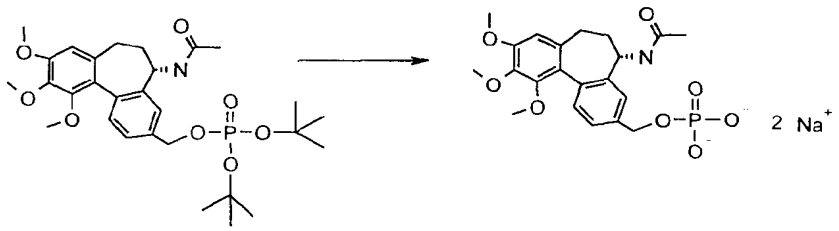
^{1}H NMR spectrum ($DMSOd_6$) : 1.9 (s, 3H), 2-2.2 (m, 2H), 2.5 (m,1H,signal obscured by DMSO peak), 3.5 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 4.5 (m, 1H), 6.77 (s, 1H), 7.1 (s, 1H), 7.2 (2s, 2H), 8.4 (d, 1H).

MS-ESI : 482 $[M\ Na]^+$

Elemental analysis:	Found	C 48.1	H 4.9	N 2.8	S 6.2	
$C_{20}H_{22}O_8NSNa$, 2 H_2O	Requires	C 48.5	H 5.3	N 2.8	S 6.5%	

Example 43



Using an analogous procedure to that described for Example 27 [(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]methyl di*tert*butyl phosphate was treated with 1M hydrogen chloride in 1,4-dioxane to give **[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]methyl dihydrogen phosphate**.

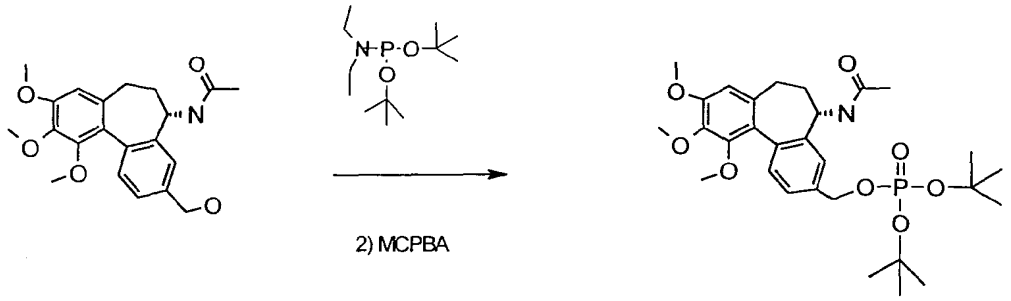
Yield : 95 %

The sodium salt was prepared by addition of 2N sodium hydroxide to a suspension of [(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]methyl dihydrogen phosphate in water until the mixture was at pH7. After freeze-drying, the sodium salt was obtained as a white solid.

^{1}H NMR Spectrum (D_2O) : 1.94 (m, 1H) ; 1.98 (s, 3H) ; 2.15 (m, 1H) ; 2.25 (m, 1H) ; 2.50 (m, 1H) ; 3.50 (s, 3H) ; 3.80 (s, 3H) ; 3.84 (s, 3H) ; 4.48 (m, 1H) ; 4.80 (m, 2H) ; 6.80 (s, 1H) ; 7.40 (m, 3H).

MS - ESI : 496 $[MH]^+$

The starting material was prepared as follows:

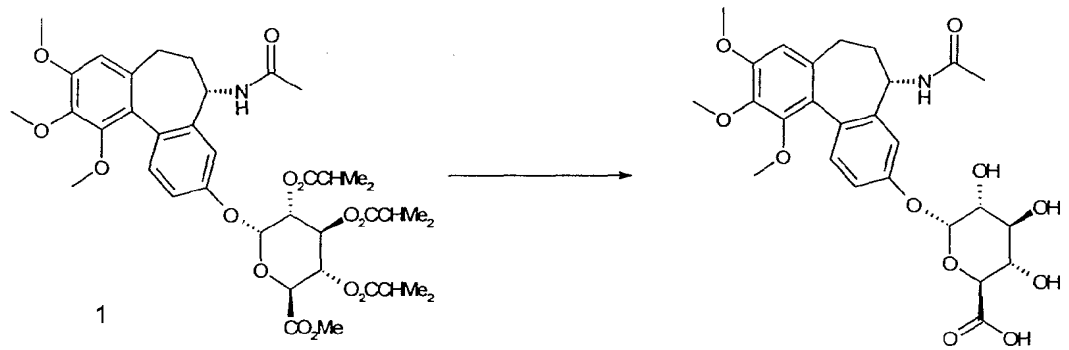


Using an analogous procedure to that described for the starting material in Example 27, *N*-[(5*S*)-3-hydroxymethyl-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl]acetamide, (prepared as described in Example 25), was reacted with di-*tert*-butyl diethylphosphoramidite to give [(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]methyl di*tert*butyl phosphate.

Yield : 59 %

^{1}H NMR spectrum (DMSOd_6) : 1.432 (s, 9H) ; 1.435 (s, 9H) ; 1.88 (s, 3H) ; 1.90 (m, 1H) ; 2.02 (m, 1H) ; 2.18 (m, 1H) ; 2.5 (m, 1H, signal obscured by DMSO peak) ; 3.50 (s, 3H) ; 3.79 (s, 3H) ; 3.85 (s, 3H) ; 4.56 (m, 1H) ; 4.97 (d, 2H) ; 6.81 (s, 1H) ; 7.35 (m, 2H) ; 7.38 (s, 1H) ; 8.46 (d, 1H).

Example 44



A solution of methyl (2*S*,3*R*,4*S*,5*R*,6*R*)-6-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]oxy-3,4,5-tris(isobutyryloxy)tetrahydro-2*H*-pyran-2-carboxylate (1) (515 mg ; 0.68 mol) in methanol (10 ml) and water (1 ml) was treated with lithium hydroxide monohydrate (214 mg ; 5.1 mmol). The reaction mixture was stirred

at ambient temperature and additional solution of lithium hydroxide monohydrate (86 mg ; 2 mmol) in H_2O (1 ml) was added after 12 hours and then again after a further 10 hours hours to complete the reaction. After a total of 30 hours at ambient temperature, the methanol was removed and the remaining solution was adjusted to pH6 with 2N hydrochloric acid. The resulting heterogeneous solution was deposited on a column of HP2O SS resin (35 ml) for purification, eluting with a 0 to 75 % aqueous solution of methanol. After removal of the solvents by evaporation, the solid was purified further by preparative HPLC on reverse phase silica eluting with a 0-50 % gradient of methanol/water to give, after removal of the methanol by evaporation and freeze drying, **(2*S*,3*S*,4*S*,5*R*,6*R*)-6-{[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]oxy}-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylic acid** as a white solid (260 mg).

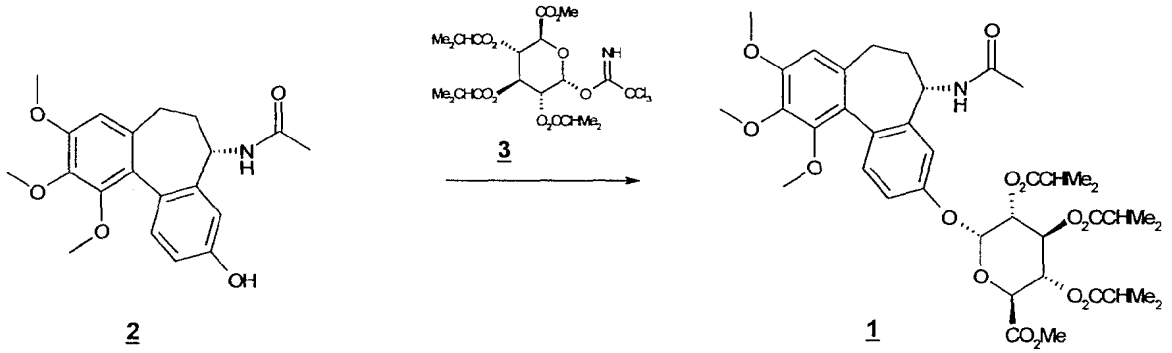
Yield : 68 %

^{1}H NMR spectrum ($DMSOd_6$, CF_3CO_2D) : 1.88 (m, 1H) ; 1.89 (s, 3H) ; 2.08 (m, 1H) ; 2.15 (m, 1H) ; 2.52 (m, 1H, signal obscured partially by DMSO peak) ; 3.25-3.36 (m, 3H) ; 3.44 (t, 1H) ; 3.51 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 3.91 (d, 1H) ; 4.50 (m, 1H) ; 5.03 (d, 1H) ; 6.77 (s, 1H) ; 6.98 (s, 1H) ; 7.00 (d, 1H) ; 7.26 (d, 1H).

MS - ESI : 534 $[MH]^+$

Elemental analysis	Found	C 55.7	H 6.1	N 2.5
$C_{26}H_{31}NO_{11}$; 1.5 H_2O	Requires	C 56.0	H 5.9	N 2.6%

The starting material was prepared as follows :



Freshly distilled boron trifluoride-diethyl ether (0.22 ml ; 1.7 mmol) was added at 0°C under argon atmosphere to a stirred solution of *N*-acetyl-colchicinol (2) (303 mg ; 0.85 mmol)

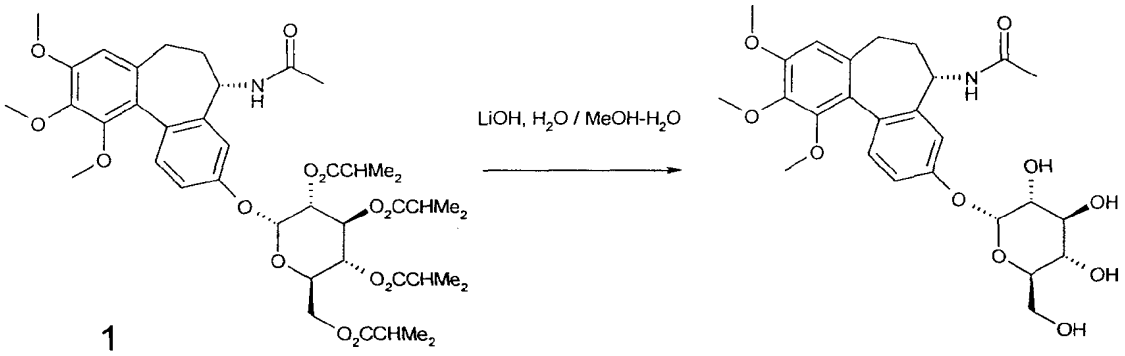
and methyl (trichloroacetimidoyl 2, 3, 4-tri-O-isobutyryl-α-D-glucopyranosid) uronate (3) (955 mg ; 1.7 mmol), (THL 36, 8601, 1995), in dichloromethane (8 ml). The mixture was stirred at 0°C for 15 minutes and then at ambient temperature for 2 hours. The reaction mixture was diluted with dichloromethane, washed with aqueous saturated sodium hydrogen carbonate, water, then dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography eluting with a 0 to 35 % gradient of dichloromethane/ether to give, after evaporation, (1) as a light yellow-green foam.

Yield : 82 %

^1H NMR spectrum ($DMSOd_6$ + CD_3CO_2D) : 1.01-1.06 (m, 18H) ; 1.87 (m, 1H) ; 1.89 (s, 3H) ; 2.13 (m, 1H) ; 2.26 (m, 1H) ; 2.50 (m, 4H, signal obscured partially by DMSO peak) ; 3.50 (s, 3H) ; 3.65 (s, 3H) ; 3.78 (s, 3H) ; 3.83 (s, 3H) ; 4.58 (m, 1H) ; 4.74 (d, 1H) ; 5.11 (t, 1H) ; 5.17 (d, 1H) ; 5.60 (t, 1H) ; 5.73 (d, 1H) ; 6.77 (s, 1H) ; 6.94 (s, 1H) ; 6.95 (d, 1H) ; 7.28 (d, 1H) ; 8.37 (d, 1H).

MS - ESI : 758 $[MH]^+$

Example 45



1

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-[(5*S*)-5-(Acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]oxy-3,5-bis(isobutyryloxy)-6-[(isobutyryloxy)methyl]tetrahydro-2*H*-pyran-4-yl 2-methylpropanoate (1) (304 mg ; 0.38 mmol) and H_2O (0.25 ml) were added to a 0.48M solution of lithium hydroxide monohydrate in methanol (6 ml). The mixture was stirred at ambient temperature for 6 hours. After removal of the methanol by evaporation, the remaining aqueous solution was adjusted to pH6.2 with 2N hydrochloric acid. The resulting heterogeneous solution was deposited on a

column of HP2O SS resin (35 ml) for purification, eluting with a 0 - 60 % gradient of methanol/water. After concentration and freeze drying ***N*-((5*S*)-9,10,11-trimethoxy-3-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl]oxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl)acetamide** was obtained as a white solid (180 mg).

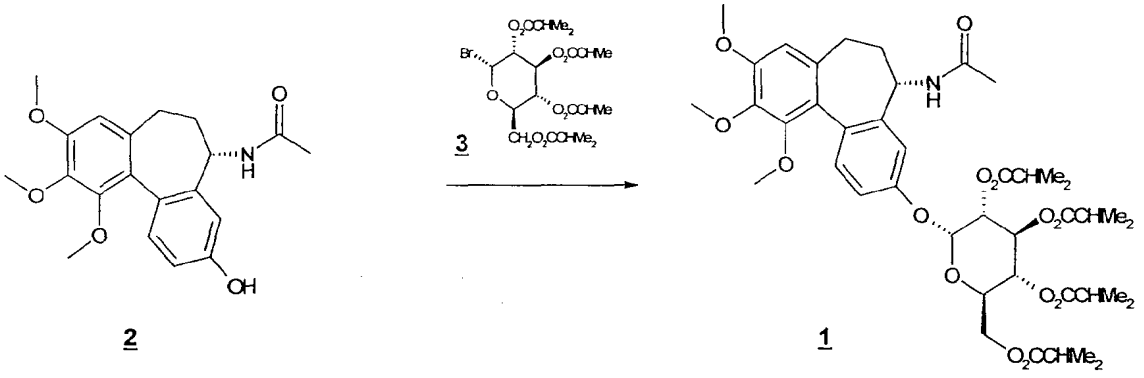
Yield : 84 %

^{1}H NMR spectrum ($DMSOd_6$, CF_3CO_2D) : 1.88 (m, 1H) ; 1.90 (s, 3H) ; 2.10 (m, 1H) ; 2.18 (m, 1H) ; 2.52 (m, 1H, signal obscured partially by DMSO peak) ; 3.21-3.37 (m, 4H) ; 3.51 (s, 3H) ; 3.48-3.58 (m, 1H) ; 3.74-3.81 (m, 1H) ; 3.80 (s, 3H) ; 3.84 (s, 3H) ; 4.50 (m, 1H) ; 4.92 (d, 1H) ; 6.78 (s, 1H) ; 6.98 (d, 1H) ; 7.00 (dd, 1H) ; 7.26 (d, 1H) ; 8.36 (d, 1H).

MS - ESI : 542 $[MNa]^+$

Elemental analysis	Found	C 55.3	H 6.6	N 2.6	
$C_{26}H_{33}NO_{10}$ 2.6 H_2O	Required	C 55.1	H 6.8	N 2.5%	

The starting material was prepared as follows:



N-Benzyltributylammomium bromide (523 mg ; 1 mmol) and *N*-acetyl-colchicinol (2) (357 mg ; 1 mmol) in a 1.25N aqueous solution of sodium hydroxide were added at 0°C to a solution of the (2*R*,3*R*,4*S*,5*S*,6*R*)-2-bromo-3,5-bis(isobutyryloxy)-6-[(isobutyryloxy)methyl]tetrahydro-2*H*-pyran-4-yl 2-methylpropanoate (3) (523 mg ; 1 mmol), (J. Chem. Soc. Perkins Trans. 1 1995 p 577), in trichloromethane (2 ml). After 1 hour the reaction mixture was stirred at ambient temperature. Additional reagent (3) (250 mg ; 0.48 mmol and 1.33 mg ; 0.33 mmol) and 1.25N sodium hydroxide (0.2 ml and 0.1 ml) were added

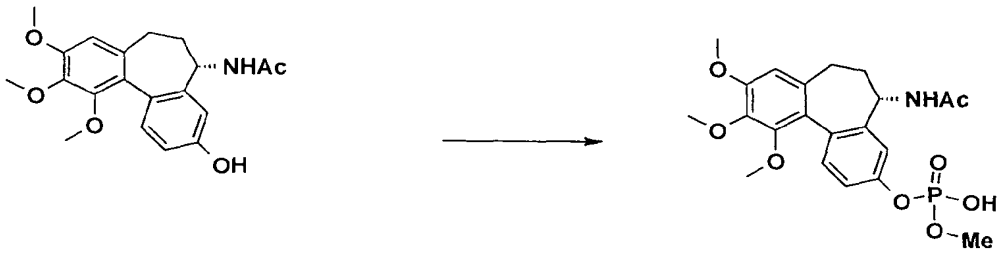
to the reaction mixture after 6 hours at ambient temperature and then again after a further 14 hours at ambient temperature. After a total of 24 hours, the reaction mixture was diluted with dichloromethane, washed successively with water, brine and then dried ($MgSO_4$). After removal of the solvent, the residue was purified by flash chromatography eluting with dichloromethane/ether (8/2 to 6/4) to give (1) (320 mg) as a foam.

Yield : 40 %

^1H NMR spectrum ($DMSOd_6$) : 1.00-1.11 (m, 24H) ; 1.88 (m, 1H) ; 1.89 (s, 3H) ; 2.08 (m, 1H) ; 2.21 (m, 1H) ; 2.46-2.66 (m, 5H, signal obscured partially by DMSO peak) ; 3.48 (s, 3H) ; 377 (s, 3H) ; 3.83 (s, 3H) ; 4.16-4.24 (m, 2H) ; 4.32 (m, 1H) ; 4.47 (m, 1H) ; 5.08 (m, 2H) ; 5.54 (t, 1H) ; 5.67 (d, 1H) ; 6.77 (s, 1H) ; 6.92 (d, 1H) ; 6.95 (dd, 1H) ; 7.25 (d, 1H) ; 8.38 (d, 1H).

MS-ESI : 800 $[MH]^+$

Example 46



1

A solution of *N*-acetyl-colchicinol (1) (0.45 g ; 1.26 mmol) in THF (40 ml) under argon was cooled to 0°C and treated with a 1.0M solution of lithiumHMDS in THF (1.39 ml ; 1.39 mmol). The mixture was stirred at 0°C for 1 hour and then added in portions over about 15 minutes to a solution of methyl dichlorophosphate (625 µl ; 4.16 mmol) in THF (150 ml). The mixture was stirred at ambient temperature for 15 minutes. After addition of water (200 ml) the THF was removed by evaporation. After removal of the insoluble material by filtration, the filtrate was purified on HP20 SS resin eluting with a gradient of 0-60% methanol/water. The appropriate fractions were freeze-dried to give **(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl methyl hydrogen phosphate** as a white solid (391 mg).

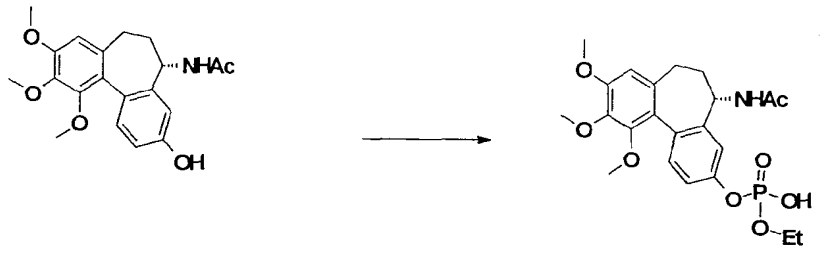
Yield : 69%

^{1}H NMR spectrum (DMSO d_6 ; CF_3CO_2D) : 1.89 (s, 3H) ; 1.9 (m, 1H) ; 2.05 (m, 1H) ; 2.18 (m, 1H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 3.53 (s, 3H) ; 3.73 (d, 3H) ; 3.79 (s, 3H) ; 3.84 (s, 3H) ; 4.51 (m, 1H) ; 6.79 (s, 1H) ; 7.14 (d, 1H) ; 7.15 (s, 1H) ; 7.32 (d, 1H) ; 8.46 (d, 1H).

MS-ESI : 451 $[MH]^+$

Elemental analysis :	Found	C 54.1	H 5.9	N 3.1
$C_{21}H_{26}NO_8P$; 0.7 H_2O	Requires	C 54.2	H 6.0	N 3.0%

Example 47



1

A solution of *N*-acetyl-colchicinol (1) (0.36 g ; 1.0 mmol) in THF (40 ml) under argon was cooled to 0°C and treated with a 1.0M solution of lithiumHMDS in THF (1.1 ml ; 1.1 mmol). The mixture was stirred at 0°C for 1 hour and then added in portions over about 2 hours to a solution of ethyl dichlorophosphate (400 µl ; 3.3 mmol) in THF (150 ml). The mixture was stirred at ambient temperature for 15 minutes. After addition of water (200 ml) the THF was removed by evaporation. After removal of the insoluble material by filtration, the filtrate was purified on HP20 SS resin eluting with a gradient of 0-60% methanol/water. The appropriate fractions were freeze-dried to give **(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl ethyl hydrogen phosphate** as a white solid (259 mg).

Yield : 56%

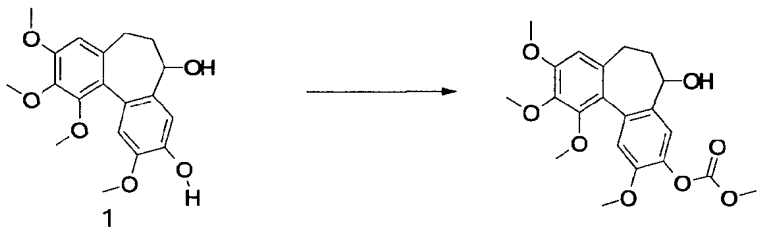
^{1}H NMR spectrum (DMSO d_6 ; CF_3CO_2D) : 1.25 (dt, 3H) ; 1.89 (s, 3H) ; 1.9 (m, 1H) ; 2.05 (m, 1H) ; 2.19 (m, 1H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 3.53 (s, 3H) ;

3.79 (s, 3H) ; 3.85 (s, 3H) ; 4.09 (m, 2H) ; 4.52 (m, 1H) ; 6.80 (s, 1H) ; 7.13 (d, 1H) ; 7.15 (s, 1H) ; 7.32 (d, 1H) ; 8.45 (d, 1H).

MS-ESI : 466 $[MH]^+$

Elemental analysis :	Found	C 54.6	H 6.0	N 3.0
$C_{22}H_{28}NO_8P$; 1.0 H_2O	Requires	C 54.7	H 6.3	N 2.9%

Example 48



1

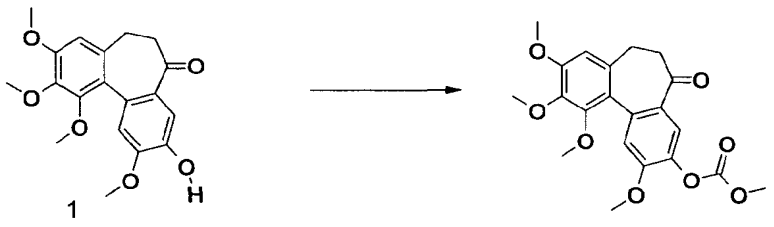
Triethylamine (140 µl ; 1.0 mmol) and methyl chloroformate (80 µl ; 1.0 mmol) were added to a solution of 5-hydroxy-2,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-ol (1) (0.18 g ; 0.5 mmol) in THF (10 ml). The mixture was stirred at ambient temperature overnight. After removal of the insoluble material by filtration the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate/hexanes (5 to 60% ethyl acetate) to give **5-hydroxy-2,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl methyl carbonate** as a hard oil/white solid (163 mg).

Yield : 81%

^{1}H NMR spectrum ($CDCl_3$) : 1.89 (m, 1H) ; 2.39 (m, 2H) ; 2.54 (m, 1H) ; 3.61 (s, 3H) ; 3.87 (s, 3H) ; 3.91 (s, 3H) ; 3.92 (s, 3H) ; 3.93 (s, 3H) ; 4.56 (m, 1H) ; 6.59 (s, 1H) ; 7.15 (s, 1H) ; 7.45 (s, 1H).

MS-ESI : 427 $[MNa]^+$

Example 49



1

Triethylamine (35 µl ; 0.225 mmol) and methyl chloroformate (20 µl ; 0.225 mmol) were added to a solution of 3-hydroxy-2,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-one (1) (0.052 g ; 0.15 mmol) in THF (5 ml). The mixture was stirred at ambient temperature for 5 hours. After removal of the insoluble material by filtration the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate/hexanes (0 to 100% ethyl acetate) to give **methyl 2,9,10,11-tetramethoxy-5-oxo-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl carbonate** as a white solid (57 mg).

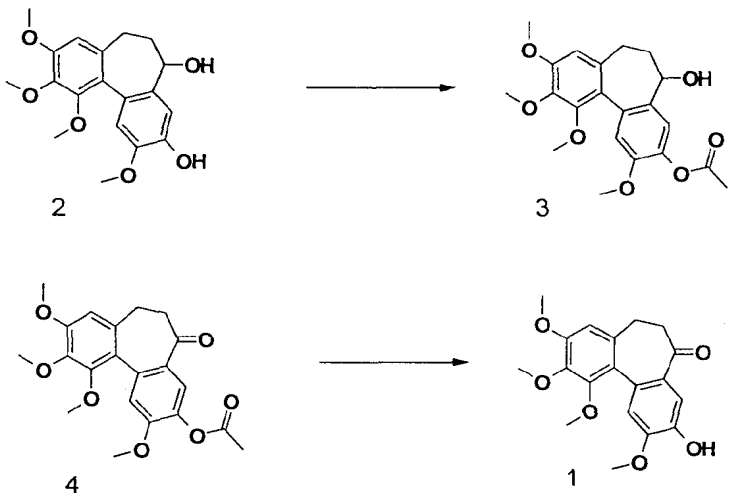
Yield : 95%

^{1}H NMR spectrum ($CDCl_3$) : 2.69 (m, 1H) ; 2.85 (m, 1H) ; 2.97 (m, 1H) ; 3.16 (m, 1H) ; 3.53 (s, 3H) ; 3.93 (s, 3H) ; 3.94 (s, 3H) ; 3.94 (s, 3H) ; 3.95 (s, 3H) ; 6.64 (s, 1H) ; 7.24 (s, 1H) ; 7.47 (s, 1H).

MS-ESI : 403 $[MH]^+$

Elemental analysis :	Found	C 62.0	H 5.5
$C_{21}H_{22}O_8$; 0.2 H_2O	Requires	C 62.1	H 5.6%

The starting material was prepared as follows:



Triethylamine (1.05 ml ; 7.5 mmol) and acetyl chloride (540 µl ; 7.5 mmol) were added to a solution of 5-hydroxy-2,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-ol (2) (1.05 g ; 3.0 mmol) in THF (50 ml). The mixture was stirred at ambient temperature overnight. After removal of the insoluble material by filtration the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate/hexanes (0 to 100% ethyl acetate) to give methyl 5-hydroxy-2,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl carboxylate (3) as a white solid (880 mg).

Yield : 76%

^{1}H NMR spectrum ($CDCl_3$) : 1.89 (m, 1H) ; 2.34 (s, 3H) ; 2.38 (m, 2H) ; 2.53 (m, 1H) ; 3.61 (s, 3H) ; 3.84 (s, 3H) ; 3.90 (s, 3H) ; 3.91 (s, 3H) ; 4.55 (m, 1H) ; 6.59 (s, 1H) ; 7.14 (s, 1H) ; 7.35 (s, 1H).

MS-ESI : 411 $[MNa]^+$

Elemental analysis :	Found	C 65.0	H 6.3
$C_{21}H_{24}O_7$	Requires	C 64.9	H 6.2%

A solution of (3) (0.776 g ; 2.0 mmol) in dichloromethane (30 ml) was added to a solution of Collins Reagent (3.1 g ; 12.0 mmol) in dichloromethane (30 ml). The mixture was stirred at ambient temperature for 30 minutes. After removal of the insoluble material by filtration the filtrate was washed with 2N hydrochloric acid, then brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of

ethyl acetate/hexanes (0 to 60% ethyl acetate) to give methyl 5-oxo-2,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl carboxylate (4) as a white solid (706 mg).

Yield : 91%

^{1}H NMR spectrum ($CDCl_3$) : 2.34 (s, 3H) ; 2.64 (m, 1H) ; 2.82 (m, 1H) ; 2.93 (m, 1H) ; 3.14 (m, 1H) ; 3.50 (s, 3H) ; 3.88 (s, 3H) ; 3.91 (s, 3H) ; 3.92 (s, 3H) ; 6.61 (s, 1H) ; 7.20 (s, 1H) ; 7.36 (s, 1H).

MS-ESI : 387 $[MH]^+$

Elemental analysis :	Found	C 65.6	H 6.0
$C_{21}H_{22}O_7$	Requires	C 65.3	H 5.7%

Water (10 ml) and saturated aqueous sodium hydrogen carbonate (10 ml) were added to a solution of (4) (0.58 g ; 1.5 mmol) in methanol (50 ml). The mixture was stirred at ambient temperature overnight. After dilution with ethyl acetate the organic phase was washed with 2N hydrochloric acid, then brine and dried over $MgSO_4$. The residue was triturated with ether and hexanes to give (1) as a white solid (441 mg).

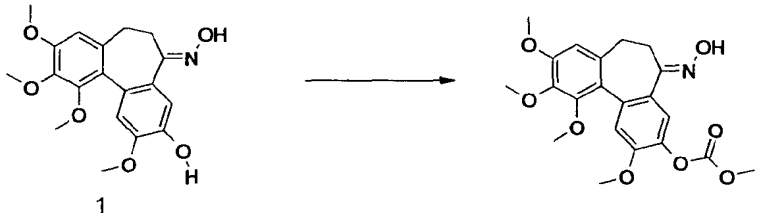
Yield : 85%

^{1}H NMR spectrum ($CDCl_3$) : 2.61 (m, 1H) ; 2.80 (m, 1H) ; 2.91 (m, 1H) ; 3.06 (m, 1H) ; 3.45 (s, 3H) ; 3.88 (s, 3H) ; 3.88 (s, 3H) ; 3.91 (s, 3H) ; 5.73 (s br, 1H) ; 6.58 (s, 1H) ; 7.09 (s, 1H) ; 7.17 (s, 1H).

MS-ESI : 345 $[MH]^+$

Elemental analysis :	Found	C 65.52	H 6.10
$C_{19}H_{20}O_6$; 0.2 H_2O	Requires	C 65.58	H 5.91

Example 50



1

Triethylamine (18 µl ; 0.12 mmol) and methyl chloroformate (10 µl ; 0.12 mmol) were added to a solution of 5-(hydroxyimino)-2,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-ol (1) (0.035 g ; 0.1 mmol) in THF (3 ml). The mixture was stirred at ambient temperature overnight. After removal of the insoluble material by filtration the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate/hexanes (0 to 100% ethyl acetate) to give **5-(hydroxyimino)-2,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl methyl carbonate** (E isomer) as a white solid (22 mg), followed by the second (Z) isomer (7 mg).

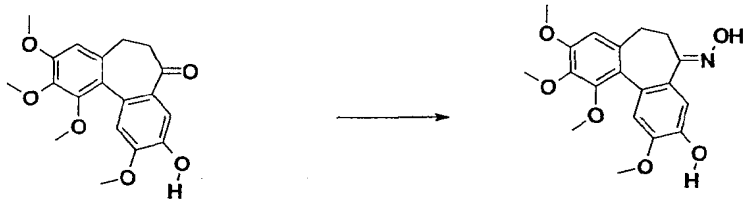
Yield : 54%

^{1}H NMR spectrum ($CDCl_3$) : 2.59 (m, 1H) ; 2.82 (m, 2H) ; 3.20 (m, 1H) ; 3.51 (s, 3H) ; 3.88 (s, 3H) ; 3.90 (s, 3H) ; 3.91 (s, 3H) ; 3.93 (s, 3H) ; 6.59 (s, 1H) ; 7.21 (s, 1H) ; 7.26 (s, 1H) ; 8.61 (br s, 1H).

MS-ESI : 418 $[MH]^+$

Elemental analysis :	Found	C 58.1	H 5.7	N 3.0
$C_{21}H_{23}NO_8$; 0.8 H_2O	Requires	C 58.4	H 5.7	N 3.2%

The starting material was prepared as follows :



2 1

Hydroxylamine hydrochloride (70 mg ; 1.0 mmol)was added to a solution of 3-hydroxy-2,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-one (2) (0.172 g ; 0.5 mmol) in pyridine (3.0 ml). The mixture was stirred at ambient temperature overnight. After dilution with 2N hydrochloric acid and extraction with ethyl acetate, the organic phase was washed with 2N hydrochloric acid, then brine and dried over $MgSO_4$. The residue was triturated with ether and hexanes to give (1) (a 3:1 mixture of E:Z isomers) as a white solid (170 mg).

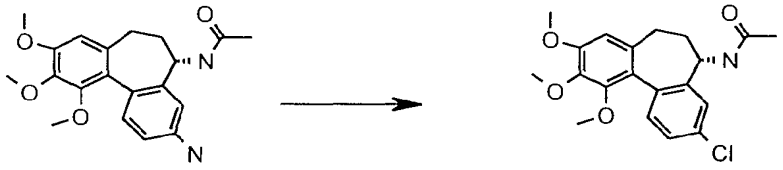
Yield : 95%

^{1}H NMR spectrum ($CDCl_3$), major isomer : 2.56 (m, 1H) ; 2.66-2.9 (m, 2H) ; 3.18 (m, 1H) ; 3.45 (s, 3H) ; 3.86 (s, 3H) ; 3.88 (s, 3H) ; 3.89 (s, 3H) ; 6.55 (s, 1H) ; 7.08 (s, 1H) ; 7.24 (s, 1H).

MS-ESI : 360 $[MH]^+$

Elemental analysis :	Found	C 62.6	H 6.3	N 3.6
$C_{19}H_{21}NO_6$; 0.3 H_2O	Requires	C 62.6	H 6.0	N 3.8%

Example 51



1

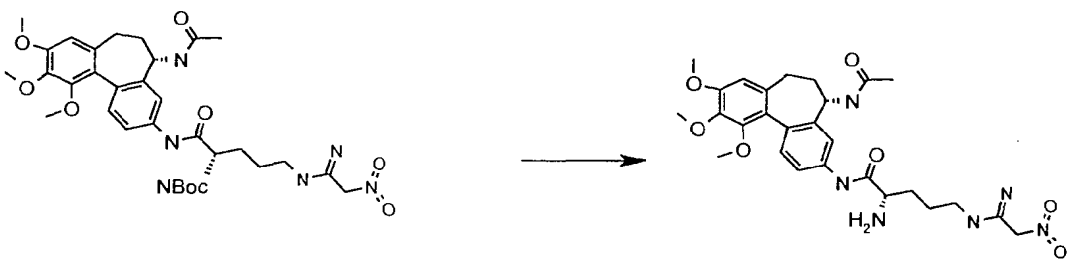
A solution of *N*-[(5*S*)-3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl]acetamide (0.712 g ; 2 mmol) in ethanol (3.75 ml) and 36% hydrochloric acid (1.57 ml) was slowly added into a mixture of ice (6 ml) and 36% hydrochloric acid (1.57 ml). At 0°C a solution of sodium nitrite (0.14 g ; 2 mmol) in water (0.25 ml) was added. The mixture was stirred at 0°C for 1 hour and then transferred into a separate flask containing a solution of copper(I) chloride (0.218 g ; 2.2 mmol) in water (0.35 ml) and 36% hydrochloric acid (0.4 ml). The resulting mixture was stirred at 30°C for 30 minutes and extracted with toluene/ethyl acetate (50/50). The organic phase was washed with water, dilute sodium hydroxide, and saturated sodium chloride solution, then dried and the volatiles were removed by evaporation. The residue was purifed by flash chromatography eluting with ethyl acetate to give ***N*-[(5*S*)-3-chloro-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl]acetamide**.

Yield : 46%.

^{1}H NMR Spectrum ($DMSOd_6$) : 1.89 (s, 3H) ; 1.90 (m, 1H) ; 2.02 (m, 1H) ; 2.15 (m, 1H) ; 2.5 (m, 1H) ; 3.50 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 4.52 (m, 1H) ; 6.80 (s, 1H) ; 7.35 (m, 3H); 8.43 (d, 1H).

