF, 2.1 mL, 4 mmol), $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) and THF (3 mL) is heated at 80 °C for 18 hours. Ethyl acetate (20 mL) is added. The organic layer is separated, dried over

magnesium sulfate, filtered, and the solvent removed in vacuo. Purification is performed via silica gel chromatography using a 3:1 mixture of hexanes and ethyl acetate as eluent to produce the title compound 325 mg (86%). ^{1}H-NMR ($CDCl_3$), δ 9.55 (m,1H); 8.10 (m, 1H); 7.73 (m,1H); 7.26 (m,1H); 6.58 (s, 1H); 3.24 (m, 1H); 2.43 (s, 3H); 2.40 (s, 3H); 2.33 (s, 3H); 1.76 (m, 4H); 0.80 (t, 6H) ppm. MS/ES$^+$ = 391 (100%, M+1).

Example 8.

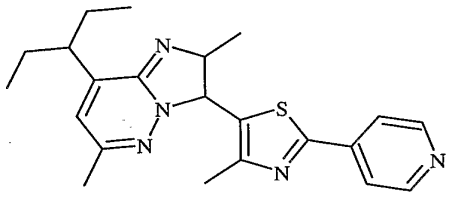
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3-pyridyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a microwave pressure tube is added 0.070 g (0.178 mmol) of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 0.066g (0.534 mmol) of pyridine-3-boronic acid, 0.103 g (0.089 mmol) of Pd(PPh3)4, 0.267mL (0.534 mmol) of 2 M aqueous Na2CO3, and 1mL 7:3:2 DME:H2O:EtOH, and the mixture is heated at 160 °C for 60 min. The reaction mixture is partitioned between 25mL of ethyl acetate and 25 mL of water. The layers are separated and the aqueous is extracted 3X 25 mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using hexanes/Ethyl acetate as a solvent system. The product containing fractions are combined to obtain 0.045 g of the product, 64% yield. MS, ES+ = 392.2 (M+1); ^{1}HNMR (DMSO-d6) δ 9.18 (s, 1H); 8.65 (m, 1H); 8.34 (d, 1H); 7.60 (m, 1H); 7.06 (s, 1H); 3.06 (m, 1H); 2.50 (s, 3H); 2.40 (s, 3H); 2.34 (s, 3H); 1.87-1.82 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 9.

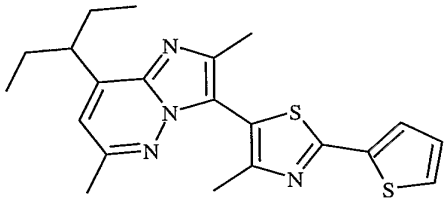
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-pyridyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, pyridine-4-boronic acid produces the title compound in 10% yield. MS, ES+ = 392.3 (M+1); ^{1}HNMR (DMSO-d6) = 8.79 (s, 2H); 7.80 (m, 2H); 7.07 (s, 1H); 3.12 (m, 1H); 2.50 (s, 3H); 2.40 (s, 3H); 2.36 (s, 3H); 1.90-1.80 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 10.

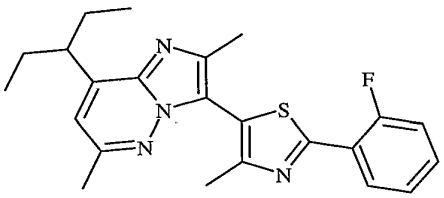
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(thiophene-2-yl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, thiophene-2-boronic acid produces the title compound in 89% yield. MS, ES+ = 397.1 (M+1); ^{1} H-NMR (DMSO-d6) = 7.81-7.79 (d, 1H); 7.78-7.77 (d, 1H); 7.21-7.20 (m, 1H); 7.05 (s, 1H); 3.19-3.15 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H); 2.27 (s, 3H); 1.85-1.83 (m, 4H); 0.82-0.79 (m, 6H) ppm.

Example 11.

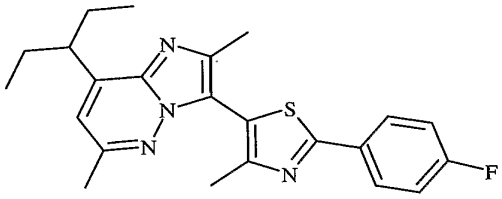
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 2-fluorophenyl boronic acid produces the title compound in 82% yield. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.32-8.28 (m, 1H); 7.60-7.58 (m, 1H); 7.57-7.41 (m, 2H); 7.05 (s, 1H); 3.13-3.12 (m, 1H); 2.49 (s, 3H); 2.40 (s, 3H); 2.35 (s, 3H); 1.91-1.780 (m, 4H); 0.87-0.79 (m, 6H) ppm.

Example 12.

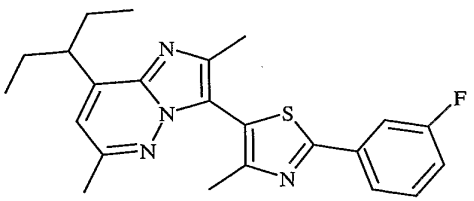
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 4-fluorophenyl boronic acid produces the title compound in 63% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.06-8.03 (m, 2H); 7.408-7.36 (m, 2H); 7.05 (s, 1H); 3.14-3.11 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H); 2.31 (s, 3H); 1.90-1.78 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 13.

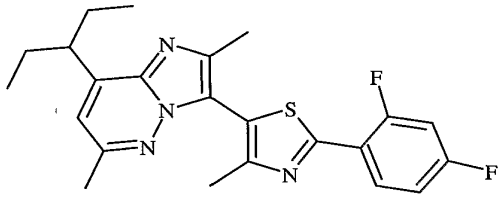
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 3-fluorophenyl boronic acid produces the title compound in 77% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 7.84-7.78 (m, 2H); 7.64-7.57 (m, 2H); 7.41-7.36 (m, 1H); 7.06 (s, 1H); 3.15-3.111 (m, 1H); 2.45 (s, 3H); 2.40(s, 3H); 2.32 (s, 3H); 1.91-1.78 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 14

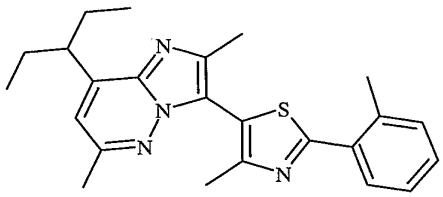
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2,4-difluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 2,4-difluorophenyl boronic acid produces the title compound in 76% yield. MS, ES+ = 427.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.370-8.310 (m, 1H); 7.586-7.540 (m, 1H); 7.36-7.32 (m, 1H); 7.054 (s, 1H); 3.14-3.13 (m, 1H); 2.492 (s, 3H); 2.391 (s, 3H); 2.345 (s, 3H); 1.906-1.797 (m, 4H); 0.826-0.788 (m, 6H) ppm.

Example 15.

Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(o-tolyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

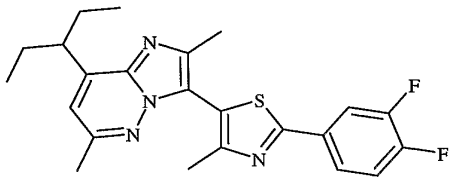


Using a procedure similar to Example 8, o-tolyl boronic acid produces the title compound in 87% yield where the crude mixture is purified by silica gel chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 405.2 (M+1); ^{1}H-

NMR (DMSO-d6) = 7.857-7.838 (d, 1H); 7.429-7.419 (d, 2H); 7.393-7.352 (m, 1H); 7.049 (s, 1H); 3.145-3.114 (m, 1H); 2.647 (s, 3H); 2.502 (s, 3H); 2.406 (s, 3H); 2.337 (s, 3H); 1.907-1.782 (m, 4H); 0.827-0.791 (m, 6H) ppm.

Example 16.

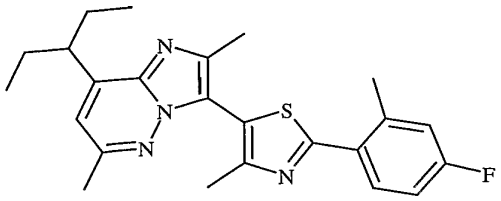
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3,4-difluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 3,4-difluorophenyl boronic acid produces the title compound in 74% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 427.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.07-8.02 (m, 1H); 7.849 (s, 1H); 7.66-7.59 (m, 1H); 7.062 (s, 1H); 3.12-3.11 (m, 1H); 2.498 (s, 3H); 2.392 (s, 3H); 2.319 (s, 3H) 1.905-1.779 (m, 4H); 0.826-0.790 (m, 6H) ppm.

Example 17.

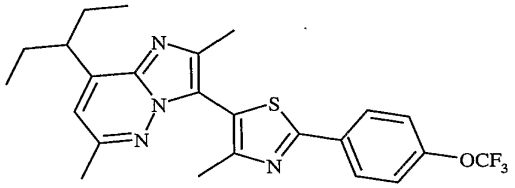
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-fluoro-2-methylphenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 4-fluoro-2-methylphenyl boronic acid produces the title compound 0.040g (37% yield). MS, ES+ = 423.2 (M+1); ^{1}H-NMR (DMSO-d6) = 7.918-7.882 (m, 1H); 7.323-7.241 (d, 1H); 7.234-7.192 (m, 1H); 7.049 (s, 1H); 3.142-3.111 (m, 1H); 2.650 (s, 3H); 2.499 (s, 3H); 2.401 (s, 3H); 2.330 (s, 3H); 1.905-1.779 (m, 4H); 0.969-0.788 (m, 6H) ppm.

Example 18.

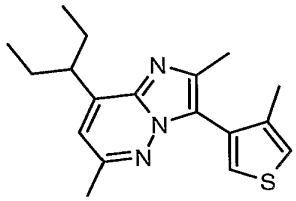
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-trifluoromethoxyphenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a microwave pressure tube is added 0.100g (0.254mmol) of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 0.157g (0.762mmol) of 4-(trifluoromethoxy)benzene boronic acid, 0.147g (0.127mmol) of Pd(PPh3)4, 0.381mL (0.762mmol) of 2 M aqueous sodium carbonate, and 2mL Ethanol. The reaction mixture is heated in the microwave at 160°C for up to 1 hour. The reaction mixture is partitioned between 50 mL of ethyl acetate and 50 mL of water. The layers are separated and the aqueous is extracted 3X50mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. The product containing fractions are combined to obtain 0.085g of the product, 70% yield. MS, ES+ = 475.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.134-8.112 (d, 2H); 7.553-7.532 (d, 2H); 7.059 (s, 1H); 3.142-3.113 (m, 1H); 2.500 (s, 3H); 2.399 (s, 3H); 2.330 (s, 3H); 1.907-1.782 (m, 4H); 0.827-0.791 (m, 6H) ppm.

Example 19.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.



A. 4,4,5,5-Tetramethyl-2-(4-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane.

To a 250 mL round bottom flask is added 3-bromo-4-methyl-thiophene (5.00 g, 28.24 mmol), bis(pinacolato)diboron (7.89 g, 31.06 mmol) and KOAc (8.32 g, 84.72 mmol) in DMSO (85 mL). The mixture is degassed by bubbling N_2 for 5 min, $PdCl_2(dppf)_2 \bullet CH_2Cl_2$ (1.15 g, 1.42 mmol) is added and the reaction mixture is heated to and stirred at 85 °C overnight. The reaction is cooled to rt, and diluted with EtOAc (400 mL), washed with H_2O (3 x 300 mL); dried with $MgSO_4$, filtered and concentrated. Purification of the crude material by chromatography to give the title compound (3.69 g, 16.5 mmol, 58%). ES-MS (m/z): calcd for $C_{11}H_{17}BO_2S$ (M^+): 224.1; found: 224.9.

B. 4-Methyl 3-thiophene boronic acid.

A solution of 4,4,5,5-tetramethyl-2-(4-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane (3.69 g, 16.47 mmol) in acetone (30 mL) is treated with H_2O (30 mL), followed by $NaIO_4$ (7.05 g, 32.95 mmol). The resulting mixture is stirred at rt overnight. The organic solvent is removed in vacuo. The residue is diluted with H_2O (50 mL), extracted with EtOAc ((2 x 100 mL). The organic extracts are combined, dried with Na_2SO_4, filtered and concentrated. Purification of the crude material by chromatography gives the title compound (0.82 g, 5.78 mmol, 35%). ^1H NMR ($CDCl_3$): δ 1.33 (s, 3H), 2.64-2.66 (m, 2H), 7.00-7.02 (m, 1H), 8.27 (d, J = 3.0 Hz, 1H). ES-MS (m/z): calcd for $C_5H_7BO_2S$ $(M-H)^-$: 141.0; found: 141.1.

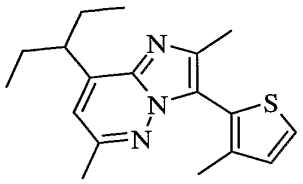
C. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.

To a 100 mL round bottom flask containing 4-methyl 3-thiophene boronic acid (0.27 g, 1.91 mmol), and 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.65 g, 1.91 mmol) in 20 mL of a stock solution (DME:H_2O:EtOH = 7:3:2) is added 2 M Na_2CO_3 (1.9 mL). The resulting mixture is degassed by bubbling N_2 for 5 min. Then $Pd(PPh_3)_4$ (0.11 g, 0.096 mmol) is added. The reaction mixture is refluxed overnight. The reaction is diluted with H_2O (20 mL); extracted with EtOAc (3 x 30 mL); dried (Na_2SO_4), filtered and purification of the crude material by chromatography gives the title compound (0.52 g, 1.66 mmol, 87%). ^1H NMR ($CDCl_3$): δ 0.89 (t, J = 7.5 Hz,

6H), 1.75-1.90 (m, 4H), 2.13 (d, J = 0.8 Hz, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 3.30-3.39 (m, 1H), 6.64 (s, 1H), 7.08-7.11 (m, 1H), 7.34 (d, J = 3.1 Hz, 1H). ES-MS (m/z): calcd for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.5; found: 314.2.

Example 20.

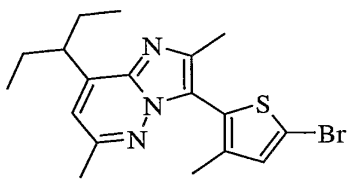
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To mixture of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (12.0 g, 34.96 mmol) and $PdCl_2$(dppf) (1.28 g, 1.75 mmol) is added a 0.5 M solution of 3-methyl-2-thienylzinc bromide in THF (100 mL, 50.0 mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (500 mL), washed with 10% citric acid (500 mL), water (400 mL), brine (400 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (10%-20% EtOAc/hexane gradient) furnish the title compound (8.83 g, 28.17 mmol, 81%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.4 Hz, 6H), 1.78-1.95 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 3.33-3.43 (m, 1H), 6.69 (s, 1H), 7.06 (d, J = 4.9 Hz, 1H), 7.46 (d, J = 4.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.6; found: 314.2.

Example 21.

Preparation of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

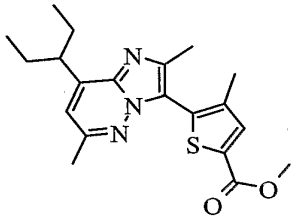


To a solution of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (8.83 g, 28.17 mmol) and CH_2Cl_2 (90 mL) is added NBS (5.26

g, 29.58 mmol). The solution is stirred at ambient temperature for 2 hours. The solution is washed with water (3 X 75 mL), dried over MgSO4, filtered and concentrated to furnish the title compound (10.5 g, 26.76 mmol, 95%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.3 Hz, 6H), 1.73-1.93 (m, 4H), 2.09 (s, 3H), 2.44 (s, 3H), 2.51 (s, 3H), 3.26-3.36 (m, 1H), 6.68 (s, 1H), 6.98 (d, J = 4.9 Hz, 1H) ppm. LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.6; found: 392.1, 394.1.

Example 22.

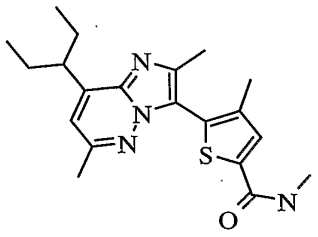
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methyl ester.



A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.00 g, 2.66 mmol) in CH_3OH (12 mL), DMSO (18 mL), Et_3N (2.0 mL) with $Pd(OAc)_2$ (0.12 g, 0.538 mmol), dppf (0.937 g, 1.69 mmol) is reacted at CO atmosphere (100 psi) at 80 °C for 24 h. The reaction mixture is diluted with EtOAc (200 mL), washed with 0.1 M HCl (2 x 50 mL), brine (50 mL); dried with Na_2SO_4; filtered through silica gel and eluted with excess EtOAc. Purification of the crude material by chromatography gives the title compound (0.79 g, 2.12 mmol, 80%). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.7 Hz, 6H), 1.75-1.93 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.32-3.42 (m, 1H), 3.91 (s, 3H), 6.72 (s, 1H), 7.73 (s, 1H). ES-MS (m/z): calcd for $C_{20}H_{25}N_3O_2S$ $(M+H)^+$: 372.5; found: 372.2.

Example 23.

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methylamide.



A. 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid.

A solution of (1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methyl ester (0.78 g, 2.10 mmol) in CH_3OH (10 mL) is treated with 5.0 M NaOH (2.1 mL, 10.5 mmol). The resulting reaction mixture is refluxed for 4 h. Organic solvent is removed in vacuo; the aqueous residue is acidified by the addition of 2.0 M HCl to pH 5~6; it is then extracted with EtOAc (3 x 50 mL); dried (Na_2SO_4); filtered and concentration to give the title compound (0.74 g, 2.07 mmol, 98%). ^{1}H NMR (DMSO-d6): δ 0.79 (t, J = 7.6 Hz, 6H), 1.75-1.86 (m, 4H), 2.06 (s, 3H), 2.36 (s, 3H), 2.47 (s, 3H), 3.06-3.14 (m, 1H), 7.01 (s, 1H), 7.68 (s, 1H), 13.1 (bs, 1H). ES-MS (m/z): calcd for $C_{19}H_{23}N_3O_2S$ $(M+H)^+$: 358.5; found: 358.2.

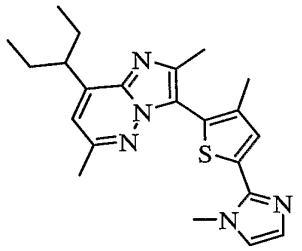
B. 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methylamide.

5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid (0.17 g, 0.47 mmol) is reacted with 2.0 M oxalyl chloride in CH_2Cl_2 (3.0 mL) at rt for 1h. The excess reagent and solvent are removed in vacuo. The residue is dissolved in CH_2Cl_2 (3mL), cooled to 0 °C and treated with 2.0 M methyl amine in THF (3 mL). The reaction is stirred at 0 °C for 10 min and rt for 30min. It is diluted with EtOAc (50 mL), washed with H_2O (15 mL0, 0.1 M NaOH (2 x 30 mL); dried (Na_2SO_4); filtered and concentrated. Purification of the crude material by chromatography to give the title compound (0.91g, 0.25 mmol, 53%). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 6H), 1.75-1.91 (m, 4H), 2.14 (s, 3H), 2.47 (s, 3H), 2.52 (s, 3H), 3.02

(d, J = 4.8 Hz, 3H), 3.28-3.36 (m, 1H), 5.90-6.01 (m, 1H), 6.69 (s, 1H), 7.43 (s, 1H). ES-MS (m/z): calcd for $C_{20}H_{26}N_4OS$ $(M+H)^+$: 371.5; found: 371.2.

Example 24.

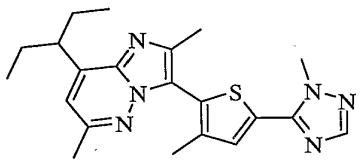
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-imidazol-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo-[*1,2-b*]pyridazine (0.98 g, 2.51 mmol) and 1-methyl-*1H*-imidazole (0.2 mL), $Pd(OAc)_2$ (34 mg, 0.15 mmol), PPh_3 (79 mg, 0.299 mmol), Cs_2CO_3 (1.95 g, 6.0 mmol) in DMF (50 mL) is stirred under N_2 at 130-140°C overnight. The reaction mixture is cooled, diluted with EtOAc (300 mL), washed with H_2O (3 x 100 mL); dried (Na_2SO_4); filtered and concentrated. Purification of the resulting crude material by chromatography yields the title compound (0.51 g, 1.29 mmol, 51%). ^1H NMR ($CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 6H), 1.77-1.92 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.54 (s, 3H), 3.30-3.40 (m, 1H), 3.81 (s, 3H), 6.69 (s, 1H), 7.02 (s, 1H), 7.24 (s, 1H), 7.52 (s, 1H). ES-MS (m/z): calcd for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.6; found: 394.3.

Example 25.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

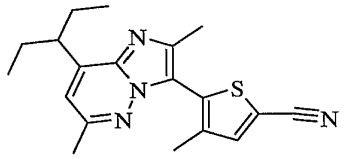


To a –78 °C solution of 1-methyl-1,2,4-triazole (0.15 mL, 2.04 mmol) and THF (3 mL) is added a 1.34 M solution of n-Bu-Li in hexanes (1.60 mL, 2.14 mmol) over 20

minutes, then stirred at –78 °C for 1.5 hours. A 0.5 M solution of $ZnCl_2$ in THF (4.28 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.019 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and the solution heated at 65 °C overnight diluted with CH_2Cl_2 (30 mL). The organic layer is washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (20%-60% EtOAc/hexane gradient). The residue is dissolved in Et_2O, treated with Darco®-60 for 15 minutes, dried with Na_2SO_4, and filtered to furnish the title compound (0.24 g, 0.61 mmol, 60%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.20 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.28-3.37 (m, 1H), 4.14 (s, 3H), 6.69 (s, 1H), 7.45 (s, 1H), 7.87 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6S$ $(M+H)^+$: 395.6; found: 395.2.

Example 26.

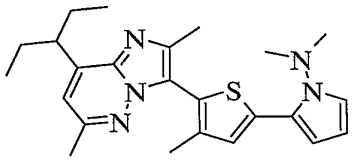
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carbonitrile.



A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.28 mmol), DMF (5 mL), and $Zn(CN)_2$ (0.090 g, 0.76 mmol) is degassed with nitrogen for 15 minutes. $Pd(PPh_3)_4$ (0.74 g, 0.064 mmol) and the solution heated at 100 °C overnight. The solution is diluted with EtOAc (50 mL), washed with 2 M NH_4OH (2 X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Purified by ISCO column chromatography (15% - 20% EtOAc/hexane gradient) furnish the title compound (0.39 g, 1.15 mmol, 91%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.15 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 3.26-3.34 (m, 1H), 6.72 (s, 1H), 7.53 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{22}N_4S$ $(M+H)^+$: 339.6; found: 339.2.

Example 27.

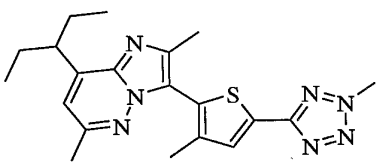
Preparation of (2-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyrrol-1-yl)-dimethyl-amine.



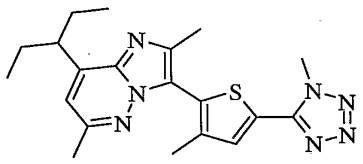
To a 0 °C solution 1-(dimethylamino)-pyrrole (0.24 mL, 2.04 mmol) and THF (4 mL) is added 1.24 M *n*-BuLi (1.73 mL, 2.14 mmol). The solution is warmed to ambient temperature and stirred for two hours. 0.5 M $ZnCl_2$ (4.28 mL, 2.14 mmol) is added and the solution is stirred for one hour. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and the solution is heated at 65 °C overnight. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (15% -20% EtOAc gradient) furnish the title compound (0.41 g, 0.97 mmol, 95%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.11 (s, 3H), 2.51 (s, 6H), 2.83 (s, 6H), 3.29-3.39 (m, 1H), 6.18-6.21 (m, 1H), 6.35 (dd, J = 4.0, 1.8 Hz, 1H), 6.65 (s, 1H), 6.98 (dd, J = 4.0, 1.8 Hz, 1H), 7.25 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{31}N_5S$ $(M+H)^+$: 422.2; found: 422.4.

Example 28 and 29.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-2,5-dihydro-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[1,2 b]pyridazine.



Ex 28.



Ex. 29.

A. 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

To a solution of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carbonitrile (0.25 g, 0.74 mmol) and DMF (2.5 mL) is added Et_3N•HCl (0.31 g, 2.22 mmol) and NaN_3 (0.14 g, 2.20 mmol). The solution is heated at 100 °C overnight. The solution is diluted with water (20 mL) and extracted with EtOAc (3 X 15 mL), the combined organic layers are washed with 0.1 M HCl (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is recrystalized from acetonitrile furnish the title compound (0.14 g, 0.37 mmol, 50%). ^{1}H NMR ($CDCl_3$), δ 0.81 (t, J = 7.5 Hz, 6H), 1.66-1.87 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.26-3.35 (m, 1H), 6.83 (s, 1H), 7.84 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{23}N_7S$ $(M+H)^+$: 382.6; found: 382.2.

B. 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-2,5-dihydro-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[1,2 b]pyridazine.

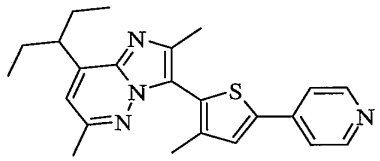
To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.14 g, 0.35 mmol) and THF (3 mL) is added Et_3N (0.1 mL, 0.71 mmol) and MeI (0.024 mL, 0.39 mmol). The solution is stirred overnight, diluted with EtOAc (20 mL), washed with water (15 mL), 0.1 M HCl (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%- 40% EtOAc/hexane gradient) furnish Ex. 28 (0.71 g, 0.18 mmol, 51%), and Ex. 29 (0.031 g, 0.078 mmol, 22%).

Ex. 28: ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.92 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.28-3.38 (m, 1H), 4.38 (s, 3H), 6.68 (s, 1H), 7.71 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{25}N_7S$ $(M+H)^+$: 396.6; found: 396.3.

Ex. 29: ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.73-1.94 (m, 4H), 2.23 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.37 (m, 1H), 4.30 (s, 3H), 6.62 (s, 1H), 7.63 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{25}N_7S$ $(M+H)^+$: 396.6; found: 396.3.

Example 30.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



A. 3-(5-Boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a -78 °C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.20 g, 3.06 mmol) and THF (10 mL) is added 1.30 M *n*-Bu-Li (2.47 mL, 3.21 mmol) drop wise. The solution is stirred at –78 °C for one hour. $B(OMe)_3$ (0.38 mL, 3.65 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hours. 1 M HCl is added and the solution stirred for 10 minutes extracted with CH_2Cl_2 (2 X 30 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.47 g, 1.32 mmol, 43%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.5 Hz, 6H), 1.71-1.98 (m, 4H), 2.02 (s, 3H), 2.64 (s, 3H), 2.69 (s, 3H), 3.64-3.83 (m, 1H), 7.06 (d, J = 5.3 Hz, 1H), 7.54 (d, J = 5.3 Hz, 1H), 7.20 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{24}BN_3O_2S$ $(M+H)^+$: 358.4; found: 358.2.

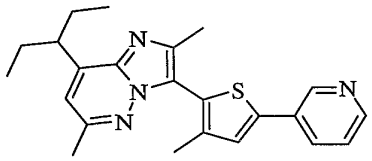
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

A solution of 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.70 mmol), 4-bromopyridine hydrochloride (0.16 g, 0.84 mmol), and 2 M Na_2CO_3 (0.87 mL, 1.75 mmol) and *n*-PrOH (2.5 mL) is degassed with nitrogen for 10 minutes. $Pd(PPh_3)_4$ (0.040 g, 0.035 mmol) is added and the solution heated at 85 °C overnight. The solution is diluted with CH_2Cl_2 (40 mL), washed with 10% Na_2CO_3 (30 mL), water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.16 g, 0.41 mmol, 59%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.52 (s,

3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.43 (s, 1H), 7.52 (d, J = 5.5 Hz, 2H), 8.62 (d, J = 5.5 Hz, 2H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.2 found: 391.2.

Example 31.

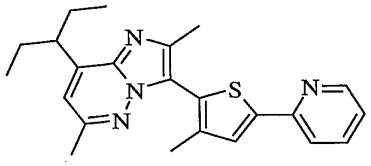
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-3-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol), and THF (5 mL) is added 1.34 M *n*-Bu-Li (1.0 mL, 1.34 mmol). The solution is stirred for at -78 °C for 30 minutes and 0.5 M $ZnCl_2$ in THF (2.7 mL, 1.34 mmol) is added and the solution warmed to ambient temperature. After 30 minutes 3-bromopyridine (0.15 mL, 1.53 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) is added and the solution heated at 65 °C overnight. The solution is diluted with CH_2Cl_2 (40 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) concentrated and re-dissolved in Et_2O. The solution is treated with Darco®-60 for 15 minutes, dried over Na_2SO_4, and filtered thru celite® furnish the title compound (0.26 g, 0.67 mmol, 52%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.26-7.32 (m, 2H), 7.86 (dt, J = 7.9, 1.8 Hz, 1H), 850 (d, J = 3.2 Hz, 1H), 8.89 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.6; found: 391.2.

Example 32.

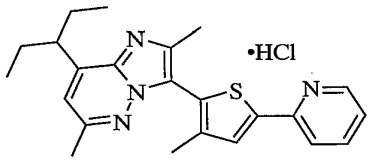
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a mixture of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) is added a 0.5 M solution of 2-pyridylzinc bromide in THF (5.1 mL, 2.55 mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (50 mL), washed with 10% citric acid (50 mL), water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.45 g, 1.15 mmol, 89%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.52 (s, 6H), 3.30-3.39 (m, 1H), 6.67 (s, 1H), 7.12-7.16 (m, 1H), 7.53 (s, 1H), 7.63-7.71 (m, 2H), 8.57 (dt, J = 1.3, 4.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.6; found: 391.2.

Example 33.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine hydrochloride.

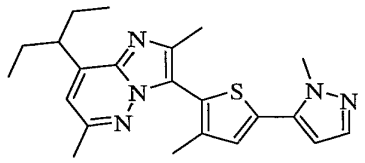


To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (0.15 g, 38 mmol) and MeOH (2 mL) is added AcCl (0.028 mL, 0.39 mmol). After one hour the solution is concentrated and the residue recrystalized from EtOAc/ hexane furnish the title compound (0.11 g, 0.26 mmol, 69%). ^{1}H NMR ($CDCl_3$), δ 0.97 (t, J = 7.4 Hz, 6H), 1.75-2.03 (m, 4H), 2.17 (s, 3H), 2.66 (s, 3H), 2.77 (s, 3H), 3.86-3.98 (m, 1H), 7.17 (s, 1H), 7.21-7.30 (m, 2H), 7.62 (bs, 1H), 7.67-

7.7.82 (m, 2H), 8.60 (d, J = 4.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}ClN_5S$ $(M+H)^+$: 428.1; found: 391.2.

Example 34.

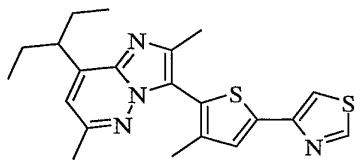
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-2*H*-pyrazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 1-methylpyrazole (0.17 g, 2.04 mmol), 1.56 M *n*-Bu-Li (1.34 mL, 2.09 mmol), $ZnCl_2$ (4.3 mL, 2.14 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.35 g, 0.89 mmol, 88%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 4.05 (s, 3H), 6.42 (d, J = 1.8 Hz, 1H), 6.68 (s, 1H), 7.08 (s, 1H), 7.46 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.7; found: 394.2.

Example 35.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-thiazol-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

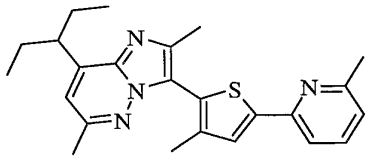


Using a procedure similar to Example 31, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.40 g, 1.02 mmol), 1.34 M *n*-Bu-Li (0.8 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 4-bromo-thiazole (0.20 mL, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.16g, 0.40 mmol, 40%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.4 Hz, 6H), 1.70-1.96 (m, 4H), 2.17 (s, 3H), 2.64 (s, 3H), 2.66 (s, 3H), 3.38-3.48 (m, 1H), 7.16 (d, J = 1.8

Hz, 1H), 7.44 (s, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.7; found: 397.2.

Example 36.

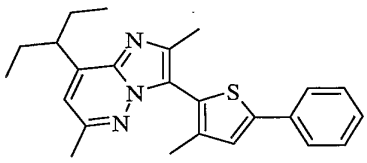
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.53 mmol) and $PdCl_2$(dppf) (0.056 g, 0.076 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (6.0 mL, 3.06 mmol) furnish the title compound (0.29 g, 0.72 mmol, 47%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 2.58 (s, 3H), 3.31-3.40 (m, 1H),
6.67 (s, 1H), 7.00 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 8.56 (t, J = 7.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4$ $(M+H)^+$: 405.7; found: 405.2.

Example 37.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-phenyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

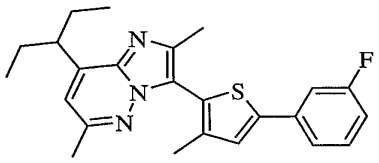


Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.05 g, 0.069 mmol) and 0.5 M solution of phenylzinc iodide in THF (5.5 mL, 2.76 mmol) furnish the title compound (0.25 g, 0.64 mmol, 50%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.17 (s, 3H), 2.52 (s, 3H), 2.53 (s,

3H), 3.31-3.41 (m, 1H), 6.68 (s, 1H), 7.26 (s, 1H), 7.27-30 (m, 1H), 7.35-7.41 (m, 2H), 7.61-7.66 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{27}N_3S$ $(M+H)^+$: 390.3; found: 390.3.

Example 38.

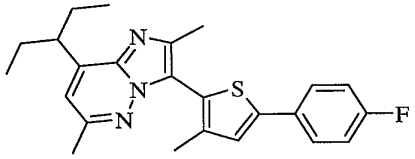
Preparation of 8-(1-ethyl-propyl)-3-[5-(3-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.063 mmol) and 0.5 M solution of 3-flourophenylzinc iodide in THF (5.1 mL, 2.55 mmol) furnish the title compound (0.24 g, 0.59 mmol, 46%). ^1H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.31-3.39 (m, 1H), 6.69 (s, 1H), 6.94-7.01 (m, 1H), 7.26 (s, 1H), 7.30-7.42 (m, 3H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.7; found: 408.2.

Example 39.

Preparation of 8-(1-ethyl-propyl)-3-[5-(4-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

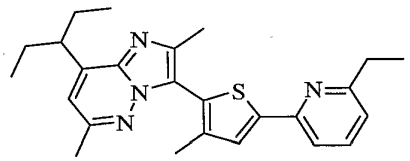


A slurry of 0.05 g/mL of Reike® Zn in THF (0.26 g, 4.01 mmol) and 1-bromo-4-fluoro-benzene (0.29 mL, 2.68 mmol) is heated at a reflux overnight. The solution is filtered under nitrogen. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.35 g, 0.89 mmol) and $PdCl_2$(dppf) (0.033 g, 0.045 mmol) are added, and the solution is heated at a reflux overnight diluted with EtOAc (30 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column

chromatography (10%-15% EtOAc/hexane gradient) furnish the title compound (0.091 g, 0.22 mmol, 25%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30-3.38 (m, 1H), 6.68 (s, 1H), 7.08 (d, J = 8.8 Hz, 2H),7.18 (s, 1H), 7.59 (dd, J = 8.5, 5.3 Hz, 2H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.7; found: 408.3.

Example 40.

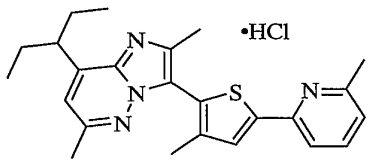
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-ethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31, 2-bromo-6-ethyl pyridine (0.26 g, 1.41 mmol), 1.56 M *n*-Bu-Li (0.94 mL, 1.47 mmol), 0.5 M $ZnCl_2$ in THF (3.0 mL, 1.53 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) produce the title compound (0.15 g, 0.36 mmol, 28%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.34 (t, J = 7.5 Hz, 3H), 1.75-1.94 (m, 4H), 2.16 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 2.85 (q, J = 16.2, 7.5 Hz, 2H), 3.31-3.41 (m, 1H), 6.67 (s, 1H), 7.01 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.53 (s, 1H), 8.59 (t, J = 7.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{25}H_{30}N_4S$ $(M+H)^+$: 419.3; found: 419.3.

Example 41.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine hydrochloride.

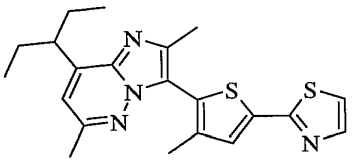


Using a procedure similar to Example 33, 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.55 g, 1.36

mmol), MeOH (6 mL) and AcCl (0.098 mL, 1.36 mmol) furnish the title compound (0.11 g, 0.25 mmol, 42%). ^{1}H NMR ($CDCl_3$), δ 0.96 (t, J = 7.2 Hz, 6H), 1.74-1.89 (m, 2H), 1.89-2.02 (m, 2H), 2.22 (s, 3H), 2.68 (s, 3H), 2.78 (s, 3H), 3.08 (s, 3H), 3.88-3.98 (m, 1H), 7.23 (s, 1H), 7.40 (d, J = 6.9 Hz, 1H), 7.71 (d, J = 4.8 Hz, 1H), 8.06 (s, 1H), 8.82 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{29}ClN_4S$ $(M+H)^+$: 441.3; found: 405.2.

Example 42.

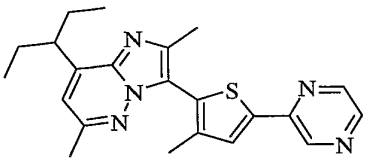
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-thiazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.46 g, 1.17 mmol), 0.5 M 2-thiazolylzinc bromide in THF (4.7 mL, 2.35 mmol) and $PdCl_2$(dppf) (0.043 g, 0.059 mmol) furnish the title compound (0.32 g, 0.81 mmol, 70%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 7.70 (s, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.47 (s, 1H), 7.78 (d, J = 3.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.7; found: 397.1.

Example 43.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrazin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

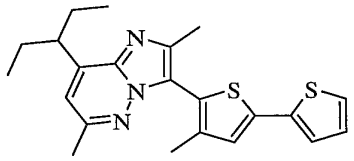


Using a procedure similar to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) (example Rupp-2), 2-chloropyrazine (0.11 mL, 1.22 mmol), 1.42 M *n*-Bu-Li (1.52 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), and $PdCl_2$(dppf) (0.037 g, 0.051

mmol) furnish the title compound (0.19 g, 0.49 mmol, 48%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.20 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 6.69 (s, 1H), 7.63 (s, 1H), 8.40 (d, J = 2.6 Hz, 1H), 8.51 (t, J = 1.9 Hz, 1H), 8.96 (d, J = 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 44.

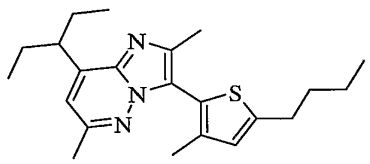
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-[2,2']bithiophenyl-5-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 0.5 M 2-thiophenlyzinc bromide in THF (3.0 mL, 1.53 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) furnish the title compound (0.25g, 0.63 mmol, 83%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.14 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.02 (dd, J = 5.0, 3.6 Hz, 1H), 7.11 (s, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.19 (dd, J = 5.0, 1.0 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_3S_2$ $(M+H)^+$: 396.7; found: 396.2.

Example 45.

Preparation of 3-(5-butyl-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

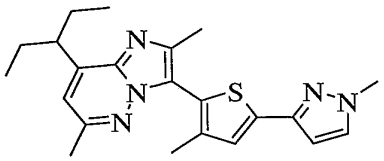


Using a procedure similar to Example 25 from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.1.02 mmol), 1.34 M *n*-Bu-Li (1.60 mL, 2.14 mmol), 0.5 M $ZnCl_2$ (4.3 mL, 2.14 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnishes the title compound (0.25g, 0.69 mmol, 68%). ^{1}H NMR

($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 0.97 (t, J = 7.5 Hz, 3H), 1.40-1.51 (m, 2H), 1.67-1.92 (m, 6H), 2.07 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 2.83 (t, J = 8.0 Hz, 2H), 3.30-3.38 (m, 1H), 6.64 (s, 1H), 6.70 (s, 1H) LC/MS (m/z): calcd. for $C_{22}H_{31}N_3S$ $(M+H)^+$: 370.3; found: 370.2.

Example 46.

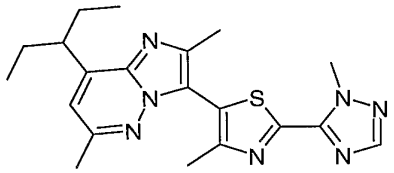
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-pyrazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.42 M *n*-Bu-Li (0.75 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 3-bromo-1-methyl-*1H*-pyrazole (Pavlik, J.; Kurzweil, E.; *J. Org. Chem.*, 1991, 56, 22, 6313) (0.20 g, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.041g, 0.10 mmol, 10%). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.15 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.31-3.41 (m, 1H), 3.95 (s, 3H), 6.47 (d, J = 2.2 Hz, 1H), 6.67 (s, 1H), 7.25 (s, 1H), 7.36 (d, J = 2.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 47.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[4-methyl-2-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.

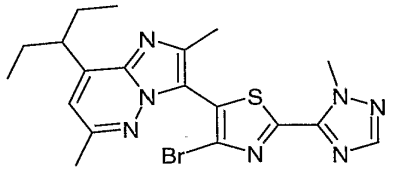


82 mg of 1-Methyl-1,2,4-triazole (0.99 mmol) is dissolved in 2 ml of dry THF and cooled to –78°C and 0.4 ml of n-butyllithium 2.5 M in hexane (0.99 mmol) is added. The reaction mixture is stirred at –78C to room temperature for 10min and cooled to –78°C

again. 1.98 ml of 0.5 M zinc chloride 0.5 M solution in THF (0.99 mmol) is added and stirred at –78C to room temperature for 15 min. 265 mg of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.66 mmol) and 27 mg of PdCl2(dppf) (0.033 mmol) are added and the vial is capped with a Teflon cap and heated at 80°C for 2 days. The reaction is cooled to room temperature and quenched with sat. NH4Cl and extracted with CH2Cl2. The separated CH2Cl2 layer is dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt : 2 M NH3 in MeOH=10:2:1) to give 57 mg of the title product. Yield 22%. mass spectrum (m/e):396(M+1). ^{1}H-NMR (CDCl3): δ 7.96 (s, 1H), 6.77 (s, 1H), 4.45 (s, 3H), 3.36 (m, 1H), 2.55 (s, 3H), 2.52 (s, 3H), 2.47 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.3Hz, 6H).

Example 48.

Preparation of 3-[4-bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

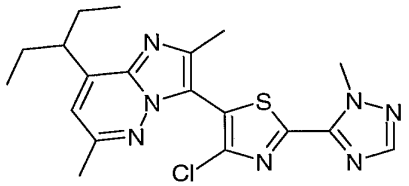


82 mg of 1-methyl-1,2,4-triazole (0.99 mmol) is dissolved in 2 ml of dry THF and cooled to –78°C and 0.4 ml of n-butyllithium 2.5 M in hexane (0.99 mmol) is added. The reaction mixture is stirred at –78°C to room temperature for 10min and cooled to –78°C again. 1.98 ml of 0.5 M zinc chloride 0.5 M solution in THF (0.99 mmol) is added and stirred at –78°C to room temperature for 15min. 152 mg of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.33 mmol) and 27 mg of PdCl2(dppf) (0.033 mmol) are added and the vial is capped with a Teflon cap and heated at 80°C for 2days. The reaction is cooled to room temperature and quenched with sat. NH4Cl and extracted with CH2Cl2. The separated CH2Cl2 layer is dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt:2M NH3 in MeOH=10:2:1) to give 88mg of the title product. Yield 54%.

mass spectrum (m/e):461(M+1). ^{1}H-NMR (CDCl3): 7.98 (s, 1H), 6.77 (s, 1H), 4.44 (s, 3H), 3.35 (m, 1H), 2.59 (s, 3H), 2.55 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.5Hz, 6H).

Example 49.

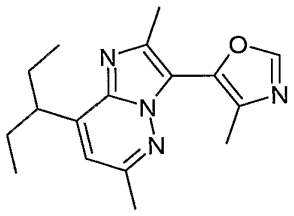
Preparation of 3-[4-chloro-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



175 mg of 3-[4-Bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.38 mmol) and 56 mg of copper chloride (0.57 mmol) are placed into 4 ml vial with 3.0 ml of dry DMF and the vial is capped with a Teflon cap. The vial is heated at 130°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1 and hexane:AcOEt=8:1) to give 91 mg of crude product. The pure product is recrystalized from Et2O/Hexane. 73 mg (46%). mass spectrum (m/e):416(M+1). ^{1}H-NMR (CDCl3): 7.98 (s, 1H), 6.80 (s, 1H), 4.44 (s, 3H), 3.35 (m, 1H), 2.59 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.5Hz, 6H).

Example 50.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-oxazol-5-yl)-imidazo[*1,2-b*]pyridazine.

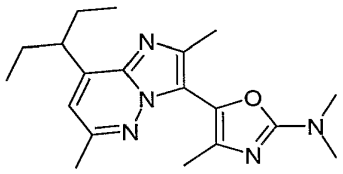


686 mg of 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 mmol), 830 mg of 4-methyl-oxazole. (10 mmol), 105 mg of triphenylphosphine (0.4 mmol) and 1.30 g of cesium carbonate (4.0 mmol) are placed into tube with 10 ml of dry

DMF. N2 gas is bubbled in for 20min and 92 mg of Pd2dba3 (0.1 mmol) is added. The tube is sealed and heated at 130°C overnight. After being cooled to room temperature, water and CHCl2 are added to the mixture. The CHCl2 layer is separated, washed with sat. NaCl , dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=5:1) to give 234 mg of the title product. Yield 39%. mass spectrum (m/e):299(M+1). ^{1}H-NMR (CDCl3): 8.06 (s, 1H), 6.75 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.50 (s, 3H), 2.29 (s, 3H), 1.86 (m, 4H), 0.90 (t, J=7.4Hz, 6H).

Example 51.

Preparation of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-oxazol-2-yl}-dimethylamine.



A. 3-(2-Bromo-4-methyl-oxazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

230 mg of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-oxazol-5-yl)-imidazo[*1,2-b*]pyridazine (0.77 mmol) is dissolved in 20 ml of CH2Cl2 and 178 mg of NBS (1.0 mmol) is added. The reaction mixture is stirred at room temperature overnight. The reaction mixture is washed with sat. Na2S2O3, sat. NaCl, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 36 mg of the title compound. Yield 12%. mass spectrum (m/e):378(M+1). ^{1}H-NMR (CDCl3): 6.82 (s, 1H), 3.39 (m, 1H), 2.58 (s, 3H), 2.53 (s, 3H), 2.26 (s, 3H), 1.85 (m, 1H), 0.89 (t, J=7.4Hz, 6H).

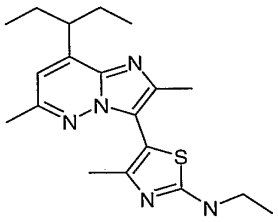
B. N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-oxazol-2-yl}-dimethylamine.

32 mg of 3-(2-Bromo-4-methyl-oxazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.08 mmol) and 78 mg of cesium carbonate (0.24 mmol) are placed into vial with 3 ml of dimethylamine 2.0 M in THF. The vial is capped with a

Teflon cap and heated at 110°C for 3days. The reaction mixture is cooled to room temperature, concentrated, and applied onto a silica-gel chromatography column (Hexane :AcOEt:2M NH3 in MeOH=10:2:1) to give 24 mg of the title product. Yield 89%. mass spectrum (m/e):342(M+1). ^{1}H-NMR (CDCl3): 6.71(s, 1H), 3.34 (m, 1H), 3.13 (s, 6H), 2.56 (s, 3H), 2.49 (s, 3H), 2.14 (s, 3H), 1.84 (m, 4H), 0.89 (t, J=7.5Hz, 6H).

Example 52.

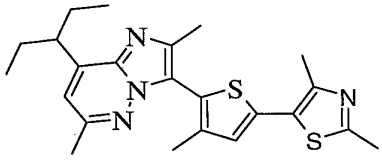
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[(4-methyl-2-ethylamino)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.



The title compound is prepared essentially as described in Example 51B. employing 2.0 ml of ethylamine 2.0 M in THF and 182 g of cesium carbonate (0.56 mmol), 78%. mass spectrum (m/e):358 (M+1); 1H-NMR (CDCl3): 6.69(s, 1H), 5.23(br, 1H), 3.38(m, 3H), 2.56(s, 3H), 2.46(s, 3H), 2.17(s, 3H), 1.85(m, 4H), 1.35(t, 3H, J=7.2Hz), 0.90(t, 6H, J=7.2Hz).

Example 53.

Preparation of 3-[5-(2,4-dimethyl-thiazol-5-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

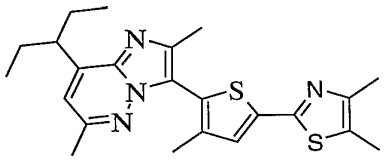


To a –78 °C mixture of 2,4-dimethylthiazole (0.23 g, 2.04 mmol) and THF (3 mL) is added 1.6 M *t*-Bu-Li in hexane (1.30 mL, 2.09 mmol). The mixture is stirred at –78°C for 15 minutes. 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-

2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65 °C overnight, diluted with EtOAc (20 mL), washed with 10% citric acid (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by silica gel chromatography (0%-15% EtOAc/hexane gradient) furnish the title compound (0.21 g, 0.49 mmol, 49%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.14 (s, 3H), 2.49 (s, 3H), 2.52 (s, 3H), 2.57 (s, 3H), 2.66 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.00 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}N_4S_2$ $(M+H)^+$: 425.3; found: 425.2.

Example 54.

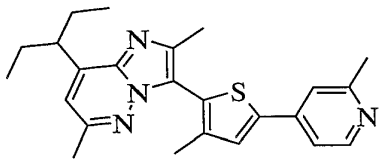
Preparation of 3-[5-(4,5-dimethyl-thiazol-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, from 4,5-dimethylthiazole (0.22 mL, 2.04 mmol), 1.56 M *n*-Bu-Li (1.34 mL, 2.09 mmol), $ZnCl_2$ (4.3 mL, 2.14 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.27 g, 0.64 mmol, 63%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.13 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.49 (s, 3H), 2.51(s, 3H), 3.29-3.38 (m, 1H), 6.67 (s, 1H), 7.32 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}N_4S_2$ $(M+H)^+$: 425.3; found: 425.2.

Example 55.

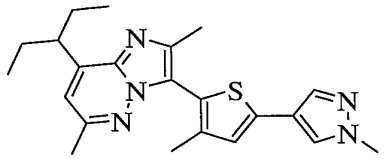
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-pyridin-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31, from 4-bromo-2-methyl pyridine (Fukaya et. el. *Chem. Pharm. Bull.*, 1990, 38, 2446) (0.21 g, 1.22 mmol), 1.56 M *n*-Bu-Li (0.69 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.2 mL, 1.12 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.058 g, 0.14 mmol, 14%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.16 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 2.58 (s, 3H), 3.27-3.37 (m, 1H), 6.68 (s, 1H), 7.29 (d, J = 5.3 Hz, 1H), 7.35 (s, 1H), 7.41 (s, 1H), 8.46 (t, J = 5.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.2.

Example 56.

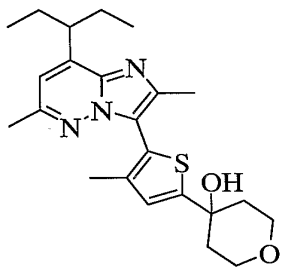
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-pyrazol-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 31, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.42 M *n*-Bu-Li (0.75 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 4-bromo-1-methyl-*1H*-pyrazole (0.25 g, 1.53 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnishes the title compound (0.092g, 0.23 mmol, 23%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 6H), 1.73-1.92 (m, 4H), 2.12 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.29-3.38 (m, 1H), 3.92 (s, 3H), 6.66 (s, 1H), 6.98 (s, 1H), 7.54 (s, 1H), 7.68 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 57.

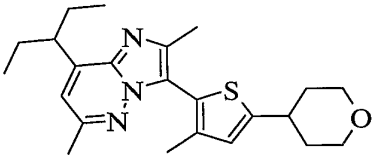
Preparation of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-tetrahydro-pyran-4-ol.



To a -78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.53 mmol) and THF (10 mL) is added 1.56 M *n*-Bu-Li (1.03 mL, 1.61 mmol). After 30 minutes tetrahydro-pyran-4-one (0.21 mL, 2.29 mmol) is added over 5 minutes. The solution is stirred at –78°C for 2 hours, warmed to ambient temperature, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-100% EtOAc/hexane gradient) furnish the title compound (0.38 g, 0.92 mmol, 60%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 1.91-2.00 (m, 2H), 2.11 (s, 3H), 2.20-2.30 (m, 2H), 2.46 (s, 3H), 2.51 (s, 3H), 3.30-3.39 (m, 1H), 3.83-3.98 (m, 5H), 6.66 (s, 1H), 6.93 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{31}N_3O_2S$ $(M+H)^+$: 414.3; found: 414.2.

Example 58.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(tetrahydro-pyran-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Method A.

To a solution of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-tetrahydro-pyran-4-ol (0.25 g, 0.604 mmol) and CH_2Cl_2

(10 mL) is added TFA (0.79 mL, 10.28 mmol) and Et_3SiH (0.25 mL, 1.57 mmol). The solution is concentrated, dissolved in EtOAc (30 mL), washed with sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-15% EtOAc/hexane gradient), is dissolved in EtOH (25 mL), 10 % Pd/C (0.07 g, 0.066 mmol) is added and the solution stirred under an atmosphere of H_2. After 2 hours the solution is filtered thru celite® and concentrated. The residue is purified by ISCO column chromatography (30% EtOAc in hexane) furnish the title compound (0.033 g, 0.083 mmol, 14%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.95 (m, 4H), 1.97-2.04 (m, 2H), 2.09 (s, 3H), 2.20-2.30 (m, 2H), 2.46 (s, 3H), 2.52 (s, 3H), 3.00-3.11 (m, 1H), 3.30-3.40 (m, 1H), 3.54 (dt, J = 11.8, 2.2 Hz, 2H), 4.08 (dd, J = 11.8, 2.2 Hz, 2H), 6.65 (s, 1H), 6.75 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{31}N_3OS$ $(M+H)^+$: 398.7; found: 398.2.

Method B.

A. 4-(5-Bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran-4-ol.

To a -78°C solution of 2-bromo-3-methyl-thiophene (2.0 g, 17.75 mmol) and THF (30 mL) is added 2.0 M LDA (9.32 mL, 18.63 mmol). After 30 minutes at –78°C tetrahydro-pyran-4-one (2.3 mL, 23.07 mmol) is added and the solution is warmed to ambient temperature. The solution is washed with sat. NH_4Cl (30 mL). The aqueous phases is extracted with EtOAc. The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (30%-100% EtOAc/hexane gradient) furnish the title compound (2.3 g, 8.30 mmol, 47%). ^1H NMR ($CDCl_3$), δ 1.82 (m, 2H), 2.00 (s, 3H), 2.06-2.15 (m, 3H), 2.16 (s, 3H), 3.77-3.84 (m, 2H), 3.87 dt, J = 11.3, 2.2 Hz, 2H), 6.67 (s, 1H). LC/MS (m/z): calcd. for $C_{10}H_{13}BrO_2S$ $(M+H)^+$: 277.0; found: 260.9.

B. 4-(5-Bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran.

To a solution of 4-(5-bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran-4-ol (2.3 g, 8.30 mmol) and 1,2-dichloroethane (50 mL) is added ZnI_2 (3.97 g, 12.45 mmol) and sodium cyanoborohydride (3.91, 62.23 mmol). The solution is stirred for 1 hour, filtered

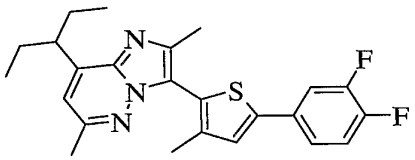
thru celite and concentrated. The residue is purified by ISCO column chromatography (5%-10% EtOAc/hexane gradient) furnish the title compound (1.53 g, 5.86 mmol, 71%). ^{1}H NMR ($CDCl_3$), δ 1.69-1.82 (m, 2H), 1.84-1.92 (m, 2H), 2.14 (s, 3H), 2.84-2.98 (m, 1H), 3.49 (dt, J = 11.8, 2.2 Hz, 2H), 4.00-4.07 (m, 2H), 6.51 (s, 1H).

C. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(tetrahydro-pyran-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 25, 4-(5-bromo-4-methyl-thiophen-2-yl)-tetrahydropyran (0.83 g, 3.19 mmol), 1.56 M *n*-Bu-Li (2.04 mL, 3.19 mmol), $ZnCl_2$ (6.4 mL, 3.19 mmol), 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.56 mmol) and $Pd(PPh_3)_4$ (0.092 g, 0.008 mmol) furnish the title compound (0.072 g, 0.18 mmol, 11%). Spectrum identical to that from Method A.

Example 59.

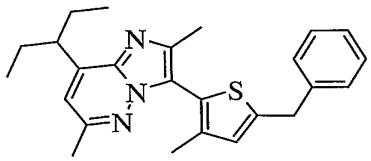
Preparation of 3-[5-(3,4-difluoro-phenyl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) and 0.5 M solution of 3,4-difluorophenylzinc bromide in THF (5.1 mL, 2.55 mmol) are reacted. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 30-80% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.18 g, 0.42 mmol, 33%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 3.31-3.40 (m, 1H), 6.69 (s, 1H), 7.13-7.21 (m, 1H), 7.18 (s, 1H), 7.31-7.36 (m, 1H), 7.39-7.46 (m, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}F_2N_3S$ $(M+H)^+$: 426.3; found: 426.2.

Example 60.

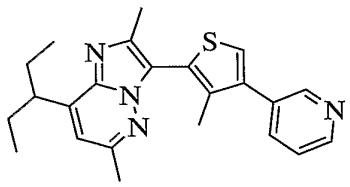
Preparation of 3-(5-benzyl-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of benzylzinc bromide in THF (4.6 mL, 2.29 mmol) are reacted. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 40-65% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.062 g, 0.15 mmol, 20%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3H), 2.45 (s, 3H), 2.51 (s, 3H), 3.29-3.39 (m, 1H), 4.16 (s, 2H), 6.65 (s, 1H), 6.68(s, 1H), 7.22-7.29 (m, 1H), 7.31-7.36 (m, 4H). LC/MS (m/z): calcd. for $C_{25}H_{29}N_3S$ $(M+H)^+$: 404.3; found: 404.2.

Example 61.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-pyridin-3-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

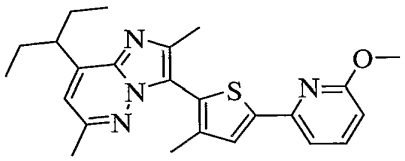


A solution of 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.64 mmol), pyridine-3-boronic acid (0.086 g, 0.70 mmol), 2 M Na_2CO_3 (0.48 mL, 0.96 mmol) and, *n*-PrOH (3 mL), is degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (2.7 mg, 0.0013 mmol) and PPh_3 (0.010 g, 0.038 mmol) are added and the solution is heated at 90 °C overnight. The solution is diluted with EtOAc (30 mL), washed with 10% Na_2CO_3 (30 mL), water (30 mL), brine (30 mL),

dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO (20-40% EtOAc gradient) furnish the title compound (0.051 g, 0.13 mmol, 20%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.09 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.29-3.40 (m, 1H), 6.69 (s, 1H), 7.33-7.43 (m, 1H), 7.47 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 8.61 (bs, 1H), 8.78 (bs, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.2; found: 391.4.

Example 62.

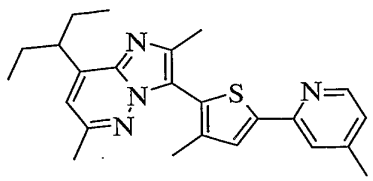
Preparation of 8-(1-ethyl-propyl)-3-[5-(6-methoxy-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 6-methoxy-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.12 g, 0.29 mmol, 38%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 3.98 (s, 3H), 6.61 (d, J = 7.5 Hz, 1H), 6.70(s, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.52 (s, 1H), 7.56 (d, J = 7.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.3; found: 421.3.

Example 63.

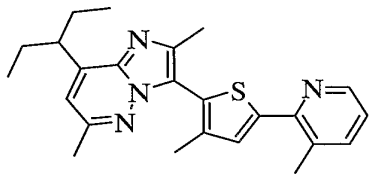
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(4-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 4-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.21 g, 0.52 mmol, 68%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.40 (s, 3H), 2.52 (s, 6H), 3.30-3.40 (m, 1H), 6.67 (s, 1H), 6.97(d, J = 4.8 Hz, 1H), 7.49 (s, 1H), 7.52 (s, 1H), 8.42 (d, J = 4.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 64.

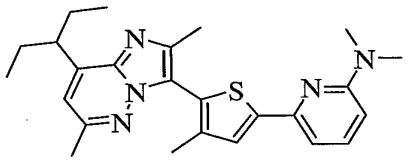
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(3-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine) (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 3-methyl-2-pyridylzinc bromide in THF (5.0 mL, 2.50 mmol) furnish the title compound (0.22 g, 0.54 mmol, 71%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 2.63 (s, 3H), 3.29-3.39 (m, 1H), 6.67 (s, 1H), 7.06-7.14 (m, 1H), 7.44 (s, 1H), 7.74 (dd, J = 7.5, 0.9 Hz, 1H), 8.47 (dd, J = 4.9, 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 65.

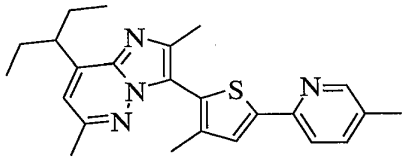
Preparation of (6-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-dimethyl-amine.



Using a procedure similar to Example 39, from Rieke® Zn in THF (0.20 g, 3.06 mmol), (6-bromo-pyridin-2-yl)-dimethyl-amine (Newkomw et. el. *J. Org. Chem.*, 1988, 3, 786) (0.41 mL, 2.04 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.35 g, 0.89 mmol), and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.16 g, 0.37 mmol, 36%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, *J* = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.15 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.21 (s, 6H), 3.30-3.40 (m, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 6.66 (s, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 7.45 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.46 (s, 1H). LC/MS (m/z): calcd. for $C_{25}H_{31}N_5S$ $(M+H)^+$: 434.3; found: 434.3.

Example 66.

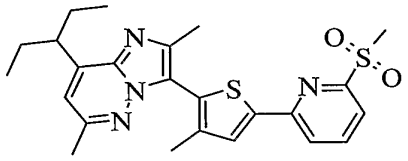
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 4-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.23 g, 0.57 mmol, 74%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, *J* = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.16 (s, 3H), 2.35 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.31-3.41 (m, 1H), 6.67 (s, 1H), 7.48(s, 1H), 7.50 (d, *J* = 2.2 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 8.39-8.40 (m, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 67.

Preparation of 8-(1-ethyl-propyl)-3-[5-(6-methanesulfonyl-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 2-Bromo-6-methanesulfonyl-pyridine.

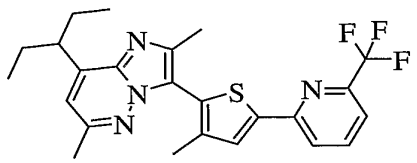
To a solution of 2-bromo-6-methylsulfanyl-pyridine (Testaferri et. el *Tetrahedron*, 1985, 41, 1373) (2.15 g, 10.53 mmol) and CH_2Cl_2 (30 mL) is added 56-87% mCPBA (12 g, 42.15 mmol). The solution is cooled with ice to ambient temperature and the solution is stirred for 2 hour, washed with sat. $Na_2S_2O_3$ (15 mL), sat. $NaHCO_3$ (2 X 15 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by recrystalization from EtOAc /hexane furnish the title compound (1.71 g, 7.24 mmol, 69%). ^1H NMR ($CDCl_3$), δ 3.26 (s, 3H), 7.73 (dd, J = 8.0, 0.9 Hz, 1H), 7.82 (dd, J = 8.0, 7.5 Hz, 1H), 8.05 (dd, J = 7.5, 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_6H_6BrNO_2S$ $(M+H)^+$: 235.9; found: 235.9.

B. 8-(1-ethyl-propyl)-3-[5-(6-methanesulfonyl-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 25, 2-bromo-6-methanesulfonyl-pyridine (0.29 mL, 1.22 mmol), 1.3 M *n*-Bu-Li (0.82 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.13 g, 0.28 mmol, 27%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30 (s, 3H), 3.30-3.38 (m, 1H), 6.70 (s, 1H), 7.64 (s, 1H), 7.83 (dd, J = 7.6, 0.8 Hz, 1H), 7.89 (dd, J = 7.9, 0.8 Hz, 1H), 7.93 (dd, J = 7.9, 7.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4O_2S_2$ $(M+H)^+$: 469.3; found: 469.2.

Example 68.

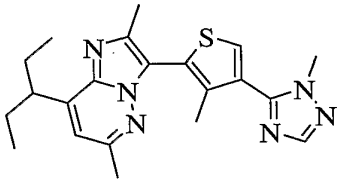
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-trifluoromethyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 2-chloro-6-trifluoromethyl-pyridine (0.29 mL, 1.22 mmol), 1.34 M *n*-Bu-Li (0.80 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.20 g, 0.44 mmol, 43%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.30-3.40 (m, 1H), 6.69 (s, 1H), 7.50 (dd, J = 7.5, 0.9 Hz, 1H), 7.65 (s, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.84 (dd, J = 7.9, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}F_3N_4S$ $(M+H)^+$: 459.3; found: 459.2.

Example 69.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-4-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

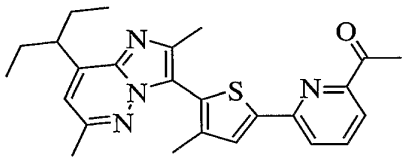


To a slurry of 0.05 g/ mL of Reike® Zn in THF (3.0 mL, 2.29 mmol) is added a solution of 5-bromo-1-methyl-*1H*-[1,2,4]triazole and THF (2 mL). The solution was heated at 65 °C for 1 hour, cooled to ambient temperature and the excess Zn allowed to settle for 1 hour. The solution was transferred to a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example Rupp-152) (0.32 g, 0.70 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat.

NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (50%-100% Et_2O) to furnish the title compound (0.058 g, 0.15 mmol, 19%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.11 (s, 3H), 2.47 (s, 3H), 2.49 (s, 3H), 3.27-3.37 (m, 1H), 3.97 (s, 3H), 6.68 (s, 1H), 7.64 (s, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6S$ $(M+H)^+$: 395.2; found: 395.4.

Example 70.

Preparation of 1-(6-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-ethanone.



A. 3-[5-(6-Bromo-pyridin-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 25, 2,6-dibromo-pyridine (0.91 g, 3.82 mmol), 1.34 M *n*-Bu-Li (1.50 mL, 2.00 mmol), $ZnCl_2$ (4.0 mL, 2.00 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.75 g, 1.92 mmol) and $PdCl_2$(dppf) (0.070 g, 0.096 mmol) furnish the title compound (0.26 g, 0.55 mmol, 29%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.74-1.93 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.31 (dd, J = 7.5, 1.3 Hz, 1H), 7.49-7.57 (m, 2H), 7.58 (s, 1H).

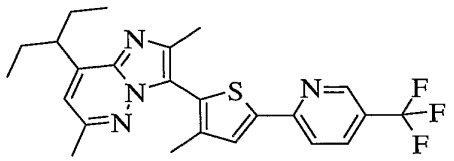
B. 1-(6-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-ethanone.

To a –78°C solution of 3-[5-(6-bromo-pyridin-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine) (0.26 g, 0.55 mmol), and THF (5 mL), is added 1.34 M *n*-Bu-Li (0.43 mL, 0.58 mmol). After 30 minutes *N*-methoxy-*N*-methyl-acetamide (0.065 mL, 0.61 mmol) is added and the solution warmed to ambient

temperature. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15-20% EtOAc/hexane gradient) furnish the title compound (0.030 g, 0.069 mmol, 13%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.19 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 2.77 (s, 3H), 3.30-3.40 (m, 1H), 6.69 (s, 1H), 7.59 (s, 1H), 7.77-7.85 (m, 2H), 7.87 (dd, J = 6.8, 2.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{25}H_{28}N_4OS$ $(M+H)^+$: 433.3; found: 433.2.

Example 71.

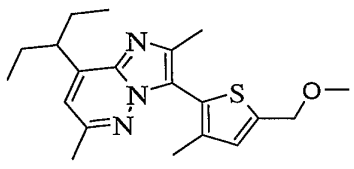
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-trifluoromethyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 2-bromo-5-trifluoromethyl-pyridine (2.14 mL, 1.07 mmol), 1.34 M *n*-Bu-Li (0.80 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.17 g, 0.37 mmol, 36%). ^1H NMR ($CDCl_3$), δ 0.90 (t, J = 7.3 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.19 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 6.70 (s, 1H), 7.63 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 8.4, 2.2 Hz, 1H), 7.79-7.82 (m, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}F_3N_4S$ $(M+H)^+$: 459.3; found: 459.2.

Example 72.

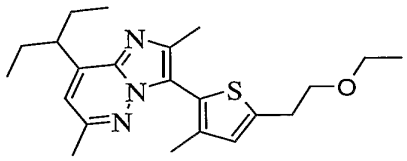
Preparation of 8-(1-ethyl-propyl)-3-(5-methoxymethyl-3-methyl-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and THF (3 mL) is added 1.34 M *n*-Bu-Li (0.50 mL, 0.80 mmol). After 30 minutes iodo-methoxy-methane (0.097 mL, 1.15 mmol) is added and the solution warmed to ambient temperature. After 1 hour the solution is diluted with EtOAc (40 mL) washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.12 g, 0.34 mmol, 44%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.09 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.28-3.37 (m, 1H), 3.44 (s, 3H), 4.61 (s, 2H), 6.65 (s, 1H), 6.93 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{27}N_3OS$ $(M+H)^+$: 358.3; found: 358.3.

Example 73.

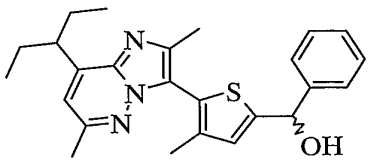
Preparation of 3-[5-(2-ethoxy-ethyl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 72, from of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 1.34 M *n*-Bu-Li (0.53 mL, 0.84 mmol), 1-bromo-2-ethoxy-ethane (0.13 mL, 1.15 mmol) and KI (0.013 g, 0.076 mmol) furnish the title compound (0.11 g, 0.29 mmol, 38%). ^{1}H NMR ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.23 (t, J = 7.0 Hz, 3H), 1.72-1.90 (m, 4H), 2.06 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.09 (t, J = 7.0 Hz, 2H), 3.28-3.37 (m, 1H), 3.55 (q, J = 7.0 Hz, 2H), 3.71 (t, J = 7.0 Hz, 2H), 6.64 (s, 1H), 6.77 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{31}N_3OS$ $(M+H)^+$: 386.3 found: 386.3.

Example 74.

Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-phenyl-methanol.



A. (5-Bromo-4-methyl-thiophen-2-yl)-phenyl-methanol.

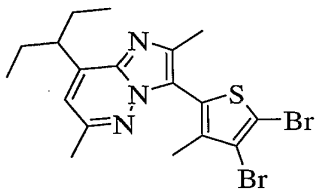
To a –78°C solution of 2-bromo-3-methyl-thiophene (4.7 g, 26.54 mmol) and Et_2O (100 mL) is added 2.0 M LDA (14.6 mL, 29.2 mmol). After 1 hour benzaldehyde (3.0 mL, 29.2 mmol) is added and the solution warmed to ambient temperature and stirred for 2 hour. The solution is washed with sat. NH_4Cl (75 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (3.29 g, 11.62 mmol, 44%). ^{1}H NMR ($CDCl_3$), δ 2.11 (s, 3H), 3.38-3.46 (m, 1H), 5.90 (s, 1H), 6.54 (s, 1H), 7.30-7.45 (m, 5H). LC/MS (m/z): calcd. for $C_{12}H_{11}BrOS$ $(M+H)^+$: 281.0, 283.0; found: 264.9, 266.9.

B. {5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-phenyl-methanol.

Using a procedure analogous to Example 30C, from 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.1.15 mmol), (5-bromo-4-methyl-thiophen-2-yl)-phenyl-methanol (0.33 g, 1.15 mmol), 2 M Na_2CO_3 (0.86 mL, 1.72 mmol) *n*-PrOH (1 mL), $Pd(OAc)_2$ (0.0052 g, 0.023 mmol), and PPh_3 (0.018 , 0.069 mmol). The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 25-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.017 g, 0.041 mmol, 3.5%). ^{1}H NMR ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.04 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 2.75 (bs, 1H), 3.26-3.38 (m, 1H), 6.05 (s, 1H), 6.65 (s, 1H), 6.76 (s, 1H), 7.30-7.45 (m, 3H), 7.50-7.56 (m, 1H). LC/MS (m/z): calcd. for $C_{25}H_{29}N_3OS$ $(M+H)^+$: 420.3; found: 420.3.

Example 75.

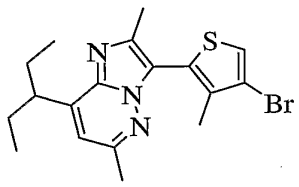
Preparation of 3-(4,5-dibromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (4.00 g, 10.20 mmol) and AcOH (40 mL) is added Br_2 (0.57 mL, 11.21 mmol) and the solution heated at 110 °C overnight. Br_2 (0.57 mL, 11.21 mmol) is added and the solution heated at 110 °C for 2 hours. The solution is poured into 5 M NaOH (200 mL) and ice (200 mL). The slurry is extracted with EtOAc (2 x 150 mL). The combined organic layers are washed with water (200 mL), 20% $NaHSO_3$ (200 mL), sat. $NaHCO_3$ (200 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (5%-15% EtOAc gradient) furnish the title compound (2.66 g, 5.64 mmol, 55%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.12 (s, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 3.25-3.35 (m, 1H), 6.69 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{21}Br_2N_3S$ $(M+H)^+$: 470.0; found: 470.3.

Example 76.

Preparation of 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

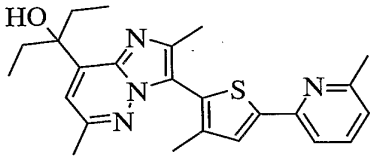


To a –78 °C solution of 3-(4,5-dibromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 g, 0.47 mmol) and THF (3 mL) is added 1.6 M *n*-BuLi (0.31 mL, 0.49 mmol). After 20 minutes the solution is quenched with water (1 mL), warmed to ambient temperature, diluted with EtOAc (30 mL), washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified

by ISCO (5%-10% EtOAc gradient) furnish the title compound (0.056 g, 0.14 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.09 (s, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 3.27-3.36 (m, 1H), 6.68 (s, 1H), 7.44 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.2; found: 392.3.

Example 77.

Preparation of 3-{2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-pentan-3-ol.



A. 2-(5-Bromo-4-methyl-thiophen-2-yl)-6-methyl-pyridine.

To a –78°C solution of 2-bromo-3-methyl-thiophene (2.0 mL, 17.75 mmol) and THF (30 mL) is added 2.0 M LDA (9.76 mL, 19.52 mmol). After 45 minutes 0.5 M $ZnCl_2$ (39.0 mL, 19.50 mmol) is added and the solution stirred for 30 minutes. 2-Bromo-6-methyl-pyridine (2.4 mL, 21.29 mmol) and $Pd(PPh_3)_4$ (0.50 g, 0.44 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hour. The solution is washed with sat. NH_4Cl (20 mL). The aqueous layer is extracted with CH_2Cl_2 (30 mL). The combined organic layers are washed with sat. NH_4Cl (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-20% EtOAc/hexane gradient) furnish the title compound (2.34 g, 8.73 mmol, 49%). ^{1}H NMR ($CDCl_3$), δ 2.21 (s, 3H), 2.54 (s, 3H), 6.99 (d, J = 7.9 Hz, 1H), 7.23 (s, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.53 (dd, J = 7.9, 7.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{11}H_{10}BrNS$ $(M+H)^+$: 267.0, 269.0; found:267.7, 269.5.

B. 2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine (below) (0.50 g, 3.39 mmol), 2-(5-bromo-4-methyl-thiophen-2-yl)-6-methyl-pyridine (1.00 g, 3.73 mmol), Cs_2CO_3 (2.32 g, 7.13 mmol) and DMF (5 mL) is de-gassed for 15 minutes with N_2. $Pd_2(dba)_3$ (0.15 g, 0.16 mmol) and PPh_3 (0.17 g, 0.65 mmol) is added and the solution is heated at 130°C overnight. The solution is diluted with CH_2Cl_2 (30 mL) washed with water (2 x 25 mL), brine (25 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (100% EtOAc), followed by recrystalization from acetonitrile / water furnish the title compound (0.45 g, 1.35 mmol, 39%). ^{1}H NMR ($CDCl_3$), δ 2.13 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 2.57 (s, 3H), 6.90 (d, J = 9.2 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, J = 8.0, 7.5 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{19}H_{18}N_4S$ $(M+H)^+$: 335.1; found: 335.1.

C. 1-{2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-propan-1-one.

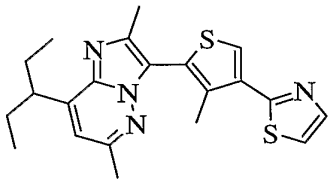
To a –78°C solution of 2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.34 g, 1.02 mmol) and THF (9 mL) is added 2.0 M LDA (0.61 mL, 1.22 mmol). After 3 minutes, *N*-methoxy-*N*-methyl-propionamide (Wolberg et. el. *Chem. Eur. J.*, 2001, 7, 4562) (1.17 g, 1.42 mmol) is added and the solution stirred for 20 minutes, warmed to ambient temperature and stirred for 30 minutes. The solution is diluted with EtOAc (50 mL) washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.10 g, 0.26 mmol, 25%). ^{1}H NMR ($CDCl_3$), δ 1.28 (t, J = 7.0 Hz, 3H), 2.13 (s, 3H), 2.54 (s, 3H), 2.58 (s, 6H), 3.59 (q, J = 7.0 Hz, 2H), 7.03 (d, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.55 (bs, 1H), 7.58 (dd, J = 7.9, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{22}N_4OS$ $(M+H)^+$: 391.2; found: 391.2.

D. 3-{2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-pentan-3-ol.

To a –0°C solution of 1-{2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-propan-1-one (0.040 g, 0.10 mmol) and Et_2O (5 mL) is added 3.0 M ethyl magnesium bromide (0.68 mL, 2.05 mmol). The solution is warmed to ambient temperature, diluted with EtOAc (30 mL) washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.016 g, 0.038 mmol, 37%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.92-2.01 (m, 4H), 2.14 (s, 3H), 2.46 (s, 3H), 2.53 (s, 3H), 3.57 (s, 3H), 6.39 (s, 1H), 6.66 (s, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 7.57 (dd, J = 7.9, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.3; found: 421.3.

Example 78.

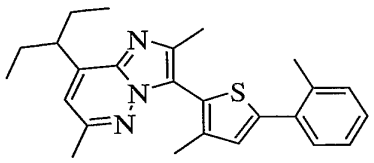
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-thiazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 g, 0.64 mmol) and $PdCl_2$(dppf) (0.023 g, 0.032 mmol) is added a 0.5 M solution of 2-thiazolylzinc bromide (3.82 mL, 1.91 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-20% EtOAc gradient) furnish the title compound (0.19 g, 0.48 mmol, 76%). ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.36 (s, 3H), 2.47 (s, 3H), 2.50 (, 3H), 3.29-3.39 (m, 1H), 6.69 (s, 1H), 7.33 (d, J = 3.3 Hz, 1H), 7.89 (d, J = 3.3 Hz, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.2; found: 397.3.

Example 79.

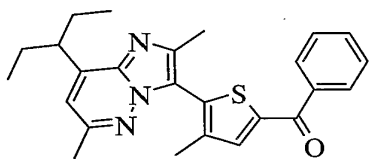
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-o-tolyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 g, 0.38 mmol) and $PdCl_2$(dppf) (0.014 g, 0.019 mmol) and 0.5M solution of 2-methylphenylzinc iodide in THF (3 mL, 1.53 mmol) furnish the title compound (0.069 g, 0.17 mmol, 46%). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.19 (s, 3H), 2.53 (s, 3H), 2.54 (s, 3H), 2.55 (s, 3H), 3.32-3.40 (m, 1H), 6.68 (s, 1H), 7.02 (s, 1H), 7.22-7.30 (m, 3H), 7.48-7.53 (m, 1H). LC/MS (m/z): calcd. for $C_{25}H_{29}N_3S$ $(M+H)^+$: 404.3; found: 404.3.

Example 80.

Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-phenyl-methanone.

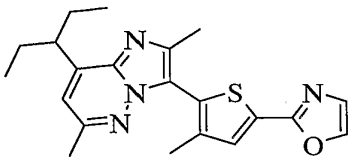


To a -78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and THF (5 mL) is added 1.30 M *n*-Bu-Li (0.50 mL, 0.80 mmol). After 30 minutes *N*-methoxy-*N*-methyl-benzamide (0.13 mL, 0.84 mmol) is added, the solution is warmed to ambient temperature, and stirred overnight. The solution is diluted with EtOAc (20 mL), washed with sat. NH_4Cl (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.066 g, 0.16 mmol, 21%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, *J* = 7.4 Hz, 6H), 1.74-1.93 (m, 4H), 2.18 (s, 3H), 2.52 (s, 3H), 2.54 (s,

3H), 3.29-3.38 (m, 1H), 6.71 (s, 1H), 7.49-7.54 (m, 2H), 7.56 (s, 1H), 7.57-7.62 (m, 1H), 7.89-7.94 (m, 2H). LC/MS (m/z): calcd. for $C_{25}H_{27}N_3OS$ $(M+H)^+$: 418.2; found: 418.2.

Example 81.

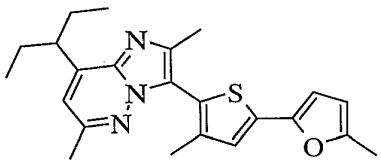
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-oxazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of oxazole (0.14 g, 2.04 mmol) and THF (3 mL) is added 1.6 M *t*-Bu-Li in hexane (1.32 mL, 2.14 mmol). The mixture is stirred at –78°C for 15 minutes. 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65 °C overnight, diluted with EtOAc (30 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 20-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) to furnish the title compound (0.020 g, 0.053 mmol, 5%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.69 (s, 1H), 7.19 (s, 1H), 7.59 (s, 1H), 7.65 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4OS$ $(M+H)^+$: 381.3; found: 381.1.

Example 82.

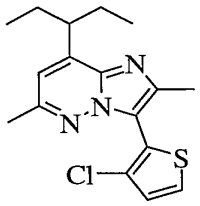
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-methyl-furan-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



To a 0°C mixture of 2-methylfuran (0.18 mL, 2.04 mmol) and Et_2O (2 mL) is added 1.6 M *t*-Bu-Li in hexane (1.30 mL, 2.14 mmol). The mixture is heated at a reflux for 30 minutes, cooled to 0°C, and 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65°C overnight, diluted with EtOAc (30 mL), washed with 10% citric acid (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20% EtOAc/hexane gradient) furnish the title compound (0.20 g, 0.51 mmol, 50%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.12 (s, 3H), 2.35 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.62 (dd, J = 3.1, 0.9 Hz, 1H), 6.40 (d, J = 3.1 Hz, 1H), 6.66 (s, 1H), 7.12 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{27}N_3OS$ $(M+H)^+$: 394.3; found: 394.2.

Example 83.

Preparation of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

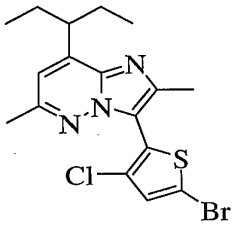


To a flask of 2-bromo-3-chloro-thiophene (Lemaire et. el., *Synth. Commun.*, 1994, 24, 95) (2.53 g, 12.82 mmol) is added 0.05 g/mL Reike® zinc in THF (25 mL, 19.24 mmol). The solution is heated at a reflux for 2 hours. The excess zinc is allowed to settle and the solution transferred to a flask containing 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example KW1-A03735-193) (2.01 g, 6.41 mmol) and $PdCl_2$(dppf) (0.23 g, 0.32 mmol). The solution is heated at a reflux overnight, quenched with sat. NH_4Cl (25 mL) and extracted with EtOAc (2 X 25 mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (2%-15% EtOAc/hexane gradient) furnish the title compound (1.32 g, 6.68 mmol, 62%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m,

4H), 2.48 (s, 3H), 2.49 (s, 3H), 3.37-3.36 (m, 1H), 6.67 (s, 1H), 7.07 (d, J = 5.4 Hz, 1H), 7.48 (d, J = 5.4 Hz, 1H). LC/MS (m/z): calcd. for $C_{17}H_{20}ClN_3S$ $(M+H)^+$: 334.1; found: 334.1.

Example 84.

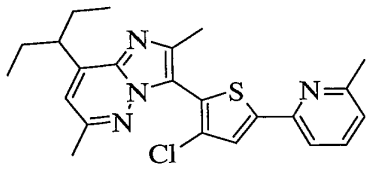
Preparation of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine. (1.15 g, 3.44 mmol) and CH_2Cl_2 (12 mL) is added NBS (0.64 g, 3.62 mmol). The solution is stirred at ambient temperature overnight, washed with water (2 x 75 mL), brine (75 mL), dried over Na_2SO_4, filtered and concentrated to furnish the title compound (1.36 g, 3.29 mmol, 96%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.49 (s, 3H), 2.53 (s, 3H), 3.26-3.36 (m, 1H), 6.70 (s, 1H), 7.07 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{19}BrClN_3S$ $(M+H)^+$: 412.1; found: 412.0.

Example 85.

Preparation of 3-[3-chloro-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Method A.

To a flask of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.73 mmol) and $PdCl_2$(dppf) (0.027 g, 0.036 mmol) is added 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (2.9 mL, 1.45

mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (50 mL), washed with sat. NH_4CL (40 mL), water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.072 g, 0.17 mmol, 23%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.58 (s, 3H), 3.30-3.39 (m, 1H), 6.70 (s, 1H), 7.06 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.60 (dd, J = 7.7, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{25}ClN_4S$ $(M+H)^+$: 425.2; found: 425.2.

Method B.

A. 2-(4-Chloro-thiophen-2-yl)-6-methyl-pyridine.

To a solution of 2-bromo-4-chloro-thiophene (Gronowitz, Rosén *Chemica Scripta*, 1971, 1, 33) (1.50 g, 7.60 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (23.00 mL, 11.39 mmol) is added $Pd(PPh_3)_4$ (0.18 g, 0.15 mmol). The solution is heated at 40°C overnight, diluted with Et_2O (50 mL), washed with sat. NH_4Cl (40 mL), dried over $MgSO_4$, filtered on concentrated. The residue is purified by ISCO column chromatography (5%-20% EtOAc/hexane gradient) furnish the title compound (0.45 g, 2.15 mmol, 28%). ^1H NMR ($CDCl_3$), δ 2.56 (s, 3H), 7.02 (d, 7.7 Hz, 1H), 7.13 (d, J = 0.9 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 0.9 Hz, 1H), 7.54 (dd, J = 7.9, 7.7, 1H).

B. 2-(5-bromo-4-chloro-thiophen-2-yl)-6-methyl-pyridine.

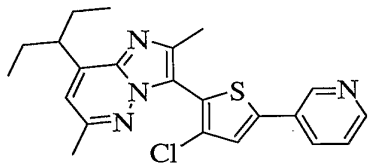
To a 0°C solution of 2-(4-chloro-thiophen-2-yl)-6-methyl-pyridine (example Rupp-96) (0.45 g, 1.45 mmol) and CH_2Cl_2 (10 mL) is added Br_2 (0.15 mL, 2.91 mmol). The solution is warmed to ambient temperature and stirred for 1 hour. The solution is washed with sat. $NaHCO_3$ (10 mL), sat. $Na_2S_2O_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.59 g, 2.04, 95%). ^1H NMR ($CDCl_3$), δ 2.55 (s, 3H), 7.05 (d, 7.9 Hz, 1H), 7.29 (s, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.58 (dd, J = 7.9, 7.9, 1H). LC/MS (m/z): calcd. for $C_{10}H_7BrClNS$ $(M+H)^+$: 288.0; found: 287.9.

C. 3-[3-Chloro-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.39 g, 1.78 mmol), 2-(5-bromo-4-chloro-thiophen-2-yl)-6-methyl-pyridine (0.59 g, 2.04 mmol), Cs_2CO_3 (1.23 g, 3.77 mmol), and DMF (5 mL), is de-gassed with N_2 for 15 minutes. PPh_3 (0.089 g, 0.34 mmol) and $Pd_2(dba)_3$ (0.079 g, 0.86 mmol) is added and the solution heated at 110°C for 48 hours. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) and is chromatographed (19 x 300 C18 Symmetry column, 20-45% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.078 g, 0.18 mmol, 10%). Spectrum identical to Method A.

Example 86.

Preparation of 3-(3-chloro-5-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Method A.

A solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), pyridine-3-boronic acid (0.082 g, 0.67 mmol), 2 M Na_2CO_3 (0.45 mL, 0.91 mmol) and, *n*-PrOH (1 mL), is degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (0.0027 g, 0.0012 mmol) and PPh_3 (0.0095 g, 0.036 mmol) are added and the solution is heated at 88°C overnight. The solution is diluted with EtOAc (15 mL), washed with water (10 mL), sat. $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated. Purified by ISCO column chromatography (15-40% EtOAc/hexane gradient) furnish the title compound (0.095 g, 0.23 mmol, 38%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.71 (s, 1H), 7.32-7.37 (m, 2H), 7.85-7.90 (m, 1H), 8.57 (d, J = 4.0 Hz, 1H), 8.89 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 411.2; found: 411.2.

Method B.

A. 3-(4-Chloro-thiophen-2-yl)-pyridine.

A solution of 2-bromo-4-chloro-thiophene (Gronowitz, Rosén *Chemica Scripta*, 1971, 1, 33) (1.45 g, 7.34 mmol), pyridine-3-boronic acid (0.95 g, 7.71 mmol), 2 M Na_2CO_3 (5.50 mL, 11.01 mmol) and, *n*-PrOH (3 mL), is degassed with N_2 for 10 minutes. $Pd(OAc)_2$ (0.033 g, 0.15 mmol) and PPh_3 (0.12 g, 0.44 mmol) are added and the solution is heated at 85°C for 48 hours, diluted with CH_2Cl_2 (50 mL), washed with 10 % Na_2CO_3 (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.74 g, 3.78 mmol, 51%). ^{1}H NMR ($CDCl_3$), δ 7.12-7.13 (m, 1H), 7.20 (d, J = 1.4 Hz, 1H), 7.31 (dd, J = 8.0, 4.9 Hz, 1H), 7.78-7.82 (m, 1H), 8.55 (d, J = 4.9 Hz, 1H), 8.82 (d, J = 2.2 Hz, 1H).

B. 3-(5-Bromo-4-chloro-thiophen-2-yl)-pyridine.

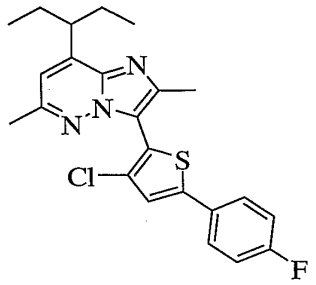
Using a procedure similar to Example 85 Method B. step B, 3-(4-chloro-thiophen-2-yl)-pyridine (0.74 g, 3.78 mmol), and Br_2 (0.39 mL, 7.56 mmol) furnish the title compound (0.99 g, 3.61 mmol, 95%). ^{1}H NMR ($CDCl_3$), δ 7.13 (s, 1H), 7.34 (dd, J = 8.1, 4.4 Hz, 1H), 7.74-7.78 (m, 1H), 8.58 (d, J = 4.4 Hz, 1H), 8.78 (s, 1H).

C. 3-(3-Chloro-5-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 85 Method B Step C, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 2.30 mmol), 3-(5-bromo-4-chloro-thiophen-2-yl)-pyridine) (0.76 g, 2.76 mmol), Cs_2CO_3 (1.57 g, 4.83 mmol), PPh_3 (0.11 g, 0.44 mmol) and $Pd_2(dba)_3$ (0.10 g, 0.11 mmol). The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.35 g, 0.85 mmol, 37%). Spectrum identical to Method A.

Example 87.

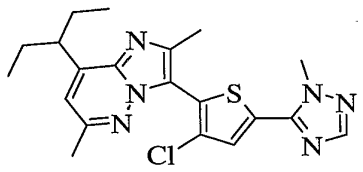
Preparation of 3-[3-chloro-5-(4-fluoro-phenyl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), 4-flourophenylboronic acid (0.093 g, 0.67 mmol), 2 M Na_2CO_3 (0.45 mL, 0.91 mmol), *n*-PrOH (2 mL), $Pd(OAc)_2$ (0.0068 g, 0.030 mmol) and PPh_3 (0.016 g, 0.061 mmol) furnish the title compound (0.041 g, 0.096 mmol, 16%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.70 (s, 1H), 7.07-7.13 (m, 2H), 7.22 (s, 1H), 7.54-7.60 (m, 2H). LC/MS (m/z): calcd. for $C_{23}H_{23}ClFN_3S$ $(M+H)^+$: 428.2; found: 428.1.

Example 88.

Preparation of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Method A.

To a –78 °C solution of 1-methyl-1,2,4-triazole (0.18 mL, 2.33 mmol) and THF (3 mL) is added a 1.56 M solution of *n*-Bu-Li in hexanes (1.49 mL, 2.33 mmol). The solution is stirred at –78°C for 30 minutes, 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g,

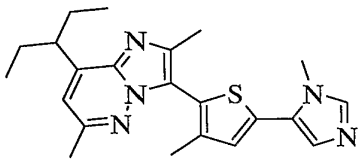
0.78 mmol) and $PdCl_2$(dppf) (0.028 g, 0.039 mmol) is added and the solution heated at 60 °C for 2 days, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (30 mL), water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-10% EtOAc/hexane gradient) furnish the title compound (0.19 g, 0.46 mmol, 59%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.37 (m, 1H), 4.16 (s, 3H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{23}ClN_6S$ $(M+H)^+$: 415.2; found: 415.1.

Method B.

A 5-L reaction flask equipped with a cooling bath, air stirrer, gas dispersion tube and thermometer probe is charged with 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-1H-[1,2,4]triazole (162.0 g, 0.745 moles), 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (250.1 g, 0.898 moles), NMP (800 mL), KOAc (366.0 g), TBABr (50.5 g), and additional NMP (700 mL) to form a mixture. While stirring, N_2 is bubbled through the mixture for 1 hour. A mixture of $Pd(OAc)_2$ (8.37 g) and TDBPP (24.56 g) are added in one portion, then heated to 120 °C for 3 hours. The reaction is cooled to 50 °C and transferred to a 12 L flask. The mixture is cooled to 20-25 °C, then added de-ionized H_2O (3.5 L) is added dropwise to precipitate out a sticky solid that gradually solidifies with stirring overnight. The solids are filtered, washed with de-ionized H_2O (2 x 2L), and fried on the filter plate for 30-60 minutes. The crude solids (595 g) are warmed in EtOAc (6.0 L) to 30 °C, then filtered through GFF paper to remove insolubles. The filtrate is dried over Na_2SO_4, treated with Darco (30.0 g), heated to 35 °C, filtered, and concentrated to give brown solids (432 g). The crude solids are eluted through a silica plug (1.0 kg) with CH_2Cl_2 (4.0 L), followed by EtOAc (16.0 L). Similar fractions are combined and concentrated under vacuum to approximately 6.0 L, then treated with Darco overnight with stirring. After filtering off the Darco through GFF paper, the filtrate is concentrated to solids (336 g). The solids are crystallized from EtOAc: heptane (1:2) to afford the title compound as a pale yellow solid (187 g, 60.5%, >98% area-% by reverse phase: Zorbax SB-C8, 4.6 mm x 250 mm, 5 microns, UV = 218 nm, flow rate 1.0 mL/min., oven temp. 25°C, isocratic = 30% water (0.1% TFA) & 70% AcCN.

Example 89.

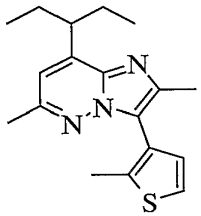
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(3-methyl-*3H*-imidazol-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.34M *n*-Bu-Li (0.80 mL, 1.07 mmol), 0.5M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 5-iodo-1-methyl-*1H*-imidazole (0.24 g, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.061g, 0.15 mmol, 15%). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.24-3.38 (m, 1H), 3.61 (s, 3H), 6.68 (s, 1H), 7.02 (s, 1H), 7.23 (s, 1H), 7.55 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 90.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.



A. 4,4,5,5-Tetramethyl-2-(2-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane.

A mixture of 3-bromo-2-methyl-thiophene (Saika et. el. *Chem. Soc. Chem. Communication*, 18, 1994, 2133; Steinkopf et. el.; *Justus Liebigs Ann. Chem.*, 513, 1934, 281; 3.1 g, 17.51 mmol), DMSO (50 mL), 4,4,5,5,4',4',5',5'-Octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (4.90g, 19.26 mmol), and KOAc (5.20 g, 52.58 mmol) is de-gassed with N_2 for 15 minutes. $PdCl_2$(dppf) (0.70 g, 0.88 mmol) is added and the solution stirred at ambient temperature overnight, then warmed to 85°C for 3 hours. The solution is diluted with water (200 mL), extracted with EtOAc (2 x 100 mL). The

combined organic layers washed with water (2 x 200 mL), brine (200 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (5%-20% EtOAc/hexane gradient) furnish the title compound (1.52 g, 6.78 mmol, 39%). ^1H NMR ($CDCl_3$), δ 1.34 (s, 12H), 2.72 (s, 3H), 7.04 (d, J = 5.0 Hz, 1H), 7.22 (d, 5.0 Hz, 1H).

B. 2-Methyl-thiophene-3-boronic acid.

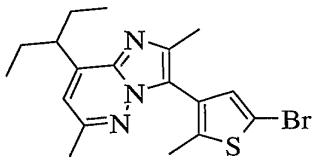
To a solution of 4,4,5,5-tetramethyl-2-(2-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane (1.52 g, 6.78 mmol), acetone (15 mL) and water (15 mL) is added $NaIO_4$ (2.90 g, 13.56 mmol). The solution is stirred at ambient temperature for 24 hours, then heated to a reflux for 24 hours. The solution is concentrated dissolved in EtOAc (1450 mL), washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.75g, 5.49 mmol, 78%). ^1H NMR ($CDCl_3$), δ 2.93 (s, 3H), 7.10 (d, J = 5.3 Hz, 1H), 7.51 (d, 5.3 Hz, 1H).

C. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(2-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.

(1.65 g, 4.80 mmol), 2-methyl-thiophene-3-boronic acid (0.75 g, 5.28 mmol), 2 M Na_2CO_3 (3.60 mL, 7.20 mmol) and *n*-PrOH (20 mL) is degassed with N_2 for 10 minutes. $Pd(OAc)_2$ (0.022 g, 0.096 mmol) PPh_3 (0.076 g, 0.29 mmol) is added and the solution heated at 60°C for 24 hours, then heated at 90°C for 24 hours. The solution is concentrated, diluted in EtOAc (50 mL) washed with 10% Na_2CO_3 (40 mL), water (40 mL), brine (40 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-15% EtOAc/hexane gradient) furnish the title compound (0.78 g, 2.49 mmol, 52%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.94 (m, 4H), 2.38 (s, 3H), 2.44 (s, 3H), 2.50 (s, 3H), 3.30-3.40 (m, 1H), 6.64 (s, 1H), 7.11 (d, J = 5.3 Hz, 1H), 7.20 (d, J = 5.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.2; found: 314.2.

Example 91.

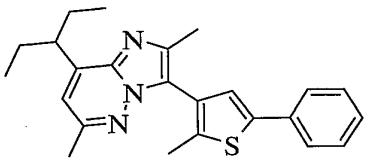
Preparation of 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine. (0.76 g, 2.42 mmol) and CH_2Cl_2 (10 mL) is added NBS (0.60 g, 3.37 mmol). The solution is stirred at ambient temperature for 2 hours and concentrated. The solution is dissolved in Et_2O (30 mL) washed with water (3 x 30 mL), brine (30 mL) dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.95 g, 2.42 mmol, >99%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.31 (s, 3H), 2.42 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.04 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.2; found: 392.1.

Example 92.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-phenyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.

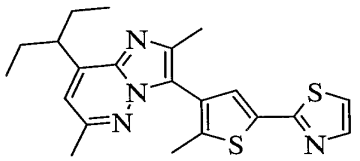


Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol) and $PdCl_2$(dppf) (0.019 g, 0.025 mmol) and 0.5 M solution of phenylzinc iodide in THF (2.0 mL, 1.02 mmol). The residue is purified by column chromatography (0-10% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 30-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.081 g, 0.21 mmol, 41%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.40 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.32-3.41 (m, 1H), 6.66 (s, 1H), 7.23-7.30 (m, 1H),

7.32 (s, 1H), 7.34-7.41 (m, 2H), 7.57-7.63 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{27}N_3S$ $(M+H)^+$: 390.2; found: 390.2.

Example 93.

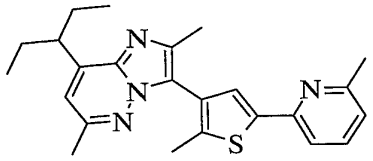
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-thiazol-2-yl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol), 0.5 M 2-thiazolylzinc bromide in THF (8.1 mL, 4.05 mmol) and $PdCl_2$(dppf) (0.019 g, 0.025 mmol) furnish the title compound (0.20 g, 0.50 mmol, >99%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.40 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.29-3.38 (m, 1H), 6.60 (s, 1H), 7.22 (d, J = 3.2 Hz, 1H), 7.52 (s, 1H), 7.75 (d, J = 3.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.1; found: 397.2.

Example 94.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[2-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-3-yl]-imidazo[*1,2-b*]pyridazine.

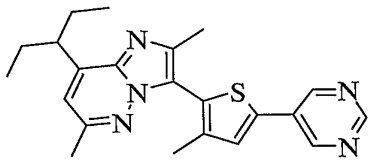


Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.24 g, 0.61 mmol) and $PdCl_2$(dppf) (0.022 g, 0.031 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (3.7 mL, 1.84 mmol) furnish the title compound (0.086 g, 0.21 mmol, 34%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.39 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 2.57 (s, 3H), 3.31-3.40 (m, 1H), 6.65 (s, 1H), 6.97 (d, J = 7.8 Hz,

1H), 7.41 (d, J = 7.8 Hz, 1H), 7.50-7.56 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4$ $(M+H)^+$: 405.2; found: 405.2.

Example 95.

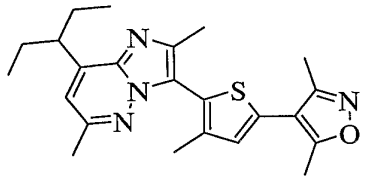
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrimidin-5-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 74B, from of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol), 5-pyrimidine boronic acid (0.076 g, 0.61 mmol), 2 M Na_2CO_3 (0.38 mL, 0.76 mmol), $Pd(OAc)_2$ (0.0023 g, 0.011 mmol), PPh_3 (0.0080 g, 0.0031 mmol), and *n*-PrOH (2 mL) is furnished the title compound (0.084 g, 0.21 mmol, 42%). ^1H NMR ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.17 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 3.26-3.36 (m, 1H), 6.69 (s, 1H), 7.74 (s, 1H), 8.95 (s, 2H), 9.10 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 96.