MS-ESI : 398 $[MNa]^+$

Example 52



1

A solution of (2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]-2-(*N*-*tert*butoxycarbonylamino)-5-[(2-nitroethanimidoyl)amino]pentanamide (1) (0.15 g, 0.28 mmol) in dichloromethane (2 ml) was treated at 0°C with TFA (2 ml). The mixture was stirred at ambient temperature for 2 hours and evaporated. The residue was taken up in methanol/dichloromethane and evaporated to give an oil which was triturated in ether to give **(2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]-2-amino-5-[(2-nitrocthanimidoyl)amino]pentanamide** as a solid.

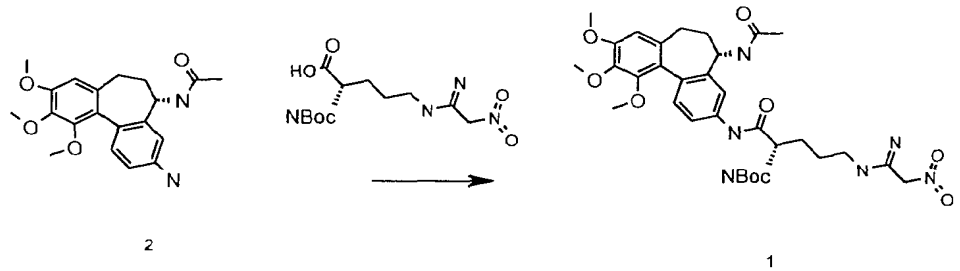
Yield : 95 %

^{1}H NMR spectrum ($DMSOd_6$) : 1.60 (m, 2H) ; 1.83 (m, 2H) ; 1.90 (s, 3H) ; 1.92 (m, 1H) ; 2.06 (m, 1H) ; 2.20 (m, 1H) ; 2.5 (m, 1H ; signal obscured by DMSO Peak) ; 3.22 (m, 2H) ; 3.50 (s, 3H) ; 3.79 (s, 3H) ; 3.85 (s, 3H) ; 3.95 (m, 1H) ; 4.48 (m, 1H) ; 6.80 (s, 1H) ; 7.32 (d, 1H) ; 7.45 (d, 1H) ; 7.75 (dd, 1H) ; 8.45 (d, 1H).

MS - ESI : 558 $[MH]^+$

Elemental analysis	Found	C 48.1	H 5.7	N 13.2
$C_{26}H_{35}N_7O_7$; 1.4 TFA; 0.5 methanol	Requires	C 48.0	H 5.3	N 13.4%

The starting material was prepared as follows:



2 1

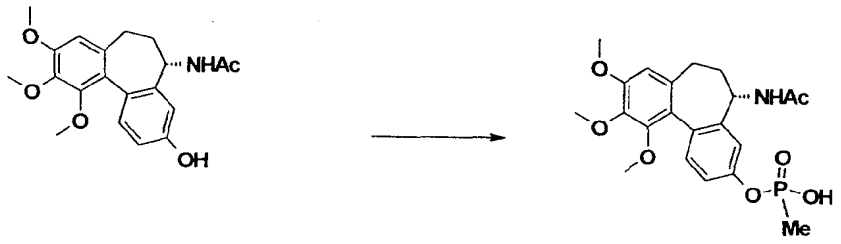
A solution of *N*-[(5*S*)-3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl]acetamide (2) (0.45 g ; 1.26 mmol), *Nα-tert*-butoxycarbonyl-ω-nitro-L-arginine (50.402 g ; 1.26 mmol), EDCI (0.312 g ; 1.63 mmol) and DMAP (0.03 g ; 0.25 mmol) in dichloromethane (18 ml) was stirred at ambient temperature overnight. After addition of water (2 ml) and extraction, the organic phase was evaporated to give an oil which was purified by flash chromatography eluting with ethyl acetate/methanol (95/5) to give (1).

Yield : 28 %

^{1}H NMR ($DMSOd_6$) : 1.38 (m, 2H) ; 1.40 (s, 9H) ; 1.60 (m, 2H) ; 1.90 (s, 3H) ; 1.91 (m, 1H) ; 2.15 (m, 2H) ; 2.5 (m, 1H, signal obscured by DMSO peak) ; 3.20 (m, 2H) ; 3.48 (s, 3H) ; 3.79 (s, 3H) ; 3.84 (s, 3H) ; 4.13 (m, 1H) ; 4.50 (m, 1H) ; 6.80 (s, 1H) ; 7.10 (d, 1H) ; 7.27 (d, 2H) ; 7.55 (s, 1H) ; 7.62 (d, 1H) ; 8.40 (d, 1H).

MS - ESI : 658 $[MH]^+$

Example 53



1

A solution of *N*-acetyl-colchicinol (0.36 g ; 1.0 mmol) in THF (40 ml) under argon was cooled to 0°C and treated with a 1.0M solution of lithiumHMDS in THF (1.1 ml ; 1.1 mmol). The mixture was stirred at 0°C for 1 hour and then added in portions over about 2

hours to a solution of methylphosphonic dichloride (0.53 mg ; 4.0 mmol) in THF (150 ml). The mixture was stirred at ambient temperature for 15 minutes. After addition of water (200 ml) the THF was removed by evaporation. After removal of the insoluble material by filtration, the filtrate was purified on HP20 SS resin eluting with a gradient of 0-60% methanol/water. The methanol was removed by evaporation and the mixture was adjusted to pH7.14 with sodium hydroxide (0.1 M). The appropriate fractions were freeze-dried to give **(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl hydrogen methylphosphonate** as a beige solid (180 mg).

Yield : 41%

^{1}H NMR spectrum (DMSO d_6 ; CF_3CO_2D) : 1.53 (d, 3H) ; 1.88 (s, 3H) ; 1.9 (m, 1H) ; 2.06 (m, 1H) ; 2.16 (m, 1H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 3.52 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 4.51 (m, 1H) ; 6.79 (s, 1H) ; 7.13 (s, 1H) ; 7.14 (d, 1H) ; 7.30 (d, 1H) ; 8.45 (d, 1H).

MS-ESI : 458 $[MNa]^+$

Example 54

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)	Tablet I	mg/tablet
	Compound X	100
	Lactose Ph.Eur	182.75
	Croscarmellose sodium	12.0
	Maize starch paste (5% w/v paste)	2.25
	Magnesium stearate	3.0

(b)	Tablet II	mg/tablet
	Compound X	50
	Lactose Ph.Eur	223.75
	Croscarmellose sodium	6.0

Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c) Tablet III — mg/tablet

Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d) Capsule — mg/capsule

Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e) Injection I — (50 mg/ml)

Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid (to adjust pH to 7.6)	
Polyethylene glycol 400	4.5% w/v
Water for injection to 100%	

(f) Injection II — 10 mg/ml)

Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection to 100%	

(g) Injection III — (1mg/ml,buffered to pH6)

Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v

Citric acid ..... 0.38% w/v

Polyethylene glycol 400 ..... 3.5% w/v

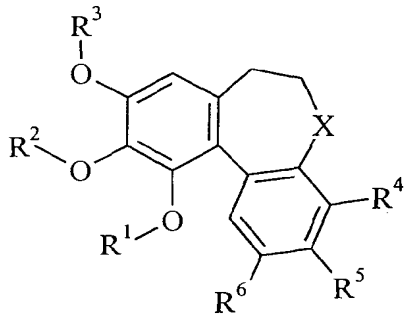
Water for injection to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIMS

1. The use of a compound of the formula I:



(I)

wherein

X is

-C(O)-, -C(S)-, -C=NOH, or -CH(R^7)- wherein R^7 is hydrogen, hydroxy, C_{1-7}alkoxy, -OR^8 or -NR^8R^9 (wherein R^8 is a group -Y^1R^{10} (wherein Y^1 is a direct bond, -C(O)-, -C(S)-, -S-, -C(O)O-, -C(O)NR^{11}-, -SO_2- or -SO_2NR^{12}- (wherein R^{11} and R^{12}, which may be the same or different, each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{10} is selected from one of the following nine groups:

1) hydrogen, C_{1-7}alkyl, C_{3-7}cycloalkyl, C_{1-4}alkylY^8C_{1-4}alkyl wherein Y^8 is as defined herein, or phenyl,

(which alkyl, cycloalkyl, alkylY^8alkyl or phenyl group may bear one or more substituents selected from:

halogeno, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, hydroxy, carboxy, carbamoyl, C_{1-4}alkoxy, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkanoyl, phenyl, nitro, sulphate, phosphate,

Z^1 (wherein Z^1 represents a 5-6 membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}aminoalkyl, C_{1-7}alkanoyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl and Z^2 (wherein Z^2 is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms,

selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}aminoalkyl, C_{1-7}alkanoyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl)),

C_{1-4}alkylZ^1 (wherein Z^1 is as defined herein), and

a group $-Y^2R^{13}$ (wherein Y^2 is $-NR^{14}C(O)-$ or $-O-C(O)-$ (wherein R^{14} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{13} is C_{1-7}alkyl, C_{3-7}cycloalkyl or a group R^{15} wherein R^{15} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, $-CONR^{16}R^{17}$ and $-NR^{18}COR^{19}$ (wherein R^{16}, R^{17}, R^{18} and R^{19}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl)));

2) R^{15} wherein R^{15} is as defined herein;

3) C_{2-7}alkenylR^{15} (wherein R^{15} is as defined herein);

4) C_{3-7}alkynylR^{15} (wherein R^{15} is as defined herein));

5) Z^1 (wherein Z^1 is as defined herein);

6) C_{1-7}alkylZ^1 (wherein Z^1 is as defined herein);

7) C_{1-7}alkylY^8Z^1 (wherein Z^1 is as defined herein and Y^8 is $-C(O)-$, $-NR^{59}C(O)-$, $-NR^{59}C(O)C_{1-4}$alkyl-, $-C(O)NR^{60}-$ or $-C(O)NR^{60}C_{1-4}$alkyl-, (wherein R^{59} and R^{60}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl, C_{1-3}hydroxyalkyl or C_{1-3}alkoxyC_{2-3}alkyl));

8) $(C_{1-7}alkyl)_cY^9Z^3$ (wherein c is 0 or 1, Z^3 is an amino acid group and Y^9 is a direct bond, $-C(O)-$ or $-NR^{61}-$ (wherein R^{61} is hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl)); and

9) C_{1-7}alkylR^{15} (wherein R^{15} is as defined herein);

and R^9 is hydrogen, C_{1-7}alkyl or C_{3-7}cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from C_{1-4}alkoxy and phenyl);

R^1, R^2 and R^3 are each independently

hydrogen, PO_3H_2, sulphate, C_{3-7}cycloalkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{1-7}alkanoyl, a group $R^{20}C_{1-7}$alkyl (wherein R^{20} is phenyl which may bear one or more substituents selected from C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}aminoalkyl and C_{1-4}hydroxyalkoxy), C_{1-7}alkyl or C_{1-7}alkylsulphonyl (which alkyl or alkylsulphonyl group may bear one or more substituents selected from: halogeno, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^2R^{21}$ (wherein Y^2 is $-NR^{22}C(O)-$ or $-O-C(O)-$ (wherein R^{22} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{21} is C_{1-7}alkyl, C_{3-7}cycloalkyl or a group R^{23} wherein R^{23} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, $-CONR^{24}R^{25}$ and $-NR^{26}COR^{27}$ (wherein R^{24}, R^{25}, R^{26} and R^{27}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl)));

with the proviso that at least two of R^1, R^2 and R^3 are C_{1-7}alkyl;

R^4, R^5 and R^6 are each independently selected from:

hydrogen, $-OPO_3H_2$, phosphonate, cyano, halogeno, nitro, amino, carboxy, carbamoyl, hydroxy, C_{1-7}alkoxy, C_{1-7}alkanoyl, C_{1-7}thioalkoxy, C_{1-7}alkyl,

(which alkyl group may bear one or more substituents selected from: halogeno, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkanoyl, carboxy, phenyl, sulphate, phosphate and a group $-Y^3R^{28}$ (wherein Y^3 is $-NR^{29}C(O)-$ or $-O-C(O)-$ (wherein R^{29} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{28} is C_{1-7}alkyl, C_{3-7}cycloalkyl or a group R^{30} wherein R^{30} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, $-CONR^{31}R^{32}$ and $-NR^{31}COR^{32}$ (wherein R^{31}, R^{32}, R^{33} and

R^{34}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl))), and

a group -Y^4R^{35}

(wherein Y^4 is -C(O)-, -OC(O)-, -O-, -SO-, -SO_2-, -OSO_2-, -NR^{36}-, -C_{1-4}alkylNR^{36}-, -C_{1-4}alkylC(O)-, -NR^{37}C(O)-, -OC(O)O-, -C(O)NR^{38}- or -NR^{39}C(O)O- (wherein R^{36}, R^{37}, R^{38} and R^{39}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and

R^{35} is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, hydroxy, amino, C_{1-7}alkyl, C_{1-7}alkoxy, C_{1-7}alkanoyl, C_{1-7}alkylamino, di(C_{1-7}alkyl)amino, aminoC_{1-7}alkylamino, C_{1-7}alkylaminoC_{1-7}alkylamino, C_{1-7}alkanoylaminoC_{1-7}alkyl, di(C_{1-7}alkyl)aminoC_{1-7}alkylamino, C_{1-7}alkylphosphate, C_{1-7}alkylphosphonate, C_{1-7}alkylcarbamoylC_{1-7}alkyl,

(which alkyl, alkoxy, alkanoyl, alkylamino, dialkylamino, aminoalkylamino, alkylaminoalkylamino, alkanoylaminoalkyl, dialkylaminoalkylamino, alkylphosphate, alkylphosphonate or alkylcarbamoylalkyl, may bear one or more substituents selected from:

halogeno, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, hydroxy, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -Y^5R^{40} (wherein Y^5 is -NR^{41}C(O)-, -C(O)NR^{42}-, -C(O)-O- or -O-C(O)- (wherein R^{41} and R^{42} which may be the same or different each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{40} is C_{1-7}alkyl, C_{3-7}cycloalkyl, carboxyC_{1-7}alkyl or a group R^{43} wherein R^{43} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, -$CONR^{44}R^{45}$ and -$NR^{46}COR^{47}$ (wherein R^{44}, R^{45}, R^{46} and R^{47}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl))),

R^{48} (wherein R^{48} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected

independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from

hydroxy, nitro, halogeno, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, di(C_{1-4}hydroxyalkyl)aminoC_{1-4}alkyl, di(C_{1-4}aminoalkyl)aminoC_{1-4}alkyl, C_{1-4}hydroxyalkoxy, carboxy, C_{1-4}carboxyalkyl, phenyl, cyano, -CONR^{49}R^{50}, -NR^{51}COR^{52} (wherein R^{49}, R^{50}, R^{51} and R^{52}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and C_{1-4}alkylR^{53} (wherein R^{53} is as defined herein),

C_{1-7}alkylR^{48} (wherein R^{48} is as defined herein),

R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}carboxyalkyl, C_{1-4}aminoalkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl and R^{54} (wherein R^{54} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

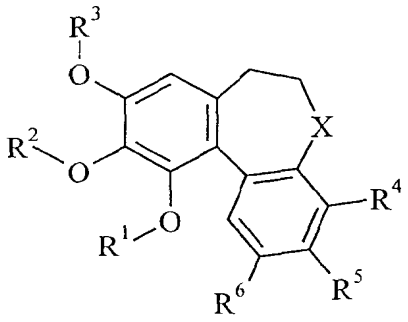
oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl)), or

$(CH_2)_aY^6(CH_2)_bR^{53}$ (wherein R^{53} is as defined herein, a is 0, or an integer 1-4, b is 0 or an integer 1-4 and Y^6 represents a direct bond, -O-, -C(O)-, -NR^{55}-, -NR^{56}C(O)- or -C(O)NR^{57}- (wherein R^{55}, R^{56}, and R^{57}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and wherein one or more of the $(CH_2)_a$ or $(CH_2)_b$ groups may bear one or more substituents selected from hydroxy, amino and halogeno));

with the proviso that R^5 is not hydroxy, alkoxy, substituted alkoxy (wherein R^5 is Y^{4}R^{35} and Y^4 is -O- and R^{35} is C_{1-7}alkyl bearing one or more substituents selected from the list given herein), $-OPO_3H_2$, -O-C_{1-7}alkanoyl or benzyloxy;

or a salt thereof, a pharmaceutically acceptable salt thereof, a solvate or hydrate thereof, or a prodrug thereof in the manufacture of a medicament for use in the production of a vascular damaging effect in warm-blooded animals such as humans.

2. A compound of the formula IIa:



(IIa)

wherein

X is

-C(O)-, -C(S)-, -C=NOH, or -CH(R^7)- wherein R^7 is hydrogen, hydroxy, C_{1-7}alkoxy, -OR^8 or -NR^8R^9 (wherein R^8 is a group -Y^1R^{10} (wherein Y^1 is a direct bond, -C(O)-, -C(S)-, -S-, -C(O)O-, -C(O)NR^{11}-, -SO_2- or -SO_2NR^{12}- (wherein R^{11} and R^{12}, which may be the same or different, each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{10} is selected from one of the following nine groups:

1) hydrogen, C_{1-7}alkyl, C_{3-7}cycloalkyl, C_{1-4}alkylY^8C_{1-4}alkyl wherein Y^8 is as defined herein, or phenyl,

(which alkyl, cycloalkyl, alkylY^8alkyl or phenyl group may bear one or more substituents selected from:

halogeno, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, hydroxy, carboxy, carbamoyl, C_{1-4}alkoxy, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkanoyl, phenyl, nitro, sulphate, phosphate,

Z^1 (wherein Z^1 represents a 5-6 membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}aminoalkyl, C_{1-7}alkanoyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl and Z^2 (wherein Z^2 is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}aminoalkyl, C_{1-7}alkanoyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl)),

C_{1-4}alkylZ^1 (wherein Z^1 is as defined herein), and

a group $-Y^2R^{13}$ (wherein Y^2 is $-NR^{14}C(O)-$ or $-O-C(O)-$ (wherein R^{14} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{13} is C_{1-7}alkyl, C_{3-7}cycloalkyl or a group R^{15} wherein R^{15} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, $-CONR^{16}R^{17}$ and $-NR^{18}COR^{19}$ (wherein R^{16}, R^{17}, R^{18} and R^{19}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl)));

2) R^{15} wherein R^{15} is as defined herein;

3) C_{2-7}alkenylR^{15} (wherein R^{15} is as defined herein);

4) C_{3-7}alkynylR^{15} (wherein R^{15} is as defined herein));

5) Z^1 (wherein Z^1 is as defined herein);

6) C_{1-7}alkylZ^1 (wherein Z^1 is as defined herein);

7) C_{1-7}alkylY^8Z^1 (wherein Z^1 is as defined herein and Y^8 is $-C(O)-$, $-NR^{59}C(O)-$, $-NR^{59}C(O)C_{1-4}$alkyl-, $-C(O)NR^{60}-$ or $-C(O)NR^{60}C_{1-4}$alkyl-, (wherein R^{59} and R^{60}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl, C_{1-3}hydroxyalkyl or C_{1-3}alkoxyC_{2-3}alkyl));

8) $(C_{1-7}alkyl)_cY^9Z^3$ (wherein c is 0 or 1, Z^3 is an amino acid group and Y^9 is a direct bond, $-C(O)-$ or $-NR^{61}-$ (wherein R^{61} is hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl)); and

9) C_{1-7}alkylR^{15} (wherein R^{15} is as defined herein);

and R^9 is hydrogen, C_{1-7}alkyl or C_{3-7}cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from C_{1-4}alkoxy and phenyl);

R^1, R^2 and R^3 are each independently

hydrogen, PO_3H_2, sulphate, C_{3-7}cycloalkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{1-7}alkanoyl, a group $R^{20}C_{1-7}$alkyl (wherein R^{20} is phenyl which may bear one or more substituents selected from C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}aminoalkyl and C_{1-4}hydroxyalkoxy), C_{1-7}alkyl or C_{1-7}alkylsulphonyl (which alkyl or alkylsulphonyl group may bear one or more substituents selected from:

halogeno, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^2R^{21}$ (wherein Y^2 is $-NR^{22}C(O)-$ or $-O-C(O)-$ (wherein R^{22} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{21} is C_{1-7}alkyl, C_{3-7}cycloalkyl or a group R^{23} wherein R^{23} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, $-CONR^{24}R^{25}$ and $-NR^{26}COR^{27}$ (wherein R^{24}, R^{25}, R^{26} and R^{27}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl)));

with the proviso that at least two of R^1, R^2 and R^3 are C_{1-7}alkyl;

R^4 is

hydrogen, cyano, halogeno, nitro, amino, hydroxy, C_{1-7}alkoxy, C_{1-7}thioalkoxy, C_{1-7}alkanoyl or C_{1-7}alkyl,

(which alkyl group may bear one or more substituents selected from:
halogeno, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^3R^{28}$ (wherein Y^3 is $-NR^{29}C(O)-$ or $-O-C(O)-$ (wherein R^{29} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{28} is C_{1-7}alkyl, C_{3-7}cycloalkyl or a group R^{30} wherein R^{30} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, $-CONR^{31}R^{32}$ and $-NR^{31}COR^{32}$ (wherein R^{31}, R^{32}, R^{33} and R^{34}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl)));

R^5 and R^6 are each independently selected from

hydrogen, $-OPO_3H_2$, phosphonate, cyano, halogeno, nitro, amino, carboxy, carbamoyl, hydroxy, C_{1-7}alkoxy, C_{1-7}alkanoyl, C_{1-7}thioalkoxy, C_{1-7}alkyl,

(which alkyl group may bear one or more substituents selected from:
halogeno, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkanoyl, carboxy, phenyl, sulphate, phosphate and a group $-Y^3R^{28}$ (wherein Y^3 is $-NR^{29}C(O)-$ or $-O-C(O)-$ (wherein R^{29} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{28} is C_{1-7}alkyl, C_{3-7}cycloalkyl or a group R^{30} wherein R^{30} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, $-CONR^{31}R^{32}$ and $-NR^{31}COR^{32}$ (wherein R^{31}, R^{32}, R^{33} and R^{34}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl))), and

a group $-Y^4R^{35}$

(wherein Y^4 is $-C(O)-$, $-OC(O)-$, $-O-$, $-SO-$, $-SO_2-$, $-OSO_2-$, $-NR^{36}-$, $-C_{1-4}$alkyl$NR^{36}-$, $-C_{1-4}$alkyl$C(O)-$, $-NR^{37}C(O)-$, $-OC(O)O-$, $-C(O)NR^{38}-$ or $-NR^{39}C(O)O-$ (wherein R^{36}, R^{37}, R^{38} and R^{39}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and

R^{35} is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, hydroxy, amino, C_{1-7}alkyl, C_{1-7}alkoxy, C_{1-7}alkanoyl, C_{1-7}alkylamino, di(C_{1-7}alkyl)amino, aminoC_{1-7}alkylamino, C_{1-7}alkylaminoC_{1-7}alkylamino, C_{1-7}alkanoylaminoC_{1-7}alkyl, di(C_{1-7}alkyl)aminoC_{1-7}alkylamino, C_{1-7}alkylphosphate, C_{1-7}alkylphosphonate, C_{1-7}alkylcarbamoylC_{1-7}alkyl,

(which alkyl, alkoxy, alkanoyl, alkylamino, dialkylamino, aminoalkylamino, alkylaminoalkylamino, alkanoylaminoalkyl, dialkylaminoalkylamino, alkylphosphate, alkylphosphonate or alkylcarbamoylalkyl, may bear one or more substituents selected from:
halogeno, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, hydroxy, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^5R^{40}$ (wherein Y^5 is $-NR^{41}C(O)-$, $-C(O)NR^{42}-$, $-C(O)-O-$ or $-O-C(O)-$ (wherein R^{41} and R^{42} which may be the same or different each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and

R^{40} is C_{1-7}alkyl, C_{3-7}cycloalkyl, carboxyC_{1-7}alkyl or a group R^{43} wherein R^{43} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, -$CONR^{44}R^{45}$ and -$NR^{46}COR^{47}$ (wherein R^{44}, R^{45}, R^{46} and R^{47}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl))),

R^{48} (wherein R^{48} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from

hydroxy, nitro, halogeno, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, di(C_{1-4}hydroxyalkyl)aminoC_{1-4}alkyl, di(C_{1-4}aminoalkyl)aminoC_{1-4}alkyl, C_{1-4}hydroxyalkoxy, carboxy, C_{1-4}carboxyalkyl, phenyl, cyano, -$CONR^{49}R^{50}$, -$NR^{51}COR^{52}$ (wherein R^{49}, R^{50}, R^{51} and R^{52}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and C_{1-4}alkylR^{53} (wherein R^{53} is as defined herein),

C_{1-7}alkylR^{48} (wherein R^{48} is as defined herein),

R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}carboxyalkyl, C_{1-4}aminoalkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl and R^{54} (wherein R^{54} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl)), or

$(CH_2)_aY^6(CH_2)_bR^{53}$ (wherein R^{53} is as defined herein, a is 0, or an integer 1-4, b is 0 or an integer 1-4 and Y^6 represents a direct bond, -O-, -C(O)-, -NR^{55}-, -NR^{56}C(O)- or -

C(O)NR^{57}- (wherein R^{55}, R^{56}, and R^{57}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and wherein one or more of the $(CH_2)_a$ or $(CH_2)_b$ groups may bear one or more substituents selected from hydroxy, amino and halogeno));

with the proviso that R^5 is not hydroxy, alkoxy, substituted alkoxy (wherein R^5 is Y^{4}R^{35} and Y^4 is -O- and R^{35} is C_{1-7}alkyl bearing one or more substituents selected from the list given herein), -OPO$_3$H$_2$, -O-C_{1-7}alkanoyl or benzyloxy;

with the further proviso that at least one of R^5 or R^6 is a group -Y^{4}R^{35} (wherein Y^4 and R^{35} are as defined herein) but with the further provisos

that when R^5 is -Y^{4}R^{35} and R^6 is hydroxy, hydroxy, methoxy or methoxycarbonyl, -Y^{4}R^{35} is not selected from cases wherein:

Y^4 is -C(O)-, -OC(O)-, -O-, -SO-, -OSO$_2$-, -NR^{36}-, -NR^{37}C(O)- or -C(O)NR^{38}- (wherein R^{36}, R^{37} and R^{38}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{35} is

a glycine, valine or lysine group, a dipeptide of glycine and valine groups, C_{1-7}alkyl, C_{1-7}alkoxy, C_{1-7}alkanoyl,

(which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno, hydroxy, and a group -Y^{5}R^{40} (wherein Y^5 is -O-C(O)- and R^{40} is C_{1-7}alkyl)), or

R^{48} (wherein R^{48} is a tetrazolyl group (which may or may not be substituted as herein defined), a phenyl group or a benzyl group which phenyl or benzyl group may bear one or more substituents selected from C_{1-4}alkyl); and

that when R^6 is -Y^{4}R^{35} and R^5 is hydrogen, hydroxy, methoxy or methoxycarbonyl, -Y^{4}R^{35} is not selected from cases wherein:

Y^4 is -C(O)-, -O- or -OSO$_2$- and R^{35} is

C_{1-7}alkyl, C_{1-7}alkoxy

(which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno),

R^{48} (wherein R^{48} is a benzyl group which benzyl group may bear one or more substituents selected from C_{1-4}alkyl), or

R^{53} (wherein R^{53} is piperidinyl);

or a salt thereof.

3. The use of a compound of the formula IIa as defined in claim 2, or a salt thereof, a pharmaceutically acceptable salt thereof, a solvate or hydrate thereof, or a prodrug thereof, in the manufacture of a medicament for use in the production of a vascular damaging effect in warm-blooded animals such as humans.

4. A compound according to claim 2 wherein X is $-CH(R^7)-$ wherein R^7 is $-OR^8$ or $-NR^8R^9$ (wherein R^8 is a group $-Y^1R^{10}$ (wherein Y^1 is -C(O)-, -C(O)O- or $-C(O)NR^{11}-$ (wherein R^{11} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{10} is as defined in claim 2) and R^9 is as defined in claim 2).

5. A compound according to claim 2 or claim 4 wherein R^1, R^2 and R^3 are each methyl.

6. A compound according to any one of claims 2, 4 or 5 wherein R^4 is hydrogen.

7. A compound according to any one of claims 2, 4, 5 or 6 wherein R^6 is hydrogen, halogeno, amino, carboxy, hydroxy, C_{1-7}alkoxy or a group Y^4R^{35} (wherein Y^4 is -C(O)-, -O- or $-OSO_2-$ and R^{35} is C_{1-7}alkyl, C_{1-7}alkoxy (which alkyl or alkoxy may bear one or more substituents selected from halogeno), R^{48} (wherein R^{48} is a benzyl group) or R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms selected independently from O, S and N)).

8. A compound according to any one of claims 2, 4, 5, 6 or 7 wherein R^6 is hydrogen, $C(O)OCH_3$ or methoxy.

9. A compound according to any one of claims 2, 4, 5, 6, 7 or 8 wherein R^5 is hydrogen, halogeno, amino, carboxy, carbamoyl, C_{1-7}alkanoyl, C_{1-7}thioalkoxy, or a group $-Y^4R^{35}$

(wherein Y^4 is -C(O)-, -OC(O)-, -O-, -SO-, $-OSO_2-$, $-NR^{36}-$, $-NR^{37}C(O)-$ or $-C(O)NR^{38}-$ (wherein R^{36}, R^{37} and R^{38}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and

R^{35} is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, C_{1-7}alkyl, C_{1-7}alkoxy, C_{1-7}alkanoyl, C_{1-7}alkanoylaminoC_{1-7}alkyl,

(which alkyl, alkoxy, alkanoyl, alkanoylaminoalkyl may bear one or more substituents selected from:

halogeno, amino, hydroxy, carboxy, and a group $-Y^5R^{40}$ (wherein Y^5 is -C(O)-O- or -O-C(O)- and R^{40} is C_{1-7}alkyl or a group R^{43} wherein R^{43} is a benzyl group),

R^{48} (wherein R^{48} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from

hydroxy, fluoro, amino, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, di(C_{1-4}hydroxyalkyl)aminoC_{1-4}alkyl, di(C_{1-4}aminoalkyl)aminoC_{1-4}alkyl, C_{1-4}hydroxyalkoxy, carboxy, C_{1-4}carboxyalkyl, cyano, $-CONR^{49}R^{50}$, $-NR^{51}COR^{52}$ (wherein R^{49}, R^{50}, R^{51} and R^{52}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and C_{1-4}alkylR^{53} (wherein R^{53} is as defined herein),

C_{1-7}alkylR^{48} (wherein R^{48} is as defined herein),

R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, fluoro, chloro, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}carboxyalkyl, C_{1-4}aminoalkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl and R^{54} (wherein R^{54} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl)), or

$(CH_2)_aY^6(CH_2)_bR^{53}$ (wherein R^{53} is as defined herein, a is 0, or an integer 1-4, b is 0 or an integer 1-4 and Y^6 represents a direct bond, -O-, -C(O)-, $-NR^{55}$-, $-NR^{56}$C(O)- or -C(O)NR^{57}- (wherein R^{55}, R^{56}, and R^{57}, which may be the same or different, each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and wherein one or more of the $(CH_2)_a$ or

$(CH_2)_b$ groups may bear one or more substituents selected from hydroxy, amino and halogeno));

with the proviso that R^5 is not alkoxy, substituted alkoxy (wherein R^5 is Y^4R^{35} and Y^4 is -O- and R^{35} is C_{1-7}alkyl bearing one or more substituents selected from the list given herein), -O-C_{1-7}alkanoyl or benzyloxy.

10. A compound according to claim 2 selected from:

(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl 3-{[(2*R*)-2,6-diaminohexanoyl]amino}propanoate,

(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl 3-[(2-aminoacetyl)amino]propanoate,

N-([(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]oxymethyl)-2-morpholinoacetamide,

(2*S*,3*S*,4*S*,5*R*,6*R*)-6-{[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]oxy}-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylic acid,

N-[(5*S*)-3-(4-{4-methylpiperazin-1-ylmethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl]acetamide,

N-[(5*S*)-3-(4-{morpholinomethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl]acetamide,

(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl 3-[4-methylpiperazin-1-ylcarbonyl]propanoate,

5-[{(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl}oxycarbonyl]pentanoic acid,

4-(3-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]oxy-3-oxopropyl)benzoic acid and

(2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]-2-amino-3-hydroxypropanamide,

and salts thereof.

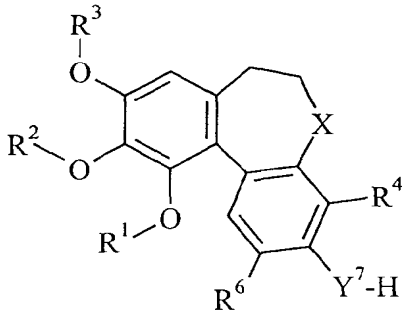
11. A compound according to claim 2 selected from

N-[(5*S*)-3-(4-{4-methylpiperazin-1-ylmethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl]acetamide and

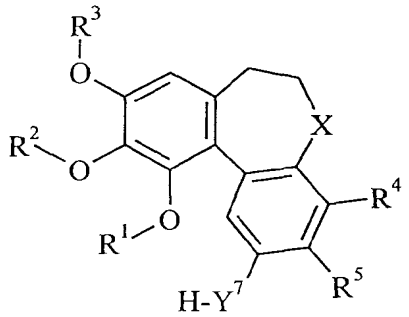
(2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]-2-amino-3-hydroxypropanamide,
and salts thereof.

12. A compound according to claim 2 selected from
(2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl]-2-amino-5-[(2-nitroethanimidoyl)amino]pentanamide
and salts thereof.

13. A process for the manufacture of a compound of formula IIa as defined in claim 2 which comprises:
(a) for the preparation of compounds of formula IIa and salts thereof in which R^5 or R^6 is a group Y^4R^{35} (wherein R^{35} is as defined in claim 2 and Y^4 is a group -OC(O)- or -NHC(O)-), the reaction of a compound of formula III or IV:



(III)



(IV)

(wherein X, R^1, R^2, R^3, R^4, R^5, R^6 are as defined in claim 2 and Y^7 is -O- or -NH-), by acylation or coupling reactions;
(b) for the preparation of compounds of formula IIa and salts thereof in which R^5 or R^6 is a group Y^4R^{35} (wherein R^{35} is C_{1-7}alkoxy which may be substituted as defined in claim 2 and Y^4 is a group -OC(O)- or -NHC(O)-), the reaction of a compound of formula III and IV, by acylation reactions;
(c) for the preparation of compounds of formula IIa and salts thereof in which R^5 or R^6 is a group Y^4R^{35} (wherein R^{35} is aminoC_{1-7}alkylamino, C_{1-7}alkylaminoC_{1-7}alkylamino, di(C_{1-7}alkyl)aminoC_{1-7}alkylamino and may be substituted as defined in claim 2, or is R^{53} (wherein

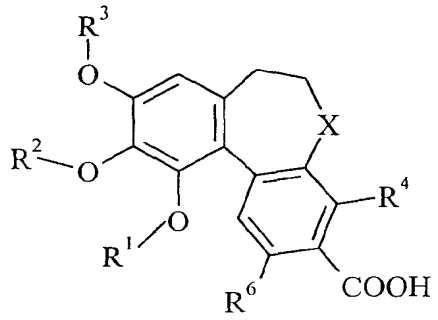
R^{53} is as defined in claim 2) and Y^4 is a group -OC(O)- or -NHC(O)-), can be prepared by the reaction of a compound of formula III or IV, acylation reactions;

(d) for the preparation of compounds of formula IIa and salts thereof in which R^5 or R^6 is a group Y^4R^{35} (wherein R^{35} is a sugar moiety and Y^4 is a group -O- or -NH-), the reaction of a compound of formula III or IV, glycosylation reactions;

(e) for the preparation of compounds of formula IIa and salts thereof in which R^5 or R^6 is a group Y^4R^{35} (wherein R^{35} is sulphate and Y^4 is a group -O- or -NH-), the reaction of a compound of formula III or IV, by sulphonylation reactions;

(f) for the preparation of compounds of formula IIa and salts thereof in which R^5 or R^6 is a group Y^4R^{35} (wherein R^{35} is C_{1-7}alkylphosphate and may be substituted as defined in claim 2 and Y^4 is a group -O- or -NH-), the reaction of a compound of formula III or IV, by phosphorylation reactions;

(g) for the preparation of compounds of formula IIa and salts thereof in which R^5 is amino the reaction of a carboxylic acid of formula V:



(V)

(wherein X, R^1, R^2, R^3, R^4 and R^6 are as defined in claim 2) via Curtius rearrangement and hydrolysis; and

(h) for the preparation of compounds of formula IIa and salts thereof in which R^5 or R^6 is chloro the reaction of a compound of formula III or IV by the Sandmeyer reaction;

and when a pharmaceutically acceptable salt of a compound of formula IIa is required, reaction of the compound obtained with an acid or base whereby to obtain the desired pharmaceutically acceptable salt.

14. A pharmaceutical composition which comprises as active ingredient a compound of formula IIa as defined in claim 2 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient or carrier.

15. A method for producing a vascular damaging effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IIa or a pharmaceutically acceptable salt thereof as defined in claim 2.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 99/04436

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C13/547 A61K31/165 A61K31/22 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 02166 A (ANGIOGENE PHARM LTD ;DOUGHERTY GRAEME (GB)) 21 January 1999 (1999-01-21) the whole document	1-15
X	FR 4 685 M (ROUSSEL-UCLAF) 23 January 1967 (1967-01-23) page 1, left-hand column	2,4-9
X	US 5 760 092 A (TIMASHEFF SERGE M ET AL) 2 June 1998 (1998-06-02) the whole document	1-15

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[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

Date of the actual completion of the international search	Date of mailing of the international search report
29 March 2000	12/04/2000

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	Engl, B

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 88, no. 17, 1978 Columbus, Ohio, US; abstract no. 121468j, KISELEV ET AL.: "Benzoid rearrangement of colchicine in the presence of ethylene glycol" page 572; XP002134241 abstract & ZH. ORG. KHIM., vol. 13, no. 11, - 1977 pages 2337-2342,	2,4-9
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X	R BRECHT ET AL: "Dihydrocolchicine 8,12-endoperoxide. a novel starting material for convenient syntheses of the allocolchicinoids N-acetylcolchinol O-methyl ether and androbiphenyline" LIEBIGS ANNALEN/RECUEIL: ORGANIC AND BIOORGANIC CHEMISTRY - A EUROPEAN JOURNAL,US,VCH PUBLISHERS, FLORIDA, no. 11, 1 January 1997 (1997-01-01), pages 2275-2279, XP002081867 ISSN: 0947-3440 Compounds 6a,6b page 2276, right-hand column	2,4-9
X	GIL-JONG KANG ET AL: "n-Acetylcolchinol O-methyl ether and thiocolchicine, potent nalogs of colchicine modified in the C-ring" JOURNAL OF BIOLOGICAL CHEMISTRY,US,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 265, no. 18, 25 June 1990 (1990-06-25), pages 10255-10259, XP002081868 ISSN: 0021-9258 page 10259, left-hand column; figure 1	2,4-9

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/GB 99/04436

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9902166 A	21-01-1999	AU 8231198 A	08-02-1999
FR 4685 M		NONE	
US 5760092 A	02-06-1998	NONE	

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(71) Applicant: **SPRUCE BIOSCIENCES, INC.** [US/US]; 548 Market Street, Suite 74589, San Francisco, California 94105 (US).

(72) Inventors: **HOWERTON, Alexis**; 548 Market Street, Suite 74589, San Francisco, California 94105 (US). **GERBER, Hal**; 548 Market Street, Suite 74589, San Francisco, California 94105 (US). **HUANG, Michael**; 548 Market Street, Suite 74589, San Francisco, California 94105 (US).

(74) Agent: **DELANEY, Simren**; WILSON SONSINI GOODRICH & ROSATI, 650 Page Mill Road, Palo Alto, California 94304 (US).

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(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).

(54) Title: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

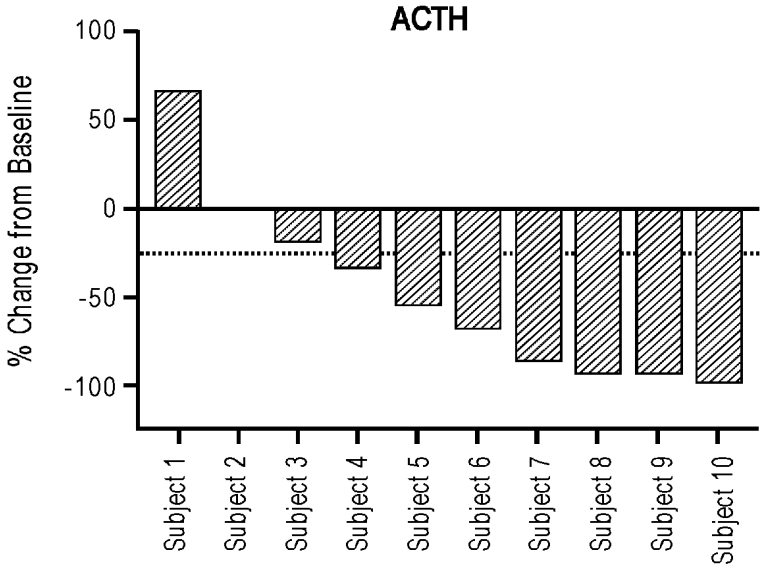


FIG. 2

(57) Abstract: The present invention provides novel pharmaceutical compositions comprising -(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine and methods of using the same for the treatment of Congenital adrenal hyperplasia (CAH).

WO 2019/036503 A1

[Continued on next page]

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

CROSS-REFERENCE

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 62/545,406, filed August 14, 2017, which is incorporated herein by reference in its entirety.

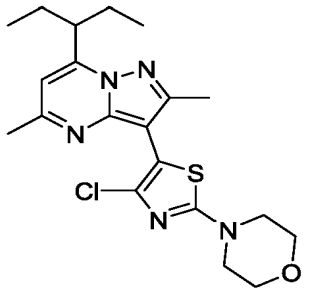
BACKGROUND OF THE INVENTION

[0002] Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

SUMMARY OF THE INVENTION

[0003] The present invention provides novel pharmaceutical compositions comprising 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine and methods using such pharmaceutical compositions for treating congenital adrenal hyperplasia (CAH).

[0004] In one aspect, the present disclosure provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

[0005] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1000 mg/day. In some

embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.

[0006] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm and about 20 μm. In some embodiments, the average size of the microparticles is between about 5 μm and about 15 μm. In some embodiments, the average size of the microparticles is less than about 10 μm.

[0007] In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the pharmaceutical composition is in the form of a capsule. 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.

[0008] 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.

[0009] 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. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition

comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0010] In some embodiments, the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0011] In some embodiments, the pharmaceutical composition provides a Compound 1 T_{max} of about 2 to about 6 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 T_{max} of about 3 to about 5 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 T_{max} of about 6 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 T_{max} of about 5 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 T_{max} of about 4 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 T_{max} of about 3 hours in a subject.

[0012] 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 once a day. In some embodiments, the pharmaceutical composition is administered twice a day. In some embodiments, the pharmaceutical composition is administered three times a day.

[0013] In some embodiments, the method further comprises administering a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the amount of glucocorticoid used is reduced from a supraphysiologic amount to a physiologic amount. In some embodiments, the amount of glucocorticoid is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%.

[0014] In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are reduced. In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone.

[0015] In some embodiments, the glucocorticoid is hydrocortisone. In some embodiments, the hydrocortisone is administered at a dose less than about 15 mg/day. In some embodiments, the hydrocortisone is administered at a dose less than about 10 mg/day. In some embodiments, the hydrocortisone is administered at a dose less than about 5 mg/day.

[0016] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 24 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 8 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 2 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 30 minutes.

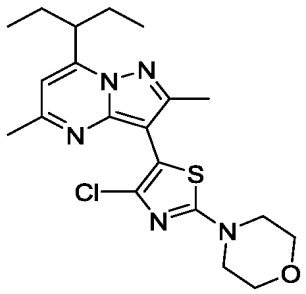
[0017] In some embodiments, the method further comprises administering a mineralocorticoid. In some embodiments, the mineralocorticoid is fludrocortisone.

[0018] 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 mins 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 pharmaceutical composition is administered at or before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the pharmaceutical composition is administered about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH).

[0019] In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.

[0020] In one aspect, the present disclosure provides 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 Compound 1:



or a pharmaceutically acceptable salt or solvate thereof; and

(iii) repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of compound 1.

[0021] In some embodiments, the hormone is 17α-Hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, or androstenedione. In some embodiments, the hormone is 17-OHP, and the pre-determined range is from about 200 ng/dL to about 400 ng/dL. In some embodiments, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL. In some embodiments, the hormone is testosterone and the pre-determined range is from about 14 ng/dL to about 76 ng/dL. In some embodiments, the hormone is androstenedione and the pre-determined range is from about 30 ng/dL to about 150 ng/dL in males. In some embodiments, the hormone is androstenedione and the pre-determined range is from about 40 ng/dL to about 200 ng/dL in females.

[0022] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is

administered at a dose between about 200 mg/day and about 1000 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 800 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.

[0023] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and 400 mg /day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between 50 mg/day and 200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 50 mg /day.

[0024] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm and about 20 μm. In some embodiments, the average size of the microparticles is between about 5 μm and about 15 μm. In some embodiments, the average size of the microparticles is less than about 10 μm.

[0025] In some embodiments, Compound 1 is formulated in a pharmaceutical composition in the form of a capsule or a tablet. In some embodiments, the pharmaceutical composition is in the form of a capsule. 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.

[0026] 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.

[0027] In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0028] In some embodiments the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments,the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate

thereof. In some embodiments, he pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0029] In some embodiments, the pharmaceutical composition provides a Compound 1 T_{max} of about 2 to about 6 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 T_{max} of about 3 to about 5 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 T_{max} of about 6 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 T_{max} of about 5 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 T_{max} of about 4 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 T_{max} of about 3 hours in a subject.

[0030] 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 once a day. In some embodiments, the pharmaceutical composition is administered twice a day. In some embodiments, the pharmaceutical composition is administered three times a day.

[0031] In some embodiments, the method further comprises administering a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the amount of glucocorticoid used is reduced from a supraphysiologic amount to a physiologic amount. In some embodiments, the amount of glucocorticoid is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%.

[0032] In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are reduced. In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the glucocorticoid is hydrocortisone.

[0033] In some embodiments, the hydrocortisone is administered at a dose less than about 15 mg/day. In some embodiments, the hydrocortisone is administered at a dose less than about 10 mg/day. In some embodiments, the hydrocortisone is administered at a dose less than about 5 mg/day.

[0034] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 24 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 8 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 2 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 30 minutes.

[0035] In some embodiments, the method further comprises administering a mineralocorticoid. In some embodiments, the mineralocorticoid is fludrocortisone.

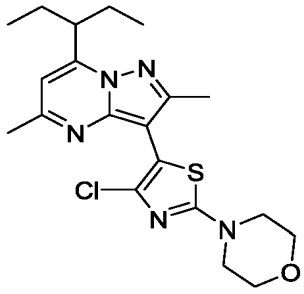
[0036] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at bedtime. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered less than about 4 hours before sleeping. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered less than about 2 hours before sleeping. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered less than about 30 mins before sleeping. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered in the evening. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at 10 pm at night.

[0037] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at or before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH).

[0038] In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.

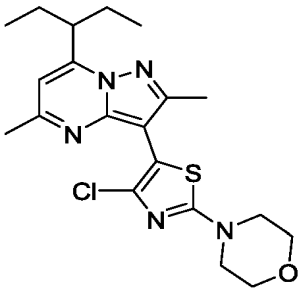
[0039] In some embodiments, the subject in need thereof is from about 12 years of age to about 20 years of age.

[0040] In one aspect, the present disclosure provides a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



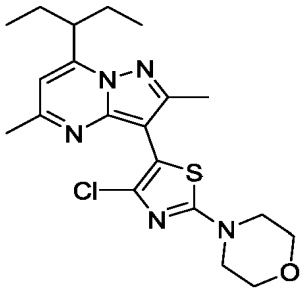
; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism and alopecia.

[0041] In one aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



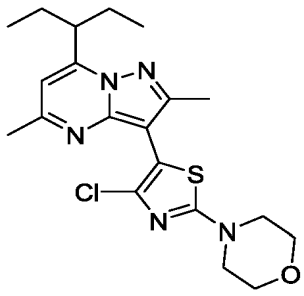
; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

[0042] In one aspect, the present disclosure provides a method of improving metabolic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the metabolic symptoms are selected from the group consisting of body weight, BMI, waist circumference, blood pressure and glycemic control.

[0043] In one aspect, the present disclosure provides a method of improving quality of life in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day, wherein treatment results in an improved quality of life.

INCORPORATION BY REFERENCE

[0044] 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] 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 of which:

[0046] FIG. 1 shows Compound 1 in patients with CAH following 14-days of once daily dosing at each level;

[0047] FIG. 2 demonstrates the attenuation of ACTH across different subjects due to the administration of Compound 1;

[0048] FIG. 3 demonstrates the reduction in 17-OHP due to the administration of Compound 1;

[0049] FIG. 4 demonstrates the reduction of Androstenedione due to the administration of Compound.

DETAILED DESCRIPTION OF THE INVENTION

[0050] 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.

[0051] CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain thereby suggesting potential functional diversity. For example, widely distributed brain CRF1 receptors are strongly implicated in emotionality accompanying exposure to environmental stressors. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors. A more discrete septallhypothalmic distribution and the availability of alternative endogenous ligands suggest a different functional role for the CRF2 receptor. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF 1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism. In other cases, CRF2 agonism produces similar effects to those reported for CRF 1 antagonists or CRF 1 gene deletion. For example, while CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well.

[0052] Treatment of CAH is based on normalization of hormone and steroid levels using a variety of medications from diagnosis in infancy through adulthood. Glucocorticoids are the current standard treatment in CAH and are used both to correct the endogenous Cortisol deficiency and for reducing the elevated ACTH levels from the pituitary, which drives increased androgen production. Unlike the treatment of Addison's disease (adrenal insufficiency), in which Cortisol replacement is sufficient, the treatment of CAH must also reduce ACTH production, to control the subsequent androgen excess as well. Thus, the goals of glucocorticoid treatment include Cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women. Mineralocorticoid replacement is needed to achieve normal plasma renin activity for maintenance of regular blood pressure, electrolyte balance, and volume status in those patients with the salt-wasting form of CAH.

[0053] The regimen of glucocorticoid treatment must support normal physiology and also ensure that sufficient Cortisol is available during events that may elicit a strong stress response (e.g., intercurrent illness, exercise, hypotension). Careful monitoring is also necessary to avoid the development of Addisonian syndrome due to under-treatment. Overtreatment with mineralocorticoids may cause hypertension while under-treatment may lead to low blood pressure, salt loss, fatigue and increased requirements for glucocorticoids. Typical laboratory

tests for monitoring treatment efficacy include measurement of plasma concentrations of 17-OHP, androstenedione, testosterone, renin activity, and electrolytes.

[0054] Adult patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension, and insulin resistance. A study of a large cohort of pediatric and adult CAH patients (n=244) demonstrated that patients are prescribed a variety of glucocorticoid treatment regimens yet frequently suffer from poor hormonal control and the aforementioned adverse outcomes. Treatment of CAH includes efforts to normalize the Cortisol deficiency with glucocorticoids (usually hydrocortisone in children but often more potent agents with narrow therapeutic indices, such as dexamethasone, in adults) and, if necessary for salt-wasting, mineralocorticoids (usually fludrocortisone). The glucocorticoid doses required to achieve sufficient suppression of excess androgens, however, are usually well above the normal physiologic dose used for Cortisol replacement alone as in patients with Addison's disease. This increased exposure to glucocorticoids can lead to increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients.

[0055] 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.

[0056] 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.

[0057] The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. Deficiencies in these enzymes as a result of mutation or deletion cause the substrate concentrations to increase. In the most common form of CAH resulting from mutations or deletions in the 21 -hydroxylase gene (CYP21A2), potent androgens are produced by the adrenal because of the accumulation of the steroid precursors, progesterone and 17-hydroxyprogesterone (17-OHP). Plasma levels of 17-OHP can reach 10-1000 times the normal concentration in these cases. These increases result in the overproduction of androgens, specifically androstenedione, testosterone, and dihydroxytestosterone causing virilization in

females. In addition, 21 -hydroxylase deficiency in CAH causes insufficient biosynthesis of glucocorticoids and mineralocorticoids, specifically Cortisol and aldosterone. Cortisol is a critical negative feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates the restraint on the hypothalamus and pituitary, which causes ACTH levels to increase. The excessive ACTH stimulation causes hypertrophy of the zona fasciculata and zona reticularis resulting in adrenal hyperplasia.

[0058] In one embodiment, the CRF receptor antagonist useful for the treatment of CAH is 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine.

Certain Definitions

[0059] 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.

[0060] 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.

[0061] The term "about" is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value.

[0062] 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."

[0063] 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.

[0064] "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.

[0065] 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.

[0066] The term "pharmaceutical composition" means a composition comprising at least one active ingredient, such as Compound 1, 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.

[0067] The term "supraphysiologic" amount" describes hormones levels that are elevated compared to average levels found in healthy individuals.

[0068] The term "physiologic amount" describes average hormone levels found in healthy individuals.

[0069] 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).

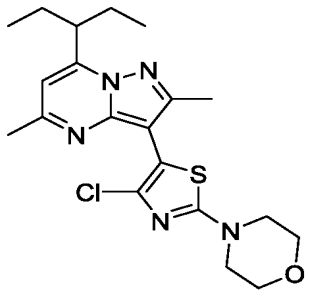
[0070] The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, 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.

[0071] 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. 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 of the invention 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.

Compound

[0072] 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), a pharmaceutically acceptable salt, and/or a solvate thereof:



. 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 1. 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 1.

Pharmaceutical Compositions

[0073] Disclosed herein is a pharmaceutical composition comprising Compound 1, a pharmaceutically acceptable salt, and/or a solvate thereof.

Dosage Form

[0074] 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 Compound 1 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.

[0075] 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.

[0076] 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

[0077] 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.

[0078] 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.

[0079] In some embodiments, the capsule comprises one or more pharmaceutically acceptable excipients. In some embodiments, the capsule is free of additional excipients.

[0080] 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

[0081] 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.

[0082] In some embodiments, the pharmaceutical composition is formulated as a tablet.

[0083] 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 Compound 1 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 Compound 1 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 Compound 1 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 Compound 1. 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.

[0084] In some embodiments, the tablet size is less than about 1000 mg, less than about 800 mg, less than about 600 mg, less than about 400 mg or less than about 200 mg. In some embodiments, the tablet has a dose strength of more than about 50 mg, more than about 100 mg, more than about 150 mg, more than about 200 mg, or more than about 250 mg. In some embodiments, the tablet size is less than about 1000 mg for a dose strength of more than about 50 mg. In some embodiments, the tablet size is less than 800 mg for a dose strength of more than about 100 mg. In some embodiments, the tablet size is less than 600 mg for a dose strength of more than about 150 mg. In some embodiment, the tablet size is less than 400 mg for a dose strength of more than about 200 mg. In some embodiments, the tablet size is less than 400 mg for a dose strength of 200 mg.

In some embodiments, more than about 20% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 24 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is

dissolved in less than 12 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 6 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 3 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 2 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than 70% of the tablet is dissolved in 60 minutes in conventional dissolution media.

[0085] In some embodiments, the tablet is produced at a commercial scale.

[0086] In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

[0087] In some embodiments, the tablet is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some embodiments, the coating material is in the form of a film coating, e.g., a glossy film, a pH independent film coating, an aqueous film coating, a dry powder film coating (e.g., complete dry powder film coating), or any combination thereof. In some embodiments, the coating material is highly adhesive. In some embodiments, the coating material provides low level of water permeation. In some embodiments, the coating material provides oxygen barrier protection. In some embodiments, the coating material allows immediate disintegration for fast release of Compound 1. In some embodiments, the coating material is pigmented, clear, or white. In some embodiments, the coating is an enteric coating. Exemplary coating materials include, without limitation, polyvinylpyrrolidone, polyvinyl alcohol, an acrylate-methacrylic acid copolymer, a methacrylate-methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, cellulose acetate trimellitate, sodium alginate, zein, and any combinations thereof.

Pharmaceutically Acceptable Excipients

[0088] 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.

[0089] 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

[0090] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 40 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 20 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 10 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 5 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule comprises about 1 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule comprises about 5 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0091] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0092] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 500 mg of Compound 1, or a

pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0093] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 80 mg of Compound 1, or a

pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0094] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0095] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt

or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0096] In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0097] In some embodiments, the pharmaceutical composition comprises about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 90 mg of Compound 1, or a pharmaceutically

acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 40 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 20 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 10 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

Particle size

[0098] In some embodiments, the pharmaceutical composition, in the form of a tablet or a capsule, comprises Compound 1, or a pharmaceutically acceptable salt or solvate thereof, in the form of microparticles. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 100 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 50 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 30 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 20 μm. In some embodiments, microparticles of Compound 1 have an average size from about 5 μm to about 15 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 3 μm to about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 4 μm to about 9 μm.

[0099] In some embodiments, microparticles of Compound 1 have an average size less than about 100 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 80 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 60 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 50 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 40 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 30 μm. In some embodiments, microparticles of Compound 1

have an average size less than about 20 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 10 μm.

Pharmacokinetics

[0100] In some embodiments, Compound 1 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, Compound 1 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, Compound 1 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, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 3 to about 5 hours in a subject.

[0101] In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 8 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 7 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 6 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 5 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 4 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 3 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 2 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 1 hour in a subject.

Stability

[0102] The pharmaceutical compositions described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to pharmaceutical compositions having about 95% or greater of the initial Compound 1 amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of Compound 1. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable pharmaceutical compositions have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable pharmaceutical compositions have about 5% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 4% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 3% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 2% w/w total impurities or related substances. In yet

other embodiments, the stable pharmaceutical compositions have about 1% w/w total impurities or related substances.

[0103] At refrigerated condition, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5±5 ºC. In some embodiments, refrigerated condition is about 0 ºC, about 0.1 ºC, about 0.2 ºC, about 0.3 ºC, about 0.4 ºC, about 0.5 ºC, about 0.6 ºC, about 0.7 ºC, about 0.8 ºC, about 0.9 ºC, about 1 ºC, about 1.1 ºC, about 1.2 ºC, about 1.3 ºC, about 1.4 ºC, about 1.5 ºC, about 1.6 ºC, about 1.7 ºC, about 1.8 ºC, about 1.9 ºC, about 2 ºC, about 2.1 ºC, about 2.2 ºC, about 2.3 ºC, about 2.4 ºC, about 2.5 ºC, about 2.6 ºC, about 2.7 ºC, about 2.8 ºC, about 2.9 ºC, about 3 ºC, about 3.1 ºC, about 3.2 ºC, about 3.3 ºC, about 3.4 ºC, about 3.5 ºC, about 3.6 ºC, about 3.7 ºC, about 3.8 ºC, about 3.9 ºC, about 4 ºC, about 4.1 ºC, about 4.2 ºC, about 4.3 ºC, about 4.4 ºC, about 4.5 ºC, about 4.6 ºC, about 4.7 ºC, about 4.8 ºC, about 4.9 ºC, about 5 ºC, about 5.1 ºC, about 5.2 ºC, about 5.3 ºC, about 5.4 ºC, about 5.5 ºC, about 5.6 ºC, about 5.7 ºC, about 5.8 ºC, about 5.9 ºC, about 6 ºC, about 6.1 ºC, about 6.2 ºC, about 6.3 ºC, about 6.4 ºC, about 6.5 ºC, about 6.6 ºC, about 6.7 ºC, about 6.8 ºC, about 6.9 ºC, about 7 ºC, about 7.1 ºC, about 7.2 ºC, about 7.3 ºC, about 7.4 ºC, about 7.5 ºC, about 7.6 ºC, about 7.7 ºC, about 7.8 ºC, about 7.9 ºC, about 8 ºC, about 8.1 ºC, about 8.2 ºC, about 8.3 ºC, about 8.4 ºC, about 8.5 ºC, about 8.6 ºC, about 8.7 ºC, about 8.8 ºC, about 8.9 ºC, about 9 ºC, about 9.1 ºC, about 9.2 ºC, about 9.3 ºC, about 9.4 ºC, about 9.5 ºC, about 9.6 ºC, about 9.7 ºC, about 9.8 ºC, about 9.9 ºC, or about 10 ºC. At accelerated conditions, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, or at least 24 month. Accelerated conditions for the pharmaceutical compositions described herein include temperatures that are at or above ambient levels (e.g. 25±5 °C). In some instances, an accelerated condition is at about 40±2 °C. In some instances, an accelerated condition is at about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C, or about 60 °C. Accelerated conditions for the pharmaceutical compositions described herein also include relative humidity (RH) that are at or above ambient levels (55±10% RH). In other instances, an accelerated condition is above about 65% RH, about 70% RH, about 75% RH, or about 80% RH. In further instances, an accelerated condition is about 40 °C or 60 °C at ambient humidity. In yet further instances, an accelerated condition is about 40±2 °C at 75±5% RH humidity.

[0104] In some embodiments, the pharmaceutical compositions are stable at about 5±5 °C to about 25±5 °C for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 5±5 °C for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 25±5 °C for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 5±5 °C for at least 24 months. In one embodiment, the pharmaceutical compositions are stable at about 25±5 °C for at least 24 months.

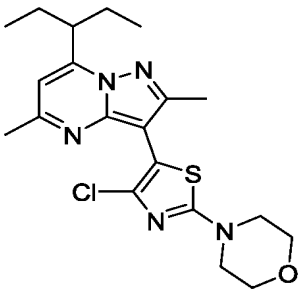
Methods of Use

[0105] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.In some embodiments, the methods described herein result in the reduction of a hormone level. Such hormones include deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, 17α-hydroxy progesterone (17-OHP), dehydroepiandrosterone, androstenediol, androstenedione, testosterone, dihydrotestosterone, estrone, estradiol, estriol, and adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein result in the reduction of 17α-hydroxy progesterone (17-OHP). In some embodiments, the methods described herein result in the reduction of adrenocorticotropic hormone (ACTH), also known as corticotropin.

[0106] Also disclosed herein 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 Compound 1:



or a pharmaceutically acceptable salt or solvate thereof;

(iii) repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of compound 1.

[0107] In some embodiment, the hormone is 17α-Hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, or androstenedione.

[0108] In some embodiment, the hormone is 17-OHP, and the pre-determined range is from about 200 ng/dL to about 400 ng/dL. In some embodiment, the hormone is 17-OHP, and the pre-determined range is less than about 400 ng/dL, less than about 350 ng/dL, less than about 300 ng/dL, less than about 250 ng/dL, or less than about 200 ng/dL.

[0109] In some embodiment, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL. In some embodiment, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL, below about 90 pg/mL, or below about 80 pg/mL.

[0110] In some embodiment, the hormone is testosterone and the pre-determined range is from about 14 ng/dL to about 76 ng/dL. In some embodiment, the hormone is testosterone and the pre-determined range is less than about 76 ng/dL, less than about 70 ng/dL, less than about 65 ng/dL, less than about 60 ng/dL, less than about 55 ng/dL, less than about 50 ng/dL, less than about 45 ng/dL, less than about 40 ng/dL, less than about 35 ng/dL, less than about 30 ng/dL, less than about 25 ng/dL, less than about 20 ng/dL, or less than about 15 ng/dL.

[0111] In some embodiment, the hormone is androstenedione and the pre-determined range is from about 30 ng/dL to about 200 ng/dL in males. In some embodiment, the hormone is androstenedione and the pre-determined range is less than about 200 ng/dL, less than about 150 ng/dL, less than about 100 ng/dL, less than about 50 ng/dL, or less than about 30 ng/dL in males

[0112] In some embodiment, the hormone is androstenedione and the pre-determined range is from about 40 ng/dL to about 150 ng/dL in females. In some embodiment, the hormone is androstenedione and the pre-determined range is less about 150 ng/dL, less about 100 ng/dL, less about 50 ng/dL, or less about 40 ng/dL in females.

[0113] In some embodiments, the methods described herein include administration of the pharmaceutical composition comprising Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt or solvate thereof once a day. In some embodiments, the methods described herein administer Compound 1, or a pharmaceutically acceptable salt or solvate thereof twice a day.

[0114] In some embodiments, the methods described herein include administration of about 1 mg to about 2000 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, per day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1500 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1400 mg/day. In some

embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1300 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1100 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 900 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 60 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 70 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 80 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 90 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 700 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 150 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 500 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 400 mg/day.

[0115] In some embodiments, Compound 1 is administered at a dose of about 500 mg/day. In some embodiments, Compound 1 is administered at a dose of about 400 mg/day. In some embodiments, Compound 1 is administered at a dose of about 300 mg/day. In some embodiments, Compound 1 is administered at a dose of about 200 mg/day. In some embodiments, Compound 1 is administered at a dose of about 100 mg/day.

[0116] In some embodiments, about 100 mg to about 1600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1000 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about

800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered each day.

[0117] In some embodiments, less than about 2000 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1800 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1600 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1400 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1200 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1000 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 800 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 600 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 500 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 400 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 300 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 200 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day.

[0118] 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.

[0119] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at bedtime.

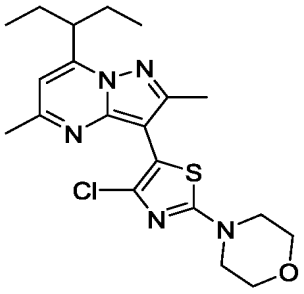
[0120] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 4 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than 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.

[0121] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in the evening.

[0122] 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.

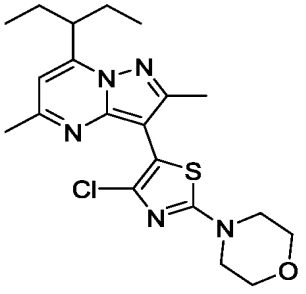
[0123] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at or before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the subject in need thereof is from about 12 years of age to about 20 years of age.

[0124] In one aspect, the present disclosure provides a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



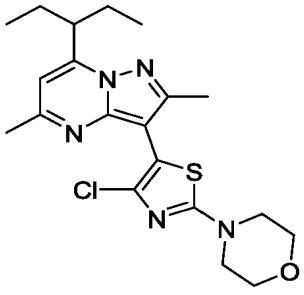
; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism and alopecia.

[0125] In one aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



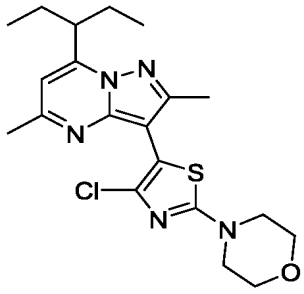
; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

[0126] In one aspect, the present disclosure provides a method of improving metabolic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the metabolic symptoms are selected from the group consisting of body weight, BMI, waist circumference, blood pressure and glycemic control.

[0127] In one aspect, the present disclosure provides a method of improving quality of life in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day, wherein treatment results in an improved quality of life.

Combination Therapy

[0128] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a combination of Compound 1, or a pharmaceutically acceptable salt or solvate thereof; and a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0129] In some embodiments, the methods described herein reduce the amount of a glucocorticoid administered from a supraphysiologic amount to a physiologic amount.

[0130] In some embodiments, the methods described herein reduce the symptoms associated with high-dose glucocorticoid therapy. In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis.

[0131] In some embodiments, the amount of glucocorticoid administered is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 80, or about 90% as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the amount of glucocorticoid administered is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60% as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0132] In some embodiments, the amount of glucocorticoid administered is reduced by about 1% to about 90%, about 1% to about 60%, about 1% to about 30%, about 1% to about 10%, about 10% to about 50%, about 10% to about 40%, about 10% to about 30%, about 15% to about 25%, about 20% to about 30%, about 5% to about 25%, about 20% to about 50%, about

30% to about 60%, or about 40% to about 70% as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0133] In some embodiments, the glucocorticoid is administered at a dose between about 0.1 mg/day and about 25 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 20 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 15 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 12 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 10 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 9 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 8 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 7 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 6 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 5 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 4 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 3 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 2 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 3 mg/day and about 13 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 5 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 8 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 9 mg/day and about 12 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 9 mg/day and about 10 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 5 mg/day and about 10 mg/day.

[0134] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered in one pharmaceutical composition. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently in separate pharmaceutical compositions.

[0135] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially. In some embodiments, Compound

1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 24 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 12 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 8 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 6 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 4 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 2 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 1 hour. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 30 minutes. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 10 minutes.

[0136] In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the glucocorticoid is hydrocortisone.

[0137] In some embodiments, the glucocorticoid is hydrocortisone and the dose administered is less than the recommended dose of 15-25 mg/day.

[0138] In some embodiments, the glucocorticoid is prednisone and the dose administered is less than the recommended dose of 5-7.5 mg/day.

[0139] In some embodiments, the glucocorticoid is prednisolone and the dose administered is less than the recommended dose of 4-6 mg/day.

[0140] In some embodiments, the glucocorticoid is dexamethasone and the dose administered is less than the recommended dose of 0.25-0.5 mg/day.

[0141] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a combination of Compound 1, or a pharmaceutically acceptable salt or solvate thereof; a glucocorticoid; and optionally a mineralcorticoid. In some embodiments, the mineralocorticoid is fludrocortisone and the dose is less than the recommended dose of 0.05-0.2 mg/day.

EXAMPLES

[0142] 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.

[0143] 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: Pharmaceutical Composition

[0144] The pharmaceutical composition is manufactured as size 1 white hard gelatin capsules containing 200 mg of Compound 1 micronized to and average size of 10 microns or less. The pharmaceutical composition contains no additional excipients.

Example 2: Stability of the Pharmaceutical Composition

Stability Data Summary

[0145] A summary of the pharmaceutical composition stability studies is provided in Table 1. The pharmaceutical composition is a Compound 1 neat-filled into size 0 capsules with no added excipients, in 3 strength configurations: 1-mg, 5-mg, and 50-mg. The capsules were blister packaged in a polyvinyl chloride (PVC)-based film.

[0146] Under long term and accelerated conditions, no significant trend was observed in the three lots for any of the attributes evaluated throughout the course of the stability study.

Table 1. Summary of Stability

Lot Number	Strength	CCS	Stability Conditions	Available Data
#1	1-mg	PVC-based blister pack	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#2	5-mg	PVC-based blister pack	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#3	50-mg	PVC-based blister pack	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#4	200-mg	75 mL HDPE bottle	25 °C/60% RH	1 month
			40 °C/75% RH	9 months
#5	200-mg	30 mL HDPE bottle	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#6	200-mg	30 mL HDPE bottle	25 °C/60% RH	6 months
			40 °C/75% RH	6 months

CCS = container closure system; CRC = child-resistant closure; DoM = date of manufacture; HDPE = high density polyethylene; PVC = polyvinyl chloride

Stability Protocols

[0147] The stability protocol for various pharmaceutical compositions is provided in Table 2, 3, and 4.

Table 2. Stability Protocol

Test	Acceptance Criteria	Time (months)			
		T_0	1	**3**	**6**
Appearance	Size 0 blue capsule containing yellow powder, blister pack and foil backing intact	X	A,B	A,B	A,B
Assay	Report (% Label Claim)	X	A,B	A,B	A,B
Related Substances	Report RRT and % each individual species and total	X	A,B	A,B	A,B
Disintegration	Report	X	A,B	A,B	A,B

RRT = relative retention time
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

Table 3. Stability Protocol (200-mg capsules in 30 mL HDPE bottles)

Test	Acceptance Criteria	Time (months)			
		T_0	1	3	6
Appearance	Size 1 white capsule containing an off-white to yellow powder	X	A,B	A,B	A,B
Assay (%LC)	90.0 – 110.0	X	A,B	A,B	A,B
Related Substances Any Unspecified Impurity (%) Total Impurities (%)	 ≤1.0 ≤2.0	X	A,B	A,B	A,B
Disintegration (min)	NMT 15	X	A,B	A,B	A,B
Water Activity	Report result	X	A,B	A,B	A,B

LC = label claim; NMT = not more than

X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

Table 4. Stability Protocol (200-mg capsules in 30 mL HDPE bottles) for Lots to be Used in Phase 2 Clinical Study

Test	Acceptance Criteria	Time (months)					
		T_0	1	3	6	9	12
Appearance	Size 1 white capsule containing an off-white to yellow powder	X	B	A,B	A,B	A	A
Assay (%LC)	90.0 – 110.0	X	B	A,B	A,B	A	A
Related Substances Any Unspecified Impurity (%) Total Impurities (%)	 ≤1.0 ≤2.0	X	B	A,B	A,B	A	A
Disintegration (min)	NMT 15	X	B	A,B	A,B	A	A
Water Activity	Report result	X	n/a	n/a	n/a	A	A
Microbial Enumeration Total Aerobic Microbial Count (CFU/g) Total Combined Yeast and Mold (CFU/g) Count	 NMT 2000 CFU/g NMT 200 CFU/g	X	n/a	n/a	n/a	A	A
Test for Specified Microorganisms *E. coli* (/g)	Absent	X	n/a	n/a	n/a	A	A

CFU = colony forming units; LC = label claim; n/a = not applicable; NMT = not more than
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

[0148] The supportive data demonstrate that the pharmaceutical composition is stable for a minimum of 6 months (end of study). No adverse trends were observed under long term and accelerated conditions. The assay results were consistent through the entire study and no new related substances species were observed during the stability study. The reported stability results for lots stored in a blister packaging configuration are considered supportive for the updated packaging configuration of a 30-mL HDPE bottle, induction seal, and a child resistant

cap. There are no excipients in either configuration and both configurations provide protection from light.