Preparation of 3-[5-(3,5-Dimethyl-isoxazol-4-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

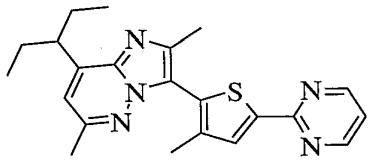


To a flask of 4-iodo-3,5-dimethyl-isoxazole (0.34 g, 1.53 mmol) is added a solution of Rieke® zinc 5g/100 mL in THF (3 mL, 2.29 mmol). The slurry is heated at a reflux for 4 hours, the zinc is allowed to settle and the solution transferred to a flask of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol). The solution is

heated at 50 °C overnight, diluted with EtOAc (20 mL), washed with 0.1 M HCl (15 mL), water (15 mL), brine (15 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.22 g, 0.54 mmol, 71%). ^1H NMR ($CDCl_3$), δ 0.92 (t, J = 7.5 Hz, 6H), 1.78-1.96 (m, 4H), 2.21 (s, 3H), 2.47 (s, 3H), 2.53 (s, 3H), 2.56 (s, 3H), 2.61 (s, 3H), 3.33-3.42 (m, 1H), 6.72 (s, 1H), 6.98 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}N_4OS$ $(M+H)^+$: 409.3; found: 409.2.

Example 97.

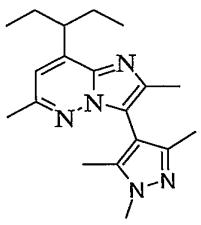
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrimidin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



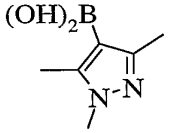
A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 2-tributylstannanyl-pyrimidine (0.34 g, 0.92 mmol) and THF (5 mL) is de-gassed with N_2 for 10 minutes Triphenylarsine (0.047 g, 0.15 mmol) and $Pd_2(dba)_3$ (0.035 g, 0.038 mmol) is added and the solution heated at 55°C for 48 hours and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient), dissolved in acetonitrile (20 mL), washed with hexane (3 x 20 mL) and concentrated to furnished the title compound (0.097 g, 0.25 mmol, 32%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.74-1.92 (m, 4H), 2.18 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.29-3.38 (m, 1H), 6.67 (s, 1H), 7.08 (t, J = 4.8, 1H), 7.93 (s, 1H), 8.69 (s, 2H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 98.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.



A. 1,3,5-Trimethylpyrazole-4-boronic acid.



To a dry flask is added 300 mg (1.59 mmol) of 4-bromo-1,3,5-trimethyl pyrazole to 4.0 ml THF. The mixture is cooled to -78^0C and 1eq of n-BuLi (1.6 M) is added via syringe. The mixture is stirred 1.5 hrs, and 0.19ml of trimethylborate (1.08 eq) is added. The reaction mixture is stirred 2 hrs, allowing bath to reach -10^0C, then 1.5 ml of 5N HCl is added and stirred 30 minutes longer. The aqueous layer is extracted 3 times with ethyl acetate. The combined organics are dried over MgSO4, filtered, and evaporated to an oil. The oil is dissolved in methanol/methylene chloride and re-evaporated. The residue is triturated with acetone/ethyl acetate then filtered to obtain title compound as a white solid 92.1 mg (37.6%). ^{1}H-NMR (DMSO-d_6): δ5.92 (s); 3.72 (s, 3H); 2.34 (s, 3H); 2.26 (s, 3H) ppm.

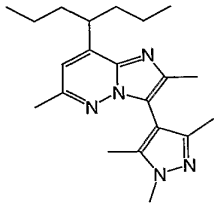
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.

3-Iodo-2,6-dimethyl-8-(1-ethyl-propyl)-imidazo[*1,2-b*]pyridazine (200mg, 0.582 mmol), 1,3,5-trimethylpyrazole-4-boronic acid (233mg, 1.53 mmol), Pd(PPh3)4 (13.4mg, 0.01 mmol) are combined in a microwave pressure tube. Then 0.58 ml of 2N Na2CO3 and 3.0ml of dimethoxyethane/H20/ethanol (7:3:2) solution is added. The mixture is microwaved at 155^0C for 20minutes. Water is added and the mixture is extracted four times with ethyl acetate. The combined organics are dried over MgSO4, filtered, then

evaporated to a residue which is chromatographed using hexanes, then 1:1 hexanes: ethyl acetate, then 100% ethyl acetate to give the title compound (6.4%) as a yellow oil. ^{1}H-NMR (DMSO-d_6): δ6.86 (s, 1H); 3.73 (s, 3H); 3.06-3.10 (m, 1H); 2.41 (s, 3H); 2.22 (s, 3H); 2.03 (s, 3H); 1.93 (s, 3H); 1.74-1.83 (m, 4H); 0.77 (t, J = 7.26 Hz, 6H) ppm. MS/ ES+ = 327 (100%, M+2).

Example 99.

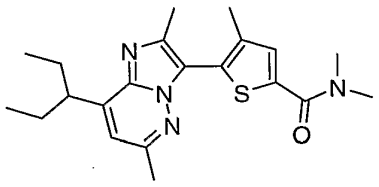
Preparation of 2,6-Dimethyl-8-(1-propyl-butyl)-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.



3-Iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine (75 mg, 0.20 mmol), 1,3,5-trimethylpyrazole-4-boronic acid (80 mg, 0.52 mmol), 2N Na2CO3 solution (0.22 ml), and 5.0mg (0.0004 mmol) of Pd(PPh3)4 are combined in microwave pressure vessel with 1.5ml of dimethylether/H2O/ethanol (7:3:2) solution. The mixture is microwaved at 140^{0}C for 25 minutes. The mixture is evaporated and chromatographed on silica gel column using hexanes then 3:1 hexane:ethyl acetate, then 1:1 hexane:ethyl acetate to give the title compound (22.8%) as a clear oil. ^{1}H-NMR (DMSO-d_6): δ6.88 (s, 1H); 3.72 (s, 3H); 3.06-3.10 (m, 1H); 2.40 (s, 3H); 2.21 (s, 3H); 2.02 (s, 3H); 1.92 (s, 3H); 1.60-1.76 (m, 4H); 1.08-1.21 (m, 4H); 0.82 (t, J = 7.49 Hz, 6H) ppm. MS/ ES+ = 354 (100%, M+1).

Example 100.

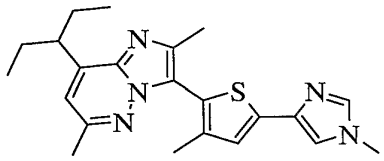
Preparation of 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid dimethylamide.



Using a procedure analogous to Example 23 B, 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid (151 mg, 0.42 mmol) and 2.0 M dimethylamine (2.0 mL, 4 mmol) give the title compound (161 mg, 0.42 mmol, 100%). 1H NMR (CDCl3): δ 0.89 (t, J = 7.4 Hz, 6H), 1.75-1.94 (m, 4H), 2.14 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.15-3.50 (m, 7H), 6.72 (s, 1H), 7.30 (s, 1H). ES-MS (m/z): calcd for C21H28N4OS (M+H)+: 385.6 found: 385.3.

Example 101.

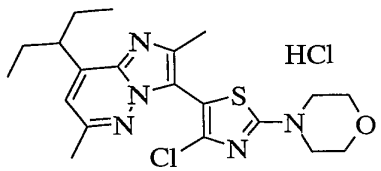
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-Imidazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31. from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.34 M *n*-BuLi (0.80 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 3-iodo-1-methyl-*1H*-imidazole (0.24 mL, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.030g, 0.076 mmol, 8%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, *J* = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.13 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.31-3.40 (m, 1H), 3.72 (s, 3H), 6.66 (s, 1H), 7.09 (d, *J* = 1.3 Hz, 1H), 7.19 (s, 1H), 7.86 (d, *J* = 1.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.2; found: 394.2.

Example 102.

Preparation of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine, hydrochloride salt.

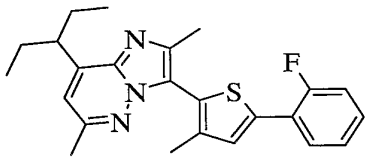


IPA (225.0 mL) is added to compound N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (18.8 g, 0.0448 mmol,

below) in a 1 L 1-neck round-bottomed flask The starting material slurry is heated to 50 °C on a Buchi bath, at which time a hazy solution resulted. Concentrated (12 M) aqueous HCl (3.73 mL, 0.0448 mmole, 1.0 eq) is added all at once, and the hazy solution is stirred at 50 °C on the Buchi for 10 minutes, then evaporated to a yellow solid under vacuum. After 20 minutes at room temperature under vacuum (weight of 20.9 g), acetone (100 mL) is added and the resulting yellow slurry is stirred at room temperature for 1 hour, then cooled with an ice bath and stirred for an additional 1 hour. The slurry is filtered, rinsed with acetone, and dried overnight under vacuum at 40°C to provide pale yellow-white crystalline solid 19.18 g (94%). ^{1}H NMR (DMSO): δ 7.52 (s, 1H), 3.73 (t, J = 4.6, 4H), 3.49 (t, J = 5.2 Hz, 4H), 3.39 (m, 1H), 2.57 (s, 3H), 2.49 (s, 3H), 1.77 (m, 4H), 0.80 (t, J = 7.4 Hz, 6H).

Example 103.

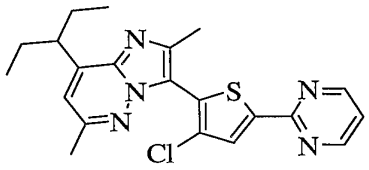
Preparation of 8-(1-ethyl-propyl)-3-[5-(2-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 30 B, 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.18 g, 0.50 mmol), 1-bromo-2-fluoro-benzene (0.072 g, 0.65 mmol), and 2 M Na_2CO_3 (0.38 mL, 0.76 mmol), *n*-PrOH (2 mL), and $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol) furnish the title compound (0.022 g, 0.054 mmol, 11%). ^{1}H NMR ($CDCl_3$), δ 0.93 (t, *J* = 7.4 Hz, 6H), 1.71-1.96 (m, 4H), 2.19 (s, 3H), 2.66 (s, 3H), 2.67 (s, 3H), 3.41-3.50 (m, 1H), 7.15 (s, 1H), 7.15-7.23 (m, 2H), 7.28-7.35 (m, 1H), 7.45 (d, *J* = 1.4 Hz, 1H), 7.66 (dt, *J* = 7.8, 1.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.2; found: 408.2.

Example 104.

Preparation of 3-(3-chloro-5-pyrimidin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 3-(3-Chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a –78 °C solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 g, 5.97 mmol) and THF (30 mL) is added 1.6 M *n*-BuLi (4.1 mL). After 30 minutes $B(OMe)_3$ (0.74 mL, 6.59 mmol) is added, the solution is warmed to ambient temperature and stirred overnight. 1 M HCl (30 mL) is added and the solution stirred for 20 minutes. The solution is made basic with 5 M NaOH. The organic layer is extracted with 1 M NaOH (30 mL). The combined aqueous layers are made acidic with 5 M HCl, $K_3PO_4 \bullet 3\ H_2O$ is added and the PH adjusted to 5.5 using 1 M NaOH. The combined aqueous layers are extracted with EtOAc (200 mL), washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (2.20 g, 5.82 mmol, 97%). LC/MS (m/z): calcd. for $C_{17}H_{21}BClN_3O_2S$ $(M+H)^+$: 378.7; found: 378.0.

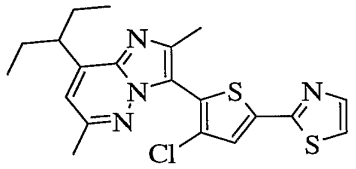
B. 3-(3-Chloro-5-pyrimidin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 2-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol), and *i*-PrOH (3 mL) are degassed with N_2 for 15 minutes. $Pd(OAc)_2$ (7.4 mg, 0.033 mmol) and PPh_3 (0.026 g, 0.099 mmol) are added and the solution is heated at 90 °C overnight. The solution is diluted with EtOAc (35 mL), washed with 10% Na_2CO_3 (35 mL), brine (35 mL), dried over Na_2SO_4, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.077 g, 0.19 mmol, 29%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H),

3.27-3.40 (m, 1H), 6.71 (s, 1H), 7.16 (t, J = 5.0 Hz, 1H), 8.00 (s, 1H), 8.74 (d, J = 5.0 Hz, 2H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 412.2.

Example 105.

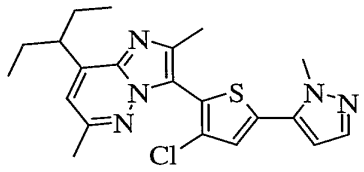
Preparation of 3-(3-chloro-5-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 2-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol) and *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.099 g, 0.24 mmol, 35%). ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (m, 1H), 6.71 (s, 1H), 7.33 (t, J = 3.3 Hz, 1H), 7.49 (s, 1H), 7.81 (d, J = 3.3 Hz, 2H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 417.1; found: 417.1.

Example 106.

Preparation of 3-[3-chloro-5-(2-methyl-*2H*-pyrazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

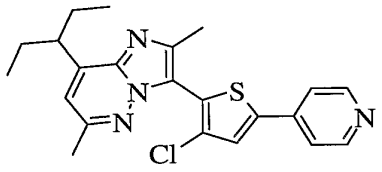


To a –78 °C solution of 1-methyl-*1H*-pyrazole (0.12 g, 1.45 mmol) and THF (4 mL) is added 1.6 M *n*-BuLi (0.91 mL, 1.45 mmol). After 45 minutes 0.5 M $ZnCl_2$ (2.9 mL, 1.45 mmol) is added and the solution is warmed to ambient temperature. After 30 minutes 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example Rupp-88) (0.30 g, 0.73 mmol) and $PdCl_2$(dppf) (0.027

g, 0.036 mmol) are added and the solution heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.15 g, 0.36 mmol, 50%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 6H), 3.26-3.36 (m, 1H), 4.05 (s, 3H), 6.45 (d, J = 1.9 Hz, 1H), 6.71 (s, 1H), 7.14(s, 1H), 7.49 (d, J = 1.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}ClN_5S$ $(M+H)^+$: 414.2; found: 414.2.

Example 107.

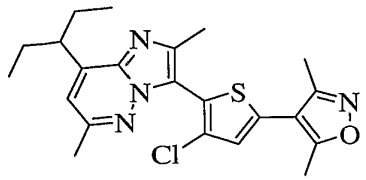
Preparation of 3-(3-chloro-5-pyridin-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 4-bromo-pyridine hydrochloride (0.26 g, 1.32 mmol), 2 M Na_2CO_3 (1.00 mL, 1.99 mmol), *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.16 g, 0.59 mmol, 59%). ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.27-3.36 (m, 1H), 6.72 (s, 1H), 7.45-7.49 (m, 3H), 8.63 (d, J = 1.3 Hz, 1H), 8.64 (d, J = 1.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 411.1; found: 411.1.

Example 108.

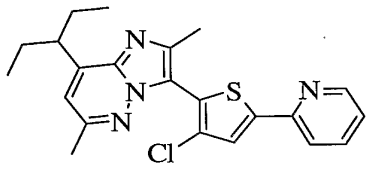
Preparation of 3-[3-chloro-5-(3,5-dimethyl-isoxazol-4-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 4-iodo-3,5-dimethyl-isoxazole (0.30 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol) and *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.14 g, 0.50 mmol, 50%). ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.43 (s, 3H), 2.53 (s, 6H), 2.57 (s, 3H), 3.27-3.38 (m, 1H), 6.71 (s, 1H), 7.01 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}ClN_4OS$ $(M+H)^+$: 429.2; found: 429.2.

Example 109.

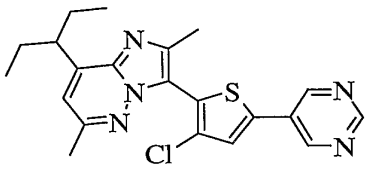
Preparation of 3-(3-chloro-5-pyridin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 g, 0.61 mmol) and $PdCl_2$(dppf) (0.022 g, 0.030 mmol) is added a 0.5 M solution of 2-pyridylzinc bromide (2.40 mL, 1.21 mmol) and the solution heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) followed by recrystallization from CH_3CN furnish the title compound (0.15 g, 0.36 mmol, 60%). ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.29-3.38 (m, 1H), 6.70 (s, 1H), 7.17-7.23 (m, 1H), 7.56 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.70-7.76 (m, 1H), 8.59 (d, J = 4.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 412.0; found: 412.4.

Example 110.

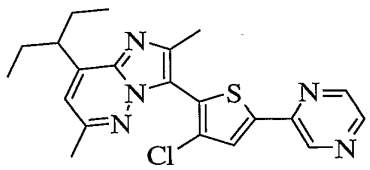
Preparation of 3-(3-chloro-5-pyrimidin-5-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 4-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol), *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.053 g, 0.13 mmol, 20%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.27-3.37 (m, 1H), 6.73 (s, 1H), 7.40 (s, 1H), 8.97 (s, 2H), 9.18 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 411.2.

Example 111.

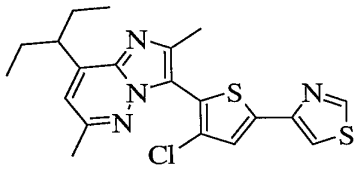
Preparation of 3-(3-chloro-5-pyrazin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.40g, 1.06 mmol), 2-iodo-pyrazine (0.16 g, 1.59 mmol), 2 M Na_2CO_3 (1.06 mL, 2.12 mmol) and *i*-PrOH (5 mL), $Pd(OAc)_2$ (0.012 g, 0.053 mmol), and PPh_3 (0.042 g, 0.16 mmol) furnish the title compound (0.15 g, 0.36 mmol, 34%). ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.25-3.37 (m, 1H), 6.71 (s, 1H), 7.66 (s, 1H), 8.45 (d, J = 2.6 Hz, 1H), 8.51-8.53 (m, 1H), 8.96 (d, J = 1.0 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 412.3.

Example 112.

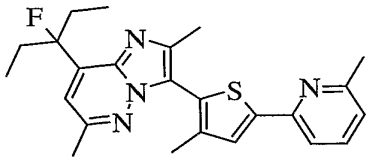
Preparation of 3-(3-chloro-5-thiazol-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a 0 °C solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.45 mmol) and THF (2 mL) is added 0.05 g/mL of Reike® Zn (3.80 mL, 2.91 mmol). The solution is heated at a reflux for 1 hour, and the excess Zn allowed to settle for 1 hour at ambient temperature. The solution is transferred to a flask of 4-bromo-thiazole (Kelly, T. et al. *Tetrahedron Lett.* 1995, 51, 9293) (0.29 g, 1.74 mmol). $PdCl_2(dppf)$ (0.027 g, 0.036 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (40 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) followed by ISCO column chromatography (100% Et_2O) to furnish the title compound (0.098 g, 0.24 mmol, 16%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (m, 1H), 6.70 (s, 1H), 7.45 (s, 1H), 7.49 (d, J = 2.0 Hz, 1H), 8.85 (d, J = 2.0 Hz, 1H). LC/MS (m/z): calcd. for $C_{20}H_{21}ClN_4S_2$ $(M+H)^+$: 417.1; found: 417.3.

Example 113.

Preparation of 8-(1-ethyl-1-fluoro-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

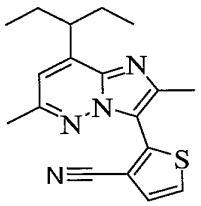


To a –78 °C solution of 3-{2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-pentan-3-ol (0.23 g, 0.55 mmol) and CH_2Cl_2 (3 mL) is added a solution of [bis(2-methoxyethyl)amino]sulfur triflouride (0.14 g, 0.60 mmol) and CH_2Cl_2 (2 mL). The solution is warmed to ambient temperature and

stirred overnight. The solution is washed with sat. $NaHCO_3$ (5 mL) and concentrated. The reside is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.13g, 0.31 mmol, 57%). ^1H NMR ($CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 6H), 2.14 (s, 3H), 2.16-2.31 (m, 2H), 2.46 (s, 3H), 2.54 (s, 3H), 2.56 (s, 3H), 2.59-2.70 (m, 2H), 6.98 (s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, J = 7.8, 7.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{27}FN_4S$ $(M+H)^+$: 423.2; found: 423.4.

Example 114.

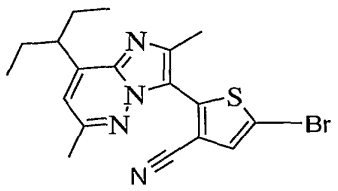
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile.



To a solution 0.05 g/mL of Reike® Zn (31 mL, 23.93 mmol) is added 2-bromo-thiophene-3-carbonitrile (Fournari, P. et al. Bull. Soc. Chim. Fr., 1967, 4115) (2.25 g, 11.96 mmol) and THF (5 mL). The solution is heated at a reflux for 2 hours, cooled to ambient temperature and the excess Zn allowed to settle. The solution is transferred via a cannula into a flask of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.5 g, 7.98 mmol) and $PdCl_2$(dppf) (0.29 g, 0.040 mmol). The mixture is heated at 65°C overnight, diluted with EtOAc (75 mL), washed with sat. NH_4Cl (2 x 75 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-20% EtOAc/hexane gradient) furnish the title compound (1.10 g, 3.39 mmol, 42%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.55 (s, 3H), 2.61 (s, 3H), 3.25-3.34 (m, 1H), 6.75 (s, 1H), 7.35 (d, J = 5.2 Hz, 1H), 7.53 (d, J = 5.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{20}N_4S$ $(M+H)^+$: 325.5; found: 325.2.

Example 115.

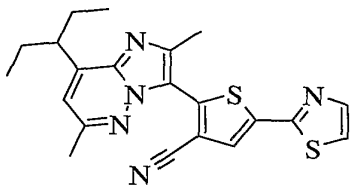
Preparation of 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile.



To a solution of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.83 g, 2.56 mmol) and CH_2Cl_2 (10 mL) is added NBS (0.48 g, 2.69 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated to furnish the title compound (1.03 g, 2.55 mmol, >99%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.56 (s, 3 H), 2.60 (s, 3H), 3.24-3.32 (m, 1H), 6.76 (s, 1H), 7.30 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{19}BrN_4S$ $(M+H)^+$: 404.4; found: 404.1.

Example 116.

Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-thiazol-2-yl-thiophene-3-carbonitrile.

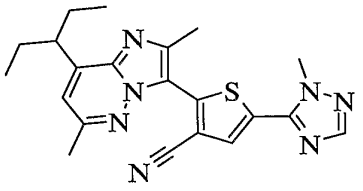


To a flask containing 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.023 g, 0.031 mmol) is added a solution of 0.5 M 2-thiazolylzinc bromide (6.0 mL, 3.10 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.16 g, 0.39 mmol, 64%). ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3H), 2.66 (s, 3H), 3.25-3.35 (m, 1H), 6.78 (s, 1H), 7.38 (d, J = 3.5

Hz, 1H), 7.70 (s, 1H), 7.84 (d, J = 3.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{21}N_5S_2$ $(M+H)^+$: 408.6; found: 408.1.

Example 117.

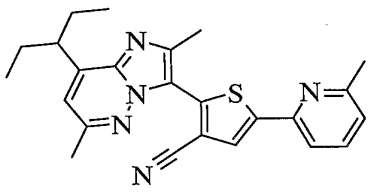
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-thiazol-2-yl-thiophene-3-carbonitrile.



To a –78 °C solution of 1-methyl-1,2,4-triazole (0.14 mL, 1.86 mmol) and THF (5 mL) is added a 1.6 M solution of *n*-BuLi in hexanes (1.20 mL, 1.86 mmol) after 30 minutes a 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature and stirred for 30 minute. 5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (example Rupp-122) (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.023 g, 0.031 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-60% EtOAc/hexane gradient), and is chromatographed (50 x 250 C18 X-Terra RP column, 30-90% 10 mM NH_4HCO_3/water/5 % ACN: ACN gradient). The residue is dissolved in Et_2O (25 mL), washed with sat. $NaHCO_3$ (25 mL), dried over MgSO4, filtered and concentrated to furnish the title compound (0.013 g, 0.032 mmol, 5%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3 H), 2.67 (s, 3H), 3.26-3.34 (m, 1H), 4.17 (s, 3H), 6.79 (s, 1H), 6.78 (s, 1H), 7.92 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{23}N_7S$ $(M+H)^+$: 406.5; found: 406.2.

Example 118.

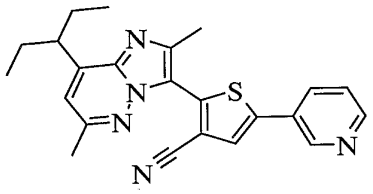
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-(6-methyl-pyridin-2-yl)-thiophene-3-carbonitrile.



To a flask containing 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.024 g, 0.033 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (2.50 mL, 1.24 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-25% EtOAc/hexane gradient), furnish the title compound (0.11 g, 0.26 mmol, 39%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.76-1.92 (m, 4H), 2.57 (s, 3 H), 2.58 (s, 3H), 2.65 (s, 3H), 3.26-3.35 (m, 1H), 6.75 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.63 (dd, J = 7.9, 7.5 Hz, 1H), 7.74 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}N_5S$ $(M+H)^+$: 416.6; found: 416.2.

Example 119.

Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-pyridin-3-yl-thiophene-3-carbonitrile.

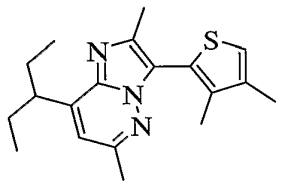


To a –78 °C solution of 3-iodo-pyridine (0.32 g, 1.56 mmol), 0.5 M $ZnCl_2$ in THF (3.20 mL, 1.59 mmol), and THF (2 mL) is added 1.7 M *t*-BuLi (1.85 mL, 3.15 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. 5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.21 g, 0.52 mmol) and $Pd(PPh_3)_4$ (0.03 g, 0.026 mmol) are added and the solution

heated at 55 °C for 1 hour, cooled to ambient temperature and stirred overnight, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (2 x 40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-40% EtOAc/hexane gradient), furnish the title compound (0.15 g, 0.37 mmol, 71%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.58 (s, 3 H), 2.66 (s, 3H), 3.26-3.35 (m, 1H), 6.78 (s, 1H), 7.34-7.46 (m, 1H), 7.56 (s 1H), 7.91 (d, J = 7.1 Hz, 1H), 8.62 (s, 1H), 8.91 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{23}N_5S$ $(M+H)^+$: 402.6; found: 402.4.

Example 120.

Preparation of 3-(3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 2-Bromo-3,4-dimethyl-thiophene.

To a solution of 3,4-dimethyl-thiophene (2.0 g, 17.82 mmol) (Minato et. al., *Tetrahedron* 1982, 38, 3347) in CH_2Cl_2 (20 mL) is added NBS (3.3 g, 18.72 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated. The residue is purified by ISCO column chromatography (100% hexane) furnish the title compound (3.0 g, 16.70 mmol). ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.17 (s, 3H), 6.85 (s, 1H).

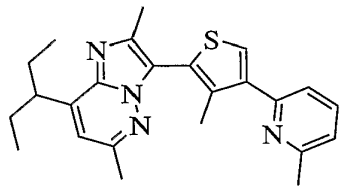
B. 3-(3,4-Dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3,4,3',4'-tetramethyl-[2,2']bithiophenyl-5-yl)-imidazo[*1,2-b*]pyridazine, respectively.

To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.30 g, 10.58 mmol), 2-bromo-3,4-dimethyl-thiophene (3.03 g, 15.88 mmol) and Cs_2CO_3 (7.24 g, 22.23 mmol) and DMF (50 mL) is de-gassed with N_2 for 20 minutes. $Pd_2(dba)_3$ (0.48 g, 0.053 mmol) and PPh_3 (0.56 g, 0.21 mmol) are added and the solution is heated at 120°C overnight. The solution is diluted with EtOAc (200 mL), washed with water (3 x

200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated. The residue is purified by ISCO column chromatography (10% -15% EtOAc/hexane gradient) furnish 2.04 g of a brown oil which is chromatographed (50 x 250 C18 Symmetry column, 30-70% water: 0.1 % TFA /ACN gradient) furnish the title compound (0.41 g, 1.25 mmol, 12%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.94 (m, 4H), 2.00 (s, 3 H), 2.24 (d, J = 1.0 Hz, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.29-3.38 (m, 1H), 6.65 (s, 1H), 7.10 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{25}N_3S$ $(M+H)^+$: 328.5; found: 328.3.

Example 121.

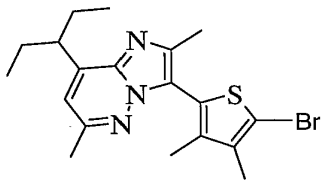
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-4-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (below) (0.25 g, 0.64 mmol) and $PdCl_2$(dppf) (0.023 g, 0.032 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (2.5 mL, 1.27 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-20% EtOAc gradient) and is chromatographed (50 x 250 C18 Symmetry column, 10-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient). The residue is dissolved in Et_2O (20 mL), washed with sat. $NaHCO_3$ (15 mL) dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.066 g, 1.57 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.20 (s, 3 H), 2.47 (s, 3H), 2.49 (s, 3H), 2.61 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.54 (dd, J = 7.5, 7.8 Hz, 1H), 7.72 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.2; found: 405.3.

Example 122.

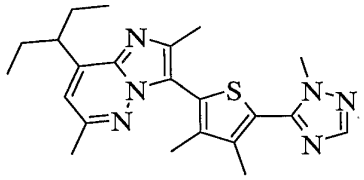
Preparation of 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.41 g, 1.25 mmol) and CH_2Cl_2 (30 mL) is added NBS (0.23 g, 1.32 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated to furnish the title compound (0.41 g, 1.01 mmol, 80%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.4 Hz, 6H), 1.72-1.94 (m, 4H), 2.02 (s, 3 H), 2.18 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 3.27-3.36 (m, 1H), 6.67 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{24}BrN_3S$ $(M+H)^+$: 407.4; found: 407.3.

Example 123.

Preparation of 3-[3,4-dimethyl-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

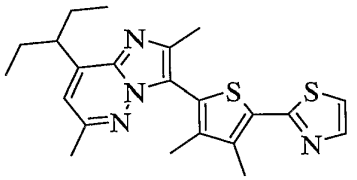


To a –78 °C solution of 1-methyl-1,2,4-triazole (0.056 mL, 0.74 mmol) and THF (2 mL) is added a 1.6 M solution of *n*-BuLi in hexanes (0.46 mL, 0.74 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. The solution is cooled to 0 °C, a 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature and stirred for 30 minute. 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $PdCl_2$(dppf) (0.009 g, 0.012 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried

over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-60% EtOAc/hexane gradient), followed by a second purification by ISCO column chromatography (100% Et_2O) furnish the title compound (0.07 g, 0.17 mmol, 70%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3 H), 2.29 (s, 3H), 2.47 (s, 3H), 2.51 (s, 3H), 3.27-3.37 (m, 1H), 3.97 (s, 3H), 6.69 (s, 1H), 8.00 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{28}N_6S$ $(M+H)^+$: 409.6; found: 409.2.

Example 124.

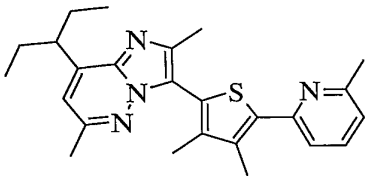
Preparation of 3-(3,4-dimethyl-5-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and THF (1 mL) is added 1.6 M *n*-BuLi (0.16 mL). The solution is stirred for 45 minutes and 0.5 M $ZnCl_2$ in THF (0.52 mL, 0.26 mmol) is added. The solution is warmed to ambient temperature and stirred for 30 minutes. 2-Bromo-thiazole (0.044 mL, 0.49 mmol), and $PdCl_2$(dppf) (0.009 g, 0.012 mmol) are added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient), furnish the title compound (6.1 mg, 0.015 mmol, 6%). ^1H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3 H), 2.49 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.29-3.39 (m, 1H), 6.68 (s, 1H), 7.35 (d, J = 3.1 Hz, 1H), 7.86 (d, J = 3.1 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{26}N_4S_2$ $(M+H)^+$: 411.6; found: 411.2.

Example 125.

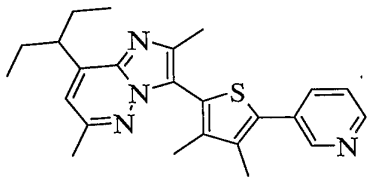
Preparation of 3-[3,4-dimethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $PdCl_2$(dppf) (9 mg, 0.012 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (0.98 mL, 0.49 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.029 g, 0.069 mmol, 29%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.04 (s, 3 H), 2.45 (s, 3H), 2.47 (s, 3H), 2.50 (s, 3H), 2.59 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 8.0, 7.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{25}H_{30}N_4S$ $(M+H)^+$: 419.6; found: 419.4.

Example 126.

Preparation of 3-[3,4-dimethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

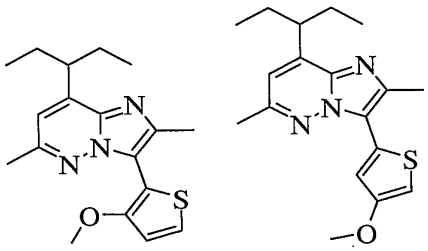


To a –78 °C solution of 3-iodo-pyridine (0.15 g, 0.74 mmol) and 0.5 M $ZnCl_2$ in THF (1.5 mL, 0.75 mmol) is added *t*-BuLi (0.88 mL, 1.49 mmol). The slurry is warmed to ambient temperature and stirred for 30 minutes. 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $Pd(PPh_3)_4$ (0.014 g, 0.012 mmol) are added and the solution stirred at ambient

temperature for 2 days, diluted with EtOAc (35 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (6.1 mg, 0.015 mmol, 6%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3 H), 2.29 (s, 3H), 2.49 (s, 3H), 2.53 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.36 (dd, J = 8.0, 4.5 Hz, 1H), 7.79-7.83 (m 1H), 8.57 (d, J = 4.5 Hz, 1H), 8.79 (d, J = 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.6; found: 405.2.

Example 127 & 128.

Preparation of 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-3-(4-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Ex. 127. Ex. 128.

To a solution of 3-methoxy-thiophene (2.19 g, 19.14 mmol) in Et_2O (50 mL) is added 1.6 M *n*-BuLi (12.20 mL, 19.46 mmol). The solution is heated at a reflux for 30 minutes and cooled to ambient temperature. As solution of 0.5 M $ZnCl_2$ (38.9 mL, 19.5 mmol) and THF (50 mL) is added and the solution is stirred for 30 minutes. 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 g, 6.38 mmol) and $PdCl_2$(dppf) (0.23 g, 0.032 mmol) are added and the solution is heated at 65 °C for 4 hours, diluted with EtOAc (250 mL), washed with sat. NH_4Cl (250 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-25% EtOAc/hexane gradient) furnish the title compounds (1.50 g, 4.55 mmol, 71%) and (0.23 g, 0.70 mmol, 11%), respectively.

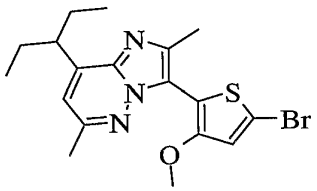
Example 127: ^1H NMR ($CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.59 (s, 3H), 2.70 (s, 3H), 3.26-3.35 (m, 1H), 3.86 (s, 3H), 6.32 (d, J = 1.6 Hz, 1H), 6.67 (s, 1H),

7.41 (d, J = 1.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3OS$ $(M+H)^+$: 330.5; found: 330.3.

Example 128: ^1H NMR ($CDCl_3$) δ 0.84 (t, J = 7.5 Hz, 6H), 1.71-1.88 (m, 4H), 2.47 (s, 3H), 2.49 (s, 3H), 3.26-3.35 (m, 1H), 3.84 (s, 3H), 6.62 (s, 1H), 6.96 (d, J = 5.5 Hz, 1H), 7.39 (d, J = 5.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3OS$ $(M+H)^+$: 330.5; found: 330.3.

Example 129.

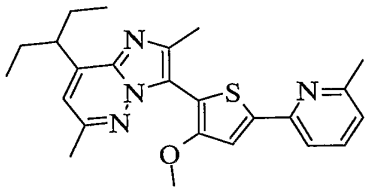
Preparation of 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.78 g, 2.37 mmol) and CH_2Cl_2 (10 mL) is added NBS (0.44 g, 2.49 mmol). The solution is stirred for 1 hour, washed with water (3 x 10 mL), concentrated and purified by ISCO column chromatography (5%-15% EtOAc/hexane gradient) to furnish the title compound (0.87 g, 2.13 mmol, 90%). ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.25-3.35 (m, 1H), 3.82 (s, 3H), 6.65 (s, 1H), 6.97 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3OS$ $(M+H)^+$: 408.1; found: 408.3.

Example 130.

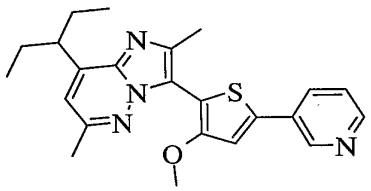
Preparation of 8-(1-ethyl-propyl)-3-[3-methoxy-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.49 mmol) and $PdCl_2$(dppf) (0.018 g, 0.024 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.47 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.066 g, 1.57 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.50 (s, 3 H), 2.51 (s, 3H), 2.55 (s, 3H), 3.26-3.37 (m, 1H), 3.90 (s, 3H), 6.63 (s, 1H), 6.99 (d, J = 7.4 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.49 (s, 1H), 7.54 (dd, J = 7.4, 7.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.6; found: 422.4.

Example 131.

Preparation of 8-(1-ethyl-propyl)-3-(3-methoxy-5-pyridin-3-yl-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

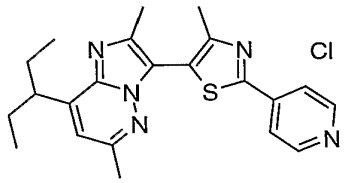


To a –78 °C solution of 3-iodo-pyridine (0.32 g, 1.56 mmol) and 0.5 M $ZnCl_2$ in THF (3.20 mL, 1.59 mmol) is added *t*-BuLi (2.27 mL, 3.85 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.26 g, 0.64 mmol) and $Pd(PPh_3)_4$ (0.037 g, 0.032 mmol) are added and the solution heated at 50 °C for 1 hour, cooled to ambient temperature and stirred overnight. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-50% EtOAc/hexane gradient), furnish the title compound (0.16 g, 0.39 mmol, 61%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 3 H), 2.55 (s, 3H), 3.28-3.38 (m, 1H), 3.93, (3H), 6.67 (s, 1H), 7.26 (d, J = 3.5 Hz, 1H), 7.31-7.36 (m, 1H), 7.88-

7.92 (m, 1H), 8.55 (d, J = 4.5 Hz, 1H), 8.92 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4OS$ $(M+H)^+$: 407.6; found: 407.4.

Example 132.

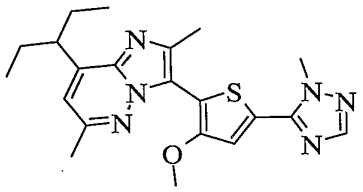
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-4-yl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine, hydrochloride salt.



A mixture of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (500 mg, 1.27 mmol), 4-pyridineboronic acid (500 mg, 4 mmol), $Pd(PPh_3)_4$ (100 mg, 0.08 mmol), toluene (2 mL), MeOH (1mL), and K_2CO_3 (2 M aqueous solution, 3.5mL) is heated at 100 °C for 18 hours. Ethyl acetate (20mL) is added, and the organic layer is separated, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification is performed via silica gel chromatography using a 3:1 mixture of hexanes and ethyl acetate to obtain the free amine of the title compound (200 mg, 40%). The purified product is dissolved in ethyl acetate and a freshly prepared solution of hydrogen chloride (0.5 M in ethyl acetate, 2 mL) is added. The solvent is removed in vacuo to give the title compound ^{1}H-NMR ($CDCl_3$), δ 8.2 (m, 2H); 7.05 (m,2H); 6.55 (s, 1H); 3.24 (m, 1H); 2.43 (s, 3H); 2.40 (s, 3H); 2.33 (s, 3H); 1.76 (m, 4H); 0.80 (t, 6H) ppm. MS/ES$^+$ = 391 (100%, M+1).

Example 133.

Preparation of 8-(1-ethyl-propyl)-3-[3-methoxy-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-1-methyl-*1H*-[1,2,4]triazole.

To a –78 °C solution of 1-methyl-*1H*-[1,2,4]triazole (1.0 mL, 13.20 mmol) and THF (100 mL) is added 1.6 M *n*-BuLi (8.70 mL, 13.86 mmol). After 45 minutes 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (1.76 mL, 14.52 mmol) is added, the solution is warmed to ambient temperature and stirred for 2 hours. The solution is diluted with EtOAc (200 mL), washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.37 g, 8.46 mmol, 64%). ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 7.78 (s, 1H). LC/MS (m/z): calcd. for $C_3H_4BrN_3$ $(M+H)^+$: 162.0; found: 161.9.

B. 8-(1-Ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.75 g, 2.28 mmol) and CH_3CN (10 mL) is added NIS (0.54 g, 2.39 mmol). The solution is stirred overnight, concentrated, diluted with EtOAc (30 mL), washed with water (30 mL), sat. NH_4Cl (30 mL), 20% ($NaHSO_3$) (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.91 g, 2.00 mmol, 88%). ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.25-3.35 (m, 1H), 3.83 (s, 3H), 6.64 (s, 1H), 7.12 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}IN_3OS$ $(M+H)^+$: 456.4; found: 456.0.

C. 5-Bromo-1-methyl-1*H*-[1,2,4]triazole.

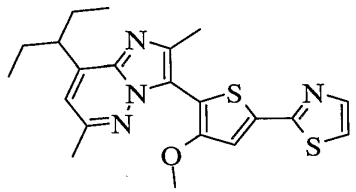
To a –78 °C solution of 1-methyl-1*H*-[1,2,4]triazole (1.0 mL, 13.20 mmol) and THF (100 mL) is added 1.6 M *n*-BuLi (8.70 mL, 13.86 mmol). After 45 minutes 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (1.76 mL, 14.52 mmol) is added, the solution warmed to ambient temperature and stirred for 2 hours. The solution is diluted with EtOAc (200 mL), washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.37 g, 8.46 mmol, 64%). ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 7.78 (s, 1H). LC/MS (m/z): calcd. for $C_3H_4BrN_3$ $(M+H)^+$: 162.0; found: 161.9.

D. 8-(1-Ethyl-propyl)-3-[3-methoxy-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a slurry of 0.05 g/ mL of Reike® Zn in THF (2.8 mL, 2.11 mmol) is added 5-bromo-1-methyl-*1H*-[1,2,4]triazole and THF (2 mL). The solution is heated at 65 °C for 1 hour, cooled to ambient temperature and the excess Zn allowed to settle for 1 hour. The solution is transferred to a flask containing 8-(1-ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g, 0.70 mmol) and $Pd(PPh_3)_4$ (0.041 g, 0.035 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL) washed with sat. NH_4Cl (30 mL). The aqueous phase is extracted with EtOAc (20 mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The reside is purified by ISCO column chromatography (20%-65% EtOAc/hexane gradient) followed by ISCO column chromatography (100% Et_2O) furnish the title compound (0.19 g, 0.46 mmol, 62%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.51 (s, 3 H), 2.52 (s, 3H), 3.26-3.37 (m, 1H), 3.92 (s, 3H), 4.15 (s, 3H), 6.67 (s, 1H), 7.48 (s, 1H), 7.89 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6OS$ $(M+H)^+$: 411.5; found: 411.3.

Example 134.

Preparation of 8-(1-ethyl-propyl)-3-(3-methoxy-5-thiazol-2-yl-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

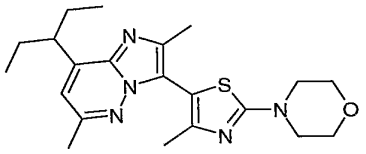


To a flask containing 8-(1-ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.45 g, 0.99 mmol) and $PdCl_2$(dppf) (0.057 g, 0.078 mmol) is added a 0.5 M solution of 2-thiazolylzinc bromide (9.9 mL, 4.94 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.29 g, 0.70 mmol, 71%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-

1.90 (m, 4H), 2.51 (s, 3H), 2.53 (s, 3H), 3.28-3.37 (m, 1H), 3.93 (s, 3H), 6.67 (s, 1H), 7.28 (d, J = 3.3 Hz, 1H), 7.41 (s, 1H), 7.80 (d, J = 3.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4OS_2$ $(M+H)^+$: 413.6; found: 414.3.

Example 135.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-morpholin-4-yl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine.



110 mg of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.28 mmol) and 122 mg of morpholine (1.4 mmol) are dissolved in 3.0 ml of THF and 182 mg of cesium carbonate (0.56 mmol) is added. The mixture is put in 4 ml vial with a Teflon® lined cap and heated at 110°C overnight. The reaction mixture is concentrated and applied to a silica-gel column chromatography column with hexane:EtOAc = 3:1 eluent to give 98 mg of the title compound (88%). mass spectrum (m/e): 400(M+1); ^{1}H-NMR(CDCl3): δ 6.70(s, 1H), 3.87(t, 4H, J=4.8Hz), 3.56(t, 4H, J=4.8Hz), 3.35(m, 1H) 2.56(s, 3H), 2.46(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.6Hz)

The following compounds are prepared essentially as described in Example 135. with 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and the named amine:

Ex	Name	Amine	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
136.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine	2M Methyl-amine/THF	6.71 (s, 1H), 5.44 (s, NH), 3.35 (m, 1H), 3.06 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.19 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.6 Hz, 6H).	344
137.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-dimethylamine	2M Dimethyl-amine/THF	6.70 (s, 1H), 3.36 (m, 1H), 3.17 (s, 6H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	358
138.	N-Ethyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine	N-Methyl-ethylamine	6.70 (s, 1H), 3.59 (q, J = 7.6 Hz, 2H), 3.37 (m, 1H), 3.15 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 1.30 (t, J = 7.5 Hz, 2H), 0.90 (t, J = 7.1 Hz, 6H).	372
139.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-diethylamine	Diethyl-amine	6.71 (s, 1H), 3.56 (q, J = 7.1 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 1.30 (t, J = 7.3 Hz, 6H), 0.90 (t, J = 7.3 Hz, 6H).	386

140.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(furan-2-ylmethyl)-methylamine	N-Methyl-(furan-2-yl)-methyl-amine	7.44 (s, 1H), 6.69 (s, 1H), 6.38 (s, 2H), 4.72 (s, 2H), 3.36 (m, 1H), 3.14 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).	424
141.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl}thiomorpholine	Thio-morpholine	6.71 (s, 1H), 3.92 (m, 4H), 3.37 (m, 1H), 2.80 (m, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	416
142	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methoxy-ethyl)-amine	2-methoxy-ethylamine	6.71 (s, 1H), 5.90 (s, NH), 3.66 (t, J = 5.4 Hz, 2H), 3.56 (t, J = 4.6 Hz, 2H), 3.44 (s, 3H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	388
143	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isopropyl-amine	i-propyl-amine	6.69 (s, 1H), 5.15 (s, NH), 3.74 (m, 1H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 1.84 (m, 4H), 1.35 (d, J = 5.4 Hz, 6H), 0.90 (t, J = 7.4 Hz, 6H).	372
144.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-pyrrolidine	Pyrrolidine	6.68 (s, 1H), 3.55 (m, 4H), 3.36(m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 2.09 (m, 4H), 1.86 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).	384

145.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	n-propyl-amine	6.70 (s, 1H), 5.21 (s, NH), 3.39 (t, J = 7.2 Hz, 2H), 3.29 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H), 1.85 (m, 4H), 1.74 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.4 Hz, 6H).	372
146	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-benzylamine	Benzyl-amine	7.47-7.23 (m, 5H), 6.70 (s, 1H), 5.52 (s, NH), 6.70 (s, 2H), 3.34 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H).	420
147	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(2-methoxy-ethyl)-ethylamine	N-(2-Methoxy-ethyl)-ethylamine		416
148	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methoxy-ethyl)-n-propylamine	N-(2-meth-oxyethyl)-n-propyl-amine	6.69 (s, 1H), 3.72 (m, 4H), 3.47 (t, J = 7.4 Hz, 2H), 3.42 (s, 3H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H), 1.87 (m, 6H), 0.99 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.5 Hz, 6H).	430
149	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidine	piperidine	6.68 (s, 1H), 3.53 (t, J = 4.7 Hz, 4H), 3.36 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.86 (m, 4H), 1.71 (m, 6H), 0.90 (t, J = 7.4 Hz,	398

			6H).	
150	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-3-pentylamine	3-amino-pentane	6.70 (s, 1H), 5.24 (s, NH), 3.32 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 1.94 (s, 3H), 1.85 (m, 4H), 1.72 (m, 2H), 1.60 (m, 2H), 1.02 (t, J = 7.5 Hz, 6H), 0.90 (t, J = 7.3 Hz, 6H).	400
151	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-cyclo-propylamine	Cyclo-propylamine	6.70 (s, 1H), 6.51 (s, NH), 3.35 (m, 1H), 2.67 (m, 1H), 2.57(s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H), 0.82 (m, 2H), 0.77 (m, 2H).	370
152	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-allylamine	Allylamine	6.70 (s, 1H), 6.0 (m, 1H), 5.60 (s, NH), 5.38 (dd, J = 1.3, 17.4 Hz, 1H), 5.27 (dd, J = 1.2, 10.3 Hz, 1H), 4.0 (d, J = 5.2 Hz, 2H), 3.45 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 6.8 Hz, 6H).	370
153	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,2,3,6-tetra-hydro-pyridine	1,2,3,6-tetra-hydro-pyridine	6.70 (s, 1H), 5.96 (m, 1H), 5.81 (m, 1H), 4.02 (t, J = 3.1 Hz, 2H), 3.72 (t, J = 5.5 Hz, 2H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.35 (m, 2H), 2.19 (s, 3H), 1.87 (m,	396

			4H), 0.90 (t, J = 7.4 Hz, 6H).	
154	N-Ethyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	N-ethyl-n-propyl-amine	6.69 (s, 1H), 3.58 (q, J = 7.1 Hz, 2H), 3.43 (t, J = 7.5 Hz, 2H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.80 (m, 4H), 1.30 (t, J = 6.9 Hz, 3H), 1.04 (t, J = 6.9 Hz, 3H), 0.91 (t, J = 7.5 Hz, 6H).	400
155	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	N-methyl-n-propyl-amine	6.68 (s, 1H), 3.46 (t, J = 8.3 Hz, 2H), 3.35 (m, 1H), 3.16 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.80 (m, 2H), 1.00 (t, J = 7.7 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).	386
156	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isopropyl-amine	N-Methyl-2-propyl-amine	6.70 (s, 1H), 4.40 (m, 1H), 3.36 (m, 1H), 2.99 (s, 3H), 2.57 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 1.29 (d, J = 6.4 Hz, 6H), 0.90 (t, J = 7.1 Hz, 6H).	386
157	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-2-propyn-1-amine	N-Methyl-2-Propyn-1-amine	6.70 (s, 1H), 4.40 (d, J = 2.5 Hz, 2H), 3.35 (m, 1H), 3.17 (s, 3H), 2.56 (s, 3H), 2.45 (s, 3H), 2.34 (m, 1H), 2.19 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	382

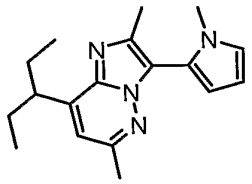
158	N-Methyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-3-amino-propionitrile	N-Methyl-3-amino-propio-nitrile	6.71 (s, 1H), 3.92 (t, J = 6.4 Hz, 2H), 3.37 (m, 1H), 3.25 (s, 3H), 2.9 (t, J = 6.4 Hz, 2H), 2.58 (s, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).	397
159	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- cyclopropyl-methylamine	Cyclo-propyl-methyl-amine	6.68 (s, 1H), 5.35 (s, NH), 3.34 (m, 1H), 3.19 (t, J = 6.3 Hz, 2H), 2.56 (s, 3H), 2.45 (s, 3H), 2.16 (s, 3H), 1.86 (m, 4H), 1.19 (m, 1H), 0.91 (t, J = 7.1 Hz, 6H), 0.61 (m, 2H), 0.31 (m, 2H).	384
160	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methylsulfanyl)-ethylamine	2-methyl-sulfanyl-ethylamine	6.72 (s, 1H), 5.58 (s, NH), 3.58 (m, 2H), 3.35 (m, J = 7.3, 14.4, 1H), 2.85 (m, 2H), 2.57 (s, 3H), 2.46 (s, 3H), 2.17 (s, 6H), 1.85 (m, 4H), 0.90 (t, J = 6.7 Hz, 6H).	404
161	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- N-{[1,3]dioxolan-2-ylmethyl-methylamine	N-{[1,3]di-oxolan-2-yl-methyl}-methyl-amine	6.72 (s, 1H), 5.22 (m, 1H), 4.05 (m, 2H), 3.94 (m, 2H), 3.73 (d, J = 4.5 Hz, 2H), 3.35 (m, J = 6.6, 14.1 Hz, 1H), 3.23 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.84 (m, 4H), 0.91 (t, J = 7.1 Hz, 6H).	430
162	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-	N-Methyl-2-propen-1-yl-amine	6.71 (s, 1H), 5.93 (m, 2H), 5.30 (m, 2H), 4.16 (d, J = 5.9 Hz, 2H), 3.39 (m, 1H),	384

	3-yl]-4-methyl-thiazol-2-yl}- N-Methyl-2-propen-1-yl-amine		3.12 (s, 3H), 2.58 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H).	
163	(R)-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(tetrahydro-furan-2-ylmethyl)-amine	(R)-(tetrahydro-furan-2-ylmethyl)-amine	6.70 (s, 1H), 5.44 (s, NH), 4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.60 (m, 1H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 2.08 (m, 1H), 1.98 (m, 2H), 1.85 (m, 4H), 1.73 (m, 2H), 0.90 (t, J = 7.3 Hz, 6H).	414
164	(S)-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(tetrahydro-furan-2-ylmethyl)-amine	(S)-(tetrahydro-furan-2-ylmethyl)-amine	6.69 (s, 1H), 5.45 (s, NH), 4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.59 (m, 1H), 3.34 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 2.08 (m, 1H), 1.98 (m, 2H), 1.85 (m, 4H), 1.73 (m, 1H), 0.90 (t, J = 7.2 Hz, 6H).	414
165	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(2-methoxyethyl)-methylamine	N-Methyl-2-methoxy-ethyl-amine	6.70 (s, 1H), 3.74 (t, J = 4.2 Hz, 2H), 3.71 (t, J = 4.1 Hz, 2H), 3.43 (s, 3H), 3.37 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	402
166	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-	N-Methyl-benzyl-amine	7.43-7.32 (m, 5H), 6.69 (s, 1H), 4.76 (s, 2H), 3.35 (m, 1H), 3.10 (s, 3H), 2.57(s, 3H), 2.48 (s, 3H), 2.21 (s,	434

	yl}-N-methyl-benzylamine		3H), 1.85 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).	
167	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-ethyl-benzylamine	N-Ethyl-benzyl-amine	7.41-7.31 (m, 5H), 6.68 (s, 1H), 4.76 (s, 2H), 3.54 (q, J = 7.3, 2H), 3.36 (m, 1H), 2.56(s, 3H), 2.49 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).	448
168	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(1-methoxy-2-butyl)-amine	1-Methoxy-2-amino-butane		416
169	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methyl-isobutylamine	N,2-Di-methyl- n-propyl-amine		400
170	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isobutyl-amine	2-Methyl-n-propyl-amine		386

Example 171.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1-methyl-^1H-pyrrol-2-yl)-imidazo[*1,2-b*]pyridazine.



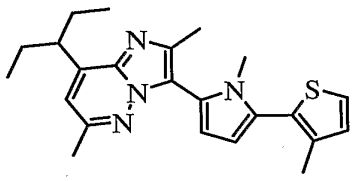
A THF solution (10 mL) of N-methylpyrrole (Aldrich, 800 μL, 9.0 mmol) is cooled to -78 °C under N_2 then treated with *tert*-BuLi (1.7 M in pentane, 5.3 mL, 9.0 mmol). The solution is warmed to room temperature for 30 minutes then cooled to -78 °C and treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 18 mL, 9.0 mmol). The resulting mixture is warmed to room temperature and treated with a THF slurry (5 mL) containing 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.02 gm, 3.0 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 140 mg, 0.17 mmol). The mixture is heated to 60 °C overnight, then poured into sat'd aq NH_4Cl (50 mL) and extracted with diethyl ether (75 mL). The organic extract is ished with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (407.5 mg, 46% yield) as an oil.

ES-MS (m/z): calc'd for $C_{18}H_{24}N_4$: 296.20; found 297.5 $(M+H)^+$

^{1}H NMR (400 mHz, $CDCl_3$): δ 6.86 (s, 1H), 6.65 (s, 1H), 6.32-6.28 (m, 2H), 3.50 (s, 3H), 3.35 (br s, 1H), 2.49 (s, 3H), 2.46 (s, 3H), 1.87-1.75 (m, 4H), 0.87 (t, J = 7.0 Hz, 6H).

Example 172.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[1-methyl-5-(3-methyl-thiophen-2-yl)-^1H-pyrrol-2-yl]- imidazo[*1,2-b*]pyridazine.



A. 3-(5-Bromo-1-methyl-^1H-pyrrol-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

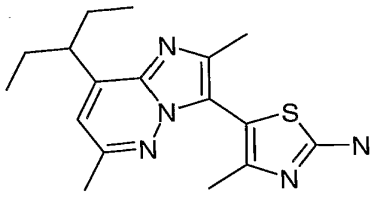
A THF solution (10 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1-methyl-^1H-pyrrol-2-yl)-imidazo[*1,2-b*]pyridazine (414 mg, 1.40 mmol) is cooled to 0 °C and treated with a THF solution of NBS (250 mg, 1.40 mmol). Within 5 min, the reaction mixture is treated with sat Na_2SO_3 (1 mL) then concentrated. The resulting residue is diluted with ethyl acetate (50 mL) and ished with 50% aq sat'd Na_2SO_3 (2x50 mL). The organic extract is dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (374 mg, 71% yield) as a solid. ES-MS (m/z): calc'd for $C_{18}H_{23}BrN_4$: 374.11; found 375 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 6.67 (s, 1H), 6.33 (d, J = 4.0 Hz, 1H), 6.30 (d, J = 4.0 Hz, 1H), 3.40 (s, 3H), 3.36 (br s, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 1.88-1.75 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H).

B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[1-methyl-5-(3-methyl-thiophen-2-yl)-^1H-pyrrol-2-yl]- imidazo[*1,2-b*]pyridazine.

A THF slurry (5 mL) of 3-(5-bromo-1-methyl-^1H-pyrrol-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (143 mg, 0.38 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 19 mg, 0.023 mmol) is treated with 3-methyl-2-thienyl zinc bromide (Aldrich, 0.5 M in THF, 3.8 mL, 1.9 mmol) then heated to 60 °C for 1 hr. The resulting mixture is poured into sat'd NH_4Cl (25 mL) and extracted with diethyl ether (35 mL). The organic extract is washed with aq. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 15% ethyl acetate in hexane) to elute the product. The material is purified a second time by flash chromatography using hexane-ethyl acetate gradient (100% hexane to 12% ethyl acetate in hexane) to elute the product. Only the fractions containing pure desired product, as judged by MS analysis, are collected and give the title compound (82.6 mg, 55% yield) as an oil. ES-MS (m/z): calc'd for $C_{23}H_{28}N_4S$: 392.20; found 393.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.28 (d, J = 5.3 Hz, 1H), 6.96 (d, J = 4.8 Hz, 1H), 6.67 (br s, 1H), 6.39 (d, J = 3.5 Hz, 1H), 6.37 (d, J = 4.0 Hz, 1H), 3.35 (br s, 1H), 3.33, (s, 3H), 2.52 (s, 3H), 2.51 (s, 3H), 2.26 (s, 3H), 1.89-1.76 (m, 4H), 0.87 (t, J = 7.5 Hz, 6H).

Example 173.

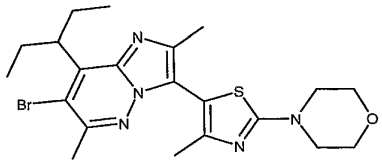
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-ylamine.



50 mg of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.13 mmol) and 10 mg of copper (I) oxide are added to 3 ml of 2 M NH3 in MeOH and vial is capped with a Teflon® lined cap, heated at 130°C for overnight. The reaction mixture is concentrated under N2 gas and applied onto a silica-gel chromatography column (Hexane: AcOEt: 2 M NH3 in MeOH = 20:20:1) to give 22 mg of the title compound. Yield 54%: mass spectrum (m/e): 330(M+1); ^{1}H-NMR(CDCl3): 6.72(s,1H), 5.24(br, 2H), 3.40(m, 1H), 2.56(s, 3H), 2.47(s, 3H), 2.18(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.4Hz).

Example 174.

Preparation of N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.



A. 7-Bromo-3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

547 mg of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine (1.74 mmol) and 341 mg of NBS (1.92 mmol) are dissolved in 20 ml of CHCl3 and stirred at room temperature overnight. The reaction mixture is washed with sat. $Na_2S_2O_3$, sat. NaCl, dried over Na_2SO_4 and evaporated. The crude materials are

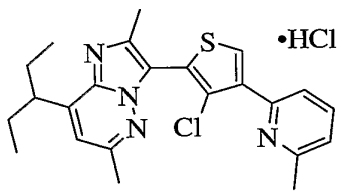
applied onto a silica-gel chromatography column (Hexane:AcOEt=8:1) to give 218 mg of the title compound. Yield 27%. mass spectrum (m/e): 473(M+1); ^{1}H-NMR(CDCl3): 3.44(m, 1H), 2.70(s, 3H), 2.45 (s, 3H), 2.37(s, 3H), 2.03(m, 4H), 0.90(m, 6H).

B. N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.

72 mg of 7-bromo-3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 mmol) and 66 mg of morpholine (0.76 mmol) and 97 mg of cesium carbonate (0.3 mmol) are put in 4 ml vial with 3 ml of dry THF. The vial is capped with a Teflon® lined cap and heated at 100°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt = 3:1) to give 30 mg of the title compound. Yield 42%.: mass spectrum (m/e): 479(M+1); ^{1}H-NMR(CDCl3): 3.87(t, 4H, J=5.0Hz), 3.55(t, 4H, J=5.0Hz), 3.45(m, 1H), 2.70(s, 3H), 2.44(s, 3H), 2.40(m, 2H), 2.18(s, 3H), 2.01(m, 2H), 0.88(t, 6H, J=7.3Hz).

Example 175.

Preparation of 3-[3-chloro-4-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, hydrochloride salt.

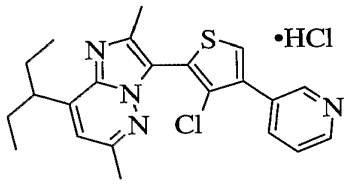


Reike® Zn (0.5 g/ mL solution in THF (1.9 mL,, 1.45 mmol) is added to a flask containing 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.73 mmol). The slurry is heated at 65 °C for 1 hour, placed in a centrifuge for 5 minutes, and the resulting solution is transferred to a flask containing 2-bromo-6-methyl-pyridine (0.12 g, 0.73 mmol) and $PdCl_2$(dppf) (0.018 g, 0.024 mmol). The reaction is heated at 65 °C overnight, diluted with ethyl acetate (20 mL), and washed with a sat. solution of NH_4Cl (15 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by silica gel chromatography using a hexanes and ethyl acetate gradient. The resulting product is dissolved in

dichloromethane (5 mL), treated with a 1 M solution of HCl in EtOH (0.35 mL, 0.35 mmol) and concentrated. The residue is recrystallized from ethyl acetate and hexanes furnish the title compound (0.033 g, 0.072 mmol, 11%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.3 Hz, 6H), 1.73-2.02 (m, 4H), 2.68 (s, 3H), 2.81 (s, 3H), 3.21 (s, 3H), 3.88-3.98 (m, 1H), 7.25 (s, 1H), 7.65 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 8.33 (dd, J = 7.5, 7.1 Hz, 1H), 9.26 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{23}H_{26}Cl_2N_4S$ $(M+H)^+$: 424.2; found: 424.2.

Example 176.

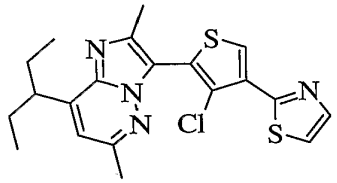
Preparation of 3-(3-chloro-4-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, hydrochloride salt.



Using a procedure analogous to Example 175, 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.97 mmol), Reike® Zn (0.5 g/ mL solution in THF, 2.5 mL, 1.94 mmol), 3-iodo-pyridine (0.30 g, 1.45 mmol), $PdCl_2$(dppf) (0.035 g, 0.048 mmol), and a 1 M solution of HCl in EtOH (0.61 mL, 0.61 mmol) furnish the title compound (0.076 g, 0.17 mmol, 18%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.0 Hz, 6H), 1.71-1.88 (m, 2H), 1.88-2.01 (m, 2H), 2.68 (s, 3H), 2.81 (s, 3H), 3.85-3.96 (m, 1H), 5.28 (s, 1H), 7.27 (bs, 1H), 8.09 (bs, 1H), 8.23 (bs, 1H), 8.70 (bs, 1H), 8.89 (bs, 1H), 9.18 (bs, 1H). LC/MS (m/z): calcd. for $C_{22}H_{24}Cl_2N_4S$ $(M+H)^+$: 411.1; found: 411.2.

Example 177.

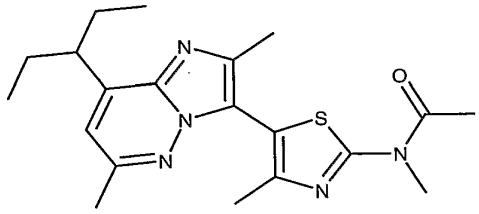
Preparation of 3-(3-chloro-4-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 175, 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), Reike® Zn (0.5 g/ mL solution in THF, 1.6 mL, 1.21 mmol), 2-bromo-thiazole (0.11 mL, 1.21 mmol), and $PdCl_2$(dppf) (0.022 g, 0.030 mmol) furnish the title compound (0.012 g, 0.29 mmol, 6.8%). ^{1}H-NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.52 (s, 6H), 3.27-3.43 (m, 1H), 6.73 (s, 1H), 7.43 (d, J = 3.3 Hz, 1H), 7.94 (d, J = 3.3 Hz, 1H), 8.30 (s,1H) ppm. LC/MS (m/z): calcd. for $C_{20}H_{21}ClN_4S_2$ $(M+H)^+$: 417.1; found: 417.2.

Example 178.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methyl-acetamide.

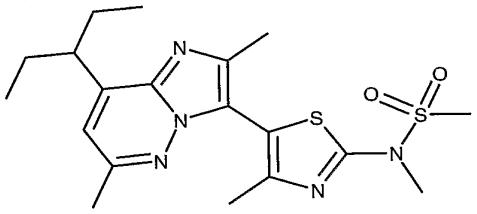


60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.17 mmol) and 86 mg of triethylamine (0.85 mmol) are dissolved in 3.0 ml of CH_2Cl_2 and 16 mg of acetylchloride (0.2 mmol) is added. The vial is capped with a Teflon® lined cap and shaken at room temperature for 2h. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt = 3:1 and Hexane :AcOEt=2:1) to give 33.8 mg of the title compound. Yield 50%: mass spectrum (m/e): 386(M+1); ^{1}H-NMR(CDCl3): 7.03(s,1H), 3.79(s, 3H),

3.47(m, 1H), 2.54 (s, 3H), 2.47(s, 3H), 2.46(s, 3H), 2.31(s, 3H), 1.86(m, 4H), 0.91(t, 6H, J=7.4Hz).

Example 179.

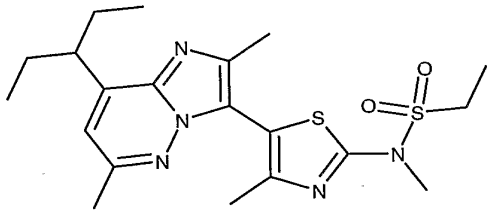
Preparation of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methanesulfonyl-methylamine.



60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.17 mmol) and 86 mg of triethylamine (0.85 mmol) are dissolved in 3.0 ml of CH2Cl2 and 23 mg of methanesulfonyl chloride (0.2 mmol) is added. The vial is capped with a Teflon® lined cap and shaken at room temperature for 2h. The reaction mixture is concentrated and applied to silica-gel chromatography (Hexane :AcOEt = 2:1) to give 53.8 mg of the title compound. Yield 75%. mass spectrum (m/e): 422(M+1); ^{1}H NMR(CDCl3): 6.96(s, 1H), 3.60(s, 3H), 3.34(m, 1H), 3.19(s, 3H), 2.56(s, 3H), 2.48(s, 3H), 2.29(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.4Hz).

Example 180.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-ethanesulfonyl-methylamine.

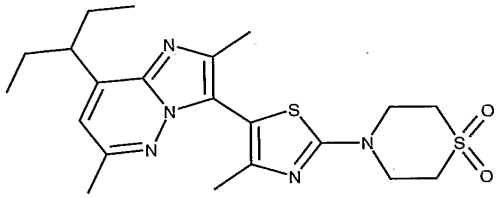


The title compound is prepared by a procedure analogous to Example 178. employing 50 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.15 mmol), 51 mg of triethylamine (0.5 mmol) and 39 mg of ethanesulfonylchloride (0.3 mmol). 48.9 mg, Yield 75%: mass spectrum

(m/e): 436(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.62(s, 3H), 3.42(q, 2H, J=7.4Hz), 3.35(m, 1H), 2.55(s, 3H), 2.48(s, 3H), 2.28(s, 3H), 1.85(m, 4H), 1.46(t, 3H, J=7.4Hz), 0.90(t, 6H, J=7.5Hz).

Example 181.

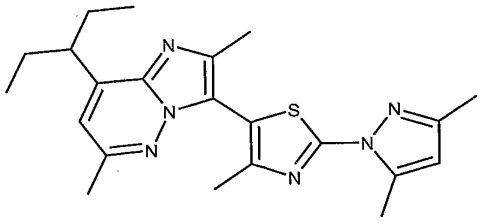
Preparation of 3-[2-(1,1-dioxo-thiomorpholin-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}thiomorpholine(0.14 mmol) is dissolved in 3 ml of CH_2Cl_2 and 62 mg of mCPBA (0.36 mmol) is added. The reaction mixture is stirred at room temperature for 30 min. The reaction mixture is diluted with CH_2Cl_2, washed with sat. NaHCO3 and sat. NaCl. The separated organic layer is dried over Na_2SO_4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt:2 M NH3 in MeOH=10:3:1) to give 20.3 mg of the title compound. Yield 33%: mass spectrum (m/e): 448(M+1). ^{1}H-NMR: 6.72 (s, 1H), 4.16 (t, J = 4.7 Hz, 4H), 3.35 (m, 1H), 3.23 (t, J = 5.2 Hz, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).

Example 182.

Preparation of 3-[2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. {5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-hydrazine.

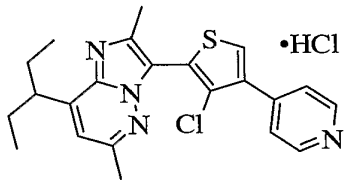
The title compound is prepared essentially as described in Example 135 using hydrazine. MS found (M+1) 345.

B. 3-[2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

28 mg of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-hydrazine (0.08 mmol) and 80 mg of 2,4-pentanedione (0.8 mmol) are dissolved in 1.0 ml of AcOH and heated at 100°C for 2 h. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane : AcOEt = 5:1) to give 23 mg of the title compound. Yield 70%: mass spectrum (m/e): 409 (M+1). 6.72 (s, 1H), 6.03 (s, 1H), 3.36 (m, J = 7.1, 14.1 Hz, 1H), 2.75 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.32(s, 3H), 2.31(s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H).

Example 183.

Preparation of 3-(3-chloro-4-pyridin-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, hydrochloride salt.

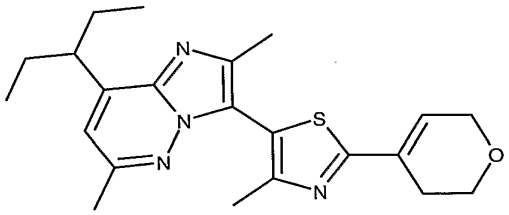


A solution of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), 4-pyridyl-boronic acid (0.82, 0.67 mmol), a 2 M solution of Na_2CO_3 (0.5 mL, 0.91 mmol), and *n*-PrOH (2.5 mL) are degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (0.0027 g, 0.012 mmol) and PPh_3 (0.0095 g, 0.036 mmol) are added, and the solution heated at a 90 °C overnight. The solution is diluted with ethyl acetate (40 mL) and washed with a 10 % solution of Na_2CO_3 (30 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO flash chromatography (20%-30% EtOAc gradient). The resulting product is dissolved in dichloromethane (5 mL), treated with a 1 M solution of HCl in

EtOH (0.35 mL, 0.35 mmol), and concentrated. The residue is recrystallized from acetonitrile and ethyl acetate furnish the title compound (0.15 g, 0.34 mmol, 56%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.5 Hz, 6H), 1.73-1.88 (m, 2H), 1.89-2.04 (m, 2H), 2.68 (s, 3H), 2.82 (s, 3H), 3.87-3.97 (m, 1H), 7.28 (s, 1H), 8.26-8.34 (m, 3H), 8.95 (d, J = 5.3 Hz, 2H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{24}Cl_2N_4S$ $(M+H)^+$: 411.1; found: 411.2.

Example 184.

Preparation of 3-[2-(3,6-dihydro-*2H*-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 4-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-tetrahydro-pyran-4-ol.

370 mg of 3-(2-Bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.93 mmol) is dissolved in 10 ml of dry THF and cooled to –78°C. 0.6 ml of n-BuLi 2.0 M in hexane (1.2 mmol) is added and stirred at –78°C for 30 min. 141 mg of tetrahydro-*4H*-pyran-4-one (1.41 mmol) is added and stirred at –78°C for 2 h. The reaction mixture is diluted with AcOEt, washed with sat. NH4Cl , dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt : 2 M NH3 in MeOH =10:3:1) to give 152 mg of the title compound. Yield 40%.: mass spectrum (m/e): 415(M+1). ^{1}H NMR ($CDCl_3$): δ 6.74 (s, 1H), 3.99 (t, J = 2.2 Hz, 4H), 3.97 (t, J = 2.2 Hz, 4H), 3.35 (m, 1H), 3.20 (s, OH), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 1.88 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).

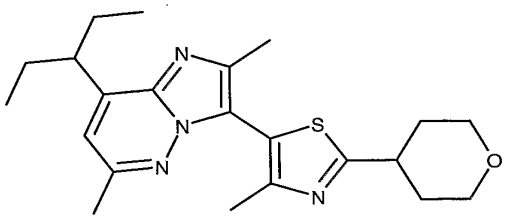
B. 3-[2-(3,6-Dihydro-*2H*-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

150 mg of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-tetrahydro-pyran-4-ol (0.36 mmol) is dissolved in 5 ml of CH2Cl2

and 112 mg of triethylsilane (0.96 mmol) and 717 mg of trifluoroacetic acid (6.3 mmol) are added. The reaction mixture is stirred at room temperature for 1h. The reaction mixture is stirred under reflux for 1 h and cooled down to room temperature. The solvent is removed in *vacuo*. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt: 2 M NH3 in MeOH =10:3:1) to give 64 mg of the title compound. Yield 45%. mass spectrum (m/e): 397(M+1). 6.94 (s, 1H), 6.71 (s, 1H), 4.41 (d, J = 2.6 Hz, 2H), 3.98 (t, J = 5.3 Hz, 2H), 3.43 (m, 1H), 2.62(s, 3H), 2.75 (m, 2H), 2.56 (s, 3H), 2.37 (s, 3H), 1.86 (m, 4H), 0.92 (t, J = 8.2 Hz, 6H).

Example 185.

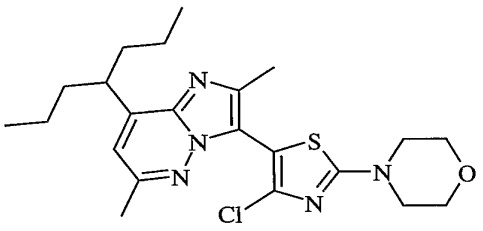
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[4-methyl-2-(tetrahydro-pyran-4-yl)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.



Add 3-[2-(3,6-dihydro-2*H*-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (55 mg, 0.14 mmol), 5% palladium on carbon (55 mg) and absolute ethanol (50 ml) to a pressure vessel. Purge the reaction vessel with nitrogen, purge the reaction vessel with hydrogen, pressurize the reaction mixture with hydrogen (415 KPa), seal the vessel, agitate the reaction and heat to 40 °C. Continue the reaction for 18 hours then turn off the heat and allow the reaction mixture to cool to ambient temperature. Vent the excess hydrogen from the vessel and purge the vessel with nitrogen. Filter the reaction mixture to remove the 5% palladium on carbon. The filtrate is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt : 2 M NH_3 in MeOH = 10:3:1) to give 12.8 mg of the title compound. Yield 23%. mass spectrum (m/e): 399(M+1). ^{1}H NMR ($CDCl_3$): δ 6.73 (s, 1H), 4.14 (m, 2H), 3.60 (m, 2H), 3.34 (m, 2H), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 2.16 (m, 2H), 2.02 (m, 2H), 1.87 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).

Example 186.

Preparation of 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.



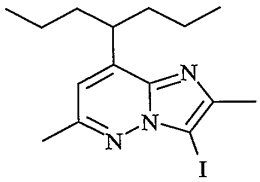
A. 6-Methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine.

6-Methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine can be made using chemistry described in J. Heterocylic Chem. **1991**, *28*, 583. A 250 mL three neck round bottom flask is charged with 3-amino-6-methyl pyridazine (2.5 g, 0.229 moles, 1.0 equiv), water (70 mL), and acetonitrile (50 mL). Concentrated sulfuric acid (3.51 g, 1.91 mL, 0.0344 moles, 1.5 equiv), silver nitrate (3.87 g, 0.0229 moles, 1.0 equiv), and valproic acid (7.21 g, 7.95 mL, 0.050 moles, 2.2 equiv) are added to the reaction mixture. The reaction is heated to 75 °C. As the reaction mixture is heating, a solution of $(NH_4)_2S_2O_8$ (7.85 g, 0.0344 moles, 1.5 equiv) in 40 mL of water is slowly added via an addition funnel over a period of 30 minutes. The reaction mixture is heated at 70-80 °C for two more hours. The reaction mixture is cooled and dichoromethane is added. The reaction is made basic with a 30% aqueous NaOH solution and filtered through a short Celite® plug. The organic layer is separated, and the aqueous layer is extracted two more times with dichoromethane. The combined organic extracts are dried over Na_2SO_4. The solvent is evaporated and the crude material is purified using silica gel chromatography with a 2.0 N solution of NH_3 in MeOH and methylene chloride as eluent. Yield = 0.61 g (13%). MS (APCI): 208 (M+1).

B. 2,6-Dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.

A 250 mL round bottom flask is charged with 6-methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine (0.611 g, 0.00295 moles, 1 equiv), ethanol 2B (30 mL), and chloroacetone (0.382 g, 0.328 ml, 0.00412 moles, 1.4 equiv). The reaction mixture is heated at 75 °C overnight and then cooled to room temp. $NaHCO_3$ (0.371 g, 0.00442 moles, 1.5 equiv) is slowly added to the reaction mixture that is then heated to 100 °C overnight. The reaction mixture is cooled and the solvent is evaporated. Dichloromethane is added and the reaction mixture is passed through filter paper. The solvent is evaporated to obtain a brown oil which is purified via silica gel chromatography. The material is eluted with a hexanes and ethyl acetate gradient to obtain 0.511 g of the final products. Two peaks are identified in the lc/ms. The mixture is used "as is" in the next reaction. MS (APCI): 246 (M+1).

C. 3-Iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.



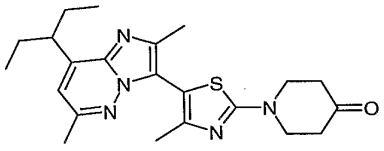
A 50 mL round bottom flask is charged with 2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-*b*]pyridazine (0.51 g, 0.0021 moles) and acetonitrile (3 mL). The reaction mixture is placed on an ice bath and NIS (0.468 g, 0.00208 moles) is added neat. The reaction is stirred overnight and the ice bath melts. The next day, the reaction mixture is partitioned between dichloromethane and a saturated aqueous solution of $NaHCO_3$. The organic layer is collected and the aqueous layer is extracted two more times with dichloromethane. The organic extracts are combined, washed with brine, and dried over Na_2SO_4. The solvent is evaporated and the crude material is purified via silica gel chromatography eluting with hexanes and then a 25:75 mixture of ethyl acetate and hexanes. Yield = 0.435 g (56%). MS (APCI): 372 (M+1).

D. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.

A 15 mL round bottom flask is charged with 3-iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-*b*]pyridazine (0.200 g, 0.000539 moles), 4-(4-chloro-thiazol-2-yl)-morpholine (0.165 g, 0.000808 moles), Cs_2CO_3 (0.361 g, 0.00108 moles, 2.0 equiv), $Pd(dba)_2$ (0.0092 g, 0.0000161 moles, 0.03 equiv), PPh_3 (0.00847 gram, 0.000323 moles, 0.060 equiv) and DMF (2.0 mL). Nitrogen is bubbled through the reaction mixture for 15 minutes; then, the reaction mixture is heated at 130 °C overnight. The next day, the reaction mixture is partitioned between Et_2O and a saturated solution of NH_4Cl. The aqueous layer is extracted twice more with Et_2O. The organic extracts are combined, washed 2-3 times with H_2O, washed once with brine, and dried over Na_2SO_4. The solvents are evaporated in vacuo and the crude reaction mixture is purified via silica gel chromatography. Yield = 0.1737 g (72%). ^{1}H-NMR ($CDCl_3$), δ 0.87 (t, *J* = 7 Hz, 6H), 1.14- 1.37 (m, 4H), 1.74 (q, *J* = 8 Hz, 4H), 2.54 (s, 3H), 2.50 (s, 3H), 3.48 (m, 1H), 3.53 (t, *J* = 5 Hz, 4H), 3.83 (t, *J* = 5 Hz, 4H), 6.71(br s, 1H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{30}ClN_5OS$ $(M+H)^+$: 448; found: 448.

Example 187.

Preparation of 1-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidin-4-one.



A. 8-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,4-dioxa-8-aza-spiro[4.5]decane.

100 mg of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 mmol), 182 mg of 4-piperidineethylene ketal (1.27 mmol) and 244 mg of Cs2CO3 (0.75 mmol) are put into 4.0 ml vial with 2.0 ml of THF. The vial is capped with a Teflon® lined cap and heated at 110°C for 3 days. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 116 mg of the title compound. Yield 100%. mass spectrum

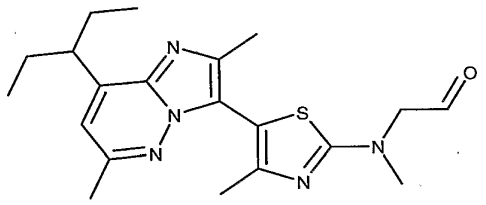
(m/e): 456(M+1). ^{1}H NMR ($CDCl_3$): δ 6.69 (s, 1H), 4.05 (s, 4H), 3.70 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.90-1.78 (m, 8H), 0.90 (t, J = 7.2 Hz, 6H).

B. 1-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidin-4-one.

70 mg of 8-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,4-dioxa-8-aza-spiro[4.5]decane (0.15 mmol) is dissolved in 10.ml of conc. HCl and stirred at room temperature for 2 h. The reaction mixture is neutralized with sat. NaHCO3, extracted with CH2Cl2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=2:1) to give 33.2 mg of the title compound . Yield 52%. mass spectrum (m/e): 412(M+1). ^{1}H NMR ($CDCl_3$): δ 6.70 (s, 1H), 3.94 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.67 (t, J = 6.5 Hz, 4H), 2.57 (s, 3H), 2.47 (s, 3H), 2.21 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.1 Hz, 6H).

Example 188.

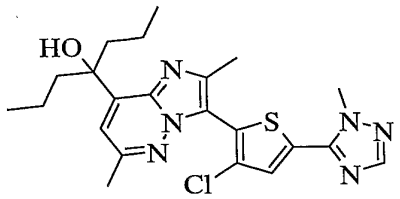
Preparation of ({5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methyl-amino)-acetaldehyde.



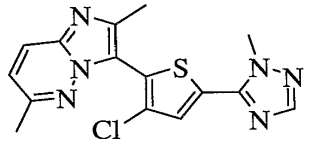
85 mg of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- N-{[1,3]dioxolan-2-ylmethyl-methylamine (0.2 mmol) is dissolved in 2 ml of conc. HCl and stirred at 50°C for 30 min. The mixture is cooled to room temperature and neutralized with sat. NaHCO3. The mixture is extracted with CH2Cl2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (CH2Cl2:MeOH=20:1) to give 73.4 mg of the title compound. Yield 76%. mass spectrum (m/e): 386(M+1). 9.79 (s, 1H), 6.72 (s, 1H), 4.39 (s, 2H), 3.36 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).

Example 189.

Preparation of 4-{3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-heptan-4-ol.

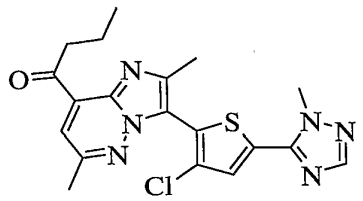


A. 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.32 g, 2.17 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}*H*-[1,2,4]triazole (0.72 g, 2.61 mmol), Cs_2CO_3 (1.49 g, 4.57 mmol) and DMF (6 mL) is de-gassed for 15 minutes with N_2. $Pd(OAc)_2$ (0.024 g, 0.11 mmol) and PPh_3 (0.057 g, 0.22 mmol) are added and the solution is heated at 135°C for 4 hours. The solution is diluted with CH_2Cl_2 (50 mL), washed with sat. NH_4Cl (2 x 50 mL), water (50 mL), filtered and concentrated. The residue is purified by ISCO flash chromatography (30%-100% EtOAc gradient) furnish the title compound (0.29 g, 0.84 mmol, 39%). ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 6.92 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H). LC/MS (m/z): calcd. for $C_{15}H_{13}ClN_6S$ $(M+H)^+$: 345.1; found: 345.2.

B. 1-{3-[3-Chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-butan-1-one.



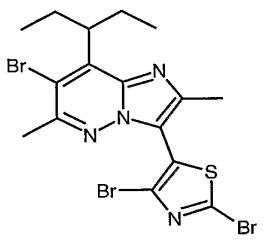
A solution of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.58 mmol), *N*-methoxy-*N*-methyl-butylamide (Wolberg, M. et. al. *Chem. Europ. J.* 2001, 7, 4562.) (0.084 g, 0.64 mmol) in THF (3 mL) is cooled to a -78 °C, and a 2.0 M solution of LDA in heptane/ THF/ ethyl benzene (0.58 mL, 1.16 mmol) is added. The solution is warmed to ambient temperature, diluted with dichloromethane (20 mL), and washed with a sat. NH_4Cl solution (15 mL). The organic layer is dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-100% EtOAc gradient) to furnish the title compound (0.11 g, 0.27 mmol, 46%). ^{1}H-NMR ($CDCl_3$), δ 1.04 (t, J = 7.0 Hz, 3H), 1.76-1.86 (m, 2H), 2.56 (s, 3H), 2.59 (s, 3H), 3.51 (t, J = 7.1 Hz, 2H), 4.15 (s, 3H), 7.36 (s, 1H), 7.49 (s, 1H), 7.90 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{19}H_{19}ClN_6OS$ $(M+H)^+$: 415.1; found: 415.3.

C. 4-{3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-heptan-4-ol.

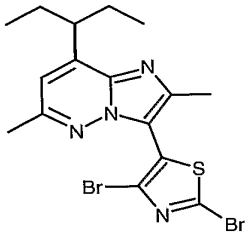
A solution of 1-{3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-butan-1-one (0.15 g, 0.36 mmol) and THF (5 mL) is cooled to 0°C, and a 2.0 M propyl magnesium bromide solution in diethylether (0.22 mL, 0.43 mmol) is added. The reaction is warmed to ambient temperature, diluted with ethyl acetate (30 mL), and washed with a sat. NH_4Cl solution (30 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO flash chromatography (20%-40% EtOAc gradient) to furnish the title compound (0.016 g, 0.017 mmol, 47%). ^{1}H-NMR ($CDCl_3$), δ 0.90 (t, J = 7.4 Hz, 6H), 1.12-1.29 (m, 2H), 1.37-1.54 (m, 2H), 1.86-2.04 (m, 4H), 2.50 (s, 3H), 2.54 (s, 3H), 4.15 (s, 3H), 6.11 (bs, 1H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{27}ClN_6OS$ $(M+H)^+$: 459.2; found: 459.3.

Example 190, 191, and 192.

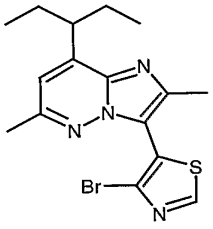
Preparation of 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; and 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



190.



191.



192.

A. 8-(1-ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine.

2.41 g (7 mmol) of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 3.00 g of thiazole (35.2 mmol), 378 mg of triphenylphosphine (1.44 mmol) and 4.71 g of Cs2CO3 (14.5 mmol) are combined with 25 ml of DMF and N2 gas is bubbled in for 30 min. 330 mg of Pd2dba3 (0.36 mmol) is added and the tube is sealed. The reaction tube is heated at 130°C overnight. To the reaction mixture is added water and CH2Cl2, and the CH2Cl2 layer is separated, washed with sat. NaCl and dried over Na2SO4. The solvents are removed *in vauo* and crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt = 3:1) to give 1.48 g of the title compound. Yield 70%. mass spectrum (m/e): 301(M+1); ^{1}H-NMR(CDCl3): 8.93(s, 1H), 8.52(s, 1H), 6.78(s, 1H), 3.35(m, 1H), 2.76(s, 3H), 2.66(s, 3H), 1.86(m, 4H), 0.89(t, 6H, J=7.5Hz).

B. 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; and 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

1.05 g (3.5 mmol) of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine and 1.56 g of NBS (8.75 mmol) are dissolved in 50 ml of CH2Cl2 and stirred at room temperature for 3 days. The reaction mixture is diluted with CH2Cl2 and washed with sat. $Na_2S_2O_3$ and sat. NaCl. The separated organic layer is dried over Na_2SO_4 and evaporated. The reaction mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 20:1→8:1) to give three products:

149 mg of 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (9%);

936 mg of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (58%); and

77 mg of 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (6%).

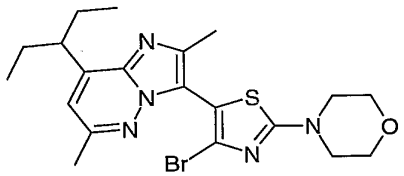
7-Bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 538(M+1); ^{1}H-NMR(CDCl3): 3.45(m, 1H), 2.71(s, 3H), 2.52(s, 3H), 2.38(m, 2H), 2.02(m, 2H), 0.88(t, 6H, J=7.5Hz);

3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 459(M+1); ^{1}H-NMR(CDCl3): 6.79(s, 1H), 5.33(m, 1H), 2.57(s, 3H), 2.55(s, 3H), 1.87(m, 4H), 0.90(t, 6H, J=7.5Hz); and

3-(4-Bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 380(M+1); ^{1}H-NMR(CDCl3): 9.01(s, 1H), 6.77(s, 1H), 3.35(m, 1H), 2.55(s, 3H), 2.54(s, 3H), 1.87(m, 4H), 0.91(t, 6H, J=7.5Hz).

Example 193.

Preparation of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



100 mg (0.22 mmol) of 3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol), 96 mg of morpholine (1.1 mmol) and 215 mg of Cs2CO3(0.66 mmol) are put in a 4 ml vial with dry THF, and the vial is

capped with a Teflon cap. The vial is heated at 120°C for overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane :AcOEt :2 M NH3 in MeOH = 9:3:1) to give 72.7 mg of the title compound. Yield 71%. mass spectrum (m/e): 465(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.87(t, 4H, J=5.1Hz), 3.58(t, 4H, J=5.1Hz), 3.35(m, 1H), 2.57(s, 3H), 2.53(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.5Hz).

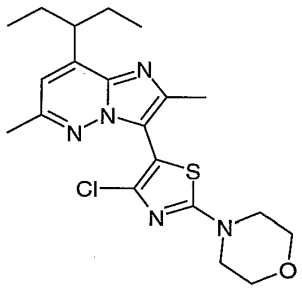
The following compounds are prepared essentially as described in Example 193. Examples 194-197 use 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol) and the named amine. Example 198. uses 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and the named amine:

Ex	Name	Amine	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
194	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-methyl-amine	Methyl-amine	6.75 (s, 1H), 5.85 (s, NH), 3.37 (m, 1H), 3.07 (d, J = 5.3 Hz, 3H), 2.59 (s, 3H), 2.55 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	409
195	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	Dimethyl-amine	6.72 (s, 1H), 3.36 (m, 1H), 3.19 (s, 6H), 2.57 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, J=7.3Hz)	423
196	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	N-2-methoxy-ethyl-methyl-amine	6.71 (s, 1H), 3.76 (m, 2H), 3.71 (m, 2H), 3.42 (s, 3H), 3.35 (s, 1H), 3.21 (s, 3H), 2.57(s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	467

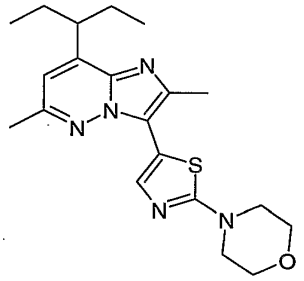
197	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	N-methyl-i-propyl-amine	6.72 (s, 1H), 4.43 (m, 1H), 3.36 (m, 1H), 3.0 (s, 3H), 2.57 (s, 3H), 2.54 (s, 3H), 1.86 (m, 4H), 1.31 (s, 3H), 1.29 (s, 3H), 0.90 (t, J = 7.4 Hz, 6H).	451
198	N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-bromo-thiazol-2-yl}-morpholine	Morpholine	3.87 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 7.8 Hz, 4H), 3.43 (m, 1H), 2.71(s, 3H), 2.50 (s, 3H), 2.38 (m, 2H), 2.01 (m, 2H), 0.88 (t, J = 7.5 Hz, 6H).	544

Example 199 and 200.

Preparation of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine and N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine.



199.



200.

Method A

40 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 25 mg of CuCl (0.25 mmol) are put in a 4 ml vial with 2 ml of dry DMF and capped with a Teflon cap. The vial is heated at 120°C overnight. The reaction mixture is filtered, washed with CH2Cl2 and the filtrate is concentrated. The crude product mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 2:1 and Hexane : AcOEt = 8:1) to give two products:

4.2 mg of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (12%), and

7.2 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (22%).

N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine mass spectrum (m/e): 420(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.88(t, 4H, J=5.0 Hz), 3.57(t, 4H, J=5.0Hz), 3.35(m, 1H), 2.57(s, 3H), 2.52(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.5Hz.

N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine mass spectrum (m/e): 386(M+1); ^{1}H-NMR(CDCl3): 7.75(s, 1H), 6.70(s, 1H), 3.91(t, 4H, J=5.0Hz), 3.61(t, 4H, J=5.0Hz), 3.34(m, 1H), 2.67(s, 3H), 2.61(s, 3H), 1.85(m, 4H), 0.88(t, 6H, J=7.5Hz).

Method B N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine.

A 20L reactor flask under nitrogen is charged with 2900 ml of dry and degassed DMF then with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[1,2-b]pyridazine (287 g, 0.836 mol), 2-morpholino-4-chlorothiazole (205.4 g, 1.01 mol, 1.2 equv.), $Pd(OAc)_2$ (3.74 g, 7.91 mmol, 0.01 equiv.), triphenylphosphine (8.77g, 33.1 mmol, 0.04 equiv.), Copper iodide (8 g, 41.59 mmol, 0.05 equiv.) and cesium carbonate (544.9 g, 1.65 mol). The reaction mixture is heated at 120°C. After 16 h at 120°C, 1.87 g of $Pd(OAc)_2$ and 4.38 g of triphenylphosphine more is added. After 1 h, the mixture is cooled, quenched with NH_4Cl solution (4300 mL) and extracted with MTBE (2900 mL), the aqueous phase is extracted twice more with 2000 ml of MTBE. The organic phases are washed with sat NaCl aq (2000 mL), then treated with charcoal 72 g in flask bottle and filtered on Celite®. The filtrate is concentrated under vacuum to afford 373.8 g (79.3%) of the title compound which is 81.4%-area HPLC analysis the rest being solvent and with no detectable Example 200 by-product.

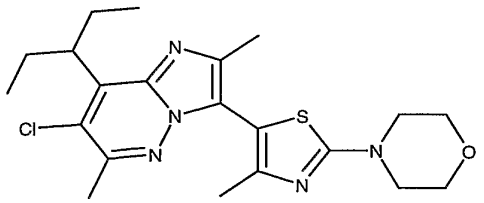
The following title compounds are prepared essentially as described in Examples 199 and 200 Method A:

Example #	Name	Starting material	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
201	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	6.72 (s, 1H), 3.36 (m, 1H), 3.19 (s, 6H), 2.57 (s, 3H), 2.51 (s, 3H), 1.84 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H).	378
202	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	7.74 (s, 1H), 6.67 (s, 1H), 3.35 (m, 1H), 2.23 (s, 6H), 2.67(s, 3H), 2.61 (s, 3H), 1.84 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	344
203	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	6.71 (s, 1H), 3.76 (t, J = 5.3 Hz, 2H), 3.71 (t, J = 5.1 Hz, 2H), 3.42 (s, 3H), 3.36 (m, 1H), 3.20 (s, 3H), 2.58 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	423
204	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-	7.72 (s, 1H), 6.68 (s, 1H), 3.80 (t, J = 5.7 Hz, 2H), 3.72 (t, J = 5.7 Hz, 2H), 3.42 (s, 3H), 3.35 (m, 1H), 3.26 (s, 3H), 2.67 (s, 3H), 2.61 (s, 3H), 1.84	388

	methylamine	methylamine	(m, 4H), 0.88 (t, J = 7.7 Hz, 6H).	
205	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	6.71 (s, 1H), 4.48 (m, J = 7.4, 13.2 Hz, 1H), 3.34 (m, J = 7.6, 14.4 Hz, 1H), 3.04 (s, 3H), 2.76 (s, 3H), 2.61 (s, 3H), 1.85 (m, 4H), 1.31 (d, J = 7.1 Hz, 6H), 0.88 (t, J = 7.3 Hz, 6H).	407
206	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-isopropyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	7.72 (s, 1H), 6.67 (s, 1H), 4.48 (m, 1H), 3.33 (m, 1H), 3.03 (s, 3H), 2.66 (s, 3H), 2.60 (s, 3H), 1.84 (m, 4H), 1.31 (d, J = 6.8, 6H), 0.88 (t, J = 7.2 Hz, 6H).	371

Example 207.

Preparation of N-{5-[7-chloro-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.

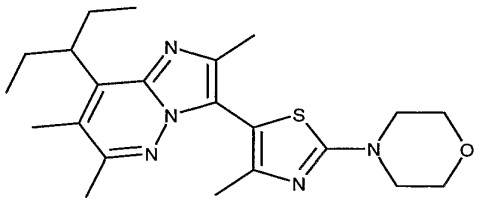


50 mg of N-{5-[7-Bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine (0.1 mmol) is dissolved in 2.0 ml of

dry DMF and 31 mg of CuCl (0.3 mmol) is added. The vial is capped with a Teflon® lined cap and heated at 120°C for overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 39.2 mg of the title compound. Yield 87%. mass spectrum (m/e): 435(M+1). 3.88 (t, J = 4.8 Hz, 4H), 3.57 (t, J = 5.1 Hz, 4H), 2.64(s, 3H), 2.44 (s, 3H), 2.18 (s, 3H), 2.00 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Example 208.

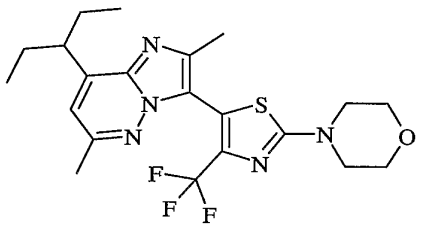
Preparation of N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6,7-trimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.



50 mg of N-{5-[7-Bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine (0.1 mmol) is dissolved in 4 ml of Et2O and cooled to –78°C. 0.09 ml of n-BuLi 1.6M in hexane (0.15 mmol) is added at –78°C and stirred at –78°C for 20 min. 43 mg of iodomethane (0.3 mmol) is added to the mixture and stirred at –78°C and allowed to come to room temperature overnight. The reaction is quenched with sat. NH4Cl and extracted with Et2O. The separated organic layer is dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=3:1) to give 29.6 mg of the title compound. Yield 69%. mass spectrum (m/e): 414(M+1). ^{1}H NMR ($CDCl_3$): δ 3.87 (t, J = 4.6 Hz, 4H), 3.56 (t, J = 4.6 Hz, 4H), 3.35 (m, 1H), 2.54 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H), 2.01 (m, 4H), 0.88 (m, 6H).

Example 209.

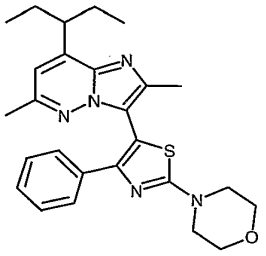
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-trifluoromethyl-thiazol-2-yl}-morpholine.



170 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.37 mmol) and 100 mg of sodium trifluoroacetate (0.74 mmol) are dissolved in 3 ml of DMF/toluene = 2/1. N2 gas is bubbled into the mixture for 20 min and 141 mg of CuI (0.74 mmol) is added. The vial is sealed and heated in the microwave at 210°C for 30 min. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1 and CH3CN : CH2Cl2 : Hexane = 5 : 45 : 50) to give 64.3 mg of the title compound. Yield 38%. mass spectrum (m/e): 454(M+1). ^{1}H NMR ($CDCl_3$): δ 6.72 (s, 1H), 3.88 (m, 4H), 3.60 (m, 4H), 3.32 (m, 1H), 2.54 (s, 3H), 2.47 (s, 3H), 1.85 (m, 4H), 0.89 (t, J = 7.0 Hz, 6H).

Example 210.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-phenyl-thiazol-2-yl}-morpholine.

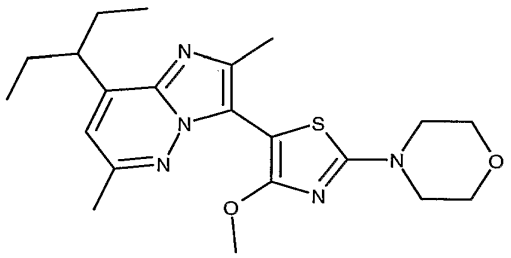


50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), 40 mg of phenylboronic acid (0.33 mmol) and 0.27 ml of 2 M Na2CO3aq.(0.55 mmol) are put in 2.5 ml of DME / water / EtOH = 7 / 3 / 1. N2 gas is bubbled in the mixture for 20 min and 20 mg of Pd(PPh3)4

(0.017 mmol) is added. The vial is sealed and heated at 160°C for 30 min in Microwave. The reaction mixture are added CH2Cl2 and water and the organic layer is separated, washed with brine, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt = 10:1) to give 27 mg of the title compound. Yield 54% mass spectrum (m/e): 462(M+1). δ 8.29(m, 1H), 7.60(m, 2H), 7.44(m, 1H), 7.22(m, 1H), 6.70 (s, 1H), 3.90 (t, J = 4.6 Hz, 4H), 3.64 (t, J = 5.0 Hz, 4H), 3.36 (m, 1H), 2.52 (s, 3H), 2.09 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Example 211.