Example 3: Phase 1 Clinical Studies

[0149] Compound 1 has been investigated in 2 Phase 1 studies in healthy adult volunteers.

[0150] Study 1 was the first-in-human study that investigated the safety, tolerability, and PK of single-escalating doses of Compound 1, given orally, to healthy adult subjects. Safety and tolerability assessments were made over a wide range of single oral doses, and dose escalation did not proceed until safety data from the preceding doses had been reviewed. The data from this study were used for the selection of doses for Study 2.

[0151] The 2-part multiple-dose study, Study 2, determined the safety and tolerability of repeated daily doses of Compound 1 and investigated the effects on biomarkers of relevance for the treatment of alcohol dependence. Part B investigated the interaction of Compound 1 with midazolam (a cytochrome P450 3A4 [CYP3A4] substrate), determining whether Compound 1 significantly inhibited the metabolism of drugs that are metabolized by CYP3A4.

[0152] In Study 1, Compound 1 was administered to healthy adult subjects as a single PO dose of 2, 10, 50, 150, 400, or 800 mg in the fed state and 150 mg in the fasted state. Absorption occurred moderately late, achieving peak C_{max} between 4 to 6 hours following dosing in the fed state.

[0153] Table 5 provides a summary of the PK parameters at each dose level. When Compound 1 was given in the fed state, median time to reach maximum plasma concentration (T_{max}) occurred between 4 and 6 hours. The median T_{max} was 10.05 hours when Compound 1 was given in the fasted state at 150 mg and ranged between 6 and 12 hours, suggesting possible delayed absorption in the fasted state. Mean half-life ($t_{1/2}$) after a single PO dose (fed and fasted state) was between 31 and 44 hours, ranging from 11 to 101 hours. Apparent volume of distribution (V_z/F) was large and appeared highly variable with greatest variability observed at the 2 highest dose levels of 400 mg and 800 mg.

Table 5. Summary of Pharmacokinetic Parameters of Compound 1 Following Single Oral Dose Administration in Healthy Volunteers (all Fed)

PK Parameters	Geometric Mean (CV%)					
	Analyte = Plasma Compound 1					
	2 mg	**10 mg**	**50 mg**	**150 mg**	**400 mg**	**800 mg**
N	6	6	6	6	6	6
C_{max} (ng/mL)	0.867 (53)	3.01 (87)	19.5 (39)	93.4 (22)	207 (92)	382 (110)
T_{max}[a] (h)	6.00 (4.00-6.00)	4.00 (2.00 -6.00)	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)	6.00 (4.00 - 6.00)
$t_{1/2}$b (h)	NC	NC	31	29.2	44.2	41.9

	(NC)	(NC)	(10.8-53.4)	(20.0 - 41.5)	(20.2 - 101)	(24.1 - 67.8)
$AUC_{0-tlast}$ (ng•h/mL)	NC (NC)	NC (NC)	152 (60)	891 (26)	2300 (103)	4390 (100)
$AUC_{0-\infty}$ (ng•h/mL)	NC (NC)	NC (NC)	165 (64)	956 (25)	2580 (93)	4850 (95)
CL/F (L/h)	NC (NC)	NC (NC)	302 (64)	157 (25)	155 (93)	165 (95)
V_z/F (L)	NC (NC)	NC (NC)	13500 (45)	6620 (38)	9890 (212)	9970 (144)
V_{ss}/F (L)	NC (NC)	NC (NC)	8080 (36)	4600 (33)	6580 (152)	6820 (120)

AUC = area under the plasma concentration-time curve; CL/F = oral clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; NC = not calculable; $t_{1/2}$ = elimination half-life; T_{max} = time to reach maximum plasma concentration; V_{ss}/F = volume of distribution at steady state; V_z/F = volume of distribution at terminal phase

a Median (range)

b Geometric mean (range)

[0154] As part of this single-dose escalation study, a food effect PK investigation was performed to examine Compound 1 exposures in both the fed and fasted states at the 150-mg dose level. A total of 6 subjects were administered 150 mg Compound 1 in each of these 2 dosing groups. Of these 6 subjects, 4 subjects received Compound 1 at the same dose in both fed and fasted states. The administration of Compound 1 in the fasted state resulted in a much flatter mean concentration-time (i.e., with significantly lower absorption) profile when compared against the mean profile at the same dose, given within 5 minutes after a standardized breakfast meal. The mean $AUC_{0-\infty}$, and C_{max} values for a 150-mg dose in the fed state was approximately 3- and 11-fold greater than that of the fasted state, respectively. Table 6 provides a summary of the PK parameters at the 150-mg dose level under both fed and fasted state conditions.

Table 6. Summary of Pharmacokinetic Parameters of Compound 1 Following Single Oral Dose Administration in Healthy Volunteers – Fed vs. Fasted State

Pharmacokinetic Parameters	**Geometric Mean (CV %)**	
	Analyte = Plasma Compound 1	
	150 mg Fed	**150 mg Fasted**
N	6	6
C_{max} (ng/mL)	93.4 (22)	8.22 (83)
T_{max}[a] (h)	4.00 (3.00 – 6.00)	10.05 (6.00 – 12.00)
$t_{1/2}$[b] (h)	29.2 (20.0 – 41.5)	38.4 (24.2 – 88.5)
$AUC_{0-tlast}$ (ng•h/mL)	891	288

	(26)	(48)
$AUC_{0-\infty}$ (ng•h/mL)	956 (25)	331 (44)
CL/F (L/h)	157 (25)	454 (44)
Vz/F (L)	6620 (38)	25100 (81)
Vss/F (L)	4600 (33)	25200 (68)

AUC = area under the plasma concentration-time curve; CL/F = apparent total body clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; N = number of subjects; NC = not calculable; PK = pharmacokinetic; T_{max} = time to reach maximum plasma concentration; t1/2 = elimination half-life; $V_{ss}F$ = apparent volume of distribution at steady state during the terminal phase after extravascular administration; V_z/F = apparent volume of distribution during the terminal phase after extravascular administration.

a Median (range)

b Geometric mean (range)

[0155] PK parameters $AUC_{0-\infty}$ and C_{max} were analyzed separately for dose proportionality for Compound 1 from 50 to 800 mg when administered in the fed state. The analysis results suggested that for every doubling of dose, $AUC_{0-\infty}$ can be expected to increase 1.74 times more than what would be expected under dose proportionality. C_{max} appeared more than dose proportional but the formal test was inconclusive as the 90% confidence interval were partially within the 0.8 – 1.25 interval. Dose proportionality across administered doses in the fed state could not be concluded on the basis of $AUC_{0-\infty}$ or C_{max}.

[0156] PK were also evaluated in the multiple-dose, dose-escalation study, Study 2. In Part A of the study, subjects were divided into 3 cohorts and received 50, 150, or 200 mg Compound 1 or placebo for 14 consecutive days (at least 6 subjects received Compound 1 and 2 subjects received placebo in each cohort). Blood concentrations of Compound 1 were close to steady-state levels after 2 weeks of dosing and the accumulation ratio was between 2.51 to 3.65. Part B investigated the interaction of Compound 1 with midazolam (a CYP3A4 substrate), thereby determining whether this compound significantly inhibited the metabolism of drugs that are metabolized by CYP3A4 serial blood samples were collected to determine plasma concentrations of study drug after a single dose of Compound 1 had been administered and at steady state. All dosing occurred in the fed state. An assessment of diurnal cortisol levels, plus when under conditions of glucose clamp, were also carried out both prior to and during the dosing period.

[0157] Overall concentration time profiles of Compound 1 showed that absorption was moderately delayed with C_{max} achieved at a median of 5 hours following oral dosing. Consistent with the single-dose study (Study 1), concentrations appeared to decline in a bi-exponential manner, characterized by a rapid decrease within the first 24 hours. Following multiple daily dosing for 2 weeks, the $t_{1/2}$ of Compound 1 exceeded 100 hours; therefore, an accumulation ratio of Compound 1 was between 2.51 to 3.65 (see Table 7). The T_{max} appeared to be consistent across doses. Overall half-lives, weight normalized CL/F and V/F were consistent for 150 and 200 mg. However, the values for these latter 2 parameters were almost doubled at the 50-mg dose level. Variability (CV%) for apparent clearance and volume of distribution were large and not reduced with weight-normalization.

Table 7. Summary of Noncompartmental Pharmacokinetic Parameters of Compound 1 After Single (Day 1) and Multiple (Day 14) Oral Doses of 50 mg, 150 mg, and 200 mg of Compound 1 in Part A of the Study

	Geometric Mean (CV%)					
	50 mg Day 1	**150 mg Day 1**	**200 mg Day 1**	**50 mg Day 14**	**150 mg Day 14**	**200 mg Day 14**
N	**8**	**9**	**7**	**8**	**9**	**6**
C_{max} (ng/mL)	22.7 (59)	127 (52)	143 (62)	50.3 (56)	222 (58)	314 (93)
T_{max} [a] (hr)	4.52 (3.00 – 10.00)	5.00 (5.00 - 6.00)	5.00 (2.00 - 5.00)	5.00 (3.00 - 5.00)	5.00 (3.00 - 5.03)	5.00 (3.00 - 5.00)
Effective $t_{1/2}$ [b] (hr)	NC NC	NC NC	NC NC	37.7 (27.4)	32.7 (29.7)	52.0
$AUC_{0-\infty}$ (ng•hr/mL)	NC NC	NC NC	NC NC	980 (53.8)	4680 (104)	5660 (122)
AUC_{0-24h} (ng•hr/mL)	97.6 (58)	590 (56)	559 (55[c])	273 (56)	1480 (66)	2040 (98)
C_{avg} (ng/mL)	NC NC	NC NC	NC NC	11.4 (56)	61.7 (66)	85.0 (98)
CL_{aa}/F (L/hr)	NC NC	NC NC	NC NC	183 (56)	101 (66)	98 (98)
WT-norm						
Cl_{aa}/F (L/hr/kg)	NC NC	NC NC	NC NC	2.88 (46.9)	1.42 (72.9)	1.50 (89.9)
Vz/F (L)	NC NC	NC NC	NC NC	33500 (90)	17600 (59)	16300 (76)
Vss/F (L)	NC NC	NC NC	NC NC	12900 (91)	6170 (40)	5080 (78)
WT-norm						
Vss/F (L/kg)	NC	NC	NC	204	86.5	77.4

	NC NC	NC NC	NC NC	(71.3) 2.80	(41.0) 2.51	(68.6) 3.65
R_A	NC	NC	NC	(27.4)	(29.7)	(34.4)

AUC = area under the plasma concentration-time curve; CL/F = apparent clearance; C_{max} = maximum plasma concentration; RA = accumulation ratio calculated as Day 14 AUC_{0-24}/Day 1 AUC_{0-24}; t1/2 = terminal half-life; effective t1/2 = half-life calculated by accumulation ratio; Tmax = time to maximum plasma concentration; Vss/F = volume of distribution at steady state; Vz/F = volume of distribution at terminal phase; WT-norm = weight normalized

[a] Median (range).

[b] Geometric mean (range).

[c] n = 6, Dropout Subject 306 not included in the calculation of summary statistics.

[0158] Table 8 presents the results of the dose proportionality assessment for the AUC_{0-24} and C_{max} over the tested dose range. For AUC_{0-24} and C_{max}, the adjusted mean slope at Day 1 and Day 14 were all above the value of 1, suggesting a slightly more than proportional increase of AUC_{0-24} and C_{max} values with increasing doses.

Table 8. Summary of Assessment of Dose Proportionality as Assessed by the Power Model for Plasma Compound 1

Parameter	Day	Mean Slope	Standard Error	90% CI for Slope	CV%
AUC_{0-24} (ng hr/mL)	1	1.40	0.194	(1.069, 1.737)	59.3
	14	1.48	0.221	(1.104, 1.864)	69.1
C_{max} (ng/mL)	1	1.41	0.185	(1.092, 1.728)	57.5
	14	1.33	0.210	(0.972, 1.693)	64.8

AUC = area under the plasma concentration-time curve; C_{max} = maximum plasma concentration

Safety

[0159] The safety of Compound 1 was evaluated in 2 Phase 1 studies in healthy adult volunteers (Study 1 and Study 2). In both studies, adverse events (AEs), clinical laboratory tests, vital signs (supine blood pressure and pulse rate), and electrocardiograms (ECGs) were evaluated. Overall, in Study 1, Compound 1 was well-tolerated.

[0160] Compound 1, when administered as multiple doses up to 200 mg, was generally well tolerated in the healthy subject population studied. In Study 1, the effects upon biomarkers of relevance for the treatment of alcohol dependence were investigated. Five clusters of an Addiction Research Center Inventory Questionnaire (ARCI-49) were used to compare the effect of Compound 1 vs. placebo: Morphine-Benzedrine Group Scale measuring euphoria; Lysergic-Acid-Diethylamide Group Scale estimating dysphoric and somatic changes; Pentobarbital-

Chlorpromazine-Alcohol Group Scale measuring sedation; Benzedrine Group (BG) Scale measuring intellectual efficiency and energy; Amphetamine Group Scale measuring effects of d-amphetamine, respectively. No systematic pattern or dose-response for the change from baseline or for the difference over placebo in each cluster was observed.

[0161] In summary, single, oral doses up to 800 mg and multiple doses up to 200 mg of Compound 1 were well-tolerated by healthy male and female subjects.

Example 4: Phase 2 Clinical Studies

[0162] Cohort A of the Phase 2 Study includes a 6-week, multiple-dose, dose escalation study of Compound 1 for the treatment of adults with classic CAH. After screening, eligible patients will be enrolled into a 6-week treatment period followed by a 4-week washout/safety follow-up period.

[0163] This cohort will be conducted in approximately 9 patients, who will receive Compound 1 daily for up to 6 weeks. Compound 1 will be administered as an oral daily dose. Patients will undergo titration of Compound 1 through three escalating dosage strengths at 2-week intervals. Patients will have overnight PK/PD assessments performed at baseline, which include an pre-dose overnight assessment and a post-dose overnight assessment for PK/PD following administration of the first dose. At the end of each 2-week dosing period, patients will return for single overnight visits for steady-state PK/PD assessments. A follow-up outpatient visit will occur 30 days after their last dose. Upon completion of the initial cohort (Cohort A), the study will proceed to a multiple ascending dose (MAD) design with up to 3 sequential cohorts (Cohorts B, C, and D) to further evaluate the safety, PK, and PD of various SPR001 dosing regimens and to identify an optimal dose regimen. Each cohort will undergo a 2-week run-in period, a 2-week treatment period, and a 30-day washout and safety follow-up period. During the run-in period, which will occur during screening, subjects will document in a paper diary each dose of glucocorticoid medication taken, the time of each meal, and the time they went to bed and woke up each day, to ensure compliance with background glucocorticoid regimens and the stability of their daily routine.

[0164] Patients in Cohort B will receive study drug at 200 mg BID, with a dose in the morning and a dose in the evening, either with a meal or consumption of a standardized snack. For Cohorts C and D, the dose level and the frequency and timing of dosing will be determined based on interim data from the previous cohorts. However, the dose level of each successive cohort will be capped at twice the daily dose level of the previous cohort.

Study Design

- Study Type: Interventional
- Primary Purpose: Treatment

- Study Phase: Phase 2
- Interventional Study Model: Sequential Assignment
- Number of Cohorts: Up to 4
- Masking: No masking
- Allocation: Non-Randomized
- Enrollment: Up to approximately 27 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Cohort A The first cohort of 9 patients will be administered Compound 1 at dose strength of 200 mg daily for 2 weeks, and escalating through 600 mg per day for 2 weeks and 1,000 mg per day for 2 weeks.	Drug: Compound 1 200-mg capsules
Experimental: Cohort B Cohort B patients will be administered Compound 1 at a dose strength of 200 mg twice daily (BID) for 2 weeks.	Drug: Compound 1 200-mg capsules
Experimental: Cohort C The dose/dose regimen for Cohort C will be determined based on an interim review of safety and PK/PD data from the previous Cohorts	Drug: Compound 1 50-mg or 200 mg capsules
Experimental: Cohort D The dose/dose regimen for Cohort C will be determined based on an interim review of safety and PK/PD data from the previous Cohorts	Drug: Compound 1 50-mg or 200 mg capsules

Outcome Measures

Primary Outcome Measure:

1. To evaluate the safety of Compound 1 in subjects with CAH.

2. To assess the efficacy of Compound 1 in subjects with classic CAH as measured by percent and absolute change in 17-OHP compared to baseline.

Secondary Outcome Measure:

3. To explore the dose(s) of Compound 1 that cause pharmacodynamics changes in plasma concentrations of ACTH, androstenedione, and testosterone, as measured by the absolute and percent change from baseline by dose.

4. To determine pharmacokinetics of Compound 1 in subjects with CAH.

5. To explore potential relationships between pharmacodynamics and pharmacokinetics.

Exploratory

6. To explore the dose(s) of Compound 1 that cause changes in pharmacodynamics biomarkers in urine, as measured by the absolute and percent change from baseline by dose.

Eligibility

- Minimum Age: 18 Years
- Maximum Age:
- Sex: All
- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- 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.

Results:

The phase 2 study showed that Compound 1 was generally well-tolerated. The study established a range of safe doses after exploring a wide range of doses (5-fold range) (see FIG. 1).

[0165] With respect to patient-level response to Compound 1, 80% showed reduced ACTH (see FIG. 2). Generally, attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism. 80% of patient subjects demonstrated reduction in ACTH. 70% of subject demonstrated more than 25% reduction in ACTH. 40% of subjects were in the normal range after treatment.

[0166] A reduction of 17-OHP demonstrates "control" of the disease based on Standard guidelines. This allows for steroid taper. 80% of subjects demonstrated reduction in 17-OHP (see FIG. 3). 50% of subjects demonstrated more than 25% reduction in 17-OHP. 50% of subjects were within the guideline range (1200 ng/dL) after treatment.

[0167] Compound 1 attenuates morning rise in A4 which indicates an ability to control excess androgen production and associated symptoms (see FIG. 4). 100% of subjects demonstrated reduction in Androstenedione (at various doses). 60% of subjects demonstrated more than 25%

reduction in Androstenedione. 50% of subjects were within normal reference range after treatment.

Example 5: 3-Month Phase 2 Study

[0168] This is a 3-month Phase 2 study to evaluate the safety and efficacy of Compound 1 in subjects with classic CAH. This study will investigate the extended use of Compound 1 over a 3-month period in combination with replacement glucocorticoids and mineralocorticoids in the treatment of CAH.

[0169] This study will enroll up to approximately 24 eligible subjects who will receive Compound 1 daily for up to 3-months. Compound 1 will be administered as an oral daily dose. At the end of each 2-week dosing period, patients will return for morning laboratory assessments. A follow-up outpatient visit will occur 30 days after their last dose.

Study Design

- Study Type: Interventional
- Primary Purpose: Treatment
- Study Phase: Phase 2
- Interventional Study Model: Sequential Assignment
- Number of Arms: 1
- Masking: No Masking
- Allocation: Non-Randomized
- Enrollment: Up to approximately 24 [anticipated]

Outcome Measures

Primary Outcome Measure:

1. To evaluate the safety of Compound 1 in subjects with CAH.

Second Outcome Measure:

2. To evaluate the efficacy of Compound 1 in subjects with CAH in terms of changes in hormones.

Exploratory:

3. To evaluate the effect of Compound 1 on quality of life, metabolic parameters, exploratory adrenal hormones, and semen analysis in subjects with CAH.

Eligibility:

- Minimum Age: 18 Years
- Maximum Age:
- Sex: All
- Gender Based: No
- Accepts Healthy Volunteers: No

- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- 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.

Example 6: Adolescent Study

[0170] This is a Phase 2, open-label, multiple-dose study designed to provide proof of concept for the use of Compound 1 to treat adolescents 12 to 17 years of age with classic CAH. The study will evaluate the safety, efficacy, and PK of 2 weeks of treatment with Compound 1. Each subject will undergo a 2-week diary run-in period during screening, a 2-week treatment period, and a 30-day washout and safety follow-up period.

[0171] An adaptive design with up to 3 sequential dose cohorts (Cohorts 1, 2, and 3) is planned to identify an optimal dose strength and regimen in adolescents with classic CAH. Each cohort will initially enroll 3 subjects and may later enroll 3 more subjects based on interim data from the first 3 subjects, for a total of 6 subjects per cohort. However, if safety, efficacy, and PK results from 6 subjects are inconclusive, a cohort may be expanded up to a maximum of 12 subjects. Cohort 1 will receive study drug at 200 mg QD. Cohorts 2 and 3 will be sequentially activated only if further investigation of an optimal dose strength or regimen is required; the dose strength and frequency and timing of dosing for these cohorts will be determined based on interim data from the previous cohort(s). However, the dose strength administered to each successive cohort will be capped at twice the daily dose strength administered to the previous cohort.

[0172] This study will enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). In practice, CAH patients are typically treated

with supraphysiologic doses of GCs which are both toxic and not effective in many adolescent patients. In this population, GCs are associated with multiple well-described short- and long-term toxicities including: growth retardation, weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

[0173] The objective of treatment of this patient population with Compound 1 is reduction (or normalization) of key hormonal outcome measures which could allow reduction of their GC replacement requirements which will improve clinical outcomes of concern, including growth velocity. Improvement of hormonal outcome measures in this population are also expected to delay premature puberty and bone maturation, ultimately leading to improvements in height in adolescents with CAH.

Outcome Measures

Primary Outcome Measures:

1. To evaluate the safety of Compound 1 in adolescent subjects with CAH.

Secondary Outcome Measures:

2. To evaluate the dose(s) of Compound 1 that cause changes in key pharmacodynamics bioamarkers in blood in adolescent subjects with CAH.
3. To investigate the effect of Compound 1 on quality of life in adolescent subjects with CAH.
4. To determine the pharmacokinetics of Compound 1 in adolescent subjects with CAH.
5. To investigate potential relationships between pharmacodynamics and pharmacokinetics in adolescent subjects with CAH.

Exploratory

6. To explore the dose(s) of Compound 1 that cause changes in exploratory pharmacodynamics biomarkers in blood and urine in adolescent subjects with CAH.

Eligibility Criteria

Inclusion Criteria:

- Male and female subjects 12 to 17 years of age, inclusive
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable regimen of glucocorticoid replacement for minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- 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.

Example 7: Phase 3 Clinical Studies

[0174] This is a 24-week, randomized, double-blind, placebo-controlled study of Compound 1 for the treatment of classic CAH. After screening, eligible patients will be enrolled into a 24-week treatment period followed by a 4-week safety follow-up period.

[0175] Subjects in the study will be randomized in a 1:1 ratio to either receive Compound 1 or a matching placebo for up to 24 weeks. Compound 1 or a placebo will be administered as an oral daily dose. Patients will return approximately monthly for study visits. A follow-up outpatient visit will occur 30 days after their last dose. It is initially planned that up to approximately 150 patients will be enrolled.

[0176] Consistent with the design of the Phase 2 study, the Phase 3 clinical study will seek to enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). In practice, CAH patients are typically treated with supraphysiologic doses of GCs which are both toxic and not effective in the majority of patients. GCs are associated with multiple well-described short- and long-term toxicities in adults including: excessive weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

Study Design:

- Study Type: Interventional
- Primary Purpose: Treatment
- Study Phase: Phase 3
- Interventional Study Model: Randomized Controlled Trial
- Allocation: Randomized
- Enrollment: 150 [Anticipated]

Outcome Measures

Primary Outcome Measures

1. Evaluate efficacy of Compound 1 in reducing A4 and 17-OHP in patients with CAH.

Secondary Outcome Measures

2. Evaluate efficacy of Compound 1 in patients with CAH in terms of changes in key hormones.
3. Evaluate efficacy of Compound 1 in improving quality of life and/or mood in patients with CAH.

4. Evaluate efficacy of Compound 1 in improving hyperandrogenic symptoms in patients with CAH.
5. Evaluate efficacy of Compound 1 in improving metabolic parameters in patients with CAH.
6. Evaluate safety of Compound 1 in patients with CAH.

Eligibility

- Minimum age: 16 Years
- Maximum Age:
- Sex: All
- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria

Inclusion Criteria:

- Male and female patients age 16 or older.
- Document diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- 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.

Example 8: Phase 3 OLE and steroid sparing studies

[0177] Upon completion of the study described in Example 7, eligible patients will then be offered the opportunity to enroll into an open label extension study lasting up to 1 year. The open label study will allow all eligible patients to receive active study drug during their participation in the Phase 3 program. Patients will undergo study assessments every 1-3 months during the open label phase, and will be evaluated for long-term safety and efficacy (including both hormonal endpoints and long-term clinical outcome measures of concern in this population).

[0178]

[0179] A further study may seek to enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen:

hydrocortisone, prednisone/prednisolone, and/or dexamethasone). Such CAH patients are typically treated with supraphysiologic doses of GCs which are both toxic and not effective in the majority of patients. GCs are associated with multiple well-described short- and long-term toxicities in adults including: excessive weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

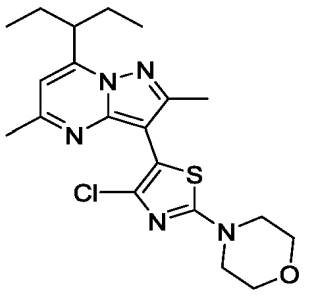
[0180] [0159] Following a period of treatment (for example 12 weeks) during the dose of GC will be kept stable, patients in this study will have their dose of GC progressively reduced from a supraphysiologic dose to a lower dose at or close to a dose equivalent to a physiologic dose of GC.

[0181] 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. 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 of the invention 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.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

2. The method of claim 1, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1200 mg/day.
3. The method of claim 1 or 2, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1000 mg/day.
4. The method of any one of claims 1 to 3, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 800 mg/day.
5. The method of any one of claims 1 to 4, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 100 mg/day and about 600 mg/day.
6. The method of any one of claims 1 to 5, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day.
7. The method of any one of claims 1 to 6, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.
8. The method of any one of claims 1 to 7, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is in the form of microparticles.
9. The method of claim 8, wherein the average size of the microparticles is between about 1 μm and about 20 μm.

10. The method of claim 8 or 9, wherein the average size of the microparticles is between about 5 μm and about 15 μm.
11. The method of any one of claims 8 to 10, wherein the average size of the microparticles is less than about 10 μm.
12. The method of any one of claims 1 to 11, wherein the pharmaceutical composition is in the form of a capsule or a tablet.
13. The method of any one of claims 1 to 12, wherein the pharmaceutical composition is in the form of a capsule.
14. The method of claim 13, wherein the capsule is a hard gelatin capsule.
15. The method of claim 13, wherein the capsule is a soft gelatin capsule.
16. The method of any one of claims 13 to 15, 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.
17. The method of any one of claims 13 to 16, wherein the pharmaceutical composition is free of additional excipients.
18. The method of any one of claims 13 to 16, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.
19. The method of any one of claims 1 to 12, wherein the pharmaceutical composition is in the form of a tablet.
20. The method of claim 19, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.
21. The method of any one of claims 1 to 20, wherein the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
22. The method of any one of claims 1 to 21, wherein the pharmaceutical composition comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
23. The method of any one of claims 1 to 22, wherein the pharmaceutical composition comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
24. The method of any one of claims 1 to 23, wherein the pharmaceutical composition comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

25. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
26. The method of any one of claims 1 to 23, wherein the pharmaceutical composition comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
27. The method of any one of claims 1 to 23, wherein the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
28. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
29. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
30. The method of any one of claims 1 to 23, wherein the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
31. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
32. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
33. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
34. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
35. The method of any one of claims 1 to 25, wherein the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

36. The method of any one of claims 1 to 25, wherein the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
37. The method of any one of claims 1 to 25, wherein the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
38. The method of any one of claims 1 to 25, wherein the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
39. The method of any one of claims 1 to 25, wherein the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
40. The method of any one of claims 1 to 39, wherein the pharmaceutical composition provides a Compound 1 T_{max} of about 2 to about 6 hours in a subject.
41. The method of any one of claims 1 to 40, wherein the pharmaceutical composition provides a Compound 1 T_{max} of about 3 to about 5 hours in a subject.
42. The method of any one of claims 1 to 40, wherein the pharmaceutical composition provides a Compound 1 T_{max} of about 6 hours in a subject.
43. The method of any one of claims 1 to 41, wherein the pharmaceutical composition provides a Compound 1 T_{max} of about 5 hours in a subject.
44. The method of any one of claims 1 to 41, wherein the pharmaceutical composition provides a Compound 1 T_{max} of about 4 hours in a subject.
45. The method of any one of claims 1 to 41, wherein the pharmaceutical composition provides a Compound 1 T_{max} of about 3 hours in a subject.
46. The method of any one of claims 1 to 45, wherein the pharmaceutical composition is administered in the fed state.
47. The method of any one of claims 1 to 45, wherein the pharmaceutical composition is administered in the fasted state.
48. The method of any one of claims 1 to 47, wherein the pharmaceutical composition is administered once a day.
49. The method of any one of claims 1 to 47, wherein the pharmaceutical composition is administered twice a day.
50. The method of any one of claims 1 to 47, wherein the pharmaceutical composition is administered three times a day.
51. The method of any of claims 1 to 50, further comprising administering a glucocorticoid.

52. The method of claim 51, wherein the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
53. The method of claim 52, wherein the amount of glucocorticoid used is reduced from a supraphysiologic amount to a physiologic amount.
54. The method of claim 52, wherein the amount of glucocorticoid is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%.
55. The method of any one of claims 52 to 54, wherein the symptoms associated with high-dose glucocorticoid therapy are reduced.
56. The method of claim 55, wherein the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis.
57. The method of any one of claims 51 to 56, wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone.
58. The method of any one of claims 51 to 57, wherein the glucocorticoid is hydrocortisone.
59. The method of claim 58, wherein the hydrocortisone is administered at a dose less than about 15 mg/day.
60. The method of claim 58 or 59, wherein the hydrocortisone is administered at a dose less than about 10 mg/day.
61. The method of any one of claims 58 to 60, wherein the hydrocortisone is administered at a dose less than about 5 mg/day.
62. The method of any one of claims 51 to 61, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently.
63. The method of any one of claims 51 to 62, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially.
64. The method of any one of claims 51 to 62, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 24 hours.
65. The method of any one of claims 51 to 62, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 8 hours.

66. The method of any one of claims 51 to 62, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 2 hours.

67. The method of any one of claims 51 to 62, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 30 minutes.

68. The method of any one of claims 1 to 67, further comprising administering a mineralocorticoid.

69. The method of claim 68, wherein the mineralocorticoid is fludrocortisone.

70. The method of any one of claims 1 to 69, wherein the pharmaceutical composition is administered at bedtime.

71. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered less than about 4 hours before sleep.

72. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered less than about 2 hours before sleep.

73. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered less than about 30 mins before sleep.

74. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered in the evening.

75. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered at about 10 pm at night.

76. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered at or before the expected circadian release of adrenocorticotropic hormone (ACTH).

77. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH).

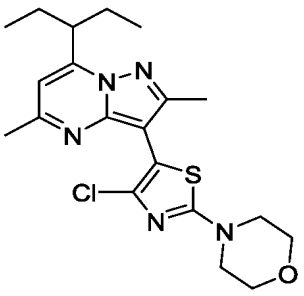
78. The method of any one of claims 1 to 77, wherein CAH is classic CAH.

79. The method of any one of claims 1 to 77, wherein CAH is non-classic CAH.

80. A method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising:

(iv)measuring a hormone level in the subject in need thereof;

(v) administering Compound 1:



or a pharmaceutically acceptable salt or solvate thereof;

(vi) repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of compound 1.

81. The method of claim 80, wherein the hormone is 17α-Hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, or androstenedione.

82. The method of claim 81, wherein the hormone is 17-OHP, and the pre-determined range is from about 200 ng/dL to about 400 ng/dL.

83. The method of claim 81, wherein the hormone is ACTH, and the pre-determined range is below about 100 pg/mL.

84. The method of claim 81, wherein the hormone is testosterone and the pre-determined range is from about 14 ng/dL to about 76 ng/dL.

85. The method of claim 81, wherein the hormone is androstenedione and the pre-determined range is from about 30 ng/dL to about 150 ng/dL in males.

86. The method of claim 81, wherein the hormone is androstenedione and the pre-determined range is from about 40 ng/dL to about 200 ng/dL in females.

87. The method of any one of claims 80 to 86, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1600 mg/day.

88. The method of any one of claims 80 to 87, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1200 mg/day.

89. The method of any one of claims 80 to 88, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1000 mg/day.

90. The method of any one of claims 80 to 89, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 800 mg/day.

91. The method of any one of claims 80 to 90, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 600 mg/day.

92. The method of any one of claims 80 to 91, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day.

93. The method of any one of claims 80 to 92, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.

94. The method of any one of claims 80 to 86, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1600 mg/day.

95. The method of claim 94, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1200 mg/day.

96. The method of claims 94 or 95, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1000 mg/day.

97. The method of any one of claims 94 to 96, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 800 mg/day.

98. The method of any one of claims 94 to 97, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 600 mg/day.

99. The method of any one of claims 94 to 98, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and 400 mg /day.

100. The method of any one of claims 94 to 99, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between 50 mg/day and 200 mg/day.

101. The method of any one of claims 94 to 99, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 50 mg /day.

102. The method of any one of claims 80 to 101, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is in the form of microparticles.

103. The method of claim 102, wherein the average size of the microparticles is between about 1 μm and about 20 μm.

104. The method of claim 102 or 103, wherein the average size of the microparticles is between about 5 μm and about 15 μm.

105. The method of any one of claims 102 to 104, wherein the average size of the microparticles is less than about 10 μm.

106. The method of any one of claims 80 to 105, wherein Compound 1 is formulated in a pharmaceutical composition in the form of a capsule or a tablet.

107. The method of claim 106, wherein the pharmaceutical composition is in the form of a capsule.

108. The method of claim 107, wherein the capsule is a hard gelatin capsule.

109. The method of claim 107, wherein the capsule is a soft gelatin capsule.

110. The method of any one of claims 106 to 109, 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.

111. The method of any one of claims 106 to 110, wherein the pharmaceutical composition is free of additional excipients.

112. The method of any one of claims 106 to 110, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

113. The method of claim 106, wherein the pharmaceutical composition is in the form of a tablet.

114. The method of claim 113, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

115. The method of any one of claims 106 to 114, wherein the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

116. The method of any one of claims 106 to 115, wherein the pharmaceutical composition comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

117. The method of any one of claims 106 to 116, wherein the pharmaceutical composition comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

118. The method of any one of claims 106 to 117, wherein the pharmaceutical composition comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

119. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

120. The method of any one of claims 106 to 117, wherein the pharmaceutical composition comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

121. The method of any one of claims 106 to 117, wherein the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

122. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

123. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

124. The method of any one of claims 106 to 117, wherein the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

125. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

126. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

127. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

128. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

129. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

130. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

131. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

132. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

133. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

134. The method of any one of claims 106 to 133, wherein the pharmaceutical composition provides a Compound 1 T_{max} of about 2 to about 6 hours in a subject.

135. The method of any one of claims 106 to 118, wherein the pharmaceutical composition provides a Compound 1 T_{max} of about 3 to about 5 hours in a subject.

136. The method of any one of claims 106 to 118, wherein the pharmaceutical composition provides a Compound 1 T_{max} of about 6 hours in a subject.

137. The method of any one of claims 106 to 135, wherein the pharmaceutical composition provides a Compound 1 T_{max} of about 5 hours in a subject.

138. The method of any one of claims 106 to 135, wherein the pharmaceutical composition provides a Compound 1 T_{max} of about 4 hours in a subject.

139. The method of any one of claims 106 to 135, wherein the pharmaceutical composition provides a Compound 1 T_{max} of about 3 hours in a subject.

140. The method of any one of claims 106 to 139, wherein the pharmaceutical composition is administered in the fed state.

141. The method of any one of claims 106 to 140, wherein the pharmaceutical composition is administered in the fasted state.

142. The method of any one of claims 106 to 141, wherein the pharmaceutical composition is administered once a day.

143. The method of any one of claims 106 to 141, wherein the pharmaceutical composition is administered twice a day.

144. The method of any one of claims 106 to 141, wherein the pharmaceutical composition is administered three times a day.

145. The method of any of claims 80 to 144, further comprising administering a glucocorticoid.

146. The method of claim 145, wherein the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

147. The method of claim 145, wherein the amount of glucocorticoid used is reduced from a supraphysiologic amount to a physiologic amount.

148. The method of claim 145, wherein the amount of glucocorticoid is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%.

149. The method of any one of claims 145 to 148, wherein the symptoms associated with high-dose glucocorticoid therapy are reduced.

150. The method of claim 149, wherein the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis.

151. The method of any one of claims 145 to 150, wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone.

152. The method of any one of claims 145 to 151, wherein the glucocorticoid is hydrocortisone.

153. The method of claim 152, wherein the hydrocortisone is administered at a dose less than about 15 mg/day.

154. The method of claim 152 or 153, wherein the hydrocortisone is administered at a dose less than about 10 mg/day.

155. The method of any one of claims 152 to 154, wherein the hydrocortisone is administered at a dose less than about 5 mg/day.

156. The method of any one of claims 152 to 155, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently.

157. The method of any one of claims 152 to 155, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially.

158. The method of any one of claims 152 to 155, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 24 hours.

159. The method of any one of claims 152 to 155, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 8 hours.

160. The method of any one of claims 152 to 155, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 2 hours.

161. The method of any one of claims 152 to 155, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 30 minutes.

162. The method of any one of claims 80 to 161, further comprising administering a mineralocorticoid.

163. The method of claim 162, wherein the mineralocorticoid is fludrocortisone.

164. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at bedtime.

165. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered less than about 4 hours before sleeping.

166. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered less than about 2 hours before sleeping.

167. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered less than about 30 mins before sleeping.

168. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered in the evening.

169. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at 10 pm at night.

170. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at or before the expected circadian release of adrenocorticotropic hormone (ACTH).

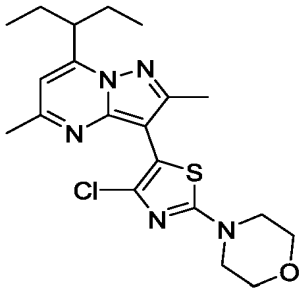
171. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH).

172. The method of any one of claims 80 to 171, wherein CAH is classic CAH.

173. The method of any one of claims 80 to 171, wherein CAH is non-classic CAH.

174. A method of any one of claims 1 to 173, wherein the subject in need thereof is from about 12 years of age to about 20 years of age.

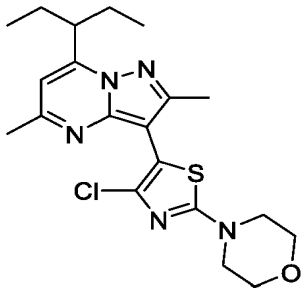
175. A method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

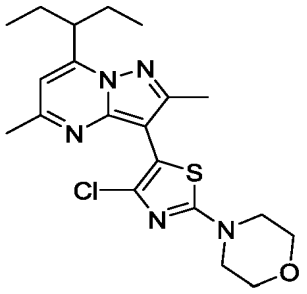
176. A method of claim 175, wherein the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism and alopecia.

177. A method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

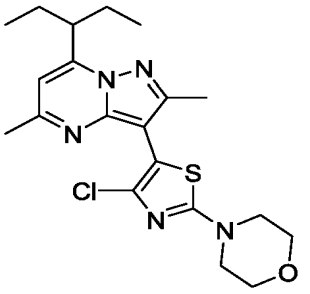
178. A method of improving metabolic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

179. A method of claim 178, wherein the metabolic symptoms are selected from the group consisting of body weight, BMI, waist circumference, blood pressure and glycemic control.

180. A method of improving quality of life in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day, wherein treatment results in an improved quality of life.

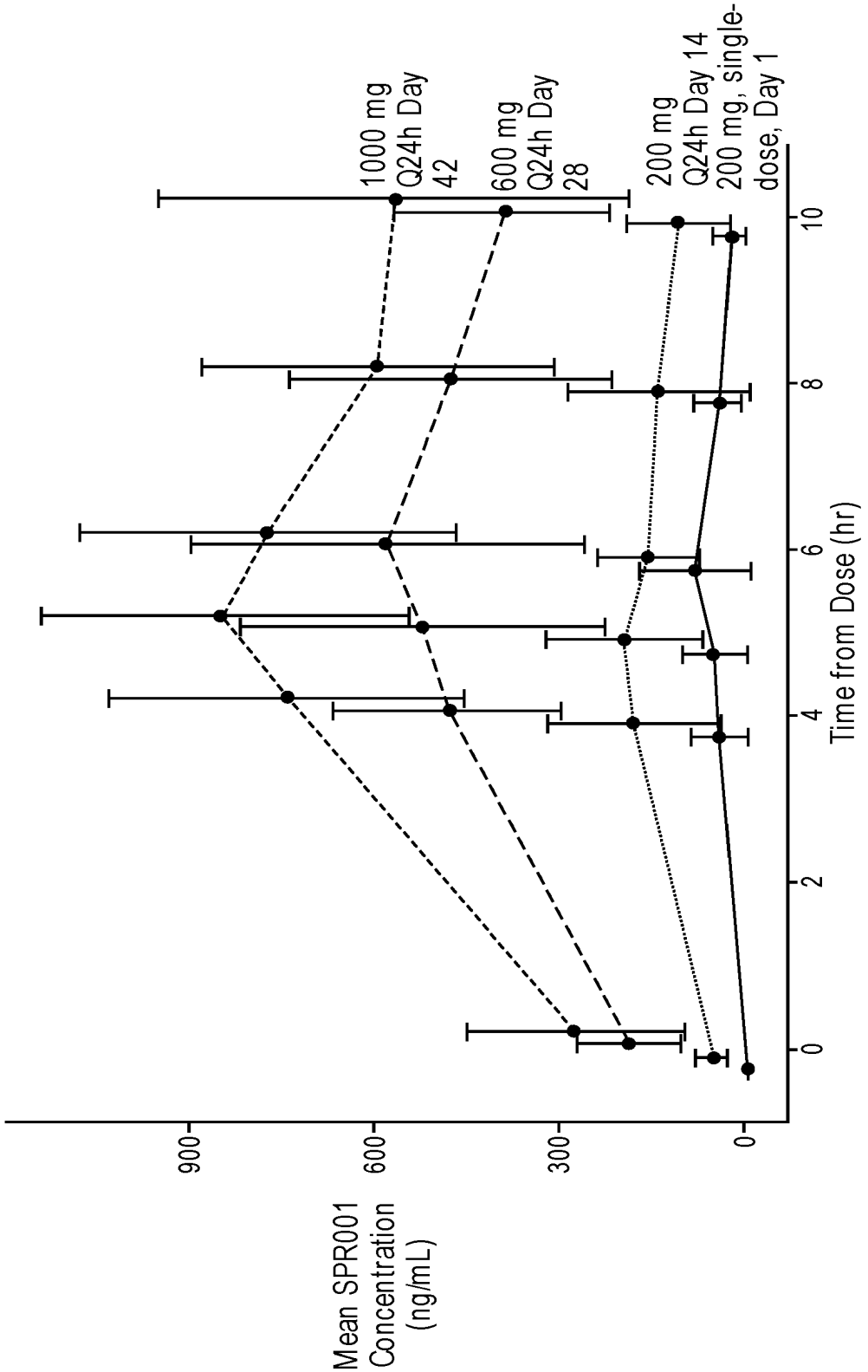

1000 mg Q24h Day 42
600 mg Q24h Day 28
200 mg Q24h Day 14
200 mg, single-dose, Day 1
Mean SPR001 Concentration (ng/mL)
0
300
600
900
Time from Dose (hr)
0
2
4
6
8
10

FIG. 1

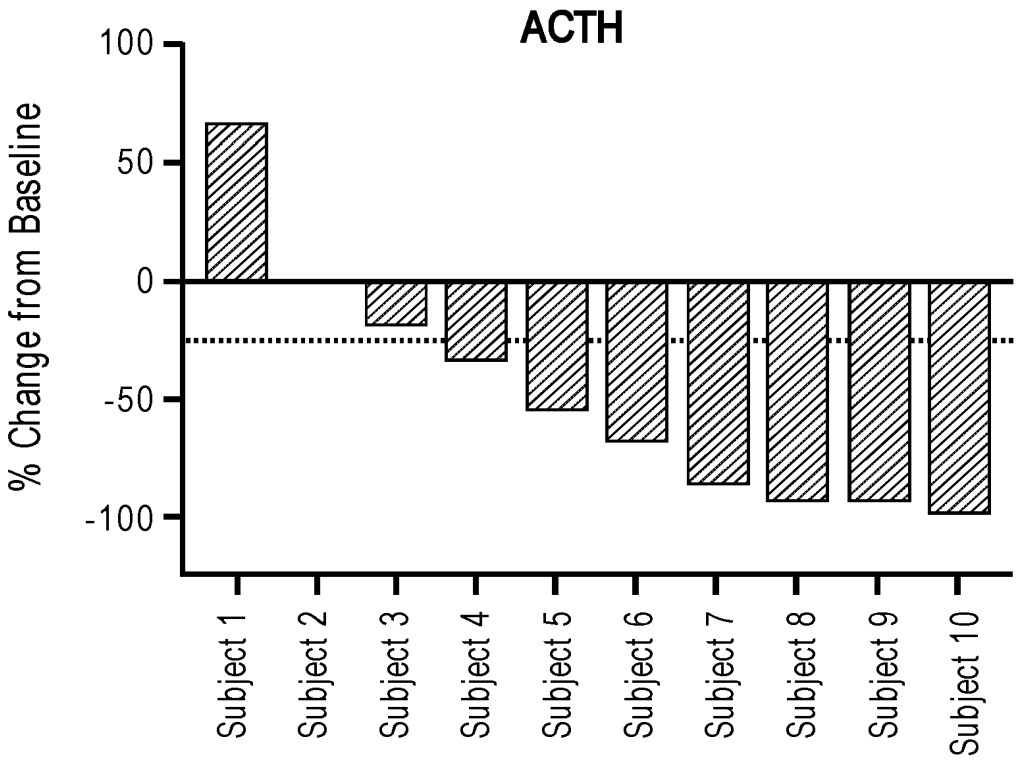

ACTH
% Change from Baseline
100
50
0
-50
-100
Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6
Subject 7
Subject 8
Subject 9
Subject 10

FIG. 2

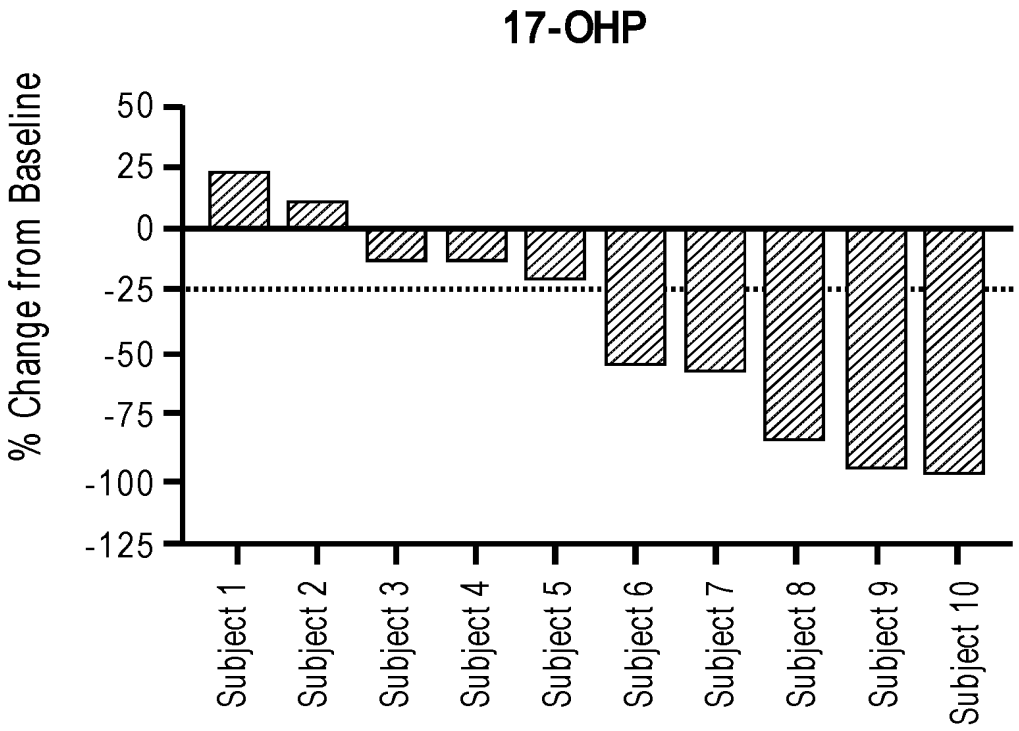

17-OHP
% Change from Baseline
50
25
0
-25
-50
-75
-100
-125
Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6
Subject 7
Subject 8
Subject 9
Subject 10

FIG. 3

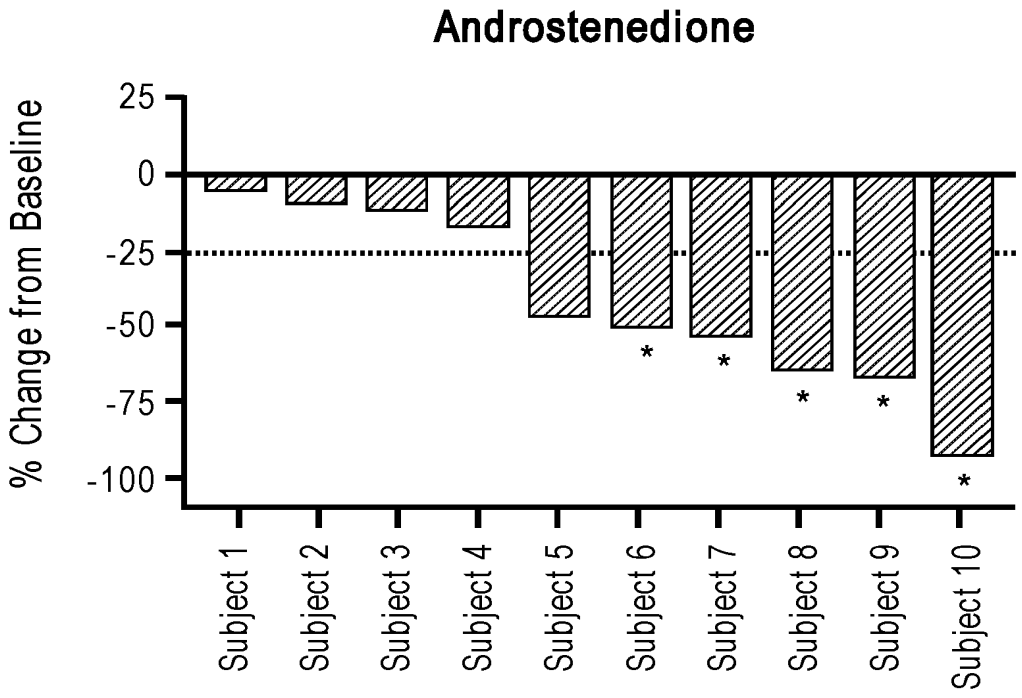

Androstenedione
% Change from Baseline
25
0
-25
-50
-75
-100
*
*
*
*
*
Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6
Subject 7
Subject 8
Subject 9
Subject 10

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/46760

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/415; 31/425; 31/519; C07D 487/04; A61P 5/24 (2018.01)
CPC - A61K 31/41; A61K 31/519; C07D 487/04; C07D 401/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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.
Y	US 8,030,304 B2 (CHEN et al.) 04 October 2011 (04.10.2011) Col 1, ln 10-15; Col 2, ln 51-56;Col 3, ln 8-12; Col 5, ln 63 to Col 6, ln 4; Col 6, ln 11-13; Col 32, Example 16	1-3, 80-87, 94-95; 175-180
Y	TURCU et al. 'Single-Dose Study of a Corticotropin-Releasing Factor Receptor-1 Antagonist in Women With 21-Hydroxylase Deficiency', J. Clin. Endocrinol. Metab. 2016, Vol. 101(3), pp. 1174-1180. Abstract; pg. 1177, Table 2; pg. 1179, Table 3; pg 1179, Col 2, para 2 to pg. 1180, Col 1, para 2	1-3, 80-87, 94-95; 175-180
A	US 2017/0020877 A1 (NEUROCRINE BIOSCIENCES, INC.) 26 January 2017 (26.01.2017) ENTIRE DOCUMENT	1-3, 80-87, 94-95; 175-180
A	US 2010/0155595 A1 (GHOSHAL et al.) 24 June 2010 (24.06.2010) ENTIRE DOCUMENT	1-3, 80-87, 94-95; 175-180
A	Lee et al. 'Attenuated Forms of Congenital Adrenal Hyperplasia due to 21-hydroxylase Deficiency', Journal of Clin Endocrin Metab 1982, Vol. 55, pp. 866-871. ENTIRE DOCUMENT	1-3, 80-87, 94-95; 175-180

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier 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
25 SEPTEMBER 2018

Date of mailing of the international search report
24 OCT 2018

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:
Lee W. Young
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/46760

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.: 4-79, 88-93 and 96-174
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.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: SIMREN DELANEY
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304

PCT

INVITATION TO PAY ADDITIONAL FEES
AND, WHERE APPLICABLE, PROTEST FEE

(PCT Article 17(3)(a) and Rules 40.1 and 40.2(e))

Applicant's or agent's file reference 50535-710601	Date of mailing *(day/month/year)* 04 JUN 2019 **PAYMENT DUE** within **ONE MONTH** from the above date of mailing
International application No. PCT/US2019/029486	International filing date *(day/month/year)* 26 April 2019
Applicant SPRUCE BIOSCIENCES, INC.	

1. This International Searching Authority

(i) considers that there are 1+ *(number of)* inventions claimed in the international application covered by the claims indicated below/on an extra sheet:

see Extra Sheet(s)

(ii) therefore considers that **the international application does not comply with the requirement of unity of invention** (Rules 13.1, 13.2 and 13.3) for the reasons indicated below/on an extra sheet:

see Extra Sheet(s)

(iii) ☐ has carried out a partial international search (see Annex) ☒ will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:

1-4, 9, 13, 14, 34

(iv) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid.

2. Consequently, the applicant is hereby **invited to pay**, within the time limit indicated above, additional fees in the amount indicated below:

$2,080.00	x	1+	=	$2,080.00+ (See Item 2 of annex)
Fee per additional invention		number of additional inventions		total amount of additional fees/currency

3. The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fees may be made under protest**, that is, a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fees is excessive, where applicable, subject to the payment of a protest fee.

Where the applicant pays additional fees under protest, the applicant is hereby invited, within the time limit indicated above, to pay a protest fee (Rule 40.2(e)) in the amount of _____ *(amount/currency)*

Where the applicant has not, within the time limit indicated above, paid the required protest fee, the protest will be considered not to have been made and the International Searching Authority will so declare.

4. ☒ Claim(s) Nos. 15-33, 35-71 have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/206 (April 2005)

INVITATION TO PAY ADDITIONAL FEES
AND, WHERE APPLICABLE, PROTEST FEE

International application No.
PCT/US2019/029486

Item 2 (continued). For International Applications filed on or after 01 January 2014, Applicant is reminded that the search fee per additional invention indicated in item 2 is the undiscounted fee per additional invention. An Applicant may pay the search fee per additional invention fee reduced by 50% (small entity assertion) or 75% (micro entity certification), as appropriate. See 37 CFR 1.27 and 1.29.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-14 and 34 are drawn to methods of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART).

The first invention of Group I+ is restricted to 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 (CRF1) antagonist or a pharmaceutically acceptable salt thereof, wherein the CRF1 antagonist is a compound of structural Formula I or a pharmaceutically acceptable salt thereof, wherein: R1 and R2 are independently ethyl; R3 is hydrogen; R4 is hydrogen; and methods of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART). It is believed that claims 1-4, 9, 13, 14, and 34 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be 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 (CRF1) antagonist or a pharmaceutically acceptable salt thereof, wherein the CRF1 antagonist is a compound of structural Formula I or a pharmaceutically acceptable salt thereof, wherein: R1 and R2 are independently ethyl; R3 is Br; R4 is hydrogen; and methods of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART). Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, R3, R4, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of 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 (CRF1) antagonist or a pharmaceutically acceptable salt thereof; 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):, and 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, these shared technical features do not represent a contribution over the prior art as disclosed by US 2017/0020877 A1 to Neurocrine Biosciences, Inc. and US 2010/0222339 A1 to Chen et al.

US 2017/0020877 A1 to Neurocrine Biosciences, Inc. teaches a method of treating or preventing testicular adrenal rest tumors (TART) (Para. [0044],...glucocorticoid treatment include cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women and to inhibit testicular adrenal rest tumors in men.; Para. [0047], Treatment of CAH includes efforts to normalize the cortisol deficiency with glucocorticoids...; Claim 1, A method for treating Congenital Adrenal Hyperplasia (CAH) by administering to a subject in need thereof a CRF1 receptor antagonist...), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF1) antagonist (Claim 1; Para. [0007]); and a method of treating or preventing testicular adrenal rest tumors (TART) (Paras. [0044] and [0047]; Claim 1), comprising administering to a subject in need thereof a pharmaceutical composition (Paras. [0061] and [0065], The pharmaceutical compositions described herein that comprise at least one of the CRF1 antagonist compounds described herein may be administered to a subject in need by any one of several routes that effectively deliver an effective amount of the compound.; Claim 1).

US 2010/0222339 A1 to Chen et al., in the field of treating congenital adrenal hyperplasia (Para. [0014]), teach a corticotropin-releasing factor type-1 (CRF1) antagonist (Para. [0125], Ex. No. 2, 3-(2,4-Dibromo-thiazol-5-yl)- 7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a] pyrimidine; Para. [0057], The compounds of Formula I are CRF-1 antagonists and, as such, are useful for treating a condition which is treatable by reducing CRF1 receptor tone or stimulation.); a compound of structural Formula (I) wherein , R1 and R2 are independently ethyl; R3 is Br; and R4 is Br (Para. [0125], Ex. No. 2, 3-(2,4-Dibromo-thiazol-5-yl)- 7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a] pyrimidine); and a pharmaceutical composition, comprising a compound of structural Formula (I) (Claim 10, A pharmaceutical composition comprising: a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.; (Para. [0125], Ex. No. 2, 3-(2,4-Dibromo-thiazol-5-yl)- 7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 December 2001 (06.12.2001)

PCT

(10) International Publication Number
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(71) Applicant *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertalje (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ARNOULD, Jean-Claude** [FR/FR]; Z.I. la Pompelle, Boîte postale 1050, F-51689 Reims Cedex 2 (FR). **BIRD, Thomas, Geoffrey** [GB/FR]; 7, rue Pierre Boileau, F-51420 Witry-les-Reims (FR). **BOYLE, Francis, Thomas** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **BLAKEY, David, Charles** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

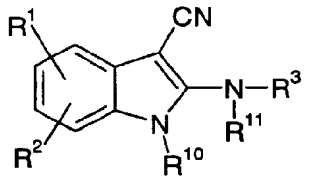
(74) Agent: **BRYANT, Tracey**; AstraZeneca, Global Intellectual Property, P.O. Box 272, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4GR (GB).

(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, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

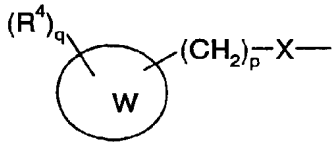
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian

[Continued on next page]

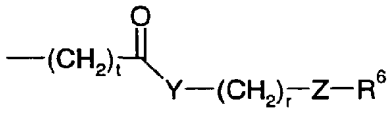
(54) Title: INDOLE DERIVATIVES WITH VASCULAR DAMAGING ACTIVITY



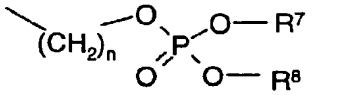
(I)



(II)



(IV)



(V)

(57) Abstract: The invention provides a compound of Formula (I) wherein: R^1 and R^2 are independently selected from hydrogen, halogen, -CN, a hydrocarbyl group or a group of Formula (II); wherein W is aryl or a heterocyclic group, R^4 is independently selected from hydrogen, halogen, -OH, amino, alkanoylamino, $-OPO_3H_2$, or a hydrocarbyl group, wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified or two R^4 groups together form an optionally substituted cyclic or heterocyclic group; X is selected from $M(y) S+-, +-O-+, -+S(O)+-, -+S(O_2)+- and -+NH--; p is an integer from 0 to 4; and q is an integer from 1 to 4; R^3 and R^{10} are independently selected from hydrogen, lower alkyl or a group of Formula (IV): wherein Y is selected from + NH+-, - $M(Y)O$M(Y)- or a bond; Z is selected from + NH+-, -+Oυ-, -+C(O)+- or a bond; r is an integer from 0 to 4; t is an integer from 0 to 1; R^6 is hydrogen, a hydrocarbyl group or a group of Formula (V): wherein n is an integer of from 1 to 6, and; R^7 and R^8 are independently selected from hydrogen or a hydrocarbyl group; and R^{11} is hydrogen or lower alkyl; or a salt or solvate thereof; provided that: I) when R^1 is an unsubstituted phenylthio group (Ph-S-), R^2 is H, R^{10} is H and R^{11} is H then R^3 is neither H nor- $C(O)-O-CH_2CH_3$; and ii) R^1, R^2 and R^3 are not all hydrogen. Such compounds are predicted to cause the selective destruction of tumour vasculature. They may therefore be used to inhibit and/or reverse, and/or alleviate symptoms of angiogenesis and/or any disease state associated with angiogenesis.

WO 01/92224 A1

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, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:
— *with international search report*

INDOLE DERIVATIVES WITH VASCULAR DAMAGING ACTIVITY

This invention relates to vascular damaging agents and their uses. In particular it relates to certain novel compounds which may be of use as vascular damaging agents, to methods for preparing the compounds, to their use as medicaments (including in methods for the treatment of angiogenesis or disease states associated with angiogenesis) and to pharmaceutical compositions containing them. The invention also relates to the use of such compounds, and of certain analogous, known compounds in the manufacture of medicaments for the production of anti-angiogenic and/or anti-vascular effects.

Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, *Trends Pharmacol. Sci.* **16**: 57-66; Folkman, 1995, *Nature Medicine* **1**: 27-31). Formation of new vasculature by angiogenesis is a key pathological feature of several diseases (J. Folkman, *New England Journal of Medicine* **333**, 1757-1763, 1995). For example, for a solid tumour to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients; if this blood supply is mechanically shut off the tumour undergoes necrotic death. Neovascularisation is also a clinical feature of skin lesions in psoriasis, of the invasive pannus in the joints of rheumatoid arthritis patients and of atherosclerotic plaques. Retinal neovascularisation is pathological in macular degeneration and in diabetic retinopathy.

Reversal of neovascularisation by damaging the newly-formed vascular endothelium is therefore expected to have a beneficial therapeutic effect.

The present invention is based on the discovery of compounds that show surprising activity in *in vitro* cell detachment assays, in particular by inducing changes in the shape of proliferating endothelial cells and by causing rapid cell detachment, which activity is a likely indicator of vascular damaging activity. The compounds are expected to cause damage to newly formed vasculature, for example the vasculature of tumours, without affecting the normal, established vascular endothelium of the host species. This vascular damage would effectively reverse the process of angiogenesis, as compared to known anti-angiogenic agents

which can prevent vasculature formation but which tend to be less effective once the vasculature has formed.

Such vascular-damaging activity would clearly be of value in the treatment of disease states associated with angiogenesis such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation.

A compound of Formula (I) in which R^1 is Ph-S- and both R^2 and R^3 are H (2-amino-3-cyano-5-(phenylthio)indole, also known as amphethinile) is disclosed in US-4,533,672 as an anti-cancer agent, as is a compound of Formula (I) in which R^1 is Ph-S-, R^2 is H and R^3 is –C(O)-O-CH_2CH_3 (ethyl 3-cyano-5-(phenylthio)indol-2-ylcarbamate). However, anti-cancer activity, in this case an apparent inhibition of tumour growth in mice, is not in itself an indicator of vascular damaging activity, for which the compounds of the present invention are of interest. Amphethinile has also been disclosed as a tubulin-binding agent (McGowan and Fox , *British Journal of Cancer* **59**, 865-868, 1989).

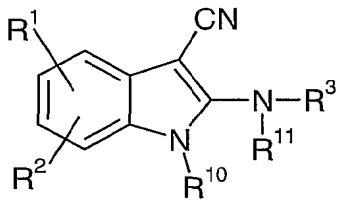
Several anticancer agents have been described which bind to tubulin, these include Taxol™ and Taxotere™ . However, these agents do not act as selective vascular targeting agents. For example, Taxol does not cause cell detachment in the HUVEC detachment assay, described herein. Other tubulin-binding agents such as colchicine and vinca alkaloids such as vincristine only elicit vascular damaging activity at doses approaching the maximum tolerated dose (MTD) (see Dark et al 1997 *Cancer Research* **57**, 1829-1834). More recently Combretastatin A4 has been described which is a tubulin binding agent which acts as a selective vascular targeting agent, producing anti-vascular effects at doses greater than 10-times less than the MTD (Dark et al 1997 *Cancer Research* **57**, 1829-1834). Thus, tubulin-binding activity is not in itself an indicator of compounds that have selective vascular damaging activity.

Tubulin binding agents that do cause selective destruction of tumour vasculature such as combretastatin and ZD6126 (N-acetylcolchinol phosphate) have been reported *in vitro* at non-cytotoxic concentrations to cause selective effects on the cell shape of proliferating endothelial cells leading to endothelial cell detachment[Dark et al, *Cancer Research* **57**, 1829-34, 1997; Galbraith et al, **21(1A)**, 93-102, 2001; Blakey D C et al, *Proceedings of the American Association for Cancer Research*, **41**, 329, 2000 abstract 2086, Davis P D et al,

Proceedings of the American Association for Cancer Research, **41**, 329, 2000 abstract 2085; Chaplin D J & Dougherty G J, *Br J Cancer*, **80**, Suppl 1, 57-64, 1999] .

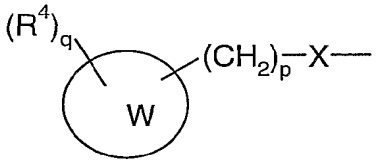
The compounds of the present in invention are tubulin binding agents that have similar activity to combretastatin and ZD6126 on proliferating endothelial cells. It can therefore be expected that the compounds of the present invention will have damaging effects on newly-formed vasculature, for example the vasculature of tumours. It can reasonably be predicted, for example, that they will be capable of causing selective destruction of tumour vasculature, both *in vitro* and *in vivo*. Destruction of tumour vasculature in turn leads to a reduction in tumour blood flow and to tumour cell death due to starvation of oxygen and nutrients, ie, to anti-tumour activity [Davis P D et al; Chaplin D J & Dougherty G J; Blakey D C et al, all *supra*].

Thus, according to the first aspect of the invention there is provided a compound of Formula (I).



Formula (I)

wherein R^1 and R^2 are independently selected from hydrogen, halogen, -CN, a hydrocarbyl group or a group of Formula (II);



Formula (II)

wherein W is aryl or a heterocyclic group,

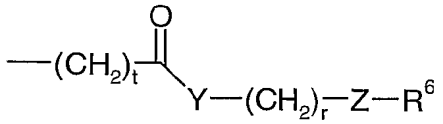
R^4 is independently selected from hydrogen, halogen, -OH, amino, alkanoylamino, —OPO_3H_2, or a hydrocarbyl group, wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified or two R^4 groups together form an optionally substituted cyclic or heterocyclic group;

X is selected from —S—, —O—, —S(O)—, —$S(O_2)$— and —NH—;

p is an integer from 0 to 4; and

q is an integer from 1 to 4;

$R^3$and R^{10} are independently selected from hydrogen, lower alkyl or a group of Formula (IV):



Formula (IV)

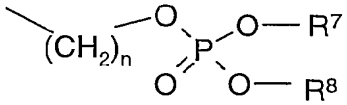
wherein Y is selected from —NH—, —O— or a bond;

Z is selected from —NH—, —O—, —C(O)— or a bond;

r is an integer from 0 to 4;

t is an integer from 0 to 1;

R^6 is hydrogen, a hydrocarbyl group or a group of Formula (V):



Formula (V)

wherein n is an integer of from 1 to 6, and;

R^7 and R^8 are independently selected from hydrogen or a hydrocarbyl group; and

R^{11} is hydrogen or lower alkyl;

or a salt or solvate thereof;

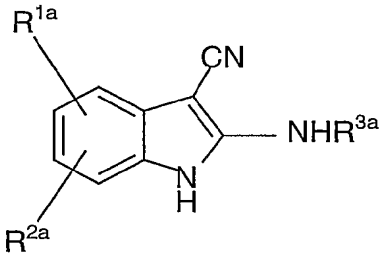
provided that:

i) when R^1 is an unsubstituted phenylthio group (Ph-S-), R^2 is H, R^{10} is H and R^{11} is H then R^3 is neither H nor –C(O)-O-CH_2CH_3; and

ii) R^1, R^2 and R^3 are not all hydrogen.

Whilst pharmaceutically acceptable salts of compounds of the invention are preferred, other non-pharmaceutically acceptable salts of the invention may be useful in the preparation of pharmaceutically-acceptable salts of compounds of the invention.

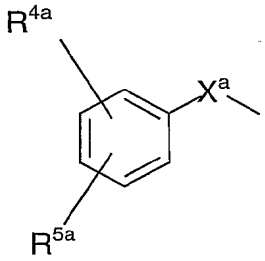
According to a further feature of the first aspect of the present invention there is provided a compound of the general Formula (Ia):



Formula (Ia)

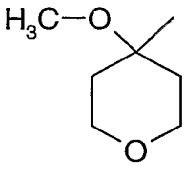
or a derivative thereof,

wherein R^{1a} and R^{2a} are independently selected from hydrogen, halogen (such as fluorine, chlorine or bromine), -OH, -CN, a hydrocarbyl group (such as a lower alkyl group) or a group of Formula (IIa):



Formula (IIa)

wherein R^{4a} and R^{5a} are independently selected from hydrogen, halogen (such as fluorine, chlorine or bromine), -OH or a hydrocarbyl group (such as a C_1-C_{10} alkyl group, an alkoxy group such as –O-alkyl or a group of Formula (IIIa);

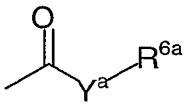


Formula (IIIa)

or a carbonyl group of the Formula –C(O)-R^{9a} where R^{9a} is hydrogen, -OH, a hydrocarbyl group such as a lower alkyl group or an alkoxy group), or R^{4a} and R^{5a} together form a cyclic or heterocyclic group, for instance to make R^{1a} into –X-naphthyl;

X^a is selected from —S—, —O—, — S(O)—, —$S(O_2)$— and —NH—;

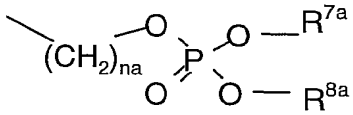
R^{3a} is either hydrogen or a group of Formula (IVa):



Formula (IVa)

wherein Y^a is selected from —NH—, —O— or a bond; and

R^{6a} is hydrogen or a hydrocarbyl group (such as an alkyl, aryl, alkoxy or phenoxy group, preferably –Ph or a lower alkyl group) or a group of Formula (Va):



Formula (Va)

wherein na is an integer of from 1 to 6, preferably 2 or 3, and R^{7a} and R^{8a} are independently selected from hydrogen or a hydrocarbyl group (in particular an alkaryl group such as $-(CH_2)_{ma}$-Ph where ma is an integer of from 1 to 6, preferably 1);

provided that:

i) when R^1 is an unsubstituted phenylthio group (Ph-S-) and R^{2a} is H, R^{10a} is H and R^{11a} is H then R^{3a} is neither H nor $-C(O)-O-CH_2CH_3$; and

ii) R^{1a}, R^{2a} and R^{3a} are not all hydrogen.

In this specification , the term **"alkyl"** refers to straight or branched chain alkyl groups, suitably containing up to 20 and preferably up to 10 or up to 6 carbon atoms, which may be substituted with one or more functional groups. The terms "**C_{1-4}alkyl**" and "**C_{1-6}alkyl**" refer to both straight-chain and branched alkyl groups containing between 1 and 4 carbon atoms and between 1 and 6 carbon atoms respectively. The terms **"alkenyl"** and **"alkynyl"** refer to optionally substituted unsaturated straight or branched chains which include for example from 2 to 20 carbon atoms, in particular from 2 to 10 or from 2 to 6 carbon atoms; these chains may include one or more double or triple bonds respectively. The term **"alkoxy"** refers to alkyl, alkenyl or alkynyl groups containing the group —O—, for example methoxy, ethoxy and propoxy. The term **"alkanoyl"** refers to alkyl, alkenyl or alkynyl groups containing the group —C(O)—, for example acetyl, propanoyl and butanoyl. The term **"alkanoylamino"** refers to alkyl, alkenyl or alkynyl groups containing the group —C(O)— followed by —N(H)—, for example acetylamino, propanoylamino and butanoylamino. The term **"carbamoyl"** refers to the group $-C(O)-NH_2$. The term **"carbamoylalkyl"** refers to an alkyl chain terminating in a

carbamoyl group, for example carbamoylmethyl which has the formula $-CH_2-C(O)-NH_2$. The term **"halogen"** refers to chloro, bromo, fluoro or iodo.