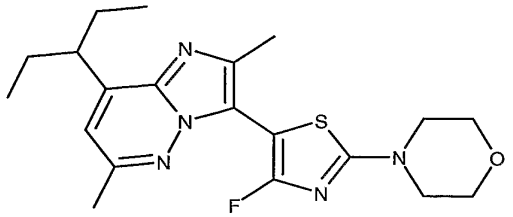
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methoxy-thiazol-2-yl}-morpholine.



100 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol), 24 mg of sodium methoxide (0.44 mmol) and 21 mg of CuI (0.11 mmol) are put into 4 ml vial with MeOH 3 ml and capped with a Teflon® lined cap. The reaction vial is heated at 130°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane : THF = 10 : 1) to give 32.8 mg of the title compound. Yield 36%. Mass spectrum (m/e): 416(M+1). ^{1}H NMR ($CDCl_3$): δ 6.64 (s, 1H), 3.96 (s, 3H), 3.86 (t, J = 4.7 Hz, 4H), 3.53 (m, 4H), 3.34 (m, 1H), 2.82 (s, 3H), 2.48 (s, 3H), 1.82 (m, 4H), 0.85 (t, J = 7.4 Hz, 6H).

Example 212.

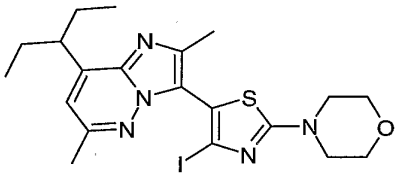
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-fluoro-thiazol-2-yl}-morpholine.



50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol) is dissolved in 4 ml of diethylether and cooled to –78°C and 0.1 ml of n-BuLi 1.6M in hexane (0.16 mmol) is added at –78°C and stirred at –78°C for 20 min. 104 mg of N-fluorobenzene sulfonimide (0.33 mmol) in 2 ml of toluene is added at –78°C and stirred at room temperature for 1h. sat. NH4Cl is added, and the mixture is extracted with Et2O, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 4.1 mg of the title compound. Yield 10%. Mass spectrum (m/e): 404 (M+1). 6.71 (s, 1H), 3.87 (t, J = 4.6 Hz, 4H), 3.55 (t, J = 5.0 Hz, 4H), 3.34 (m, 1H), 2.58 (s, 3H), 2.54 (s, 3H), 1.84 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Example 213.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-iodo-thiazol-2-yl}-morpholine.

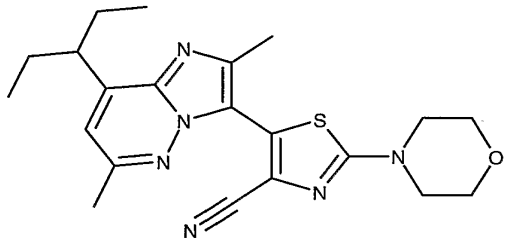


50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), 30 mg of CF_3CO_2Na (0.22 mmol) and 42 mg of CuI (0.22 mmol) are put into 4 ml vial with DMF / toluene = 2:1. The vial is capped with a Teflon cap and heated at 150°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane :AcOEt = 5 : 1) to give 54 mg of the

title compound. 96%. Mass spectrum (m/e): 512 (M+1). ^{1}H NMR ($CDCl_3$): δ 6.71 (s, 1H), 3.87 (t, J = 5.4 Hz, 4H), 3.58 (t, J = 5.4 Hz, 4H), 3.36 (m, 1H), 2.57 (s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 5.4 Hz, 6H).

Example 214.

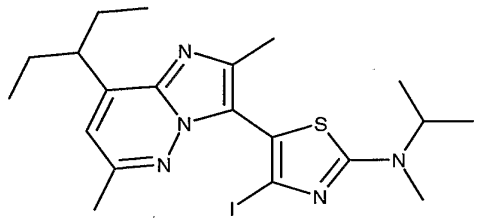
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-2-morpholin-4-yl-thiazole-4-carbonitrile



50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), and 30 mg of CuCN (0.33 mmol) are put into 4 ml vial with 2 ml of DMF and the vial is capped with a Teflon cap. The vial is heated at 150°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=5:1) to give 12.3 mg of the title compound. Yield 28%. Mass spectrum (m/e): 411(M+1). 6.77 (s, 1H), 3.89 (t, J = 4.8 Hz, 4H), 3.61 (t, J = 5.0 Hz, 4H), 3.32 (m, 1H), 2.62 (s, 3H), 2.59 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Example 215.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-iodo-thiazol-2-yl}-N-isopropyl-methylamine.

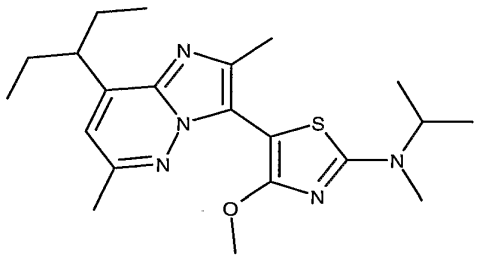


The title compound is prepared essentially as described in Example 213, employing N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-

bromo-thiazol-2-yl}-N-isopropyl-methylamine to give 17.9 mg. Yield 22%: mass spectrum (m/e):498 (M+1). ^{1}H NMR ($CDCl_3$): δ 6.71 (s, 1H), 4.41 (m, 1H), 3.35 (m, 1H), 2.97 (s, 3H), 2.57 (s, 3H), 2.53 (s, 3H), 1.84 (m, 4H), 1.29 (d, J = 5.8 Hz, 6H), 0.90 (t, J = 7.2 Hz, 6H).

Example 216.

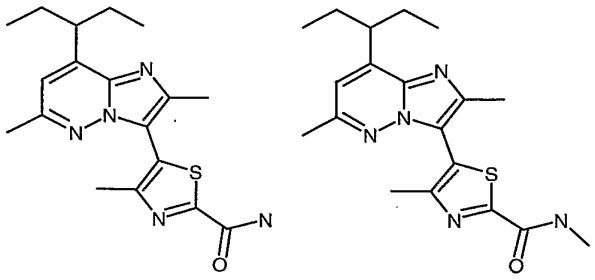
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methoxy-thiazol-2-yl}-N-isopropyl-methylamine.



The title compound is prepared essentially as described in Example 211, employing N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-bromo-thiazol-2-yl}-N-isopropyl-methylamine to give 52.7. Yield 36%: mass spectrum (m/e):402(M+1). ^{1}H NMR ($CDCl_3$): δ 6.63 (s, 1H), 4.44 (m, 1H), 3.96 (s, 3H), 3.35 (m, 1H), 2.97 (s, 3H), 2.57 (s, 3H), 2.50 (s, 3H), 1.83 (m, 4H), 1.29 (d, J = 6.7 Hz, 6H), 0.88 (t, J = 8 Hz, 6H).

Example 217 and 218.

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide and 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid N-methylamide.



217. 218.

180 mg of 8-(1-Ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.46 mmol) and 124 mg of copper(I) cyanide are put into 4 ml vial with 2 ml of dry DMF. The vial is closed with a Teflon can and heated at 130°C overnight. The crude reaction mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 1:1 →1:3) to give

52.1 mg of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide (32%) and

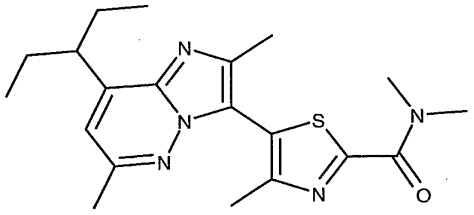
7.6 mg of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid methylamide.

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide: mass spectrum (m/e): 358(M+1) ^{1}H NMR ($CDCl_3$): δ 7.21 (s, NH), 6.76 (s, 1H), 5.59 (s, NH), 3.34 (m, 1H), 2.55 (s, 3H), 2.50 (s, 3H), 2.42 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H). and

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid methylamide: mass spectrum (m/e): 372(M+1). ^{1}H NMR ($CDCl_3$): 8.77 (s, NH), 6.75 (s, 1H), 4.06 (s, 3H), 3.35 (m, 1H), 2.55 (s, 3H), 2.49 (s, 3H), 2.43 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).

Example 219.

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid dimethylamide.

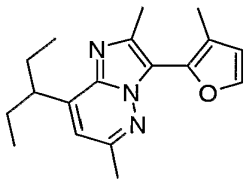


5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide (46 mg, 0.13 mmol) and 28 mg of sodium *tert*-Butoxide (0.30 mmol) are put into 4 ml of dry DMSO and stirred at room temperature for 5 min. 141 mg of iodomethane (1.0 mmol) is added and stirred at room temperature for 1 h.

Water is added, and the mixture is extracted with CH_2Cl_2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=3:1) to give 22.3 mg of the title compound. Yield 45%: mass spectrum (m/e):386(M+1). 6.75 (s, 1H), 3.70 (s, 3H), 3.35 (m, 1H), 3.21 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.41 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).

Example 220.

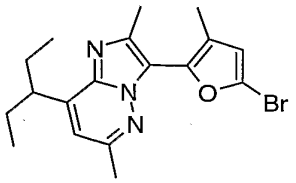
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-furan-2-yl)-imidazo[*1,2-b*]pyridazine.



A THF solution (5 mL) of 3-methylfuran (Acros, 232 mg, 2.83 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 1.8 mL, 2.9 mmol). After addition of the nBuLi, the solution is warmed to 0 °C for 15 minutes, then to room temperature for an additional 5 minutes. The reaction mixture is then cooled to -78 °C and treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 5.8 mL, 2.9 mmol). The resulting mixture is warmed to room temperature and treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (400 mg, 1.17 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 95 mg, 0.12 mmol). The mixture is heated to 60 °C for 4 hours, then poured into 1 N HCl (60 mL) and extracted with ethyl acetate (2x60 mL). The combined organic extracts are washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound as an oil pyridazine (149 mg, 43% yield). ES-MS (m/z): calc'd for $C_{18}H_{23}N_3O$: 297.2; found 298.5 (M+H); ^{1}H NMR (400 mHz, $CDCl_3$): δ 7.59 (d, J = 1.8 Hz, 1H), 6.71 (s, 1H), 6.47 (d, J = 1.8 Hz, 1H), 3.36 (m, 1H), 2.55 (s, 3H), 2.50 (s, 3H), 2.10 (s, 3H), 1.92-1.79 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H).

Example 221.

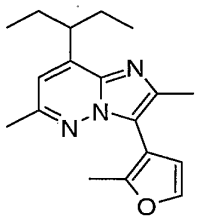
Preparation of 3-(5-bromo-3-methyl-furan-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A CH_2Cl_2 solution (4 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-furan-2-yl)-imidazo[*1,2-b*]pyridazine (32.4 mg, 0.11 mmol) is cooled to 0 °C under a $CaSO_4$ drying tube and treated with NBS (20.1 mg, 0.11 mmol). After 15 minutes at 0 °C, the mixture is warmed to room temperature. After an additional 10 minutes, the reaction mixture is poured into H_2O (25 mL) and extracted into CH_2Cl_2 (2x25 mL). The combined organic extracts are washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 10% ethyl acetate in hexane) to elute the title compound (26.3 mg, 64% yield) as a solid. ES-MS (m/z): calc'd for $C_{18}H_{22}BrN_3O$: 375.1; found 376.2 (M+H); ^1H NMR (400 mHz, $CDCl_3$): δ 6.72 (s, 1H), 6.40 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.49 (s, 3H), 2.07 (s, 3H), 1.93-1.77 (m, 4H), 0.89 (t, J = 7.5 Hz, 6H).

Example 222.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo[*1,2-b*]pyridazine.



A. 3-Bromo-2-methyl furan.

A THF solution (10 mL) of 2,3-dibromofuran (Lancaster, 5.54 gm, 24.5 mmol) under N_2 is treated with $PdCl_2(PPh_3)_2$ (860 mg, 1.2 mmol) and stirred for 10 minutes at

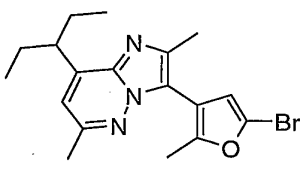
room temperature. The solution is then treated with CH_3ZnCl (Aldrich, 2.0 M in THF, 15 mL, 30 mmol). The resulting mixture is stirred at room temperature overnight then poured into 1 N HCl and extracted into diethyl ether. The organic extract is washed with sat. NaCl, dried over Na_2SO_4, and filtered. The filtrate is then distilled and the product is collected at 120-125 °C to give the title compound as a colorless oil (1.71 gm, 43% yield). ^1H NMR (400 mHz, $CDCl_3$): δ 7.25 (d, J = 1.8 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 2.28 (s, 3H).

B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo[*1,2-b*]pyridazine.

A THF solution (10 mL) of 3-bromo-2-methyl furan (prepared as described above) (1.06 gm, 6.58 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 4.1 mL, 6.6 mmol). After 10 minutes at -78 °C, the mixture is treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 13.2 mL, 6.6 mmol). The resulting mixture is warmed to room temperature then treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.13 gm, 3.29 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 257 mg, 0.31 mmol). The mixture is heated to 60 °C for 4 hours, then poured into sat. NH_4Cl (50 mL) and extracted with diethyl ether (2x50 mL). The combined organic extracts are washed with sat. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title product (685 mg, 70% yield) as an oil. ES-MS (m/z): calc'd for $C_{18}H_{23}N_3O$: 297.2; found 298.2 (M+H); ^1H NMR (400 mHz, $CDCl_3$): δ 7.45 (d, J = 2.0 Hz, 1H), 6.63 (s, 1H), 6.60 (d, J = 2.0 Hz, 1H), 3.35-3.31 (m, 1H), 2.51 (s, 3H), 2.44 (s, 3H), 2.30 (s, 3H), 1.88-1.75 (m, 4H), 0.86 (t, J = 7.5 Hz, 6H).

Example 223.

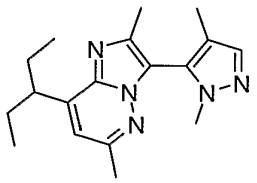
Preparation of 3-(5-bromo-2-methyl-furan-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A CH_2Cl_2 solution (2 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo[*1,2-b*]pyridazine (42.3 mg, 0.14 mmol) under a $CaSO_4$ drying tube is treated with N-bromosuccinimide (27.6 mg, 0.16 mg). After 30 minutes the reaction mixture is poured into H_2O (25 mL) and extracted into CH_2Cl_2 (2x25 mL). The combined organic extracts are washed with sat. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 12% ethyl acetate in hexane) to elute the title product (36.9 mg, 70% yield) as a white solid. ES-MS (m/z): calc'd for $C_{18}H_{22}BrN_3O$: 375.1; found 376.3 (M+H); ^1H NMR (400 mHz, $CDCl_3$): δ 6.67 (s, 1H), 6.50 (s, 1H), 3.33 (m, 1H), 2.53 (s, 3H), 2.44 (s, 3H), 2.29 (s, 3H), 1.90-1.73 (m, 4H), 0.86 (t, J = 7.3 Hz, 6H).

Example 224.

Preparation of 3-(2,4-dimethyl-*2H*-pyrazol-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

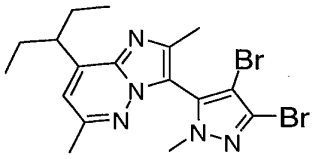


n-BuLi (1.3 ml, 2.09 mmol) is stirred in THF (4 ml), under N_2, and cooled to –72°C. 1,4-dimethyl-*1H*-pyrazole (170 mg, 2.04 mmol, in THF, 1 ml) is added slowly, stirred for 5 min. then allowed to warm to ambient temp. and stirred for 45 min. The mixture is cooled to –72°C and a zinc chloride solution (4.3 ml, 2.14 mmol, 0.5 M in toluene) added, warmed to ambient temp. and treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 40 mg, 0.05 mmol). The mixture is heated to 65°C overnight, cooled to ambient temp., added to water and extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 50 % ethyl acetate in hexane) to elute the product. The title compound is obtained (0.7% yield). ES-MS (m/z): calc'd for $C_{18}H_{25}N_5$: 311.4; found 312.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$):

δ 7.51 (s, 1H), 6.75 (s, 1H), 3.72 (s, 3H), 3.33 (m, 1H), 2.53 (s, 3H), 2.43 (s, 3H), 2.00 (s, 3H), 1.87 (m, 4H), 0.92 (m, 6H).

Example 225.

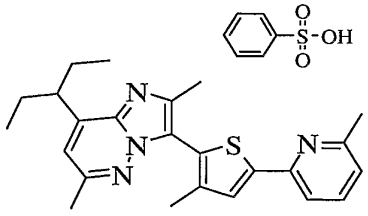
Preparation of 3-(4,5-dibromo-2-methyl-*2H*-pyrazol-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (300 mg, 1.4 mmol), 3,4,5-tribromo-1-methyl-*1H*-pyrazole (700 mg, 2.1 mmol) and cesium carbonate (900 mg, 2.8 mmol) are stirred in DMF (5 ml) and degassed by bubbling a stream of nitrogen through the mixture. $PdCl_2(PPh_3)_2$ (14 mg) is added and the mixture heated to 130°C overnight. The mixture is added to water and extracted twice with EtOAc. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title product (204 mg, 32% yield). ES-MS (m/z): calc'd for $C_{17}H_{21}Br_2N_5$: 455.2; found 455.9 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 6.75 (s, 1H), 3.72 (s, 3H), 3.33 (m, 1H), 2.51 (s, 3H), 2.45 (s, 3H), 1.84 (m, 4H), 0.88 (t, 6H).

Example 226.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine benzenesulfonic acid.

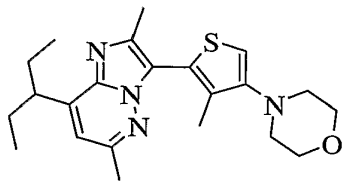


To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.23 g, 0.57 mmol) and MeOH (1

mL) is added a solution of benzenesulfonic acid (0.096 g, 0.57 mmol) and MeOH (1 mL). The solution is concentrated to furnish the title compound (0.32 g, 0.57 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 7.0 Hz, 6H), 1.59-1.82 (m, 4H), 2.06 (s, 3H), 2.61 (s, 6H), 2.88 (s, 3H), 3.22-3.32 (m, 1H), 6.79 (bs, 2H), 7.25 (s, 1H), 7.33-7.42 (m, 3H), 7.49 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.4 Hz, 2H), 7.92 (dd, J = 7.4, 1.6 Hz, 1H) 8.23 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.2; found: 405.4.

Example 227.

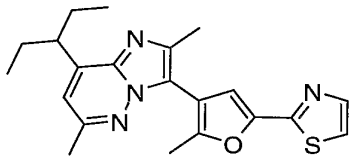
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-morpholin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30g, 0.76 mmol), morpholine (0.10 mL, 1.15 mmol), $Pd_2(dba)_3$ (0.035 g, 0.038 mmol), and 2-dicyclohexylphosphino-biphenyl-2'-(N,N-dimethyl-amino)biphenyl (0.018 g, 0.046 mmol) is added 1 M LiHMDS (1.9 mL, 1.91 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-30% EtOAc gradient), dissolved in Et_2O (20 mL) and extracted with 1 M HCl (2 x 30 mL). The aqueous layer is washed with Et_2O (20 mL), made basic with 5 M NaOH (15 mL), extracted with EtOAc (2 x 20 mL), the combined organic layers washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.047 g, 0.12 mmol, 16%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.01 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 2.99-3.05 (m, 4H), 3.28-3.37 (m, 1H), 3.84-3.88 (m, 4H), 6.65 (s, 1H), 6.71 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{30}N_4OS$ $(M+H)^+$: 399.2; found: 399.2.

Example 228.

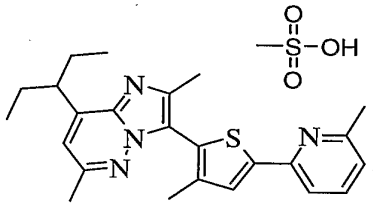
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-thiazol-2-yl-furan-3-yl)-imidazo[*1,2-b*]pyridazine.



A THF solution (5 mL) of 2-bromothiazole (Aldrich, freshly distilled, 75.0 μL, 0.84 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 0.52 mL, 0.83 mmol). After 15 minutes at -78 °C, the mixture is treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 1.8 mL, 0.90 mmol). The resulting mixture is warmed to room temperature then treated with a THF slurry (1 mL) containing 3-(5-bromo-2-methyl-furan-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (60.1 mg, 0.16 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 22 mg, 0.027 mmol). The mixture is heated overnight at 60 °C, then poured into sat'd NH_4Cl and extracted with diethyl ether. The organic extract is washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (45.8 mg, 75% yield) as an oil. ES-MS (m/z): calc'd for $C_{21}H_{24}N_4OS$: 380.17; found 381.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.83 (d, J = 3.5 Hz, 1H), 7.29 (d, J = 3.1 Hz, 1H), 7.20 (s, 1H), 6.68 (br s, 1H), 3.35 (br s, 1H), 2.53 (s, 3H), 2.49 (s, 3H), 2.40 (s, 3H), 1.90-1.76 (m, 4H), 0.88 (t, J = 7.5 Hz, 6H).

Example 229.

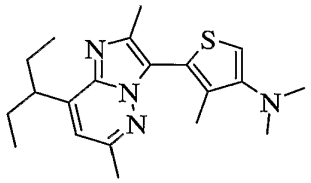
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine; compound with methanesulfonic acid.



To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (0.55 g, 1.36 mmol) and MeOH (6 mL) is added methane sulfonic acid (0.088 mL, 1.36 mmol). After one hour the solution is concentrated and the solution is treated with Darco-60® for 1 hour, filtered and concentrated to furnish the title compound (0.68 g, 1.36 mmol, >99%). ^{1}H NMR ($CDCl_3$: CD_3OD 95:5) δ 0.85 (t, J = 7.4 Hz, 6H), 1.67-1.91 (m, 4H), 1.96 (s, 3H), 1.97 (s, 3H), 2.20 (s, 3H), 2.61 (s, 3H), 2.90 (s, 3H), 3.17-3.29 (m, 1H), 7.33 (s, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 8.18 (s, 1H), 8.34 (t, J = 7.9 Hz, 1H), 9.95 (bs, 1H). LC/MS (m/z): calcd. for $C_{25}H_{32}N_4O_2S_2$ $(M+H)^+$: 405.6; found: 405.6.

Example 230.

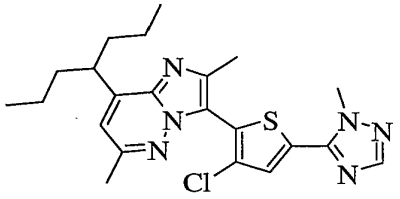
Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-3-yl}-dimethyl-amine.



To a –78 °C solution of dimethyl-(4-methyl-thiophen-3-yl)-amine (0.43 g, 3.06 mmol) and THF (5 mL) is added 1.6 M *n*-BuLi (1.91 mL, 3.06 mmol). The solution is stirred for 1 hour, then 0.5 M $ZnCl_2$ (6.1 mL, 3.06 mmol) is added and the solution warmed to ambient temperature. After 30 minutes 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.70 g, 2.04 mmol) and $PdCl_2$(dppf) (0.075 g, 0.10 mmol) is added and the solution heated at 65 °C overnight. The solution is diluted with EtOAc (35 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (15% -30% EtOAc gradient) furnish the title compound (0.13 g, 0.36 mmol, 18%). ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.03 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 2.77 (s, 6H), 3.28-3.37 (m, 1H), 6.63 (s, 1H), 6.65 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{28}N_4S$ $(M+H)^+$: 357.2; found: 357.2

Example 231.

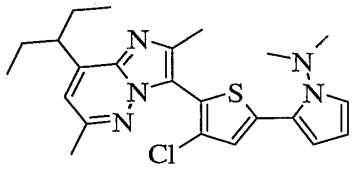
Preparation of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.



A slurry of 2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine (below) (0.30 g, 1.22 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-[1,2,4]triazole (below) (0.41 g, 1.47 mmol), KOAc (0.60 g, 6.11 mmol), TBABr (0.39 g, 1.22 mmol), and NMP (3 mL) is de-gassed with N_2 for 30 minutes. $Pd(OAc)_2$ (0.014 g, 0.061 mmol) and TDBPP (0.040 g, 0.061 mmol) are added and the solution heated at 125 °C for 2.5 hours. The solution is diluted with EtOAc (50 mL), washed with water (3 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-40% EtOAc gradient) furnish the title compound (0.30 g, 0.68 mmol, 56%). ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 6H), 1.14-1.39 (m, 4H), 1.76 (q, J = 16.3, 7.7 Hz, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.41-3.50 (m, 1H), 4.15 (s, 3H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}ClN_6S$ $(M+H)^+$: 443.2; found: 443.3.

Example 232.

Preparation of (2-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophen-2-yl}-pyrrol-1-yl)-dimethyl-amine.

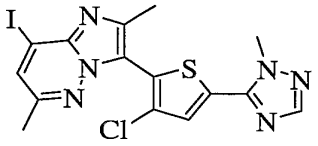


Using a procedure analogous to Example 27, 1-(dimethylamino)-pyrrole (0.20 mL, 1.65 mmol), THF (4 mL), 1.6 M *n*-BuLi (1.10 mL, 1.73 mmol), 0.5 M $ZnCl_2$ (3.46 mL, 1.73 mmol), 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.34 g, 0.82 mmol) and $PdCl_2$(dppf) (0.030 g, 0.041 mmol),

furnish the title compound (0.17 g, 0.38 mmol, 46%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 6H), 2.84 (s, 6H), 3.28-3.39 (m, 1H), 6.21 (dd, J = 4.1, 3.2 Hz, 1H), 6.38 (dd, J = 4.1, 1.8 Hz, 1H), 6.68 (s, 1H), 7.02 (dd, J = 3.2, 1.8 Hz, 1H), 7.29 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}ClN_5S$ $(M+H)^+$: 442.2; found: 442.3.

Example 233.

Preparation of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 4-Chloro-thiophene-2-carbonitrile.

A 22-L reaction flask is equipped with a cooling bath, air stirrer, gas addition tube, and thermometer probe. The flask is purged with nitrogen, then charged $AlCl_3$ (1025 g, 7.69 moles) and $CHCl_3$(6.6 L, 16.5 vol.). After cooling the mixture to 0-5 °C, it is charged with 2-thiophene carbonitrile (400 g, 3.66 moles) dropwise via an addition funnel over 10-15 minutes while maintaining the temperature at ≤ 10 °C. The mixture is charged with Cl_2 gas (300g, 4.23 moles, 1.16 EQ) subsurface at ≤ 10 °C over 1.25 hours. The progress of the reaction is monitored by GC, wherein the GC sampling method is quenching an aliquot of the reaction mixture into 6N HCl, extracting with EtOAc, drying over Na_2SO_4, filtering, and injecting the filtrate.

When the reaction is deemed complete by GC analysis [the reaction was deemed complete when the ratio of (sm : prod : dichloro) was approximately (1 : 5.8 : 1) by area % GC.], 6N HCl (8.0 L) is added dropwise via addition funnel over 1.5 hours, while maintaining the temperature at ≤ 20 °C [The HCl addition is extremely exothermic and evolves gas]. The reaction is transferred to a separatory funnel and the layers are separated. After extracting the aqueous layer with $CHCl_3$ (4.0 L), the chloroform layers are combined and washed with de-ionized H_2O (6.0L). The organic layer is dried over Na_2SO_4, filtered and concentrated under vacuum to give a pale yellow semi solid 575g, 109.3%). GC (60°C to 280°C temperature gradient) Area-% analysis shows ~68%

product (t_{ret} = 6.5 min) with major impurities being the unreacted starting material (t_{ret} = 5.1 min) and the dichlorinated product (t_{ret} = 7.4 min). GC Method: Column: DB1; $T_{injecyt}$ = 300 °C ; $T_{initial}$ = 60 °C, t = 2.0 min; T_{final} = 280 °C, rate = 18 °C/min.

B. 4-Chloro-2-thiophene carboxamide.

A 12-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with KOH (288.6 g, 5.143 moles) and De-ionized H_2O (6.04 L) to form a solution that exotherms to ~31 °C. After allowing the solution to cool to ~28.0 °C, th mixture is charged with 4-chloro-2-thiophene carbonitrile (671.3 g, 4.675 moles)[1] followed by EtOH (675 mL). A gradual exotherm occurs upon the addition of EtOH and continues over 1-1.5 hours to ~38 °C. The reaction is stirred at ambient temperature overnight.

The reaction mixture is filtered under vacuum, washed with de-ionized H_2O and dried to give crude product. The solids are dissolved in EtOAc (10.0 L) treated with Na_2SO_4 and Darco for 1-2 hours; then, filtered and washed with EtOAc. The filtrate is concentrated on the Büchi until solids began to precipitate out at 45 °C at which time the vacuum is released, and the temperature is increased to 60-65 °C to redissolve the solids. With stirring at 60 °C, heptane (3.5 L) is added slowly to precipitate solids. After stirring for 15-20 minutes at 60 °C, the mixture is cooled to 30-40 °C and filtered. The solids are washed with heptane (2 x 0.75 L), and dried to give the title compound (t_{ret} = 9.9 min) as a white solid (235.4 g, 31.2 % 96.4 area % by GC analysis). A second crop is obtained from the filtrate to give 67.8 g, 9.0 %; 94.5% area-% by GC analysis). The Overall yield is 303.2 g, 40.1 %.

C. 4-Chloro-N-dimethylaminomethylene-2-thiophene carboxamide.

A 5-L reaction flask equipped with a heating mantle, air stirrer, Dean-Stark apparatus, and thermometer probe is charged with 4-chloro-2-thiophene carboxamide. (300 g, 1.856 moles) and dimethylformamide dimethylacetal (872 mL) to form a slurry that endotherms 1-2 °C from 22-20 °C. The mixture is heated gradually to 96 °C while collecting the distillate (mostly MeOH). The heating mantle is removed, and the mixture is cooled to $\leq$ 25 °C. De-ionized H_2O (3.0 L) is added via an addition funnel and the

[1] A small amount of solids were undissolved at this point.

temperature is maintained at $\leq$ 35 °C. The reaction mixture is extracted with EtOAc (1 x 3.0 L, 1 x 1.5 L), then combined the organics are washed with de-ionized H_2O (1.5 L). The organic phase is dried over Na_2SO_4, filtered, and concentrated under vacuum to give crude product (400 g).

The crude product is dissolved in EtOAc (320 mL, 0.8 Vol) at 50-60 °C; then, heptane (1700 mL, 4.25 Vol) is added slowly while gradually increasing the temperature to 70 °C. A seed crystal (Lot: PP6-H00086-075-1) is added to the cloudy solution to initiate precipitation. The resulting mixture is stirred to room temperature overnight, then filtered and washed with heptane. The solids are dried to give the title compound (t_{ret} = 13.0 min) as a white solid (329.8 g, 82%; 98.2 % area-% by GC analysis).

D. 5-(4-Chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole.

A 3-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide. (155 g, 0.715 moles) and HOAc (1500 mL) to form a solution. Using an ice-water cooling bath to maintain the temperature at $\leq$ 30 °C, methylhydrazine (33.2 g, 0.721 moles) is added dropwise via an addition funnel over 15-20 minutes to form a light yellow slurry. Gradually, the reaction is heated to 90 °C and held at 90 °C for 30 minutes. After analysis of the mixture by GC, the reaction is cooled to ~70 °C; then, concentrated to a thick oil/slurry. De-ionized H_2O (1.67 L) is slowly added to precipitate solids; then, the mixture is cooled to < 30 °C, filtered and washed with de-ionized H_2O (1.67 L). The wet solids (125.8 g) are re-dissolved in warm MTBE (1.64 L), dried over Na_2SO_4, filtered and concentrated to dryness giving the title compound as a pale yellow solid (85.8 g, 60.1% 91.9 % area % by GC).

E. 5-(5-Bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole.

A 3-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with 5-(4-Chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole (105.3 g, 0.527 moles), ACN (1053 mL) and HOAc (105 mL) to form a solution. NBS

(103.2 g, 0.580 moles) is added portion-wise over 30-60 minutes while maintaining the temperature at ≤ 31 °C. After stirring for 1 hour[2], GC analysis indicated reaction completion. The reaction mixture is poured into de-ionized H_2O (2.1 L, 20vol), stirred for 30 minutes, filtered, and washed with de-ionized H_2O (2 x 1 L). The product is dried in a vacuum oven at 45 °C overnight to give the title compound as a pale yellow solid (123.0 g, 83.8 %; 96.6 % area-% by GC).

F. 2,6-Dimethyl-imidazo[1,2-*b*]pyridazine.

A 3 neck 1L round bottom flask is charged with 6-methyl-pyridazin-3-ylamine (20 g, 0.18 moles), ethanol 2B (200 mL), and chloroacetone (23.7 g, 20.4 mL, 0.256 moles, 1.4 equiv). The reaction mixture is heated at 70 °C overnight. NaHCO3 (23.2 g, 0.276 moles, 1.5 equiv) is added portion wise. After most of bubbling subsides, the reaction is heated at 100 °C overnight. The solvents are removed in vacuo and the residue is taken up in dichloromethane and filtered through a filter paper. The solvent is again removed in vacuo. The residue is purified using silica gel chromatography with a hexanes:ethyl acetate gradient to obtain the title compound (15.5 g, 57%). ^{1}H-NMR (DMSO-d6), δ 2.34 (s, 3H), 2.47 (s, 3H), 7.03, (d, J = 10 Hz, 1H), 7.85 (d, J = 10 Hz, 1H), 7.91 (s, 1H) ppm. MS (APCI): 148 (M+1).

G. 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g, 2..17 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-*1H*-[1,2,4]triazole (0.72 g, 2.61 mmol), Cs_2CO_3 (1.49 g, 4.57 mmol) and DMF (6 mL) is de-gassed for 15 minutes with N_2. $Pd(OAc)_2$ (0.024 g, 0.11 mmol) and PPh_3 (0.057 g, 0.22 mmol) are added and the solution is heated at 135°C for 4 hours. The solution is diluted with CH_2Cl_2 (50 mL), washed with sat. NH_4Cl (2 x 50 mL), water (50 mL), filtered and concentrated. The residue is purified by ISCO flash chromatography (30%-100% EtOAc gradient) furnish the title compound (0.29 g, 0.84 mmol, 39%). ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 6.92 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H). LC/MS (m/z): calcd. for $C_{15}H_{13}ClN_6S$ $(M+H)^+$: 345.1; found: 345.2.

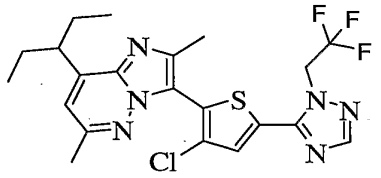
[2] The reaction temperature decreased after 1 hour to 26.7 °C

H. 3-[3-Chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a –78 °C solution of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.50 g, 4.35 mmol) and THF (50 mL) is added I_2 (1.21 g, 4.78 mmol). After 10 minutes 2 M LDA (5.44 mL, 10.87 mmol) is added. The solution is stirred for 30 minutes, quenched with water, diluted with EtOAc (100 mL), washed with water (100 mL), sat. $Na_2S_2O_3$ (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (100% EtOAc) furnish the title compound (0.61 g, 1.30 mmol, 30%). ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 2.55 (s, 3H), 4.14 (s, 3H), 7.47 (s, 1H), 7.51 (s, 1H), 7.89 (s, 1H),. LC/MS (m/z): calcd. for $C_{15}H_{12}ClIN_6S$ $(M+H)^+$: 471.0; found: 471.0.

Example 234.

Preparation of 3-{3-chloro-5-[2-(2,2,2-trifluoro-ethyl)-*2H*-[1,2,4]triazol-3-yl]-thiophen-2-yl}-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-(4-Chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole.

To a solution of 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide (1.00 g, 4.62 mmol) and AcOH (1. mL) is added 70 % aqueous 2,2,2-trifluoroethyl-hydrazine (0.79 mL, 4.85 mmol). The solution is heated at 90 °C for 45 minutes, concentrated, dissolved in Et_2O (40 mL), washed with water (30 mL), sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.24 g, 4.62 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 4.88 (q, J = 16.8, 7.8 Hz, 2H), 7.28 (d, J = 0.9 Hz, 1H), 7.31-7.33 (m, 1H), 7.94 (s, 1H). LC/MS (m/z): calcd. for $C_8H_5ClF_3N_3S$ $(M+H)^+$: 268.0; found: 268.0.

B. 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole.

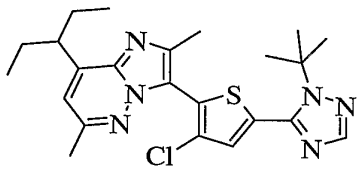
To a solution of 5-(4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole (1.13 g, 4.22 mmol) and AcOH (10 mL) in a sealed tube, is added Br_2 (0.23 mL, 4.43 mmol). The solution is heated at 120 °C for 2 hours, and 140 °C for 5 hours. The solution is concentrated, diluted with Et_2O (150 mL), washed with sat $NaHCO_3$ (75 mL), sat. $Na_2S_2O_3$ (75 mL), brine (75 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (5%-15% EtOAc gradient) furnish the title compound (1.04 g, 3.00 mmol, 71%). ^{1}H NMR ($CDCl_3$) δ 4.88 (q, J = 16.0, 7.9 Hz, 2H), 7.22 (s, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_8H_4BrClF_3N_3S$ $(M+H)^+$: 345.9; found: 346.0.

C. 3-{3-Chloro-5-[2-(2,2,2-trifluoro-ethyl)-*2H*-[1,2,4]triazol-3-yl]-thiophen-2-yl}-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure analogous to Example 231, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 1.14 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole (0.47 g, 1.37 mmol), KOAc (0.56 g, 5.60 mmol), TBABr (0.37 g, 1.14 mmol), and NMP (3 mL), $Pd(OAc)_2$ (0.013 g, 0.057 mmol) and TDBPP (0.037 g, 0.057 mmol) furnish the title compound (0.43 g, 0.89 mmol, 78%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.27-3.36 (m, 1H), 4.98 (q, J = 15.7, 7.9 Hz, 2H), 6.74 (s, 1H), 7.45 (s, 1H), 8.03 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClF_3N_6S$ $(M+H)^+$: 483.1; found: 483.2.

Example 235.

Preparation of 3-[5-(2-tert-butyl-*2H*-[1,2,4]triazol-3-yl)-3-chloro-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 1-*tert*-Butyl-5-(4-chloro-thiophen-2-yl)-*1H*-[1,2,4]triazole.

Using a procedure analogous to Example 234A, 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide (5.00 g, 23.07 mmol) and AcOH (50.

mL), *tert*-butylhydrazine hydrochloride (3.16 g, 25.38 mmol) furnish the title compound (0.20 g, 0.83 mmol, 3.6%). ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 9H), 7.07 (d, J = 1.3 Hz, 1H), 7.51 (d, J = 1.3 Hz,1H), 8.08 (s, 1H).

B. 5-(5-Bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-^{1}*H*-[1,2,4]triazole.

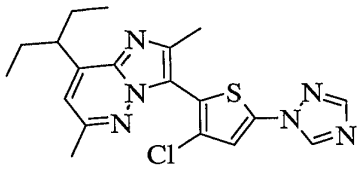
Using a procedure analogous to Example 249B, 1-*tert*-butyl-5-(4-chloro-thiophen-2-yl)-^{1}*H*-[1,2,4]triazole (0.20 g, 0.83 mmol), AcOH (3 mL) and Br_2 (0.051 mL, 0.99 mmol) furnish the title compound (0.27 g, 0.83 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 9H), 7.42 (s, 1H), 8.08 (s, 1H). LC/MS (m/z): calcd. for $C_{10}H_{11}BrClN_3S$ $(M+H)^+$: 320.0; found: 320.0.

C. 3-[5-(2-tert-Butyl-2*H*-[1,2,4]triazol-3-yl)-3-chloro-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure analogous to Example 231, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 g, 0.68 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-^{1}*H*-[1,2,4]triazole (0.20 g, 0.82 mmol), KOAc (0.34 g, 3.42 mmol), TBABr (0.22 g, 0.68 mmol), and NMP (3 mL), $Pd(OAc)_2$ (0.0077 g, 0.034 mmol) and TDBPP (0.022 g, 0.034 mmol) furnish the title compound (0.039 g, 0.085 mmol, 13%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.65 (s, 9H), 1.73-1.91 (m, 4H), 2.51 (s, 6H), 3.26-3.37 (m, 1H), 6.69 (s, 1H), 7.65 (s, 1H), 8.11 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{29}ClN_6S$ $(M+H)^+$: 457.2; found: 457.3.

Example 236.

Preparation of 3-(3-chloro-5-[1,2,4]triazol-1-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 3-(3-Chloro-5-iodo-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

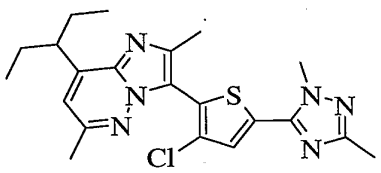
To a solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (2 g, 6 mmol) in 10 mL of anhydrous CH_3CN under nitrogen was added portionwise NIS (1.6 g, 7.2 mmol). The reaction mixture is stirred at reflux for 14 hours. After cooling, the solvent is concentrated under vacuum, the residue is disolved in EtOAc and washed with H_2O, 5% solution of sodium bisulfite, H_2O and brine. The organic layer is dried over magnesium sulfate, filtered and concentrated under vacuum. The crude residue is purified by silica gel chromatography using hex/EtOAc 8:2 as eluent mixture, to obtain 2.4 g (90%) of the title compound; mass spectrum 460 (M+1); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.24 (s, 1H), 6.71 (s, 1H), 3.32 (q, 1H, J = 7.2 Hz), 2.52 (s, 3H), 2.49 (s, 3H), 1.84 (q, 4H, J = 7.2 Hz); 0.88 (t, 6H, J = 7.2 Hz) ppm.

B. 3-(3-Chloro-5-[1,2,4]triazol-1-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(3-chloro-5-iodo-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.65 mmol), *1H*-triazole (0.047 g, 0.69 mmol), CuI (0.0062, 0.033 mmol), Cs_2CO_3 (0.45 g, 1.37 mmol) and DMF (3 mL) is added (*1S, 2S*)-(+)-*N,N'*- dimethylcyclohexane-1,2-diamine (0.014 mL, 0.098 mmol). The solution is heated at 112 °C overnight, diluted with CH_2Cl_2 (10 mL) and filtered thru Celite® and concentrated. The residue is purified by ISCO flash chromatography (30%-40% EtOAc gradient furnish the title compound (0.028 g, 0.070 mmol, 11%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.35 (m, 1H), 6.72 (s, 1H), 7.22 (s, 1H), 8.10 (s, 1H), 8.50 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{21}ClN_6S$ $(M+H)^+$: 401.1; found: 401.2.

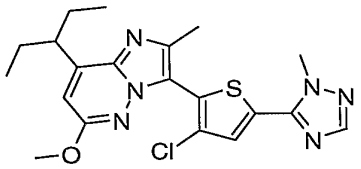
Example 237.

Preparation of 3-[3-chloro-5-(2,5-dimethyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.72 mmol) and THF (5 mL) is added 1.7 M *tert*-BuLi (0.47 mL, 0.80 mmol). After 15 minutes MeI (0.052 mL, 0.83 mmol) is added and the solution warmed to ambient temperature. The solution is diluted with EtOAc (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The solution is recrystalized from acetone: hexane furnish the title compound (0.13 g, 0.30 mmol, 42%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.36 (s, 3H), 2.51 (s, 6H), 3.27-3.39(m, 1H), 3.40 (s, 3H), 6.72 (s, 1H), 8.02 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{25}ClN_6S$ $(M+H)^+$: 429.2; found: 429.2.

Example 238.Preparation of 3-[3-Chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. N-(6-Methoxy-pyridazin-3-yl)-2,2-dimethyl-propionamide.

3-Chloro-6-methoxy-pyridazine (10.0 g, 69. 18 mmol) is mixed with 2,2-dimethyl-propionamide (8.40 g, 83.01 mmol), BINAP (2.15 g, 3.46 mmol), Cs_2CO_3 (33.8 g, 103.77 mmol) in 1,4-dioxane (150 mL). It is degassed by passing N_2 through for 10 min at rt. $Pd_2(dba)_3$ (3.16 g, 3.46 mmol) is added and the resulting mixture is refluxed overnight. The mixture is cooled to rt, diluted with EtoAc (150 mL); filtered through silica gel; washed with EtOAc (2 x 150 mL). The filtrate is washed with H2O (2 x 300 mL); dried with $MgSO_4$; filtered and concentrated. Purification of the crude material by silica gel chromatography gives the title compound (6.59 g, 31.53 mmol, 46%). 1H NMR (CDCl3): δ. 1.35 (s, 9H), 4.08 (s, 3H), 7.01 (d, J = 9.7 Hz, 1H), 8.41 (d, J = 9.7 Hz, 1H), 8.44 (bs, 1H). ES-MS (m/z): calcd for $C_{10}H_{15}N_3O_2$ $(M+H)^+$: 210.3; found : 210.1.

B. N-[4-(1-Ethyl-propyl)-6-methoxy-pyridazin-3-yl]-2,2-dimethyl-propionamide.

Using a procedure analogous to Example 6a, from N-(6-methoxy-pyridazin-3-yl)-2,2-dimethyl-propionamide (6.09 g, 29.14 mmol) and a Grignard reagent prepared from 3-pentyl bromide (18.1 mL, 160.3 mmol) and Mg (3.84 g, 160.26 mmol) gives the title

compound (5.32 g, 19.08 mmol, 65%). 1H NMR (CDCl3): δ. 0.84 (t, J = 7.5 Hz, 6H), 1.36 (s, 9H), 1.50-1.72 (m, 4H), 3.50-3.70 (m, 1H), 4.07 (s, 3H), 6.96 (s, 1H). ES-MS (m/z): calcd for $C_{15}H_{25}N_3O_2$ $(M+H)^+$: 280.4; found : 280.2.

C. 4-(1-Ethyl-propyl)-2-methoxy-6-methyl-pyrrolo[1,2-b]pyridazine.

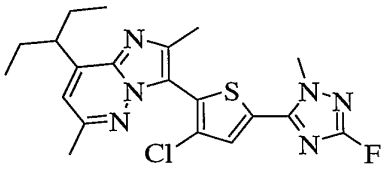
A solution of N-[4-(1-ethyl-propyl)-6-methoxy-pyridazin-3-yl]-2,2-dimethyl-propionamide (5.32 g, 19.08 mmol) in EtOH (250 mL) is treated with $ZnCl_2$ (26.0 g, 190.8 mmol) and refluxed for 48 h. The reaction is cooled to rt and concentrated. The residue is taken up with EtOAc (250 mL), and H_2O (100 mL). It is washed with H_2O (2 x 100 mL); dried with Na_2SO_4; filtered and concentrated. The residue is then dissolved in EtOAc (80 mL), reacted with chloroacetone (1.6 mL, 20.03 mmoL) at reflux overnight. While it is hot, $NaHCO_3$ (8.10 g) is added and the reaction is refluxed for 1 h. It is cooled to rt and filtered through silica gel washed with EtOAc and concentrated. Purification of the crude material by chromatography gives the title compound (0.48 g, 2.07 mmol, 11%). 1H NMR (CDCl3): δ. 0.84 (t, J = 7.5 Hz, 6H), 1.69-1.869 (m, 4H), 2.45 (s, 3H), 3.19-3.30 (m, 1H), 3.94 (s, 3H), 6.39 (s, 1H), 7.49 (s, 1H). ES-MS (m/z): calcd for $C_{14}H_{20}N_2O$ $(M+H)^+$: 233.3; found : 234.1.

D. 3-[3-Chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 4-(1-ethyl-propyl)-2-methoxy-6-methyl-pyrrolo[*1,2-b*]pyridazine (74.8 mg, 0.32 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^1H-[1,2,4]triazole (107.5 mg, 0.38 mmol), TDBPP (10.4 mg, 0.016 mmol), tetrabutylammonium bromide (103.0 mg, 0.32 mmol), KOAc (158 mg, 1.61 mmol) in NMP (15 mL) is purged with N2 for 5 min. Pd(OAc)2 (3.6 mg, 0.016 mmol) is added and the resulting mixture is stirred at 125 °C for 6 h. The reaction is cooled to rt, and diluted with EtOAc (10 mL); filtered through silica gel; washed with EtOAc (3 x 30 mL). The filtrate is washed with H2O (3 x 30 m); dried with Na2SO4, filtered and concentrated. Purification of the crude material by silica gel chromatography gives the title compound (0.1062 g, 0.2469 mmol, 77%). 1H NMR (CDCl3): δ. 0.89 (t, J = 7.6 Hz, 6H), 1.75-1.90 (m, 4H), 2.52 (s, 3H), 3.22-3.38 (m, 1H), 3.93 (s, 3H), 4.15 (s, 3H), 6.52 (s, 1H), 7.48 (s, 1H), 7.91 (s, 1H). ES-MS (m/z): calcd for $C_{20}H_{23}ClN_6OS$ $(M+H)^+$: 431.9; found: 431.3.

Example 239.

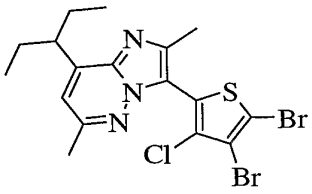
Preparation of 3-[3-chloro-5-(5-fluoro-2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.72 mmol) and THF (8 mL) is added 1.7 M *tert*-BuLi (0.47 mL, 0.80 mmol). After 30 minutes the solution is transferred via a cannula into a solution of N-fluorobenzenesulfonamide (0.40 g, 1.25 mmol) and THF. After 30 minutes the solution warmed to ambient temperature. The solution is diluted with EtOAc (40 mL), washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The solution is purified by ISCO (20%-30% EtOAc gradient) furnish the title compound (0.068 g, 0.16 mmol, 16%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.71-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.26-3.36 (m, 1H), 4.08 (d J = 2.7 Hz, 3H), 6.75 (s, 1H), 7.97 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{22}ClFN_6S$ $(M+H)^+$: 433.2; found: 433.2.

Example 240.

Preparation of Preparation of 3-(4,5-dibromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

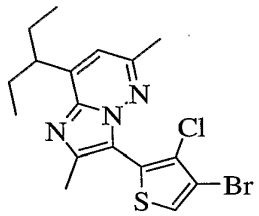


To a solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (5.92 g, 14.34 mmol) and triflouroacetic acid (40 mL) and 98% H_2SO_4 (10 ml) is added NBS (3.83 g, 21.15 mmol). After 10 minutes the solution is poured into ice, and made basic with 5M NaOH. The slurry is extracted with

EtOAc (3 x 100 mL), the combined organic layers washed with water (2 x 400 mL), brine (400 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (6.61 g, 13.44 mmol, 94%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.47 (s, 3H), 2.52 (s, 3H), 3.25-3.34 (m, 1H), 6.72 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{18}Br_2ClN_3S$ $(M+H)^+$: 489.9; found: 490.0.

Example 241.

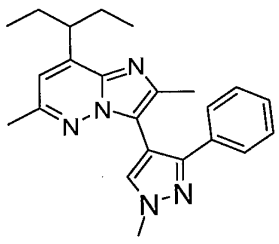
Preparation of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 76, 3-(4,5-dibromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.83 g, 3.72 mmol), 1.6 M *n*-BuLi (2.56 mL, 4.09 mmol), and THF (30 mL) furnish the title compound (1.05 g, 2.54 mmol, 68%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.48 (s, 3H), 2.51 (s, 3H), 3.27-3.36 (m, 1H), 6.71 (s, 1H), 7.55 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{19}BrClN_3S$ $(M+H)^+$: 412.0; found: 412.1.

Example 242.

Preparation of 3-(1-methyl-3-phenyl-^{1}*H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 1-methyl-3-phenyl-^{1}*H*-pyrazole and 1-methyl-5-phenyl-^{1}*H*-pyrazole.

Sodium hydride (60% dispersion in mineral oil, 0.83 g, 20.8 mmol) is suspended in THF (45 ml) and stirred under a nitrogen atmosphere. 3-Phenyl pyrazole (2.5 g, 17.3 mmol dissolved in THF, 15 ml) is added slowly, stirred for 30 minutes then iodomethane (1.3 ml, 20..8 mmol) added and stirred for 3 hrs. The reaction is added to water and extracted twice with ethyl acetate. The combined organic extracts are ished with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 40% ethyl acetate in hexane) to elute the title compound. Obtained is a mixture of 1-methyl-3-phenyl-*1H*-pyrazole and 1-methyl-5-phenyl-*1H*-pyrazole (2.6g, 95% yield).

B. 4-Bromo-1-methyl-3-phenyl-*1H*-pyrazole and 4-bromo-1-methyl-5-phenyl-*1H*-pyrazole.

The mixture of isomers, 1-methyl-3-phenyl-*1H*-pyrazole and 1-methyl-5-phenyl-*1H*-pyrazole (1.0g, 6.3 mmol) and NBS (1.1g, 6.3 mmol) are combined in acetonitrile (25 ml), stirred and heated to 70 °C for 1 hr. The solution is concentrated and the crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 25% ethyl acetate in hexane) to elute 4-bromo-1-methyl-3-phenyl-*1H*-pyrazole (504 mg, 34% yield) and 4-bromo-1-methyl-5-phenyl-*1H*-pyrazole (295 mg, 20% yield), respectively:

^{1}H NMR: (400 mHz, DMSO): δ 8.01 (s, 1H), 7.95 (d, 2H), 7.41 (t, 2H), 7.38 (d, 1H), 3.85 (s, 3H).
^{1}H NMR: (400 mHz, DMSO): δ 7.63 (s, 1H), 7.50 (m, 5H) 3.77 (s, 3H).

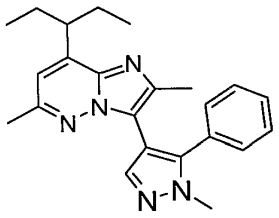
C. 3-(1-Methyl-3-phenyl-*1H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (160 mg, 0.73 mmol), 4-bromo-1-methyl-3-phenyl-*1H*-pyrazole (250 mg, 1.1 mmol) and cesium carbonate (490 mg, 1.50 mmol) are stirred in DMF (5 ml) and degassed by bubbling a stream of nitrogen through the mixture. $PdCl_2(PPh_3)_2$ (15mg) is added and the mixture is heated to 130^{0}C overnight. The mixture is added to water and extracted twice with ethyl acetate. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude

product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 50% ethyl acetate in hexane) to elute the title compound (17.5 mg, 4% yield). ES-MS (m/z): calc'd for $C_{23}H_{27}N_5$: 373.5; found 374.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.68 (s, 1H), 7.37 (m, 2H), 7.20 (m, 3H), 6.59 (s, 1H), 4.04 (s, 3H), 3.36 (m, 1H), 2.38 (s, 3H), 2.15 (s, 3H), 1.82 (m, 4H), 0.86 (t, 6H).

Example 243.

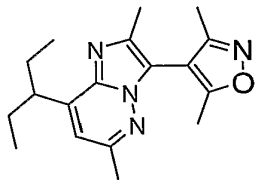
Preparation of 3-(1-methyl-5-phenyl-*1H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 242, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (160 mg, 0.73 mmol), 4-bromo-1-methyl-5-phenyl-^1H-pyrazole (250 mg, 1.1 mmol), cesium carbonate (490 mg, 1.50 mmol) and $PdCl_2(PPh_3)_2$ (15 mg) in DMF (5 ml) gives the title compound (18 mg, 4% yield). ES-MS (m/z): calc'd for $C_{23}H_{27}N_5$: 373.5; found 374.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.85 (s, 1H), 7.32 (m, 3H), 7.23 (m, 2H), 6.55 (s, 1H), 3.94 (s, 3H), 3.27 (m, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.76 (m, 4H), 0.83 (t, 6H).

Example 244.

Preparation of 3-(3,5-dimethyl isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.,

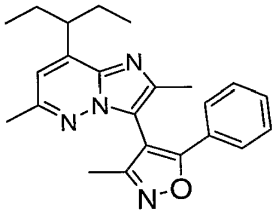


Using the procedure analogous to Example 242, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (200 mg, 0.90 mmol), 4-bromo-3,5-dimethyl

isoxazole (Alfa, 320 mg, 1.8 mmol), cesium carbonate (880 mg, 2.70 mmol) and $PdCl_2(PPh_3)_2$ (25mg) in DMF (5 ml), heated at 130 for 4 hrs, then overnight at ambient temperature gives the title compound (65 mg, 23% yield). ES-MS (m/z): calc'd for $C_{18}H_{24}N_4O$: 312.4; found 313.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 6.68 (s, 1H), 3.32 (m, 1H), 2.50 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 2.19 (s, 3H), 1.82 (m, 4H), 0.87 (m, 6H).

Example 245.

Preparation of 3-(3-methyl-5-phenyl-isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 4-Bromo-3-methyl-5-phenyl isoxazole.

3-Methyl-5-phenyl isoxazole (Synthesis, **1997**, 439-442) (1.0g, 6.3 mmol) and N-bromosuccinimide (1.2 g, 6.9 mmol) are combined together in acetic acid (30 ml) and heated to reflux with stirring for 2 hrs. The solution is added to water and extracted twice with ethyl acetate. The combined organic extracts are washed with sodium bicarbonate (sat'd) and sat. NaCl then dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 10% ethyl acetate in hexane) to elute the title compound (1.5 g, 100% yield). ^1H NMR (400 mHz, $CDCl_3$): δ 8.02 (m, 2H), 7.49 (m, 3H), 6.34, 2.35 (s, 3H).

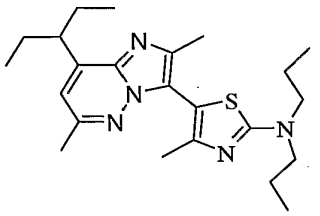
B. 3-(3-Methyl-5-phenyl-isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using the procedure analogous to Example 257, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (200 mg, 0.90 mmol), 4-bromo-3-methyl-5-phenyl isoxazole (430 mg, 1.8 mmol), cesium carbonate (880 mg, 2.70 mmol) and $PdCl_2(PPh_3)_2$ (25mg) in DMF (5 ml) are combined and heated at 130 °C. for 5 hrs to give the title compound (65

mg, 23% yield). ES-MS (m/z): calc'd for $C_{23}H_{26}N_4O$: 374.5; found 375.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.50 (d, 2H), 7.31 (m, 3H), 6.69 (s, 1H), 3.39 (m, 1H), 2.48 (s, 3H), 2.20 (s, 6H), 2.33 (s, 3H), 1.84 (m, 4H), 0.88 (m, 6H).

Example 246.

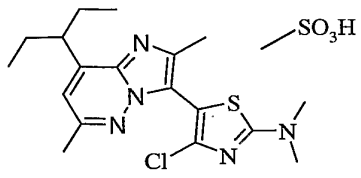
{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-dipropyl-amine.



35 mg of 3-(2-Bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.09mmol) and 45 mg of di-n-propylamine (0.44 mmol) and 57 mg of cesium carbonate(0.18 mmol) are place into 4 ml reaction vial with 3 ml of dry THF and the vial is capped with a Teflon cap. The reaction vial is heated at 100°C for 4h. The reaction mixture is transferred into microwave reaction vessel and sealed. The reaction mixture is heated at 160°C for 30 min by microwave. The mixture is concentrated and applied onto silica-gel chromatography column (Hexane:AcOEt=3:1) to give the title compound. 5.3 mg (14%); mass spectrum(m/e): 414; ^1H-NMR($CDCl_3$):5.59(s, 1H), 3.45(m, 4H), 3.36(m, 1H), 2.57(s, 3H), 2.47(s, 3H), 2.17(s, 3H), 1.80(m, 8H), 0.99(t, 6H, J=7.5Hz), 0.89(t, 6H, J=9.4Hz).

Example 247.

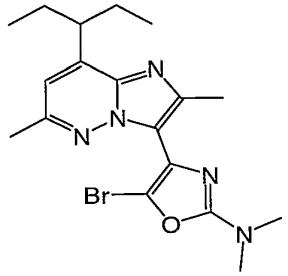
N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-chloro-thiazol-2-yl}-dimethylamine, mesylate salt.



89 mg of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-chloro-thiazol-2-yl}-dimethylamine (0.236 mmol) is dissolved in 2.0 ml of ethylacetate and 0.236ml of 1M methanesulfonic acid in ethylacetate (0.236 mmol) is added. The solvents are removed under N_2 gas and precipitated crystals are collected, washed with Et2O and dried. 92mg (83%); mass spectrum(m/e): 378(M+1); ^{1}H-NMR($CDCl_3$): 7.30(s, 1H), 3.67(m, 1H), 3.22(s, 6H), 2.93(s, 3H), 2.78(s, 3H), 2.78(s, 3H), 2.71(s, 3H), 1.95(m, 2H), 1.82(m, 2H), 0.96(t, 6H, J=7.3Hz).

Example 248.

Preparation of {5-Bromo-4-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-oxazol-2-yl}-dimethyl-amine.



A. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-oxazol-4-yl-imidazo[*1,2-b*]pyridazine.

500 mg of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.46 mmol) , 622 mg of oxazole (9.0mmol), 79 mg of triphenylphosphine (0.3 mmol) and 989 mg of cesium carbonate (3.03 mmol) are placed into reaction vial with 7 ml of dry DMF. N_2 gas is bubbled into the mixture for 30 min and 67 mg of Pd_2dba_3 (0.07 mmol) is added. The reaction vial is capped with a Teflon cap and stirred at 130°C for 3 days. The reaction mixture is diluted with dichloromethane, washed with sat NaCl, dried over Na_2SO_4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:EtOAc = 3:1) to give the title compound 172 mg (42%); mass spectrum(m/e): 285; ^{1}H-NMR($CDCl_3$): 8.04(s, 1H), 7.97(s, 1H), 6.78(s, 1H), 3.35(m, 1H), 2.80(s, 3H), 2.65(s, 3H), 1.86(m, 4H), 0.88(t, 6H).

B. 3-(2,5-Dibromo-oxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

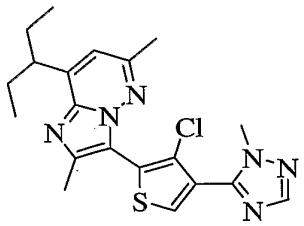
172 mg of 8-(1-ethyl-propyl)-2,6-dimethyl-3-oxazol-4-yl-imidazo[*1,2-b*]pyridazine (0.60 mmol) and 270 mg of NBS (1.51 mmol) are dissolved in 8.0 ml of dichloromethane and stirred at room temperature overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:EtOAc = 3:1) to give 70 mg of the title compound (26%); mass spectrum(m/e): 442; ^{1}H-NMR($CDCl_3$): 6.82(s, 1H), 3.32(m, 1H), 2.59(s, 3H), 2.54(s, 3H), 1.86(m, 4H), 0.89(t, 6H, J=7.4Hz).

C. {5-Bromo-4-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-oxazol-2-yl}-dimethyl-amine.

67 mg of 3-(2,5-Dibromo-oxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 mmol), 146 mg of cesium carbonate (0.45 mmol) and 3.0 ml of dimethylamine 2.0M in THF (6 mmol) are placed into a 4 ml of reaction vial and the vial is capped with a Teflon cap. The reaction vial is heated at 130°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:AcOE t = 3:1) to give 53 mg of the title compound (87%); mass spectrum(m/e): 406; ^{1}H-NMR($CDCl_3$): 6.72(s, 1H), 3.37(m, 1H), 3.15(s, 6H), 2.58(s, 3H), 2.53(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.2Hz).

Example 249.

Preparation of 3-[3-chloro-4-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

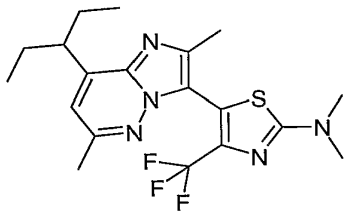


To a flask of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.49 mmol) is added 0.5 g/ mL Reike® Zn (1.3 mL, 0.97 mmol). The slurry is heated at 65 °C for 1 hour, placed in a centrifuge for 5 minutes, and the solution transferred to a flask containing 5-bromo-1-methyl-*1H*-[1,2,4]triazole (0.12 g, 0.73 mmol) and PdCl2(dppf) (0.018 g, 0.024 mmol). The

solution is heated at 65 °C overnight, diluted with EtOAc (20 mL), washed with sat. NH_4Cl (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-50% EtOAc gradient) furnish the title compound (0.018 g, 0.043 mmol, 9%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.37 (m, 1H), 3.95 (s, 3H), 6.72 (s, 1H), 7.82 (s, 1H), 8.01 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{23}ClN_6S$ $(M+H)^+$: 415.2; found: 415.3.

Example 250.

Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-dimethyl-amine.



A. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine.

Iodoimidazopiridazine (6.75 g, 19.7 mmol), triphenylphosphine (1.03 g, 3.94 mmol), Cs_2CO_3 (12.84 g, 39.4 mmol) and $Pd_2(dba)_3$ (900 mg, 0.98 mmol) are put into a sealed tube with 65 mL of dry DMF and N_2 gas is bubbled into the mixture for 5 minutes. Thiazole (8.36 g, 6.7 mL, 98.4 mmol) is added, and the mixture is heated at 130°C overnight. The mixture is cooled to r.t. and quenched by addition of NH_4Cl saturated solution (200 mL). The mixture is extracted with Et_2O (3 x 100 mL) and the organic layers washed with water (2 x 100 mL) and sat. NaCl (100 mL), dried over $MgSO_4$ and concentrated. The crude product is purified by flash chromatography on silica gel (eluent; hexane:EtOAc= 4:1) to give 3.80 g of the title compound (Yield: 64%). ESIMS: m/z 301 $[M+H]^+$.

B. 3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine. (3.80 g, 12.6 mmol) in CH_3CN (55 mL) at room temperature is added NBS (5.18 g, 29.1 mmol), and the mixture is stirred at room temperature for 3 hours. A white precipitate is formed that is filtered in vacuo, to give 4.86 g of the title compound (Yield: 84%). ESIMS: m/z 459, 461 $[M+H]^+$.

C. 3-(4-Bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (4.86 g, 10.6 mmol) in THF (150 mL) under N_2 atmosphere at –78°C, BuLi (6.63 mL 1.6 M in hexane, 10.6 mmol) is added dropwise for a period of 10 minutes. The mixture is stirred at –78°C for 30 minutes. Water is added, and the mixture is extracted with Et_2O (3 x 100 mL), dried over $MgSO_4$ and concentrated in vacuo. Crude product is purified by flash chromatography on silica gel (eluent hexane:EtOAc 5:1) to give 3.28 g of the title compound (Yield: 82%). ESIMS: m/z 379, 381 $[M+H]^+$.

D. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-trifluoromethyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.45 g, 6.5 mmol) in NMP (35 mL) in a sealed tube is added $FSO_2CF_2CO_2Me$ (2.5 g, 1.65 mL, 13 mmol) and CuI (2.48 g, 13 mmol). N_2 gas is bubbled into the mixture for 5 minutes, and the mixture is heated at 120°C for 9 hours. After cooling to room temperature, water (100 mL) and NaCl saturated solution (100 mL) are added to the mixture. The mixture is extracted with Et_2O (5 x 80 mL); washed with water (2 x 100 mL), and dried over $MgSO_4$ and concentrated. The crude product is purified by flash chromatography on silica gel (eluent hexane:EtOAc 5:1) to obtain 960 mg of the title compound (Yield: 40%). ESIMS: m/z 369 $[M+H]^+$.

E. 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

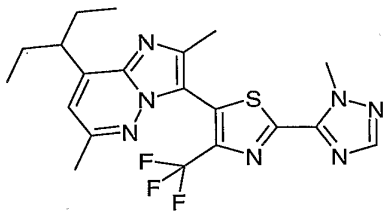
To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-trifluoromethyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine (915 mg, 2.48 mmol) in 40 mL of THF under N_2 atmosphere al –78°C, BuLi (1.86 mL 1.6 M in hexane, 2.98 mmol) is slowly added. The mixture is stirred at –78°C for 30 minutes. Then, a solution of CBr_4 (989 mg, 2.98 mmol) in 3 mL of THF is added, and the mixture is stirred at –78°C for 45 minutes. The reaction is quenched by addition of NH_4Cl saturated solution (50 mL), extracted with Et_2O (2 x 50 mL), dried over $MgSO_4$, and concentrated in vacuo. Crude product is purified by flash chromatography on silica gel (eluent CH_2Cl_2) to obtain 685 mg of the title compound (Yield: 62%). ^1H NMR ($CDCl_3$): δ0.86 (t, J = 7.5 Hz, 6H), 1.82 (m, 4H), 2.45 (s, 3H), 2.51 (s, 3H), 3.27 (m, 1H), 6.74 (s, 1H). ESIMS: m/z 447, 449 $[M+H]^+$.

F. {5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-dimethyl-amine.

100 mg of 3-(2-Bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol) and 218 mg of cesium carbonate (0.66 mmol) are placed in 4 ml reaction vial and 3 ml of dimethylamine 2 M in THF is added. The reaction vial is capped with a Teflon cap and heated at 120°C overnight. The reaction mixture is filtered and concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt =3:1) to give 85 mg of the title compound. Yield 94%. mass spectrum (m/e) : 412 (M+1).

Example 251.

Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-4-trifluoromethyl-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine

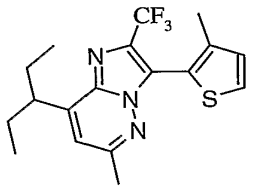


164 mg of 1-Methyl-1,2,4-triazole (1.96 mmol) is dissolved in 2 ml of THF and cooled to –78 °C. 0.8 ml of 2.5M n-butyllithium in hexane (1.96 mmol) is added slowly and stirred at –78 °C, warmed up to room temperature and stirred at r.t. for 15min and

cooled to –78 °C. 3.96 ml of 0.5 M $ZnCl_2$ in THF (1.98 mmol) is added and stirred at room temperature for 15 min. 180 mg of 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 54 mg of PdCl2(pddf) (0.06 mmol) are added. The vial is capped with a Teflon cap and heated at 80 °C overnight. NH_4Cl aq. is added to quench the reaction and the mixture is extracted by CH_2Cl_2, dried over Na2SO4 and evaporated. The crude product is applied onto silica-gel chromatography column (Hexane :AcOEt=3:1) to give 119 mg of the title compound. Yield 58%. mass spectrum (m/e) : 449(M+1).

Example 252.

Preparation of 8-(1-Ethyl-propyl)-6-methyl-3-(3-methyl-thiophen-2-yl)-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.



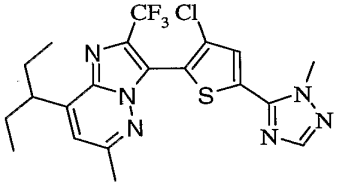
A. 8-(1-Ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

α-Bromotrifluoroacetone (402 mg, 2.93 mmol) is added to a dry 10 mL microwave reaction tube containing 4-(1-ethyl-propyl)-6-methyl-pyridazin-3-ylamine (500 mg, 2.79 mmol) in EtOH (2.0 mL). The resulting mixture is heated at 110 °C in the microwave for 1 hour. $NaHCO_3$ (246.5 mg, 2.93 mmol) is added, and the reaction is mixed well for 5 minutes. Then, the reaction is heated at 110 °C in the microwave for 1 hour. The solvent is removed via reduced pressure, and the reaction is diluted with ethyl acetate (30 mL). The organic layer is washed with H_2O (3 X 10 mL), and the combined aqueous layers are extracted with ethyl acetate (2 X 20 mL). The combined organic extracts are dried over Na_2SO_4, filtered, and purified by silica gel chromatography to give the title compound (29.5 mg, 0.068 mmol, 9.8 %). ^{1}H-NMR ($CDCl_3$), δ 0.87 (t, J = 7.6 Hz, 6H), 1.86 (m, 4H), 2.60 (s, 3H), 3.30 (m, 1H), 6.80 (s, 1H), 8.14 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{13}H_{16}F_3N_3$ $(M+H)^+$: 271.29; found: 272.2

B. 8-(1-Ethyl-propyl)-6-methyl-3-(3-methyl-thiophen-2-yl)-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

To a dry 10 ml round bottom flask with reflux condenser containing 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (300 mg, 1.11 mmol), 2-bromo-3-methyl-thiophene (216 mg, 1.22 mmol), and Cs_2CO_3 (760 mg, 2.33 mmol) is added NMP (1.7 ml). The mixture is degassed with bubbling N_2 for 15 min and $Pd_2(dba)_3$ (50.8 mg, 0.055 mmol) and PPh_3 (58.2 mg, 0.222 mmol) are added. The reaction mixture is stirred at 130°C overnight. The mixture is cooled to rt, diluted with H_2O; and extracted with EtOAc (3 x 20 ml). The organic layers are dried (Na_2SO_4), filtered and purified by HPLC to give title compound (32 mg, 0.087 mmol, 8%). ^{1}H-NMR ($CDCl_3$), δ 0.93 (t, J = 7.2 Hz, 6H), 1.91 (m, 4H), 2.15 (s, 3H), 2.58 (s, 3H), 3.36 (m, 1H), 6.91 (s, 1H), 7.08 (d, J = 5.3 Hz, 1H), 7.55 (d, J = 5.5 Hz, 1H) ppm. ES-MS (m/z): calcd for $C_{18}H_{20}F_3N_3S$ $(M+H)^+$: 367.44; found: 368.1.

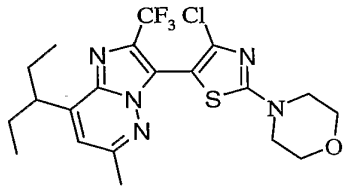
Example 253.Preparation of 3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.



In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (182 mg, 0.671 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}*H*-[1,2,4]triazole (225 mg, 0.805 mmol), KOAc (330.2 mg, 3.36 mmol), and TBAB (217 mg, 0.671 mmol) are dissolved in NMP (3 mL). The mixture is degassed with bubbling nitrogen for 20 minutes. Then, $Pd(OAc)_2$ (8 mg, 0.034 mmol) and TDBPP (20.4 g, 0.34 moles) are added. The reaction mixture is heated to 125 °C for 3 hours to give the title compound (125 mg, 0.267 mmol, 40%). ^{1}H-NMR ($CDCl_3$), δ 0.88 (t, J = 7.2 Hz, 6H), 1.87 (m, 4H), 2.537 (s, 3H), 3.32 (m, 1H), 4.16 (s, 3H), 6.86 (s, 1H), 7.51 (s, 1H), 7.91 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{20}H_{20}ClF_3N_6S$ $(M+H)^+$: 468.93; found: 469.2.

Example 254.

Preparation of 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.



A. 8-(1-Ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (460 mg, 1.70 mmol) are dissolved in dry THF (3.5 mL) and cooled to -78°C. A solution of 2.5 M *n*-butyllithium in hexanes (748 µL, 1.87 mmol) is added dropwise. The reaction mixture is stirred for 20 minutes at -78 °C, then warmed to 0 °C for 15 minutes. A solution of I_2 (453 mg, 1.79 moles) in THF (2.0 mL) is added dropwise. The reaction is stirred for 15 minutes at 0 °C, and then warmed to room temp. The reaction is stirred overnight, and the solvent is removed via reduced pressure. The reaction mixture is redissolved in ethyl acetate (50 mL) and washed with a 1 N solution of $Na_2S_2O_3$ (2 X 20 mL). The aqueous layer is extracted with ethyl acetate (2 X 40 mL). The combined organic extracts are dried with Na_2SO_4, filtered, and purified via silica gel chromatography to give the title compound (595 mg, 1.50 mmol, 88%). ^{1}H-NMR ($CDCl_3$), δ 0.82 (t, J = 8.0 Hz, 6H), 1.83 (m, 4H), 2.64 (s, 3H), 3.27 (m, 1H), 6.82 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_{13}H_{15}F_3IN_3$ $(M+H)^+$: 397.18; found: 398.3.

B. 2,4-Dichloro-thiazole.

In a 250 mL round bottom flask, 2.4-thiazolidine dione (12.5 g, 107 mmol) is dissolved in phosphorousoxychloride (70 mL) and pyridine (8.5 mL). The mixture is stirred under reflux for 3 hours and cooled to room temp. The reaction mixture is poured into ice water slowly and extracted with dichloromethane. The combined organic extracts are dried with Na_2SO_4, filtered, and concentrated. The residue is purified via silica gel

chromatography to give title compound (9.18 g, 59.6 mmol, 56%). ^{1}H-NMR ($CDCl_3$), δ 7.01 (s, 1H) ppm.

C. 4-(4-Chloro-thiazol-2-yl)-morpholine.

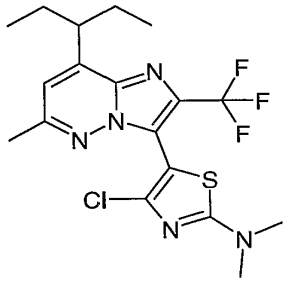
In a 75 mL dry pressure vessel, 2,4-dichloro-thiazole (500 mg, 3.2 mmol) and morpholine (560 μL, 6.4 mmol) are dissolved in dry THF (2.0 mL). Cs_2CO_3 (1.56 g, 4.8 mmol) is added, and the reaction vessel is sealed. The reaction mixture is heated to 110 °C overnight. Solvent is removed via reduced pressure, and the crude reaction mixture is purified via silica gel chromatography to give the title compound (597 mg, 2.92 mmol, 91%). ^{1}H-NMR ($CDCl_3$), δ 3.45 (m, 4H), 3.79 (m, 4H), 6.31 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_7H_9ClN_2OS$ $(M+H)^+$: 204.68; found: 205.2.

D. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (250 mg, 0.630 mmol), 4-(4-chloro-thiazol-2-yl)-morpholine (194 mg, 0.945 mmol), and Cs_2CO_3 (410 mg, 1.26 mmol) are dissolved in DMF. The mixture is degassed with bubbling nitrogen for 15 minutes. Then, $Pd_2(dba)_3$ (18 mg, 0.032 mmol) and PPh_3 (33 mg, 0.126 mmol) are added. The reaction mixture is heated to 130 °C overnight. The reaction is cooled to room temp., quenched with a solution of NH_4Cl sat? (20 mL), and extracted with Et_2O (3 X 50 mL). The combined organic extracts are washed with brine (30 mL), dried with Na_2SO_4, filtered and concentrated. The residue is purified via reverse phase HPLC with a 30-80% gradient of CH_3CN in 10mM NH_4HCO_3/H_2O/5%CH_3CN (pH 10.0)to give the title compound (11 mg, 0.023 mmol, 4%). ^{1}H-NMR ($CDCl_3$), δ 0.86 (t, J = 7.3 Hz, 6H), 1.84 (m, 4H), 2.55 (s, 3H), 3.31 (m, 1H), 3.54 (dd, J = 5.2, 4H), 3.84 (dd, J = 5.2 Hz, 4H), 6.82 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_{20}H_{23}ClF_3N_5OS$ $(M+H)^+$: 473.95; found: 474.2.

Example 255.

Preparation of {4-Chloro-5-[8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine.



A. (4-Chloro-thiazol-2-yl)-dimethyl-amine.

Using a procedure analogous to Example 254C, 2,4-dichloro-thiazole (500 mg, 3.2 mmol) and dimethylamine (a 2.0 M solution in THF, 3 mL, 6.4 mmol) are reacted to give the title compound (60 mg, 0.152 mmol, 15%). ^{1}H-NMR ($CDCl_3$), δ 3.09 (s, 6H), 6.22 (s, 1H) ppm. ES-MS (m/z): calcd for $C_5H_7ClN_2S$ $(M+H)^+$: 162.64; found: 163.2.

B. {4-Chloro-5-[8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine.

Using a procedure analogous to Example 254D, 8-(1-ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (250 mg, 0.630 mmol) is coupled with (4-chloro-thiazol-2-yl)-dimethyl-amine (154 mg, 0.945 mmol) to provide desired product. ^{1}H-NMR ($CDCl_3$), δ 0.85 (t, J = 7.4 Hz, 6H), 1.83 (m, 4H), 2.55 (s, 3H), 3.16 (s, 6H), 3.31 (m, 1H), 6.81 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{18}H_{21}ClF_3N_5S$ $(M+H)^+$: 431.91; found: 432.2.

Example A

In Vivo Potency Assessment Using Ex Vivo Binding

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 ^{125}I-

sauvagine to the cerebellum is then assessed ex vivo as described in Gehlert *et al.* For example, Example 199 provides an ED_{50} result of 1.3 mg/kg.

Example B

CRF1 Filter Binding Assay

The limitations of plasmid-based human CRF1 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 ^{125}I-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 hours and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are wash twice with ice-cold assay buffer (50 mM tris, 12.5 mM NaCl, 1mM EDTA, 10 mM $MgCl_2$, 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.

Using this assay, the claimed exemplified compounds of the present invention inhibit the binding of ^{125}I-Sauvagine (4 nM) in roller/adherent cells with a Ki (inhibition constant) below 1 µM. For example, Examples 102 and 199 exhibit a Ki of 4.92 ± 0.57 nM and 9.98 ± 0.72 nM, respectively.

Example C

CRF2 Filter Binding Assay

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 ul of ^{125}I-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, 1mM EDTA, 10 mM $MgCl_2$, 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: 50ul of ^{125}I-Sauvagine (0.2 nM final concentration), 50 µl compound or non-labelled sauvagine (NSB) and 100 µl containing 250 µg wheat germ agglutinin (WGA) SPA beads and CRF2 membrane (1.5 µg/reaction). Plates are incubated for 4-5 hours at room temperature and then centrifuged at 200 X g for 10 minutes. 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.

Compounds of the present invention are tested in the CRF2 binding assay and exhibit weak affinity for the CRF2 receptor. For example, Examples 102 and 199 exhibit a percent inhibition at 50 µM of 9.0 ± 2.6 and 16.9 ± 1.9, respectively. These results suggest that the compounds of the present invention are highly selective for the CRF1 receptor.

Example D

Bioavailability and Pharmacokinetic Properties

The compounds of Formula I are antagonists of CRF1, and possess surprisingly useful properties related to their pharmacokinetics and bioavailability.

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: Vdist = amount of drug in the body/ 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

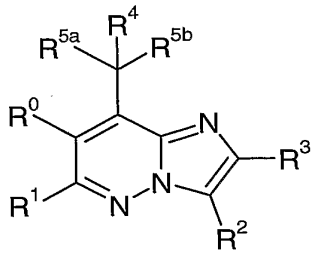
setting, Vdist can be used to determine a loading dose achieve a steady state concentration.

To test for volume of distribution, Male Sprague Dawley rats (N=3) are administered a single 3 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).

An overwhelming 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, following a single intravenous dose, thiazole Examples 48 and 199 of the present invention exhibits a rat Vdist of only 9 and 2 L/Kg, respectively. Furthermore, thiophene Examples 88 and 39 of the present invention exhibit a rat Vdist of only 44 and 17 L/kg, respectively.

WE CLAIM:

1. A compound of Formula I



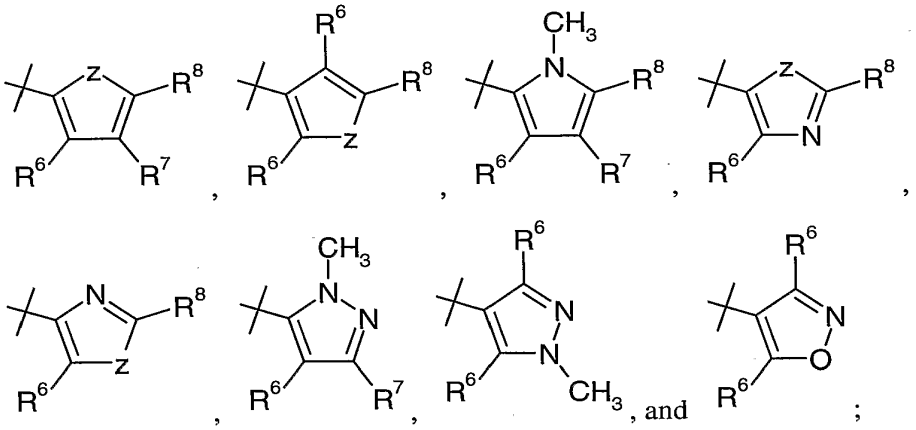
Formula I

wherein:

R^0 is hydrogen, halo, methyl or ethyl;

R^1 and R^3 are independently methyl, methoxy, or trifluoromethyl;

R^2 is selected from the group consisting of:

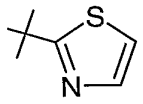


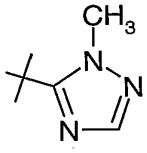
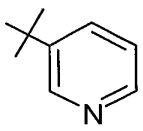
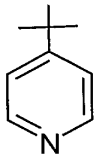
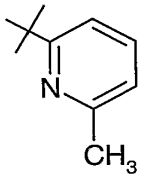
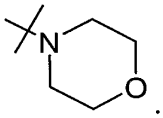
, and ;

R^4 is hydrogen, halo, or hydroxy;

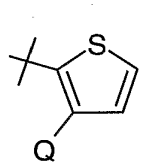
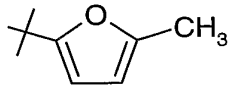
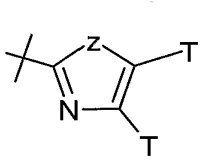
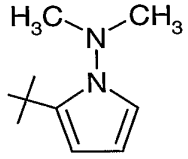
R^{5a} and R^{5b} are independently ethyl or n-propyl;

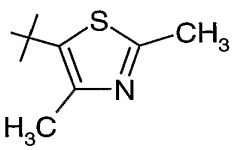
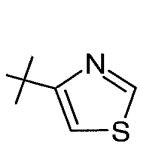
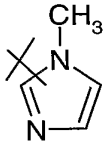
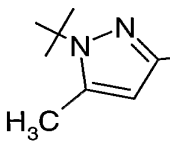
R^6 at each occurrence is independently hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, trifluoromethyl, methoxy, or phenyl;

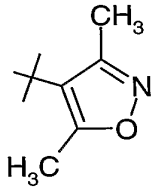
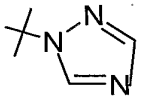
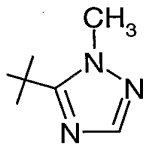
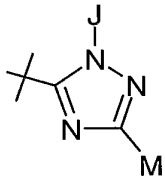
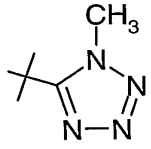
R^7 is hydrogen, halo, methyl, methoxy, dimethylamino,  ,

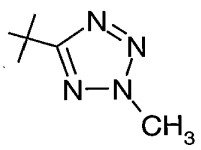
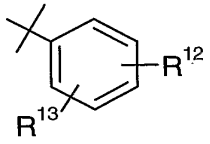
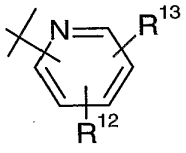
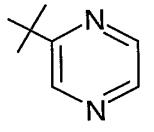
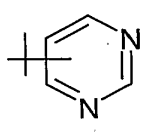
 ,  ,  ,  , or  ;

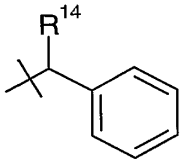
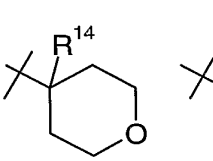
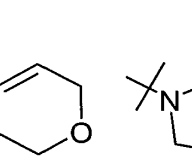
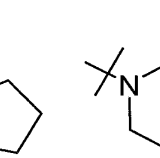
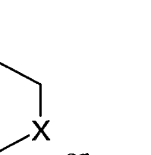
R^8 is selected from the group consisting of hydrogen, halo, cyano, $(C_1$-$C_4)$alkyl, R^aR^bN-, carbamyl, $(C_1$-$C_2)$alkoxy$(C_1$-$C_2)$alkyl, R^{11}-C(O)-,

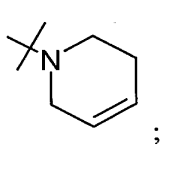
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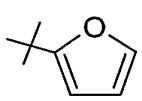
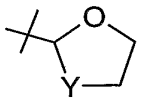
;

R^{11} is methoxy, methylamino, dimethylamino, or phenyl;

R^{12} is hydrogen, halo, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxy dimethylamino, acetyl, or methylsulfonyl;

R^{13} is hydrogen, methyl or halo;

R^{14} is hydrogen or hydroxy;

R^{15} is methylthio, cyclopropyl, phenyl,  or  ;

R^a is hydrogen, $(C_1\text{-}C_5)$alkyl, $(C_3\text{-}C_5)$cycloalkyl, methoxy$(C_2\text{-}C_4)$alkyl, acetyl, $(C_1\text{-}C_2)$alkylsulfonyl, (C_3)alkenyl, $R^{15}\text{-}(CH_2)n$-, or $(C_1\text{-}C_2)$alkyl substituted with cyano, formyl, vinyl, or ethynyl;

R^b is hydrogen or $(C_1\text{-}C_3)$alkyl;

X is $-CH_2-$, -CO-, -O-, -S- or $-SO_2-$;

Y is $-CH_2-$ or -O-;

z is S or O;

n is 1 or 2;

Q is hydrogen or methyl;

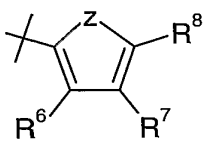
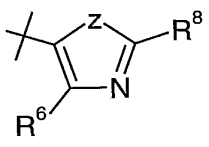
T is hydrogen or methyl;

J is methyl, trifluoroethyl, or tert-butyl; and

M is methyl or halo;

and pharmaceutically acceptable salts thereof.

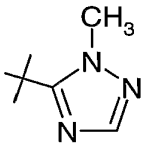
2. The compound of Claim 1 wherein R^0 and R^4 are hydrogen, R^1 and R^3 are methyl, and R^{5a} and R^{5b} are ethyl.

3. The compound according to any one of claims 1 to 2, wherein R^2 is selected from the group consisting of  or  and where z is S.

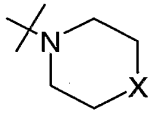
4. The compound according to any one of claims 1 to 3, wherein R^7 is hydrogen.

5. The compound according to any one of claims 1 to 4, wherein R^6 is halo or methyl.

6. The compound according to any one of claims 1 to 5, wherein R^8 is



or



and where X is O.

7. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

8. A compound according to any one of Claims 1 to 6 for use as a medicament.

9. Use of a compound according to any one of Claims 1 to 6 for the manufacture of a medicament for treating anxiety, depression, major depressive disorder, alcohol withdrawal symptoms, or irritable bowel syndrome in a mammal.

10. Use of a compound according to Claim 9 wherein the mammal is a human.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/009942

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5025 A61P25/20

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 364 952 A (EISAI CO., LTD) 26 November 2003 (2003-11-26) examples	1-10
A	WO 97/29109 A (JANSSEN PHARMACEUTICA N.V; NEUROCRINE BIOSCIENCES INC; CHEN, CHEN; WEB) 14 August 1997 (1997-08-14) examples	1-10
A	EP 1 466 527 A (SUMITOMO CHEMICAL TAKEDA AGRO COMPANY, LIMITED) 13 October 2004 (2004-10-13) examples	1-10

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2006	16/08/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Menegaki, F

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/009942

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOREAU S ET AL: "Synthesis and anticonvulsant Properties of Triazolo- and Imidazopyridazinyl Carboxamides and Carboxylic Acids" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 6, no. 7, July 1998 (1998-07), pages 983-991, XP002991062 ISSN: 0968-0896 compounds 9,10,11 -----	1-10

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/009942

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1364952 A	26-11-2003	WO 02062800 A1	15-08-2002
		US 2004082781 A1	29-04-2004
WO 9729109 A	14-08-1997	AU 713673 B2	09-12-1999
		AU 1599197 A	28-08-1997
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EP 1466527 A	13-10-2004	BR 0306810 A	26-10-2004
		CN 1617666 A	18-05-2005
		WO 03061388 A1	31-07-2003
		US 2005032650 A1	10-02-2005

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 September 2002 (19.09.2002)

PCT

(10) International Publication Number
WO 02/072202 A1

(51) International Patent Classification[7]: A61P 25/00, 25/24, A61K 31/53, C07D 403/00

(21) International Application Number: PCT/US02/06837

(22) International Filing Date: 6 March 2002 (06.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/275,403 13 March 2001 (13.03.2001) US

(71) Applicant: **BRISTOL-MYERS SQUIBB PHARMA COMPANY** [US/US]; Patent Department, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(72) Inventor: **GILLIGAN, Paul, J.**; 2629 Pennington Drive, Wilmington, DE 19810 (US).

(74) Agents: **DOLAN, Peter, L.** et al.; Patent Department, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

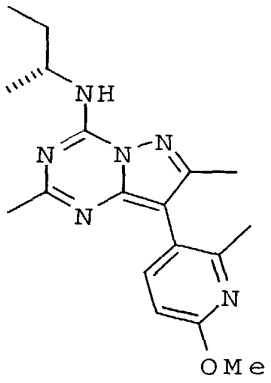
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), 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, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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(54) Title: 4-(2-BUTYLAMINO)-2,7-DIMETHYL-8-(2-METHYL-6-METHOXYPYRID-3-YL) PYRAZOLO-[1,5-A]-1,3,5-TRIAZINE, ITS ENANTIOMERS AND PHARMACEUTICALLY ACCEPTABLE SALTS AS CORTICOTROPIN RELEASING FACTOR RECEPTOR LIGANDS



(I)

(57) Abstract: Corticotropin releasing factor (CRF) antagonists of Formula (I), and its 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.

WO 02/072202 A1

4-(2-BUTYLAMINO)-2,7-DIMETHYL-8-(2-METHYL-6-METHOXYPYRID-3-YL)PYRAZOLO-[1,5-A]-1,3,5-TRIAZINE, ITS ENANTIOMERS AND PHARMACEUTICALLY ACCEPTABLE SALTS AS CORTICOTROPIN RELEASING FACTOR RECEPTOR LIGANDS

Field of the Invention

This invention relates to a 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 psycho-pathological disturbances and stress, by administration of 4-(2-Butylamino)-2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)pyrazolo-[1,5-a]-1,3,5-triazine, its enantiomer and pharmaceutically acceptable salts as a corticotropin releasing factor receptor ligand.

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 cerebrospinal 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 a-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)].

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)].

It has been further postulated that CRF has a role in cardiovascular or heart-related diseases as well as

gastrointestinal disorders arising from stress such as hypertension, tachycardia and congestive heart failure, stroke, irritable bowel syndrome post-operative ileus and colonic hypersensitivity associated with psychopathological disturbance and stress [for reviews see E.D. DeSouza, C.B. Nemeroff, Editors; Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990) and C. Maillot, M. Million, J.Y. Wei, A. Gauthier, Y. Tache, Gastroenterology, 119, 1569-1579 (2000)].

Over-expression or under -expression of CRF has been proposed as an underlying cause for several medical disorders. Such treatable disorders include, for example and without limitation: 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, 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 [for reviews see J.R. McCarthy, S.C. Heinrichs and D.E. Grigoriadis, Cuur. Pharm. Res., 5, 289-315 (1999); P.J. Gilligan, D.W. Robertson and R. Zaczek, J. Medicinal Chem., 43, 1641-1660 (2000), G. P. Chrousos, Int. J. Obesity, 24, Suppl. 2, S50-S55 (2000); E. Webster, D.J. Torpy, I.J. Elenkov, G.P. Chrousos, Ann. N.Y. Acad. Sci., 840, 21-32 (1998); D.J. Newport and C.B. Nemeroff, Curr. Opin. Neurobiology, 10, 211-218 (2000); G. Mastorakos and I. Ilias, Ann. N.Y. Acad. Sci., 900, 95-106 (2000); M.J. Owens and C.B. Nemeroff, Expert Opin. Invest. Drugs, 8, 1849-1858 (1999); G. F. Koob, Ann. N.Y. Acad. Sci., 909, 170-185 (2000)].

The following publications each describe CRF antagonist compounds; however, none disclose the compounds provided herein: WO95/10506; WO99/51608; WO97/35539; WO99/01439; WO97/44308; WO97/35846; WO98/03510; WO99/11643; PCT/US99/18707; WO99/01454; and, WO00/01675.

Summary of the Invention

In accordance with one aspect, the present invention provides a novel compound, 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; 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 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., 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 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 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, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism; and hypoglycemia in a mammal.

The present invention provides a novel compound that binds to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compound of the present invention is useful for the treatment of psychiatric disorders and neurological diseases, 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 a mammal.

According to another aspect, the present invention provides a novel compound of Formula (I) (described below) which is useful as an antagonist of the corticotropin releasing factor. The compound of the present invention exhibits activity as a corticotropin releasing factor antagonist and appears to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such a compound of Formula (I), and methods of using such a compound for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

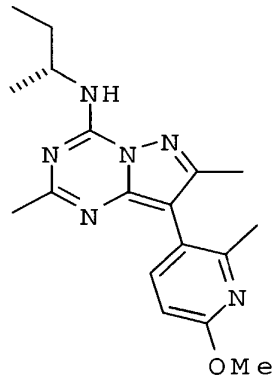
The use of competitive binding assays is considered particularly valuable for screening candidates for new drugs, e.g. to identify new CRF ligands or other compounds having even greater or more selective binding affinity for CRF receptors, which candidates would therefore be potentially useful as drugs. In the assay, one determines the ability of the candidate ligand to displace the labelled compound.

Therefore, another embodiment of the invention includes the use of a compound of the invention is a binding assay, wherein one or more of the compounds may be joined to a label, where the label can directly or indirectly provide a detectable signal. Various labels include radioisotopes, fluorescers, chemiluminescers, specific binding molecules, particles, e.g. magnetic particles, and the like.

Another embodiment of the invention is directed to the use of the compounds of the invention (particularly labeled compounds of this invention) as probes for the localization of receptors in cells and tissues and as standards and reagents for use in determining the receptor-binding characteristics of test compounds. Labeled compounds of the invention may be used for in vitro studies such as autoradiography of tissue sections or for in vivo methods, e.g. PET or SPECT scanning. Particularly, preferred compounds of the invention are useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF1 receptor.

Detailed Description of the Invention

[1] In a first embodiment, the present invention provides a compound of Formula (I):



(I)

and stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[2] In another embodiment, the present invention provides a compound of embodiment [1], isomers thereof, stereoisomeric forms thereof, mixtures of stereoisomeric forms thereof, pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms thereof, wherein said compound is 4-((R)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine or 4-((S)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

[3] In another embodiment, the present invention provides a compound of any one of embodiments [1] to [2], pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms thereof, wherein

said compound is substantially free of its (S) stereoisomer

[4] In another embodiment, the present invention provides a compound of embodiment [1], wherein said compound is 4-(2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

[5] In another embodiment, the present invention provides a compound of embodiment [1], wherein said compound is 4-((R)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

[6] A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of any one of embodiments [1] to [5].

[7] In another embodiment, the present invention provides a method of antagonizing a CRF receptor in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound of any one of embodiments [1] to [5].

[8] In another embodiment, the present invention provides a method of treating a disorder manifesting hypersecretion of CRF in a warm-blooded animal, comprising administering to the animal a therapeutically effective amount of a compound of any one of embodiments [1] to [5].

[9] In another embodiment, the present invention provides a method for the treatment of a disorder, the treatment of which can be effected or facilitated by antagonizing CRF, comprising administering to the mammal

a therapeutically effective of a compound of any one of embodiments [1] to [5].

[10] In another embodiment, the present invention provides a method of antagonizing a CRF receptor in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound of any one of embodiments [1] to [5].

[11] In another embodiment, the present invention provides a method of treating anxiety or depression in mammals, comprising administering to the mammal a therapeutically effective amount of a compound of any one of embodiments [1] to [5].

[12] In another embodiment, the present invention provides a method for screening for ligands for CRF receptors, which method comprises:

a) carrying out a competitive binding assay with a CRF receptor, a compound of any one of embodiments [1] to [5] which is labelled with a detectable label, and a candidate ligand; and

b) determining the ability of said candidate ligand to displace said labelled compound.

[13] In another embodiment, the present invention provides a method for detecting CRF receptors in tissue comprising:

a) contacting a compound of any one of embodiments [1] to [5], which is labelled with a detectable label, with a tissue, under conditions that permit binding of the compound to the tissue; and

b) detecting the labelled compound bound to the tissue.

[14] In another embodiment, the present invention provides a method of inhibiting the binding of CRF to a CRF-1 receptor, comprising contacting a compound of any one of embodiments [1] to [5] with a solution comprising cells expressing the CRF1 receptor, wherein the compound is present in the solution at a concentration sufficient to inhibit the binding of CRF to the CRF-1 receptor.

[15] In another embodiment, the present invention provides a article of manufacture comprising:

a) a packaging material;

b) a compound of any one of embodiments [1] to [5]; and

c) a label or package insert contained within said packaging material idicating that said compound is effective for treating anxiety or depression.

[16] The present invention also comprises 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 any one of embodiments [1] to [5].

Definitions

As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic acids and organic acids. Suitable non-toxic acids include inorganic and organic acids of basic residues such as amines, for example, acetic, benzenesulfonic, benzoic, amphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic and the like; and alkali or organic salts of acidic residues such as carboxylic acids, for example, alkali and alkaline earth metal salts derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, trimethylammonia, triethylammonia, ethylenediamine, n-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine,chloroprocaine, diethanolamine, procaine, n-benzylphenethylamine,

diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide,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.

"Pharmaceutically acceptable prodrugs" as used herein means 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, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" means compounds that are rapidly transformed *in vivo* to

yield the parent compound of formula (I), for example by hydrolysis in blood. Functional groups which may be rapidly transformed, by metabolic cleavage, in vivo form a class of groups reactive with the carboxyl group of the compounds of this invention. They include, but are not limited to such groups as alkanoyl (such as acetyl, propionyl, butyryl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethysilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the compounds useful according to this invention are cleaved in vivo, the compounds bearing such groups act as pro-drugs. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. A thorough discussion of prodrugs is provided in the following: Design of Prodrugs, H. Bundgaard, ed., Elsevier, 1985; Methods in Enzymology, K. Widder et al, Ed., Academic Press, 42, p.309-396, 1985; A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard, ed., Chapter 5; "Design and Applications of Prodrugs" p.113-191, 1991; Advanced Drug Delivery Reviews, H. Bundgard, 8, p.1-38, 1992; Journal of Pharmaceutical Sciences, 77, p. 285, 1988; Chem. Pharm. Bull., N. Nakeya et al, 32, p. 692,

1984; Pro-drugs as Novel Delivery Systems, T. Higuchi and V. Stella, Vol. 14 of the A.C.S. Symposium Series, and Bioreversible Carriers in Drug Design, Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, 1987, which are incorporated herein 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 Formula (I), and the like.

As used herein to describe a compound, the term "substantially free of its (S) stereoisomer" means that the compound is made up of a significantly greater proportion of its (R) stereoisomer than of its optical antipode (i.e., its (S) stereoisomer). In a preferred embodiment of the invention, the term "substantially free of its (S) stereoisomer" means that the compound is made up of at least about 90% by weight of its (R)

stereoisomer and about 10% by weight or less of its (S) stereoisomer.

In a more preferred embodiment of the invention, the term "substantially free of its (S) stereoisomer" means that the compound is made up of at least about 95% by weight of its (R) stereoisomer and about 5% by weight or less of its (S) stereoisomer. In an even more preferred embodiment, the term "substantially free of its (S) stereoisomer" means that the compound is made up of at least about 99% by weight of its (R) stereoisomer and about 1% or less of its (S) stereoisomer. In another preferred embodiment, the term "substantially free of its (S) stereoisomer" means that the compound is made up of nearly 100% by weight of its (R) stereoisomer. The above percentages are based on the total amount of the combined stereoisomers of the compound.

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.

As used herein, the term "labeled" is meant that the compound is either directly or indirectly labeled with a label which provides a detectable signal, e.g. radioisotope, fluorescers, enzyme, antibodies, particles such as magnetic particles, chemiluminescer, P^{32}, I^{131}, and At^{211}, etc.