The term **"cyclic group"** refers to an optionally substituted carbon ring structure, which may contain one or more double or triple bonds, the term encompassing aryl and aralkyl groups.

The term **"aryl"** refers to wholly or partially aromatic groups such as phenyl (for which the abbreviation "Ph" is used) or naphthyl, which may be substituted with one or more functional groups. The term **"alkaryl"** means an alkyl group having at least one (optionally substituted) aryl substituent, and the term **"aralkyl"** an aryl group having at least one (optionally substituted) alkyl substituent.

The term **"lower"**, applied to the terms alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkanoylamino, alkaryl and aralkyl, means a group containing from 1 to 6 carbon atoms, preferably from 1 to 4.

The term **"hydrocarbyl"** refers to any structure comprising carbon and hydrogen atoms. For example, these may be alkyl, alkenyl, alkynyl, alkoxy, aryl such as phenyl or naphthyl, alkaryl, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl. Suitably they will contain up to 20 and preferably up to 10 carbon atoms. They may be substituted with other functional groups, or an alkyl chain optionally substituted with other functional groups and they may include heteroatoms such as oxygen, nitrogen, sulphur and/or phosphorous within a carbon chain or ring.

The term **"heterocyclic group"** includes optionally substituted aromatic, partially aromatic or non-aromatic rings or mixtures thereof, for example containing from 3 to 20, suitably from 5 to 10 ring atoms, at least one of which is a heteroatom such as oxygen, sulphur or nitrogen. Examples of such groups include morpholinyl, morpholino, piperazinyl, piperidino, furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, iosquinolinyl, quinoxalinyl, benzthiazolyl, benzoxazolyl, benzothienyl or benzofuryl.

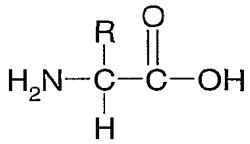
The term **"functional group"** refers to reactive groups such as halogen, cyano, nitro, oxo, $C(O)_yR^a$, OR^a, $S(O)_zR^a$, NR^bR^c, $OC(O)NR^bR^c$, $C(O)NR^bR^c$, $-NR^7C(O)_yR^6$, $-NR^aCONR^bR^c$, $-C{=}NOR^a$, $-N{=}CR^bR^c$, $S(O)_zNR^bR^c$, $C(S)_yR^a$, $C(S)OR^a$, $C(S)NR^bR^c$ or $-NR^bS(O)_zR^a$ where R^a, R^b and R^c are independently selected from hydrogen or optionally

substituted hydrocarbyl, or R^b and R^c together form an optionally substituted ring which optionally contains further heteroatoms such as $S(O)_z$, oxygen and nitrogen. In this paragraph, y is an integer of 1 or 2 and z is 0 or an integer from 1 to 3.

The term **"heteroatom"** as used herein refers to non-carbon atoms such as oxygen, nitrogen, sulphur or phosphorous atoms. Where nitrogen atoms are present, they will generally be present as part of an amino or amido residue so that they will be substituted for example by hydrogen, alkyl or carbonyl.

The term **"derivative"** as used herein refers to salts, solvates and pro-drugs of compounds of the invention.

An **"amino acid residue"** is defined as that derived from the coupling of an L-amino acid with an amino group via an amide bond. This bond can either be formed via a carboxylate group on the amino acid backbone or via a side chain carboxylate group, preferably via a carboxylate group on the amino acid backbone. Amino acid residues include those derived from natural and non-natural amino acids, preferably natural amino acids and include α-amino acid residues β-amino acid residues and γ-amino acid residues. For the avoidance of doubt amino acids include those with the generic structure:



where R is the amino acid side chain. The definition of amino acid also includes amino acid analogues which have additional methylene groups within the amino acid backbone, for example β-alanine and amino acids which are not naturally occurring such as cyclohexylalanine. Preferred amino acid residues are those derived from naturally occurring amino acids. For avoidance of doubt the term **'naturally occurring amino acids'** is defined as those amino acids which occur in the proteins of animals.

Preferred amino acids include glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparaginine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, β-alanine and ornithine. More preferred amino acids include glutamic acid, serine, threonine, arginine, glycine, alanine, β-alanine and lysine. Especially preferred amino acids include glutamic acid, serine, and glycine.

"Esterifying groups at R_4" are esterifying groups which increase the solubility of the molecule in water at a pH of approximately pH=7. Such groups include groups with ionisable groups, such as acidic functions or basic functions and groups containing a hydrophilic function. Basic functions include: amino, morpholino, piperidino, piperazinyl, pyrrolidino, amino acids and imidazolino. Acidic functions include: carboxy, sulphonic acid, phosphate, sulphate and acid mimetics such as tetrazolyl. Hydrophilic groups include hydroxyl.

Suitable R_4 groups wherein hydroxy is esterfied include: C_{1-6}alkanoyloxy, arylcarbonyloxy, heterocyclylcarbonyloxy, heteroarylcarbonyloxy wherein the R_1 group is optionally substituted with between 1 and 3 groups selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkanoylC_{1-4}alkyl, C_{1-4}alkanoylheterocyclyl, hydroxy, hydroxyC_{1-4}alkyl, carboxy, carboxyphenyl, phosphono, phosphonoC_{1-4}alkyl, amino, aminoC_{1-4}alkyl, N-C_{1-4}alkylamino, N,N-diC_{1-4}alkylamino, carbamoyl, carbamoylC_{1-4}alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylcarbonyl, heterocyclC_{1-4}alkanoylamino, carbamoylheterocyclyl, [wherein optional substituents comprising heterocyclyl are optionally further substituted by C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkanoyl and formyl, wherein the carbamoyl and amino optional substituents are optionally further N-substituted by C_{1-4}alkyl, di-C_{1-4}alkyl, hydroxyC_{1-4}alkyl, di-(hydroxyC_{1-4}alkyl), carboxyC_{1-4}alkyl, and wherein the amino group is optionally substituted by an amino acid residue] with the proviso that when R_1 is C_{1-6}alkanoyloxy or arylcarbonyloxy R_1 is not unsubstituted and R_1 is not substituted by C_{1-4}alkyl.

More preferred R_4 groups wherein hydroxy is esterfied include: carboxypentanoyloxy, 4-carboxyphenylpropanoyloxy; 4-(N-methylpiperazin-1-ylethyl)phenylcarbonyloxy, 4-(piperazin-1-ylethyl)phenylcarbonyloxy, 4-[N-di-(hydroxyethyl)aminomethyl]phenylcarbonyloxy, 3-(N-acetylpiperazin-1-ylethyl)phenylcarbonyloxy, 3-[N-di-(hydroxyethyl)aminomethyl]phenylcarbonyloxy, 4-(N-methylpiperazin-1-ylpropanoylamino)phenylcarbonyloxy, N-methylpiperazin-1-ylcarbonylpropanoyloxy, N-di-(hydroxyethyl)aminocarbonylpropanoyloxy, piperazin-1-ylcarbonylpropanoyloxy, (N-acetylpiperazin-1-yl)carbonylpropanoyloxy, (N-di-(hydroxyethyl)aminocarbonylpropanoyloxy, and 4-(piperazin-1-ylmethyl)phenylcarbonyloxy.

Further preferred R_1 groups wherein hydroxy is esterfied include:
4-(N-methylpiperazin-1-ylpropanoylamino)phenylcarbonyloxy,
N-methylpiperazin-1-ylcarbonylpropanoyloxy and
N-di-(hydroxyethyl)aminocarbonylpropanoyloxy.

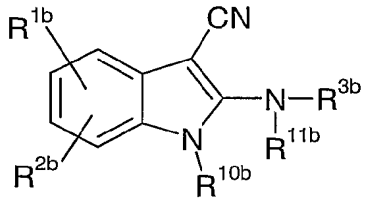
A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a carbazole derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

It is to be understood that, insofar as certain of the compounds in the different features of the invention may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of inhibiting and/or reversing and/or alleviating the symptoms of angiogenesis and/or any disease states associated with angiogenesis. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, activity of these compounds may be evaluated using the standard laboratory techniques referred to hereinafter.

The invention also relates to any and all tautomeric forms of the compounds of the different aspects of the invention that possess the property of inhibiting and/or reversing and/or alleviating the symptoms of angiogenesis and/or any disease states associated with angiogenesis.

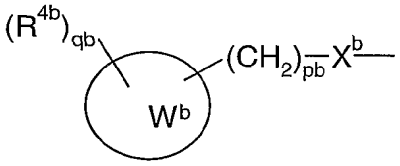
It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of the property of inhibiting and/or reversing and/or alleviating the symptoms of angiogenesis and/or any disease states associated with angiogenesis.

According to the second aspect of the invention there is provided the use of a compound of Formula (Ib) as a medicament:



Formula (Ib)

wherein R^{1b} and R^{2b} are independently selected from hydrogen, halogen, -CN, a hydrocarbyl group or a group of Formula (IIb);



Formula (IIb)

wherein W^b is aryl or a heterocyclic group,

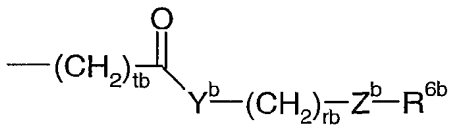
R^{4b} is independently selected from hydrogen, halogen, -OH, amino, alkanoylamino, —OPO_3H_2, or a hydrocarbyl group, wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified or two R^{4b} groups together form an optionally substituted cyclic or heterocyclic group;

X^b is selected from —S—, —O—, —S(O)—, —$S(O_2)$— and —NH—;

pb is an integer from 0 to 4; and

qb is an integer from 1 to 4;

$R^{3b}$and R^{10b} are independently selected from hydrogen, lower alkyl or a group of Formula (IVb):



Formula (IVb)

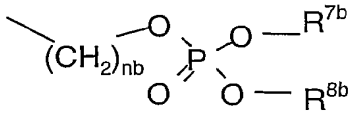
wherein Y^b is selected from —NH—, —O— or a bond;

Z^b is selected from —NH—, —O—, —C(O)— or a bond;

rb is an integer from 0 to 4;

tb is an integer from 0 to 1;

R^{6b} is hydrogen, a hydrocarbyl group or a group of Formula (Vb):



Formula (Vb)

wherein nb is an integer of from 1 to 6, and;

R^{7b} and R^{8b} are independently selected from hydrogen or a hydrocarbyl group; and

R^{11b} is hydrogen or lower alkyl;

or a salt or solvate thereof;

provided that:

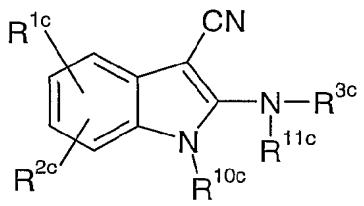
i) when R^{1b} is an unsubstituted phenylthio group (Ph-S-), R^{2b} is H, R^{10b} is H and R^{11b} is H then R^{3b} is neither H nor $-C(O)-O-CH_2CH_3$.

According to a further feature of the second aspect of the invention there is provided a compound of Formula (Ib) for use in any surgical, therapeutic or diagnostic method practised on a human or animal patient.

According to a further feature of the second aspect of the invention there is provided a compound of Formula (Ib) for use in the preparation of a medicament for use in any surgical, therapeutic or diagnostic method practiced on a human or animal patient.

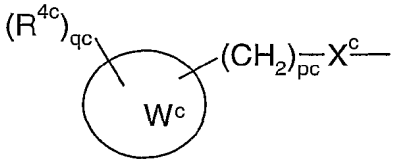
For each feature of the second aspect of the invention, the surgical, therapeutic or diagnostic method preferably involves the treatment of a human or animal patient to inhibit and/or reverse, and/or to alleviate a symptom of, angiogenesis and/or any disease state associated with angiogenesis. In other words, compounds and derivatives according to the second aspect of the invention are preferably used as vascular damaging and/or anti-angiogenic agents.

Thus, according to the third aspect of the present invention there is provided the use of a compound of Formula (Ic) or a pharmaceutically-acceptable salt or solvate thereof, for the manufacture of a medicament to inhibit and/or reverse and/or alleviate symptoms of angiogenesis and/or any disease state associated with angiogenesis:



Formula (Ic)

wherein R^{1c} and R^{2c} are independently selected from hydrogen, halogen, -CN, a hydrocarbyl group or a group of Formula (IIc);



Formula (IIc)

wherein W^c is aryl or a heterocyclic group,

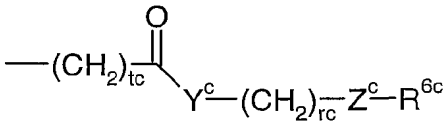
R^{4c} is independently selected from hydrogen, halogen, -OH, amino, alkanoylamino, —OPO_3H_2, or a hydrocarbyl group, wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified or two R^{4c} groups together form an optionally substituted cyclic or heterocyclic group;

X^c is selected from —S—, —O—, —S(O)—, —$S(O_2)$— and —NH—;

pc is an integer from 0 to 4; and

qc is an integer from 1 to 4;

R^{3c} and R^{10c} are independently selected from hydrogen, lower alkyl or a group of Formula (IVc):



Formula (IVc)

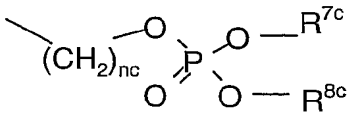
wherein Y^c is selected from —NH—, —O— or a bond;

Z^c is selected from —NH—, —O—, —C(O)— or a bond;

rc is an integer from 0 to 4;

tc is an integer from 0 to 1;

R^{6c} is hydrogen, a hydrocarbyl group or a group of Formula (Vc):



Formula (Vc)

wherein nc is an integer of from 1 to 6, and;

R^{7c} and R^{8c} are independently selected from hydrogen or a hydrocarbyl group; and

R^{11c} is hydrogen or lower alkyl;

According to a further feature of the third aspect of the invention there is provided a method of treatment, in an animal, to inhibit and/or reverse and/or alleviate symptoms of angiogenesis and/or any disease state associated with angiogenesis, comprising administering to said animal a therapeutically effective amount of a compound of Formula (Ic), or a pharmaceutically-acceptable salt or solvate thereof.

An animal is preferably a warm-blooded animal, more preferably a mammal, most preferably a human.

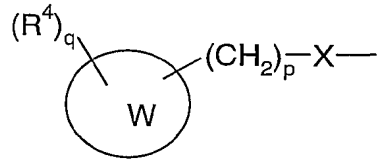
According to a further feature of the third aspect of the invention provides a method of treatment of a patient to inhibit and/or reverse, and/or to alleviate a symptom of, angiogenesis and/or any disease state associated with angiogenesis, the method involving administering to the patient a therapeutically (including prophylactically) effective amount of a compound of Formula (Ia) or derivative thereof , or of a compound of Formula (Ia) (or derivative thereof) in which R^1 is an unsubstituted phenylthio group (Ph-S-), R^2 is H and R^3 is either H or –C(O)-O-CH_2CH_3.

A patient is preferably a warm-blooded animal, more preferably a mammal, most preferably a human.

The term **"therapy"** and **"therapeutically effective"** as used here includes prophylaxis.

A series of preferences for groups of values and for groups of compounds of the invention follow, these relate to compounds of Formula (I) and also relate to the respective groups in compounds of Formula (Ia), Formula (Ib) and Formula (Ic). For example, preferences for R^1 also relate to R^{1a}, R^{1b}, and R^{1c}, and preferences for R^4 also relate to R^{4a}, R^{5a}, R^{4b} and R^{4c}.

A preferred group of values for R^1 in each aspect of the invention is hydrogen, halogen, -CN, lower alkyl or a group of Formula (II);



Formula (II)

wherein W, R^4, X, p and q are as defined above. More preferably R^1 is hydrogen, halogen, lower alkyl or a group of Formula (II) wherein W, R^4, X, p and q are as defined above. More preferably R^1 is fluoro, chloro, methyl, or a group of Formula (II) wherein W, R^4, X, p and q are as defined above. Most preferably R^1 is a group of Formula (II) wherein W, R^4, X, p and q are as defined above.

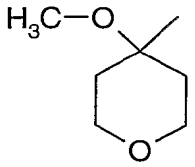
A preferred group of values for R^2 in each aspect of the invention is hydrogen, halogen, preferably fluoro or chloro, a lower alkyl group, preferably methyl, ethyl, propyl, isopropyl, butyl or *t*-butyl. More preferably R^2 is hydrogen, fluoro, chloro or methyl. Most preferably R^2 is hydrogen.

A preferred group of values for W in each aspect of the invention is aryl or a heterocyclic group. More preferably W is phenyl, naphthyl or pyridyl. Most preferably W is phenyl.

A preferred group of values for X in each feature of the invention is —O—, —NH—, —S— or —S(O_2)—. More preferably X is —O— or —S—. Most preferably X is —O—.

A preferred group of values for p in each aspect of the invention is when p is 0 or 1. Most preferably p is 0.

A preferred group of values for R^4 , when q is an integer between 1 and 4, in each aspect of the invention is hydrogen, halogen, -OH, amino, —OPO_3H_2,or C_1-C_{10} alkyl group, a lower alkoxy group, a lower alkanoyl group, a lower alkanoylamino group, a group of Formula (III),

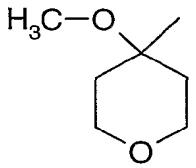


Formula (III)

or a carbonyl group of the Formula –C(O)-R^9 where R^9 is hydrogen, -OH, a hydrocarbyl group (such as a lower alkyl group or an alkoxy group) , wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified. More preferably R^4 is hydrogen, fluoro, -OH, amino, —OPO_3H_2, a lower alkanoylamino group, or a

lower alkoxy group, wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified. Further preferably R^4 is hydrogen, -OH, amino, —OPO_3H_2, acetylamino, methoxy, serylamino, glutamylamino preferably α-glutamylamino, glycylamino, alanylamino and 4-methylpiperazin-1-ylcarbonylpropanoyloxy. Most preferably R^4 is amino, -OH, acetylamino or methoxy.

A preferred group of values for R^4 , when q is 1, in each aspect of the invention is hydrogen, halogen, -OH, amino, —OPO_3H_2, or C_1-C_{10} alkyl group, a lower alkoxy group, a lower alkanoyl group, a lower alkanoylamino group, a group of Formula (III),



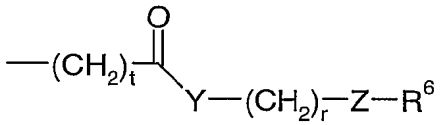
Formula (III)

or a carbonyl group of the Formula –C(O)-R^9 where R^9 is hydrogen, -OH, a hydrocarbyl group such as a lower alkyl group or an alkoxy group) , wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified. More preferably R^4 is hydrogen, fluoro, -OH, amino, —OPO_3H_2, a lower alkanoylamino group, or a lower alkoxy group, wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified. Further preferably R^4 is hydrogen, -OH, amino, —OPO_3H_2, acetylamino, methoxy, serylamino, glutamylamino preferably α-glutamylamino, glycylamino, alanylamino and 4-methylpiperazin-1-ylcarbonylpropanoyloxy. Most preferably serylamino, α-glutamylamino, glycylamino, —OPO_3H_2, amino, -OH, acetylamino or methoxy.

A preferred group of values for R^4 , when q is 2 or 3, in each aspect of the invention is when R^4 is independently selected from hydrogen, halogen, -OH, —OPO_3H_2,or a C_1-$_{10}$ alkyl group, or a lower alkoxy group, a lower alkanoyl group, or a carbonyl group of the Formula -C(O)-R^9 where R^9 is hydrogen, lower alkyl or alkoxy. More preferably R^4 is independently selected from hydrogen, fluoro, -OH, —OPO_3H_2, or a lower alkoxy group. Further preferably R^4 is hydrogen, -OH, —OPO_3H_2 or methoxy. Most preferably R^4 is —OPO_3H_2, -OH or methoxy.

A preferred group of values for q is 2 or 3. More preferably q is 3.

A preferred group of values for R^3 in each aspect of the invention is when R^3 is hydrogen, lower alkyl or a group of Formula (IV):



Formula (IV)

wherein t, Y, r, Z and R^6 are as defined above. More preferably R^3 is hydrogen or a group of Formula (IV). Most preferably R^3 is hydrogen.

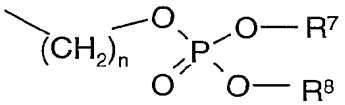
A preferred group of values for t in each aspect of the invention is 0 or 1. Preferably t is 0.

A preferred group of values for Y in each aspect of the invention is —O— or—NH—. More preferably Y is —O— or a bond. Most preferably —Y— is —O—.

A preferred group of values for r in each aspect of the invention is 2 or 3. Preferably r is 3.

A preferred group of values for Z in each aspect of the invention is —C(O)— or a bond. Preferably Z is a bond.

A preferred group of values for R^6 in each aspect of the invention is hydrogen, lower alkyl, a lower alkoxy group, an aryl group, a heterocyclic group or a group of Formula (V), wherein the aryl group and heterocyclic group are optionally substituted by lower alkyl or a lower alkanoyl group:



Formula (V).

More preferably R^6 is a non-aromatic heterocyclic group, an aryl group or a group of Formula (V), wherein the aryl group and non-aromatic heterocyclic group are optionally substituted by lower alkyl or a lower alkanoyl group. Further preferably R^6 is –Ph, morpholino, piperazinyl or a group of Formula (V), wherein the –Ph, morpholino and piperazinyl group are optionally substituted by methyl or acetyl and R^7 and R^8 are both hydrogen. Most preferably R^6 is –Ph, morpholino or 4-methyl-piperazin-1-yl.

A preferred group of values for n in each aspect of the invention is 2 or 3. Preferably n is 2.

A preferred group of values for R^7 and R^8 in each aspect of the invention is R^7 and R^8 are independently selected from hydrogen or an alkaryl group, preferably $-(CH_2)_m$-Ph where m is an integer of from 1 to 6, preferably m is 1. More preferably R^7 and R^8 are independently selected from hydrogen or benzyl (-CH_2-Ph). Preferably R^7 and R^8 are both hydrogen.

A preferred group of values for R^{10} in each aspect of the invention is hydrogen, lower alkyl or a group of Formula (IV), wherein t, Y, r, Z and R^6 are as defined above. More preferably R^{10} is hydrogen, lower alkyl or lower carbamoylalkyl group. Most preferably R^{10} is hydrogen, methyl or carbamoylmethyl.

A preferred group of values for a group of Formula (IV) is phenoxycarbonyl, phosphonooxyethylaminocarbonyl, 4-methylpiperazin-1-ylpropoxycarbonyl, carbamoylmethyl, 4-acetyl-piperazin-1-ylethoxycarbonyl, 4-methyl-piperazin-1-ylcarbonylpropanoyl and morpholinoethoxycarbonyl. Preferably phenoxycarbonyl, 4-methylpiperazin-1-ylpropoxycarbonyl or carbamoylmethyl.

Preferably only one of R^3 and R^{10} is a group of Formula (IV).

A preferred group of values for R^{11} in each aspect of the invention is hydrogen or lower alkyl. More preferably R^{11} is hydrogen or methyl. Most preferably R^{11} is hydrogen.

In the following preferred groups of compounds of each aspect of the invention values for R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, n, m, p, q, r, t, W, X, Y and Z are as hereinbefore defined, unless specifically defined with a preferred group of compounds.

A further preferred group of compounds of each aspect of the invention described herein, comprise compounds wherein:

R^1 is a group of Formula (II);

X is —O—;

p is 0 or 1; and

W is phenyl;

or a salt or solvate thereof.

A further preferred group of compounds of each aspect of the invention described herein, comprise compounds wherein:

R^1 is a group of Formula (II);

X is —NH—;

p is 0 or 1; and

W is phenyl;

or a salt or solvate thereof.

A further preferred group of compounds of each aspect of the invention described herein, comprise compounds wherein:

R^1 is a group of Formula (II);

X is —S—, —SO— or —$S(O_2)$—, preferably X is —S— or —$S(O_2)$—, most preferably X is —S—;

p is 0 or 1; and

W is phenyl;

or a salt or solvate thereof.

A further preferred group of compounds of each aspect of the invention described herein, comprise compounds wherein:

R^1 is a group of Formula (II);

X is —S—, —$S(O_2)$—, —O— or —NH—; preferably X is —O— or —S—; most preferably X is —O—;

p is 0 or 1; and

W is phenyl;

R^4 is hydrogen, -OH, amino, —OPO_3H_2, or a C_{1-4}alkoxy group, wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified;

q is an integer between 1 and 3;

or a salt or solvate thereof.

A further preferred group of compounds of each aspect of the invention described herein, comprise compounds wherein:

R^1 is a group of Formula (II);

X is —S—, —$S(O_2)$—, —O— or —NH—; preferably X is —O— or —S—, most preferably X is —O—;

p is 0 or 1;

W is phenyl;

R^4 is an amino group or —OPO_3H_2, wherein the amino group is substituted by an amino acid residue. Preferably R^4 is serylamino, glutamylamino, glycylamino, or alanylamino. Most preferably R^4 is serylamino, α-glutamylamino, glycylamino, or alanylamino; and

q is 1;

or a salt or solvate thereof.

A further preferred group of compounds of each aspect of the invention described herein, comprise compounds wherein:

R^1 is a group of Formula (II);

X is —S—, —S(O_2)—, —O— or —NH—; preferably X is —O— or —S—; most preferably X is —O—;

p is 0 or 1; and

W is phenyl;

R^4 is independently selected from hydrogen, -OH, —OPO_3H_2, or a C_{1-4}alkoxy group, preferably R^4 is independently selected from —OPO_3H_2, methoxy or ethoxy, most preferably R^4 is methoxy;

q is an integer between 1 and 4, preferably q is 2 or 3, most preferably q is 3;

or a salt or solvate thereof.

A further preferred group of compounds of each aspect of the invention described herein, comprise compounds wherein:

R^3 and R^{10} are independently selected from hydrogen, methyl , ethyl or a group of Formula (IV), preferably methyl or a group of Formula (IV);

or a salt or solvate thereof.

A further preferred groups of compounds of each aspect of the invention described herein comprise compounds wherein:

R^3 is a group of Formula (IV) and R^{10} is hydrogen or lower alkyl or R^3 is hydrogen or lower alkyl and R^{10} is a group of Formula (IV);

t is 0 or 1, preferably 0;

Y is —NH— or —O—, preferably Y is —O—;

r is an integer between 2 and 4, preferably 2 or 3;

Z is a bond; and

R^6 is a –Ph or a non-aromatic heterocyclic group, wherein –Ph and the non-aromatic heterocyclic group are optionally substituted by lower alkyl or a lower alkanoyl group, preferably R^6 is a non-aromatic heterocyclic group optionally substituted by lower alkyl or a lower alkanoyl group;

or a salt or solvate thereof.

Preferred compounds of the invention include:

2-phenoxycarbonylamino-5-phenylsulphanyl-1*H*-indole-3-carbonitrile;

5-(4-hydroxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile;

5-(3,6-dimethoxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile;

5-phenylsulphanyl-2-(4-methylpiperazin-1-ylpropoxycarbonylamino)-1*H*-indole-3-carbonitrile;

5-phenylsulphanyl-1-(4-methylpiperazin-1-ylpropoxycarbonyl)-2-amino-1*H*-indole-3-carbonitrile;

6-benzyloxy-2-amino-1*H*-indole-3-carbonitrile;

5-[4-(4-methylpiperazin-1-yl-4-oxobutanoyloxy)phenoxy]-2-amino-1*H*-indole-3-carbonitrile;

5-(4-glycylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(4-alanylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(4-glutamylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(3-glycylbenzyloxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(4-hydroxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(4-phosponooxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(3-serylbenzyloxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(4-acetylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile; and

5-(4-serylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile;

or salt or solvate thereof.

More preferred compounds of the invention include:

5-(4-aminophenoxy)-2-amino-1*H*-indole-3-carbonitrile; and

5-(3,4,5-trimethoxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile,

or salt or solvate thereof.

Most preferred compounds of the invention include:

5-(3,4-dimethoxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile; and (Example 3)

5-(3,4,5-trimethoxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile; (Example 11)

or salt or solvate thereof.

In any aspect of the invention it is desirable to include in the compound of the invention, at any appropriate position, a water solubilising group such as (but not limited to) a phosphate,

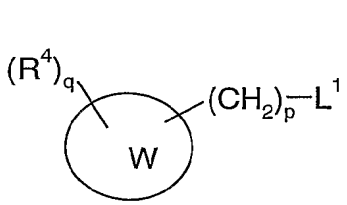
sulphate or sugar group, to enhance the bioavailability of the compound on administration to a patient.

The first aspect of the invention also encompasses derivatives of compounds of Formula (I), such as pharmaceutically acceptable salts and/or ionic forms (for instance where a terminal hydroxyl group is actually present as $-O^-$ or a terminal amine is in it's protonated form), co-ordination complexes for example with metal ions, hydrated forms, labelled forms for instance for use in diagnostic methods and pharmaceutical precursors which are convertible, either *in vitro* or *in vivo*, into the relevant compound.

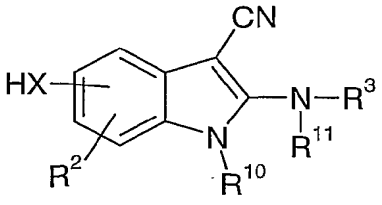
A compound of the invention or a pharmaceutically-acceptable salt, or solvate thereof, may be prepared by any process known to be applicable to the preparation of chemically related compounds. Such processes, when used to prepare a compound of the invention or a pharmaceutically-acceptable salt, or solvate thereof, are provided as a further feature of the invention and are illustrated by the following representative examples in which R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, m, n, p, q, r, t, W, X, Y and Z have the same meaning as herein before defined. The reader is referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents. The reader is referred to Protective Groups in Organic Synthesis 2nd Edition, by Green et al, published by John Wiley & Sons for general guidance on protecting groups.

Thus, according to the fourth aspect of the invention there is provided a process for preparing a compound of Formula (I), or salt, or solvate thereof, which process (wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, m, n, p, q, r, t, W, X, Y and Z are unless otherwise specified as defined in Formula (I)) comprises:

a) for compounds of Formula (I) wherein R^1 is of the Formula (II) and X is —O—, —S— or —NH—, reacting a compound of Formula (A) with a compound of Formula (B),



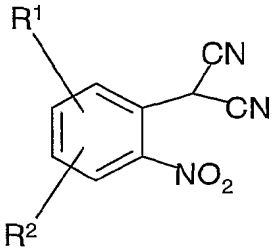
Formula (A)



Formula (B)

wherein L^1 is a leaving group;

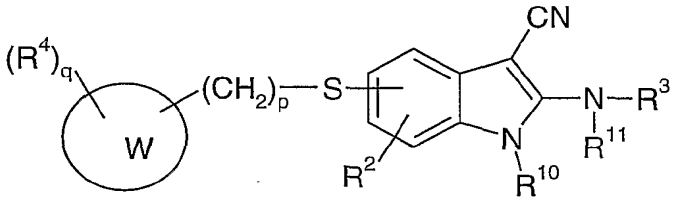
b) for compounds of Formula (I) in which R^3 is hydrogen and R^{11} is hydrogen may be prepared by reduction followed by ring closure of compounds of Formula (C):



Formula (C)

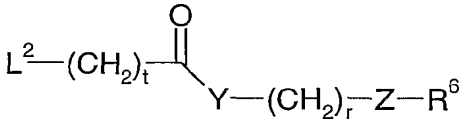
c) for compounds of Formula (I) wherein R^{10} is lower alkyl, reacting a compound of Formula (I) wherein R^{10} is hydrogen with a suitable alkylhalide,

d) for compounds of Formula (I) wherein R^1 is of the Formula (II) and X is —S(O)—, —$S(O_2)$—, oxidising a compound of Formula (D),



Formula (D)

e) for compounds of Formula (I) in which R^3 is a group of Formula (IV) may be prepared by the reaction of compounds of Formula (I) in which R^3 is hydrogen with compounds of Formula (F) below, in which L^2 is a leaving group.:



Formula (F)

and thereafter if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups;

iii) forming a salt, or solvate.

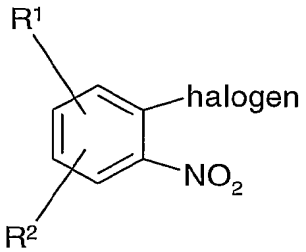
According to a further feature of the fourth aspect of the invention there is provided the processes a), b), c), d) and e) described above for the preparation of compounds of the Formula (I), or a salt, or solvate thereof.

Specific reaction conditions for the above reactions are as follows:

Process a) Compounds of Formula (A) and compound of Formula (B) can be reacted together in an organic solvent, at a temperature between room temperature and about 80°C, optionally in the presence of a base such as sodium hydride, potassium carbonate or triethylamine.

Process b) The conditions for reduction of a compound of Formula (C) are well known in the art. Examples of reducing agents include hydrogen and a hydrogenation catalyst (for example palladium on carbon), iron and acetic acid, and zinc and hydrochloric acid. The reaction is preferably carried out in the presence of a suitable solvent such as an alcohol, for example methanol or ethanol, and at a temperature in the range of 0-80°C, preferably at or near room temperature. Further examples of reducing conditions include sodium dithionite in the presence of a base, preferably sodium bicarbonate in a suitable solvent such as DMF or N-methyl-pyrrolidone.

Compounds of Formula (C) can be prepared by displacement of a halogen atom, preferably F or Cl , from compounds of Formula (E), using a salt of malononitrile, preferably the sodium salt:



Formula (E)

A method for reduction and ring closure of a compound of Formula (C) can be found in US-4,533,672.

Process c) Compounds of Formula (I) wherein R_2 is hydrogen and a suitable alkyl halide may be reacted together in a suitable organic solvent such as DMF or DMSO, in the presence of a base, such as sodium hydride or potassium carbonate at a temperature between about room temperature and about 80°C.

Process d) The oxidization of a compound of Formula (D) can be carried out, for example, by reaction with metachloroperbenzoic acid (MCPBA) is the presence of a suitable solvent such as dichloromethane at ambient temperature. If an excess of MCPBA is used a compound of Formula (I) wherein X is —$S(O_2)$— is obtained.

Process e) Compounds of Formula (I) in which R^3 is hydrogen can be reacted with compounds of Formula (F) under conditions well known in the art. For example L^2 may be -Cl or p-nitrophenoxy. When L^2 is Cl this is carried out in the presence of a base, preferably pyridine

The synthesis of a compound of Formula (I) in which R^1, R^2 and R^3 are all hydrogen (2-aminoindole-3-carbonitrile) is described by Eger et al in *Liebigs Ann. Chem.* **1993**, 465-470.

The compounds used as starting points for the reactions described above are commercially available or they are known compounds or they are prepared by processes known in the art.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

According to the fifth aspect of the invention there is provided a pharmaceutical composition comprising a compound of Formula (I) or pharmaceutically acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof.

According to a further feature of the fifth aspect of the invention there is provided a pharmaceutical composition comprising a compound of Formula (I) or pharmaceutically acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof, in admixture with a pharmaceutically-acceptable diluent or carrier.

In order to use a compound of Formula (I) or pharmaceutically acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof, for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible

powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically-acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and

hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate), anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a

solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient 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. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedures well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μm or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in

Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 50 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.2 mg to 10 mg per kg body weight will generally be used. Typically, intravenous doses of about 10 mg to 500 mg per patient of a compound of this invention will be used..

The compounds of this invention may be used in combination with other drugs and therapies used to inhibit and/or reverse and/or alleviate symptom of angiogenesis and/or any disease state associated with angiogenesis. Examples of such disease states include: cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

Possible uses for the pharmaceutical composition include both therapeutic and diagnostic uses. In particular, it may be used to treat and/or diagnose any condition which is related to (ie, which is or can be caused or mediated, directly or indirectly, by, or which is in any way associated with) angiogenesis or vasculature formation, especially of tumours.

A therapeutic treatment method in which a compound or derivative according to the invention may be used involves the administration to a patient suffering from a relevant condition of a therapeutically (which includes prophylactically) effective amount of the compound or derivative, preferably in the form of a pharmaceutical composition according to

the fifth aspect of the invention. **"Effective amount"** means an amount sufficient to cause a benefit (which may be prophylactic) to the patient or at least to cause a change in the patient's condition, eg, to cause a medically significant inhibition of tumour development. The actual amount administered to the patient, and the rate and time-course of administration, will depend on the nature of the patient, the nature and severity of the condition, the administration method used, etc. Appropriate values can be selected by the trained medical practitioner. The compound or derivative may be administered alone or in combination with other treatments, either simultaneously or sequentially. It may be administered by any suitable route, preferably orally. It may be administered directly to a suitable site or in a manner in which it targets a particular site - suitable targeting methods are already known.