Syntheses

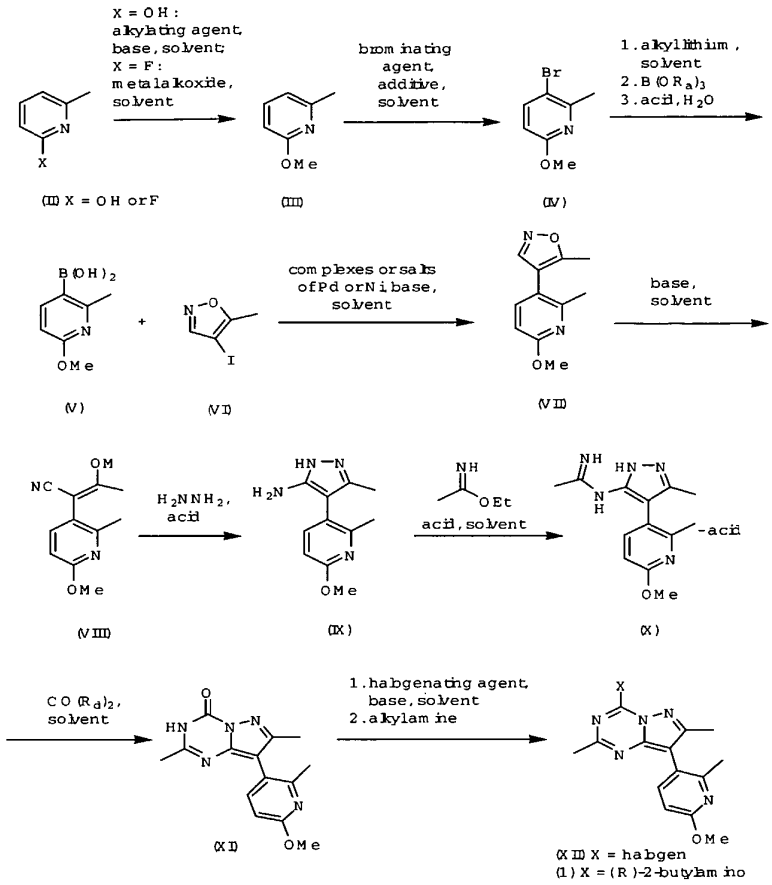
Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and 1 or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture.

The present invention includes all stereoisomeric forms of the compounds of the formula I. Centers of asymmetry that are present in the compounds of formula I can all independently of one another have S configuration or R configuration. The prefixes d and 1 or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or

diastereomers, in all ratios. Thus, enantiomers are a subject of the invention in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism the invention includes both the cis form and the trans form as well as mixtures of these forms in all ratios. The preparation of individual stereoisomers can be carried out, if desired, by separation of a mixture by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials for the synthesis or by stereoselective synthesis. Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compounds of the formula I or at the stage of an intermediate during the synthesis. The present invention also includes all tautomeric forms of the compounds of formula (I).

The compound of Formula (I) may be prepared from using the procedures outlined in Scheme 1.

Scheme 1



A compound of Formula (II), where X = F, may be treated with a metal alkoxide (e.g. sodium methoxide, potassium methoxide; pre-formed or generated in situ) in an inert solvent to generate an intermediate of Formula (III). 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.

Alternatively, a compound of Formula (II), where X = OH, may be treated with an alkylating agent in the presence of a base in an inert solvent to generate an intermediate of Formula (III). Alkylating agents include, but are not limited to, haloalkanes (e.g. CH_3I), dialkyl sulfates (e.g. Me_2SO_4) or alkyl trifluoro-sulfonates (e.g. $CH_3O_3SCF_3$).

Bases may include, but are not limited to, alkali metals, 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 carbonates, alkaline metal carbonates, transition metal carbonates (e.g. silver carbonate), alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bicarbonates, 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, halocarbons (1 to 8 carbons, 1 to 8 halogens), 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 50°C to 150°C.

A compound of Formula (III) may be transformed to a compound of Formula (IV) by reaction with a brominating agent in the presence or absence of an additive in an inert solvent. Brominating agents include, but are not limited to, N-bromosuccinimide - 2,2'-azobisisobutyro-nitrile (AIBN), N-bromophthalimide - 2,2'-azobisiso-butyronitrile (AIBN)), bromine. Additives include, but are not limited to, alkali metal phosphates (e.g. K_3PO_4, Na_3PO_4), alkali metal hydrogen phosphates (e.g. Na_2HPO_4, K_2HPO_4), alkali metal dihydrogen phosphates (e.g. NaH_2PO_4, KH_2PO_4). Inert solvents include, but are not

limited to, halocarbons (1 to 6 carbons, 1 to 6 halogens (preferably chlorine), water, N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one). Reaction temperatures range from 0°C to 200°C (preferably 20°C to 120°C).

A compound of Formula (IV) may be converted to a compound of Formula (V) by sequential reactions with (1) an alkyl lithium in an inert solvent at temperatures ranging from -100°C to 50°C; (2) a compound of the Formula $B(OR^a)_3$ (where R^a is branched or straight chain alkyl of 1 to 20 carbons) at temperatures ranging from -100°C to 50°C and (3) an acid in the presence or absence of water at temperatures ranging from -100°C to 100°C. Alkyl lithiums may be branched or straight chain compounds containing 1 to 20 carbons. Inert solvents include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or aromatic hydrocarbons (preferably benzene or toluene).

Acids may include, but are not limited to, alkanoic 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 benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid.

A compound of Formula (VII) may be produced by reaction of a compound of Formula (V) with a compound of Formula (VI) in the presence of a complex or salt of palladium or nickel, a base and an inert solvent. Complexes of palladium or nickel include, but are not limited to, phosphine complexes such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $NiCl_2(PPh_3)_2$, or [1,1-bis(diphenylphosphino)ferrocene]-dichloropalladium. Bases may include, but are not limited to, alkali metals, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkali metal carbonates, alkaline metal carbonates (e.g. barium carbonate), transition metal carbonates (e.g. silver carbonate) or trialkyl amines (e.g. triethyl amine). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -100°C to 100°C.

An intermediate of Formula (VII) may be reacted with a base in the presence of an inert solvent to afford a compound of Formula (VIII), where M is an alkali metal cation (e.g. sodium or potassium). Bases may include, but are not limited to, alkali metal hydroxides (e.g. NaOH or KOH), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide) or alkaline earth metal hydroxides. Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, 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). Preferred reaction temperatures range from 0°C to 150°C.

Compounds of Formula (VIII) may be treated with hydrazine-hydrate in the presence of an acid and an inert solvent at temperatures ranging from 0°C to 200°C, preferably 70°C to 150°C, to produce compounds of Formula (IX). Acids may include, but are not limited to, alkanoic 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 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, 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).

A compound of Formula (IX) may be reacted with compounds of Formula $H_3C(C=NH)OR^c$ (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 a compound of Formula (X). Acids may include, but are not limited to alkanoic 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 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, alkanenitriles (1 to 6 carbons, preferably acetonitrile), halocarbons of 1 to 6 carbons and 1 to 6 halogens (preferably dichloroethane or chloroform), alkyl alcohols of 1 to 10 carbons (preferably ethanol), dialkyl ethers (4 to 12 carbons, preferably diethyl ether or di-isopropylether) or cyclic ethers such as dioxan or tetrahydrofuran. Preferred temperatures range from 0°C to 100°C.

A compound of Formula (X) may be converted to an intermediate compound of Formula (XI) by treatment with compounds $C=O(R^d)_2$ (where 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 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-

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 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).

A compound of Formula (XI) may be treated with a halogenating 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 a halogenated intermediate (XII) (where X is halogen). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3 or PBr_5. Bases may include, but are not limited to, trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably N,N-diethylaniline).

Inert solvents may include, but are not limited to, N,N-dialkylformamides (preferably dimethylformamide),

N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 20°C to 200°C.

A compound of Formula (XII) may be reacted with an alkyl amine 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 (I). 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 dichloroethane). Preferred reaction temperatures range from 0°C to 140°C.

The compounds of the invention may be prepared as radiolabeled compounds by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^{3}H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I). Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds. Such suppliers include Amersham Corporation, Arlington Heights, Ill.; Cambridge Isotope Laboratories, Inc. Andover, Mass.; SRI International, Menlo Park, Calif.; Wizard Laboratories, West Sacramento, Calif.; ChemSyn Laboratories, Lexena, KS; American Radiolabeled Chemicals, Inc., St.Louis, Mo.; and Moravek Biochemicals Inc., Brea, Calif.

Tritium labeled probe compounds may also conveniently be prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-

catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas. Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate.

Receptor autoradiography (receptor mapping) may be carried out in vitro as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention.

EXAMPLES

Analytical data were recorded for the compounds described below using the following general procedures. Proton NMR spectra were recorded on a Varian VXR or Unity 300 FT-NMR instruments(300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethysilane standard in deuterochloroform or deuterodimethylsulfoxide as specified below. Mass spectra (MS) or high resolution mass spectra (HRMS) were recorded on a Finnegan MAT 8230 spectrometer or a Hewlett Packard 5988A model spectrometer (using chemi-ionization (CI) with NH_3 as the carrier gas,

electrospray (ESI), atmospheric pressure chemi-ionization (APCI) or gas chromatography (GC)). Melting points were recorded on a MelTemp 3.0 heating block 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. Commonly used abbreviations are: DMF (N,N-dimethylformamide), EtOH (ethanol), MeOH (methanol), EtOAc (ethyl acetate), HOAc (acetic acid), DME (1,2-diethoxyethane) and THF (tetrahydrofuran).

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.

EXAMPLE 1

Preparation of 2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-[1,3,5]-triazin-4(3H)-one

A. 2-Methoxy-6-methylpyridine.

Sodium (31.0 g, 1.35 mol) was added portionwise to methanol (500 mL) over 30 min with stirring in a flask equipped with a reflux cindenser. After the addition was complete, the reaction mixture was allowed to cool to ambient temperature. 2-Fluoro-6-methylpyridine (50 g, 450 mmol) was added portionwise with stirring. The reaction mixture was then heated to reflux temperature and stirred for 48 h. The mix was then cooled to ambient temperature and solvent was removed in vacuo to provide a yellow oil. The residue was taken up in water (500 mL) and three extractions with ether (200 mL) were performed. The combined organic layers were dried over $MgSO_4$, filtered and solvent was removed in vacuo from the filtrate to give a yellow liquid: ^{1}H-NMR($CDCl_3$, 300 MHz): δ 7.44 (dd, 1H, J = 8, 7), 6.71 (d, 1H, J = 7), 6.53 (d, 1H, J = 8), 3.91 (s, 3H), 2.45 (s, 3H).

B. 2-Methoxy-6-methylpyridine.

A mixture of 2-hydroxy-6-methylpyridine (6.85 g, 62.8 mmol), silver carbonate (22.5 g, 81.6 mmol), iodomethane (39.1 mL, 628 mmol) and chloroform (200 mL) was stirred at ambient temperature for 40 h in the dark. The reaction mixture was filtered through celite. The

collected solid was washed with ether. The combined filtrates were concentrated in vacuo to give a liquid (6.25 g), which was identical to the product from Part A.

C. 6-Methoxy-3-bromo-2-methylpyridine.

A mixture of 2-methoxy-6-methylpyridine (17.0 g, 138 mmol) and a solution of disodium hydrogen phosphate (0.15M in water, 250 mL) was stirred at room temperature. Bromine (7.1 mL, 138 mmol) was added dropwise over 15 min via an addition funnel. The reaction mixture was then stirred at room temperature for 4 h. The clear colorless solution was diluted with water (500 mL) and extracted with dichloromethane (200 mL) three times. The combined organic layers were dried over $MgSO_4$, filtered and solvent was removed in vacuo from the filtrate to give a yellow liquid. Flash chromatography on silica gel (EtOAc:hexane::1:20) and removal of solvent from the desired combined fractions afforded a clear colorless liquid (15.4 g): ^{1}H-NMR($CDCl_3$, 300 MHz): δ 7.60(d, 1H, J = 8), 6.46 (d, 1H, J = 8), 3.89 (s, 3H), 2.54 (s, 3H).

D. 6-Methoxy-2-methylpyridine-3-boronic acid.

A solution of 6-methoxy-3-bromo-2-methylpyridine (59.8 g, 296 mmol) in dry THF (429 mL) was cooled with

stirring to ~ -78 °C under a nitrogen atmosphere. A solution of n-butyl lithium (2.5 M, 130.4 mL, 326 mmol) in hexane was added dropwise over 30 min. The reaction mixture was stirred for 3 h at ~ -78 °C. A solution of tri-isopropyl borate (102.7 mL, 445 mmol) in dry THF (100 mL) was added dropwise over 30 min. The reaction mixture was warmed to ambient temperature with stirring over 16 h. Acetic acid (37.35 g, 622 mmol), then water (110 mL) were added to the reaction mixture with stirring. After 2h, the layers were separated and the organic layer was concentrated in vacuo. The residue was taken up in 2-propanol (750 mL) and solvent was removed on a rotary evaporator (bath temperature ~ 50 °C). The residue was triturated with ether. The product was collected by filtration and dried in vacuo (48.4 g) : mp > 200 °C; ^{1}H-NMR(CD_3OH, 300 MHz): δ 7.83 (d, 1H, J = 8), 6.56 (d, 1H, J = 8), 3.85 (s, 3H), 2.44 (s, 3H); GC-MS: 168 (M^+ + H).

E. 2-Methyl-3-(5-methylisoxazol-4-yl)-6-methoxypyridine.

A mixture of 4-iodo-5-methylisoxazole (18.2 g, 87 mmol), 6-methoxy-2-methylpyridine-3-boronic acid (14.6 g, 87 mmol), sodium bicarbonate (22.0 g, 262 mmol), water (150 mL) and DME (150 mL) was degassed three times

with stirring by the application of a vacuum and then introduction of a nitrogen atmosphere. [1,1-Bis(diphenylphosphino)ferrocene]-dichloropalladium (II) (2.14 g, 2.6 mmol) was added in one portion. The reaction mixture was degassed as before. The reaction mixture was then stirred at 80 °C for 4 h, then it was cooled to ambient temperature. Three extractions with EtOAc, drying the combined organic layers over $MgSO_4$, filtration and removal of solvent in vacuo afforded an oil. Flash chromatography (EtOAc:hexane::1:9) and removal of solvent in vacuo from the desired fractions gave the product (7.15 g): ^{1}H-NMR($CDCl_3$, 300 MHz): δ 8.16 (s, 1H), 7.33 (d, 1H, J = 8), 6.63 (d, 1H, J = 8), 3.95 (s, 3H), 2.35 (s, 6H); APCI$^+$-MS: 205 (M^+ + H).

F. 1-Cyano-1-(2-methyl-6-methoxypyrid-3-yl)propan-2-one, sodium salt.

A mixture of sodium methoxide (25% w/w, 13 mL, 70 mmol), 2-methyl-3-(5-methylisoxazol-4-yl)-6-methoxypyridine (7.15 g, 35 mmol) and methanol (50 mL) was stirred at room temperature for 16 h. Solvent was removed in vacuo to give a yellow oil. Trituration with ether, filtration and drying in vacuo afforded the crude product as a white solid (9.3 g).

G. 5-Amino-4-(2-methyl-6-methoxypyrid-3-yl)-3-methylpyrazole.

A mixture of 1-cyano-1-(2-methyl-6-methoxypyrid-3-yl)propan-2-one, sodium salt (9.3 g), hydrazine-hydrate (6 mL, 123.3 mmol) and glacial acetic acid (150 mL) was stirred at room temperature for 4 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in 1N HCl and the resulting solution was extracted with EtOAc two times. A 1N NaOH solution was added to the aqueous layer until pH = 12. The resulting semi-solution was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed in vacuo to give a viscous oil (5.8 g): ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.37 (d, 2H, J = 8), 6.62 (d, 2H, J = 8), 3.95 (s, 3H), 2.36 (s, 3H), 2.08 (s, 3H); APCI$^+$-MS: 219 (M^+ + H); 260 (M^+ + CH_3CN).

H. 5-Acetamidino-4-(2-methyl-6-methoxypyrid-3-yl)-3-methylpyrazole, acetic acid salt.

Ethyl acetamidate hydrochloride (6.46g, 52.2 mmol) was added quickly to a rapidly stirred mixture of potassium carbonate (6.95g, 50.0 mol), dichloromethane (60 mL) and water (150 mL). The layers were separated and the aqueous layer was extracted with dichloromethane

(2 X 60 mL). The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed by simple distillation and the pot residue, a clear pale yellow liquid, was used without further purification.

Glacial acetic acid (1.0 mL, 17.4 mmol) was added to a stirred mixture of 5-amino-4-(2-methyl-6-methoxypyrid-3-yl)-3-methylpyrazole (3.8g, 17.4 mmol), ethyl acetamidate free base and dichloromethane (100 mL). The resulting reaction mixture was stirred at room temperature for 16 h; at the end of which time, it was concentrated in vacuo. The residue was triturated with ether, the product was filtered and washed with copious amounts of ether. The white solid was dried in vacuo (5.4 g): ^{1}H-NMR (CD_3OH, 300 MHz): 7.43 (d, 2H, J = 8), 6.69 (d, 2H, J = 8), 4.9 (br s, 2H), 3.93 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 2.13 (s, 3H), 1.88 (s, 3H); $APCI^+$-MS: 260 (M^+ + H).

I. 2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-[1,3,5]-triazin-4(3H)-one.

Sodium pellets (3.9 g, 169 mmol) were added portionwise to ethanol (200 mL) with vigorous stirring. After all the sodium reacted, 5-acetamidino-4-(2-methyl-6-methoxypyrid-3-yl)-3-methylpyrazole, acetic acid salt (5.4 g, 16.9 mmol) and diethyl carbonate (16.4 mL, 135.3 mmol) were added. The resulting reaction mixture

was heated to reflux temperature and stirred for 18 hours. The mix 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 ~ 6. The aqueous layer was extracted with EtOAc three times; the combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed in vacuo to give a solid. Trituration with ether, filtration and drying in vacuo afforded a white solid (3.9 g): ^{1}H-NMR (CD_3OH, 300 MHz): 7.49 (d, 2H, J = 8), 6.69 (d, 2H, J = 8), 3.93 (s, 3H), 2.35 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H); $APCI^+$-MS: 286 (M^+ + H).

EXAMPLE 2

Preparation of 4-((R)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine

A. 4-Chloro-2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolotriazine.

A mixture of 2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazin-4-one (Example 1, 3.9 g, 13.7 mmol), di-isopropyl-ethylamine (9.5 mL, 54.7 mmol), phosphorus oxychloride (5.1 mL, 54.7 mmol) and toluene (75 mL) was stirred at reflux temperature for 4 h. The volatiles were removed in vacuo. The residue was loaded on a pad of silica gel on celite and eluted with a 1:1 mixture of EtOAc and

hexane. Solvent was removed in vacuo from the filtrate to give an oil.

B. 4-((R)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

A mixture of 4-chloro-2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolotriazine, (R)-2-butylamine (2.0 mL, 20.5 mmol), di-isopropyl-ethylamine (9.5 mL, 54.7 mmol) and dry THF (25 mL) was stirred at ambient temperature for 18 hours. Solvent was removed in vacuo. Column chromatography of the residue (first using EtOAc:hexane::1:2, then using EtOAc:hexane::1:4) afforded the product. Removal of solvent in vacuo gave a white solid (2.3 g): mp = 118.3 ^{o}C ; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.41 (d, 1H, J = 8), 6.63 (d, 1H, J = 8), 6.25 (br d, 1H, J = 9), 4.35-4.30 (m, 1H), 3.95 (s, 3H), 2.49 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H), 1.76-1.66 (m, 2H), 1.34 (d, 3H, J = 7), 1.02 (t, 3H, J = 7); ^{13}C-NMR ($CDCl_3$, 100.52 MHz): δ 163.8, 163.0, 155.7, 153.7, 147.8, 146.6, 141.6, 118.5, 107.4, 106.6, 53.3, 48.2, 29.7, 26.1, 22.9, 20.4, 13.1, 10.3; IR (neat, KBr, cm^{-1}): 3380 (m), 3371 (m), 2968 (m), 2928 (m), 2872 (w), 1621 (s), 1588 (s), 1544 (s), 1489 (s), 1460 (s), 1425 (s), 1413 (s), 1364 (s), 1346 (m), 1304 (s), 1275 (s), 1247 (s), 1198 (m), 1152 (m), 1134 (m), 1112 (m), 1034

(s), 1003 (m); ESI(+)-HRMS: Calcd for $C_{18}H_{24}N_6O$: 341.2089; Found: 341.2093 (M^+ + H). Anal. Calcd for $C_{18}H_{24}N_6O$: C, 63.51, H, 7.12, N, 24.69; Found: C, 63.67, H, 7.00, N, 24.49.

Utility

Rat CRF Receptor Binding Assay for the Evaluation of Biological Activity.

Receptor binding affinity to rat cortical receptors was assayed according to the published methods (E.B. De Souza, J. Neuroscience, 7: 88 (1987).

Curves of the inhibition of [^{125}I-Tyr^0]-o-CRF binding to cell membranes at various dilutions of test drug were analyzed by the iterative curve fitting program LIGAND [P.J. Munson and D. Rodbard, Anal. Biochem. 107:220 (1980), which provides Ki values for inhibition which are then used to assess biological activity.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

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° C), 10 mM $MgCl_2$, 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^{-6}m) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/^{32}P]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 [^{3}H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [^{32}P]cAMP from [^{32}P]ATP is performed by sequential elution over Dowex and alumina columns.

In vivo Biological Assay

The in vivo activity of a compound 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 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).

A compound may be tested in any species of rodent or small mammal.

A compound of this invention has utility in the treatment of imbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

A compound 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 conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. It 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 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 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, a compound of this invention can be orally administered

daily at a 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 is 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, butter substances. 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 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.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

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.

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 displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

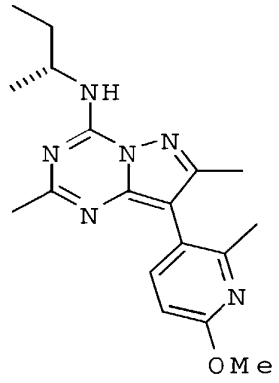
A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase 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.

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 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.

What is claimed is:

1. A compound of Formula (I):



(I)

isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms.

2. A compound of claim 1, pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms thereof, wherein said compound is 4-((R)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

3. A compound of claim 1, pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms thereof, wherein said compound is substantially free of its (S) stereoisomer.

4. A compound of claim 1, wherein said compound is 4-(2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

5. A compound of claim 1, wherein said compound is 4-((R)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 5.

8. A method of antagonizing a CRF receptor in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound as claimed in claim 1.

9. A method of treating a disorder manifesting hypersecretion of CRF in a warm-blooded animal, comprising administering to the animal a therapeutically effective amount of a compound as claimed in claim 1.

10. A method for the treatment of a disorder, the treatment of which can be effected or facilitated by antagonizing CRF, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

11. A method of antagonizing a CRF receptor in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound as claimed in claim 5.

12. A method of treating anxiety or depression in mammals, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

13. A method of treating anxiety or depression in mammals, comprising administering to the mammal a therapeutically effective amount of a compound of claim 5.

14. A method for screening for ligands for CRF receptors, which method comprises:

a) carrying out a competitive binding assay with a CRF receptor, a compound according to claim 1 which is labelled with a detectable label, and a candidate ligand; and

b) determining the ability of said candidate ligand to displace said labelled compound.

15. A method for detecting CRF receptors in tissue comprising:

a) contacting a compound of claim 1, which is labelled with a detectable label, with a tissue, under conditions that permit binding of the compound to the tissue; and

b) detecting the labelled compound bound to the tissue.

16. A method of inhibiting the binding of CRF to a CRF-1 receptor, comprising contacting a compound of claim 1 with a solution comprising cells expressing the CRF1 receptor, wherein the compound is present in the solution at a concentration sufficient to inhibit the binding of CRF to the CRF-1 receptor.

17. An article of manufacture comprising:

a) a packaging material;

b) a compound of claim 1; and

c) a label or package insert contained within said packaging material idicating that said compound is effective for treating anxiety or depression.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/06837

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61P 25/00, 25/24; A61K 31/53; C07D 403/00
US CL : 514/245; 544/212
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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U.S. : 514/245; 544/212

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)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,191,131 B1 (HE et al.) 20 February 2001, see entire document, especially Table 7.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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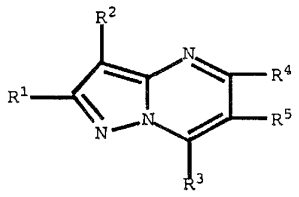
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(54) Title: PYRAZOLOPYRIMIDINES AS CRF ANTAGONISTS



(I)

(57) Abstract

The present invention relates to pyrazolopyrimidines according to formula (I) and stereoisomers, isomers and salts thereof wherein R^1–R^5 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.

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TITLE

PYRAZOLOPYRIMIDINES AS CRF ANTAGONISTS

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 a-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)].

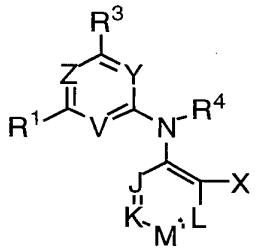
Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton 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)].

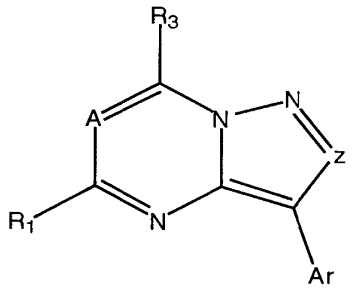
DuPont Merck PCT application US94/11050 describes corticotropin releasing factor antagonist compounds of the formula:



and their use to treat psychiatric disorders and neurological diseases. Included in the description are fused pyridines and pyrimidines of the formula:

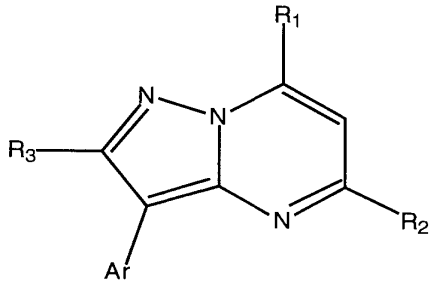
where: V is CR^{1a} or N; Z is CR^2 or N; A is CR^30 or N; and D is CR^{28} or N.

WO 98/03510, published in January, 1998, also describes a series of CRF antagonist compounds having the formula:



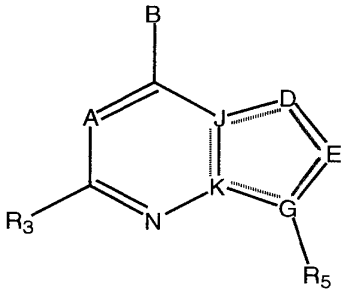
wherein z is N or CR^2 and A is N or CR.

WO 97/29109, published in August, 1997, similarly describes certain CRF antagonist compounds having the formula:



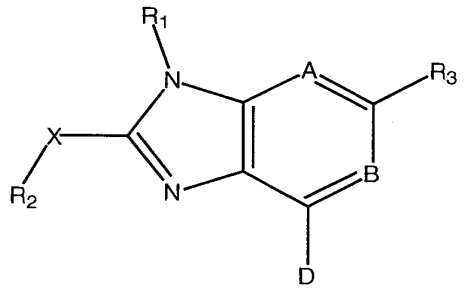
wherein Ar is phenyl, pyridyl and substituted versions thereof.

WO 98/08847, published March 5, 1998, discloses CRF antagonist compounds of the formula:



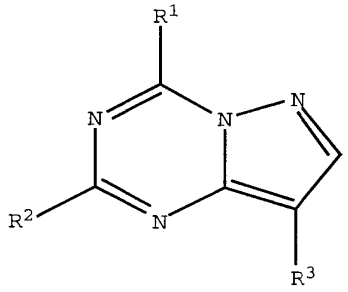
wherein B is selected from a variety of non-aryl groups and R^5 is selected from certain groups such as phenyl or pyridyl or substituted versions thereof.

WO 99/01454, published on January 14, 1999, discloses CRF antagonist compounds of the formula:



wherein D is an aryl or heteroaryl group and R^1 is selected from certain non-aryl or non-heteroaryl groups.

EP 0 269 859 (Ostuka, 1988) discloses pyrazolotriazine compounds of the formula



where R^1 is OH or alkanoyl, R^2 is H, OH, or SH, and R^3 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.

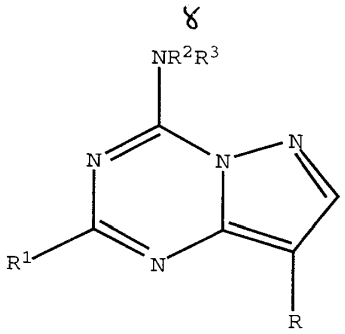
EP 0 594 149 (Ostuka, 1994) discloses pyrazolotriazine and pyrazolopyrimidine compounds of the formula

where A is CH or N, R^0 and R^3 are H or alkyl, and R^1 and R^2 are H, alkyl, alkoxyl, alkylthio, nitro, etc., and 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:

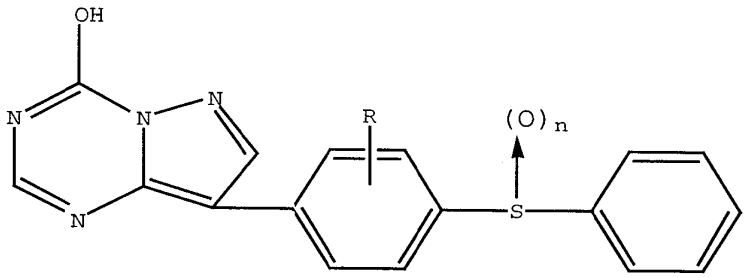
where R1 is CH_3, C_2H_5 or C_6H_5, X is H, C_6H_5, m-$CH_3C_6H_4$, CN, COOEt, Cl, I or Br, Y is H, C_6H_5, o-$CH_3C_6H_4$, or p-$CH_3C_6H_4$, and Z is OH, H, CH_3, C_2H_5, C_6H_5, n-C_3H_7, i-C_3H_7, SH, SCH_3, NHC_4H_9, or $N(C_2H_5)_2$, and states that the compounds are c-AMP phosphodiesterase inhibitors useful as bronchodilators.

US 3,995,039 discloses pyrazolotriazines of the 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 pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

US 5,137,887 discloses pyrazolotriazines of the formula



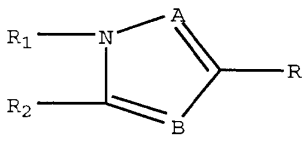
where R is lower alkoxy, and teaches that the compounds are xanthine oxidase inhibitors and are useful for treatment of gout.

US 4,892,576 discloses pyrazolotriazines of the formula

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,

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 compound of the formula



where A can be N, B can be CR_3, R_3 can be phenyl or substituted phenyl, etc., R is $-N(R_4)SO_2R_5$ or $-SO_2N(R_6)R_7$ and R_1 and R_2 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, CH_3, C_2H_5, C_6H_5, n-C_3H_7, iso-C_3H_7, SH, SCH_3, NH(n-C_4H_9), or $N(C_2H_5)_2$, R is H or CH_3, and R_1 is CH_3 or C_2H_5. 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

where Q is carbonyl or sulfonyl, n is 0 or 1, A is a single bond, alkylene or alkenylene, R^1 is H, alkyl, etc., R^2 is naphthyl, cycloalkyl, heteroaryl, substituted phenyl or phenoxy, R^3 is H, alkyl or phenyl, R^4 is H, alkyl, alkoxycarbonyl, phenylalkyl, optionally phenylthio-substituted phenyl, or halogen, R^5 and R^6 are H or alkyl.

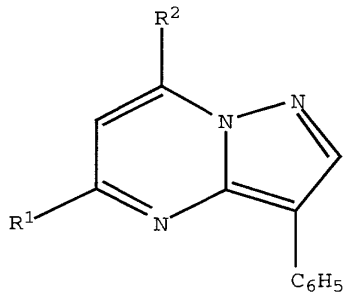
EP 0 591 528 (Otsuka,1991) discloses anti-inflammatory use of pyrazolopyrimidines represented by the formula

where R_1, R_2, R_3 and R_4 are H, carboxyl, alkoxycarbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, R_5 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.

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

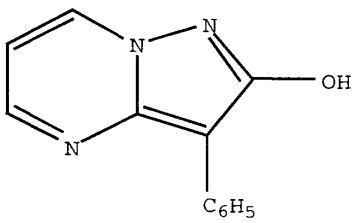
where R can be phenyl, substituted phenyl or pyridyl, and their use to treat gout, based on their ability to inhibit xanthine oxidase.

Joshi et al., J. Prakt. Chemie, 321, 2, 1979, 341-344, discloses compounds of the formula



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

5

where R is NH2 or OH and Ar is 4-phenyl-3-cyano-2-aminopyrid-2-yl.

Other references which disclose azolopyrimidines
10 inclued 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

hypersensitivity associated with psychopathological disturbance and stress in mammals.

According to another aspect, the present invention 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 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.

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, 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; 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 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., 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 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 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, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in mammals. The preferred uses include treatment of depression and anxiety.

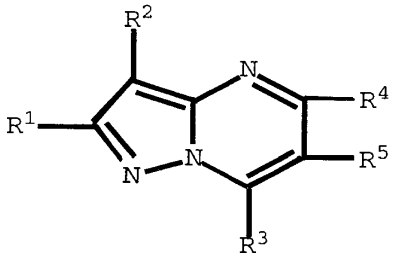
The present invention also relates to the use of a compound of formula I and other compounds generically and specifically disclosed herein in therapy.

According to a still further aspect of the invention, the compounds provided by this invention (and especially labelled compounds of this invention)

are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

DETAILED DESCRIPTION OF INVENTION

[1] Thus, in a first embodiment, the present invention provides a novel compound of formula I:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of

C_{1-6} alkyl,
C_{2-10} alkenyl,
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 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 0 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, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

R^2 is selected from the group consisting of
C_{1-10} alkyl,
C_{2-10} alkenyl,
C_{2-10} alkynyl,
C_{3-8} cycloalkyl,
C_{3-6} cycloalkyl C_{1-6} alkyl,
C_{1-10} alkyloxy,
C_{1-10} alkyloxyC_{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,
$-SO_2R^{2b}$ 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} alkyloxyC_{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,

- halogen,
$-CN$,
$-C(O)L$ wherein L is selected from $NR^{2c}R^{2d}$, C_{1-6} alkyl, H, $-OC_{1-6}$ alkyl, $O(CH_2)_mOC_{1-6}$alkyl, $O(CH_2)_mNR^{2c}R^{2d}$, -OH, aryl, heteroaryl or $C(O)OC_{1-6}$ alkyl, wherein m is 1-3, or more particularly from,
$-C(O)NR^{2c}R^{2d}$,
$-C(O)R$ 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,

$-C(O)O(CH_2)_2-NR^2$,

$-C(O)OH$,

$-C(O)H$,

$-C(O)Ph$,

$-C(O)R'$ wherein R' is aryl, heteroaryl or carboalkoxy;

n is 0, 1 or 2;

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, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy, or

R^2 is substituted with 0-3 substituents independently selected from:

halogen,

$-CN$,

$-S(O)_nR^{2e}$ 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} cycloalkyl, and C_{3-6} cycloalkylC_{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;

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, 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} cycloalkylC_{1-6} alkyl;

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

1-piperidinyl,

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 -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 SO_2R^{2e}; or

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^{2l} and in wich 0-1 carbons of C_{4-8} 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 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, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{20}R^{2p}$, $-NR^{2g}CO_2R^{2n}$, $-NR^{20}R^{2p}$ and $-CONR^{20}R^{2p}$;

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^{2l} is H, C_{1-4} alkyl, C_{3-6} cycloalky-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;

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cyloalkyl, 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^{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 heleroaryl (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;

$R^{2r}R^{2s}$ 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};

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);

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, $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ 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;

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 substitued 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,

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;

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, $(C_{1-4}$ alkyl$)_2$ amino and phenyl, each phenyl is substituted 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 $(C_{1-4}$ alkyl$)_2$ amino and wherein R^4 and R^5 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} alkyl$(OH)_nCO_2R$ 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 Formula I with R^1, R^2, R^3, R^4 and R^5 as specifically defined below are excluded:

(a) a compound of formula I wherein R^1 is unsubstituted, unbranched (linear) C_{1-3} alkyl and R^2 is -C(O)-Ph (EP O 129 847 A2, US 4,521,422, US 4,654,347);

(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 (US 4,281,000);

(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)

(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 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, 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

(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 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 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, 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);

(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);

(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 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);

(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 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);

(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 (reg. ref. 147);

(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 (reg. ref. 148);

(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 (reg. ref. 154);

(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 (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);

(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 (reg. ref. 157);

(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 (reg. ref. 157);

(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 (reg. ref. 163);

(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 (reg. ref. 164);

(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 (reg. ref. 165);

(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 (reg. ref. 166);

(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 (reg. ref. 167);

(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 (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);

(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_3Ph, R^4 and R^5 are H (reg. ref. 172);

(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 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);

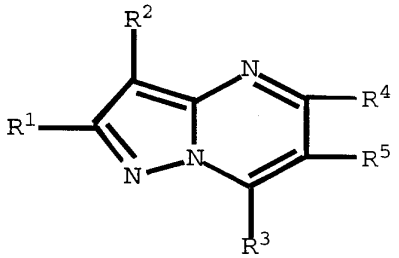
(nnn) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is m-CF_3-Ph, R^4 is H and R^5 is CH_3 (reg. ref. 178);

(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 $C(O)NH_2$, R^3 is m-CF_3-Ph, R^4 and R^5 are H (reg. ref. 180);

(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 invention provides a novel compound of formula I:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of

C_{1-6} alkyl,
C_{2-10} alkenyl,
C_{2-10} alkynyl,
C_{3-6} cycloalkyl,
C_{1-6} alkyloxy,
C_{1-6} alkyl$S(O)_n$,
$-NR^{1a}R^{1B}$ 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,

$-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl;
X is selected from 0 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, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

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,
C_{3-6} cycloalkyl C_{1-6} alkyl,
C_{1-10} alkyloxy,
C_{1-10} alkyloxyC_{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,

$-SO_2R^{2b}$ 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} alkyloxyC_{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,

n is 0, 1 or 2;

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, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy, or

R^2 is substituted with 0-3 substituents independently selected from:

-CN,

$-S(O)_nR^{2e}$ 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} cycloalkyl, and C_{3-6} cycloalkylC_{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;

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, 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} cycloalkylC_{1-6} alkyl;

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

1-piperidinyl,

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 $-O-$, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2R^{2e}$, $-NCOR^{2e}$, 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 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 substituted with 0-1 R^{2i} and in wich 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, 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} cycloalky-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;

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cyloalkyl, 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^{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 heleroaryl (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;

$R^{2r}R^{2s}$ 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};

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);

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, $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ 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;

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 substitued 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,

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;

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, $(C_{1-4}$ alkyl$)_2$ amino and phenyl, each phenyl is substituted 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 $(C_{1-4}$ alkyl$)_2$ amino and wherein R^4 and R^5 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} alkyl$(OH)_nCO_2R$ 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.

[2] The present invention relates to a compound as described directly above in [1] or [1'] wherein

R^1 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, $-XR^{1c}$ wherein R^1 is substituted with 0-6 substituents selected from halogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

R^2 is selected from substituted-C_{1-10} alkyl, branched C_{3-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-8} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl, $-NR^{2c}R^{2d}$ wherein, in the case of substituted-C_{1-10} alkyl, 1-3 substitutents are independently selected from 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^{21} and in wich 0-1 carbons of C_{4-8} cycloalkyl is replaced by -O- and wherein the R^2 groups, other than substituted-C_{1-10} alkyl, are substituted with 0-3 substituents independently selected from 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^{21} and in wich 0-1 carbons of C_{4-8} cycloalkyl is replaced by -O-.

[3] The present invention also relates to a compound described in groups [1], [1'] or [2] wherein R^3 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 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.

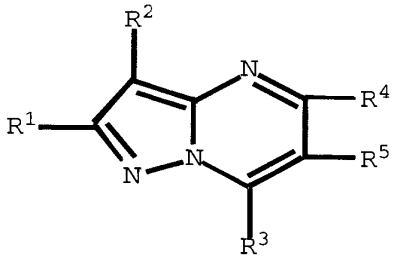
[5] The present invention preferrably relates to a compound as described directly above in groups [1'] and [1]-[4] wherein R^3 is selected from 2,4-dichlorophenyl, 2-chloro-4-methoxyphenyl, 2,4,6-trimethylphenyl, 2,4,6-trimethoxyphenyl, 2-dimethylamino-4-methyl-pyridin-5-yl, 2,4-dichloro-5-fluorophenyl, 2-chloro-4-methoxy-5-fluorophenyl, 2-chloro-4,5-dimethoxyphenyl or 2-chloro-4,5-dimethoxyphenyl.

[6] The present invention also preferrably relates to a compound as described in groups [1'] and [2]-[5] 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, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{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.

[7] The present invention preferrably 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 substitued 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 preferrably relates to a compound of formula (I)



(I)

or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof, wherein

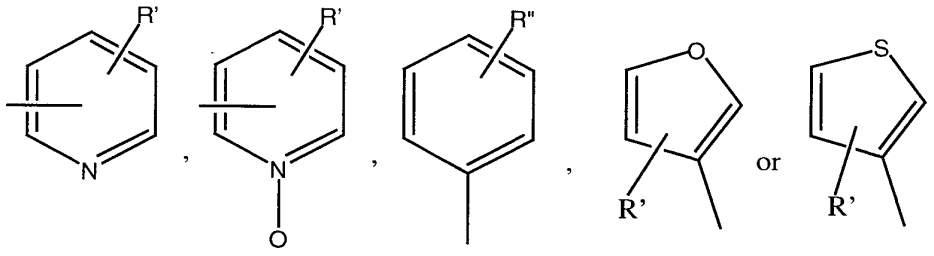
R^1 is selected from C_{1-6} alkyl, C_{1-6} alkyloxy, -SH or OH;

R^2 is selected from C_{1-4} alkyl which is unsubstituted or substituted with 1-4 substitutents 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;

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, CF_3, $S(O)_nC_{1-6}$ alkyl, $-OC_{1-6}$ 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;

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 C_{1-3} alkyl and R″ is H or o-trifluoromethyl, m-trifluoromethyl or m-methoxy (see 4,281,000).

[9] The present invention also relates to a compound according to group [8] wherein R^3 is substituted with 2-4 substituents.

[10] The present invention also relates to a compound according to group [8] or[9] wherein R^2 is substituted with 1-4 substituents.

[11] The present invention also relates to a compound according to groups [8]-[10] having the formulae shown in Table 1.

[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-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 Formula (I) wherein

R^1 is selected from the group consisting of

C_{1-6} alkyl,

C_{2-10} alkenyl,

C_{2-10} alkynyl,

C_{3-6} cycloalkyl,

C_{1-6} alkyloxy,

C_{1-6} alkyl$S(O)_n$,

$-NR^{1a}R^{1B}$ 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,

$-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl;
X is selected from 0 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, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

R^2 is selected from the group consisting of

C_{1-10} alkyl,

C_{2-10} alkenyl,

C_{2-10} alkynyl,

C_{3-8} cycloalkyl,

C_{3-6} cycloalkyl C_{1-6} alkyl,

C_{1-10} alkyloxy,

C_{1-10} alkyloxyC_{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,

$-SO_2R^{2b}$ 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} alkyloxyC_{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,

- halogen,

-CN,

$-C(O)NR^{2c}R^{2d}$,

-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,

$-C(O)O(CH_2)_2-NR^2$,

-C(O)OH,

-C(O)H,

-C(O)Ph,

-C(O)R' wherein R' is aryl, heteroaryl or carboalkoxy;

n is 0, 1 or 2;

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, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy, or

R^2 is substituted with 0-3 substituents independently selected from

halogen,

-CN,

$-S(O)_nR^{2e}$ 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} cycloalkyl, and C_{3-6} cycloalkylC_{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;

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, 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} cycloalkylC_{1-6} alkyl;

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

1-piperidinyl,

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

$-O-$, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2R^{2e}$, $-NCOR^{2e}$,

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 SO_2R^{2e}; or

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^{2l} and in wich 0-1 carbons of C_{4-8} 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 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 $-CONR^{2o}R^{2p}$;

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^{2l} is H, C_{1-4} alkyl, C_{3-6} cycloalky-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;

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cyloalkyl, 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^{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 heleroaryl (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;

$R^{2r}R^{2s}$ 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};

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);

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, $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ 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;

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 substitued 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,

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;

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, $(C_{1-4}$ alkyl$)_2$ amino and phenyl, each phenyl is substituted 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 $(C_{1-4}$ alkyl$)_2$ amino and wherein R^4 and R^5 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}

alkyl$(OH)_nCO_2R$ 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.

[13] The present invention also relates to a method as described directly above in group [12] wherein

R^1 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, $-XR^{1c}$ wherein R^1 is substituted with 0-6 substituents selected from halogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

R^2 is selected from substituted-C_{1-10} alkyl, branched C_{3-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-8} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl, $-NR^{2c}R^{2d}$ wherein, in the case of substituted-C_{1-10} alkyl, 1-3 substitutents are independently selected from 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^{21} and in wich 0-1 carbons of C_{4-8} cycloalkyl is replaced by -O- and wherein the R^2 groups, other than substituted-C_{1-10} alkyl, are substituted with 0-3 substituents independently selected from 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^{21} and in wich 0-1 carbons of C_{4-8} cycloalkyl is replaced by -O-.

[14] The present invention also relates to a method described directly above in [12] or [13] wherein R^3 is selected from an aryl group selected from phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

[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 preferrably 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.

[17] The present invention also preferrably 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, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{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;

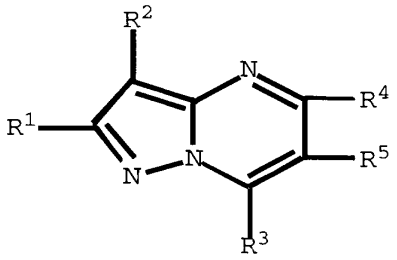
or R^2 is selected from NR'R" wherein R' and R" are independently selected from H or C_{1-6} alkyl.

[18] The present invention preferrably 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}

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 substitued 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} .

[19] The present invention preferrably 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

induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of formula (I)



(I)

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;

R^2 is selected from C_{1-4} alkyl which is unsubstituted or substituted with 1-4 substitutents 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;

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, CF_3, $S(O)_nC_{1-6}$ alkyl, $-OC_{1-6}$ 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;

R^4 and R^5 are independently selected from H, C_{1-6} alkyl or C_{1-6} alkyloxy.

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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.

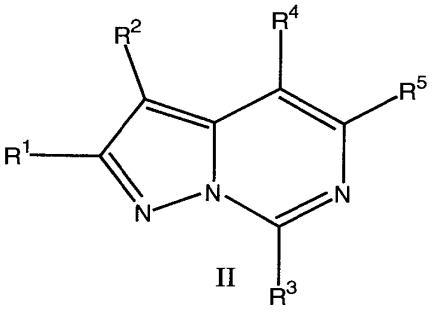
[21] The present invention also relates to a method according to group [19]-[20] wherein R^2 is substituted with 1-4 substituents.

[22] The present invention also relates to a method according to group [19]-[21] using the formulae shown in Table 1.

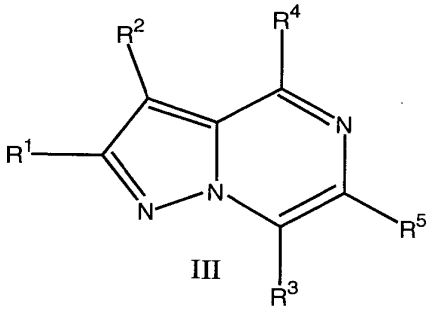
[23] The present invention also provides pharmaceutical compositions comprising compounds of Formula (1) with the variables as recited above in group [1] and [1'] with the proviso that the compounds excluded in proviso (d) in group [1] are included herein and a pharmaceutically acceptable carrier.

[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 of the formulae shown below having the variables recited above in groups [1'] and [1]-[24]:



II



III

except that the provisos listed in group I are not included for the compounds of formula II and III.

[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

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 substitent 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 "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 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) 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:

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-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

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

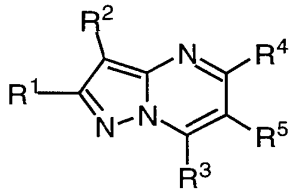
2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine

Synthesis

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.

Synthesis of compounds of formula (I) may be prepared by the reaction shown in Scheme 1.

The embodiment of this invention concerning compounds of Formula (I) with the structure



may be prepared according to the following methods:

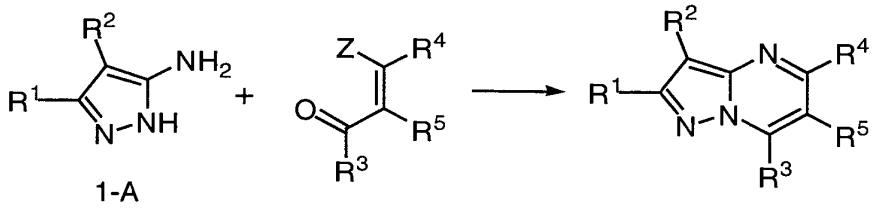
The pyrazolo[1,5-a]pyrimidine ring system is best prepared by the condensation reaction of a 3-aminopyrazole (1-A, Scheme 1A) with a compound of formula

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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



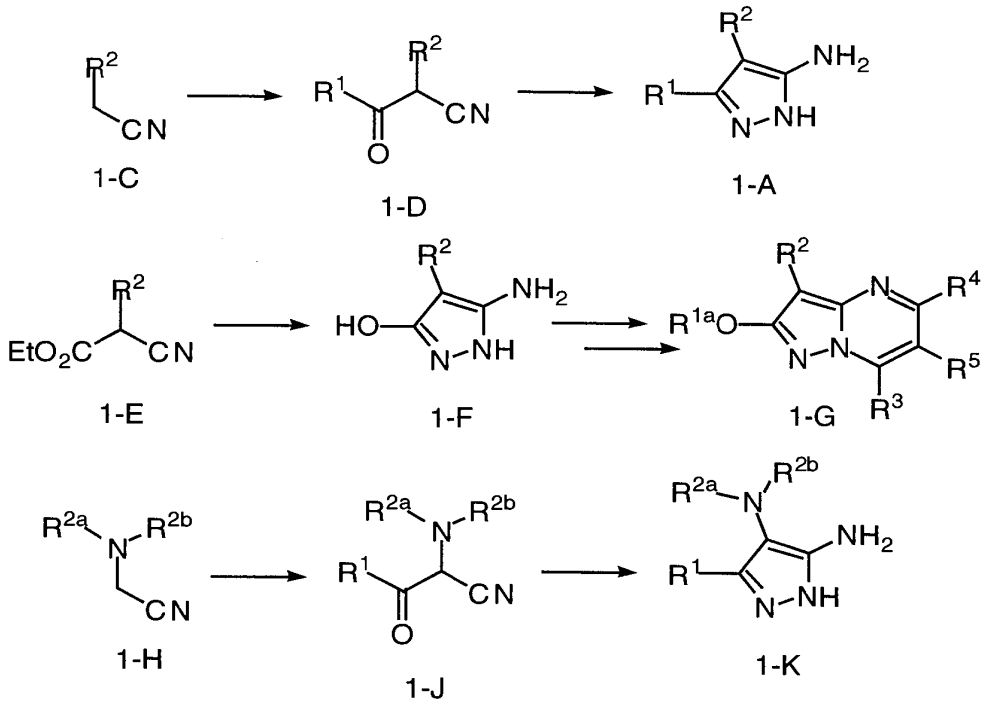
1-A 1-B

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.

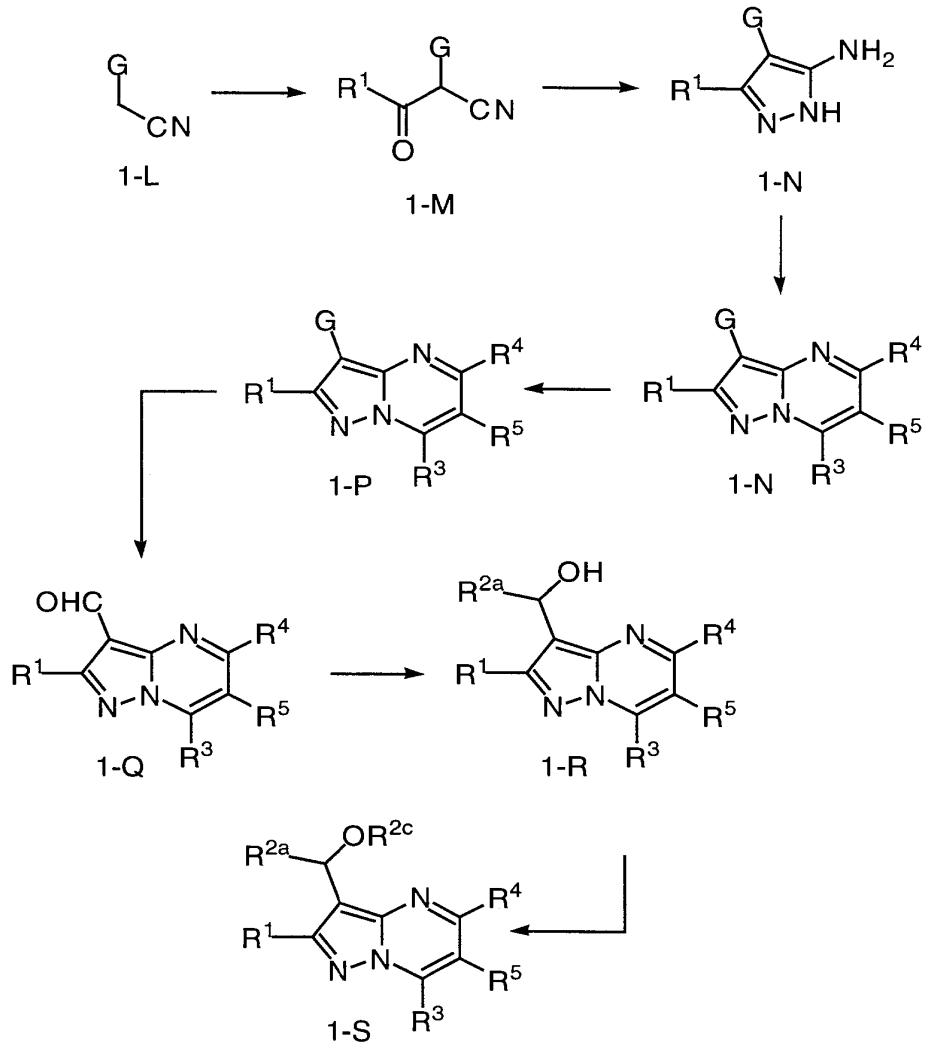
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Cyclization with reagent 1-B and O-alkylation with a reagent $R^{1a}X$, wherein X is a halide or pseudohalide group, gives compound 1-G. Finally, strong base treatment of aminonitrile 1-H, usually in the presence of a solvent mixture such as THF/HMPA, followed by acylation and ring-forming, gives diamine 1-K.

Scheme 1B



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 R^2 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 R^2 group of

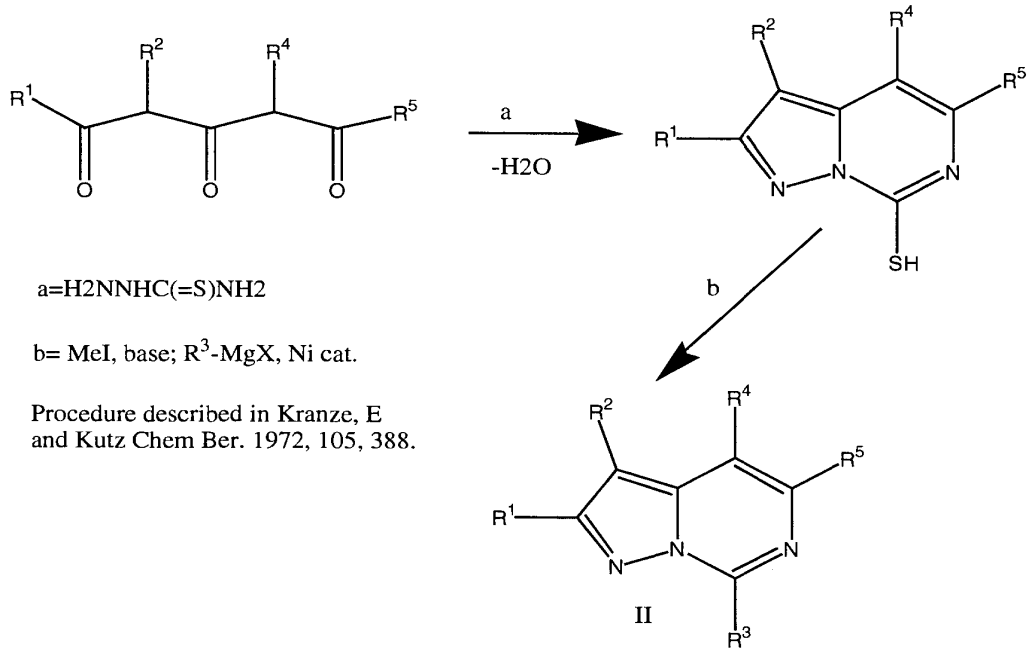
choice wherein R^2 and substituted versions thereof is as defined in the claims and as above in the specification; the following method is one example. Use of a reducing agent such as diisobutylaluminum hydride in a solvent like toluene or dichloromethane at low temperatures can be used to obtain the 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 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.

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 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 be accomplished by the general schemes shown below in Scheme 2 and in Scheme 3.

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SCHEME 2



a=H2NNHC(=S)NH2

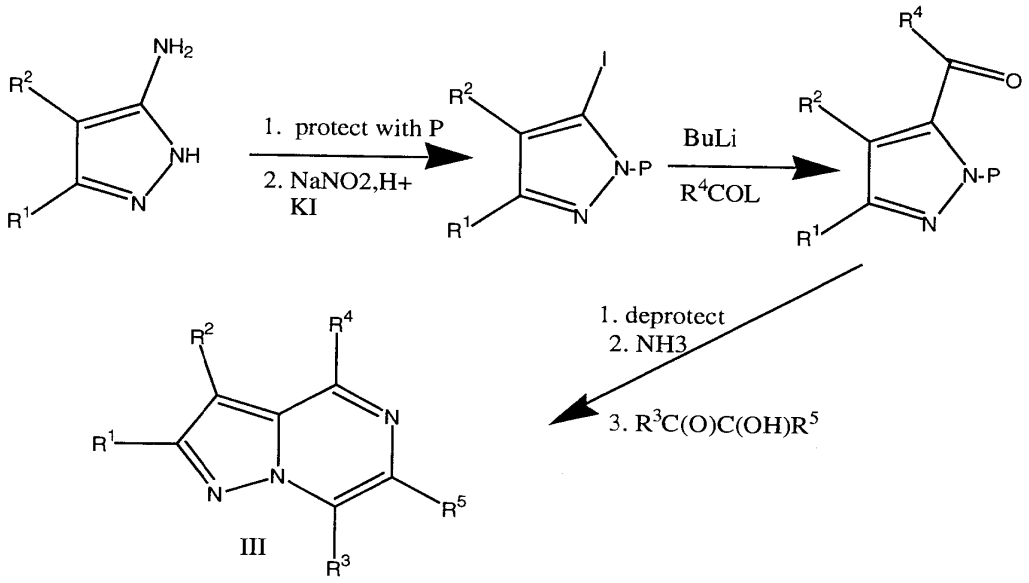
b= MeI, base; R^3-MgX, Ni cat.

Procedure described in Kranze, E and Kutz Chem Ber. 1972, 105, 388.

The variables for R^1-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 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



III

The variables for R^1-R^5 in Scheme 3 are selected from those described in groups [1]-[24]. Compounds II and III with the variables as defined above are useful as CRF antagonists.

Utility

CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

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 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 CRH_1 receptor using a modified version of methods described earlier (see E.B. DeSouza, J. Neurosci, 7:88, 1987). Rat cortex was homogenized in tissue buffer (containing 50 mM HEPES, 10 mM $MgCl_2$, 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 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 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 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, [^{125}I] tyr° ovine CRH; New England 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 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, containing 0.01% Triton X-100), dried, and counted in a gamma counter at 80% efficiency.

Binding affinities (K_i's) of ligands for the CRH_1 receptor were calculated using the iterative nonlinear regression curve-fitting programs (LIGAND) of Munson and Rodbard (Anal. Biochem. 1980, 107, 220-239) or 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 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 $MgCl_2$, 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 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/^{32}P]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 [^{3}H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [^{32}P]cAMP from [^{32}P]ATP is performed by sequential elution over Dowex and alumina columns.

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 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).

Compounds may be tested in any species of rodent or small mammal.

Compounds of this invention have utility in the treatment of inbalances 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 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 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 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 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 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 is 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, butter substances. 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 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.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

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.

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 displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

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 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.

The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

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: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (2H, d, J = 5.8 Hz), 1.62-1.36 (5H, m), 0.92 (6H, t, J = 7.3 Hz). MS (H_2O-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,

13.7 mmol, 56%). Spectral data: ^{1}H 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: ^{1}H 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

product, which was the title compound. TLC R_F 0.32 (10:90 ethyl acetate-hexane). Spectral data: ^{1}H 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 (NH_3-CI): m/e 367 (2), 366 (11), 365 (15), 364 (65), 363 (25), 362 (100). Analysis calc'd for $C_{19}H_{21}Cl_2N_3$: 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 31

Preparation of 7-(2,4-dichlorophenyl)-3-(N,N-diethylamino)-2-ethylpyrazolo[1,5-a]pyrimidine

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 -78 °C. To this was added first, N,N'-dimethylpropyleneurea as cosolvent (15 mL), then, diethylaminoacetontrile (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 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, 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%).

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) 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. $NaHCO_3$ 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%).

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 columnm chromatography (silica gel, 20:80 ethyl acetate-hexane) to afford the title product as a red oil (411 mg, 1.13 mmol, 64%). Spectral data: ^{1}H 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 (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 (NH_3-CI): calculated for $C_{18}H_{21}Cl_2N_4$ 363.1143, measured 363.1146; m/e 367 (6), 366 (14), 365 (81), 364 (28), 363 (100).

Examples 32-45 were and/or may be prepared in an analogous manner.

Examples 51 and 92

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)

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 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 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: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27 (2H, q, J = 7.0 Hz), 3.61 (1H, d, J = 4.4 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 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 and evaporated. The resulting oil was sufficiently pure product, 3-amino-5-hydroxy-4-(3-pentyl)pyrazole (1.29 g, 7.62 mmol, 41%).

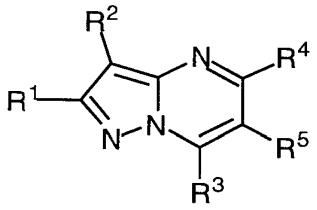
Part C. A solution of the pyrazole compound from Part B (478 mg, 2.82 mmol) and 2-(2,4-dichlorobenzoyl)-1-(N,N-dimethylamino)-1-propene (729 mg, 2.82 mmol) in acetic acid (10 mL) was heated to reflux for 10 hours. The solution was cooled and poured into water (100 mL). This was neutralized by the addition of solid $NaHCO_3$, 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, $CDCl_3$): 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, $CDCl_3$): 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 (6H, t, J = 7.4 Hz). MS (NH_3-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 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.

Table 1



Ex No	R^1	R^2	R^4	R^5	R^3	m.p. °C
1	C_2H_5	$(C_2H_5)_2CH$	H	H	2,4-Cl_2-C_6H_3	oil[a]
2	C_2H_5	$(C_2H_5)_2CH$	H	H	2-Cl-4-CH_3O-C_6H_3	88-89
3	C_2H_5	$(C_2H_5)_2CH$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	oil[b]
4	C_2H_5	$(C_2H_5)_2CH$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	166-167
5	C_2H_5	$(C_2H_5)_2CH$	H	H	2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl	-
6	C_2H_5	$(C_2H_5)_2CH$	H	CH_3	2,4-Cl_2-C_6H_3	90-91
7	C_2H_5	$(C_2H_5)_2CH$	H	CH_3	2-Cl-4-CH_3O-C_6H_3	-
8	C_2H_5	$(C_2H_5)_2CH$	H	CH_3	2,4,6-$(CH_3)_3$-C_6H_2	-
9	C_2H_5	$(C_2H_5)_2CH$	H	CH_3	2,4,6-$(OCH_3)_3$-C_6H_2	-
10	C_2H_5	$(C_2H_5)_2CH$	H	CH_3	2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl	-
11	C_2H_5	$(C_2H_5)_2CH$	CH_3	H	2,4-Cl_2-C_6H_3	-
12	C_2H_5	$(C_2H_5)_2CH$	CH_3	H	2-Cl-4-CH_3O-C_6H_3	-
13	C_2H_5	$(C_2H_5)_2CH$	CH_3	H	2,4,6-$(CH_3)_3$-C_6H_2	-
14	C_2H_5	$(C_2H_5)_2CH$	CH_3	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
15	C_2H_5	$(C_2H_5)_2CH$	CH_3	H	2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl	-
16	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2,4-Cl_2-C_6H_3	oil[c]
17	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2-Cl-4-CH_3O-C_6H_3	-
18	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	oil[d]
19	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-

20	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
21	C_2H_5	$C_4H_9(C_2H_5)CH$	H	CH_3	2,4-Cl_2-C_6H_3	78-79
22	C_2H_5	$C_4H_9(C_2H_5)CH$	H	CH_3	2-Cl-4-CH_3O-C_6H_3	-
23	C_2H_5	$C_4H_9(C_2H_5)CH$	H	CH_3	2,4,6-$(CH_3)_3$-C_6H_2	-
24	C_2H_5	$C_4H_9(C_2H_5)CH$	H	CH_3	2,4,6-$(OCH_3)_3$-C_6H_2	-
25	C_2H_5	$C_4H_9(C_2H_5)CH$	H	CH_3	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
26	C_2H_5	$C_4H_9(C_2H_5)CH$	CH_3	H	2,4-Cl_2-C_6H_3	-
27	C_2H_5	$C_4H_9(C_2H_5)CH$	CH_3	H	2-Cl-4-CH_3O-C_6H_3	-
28	C_2H_5	$C_4H_9(C_2H_5)CH$	CH_3	H	2,4,6-$(CH_3)_3$-C_6H_2	-
29	C_2H_5	$C_4H_9(C_2H_5)CH$	CH_3	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
30	C_2H_5	$C_4H_9(C_2H_5)CH$	CH_3	H	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
31	C_2H_5	$(C_2H_5)_2N$	H	H	2,4-Cl_2-C_6H_3	oil[e]
32	C_2H_5	$(C_2H_5)_2N$	H	H	2-Cl-4-CH_3O-C_6H_3	97-98
33	C_2H_5	$(C_2H_5)_2N$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	-
34	C_2H_5	$(C_2H_5)_2N$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
35	C_2H_5	$(C_2H_5)_2N$	H	H	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
36	C_2H_5	$(C_2H_5)_2N$	H	CH_3	2,4-Cl_2-C_6H_3	-
37	C_2H_5	$(C_2H_5)_2N$	H	CH_3	2-Cl-4-CH_3O-C_6H_3	-
38	C_2H_5	$(C_2H_5)_2N$	H	CH_3	2,4,6-$(CH_3)_3$-C_6H_2	-
39	C_2H_5	$(C_2H_5)_2N$	H	CH_3	2,4,6-$(OCH_3)_3$-C_6H_2	-
40	C_2H_5	$(C_2H_5)_2N$	H	CH_3	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
41	C_2H_5	$(C_2H_5)_2N$	CH_3	H	2,4-Cl_2-C_6H_3	-
42	C_2H_5	$(C_2H_5)_2N$	CH_3	H	2-Cl-4-CH_3O-C_6H_3	-
43	C_2H_5	$(C_2H_5)_2N$	CH_3	H	2,4,6-$(CH_3)_3$-C_6H_2	-
44	C_2H_5	$(C_2H_5)_2N$	CH_3	H	2,4,6-$(OCH_3)_3$-C_6H_2	-

45	C_2H_5	$(C_2H_5)_2N$	CH_3	H	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
46	OCH_3	$(C_2H_5)_2CH$	H	H	2,4-Cl_2-C_6H_3	-
47	OCH_3	$(C_2H_5)_2CH$	H	H	2-Cl-4-CH_3O-C_6H_3	-
48	OCH_3	$(C_2H_5)_2CH$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	-
49	OCH_3	$(C_2H_5)_2CH$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
50	OCH_3	$(C_2H_5)_2CH$	H	H	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
51	OCH_3	$(C_2H_5)_2CH$	H	CH_3	2,4-Cl_2-C_6H_3	oil[f]
52	OCH_3	$(C_2H_5)_2CH$	H	CH_3	2-Cl-4-CH_3O-C_6H_3	-
53	OCH_3	$(C_2H_5)_2CH$	H	CH_3	2,4,6-$(CH_3)_3$-C_6H_2	-
54	OCH_3	$(C_2H_5)_2CH$	H	CH_3	2,4,6-$(OCH_3)_3$-C_6H_2	-
55	OCH_3	$(C_2H_5)_2CH$	H	CH_3	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
56	OCH_3	$(C_2H_5)_2CH$	CH_3	H	2,4-Cl_2-C_6H_3	-
57	OCH_3	$(C_2H_5)_2CH$	CH_3	H	2-Cl-4-CH_3O-C_6H_3	-
58	OCH_3	$(C_2H_5)_2CH$	CH_3	H	2,4,6-$(CH_3)_3$-C_6H_2	-
59	OCH_3	$(C_2H_5)_2CH$	CH_3	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
60	OCH_3	$(C_2H_5)_2CH$	CH_3	H	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
61	OCH_3	$C_4H_9(C_2H_5)CH$	H	H	2,4-Cl_2-C_6H_3	-
62	OCH_3	$C_4H_9(C_2H_5)CH$	H	H	2-Cl-4-CH_3O-C_6H_3	-
63	OCH_3	$C_4H_9(C_2H_5)CH$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	-
64	OCH_3	$C_4H_9(C_2H_5)CH$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
65	OCH_3	$C_4H_9(C_2H_5)CH$	H	H	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
66	OCH_3	$C_4H_9(C_2H_5)CH$	H	CH_3	2,4-Cl_2-C_6H_3	-
67	OCH_3	$C_4H_9(C_2H_5)CH$	H	CH_3	2-Cl-4-CH_3O-C_6H_3	-
68	OCH_3	$C_4H_9(C_2H_5)CH$	H	CH_3	2,4,6-$(CH_3)_3$-C_6H_2	-
69	OCH_3	$C_4H_9(C_2H_5)CH$	H	CH_3	2,4,6-$(OCH_3)_3$-C_6H_2	-
70	OCH_3	$C_4H_9(C_2H_5)CH$	H	CH_3	2-$(CH_3)_2$N-4-CH_3-	-

					pyridin-5-yl	
71	OCH_3	$C_4H_9(C_2H_5)CH$	CH_3	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
72	OCH_3	$C_4H_9(C_2H_5)CH$	CH_3	H	$2\text{-}Cl\text{-}4\text{-}CH_3O\text{-}C_6H_3$	-
73	OCH_3	$C_4H_9(C_2H_5)CH$	CH_3	H	$2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$	-
74	OCH_3	$C_4H_9(C_2H_5)CH$	CH_3	H	$2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$	-
75	OCH_3	$C_4H_9(C_2H_5)CH$	CH_3	H	$2\text{-}(CH_3)_2N\text{-}4\text{-}CH_3$-pyridin-5-yl	-
76	OCH_3	$(C_2H_5)_2N$	H	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
77	OCH_3	$(C_2H_5)_2N$	H	H	$2\text{-}Cl\text{-}4\text{-}CH_3O\text{-}C_6H_3$	-
78	OCH_3	$(C_2H_5)_2N$	H	H	$2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$	-
79	OCH_3	$(C_2H_5)_2N$	H	H	$2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$	-
80	OCH_3	$(C_2H_5)_2N$	H	H	$2\text{-}(CH_3)_2N\text{-}4\text{-}CH_3$-pyridin-5-yl	-
81	OCH_3	$(C_2H_5)_2N$	H	CH_3	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
82	OCH_3	$(C_2H_5)_2N$	H	CH_3	$2\text{-}Cl\text{-}4\text{-}CH_3O\text{-}C_6H_3$	-
83	OCH_3	$(C_2H_5)_2N$	H	CH_3	$2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$	-
84	OCH_3	$(C_2H_5)_2N$	H	CH_3	$2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$	-
85	OCH_3	$(C_2H_5)_2N$	H	CH_3	$2\text{-}(CH_3)_2N\text{-}4\text{-}CH_3$-pyridin-5-yl	-
86	OCH_3	$(C_2H_5)_2N$	CH_3	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
87	OCH_3	$(C_2H_5)_2N$	CH_3	H	$2\text{-}Cl\text{-}4\text{-}CH_3O\text{-}C_6H_3$	-
88	OCH_3	$(C_2H_5)_2N$	CH_3	H	$2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$	-
89	OCH_3	$(C_2H_5)_2N$	CH_3	H	$2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$	-
90	OCH_3	$(C_2H_5)_2N$	CH_3	H	$2\text{-}(CH_3)_2N\text{-}4\text{-}CH_3$-pyridin-5-yl	-
91	CH_3	$(C_2H_5)_2CH$	H	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
92	OH	$(C_2H_5)_2CH$	H	CH_3	$2,4\text{-}Cl_2\text{-}C_6H_3$	227-228
93	C_2H_5	$(C_2H_5)_2CH$	OCH_3	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
94	C_2H_5	$(C_2H_5)_2CH$	H	OCH_3	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
95	C_2H_5	$C_3H_7(CH_3)CH$	H	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
96	C_2H_5	$CH_3(c\text{-}C_3H_5)CH$	H	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-

97	C_2H_5	$CH_3(c\text{-}C_4H_7)CH$	H	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
98	C_2H_5	$(c\text{-}C_3H_5)_2CH$	H	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
99	C_2H_5	$C_2H_5(c\text{-}C_3H_5)CH$	H	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
100	C_2H_5	$CH_3(c\text{-}C_4H_7)CH$	H	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
101	C_2H_5	$(HOCH_2)_2(CH_3)C$	H	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
102	C_2H_5	$(HOCH_2)_2(CH_3)C$	H	H	$2\text{-}Cl\text{-}4\text{-}CH_3O\text{-}C_6H_3$	-
103	C_2H_5	$(HOCH_2)_2(CH_3)C$	H	H	$2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$	-
104	C_2H_5	$(HOCH_2)_2(CH_3)C$	H	H	$2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$	-
105	C_2H_5	$(HOCH_2)_2(CH_3)C$	H	H	$2\text{-}(CH_3)_2N\text{-}4\text{-}CH_3$-pyridin-5-yl	-
106	C_2H_5	$(HOCH_2)_2(CH_3)C$	H	H	$2,4\text{-}Cl_2\text{-}5\text{-}F\text{-}C_6H_2$	-
107	C_2H_5	$(HOCH_2)_2(CH_3)C$	H	H	$2\text{-}Cl\text{-}4\text{-}OCH_3\text{-}5\text{-}F$	-
108	C_2H_5	$(HOCH_2)_2(CH_3)C$	H	H	$2\text{-}Cl\text{-}4,5\text{-}(OCH_3)_2$	-
109	C_2H_5	$(CH_3OCH_2)_2(CH_3)C$	H	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-
110	C_2H_5	$(CH_3OCH_2)_2(CH_3)C$	H	H	$2\text{-}Cl\text{-}4\text{-}CH_3O\text{-}C_6H_3$	-
111	C_2H_5	$(CH_3OCH_2)_2(CH_3)C$	H	H	$2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$	-
112	C_2H_5	$(CH_3OCH_2)_2(CH_3)C$	H	H	$2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$	-
113	C_2H_5	$(CH_3OCH_2)_2(CH_3)C$	H	H	$2\text{-}(CH_3)_2N\text{-}4\text{-}CH_3$-pyridin-5-yl	-
114	C_2H_5	$(CH_3OCH_2)_2(CH_3)C$	H	H	$2,4\text{-}Cl_2\text{-}5\text{-}F\text{-}C_6H_2$	-
115	C_2H_5	$(CH_3OCH_2)_2(CH_3)C$	H	H	$2\text{-}Cl\text{-}4\text{-}OCH_3\text{-}5\text{-}F$	-
116	C_2H_5	$(CH_3OCH_2)_2(CH_3)C$	H	H	$2\text{-}Cl\text{-}4,5\text{-}(OCH_3)_2$	-
117	C_2H_5	$(H_2C{=}CH)_2(CH_3)C$	H	H	$2,4\text{-}Cl_2\text{-}C_6H_3$	-

118	C_2H_5	$(H_2C=CH)_2(CH_3)C$	H	H	2-Cl-4-CH_3O-C_6H_3	-
119	C_2H_5	$(H_2C=CH)_2(CH_3)C$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	-
120	C_2H_5	$(H_2C=CH)_2(CH_3)C$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
121	C_2H_5	$(H_2C=CH)_2(CH_3)C$	H	H	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
122	C_2H_5	$(H_2C=CH)_2(CH_3)C$	H	H	2,4-Cl_2-5-F-C_6H_2	-
123	C_2H_5	$(H_2C=CH)_2(CH_3)C$	H	H	2-Cl-4-OCH_3-5-F	-
124	C_2H_5	$(H_2C=CH)_2(CH_3)C$	H	H	2-Cl-4,5-$(OCH_3)_2$	-
125	C_2H_5	$(c\text{-}C_3H_5)_2(CH_3)C$	H	H	2,4-Cl_2-C_6H_3	-
126	C_2H_5	$(c\text{-}C_3H_5)_2(CH_3)C$	H	H	2-Cl-4-CH_3O-C_6H_3	-
127	C_2H_5	$(c\text{-}C_3H_5)_2(CH_3)C$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	-
128	C_2H_5	$(c\text{-}C_3H_5)_2(CH_3)C$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
129	C_2H_5	$(c\text{-}C_3H_5)_2(CH_3)C$	H	H	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
130	C_2H_5	$(c\text{-}C_3H_5)_2(CH_3)C$	H	H	2,4-Cl_2-5-F-C_6H_2	-
131	C_2H_5	$(c\text{-}C_3H_5)_2(CH_3)C$	H	H	2-Cl-4-OCH_3-5-F	-
132	C_2H_5	$(c\text{-}C_3H_5)_2(CH_3)C$	H	H	2-Cl-4,5-$(OCH_3)_2$	-
133	C_2H_5	$(C_2H_5)_2(OH)C$	H	H	2,4-Cl_2-C_6H_3	-
134	C_2H_5	$(C_2H_5)_2(OH)C$	H	H	2-Cl-4-CH_3O-C_6H_3	-
135	C_2H_5	$(C_2H_5)_2(OH)C$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	-
136	C_2H_5	$(C_2H_5)_2(OH)C$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
137	C_2H_5	$(C_2H_5)_2(OH)C$	H	H	2-$(CH_3)_2$N-4-CH_3-pyridin-5-yl	-
138	C_2H_5	$(C_2H_5)_2(OH)C$	H	H	2,4-Cl_2-5-F-C_6H_2	-

139	C_2H_5	$(C_2H_5)_2(OH)C$	H	H	2-Cl-4-OCH_3-5-F	-
140	C_2H_5	$(C_2H_5)_2(OH)C$	H	H	2-Cl-4,5-$(OCH_3)_2$	-
141	C_2H_5	$C_2H_5(OCH_3)CH$	H	H	2,4-Cl_2-C_6H_3	
142	C_2H_5	$C_2H_5(OCH_3)CH$	H	H	2-Cl-4-CH_3O-C_6H_3	-
143	C_2H_5	$C_2H_5(OCH_3)CH$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	-
144	C_2H_5	$C_2H_5(OCH_3)CH$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
145	C_2H_5	$C_2H_5(OCH_3)CH$	H	H	2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl	-
146	C_2H_5	$C_2H_5(OCH_3)CH$	H	H	2,4-Cl_2-5-F-C_6H_2	-
147	C_2H_5	$C_2H_5(OCH_3)CH$	H	H	2-Cl-4-OCH_3-5-F	-
148	C_2H_5	$C_2H_5(OCH_3)CH$	H	H	2-Cl-4,5-$(OCH_3)_2$	-
149	C_2H_5	$(C_2H_5)_2CH$	H	H	2,4-Cl_2-5-F-C_6H_2	oil
150	C_2H_5	$(C_2H_5)_2CH$	H	H	2-Cl-4-OCH_3-5-F	-
151	C_2H_5	$(C_2H_5)_2CH$	H	H	2-Cl-4,5-$(OCH_3)_2$	-
152	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2,4-Cl_2-5-F-C_6H_2	-
153	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2-Cl-4-OCH_3-5-F	-
154	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2-Cl-4,5-$(OCH_3)_2$	-
155	OCH_3	$(C_2H_5)_2CH$	H	H	2,4-Cl_2-5-F-C_6H_2	oil[g]
156	OCH_3	$(C_2H_5)_2CH$	H	H	2-Cl-4-OCH_3-5-F	-
157	OCH_3	$(C_2H_5)_2CH$	H	H	2-Cl-4,5-$(OCH_3)_2$	-
158	C_2H_5	$(C_2H_5)_2N$	H	H	2,4-Cl_2-5-F-C_6H_2	-
159	C_2H_5	$(C_2H_5)_2N$	H	H	2-Cl-4-OCH_3-5-F	-
160	C_2H_5	$(C_2H_5)_2N$	H	H	2-Cl-4,5-$(OCH_3)_2$	-
161	C_2H_5	$C_3H_7(CH_3)CH$	H	H	2-Cl-4-CH_3O-C_6H_3	-
162	C_2H_5	$C_3H_7(CH_3)CH$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	-
163	C_2H_5	$C_3H_7(CH_3)CH$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
164	C_2H_5	$C_3H_7(CH_3)CH$	H	H	2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl	-
165	C_2H_5	$C_3H_7(CH_3)CH$	H	H	2,4-Cl_2-5-F-C_6H_2	-
166	C_2H_5	$C_3H_7(CH_3)CH$	H	H	2-Cl-4-OCH_3-5-F	-
167	C_2H_5	$C_3H_7(CH_3)CH$	H	H	2-Cl-4,5-$(OCH_3)_2$	-
168	C_2H_5	$(C_2H_5)_2CH$	H	H	2-CH_3-4-OCH_3-5-	-

169	OCH_3	$(C_2H_5)_2CH$	H	H	2-CH_3-4-OCH_3-5-F-C_6H_2	-
170	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2-CH_3-4-OCH_3-5-F-C_6H_2	-
171	OCH_3	$C_4H_9(C_2H_5)CH$	H	H	2-CH_3-4-OCH_3-5-F-C_6H_2	-
172	C_2H_5	$(C_2H_5)_2N$	H	H	2-CH_3-4-OCH_3-5-F-C_6H_2	-
173	OCH_3	$(C_2H_5)_2N$	H	H	2-CH_3-4-OCH_3-5-F-C_6H_2	-
174	C_2H_5	$C_3H_7(CH_3)CH$	H	H	2-CH_3-4-OCH_3-5-F-C_6H_2	-
175	OCH_3	$C_3H_7(CH_3)CH$	H	H	2-CH_3-4-OCH_3-5-F-C_6H_2	-
176	C_2H_5	$C_2H_5(OCH_3)CH$	H	H	2-CH_3-4-OCH_3-5-F-C_6H_2	-
177	OCH_3	$C_2H_5(OCH_3)CH$	H	H	2-CH_3-4-OCH_3-5-F-C_6H_2	-
178	C_2H_5	$(C_2H_5)_2CH$	H	H	2-CH_3-4-OCH_3-C_6H_3	-
179	OCH_3	$(C_2H_5)_2CH$	H	H	2-CH_3-4-OCH_3-C_6H_3	-
180	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2-CH_3-4-OCH_3-C_6H_3	-
181	OCH_3	$C_4H_9(C_2H_5)CH$	H	H	2-CH_3-4-OCH_3-C_6H_3	-
182	C_2H_5	$(C_2H_5)_2N$	H	H	2-CH_3-4-OCH_3-C_6H_3	-
183	OCH_3	$(C_2H_5)_2N$	H	H	2-CH_3-4-OCH_3-C_6H_3	-
184	C_2H_5	$C_3H_7(CH_3)CH$	H	H	2-CH_3-4-OCH_3-C_6H_3	-
185	OCH_3	$C_3H_7(CH_3)CH$	H	H	2-CH_3-4-OCH_3-C_6H_3	-
186	C_2H_5	$C_2H_5(OCH_3)CH$	H	H	2-CH_3-4-OCH_3-C_6H_3	-
187	OCH_3	$C_2H_5(OCH_3)CH$	H	H	2-CH_3-4-OCH_3-C_6H_3	-
188	C_2H_5	$(C_2H_5)_2CH$	H	H	2-CH_3-4-Cl-C_6H_3	-
189	OCH_3	$(C_2H_5)_2CH$	H	H	2-CH_3-4-Cl-C_6H_3	-
190	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2-CH_3-4-Cl-C_6H_3	-
191	OCH_3	$C_4H_9(C_2H_5)CH$	H	H	2-CH_3-4-Cl-C_6H_3	-

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192	C_2H_5	$(C_2H_5)_2N$	H	H	2-CH_3-4-Cl-C_6H_3	-
193	OCH_3	$(C_2H_5)_2N$	H	H	2-CH_3-4-Cl-C_6H_3	-
194	C_2H_5	$C_3H_7(CH_3)CH$	H	H	2-CH_3-4-Cl-C_6H_3	-
195	OCH_3	$C_3H_7(CH_3)CH$	H	H	2-CH_3-4-Cl-C_6H_3	-
196	C_2H_5	$C_2H_5(OCH_3)CH$	H	H	2-CH_3-4-Cl-C_6H_3	-
197	OCH_3	$C_2H_5(OCH_3)CH$	H	H	2-CH_3-4-Cl-C_6H_3	-
198	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	2,4-Cl_2-C_6H_3	oil[h]
199	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	2-Cl-4-CH_3O-C_6H_3	-
200	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	-
201	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
202	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl	-
203	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
204	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	2,4-Cl_2-5-F-C_6H_2	-
205	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	2-Cl-4-OCH_3-5-F	-
206	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	2-Cl-4,5-$(OCH_3)_2$	-
207	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	2-CH_3-4-OCH_3-5-F-C_6H_2	-
208	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	2-CH_3-4-OCH_3-C_6H_3	-
209	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	2-CH_3-4-Cl-C_6H_3	-
210	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	2,4-Cl_2-C_6H_3	-
211	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	2-Cl-4-CH_3O-C_6H_3	-
212	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	-
213	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
214	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl	-
215	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-

216	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	$2,4-Cl_2-5-F-C_6H_2$	-
217	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	$2-Cl-4-OCH_3-5-F$	-
218	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	$2-Cl-4,5-(OCH_3)_2$	-
219	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	$2-CH_3-4-OCH_3-5-F-C_6H_2$	-
220	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	$2-CH_3-4-OCH_3-C_6H_3$	-
221	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	$2-CH_3-4-Cl-C_6H_3$	-
222	C_2H_5	$C_2H_5OCH_2(CH_3)CH$	H	H	$2,4-Cl_2-C_6H_3$	-
223	C_2H_5	$C_2H_5OCH_2(CH_3)CH$	H	H	$2-Cl-4-CH_3O-C_6H_3$	-
224	C_2H_5	$C_2H_5OCH_2(CH_3)CH$	H	H	$2,4,6-(CH_3)_3-C_6H_2$	-
225	C_2H_5	$C_2H_5OCH_2(CH_3)CH$	H	H	$2,4,6-(OCH_3)_3-C_6H_2$	-
226	C_2H_5	$C_2H_5OCH_2(CH_3)CH$	H	H	$2-(CH_3)_2N-4-CH_3-$pyridin-5-yl	-
227	C_2H_5	$C_2H_5OCH_2(CH_3)CH$	H	H	$2,4,6-(OCH_3)_3-C_6H_2$	-
228	C_2H_5	$C_2H_5OCH_2(CH_3)CH$	H	H	$2,4-Cl_2-5-F-C_6H_2$	-
229	C_2H_5	$C_2H_5OCH_2(CH_3)CH$	H	H	$2-Cl-4-OCH_3-5-F$	-
230	C_2H_5	$C_2H_5OCH_2(CH_3)CH$	H	H	$2-Cl-4,5-(OCH_3)_2$	-
231	C_2H_5	$C_2H_5OCH_2(CH_3)CH$	H	H	$2-CH_3-4-OCH_3-5-F-C_6H_2$	-
232	C_2H_5	$C_2H_5OCH_2(CH_3)CH$	H	H	$2-CH_3-4-OCH_3-C_6H_3$	-
233	C_2H_5	$C_2H_5OCH_2(CH_3)CH$	H	H	$2-CH_3-4-Cl-C_6H_3$	-
234	OCH_3	$C_2H_5OCH_2(CH_3)CH$	H	H	$2,4-Cl_2-C_6H_3$	-
235	OCH_3	$C_2H_5OCH_2(CH_3)CH$	H	H	$2-Cl-4-CH_3O-C_6H_3$	-
236	OCH_3	$C_2H_5OCH_2(CH_3)CH$	H	H	$2,4,6-(CH_3)_3-C_6H_2$	-
237	OCH_3	$C_2H_5OCH_2(CH_3)CH$	H	H	$2,4,6-(OCH_3)_3-C_6H_2$	-
238	OCH_3	$C_2H_5OCH_2(CH_3)C$	H	H	$2-(CH_3)_2N-4-CH_3-$	-

		H			pyridin-5-yl
239	OCH_3	$C_2H_5OCH_2(CH_3)C$ H	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
240	OCH_3	$C_2H_5OCH_2(CH_3)C$ H	H	H	2,4-Cl_2-5-F-C_6H_2	-
241	OCH_3	$C_2H_5OCH_2(CH_3)C$ H	H	H	2-Cl-4-OCH_3-5-F	-
242	OCH_3	$C_2H_5OCH_2(CH_3)C$ H	H	H	2-Cl-4,5-$(OCH_3)_2$	-
243	OCH_3	$C_2H_5OCH_2(CH_3)C$ H	H	H	2-CH_3-4-OCH_3-5-F-C_6H_2	-
244	OCH_3	$C_2H_5OCH_2(CH_3)C$ H	H	H	2-CH_3-4-OCH_3-C_6H_3	-
245	OCH_3	$C_2H_5OCH_2(CH_3)C$ H	H	H	2-CH_3-4-Cl-C_6H_3	-
246	C_2H_5	$CH_3OCH_2(C_2H_5)C$ H	H	H	2,4-Cl_2-C_6H_3	-
247	C_2H_5	$CH_3OCH_2(C_2H_5)C$ H	H	H	2-Cl-4-CH_3O-C_6H_3	-
248	C_2H_5	$CH_3OCH_2(C_2H_5)C$ H	H	H	2,4,6-$(CH_3)_3$-C_6H_2	-
249	C_2H_5	$CH_3OCH_2(C_2H_5)C$ H	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
250	C_2H_5	$CH_3OCH_2(C_2H_5)C$ H	H	H	2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl	-
251	C_2H_5	$CH_3OCH_2(C_2H_5)C$ H	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
252	C_2H_5	$CH_3OCH_2(C_2H_5)C$ H	H	H	2,4-Cl_2-5-F-C_6H_2	-
253	C_2H_5	$CH_3OCH_2(C_2H_5)C$ H	H	H	2-Cl-4-OCH_3-5-F	-
254	C_2H_5	$CH_3OCH_2(C_2H_5)C$ H	H	H	2-Cl-4,5-$(OCH_3)_2$	-
255	C_2H_5	$CH_3OCH_2(C_2H_5)C$ H	H	H	2-CH_3-4-OCH_3-5-F-C_6H_2	-
256	C_2H_5	$CH_3OCH_2(C_2H_5)C$ H	H	H	2-CH_3-4-OCH_3-C_6H_3	-
257	C_2H_5	$CH_3OCH_2(C_2H_5)C$ H	H	H	2-CH_3-4-Cl-C_6H_3	-
258	OCH_3	$CH_3OCH_2(C_2H_5)C$ H	H	H	2,4-Cl_2-C_6H_3	-
259	OCH_3	$CH_3OCH_2(C_2H_5)C$ H	H	H	2-Cl-4-CH_3O-C_6H_3	-
260	OCH_3	$CH_3OCH_2(C_2H_5)C$ H	H	H	2,4,6-$(CH_3)_3$-C_6H_2	-

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261	OCH_3	$CH_3OCH_2(C_2H_5)CH$	H	H	$2,4,6-(OCH_3)_3-C_6H_2$	-
262	OCH_3	$CH_3OCH_2(C_2H_5)CH$	H	H	$2-(CH_3)_2N-4-CH_3-$ pyridin-5-yl	-
263	OCH_3	$CH_3OCH_2(C_2H_5)CH$	H	H	$2,4,6-(OCH_3)_3-C_6H_2$	-
264	OCH_3	$CH_3OCH_2(C_2H_5)CH$	H	H	$2,4-Cl_2-5-F-C_6H_2$	-
265	OCH_3	$CH_3OCH_2(C_2H_5)CH$	H	H	$2-Cl-4-OCH_3-5-F$	-
266	OCH_3	$CH_3OCH_2(C_2H_5)CH$	H	H	$2-Cl-4,5-(OCH_3)_2$	-
267	OCH_3	$CH_3OCH_2(C_2H_5)CH$	H	H	$2-CH_3-4-OCH_3-5-F-C_6H_2$	-
268	OCH_3	$CH_3OCH_2(C_2H_5)CH$	H	H	$2-CH_3-4-OCH_3-C_6H_3$	-
269	OCH_3	$CH_3OCH_2(C_2H_5)CH$	H	H	$2-CH_3-4-Cl-C_6H_3$	-
270	C_2H_5	$(C_2H_5)_2CH$	H	H	$2-Cl-4-CF_3-C_6H_3$	oil[i]
271	OCH_3	$(C_2H_5)_2CH$	H	H	$2-Cl-4-CF_3-C_6H_3$	-
272	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	$2-Cl-4-CF_3-C_6H_3$	-
273	OCH_3	$C_4H_9(C_2H_5)CH$	H	H	$2-Cl-4-CF_3-C_6H_3$	-
274	C_2H_5	$(C_2H_5)_2N$	H	H	$2-Cl-4-CF_3-C_6H_3$	-
275	OCH_3	$(C_2H_5)_2N$	H	H	$2-Cl-4-CF_3-C_6H_3$	-
276	C_2H_5	$C_3H_7(CH_3)CH$	H	H	$2-Cl-4-CF_3-C_6H_3$	-
277	OCH_3	$C_3H_7(CH_3)CH$	H	H	$2-Cl-4-CF_3-C_6H_3$	-
278	C_2H_5	$C_2H_5(OCH_3)CH$	H	H	$2-Cl-4-CF_3-C_6H_3$	-
279	OCH_3	$C_2H_5(OCH_3)CH$	H	H	$2-Cl-4-CF_3-C_6H_3$	-
280	C_2H_5	$CH_3OCH_2(CH_3)CH$	H	H	$2-Cl-4-CF_3-C_6H_3$	-
281	OCH_3	$CH_3OCH_2(CH_3)CH$	H	H	$2-Cl-4-CF_3-C_6H_3$	-

Key:

a) Spectral data for Example 1: ^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 (NH_3-CI): m/e 367 (2), 366 (11), 365 (15), 364 (65), 363 (25), 362 (100). Analysis calc'd for $C_{19}H_{21}Cl_2N_3$: C, 62.99; H, 5.84; N, 11.60; found: 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, t, J = 7.7 Hz), 0.83 (6H, t, J = 7.5 Hz). MS (NH_3-CI): m/e 338 (3), 337 (24), 336 (100). Analysis calc'd for $C_{22}H_{29}N_3$: 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 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 = 7.5 Hz). MS (NH_3-CI): m/e calculated for $C_{21}H_{26}Cl_2N_3$: 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 = 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 (NH_3-CI): m/e calc'd for $C_{24}H_{34}N_3$: 364.2753, found 364.2754; 366 (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

(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 (NH_3-CI): calculated for $C_{18}H_{21}Cl_2N_4$: 363.1143, found 363.1146; m/e 367 (6), 366 (14), 365 (81), 364 (28), 363 (100).

f) Spectral data for Example 51: ^{1}H 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 (6H, t, J = 7.4 Hz). MS (NH_3-CI): m/e 383 (2), 382 (12), 381 (14), 380 (65), 379 (25), 378 (100).

g) Spectral data for Example 155: ^{1}H 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 (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 (NH_3-CI): m/e 384 (11), 383 (16), 382 (79), 381 (20), 380 (100).

h) Spectral data for Example 198: ^{1}H NMR (300 MHz, $CDCl_3$): 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 Spectrum (AP-CI): m/e 364 (100), 366 (65), 368 (12.5). High resolution mass spectrum: for $C_{18}H_20C_{12}N_3O$ m/e calculated: 364.0984, observed 364.0988.

i) Spectral data for Example 270: TLC R_F 0.19 (5:95 ethyl acetate-hexane). ^{1}H 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 (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).

MS (NH_3-CI): m/e 399 (7), 398 (33), 397 (25), 396 (100). Analysis calc'd for $C_{20}H_{21}ClF_3N_3$: 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

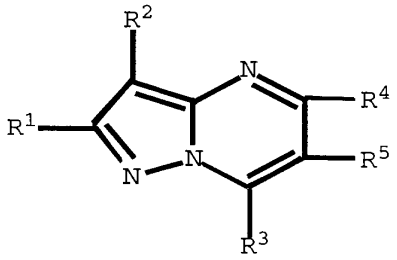
2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine

Although the present invention has been described 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 variation without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

WHAT IS CLAIMED IS:

1. A compound of formula I:



(I)

or a stereoisomer or pharmaceutically accetable salt thereof, wherein:

R^1 is selected from the group consisting of
C_{1-6} alkyl,
C_{2-10} alkenyl,
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 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 0 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, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

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,

C_{1-10} alkyloxyC_{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 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} alkyloxyC_{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,

- halogen,

-CN,

$-C(O)L$ wherein L is selected from $NR^{2c}R^{2d}$, C_{1-6} alkyl, H, $-OC_{1-6}$ alkyl, $O(CH_2)_mOC_{1-6}$alkyl, $O(CH_2)_mNR^{2c}R^{2d}$, -OH, aryl, heteroaryl or $C(O)OC_{1-6}$ alkyl wherein m is 1-3;

n is 0, 1 or 2;

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, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy; or

R^2 is substituted with 0-3 substitutents independently selected from

halogen,

-CN,

$-S(O)_nR^{2e}$ 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} cycloalkyl, and C_{3-6} cycloalkylC_{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;

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, 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} cycloalkylC_{1-6} alkyl;

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

1-piperidinyl,

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 $-O-$, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2R^{2e}$, $-NCOR^{2e}$, 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 SO_2R^{2e}; or

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^{21} and in wich 0-1 carbons of C_{4-8}

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 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 $-CONR^{2o}R^{2p}$;

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^{2l} is H, C_{1-4} alkyl, C_{3-6} cycloalky-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;

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cyloalkyl, 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^{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 heleroaryl (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;

$R^{2r}R^{2s}$ 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};

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);

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, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ 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;

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 substitued 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,

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;

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, $(C_{1-4}$ alkyl$)_2$ amino and phenyl, each phenyl is substituted 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 $(C_{1-4}$ alkyl$)_2$ amino and wherein R^4 and R^5 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} alkyl$(OH)_nCO_2R$ 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 Formula I with R^1, R^2, R^3, R^4 and R^5 as specifically defined below are excluded:

(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$(CH_2)_2$OR, -C(O)O$(CH_2)_2$NHR, 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$(CH_2)_2$OR, -C(O)O$(CH_2)_2$NHR 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;

(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 ;

(j) in a compound of formula I, R^2 is CN, R^1 is SCH_3, R^3 is Ph, R^4 is SCH_3 and R^5 is H ;

(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 ;

(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 ;

(m) in a compound of formula I, R^2 is C(O)OEt, R^1 is SCH_3, R^3 is Ph, R^4 is SCH_3 (or Ph) and R^5 is H ;

(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;

(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 ;

(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;

(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;

(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;

(t) in a compound of formula I, R^2 is $C(O)NH_2$, R^1 is CH_3, R^3 is m-CF_3Ph, R^4 and R^5 are H ;

(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 ;

(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 ;

(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;

(y) 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-$CH(OH)CH_2CH(OH)CH_2C(O)O$-nPr;

(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-$CH(OH)CH_2CH(OH)CH_2C(O)OMe$;

(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-$CH(OH)CH_2CH(OH)CH_2C(O)OH$;

(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 $-CH_2OH$;

(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;

(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 ;

(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-$CH(OH)CH_2CH(OH)CH_2C(O)OEt$;

(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-$CH(OH)CH_2CH(OH)CH_2C(O)O^-Na^+$;

(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;

(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;

(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;

(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 o-Cl,m-Cl-Ph, R^4 is H and R^5 is H;

(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 ;

(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 ;

(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 ;

(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 ;

(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 ;

(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;

(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 ;

(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 ;

(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 ;

(hhh) in a compound of formula I, R^2 is CN, R^1 is CH_3, R^3 is m-CF_3Ph, 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 ;

(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, 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 ;

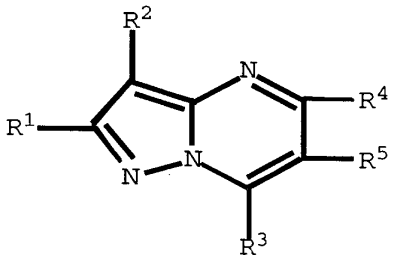
(nnn) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is m-CF_3-Ph, R^4 is H and R^5 is CH_3 ;

(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 $C(O)NH_2$, 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 Ph, R^4 and R^5 are H.

2. A compound of formula I:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of
C_{1-6} alkyl,
C_{2-10} alkenyl,
C_{2-10} alkynyl,
C_{3-6} cycloalkyl,
C_{1-6} alkyloxy,
C_{1-6} alkyl$S(O)_n$,
$-NR^{1a}R^{1B}$ 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,
$-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl;
X is selected from 0 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, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

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,
C_{3-6} cycloalkyl C_{1-6} alkyl,
C_{1-10} alkyloxy,
C_{1-10} alkyloxyC_{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,
$-SO_2R^{2b}$ 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} alkyloxyC_{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,

n is 0, 1 or 2;

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, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy, or

R^2 is substituted with 0-3 substituents independently selected from:

-CN,

$-S(O)_nR^{2e}$ 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} cycloalkyl, and C_{3-6} cycloalkylC_{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;

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, 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} cycloalkylC_{1-6} alkyl;

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

1-piperidinyl,
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 -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 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 substituted with 0-1 R^{21} and in wich 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, 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} cycloalky-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;

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cyloalkyl, 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^{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 heleroaryl (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;

$R^{2r}R^{2s}$ 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};

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);

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, $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ 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;

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 substitued 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,

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;

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, $(C_{1-4}$ alkyl$)_2$ amino and phenyl, each phenyl is substituted 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 $(C_{1-4}$ alkyl$)_2$ amino and wherein R^4 and R^5 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}

alkyl$(OH)_nCO_2R$ 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.

3. The compound according to Claim 1 or 2 wherein

R^1 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, $-XR^{1c}$ wherein R^1 is substituted with 0-6 substituents selected from halogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

R^2 is selected from substituted-C_{1-10} alkyl, branched C_{3-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-8} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl, $-NR^{2c}R^{2d}$ wherein, in the case of substituted-C_{1-10} alkyl, 1-3 substitutents are independently selected from 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^{21} and in wich 0-1 carbons of C_{4-8} cycloalkyl is replaced by -O- and wherein the R^2 groups, other than substituted-C_{1-10} alkyl, are substituted with 0-3 substituents independently selected from 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^{21} and in wich 0-1 carbons of C_{4-8} cycloalkyl is replaced by -O-.

4. The compound according to Claims 1 or 2 or 3 wherein R^3 is selected from an aryl group selected from phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

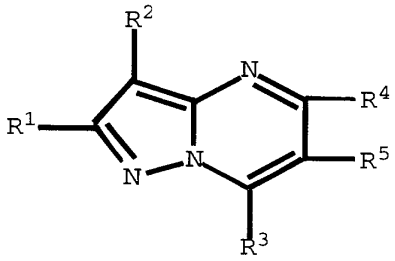
5. The compound according to Claims 1,2,3 or 4 wherein R^2 is selected from C_1 alkyl of the formula -CR'R"R"' wherein R', R" and R"' are independently selected from H, C_{1-6} alkyl, C_{3-7} cycloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy, 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.

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 substitued 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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(I)

or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof, wherein

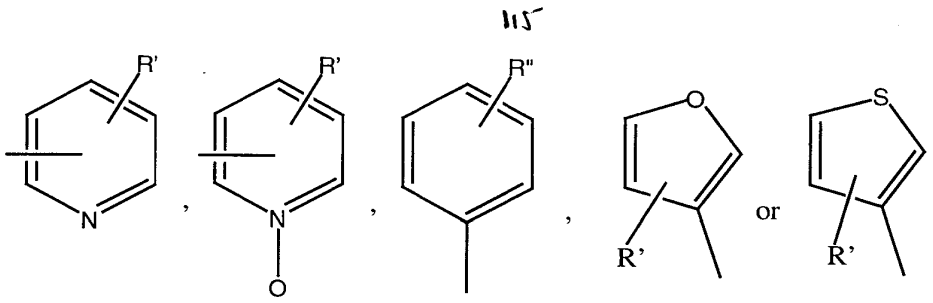
R^1 is selected from C_{1-6} alkyl, C_{1-6} alkyloxy, -SH or OH;

R^2 is selected from C_{1-4} alkyl which is unsubstituted or substituted with 1-4 substitutents 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;

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, CF_3, $S(O)_nC_{1-6}$ alkyl, $-OC_{1-6}$ 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;

R^4 and R^5 are independently selected from H, C_{1-6} alkyl or C_{1-6} alkyloxy,

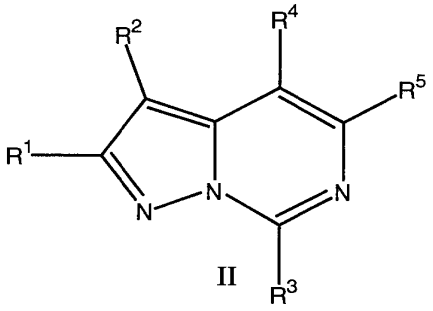
with the proviso that when R^1 and R^2 are unsubstituted, unbranched C_{1-3} alkyl, R^3 may not be



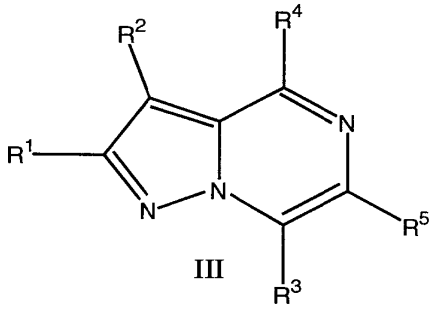
wherein R' is H or C_{1-3} alkyl and R" is H or o-trifluoromethyl, m-trifluoromethyl or m-methoxy.

8. The compound according to Claims 1-7 wherein R^3 is substituted with 2-4 substituents.

9. A compound of the formula:



II



III

or a pharmaceutically acceptable salt or isomer thereof wherein R^1-R^5 and other variables are as defined in claims 1-8.

10. Use of a compound according to Claims 1-9 in therapy.

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

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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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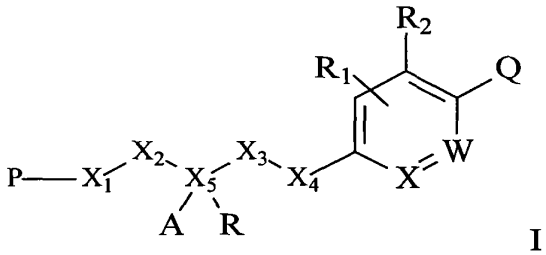
[54] 发明名称

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：



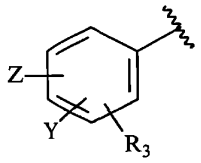
I

其中

X 是 C 或 N；W 是 C 或 N；

X_1 是 N、NH、N(C_{1-4} 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：



II

X_2 是 C_{1-4} 亚烷基、SO_2、C(O)、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；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；

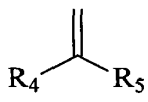
X_3 是 C_{1-4} 亚烷基、NH、N、CH(OH)、键；或者 X_1 和 X_3 与 X_1 和 X_3 所连接的 X_2 和 X_5 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X_3 和 X_5 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_3 和 X_4 一起形成双键或一起形成饱和的或不饱和

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} 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 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、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：



III

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、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

6420

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、$NHC(O)CH_3$ 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

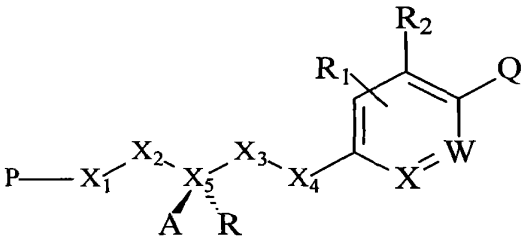
如果 P 是 H，X 是 C，X_1 是 NH，X_2 是 C(O)，R 是 OH，A 是烷基，X_3 是键或 CH_2 并且 X_4 是键或 CH_2，R_1 和 R_2 是 H，那么 Q 不是 H 或卤素；

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

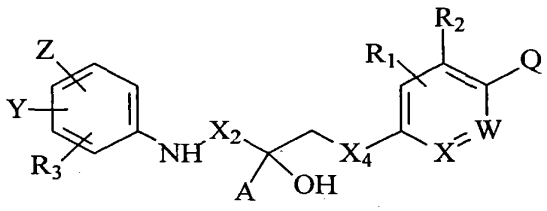
X_2 一起形成噁唑烷二酮，R 是烷基，X_3 是 CH_2 并且 X_4 是 O、NH、S、SO_2 或 CH_2，那么 Q 不是卤化物。

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} 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)[=$CHCH_2N(CH_3)_2$]、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} 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、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、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 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；

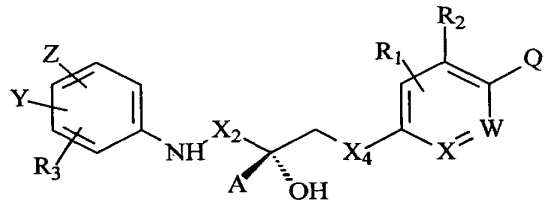
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2；

R'是 NH_2、OH 或 CH_3；并且

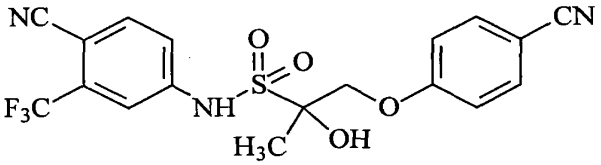
R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

4. 权利要求 3 的化合物，其由以下结构表示：



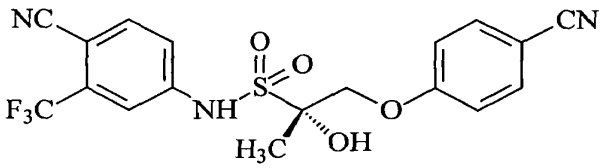
。

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：



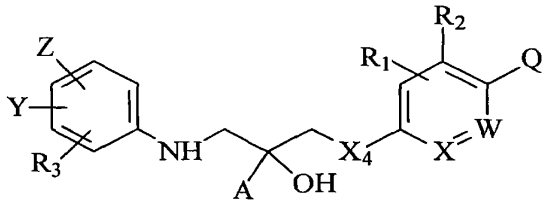
V 。

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；

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

A 是 H、OH、SH、NH$_2$、C_{1-4} 烷基、CHF$_2$、CH$_2$F、CF$_3$、CN、CH$_2$OH、CH$_2$O(C_{1-4} 烷基)、CH$_2$O(C_{1-4} 酰基)、CH$_2$CN、CH$_2$N$_3$、CH$_2$NCS、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$_2$CF$_3$、CF$_2$CF$_3$、CH$_2$OR'CH$_2$C(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$_2$NH$_2$、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$_2$C(O)NH$_2$、NHC(O)NH$_2$、NHCO(C_{1-4} 烷基)、NHSO$_2$(C_{1-4} 烷基)、O-[CH$_2$CH$_2$CH(CH$_3$)$_2$]、O-[CH$_2$CH$_2$(C_{4-8} 环烷基)]、O-[CH$_2$CH$_2$(C_{4-8} 杂环烷基)]或 O-[CH$_2$CH$_2$N(CH$_3$)$_2$]；

R 是 H、OH、C_{1-4} 烷基、CF$_3$、CH$_2$OH、O(C_{1-4} 烷基)或 O(C_{1-4} 酰基)；

R_1 是 H、OH、F、Cl、Br 或 I；

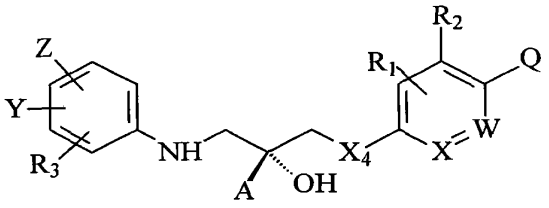
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2；

R'是 NH_2、OH 或 CH_3；并且

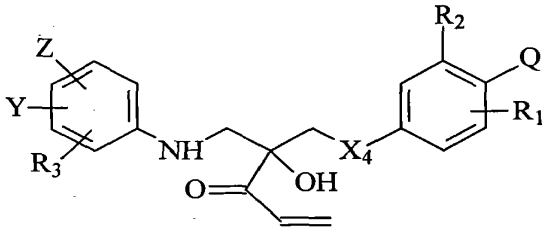
R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

8. 权利要求 7 的化合物，其由以下结构表示：



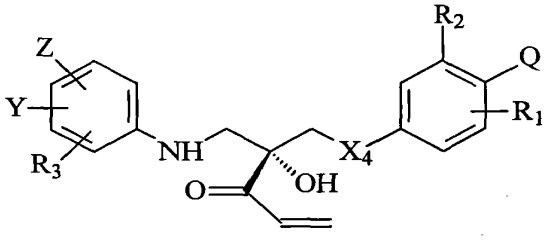
。

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：



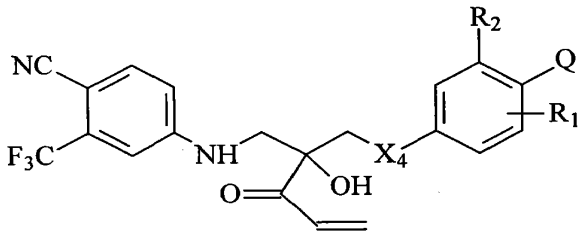
VII 。

10. 权利要求 9 的化合物，其由以下结构表示：



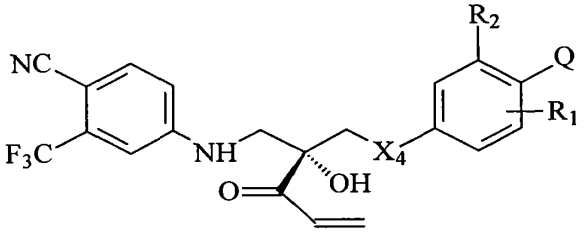
。

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：



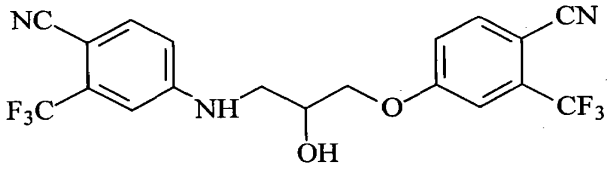
VIII 。

12. 权利要求 11 的化合物，其由以下结构表示：



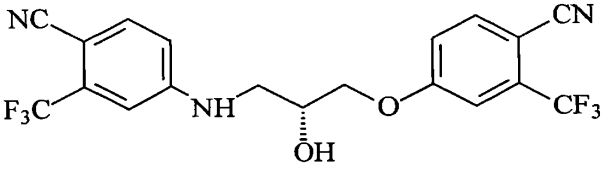
。

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：



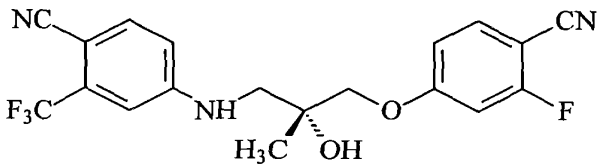
IX 。

14. 权利要求 13 的化合物，其由以下结构表示：



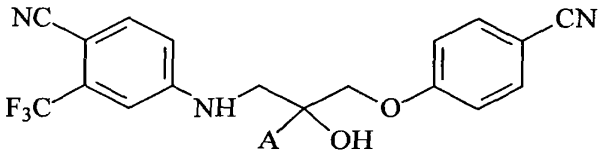
。

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：



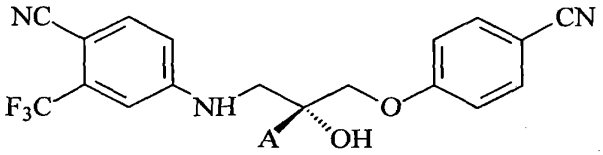
X 。

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：



XI 。

17. 权利要求 16 的化合物，其由以下结构表示：



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18. 权利要求 15 的化合物，其中 A 是 CH_2OH。

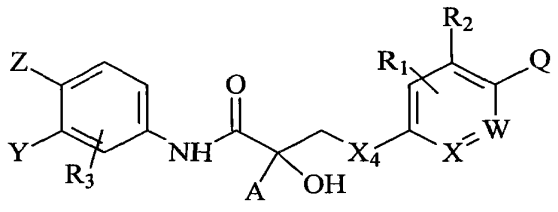
19. 权利要求 17 的化合物，其中 A 是 CH_2OMe。

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：



XII

其中

X 是 C 或 N；W 是 C 或 N；

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

A 是 CN、CH$_2$OH、CH$_2$O(C_{1-4} 烷基)、CH$_2$O(C_{1-4} 酰基)、CH$_2$CN、CH$_2$N$_3$、CH$_2$NCS、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$_2$OR'CH$_2$C(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$_2$NH$_2$、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$_2$C(O)NH$_2$、NHC(O)NH$_2$、NHCO(C_{1-4} 烷基)、NHSO$_2$(C_{1-4} 烷基)、O-[CH$_2$CH$_2$CH(CH$_3$)$_2$]、O-[CH$_2$CH$_2$(C_{4-8} 环烷基)]、O-[CH$_2$CH$_2$(C_{4-8} 杂环烷基)]或 O-[CH$_2$CH$_2$N(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。

24. 权利要求 23 的化合物，其中 X_4 是 O。

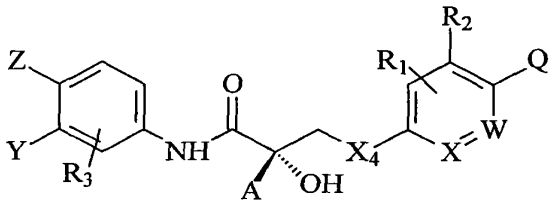
25. 权利要求 24 的化合物，其中 A 是 CH$_2$OH。

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。

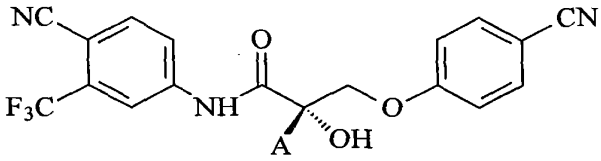
28. 权利要求 23 的化合物，其中 Q 是 CN，Z 是 CN，Y 是 CF_3，并且 R_1、R_2 和 R_3 是 H。

29. 权利要求 23 的化合物，其由以下结构表示：



。

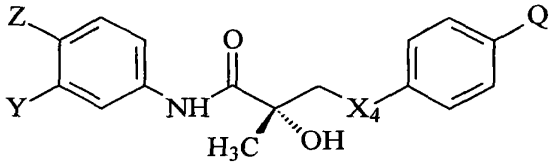
30. 权利要求 23 的化合物，其中所述化合物由式 XIII 的结构表示：



XIII

。

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：



XVII

其中

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

NO[$CH_2CH_2N(CH_3)_2$]；

Q 是 H、CN、OH、NO_2、卤化物、C_{2-6}烯基、C_{2-6}炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 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-[$CH_2CH_2N(CH_3)_2$]；

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。

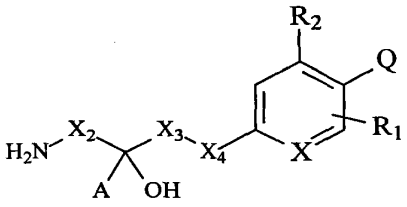
32. 权利要求 31 的化合物，其中 Q 是 F。

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、C(O)、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_3 是 C_{1-4} 亚烷基、NH、N、CH(OH)或键；

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[=$CHCH_2N(CH_3)_2$]、$PO(C_{1-4}$

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。

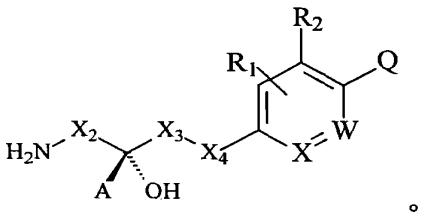
37. 权利要求 36 的化合物，其中 X_2是 CH_2。

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：

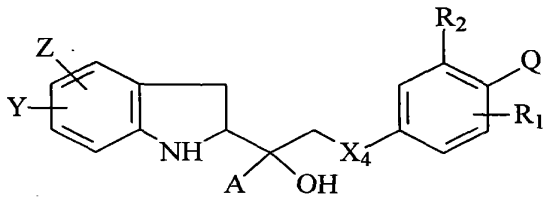


。

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：



XX

其中

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

A 是 H、OH、SH、NH$_2$、C_{1-4} 烷基、CHF$_2$、CH$_2$F、CF$_3$、CN、CH$_2$OH、CH$_2$O(C_{1-4} 烷基)、CH$_2$O(C_{1-4} 酰基)、CH$_2$CN、CH$_2$N$_3$、CH$_2$NCS、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$_2$CF$_3$、CF$_2$CF$_3$、CH$_2$OR'CH$_2$C(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、CF$_3$、NO$_2$、卤化物、C_{2-6} 烯基、C_{2-6} 炔基、C(O)CH$_2$NH$_2$、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$_2$C(O)NH$_2$、NHC(O)NH$_2$、NHCO(C_{1-4} 烷基)、

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$NHSO_2(C_{1-4}$ 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。

45. 权利要求 44 的化合物,其中 A 是 CH_3。

46. 权利要求 44 的化合物,其中 X_4 是 O。

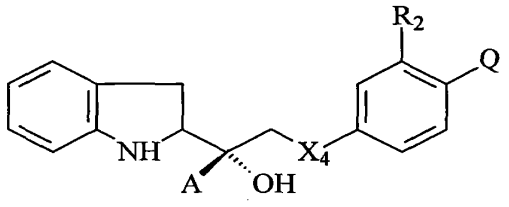
47. 权利要求 44 的化合物,其中 Q 是 CN。

48. 权利要求 44 的化合物,其中 Z 是 CN 且 Y 是 CF_3。

49. 权利要求 44 的化合物,其中 Z 是 CN,Q 是 CN 且 Y 是 CF_3。

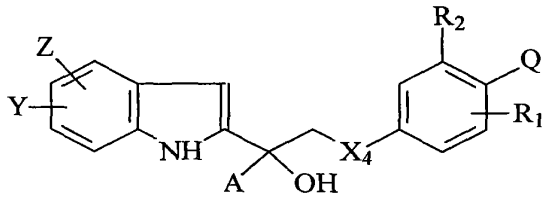
50. 权利要求 44 的化合物,其中 A 是 CH_3,X_4 是 O,Z 是 CN,Q 是 CN,R_1 和 R_2 是 H,并且 Y 是 CF_3。

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:



XXI 。

53. 权利要求 52 的化合物，其中 A 是 CH_3。

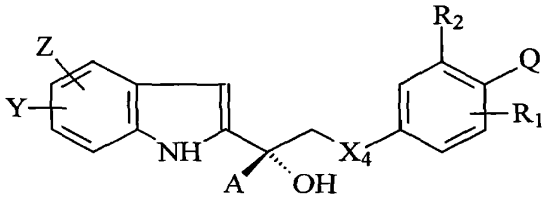
54. 权利要求 52 的化合物，其中 X_4 是 O。

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 CF_3。

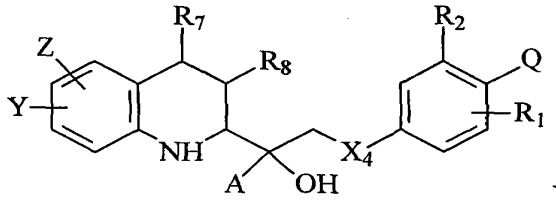
57. 权利要求 52 的化合物，其中 A 是 CH_3，X_4 是 O，Z 是 CN，Q 是 CN，R_1 和 R_2 是 H，并且 Y 是 CF_3。

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：



XXII

其中 A、Z、Y、X_4、Q、R_1 和 R_2 如式 XX 中所述，R_7 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。

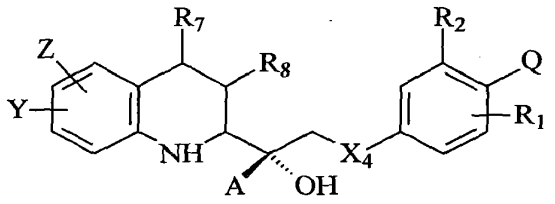
63. 权利要求 58 的化合物，其中 R_7 是=CH_2 且 R_8 是氧代。

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：



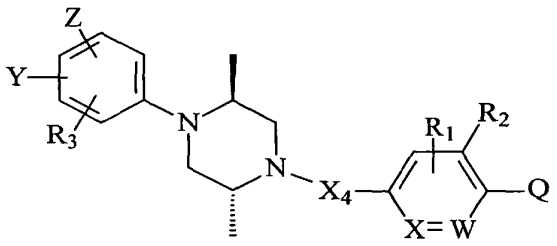
。

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；

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} 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、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 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_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。

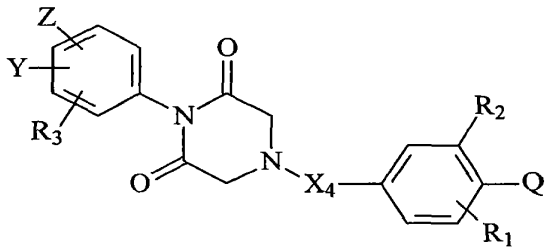
71. 权利要求 70 的化合物，其中 X_4 是 O。

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 CF_3。

74. 权利要求 70 的化合物，其中 X_4 是 O，Z 是 CN，Q 是 CN，R_1、R_2 和 R_3 是 H 且 Y 是 CF_3。

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 X_4 是 O。

77. 权利要求 75 的化合物，其中 Q 是 CN。

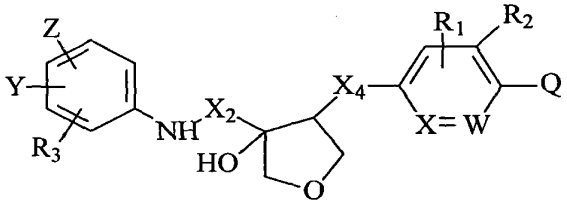
78. 权利要求 75 的化合物，其中 Z 是 CN 且 Y 是 CF_3。

79. 权利要求 75 的化合物，其中 X_4 是 O，Z 是 CN，Q 是 CN，R_1、R_2 和 R_3 是 H 且 Y 是 CF_3。

80. 权利要求 1 的化合物，其中 P 是式 II，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。

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；

X_2是C_{1-4}亚烷基、SO_2、C(O)、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)[=$CHCH_2N(CH_3)_2$]、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}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、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_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。

83. 权利要求82的化合物，其中X_4是O。

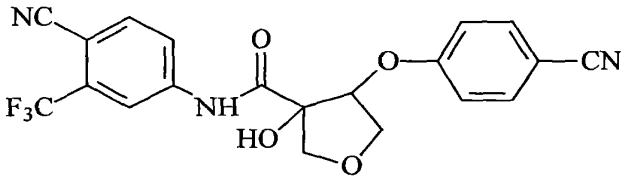
84. 权利要求82的化合物，其中Q是CN。

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)。

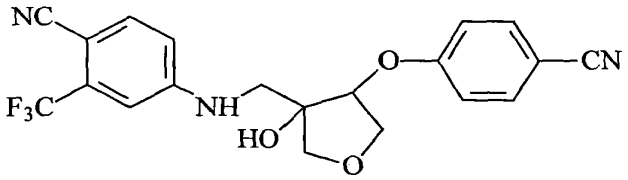
87. 权利要求 82 的化合物，其中 Z 是 CN 且 Y 是 CF_3。

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：



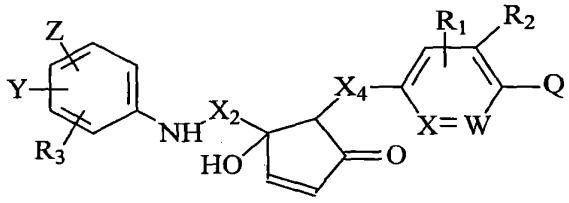
XXXV 。

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。

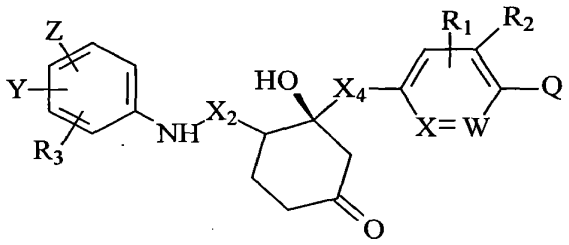
92. 权利要求 90 的化合物，其中 X_2 是 C(O)。

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；

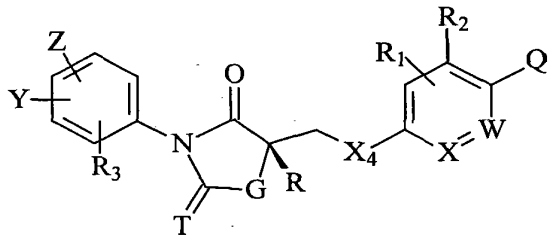
其中

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、$C(C_{1-4}$ 酰基$)_2$、$C(C_{1-4}$ 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} 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、$C(O)CH_2NH_2$、

$C(O)NH(C_{1-4}$ 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；

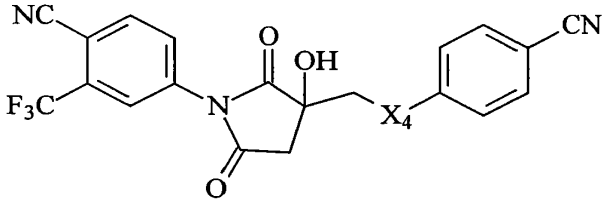
R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2；

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：

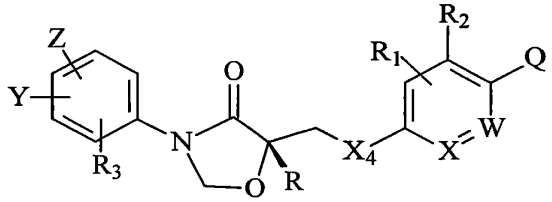


XLV

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

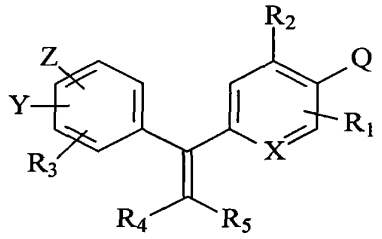
其中：

X、X_4、R、R_1、R_2、R_3、Z、Y 和 Q 如以上关于化合物 XXXIV 所述；

其中

如果 X 是 C，X_4 是 O、NH 或 S，R_1、R_2 和 R_3 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、NO_2、$NHC(O)CH_3$、CH_3、F、Cl、I 或 Br；

Y 是 H、CH_3、CF_3、CN、F、Cl、I 或 Br；

Q 是 H、$O\text{-}(CH_2)_2CH(CH_3)_2$ 或 $O\text{-}(CH_2)_2N(CH_3)_2$；

R_1 是 H、OH、F、Cl、Br 或 I；

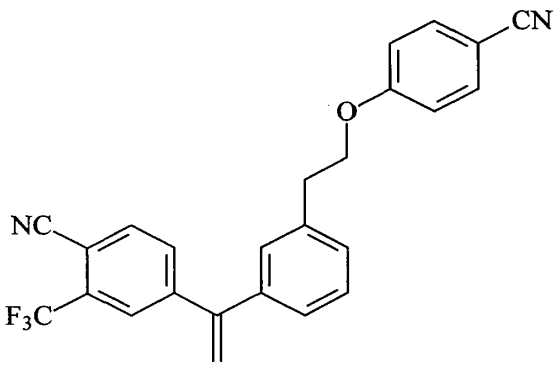
R_2 是由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、CH_3、卤化物、CN 或 NO_2；

R_4 和 R_5 独立地是 H、CH_3、卤化物、OH、$C_{1\text{-}4}$ 烷基、$C_{1\text{-}6}$ 环烷基、卤代-$C_{1\text{-}4}$ 烷基、苯基、芳基、杂环或羟基-$C_{1\text{-}4}$ 烷基；并且

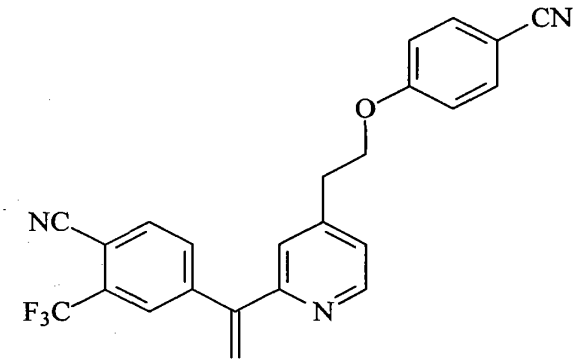
R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

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：



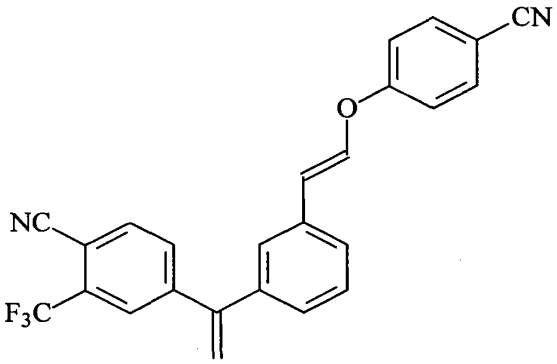
XLVIII 。

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 。

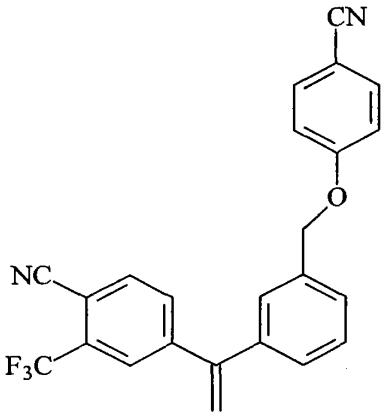
111. 权利要求 108 的化合物，其中所述化合物由式 L 的结构表示：



L 。

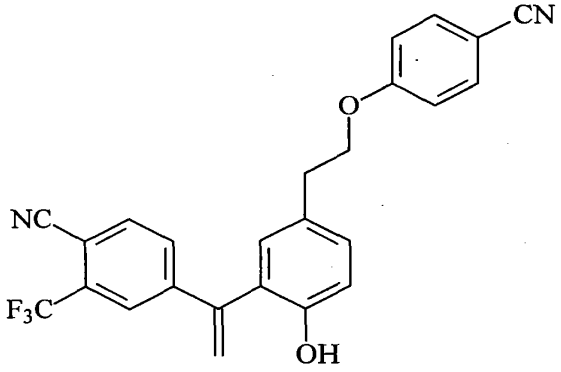
6444

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或心肌病。

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。

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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，每周肌内注射庚酸睾酮造成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，它们在肌内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量的分期系统来诊断（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。

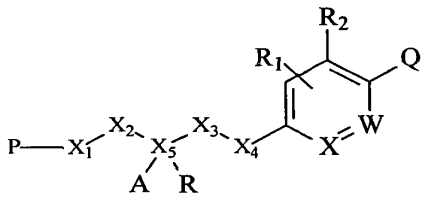
脊髓损伤（SCI）可能会导致改变中枢神经递质的分泌和产生，这继而可能造成下丘脑-垂体-肾上腺轴功能障碍，导致睾酮和其它激素水平的下降。SCI 或其它急性疾病或创伤在特征上包括分解代谢增强伴随合成代谢活动减弱，引发易于损失瘦身体组织的病症。只要分解代谢过程不中断，那么紊乱的营养利用将继续下去。损失瘦体重的影响包括伤口扩展和愈合机制受损。由于营养不良和蛋白缺乏加上固定，脊髓损伤的患者处于高度的患褥疮的风险中。

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：



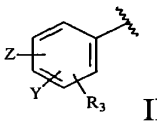
I

其中

X 是 C 或 N；W 是 C 或 N；

X_1 是 N、NH、N(C_{1-4} 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：



II；

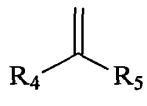
X_2 是 C_{1-4} 亚烷基、SO_2、C(O)、CH-[CH_2-(C_{4-8} 环)]、CH(C_{1-4} 烷基)、CH(NH_2)、CH(OH)、CH(C_{1-4} 卤代烷基)、键；或者 X_2 和 R_3 与 X_2 所连接的 X_1 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X_2 和 X_5 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

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} 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 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 3-6 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：



III

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 $S(O)[=CHCH_2N(CH_3)_2]$、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$N[CH_2CH_2N(CH_3)_2]$、$P(O)(C_{1-4}$ 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；

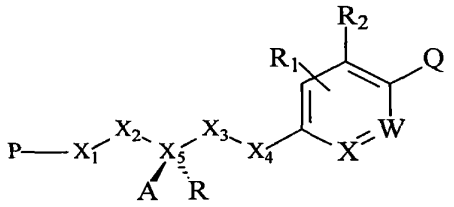
或者

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，R1 和 R_2 是 H，那么 Q 不是 H 或卤素

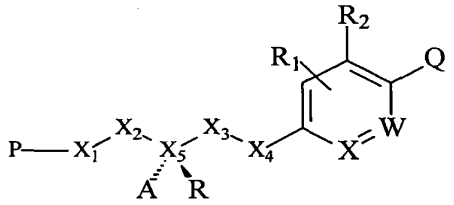
或者

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。

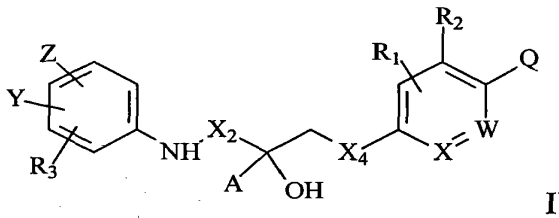
在另一个实施方案中，式 I 的化合物由以下结构表示：



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：



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} 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)[=$CHCH_2N(CH_3)_2$]、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} 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、CH_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、$C(O)CH_2NH_2$、

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

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；

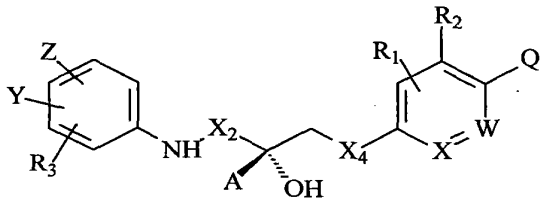
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2；

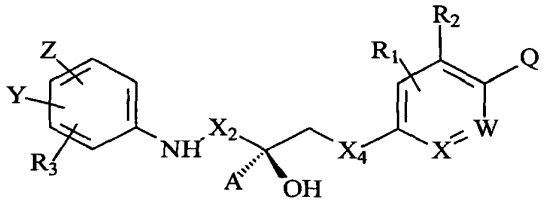
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

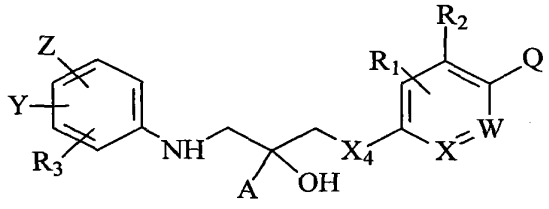
在另一个实施方案中，式 IV 的化合物由以下结构表示：



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：



VI

其中

X 是 C 或 N；W 是 C 或 N；

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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}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、CH_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、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$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；

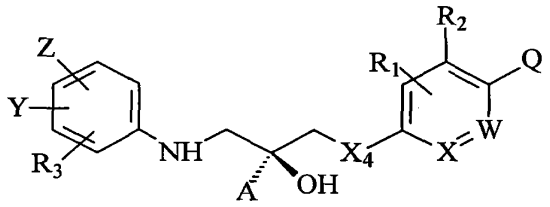
R_2是H、由R_6取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或CH=CH-O-对氰基苯基；

R_3是H、C_{1-4}烷基、卤化物、CN或NO_2；

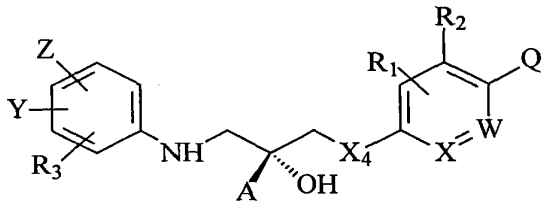
R'是NH_2、OH或CH_3；并且

R_6是CN、NO_2、$NHC(O)CH_3$或卤化物。

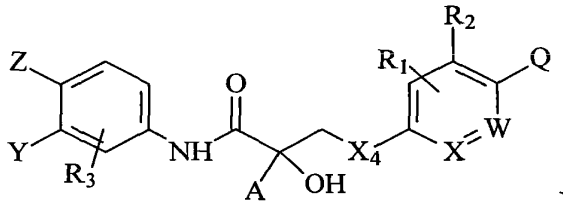
在另一个实施方案中，式VI的化合物由以下结构表示：



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；

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

A 是 CN、CH$_2$OH、CH$_2$O(C_{1-4} 烷基)、CH$_2$O(C_{1-4} 酰基)、CH$_2$CN、CH$_2$N$_3$、CH$_2$NCS、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$_2$OR'CH$_2$C(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$_2$NH$_2$、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$_2$C(O)NH$_2$、NHC(O)NH$_2$、NHCO(C_{1-4} 烷基)、NHSO$_2$(C_{1-4} 烷基)、O-[CH$_2$CH$_2$CH(CH$_3$)$_2$]、O-[CH$_2$CH$_2$(C_{4-8} 环烷基)]、O-[CH$_2$CH$_2$(C_{4-8} 杂环烷基)]或 O-[CH$_2$CH$_2$N(CH$_3$)$_2$]；

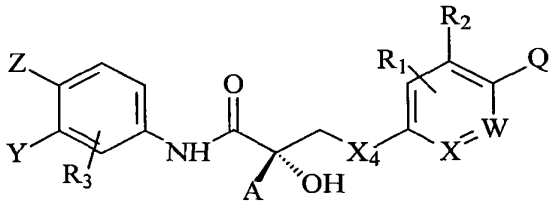
R_1 是 H、OH、F、Cl、Br 或 I；

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；

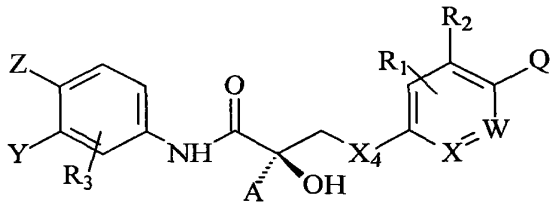
R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO$_2$；

R'是 NH$_2$、OH 或 CH$_3$；并且

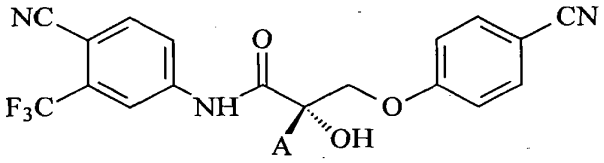
R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。在另一个实施方案中，式 XII 的化合物由以下结构表示：



在另一个实施方案中，式 XII 的化合物由以下结构表示：



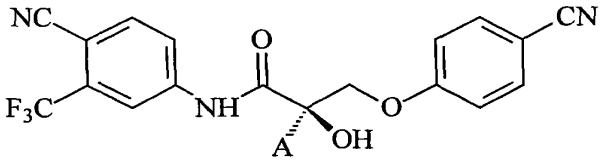
在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：



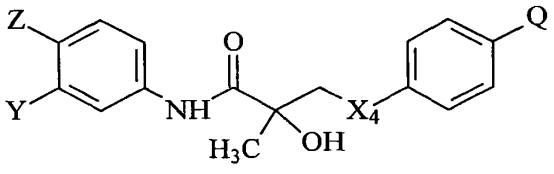
XIII

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：



XVII

其中

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

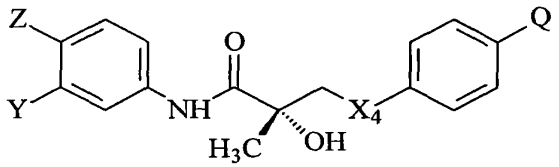
C[=CHCH$_2$N(CH$_3$)$_2$]、PO(C$_{1-4}$烷基)、N[CH$_2$CH$_2$N(CH$_3$)$_2$]、NO[CH$_2$CH$_2$N(CH$_3$)$_2$]；

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$_2$NH$_2$、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$_2$C(O)NH$_2$、NHC(O)NH$_2$、NHCO(C$_{1-4}$烷基)、NHSO$_2$(C$_{1-4}$烷基)、O-[CH$_2$CH$_2$CH(CH$_3$)$_2$]、O-[CH$_2$CH$_2$(C$_{4-8}$环烷基)]、O-[CH$_2$CH$_2$(C$_{4-8}$杂环烷基)]或O-[CH$_2$CH$_2$N(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

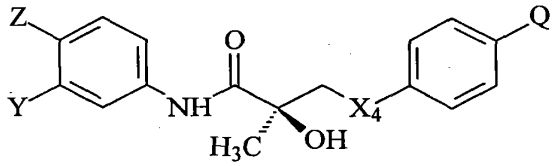
Y是H、C$_{1-4}$烷基、CF$_3$、CN、NO$_2$、F、Cl、I或Br。

在另一个实施方案中，式XVII的化合物由以下结构表示：

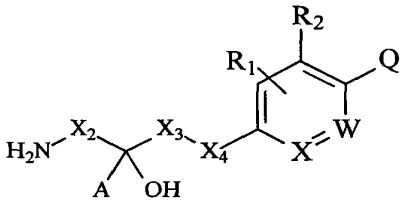


XVII

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$_{4-8}$环)]、CH(C$_{1-4}$烷基)、CH(NH$_2$)、CH(OH)、CH(C$_{1-4}$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)[=$CHCH_2N(CH_3)_2$]、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} 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；

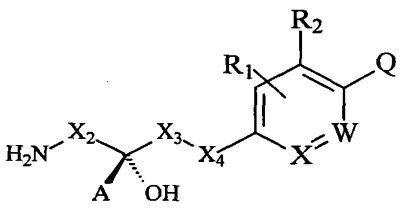
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物；

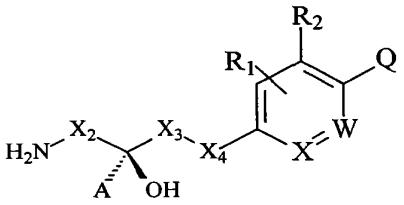
其中

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。

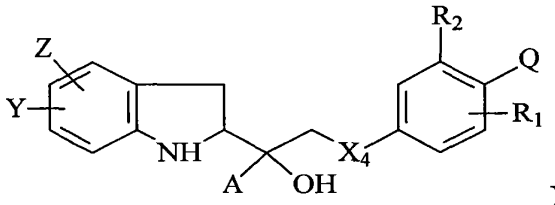
在另一个实施方案中，式 XIX 的化合物由以下结构表示：



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：



XX

其中

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} 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-[$CH_2CH_2N(CH_3)_2$]；

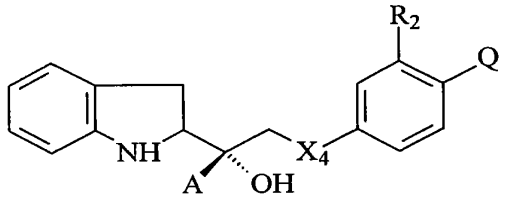
R_1 是 H、OH、F、Cl、Br 或 I；

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；

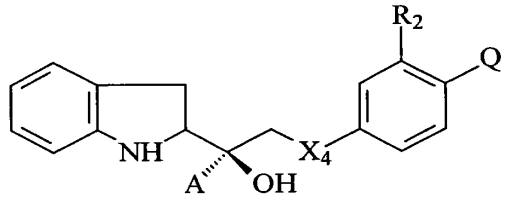
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

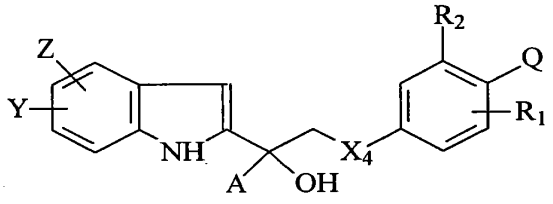
在另一个实施方案中，式 I 的化合物由以下结构表示：



或在另一个实施方案中，



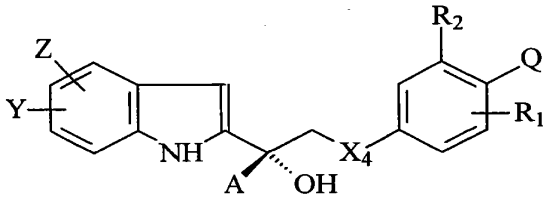
在一个实施方案中，本发明提供由式 XXI 的结构表示的化合物：



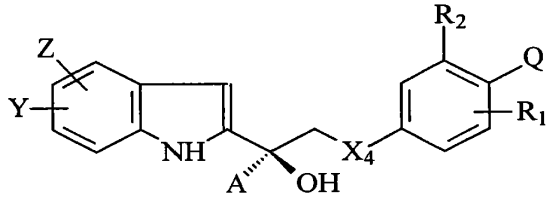
XXI

其中 A、Z、Y、X_4、Q、R_1 和 R_2 如在化合物 XX 中所述。

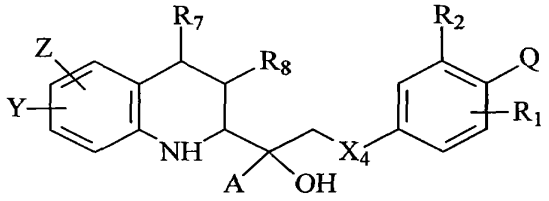
在另一个实施方案中，式 XXI 的化合物由以下结构表示：



或在另一个实施方案中，



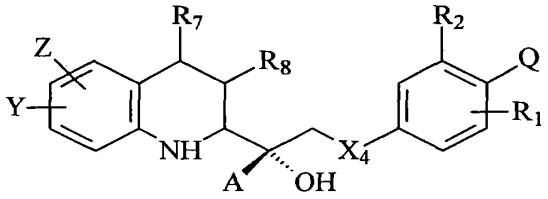
在一个实施方案中，本发明提供由式 XXII 的结构表示的化合物：



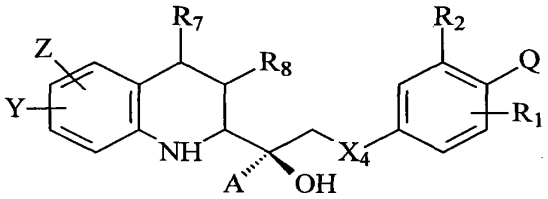
XXII

其中 A、Z、Y、X_4、Q、R_1 和 R_2 如在化合物 XX 中所述，R_7 是 H 或氧代，R_8 是 H 或=CH_2。

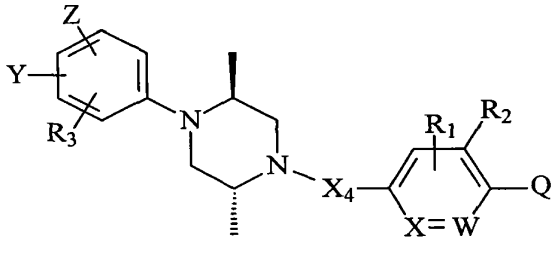
在另一个实施方案中，式 XXII 的化合物由以下结构表示：



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：



XXIII

其中

X 是 C 或 N；W 是 C 或 N；

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} 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、NO_2、卤化物、C_{2-6} 烯基、C_{2-6} 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 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；

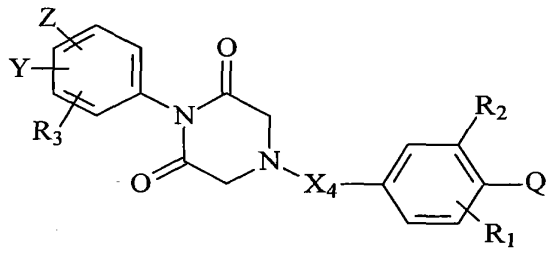
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_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。

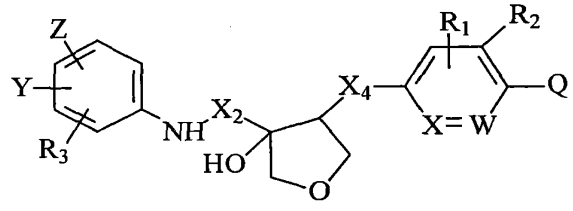
在一个实施方案中，本发明提供由式 XXXIII 的结构表示的化合物：



XXXIII

其中 Z、Y、X_4、Q、R_1、R_2 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：



XXXIV

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)、$CH-[CH_2-(C_{4-8}$ 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)、$S(O)[=CHCH_2N(CH_3)_2]$、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}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、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-[$CH_2CH_2N(CH_3)_2$]；

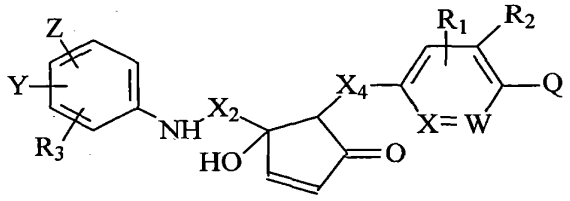
R_1是H、OH、F、Cl、Br或I；

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_3是H、C_{1-4}烷基、卤化物、CN或NO_2；

R_6是CN、NO_2、$NHC(O)CH_3$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：

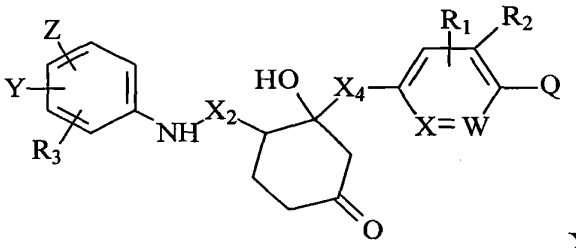


XXXVII

其中

X、X_2、X_4、Z、Y、Q、R1和R_3如以上在化合物XXXIV中所述。

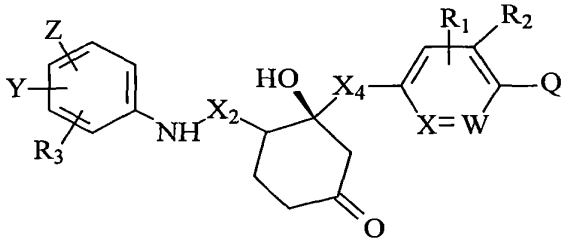
在一个实施方案中，本发明提供由式XXXVIII的结构表示的化合物：



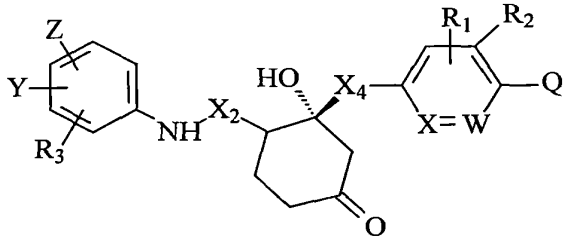
XXXVIII

其中X、X_2、X_4、Z、Y、Q、R1和R_3如以上在化合物XXXIV中所述。

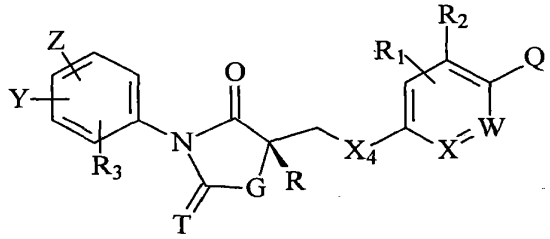
在另一个实施方案中，式XXXVIII的化合物由以下结构表示：



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：



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、$C(C_{1-4}$ 酰基$)_2$、$C(C_{1-4}$ 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} 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、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 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；

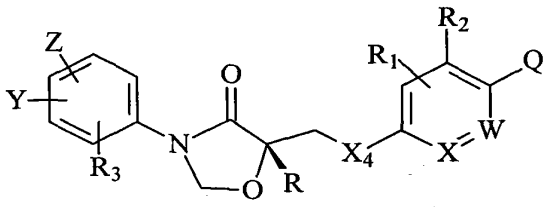
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、C_{1-4} 烷基、卤化物、CN 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。

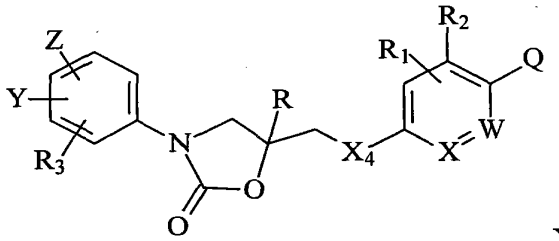
在一个实施方案中，本发明提供式 XLII 的化合物：



XLII

其中 X、X_4、Z、Y、Q、R1、R_2 和 R_3 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：



XLIV

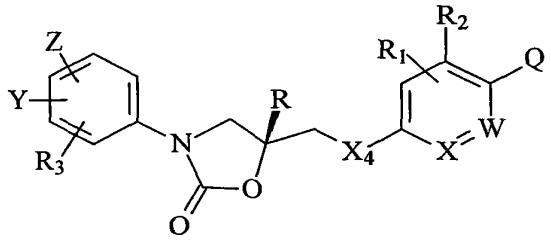
其中：

X、X_4、R、R_1、R_2、R_3、Z、Y 和 Q 如以上在化合物 XXXIX 中所述；

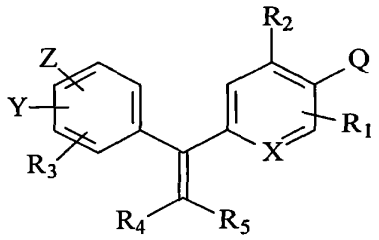
其中

如果 X 是 C，X_4 是 O、NH 或 S，R_1、R_2 和 R_3 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：



XLVII

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（oxatidyldione）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、SO_2、CH_2 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）。

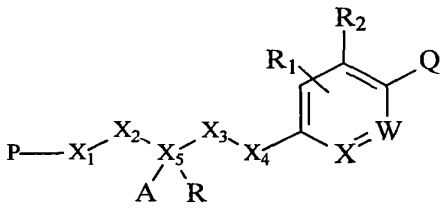
图14描绘了与*R*-比卡鲁胺结合的突变型W741L雄激素受体配体结合域。图14A显示与*R*-比卡鲁胺结合的AR LBD(W741L)的总体结构的侧视图。AF2区（螺旋3、4和12）以绿色突出显示。保守的电荷-发夹（charge-clamp）残基是H3中的K720和H12中的E897。图14B显示与DHT结合的野生型AR LBD的AF2区的结构细节。W741侧链显示在充满原子的空间中。

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：



I

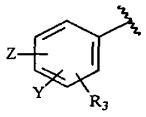
其中

X是C或N；W是C或N；

X_1是N、NH、N(C_{1-4}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：



II；

X_2 是 C_{1-4} 亚烷基、SO_2、C(O)、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；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；

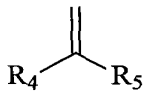
X_3 是 C_{1-4} 亚烷基、NH、N、CH(OH)、键；或者 X_1 和 X_3 与 X_1 和 X_3 所连接的 X_2 和 X_5 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X_3 和 X_5 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_3 和 X_4 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

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} 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、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：



III

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)、$O\text{-}[CH_2CH_2CH(CH_3)_2]$、$O\text{-}[CH_2CH_2(C_{4-8}$ 环烷基)]、$O\text{-}[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O\text{-}[CH_2CH_2N(CH_3)_2]$；

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、$NHC(O)CH_3$ 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 或烯基，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 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；

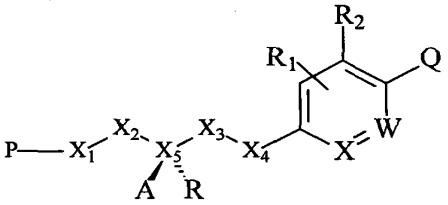
或者

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；

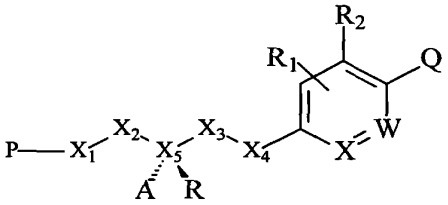
或者

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。

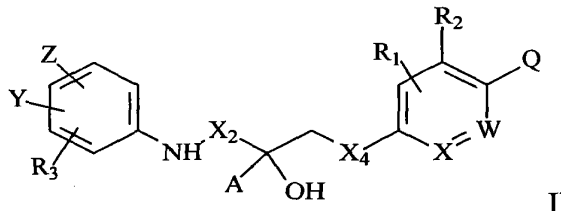
在另一个实施方案中，式 I 的化合物由以下结构表示：



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：



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} 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)[=$CHCH_2N(CH_3)_2$]、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} 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、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} 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；

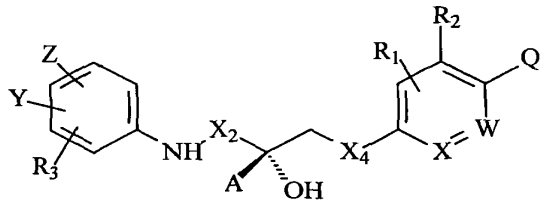
R_2 是 H、R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2；

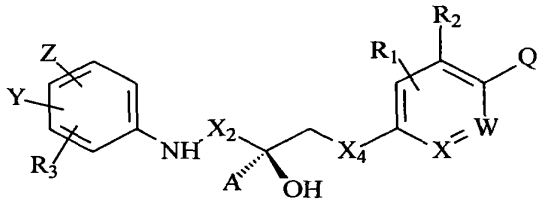
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

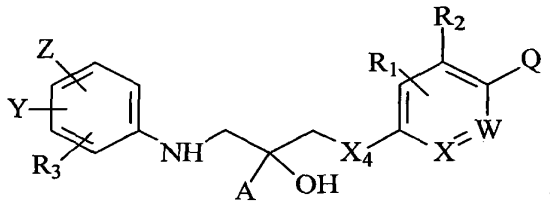
在另一个实施方案中，式 IV 的化合物由以下结构表示：



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：



VI

其中

X 是 C 或 N； W 是 C 或 N；

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} 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、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} 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；

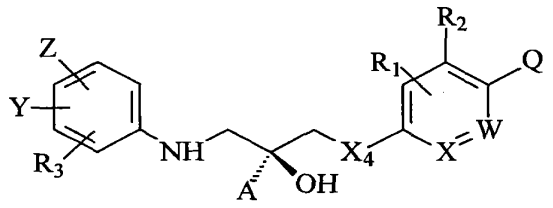
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2；

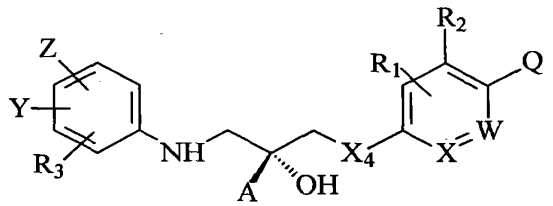
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

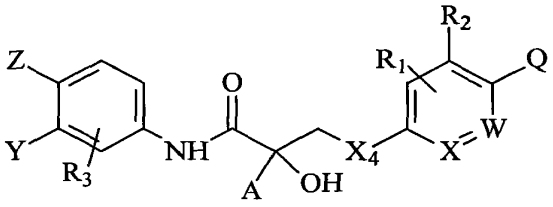
在另一个实施方案中，式 VI 的化合物由以下结构表示：



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；

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

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

A 是 CN、CH_2OH、$CH_2O(C_{1-4}$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 $C(O)CH=CH_2$；

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、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$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；

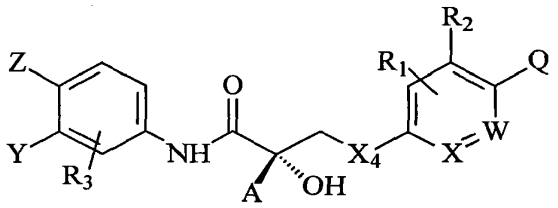
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、C_{1-4}烷基、卤化物、CN 或 NO_2；

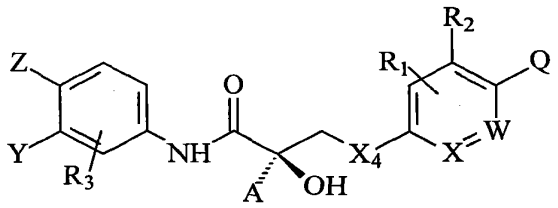
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

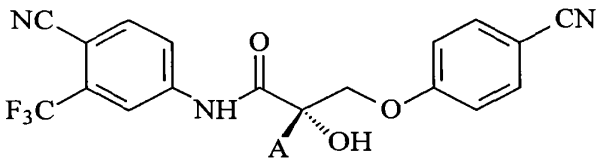
在另一个实施方案中，式 XII 的化合物由以下结构表示：



在另一个实施方案中，式 XII 的化合物由以下结构表示：



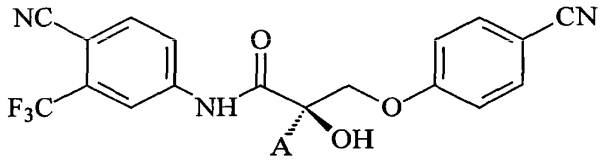
在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：



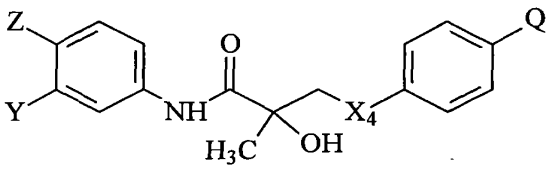
XIII

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：



XVII

其中

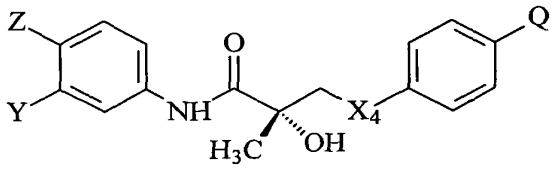
X_4 是 $S(O)[=CHCH_2N(CH_3)_2]$、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$PO(C_{1-4}$ 烷基)、$N[CH_2CH_2N(CH_3)_2]$、$NO[CH_2CH_2N(CH_3)_2]$；

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

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

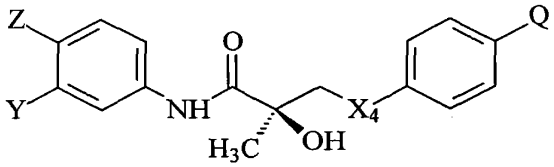
Y 是 H、C_{1-4} 烷基、CF_3、CN、NO_2、F、Cl、I 或 Br。

在另一个实施方案中，式 XVII 的化合物由以下结构表示：

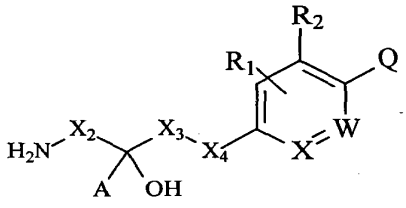


XVII

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；

X_2 是 C_{1-4} 亚烷基、SO_2、C(O)、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_3 是 C_{1-4} 亚烷基、NH、N、CH(OH)或键；

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} 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)、$O\text{-}[CH_2CH_2CH(CH_3)_2]$、$O\text{-}[CH_2CH_2(C_{4-8}$ 环烷基)]、$O\text{-}[CH_2CH_2(C_{4-8}$ 杂环烷基)]或 $O\text{-}[CH_2CH_2N(CH_3)_2]$；

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；

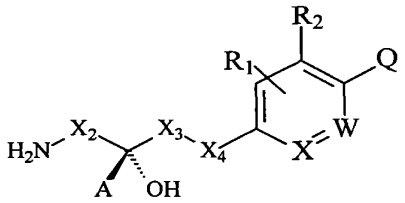
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物；

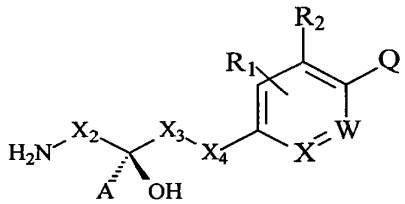
其中

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，R1 和 R_2 是 H，那么 Q 不是 H 或卤素。

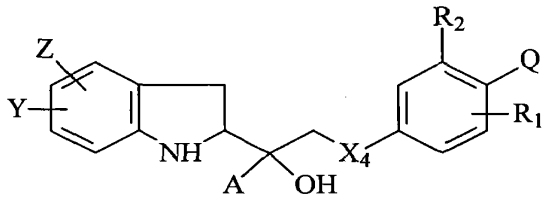
在另一个实施方案中，式 XIX 的化合物由以下结构表示：



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：



XX

其中

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}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-[$CH_2CH_2N(CH_3)_2$]；

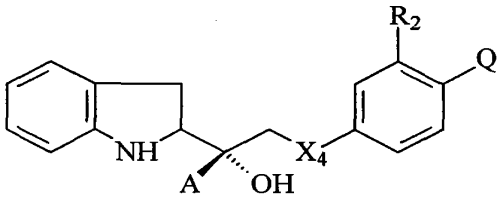
R_1是 H、OH、F、Cl、Br 或 I；

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；

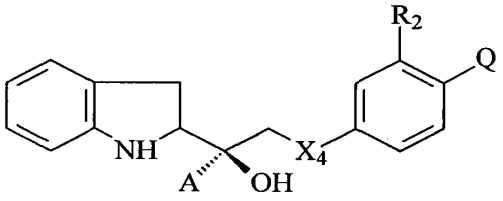
R'是 NH_2、OH 或 CH_3；并且

R_6是 CN、NO_2、$NHC(O)CH_3$或卤化物。

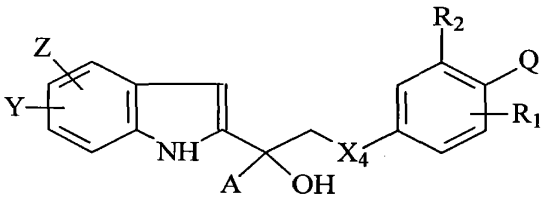
在另一个实施方案中，式 I 的化合物由以下结构表示：



或在另一个实施方案中，



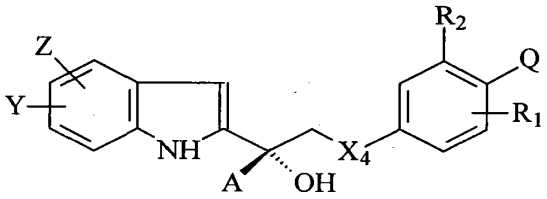
在一个实施方案中，本发明提供由式 XXI 的结构表示的化合物：



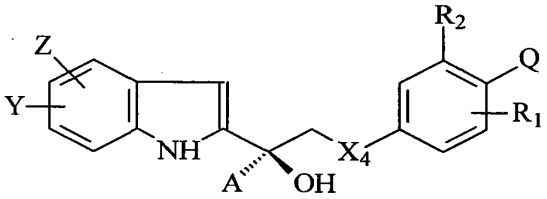
XXI

其中 A、Z、Y、X_4、Q、R_1 和 R_2 如在化合物 XX 中所述。

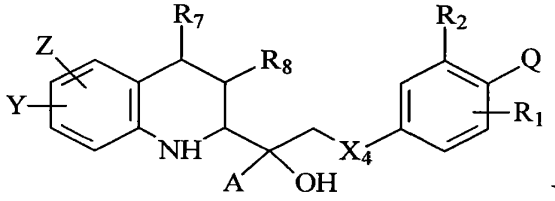
在另一个实施方案中，式 XXI 的化合物由以下结构表示：



或在另一个实施方案中，



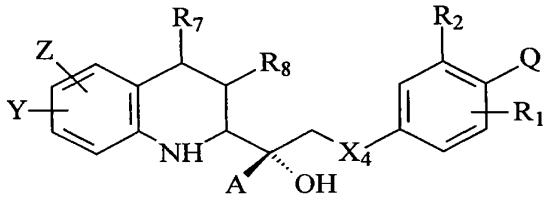
在一个实施方案中，本发明提供由式 XXII 的结构表示的化合物：



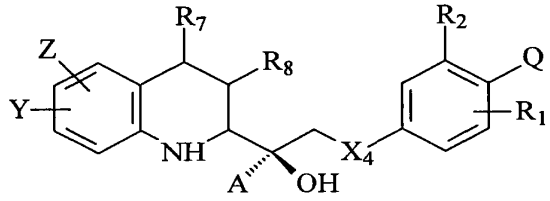
XXII

其中 A、Z、Y、X_4、Q、R_1 和 R_2 如在化合物 XX 中所述，R_7 是 H 或氧代，R_8 是 H 或=CH_2。

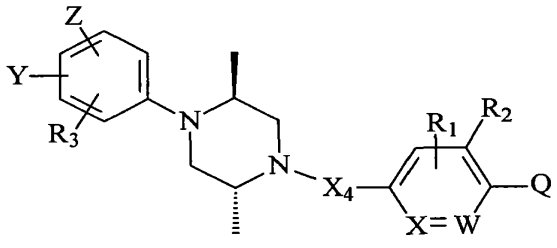
在另一个实施方案中，式 XXII 的化合物由以下结构表示：



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：



XXIII

其中

X 是 C 或 N；W 是 C 或 N；

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} 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、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 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

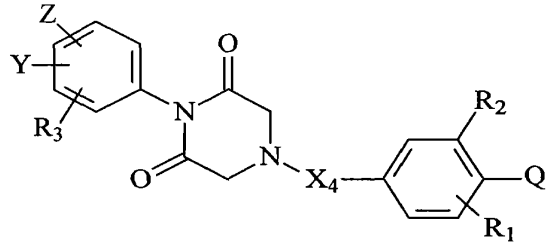
或 CH=CH-O-对氰基苯基；

R_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。

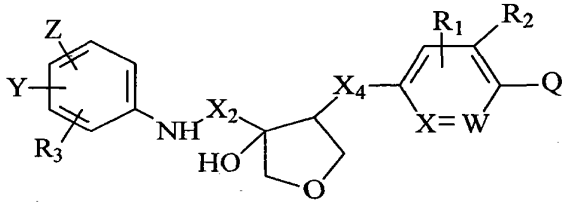
在一个实施方案中，本发明提供由式 XXXIII 的结构表示的化合物：



XXXIII

其中 Z、Y、X_4、Q、R1 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：



XXXIV

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} 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)[=$CHCH_2N(CH_3)_2$]、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} 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、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-[$CH_2CH_2N(CH_3)_2$]；

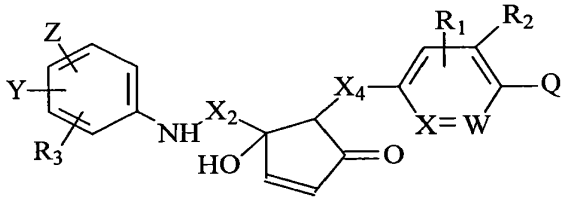
R_1是 H、OH、F、Cl、Br 或 I；

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_3是 H、C_{1-4}烷基、卤化物、CN 或 NO_2；

R_6是 CN、NO_2、$NHC(O)CH_3$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：

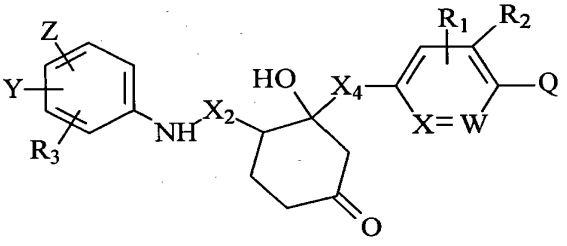


XXXVII

其中

X、X_2、X_4、Z、Y、Q、R_1和 R_3如以上在化合物 XXXIV 中所述。

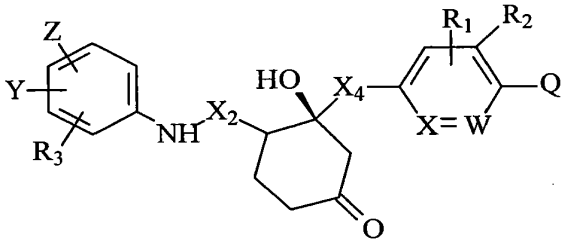
在一个实施方案中，本发明提供由式 XXXVIII 的结构表示的化合物：



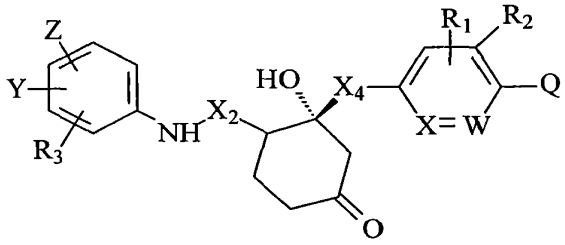
XXXVIII

其中 X、X_2、X_4、Z、Y、Q、R1 和 R_3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

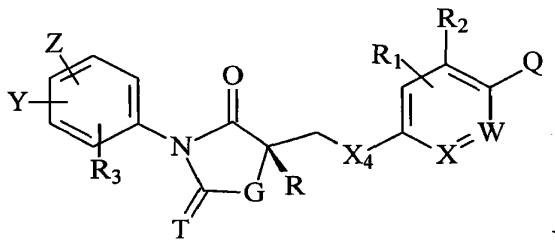
如果 P 是式 II，X 是 C，X_3 是 CH_2，X_4 是 O 或 NH，R_1、R_2 和 R_3 是 H，并且 X_5 和 X_1 形成 5 元环噁唑烷-2-酮，那么 Q 不是卤素或 H；

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：



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、$C(C_{1-4}$ 酰基$)_2$、$C(C_{1-4}$ 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} 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、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 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 或 NO_2；

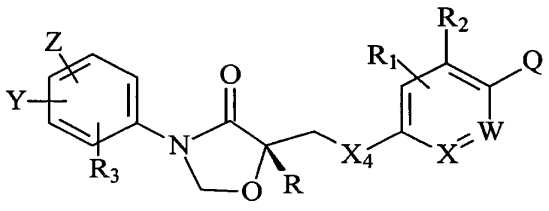
R'是 NH_2、OH 或 CH_3；并且

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。

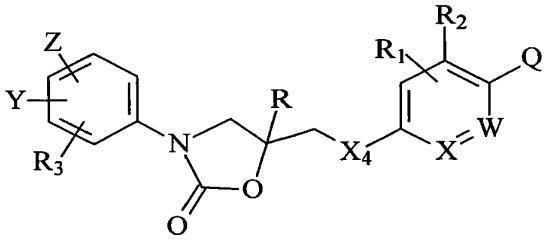
在一个实施方案中，本发明提供式 XLII 的化合物：



XLII

其中 X、X_4、Z、Y、Q、R1、R_2 和 R_3 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：



XLIV

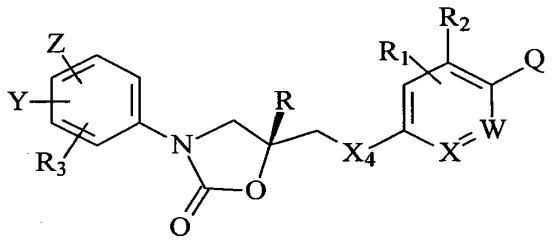
其中：

X、X_4、R、R_1、R_2、R_3、Z、Y 和 Q 如以上在化合物 XXXIX 中所述；

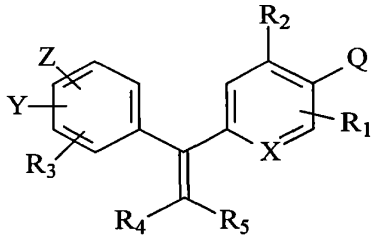
其中

如果 X 是 C，X_4 是 O、NH 或 S，R_1、R_2 和 R_3 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：

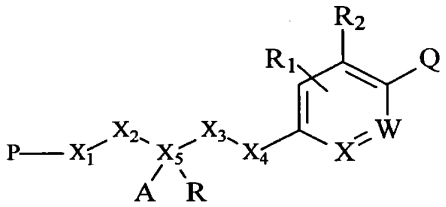


在一个实施方案中，本发明提供由式 XLVII 的结构表示的化合物：



XLVII

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：



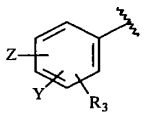
I

其中

X 是 C 或 N；W 是 C 或 N；

X_1 是 N、NH、N(C_{1-4} 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：



II；

X_2 是 C_{1-4} 亚烷基、SO_2、C(O)、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；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；

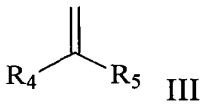
X_3 是 C_{1-4} 亚烷基、NH、N、CH(OH)、键；或者 X_1 和 X_3 与 X_1 和 X_3 所连接的 X_2 和 X_5 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X_3 和 X_5 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_3 和 X_4 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

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} 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 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：



III

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；

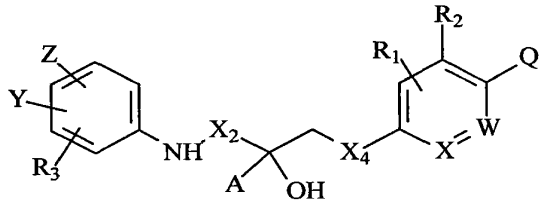
或者

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，R1 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：



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}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)[=$CHCH_2N(CH_3)_2$]、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}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、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、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$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；

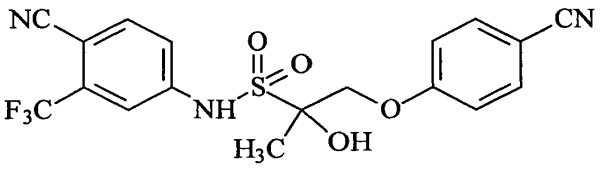
R_2是 H、由 R_6取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3是 H、C_{1-4}烷基、卤化物、CN 或 NO_2；

R'是 NH_2、OH 或 CH_3；并且

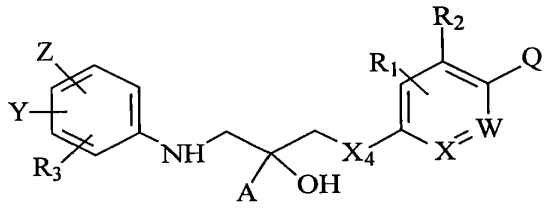
R_6是 CN、NO_2、$NHC(O)CH_3$或卤化物。

在一个实施方案中，本发明提供由式 V 的结构表示的化合物：



V

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：



VI

其中

X 是 C 或 N；W 是 C 或 N；

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} 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、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、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 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；

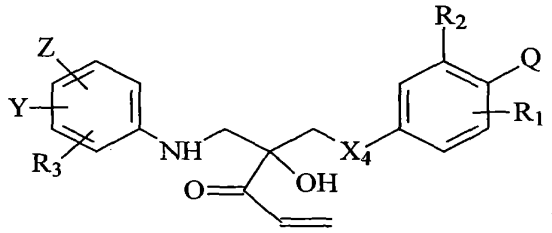
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、C_{1-4} 烷基、卤化物、CN 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。

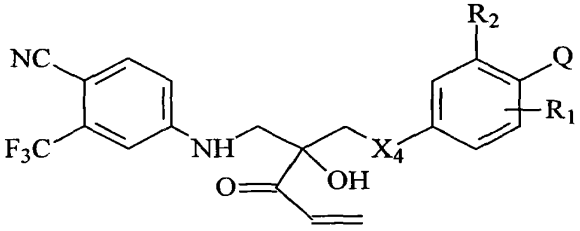
在一个实施方案中，本发明提供由式 VII 的结构表示的化合物：



VII

其中 Z、Y、R_1、R_2、R_3、Q 和 X_4 如以上在化合物 VI 中所述。

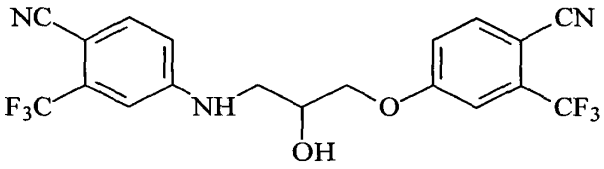
在另一个实施方案中，本发明提供由式 VIII 的结构表示的化合物：



VIII

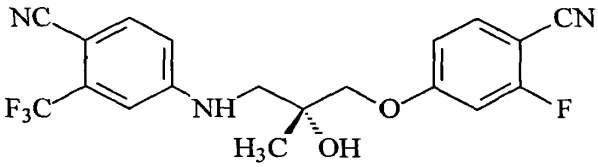
其中 R_1、R_2、Q 和 X_4 如以上在化合物 VI 中所述。

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：



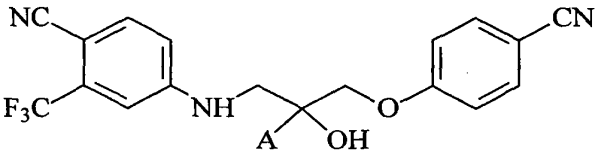
IX **8**

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：



X

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：



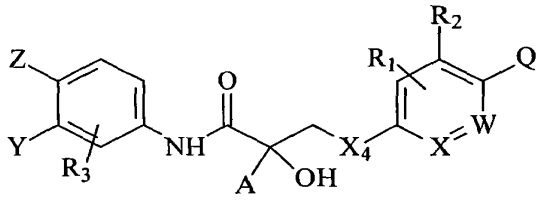
XI

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 CH_2OH。在另一个实施方案中，化合物 XI 的 A 是 CH_2OMe。在另一个实施方案中，化合物 XI 的 A 是

CF_3。在另一个实施方案中，化合物 XI 的 A 是 CH_3。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：



XII

其中

X 是 C 或 N；W 是 C 或 N；

X_4 是 O、S、SO、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} 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} 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 $C(O)CH=CH_2$；

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} 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、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；

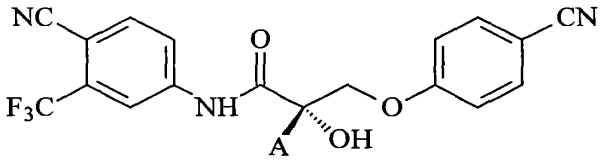
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

在另一个实施方案中，化合物 XII 的 X_4 是 O。在另一个实施方案中，化合物 XII 的 Q 是 CN，并且 R_1 和 R_2 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。

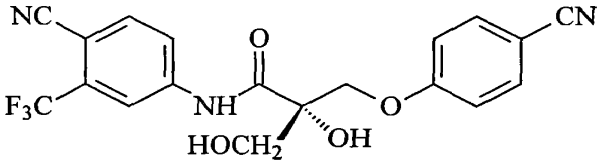
在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：



XIII

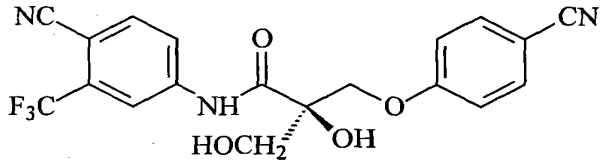
其中 A 如以上在化合物 XII 中所述。

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：

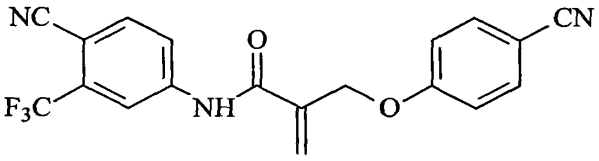


XIV

或在另一个实施方案中，

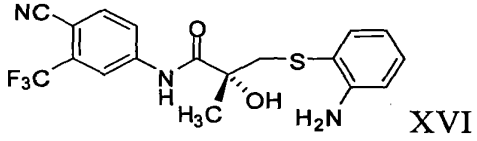


在一个实施方案中，本发明提供由式 XV 的结构表示的化合物：



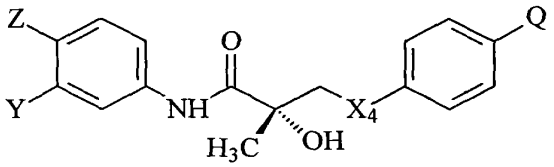
XV

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：



XVI

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：



XVII

其中

X_4 是 $S(O)[=CHCH_2N(CH_3)_2]$、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$PO(C_{1-4}$ 烷基)、$N[CH_2CH_2N(CH_3)_2]$、$NO[CH_2CH_2N(CH_3)_2]$；

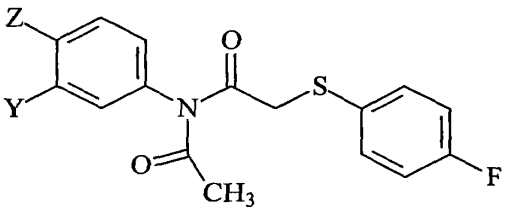
Q 是 H、CN、OH、NO_2、CF_3、卤化物、C_{2-6} 烯基、C_{2-6} 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$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

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：



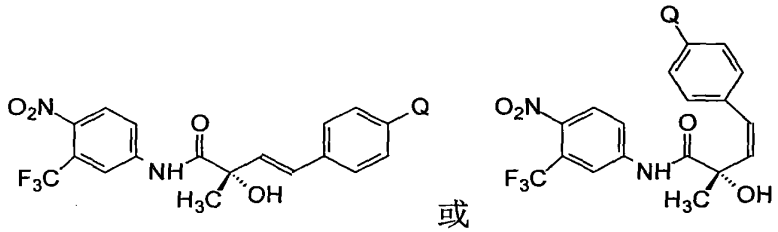
XVIII

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、环已基、环丁烯基、环戊烯基、环已烯基、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。

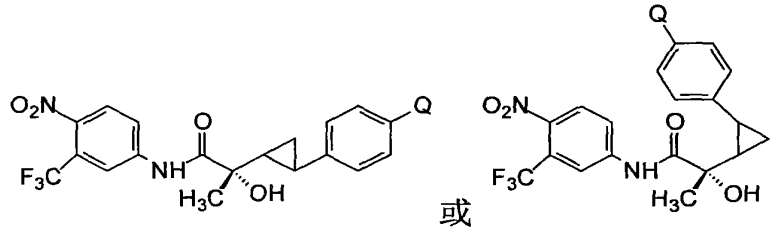
在另一个实施方案中，本发明提供由式 LIII 的结构表示的化合物：



或

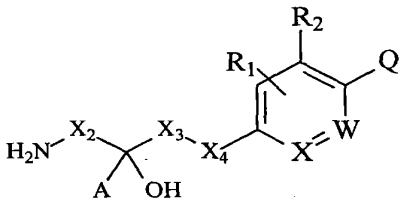
LIII-反式 LIII-顺式

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：



或

LIV LIV



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} 环)]、CH(C_{1-4} 烷基)、CH(NH_2)、CH(OH)、CH(C_{1-4} 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)[=$CHCH_2N(CH_3)_2$]、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} 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；

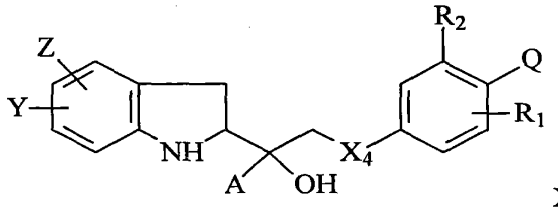
其中

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。

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CH2。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：



XX

I

其中

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} 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；

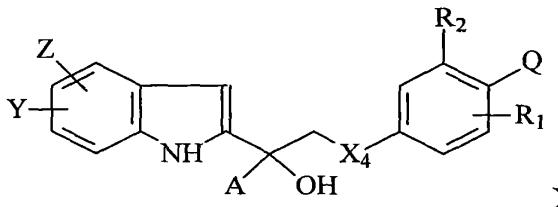
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

在另一个实施方案中，化合物 XX 的 A 是 CH_3。在另一个实施方案中，化合物 XX 的 X_4 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 CF_3。在另一个实施方案中，化合物 XX 的 Q 是 CN，Z 是 CN，并且 Y 是 CF_3。在另一个实施方案中，化合物 XX 的 A 是 CH_3，X_4 是 O，Q 是 CN，Z 是 CN，R_1 和 R_2 是 H，并且 Y 是 CF_3。

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：

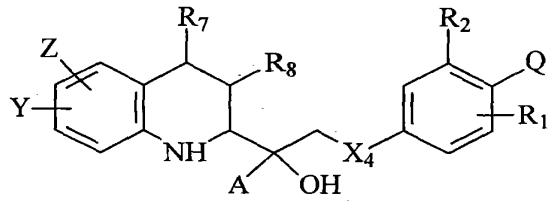


XXI

其中 A、Z、Y、X_4、Q、R_1 和 R_2 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 CH_3。在另一个实施方案中，化合物 XXI 的 X_4 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 CF_3。在另一个实施方案中，化合物 XXI 的 Q 是 CN，Z 是 CN，并且 Y 是 CF_3。在另一个实施方案中，化合物 XXI 的 A 是 CH_3，X_4 是 O，Q 是 CN，Z 是 CN，R_1 和 R_2 是 H，并且 Y 是 CF_3。

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：



XXII

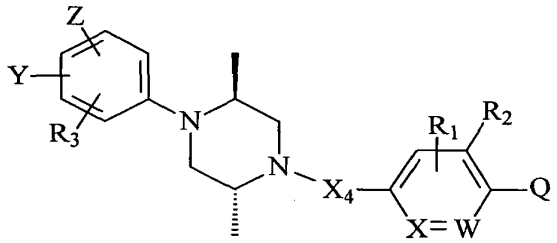
其中 A、Z、Y、X_4、Q、R_1 和 R_2 如在化合物 XX 中所述，R_7 是 H 或氧代，R_8 是 H 或=CH_2。

在另一个实施方案中，化合物 XXII 的 A 是 CH_3。在另一个实施方案中，化合物 XXII 的 X_4 是 O。在另一个实施方案中，化合物 XXI 的 R_7 和 R_8 是 H。在另一个实施方案中，化合物 XXII 的 R_7 是=CH_2，并且 R_8 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 CF_3。在另一个实施方案中，化合物 XXII 的 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。

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_3 和 X_1 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。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：



XXIII

其中

X 是 C 或 N；W 是 C 或 N；

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} 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、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 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；

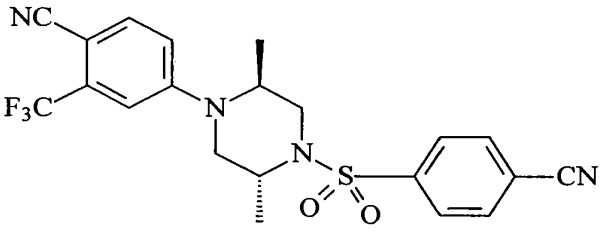
R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2；

R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

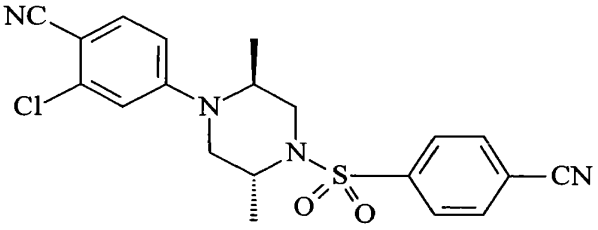
在另一个实施方案中，化合物 XXIII 的 X_4 是 O。在另一个实施方案中，化合物 XXIII 的 Q 是 CN。在另一个实施方案中，化合物 XXIII 的 Z 是 CN，并且 Y 是 CF_3。在另一个实施方案中，化合物 XXIII 的 X_4 是 O，Z 是 CN，Q 是 CN，R_1、R_2 和 R_3 是 H，并且 Y 是 CF_3。

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：



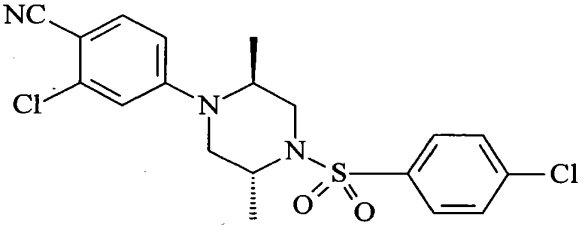
XXIV

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：



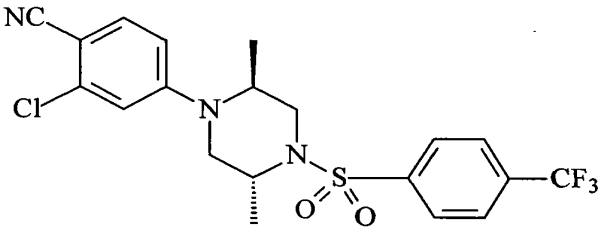
XXV

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：



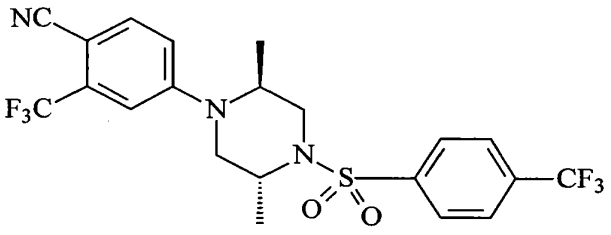
XXVI

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：



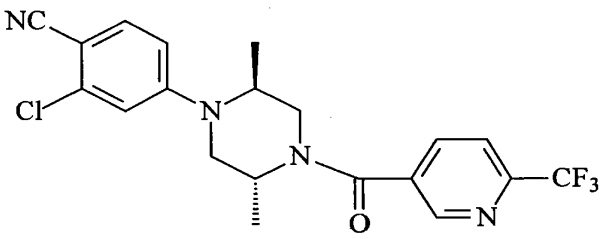
XXVII

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：



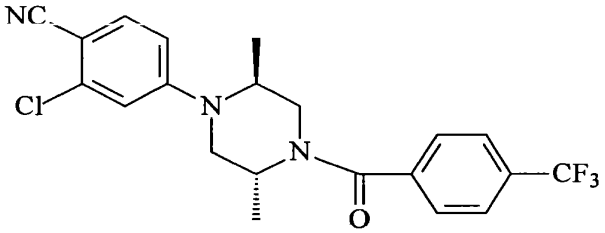
XXVIII

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：



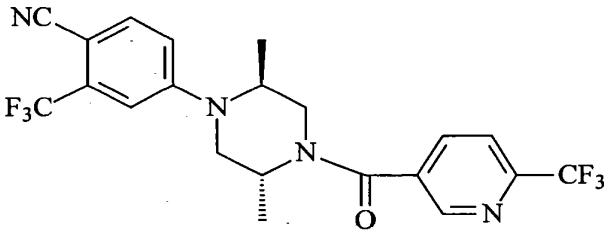
XXIX

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：



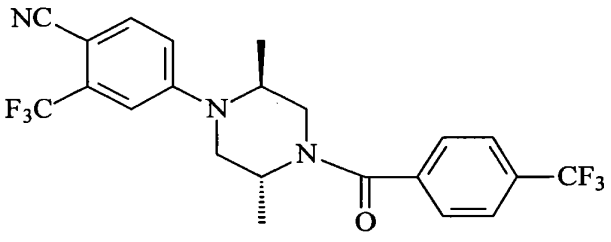
XXX

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：



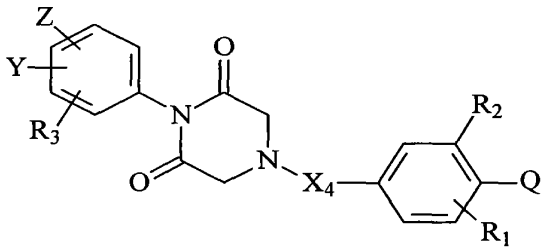
XXXI

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：



XXXII

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：



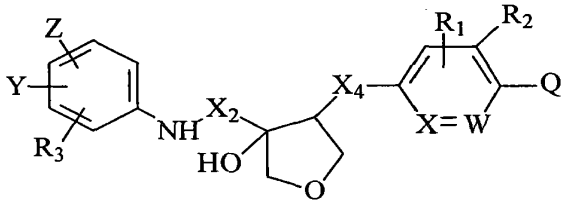
XXXIII

其中 Z、Y、X_4、Q、R_1、R_2 和 R_3 如在化合物 XXIII 中所述。

在另一个实施方案中，化合物 XXXIII 的 X_4 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 CF_3。在另一个实施方案中，化合物 XXXIII 的 X_4 是 O，Z 是 CN，Q 是 CN，R_1、R_2 和 R_3 是 H，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_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。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：



XXXIV

XXXIV

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} 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)[=$CHCH_2N(CH_3)_2$]、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} 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、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；

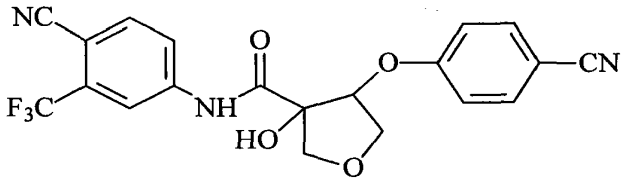
R_3 是 H、C_{1-4}烷基、卤化物、CN 或 NO_2；

R'是 NH_2、OH 或 CH_3；和

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

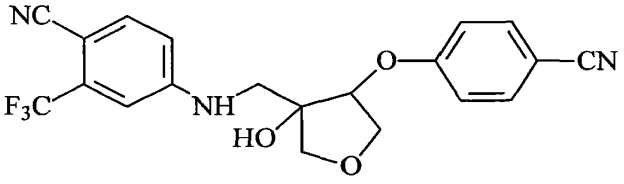
在另一个实施方案中，化合物 XXXIV 的 X_4 是 O。在另一个实施方案中，化合物 XXXIV 的 Q 是 CN。在另一个实施方案中，化合物 XXXIV 的 X_2 是 CH_2。在另一个实施方案中，化合物 XXXIV 的 X_2 是 C(O)。在另一个实施方案中，化合物 XXXIV 的 Z 是 CN，并且 Y 是 CF_3。在另一个实施方案中，化合物 XXXIV 的 X_4 是 O，Z 是 CN，Q 是 CN，R_1、R_2 和 R_3 是 H，并且 Y 是 CF_3。

在另一个实施方案中，本发明提供式 XXXV 的化合物：



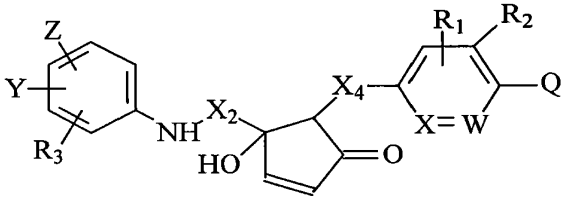
XXXV

在另一个实施方案中，本发明提供式 XXXVI 的化合物：



XXXVI

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：



XXXVII

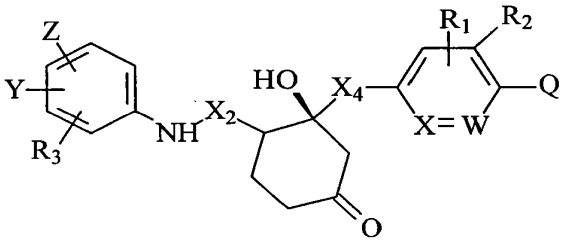
XXXVII

其中

X、X_2、X_4、Z、Y、Q、R_1、R_2和R_3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X_4是 O。在另一个实施方案中，化合物 XXXVII 的X_2是 C(O)。在另一个实施方案中，化合物 XXXVII 的X_2是CH_2。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CF_3。

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：



XXXVIII

其中 X、X_2、X_4、Z、Y、Q、R_1、R_2和R_3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

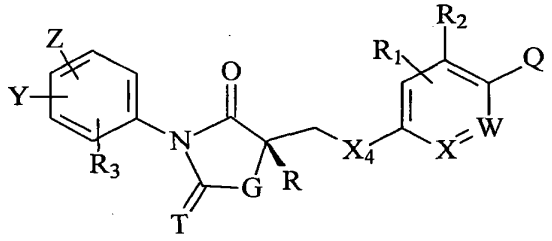
如果 P 是式 II，X 是 C，X_3 是 CH_2，X_4 是 O 或 NH，R_1、R_2 和 R_3 是 H，并且 X_5 和 X_1 形成 5 元环噁唑烷-2-酮，那么 Q 不是卤素或 H；

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：



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、$C(C_{1-4}$ 酰基$)_2$、$C(C_{1-4}$ 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} 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、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$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；

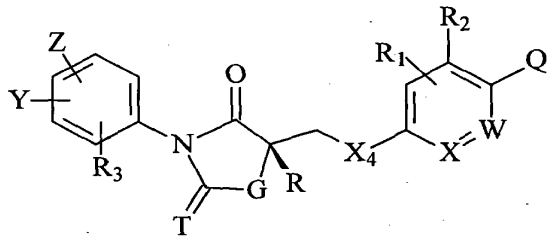
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、C_{1-4}烷基、卤化物、CN 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。

在一个实施方案中，本发明提供由式 XXXIX 的结构表示的化合物：



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、$C(C_{1-4}$酰基$)_2$、$C(C_{1-4}$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、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$PO(C_{1-4}$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、$C(O)CH_2NH_2$、

$C(O)NH(C_{1-4}$ 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;

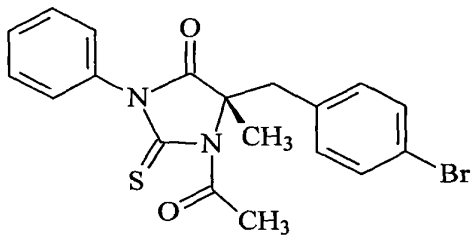
R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2;

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

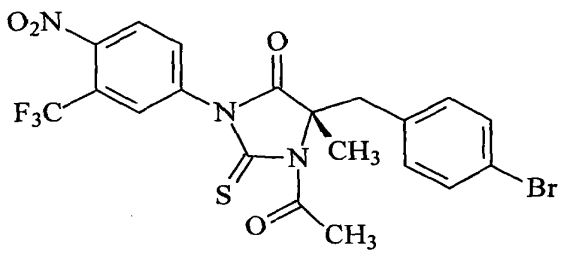
如果 R_3 是 H,X 和 W 是 C,G 是 O,T 是 O,R 是烷基,X_3 是 CH_2,并且 X_4 是 O、NH、S、SO_2 或 CH_2,那么 Q 不是卤化物。

在一个实施方案中,本发明提供式 XL 的化合物:



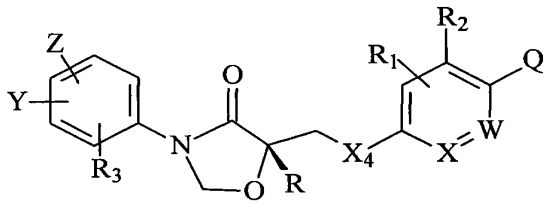
XL

在一个实施方案中,本发明提供式 XLI 的化合物:



XLI

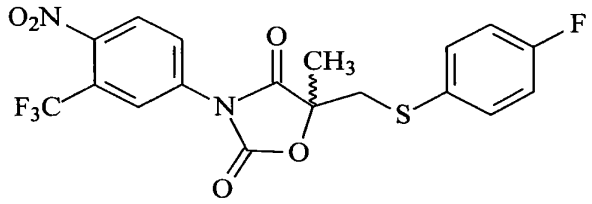
在一个实施方案中,本发明提供式 XLII 的化合物:



XLII

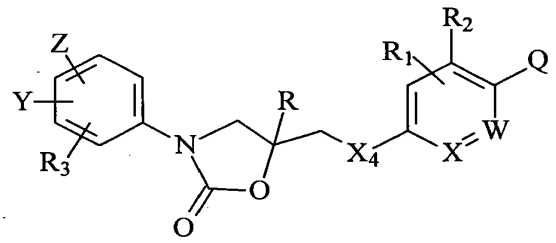
其中 X、X_4、Z、Y、Q、R_1、R_2 和 R_3 如以上在化合物 XXXIX 中所述。

在一个实施方案中，本发明提供式 XLIII 的化合物：



XLIII

在一个实施方案中，本发明提供式 XLIV 的化合物：



XLIV

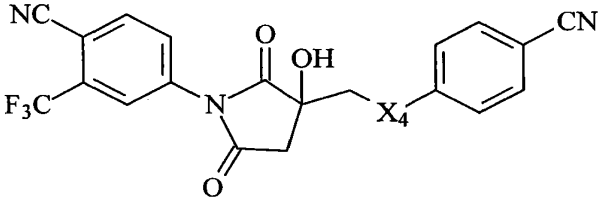
其中：

X、X_4、R、R_1、R_2、R_3、Z、Y 和 Q 如以上在化合物 XXXIXV 中所述；

其中

如果 X 是 C，X_4 是 O、NH 或 S，R_1、R_2 和 R_3 是 H 并且 R 是 H，那么 Q 不是卤素、H 或 CN。

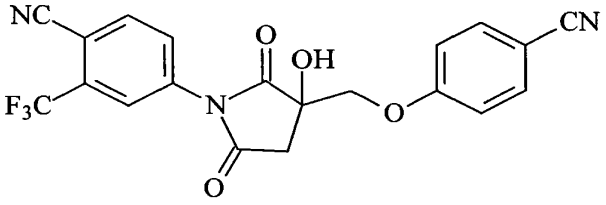
在一个实施方案中，本发明提供由式 XLV 的结构表示的化合物：



XLV

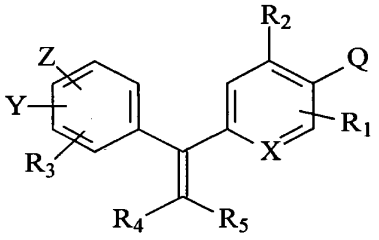
其中 X_4 如以上在化合物 XXXIX 中所述。

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、NO_2、$NHC(O)CH_3$、CH_3、F、Cl、I 或 Br；

Y 是 H、CH_3、CF_3、CN、F、Cl、I 或 Br；

Q 是 H、$O\text{-}(CH_2)_2CH(CH_3)_2$ 或 $O\text{-}(CH_2)_2N(CH_3)_2$；

R_1 是 H、OH、F、Cl、Br 或 I；

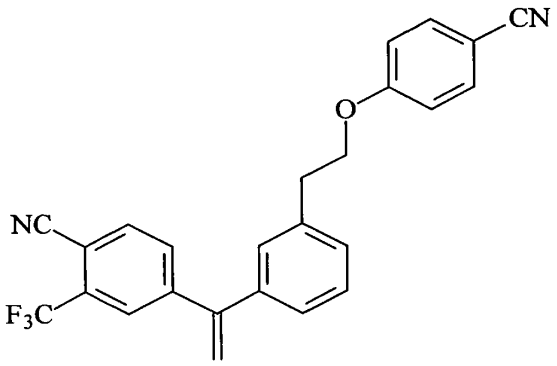
R_2 是由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、CH_3、卤化物、CN 或 NO_2；

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

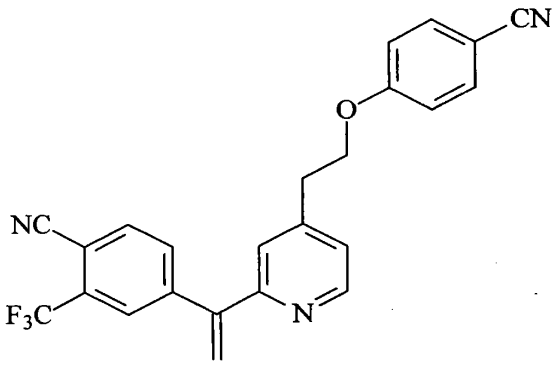
R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

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：



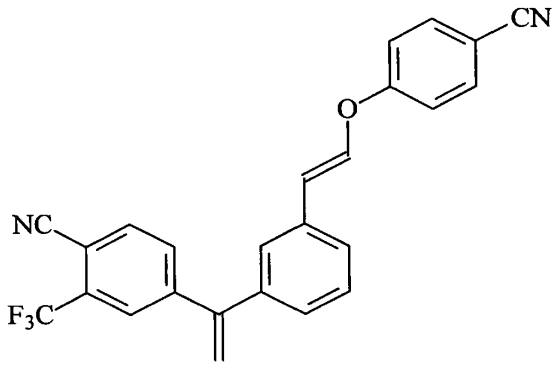
XLVIII

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：



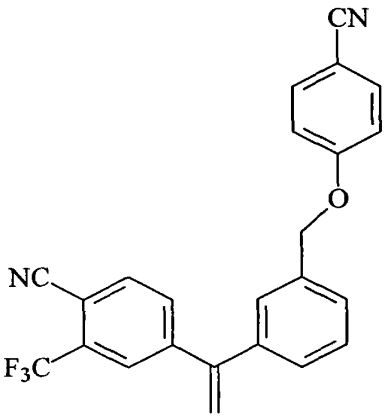
XLIX

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：



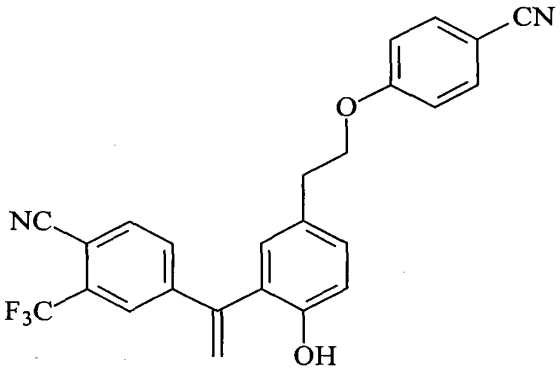
L

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：



LI

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：



LII

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，本发明包括任意的外消旋形式、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、二葡糖酸盐、十二烷基磺酸盐、二氢氯化物、癸酸盐、庚酸盐（enanthuates）、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、葡糖酸盐、谷氨酸盐、乙醇酸盐（glycolates）、葡糖酸盐、葡糖庚酸盐（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、已酸盐、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、苯乙苄胺(*N*-苄基苯乙胺)、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（picolies）、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、吡唑基、吡啶基、呋喃基、苯硫基、噻唑基、咪唑基、异噁唑基等。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的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（croscarmelose 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 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 5α-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（例如但不局限于阿那曲唑（anastrazole）、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 17β-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、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（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，PPARα配体例如苯扎贝特、非诺贝特、吉非贝齐；PPARγ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，3β-DHΔ4,6-异构酶抑制剂，3β-DHΔ4,5-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、髋、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的步骤。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所指的活性成分，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所意识

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，所述个体是雄性。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（ewings 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、骨肉瘤癌、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、髋部或关节的）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（如在髋骨折中）或压缩性骨折的形式（如在脊椎压迫性骨折中）。脊柱、髋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，骨原细胞可以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、秦哚昔芬、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（tiludroate）、氯屈膦酸钠（clodroniate）、帕米磷酸钠、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) αvβ3 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) 麦芽糖镓（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) 依普黄铜；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,在慢性下腰痛的严重病例中,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（influenze）、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。心原性恶病质，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、弯曲杆菌传染、念珠菌病、猫抓病、衣原体传染、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、诺卡尔菌感染、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、神经原性滑囊炎、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、皮肌炎、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、弗莱尔伯格二蹠骨远端缺血坏死、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颚病、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，口颚病包括舌系带过短、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、胸腔积脓、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、痱、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能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、瘘、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、瘘、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、消耗性病症、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、血小板存贮池缺如、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、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、蜱性麻痹或伤口(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、原发性胆汁性肝硬变、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（polyartekidney 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 μg/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 μg/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）、皮肌炎、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、甘油三脂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（包括心肌病、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肪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环死（NLD）、糖尿病大水疱（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 μg/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 μg/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）。

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 μg/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 μg/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。这些药剂包括但不局限于：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 OsO_4 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 $NaClO_4$ 进行氧化，形成酸 64。使用亚硫酰二氯和 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 (^{1}H, 300MHz, DMSO): 1.35 (s, 3H, CH_3), 3.5 (s, 1H, CH), 3.6 (s, 1H, CH), 4.0 (br, 1H, OH) MS: 205 ($M + Na^+$) $C_4H_7BrO_3$ 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℃，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 (^{1}H, 300MHz, $CDCl_3$): 1.8 (s, 3H, CH_3), 3.7 (s, 2H, CH_2), 5.8 (s, 1H, CH) $C_6H_6Br_4O_3$ 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℃; $[\alpha]_D^{25}$ = +24.85 (c=1.0, MeOH) NMR (^{1}H, 300MHz, $CDCl_3$):1.5 (s, 3H,

CH_3), 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 $C_{10}H_{11}FO_3S$，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，通过使用已烷-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。通过使用已烷-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 (^{1}H, 500MHz, DMSO): 1.8 (s, 3H, CH_3), 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 = 0.5Hz, 2.1 Hz) 8.1 (m, 1H, Ar, J = 0.5Hz, 9.0Hz) NMR (^{13}C, 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 $C_{10}H_{11}FO_3S$，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

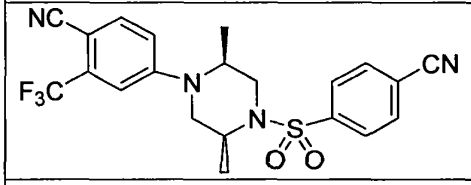
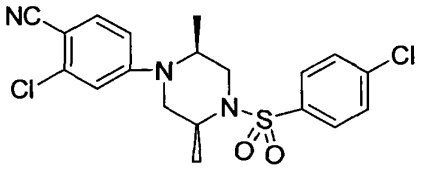
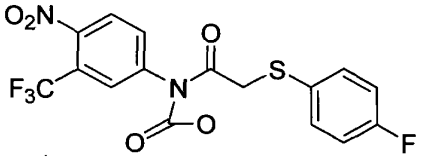
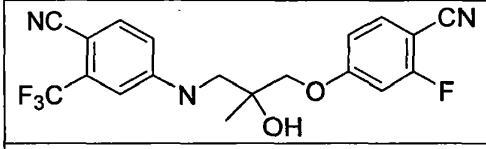
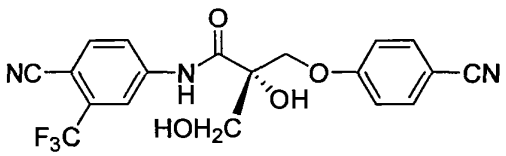
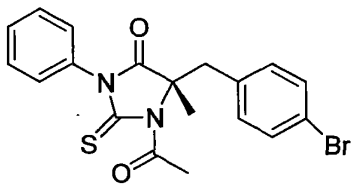
雄激素受体（AR）与 SARM 的结合以及 AR-SARM 晶体结构方法

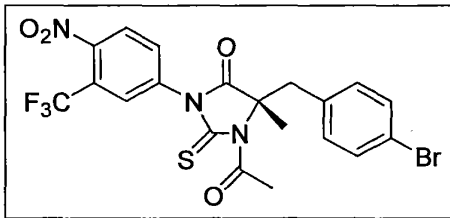
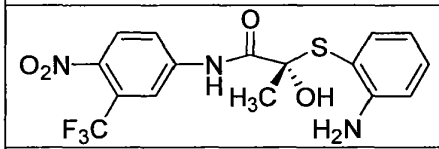
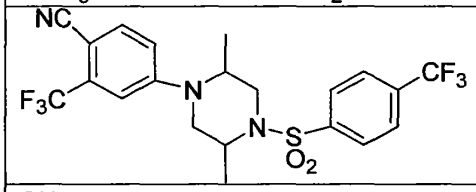
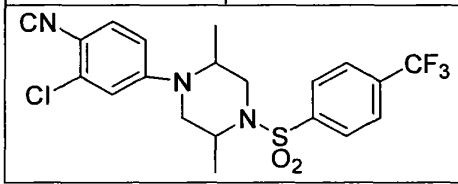
亲合力测定

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 m MEDTA 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℃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℃下用饱和浓度的 ^{3}H-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 ^{3}H-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 ^{3}H-MIB 的浓度。使用非线性回归测定 IC_{50}，即抑制 50% ^{3}H-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合力并显示在下表中：

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 μg CMVhAR 表达载体、30 μg 雄激素依赖型萤光素酶报道基因构建体(pMMTV-luc)和 30 μg β-半乳糖苷酶表达构建体（pSV-β-半乳糖苷酶；Promega, 5 Madison, WI）经 30 mLPlus 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30μM 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/mLDNA酶I、10 mM $MgCl_2$、10 mM DTT、0.5% CHAPS、100 μM配体和100 μM 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 μM配体、0.1% *n*-辛基-β-葡糖苷、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中用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 μM配体、0.1% *n*-辛基-β-葡糖苷和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。

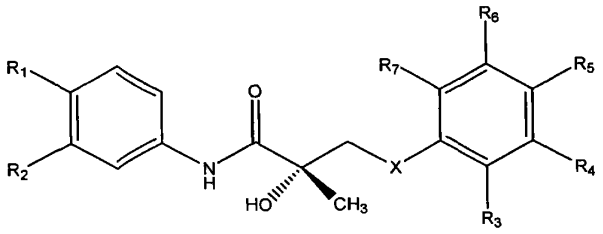
实施例 15

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 ^{1}H 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	COCH3	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	COCH3	H	H	36.6±2.3
S-3	NO_2	CF_3	O	H	H	$COCH_2CH_3$	H	H	6.1±0.14
S-4	NO_2	CF_3	O	H	H	NHCOCH3	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	OCH3	H	H	13.7±0.68
S-7	NO_2	CF_3	O	H	H	$NHCO_2C(CH_3)3$	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	CH3	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

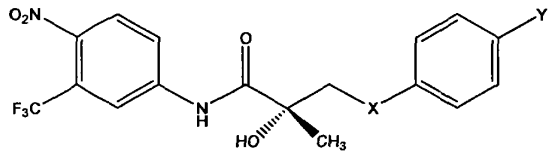
对 AR 介导的转录激活的体外研究（图 8）显示，将 X 连接由砜变为氧或将 B 环对位取代由氟变为乙酰胺基都将纯粹的 AR 拮抗剂转化为激动剂，例如在化合物 S-5 和 R-20 中。在体内试验中，先导化合物 S-1 和 S-4 在体内用作 AR 激动剂并显示出组织选择性（图 9A-9B)。S-1 和 S-4 在前列腺中都是部分激动剂，但是在肛提肌、骨和垂体中是完全激动剂，这些是对理想的选择性雄激素受体调节剂提出的特征。

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 5α-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 5α-还原酶放大，5α-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 配体下分析疗力（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 ± 0.19	43.40 ± 2.60
X-2	S	F	11 ± 2	77.4 ± 5.6
X-3	SO_2	F	28 ± 10	18.8 ± 9.3
X-4	NH	F	7.96 ± 0.43	21.33 ± 2.22
X-5	CH_2	F	9 ± 0.2	28.9 ± 2.4
S-4	O	$NH(CO)CH_3$	3.98 ± 0.70	92.92 ± 7.00
S-23	O	I	23 ± 1.6	47.2 ± 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=SO_2, Y=F)和 X-4(X=NH, Y=F)和 X-5(X=CH_2 ,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 所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，使用亲合力更高的比卡鲁胺 *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。这种结象说明，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）。

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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 17β-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-比卡鲁胺的砜连接基和 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 吲哚环(在突变体中不存在)的空间。在 T877A-HF 和 WT-DHT 复合物中，W741 吲哚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，该吲哚环距离结合口袋(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 吲哚环的位置中。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

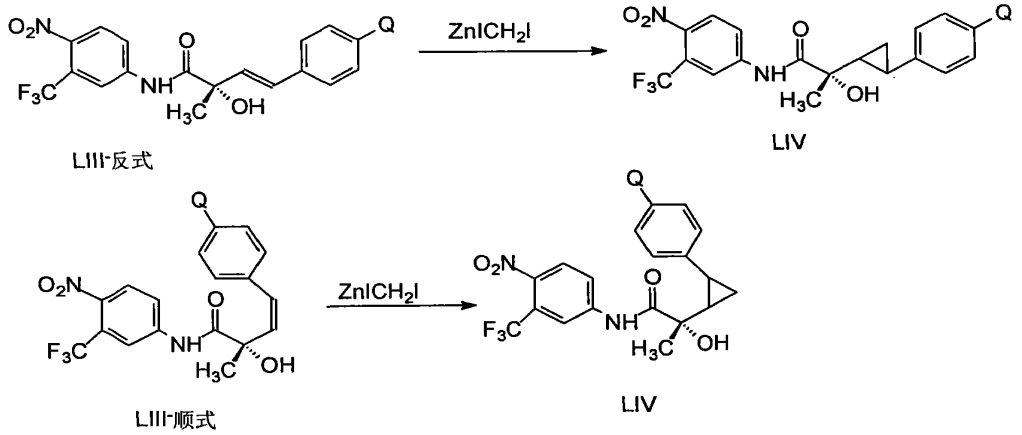
AR 配体结合的计算预测的确认

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

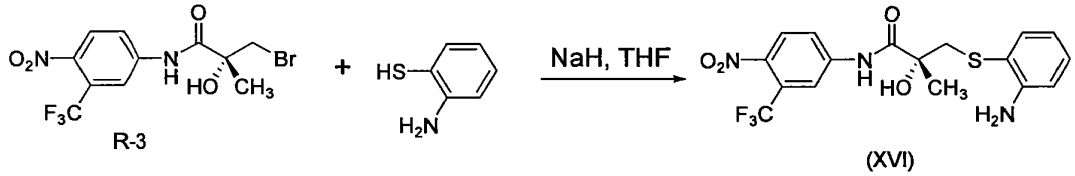
化合物 LIV 的合成

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，如以下路线所示。



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}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}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}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}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℃。

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}H NMR ($CDCl_3$)：10.80, 8.35, 8.18, 7.99, 4.49, 1.43。

化合物 XLI 的 ^{1}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。

6612

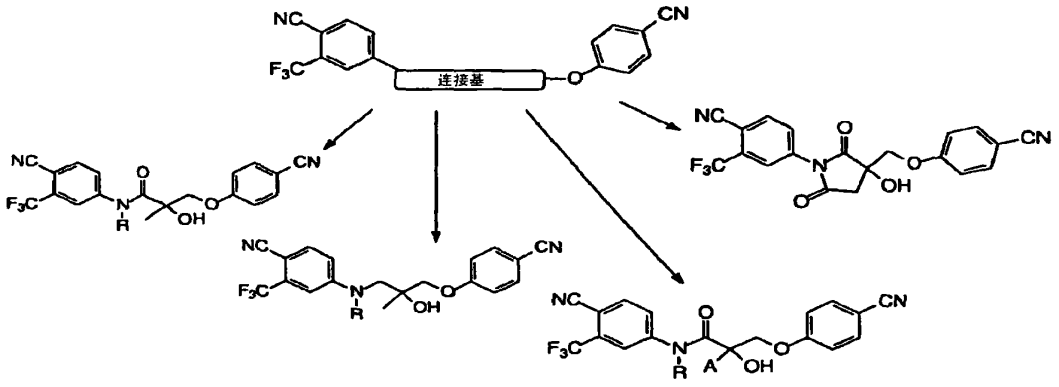

NC
CN
F3C
连接基
O
NC
CN
F3C
N
H
O
OH
NC
CN
F3C
N
R
O
OH
NC
CN
F3C
N
R
O
OH
NC
CN
F3C
N
O
O
OH
NC
CN
F3C
N
R
A
O
OH

图1A

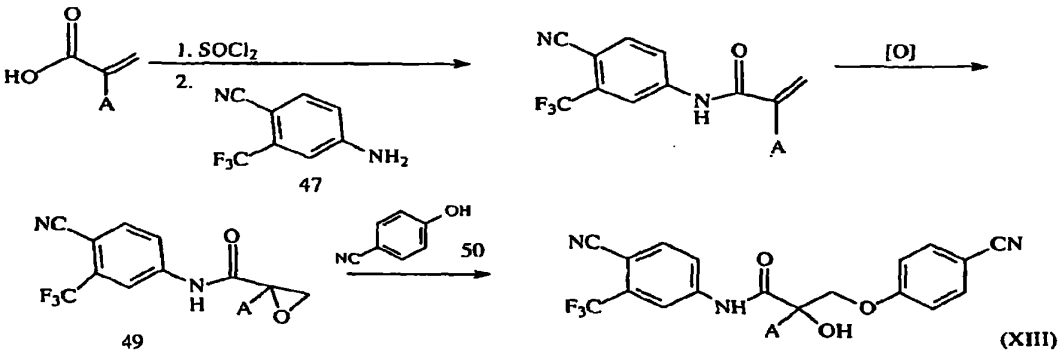

HO
O
A
1. SOCl2
2.
NC
F3C
NH2
47
NC
F3C
N
H
O
A
[O]
NC
F3C
N
H
O
A
49
OH
NC
50
NC
F3C
NH
O
A
OH
O
CN
(XIII)

图1B

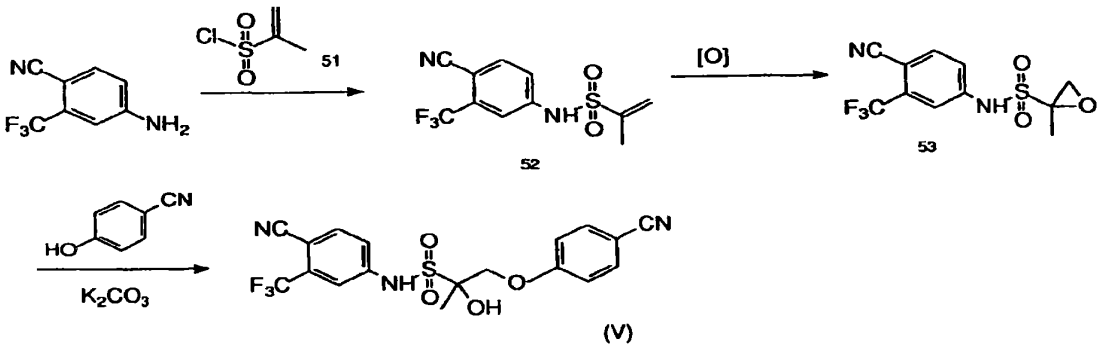

NC
F3C
NH2
Cl
O
S
O
51
52
[O]
53
HO
CN
K2CO3
NH
OH
(V)

图1C

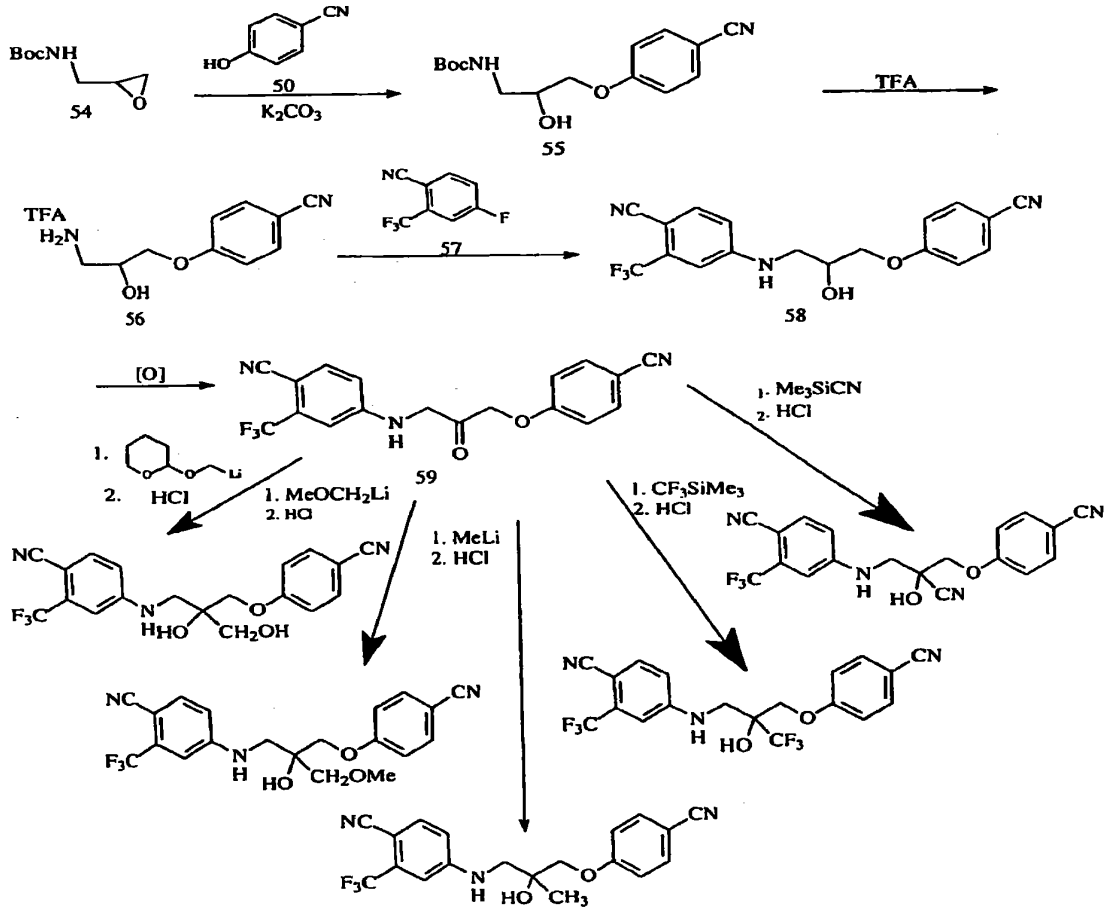

BocNH
54
50
K2CO3
55
TFA
H2N
56
F3C
F
57
58
[O]
59
1. Me3SiCN
2. HCl
1. MeOCH2Li
2. HCl
1. MeLi
2. HCl
1. CF3SiMe3
2. HCl
HO
CH2OH
CH2OMe
CF3
CH3
N
H
O
CN

图1D

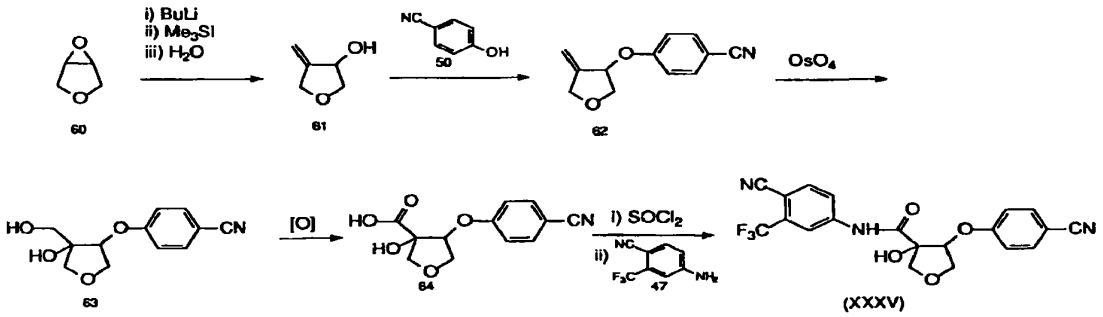


图1E

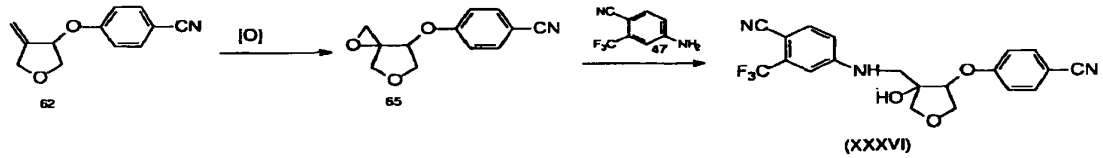


图1F

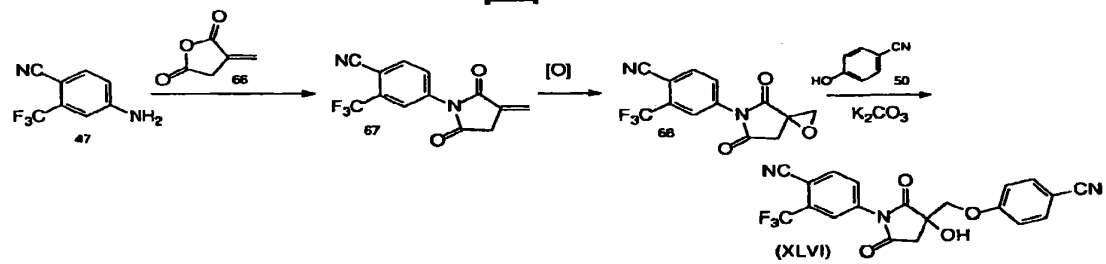


图1G

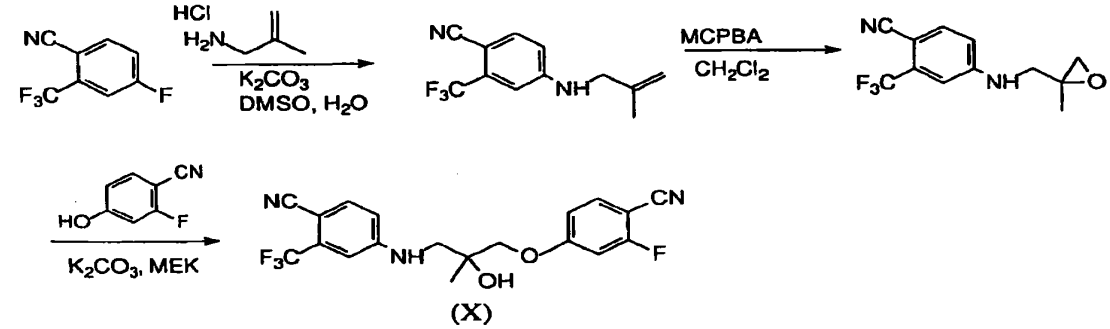
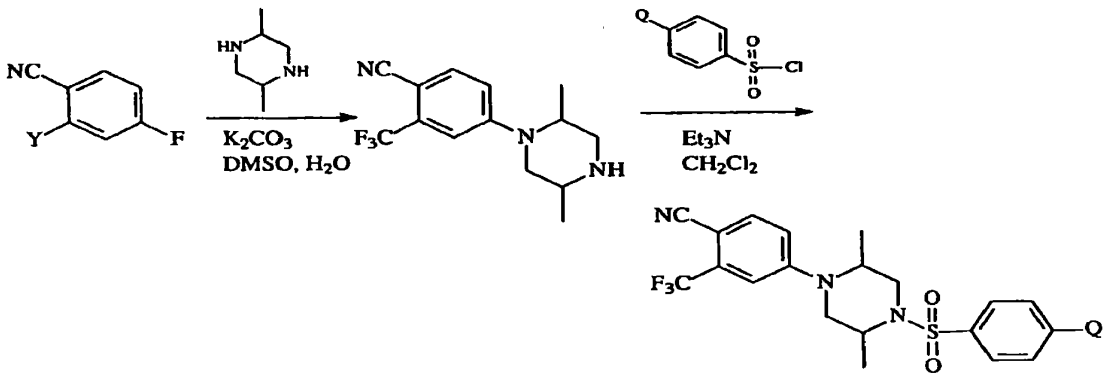


图1H



Q=CN, Y=CF_3(化合物XXIV)
Q=CN, Y=Cl(化合物XXV)
Q=Cl, Y=CN(化合物XXVI)
Q=CF_3, Y=Cl(化合物XXVII)
Q=CF_3, Y=CF_3(化合物XXVIII)

图1I

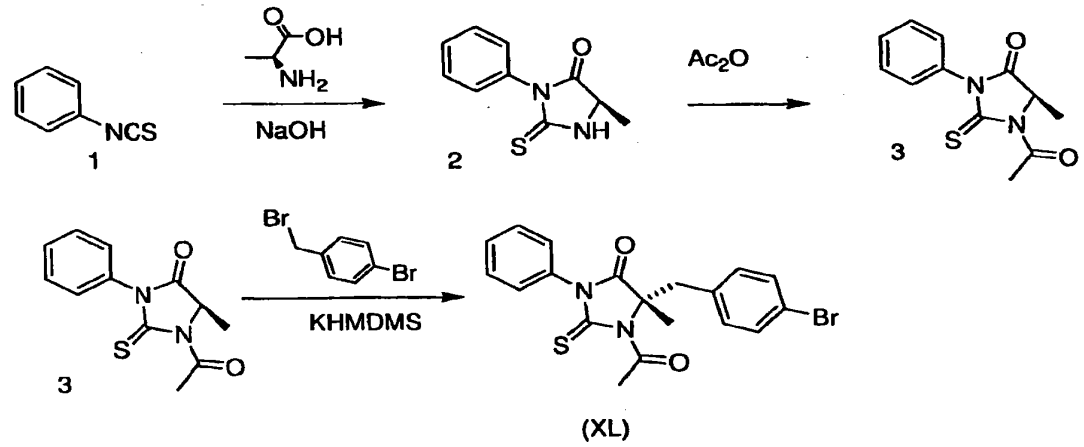


图1J

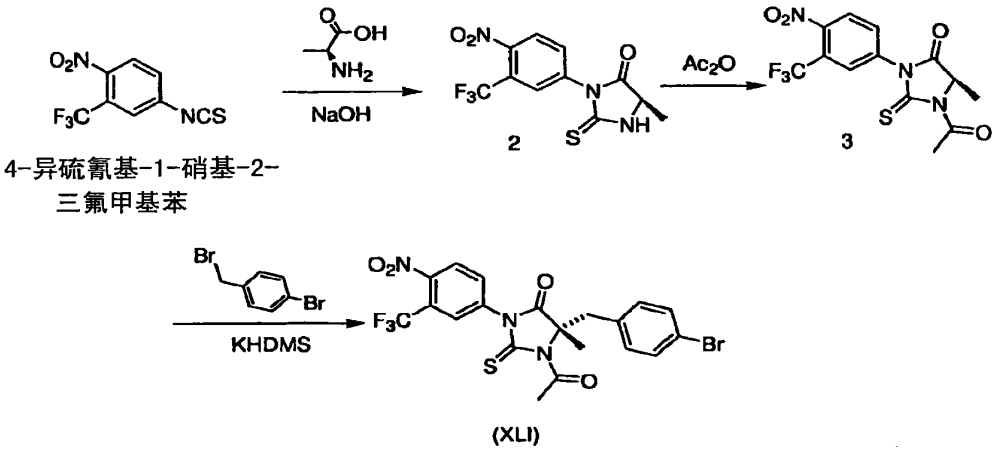
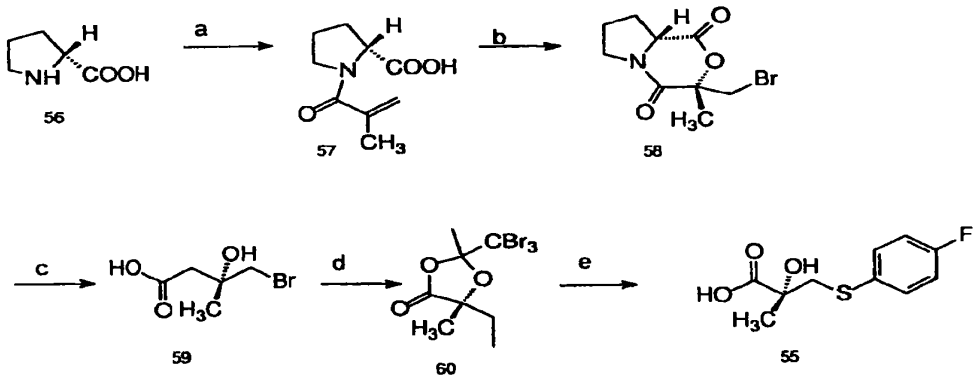
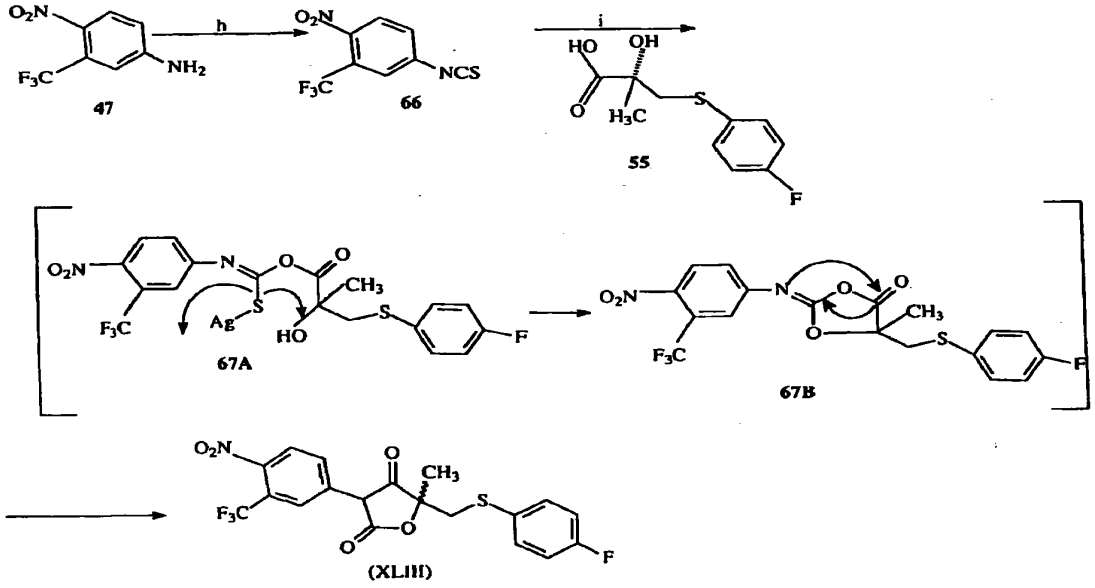


图1K



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、NaCO3， i-三氟乙酸银、三乙胺、乙腈。

图2

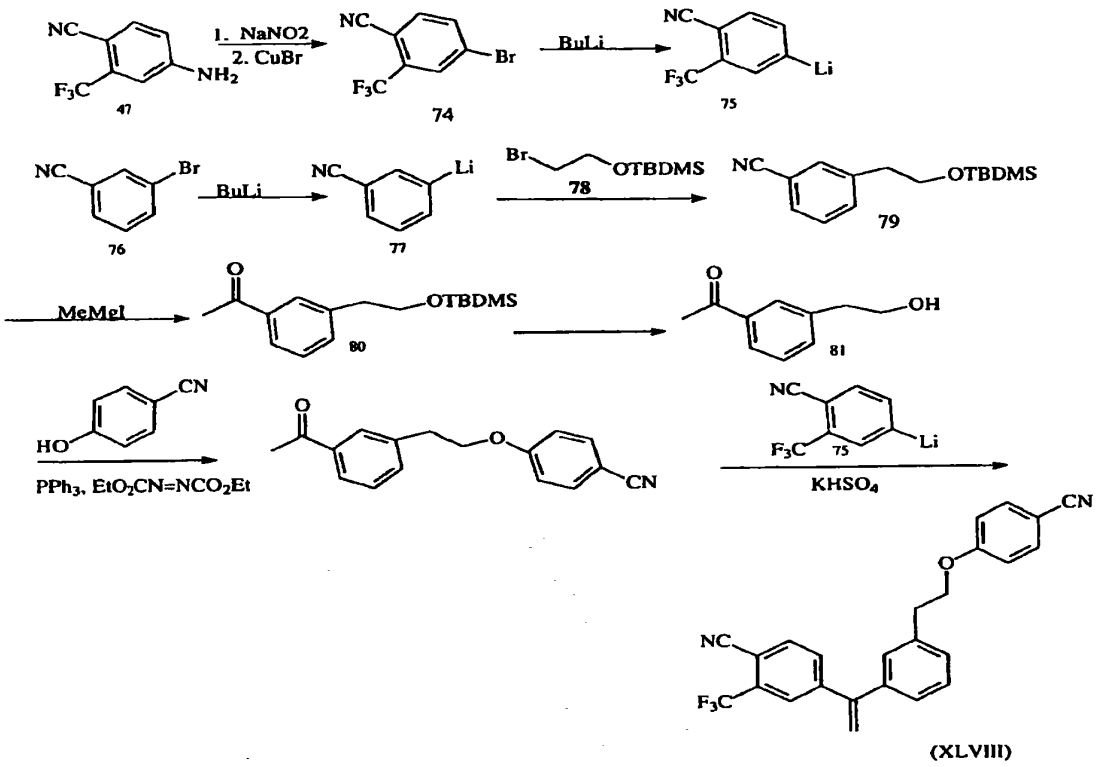

NC
F3C
NH2
47
1. NaNO2
2. CuBr
Br
74
BuLi
Li
75
76
77
78
OTBDMS
79
MeMgI
O
80
OH
81
HO
CN
PPh3, EtO2CN=NCO2Et
KHSO4
(XLVIII)

图3

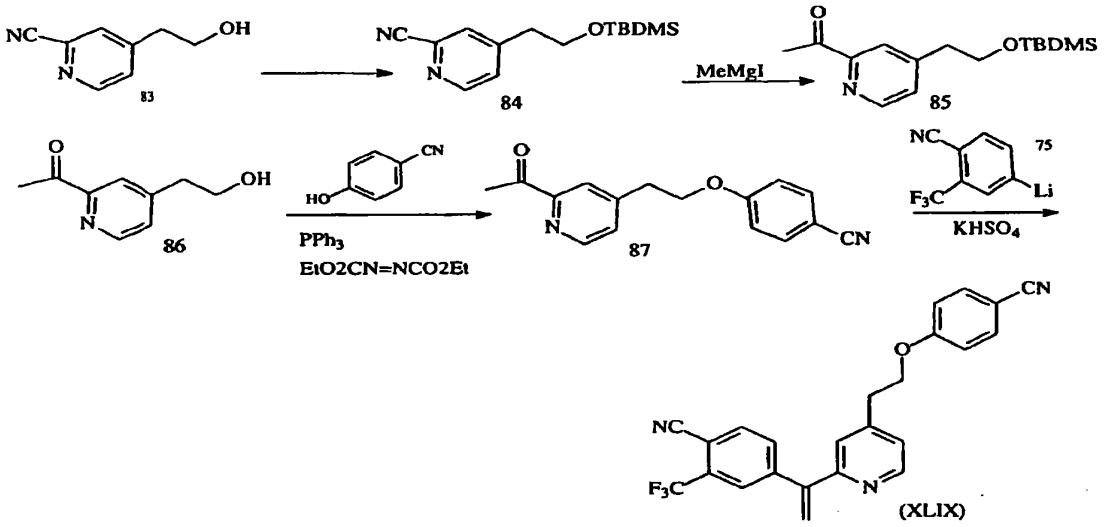

NC
OH
N
83
NC
OTBDMS
N
84
MeMgI
O
OTBDMS
N
85
O
OH
N
86
HO
CN
PPh3
EtO2CN=NCO2Et
O
O
N
CN
87
NC
75
F3C
Li
KHSO4
CN
O
NC
F3C
N
(XLIX)

图4

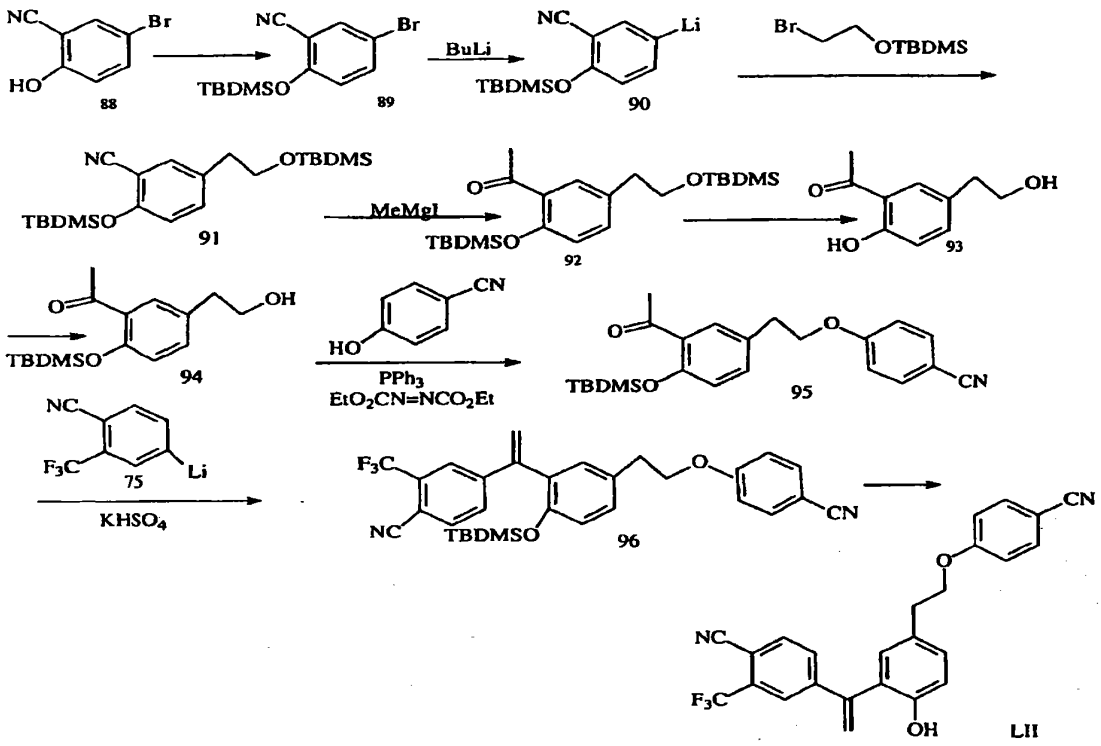

NC
Br
HO
88
TBDMSO
89
BuLi
Li
90
OTBDMS
91
MeMgI
92
OH
93
94
CN
PPh3
EtO2CN=NCO2Et
95
F3C
75
KHSO4
96
LII

图5

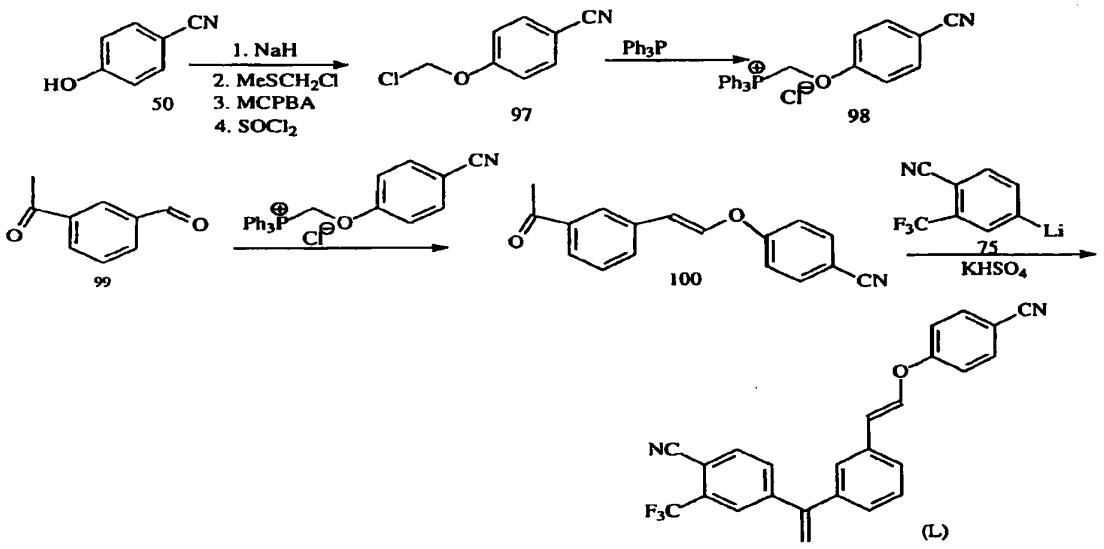

CN
HO
50
1. NaH
2. MeSCH2Cl
3. MCPBA
4. SOCl2
Cl
O
97
Ph3P
Ph3P
Cl
98
99
100
NC
F3C
Li
75
KHSO4
(L)

图6

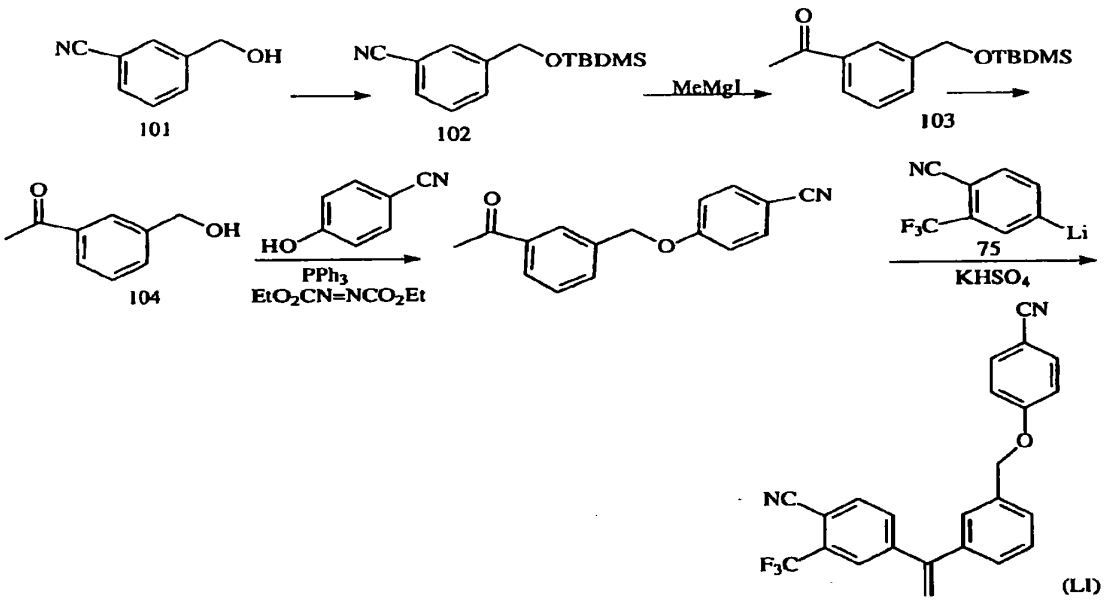

NC
OH
101
NC
OTBDMS
102
MeMgI
O
OTBDMS
103
O
OH
104
HO
CN
PPh3
EtO2CN=NCO2Et
O
CN
O
NC
F3C
Li
75
KHSO4
CN
O
NC
F3C
(LI)

图7

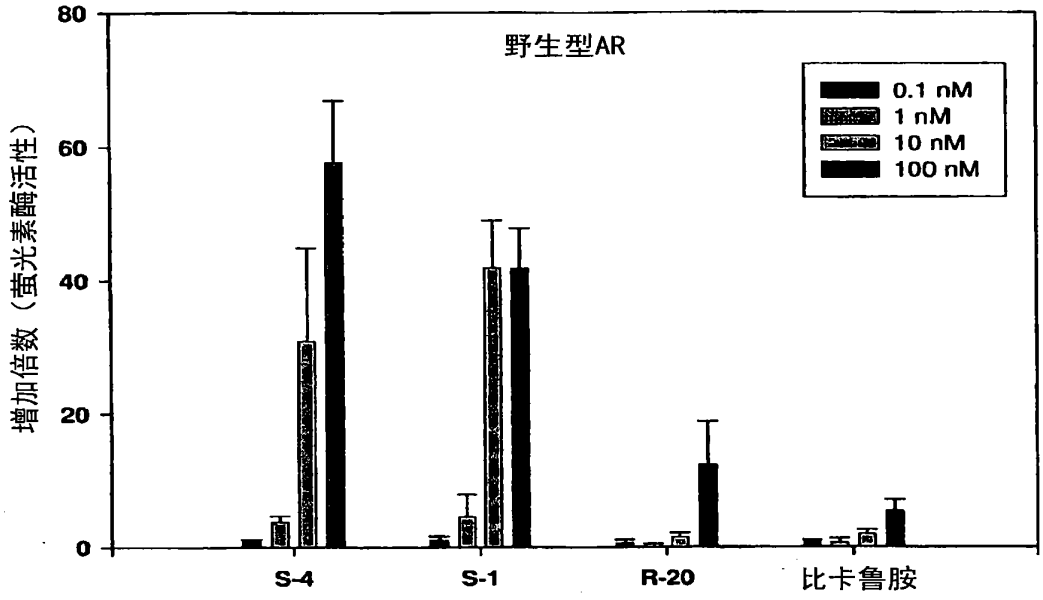

野生型AR
0.1 nM
1 nM
10 nM
100 nM
增加倍数（萤光素酶活性）
80
60
40
20
0
S-4
S-1
R-20
比卡鲁胺

图8

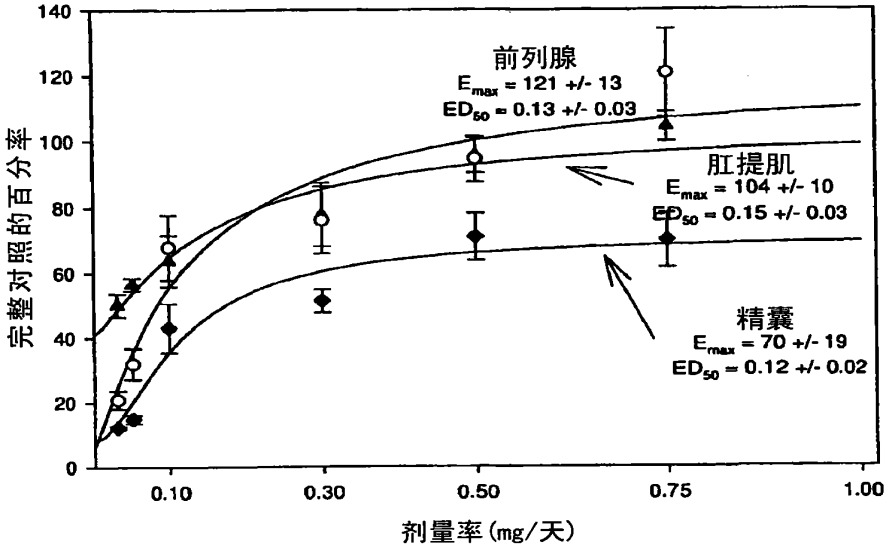

140
120
100
80
60
40
20
0
完整对照的百分率
前列腺
E_{max} = 121 +/- 13
ED_{50} = 0.13 +/- 0.03
肛提肌
E_{max} = 104 +/- 10
ED_{50} = 0.15 +/- 0.03
精囊
E_{max} = 70 +/- 19
ED_{50} = 0.12 +/- 0.02
0.10
0.30
0.50
0.75
1.00
剂量率(mg/天)

图9A

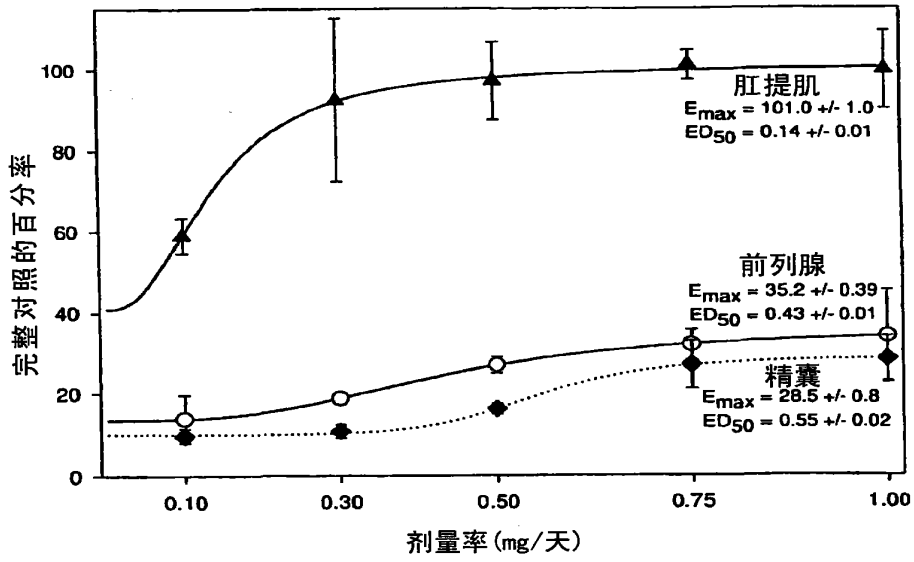

100
80
60
40
20
0
完整对照的百分率
肛提肌
E_{max} = 101.0 +/- 1.0
ED_{50} = 0.14 +/- 0.01
前列腺
E_{max} = 35.2 +/- 0.39
ED_{50} = 0.43 +/- 0.01
精囊
E_{max} = 28.5 +/- 0.8
ED_{50} = 0.55 +/- 0.02
0.10
0.30
0.50
0.75
1.00
剂量率(mg/天)

图9B

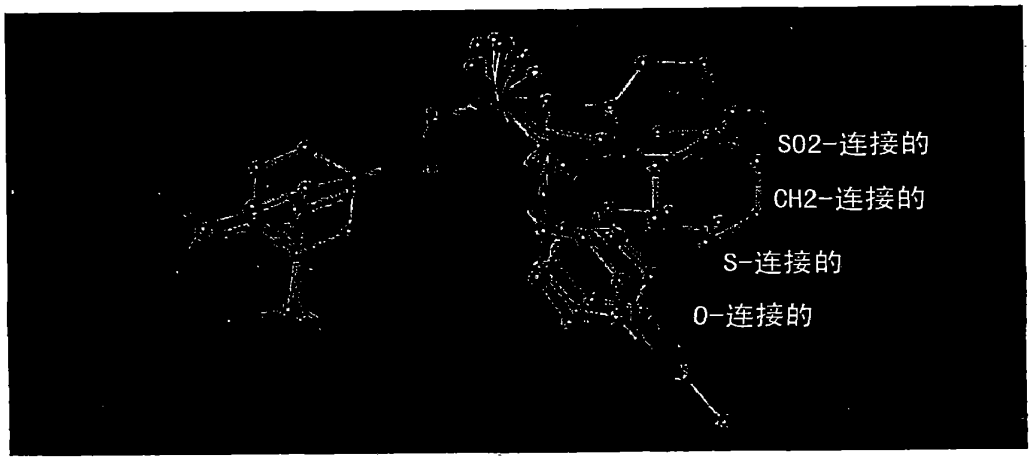


图10

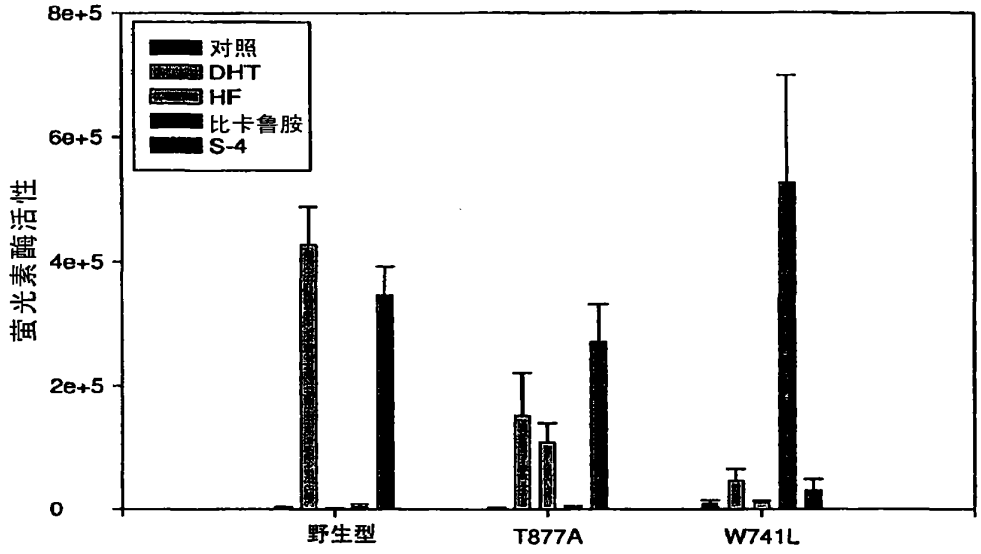


图11

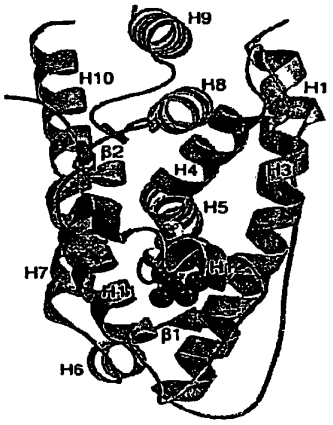

H9
H10
H8
H1
β2
H4
H3
H5
H7
β1
H6

图12A

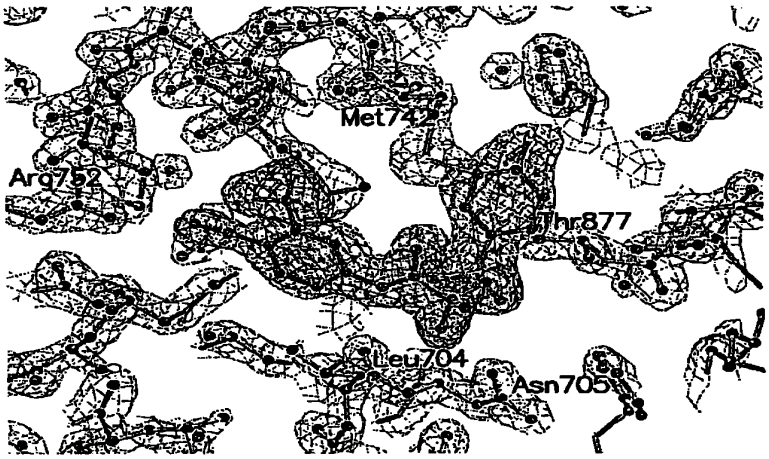

Met742
Arg752
Thr877
Leu704
Asn705

图12B

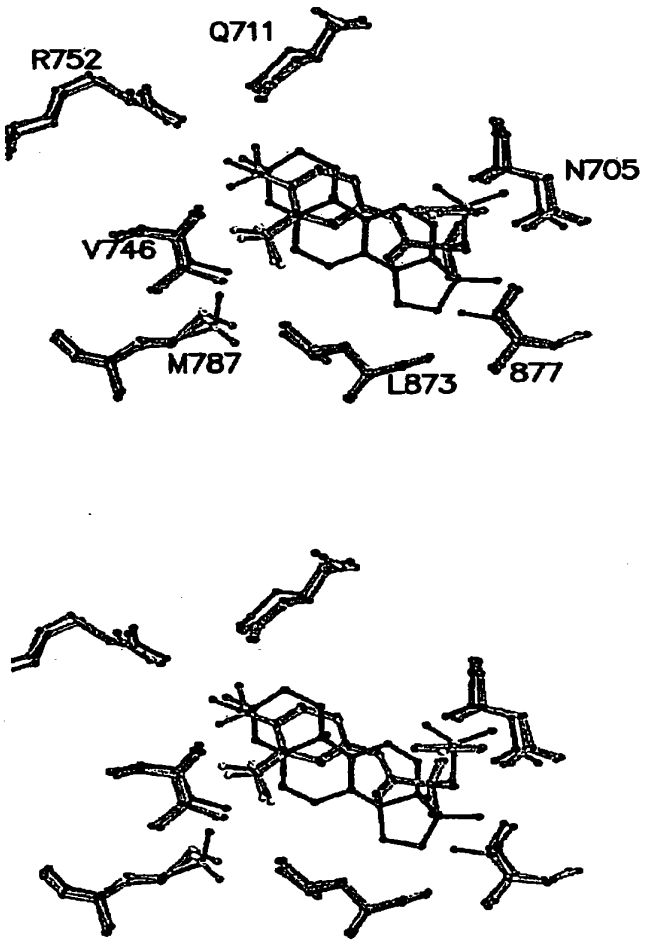


图13A

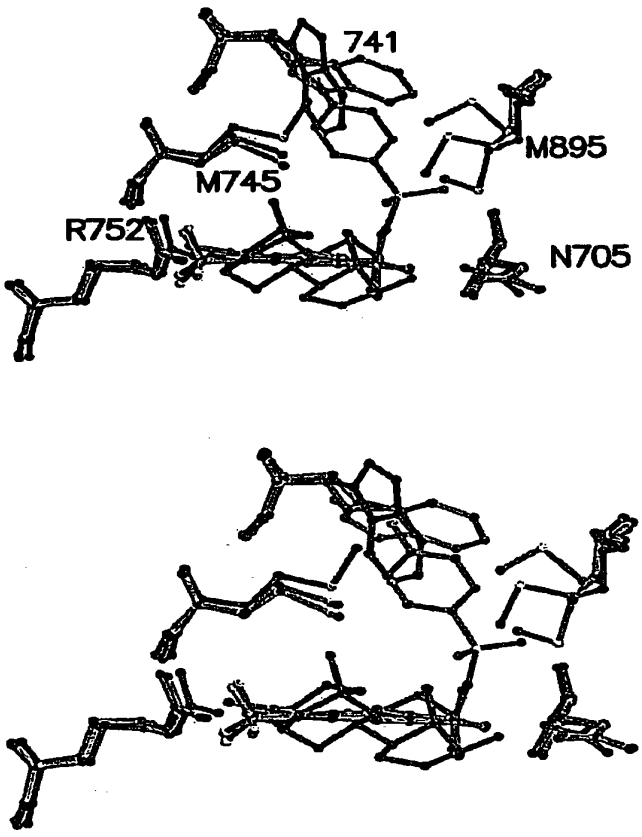


图13B

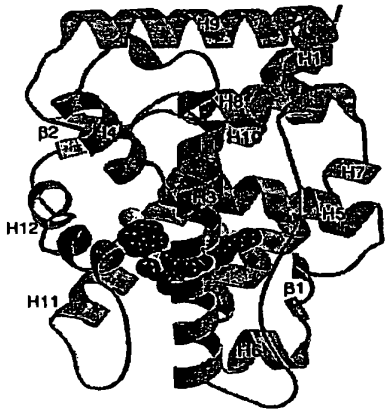

H9
H7
H6
H10
β2
H8
H7
H12
H5
H11
β1
H1

图14A

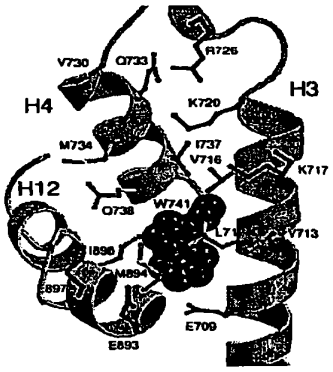

V730
Q733
R726
H4
H3
K720
M734
I737
V716
K717
H12
Q738
W741
L71
V713
I896
M894
S897
E709
E893

图14B

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, 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, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: METHODS AND COMPOSITIONS FOR TREATING POLYCYSTIC OVARY SYNDROME

(57) Abstract: Polycystic ovary syndrome (PCOS) is characterized by elevated levels of androgens, cysts in the ovaries, and irregular periods. Women with PCOS present with additional symptoms, including hirsutism, alopecia, acne, infertility, weight gain, fatigue, depression and mood changes. The present disclosure provides new compounds, salts, compositions and uses thereof in the treatment of PCOS due to elevated adrenal androgens. Further, the present disclosure provides methods for treating PCOS due to elevated adrenal androgens.

WO 2022/036123 A1

METHODS AND COMPOSITIONS FOR TREATING POLYCYSTIC OVARY SYNDROME

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/064,863, filed August 12, 2020; which is referenced herein in its entirety.

BACKGROUND

[0002] Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting an estimated 12% of reproductive aged women. Women with PCOS may have polycystic ovarian morphologic features, ovulatory dysfunction in the form of infrequent or prolonged menstrual periods, and hyperandrogenism in the form of excess male hormone levels. This complex disorder has both environmental influences, such as obesity and insulin resistance, and inappropriate endocrine signaling from the hypothalamus and pituitary glands as contributors. Hyperandrogenism presents clinically as hirsutism and acne and biochemically with elevated serum androgen levels. Androgen and androgen precursors can be produced and secreted by the ovaries and also by the adrenal cortices in about the same amount in response to stimulation by pituitary derived luteinizing hormone (LH) to the ovaries and adrenocorticotropic hormone (ACTH) to the adrenal gland, respectively. Emerging data indicate that PCOS patients can be categorized according to whether the source of excessive androgen is primarily from the ovaries, namely, functional ovarian hyperandrogenism (FOH), or the adrenal glands, namely, functional adrenal hyperandrogenism (FAH), both (FOH and FAH), or neither and attributable to either insulin resistance /obesity or of unknown origin. A majority or about two-thirds of cases have functionally typical PCOS (PCOS-T) that is due to typical FOH, characterized by hyperresponsiveness of 17-hydroxyprogesterone (17-OHP). About one fifth of cases have functionally atypical FOH (PCOS-A), lacking 17-OHP hyperresponsiveness. Within these two FOH populations, about one-third may have both FOH and FAH. About 8% of PCOS cases are attributed to either obesity and the remainder are unknown or idiopathic in nature. Only about 3-5% PCOS cases are due to isolated FAH with androgen responsiveness to ACTH.

SUMMARY

[0003] Adrenal androgen excess in PCOS appears to occur independently of ovarian androgen excess, suggesting it may represent an intrinsic, and possible primary source of abnormal synthesis of adrenal androgens. Adrenal androgen excess of PCOS may not result from deficiencies in specific enzymatic steps, rather it may represent an altered pituitary responsivity to corticotropin releasing factor (CRF) and adrenocorticotropic hormone (ACTH).

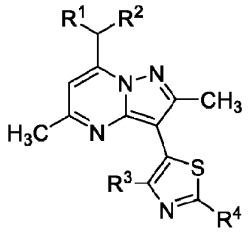
[0004] In an aspect, the present disclosure provides methods for treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

[0005] In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

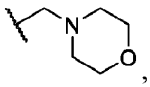
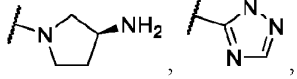
[0006] In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome (PCOS) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

[0007] In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome (PCOS) in a subject in need thereof, comprising accessing a source of excessive androgen; and administering a CRF1 antagonist or pharmaceutically acceptable salt thereof. In some embodiments, the cosyntropin is administered at a dose about 1 $\mu g/m^2$. In some embodiments, the cosyntropin is administered at a dose about 10 $\mu g/m^2$. In some embodiments, the cosyntropin is administered at a dose about 250 $\mu g/m^2$. In some embodiments, the source of excessive androgen is adrenal glands. In some embodiments, the source of excessive androgen is ovaries.

[0008] In some embodiments, the CRF_1 antagonist is a compound of Formula (I):

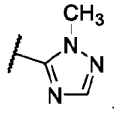


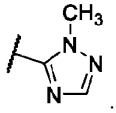
Formula (I)

or a pharmaceutically acceptable salt thereof, wherein: R^1 and R^2 are independently ethyl or *n*-propyl; R^3 is hydrogen, F, Cl, Br, methyl, trifluoromethyl, or methoxy; R^4 is hydrogen, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ; R^a and R^b are independently hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

[0009] In some embodiments, R^3 is F, Cl, Br, methyl, or trifluoromethyl.

[0010] In some embodiments, R^3 is Cl or Br.

[0011] In some embodiments, R^4 is $-NR^aR^b$, pyridin-4-yl, morpholin-4-yl, or  .

[0012] In some embodiments, R^4 is morpholin-4-yl or  .

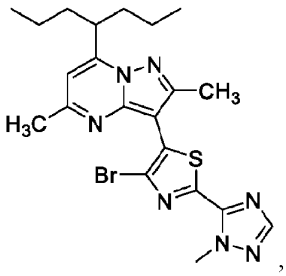
[0013] In some embodiments, R^4 is $-NR^aR^b$, and R^a and R^b are independently C_1-C_3alkyl.

[0014] In some embodiments, the CRF_1 antagonist or a pharmaceutically acceptable salt thereof is 3-[4-bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)- pyrazolo[1,5-*a*]pyrimidine.

[0015] In some embodiments, the CRF_1 antagonist or a pharmaceutically acceptable salt thereof 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.

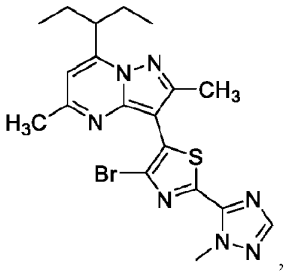
[0016] In some embodiments, the CRF_1 antagonist or a pharmaceutically acceptable salt thereof is 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.

[0017] In some embodiments, the CRF_1 antagonist is



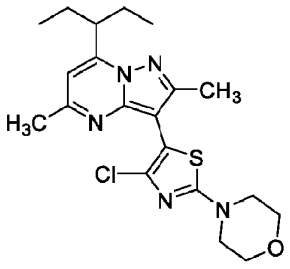
, or a pharmaceutically acceptable salt thereof.

[0018] In some embodiments, the CRF_1 antagonist is



, or a pharmaceutically acceptable salt thereof.

[0019] In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0020] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, CP-154,526, CP-376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SSR125543 (crinecerfont), and SN003.

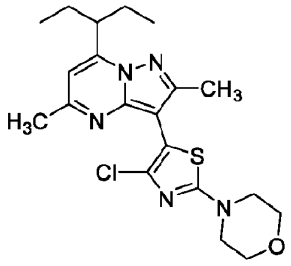
[0021] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 5 mg to about 400 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 300 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 75 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

[0022] In some embodiments, an adrenocorticotropic hormone (ACTH) level is reduced by at least 5% from baseline. In some embodiments, an adrenocorticotropic hormone (ACTH) level is reduced by at least 10% from baseline. In some embodiments, a dehydroepiandrosterone sulfate (DHEAS) level is reduced by at least 5% from baseline. In some embodiments, a dehydroepiandrosterone sulfate (DHEAS) level is reduced by at least 10% from baseline. In some embodiments, the androstenedione (A4) level is reduced by at least 5% from baseline. In some embodiments, the androstenedione (A4) level is reduced by at least 10% from baseline. In some embodiments, the 1β-hydroxyandrostenedione (11OHA4) level is reduced by at least 5%

from baseline. In some embodiments, the 1β-hydroxyandrostenedione (11OHA4) level is reduced by at least 10% from baseline. In some embodiments, the 11β-hydroxytestosterone (11OHT) level is reduced by at least 5% from baseline. In some embodiments, the 11β-hydroxytestosterone (11OHT) level is reduced by at least 10% from baseline.

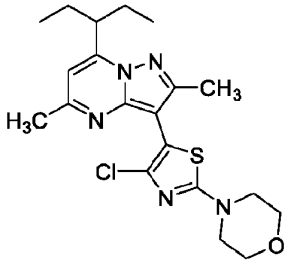
[0023] In some embodiments, a reduced ACTH, DHEAS, A4, 11OHA4 or 11OHT level from baseline is maintained for at least 24 hours. In some embodiments, a reduced ACTH, DHEAS, A4, 11OHA4 or 11OHT level from baseline is maintained for at least 4 weeks.

[0024] In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 3:



; or a pharmaceutically acceptable salt or solvate thereof.

[0025] In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH+FAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 3:



; or a pharmaceutically acceptable salt or solvate thereof.

[0026] In some embodiments, the Compound 3 is administered at a dose between about 1 mg/day and about 400 mg/day.

[0027] In some embodiments, the pharmaceutical composition comprises about 25 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 75 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments,

the pharmaceutical composition comprises about 200 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 300 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

[0028] In some embodiments, the pharmaceutical composition is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm to about 20 μm. In some embodiments, the average size of the microparticles is between about 5 μm to about 15 μm. In some embodiments, the average size of the microparticles is less than about 10 μm.

[0029] In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule.

[0030] In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof. In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

[0031] In some embodiments, the subject is a pediatric patient. In some embodiments, the subject is from about 9 years old to about 18 years old. In some embodiments, the subject is from about 8 years of age to about 55 years of age. In some embodiments, the subject is an adult patient.

[0032] In some embodiments, the subject is treated for a period of about 2 weeks to about 36 weeks. In some embodiments, the subject is treated for a period of about 1 month to 12 months. In some embodiments, the subject is treated for a period of about 10 months to 50 years.

[0033] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0034] 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. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

DETAILED DESCRIPTION

[0035] While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

Polycystic Ovary Syndrome (PCOS)

[0036] Polycystic ovarian syndrome (PCOS) is a heterogeneous disorder with multiple phenotypes and is one of the most common endocrine metabolic disorders in reproductive aged women. PCOS was first diagnosed and described as a syndrome of oligo-amenorrhea and polycystic ovaries that was variably accompanied by hirsutism, acne, and obesity. There are various diagnostic criteria for adolescent and adult patients considering the core diagnostic features, such as hyperandrogenism, persistent ovulatory dysfunction, and polycystic ovarian morphology (PCOM). The exact etiology of this disorder is not entirely clear, however, both genetic and environmental factors seem to play roles in causing the disorder. Generally, PCOS presents as a phenotype reflecting a self-perpetuating vicious cycle involving neuroendocrine, metabolic, and ovarian dysfunction and is characterized by excessive ovarian and/or adrenal androgen secretion. For example, intrinsic ovarian factors such as altered steroidogenesis and factors external to the ovary such as hyperinsulinemia contribute to the excessive ovarian androgen production. The classic ovarian phenotype of enlarged ovaries with string-of-pearl morphology and theca interstitial hyperplasia reflects androgen exposure; this morphology has also been observed in women with congenital adrenal hyperplasia (CAH).

[0037] In order to attempt to understand the pathophysiology of PCOS, it is important to understand the molecular basis of steroidogenesis and androgen source, production and physiology. Under normal circumstances in women, the ovaries and adrenal glands contribute about equally to testosterone production. Approximately half of testosterone originates from direct testosterone secretion by the ovaries and adrenal glands, whereas half is produced by

peripheral conversion of circulating androstenedione, which itself arises from approximately equal ovarian and adrenal secretion. Androgen production is not under direct negative feedback regulation by the neuroendocrine system in females, as is the case for estradiol and cortisol secretion. Androgens are secreted by both the ovaries and adrenal glands in response to their respective tropic hormones, LH and ACTH. The zona reticularis of the adrenal gland resembles the theca cell compartment of the ovary in its expression of the core enzymatic pattern for androgen production.

[0038] PCOS patients can be functionally categorized as distinct subtypes based on the source of androgen excess listed in Table 1 below. Androgen excess can be derived from the ovaries, the adrenal glands, both, or neither. Primary PCOS is the most common variety of PCOS without any known cause and a proposed theory suggests that functional ovarian hyperandrogenism (FOH) along with disturbance of hypothalamo-pituitary-ovarian (HPO) axis function may be the underlying cause. Further, functional adrenal hyperandrogenism (FAH) other than HPO axis disturbance may be explained for a certain population of PCOS patients. The PCOS patients with primary FAH may experience an average 50% increase in adrenal volume that correlates with hyperandrogenemia severity.

[0039] Table 1 Functional classification of PCOS based on source of androgen excess

PCOS Functional Type	Source of Androgen	GnRHag Test 17OHP Response	DAST Testosterone Response	ACTH test DHEA Response	Prevalence Among PCOS
PCOS-T	Primary FOH (typical FOH)	High*	High in 92.5%	High in 28% (associated FAH)	67%*
PCOS-A	Primary FOH (atypical FOH)	Normal*	High	High in 30% (associated FAH)	20%
	Primary FAH (isolated FAH)	Normal	Normal	High	5%
	PCOS without FOH or FAH (PCOS-A of obesity or idiopathic PCOS-A)	Normal	Normal	Normal	8%

[0040] Test procedures to determine the source of androgen are listed below in Table 2. The ovarian hyperandrogenism of PCOS is demonstrated directly by the GnRHag test or the hCG test and in combination with the dexamethasone androgen-suppression test (DAST). The GnRHag test determines the coordinated function of the ovarian follicle. Leuprolide acetate 10 µg/kg sc (or a comparable dose of any other short-acting GnRHag) stimulates endogenous LH and FSH release that peaks at 3–4 hours and persists for 24 hours; this in turn stimulates increased secretion of sex steroids and their precursors, with serum levels peaking at 18–24 hours. In the absence of evidence of a steroidogenic block, an elevated 17OHP response is typical of PCOS. Ovarian steroidogenic enzyme deficiency, which is rare, can be detected by an abnormal pattern of steroid intermediates in response to the test. hCG is an LH analog: 5000 IU intramuscularly stimulates steroidogenic responses comparable with those of a GnRHag test at 24 hours. DAST indirectly tests for ovarian source of androgens by suppressing ACTH-dependent androgen production of androgens. In the presence of normal adrenocortical

suppression an inappropriately elevated serum testosterone post-DAST indicates an ACTH-independent source of androgen, which is ordinarily of ovarian origin.

[0041] Adrenal hyperandrogenism may be demonstrated by a rapid ACTH test: cosyntropin is administered iv and peak steroid responses occur at 15–60 minutes. An elevated DHEA post this test indicates an ACTH-dependent source of androgen, which is ordinarily of adrenal origin. The test may be performed using cosyntropin 250 μg, this is a supramaximal dose. Lower doses of cosyntropin may be used (10 μg/m2) which elicit a similar peak response. A low-dose ACTH test (1.0-μg cosyntropin) may be used and may be more physiologic. It usually elicits nearly as great a peak response that promptly wanes, and in PCOS, does not elicit such a wide spectrum of elevated steroid intermediates as do larger doses.

[0042] Table 2 Methods to determine source of female androgen excess

Test	Rationale	Method	Outcome Measures	Interpretation*
GnRHag	Endogenous LH and FSH release stimulates coordinated function of ovarian follicles	Leuprolide acetate 30 μg/kg sc (for maximum stimulation)	Ovarian steroid secretion peaks at 20–24 h	17OHP >152 ng/dL without steroidogenic block indicates typical FOH (PCOS-T)
hCG	Exogenous administration of LH analog stimulates theca-interstitial cells	hCG 3000 IU/m^2 (for maximum stimulation)	Ovarian steroid secretion peaks at 24 h	17OHP >152 ng/dL without steroidogenic block indicates typical FOH (PCOS-T)
LDAST	Long DAST: dexamethasone profoundly suppresses adrenal androgens over several days	Dexamethasone 0.5 mg OID per os × 4–5 d	Free testosterone, DHEAS, cortisol; sample early morning d 5	Free testosterone ≥8 pg/mL with DHEAS <70 and cortisol <1 μg/dL characteristic of FOH
SDAST	Short DAST: dexamethasone rapidly suppresses adrenal testosterone and cortisol	Dexamethasone 0.25 mg/m^2 per os at 12 noon	Total testosterone, cortisol, sample 4 PM (4 h)	Total testosterone >26 ng/mL, cortisol <5 μg/dL suggests FOH
ACTH	Exogenous ACTH stimulates adrenal steroidogenesis	Cosyntropin ≥10 μg/m^2 (for maximum stimulation)	DHEA,17OHP, steroid intermediates, cortisol peak at 30–60 min	DHEA 1500–3000 μg/dL without steroidogenic block indicates FAH

Corticotropin releasing factor

[0043] Currently, no single universal treatment for PCOS is available. As a result, current treatments tend to be individualized and adapted to the actual needs of the individual patient. Furthermore, treatment may be symptom-oriented. For example, targets for pharmacological treatment may include androgen excess. For PCOS patients with elevated adrenal androgens, FOH+FAH and PCOS-FAH patients, in some embodiments, pharmacological treatment, such as corticotropin releasing factor (CRF) receptor antagonist targeting ACTH production may be used.

[0044] 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.

[0045] 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 (CAH), 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.

[0046] CRF is believed to be the major physiological regulator of the basal and stress-induced release of adrenocorticotropic hormone ("ACTH"), β-endorphin, and other proopiomelanocortin ("POMC")-derived peptides from the anterior pituitary. Secretion of CRF causes release of ACTH from corticotrophs in the anterior pituitary via binding to the CRF_1 receptor, a member of the class B family of G-protein coupled receptors.

[0047] Due to the physiological significance of CRF_1, the development of biologically-active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF_1 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, and congenital adrenal hyperplasia.

[0048] 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. The middle layer, the zona reticularis is responsible for the production of androgens such as DHEA, DHEAS and androstenedione, (A4) the precursor to testosterone (T) and dihydrotestosterone (DHT). This layer is also responsible for the production of the 11-oxyandrogens, 11β-hydroxyandrostenedione (11OHA4) and 11β-hydroxytestosterone (11OHT), which are major bioactive androgens, particularly in women. Due to an unknown cause in PCOS patients with elevated androgens, the zone reticularis displays a hyperresponsiveness to ACTH resulting excessive levels of DHEA, DHEAS, 11OHA4, 11OHT and A4. The excessive ACTH stimulation causes hypertrophy of the zona reticularis resulting in

adrenal hyperplasia and clinically manifests with physical features typical of PCOS and hyperandrogenism. Reducing the stimulatory effect on the pituitary's ACTH secretion by inhibiting the CRF1 receptor is expected is reduce excessive androgen synthesis from the ACTH responsive zone of the adrenal gland in PCOS. The normalization of elevated androgen levels in the short term would be expected to ameliorate cardinal features of PCOS - hirsutism, acne and menstrual irregularities – over the long term.

Certain Definitions

[0049] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

[0050] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

[0051] The term "about" is used to indicate that a value includes 10% level of error for the device or method being employed to determine the value.

[0052] The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to "and/or."

[0053] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, and preferably having from one to five carbon atoms (i.e. C_1-C_5alkyl). In some embodiments, an alkyl comprises one to four carbon atoms (i.e., C_1-C_4alkyl).). In some embodiments, an alkyl comprises one to three carbon atoms (i.e., C_1-C_3alkyl).). In some embodiments, an alkyl comprises one to two carbon atoms (i.e., C_1-C_2alkyl). In some embodiments, an alkyl comprises one carbon atom (i.e., C_1alkyl). In certain embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (iso-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (sec-butyl), 2-methylpropyl (isobutyl), 1,1-dimethylethyl (tert-butyl), or 1-pentyl (n-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more substituents such as those described herein.

[0054] The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises,"

"has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

[0055] "Administering" when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. "Administering" a pharmaceutical composition may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

[0056] By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

[0057] The term "pharmaceutical composition" means a composition comprising at least one active ingredient, such as a steroid or a pharmaceutically acceptable salt thereof or a CRF_1 antagonist or a pharmaceutically acceptable salt thereof, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

[0058] The term "supraphysiologic amount" describes glucocorticoid dose levels that are above the daily glucocorticoid requirement (production rate) found in healthy individuals.

[0059] The term "physiologic amount" describes glucocorticoid dose levels that meet the daily glucocorticoid requirement (production rate) found in healthy individuals.

[0060] The term "hydrocortisone equivalents" as used herein is understood by a person skilled in the art to be the conversion calculations needed to be considered when substituting one glucocorticoid for another as the potency and duration of action of various glucocorticoids may vary. Hence, the term "hydrocortisone equivalents" is the standard used for comparison of glucocorticoid potency.

[0061] A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the

pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

[0062] The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

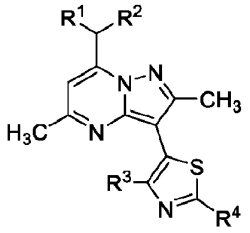
Compounds

[0063] Disclosed herein are CRF_1 antagonists or pharmaceutically acceptable salt thereof such as Antalarmin hydrochloride, CP-154,526, CP-376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003, and SSR125543 (crinecerfont).

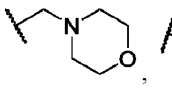
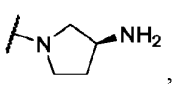
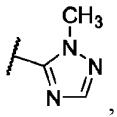
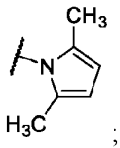
[0064] In one aspect, the CRF_1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: *n*-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine hydrochloride (Antalarmin hydrochloride), *n*-butyl-N-ethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine hydrochloride (Pfizer CP154526), N-(1-Ethylpropyl)-3,6-dimethyl-2-(2,4,6-trimethylphenox y)-4-pyridinamine hydrochloride (Pfizer CP376395 hydrochloride), 5-Chloro-N-(cyclopropylmethyl)-2-methyl-*n*-propyl-N'-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride (NBI27914 hydrochloride), (7S)-6-(Cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-ethyl-7,8-dihydro-4-methyl-6H-1,3,6,8a-tetraazaacenaphthylene hydrochloride (NBI35965 hydrochloride), N-(1-Ethylpropyl)-3-methoxy-5-[2-methoxy-4-

(trifluoromethoxy)phenyl]-6-methyl-2-pyrazinamine hydrochloride (NGD 98-2 hydrochloride), 8-(6-Methoxy-2-methyl-3-pyridinyl)-2,7-dimethyl-N-[(1R)-1-methylpropyl]pyrazolo[1,5-a]-1,3,5-triazin-4-amine (Pexacerfont), 3-[6-(Dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo[1,5-a]pyrimidin-7-amine hydrochloride (R 121919 hydrochloride), and N-(4-Methoxy-2-methylphenyl)-1-[1-(methoxymethyl)propyl]-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridine-4-amine (SN003), (S)-4-(2-chloro-4-methoxy-5-methylphenyl)-N-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-(prop-2-yn-1-yl)thiazol-2-amine (SSR125543).

[0065] Disclosed herein is a compound of Formula (I):



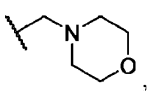
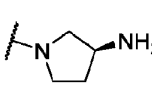
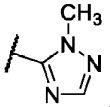
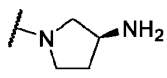
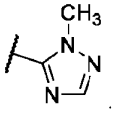
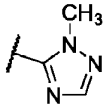
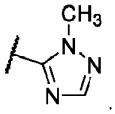
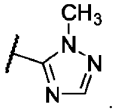
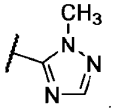
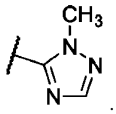
Formula (I)

or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are independently ethyl or *n*-propyl; R^3 is H, Cl, Br, methyl, trifluoromethyl, or methoxy; R^4 is H, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and

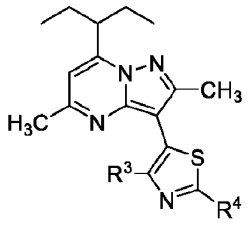
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

[0066] In some embodiments, R^1 and R^2 are independently ethyl or *n*-propyl. In some embodiments, R^1 is ethyl and R^2 is *n*-propyl. In some embodiments, R^1 is *n*-propyl and R^2 is ethyl. In some embodiments, R^1 and R^2 are both ethyl. In some embodiments, R^1 and R^2 are both *n*-propyl.

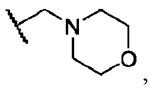
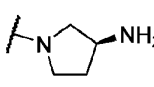
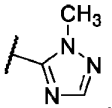
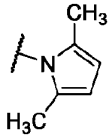
[0067] In some embodiments, R^3 is hydrogen, Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is hydrogen, Cl, Br, or methyl. In some embodiments, R^3 is hydrogen, Cl, or Br. In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is Cl. In some embodiments, R^3 is Br.

[0068] In some embodiments, R^4 is hydrogen, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  , or  . In some embodiments, R^4 is Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  , or  . In some embodiments, R^4 is $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is $-NR^aR^b$, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is $-NR^aR^b$,pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is morpholin-4-yl or  . In some embodiments, R^4 is morpholin-4-yl. In some embodiments, R^4 is  . In some embodiments, R^4 is $-NR^aR^b$ and R^a and R^b are independently C_1-C_3alkyl.

[0069] Disclosed herein is a compound of Formula (II):

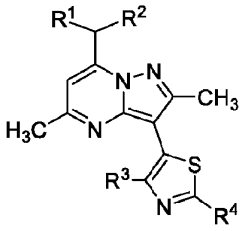


Formula (II)

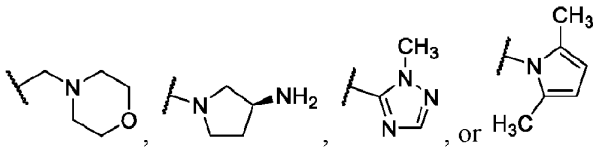
or a pharmaceutically acceptable salt thereof, wherein R^3 is H, Cl, Br, methyl, trifluoromethyl, or methoxy; R^4 is H, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and R^a and R^b are independently

hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$–$CH_2CH_2NHCH_2CH_2CH_3$.

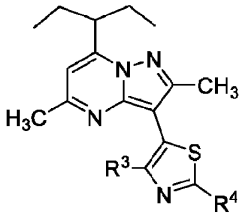
[0070] Disclosed herein is a compound of Formula (III):



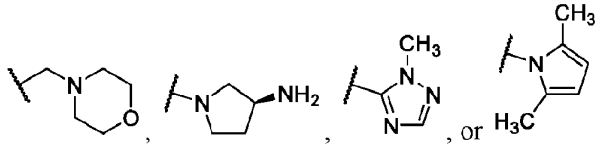
Formula (III)

or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are *n*-propyl; R^3 is H, Cl, Br, methyl, trifluoromethyl, or methoxy; R^4 is H, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ; and R^a and R^b are independently hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

[0071] Disclosed herein is a compound of Formula (IV):

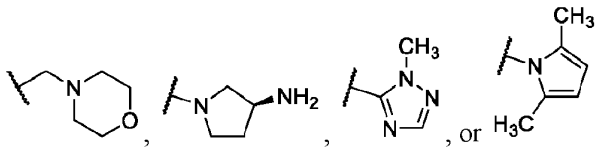
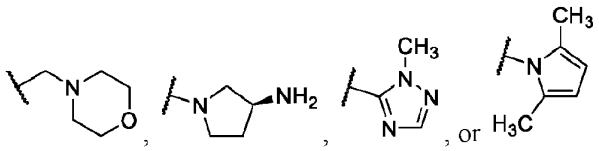
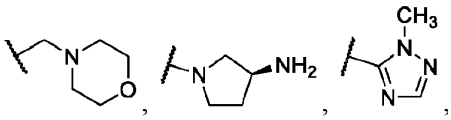
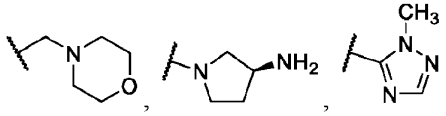
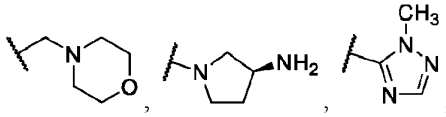


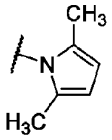
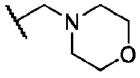
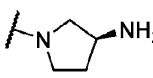
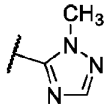
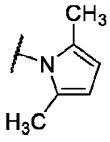
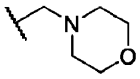
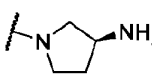
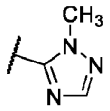
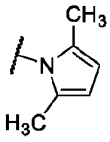
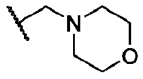
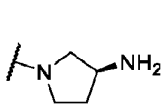
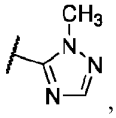
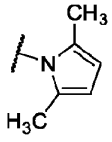
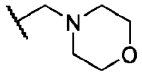
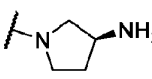
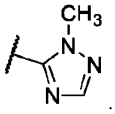
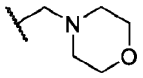
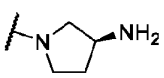
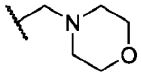
Formula IV

or a pharmaceutically acceptable salt thereof, wherein R^3 is Cl, Br, methyl, trifluoromethyl, or methoxy; R^4 is H, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ; and R^a and R^b are independently hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

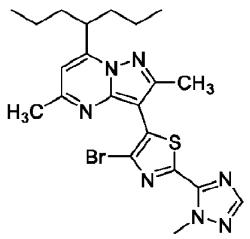
[0072] For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^3 may be hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^3 may be Cl, Br, methyl, trifluoromethyl, or methoxy. For a compound or pharmaceutically acceptable salt of Formula

(I), (II), (III), and (IV), R^3 may be Cl, Br, methyl, or trifluoromethyl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^3 may be Cl, Br, or methyl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^3 may be Cl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^3 may be Br. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^3 may be methyl.

[0073] For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is Br, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is Br, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is Br, acetamido, pyridin-4-yl, morpholin-4-yl,  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is Br, pyridin-4-yl, morpholin-4-yl,  .

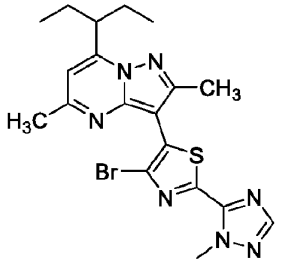

. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is morpholin-4-yl,  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is morpholin-4-yl.

[0074] Disclosed herein 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 (Compound 1) or a pharmaceutically acceptable salt thereof:



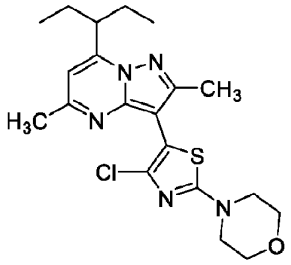
Compound 1.

[0075] Disclosed herein 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 (Compound 2) or a pharmaceutically acceptable salt thereof:



Compound 2.

[0076] Disclosed herein is 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine (or alternatively 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine) (Compound 3) or a pharmaceutically acceptable salt thereof:



Compound 3.

[0077] In some embodiments, 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine is referred to as Compound 3. In some embodiments, 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine is referred to as Compound 3.

[0078] In one aspect, the CRF_1 antagonist or pharmaceutically acceptable salt thereof may be an astressin. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

Pharmaceutical Compositions

[0079] Disclosed herein are pharmaceutical compositions comprising a compound or pharmaceutically acceptable salt described herein. In certain embodiments, the composition comprises a steroid or a pharmaceutically acceptable salt thereof and a CRF_1 antagonist or pharmaceutically acceptable salt thereof as disclosed above. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is exogenous glucocorticoids (GC) or a pharmaceutically acceptable salt thereof.

Dosage Form

[0080] In some embodiments, the pharmaceutical compositions described herein are provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a compound or pharmaceutically acceptable salt described herein that is suitable for administration to an animal, preferably mammal, subject in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. 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.

[0081] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[0082] 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

[0083] In some embodiments, the pharmaceutical composition is formulated as a 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.

[0084] 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 according to 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.

[0085] In some embodiments, the capsule comprises one or more pharmaceutically acceptable excipients. In some embodiments, the capsule is free of additional excipients.

[0086] In some embodiments, a capsule is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the capsule has a dose strength of up to 200 mg. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus II.

Tablet

[0087] Poorly soluble drugs may be difficult to formulate using standard technologies such as high shear wet granulation. Optimum delivery of poorly soluble drugs may require complex technologies such as solid solutions amorphous dispersions (hot melt extrusion or spray drying), nano-formulations or lipid-based formulations. Hydrophobic drug substances may be considered poorly soluble according to USP criteria and may be known to be difficult to granulate with water and other excipients. This is likely due to most known excipients for

immediate release formulations being water soluble or water-swellable. Making a tablet of a high dose drug substance that is poorly soluble may require a high concentration of the drug substance. However, as the drug concentration is increased above a certain level, formation of granules may become more and more difficult. Furthermore, at a certain drug load, it may become impossible.

[0088] In some embodiments, the pharmaceutical composition is formulated as a tablet.

[0089] In some embodiments, the tablet is made by compression, molding, or extrusion, optionally with one or more pharmaceutically acceptable excipient. In some embodiments, compressed tablets are prepared by compressing a compound or pharmaceutically acceptable salt described herein in a free-flowing form, optionally mixed with pharmaceutically acceptable excipients. In some embodiments, molded tablets are made by molding a mixture of the powdered a compound or pharmaceutically acceptable salt described herein, moistened with an inert liquid diluent. In some embodiments, the tablet is prepared by hot-melt extrusion. In some embodiments, extruded tablets are made by forcing a mixture comprising a compound or pharmaceutically acceptable salt described herein, through an orifice or die under controlled conditions. In some embodiments, the tablet is coated or scored. In some embodiments, the tablet is formulated so as to provide slow or controlled release of a compound or pharmaceutically acceptable salt described herein. In some embodiments, a tablet is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the tablet has a dose strength of up to 200 mg. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus II.

[0090] 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, less than about 200 mg, less than about 100 mg or less than 50 mg. In some embodiments, the tablet has a dose strength of more than about 10 mg, 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 100 mg. In some

embodiments, the tablet size is less than 200 mg for a dose strength of 50 mg. In some embodiments, the tablet size is less than 50 mg for a dose strength of 10 mg.

[0091] 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 about 90% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 100% of the tablet is dissolved in less than 60 minutes in conventional dissolution media.

[0092] In some embodiments, the tablet is produced at a commercial scale.

[0093] In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

[0094] 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 a compound or pharmaceutically acceptable salt described herein. 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.

Pharmaceutically Acceptable Excipients

[0095] In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable excipient. In some embodiments, the 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.

[0096] 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.
- 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.
- Cationic surfactants such as cetrimide, benzalkonium chloride and cetylpyridinium chloride.
- Anion surfactants such as alkyl sulphates, alkyl ethoxylate sulphates, soaps, carboxylates, sulfates, and sulfonates.
- Non-ionic surfactants such as polyoxyethylene derivatives, polyoxypropylene derivatives, polyol derivatives, polyol esters, polyoxyethylene esters, poloxamers, glyol

esters, glycerol esters, sorbitan derivatives, polyethylene glycol (PEG-40, PEG-50, PEG-55), and ethers of fatty alcohols.

- Organic materials such as carbohydrate and modified carbohydrates, lactose, a-lactose monohydrate, spray dried lactose and anhydrous lactose, starch and pre-gelatinized starch, sucrose, manitol, sorbitol, cellulose, powdered cellulose and microcrystalline cellulose.
- Inorganic materials such as calcium phosphates (anhydrous dibasic calcium phosphate, dibasic calcium phosphate and tribasic calcium phosphate).
- Co-processed diluents.
- Surfactants such as sodium lauryl sulfate.
- Compression aids.
- Anti-tacking agents such as silicon dioxide and talc

Amounts

[0097] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 400 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 300 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 200 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 100 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 90 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 80 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 70 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 60 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 50 mg of a compound or pharmaceutically acceptable salt

described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 40 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 30 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 20 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 10 mg of a compound or pharmaceutically acceptable salt described herein.

[0098] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 500 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 400 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 300 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 200 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 100 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 90 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 80 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 70 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 60 mg of a compound or pharmaceutically acceptable salt described herein f. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 50 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 40 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg

and about 30 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 20 mg of a compound or pharmaceutically acceptable salt described herein.

Particle size

[0099] In some embodiments, the pharmaceutical composition, in the form of a tablet or a capsule, comprises a compound or pharmaceutically acceptable salt described herein, in the form of microparticles. In some embodiments, the microparticles have an average size from about 1 μm to about 100 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 50 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 30 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 20 μm. In some embodiments, the microparticles have an average size from about 5 μm to about 15 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 10 μm. In some embodiments, the microparticles have an average size from about 3 μm to about 10 μm. In some embodiments, the microparticles have an average size from about 4 μm to about 9 μm.

Methods of Treatment

[0100] Disclosed herein are methods of treating polycystic ovary syndrome (PCOS) in a subject in need thereof, comprising administering a compound or pharmaceutically acceptable salt described herein. In some embodiments, the subject in need thereof has PCOS-FAH. In some embodiments, the subject in need thereof has PCOS-FOH+FAH. In some embodiments, the methods described herein result in the reduction of a level of a hormone. Such hormones include deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, 17-OHP, dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEAS), androstenediol, androstenedione (A4), testosterone (T), dihydrotestosterone (DHT), estrone, estradiol, estriol, 11β-hydroxyandrostenedione (11OHA4), 11β-hydroxytestosterone (11OHT), 11-ketoandrostenedione (11KA4), 11-ketotestosterone (11KT), 11β-hydroxy-5α-androstenedione (11OHDHA4), 11-keto-5α-androstenedione (11KDHA4), 11β-hydroxydihydrotestosterone (11OHDHT), 11-ketodihydrotestosterone (11KDHT) and ACTH. In some embodiments, the methods described herein result in the reduction of 17-OHP levels. In some embodiments, the methods described herein result in the reduction of A4 levels. In some embodiments, the methods described herein result in the reduction of ACTH levels. In some embodiments, the methods described herein result in the reduction of DHEA levels. In some embodiments, the methods described herein result in the reduction of DHEAS levels. In some embodiments, the methods described herein

result in the reduction of testosterone (T) levels. In some embodiments, the methods described herein result in the reduction of DHT levels. In some embodiments, the methods described herein result in the reduction of 11OHA4 levels. In some embodiments, the methods described herein result in the reduction of 11OHT levels. In some embodiments, the methods described herein result in the reduction of 11KA4 levels. In some embodiments, the methods described herein result in the reduction of 11KT levels.