A diagnostic method according to the invention might involve the use of the compound or derivative to determine, either qualitatively or quantitatively, the existence of a particular medical condition or change in condition. Such a method may be carried out either *in vitro* or *in vivo*. One or more of the materials used in the method may be appropriately labelled.

According to a sixth aspect of the present invention there is provided a method for producing a pharmaceutical composition according to the fifth aspect of the invention, said method comprising providing (for example by synthesising) a compound of Formula (I) or pharmaceutically-acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof, and then mixing it with one or more pharmaceutically acceptable adjuvants, and/or with one or more other therapeutically or diagnostically active agents.

According to a seventh aspect of the present invention there is provided a compound of Formula (I) or pharmaceutically-acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof, preferably in the form of a pharmaceutical composition according to the fifth aspect of the invention, when dosed in divided doses (also known as split doses) produces a greater anti-tumour effect than when a single dose is given.

Anti-tumour effects of a method of treatment of the present invention include but are not limited to, inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment, slowing of disease progression. It is expected that when a method of treatment of the present invention is administered to a warm-blooded animal such as a human, in need of treatment for

cancer involving a solid tumour, said method of treatment will produce an effect, as measured by, for example, one or more of: the extent of the anti-tumour effect, the response rate, the time to disease progression and the survival rate.

According to a further feature of the seventh aspect of the present invention there is provided a method for the production of a vascular damaging effect in a warm-blooded animal such as a human, which comprises administering to said animal in divided doses an effective amount of a compound of Formula (I) or pharmaceutically-acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof, preferably in the form of a pharmaceutical composition according to the fifth aspect of the present invention.

According to a further feature of the seventh aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal in divided doses an effective amount of a compound of Formula (I) or pharmaceutically-acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof, preferably in the form of a pharmaceutical composition according to the fifth aspect of the present invention.

According to a further feature of the seventh aspect of the present invention there is provided a medicament comprising two or more fractions of doses of a compound of Formula (I) or pharmaceutically-acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof, preferably in the form of a pharmaceutical composition according to the fifth aspect of the present invention, which together add up to a total daily dose, for administration in divided doses for use in a method of treatment of a human or animal body by therapy.

According to a further feature of the seventh aspect of the present invention there is provided a kit comprising two or more fractions of doses of a compound of Formula (I) or pharmaceutically-acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof, preferably in the form of a pharmaceutical composition according to the fifth aspect of the present invention, which together add up to a total daily dose, for administration in divided doses.

According to a further feature of the seventh aspect of the present invention there is provided a kit comprising:

a) two or more fractions of doses of a compound of Formula (I) or pharmaceutically-acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof, which together add up to a total daily dose, in unit dosage forms for administration in divided doses; and

b) container means for containing said dosage forms.

According to a further feature of the seventh aspect of the present invention there is provided a kit comprising:

a) two or more fractions of doses of a compound of Formula (I) or pharmaceutically-acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof, which together add up to a total daily dose, together with a pharmaceutically acceptable excipient or carrier, in unit dosage forms; and

b) container means for containing said dosage forms.

According to a further feature of the seventh aspect of the present invention there is provided the use of compound of Formula (I) or pharmaceutically-acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof in the manufacture of a medicament for administration in divided doses for use in the production of a vascular damaging effect in a warm-blooded animal such as a human.

According to a further feature of the seventh aspect of the present invention there is provided the use of a compound of Formula (I) or pharmaceutically-acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof in the manufacture of a medicament for administraton in divided doses for use in the production of an anti-cancer effect in a warm-blooded animal such as a human.

According to a further feature of the seventh aspect of the present invention there is provided the use of a compound of Formula (I) or pharmaceutically-acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof in the manufacture of a medicament for administration in divided doses for use in the production of an anti-tumour effect in a warm-blooded animal such as a human.

Divided doses, also called split doses, means that the total dose to be administered to a warm-blooded animal, such as a human, in any one day period (for example one 24 hour period from midnight to midnight) is divided up into two or more fractions of the total dose and these fractions are administered with a time period between each fraction of about greater

than 0 hours to about 10 hours, preferably about 1 hour to about 6 hours, more preferably about 2 hours to about 4 hours. The fractions of total dose may be about equal or unequal.

Preferably the total dose is divided into two parts which may be about equal or unequal.

The time intervals between doses may be for example selected from:

about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 3 hours, about 3.5 hours, about 4 hours, about 4.5 hours, about 5 hours, about 5.5 hours and about 6 hours.

The time intervals between doses may be any number (including non-integers) of minutes between greater than 0 minutes and 600 minutes, preferably between 45 and 375 minutes inclusive. If more than two doses are administered the time intervals between each dose may be about equal or unequal.

Preferably two doses are given with a time interval in between them of greater than or equal to 1 hour and less than 6 hours.

More preferably two doses are given with a time interval in between them of greater than or equal to two hours and less than 5 hours.

Yet more preferably two doses are given with a time interval in between them of greater than or equal to two hours and less than or equal to 4 hours.

Particularly the total dose is divided into two parts which may be about equal or unequal with a time interval between doses of greater than or equal to about two hours and less than or equal to about 4 hours.

More particularly the total dose is divided into two parts which may be about equal with a time interval between doses of greater than or equal to about two hours and less than or equal to about 4 hours.

For the avoidance of doubt the term 'about' in the description of time periods means the time given plus or minus 15 minutes, thus for example about 1 hour means 45 to 75 minutes, about 1.5 hours means 75 to 105 minutes. Elsewhere the term 'about' has its usual dictionary meaning.

An anti-vascular/anti-angiogenic treatment in accordance with the present invention may be applied as a sole therapy or may involve, in addition to the compound of Formula (I) or pharmaceutically-acceptable salt or solvate thereof or a compound of Formula (Ia) or pharmaceutically-acceptable derivative thereof, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of

medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the anti-vascular/anti-angiogenic treatment according to the invention may be, for example, surgery, radiotherapy or chemotherapy. Such chemotherapy may include the following categories of therapeutic agent:

i) anti-angiogenic agents that work by different mechanisms from the compounds of Formula (I) (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, endostatin, razoxin, thalidomide) and including vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (RTKIs) (for example those described in international patent applications publication nos. WO-97/22596, WO-97/30035, WO-97/32856 and WO-98/13354, the entire disclosure of which documents is incorporated herein by reference);

ii) cytostatic agents such as anti-oestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), anti-progestogens, anti-androgens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example epidermal growth factor (EGF), platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);

iii) biological response modifiers (for example interferon);

iv) antibodies (for example edrecolomab); and

v) anti-proliferative/anti-neoplastic drugs and combinations thereof, as used in medical oncology, such as anti-metabolites (for example anti-folates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); anti-tumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); anti-mitotic

agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, irinotecan).

As stated above compounds of Formula (I) or Formula (Ia) are of interest for their potential vascular damaging effects. They are expected to be useful in the prophylaxis and treatment of a wide range of disease states where inappropriate angiogenesis occurs including cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. In particular the compounds are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin.

In addition to their use in therapeutic medicine, compounds of Formula (I) and their pharmaceutically acceptable derivatives may also be useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of vascular damaging agents in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

Compounds of Formula (I) and compounds of Formula (Ia) encompass vascular damaging agents and pro-drugs of vascular damaging agents. Pro-drugs of vascular damaging agents are believed to be cleaved *in-vivo*. Without being bound by theoretical considerations these pro-drugs may have lower activity in the in-vitro colchicine binding site competitive assay, than would be anticipated when the activity of these compounds is measured in cell based assays or *in-vivo*.

Biological Assays

(i) Colchicine Binding site competitive assay kit.

The ability of a ligand to bind specifically to the colchicine binding site on tubulin, an indicator of the vascular damaging activity, was assessed using a size exclusion chromatography assay kit from "Cytoskeleton" (1650 Fillmore St. #240, Denver, CO 80206, U.S.A.) Catalogue number of kit: BK023.

The following reagents were used:

tubulin buffer, to give 0.1mM GTP, 0.5mM $MgCl_2$, 0.5mM EGTA, 40mM PIPES buffer at pH6.9 in the final reaction mix;

purified tubulin protein from bovine brain at 1mg/ml in tubulin buffer;

0.02mM fluorescent colchicine in tubulin buffer [FITC (fluorescein isothiocyanate)-labelled];

2mM colchicine in tubulin buffer;

0.2mM vinblastine in tubulin buffer; and

G-25 Sephadex™ Fine - particle size 34-138μm.

The reaction was performed as follows:

8μl of test compound (dissolved in DMSO) was gently mixed with 150μl of tubulin. This was then incubated at 37°C for 30 minutes. Then 4μl of the fluorescent colchicine was added, the incubation mix vortexed for 5 seconds and then incubated for a further 30 minutes at 37°C. At the end of the reaction incubation size exclusion chromatography was performed to separate the tubulin with fluorescent colchicine bound from the free, unbound colchicine. If a test compound inhibited fluorescent colchicine binding then a reduced signal is measured and the compound is confirmed as a colchicine site binding moiety.

Chromatography was performed as follows, using chromatography columns filled with 3mls of G-25 Sephadex™ Fine slurry. The incubation mixture was pipetted onto the column and up to 12 elutions of 160μl were collected. The fluorescence of the tubulin-containing fractions was detected on a spectrophotometer which excites at 485nm and emits at 535nm. Control incubations were also performed, 8μl DMSO (negative control) and 8μl colchicine stock (positive competition control), instead of the 8μl of test compound in the incubation mixture.

The degree of competition of colchicine binding by either unlabelled colchicine or test compound was calculated relative to the DMSO negative control.

(ii) HUVEC detachment assay

Compounds according to the invention are expected to be able to damage vasculature, such as tumour vasculature, that has been newly formed whilst leaving normal, mature vasculature unaffected. The identification of compounds which can selectively, and preferably potently, damage newly-formed vasculature is desirable and is the subject of the

present invention. The ability of the compounds to act in this way may be assessed, for example, using the procedure set out below:

This assay examined the effects of compounds on the adherence of HUVECs (Human umbilical cord vein endothelial cells) to tissue culture plasticware.

HUVECs (supplied by TCS Biologicals Ltd, Buckingham, United Kingdom) were plated in 0.2% gelatin-coated 12 well tissue culture plates at a concentration of $3x10^4$ cells per well in 1ml TCS medium. After 24 hours, when the cells were at ~30% confluency, they were dosed with a compound under test for 40 minutes at 37°C, 5% CO_2. After this incubation the medium containing drug was pipetted off, and the cells were then gently washed in 2mls of HBSS (Hanks' Balanced Salt Solution purchased from Life Technologies Ltd, Paisley UK; Catalogue # 24020-083) to remove any detached cells. The washing solution was then removed, and the adherent cells remaining were trypsinised using 300µl of 1x Trypsin-EDTA solution (Life Technologies Ltd, Paisley, UK; Catalogue # 43500-019) at ambient temperature for 2 minutes. The trypsinised cells were then made up to 1ml with TCS Biologicals medium, then centrifuged at 2000rpm for 2 minutes. The cell pellet was then resuspended in a volume of 50µl of TCS Biologicals medium. Total cell counts were obtained by counting the cells on a haemocytometer. The amount of cell detachment was calculated by comparing the number of cells remaining attached following treatment with the number in undosed control wells.

Although the pharmacological properties of the compounds of the Formula (I) vary with structural change as expected, in general compounds of the Formula (I) possess an activity in the colchicine binding site competitive assay of greater than 20% competition at a dose of compound of 10µM and an activity in the HUVEC detachment assay of between 15-70% detachment at a dose of compound of 100µM. For example 5-(4-hydroxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile (Example 2) has an activity of 36% in the colchicine binding site competitive assay at 10µM and 55% in the cell detachment assay at 100µM and 6-methyl-5-fluoro-2-amino-1*H*-indole-3-carbonitrile (Example 8) has an activity of 31% in the colchicine binding site competitive assay at 10µM and 34% in the cell detachment assay at 100µM.

The invention will now be illustrated by the following non-limiting Examples in which, unless otherwise stated:-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral (MS or LCMS) techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) flash chromatography was performed on silica (Merck Keiselgel: Art.9385);

(vii) concentrations of solvent in the elemental analyses are quoted in molar (M);

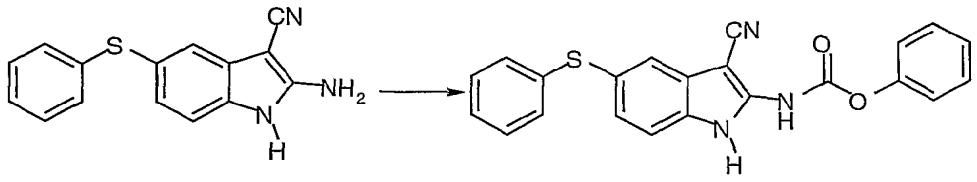
(viii) HP20SS resin (DIAION® HP20SS) was obtained from Mitsubishi Chemical America Inc.

Abbreviations

Dimethylacetamide	DMA
4-Dimethylaminopyridine	DMAP
Dimethylformamide	DMF
Dimethyl sulphoxide	DMSO
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride	EDCI
Liquid chromatographic mass spectroscopy	LCMS
Mass spectroscopy	MS
N-(9-fluorenylmethoxycarbonyl)	N-FMOC
N-methyl-pyrrolidone	NMP
Tetrahydrofuran	THF

Example 1

2-Phenoxycarbonylamino-5-phenylsulphanyl-1*H*-indole-3-carbonitrile



Example 1

A solution of 5-phenylsulphanyl-2-amino-1*H*-indole-3-carbonitrile (0.43 g ; 1.62 mmol) [Amphethinile, US 4,533,672] in THF (5 ml) and pyridine (0.17 ml ; 2.1 mmol) under argon was cooled to 0°C and treated dropwise with phenyl chloroformate (0.25 ml ; 2.0 mmol). The mixture was allowed to warm to room temperature overnight. After dilution with CH_2Cl_2 the organic phase was washed with water, then brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of Et_2O/CH_2Cl_2 (5 to 10% Et_2O) to give 2-phenoxycarbonylamino-5-phenylsulphanyl-1*H*-indole-3-carbonitrile as a beige solid (310 mg).

Yield : 50%

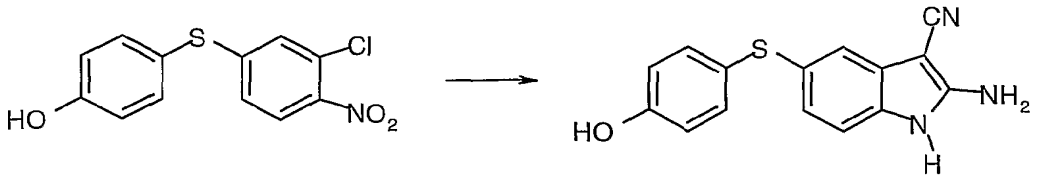
^1H NMR spectrum ($CDCl_3$) : 7.14-7.35 (m, 10H) ; 7.44 (t, 2H) ; 7.71 (d, 1H) ; 10.83 (s, 1H) ; 10.99 (br s, 1H).

MS-ESI : 408 $[MNa]^+$

Elemental analysis :	Found	C 67.14	H 3.94	N 10.76	S 7.79
$C_{22}H_{15}N_3O_2S$; 0.4 H_2O	Requires	C 67.30	H 4.06	N 10.7	S 8.17

Example 2

5-(4-Hydroxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile



Example 2

A stirred solution of 4-(4-hydroxyphenylsulphanyl)-2-chloro-nitrobenzene (42 g ; 150 mmol) and malononitrile (9.9 g ; 150 mmol) in N-methyl-2-pyrrolidinone (150 ml) was

treated dropwise with a 10 M aqueous solution of sodium hydroxide (45 ml ; 450 mmol). The mixture was stirred at room temperature for 50 hours.

The mixture was diluted with DMF (300 ml) and a solution of $NaHCO_3$ (105 g ; 1.25 mol) in water (420 ml) was added. To this solution was added sodium dithionite (74 g ; 0.425 mol) followed by further solid $NaHCO_3$ (105 g) and sodium dithionite (74 g). The resulting suspension was well stirred at room temperature until the purple colouration had disappeared (at least one night). Mineral salts were filtered and the filtrate was poured into water (4 l). The mixture was extracted with EtOAc (2x) and the combined extracts washed well with water, then brine and dried over $MgSO_4$.

The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (60 to 75% EtOAc). The appropriate fractions were evaporated to give 5-(4-hydroxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile as a beige solid (26.2 g).

Yield : 62%.

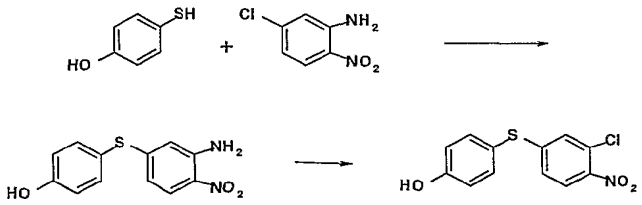
Further flash chromatography of a small sample eluting with increasingly polar mixtures of EtOAc / hexanes (60-70% EtOAc) gave colourless crystals, Melting Point 241-242°C.

^{1}H NMR spectrum (DMSO d_6) : 6.76 (d, 2H) ; 6.85 (s, 2H) ; 6.87 (dd, 1H) ; 6.98 (d, 1H) ; 7.09 (d, 1H) ; 7.2 (d, 2H) ; 9.66 (br s, 1H) ; 10.79 (br s, 1H).

MS-ESI : 282 $[MH]^+$

Elemental analysis :	Found	C 64.22	H 4.19	N 14.84	S 11.11
$C_{15}H_{11}N_3OS$	Requires	C 64.04	H 3.94	N 14.94	S 11.4

4-(4-Hydroxyphenylsulphanyl)-2-chloro-nitrobenzene was prepared as follows:-



4-(4-Hydroxyphenylsulphanyl)-2-amino-nitrobenzene

A solution of 4-hydroxybenzenethiol (46 g ; 328 mmol) in DMA (500 ml) under argon was cooled to 0°C and treated portionwise with NaH (28.9 g ; 722 mmol ; 60 % dispersion in oil). The mixture was stirred at room temperature for 2 hours and then solid 4-chloro-2-

amino-nitrobenzene (56.6 g ; 328 mmol) was added rapidly portionwise. The mixture was stirred and heated at 80°C for 30 minutes and allowed to cool overnight. The mixture was poured into aqueous HCl (2N) and the precipitate was filtered, washed with water, then pentane and dried *in vacuo* to give 4-(4-hydroxyphenylsulphanyl)-2-amino-nitrobenzene as a beige solid (86.6 g).

Yield : 100%

Purification of a small sample by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (40 to 60% EtOAc) gave analytically pure 4-(4-hydroxyphenylsulphanyl)-2-amino-nitrobenzene as a white solid.

^{1}H NMR spectrum (DMSO d_6) : 6.27 (dd, 1H) ; 6.5 (d, 1H) ; 6.92 (d, 2H) ; 7.41 (d, 2H) ; 7.44 (s, 2H) ; 7.86 (d, 1H) ; 10.08 (br s, 1H).

MS-ESI : 262 $[M]^+$

Elemental analysis :	Found	C 54.83	H 3.95	N 10.52	S 11.99
$C_{21}H_{26}NO_8P$; 0.7 H_2O	Requires	C 54.95	H 3.84	N 10.68	S 12.22

4-(4-Hydroxyphenylsulphanyl)-2-chloro-nitrobenzene

4-(4-Hydroxyphenylsulphanyl)-2-amino-nitrobenzene (85.9 g ; 327 mmol) was dissolved in a mixture of AcOH (1.0 l) and concentrated HCl (400 ml) by stirring and warming to 60°C. The cooled solution was added slowly to a mechanically stirred mixture of ice (1.6 kg) and concentrated HCl (400 ml) to obtain a fine suspension which was further stirred overnight. The suspension was cooled to 5°C and a chilled solution of $NaNO_2$ (22.6 g ; 327 mmol) in water (80 ml) was added dropwise, while maintaining the temperature of the mixture between 0°C and 5°C. The mixture was stirred for a further 3 hours and was poured slowly into a solution of CuCl (32.3 g ; 327 mmol) in a mixture of concentrated HCl (160 ml) and water (120 ml) at 35°C. After the addition was complete, the mixture was warmed at 50°C for 1 hour and then allowed to cool.

The solid which separated was filtered and digested in EtOAc (4 l). The organic phase was washed with sat. aqueous $NaHCO_3$, then brine and dried over $MgSO_4$.

The residue (85 g) was purified by flash chromatography eluting with CH_2Cl_2. The appropriate fractions were evaporated to give 4-(4-hydroxyphenylsulphanyl)-2-chloro-nitrobenzene as a yellow solid (45.1 g).

Yield : 49%

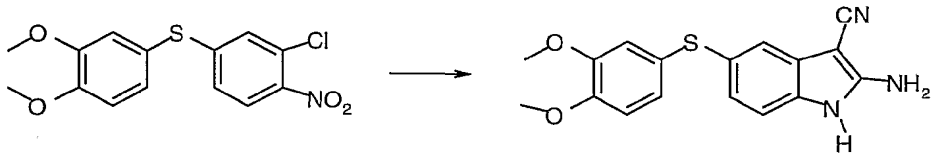
^{1}H NMR spectrum ($CDCl_3$) : 5.18 (s, 1H) ; 6.93 - 6.99 (m, 3H) ; 7.09 (d, 1H) ; 7.44 (d, 2H) ; 7.79 (d, 1H).

MS-ESI : 280 $[M-H]^-$

Elemental analysis :	Found	C 51.1	H 2.85	N 5.03	S 11.16
$C_{12}H_8ClNO_3S$	Requires	C 51.16	H 2.86	N 4.97	S 11.38

Example 3

5-(3,4-Dimethoxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile



Example 3

Using the general method described for Example 2, except that two equivalents of aqueous NaOH were employed, 5-(3,4-dimethoxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile was obtained from 4-(3,4-dimethoxyphenylsulphanyl)-2-chloro-nitrobenzene (1.7 g; 5.2 mmol) after purification by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (50 to 60% EtOAc). The product was a beige solid (745 mg), Melting Point 169-173°C.

Yield : 44%

^{1}H NMR spectrum (DMSO d_6) : 3.71 (s, 3H) ; 3.75 (s, 3H) ; 6.82 (dd, 1H) ; 6.88 (s, 2H) ; 6.93 (m, 3H) ; 7.08 (d, 1H) ; 7.12 (d, 1H) ; 10.85 (br s, 1H).

MS-ESI : 325 $[M]^+$

4-(3,4-Dimethoxyphenylsulphanyl)-2-chloro-nitrobenzene was prepared using the general method described for 4-(4-hydroxyphenylsulphanyl)-2-chloro-nitrobenzene in Example 2, except that one equivalent of NaH was used in the first step.

4-(3,4-Dimethoxyphenylsulphanyl)-2-amino-nitrobenzene

In the first step 4-(3,4-dimethoxyphenylsulphanyl)-2-amino-nitrobenzene was prepared (15.45 g):

Yield : 100%

^{1}H NMR spectrum (DMSO d_6) : 3.78 (s, 3H) ; 3.82 (s, 3H) ; 6.31 (dd, 1H) ; 6.54 (d, 1H) ; 7.08 - 7.41 (m, 3H) ; 7.45 (s, 2H) ; 7.86 (d, 1H).

MS-ESI : 306 $[M]^+$

Elemental analysis :	Found	C 54.57	H 4.59	N 9.15	S 9.87
$C_{14}H_{14}N_2O_4S$	Requires	C 54.89	H 4.61	N 9.14	S 10.47

4-(3,4-Dimethoxyphenylsulphanyl)-2-chloro-nitrobenzene

In the second step 4-(3,4-dimethoxyphenylsulphanyl)-2-chloro-nitrobenzene was prepared (2.27 g):

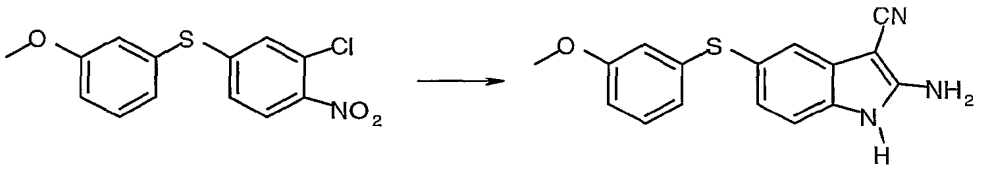
Yield : 56%

^{1}H NMR spectrum ($CDCl_3$) : 3.89 (s, 3H) ; 3.95 (s, 3H) ; 6.85 - 6.99 (m, 2H) ; 7.02 (d, 1H) ; 7.11 (d, 1H) ; 7.17 (dd, 2H) ; 7.79 (d, 1H).

Elemental analysis :	Found	C 51.45	H 3.78	N 4.38	S 9.77
$C_{14}H_{12}ClNO_4S$	Requires	C 51.62	H 3.71	N 4.3	S 9.84

Example 4

5-(3-Methoxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile



Example 4

This compound was prepared by the use of a Zymate (trade mark) Laboratory Automation System XP2 Robot (Zymark Corp.).

Thus, 4-(3-methoxyphenylsulphanyl)-2-chloro-nitrobenzene (2.45 g ; 8.28 mmol) was introduced into a robot tube. A solution of malononitrile (2M, 8.3 mmol) in N-methyl-2-pyrrolidinone was pumped into the tube and the mixture vortexed. Aqueous sodium hydroxide (10M, 16.6 mmol) was pumped in and the mixture was then vortexed and stirred for 3 days at room temperature. The contents of the tube were divided equally into a further five tubes. To each was added DMF (3 ml), water (4 ml), $NaHCO_3$ (1 g), sodium dithionate (700 mg) followed by further $NaHCO_3$ (1 g) and sodium dithionate (700 mg) with vortexing between each addition. The mixture was stirred overnight at room temperature.

Each tube was diluted with water (4 ml) and extracted with EtOAc (2x 7 ml). The organic phase was evaporated, the residues were combined in CH_2Cl_2, treated SiO_2 (5 g) and evaporated to dryness. The residue was purified by flash chromatography eluting automatically with CH_2Cl_2 and then EtOAc/CH_2Cl_2 (50/50). The appropriate fractions were evaporated, triturated with EtOAc/hexanes, filtered, rinsed and dried to give 5-(3-methoxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile as a cream solid (473 mg).

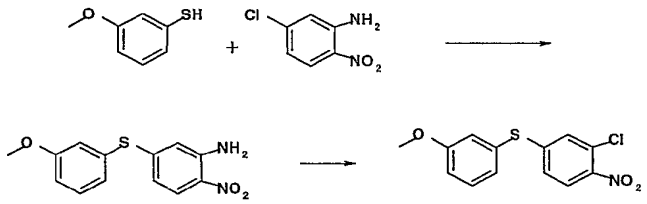
Yield : 19%

^{1}H NMR spectrum (DMSO d_6) : 3.68 (s, 3H) ; 6.62 - 6.66 (m, 2H) ; 6.73 (dd, 1H) ; 6.95 (s, 2H) ; 7.05 (dd, 1H) ; 7.15 - 7.2 (m, 3H) ; 10.93 (br s, 1H).

MS-ESI : 296 $[M]^+$

All samples prepared by the Robot contained small quantities of DMF and N-methyl-2-pyrrolidinone and were not analysed for elemental composition.

The starting material was prepared as follows:-



Using the general method described in Example 2, except that one equivalent of NaH was used in the first step, 3-methoxybenzenethiol (2.1 g ; 15 mmol) was used to prepare:

4-(3-Methoxyphenylsulphanyl)-2-amino-nitrobenzene (4.0 g):

Yield : 97%

^{1}H NMR spectrum ($CDCl_3$) : 3.82 (s, 3H) ; 6.03 (br s, 2H) ; 6.39 (d, 1H) ; 6.45 (dd, 1H) ; 6.98 (dt, 1H) ; 7.06 (t, 1H) ; 7.13 (dt, 1H) ; 7.35 (t, 1H) ; 7.98 (d, 1H).

MS-ESI : 277 $[MH]^+$

And then:

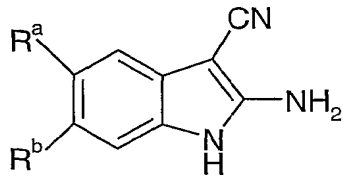
4-(3-Methoxyphenylsulphanyl)-2-chloro-nitrobenzene (2.27 g):

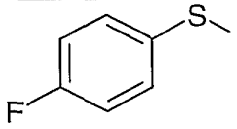
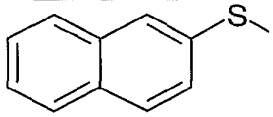
Yield : 53%

^{1}H NMR spectrum ($CDCl_3$) : 3.85 (s, 3H) ; 7.03 (dd, 1H) ; 7.07 - 7.1 (m, 2H) ; 7.14 (dd, 1H) ; 7.23 (d, 1H) ; 7.39 (t, 1H) ; 7.82 (d, 1H).

Examples 5-8

The examples in the following table were prepared using the Zymate (trade mark) Robot as described in Example 4, from the corresponding substituted 2-chloro-nitrobenzene.



Example	R^a	R^b	Footnote
5		H	a
6		H	b
7	H	F	c
8	F	CH_3-	d

Footnotes

a) Starting material: 4-(4-fluorophenylsulphanyl)-2-chloro-nitrobenzene 2.3 g8.11 mmol
Yield: 289 mg 13%
^{1}H NMR spectrum (DMSO d_6) : 6.94 (s, 2H) ; 7.03 (dd, 1H) ; 7.12 - 7.23 (m, 6H) ; 10.91 (br s, 1H).
MS-ESI : 284 $[MH]^+$

b) Starting material: 4-(2-naphthylsulphanyl)-2-chloro-nitrobenzene 1.7 g 5.4 mmol
Yield: 366 mg 21%
^{1}H NMR spectrum (DMSO d_6) : 6.95 (s, 2H) ; 7.08 (dd, 1H) ; 7.2 - 7.27 (m, 3H) ; 7.47 (m, 2H) ; 7.65 (s, 1H) ; 7.76 (d, 1H) ; 7.84 (t, 2H) ; 10.94 (br s, 1H).
MS-ESI : 314 $[M-H]^-$

c) Starting material: 5-fluoro-2-chloro-nitrobenzene 1.75 g 9.97 mmol
Yield: 18 mg 1%
^{1}H NMR spectrum (DMSO d_6) : 6.78 (s, 2H) ; 6.79 (ddd, 1H) ; 6.96 (dd, 1H) 7.07 (dd, 1H) ; 10.76 (br s, 1H).

MS-ESI : 175 $[M]^+$

d) Starting material: 4-fluoro-5-methyl-2-chloro-nitrobenzene 1.89 g 9.97 mmol

Yield: 53 mg 3%

^{1}H NMR spectrum (DMSO d_6) : 6.74 (s, 2H) ; 6.81 (d, 1H) ; 6.96 (d, 1H) ; 10.62 (br s, 1H).

MS-ESI : 188 $[M-H]^-$

Starting Materials – Example 5

Starting material 4-(4-fluorophenylsulphanyl)-2-chloro-nitrobenzene was prepared as described in Example 4.

4-(4-Fluorophenylsulphanyl)-2-amino-nitrobenzene:

Starting material: 4-fluorobenzenethiol 1.92 g 15 mmol

Yield: 3.69 g 93%

^{1}H NMR spectrum ($CDCl_3$) : 6.03 (br s, 2H) ; 6.31 (d, 1H) ; 6.38 (dd, 1H) ; 7.15 (t, 2H) ; 7.54 (dd, 2H) ; 7.98 (d, 1H).

MS-ESI : 265 $[MH]^+$.

4-(4-Fluorophenylsulphanyl)-2-chloro-nitrobenzene:

Yield: 1.72 g 44%

^{1}H NMR spectrum (DMSO d_6) : 7.0 (dd, 1H) ; 7.13 - 7.2 (m, 3H) ; 7.55 (m, 2H) ; 7.81 (d, 1H).

MS-EI : 283 $[M]^+$

Starting Materials – Example 6

Starting material 4-(2-naphthylsulphanyl)-2-chloro-nitrobenzene was prepared as described in Example 4.

4-(2-Naphthylsulphanyl)-2-amino-nitrobenzene:

Starting material: naphthalene-2-thiol 2.4 g 15 mmol

Yield: 4.45 g 100%

^{1}H NMR spectrum (DMSO d_6) : 6.40 (dd, 1H) ; 6.66 (s, 1H) ; 7.43 (br s, 2H) ; 7.54 (dd, 1H) ; 7.63 (m, 2H) ; 7.89 (d, 1H) ; 8.03 (m, 3H) ; 8.24 (s, 1H).

MS-ESI : 295 $[M-H]^-$

4-(2-Naphthylsulphanyl)-2-chloro-nitrobenzene:

Yield: 1.75 g 37%

^{1}H NMR spectrum ($CDCl_3$) : 7.07 (dd, 1H) ; 7.23 (d, 1H) ; 7.5 (dd, 1H) ; 7.59 (m, 2H) ; 7.79 (d, 1H) ; 7.83 - 7.93 (m, 3H) ; 8.1 (s, 1H).

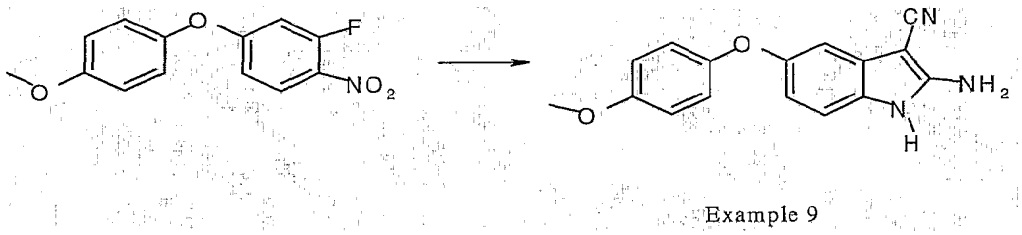
MS-EI : 315 $[M]^+$

Starting Materials – Examples 7 and 8

Starting materials 5-fluoro-2-chloro-nitrobenzene and 5-methyl-4-fluoro-2-chloro-nitrobenzene are commercially available.

Example 9

5-(4-Methoxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile



Example 9

Using the general method described for Example 2, Example 9 was prepared from a 1:2 mixture of 4-(4-methoxyphenoxy)-2-fluoro-nitrobenzene (**a**) and its isomer 2-(4-methoxyphenoxy)-4-fluoro-nitrobenzene was used (**b**) (see below) (5.97 g ; 22.7 mmol), except that two equivalents of aqueous NaOH were employed, after purification by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (40 to 100% EtOAc), 5-(4-methoxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile was obtained as a light beige solid (1.32 g), Melting Point 216-217°C.

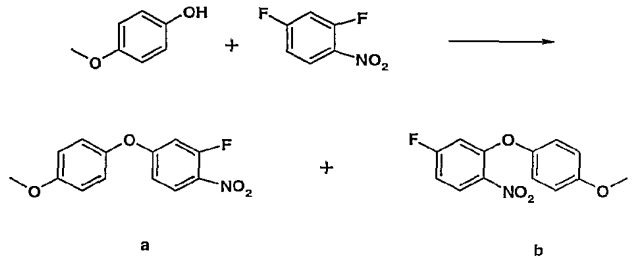
Yield : 21%

^{1}H NMR spectrum (DMSO d_6) : 3.75 (s, 3H) ; 6.58 (dd, 1H) ; 6.63 (d, 1H) ; 6.80 (s, 2H) ; 6.93 (s, 4H) ; 7.09 (d, 1H) ; 10.69 (br s, 1H).

MS-ESI : 278 $[M-H]^-$

Elemental analysis :	Found	C 65.78	H 4.52	N 14.68
$C_{16}H_{13}N_3O_2$; 0.7 H_2O	Requires	C 65.83	H 4.97	N 14.39

The 1:2 mixture of 4-(4-methoxyphenoxy)-2-fluoronitrobenzene (**a**) and its isomer 2-(4-methoxyphenoxy)-4-fluoronitrobenzene (**b**) was prepared as follows:-



a b

A solution of 4-methoxyphenol (3.75 g ; 30 mmol) in DMA (40 ml) under argon was cooled to 0°C and treated portionwise with NaH (1.35 g ; 33 mmol ; 60 % dispersion in oil). The mixture was stirred at room temperature for 1 hour. This mixture was added dropwise to a solution of 2,4-difluoro-nitrobenzene(3.3 ml ; 30 mmol) in DMA (10 ml) over 1 hour. The mixture was allowed to stir overnight and was then poured into aqueous HCl (10 %) and extracted with Et_2O (3x). The organic phase was washed with water, then brine, and dried over $MgSO_4$.

The residue (9.14 g) was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (0 to 20% EtOAc). The appropriate fractions were evaporated to give a mixture of 4-(4-methoxyphenoxy)-2-fluoronitrobenzene (**a**) and its isomer 2-(4-methoxyphenoxy)-4-fluoronitrobenzene (**b**) (5.97 g ; 1:2 as determined by ^1H NMR).