[0101] Further, in some embodiments, the methods described herein result in the maintenance of the reduction of 17-OHP, A4, ACTH, DHEA, DHEAS, T, DHT, 11OHA4, 11OHT, 11KA4,and/or 11KT levels. In some embodiments, the reductions of 17-OHP, A4, ACTH, DHEA, DHEAS, T, DHT, 11OHA4, 11OHT, 11KA4 and/or 11KT levels may last for at least 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, 2 years, 5 years, 10 years, 15 years, 20 years, 25 years, 30 years, 35 years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years, or 100 years.

[0102] In some embodiments, the methods described herein result in the reduction of DHEAS levels. In some embodiments, the DHEAS level is reduced by at least about 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% from baseline. The baseline level of the DHEAS may be measured in a subject before beginning the treatment disclosed herein. In some embodiments, the DHEAS level is reduced by at least 5% from baseline. In some embodiments, the reduced DHEAS level from baseline may be maintained for at least about 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, 48 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, or 30 weeks.

[0103] Further, in some embodiments, the methods described herein result in the maintenance of the reduction of 17-OHP, A4, ACTH, T, DHT, 11OHA4, 11OHT, 11KA4 and/or 11KT levels. In some embodiments, the reductions of 17-OHP, A4, ACTH T, DHT, 11OHA4, 11OHT, 11KA4 and/or 11KT levels may last for at least 24 hours, 36 hours, 48 hours, 60 hours, 72

hours, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, 2 years, 5 years, 10 years, 15 years, 20 years, 25 years, 30 years, 35 years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years, or 100 years.

[0104] In some embodiments, disclosed herein are methods for treating PCOS in a subject in need thereof, and the methods further comprise accessing a source of excessive androgen; and administering a CRF_1 antagonist or pharmaceutically acceptable salt thereof. In some embodiments, accessing a source of excessive androgen comprises measuring the primary source of excessive androgen produced in the subject suffering PCOS. In some embodiments, the primary source is the ovaries. In some embodiments, the primary source is the adrenal glands. In some embodiments, the primary source is both the ovaries and the adrenal glands. In some embodiments, the primary source is an organ that is able to produce androgen.

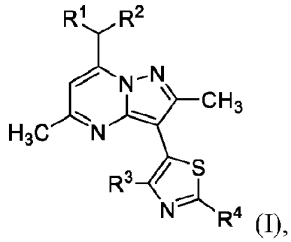
[0105] In some embodiments, cosyntropin or any other suitable hormones or chemical compounds may be administered to a subject for ACTH response in order to test for adrenal hyperandrogenism. In some embodiments, the cosyntropin is administered at a dose at least about 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 250or $\mu g/m^2$. In some embodiments, the cosyntropin is administered at a dose at about the range between the doses disclosed herein. In some embodiments, the cosyntropin is administered at a dose at most about 250, 200, 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, 5, 4, 3, 2, 1 $\mu g/m^2$.

[0106] In some embodiments, the subject will be treated for a period of about 1 week to about 40 weeks. In some embodiments, the subject will be treated for a period of about 2 weeks to about 39 weeks. In some embodiments, the subject will be treated for a period of about 3 weeks to about 38 weeks. In some embodiments, the subject will be treated for a period of about 4 weeks to about 36 weeks. In some embodiments, the subject will be treated for a period of about 1 month to 12 months. In some embodiments, the subject will be treated for a period of about 10 months to 10 years. In some embodiments, the subject will be treated for a period of about 1 months to 10 years. In some embodiments, the subject will be treated for a period of about 10 months to 20 years. In some embodiments, the subject will be treated for a period of about 1 months to 20 years. In some embodiments, the subject will be treated for a period of about 10

months to 30 years. In some embodiments, the subject will be treated for a period of about 1 months to 30 years. In some embodiments, the subject will be treated for a period of about 10 months to 40 years. In some embodiments, the subject will be treated for a period of about 1 months to 40 years. In some embodiments, the subject will be treated for a period of about 10 months to 50 years. In some embodiments, the subject will be treated for a period of about 1 months to 50 years.

[0107] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, CP-154,526, CP-376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SSR125543 (crinecerfont), AND SN003.

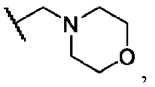
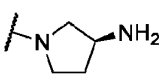
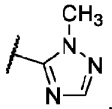
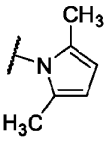
[0108] In some embodiments, the CRF_1 antagonist is a compound of Formula (I):


(I),

or a pharmaceutically acceptable salt thereof, wherein:

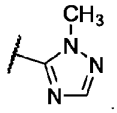
R^1 and R^2 are independently ethyl or *n*-propyl;

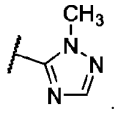
R^3 is hydrogen, F, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and

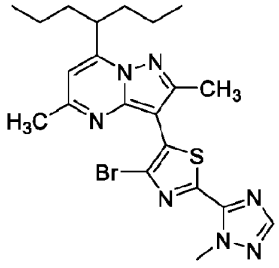
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$–$CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$–.

[0109] In some embodiments, R^3 is F, Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is Cl, Br, or methyl.

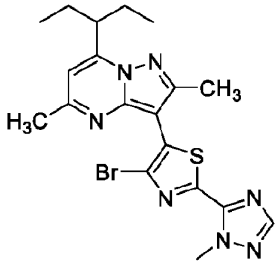
[0110] In some embodiments, R^4 is Br, $-NR^aR^b$–NR^aR^b, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is morpholin-4-yl or


. In some embodiments, R^4 is hydrogen, Br, $-NR^aR^b$ and R^a and R^b are independently C_1-C_3alkyl.

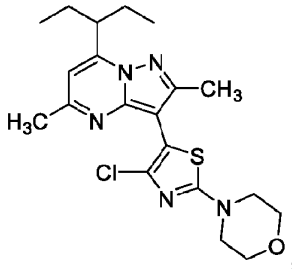
[0111] In some embodiments, the compound is


, or a pharmaceutically acceptable salt thereof.

[0112] In some embodiments, the compound is


, or a pharmaceutically acceptable salt thereof.

[0113] In some embodiments, the compound is


, or a pharmaceutically acceptable salt thereof.

[0114] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg to about 200 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject.

[0115] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is

administered in a dose of about 40 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 30 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 20 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 15 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 5 mg total daily dose to the subject.

[0116] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm to about 20 μm. In some embodiments, the average size of the microparticles is between about 5 μm to about 15 μm. In some embodiments, the average size of the microparticles is less than about 10 μ.

[0117] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

[0118] In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

[0119] In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

[0120] In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 1 to about 8 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 2 to about 7 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or

a tablet as to provide a Tmax of about 2 to about 6 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 3 to about 5 hours in a subject.

[0121] In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 8 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 7 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 6 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 5 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 4 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 3 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 2 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 1 hour in a subject.

[0122] In some embodiments, the methods described herein include administration of the pharmaceutical composition comprising CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof once a month, twice a month, three times a month, once a week, twice a week, three times a week, once every two days, once a day, twice a day, three times a day, or four times a day. In some embodiments, the methods described herein administer CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof once a day. In some embodiments, the methods described herein administer CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof twice a day.

[0123] In some embodiments, the methods described herein include administration of about 1 mg to about 2000 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, per day. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1500 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1400 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1300

mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1100 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 900 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 60 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 70 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 80 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 90 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 100 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 100 mg/day and about 700 mg/day. In some embodiments, Compound 3 is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 3 is administered at a dose between 150 mg/day and about 600 mg/day. In some embodiments, Compound 3 is administered at a dose between 200 mg/day and about 600 mg/day. In some embodiments, Compound 3 is administered at a dose between 200 mg/day and about 500 mg/day. In some embodiments, Compound 3 is administered at a dose between 200 mg/day and about 400 mg/day. In some embodiments, Compound 3 is administered at a dose between 25 mg/day and about 200 mg/day.

[0124] In some embodiments, Compound 3 is administered at a dose of about 500 mg/day. In some embodiments, Compound 3 is administered at a dose of about 400 mg/day. In some embodiments, Compound 3 is administered at a dose of about 300 mg/day. In some embodiments, Compound 3 is administered at a dose of about 200 mg/day. In some embodiments, Compound 3 is administered at a dose of about 150 mg/day. In some embodiments, Compound 3 is administered at a dose of about 100 mg/day. In some embodiments, Compound 3 is administered at a dose of about 50 mg/day.

[0125] In some embodiments, about 50 mg to about 1600 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 1600 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1600 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1200 mg of CRF_1

antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1000 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 800 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 600 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 600 mg of CRF_1 antagonist or pharmaceutically acceptable salt is administered per day. In some embodiments, about 300 mg to about 600 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 400 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 400 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 400 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered each day.

[0126] In some embodiments, less than about 2000 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1800 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1600 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1400 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1200 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1000 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 800 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some

embodiments, less than about 600 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 500 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 400 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 300 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 200 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day.

[0127] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein wherein the subject is in the fed state. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein wherein the subject is in the fasted state.

[0128] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at bedtime.

[0129] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 4 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 3 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 2 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 1 hour before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 30 mins before sleep.

[0130] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in the evening.

[0131] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 11 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 10 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 9 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 8 pm at night.

[0132] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in combination with eflornithine and/or retinoids. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in combination with contraceptive pills containing androgen receptor blockers such as cyproterone acetate, spironolactone, flutamide, or 5α-reductase inhibitors.

[0133] In some embodiments, the levels of DHEA, DHEAS, A4, 11OHA4, T, 11OHT, DHT and/or ACTH in the subject are determined from a biological sample from the subject. In some embodiments, the biological sample is selected from the group of blood, blood fractions, plasma, serum, urine, other types of bodily secretions, and saliva. In some embodiments, the biological sample is obtained non-invasively.

[0134] In some embodiments, the subject is a pediatric patient. In some embodiments, the subject is an adolescent. In some embodiments, the subject is from about 8 years old to about 18 years old. In some embodiments, the subject is an adult patient. In some embodiments, the subject is from about 18 years old to about 55 years old. In some embodiments, the subject is from about 18 years old to about 50 years old.

[0135] In some embodiments, the steroid and the CRF_1 antagonist are administered concurrently. In some embodiments, the steroid and the CRF_1 antagonist are administered in one pharmaceutical composition. In some embodiments, the steroid and the CRF_1 antagonist are administered concurrently in separate pharmaceutical compositions. In some embodiments, the steroid and the CRF_1 antagonist are administered sequentially.

EXAMPLES

[0136] The following examples further illustrate the invention but should not be construed as in any way limiting its scope. In particular, the processing conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

[0137] All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

Example 1 – Reduction of DHEAS level in a subject who has polycystic ovary syndrome (PCOS) and elevated adrenal androgens

[0138] Study Compound 3 in a double-blind, proof-of-concept study, evaluating the safety and efficacy of repeated doses of Compound 3 in adults with elevated adrenal androgens, PCOS-FAH or PCOS-FAH+FOH. After screening, eligible subjects with elevated adrenal androgens documented by elevated DHEAS will be randomized to either a compound 3 dose escalation arm or matching placebo arm.

[0139] The study is planned as a 3-period study with a duration of 4 weeks for Periods 1 and 2 and a duration of 8 weeks in Period 3 for a total treatment duration of 16 weeks. Subjects randomized to the compound 3 dose escalation arm will be treated with escalating doses of 50-mg, 100-mg or 200 mg based on achieving a DHEAS positive response criteria within each treatment period. Subjects not meeting the criteria will be dose escalated to the next highest dose in the preceding period. Subjects meeting the criteria will remain on their current dose level. Placebo subjects will remain on placebo through the full 16 weeks.

[0140] The population are composed of approximately 40 patients, who receive Compound 3 or matching placebo daily for up to 16 weeks. Compound 3 is administered as an oral daily dose. Patients are undergo PK/PD or PD only assessments, approximately every 2 weeks. A follow-up outpatient visit occurs 30 days after the last dose.

[0141] Study Design

- Study Type: Interventional
- Primary Purpose: Treatment
- Study Phase: Phase 2
- Interventional Study Model: Randomized
- Number of Arms: 2
- Masking: Masking of Study drug
- Allocation: Randomized (1:1)
- Enrollment: 40

Arms and Interventions:

Arms	**Assigned Intervention**
Arm 1	Drug: Compound 3 dose escalation (50, 100 and 200-mg)
Arm 2	Drug: Matching Placebo

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability of Compound 3 in patients with elevated adrenal androgens (adverse effects, serious adverse effects, clinical laboratory parameters, etc.)

[Time Frame: 16 weeks]

Secondary Outcome Measures:

2. Proportion of subjects with:

   a. ≥ 30% change from baseline in dehydroepiandrosterone sulfate (DHEAS)

   b. DHEAS <upper limit of normal (ULN)

   c. DHEAS <75th percentile of normal range (Q3)

[Time Fame: 4 to up to 16 weeks]

3. Pharmacokinetics of compound 3

[Time Frame: 4 weeks]

Exploratory Outcome Measure:

4. Changes in PD markers: Changes in cortisol, ACTH, DHEAS, DHEA, A4, T, 17-OHP, 11OHA4, 11OHT, 11KA4, 11KT

[Time Frame: up to 16 weeks]

Eligibility

- Minimum Age: 18 Years
- Maximum Age: 30 years
- Sex: Female only
- Gender Based: Yes
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Female subjects 18 to 30 years old, inclusive
- Subjects must have documented PCOS according to the NIH (1990) criteria
- BMI ≤38 kg/m^2
- DHEAS level > age matched reference ULN at Screening
- Evidence of DHEA hyperresponsiveness to ACTH stimulation during Screening

Exclusion Criteria:

- Has a BMI >38kg/m^2
- Has PCOS-FOH
- Has HbA1c > 6.5% or Fasting plasma glucose >126 mg/dL
- Has a history that includes bilateral adrenalectomy or hypopituitarism
- Has a history of allergy or hypersensitivity to tildacerfont or any other CRF_1 receptor antagonist
- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant uncontrolled psychiatric disorder
- Clinically significant abnormal laboratory finding or assessment
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

[0142] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

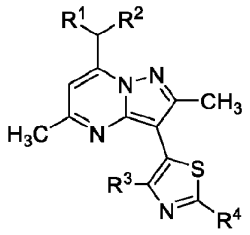
CLAIMS

WHAT IS CLAIMED IS:

1. 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 a CRF1 antagonist or pharmaceutically acceptable salt thereof.

2. A method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

3. The method of any of claims 1-2, wherein said CRF_1 antagonist is a compound of Formula (I):

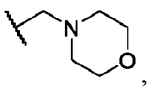
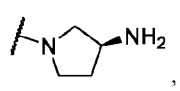
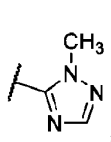
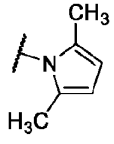


Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently ethyl or *n*-propyl;

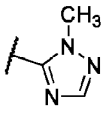
R^3 is hydrogen, F, Cl, Br, methyl, trifluoromethyl, or methoxy;

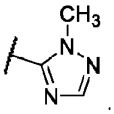
R^4 is hydrogen, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

4. The method of claim 3, wherein R^3 is F, Cl, Br, methyl, or trifluoromethyl.

5. The method of claim 3 or claim 4, wherein R^3 is Cl or Br.

6. The method of any one of claims 4 to 5, wherein R^4 is $-NR^aR^b$, pyridin-4-yl, morpholin-4-yl, or  .

7. The method of any one of claims 4 to 6, wherein R^4 is morpholin-4-yl or  .

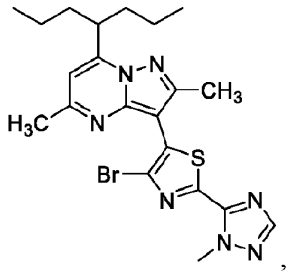
8. The method of any one of claims 4 to 6, wherein R^4 is $-NR^aR^b$, and R^a and R^b are independently C_1-C_3alkyl.

9. The method of claim 4, wherein said CRF_1 antagonist or a pharmaceutically acceptable salt thereof is 3-[4-bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)- pyrazolo[1,5-*a*]pyrimidine.

10. The method of claim 4, wherein said CRF_1 antagonist or a pharmaceutically acceptable salt thereof 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.

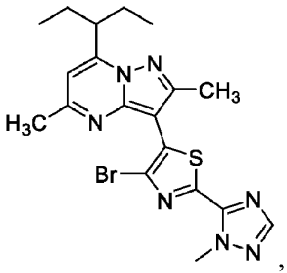
11. The method of claim 4, wherein said CRF_1 antagonist or a pharmaceutically acceptable salt thereof is 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.

12. The method of claim 4, wherein said CRF_1 antagonist is



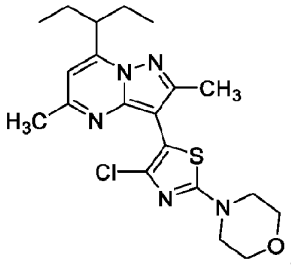
, or a pharmaceutically acceptable salt thereof.

13. The method of claim 4, wherein said CRF_1 antagonist is



, or a pharmaceutically acceptable salt thereof.

14. The method of claim 4, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

15. The method of any of claims 1-2, wherein said CRF_1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, CP-154,526, CP-376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SSR125543 (crinecerfont), and SN003.

16. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 5 mg to about 400 mg total daily dose to the subject.

17. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 300 mg total daily dose to the subject.

18. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject.

19. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject.

20. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject.

21. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 75 mg total daily dose to the subject.

22. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject.

23. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject.

24. The method of any one of claims 1-15, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg total daily dose to the subject.

25. The method of any one of claims 1-24, wherein the CRF_1 antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

26. The method of any one of claims 1-25, wherein an adrenocorticotropic hormone (ACTH) level is reduced by at least 5% from baseline.

27. The method of any one of claims 1-25, wherein an adrenocorticotropic hormone (ACTH) level is reduced by at least 10% from baseline.

28. The method of any one of claims 1-25, wherein a dehydroepiandrosterone sulfate (DHEAS) level is reduced by at least 5% from baseline.

29. The method of any one of claims 1-25, wherein a dehydroepiandrosterone sulfate (DHEAS) level is reduced by at least 10% from baseline.

30. The method of any one of claims 1-25, wherein androstenedione (A4) level is reduced by at least 5% from baseline.

31. The method of any one of claims 1-25, wherein androstenedione (A4) level is reduced by at least 10% from baseline.

32. The method of any one of claims 1-25, wherein 1β-hydroxyandrostenedione (11OHA4) level is reduced by at least 5% from baseline.

33. The method of any one of claims 1-25, wherein 1β-hydroxyandrostenedione (11OHA4) level is reduced by at least 10% from baseline.

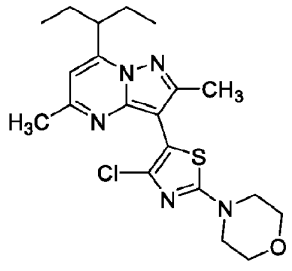
34. The method of any one of claims 1-25, wherein 11β-hydroxytestosterone (11OHT) level is reduced by at least 5% from baseline.

35. The method of any one of claims 1-25, wherein 11β-hydroxytestosterone (11OHT) level is reduced by at least 10% from baseline.

36. The method of any one of claims 25-35, wherein a reduced ACTH, DHEAS, A4, 11OHA4 or 11OHT level from baseline is maintained for at least 24 hours.

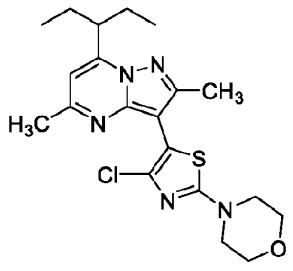
37. The method of any one of claims 25-35, wherein a reduced ACTH, DHEAS, A4, 11OHA4 or 11OHT level from baseline is maintained for at least 4 weeks.

38. A method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 3:



; or a pharmaceutically acceptable salt or solvate thereof.

39. 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 a pharmaceutical composition comprising Compound 3:



; or a pharmaceutically acceptable salt or solvate thereof.

40. The method of either claim 38 or claim 39, wherein Compound 3 is administered at a dose between about 1 mg/day and about 200 mg/day.

41. The method of any of claims 38-40, wherein the pharmaceutical composition comprises between about 1 mg and about 400 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

42. The method of claim 41, wherein the pharmaceutical composition comprises about 25 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

43. The method of claim 41, wherein the pharmaceutical composition comprises about 50 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

44. The method of claim 41, wherein the pharmaceutical composition comprises between about 75 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

45. The method of claim 41, wherein the pharmaceutical composition comprises about 100 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

46. The method of claim 41, wherein the pharmaceutical composition comprises about 200 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

47. The method of claim 41, wherein the pharmaceutical composition comprises about 300 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

48. The method of any one of claims 1-47, wherein the pharmaceutical composition is in the form of microparticles.

49. The method of claim 48, wherein the average size of the microparticles is between about 1 μm to about 20 μm.

50. The method of claim 48, wherein the average size of the microparticles is between about 5 μm to about 15 μm.

51. The method of claim 48, wherein the average size of the microparticles is less than about 10 μm.

52. The method of any of claims 1-47, wherein the pharmaceutical composition is in the form of a capsule or a tablet.

53. The method of claim 52, wherein the capsule is a hard gelatin capsule.

54. The method of claim 52, wherein the capsule is a soft gelatin capsule.

55. The method of any one of claims 52-54, wherein the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

56. The method of any one of claims 52-54, wherein the pharmaceutical composition is free of additional excipients.

57. The method of any one of claims 52-54, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

58. The method of claim 52, wherein the pharmaceutical composition is in the form of a tablet.

59. The method of claim 58, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

60. The method of any one of claims 1-59, wherein the subject is a pediatric patient.

61. The method of any one of claims 1-59, wherein the subject is from about 9 years old to about 18 years old.

62. The method of any one of claims 1-59, wherein the subject is from about 8 years of age to about 55 years of age.

63. The method of any one of claims 1-59, wherein the subject is an adult patient.

64. The method of any of claims 1-63, wherein said subject is treated for a period of about 2 weeks to about 36 weeks.

65. The method of any of claims 1-63, wherein said subject is treated for a period of about 1 month to 12 months.

66. The method of any of claims 1-63, wherein said subject is treated for a period of about 10 months to 50 years.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/45780

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61B 18/14; A61B 18/02; A61B 18/04 (2021.01)

CPC - A61N 1/36117; A61B 18/04; A61B 18/1492

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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2017/0333126 A1 (Medtronic Ardian Luxembourg S.a.r.l.) 23 November 2017 (23.11.2017); abstract	1-4, 9-15, 38-40
A	US 2010/0222339 A1 (Chen et al.) 02 September 2010 (02.09.2010); abstract, para [0144]	1-4, 9-15, 38-40
A	US 2018/0110554 A1 (Ziva Medicinal, Inc.) 26 April 2018 (26.04.2018); abstract	1-4, 9-15, 38-40
A	WO 2019/036472 A1 (SPRUCE BIOSCIENCES, INC.) 21 February 2019 (21.02.2019); entire document	1-4, 9-15, 38-40
A	US 2013/0045979 A1 (Sanfilippo) 21 February 2013 (21.02.2013); entire document	1-4, 9-15, 38-40

☐ 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
"D" document cited by the applicant in the international application
"E" earlier application or patent 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	Date of mailing of the international search report
21 November 2021	DEC 17 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/45780

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:

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.: 5-8, 16-37, 41-66
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:

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.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 487/04, A61K 31/495 | A1

(11) International Publication Number: WO 97/29109

(43) International Publication Date: 14 August 1997 (14.08.97)

(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

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(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).

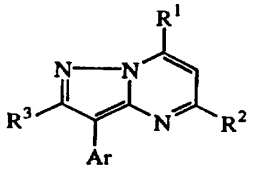
(74) Agent: WANTE, Dirk; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).

(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



(I)

This invention concerns compounds of formula (I), 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; R^4 is hydrogen, C_{1-6}alkyl, mono- or di(C_{3-6}cycloalkyl)methyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl; R^5 is C_{1-8}alkyl, mono- or di(C_{3-6}cycloalkyl)methyl, Ar^1CH_2, C_{1-6}alkyloxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-6}alkenyl, thienylmethyl, furanylmethyl, C_{1-6}alkylthioC_{1-6}alkyl, morpholinyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylC_{1-6}alkyl, C_{1-6}alkyl substituted with imidazolyl; or a radical of the 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 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

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.

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). 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 adrenocorticotropic 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 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 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 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.* 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).

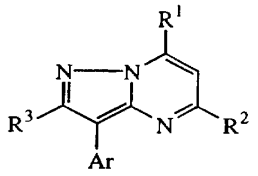
Accordingly, clinical data suggest that CRF receptor antagonists may represent novel antidepressant and/or anxiolytic drugs that may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF.

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)



(I),

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;

R^4 is hydrogen, C_{1-6}alkyl, mono- or di(C_{3-6}cycloalkyl)methyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl;

R^5 is C_{1-8}alkyl, mono- or di(C_{3-6}cycloalkyl)methyl, Ar^1CH_2, C_{1-6}alkyloxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-6}alkenyl, thienylmethyl, furanylmethyl, C_{1-6}alkylthioC_{1-6}alkyl, morpholinyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylC_{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, optionally substituted with C_{1-6}alkyl or C_{1-6}alkyloxyC_{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 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 selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, di(C_{1-6}alkyl)aminoC_{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; C_{1-6}alkanediyl 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; C_{1-2}alkyl defines straight saturated hydrocarbon radicals having from 1 to 2 carbon atoms such as methyl and ethyl; C_{2-4}alkyl 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; C_{3-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 3 to 4 carbon atoms such as propyl, butyl, 1-methylethyl and the like; C_{1-6}alkyl includes C_{1-2}alkyl and C_{3-4}alkyl 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; C_{1-8}alkyl includes C_{1-6}alkyl and the higher homologues thereof having from 7 to 8 carbon atoms such as, for example, heptyl, octyl and the like; C_{3-6}alkenyl 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 C_{3-6}alkenyl is linked to a nitrogen or oxygen, the carbon atom making the link preferably is saturated. C_{3-6}cycloalkyl comprises cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. HydroxyC_{1-6}alkyl refers to C_{1-6}alkyl 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, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl or C_{3-6}alkenyl; in particular C_{2-4}alkyl, hydroxyC_{1-2}alkyl, C_{3-4}alkenyl or C_{1-2}alkylcarbonyloxyC_{2-4}alkyl; and R^5 is C_{1-8}alkyl, C_{3-6}alkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, phenylmethyl or C_{3-6}cycloalkylmethyl; in particular C_{2-4}alkyl, C_{3-4}alkenyl, hydroxyC_{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}alkyloxyC_{1-6}alkyl.

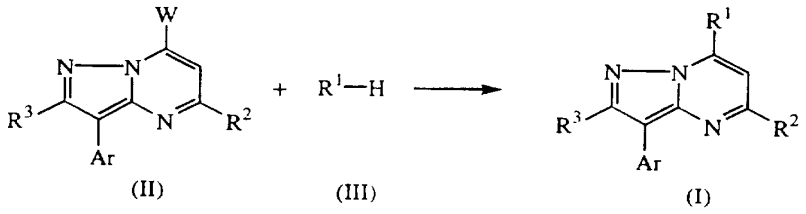
Preferred compounds are those compounds of formula (I) wherein R^1 is NR^4R^5 and R^4 is C_{3-4}alkyl or allyl, preferably propyl; R^5 is C_{2-4}alkyl, allyl or cyclopropylmethyl, preferably propyl; R^2 is methyl; R^3 is hydrogen, methyl or methylthio, preferably

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.

More preferably Ar is 3-pyridinyl substituted in the 4- and/or 6-position with methyl or dimethylamino.

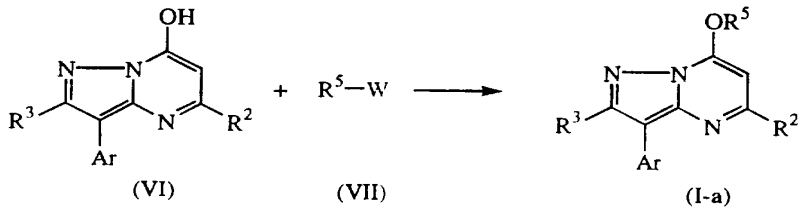
Most preferred are those compounds selected from
3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-propyl-*N*-cyclopropanemethylamino)-pyrazolo[2,3-a]pyrimidine;
3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-allyl-*N*-cyclopropanemethylamino)-pyrazolo[2,3-a]pyrimidine;
2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(*N*,*N*-diallylamino)-pyrazolo[2,3-a]pyrimidine;
2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-butyl-*N*-cyclopropanemethyl-amino)pyrazolo[2,3-a]pyrimidine;
2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-propyl-*N*-cyclopropanemethyl-amino)pyrazolo[2,3-a]pyrimidine;
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-pyrazolo[2,3-a]pyrimidine-7-amine; or
3-(2,4-dimethoxyphenyl)-2,5-dimethyl-7-(*N*-propyl-*N*-methyloxyethylamino)-pyrazolo[2,3-a]pyrimidine;
the stereoisomeric forms and the pharmaceutically acceptable acid addition salts thereof.

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.



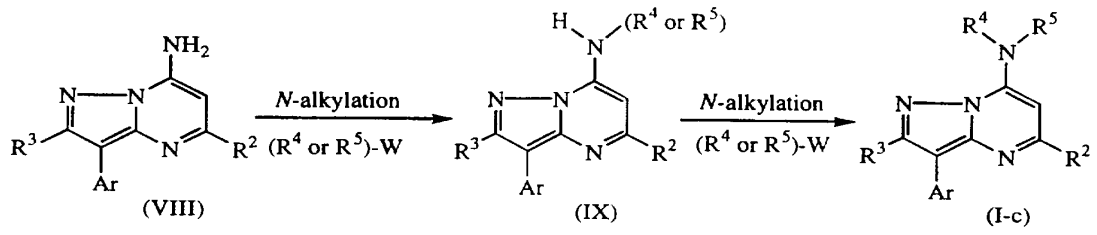
The above reaction is typically conducted in a suitable solvent, e.g. an aprotic solvent such as DMF or acetonitrile, an ether, e.g. tetrahydrofuran, preferably at an elevated temperature and, when the intermediates of formula (III) are volatile amines, in a sealed reaction vial.

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. tetrahydofuran 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 or R^5)–W, in particular where R^2 is methyl and R^4 or R^5 is C_{1-6}alkyl.

As outlined below, compounds of formula (I) may be converted into each other following art-known transformation procedures.

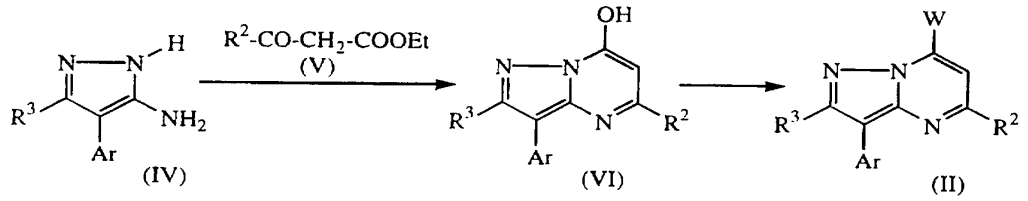
The compounds of formula (I) wherein R^3 is C_{1-6}alkylthio can be converted into compounds of formula (I) wherein R^3 is C_{1-6}alkylsulfonyl or C_{1-6}alkylsulfoxy by an oxidation reaction, e.g. treatment with a peroxide such as 3-chloroperbenzoic acid in a reaction-inert solvent, e.g. dichloromethane. 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.

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 hydroxyC_{1-6}alkyl group may be converted into compounds of formula (I) bearing a C_{1-6}alkylcarbonyloxyC_{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 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 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 room temperature and the reflux temperature of the reaction mixture.

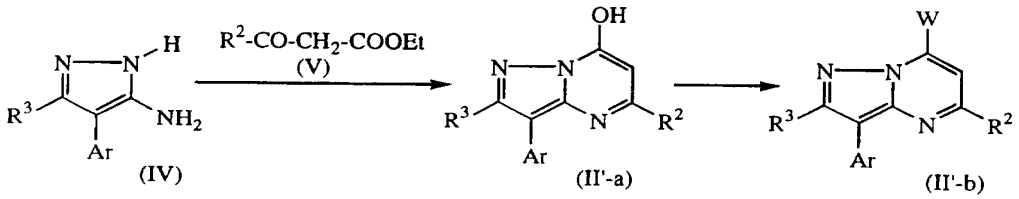
Intermediates of formula (II) can be prepared according to the procedure as described in Robins et al., *J. Heterocyclic Chem.* 22:601-634, 1985.



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. $POCl_3$.

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* I: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.* [^{125}I]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 IC_{50} 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 limition.

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 $POCl_3$ (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 $MgSO_4$ 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).

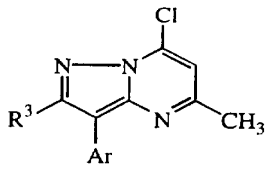
b) A mixture of intermediate 7 and hydrazine hydrobromide (100 mmol) was dissolved in ethanol/water (9:1, total 100 ml) and refluxed for 1 hour. The reaction mixture was concentrated and the residue was partitioned between ethyl acetate and sodium bicarbonate solution. The combined extracts were dried 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-amino)-5-pyridinyl]-2,5-dimethyl-7-hydroxypyrazolo[2,3-a]pyrimidine (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 (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-(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.

Table 1 :



Interm. No.	Ex. No.	R^3	Ar
2	A.1	H	2,4-dichlorophenyl
3	A.1	CH_3S	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_3CH_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

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*-cyclopropane-methylamino)-pyrazolo[2,3-a]pyrimidine (compound 8) (1 mg).

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.

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).

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. 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*-dipropyl-pyrazolo[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).

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

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 ($CH_2Cl_2/CH_3OH/NH_4OH$ 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

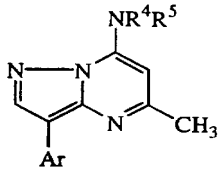
To a solution of compound 56 (100 mg) in a mixture of concentrated HCl (1 ml) and water (1 ml), cooled in an ice bath, was added a solution of sodium nitrite (21 mg) in water (1 ml). The solution was added to a mixture of copper(I)chloride (281 mg) in concentrated HCl with stirring in an ice bath. A 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.

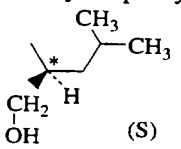
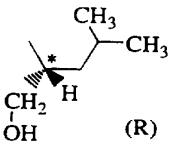
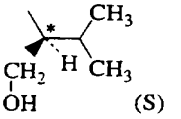
Example B.10

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.

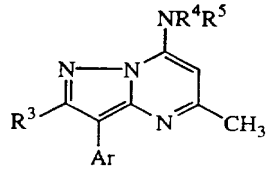
Table 2 :



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	$CH_3O(CH_2)_3$-	2,4-dichlorophenyl
7	B.1	hydrogen	$(CH_3)_2CHO(CH_2)_3$-	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	 (S)	2,4-dichlorophenyl
12	B.1	hydrogen	 (R)	2,4-dichlorophenyl
13	B.1	hydrogen	 (S)	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	$HOCH_2CH_2$-	2,4-dichlorophenyl
19	B.1	n-propyl	$CH_3O(CH_2)_2$-	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	$CH_3O(CH_2)_2$	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	$HOCH_2CH_2$-	phenylmethyl	2,4-dichlorophenyl
27	B.5	$CH_3COO(CH_2)_2$-	phenylmethyl	2,4-dichlorophenyl
28	B.5	$CH_3COO(CH_2)_2$-	n-propyl	2,4-dichlorophenyl
29	B.4	allyl	cyclopropylmethyl	2,4-dichlorophenyl
45	B.4	n-propyl	$CH_3O(CH_2)_3$	2,4-dichlorophenyl
58	B.1	$CH_3O(CH_2)_2$-	$CH_3O(CH_2)_2$-	2,4-dichlorophenyl
59	B.1	hydrogen	$CH_3OCH_2CH(CH_3)$-	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	$CH_3O(CH_2)_2$-	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

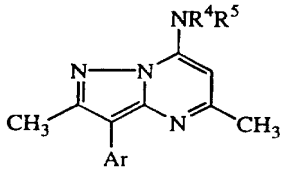
Table 3 :



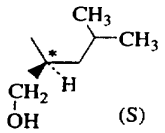
Co. No.	Ex. No.	R^3	R^4	R^5	Ar
30	B.1	CH_3S	hydrogen	n-propyl	2,4-dichlorophenyl
31	B.1	CH_3S	hydrogen	2-propyl	2,4-dichlorophenyl

Co. No.	Ex. No.	R^3	R^4	R^5	Ar
32	B.1	CH_3S	hydrogen	3-heptyl	2,4-dichlorophenyl
34	B.1	CH_3S	hydrogen	2-methoxyphenylmethyl	2,4-dichlorophenyl
35	B.1	CH_3S	methyl	methyl	2,4-dichlorophenyl
36	B.1	CH_3S	ethyl	ethyl	2,4-dichlorophenyl
37	B.2	CH_3S	n-propyl	n-propyl	2,4-dichlorophenyl
38	B.1	CH_3S	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
39	B.1	CH_3S	2-propyl	2-propyl	2,4-dichlorophenyl
40	B.1	CH_3S	n-butyl	n-butyl	2,4-dichlorophenyl
41	B.1	CH_3S	n-butyl	cyclopropylmethyl	2,4-dichlorophenyl
42	B.1	CH_3S	allyl	allyl	2,4-dichlorophenyl
43	B.6	CH_3SO	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
44	B.6	CH_3SO_2	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
73	B.2	CH_3CH_2	n-propyl	n-propyl	3,4-dimethoxy-phenyl

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	$CH_3O(CH_2)_2$-	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	$CH_3O(CH_2)_2$-	$CH_3O(CH_2)_2$-	4-chlorophenyl
75	B.1	$HOCH_2CH_2$-	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	$CH_3S(CH_2)_2$-	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	$CH_3O(CH_2)_2$-	$CH_3O(CH_2)_2$-	3-chloro-5-trifluoromethyl-2-pyridinyl
103	B.2	n-propyl	n-propyl	3,5-dichloro-2-pyridinyl
104	B.1	n-propyl	$CH_3O(CH_2)_2$-	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	$CH_3O(CH_2)_2$-	3,4-dimethoxyphenyl
118	B.1	n-propyl	cyclopropyl	2,4-dimethoxyphenyl
119	B.1	hydrogen	$CH_3O(CH_2)_2$-	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

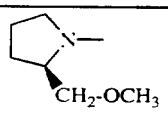
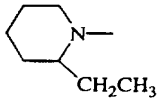
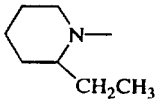
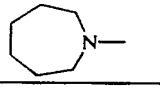
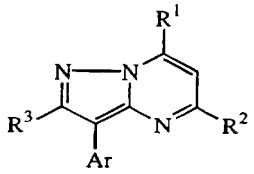
Co. No.	Ex. No.	R^4 and R^5 taken together	Ar
128	B.1		4-chlorophenyl
129	B.1		4-chlorophenyl
130	B.1		6-dimethylamino-4-methyl-3-pyridinyl
131	B.1		6-dimethylamino-4-methyl-3-pyridinyl

Table 5 :



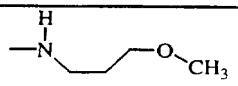
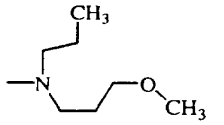
Co. No.	Ex. No.	R^1	R^2	R^3	Ar
46	B.4		n-C_4H_9	H	2,4-dichlorophenyl
47	B.4		n-C_4H_9	H	2,4-dichlorophenyl
50	B.3	CH_3CH_2O-	CH_3	CH_3-S-	2,4-dichlorophenyl

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.	^{1}H 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_2O)
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 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 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 x 10^6 cells per tube stably transfected with human CRF receptors. Each tube received about 0.1 ml of assay buffer *(e.g.,* Dulbecco's phosphate buffered saline, 10 mM magnesium chloride, 20 µM bacitracin) with or without unlabeled sauvagine, urotensin I or CRF (final concentration, 1 µM) to determine nonspecific binding, 0.1 ml of [^{125}I] tyrosine - ovine CRF (final concentration ~200 pM or approximately the K_D as determined by Scatchard analysis) and 0.1 ml of a membrane 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 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 - 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.2

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 0.5 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 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 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 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 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 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 an 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.

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 CFR antagonist is also exerted following intracerebral administration into the central nucleus of amygdala [250 ng IC].

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

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.

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. 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 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). 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 resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I..

Example D.3 : Film-coated tablets

Preparation of tablet core

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 polyvinyl-pyrrolidone 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, 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 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 apparatus.

Example D.4 : Injectable solution

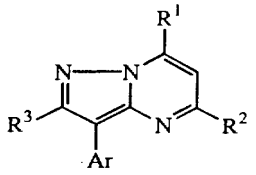
1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I. The solution was cooled to room temperature and supplemented 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

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



(I),

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;

R^4 is hydrogen, C_{1-6}alkyl, mono- or di(C_{3-6}cycloalkyl)methyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl or C_{1-6}alkyloxyC_{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}alkyloxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, thienylmethyl, furanylmethyl, C_{1-6}alkylthioC_{1-6}alkyl, morpholinyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylC_{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, optionally substituted with C_{1-6}alkyl or C_{1-6}alkyloxyC_{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 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 selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, di(C_{1-6}alkyl)aminoC_{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.

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, hydroxyC_{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, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{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 pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_{1-6}alkyl or C_{1-6}alkyloxyC_{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 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.

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, hydroxyC_{1-2}alkyl, C_{3-4}alkenyl or C_{1-2}alkylcarbonyloxyC_{2-4}alkyl; R^5 is C_{2-4}alkyl, C_{3-4}alkenyl, hydroxyC_{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 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 methyl; and Ar is 3-pyridinyl substituted on the 4- and/or 6-position with methyl or dimethylamino.

6. A compound according to claim 1 wherein the compound is
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*-dipropylpyrazolo[2,3-a]pyrimidin-7-amine;

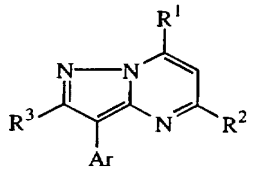
the stereochemically isomeric forms, or the pharmaceutically acceptable acid addition salts thereof.

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.

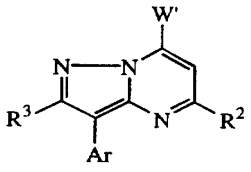
10. The use of compounds of formula



(I),

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).

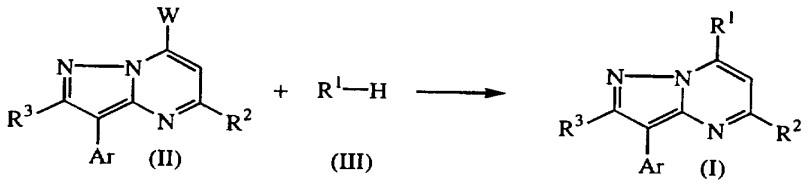
11. A compound of formula (II') wherein the radicals R^2, R^3 and Ar are as defined in any of claims 1 to 5 and radical W' is hydroxy, halo, mesyloxy or tosyloxy; a stereoisomeric form or an acid addition salt form thereof, with the proviso that compounds wherein Ar is unsubstituted phenyl are not included.



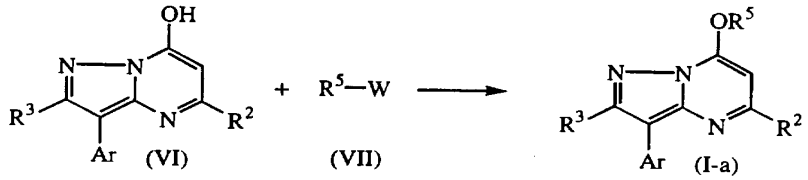
(II')

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,



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 R^1 is OR^5,

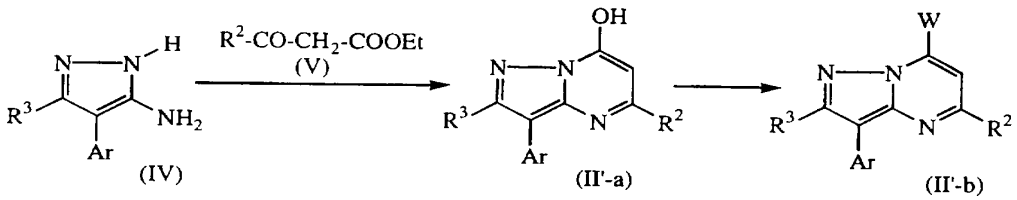


wherein in the above reaction schemes the radicals R^1, R^2, R^3, R^5 and Ar are as defined in claim 1 and W is an appropriate leaving group;

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

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;



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;

wherein in the above reaction schemes the radicals R^2, R^3 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.
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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

[X] Further documents are listed in the continuation of box C.

[X] 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

4

Date of the actual completion of the international search	Date of mailing of the international search report
15 May 1997	29. 05. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	De Jong, B

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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

4

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/EP 97/00459

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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JP 42011753 A		NONE	
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		ZA 9309405 A	15-06-95

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,303	**01/12/2026 06:01:45 PM Z ET**	**50535-710.305**

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 #	1040	FILED BY	JENNIFER VAIL
PATENT CENTER #	73944007	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

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TOTAL DOCUMENTS: 100

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WILSON SONSINI GOODRICH & ROSATI
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EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 01/29/2026

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,303	01/31/2025	Alexis HOWERTON	50535-710.305	1040

TITLE OF INVENTION: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1290	$0.00	$0.00	$1290	04/29/2026

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,303	01/31/2025	Alexis HOWERTON	50535-710.305	1040

TITLE OF INVENTION: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1290	$0.00	$0.00	$1290	04/29/2026

EXAMINER	ART UNIT	CLASS-SUBCLASS
PIHONAK, SARAH	1627	514-233200

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2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,303	01/31/2025	Alexis HOWERTON	50535-710.305	1040

21971 7590 01/29/2026

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 01/29/2026

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/ owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 19/043,303	Applicant(s) HOWERTON et al.	
	Examiner SARAH PIHONAK	Art Unit 1627	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 1/12/26.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-19 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 1/12/26 has been entered.

Status of Claims

1. Claims 1-19 were allowed for the reasons stated in the notice of allowance mailed on 12/19/25.

Information Disclosure Statement

2. The IDS filed on 1/12/26 has been considered.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached Monday-Friday 9:00-5:30 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney Klinkel can be reached at 571-270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SARAH . PIHONAK
Primary Examiner
Art Unit 1627

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,303	HOWERTON et al.
	Examiner	**Art Unit**
	SARAH PIHONAK	1627

CPC							
Symbol						**Type**	**Version**
A61K	/	31	/	519		F	2013-01-01
A61K	/	9	/	0053		A	2013-01-01
A61K	/	9	/	20		A	2013-01-01
A61K	/	9	/	48		A	2013-01-01
A61K	/	45	/	06		A	2013-01-01
A61P	/	5	/	06		A	2018-01-01
A61P	/	5	/	08		A	2018-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 19	
/SARAH PIHONAK/ Primary Examiner, Art Unit 1627 (Primary Examiner)	20 January 2026 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office — Part of Paper No.: 20260120

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,303	HOWERTON et al.
	Examiner	Art Unit
	SARAH PIHONAK	1627

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	31	/	519
A61K	/	9	/	20
A61K	/	9	/	48
A61K	/	9	/	00
A61P	/	5	/	06
A61P	/	5	/	08

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE (Assistant Examiner)	(Date)	Total Claims Allowed: 19	
/SARAH PIHONAK/ Primary Examiner, Art Unit 1627 (Primary Examiner)	20 January 2026 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office

Part of Paper No.: 20260120

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,303	HOWERTON et al.
	Examiner	Art Unit
	SARAH PIHONAK	1627

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		10		19										
	2		11												
	3		12												
	4		13												
	5		14												
	6		15												
	7		16												
	8		17												
	9		18												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 19	
/SARAH PIHONAK/ Primary Examiner, Art Unit 1627 (Primary Examiner)	20 January 2026 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office

Part of Paper No.: 20260120

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,303	HOWERTON et al.
	Examiner	Art Unit
	SARAH PIHONAK	1627

CPC - Searched*		
Symbol	**Date**	**Examiner**
a61k31/519,5377; a61p5/06,08; a61p35/00	09/02/2025	s.p.
a61k31/519,5377; a61k9/0053,20,2004,48,4841; a61p5/06,08; a61p35/00	12/03/2025	s.p.
a61k31/519,5377; a61k9/0053,20,2004,48,4841; a61p5/06,08; a61p35/00	01/20/2026	s.p.

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,303	HOWERTON et al.
	Examiner	Art Unit
	SARAH PIHONAK	1627

Search Notes		
Search Notes	**Date**	**Examiner**
a61k31/519,5377; a61p5/06,08; a61p35/00	09/02/2025	s.p.
inventor & applicant search in PE2E, patent data portal	09/02/2025	s.p.
invention & claims search in PE2E (incl. similarity search), stnext	09/02/2025	s.p.
a61k31/519,5377; a61k9/0053,20,2004,48,4841; a61p5/06,08; a61p35/00	12/03/2025	s.p.
inventor & applicant search in PE2E, patent data portal	12/03/2025	s.p.
invention & claims search in PE2E (incl. similarity search), stnext	12/03/2025	s.p.
a61k31/519,5377; a61k9/0053,20,2004,48,4841; a61p5/06,08; a61p35/00	01/20/2026	s.p.
inventor & applicant search in PE2E, patent data portal	01/20/2026	s.p.
invention & claims search in PE2E (incl. similarity search)	01/20/2026	s.p.

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
a61k	31/519,5377; 9/0053,20,2004,48,4841	12/03/2025	s.p.
a61p	5/06,08; 35/00	12/03/2025	s.p.
a61k	31/519,5377; 9/0053,20,2004,48,4841	01/20/2026	s.p.
a61p	5/06,08; 35/00	01/20/2026	s.p.

/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	19	("10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220143037" OR "20220211711" OR "4328245" OR "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2025/05/07 05:21 PM
L2	127	((testicular OR testicle OR ovarian OR ovary) WITH adrenal WITH rest WITH tumor*) AND (corticotropin adj10 releasing adj10 factor adj10 (antagon* OR block*))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/05/07 05:53 PM
L3	1	"20250195527".pn.	(US-PGPUB)	OR	ON	ON	2025/09/02 04:12 PM
L4	28	(Artificial Intelligence) More like doc: US-20250195527-A1 Text: (JP-H0971528-A OR WO-2007109853-A1 OR BR-PI0717023-B8 OR US-20100203048-A1 OR CN-106102740-A OR TW-202400179-A OR EA-202090450-A1 OR US-20250195527-A1 OR US-20250177403-A1 OR	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO;	OR	ON	ON	2025/09/02 04:12 PM

		EP-3784233-B1 OR HK-40040045-A OR US-20250177404-A1 OR HK-40040045-B OR AU-2023203095-A1 OR CA-3098562-A1 OR US-20220211711-A1 OR US-11304950-B2 OR US-20240285593-A1 OR US-20250064812-A1 OR US-11304952-B2).did.	JPO; DERWENT; IBM_TDB)				
L5	11	L4 AND ((testicular OR ovar*) adj10 adrenal adj10 rest adj10 (tumor OR neoplasm))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/09/02 04:16 PM
L6	86	(a61k31/519,5377 OR a61p5/06,08 OR a61p35/00).cpc. AND ((testicular OR ovar*) adj10 adrenal adj10 rest adj10 (tumor* OR neoplasm*))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/09/02 04:18 PM
L7	35	((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2025/09/02 04:21 PM
L8	24	((("HOWERTON") near3 ("Alexis")) OR (("GERBER") near3 ("Hal"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2025/09/02 04:22 PM
L9	11	(L7 OR L8) AND ((testicular OR ovar*) adj10 adrenal adj10 rest adj10 (tumor* OR neoplasm*))	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/09/02 04:22 PM

L10	42	(corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR suppress* OR reduc* OR decreas*)) AND ((testicular OR ovar*) adj10 adrenal adj10 rest adj10 (tumor* OR neoplasm*))	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/09/02 04:24 PM
L11	1	"11459324".pn.	(USPAT)	OR	ON	ON	2025/09/03 09:13 AM
L12	1	"6586456".pn.	(USPAT)	OR	ON	ON	2025/12/03 11:50 AM
L13	1	"20250195527".pn.	(US-PGPUB)	OR	ON	ON	2025/12/03 12:15 PM
L14	29	(Artificial Intelligence) More like doc: US-20250195527-A1 Text: (JP-H0971528-A OR EP-2004205-A4 OR EP-2094709-B1 OR US-20100203048-A1 OR JP-7285222-B2 OR AU-2018317398-A1 OR EP-3784233-B1 OR HK-40040045-A OR HK-40040045-B OR US-20250195527-A1 OR US-20250177403-A1 OR US-20250177404-A1 OR CA-3098562-A1 OR US-20250064812-A1 OR US-20240285593-A1 OR US-20210038604-A1 OR AU-2023203095-A1 OR US-11304950-B2 OR US-20210395255-A1 OR AU-2019260793-B2).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/12/03 12:15 PM
L15	12	L14 AND (adrenal adj8 rest adj8 (tumor* OR neoplasm* OR growth))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS,	OR	ON	ON	2025/12/03 12:21 PM

			IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L16	37	(a61k31/519,5377 OR a61k9/0053,20,2004,48,4841 OR a61p5/06,08 OR a61p35/00).cpc. AND (corticotropin adj8 releas* adj8 factor adj8 (antagon* OR block* OR suppress* OR decreas* OR reduc*)) AND (adrenal adj8 rest adj8 (tumor* OR neoplasm* OR growth*))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/12/03 12:27 PM
L17	8	(L7 OR L8) AND (corticotropin adj8 releas* adj8 factor adj8 (antagon* OR block* OR suppress* OR decreas* OR reduc*)) AND (adrenal adj8 rest adj8 (tumor* OR neoplasm* OR growth*))	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/12/03 12:30 PM
L18	35	("11708372" OR "11858932" OR "12098152" OR "20020013357" OR "20030008885" OR "20050209250" OR "20060078623" OR "20090076266" OR "20100022560" OR "20100155595" OR "20110136865" OR "20110160168" OR "20110166345" OR "20130045979" OR "20170333126" OR "20180110554" OR "20190262349" OR "20200255436" OR "20210015827" OR "20210038604" OR "20210137935" OR "20210322430" OR	(US-PGPUB; USPAT)	OR	ON	ON	2026/01/20 11:12 AM

		"20210361664" OR "20220133742" OR "20230159533" OR "20230321112" OR "20230414627" OR "20240043432" OR "20240261300" OR "20240293421" OR "20250064812" OR "20250177403" OR "20250177404" OR "8030304" OR "8563718").pn.					
L19	1	"20250195527".pn.	(US-PGPUB)	OR	ON	ON	2026/01/20 12:34 PM
L20	28	(Artificial Intelligence) More like doc: US-20250195527-A1 Text: (JP-H0971528-A OR AU-2007231549-A1 OR US-20100203048-A1 OR HU-E068315-T2 OR BR-112020002967-A2 OR WO-2019036472-A1 OR US-20250177404-A1 OR EP-3784233-B1 OR HK-40040045-B OR US-20250195527-A1 OR US-20250177403-A1 OR HK-40040045-A OR US-20250064812-A1 OR AU-2023203095-A1 OR CA-3098562-A1 OR BR-112020024062-A2 OR US-20210038604-A1 OR US-20240285593-A1 OR EP-4643950-A2 OR EP-4438124-A2).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2026/01/20 12:34 PM
L21	13	L20 AND (adrenal adj6 rest adj6 (tumor* OR tumour* OR neoplasm*))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT;	OR	ON	ON	2026/01/20 12:36 PM

			IBM_TDB)				
L22	162	(a61k31/519,5377 OR a61k9/0053,20,2004,48,4841 OR a61p5/06,08 OR a61p35/00).cpc. AND (adrenal adj8 rest adj8 (tumor* OR tumour* OR neoplasm*))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2026/01/20 12:39 PM
L23	90	L22 AND (CRF1 OR CRFI OR (corticotropin WITH releas* WITH factor))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2026/01/20 12:41 PM
L24	11	(CRF1 OR CRFI OR (corticotropin WITH releas* WITH factor)) AND (adrenal adj8 rest adj8 (tumor* OR tumour* OR neoplasm*)) AND (L7 OR L8)	(US-PGPUB; USPAT)	OR	ON	ON	2026/01/20 12:46 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	10	(a61k31/519,5377 OR a61k9/0053,20,2004,48,4841 OR a61p5/06,08 OR a61p35/00).cpc. AND (corticotropin adj8 releas* adj8 factor adj8 (antagon* OR block* OR suppress* OR decreas* OR reduc*)) AND (adrenal adj8 rest	(US-PGPUB; USPAT)	OR	ON	ON	2025/12/03 12:28 PM

		adj8 (tumor* OR neoplasm* OR growth*))					
N2	34	(CRF1 OR CRFI OR (corticotropin WITH releas* WITH factor)) AND (adrenal adj8 rest adj8 (tumor* OR tumour* OR neoplasm*))	(US-PGPUB; USPAT)	OR	ON	ON	2026/01/20 12:43 PM

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	21	Attorney Docket Number	50535-710.305

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	001	US-8030304	10-04-2011	CHEN et al.	
	002	US-8563718	10-22-2013	RIZZO; John Robert et al.	
	003	US-11708372	07-25-2023	REDDY; Dasharatha et al.	
	004	US-11858932	01-02-2024	BARNES; Christopher et al.	
	005	US-12098152	09-24-2024	BARNES; Christopher et al.	
	006	US-20020013357	01-31-2002	NADKARNI; Sreekant et al.	
	007	US-20030008885	01-09-2003	HE; Liqi et al.	
	008	US-20050209250	09-22-2005	ROMANO; Steve	
	009	US-20060078623	04-13-2006	DHOOT; Nikhil et al.	
	010	US-20090076266	03-19-2009	DAUGULIS; Olafs et al.	
	011	US-20100022560	01-28-2010	CHEN; Zhaogen et al.	
	012	US-20100155595	06-24-2010	GHOSHAL; Amit et al.	
	013	US-20110136865	06-09-2011	BUNTINX; Erik	
	014	US-20110160168	06-30-2011	DHINGRA; Om	
	015	US-20110166345	07-07-2011	RIZZO; John Robert et al.	
	016	US-20130045979	02-21-2013	SANFILIPPO; Louis	
	017	US-20170333126	11-23-2017	SOBOTKA; Paul	

EXAMINER SIGNATURE			
Examiner Signature	/SARAH PIHONAK/	Date Considered	01/20/2026

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				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	2	of	21	Attorney Docket Number	50535-710.305

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	018	US-20180110554	04-26-2018	ZARINS; Denise Marie et al.	
	019	US-20190262349	08-29-2019	HOWERTON; Alexis et al.	
	020	US-20200255436	08-13-2020	HOWERTON; Alexis et al.	
	021	US-20210015827	01-21-2021	HOWERTON; Alexis et al.	
	022	US-20210038604	02-11-2021	HOWERTON; Alexis et al.	
	023	US-20210137935	05-13-2021	HOWERTON; Alexis et al.	
	024	US-20210322430	10-21-2021	HOWERTON; Alexis et al.	
	025	US-20210361664	11-25-2021	HOWERTON; Alexis et al.	
	026	US-20220133742	05-05-2022	GHOSH; Sangita et al.	
	027	US-20220133742	05-05-2022	GHOSH; Sangita et al.	
	028	US-20230159533	05-25-2023	REDDY; Dasharatha et al.	
	029	US-20230321112	10-12-2023	HOWERTON; Alexis et al.	
	030	US-20230414627	12-28-2023	HOWERTON; Alexis et al.	
	031	US-20240043432	02-08-2024	REDDY; Dasharatha et al.	
	032	US-20240261300	08-08-2024	GHOSH; Sangita et al.	
	033	US-20240293421	09-05-2024	REDDY; Dasharatha et al.	

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Examiner Signature	/SARAH PIHONAK/	Date Considered	01/20/2026

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	034	US-20250064812	02-27-2025	HOWERTON; Alexis et al.	
	035	US-20250177403	06-05-2025	HOWERTON; Alexis et al.	
	036	US-20250177404	06-05-2025	HOWERTON; Alexis et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	CN-101516835-A	08-26-2009	OSURF OHIO STATE UNIVERSITY RE [US]	Abstract:	☒
	002	JP-2000302693-A	10-31-2000	PFIZER PROD INC	Abstract:	☒
	003	WO-0059908-A2	10-12-2000	DU PONT PHARM CO [US]		☐
	004	WO-0123388-A2	04-05-2001	NEUROGEN CORP [US], et al.		☐
	005	WO-02072202-A1	09-19-2002	BRISTOL MYERS SQUIBB PHARMA CO [US]		☐

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				Examiner Name	PIHONAK, SARAH
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	006	WO-2005020910-A2	03-10-2005	PHARMACIA CORP [US], et al.		☐
	007	WO-2005063755-A1	07-14-2005	SB PHARMCO INC [US], et al.		☐
	008	WO-2005079868-A2	09-01-2005	SB PHARMCO INC [US], et al.		☐
	009	WO-2006102194-A1	09-28-2006	LILLY CO ELI [US], et al.		☐
	010	WO-2010039678-A1	04-08-2010	LILLY CO ELI [US], et al.		☐
	011	WO-2013160317-A2	10-31-2013	HOLSBOERMASCHMEYER NEUROCHEMIE GMBH [DE]		☐
	012	WO-2020115555-A2	06-11-2020	NEUROCRINE BIOSCIENCES INC [US], et al.		☐
	013	WO-2021016208-A1	01-28-2021	SPRUCE BIOSCIENCES INC [US]		☐
	014	WO-2022036123-A1	02-17-2022	SPRUCE BIOSCIENCES INC [US]		☐
	015	WO-2023091684-A1	05-25-2023	SPRUCE BIOSCIENCES INC [US]		☐

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Sheet	5	of	21	Attorney Docket Number	50535-710.305

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	016	WO-9413676-A1	06-23-1994	PFIZER [US], et al.		☐
	017	WO-9729109-A1	08-14-1997	JANSSEN PHARMACEUTICA NV [BE], et al.		☐
	018	WO-9803510-A1	01-29-1998	DU PONT MERCK PHARMA [US]		☐
	019	WO-9808847-A1	03-05-1998	PFIZER [US], et al.		☐

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				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	6	of	21	Attorney Docket Number	50535-710.305

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	001	ABCAM CP 154526 Hydrochloride, Non-Peptide CRF1 Receptor Antagonist AB141429. [Internet] ABCAM. Retrieved from URL: https://www.abcam.com/products/biochemicals/cp-154526-hydrochloride-non-peptide-crf1-receptor-antagonist-ab141429.html. 2 pages.	☐
	002	AUCHUS, Richard J. et al. Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. New England Journal of Medicine 391(6):504-514 (2024).	☐
	003	AUCHUS, Richard J. et al. Supplemental Information: Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. New England Journal of Medicine 391(6):504-514 (2024).	☐
	004	AUCHUS, Richard J. Management Considerations for the Adult With Congenital Adrenal Hyperplasia. Molecular and Cellular Endocrinology 408:190-197 (2015).	☐
	005	AVILA, N. A. et al. Testicular adrenal rest tissue in congenital adrenal hyperplasia: serial sonographic and clinical findings. AJR. American journal of roentgenology 172(5):1235-1238 (1999).	☐
	006	AYCAN, Zehra et al. Prevalence and long-term follow-up outcomes of testicular adrenal rest tumours in children and adolescent males with congenital adrenal hyperplasia. Clinical endocrinology 78(5):667-672 (2013).	☐
	007	BORNSTEIN et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 101(2):364-389 (2016).	☐
	008	CHEN, C., Recent Advances in Small Molecule Antagonists of the Corticotropin-Releasing Factor Type-1 Receptor-Focus on Pharmacology and Pharmacokinetics. Current Medicinal Chemistry 13:1261-1282 (2006).	☐

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Examiner Signature		Date Considered	

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
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	009	CHEN et al. Design of 2,5-Dimethyl-3-(6-dimethyl-4-methylpyridin-3-yl)-7-dipropyl aminopryazolo[1,5-a]pyrimidine (NBI 30775/R121919) and Structure-Activity Relationships of a Series of Potent and Orally Active Corticotropin- Releasing Factor Receptor Antagonists. J Med Chem 47(19):4787-4798 (2004).	☐
	010	CLAAHSEN-VAN DER GRINTEN, H. L. et al. Testicular adrenal rest tumours in congenital adrenal hyperplasia. International Journal of pediatric endocrinology 2009:624823, 1-8 (2009).	☐
	011	CLAAHSEN-VAN DER GRINTEN, Hedi L. et al. Prevalence of testicular adrenal rest tumours in male children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. European journal of endocrinology 157(3):339-344 (2007).	☐
	012	CLAAHSEN-VAN DER GRINTEN, Hedi L. et al. Repeated successful induction of fertility after replacing hydrocortisone with dexamethasone in a patient with congenital adrenal hyperplasia and testicular adrenal rest tumors. Fertility and Sterility 88(3):705.e5-705.e8 (2007).	☐
	013	ClinicalTrials.gov Identifier: NCT04457336. A Ph2b to Evaluate Clinical Efficacy and Safety of Tildacerfont in Adult CAH, Record created June 25, 2020. pp. 1-17. [retrieved on 2025-08-12] Available at URL: https://clinicaltrials.gov/study/NCT04457336.	☐
	014	DAVE. Overview of pharmaceutical excipients used in tablets and capsules. https://www.drugtopics.com/view/overview-pharmaceutical-excipients-used-tablets-and-capsules (10/24/2008) 52 pages.	☐
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	016	DELFINO, Michele et al. Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia: prevalence and sonographic, hormonal, and seminal characteristics. Journal of ultrasound in medicine 31(3):383-388 (2012).	☐
	017	DO, Hien-Quang et al. A General Method for Copper-Catalyzed Arylation of Arene C-H Bonds. J Am Chem Soc. 130(45):15185-15192 (2008).	☐
	018	DO, Hien-Quang et al. Copper-Catalyzed Arylation and Alkenylation of Polyfluoroarene C-H Bonds. Journal of American Chemical Society 130(4):1128-1129 (2008).	☐
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	020	DO, Hien-Quang et al. Copper-Catalyzed Arylation of Heterocycle C-H Bonds. J Am Chem Soc. 129(41):12404-12405 (2007).	☐
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	023	EP19793181.9 Brief Communication - Opposition Proceedings dated August 5, 2025.	☐
	024	EP19793181.9 Letter from the Opponent - Opposition Proceedings dated March 6, 2025.	☐
	025	EP19793181.9 Reply from the opponent to submission of proprietor dated July 18, 2025.	☐
	026	EP19793181.9 Reply of the Patent Proprietor to the notice(s) of opposition dated June 18, 2025.	☐

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	027	ESCOBAR-MORREALE, HF., Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 14(5):270-284 (2018).	☐
	028	FAHMY, Hesham et al. Structure and Function of Small Non-Peptide CRF Antagonists and their Potential Clinical Use. Current Molecular Pharmacology 10(4):270-281 (2017).	☐
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	030	FUQUA et al. Duration of suppression of adrenal steroids after glucocorticoid administration. Int J Pediatr Endocrinol 2010:712549 (2010).	☐
	031	GEHLERT, Donald R. 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 27(10):2718-2726 (2007).	☐
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	035	JOSEPH, Dana N. et al. Stress and the HPA axis: balancing homeostasis and fertility. International journal of molecular sciences 18(10):2224, 1-15 (2017).	☐
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	038	MA, Li et al. Sonographic features of the testicular adrenal rests tumors in patients with congenital adrenal hyperplasia: a single-center experience and literature review. Orphanet Journal of Rare Diseases 14(1):242, 1-8 (2019).	☐
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	043	MILLION, Mulugeta et al., A Novel Water-Soluble Selective CRF1 Receptor Antagonist, NBI 35965, Blunts Stress-Induced Visceral Hyperalgesia and Colonic Motor Function in Rats. Brain Research, 985(1):32-42 (2003).	☐
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	046	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Defence dated March 13, 2025 (Claim No. HP-2025-000005) (pp. 1-3).	☐
	047	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Grounds of Invalidity dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	048	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Particulars of Claim dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	049	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Granting Institution of Post-Grant Review of U.S. Patent No. 10,849,908 dated December 1, 2023 (pp 1-57) (PGR2021-00088).	☐
	050	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Patent Owner's Response in U.S. Patent No. 12,115,166 dated July 8, 2025 (pp 1-6) (PGR-2025-00032).	☐

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	051	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petition for Post Grant Review of U.S. Patent No. 12,115,166 dated February 10, 2025 (pp 1-59).	☐
	052	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petitioner's Reply to Patent Owner's Response in U.S. Patent No. 10,849,908 dated June 20, 2024 (pp. 1-38) (PGR2021-00088).	☐
	053	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petitioner's Reply to Patent Owner's Response in U.S. Patent No. 11,007,201 dated June 20, 2024 (pp. 1-36) (PGR2022-00025).	☐
	054	Neurocrine Biosciences, Inc. (Plaintiff) v. Spruce Biosciences, Inc. (Defendant). Memorandum dated June 9, 2025 (Case No. 1:25-cv-00059-JDW (pp. 1-10).	☐
	055	NISSEN, Trygve et al. The clinical case report: a review of its merits and limitations. BMC Research Notes 7:264, 1-7 (2014).	☐
	056	O'REILLY, Michael W. et al. 11-oxygenated C19 steroids are the predominant androgens in polycystic ovary syndrome. J Clin Endocrinol Metab. 102(3):840-848 (2017).	☐
	057	PCT/US2007/078605 International Search Report and Written Opinion dated January 31, 2008.	☐
	058	PCT/US2009/058722 International Search Report and Written opinion dated January 25, 2010.	☐
	059	PCT/US2018/046707 International Search Report and Written Opinion dated October 24, 2018.	☐
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	061	PCT/US2020/042820 International Search Report and Written Opinion dated November 25, 2020.	☐
	062	PCT/US2021/045780 International Search Report and Written Opinion dated December 17, 2021.	☐
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	064	REISCH, Nicole et al. High prevalence of reduced fecundity in men with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology and Metabolism 94(5):1665-1670 (2009).	☐
	065	ROSENFIELD et al., The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocrine Reviews 37(5):467-520 (2016).	☐
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	070	Spruce Biosciences announces topline results from CAHMELIA-204 in adult CAH and CAHPTAIN-205 in adult and pediatric CAH. Spruce Biosciences :1-4 (2024).	☐
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	075	The Journal of Clinical Endocrinology and Metabolism Author Guidelines. Oxford Academic (2025); [retrieved on 2025-06-09]. Available at URL: https://academic.oup.com/jcem/pages/author_guidelines.	☐
	076	TRAPP et al. Congenital adrenal hyperplasia: an update in children. Curr Opin Endocrinol Diabetes Obes. 18(3):166-70 (2011).	☐
	077	TURCU, Adina F. et al. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinology and Metabolism Clinics 44(2):275-296 (2015).	☐
	078	TURCU, Adina F. et al. Novel treatment strategies in congenital adrenal hyperplasia. Current Opinion in Endocrinology, Diabetes and Obesity 23(3):225-232 (2016).	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	15	of	21	Attorney Docket Number	50535-710.305

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	079	TURCU, Adina F. et al. Single-dose study of a corticotropin-releasing factor receptor-1 antagonist in women with 21-hydroxylase deficiency. The Journal of Clinical Endocrinology and Metabolism 101(3):1174-1180 (2016).	☐
	080	TURCU, Adina F. et al. Supplemental Information: Single-dose study of a corticotropin-releasing factor receptor-1 antagonist in women with 21-hydroxylase deficiency. The Journal of Clinical Endocrinology and Metabolism 101(3):1174-1180 (2016).	☐
	081	U.S. Provisional Application No. 62/822,815 filed on March 23, 2019.	☐
	082	U.S. Serial No. 17/586,228 Office Action dated June 10, 2022.	☐
	083	U.S. Serial No. 13/063,226 Office Action dated January 24, 2013.	☐
	084	U.S. Serial No. 16/388,620 Office Action dated July 15, 2019.	☐
	085	U.S. Serial No. 16/388,620 Office Action dated November 25, 2019.	☐
	086	U.S. Serial No. 16/639,540 Office Action dated July 11, 2022.	☐
	087	U.S. Serial No. 16/639,540 Office Action dated March 28, 2024.	☐
	088	U.S. Serial No. 16/639,540 Office Action dated May 25, 2023.	☐
	089	U.S. Serial No. 16/639,540 Office Action dated November 16, 2021.	☐
	090	U.S. Serial No. 16/639,540 Office Action dated September 28, 2023.	☐

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Examiner Signature		Date Considered	

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				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	16	of	21	Attorney Docket Number	50535-710.305

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	091	U.S. Serial No. 16/639,541 Office Action dated April 4, 2022.	☐
	092	U.S. Serial No. 17/063,592 Office Action dated December 7, 2021.	☐
	093	U.S. Serial No. 17/078,054 Office Action dated December 14, 2020.	☐
	094	U.S. Serial No. 17/359,411 Office Action dated January 6, 2022.	☐
	095	U.S. Serial No. 17/359,414 Office Action dated November 16, 2021.	☐
	096	U.S. Serial No. 17/586,228 Office Action dated March 30, 2022.	☐
	097	U.S. Serial No. 17/720,074 Office Action dated August 26, 2022.	☐
	098	U.S. Serial No. 18/078,649 Office Action dated March 21,2024.	☐
	099	U.S. Serial No. 18/078,649 Office Action dated November 18, 2025.	☐
	100	U.S. Serial No. 18/078,649 Office Action dated October 9, 2024.	☐
	101	U.S. Serial No. 18/078,649 Office Action dated September 8, 2023.	☐
	102	U.S. Serial No. 18/307,718 Office Action dated October 12, 2023.	☐
	103	U.S. Serial No. 18/310,463 Office Action dated October 31, 2024.	☐
	104	U.S. Serial No. 19/043,264 Office Action dated April 25, 2025.	☐

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Examiner Signature		Date Considered	

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				Examiner Name	PIHONAK, SARAH
Sheet	17	of	21	Attorney Docket Number	50535-710.305

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	105	U.S. Serial No. 19/043,275 Office Action dated May 30, 2025.	☐
	106	U.S. Serial No. 19/043,303 Office Action dated September 5, 2025.	☐
	107	VARMA. Excipients used in the Formulation of Tablets. https://www.rroij.com/openaccess/excipients-used-in-the-formulationof-tablets-.php?aid=78260 Revised date: 26/07/2016.	☐
	108	WALDRON, James. Spruce saws off only drug after 2nd hyperplasia fail, leaving biotech's direction in doubt. Fierce Biotech :1-2 (2024).	☐
	109	WANG, Zhu et al. Diagnosis of testicular adrenal rest tumors on ultrasound: a retrospective study of 15 cases report. Medicine 94(36):e1471, 1-6 (2015).	☐
	110	WILLIAMS, John P. Corticotropin-releasing factor 1 receptor antagonists: a patent review. Expert Opin Ther Pat 23(8):1057-68 (2013).	☐
	111	World Health Organization Drug Information, 32(2):369-370 (2018).	☐
	112	YAMADA, Yasuki et al. New class of corticotropin-releasing factor (CRF) antagonists: small peptides having high binding affinity for CRF receptor. Journal of medicinal chemistry 47(5):1075-1078 (2004).	☐
	113	YASIR, Muhammad et al. Corticosteroid Adverse Effects. StatPearls, July 3, 2023; [retrieved on 2025-06-17]. Available at URL: https://www.ncbi.nlm.nih.gov/books/NBK531462/ pp. 1-14.	☐

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Sheet	18	of	21	Attorney Docket Number	50535-710.305

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	114	YU, Min Kyung et al. Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia. Annals of pediatric endocrinology and metabolism 20(3):155-161 (2015).	☐
	115	ZHANG et al. D-Level Essay in Statistics, 2009, How to Analyze Change from Baseline. Available at http://www.statistics.du.se/essays/D09 Zhang%20Ling%20&%20Han%20Kun.pdf (6/10/2009).	☐
	116	ZORRILLA, Eric P. et al., Progress in Corticotropin-Releasing Factor-1 Antagonist Development. Drug Discov Today 15(9-10):371-383 (2010).	☐
	117	ZORRILLA, Eric P. et al. The therapeutic potential of CRF1 antagonists for anxiety. Expert opinion on investigational drugs 13(7):799-828 (2004).	☐

EXAMINER SIGNATURE			
Examiner Signature	/SARAH PIHONAK/	Date Considered	01/20/2026

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	19	of	21	Attorney Docket Number	50535-710.305

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Victoria Cheng/	Date (YYYY-MM-DD)	2026-01-12
Name/Print	Victoria Cheng	Registration Number	79641

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	20	of	21	Attorney Docket Number	50535-710.305

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 01/29/2026
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

Jennifer Vail	(Typed or printed name)
/jvail/	(Signature)
2/6/2026	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,303	01/31/2025	Alexis HOWERTON	50535-710.305	1040

TITLE OF INVENTION: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1290	$0.00	$0.00	$1290	04/29/2026

EXAMINER	ART UNIT	CLASS-SUBCLASS
PIHONAK, SARAH	1627	514-233200

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 WILSON SONSINI GOODRICH & ROSATI
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: SPRUCE BIOSCIENCES, INC.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): South San Francisco, California

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☑ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☑ Electronic Payment via the USPTO patent electronic filing system ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 23-2415

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Kaia R. Parenti/ Date February 6, 2026

Typed or printed name Kaia R. Parenti Registration No. 81050

6783

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,303	**02/06/2026 01:01:53 PM Z ET**	**50535-710.305**

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 #	1040	FILED BY	JENNIFER VAIL
PATENT CENTER #	74365444	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kaia Parenti

Documents

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Spruce 50535-710.305 Issue Fee Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	106 KB

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,303	**02/06/2026 01:01:53 PM Z ET**	**50535-710.305**

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 #	1040	FILED BY	JENNIFER VAIL
PATENT CENTER #	74365444	AUTHORIZED BY	Kaia Parenti
CUSTOMER #	21971	FILING DATE	01/31/2025
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Alexis HOWERTON

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
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FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,303	03/17/2026	12576084	50535-710.305	1040

21971 7590 03/04/2026

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(application filed on or after May 29, 2000)

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If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

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INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

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Spruce Biosciences, Inc., South San Francisco, CA;

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1776 – 2026

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The Director

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If the application for this patent was filed on or after June 8, 1995, the term of this patent begins on the date on which this patent issues and ends twenty years from the filing date of the application or, if the application contains a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121, 365(c), or 386(c), twenty years from the filing date of the earliest such application ("the twenty-year term"), subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b), and any extension as provided by 35 U.S.C. 154(b) or 156 or any disclaimer under 35 U.S.C. 253.

If this application was filed prior to June 8, 1995, the term of this patent begins on the date on which this patent issues and ends on the later of seventeen years from the date of the grant of this patent or the twenty-year term set forth above for patents resulting from applications filed on or after June 8, 1995, subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b) and any extension as provided by 35 U.S.C. 156 or any disclaimer under 35 U.S.C. 253.

Form PTO-377C (Rev 09/17)

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(12) **United States Patent**
Howerton et al.

(10) **Patent No.: US 12,576,084 B2**
(45) **Date of Patent: *Mar. 17, 2026**

(54) **METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS**

(71) Applicant: **Spruce Biosciences, Inc.**, South San Francisco, CA (US)

(72) Inventors: **Alexis Howerton**, San Francisco, CA (US); **Hal Gerber**, San Francisco, CA (US)

(73) Assignee: **SPRUCE BIOSCIENCES, INC.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **19/043,303**

(22) Filed: **Jan. 31, 2025**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 18/941,832, filed on Nov. 8, 2024, which is a continuation of application No. 17/667,285, filed on Feb. 8, 2022, now abandoned, which is a continuation of application No. 17/081,694, filed on Oct. 27, 2020, now Pat. No. 11,304,950, which is a continuation of application No. PCT/US2019/029486, filed on Apr. 26, 2019.

(60) Provisional application No. 62/822,815, filed on Mar. 23, 2019, provisional application No. 62/663,951, filed on Apr. 27, 2018.

(51) **Int. Cl.**

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CPC ***A61K 31/519*** (2013.01); *A61K 9/0053* (2013.01); *A61K 9/20* (2013.01); *A61K 9/48* (2013.01); *A61K 45/06* (2013.01); *A61P 5/06* (2018.01); *A61P 5/08* (2018.01)

(58) **Field of Classification Search**

CPC A61K 31/519; A61K 31/5377; A61K 9/0053; A61K 9/20; A61K 9/2004; A61K 9/48; A61K 9/4841; A61P 5/06; A61P 5/08; A61P 35/00

See application file for complete search history.

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Primary Examiner — Sarah Pihonak

(74) *Attorney, Agent, or Firm* — WILSON SONSINI GOODRICH & ROSATI

(57) **ABSTRACT**

Provided herein are compounds and pharmaceutical compositions for the prevention and treatment of testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART).

19 Claims, 14 Drawing Sheets

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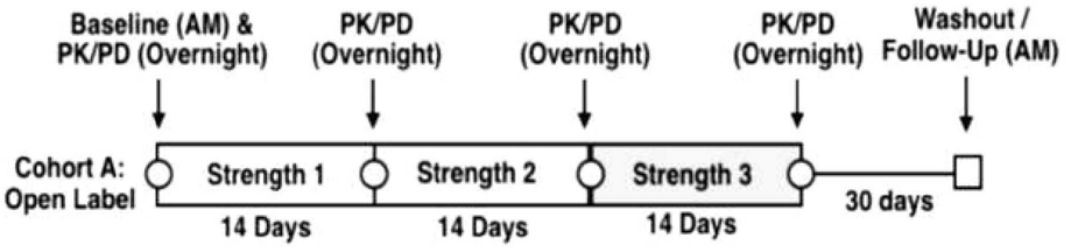

Baseline (AM) & PK/PD (Overnight)
PK/PD (Overnight)
PK/PD (Overnight)
PK/PD (Overnight)
Washout / Follow-Up (AM)
Cohort A: Open Label
Strength 1
Strength 2
Strength 3
30 days
14 Days
14 Days
14 Days

FIG. 1A

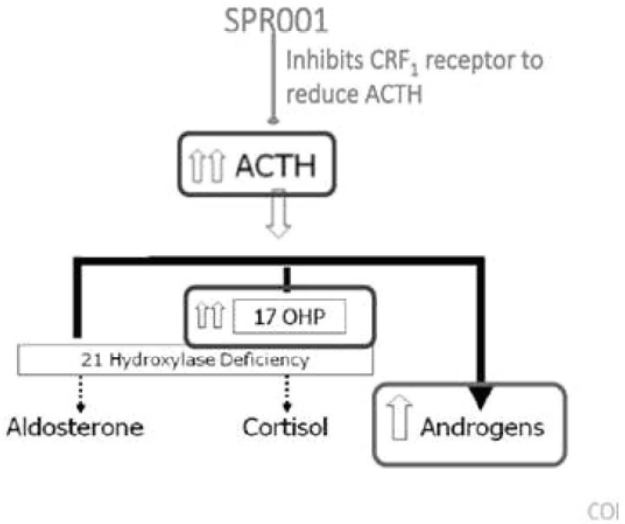

SPR001
Inhibits CRF1 receptor to reduce ACTH
ACTH
17 OHP
21 Hydroxylase Deficiency
Aldosterone
Cortisol
Androgens

FIG. 1B

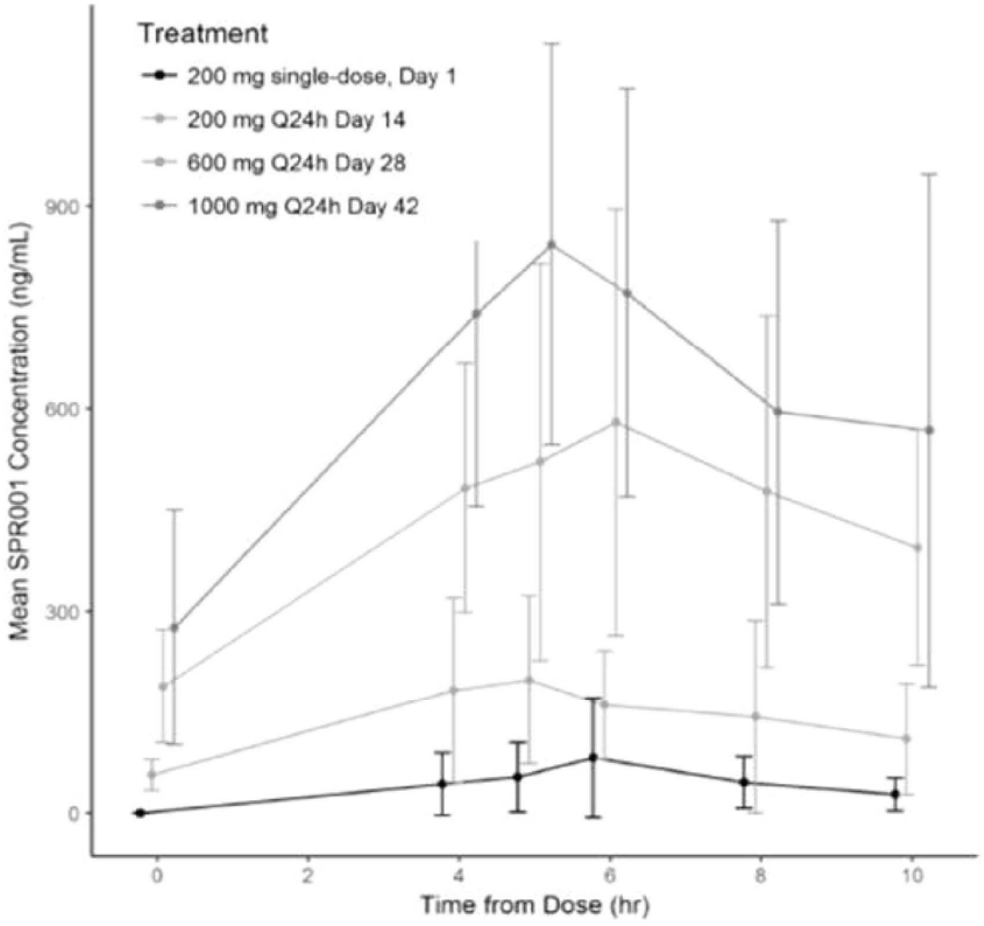

Treatment
200 mg single-dose, Day 1
200 mg Q24h Day 14
600 mg Q24h Day 28
1000 mg Q24h Day 42
Mean SPR001 Concentration (ng/mL)
0
300
600
900
0
2
4
6
8
10
Time from Dose (hr)

FIG. 2

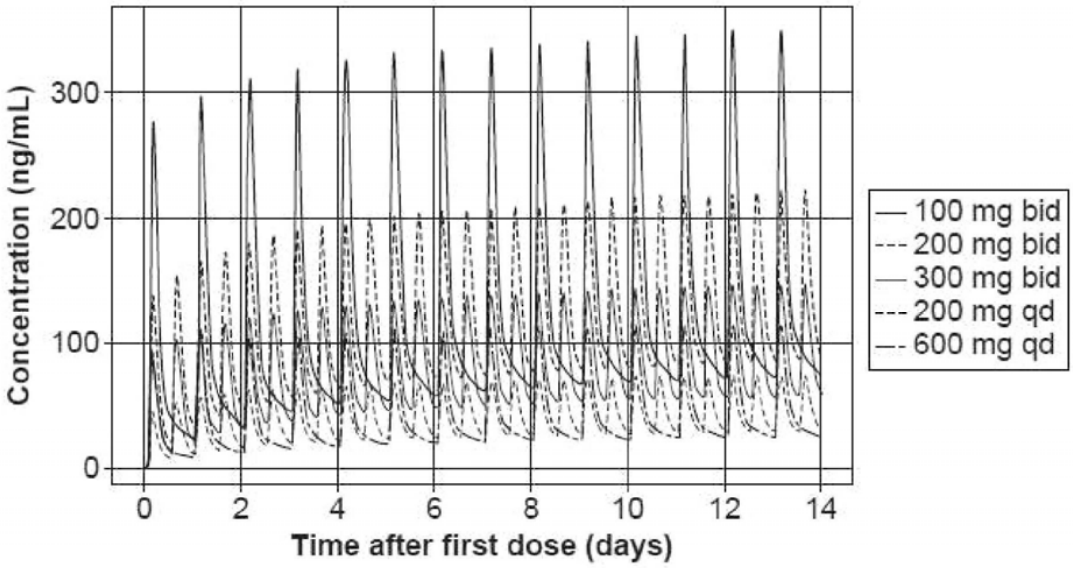

Concentration (ng/mL)
300
200
100
0
0
2
4
6
8
10
12
14
Time after first dose (days)
100 mg bid
200 mg bid
300 mg bid
200 mg qd
600 mg qd

FIG. 3

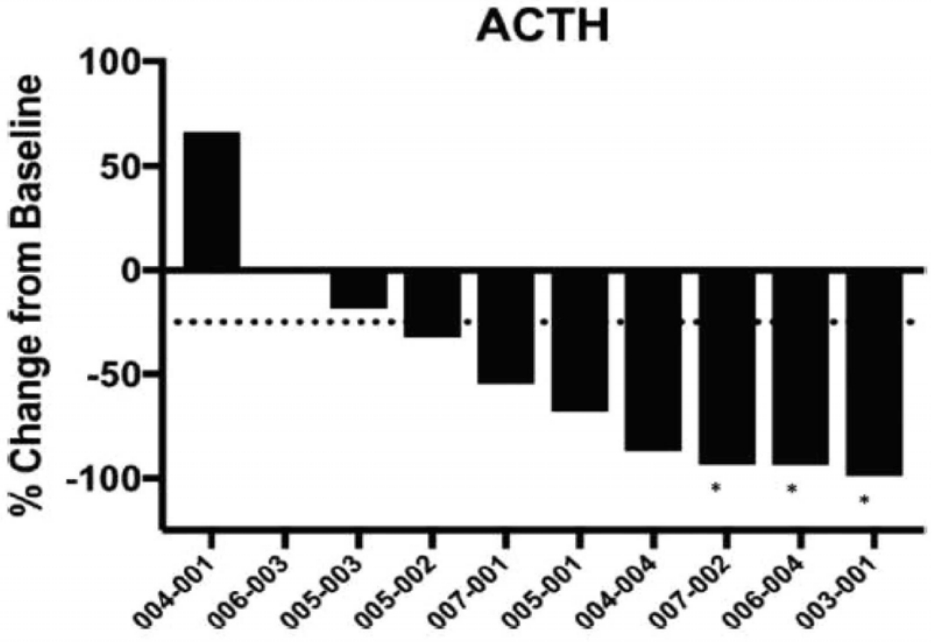

ACTH
% Change from Baseline
100
50
0
-50
-100
*
*
*
004-001
006-003
005-003
005-002
007-001
005-001
004-004
007-002
006-004
003-001

FIG. 4

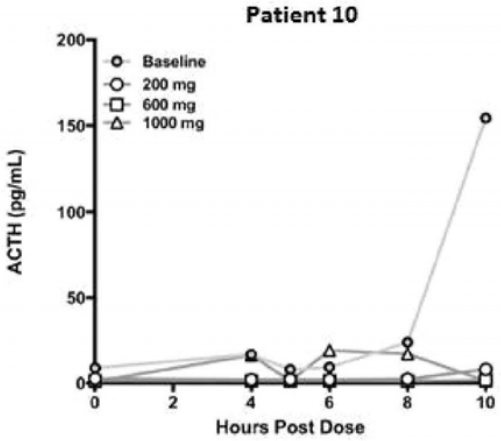


FIG. 5A

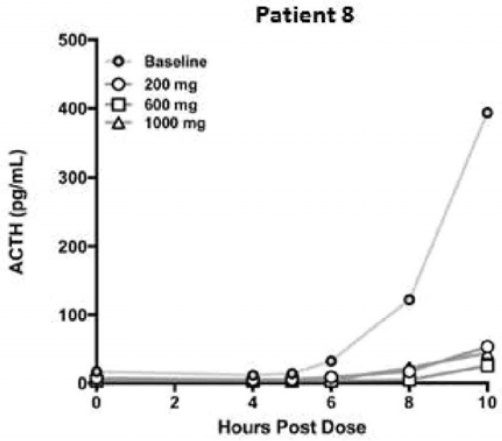


FIG. 5B

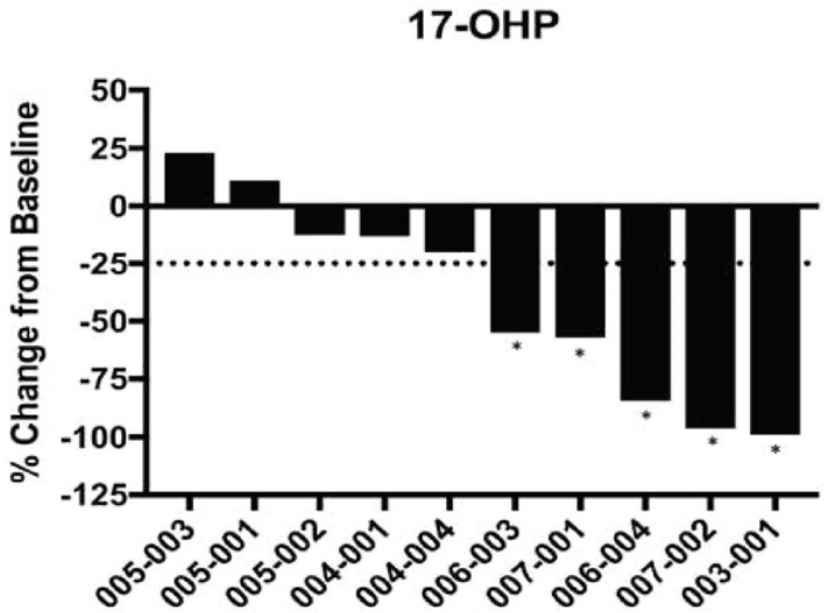


FIG. 6

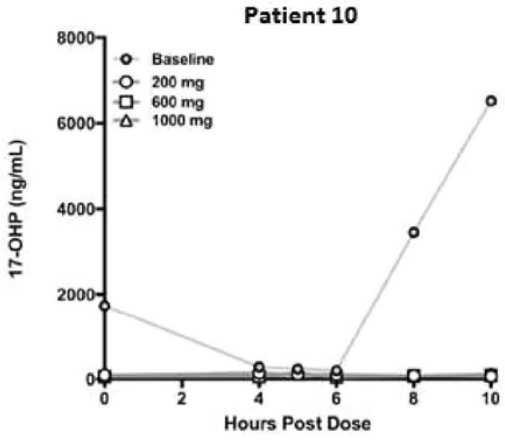


FIG. 7A

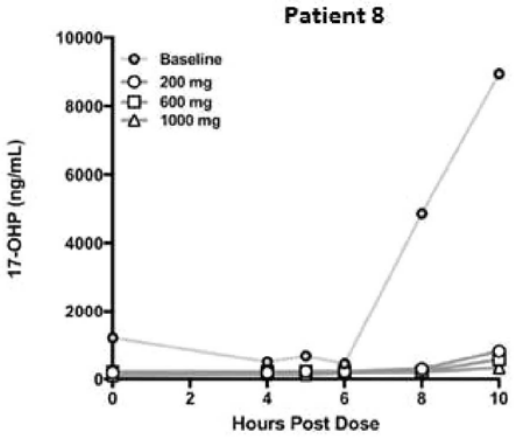


FIG. 7B

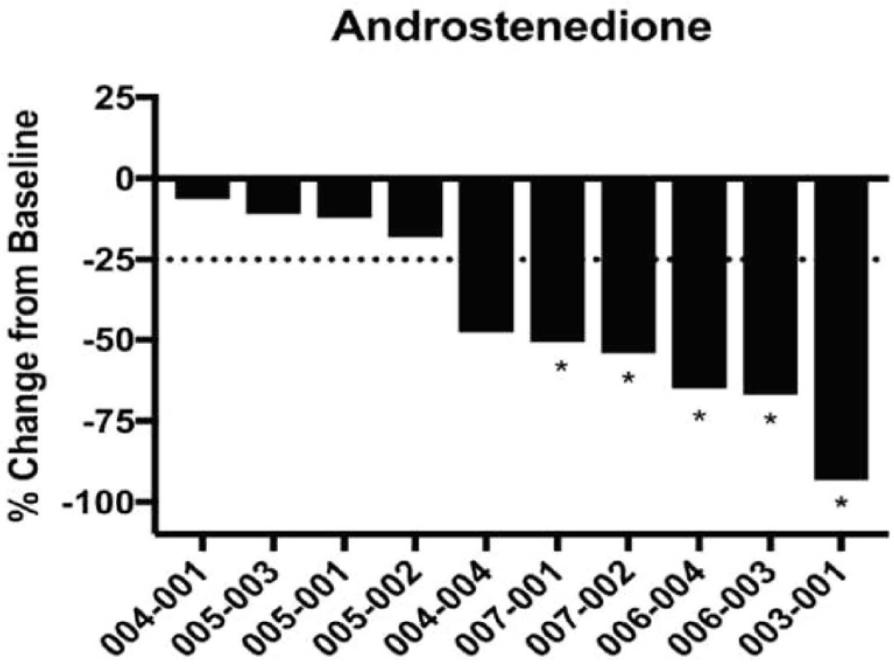


FIG. 8

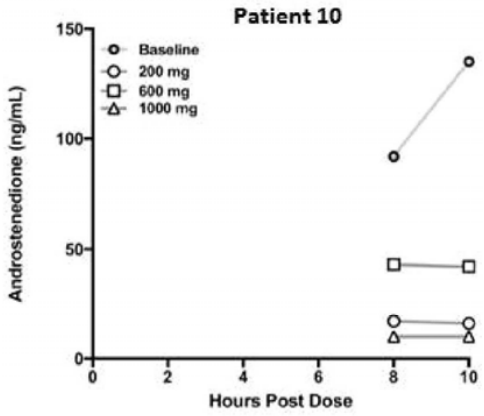


FIG. 9A

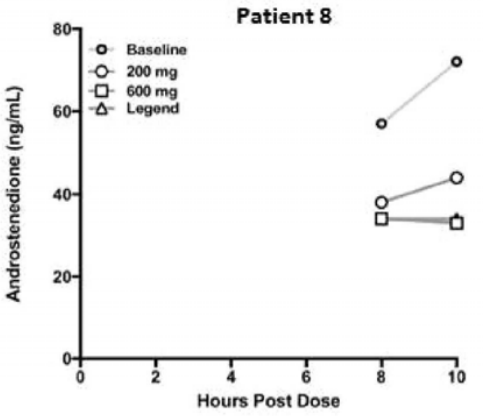


FIG. 9B

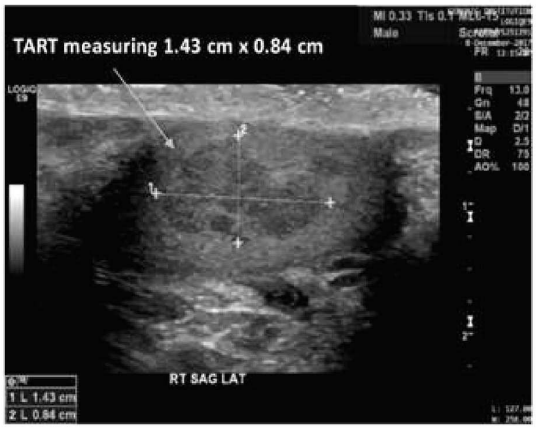


FIG. 10A

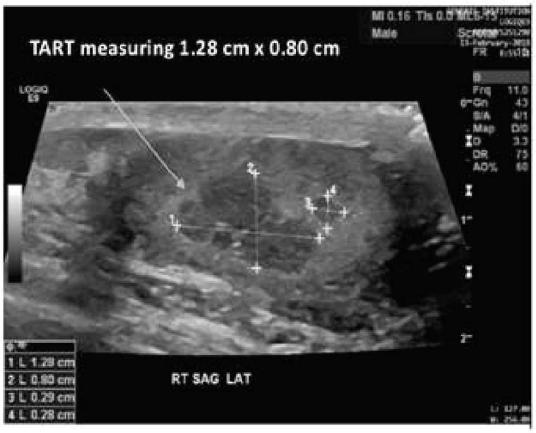


FIG. 10B

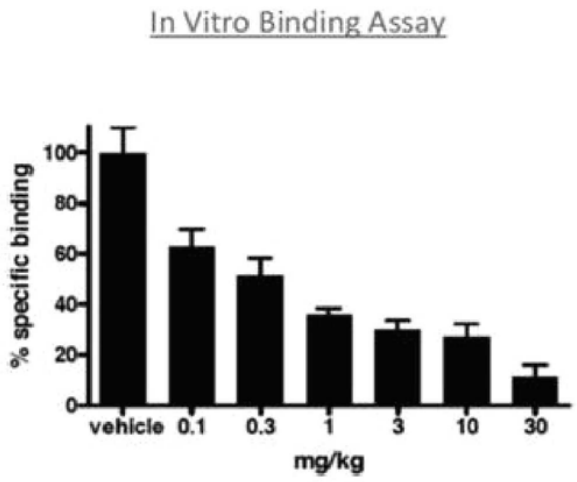


FIG. 11A

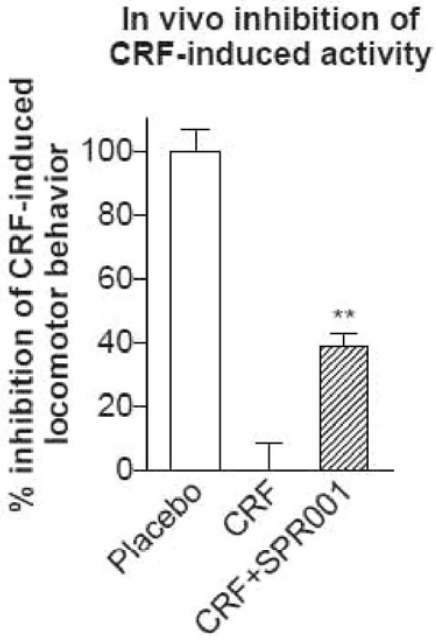


FIG. 11B

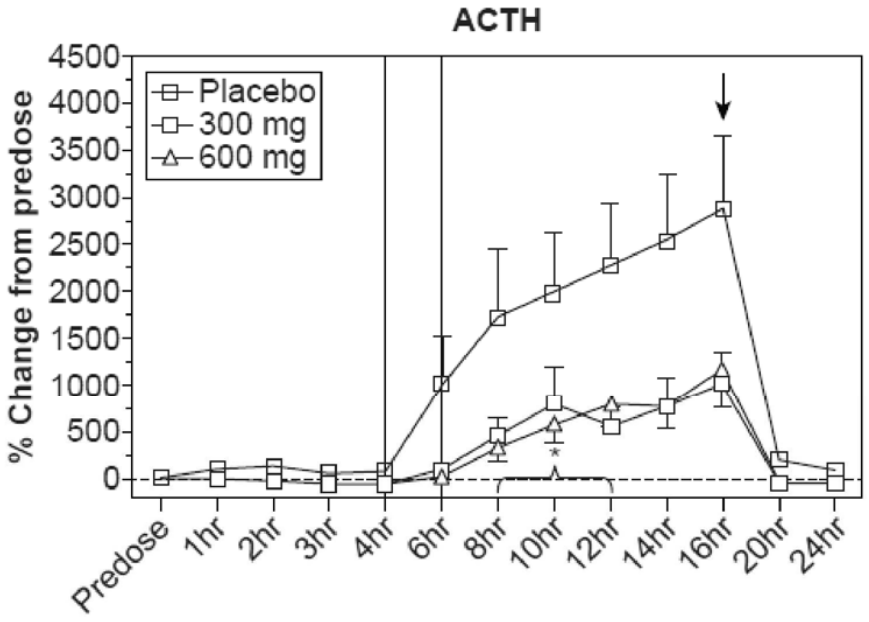


FIG. 12A

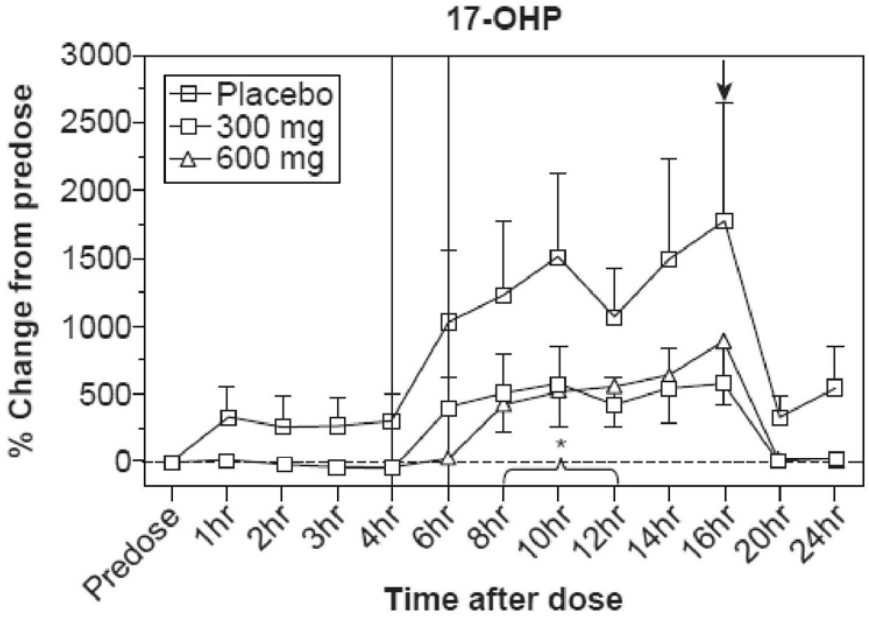


FIG. 12B

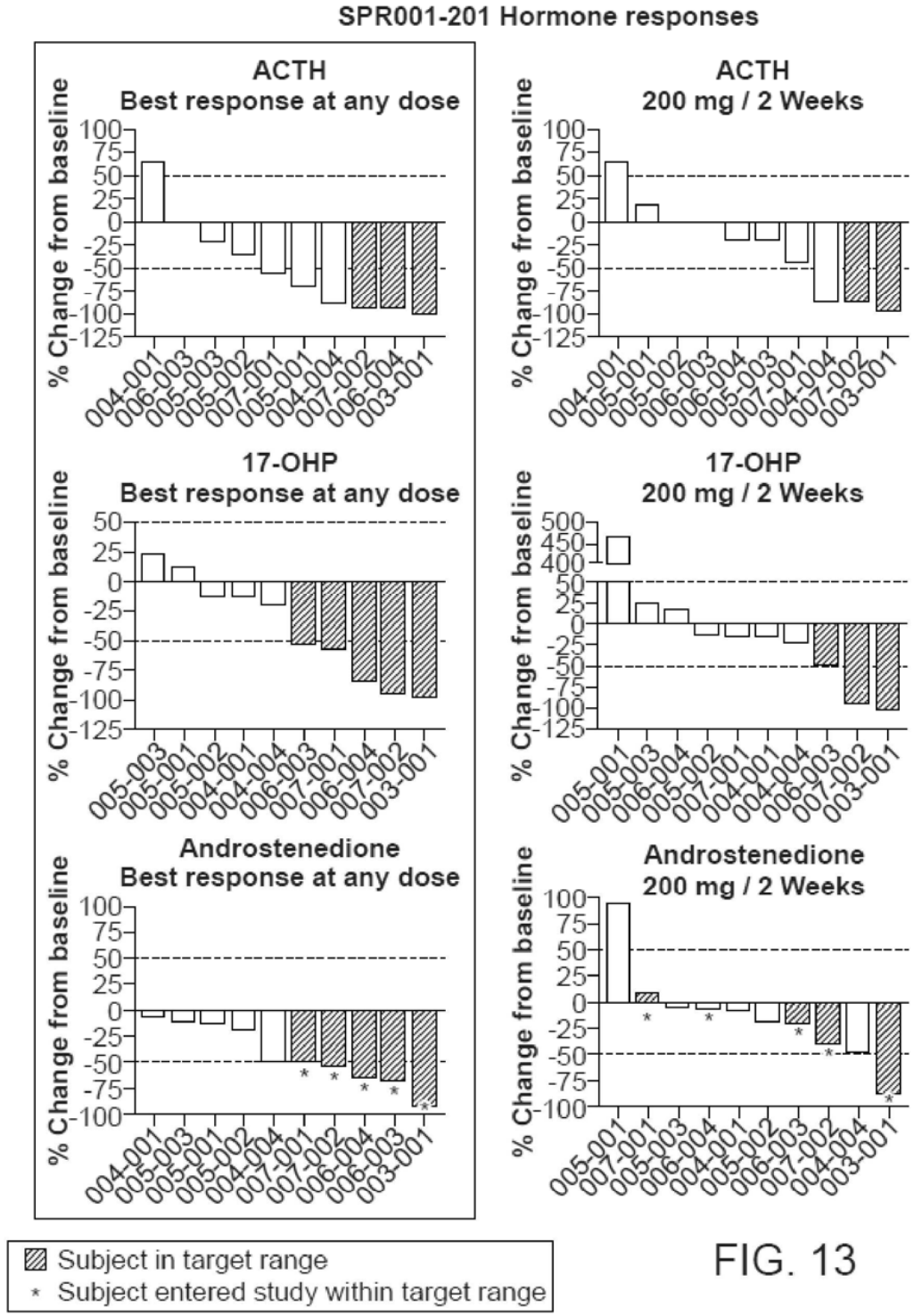


FIG. 13

ACTH: 7.2-63.3 pg/mL 17-OHP: <1200 ng/dL A4: 41-262 ng/dL (M) 27-152 ng/dL (F)

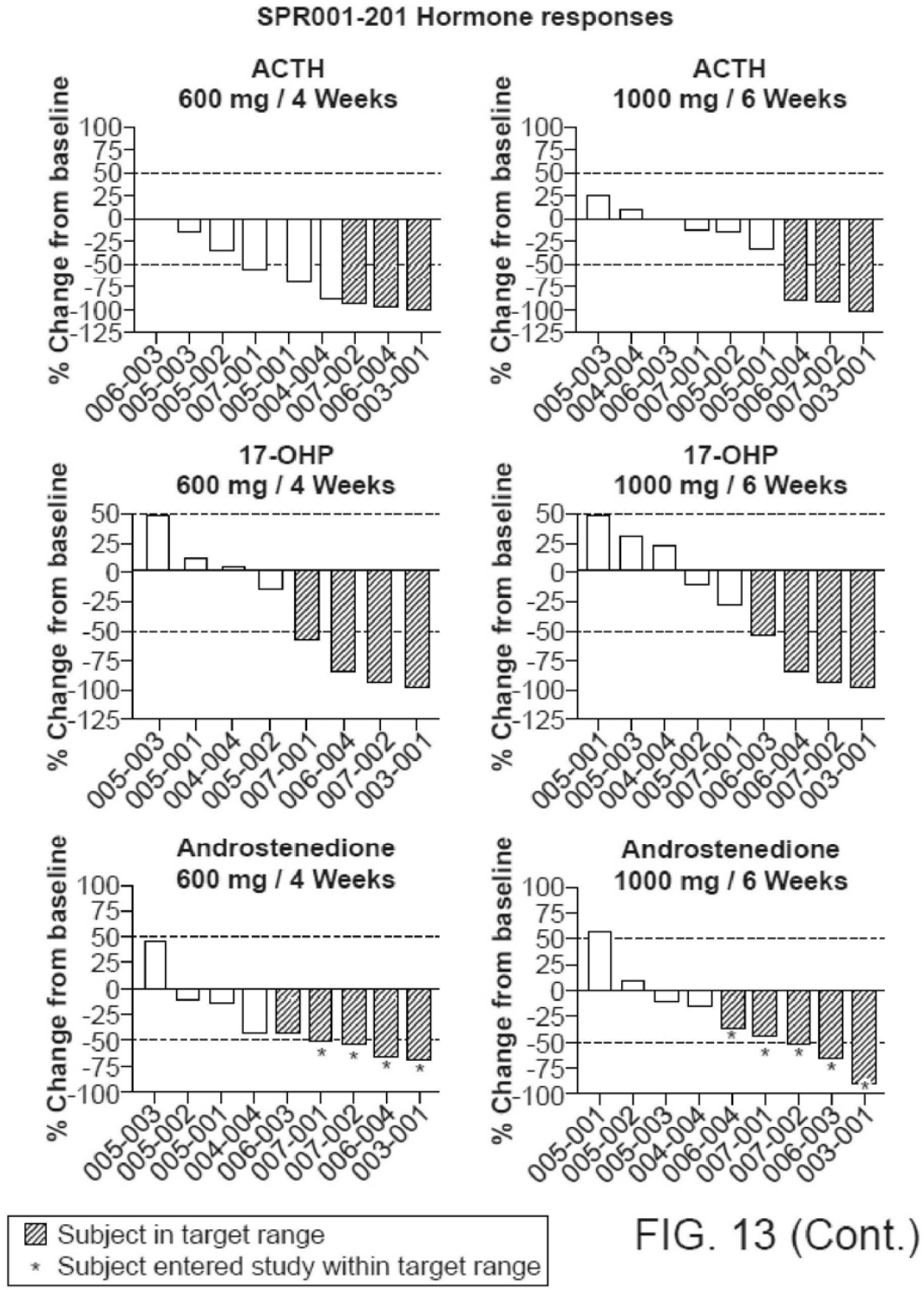


FIG. 13 (Cont.)

ACTH: 7.2-63.3 pg/mL 17-OHP: <1200 ng/dL A4: 41-262 ng/dL (M) 27-152 ng/dL (F)

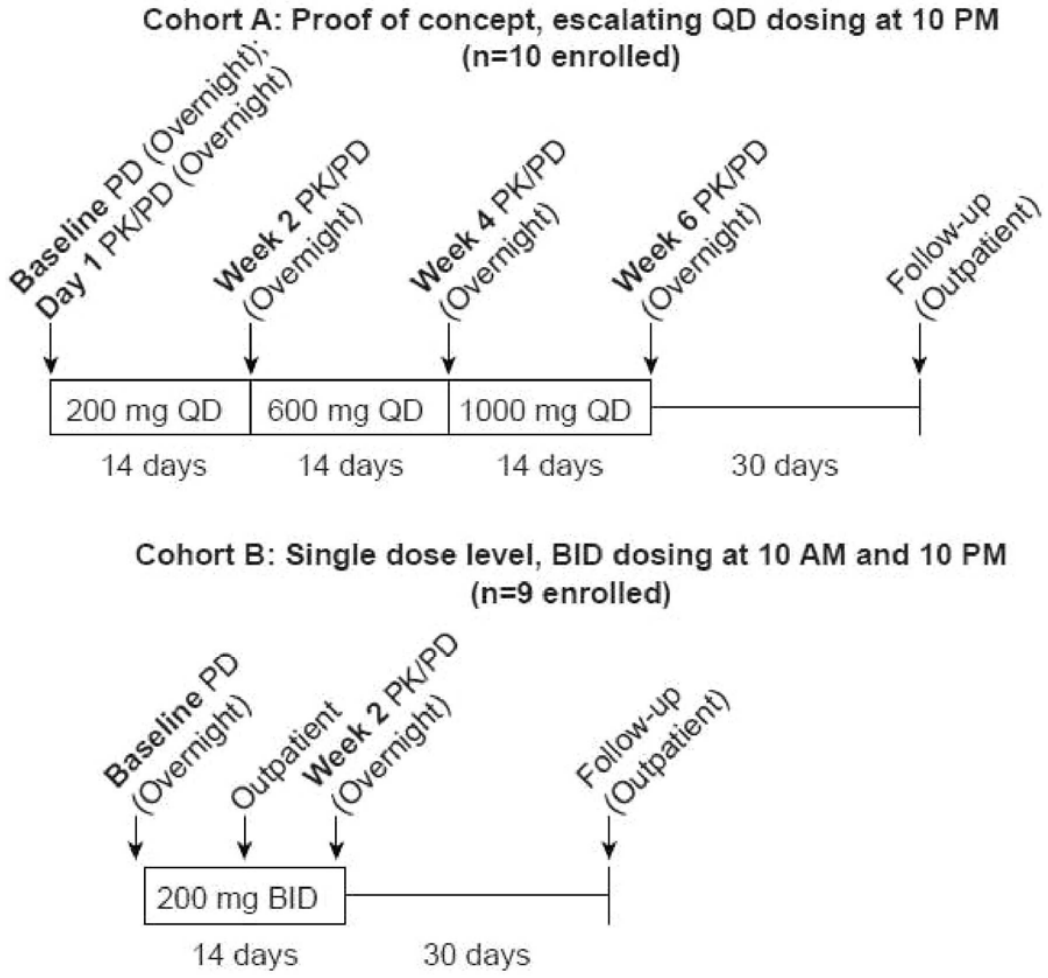

Cohort A: Proof of concept, escalating QD dosing at 10 PM
(n=10 enrolled)
Baseline PD (Overnight);
Day 1 PK/PD (Overnight)
Week 2 PK/PD
(Overnight)
Week 4 PK/PD
(Overnight)
Week 6 PK/PD
(Overnight)
Follow-up
(Outpatient)
200 mg QD
600 mg QD
1000 mg QD
14 days
14 days
14 days
30 days
Cohort B: Single dose level, BID dosing at 10 AM and 10 PM
(n=9 enrolled)
Baseline PD
(Overnight)
Outpatient
Week 2 PK/PD
(Overnight)
Follow-up
(Outpatient)
200 mg BID
14 days
30 days

FIG. 14

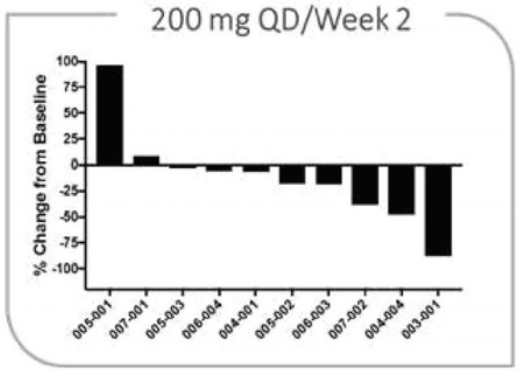


FIG. 15A

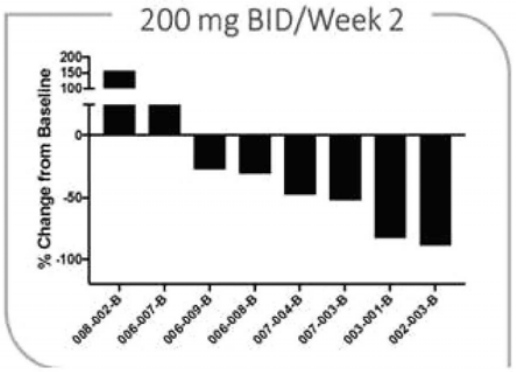


FIG. 15B

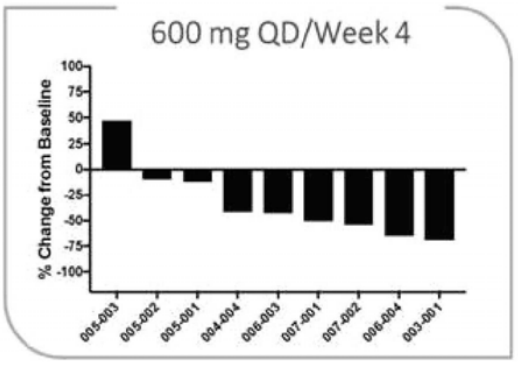


FIG. 15C

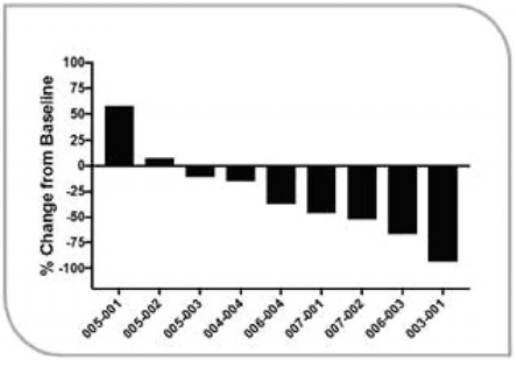


FIG. 15D

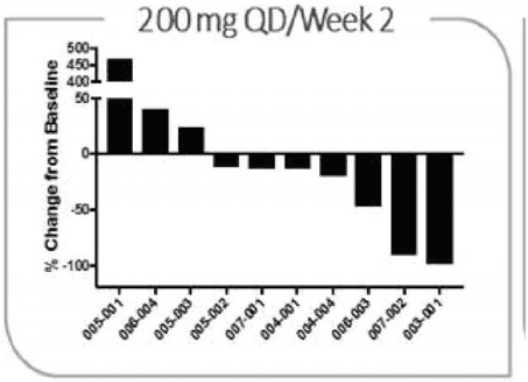


FIG. 16A

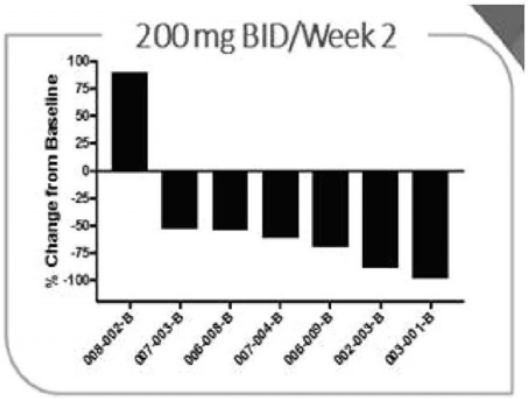


FIG. 16B

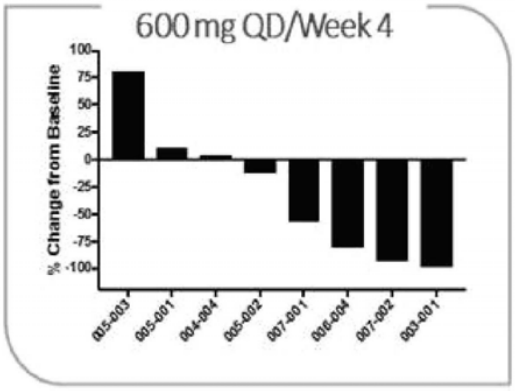


FIG. 16C

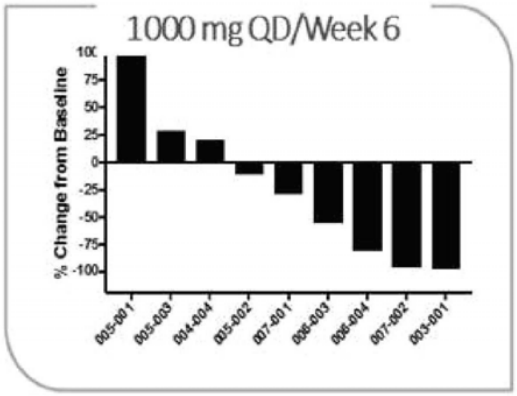


FIG. 16D

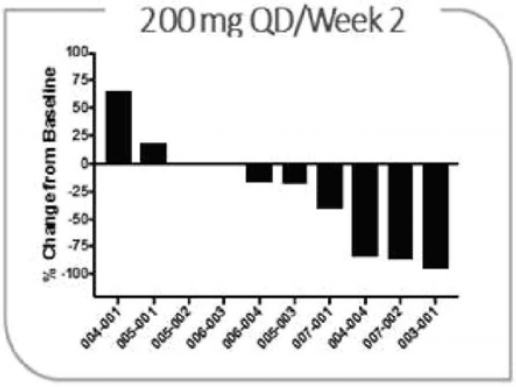


FIG. 17A

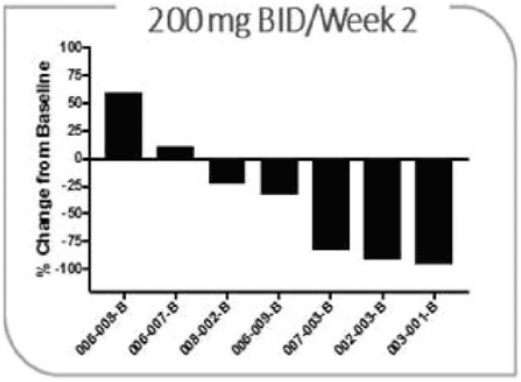


FIG. 17B

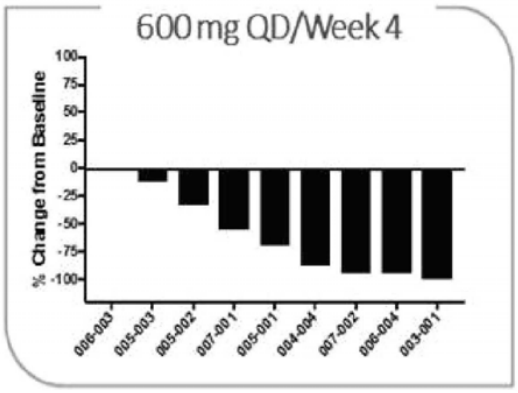


FIG. 17C

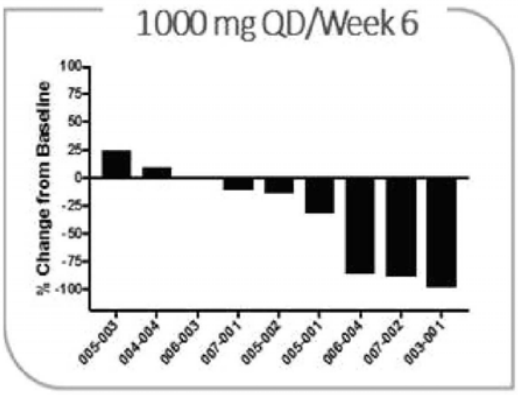


FIG. 17D

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

CROSS-REFERENCE

This application is a continuation of U.S. application Ser. No. 18/941,832, filed Nov. 8, 2024, which is a continuation of U.S. application Ser. No. 17/667,285, filed on Feb. 8, 2022, which is a continuation of U.S. application Ser. No. 17/081,694 filed on Oct. 27, 2020, which issued as U.S. Pat. No. 11,304,950 on Apr. 19, 2022, and which is a continuation of International Application No. PCT/US2019/029486 filed on Apr. 26, 2019, which claims the benefit of U.S. Provisional Patent Application No. 62/663,951, filed Apr. 27, 2018, and U.S. Provisional Patent Application No. 62/822,815, filed Mar. 23, 2019, each of which is entirely incorporated herein by reference.

BACKGROUND

Corticotropes are basophilic cells in the anterior pituitary that produce melanocyte-stimulating hormone, adrenocorticotropic hormone (ACTH) and lipotropin. The cells produce pro-opiomelanocortin (POMC) which undergoes cleavage to ACTH and β-lipotropin (β-LPH). These cells respond to corticotropin-releasing factor (CRF) and make up about 20% of the cells in the anterior pituitary. CRF is a releasing hormone that belongs to the corticotropin-releasing factor family and is the primary physiological regulator of proopiomelanocortin (POMC).

CRF is produced by parvocellular neuroendocrine cells within the paraventricular nucleus of the hypothalamus and is released at the median eminence from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamo-hypophyseal portal system. The portal system carries the CRF to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete ACTH and other biologically-active substances. ACTH, in turn, stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and DHEA.

Testicular adrenal rest tumors (TART) and ovarian adrenal rest tumors (OART) are ACTH-responsive lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility. The identification of compounds that modulate CRF function and downstream processes is an ongoing challenge. Currently, there are no non-steroidal, non-surgical solutions to control, shrink, or reduce TART. Disclosed herein, inter alia, are solutions to these and other problems in the art.

SUMMARY

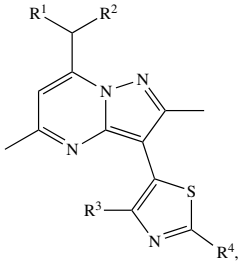
Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a serious genetic disorder characterized by impaired adrenal synthesis of cortisol and consequent overproduction of adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), and adrenal androgens such as androstenedione (A4). CAH is an orphan condition with no FDA-approved therapy. To suppress androgen production, patients are often prescribed long-term supraphysiologic doses of glucocorticoid (GC), which has adverse effects and fail to suppress 17OHP and A4 in the majority of patients.

Compound 1 may be a potent, selective, nonsteroidal, oral corticotropin-releasing factor type-1 (CRF1) receptor antagonist that reduces excess ACTH, 17OHP, and A4 to improve clinical and biochemical sequelae of CAH. This may obviate the need for high dose steroids.

One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



(I)

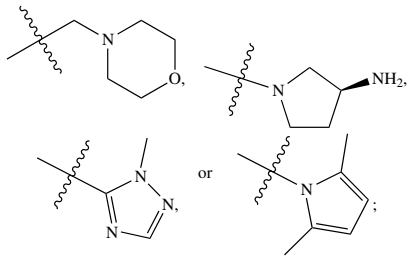
or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 are independently ethyl or n-propyl;

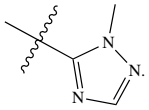
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, R^aR^bN—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,

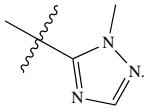


R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—.

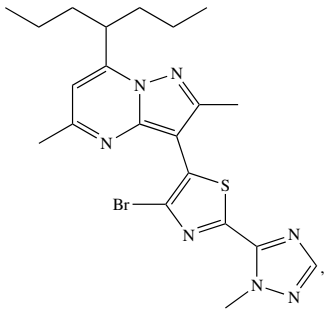
In some embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is Cl, Br, or methyl. In some embodiments, R^4 is Br, R^aR^bN—, pyridin-4-yl, morpholin-4-yl, or



In some embodiments, R^4 is morpholin-4-yl or

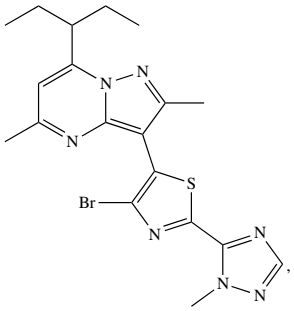


In some embodiments, R^4 is hydrogen, Br, R^aR^bN— and R^a and R^b are independently C_1-C_3alkyl. In some embodiments, the compound is



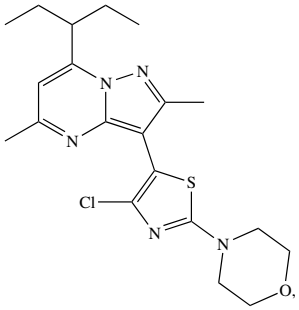
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

In some embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

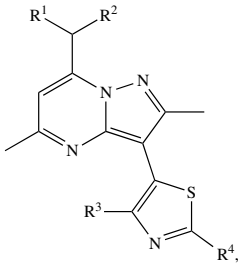
In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 5 mg/day to about 25 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 10 mg/day to about 400 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day is administered to the subject.

In some embodiments, the compound is administered orally. In some embodiments, the compound is formulated as a capsule or tablet. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

One aspect described herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I) and a pharmaceutically acceptable excipient:

(I)



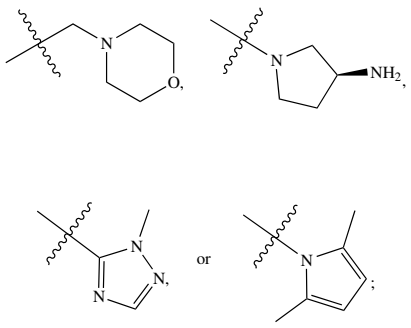
or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 are independently ethyl or n-propyl;

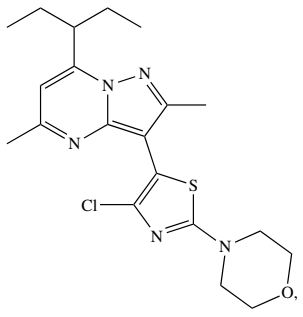
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, R^aR^bN—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—.

In some embodiments, the compound of Formula (I) has the structure:



or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370) mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

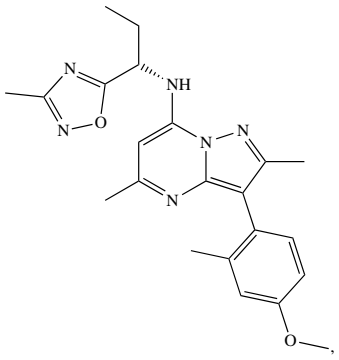
In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

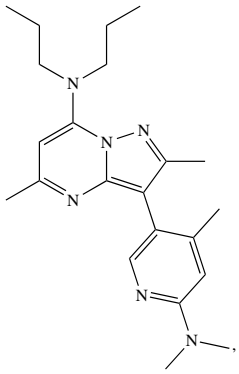
In some embodiments, the pharmaceutical composition is administered orally. In some embodiments, the pharmaceutical composition is formulated as capsule or a tablet. In some embodiments, the pharmaceutical composition is administered in the fed state. In some embodiments, the pharmaceutical composition is administered in the fasted state. In some embodiments, the pharmaceutical composition is administered at least once per day.

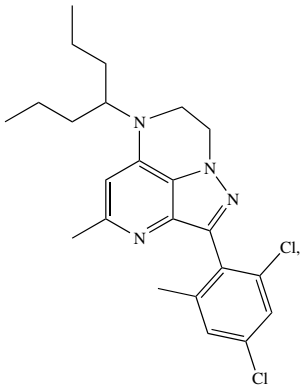
In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night.

In some embodiments, the method further comprises administering to the subject an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone.

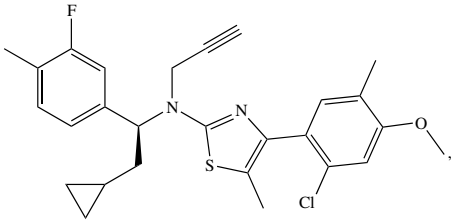
In some embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In some embodiments, the CRF_1 antagonist is



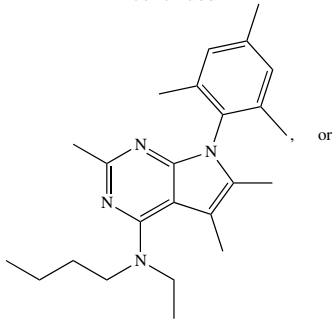




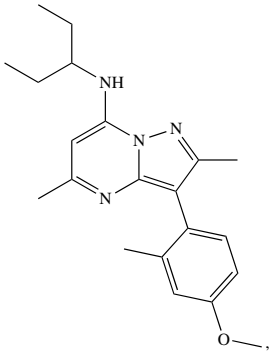
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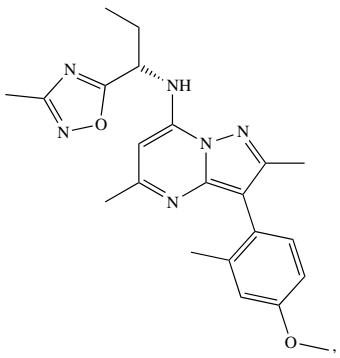


or



or a pharmaceutically acceptable salt thereof.

In some embodiments, the CRF_1 antagonist is



or a pharmaceutically acceptable salt thereof.

In some embodiments, 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 compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof.

In some embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt

thereof or the pharmaceutical composition. In some embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

In some embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In some embodiments, the radiation therapy is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

In some embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

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. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG." herein), of which:

FIG. **1**A-**1**B. A schematic representation of intra-patient dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics (A). A schematic representation of inhibition of CRF_1 with a CRF_1 antagonist (Compound 1) (B).

FIG. **2**. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

FIG. **3**. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

FIG. **4**. Graphic representation of patient-level response (measuring ACTH levels) to a CRF_1 antagonist (Compound 1).

FIG. **5**A-**5**B. Graphic representation of patient-level response of sample responders (measuring ACTH levels) to a CRF_1 antagonist [Patient 10 (A); Patient 8 (B)].

FIG. **6**. Graphic representation of patient-level response (measuring 17-OHP levels) to a CRF_1 antagonist (Compound 1).

FIG. **7**A-**7**B. Graphic representation of patient-level response of sample responders (measuring 17-OHP levels) to a CRF_1 antagonist [Patient 10 (A); Patient 8 (B)].

FIG. **8**. Graphic representation of patient-level response (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1).

FIG. **9**A-**9**B. Graphic representation of patient-level response of sample responders (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1) [Patient 10 (A); Patient 8 (B)].

FIG. **10**A-**10**B. Images of a patient with TART pretreatment with a CRF_1 antagonist (Compound 1) (A) and 6-weeks post-treatment with a CRF_1 antagonist (Compound 1) (B).

FIG. **11**A-**11**B. Graphic representation of an in vitro binding assay of a CRF_1 antagonist (Compound 1); ^{125}I-sauvagine binding to rat cerebellar membranes one hour after oral administration of increasing Compound 1 doses (A) and in vivo inhibition of CRF-induced activity after treatment with a CRF_1 antagonist; Compound 1 (oral, 10 mg/kg) (B).

FIG. **12**A-**12**B. Graphic representation of ACTH levels (A) and 17-OHP levels (B) after treatment with a CRF_1 antagonist.

FIG. **13**. Graphic representation of hormone responses after treatment with a CRF_1 antagonist (Compound 1).

FIG. **14** depicts the proof of concept and escalating QD dosing at 10 pm for Cohort A and the single dose level and BID dosing at 10 am and 10 pm for Cohort B.

FIG. **15**A-**15**D are graphic representations of changes in androstenedione seen in participants in Cohort A and Cohort B.

FIG. **16**A-**16**D are graphic representations of changes in 17-hydroxyprogesterone seen in participants in Cohort A and Cohort B.

FIG. **17**A-**17**D are graphic representations of changes in adrenocorticotropic hormone seen in participants in Cohort A and Cohort B.

DETAILED DESCRIPTION

While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

I. DEFINITIONS

The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., —CH_2O— is equivalent to —OCH_2—.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl) methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (—O—).

The term "alkylene." by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, —$CH_2CH_2CH_2CH_2$—. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: —CH_2—CH_2—O—CH_3, —CH_2—CH_2—NH—CH_3, —CH_2—CH_2—$N(CH_3)$—CH_3, —CH_2—S—CH_2—CH_3, —CH_2—CH_2, —S(O)—CH_3, —CH_2—CH_2—$S(O)_2$—CH_3, —CH═CH—O—CH_3, —$Si(CH_3)_3$, —CH_2—CH═N—OCH_3, —CH═CH—$N(CH_3)$—CH_3, —O—CH_3, —O—CH_2—CH_3, and —CN. Up to two or three heteroatoms may be consecutive, such as, for example, —CH_2—NH—OCH_3 and —CH_2—O—$Si(CH_3)_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, —CH_2—CH_2—S—CH_2—CH_2— and —CH_2—S—CH_2—CH_2—NH—CH_2—. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula —$C(O)_2R'$— represents both —$C(O)_2R'$— and —$R'C(O)_2$—. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as —C(O)R', —C(O)NR', —NR'R", —OR', —SR', and/or —SO_2R'. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as —NR'R" or the like, it will be understood that the terms heteroalkyl and —NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as —NR'R" or the like.

The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4) alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "acyl" means, unless otherwise stated, —C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least

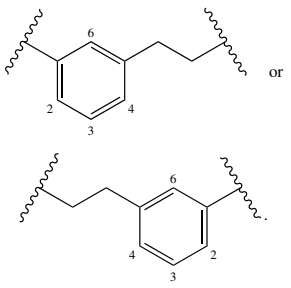
one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridavinyl, triavinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene." alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be —O— bonded to a ring heteroatom nitrogen.

Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

The symbol "  " denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

The term "Oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:



An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, —N_3, —CF_3, —CCl_3, —CBr_3, —CI_3, —CN, —CHO, —OH, —NH_2, —COOH, —$CONH_2$, —NO_2, —SH, —SO_2CH_3—SO_3H, —OSO_3H, —SO_2NH_2, —$NHNH_2$, —ONH_2, —$NHC(O)NHNH_2$, substituted or unsubstituted C_1-C_5 alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, —OR', =O, =NR', =N—OR', —NR'R", —SR', -halogen, —SiR'R"R", —OC(O)R', —C(O)R', —CO_2R', —CONR'R", —OC(O)NR'R", —NR"C(O)R', —NR'—C(O)NR"R'", —NR"$C(O)_2$R', —NR—C(NR'R"R'")=NR"", —NR—C(NR'R")=NR'", —S(O)R', —$S(O)_2$R', —$S(O)_2$NR'R", —$NRSO_2$R', —NR'NR"R'", —ONR'R", —NR'C(O)NR"NR'"R"", —CN, —NO_2, —NR'SO_2R", —NR'C(O)R", —NR'C(O)—OR", —NR'OR", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R'", and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, —NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., —CF_3 and —CH_2CF_3) and acyl (e.g., —$C(O)CH_3$, —$C(O)CF_3$, —$C(O)CH_2OCH_3$, and the like).

Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: —OR', —NR'R", —SR',

-halogen, —SiR'R"R"', —OC(O)R', —C(O)R', —CO_2R', —CONR'R", —OC(O)NR'R", —NR"C(O)R', —NR'—C(O)NR"R"', —NR"$C(O)_2$R', —NR—C(NR'R"R"')═NR"", —NR—C(NR'R")═NR"', —S(O)R', —$S(O)_2$R', —$S(O)_2$NR'R", —NRSO_2R', —NR'NR"R"', —ONR'R", —NR'C(O)NR'NR"R"", —CN, —NO_2, —R', —N_3, —$CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, —NR'SO_2R", —NR'C(O)R", —NR'C(O)—OR", —NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R"', and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"', and R"" groups when more than one of these groups is present.

Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)—$(CRR')_q$—U—, wherein T and U are independently —NR—, —O—, —CRR'—, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$—B—, wherein A and B are independently —CRR'—, —O—, —NR—, —S—, —S(O)—, —$S(O)_2$—, —$S(O)_2$NR'—, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula —$(CRR')_s$—X'—$(C"R"R"')_d$—, where s and d are independently integers of from 0 to 3, and X is —O—, —NR'—, —S—, —S(O)—, —$S(O)_2$—, or —$S(O)_2$NR'—. The substituents R, R', R", and R"' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, —CF_3, —CN, —OH, —NH_2, —COOH, —$CONH_2$, —NO_2, —SH, —SO_3H, —SO_4H, —SO_2NH_2, —$NHNH_2$, —ONH_2, —NHC═(O)$NHNH_2$, —NHC═(O)NH_2, —$NHSO_2H$, —NHC═(O)H, —NHC(O)—OH, —NHOH, —OCF_3, —$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, —CF_3, —CN, —OH, —NH_2, —COOH, —$CONH_2$, —NO_2, —SH, —SO_3H, —SO_4H, —SO_2NH_2, —$NHNH_2$, —ONH_2, —NHC═(O)$NHNH_2$, —NHC═(O)NH_2, —$NHSO_2H$, —NHC═(O)H, —NHC(O)—OH, —NHOH, —OCF_3, —$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, —CF_3, —CN, —OH, —NH_2, —COOH, —$CONH_2$, —NO_2, —SH, —SO_3H, —SO_4H, —SO_2NH_2, —$NHNH_2$, —ONH_2, —NHC═(O)$NHNH_2$, —NHC═(O)NH_2, —$NHSO_2H$, —NHC═(O)H, —NHC(O)—OH, —NHOH, —OCF_3, —$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, —CF_3, —CN, —OH, —NH_2, —COOH, —$CONH_2$, —NO_2, —SH, —SO_3H, —SO_4H, —SO_2NH_2, —$NHNH_2$, —ONH_2, —NHC═(O)$NHNH_2$, —NHC═(O)NH_2, —$NHSO_2H$, —NHC═(O)H, —NHC(O)—OH, —NHOH, —OCF_3, —$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

A "size-limited substituent" or "size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

A "lower substituent" or "lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_{20} alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_8 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric

center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{121}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

"Analog" or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C_1-C_{20}alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C_1-C_{20}alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple R^{13} substituents are present, each R^{13} substituent may be distinguished as R^{13A}, R^{13B}, R^{3C}, R^{13D}, etc., wherein each of R^{13A}, R^{13B}, R^{3C}, R^{13D}, etc. is defined within the scope of the definition of R^{13} and optionally differently.

A "detectable moiety" as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dies, radiolabeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., "Pharmaceutical Salts", *Journal of Pharmaceutical Science,* 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (−)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents. In embodiments, compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted in vivo after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

"Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of a compound 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, hydroxymethycellulose, polyvinyl pyrrolidine, 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.

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.

A "CRF1 inhibitor" refers to a compound (e.g., compounds described herein) that reduces the activity of CRF1 when compared to a control, such as absence of the compound or a compound with known inactivity.

The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. In embodiments, the terms "polypeptide," "peptide," and "protein", used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include genetically coded and non-genetically coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified polypeptide backbones. The terms include fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence; fusion proteins with heterologous and homologous leader sequences, with or without N-terminus methionine residues; immunologically tagged proteins; and the like.

A polypeptide, or a cell is "recombinant" when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (e.g. non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, e.g., in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed in vitro or in vivo from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

"Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.

The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g., MAP kinase pathway).

As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein refers to conversion of a protein into a biologically active derivative from an initial inactive or deactivated state. The terms reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

The terms "agonist," "activator," "upregulator," etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the agonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the agonist. In embodiments, an agonist is a molecule that

interacts with a target to cause or promote an increase in the activation of the target. In embodiments, activators are molecules that increase, activate, facilitate, enhance activation, sensitize, or up-regulate, e.g., a gene, protein, ligand, receptor, or cell.

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. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. 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. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

The terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist. An antagonist prevents, reduces, inhibits, or neutralizes the activity of an agonist, and an antagonist can also prevent, inhibit, or reduce constitutive activity of a target, e.g., a target receptor, even where there is no identified agonist. In embodiments, inhibitors are molecules that decrease, block, prevent, delay activation, inactivate, desensitize, or down-regulate, e.g., a gene, protein, ligand, receptor, or cell. An inhibitor may also be defined as a molecule that reduces, blocks, or inactivates a constitutive activity. An "antagonist" is a molecule that opposes the action(s) of an agonist.

The terms "corticotropin-releasing factor type-1," "CRF_1," "corticotropin-releasing hormone receptor 1," and "CHHR1" refer to a protein (including homologs, isoforms, and functional fragments thereof) and is a receptor for corticotropin releasing-hormone. The terms include any recombinant or naturally-occurring form of CRF_1 variants thereof that maintain CRF_1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF1). The terms include any mutant form of CRF_1 variants (e.g., frameshift mutations) thereof that maintain CRF_1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF_1). In embodiments, the CRF_1 protein encoded by the CRHR1 gene has the amino acid sequence set forth in or corresponding to Entrez 1233, UniProt P34998.

The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (e.g., ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, etc.).

The terms "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. The disease may be a malignant or benign tumor (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)). The disease may be cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, adrenal, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (e.g., Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including MDS, AML, ALL, ATLL and CML), or multiple myeloma.

As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include adrenal cancer and tumors (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

The term "congenital adrenal hyperplasia" or "CAH" are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis). These conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected infants, children, or adults.

"Adrenal rest tumor" refers to a neoplasm of the testis (or ovaries) consisting of adrenal tissue. It may be secondary to hyperplasia of an adrenal gland.

"Testicular adrenal rest tumor(s)" or "TART" and/or ovarian adrenal rest tumor(s) are a complication of congenital adrenal hyperplasia (CAH), which may develop from ectopic remnants of intra-testicular adrenal tissue stimulated by adrenocorticotropic hormone (ACTH) hypersecretion. TART lesions are typically located within the rete testis and are bilateral, synchronous, nodular and multiple. TART can lead to testicular structural damage, spermatogenesis disorders, infertility and mass-forming lesions.

The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma *cutaneum*, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypemephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma *mucosum*, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma *tuberosum*, tuberous carcinoma, verrucous carcinoma, or carcinoma *villosum.*

The terms "treating" or "treatment" refer to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-

being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term "treating" and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing.

"Treating" or "treatment" as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject's condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (i.e., not worsening) the state of disease, prevention of a disease's transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms (e.g., ocular pain, seeing halos around lights, red eye, very high intraocular pressure), fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

"Treating" and "treatment" as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of the compound, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

The term "prevent" refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment. In embodiments, prevent refers to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

"Patient" or "subject in need thereof" refers 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.

An "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy,* 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example, measurement of the serum level of a CRF1 inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been administered.

For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan. Adjusting the dose to achieve maximal therapeutic window efficacy or toxicity in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically

effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

The terms "QD," "qd," and "q.d." refer to once a day, i.e., a drug or therapeutic agent is administered once a day for the duration of the therapeutic regimen.

The terms "BD," "bd," and "b.i.d." refer to twice a day, i.e., a drug or therapeutic agent is administered two times a day for the duration of the therapeutic regimen.

The terms "QID," "qid," and "q.i.d." refer to three times a day, i.e., a drug or therapeutic agent is administered three times a day for the duration of the therapeutic regimen.

Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, 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. By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration 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. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, e.g., Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient.

Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 2 days, 4 days, 1 week or 1 month 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. In some embodiments, 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 another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

The compounds described herein can be administered to treat a fertility disease or disorder and/or cancer. In this regard, the compounds disclosed herein may be administered either alone to treat such diseases or disorders or may be co-administered with another therapeutic agent to treat such diseases or disorders.

The compounds disclosed herein may be co-administered with an agonist or antagonist of CRF_1 function. The compounds described herein can be co-administered with conventional anti-cancer/chemotherapeutic.

"Anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/AZD6244, GSK1120212/trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (e.g., 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), etc.), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, etc.), topoisomerase inhibitors (e.g., irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, etc.), antitumor antibiotics (e.g., doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, etc.), platinum-based compounds (e.g. cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec®), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; daclixmab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflomithine; elemene; emitefur; epirubicin; episteride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lov-

astatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin I1 (including recombinant interleukin II, or rlL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-Ib; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol™ (i.e. paclitaxel), Taxotere™, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP—XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1,

Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39·HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser·HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, inanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (−)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta *Medica*), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NC), Resverastatin phosphate sodium, BPR—OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethylstilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., *Bacillus* Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, etc.), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, etc.), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{111}In, ^{90}Y, or ^{131}I, etc.), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa™), erlotinib (Tarceva™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

"Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

The compounds disclosed herein may be co-administered with an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin); (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5.alpha.-reductase such as finasteride; (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function); (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoli-n-4-amine (gefitinib, AZD 1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazoli-n-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family; (v) an antiangiogenic agent such as one which

inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin .alpha.v.beta.3 function or an angiostatin); (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213; (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense; (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

In embodiments, the compounds disclosed herein can be co-administered with an antibody, such as a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax I1-15) or antibody modulating Ig function such as anti-IgE (for example omalizumab).

In embodiments, treatment of cancer includes administration of an effective amount of at least two of the following: a CRF1 inhibitor, an inhibitor of the PD-L1/PD-1 pathway, an inhibitor of CTLA-4, an agonistic antibody of CD137 (4-1BB). In some embodiments, the method may comprise the use of two or more combinations.

In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as conventional radiotherapeutic agents including, but not limited to, radionuclides such as ^{47}Sc, ^{64}Cu, ^{67}Cu, ^{89}Sr, ^{86}Y, ^{87}Y, ^{90}Y, ^{105}Rh, ^{111}Ag, ^{111}In, ^{117m}Sn, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi, optionally conjugated to antibodies directed against tumor antigens.

In addition, a CRF_1 inhibitor may be combined with the therapeutic administration of immune cells, sometimes referred to as adoptive cell transfer. These cells may be cells from the patient, a genetically related or unrelated donor, they may be genetically modified (e.g. CAR-T cells, NK cells, etc), cell lines, genetically modified cell lines and live or dead versions of the above. CRF1 inhibitors may also be combined with vaccines of any kind (e.g. protein/peptide, viral, bacterial, cellular) to stimulate immune responses to cancer.

The CRF_1 inhibitors/CRF_1 antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

The CRF_1 inhibitors/CRF_1 antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

The CRF_1 inhibitors/CRF_1 antagonists disclosed herein may be administered once daily until study reached endpoint. The CRF_1 inhibitors/CRF_1 antagonists disclosed herein may be administered at least three times but in some studies four or more times depending on the length of the study and/or the design of the study.

The methods disclosed herein may be used in combination with additional cancer therapy. In some embodiments, the distinct cancer therapy comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy. In some embodiments, the cancer is a chemotherapy-resistant or radio-resistant cancer.

A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaryotic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (e.g., spodoptera) and human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

"Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

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. In some embodiments, a CRF1 associated disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with CRF_1 (e.g. an endocrine disorder, a cancer including but not limited to TART or OART). A CRF_1 modulator is a compound that increases or decreases the activity or function or level of activity or level of function of CRF_1. A

modulator may act alone, or it may use a cofactor, e.g., a protein, metal ion, or small molecule. Examples of modulators include small molecule compounds and other bioorganic molecules. Numerous libraries of small molecule compounds (e.g., combinatorial libraries) are commercially available and can serve as a starting point for identifying a modulator. The skilled artisan is able to develop one or more assays (e.g., biochemical or cell-based assays) in which such compound libraries can be screened in order to identify one or more compounds having the desired properties; thereafter, the skilled medicinal chemist is able to optimize such one or more compounds by, for example, synthesizing and evaluating analogs and derivatives thereof. Synthetic and/or molecular modeling studies can also be utilized in the identification of an activator.

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, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. In embodiments, the terms "modulate", "modulation" and the like refer to the ability of a molecule (e.g., an activator or an inhibitor) to increase or decrease the function or activity of CRF_1, either directly or indirectly, relative to the absence of the molecule.

The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease, an endocrine disorder, a disease associated with CRF_1 activity, a CRF_1 associated disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) means that the disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, an endocrine disorder associated with CRF_1 activity or function may be an endocrine disorder that results (entirely or partially) from aberrant CRF_1 function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or an endocrine disorder wherein a particular symptom of the disease is caused (entirely or partially) by aberrant CRF_1 activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, an endocrine disorder associated with CRF_1 activity or function or a CRF_1 associated disease (e.g., an endocrine disorder including but not limited to TART or OART), may be treated with a compound described herein (e.g., CRF_1 modulator, CRF_1 inhibitor, or CRF_1 antagonist), in the instance where increased CRF_1 activity or function (e.g. signaling pathway activity) causes the disease (e.g., an endocrine disorder such as TART or OART). For example, an endocrine disorder associated with CRF_1 activity or function or a CRF_1 associated endocrine disorder, may be treated with an CRF_1 modulator or CRF_1 inhibitor, in the instance where increased CRF_1 activity or function (e.g. signaling pathway activity) causes the disease.

The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms.

The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extracellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propogated to other signaling pathway components. For example, binding of a CRF_1 with a compound as described herein may reduce the level of a product of the CRF_1 catalyzed reaction or the level of a downstream derivative of the product or binding may reduce the interactions between the CRF_1 or a reaction product and downstream effectors or signaling pathway components (e.g., MAP kinase pathway), resulting in changes in cell growth, proliferation, or survival.

As used herein, the terms "corticotropin-releasing factor type-1," "CRF_1," "corticotropin-releasing hormone receptor 1," and "CHHR1" and all other related art-accepted terms, many of which are set forth below, refer to a compound capable of modulating, either directly or indirectly, the CRF_1 receptor in an in vitro assay, an in vivo model, and/or other means indicative of therapeutic efficacy. The terms also refer to a compound that exhibits at least some therapeutic benefit in a human subject.

The phrase "in a sufficient amount to effect a change" means that there is a detectable difference between a level of an indicator measured before (e.g., a baseline level) and after administration of a particular therapy. Indicators include any objective parameter (e.g., serum concentration) or subjective parameter (e.g., a subject's feeling of well-being).

The "activity" of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor; to catalytic activity; to the ability to stimulate gene expression or cell signaling, differentiation, or maturation; to antigenic activity; to the modulation of activities of other molecules; and the like. The term "proliferative activity" encompasses an activity that promotes, that is necessary for, or that is specifically associated with, for example, normal cell division, as well as cancer, tumors, dysplasia, cell transformation, metastasis, and angiogenesis.

"Substantially pure" indicates that a component makes up greater than about 50% of the total content of the composition, and typically greater than about 60% of the total polypeptide content. More typically, "substantially pure" refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest. In some cases, the polypeptide will make up greater than about 90%, or greater than about 95% of the total content of the composition (percentage in a weight per weight basis).

The terms "specifically binds" and "selectively binds," when referring to a ligand/receptor, antibody/antigen, or other binding pair, indicates a binding reaction which is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated conditions, a specified ligand binds to a particular receptor and does not bind in a significant amount to other proteins present in the sample. The antibody, or binding composition derived from the antigen-binding site of an antibody, of the contemplated method binds to its antigen, or a variant or mutein thereof, with an affinity that is at least two-fold greater, at least 10-times greater, at least 20-times greater, or at least 100-times greater than the affinity with any other antibody, or binding composition derived therefrom. In embodiments, the antibody will have an affinity that is greater than about 10^9 liters/mol, as

determined by, e.g., Scatchard analysis (Munsen, et al. (1980) Analyt. Biochem. 107:220-239).

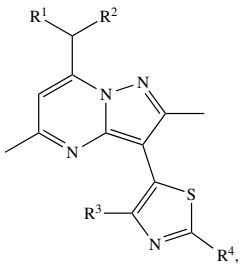
The terms "DNA," "nucleic acid," "nucleic acid molecule," "polynucleotide" and the like are used interchangeably herein to refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Non-limiting examples of polynucleotides include linear and circular nucleic acids, messenger RNA (mRNA), complementary DNA (cDNA), recombinant polynucleotides, vectors, probes, primers and the like.

As used herein, the terms "variants" and "homologs" are used interchangeably to refer to amino acid or nucleic acid sequences that are similar to reference amino acid or nucleic acid sequences, respectively. The term encompasses naturally-occurring variants and non-naturally-occurring variants. Naturally-occurring variants include homologs (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one species to another), and allelic variants (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one individual to another within a species). Thus, variants and homologs encompass naturally occurring amino acid and nucleic acid sequences encoded thereby and their isoforms, as well as splice variants of a protein or gene. The terms also encompass nucleic acid sequences that vary in one or more bases from a naturally-occurring nucleic acid sequence but still translate into an amino acid sequence that corresponds to the naturally-occurring protein due to degeneracy of the genetic code. Non-naturally-occurring variants and homologs include polypeptides and nucleic acids that comprise a change in amino acid or nucleotide sequence, respectively, where the change in sequence is artificially introduced (e.g., muteins); for example, the change is generated in the laboratory by human intervention ("hand of man"). Therefore, non-naturally occurring variants and homologs may also refer to those that differ from the naturally-occurring sequences by one or more conservative substitutions and/or tags and/or conjugates.

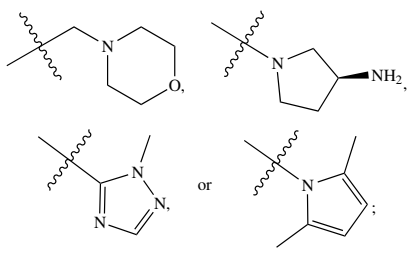
The term "muteins" as used herein refers broadly to mutated recombinant proteins. These proteins usually carry single or multiple amino acid substitutions and are frequently derived from cloned genes that have been subjected to site-directed or random mutagenesis, or from completely synthetic genes.

II. COMPOUNDS

In an aspect provided herein, is a compound of Formula (I):



or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,

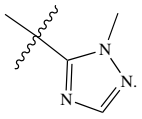


R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$— In embodiments, the inhibitor forms an irreversible bond with the amino acid residue. In embodiments, the bond is a covalent bond.

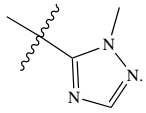
In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

In certain embodiments, R^3 is Cl, Br, or methyl.

In certain embodiments, R^4 is Br, R^aR^bN—, pyridin-4-yl, morpholin-4-yl, or

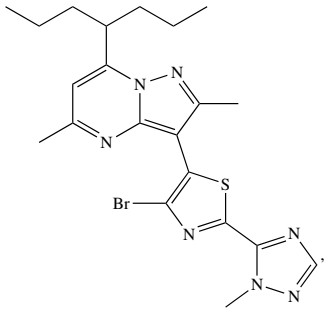


In certain embodiments, R^4 is morpholin-4-yl or



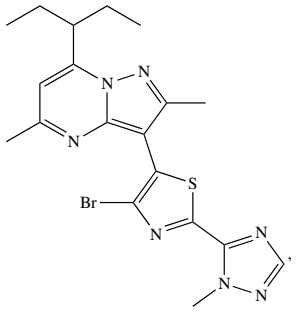
In certain embodiments, R^4 is hydrogen, Br, R^aR^bN— and R^a and R^b are independently C_1-C_3alkyl.

In certain embodiments, the compound is



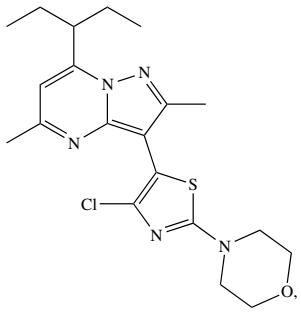
or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In one aspect described herein, there is a method of treating a subject in need thereof comprising administering an astressin or a pharmaceutically acceptable salt or solvate thereof. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof; and repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of said astressin.

In one aspect described herein, there is a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of improving metabolic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto; or a pharmaceutically acceptable salt or solvate thereof.

In one aspect described herein, there is a method of improving quality of life in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

III. PHARMACEUTICAL COMPOSITIONS

In an aspect, there is provided a pharmaceutical composition, including a compound as described herein, including embodiments, or the structural Formula (I), and a pharmaceutically acceptable excipient.

The compounds (e.g., CRF_1 inhibitors/antagonists) of the present disclosure may be in the form of compositions suitable for administration to a subject. In general, such compositions are "pharmaceutical compositions" comprising a compound (e.g., CRF_1 inhibitor(s)/antagonist(s)) and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients. In certain embodiments, the compound (e.g., CRF_1 inhibitor/antagonist) are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in the methods of the present disclosure; thus, for example, the pharmaceutical compositions can be administered ex vivo or in vivo to a subject in order to practice the therapeutic and prophylactic methods and uses described herein.

In one aspect described herein, there is a pharmaceutical composition in the form of a capsule comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a pharmaceutical composition in the form of a tablet comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

The pharmaceutical compositions of the present disclosure can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of CRF_1 function) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture thereof. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

The tablets, capsules and the like suitable for oral administration may be uncoated or coated to delay disintegration and absorption in the gastrointestinal tract and thereby

provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethylcellulose or gelatin-microcapsules or poly (methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations will be apparent to those skilled in the art.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., polyoxy-ethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptadecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example *arachis* oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, and optionally one or more suspending agents and/or preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

The pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or *arachis* oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

The pharmaceutical compositions typically comprise a therapeutically effective amount of a CRF_1 inhibitor/antagonist contemplated by the present disclosure and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate-buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer; N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES); 2-(N-Morpholino)ethanesulfonic acid (MES); 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES); 3-(N-Morpholino)propanesulfonic acid (MOPS); and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container (e.g., a single-use vial, ampule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time-delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a CRF_1 inhibitor/antagonist, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound (e.g., CRF_1 inhibitor/antagonist) disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein.

One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor® EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium; for this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids, such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

The present disclosure contemplates the administration of the compound (e.g., CRF_1 inhibitor/antagonist) in the form of suppositories for rectal administration. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

The compound (e.g., CRF_1 inhibitor/antagonist) contemplated by the present disclosure may be in the form of any other suitable pharmaceutical composition (e.g., sprays for nasal or inhalation use) currently known or developed in the future.

IV. METHODS

In certain embodiments, provided herein are methods for treating or preventing a disease comprising administering an effective amount of a compound of Formula (I), or an isotopic variant thereof or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In one embodiment, provided herein are methods for treating or preventing a tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a benign tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a malignant tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal rest tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In one embodiment, provided herein are methods for treating or preventing infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing male infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm count, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm motility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm morphology, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing female infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In one embodiment, provided herein are methods for treating or preventing a proliferative or hyperproliferative disease or disorder, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, the proliferative disease is cancer. In certain embodiments, the proliferative disease is a cancer of the breast, skin, prostate, cervix, uterus, ovary, testes, bladder, lung, liver, larynx, oral cavity, colon and gastrointestinal tract (e.g., esophagus, stomach, pancreas), brain, thyroid, blood, and lymphatic system.

In certain embodiments, the cancer treatable with the methods provided herein includes, but is not limited to, (1) leukemias, including, but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome or a symptom thereof (such as anemia, thrombocytopenia, neutropenia, bicytopenia or pancytopenia), refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), preleukemia, and chronic myelomonocytic leukemia (CMML), (2) chronic leukemias, including, but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, and hairy cell leukemia; (3) polycythemia vera; (4) lymphomas, including, but not limited to, Hodgkin's disease and non-Hodgkin's disease; (5) multiple myelomas, including, but not limited to, smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, and extramedullary plasmacytoma; (6) Waldenstrom's macroglobulinemia; (7) monoclonal gammopathy of undetermined significance; (8) benign monoclonal gammopathy; (9) heavy chain disease; (10) bone and connective tissue sarcomas, including, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemmoma, rhab-

domyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, aligodendroglioma, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; (12) breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mutinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget's disease, and inflammatory breast cancer; (13) adrenal cancer, including, but not limited to, pheochromocytom and adrenocortical carcinoma; (14) thyroid cancer, including, but not limited to, papillary or follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer; (15) pancreatic cancer, including, but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; (16) pituitary cancer, including, but limited to, Cushing's disease, prol actin-secreting tumor, acromegaly, and diabetes insipius; (17) eye cancer, including, but not limited, to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; (18) vaginal cancer, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; (19) vulvar cancer, including, but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; (20) cervical cancers, including, but not limited to, squamous cell carcinoma, and adenocarcinoma; (21) uterine cancer, including, but not limited to, endometrial carcinoma and uterine sarcoma; (22) ovarian cancer, including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; (23) esophageal cancer, including, but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; (24) stomach cancer, including, but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; (25) colon cancer; (26) rectal cancer; (27) liver cancer, including, but not limited to, hepatocellular carcinoma and hepatoblastoma; (28) gallbladder cancer, including, but not limited to, adenocarcinoma; (29) cholangiocarcinomas, including, but not limited to, pappillary, nodular, and diffuse; (30) lung cancer, including, but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma, and small-cell lung cancer; (31) testicular cancer, including, but not limited to, germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; (33) penal cancer; (34) oral cancer, including, but not limited to, squamous cell carcinoma; (35) basal cancer; (36) salivary gland cancer, including, but not limited to, adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; (37) pharynx cancer, including, but not limited to, squamous cell cancer and verrucous; (38) skin cancer, including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentiginous melanoma; (39) kidney cancer, including, but not limited to, renal cell cancer, adenocarcinoma, hypemephroma, fibrosarcoma, and transitional cell cancer (renal pelvis and/or uterer); (40) Wilms' tumor; (41) bladder cancer, including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma; and other cancer, including, not limited to, myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangio-endotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, and papillary adenocarcinomas (See Fishman et al., 1985, *Medicine,* 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy et al., 1997, *Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery*, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

Depending on the disorder, disease, or condition to be treated, and the subject's condition, the compounds or pharmaceutical compositions provided herein can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration and can be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants, and vehicles appropriate for each route of administration as described elsewhere herein.

The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. Recommended routes of administration for the second active agents are known to those of ordinary skill in the art. See, e.g., Physicians' Desk Reference, 1755-1760 (56th ed., 2002).

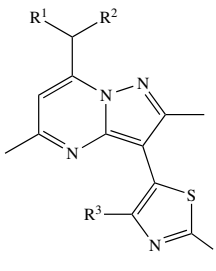
In one embodiment, provided herein are methods for treating or preventing testicular adrenal rest tumors (TART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

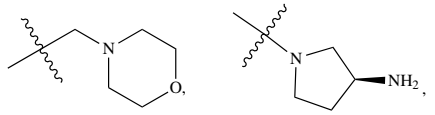
In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

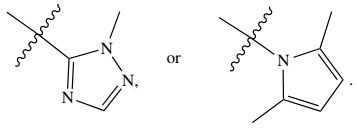
In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a compound of structural Formula (I):



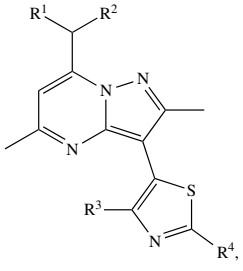
or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,





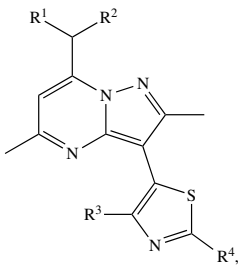
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—.

In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments.

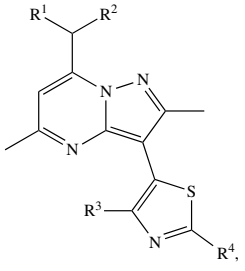
In an aspect provided herein, is a method of decreasing or reducing adrenocorticotropic hormone (ACTH) levels in a subject in need thereof, comprising administering to the subject contacting the ACTH with a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 60% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 70% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 80% of the subjects demonstrate reduction in ACTH. In embodiments, at least about 10% of subjects were in the standard or normal range for ACTH after treatment.

In embodiments, at least about 20% of subjects were in the standard or normal range for ACTH after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for ACTH after treatment. In certain embodiments, ACTH levels are decreased or reduced within about 30 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 1 hour post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 90 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 2 hours post dosing.

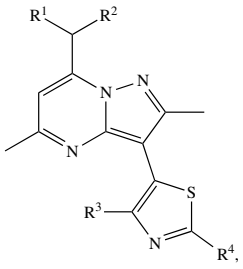
In an aspect provided herein, is a method of decreasing or reducing 17α-hydroxyprogesterone (17-OHP) levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 60% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 70% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 80% of the subjects demonstrate reduction in 17-OHP. In embodiments, at least about 30% of subjects were in the standard or normal range of

1200 ng/dL after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 60% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 60% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment.

In an aspect provided herein, is a method of decreasing or reducing androstenedione levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

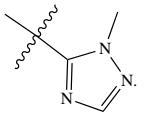


or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 60% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 70% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 80% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 90% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least 100% of the subjects demonstrate reduction in androstenedione. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least 60% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range for androstenedione after treatment.

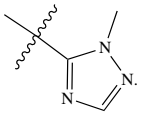
In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

In certain embodiments, R^3 is Cl, Br, or methyl.

In certain embodiments, R^4 is Br, R^aR^bN—, pyridin-4-yl, morpholin-4-yl, or

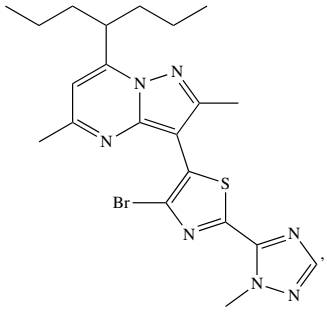


In certain embodiments, R^4 is morpholin-4-yl or



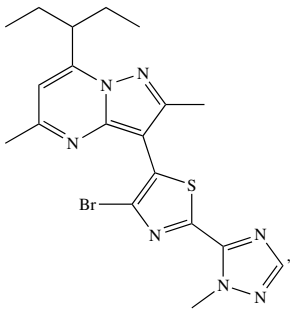
In certain embodiments, R^4 is hydrogen, Br, R^aR^bN— and R^a and R^b are independently C_1-C_3alkyl.

In certain embodiments, the compound is



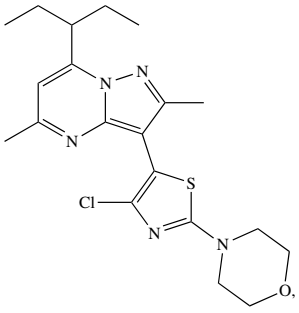
or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In certain embodiments, a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is cyclically administered to a patient. Cycling therapy involves the administration of an active agent or a combination of active agents for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

In certain embodiments, in the treatment, prevention, or amelioration of one or more symptoms of the disorders, diseases, or conditions described herein (e.g., treatment or prevention of testicular adrenal rest tumors (TART) or treatment or prevention of ovarian adrenal rest tumors (OART)), an appropriate dosage level of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof generally is ranging from about 1 mg to 3000 mg, from about 1 mg to 2000 mg, from about 1 mg to 1000 mg, from about 1 mg to about 500 mg, from about 5 mg to about 500 mg, from about 5 mg to about 400 mg, from about 5 mg to about 300 mg, from about 5 mg to about 250 mg, from about 5 mg to about 200 mg, from about 50 mg to about 200 mg, from about 10 mg to about 400 mg, from about 5 mg to about 25 mg, from about 10 mg to about 25 mg, or from about 25 to about 200 mg, which can be administered in single or multiple doses. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg/day.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable

salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, or about 1000 mg.

For oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing from about 1.0 mg to about 1,000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465

mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof for the symptomatic adjustment of the dosage to the patient to be treated. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 50 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 200 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. The pharmaceutical compositions can be administered on a regimen of one (1) to four (4) times per day, including once, twice, three times, and four times per day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg,

about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered three times per day.

In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of one day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of two days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of three days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of four days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of five days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of six days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of seven days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of eight days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of nine days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of ten days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 11 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 12 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 13 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 14 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 15 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 16 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 17 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 18 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 19 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 20 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 21 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 22 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 23 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 24 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 25 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 26 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 27 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 28 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 29 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 30 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 31 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 32 days. In some embodiments, the compound of Formula (I), or an isotopic

variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 33 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 34 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 35 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 36 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 37 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 38 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 39 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 40 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 41 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 42 days or more.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an

isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 14 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg twice daily for a period of up to

at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 14 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an

amount of about 220 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 28 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable

salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an

isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 28 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 255 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 42 days. In

certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 42 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg

twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 42 days.

In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, or about 800 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered at least once per day.

In certain embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet.

In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day.

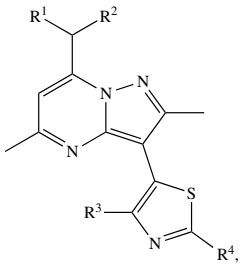
In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 6 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than

about 5 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 3 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 1 hour before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

In another aspect is provided a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I): and a pharmaceutically acceptable excipient comprising with a compound as described herein, including embodiments, or the structural Formulae (I) and a pharmaceutically acceptable excipient:



or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3, and R^4 are as described herein, including embodiments.

In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the pharmaceutical composition comprises about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the pharmaceutical composition is administered orally.

In certain embodiments, the pharmaceutical composition is formulated as a capsule or tablet. In certain embodiments, the capsule or tablet comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, or about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 50 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 200 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

In certain embodiments, the pharmaceutical composition is administered in the fed state. In certain embodiments, the pharmaceutical composition is administered in the fasted state. In certain embodiments, the pharmaceutical composition is administered at least once per day.

In certain embodiments, the pharmaceutical composition is administered at bedtime. In certain embodiments, the pharmaceutical composition is administered less than about 6 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 5 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 3 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 1 hour before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep.

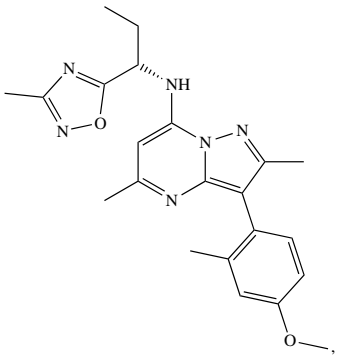
In certain embodiments, the pharmaceutical composition is administered in the evening. In certain embodiments, the pharmaceutical composition is administered at about 10 pm at night.

In certain embodiments, the subject has congenital adrenal hyperplasia (CAH).

In certain embodiments, the size and/or number of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced.

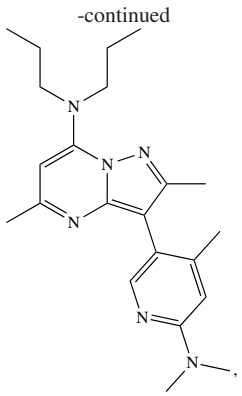
In certain embodiments of the methods disclosed herein, the method further comprises administering to the subject an additional chemotherapeutic agent.

In certain embodiments, the the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In certain embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In certain embodiments, the mineralocorticoid is fludrocortisone. In certain embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In certain embodiments, the CRF_1 antagonist is:

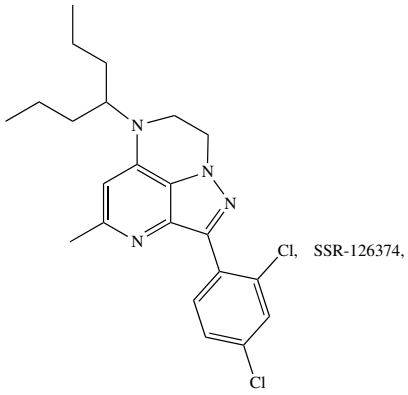


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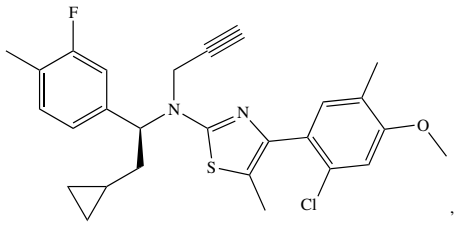
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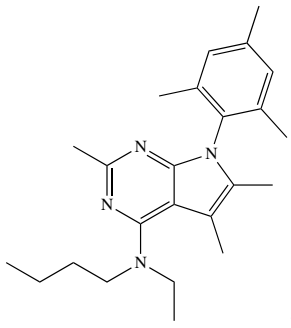
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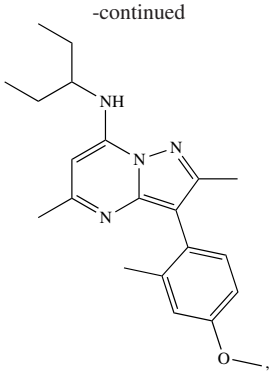


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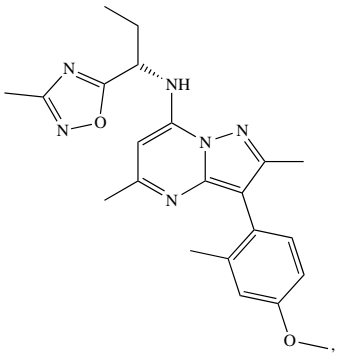


, or

-continued



or a pharmaceutically acceptable salt thereof. In certain embodiments, the CRF_1 antagonist is



or a pharmaceutically acceptable salt thereof.

In certain embodiments of the methods disclosed herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In certain embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

In certain embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the radiation therapy is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. The pharmaceutical compositions provided herein that are formulated for oral administration may be in tablet, capsule, powder, or liquid form. In some embodiments, a tablet comprises a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil, or synthetic oil. Physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol may be included. In some embodiments, a capsule comprises a solid carrier such as gelatin.

In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. Where pharmaceutical compositions may be formulated for intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution, which is pyrogen-free and has a suitable pH, isotonicity, and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride injection, Ringer's injection, or Lactated Ringer's injection. In some embodiments, preservatives, stabilisers, buffers, antioxidants, and/or other additives are included as required.

In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers.

The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, and programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (see. *Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology,* 2nd Edition, Rathbone et al., Eds., Marcel Dekker, Inc.: New York, NY, 2008).

The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

In certain embodiments, the pharmaceutical compositions provided herein further comprise one or more chemotherapeutic agents as defined herein.

A. Oral Administration

The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxy-

ethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

Coloring and flavoring agents can be used in all of the above dosage forms.

The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (see, *Remington: The Science and Practice of Pharmacy*, supra).

The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, N-methy1-2-pyrrolidone, N,N-dimethylacetamide, and dimethyl sulfoxide.

Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride.

Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydro-

chloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungi static concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and metliacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

V. EXAMPLES

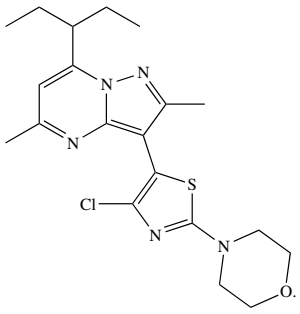
While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Example 1. A Phase 2, Open-Label Study to Evaluate the Efficacy and Safety of Compound 1 in Subjects with Testicular Adrenal Rest Tumors

Testicular adrenal rest tumors (TART) is a common complication in congenital adrenal hyperplasia (CAH) that is caused by adrenocorticotropin hormone (ACTH)-driven overstimulation of aberrant adrenal cells within the testes and results in impaired spermatogenesis and infertility. TARTS can be found anywhere on the testes, though a typical (very common) location is within the mediastinum. This is a particularly problematic location. Because of the central location of TARTs being in the mediastinum, compression of the nearby seminiferous tubules is common and can lead to obstructive azoospermia, irreversible damage to surrounding tissue, and permanent infertility in males.

Current treatment for TART consists of chronic high-dose glucocorticoids, a problematic therapy with significant side effects and a narrow therapeutic window. Given the serious nature of TART and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with TART. Compound 1, a high-affinity and selective small-molecule antagonist of the corticotropin-releasing factor type-1 (CRF_1) receptor, may be effective in blocking ACTH synthesis, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of glucocorticoids. This mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-hydroxyprogesterone (17-OHP) in subjects with CAH (FIG. **12**A-**12**B). Compound 1 has been shown to have an acceptable safety and tolerability profile in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. These promising results provide a rationale for investigating the use of Compound 1 in the treatment of TART, in combination with replacement glucocorticoids and mineralocorticoids.

The structure of Compound 1 is:



Building upon the 2 completed Phase 1 studies of Compound 1 in healthy volunteers and the ongoing Phase 2 proof-of-concept study of Compound 1 in subjects with CAH, this Phase 2 will study Compound 1 specifically in male CAH subjects with TART for the first time. A sample

size of approximately 12 subjects was selected to provide sufficient data for an initial evaluation of efficacy and safety in subjects with TART while maintaining feasible subject recruitment goals for this rare condition. Given the rarity of the disease and thus the small sample size that can be recruited, this study will be open label, and all enrolled subjects will receive active study drug. Subjects will serve as their own controls in that their outcome measures after 12 weeks of study drug dosing will be compared to their baseline measures.

The schedule of study visits (every 2 weeks through Week 4, then every 4 weeks for the remainder of the study) provides an appropriate balance between minimizing subject burden and closely monitoring subject safety and response to therapy. The 4-week post-treatment washout period will allow for adequate safety follow-up and analysis of any HPA axis rebound after the last dose of study drug.

The specification of study drug dosing at 10 pm and after consumption of a snack is based on information from the Phase 1 studies in healthy volunteers. The plasma C_{max} (maximum concentration) for Compound 1 in the Phase 1 studies occurred approximately 5 hours after dosing. Therefore, Compound 1 will be dosed daily at 10 pm in this study in order to achieve peak plasma study drug concentration at the time of day when most adrenal androgens are produced. Subjects will consume a standardized snack before taking study drug because the Phase 1 studies showed minimal study drug absorption when subjects were dosed in a fasted state. Specific dose reduction criteria, strict individual treatment stopping criteria, and appropriate laboratory and medical assessments have been established to ensure subject safety. (FIGS. **1**A-**1**B).

Objectives	Endpoints
Primary	
To assess the efficacy of Compound 1 in subjects with TART	Reduction in the size/volume of TART on testicular ultrasound from screening to Week 12
Secondary	
To evaluate the safety of Compound 1 in subjects with TART	Adverse events (AEs), serious adverse events (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs) Physical examination findings Vital signs Changes in electrocardiogram (ECG) Changes in clinical laboratory values
To assess the pharmacodynamic (PD) biomarker effects of Compound 1	Changes in plasma concentrations of key PD biomarkers, including ACTH, 17-OHP, testosterone, androstenedione, luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, sex hormone-binding globulin (SHBG), renin, and aldosterone from baseline to Week 12
To assess changes on semen analysis	Changes in sperm count, morphology, and motility from baseline to Week 12
To assess changes in metabolism	Changes in metabolic parameters, including fasting glucose, HbA1c, insulin sensitivity, and lipid profile (including LDL cholesterol, HDL cholesterol, and triglycerides), from baseline to Week 12 Changes in body weight, body mass index (BMI), waist circumference, and blood pressure
To evaluate changes in quality of life (QoL) and mood	Changes in QoL measured using the Short Form 36 (SF-36) Changes in mood measured using the Hospital Anxiety and Depression Scale (HADS)

Study Population

Approximately 12 male subjects with TART will be enrolled at approximately 6 investigative sites in the United States, United Kingdom, and possibly other countries. Up to 12 additional subjects may be added to further evaluate specific safety, PD, or efficacy findings.

Eligibility Criteria

Inclusion Criteria

- Adult male subjects aged 18 to 30, inclusive
- Documented historical diagnosis of CAH based on documented genetic mutation or historical documentation of elevated 17-OHP
- Diagnosis of TART via testicular ultrasound and/or magnetic resonance imaging (MRI) at screening with ≥1 lesion(s) measuring ≥2 cm in diameter
- On a stable regimen of GC replacement for ≥30 days before baseline
- Agree to follow contraception guidelines and refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug
- Subject is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

Exclusion Criteria

- Any clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:
  - A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
  - Presence of clinically significant renal disease, as evidenced by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2
  - Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
  - Confirmed positive test at screening for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
- Any clinically significant psychiatric disorders, including any current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months
- HADS score >12 for either depression or anxiety
- At increased risk of suicide on the basis of the Investigator's judgment or the results of the Columbia-Suicide Severity Rating Scale (C—SSRS) conducted at screening and baseline (eg, C—SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)
- Clinically significant and abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:

- Clinically meaningful abnormal ECG results, in the opinion of the Investigator
- Fridericia-corrected QT interval (QTcF) >450 msec
- Alanine aminotransferase (ALT) >2× upper limit of normal (ULN)
- Bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- A history that includes bilateral adrenalectomy or hypopituitarism
- Use of any other investigational drug within 30 days or 5 half-lives, whichever is longer, before initial screening
- Require use of prohibited concomitant medications, including strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids, hydrocortisone, and dexamethasone) within 30 days or 5 half-lives (whichever is longer) of first dose of study drug. Medications that are sensitive substrates or substrates with narrow therapeutic ranges (metabolized by CYP3A4, 2C8, 2C9, or 2C19) should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.
- Donation of blood within 60 days before first dose of study drug, or donation of platelets, white blood cells, or plasma within 15 days before first dose of study drug.

Study Duration

The expected duration of study participation for each subject is up to approximately 20 weeks. This includes a screening period of ≤4 weeks, a treatment period of 12 weeks, and a safety follow-up period of 4 weeks.

Study Design

This is a Phase 2, open-label efficacy and safety study of Compound 1 for the treatment of TART. All subjects will receive a daily oral dose of Compound 1 for 12 weeks. In-clinic study visits will occur for screening and at Day 1 (baseline) and Weeks 2, 4, 8, 12 (end of treatment), and 16 (follow-up).

Dose, Route, Regimen

All subjects will receive a daily oral dose of Compound 1 for 12 weeks. Subjects will receive 600 mg/day during the first 2 weeks and 1000 mg/day during the remaining 10 weeks of the treatment period. Study drug will be taken daily at 10 pm (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack.

On mornings of study visits with 8 am blood draws for laboratory assessments, subjects should take their morning glucocorticoid replacement after the blood draws. For all other days during the study, subjects may take their morning glucocorticoid replacement at their usual time (generally between 6 am and 8 am).

If a subject experiences a Grade 3 or higher TEAE considered at least possibly related to study drug, the Investigator may reduce the subject's daily dose of Compound 1 down in increments of 200 mg. Study drug will be discontinued in subjects who experience clinically significant liver chemistry, QTcF, or other individual treatment stopping criteria.

Investigational Drug

Compound 1 is a small-molecule CRF_1 receptor antagonist and will be supplied as 200-mg, size 1, white, hard gelatin capsules.

Example 2

Since elevated ACTH is the primary driver for TART growth, blocking ACTH synthesis using Compound 1, a small-molecule antagonist of the CRF_1 receptor, may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of GCs. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. **12**A-**12**B). The safety profile of Compound 1 has been established in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. A Phase 2 study in subjects with CAH is currently ongoing.

Nonclinical Toxicology of Compound 1

The nonclinical safety profile of Compound 1 has been evaluated in repeat-dose range-finding and definitive toxicology studies of up to 91 days in duration in rats and dogs using the clinically relevant route (oral) and schedule of administration (once daily). In rats and beagle dogs administered oral Compound 1 once daily for 91 consecutive days at doses up to 2000 mg/kg/day, toxicologic findings were all mild and limited to the male reproductive tract, and all Compound 1-related findings were reversible following a 6-week treatment-free recovery period.

Additionally, a fertility toxicology study was conducted in rats. In this study, male rats were administered oral Compound 1 once daily at 0, 5, 20, or 1000 mg/kg for 85 to 87 days (70 days before mating, during mating, and ≤4 days between mating and necropsy). Male reproductive performance (mean day of mating, mating and fertility indices, and conception rates) was unaffected by Compound 1 treatment. Untreated females mated with the Compound 1-treated males had no ovarian and uterine effects.

In addition, a complete battery of standard genotoxicity tests consisting of in vitro bacterial reverse mutation and chromosome aberration assays and an in vivo (rat) bone marrow micronucleus assay has been conducted. Exploratory and definitive embryo-fetal development studies in rabbits and a bovine corneal opacity and permeability assay have also been conducted.

Clinical Experience with Compound 1

To date, a total of 53 subjects, all healthy adults aged 21 to 65 years, have been treated with at least 1 dose of Compound 1 in 2 Phase 1 studies. The first-in-human study of Compound 1 (Study I3C-FW-BLAA) evaluated single ascending doses of 2 mg to 800 mg. In this study, a small number of subjects experienced diarrhea and headache of mild or moderate severity. A subsequent study (Study I3C-FW-BLAB) evaluated repeat doses of 50 mg, 100 mg, or 200 mg Compound 1 once daily for 14 consecutive days. A small number of subjects in the repeat-dose study experienced dyspnea, rhinorrhea, palpitations, and headache. The Phase 1 studies showed no clinically significant alterations in safety laboratory values, vital signs, or electrocardiograms (ECGs). Compound 1 has been well tolerated in healthy human subjects, with no SAEs, AEs leading to discontinuation, or dose-limiting toxicities (DLTs). A maximum tolerated dose has not been reached in humans.

An ongoing Phase 2 open-label study (Study Compound 2) is currently evaluating the safety and efficacy of Compound 1 dosed once daily for 6 weeks in adults with classic CAH. In the initial Cohort A of this study, all subjects are dosed starting at 200 mg/day for 14 days, escalating for each

subject to 600 mg/day for 14 days, then 1000 mg/day for 14 days if the subject experiences no DLTs at the previous dose level. (FIGS. **2**-**3**).

Known Potential Risks

Because the reversible testicular effects (degeneration/atrophy) observed in rats and dogs treated with high-dose Compound 1 (2,000 mg/kg/day) are likely associated with on-target (mechanism-driven) effects, these effects are likely to be relevant to human risk. However, male reproductive studies in rodents showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day). Additionally, there were no effects on clinical laboratory markers of testicular function (LH and FSH) when Compound 1 was administered to healthy male volunteers at doses up to 200 mg per day for 14 consecutive days. Clinical laboratory measures of testicular function (LH, FSH, inhibin B, and SHBG) will be assessed throughout this study to monitor the risk of testicular injury. Testicular ultrasounds and semen analysis will also be performed at screening/baseline and the end of the treatment period.

Laboratory abnormalities in liver function tests (LFTs) have been observed at significantly higher doses in nonclinical studies. However, these events were not observed in the Phase 1 clinical studies. Clinical laboratory measures of liver chemistry will be assessed throughout this study, and strict individual treatment stopping criteria for liver chemistry findings are in place.

Compound 1-induced effects on the thyroid gland were noted in dogs after 91 days of high-dose (2,000 mg/kg/day) treatment but not in any other nonclinical studies. Clinical pathology parameters of thyroid function (eg, T4, T3, thyroid-stimulating hormone [TSH]) were not evaluated in the Phase 1 studies but will be monitored throughout this study.

Known Potential Benefits

Early clinical studies suggests that Compound 1 is effective as a CRF_1 receptor antagonist, a mechanism of action that supports the clinical investigation of Compound 1 for treatment of TART. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. **12**A-**12**B).

Assessment of Potential Risks and Benefits

The mild and reversible toxicologic effects of Compound 1 on the male reproductive tract in nonclinical studies occurred in the context of animals with normal, rather than elevated, baseline hormone function. As a CRF_1 receptor antagonist, Compound 1 is intended to reduce abnormally elevated ACTH levels, which in TART drives overstimulation of aberrant adrenal cells within the testes. In nonclinical models where baseline hormone levels are within normal ranges, clinical benefits are not expected, and indeed, toxicities may be expected as a result of androgen reduction outside of the normal range. In TART, where baseline ACTH and androgen levels are pathologically elevated, androgen reduction would be considered a positive, therapeutic effect.

Given the serious nature of TART and the limitations (and risks) of chronic steroid therapy, new treatment modalities are needed for patients with TART. Given the acceptable safety and tolerability profile of Compound 1 in healthy volunteers from the Phase 1 program, the low probability of demonstrating meaningful PD marker changes in healthy subjects, and the lack of any clear benefit to exposing more healthy subjects to study drug, the Sponsor believes the benefit-to-risk profile favors the entry of Compound 1 into Phase 2 in subjects with TART.

Example 3. Congenital Andrenal Hyperplasia (CAH)

CAH results from a genetic defect in the 21-hydroxylase enzyme. CAH patients are thus unable to produce cortisol. Without cortisol to provide negative feedback, patients over-produce ACTH. High ACTH promotes the overproduction of potent androgens (male sex hormones). Without wishing to be bound by theory, Compound 1 blocks CRF_1 receptor to prevent ACTH release by the pituitary and associated drive on the hypothalamic-pituitary-adrenal axis. Replacement of cortisol to physiological levels will correct cortisol deficiency, however, will not lower ACTH, resulting in hyperplasia of adrenal gland and associated overproduction of adrenal androgens.

As shown in FIGS. **4** and **5**A-**5**B, the attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism. 80% of subjects demonstrated reduction in ACTH. 70% of subjects demonstrated >25% reduction in ACTH. 30% of subjects were in the normal range (*) after treatment with a CRF_1 receptor antagonist.

FIGS. **6** and **7**A-**7**B demonstrate "control" of disease based on standard guidelines, which would then allow steroid taper. 80% of subjects demonstrated reduction in 17-OHP. 50% of subjects demonstrated >25% reduction in ACTH. 50% of subjects were in the guideline range (*; 1200 ng/dL) after treatment with a CRF_1 receptor antagonist.

FIGS. **8** and **9**A-**9**B demonstrate attenuation of morning rise in A4 upon treatment with a CRF1 antagonist, indicative of its ability to control excess androgen production and associated symptoms. 100% of subjects demonstrated reduction in androstenedione (at various doses). 60% of subjects demonstrated >25% reduction in androstenedione. 50% of subjects were within the normal reference range after treatment with a CRF_1 receptor antagonist.

FIGS. **10**A-**10**B show approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a CRF_1 receptor antagonist.

FIGS. **11**A-**11**B demonstrate Compound 1 is a potent, selective, and functional CRF_1 receptor antagonist. In in vitro and ex vivo studies, Compound 1 was determined to be a potent and selective CRF_1 receptor antagonist with high affinity and selective for the $hCRF_1$ receptor. Compound 1 was found to have functional potency to inhibit adenylate cyclase activity (CRF_1 receptor-mediated downstream cascade), demonstrating in vitro efficacy as a CRF_1 receptor antagonist. Compound 1 was found to significantly inhibit CRF-induced locomotor behavior in response to i.c.v. administration of CRF (FIG. **11**B).

FIGS. **12**A-**12**B demonstrate single pill of CRF_1 receptor antagonist (i.e., as described in US 2017/0020877 A1) improves ACTH and 17-OHP in CAH patients.

FIG. **13** shows the subject level hormone changes (ACTH, 17-OHP, and androstenedione) by dose of a CRF_1 receptor antagonist.

Example 4. Assess Reduction in Excess ACTH and Adrenal Steroid Production

The objectives of the study are: to assess the ability of Compound 1 to reduce excess ACTH and adrenal steroid production in participants with classic CAH on a stable gluococorticoid regimen; to evaluate the safety and toler-

ability of tildacerfont in participants with classic CAH; and to evaluate the pharmacokinetics (PK) of tildacerfont.

Eligibility Criteria

Inclusion Criteria:

- Adult males and females 18 years or older
- Diagnosis of classic CAH due to 21-hydroxylase deficiency
- Morning 17OHP≥800 ng/dL, before taking any morning GC dose
- On a stable regimen of gluococorticoid replacement for ≥30 days before enrollment

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease within 30 days of screening
- Clinically significant psychiatric disorder
- History of bilateral adrenalectomy or hypopituitarism

Study Design

FIG. **14** depicts the proof of concept and escalating QD dosing at 10 PM for Cohort A and the single dose level and BID dosing at 10 AM and 10 pm for Cohort B.

Baseline Characteristics

Table 1 provides a description of the baseline characteristics displayed by Cohort A and Cohort B. In Cohort A, 10 participants were enrolled and received at least 1 dose of Compound 1. One participant withdrew early because of an occupation-related scheduling conflict. In Cohort B, 9 participants were enrolled and received at least one dose of Compound 1. One participant was withdrawn upon discovery of a major protocol violation at Baseline and did not have postbaseline efficacy/PK data. Thus, baseline characteristics are calculated for n=8 in Cohort B. One participant in Cohort B was taking both HC and prednisone.

TABLE 1

Baseline characteristics of each cohort

Parameter	Cohort A (n = 10)	Cohort B (n = 8)
Demographics		
Age (years), mean (range)	39.3 (24-66)	36.8 (19-66)
Sex	5 M, 5 F	1 M, 7 F
Bmi (kg/m^2), mean ± SD	31.5 ± 12.0	31.1 ± 6.7
Daily GC dose (mg HC equivalents), mean range	28 (13-40)	35 (20-50)
Types of GCs	4 JC, 3 pred, 3 dex	2 HC, 4 pred, 3 dex
17OHP at screening[a] (ng/dl), mean ± SD	5,985 ± 6,347	4,592 ± 4,624

Abbreviations:
17OHP: 17-hydroxyprogesterone;
BMI: body mass index;
dex: dexamethasone;
F: female;
GC: glucocorticoid;
HC: hydrocortisone;
M: male;
pred: prednisone;
SD: standard deviation.
[a]17OHP reference ranges: 27-199 ng/dL males, 15-290 ng/dL females.

Safety

Across both cohorts, Compound 1 was generally well tolerated. The most common type of adverse event (AE) was gastrointestinal disorders There were no serious AEs and no AEs leading to withdrawal.

Pharmacokinetics

Over a wide range of doses (200 to 1000 mg QD), Compound 1 exhibited a predictable, dose-dependent PK profile.

Efficacy

FIG. **15**A-**15**D show the changes in levels of Androstenedione (A4) across both cohorts. Levels of A4 improved at ≥1 dose level for 10 out of 10 participants in Cohort A and 6 out of 8 participants in Cohort B. Excess A4 is associated with clinical sequelae in CAH. Attenuation of A4 demonstrates control of adrenal androgen.

FIG. **16**A-**16**D show the changes in levels of 17-hydroxyprogesterone (17-OHP) across both cohorts. Levels of 17OHP improved at 21 dose level for 8 out of 10 participants in Cohort A and 6 out of 7 participants in Cohort B. 17OHP is a critical hormone in CAH diagnosis and management. Attenuation of 17OHP demonstrates control of adrenal steroid production.

FIG. **17**A-**17**D show the changes in levels of adrenocorticotropic hormone (ACTH) across both cohorts. Levels of ACTH improved at 21 dose level for 8 out of 10 participants in Cohort A and 5 out of 7 participants in Cohort B. Attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism.

TABLE 2

Percentage change from baseline in ACTH, 17OHP and A4.

	Cohort A			Cohort B
	200 mg QD (Week 2)	600 mg QD (Week 4)	1000 mg QD (Week 6)	200 mg BID (Weed 2)
ACTH	−25.7 (±51.6)	−60.1 (±37.5)	−32.7 (±47.0)	−36.5 (±58.0)
17OHP	+22.2 (±172.3)	−23.7 (±64.2)	−13.8 (±74.7)	−47.8 (±63.3)
A4	−12.1 (±47.4)	−33.2 (±36.5)	−28.6 (±44.6)	−16.0 (±81.4)

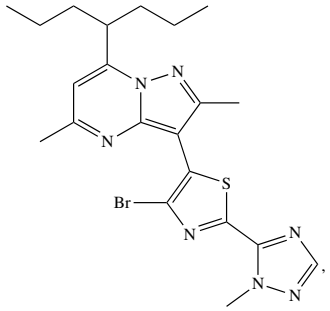
CONCLUSIONS

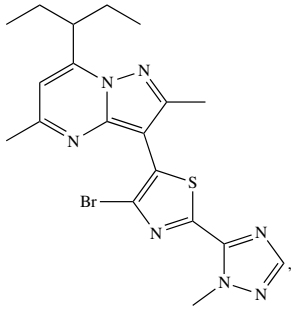
Compound 1, a potent and selective CRF_1 receptor antagonist, offers a novel nonsteroidal oral treatment approach for CAH. Compound 1 was well tolerated and efficacious in reducing excess ACTH, 17OHP, and androstenedione in patients with classic CAN. Compound 1 exhibited a predictable, dose-dependent PK profile suitable for the target population.

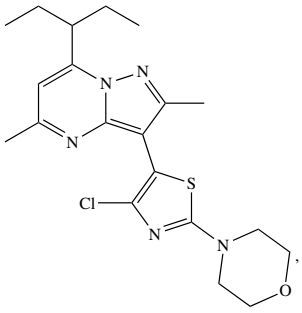
While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

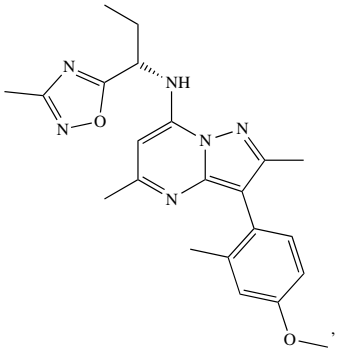
What is claimed is:

1. A method of changing a metabolic parameter of a subject having a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART), comprising administering to the subject in need thereof a small molecule corticotropin-releasing factor type-1 (CRF_1) antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule CRF_1 antagonist is:

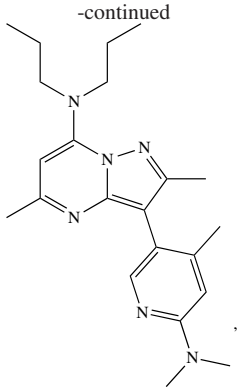


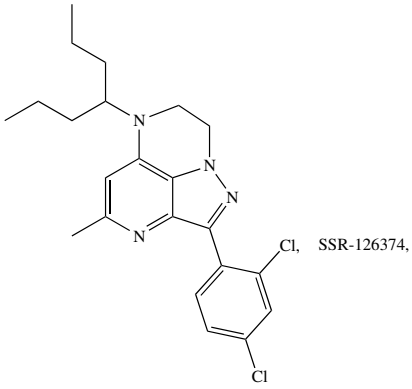




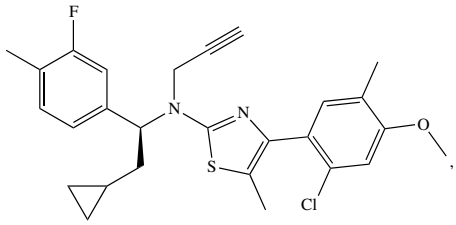


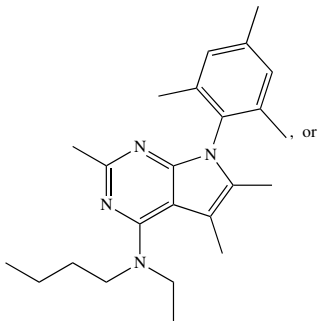
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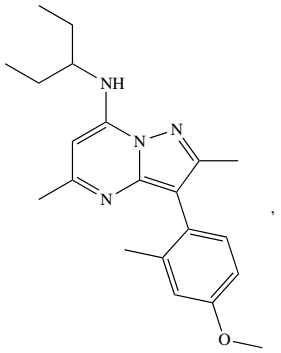
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, or

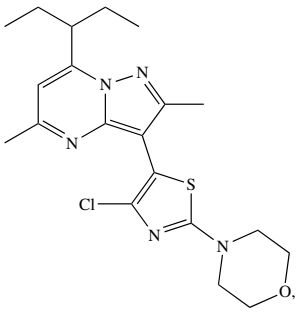
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or a pharmaceutically acceptable salt thereof, and

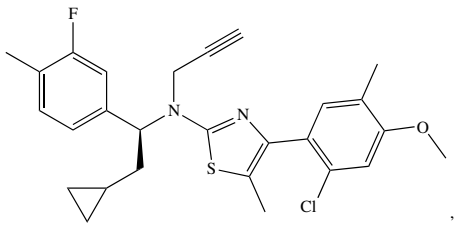
wherein the metabolic parameter comprises fasting glucose, HbA1c level, insulin sensitivity, or a lipid profile, or a combination thereof.

2. The method of claim **1**, wherein the small molecule CRF_1 antagonist is:



or a pharmaceutically acceptable salt thereof.

3. The method of claim **1**, wherein the small molecule CRF_1 antagonist is:



or a pharmaceutically acceptable salt thereof.

4. The method of claim **1**, wherein the metabolic parameter is insulin sensitivity.

5. The method of claim **1**, wherein the subject has congenital adrenal hyperplasia (CAH).

6. The method of claim **1**, wherein the administering reduces a size of the TART or the OART.

7. The method of claim **1**, wherein the administering reduces a number of the TART or the OART.

8. The method of claim **1**, wherein the small molecule CRF_1 antagonist is administered at a dose of about 10 mg/day to about 400 mg/day to the subject.

9. The method of claim **8**, wherein the small molecule CRF_1 antagonist is administered at a dose of about 50 mg.

10. The method of claim **8**, wherein the small molecule CRF_1 antagonist is administered at a dose of about 100 mg.

11. The method of claim **8**, wherein the small molecule CRF_1 antagonist is administered at a dose of about 200 mg.

12. The method of claim **8**, wherein the small molecule CRF_1 antagonist is administered at a dose of about 400 mg.

13. The method of claim **1**, wherein the small molecule CRF_1 antagonist is administered to the subject once per day.

14. The method of claim **1**, wherein the small molecule CRF_1 antagonist is administered to the subject twice per day.

15. The method of claim **1**, wherein the small molecule CRF_1 antagonist is administered orally.

16. The method of claim **1**, wherein the small molecule CRF_1 antagonist is formulated as a capsule or tablet.

17. The method of claim **1**, wherein the administering reduces a plasma concentration of a biomarker comprising 17α-hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, androstenedione (A4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, sex hormone-binding globulin (SHBG), renin, or aldosterone, or a combination thereof.

18. The method of claim **17**, wherein the biomarker is selected from the group consisting of 17-OHP, ACTH, and A4.

19. The method of claim **17**, wherein the plasma concentration of the biomarker is at least 10% from baseline.

* * * * *

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