Yield : 76%

^1H NMR spectrum ($CDCl_3$) : 3.83 (s, 3H, **b**) ; 3.84 (s, 3H, **a**) ; 6.56 (dd, 1H, **b**) ; 6.71 (dd, 1H, **a**) ; 6.76-6.82 (m, 1H, **b** and 1H, **a**) ; 6.94-6.97 (m, 2H, **b** and 2H, **a**) ; 7.02-7.06 (m, 2H, **b** and 2H, **a**) ; 8.02 (dd, 1H, **b**); 8.07 (dd, 1H, **a**).

Example 10

5-(3,6-Dimethoxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile

Example 10

5-(3,6-Dimethoxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile (1.22 g) was prepared using the general method described in Example 2, except that two equivalents of aqueous NaOH were employed, it was obtained as a white solid from 4-(3,6-dimethoxyphenylsulphanyl)-2-chloro-nitrobenzene (2.1 g ; 6.45 mmol) after purification by flash chromatography eluting with increasingly polar mixtures of CH_2Cl_2/EtOAc (0 to 50% EtOAc).

Yield : 58%

^{1}H NMR spectrum (DMSO d_6) : 3.54 (s, 3H) ; 3.80 (s, 3H) ; 6.08 (d, 1H) ; 6.68 (dd, 1H) ; 6.93 (d, 1H) ; 6.98 (s, 2H) ; 7.05 (dd, 1H) ; 7.20 (d, 1H) ; 7.24 (d, 1H) ; 10.98 (br s, 1H).

LCMS-ESI : 326 $[M+H]^+$

Elemental analysis :	Found	C 61.8	H 5.07	N 12.1	S 8.78
$C_{17}H_{15}N_3O_2S$; 0.35 EtOAc	Requires	C 62.04	H 5.04	N 11.8	S 9.0

4-(3,6-Dimethoxyphenylsulphanyl)-2-amino-nitrobenzene

Using the general method described for 4-(4-hydroxyphenylsulphanyl)–2-amino-nitrobenzene in Example 2, except that one equivalent of NaH was used, 4-(3,6-dimethoxyphenylsulphanyl)-2-amino-nitrobenzene (4.19g) was prepared from 3,6-dimethoxybenzenethiol (2.55 g ; 15 mmol).

Yield : 91%

^{1}H NMR spectrum ($CDCl_3$) : 3.78 (s, 3H) ; 3.79 (s, 3H) ; 6.02 (s, 2H) ; 6.37 (d, 1H) ; 6.41 (dd, 1H) ; 6.90 - 7.07 (m, 3H) ; 7.96 (d, 1H).

MS-ESI : 307 $[M+H]^+$

4-(3,6-dimethoxyphenylsulphanyl)-2-chloro-nitrobenzene

Similarly, using the general method described for 4-(4-hydroxyphenylsulphanyl)–2-chloro-nitrobenzene in Example 2, 4-(3,6-dimethoxyphenylsulphanyl)-2-chloro-nitrobenzene

(2.22 g) was prepared from 4-(3,6-dimethoxyphenylsulphanyl)-2-amino-nitrobenzene (4.15 g; 15 mmol) after purification by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (10 to 20% EtOAc).

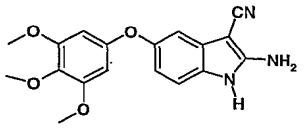
Yield : 50%

^{1}H NMR spectrum ($CDCl_3$) : 3.78 (s, 3H) ; 3.79 (s, 3H) ; 6.96 (d, 1H) ; 7.02 (m, 2H) ; 7.08 (d, 1H) ; 7.15 (d, 2H) ; 7.79 (d, 1H).

MS-ESI : 326 $[M]^+$

Example 11

5-(3,4,5-Trimethoxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile



Example 11

5-(3,4,5-Trimethoxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile (1.49 g) was prepared using the general method described in Example 2, except that two equivalents of aqueous NaOH were employed, it was obtained as a beige solid, melting point 208-209°C, from a 1:2 mixture of 4-(3,4,5-trimethoxyphenoxy)-2-fluoro-nitrobenzene (**c**) and its isomer 2-(3,4,5-trimethoxyphenoxy)-4-fluoro-nitrobenzene (**d**) (8.01 g ; 25 mmol; present in a 1:2 mixture of isomers) after purification by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (40 to 100% EtOAc).

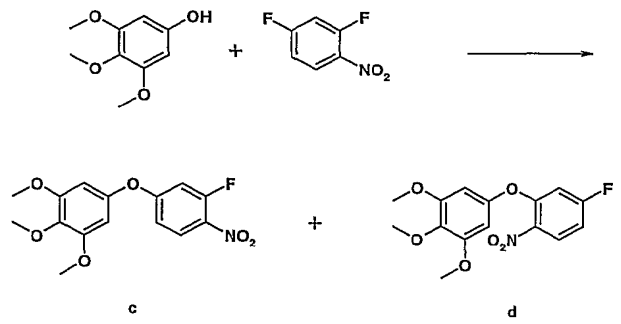
Yield : 18%

^{1}H NMR spectrum (DMSO d_6) : 3.64 (s, 3H) ; 3.70 (s, 6H) ; 6.28 (s, 2H) ; 6.64 (dd, 1H) ; 6.74 (s, 1H) ; 6.83 (s, 2H) ; 7.13 (d, 1H) ; 10.72 (br s, 1H).

LCMS-ESI : 340 $[M+H]^+$

Elemental analysis :	Found	C 62.66	H 5.12	N 12.22
$C_{18}H_{17}N_3O_4$; 0.3 H_2O	Requires	C 62.71	H 5.15	N 12.19

The starting material was prepared as follows:-



c d

Using the general method described in Example 9, a mixture of 4-(3,4,5-trimethoxyphenoxy)-2-fluoro-nitrobenzene (**c**) and its isomer 2-(3,4,5-trimethoxyphenoxy)-4-fluoro-nitrobenzene (**d**) (8.01 g ; proportions of b/bi 1:2 as determined by ^{1}H NMR) was obtained from 3,4,5-trimethoxyphenol (5.52 g ; 30 mmol) after purification by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (0 to 50% EtOAc).

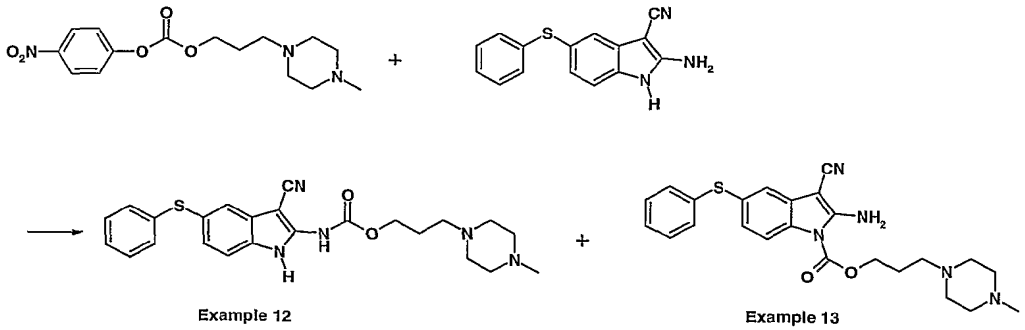
Yield : 83%

^{1}H NMR spectrum ($CDCl_3$) : 3.8 - 3.84 (m, 9H, **c** and 9H, **d**) ; 6.31 (s, 2H, **c**) ; 6.33 (s, 2H, **d**) ; 6.63 (dd, 1H, **d**) ; 6.75 (dd, 1H, **c**) ; 6.77 - 6.84 (m, 1H, **c** and 1H, **d**) ; 7.99 - 8.09 (m, 1H, **c** and 1H, **d**).

Examples 12 and Example 13

5-Phenylsulphanyl-2-(4-methylpiperazin-1-ylpropoxycarbonylamino)-1*H*-indole-3-carbonitrile, and

5-Phenylsulphanyl-1-(4-methylpiperazin-1-ylpropoxycarbonyl)-2-amino-1*H*-indole-3-carbonitrile respectively



Example 12 Example 13

A solution of 5-phenylsulphanyl-2-amino-1*H*-indole-3-carbonitrile (265 mg ; 1.0 mmol) in DMF (40 ml) under argon at room temperature was treated portionwise with NaH (200 g ; 5 mmol ; 60 % dispersion in oil). The mixture was stirred at room temperature for 30 minutes and 3-(4-methylpiperazin-1-yl)propyl 4-nitrophenyl carbonate (627 mg ; 1.5 mmol) was added

portionwise. The mixture was stirred for 1 hour, poured into water and extracted with EtOAc. The organic phase was washed with H_2O, brine and dried over $MgSO_4$. The residue was triturated with Et_2O to give5-phenylsulphanyl-1-(4-methylpiperazin-1-ylpropoxycarbonyl)-2-amino-1*H*-indole-3-carbonitrile as a beige solid (162 mg).

Yield : 36%

^{1}H NMR spectrum (DMSO d_6) : 1.95 (t, 2H) ; 2.05 (s, 3H) ; 2.05 - 2.55 (m, 10H) ; 4.52 (t, 2H) ; 7.11 (m, 2H) ; 7.26 (m, 3H) ; 7.34 (m, 2H) ; 7.82 (d, 1H) ; 7.89 (s, 2H).

LCMS-ESI : 450 $[M+H]^+$

Elemental analysis :	Found	C 53.93	H 5.48	N 13.10	S 5.55
$C_{24}H_{27}N_5O_2S$ 2.35 HCl	Requires	C 53.86	H 5.53	N 13.08	S 5.99

The filtrate was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (10 % MeOH) and the appropriate fractions were evaporated to give 5-phenylsulphanyl-2-(4-methylpiperazin-1-ylpropoxycarbonylamino)-1*H*-indole-3-carbonitrile (40 mg).

Yield : 9%

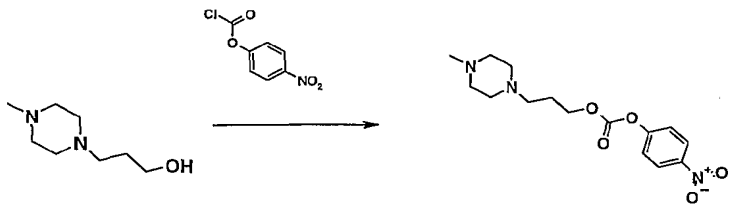
^{1}H NMR spectrum (DMSO d_6) : 1.81 (t, 2H) ; 2.15 (s, 3H) ; 2.2 - 2.25 (m, 10H) ; 4.21 (t, 2H) ; 7.16 - 7.25 (m, 4H) ; 7.3 (m, 2H) ; 7.46 (d, 1H) ; 7.55 (d, 1H) ; 11.2 (br s, 1H) ; 12.1 (br s, 1H).

LCMS-ESI : 450 $[M+H]^+$.

Elemental analysis :	Found	C 62.04	H 5.99	N 14.30	S 5.98
$C_{24}H_{27}N_5O_2S$; 0.4 HCl 0.2 EtOAc	Requires	C 61.83	H 6.07	N 14.54	S 6.66

3-(4-Methylpiperazin-1-yl)-propyl-4-nitrophenyl carbonate

This starting material was prepared as follows :



4-Nitrophenyl chloroformate (636 mg ; 3.16 mmol) was added to a solution of 3-(4-methylpiperazin-1-yl) propanol [Synthesis (1997), 6, 643-648] (500 mg ; 3.16 mmol) and triethylamine (440 ul ; 3.16 mmol) in dichloromethane (20 ml) under argon atmosphere at

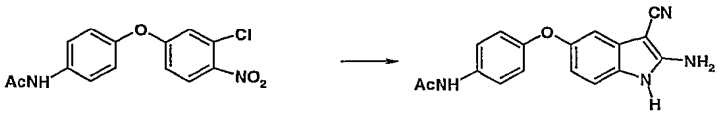
0°C. The mixture was stirred at ambient temperature for 3 hours, evaporated to dryness and triturated with Et_2O/aq. HCl (2N). The precipitate was filtered, washed with Et_2O and dried to give the dihydrochloride of 3-(4-methylpiperazin-1-yl)-propyl 4-nitrophenyl carbonate (1.22g).

Yield : 98 %.

^{1}H NMR (DMSO d_6) : 2.16 (m, 2H) ; 2.81 (s, 3H) ; 3.1-3.8 (m, 10H) ; 4.33 (t, 2H) ; 7.57 (d, 2H) ; 8.31 (d, 2H).

Example 14

5-(4-Acetylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile



Example 14

5-(4-Acetylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile (4.82 g) was prepared using the general method described in Example 2, except that two equivalents of aqueous NaOH were employed, it was obtained as a beige solid from 4-(4-acetylaminophenoxy)-2-chloro-nitrobenzene (6.13 g ; 20 mmol) after purification by trituration with a mixture of EtOAc/CH_2Cl_2.

Yield : 79%

^{1}H NMR spectrum (DMSO d_6) : 2.02 (s, 3H) ; 6.59 (dd, 1H) ; 6.66 (d, 1H) ; 6.79 (s, 2H) ; 6.89 (d, 2H) ; 7.10 (d, 1H) ; 7.53 (d, 2H) ; 9.88 (s, 1H) ; 10.69 (br s, 1H).

LCMS-ESI : 307 $[M+H]^+$

Elemental analysis :	Found	C 66.39	H 4.77	N 17.67
$C_{17}H_{14}N_4O_2$ 0.1 EtOAc	Requires	C 66.32	H 4.73	N 17.78

The starting material was prepared as follows:-

4-(4-Acetylaminophenoxy)-2-amino-nitrobenzene

4-(4-Acetylaminophenoxy)-2-amino-nitrobenzene (46.57g) was prepared from 4-acetylaminophenol (30.2 g ; 0.2 mol) using the general method described for

4-(4-hydroxyphenylsulphanyl)-2-amino-nitrobenzene in Example 2, except that one equivalent of NaH was used.

Yield : 81%

^{1}H NMR spectrum (DMSO d_6) : 2.07 (s, 3H) ; 6.3 (m, 2H) ; 7.12 (d, 2H) ; 7.48 (s, 2H) ; 7.68 (d, 2H) ; 8.01 (d, 1H) ; 10.06 (s, 1H).

4-(4-Acetylaminophenoxy)-2-chloro-nitrobenzene

Similarly, using the general method described for 4-(4-hydroxyphenylsulphanyl)-2-chloro-nitrobenzene in Example 2, 4-(4-acetylaminophenoxy)-2-chloro-nitrobenzene (11.05 g) was prepared from 4-(4-acetylaminophenoxy)-2-amino-nitrobenzene (14.35 g ; 0.5 mol) after purification by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (60 to 100% EtOAc).

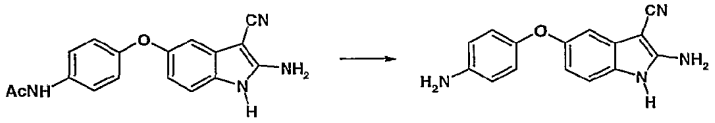
Yield : 72%

^{1}H NMR spectrum (DMSO d_6) : 2.07 (s, 3H) ; 7.05 (dd, 1H) ; 7.17 (d, 2H) ; 7.27 (d, 1H) ; 7.70 (d, 2H) ; 8.14 (d, 1H) ; 10.09 (s, 1H).

LCMS-ESI : 307 $[M+H]^+$

Example 15

5-(4-Aminophenoxy)-2-amino-1*H*-indole-3-carbonitrile



Example 15

A suspension of 5-(4-acetylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile (Example 14)(306 mg ; 1 mmol) in MeOH (10 ml) was treated with water (2 ml) and conc. HCl (1 ml) and the mixture heated under reflux for 30 hours. After cooling the mixture was poured into sat. aqueous $NaHCO_3$ and extracted with EtOAc. The organic phase was washed with brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (80 to 100% EtOAc) to give 5-(4-aminophenoxy)-2-amino-1*H*-indole-3-carbonitrile as a pale beige solid (251 mg).

Yield : 95%

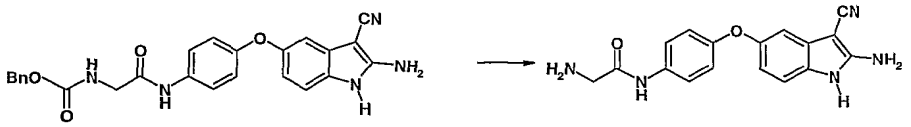
^{1}H NMR spectrum (DMSO d_6) : 4.89 (s, 2H) ; 6.55 (m, 4H) ; 6.73 (m, 4H) ; 7.06 (d, 1H) ; 10.61 (br s, 1H).

LCMS-ESI : 265 $[M+H]^+$

Elemental analysis :	Found	C 67.40	H 4.72	N 20.38
$C_{15}H_{12}N_4O$; 0.1 H_2O 0.1 EtOAc	Requires	C 67.29	H 4.77	N 20.38

Example 16

5-(4-Glycylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile



Example 16

A solution of 5-[4-({N-benzyoxycarbonylglycyl}amino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile (368 mg ; 0.8 mmol) in EtOAc (10 ml) and MeOH (10 ml) was hydrogenated over Pd/C (100 mg) at 1 Atmosphere at room temperature for 1 hour. After filtration and evaporation to dryness, the residue was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (10 % MeOH) and the appropriate fractions were evaporated to give 5-(4-glycylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile (163 mg).

Yield : 63%

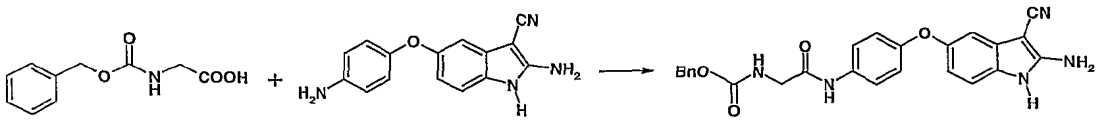
^{1}H NMR spectrum (DMSO d_6) : 2.03 (s, 2H) ; 3.24 (m, 2H) ; 6.59 (dd, 1H) ; 6.66 (d, 1H) ; 6.79 (s, 2H) ; 6.91 (d, 2H) ; 7.10 (d, 1H) ; 7.59 (d, 2H) ; 9.72 (br s, 1H) ; 10.69 (br s, 1H).

LCMS-ESI : 322 $[M+H]^+$

Elemental analysis :	Found	C 62.29	H 5.03	N 20.83
$C_{17}H_{15}N_5O_2$; 0.2 H_2O 0.2 MeOH	Requires	C 62.35	H 4.93	N 21.14

5-[4-({N-Benzyoxycarbonylglycyl}amino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile

This was prepared as follows:-



A solution of carbobenzyloxyglycine (480 mg ; 2.26 mmol) and 5-(4-aminophenoxy)-2-amino-1*H*-indole-3-carbonitrile (Example 15) (300 mg ; 1.13 mmol) in CH_2Cl_2 (10 ml) was treated at room temperature with EDCI (546 mg ; 2.8 mmol) and a catalytic quantity of DMAP (20 mg). The mixture was stirred for 1 hour and was directly purified by flash

chromatography eluting with CH_2Cl_2/EtOAc (50/50). The appropriate fractions were evaporated to give 5-[4-({N-benzyoxycarbonylglycyl}amino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile as a white solid (425 mg).

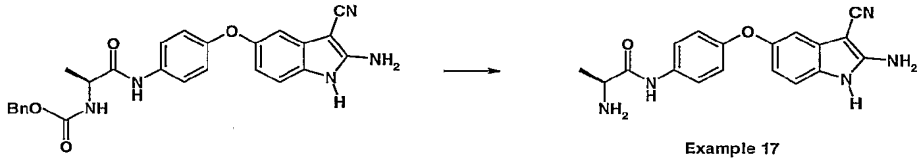
Yield : 83%

^{1}H NMR spectrum (DMSO d_6) : 3.79 (d, 2H) ; 5.05 (s, 2H) ; 6.59 (dd, 1H) ; 6.67 (d, 1H) ; 6.80 (s, 2H) ; 6.91 (d, 2H) ; 7.10 (d, 1H) ; 7.2 - 7.45 (m, 5H) ; 7.5 - 7.6 (m, 3H) ; 9.92 (s, 1H); 10.69 (s, 1H).

LCMS-ESI : 454 $[M-H]^-$

Example 17

5-(4-Alanylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile



Example 17

Using the general method of hydrogenolysis described in Example 16, 5-(4-alanylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile (213 mg) was obtained as a white solid from 5-[4-({N-benzyloxycarbonylalanyl}amino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile (514 mg ; 1.1 mmol) after purification by flash chromatography eluting with MeOH/CH_2Cl_2 (10 % MeOH).

Yield : 58%

^{1}H NMR spectrum (DMSO d_6) : 1.20 (d, 3H) ; 1.98 (m, 2H) ; 3.40 (q, 1H) ; 6.59 (dd, 1H) ; 6.65 (d, 1H) ; 6.80 (s, 2H) ; 6.90 (m, 2H) ; 7.09 (d, 1H) ; 7.59 (m, 2H) ; 9.7 (br s, 1H) ; 10.6 (br s, 1H).

LCMS-ESI : 336 $[M+H]^+$

Elemental analysis :	Found	C 63.79	H 5.21	N 20.52
$C_{18}H_{17}N_5O_2$; 0.1 H_2O 0.1 MeOH	Requires	C 63.87	H 5.21	N 20.58

5-[4-({N-Benzyloxycarbonylalanyl}amino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile

This was prepared using the general coupling method described in Example 16, 5-[4-({N-benzyloxycarbonylalanyl}amino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile (514 mg) was obtained as a white solid from 5-(4-aminophenoxy)-2-amino-1*H*-indole-3-

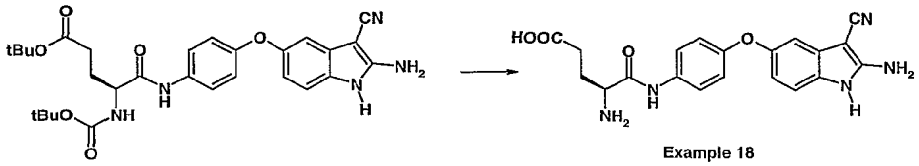
carbonitrile (Example 15)(400 mg ; 1.51 mmol) after purification by flash chromatography eluting with EtOAc/CH_2Cl_2 (50/50).

Yield : 72%

^{1}H NMR spectrum (DMSO d_6) : 1.29 (d, 3H) ; 4.18 (m, 1H) ; 5.03 (d, 2H) ; 6.58 (dd, 1H) ; 6.67 (d, 1H) ; 6.80 (s, 2H) ; 6.91 (d, 2H) ; 7.10 (d, 1H) ; 7.25 - 7.45 (m, 5H) ; 7.5 - 7.6 (m, 3H) ; 9.94 (s, 1H) ; 10.71 (s, 1H).

Example 18

5-(4-α-Glutamylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile



A suspension of a tertiary butoxycarbonyl protected derivative of 5-(4-α-glutamylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile (1.21 g ; 2.2 mmol) in CH_2Cl_2 (100 ml) was treated with a rapid stream of gaseous HCl for 2 hours at room temperature. The mixture was evaporated to dryness, taken up in water, filtered and the filtrate freeze-dried to give the hydrochloride salt of 5-(4-α-glutamylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile as a white powder (975 mg).

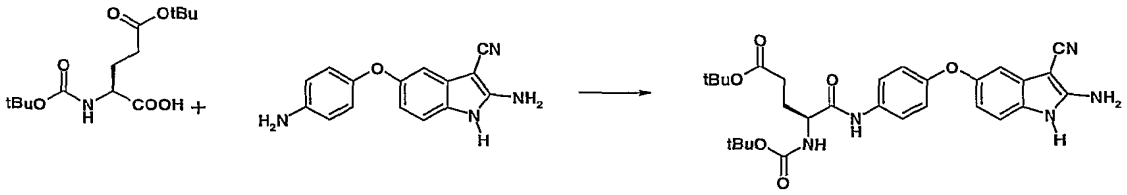
Yield : 100%

^{1}H NMR spectrum (DMSO d_6) : 2.0 - 2.15 (m, 2H) ; 2.40 (m, 2H) ; 3.8 (br s, 1H) ; 4.04 (m, 1H) ; 6.60 (dd, 1H) ; 6.69 (d, 1H) ; 6.75 (br s, 1H) ; 6.95 (d, 2H) ; 7.12 (d, 1H) ; 7.59 (d, 2H) ; 8.43 (m, 3H) ; 10.79 (br s, 1H) ; 10.81 (br s, 1H) 12.2 (br s, 1H).

LCMS-ESI : 394 $[M+H]^+$

Elemental analysis :	Found	C 52.88	H 4.83	N 15.06	Cl 8.97
$C_{17}H_{15}N_3O_2S$; 1.0 H_2O 1.15 HCl	Requires	C 52.97	H 4.93	N 15.44	Cl 8.99

The tertiary butoxycarbonyl protected derivative of 5-(4-α-glutamylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile (1.49g) was prepared using the general coupling method described in



Example 16, as a white solid from 5-(4-aminophenoxy)-2-amino-1*H*-indole-3-carbonitrile (Example 15) (800 mg ; 3.00 mmol) after purification by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (70 to 100% EtOAc).

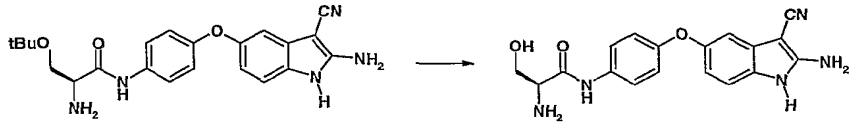
Yield : 91%

^{1}H NMR spectrum (DMSO d_6) : 1.38 (s, 18H) ; 1.80 (m, 1H) ; 1.90 (m, 1H) ; 2.26 (m, 2H); 4.05 (m, 1H) ; 6.59 (dd, 1H) ; 6.68 (d, 1H) ; 6.80 (s, 2H) ; 6.91 (d, 2H) ; 7.01 (d, 1H) ; 7.10 (d, 1H) ; 7.56 (d, 2H) ; 9.91 (s, 1H) ; 10.69 (s, 1H).

MS-ESI : 548 $[M-H]^-$

Example 19

5-(4-Serylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile



Example 19

Using the general method of deprotection described in Example 18, 5-(4-serylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile (554 mg) was obtained as its hydrochloride as a white solid from 5-[4-(O-*t*-butoxycarbonylserylamino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile (800 mg ; 2.0 mmol) after trituration with water, filtration and drying.

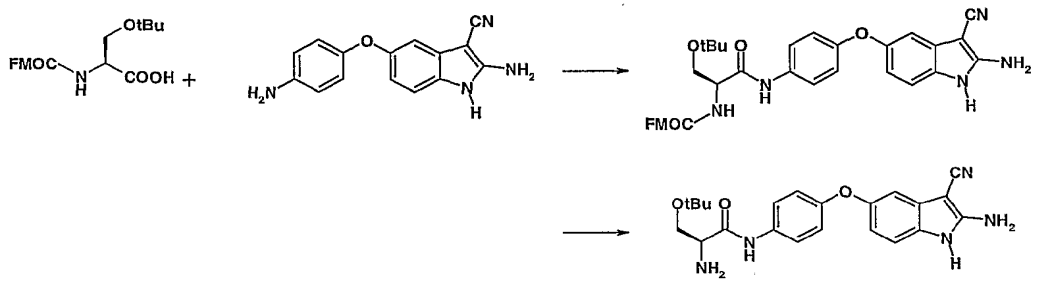
Yield : 73%

^{1}H NMR spectrum (DMSO d_6) : 3.87 (m, 2H) ; 4.03 (m, 1H) ; 5.58 (m, 1H) ; 6.61 (dd, 1H) ; 6.68 (d, 1H) ; 6.85 (s, 2H) ; 6.96 (d, 2H) ; 7.13 (d, 1H) ; 7.62 (d, 2H) ; 8.31 (br s, 3H) ; 10.69 (s, 1H) ; 10.82 (s, 1H).

LCMS-ESI : 352 $[M+H]^+$

Elemental analysis :	Found	C 53.55	H 4.87	N 17.27
$C_{18}H_{17}N_5O_3$; 1.4 HCl	Requires	C 53.73	H 4.61	N 17.40

5-[4-(O-*t*-Butyloxycarbonylserylamino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile was prepared as follows:-



5-[4-({N-FMOC-O-*t*-butoxycarbonylseryl}amino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile

Using the general coupling method described in Example 16, 5-[4-({N-FMOC-O-*t*-butoxycarbonylseryl}amino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile (1.68 g) was obtained as a white solid from 5-(4-aminophenoxy)-2-amino-1*H*-indole-3-carbonitrile (Example 15)(800 mg ; 3.00 mmol) after purification by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (70 to 100% EtOAc).

Yield : 89%

^{1}H NMR spectrum (DMSO d_6) : 1.12 (s, 9H) ; 3.55 (m, 2H) ; 4.15 - 4.35 (m, 4H) ; 6.59 (dd, 1H) ; 6.69 (d, 1H) ; 6.80 (s, 2H) ; 6.92 (d, 2H) ; 7.11 (d, 1H) ; 7.33 (m, 2H) ; 7.42 (m, 2H) ; 7.5 - 7.7 (m, 3H) ; 7.75 (m, 2H) ; 7.89 (d, 2H) ; 9.98 (s, 1H) ; 10.70 (s, 1H).

MS-ESI : 630 $[M+H]^+$

5-[4-(O-*t*-Butyloxycarbonylserylamino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile

A solution of 5-[4-({N-FMOC-O-*t*-butoxycarbonylseryl}amino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile (1.45 g ; 2.3 mmol) in $CHCl_3$ (30 ml) was treated dropwise with piperidine (3.25 ml). The mixture was stirred for 3 hours at room temperature and was directly purified by flash chromatography eluting with increasingly polar mixtures of MeOH/CH_2Cl_2 (2.5 to 10% MeOH). The appropriate fractions were evaporated to give 5-[4-(O-*t*-butoxycarbonylserylamino)phenoxy]-2-amino-1*H*-indole-3-carbonitrile as a white solid (878 mg).

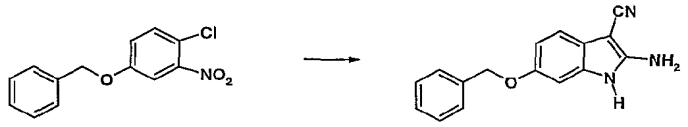
Yield : 94%

^{1}H NMR spectrum (DMSO d_6) : 1.34 (s, 9H) ; 1.93 (br s, 2H) ; 3.4 - 3.55 (m, 3H) ; 6.61 (dd, 1H) ; 6.69 (d, 1H) ; 6.82 (s, 2H) ; 6.92 (d, 2H) ; 7.12 (d, 1H) ; 7.62 (d, 2H) ; 9.83 (br s, 1H) ; 10.73 (br s, 1H).

MS-ESI : 408 $[M+H]^+$

Example 20

6-Benzyloxy-2-amino-1*H*-indole-3-carbonitrile



Example 20

Using the general method described in Example 2, except that two equivalents of aqueous NaOH were employed and the reaction was warmed to 100°C in the first step, 6-benzyloxy-2-amino-1*H*-indole-3-carbonitrile (110 mg) was obtained as a beige solid from 5-benzyloxy-2-chloro-nitrobenzene (1.31 g ; 5.0 mmol) after purification by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (30 to 70% EtOAc).

Yield : 8%

^{1}H NMR spectrum (DMSO d_6) : 5.05 (s, 2H) ; 6.59 (s, 2H) ; 6.70 (dd, 1H) ; 6.82 (d, 1H) ; 7.01 (d, 1H) ; 7.31 (t, 1H) ; 7.38 (t, 2H) ; 7.44 (d, 2H) ; 10.56 (s, 1H).

LCMS-ESI : 264 $[M+H]^+$

Elemental analysis :	Found	C 72.11	H 4.91	N 15.84
$C_{16}H_{13}N_3O$; 0.2 H_2O	Requires	C 72.0	H 5.06	N 15.74

5-Benzyloxy-2-chloro-nitrobenzene

This was prepared as follows:- A solution of benzyl bromide (10.26 g ; 60 mmol) and 4-chloro-3-nitrophenol (8.7 g ; 50 mmol) in DMF (250 ml) was treated with Na_2CO_3 (10.6 g ; 0.1 mol) and the mixture was stirred at room temperature for 3 days. The mixture was poured into water and extracted with Et_2O. The organic phase was washed with brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with CH_2Cl_2 to give 5-benzyloxy-2-chloro-nitrobenzene as a pale yellow solid (12.32 g).

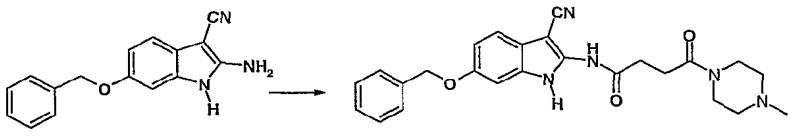
Yield : 94%

^{1}H NMR spectrum ($CDCl_3$) : 5.10 (s, 2H) ; 7.12 (dd, 1H) ; 7.36 - 7.43 (m, 6H) ; 7.47 (d, 1H).

Elemental analysis :	Found	C 58.72	H 3.81	N 5.26
$C_{13}H_{10}ClNO_3$; 0.1 H_2O	Requires	C 58.82	H 3.87	N 5.28

Example 21

6-Benzyloxy-2-(4-methylpiperazin-1-yl-4-oxobutanoylamino)-1*H*-indole-3-carbonitrile



Example 21

Using the general method described for Examples 12 and 13 , 6-benzyloxy-2-(4-methylpiperazin-1-yl-4-oxobutanoylamino)-1*H*-indole-3-carbonitrile (128 mg) was obtained as a white solid from 6-benzyloxy-2-amino-1*H*-indole-3-carbonitrile (Example 20)(120 mg ; 0.46 mmol) after purification by flash chromatography eluting with increasingly polar mixtures of MeOH/CH_2Cl_2 (3 to 10% MeOH).

Yield : 63%

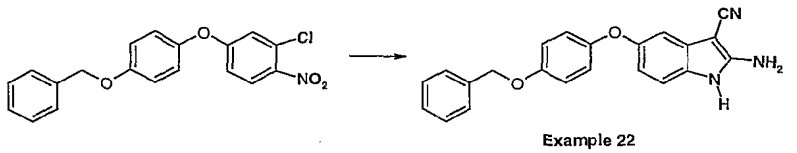
^{1}H NMR spectrum (DMSO d_6) : 2.18 (s, 3H) ; 2.22 (m, 2H) ; 2.31 (m, 2H) ; 2.6 - 2.75 (m, 4H) ; 3.4 - 3.5 (m, 4H) ; 5.08 (s, 2H) ; 6.68 (dd, 1H) ; 7.18 (d, 1H) ; 7.31 (d, 1H) ; 7.33 (t, 1H) ; 7.39 (t, 2H) ; 7.46 (d, 2H) ; 11.4 (br s, 1H) ; 11.9 (br s, 1H).

LCMS-ESI : 446 $[M+H]^+$

Elemental analysis :	Found	C 61.52	H 6.11	N 14.03
$C_{25}H_{27}N_5O_3$; 1.1 HCl 0.2 H_2O	Requires	C 61.38	H 5.87	N 14.31

Example 22

5-(4-Benzyloxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile



Example 22

Using the general method described in Example 2, except that two equivalents of aqueous NaOH were employed, 5-(4-benzyloxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile (1.28 g) was obtained as a white solid from 4-(4-benzyloxyphenoxy)-2-chloro-nitrobenzene (2.1 g ; 5.9

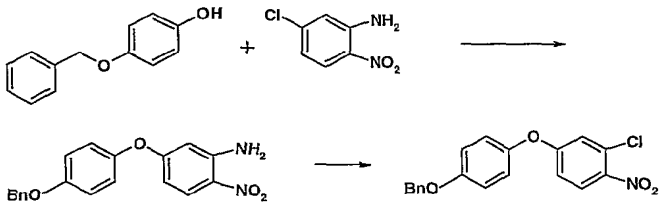
mmol) after purification by flash chromatography eluting with increasingly polar mixtures of CH_2Cl_2/EtOAc (0 to 80% EtOAc).

Yield : 61%

^{1}H NMR spectrum (DMSO d_6) : 5.07 (s, 2H) ; 6.58 (dd, 1H) ; 6.63 (d, 1H) ; 6.78 (s, 2H) ; 6.92 (m, 2H) ; 7.00 (m, 2H) ; 7.09 (d, 1H) ; 7.34 (t, 1H) ; 7.40 (t, 2H) ; 7.46 (d, 2H) ; 10.69 (br s, 1H).

LCMS-ESI : 356 $[M+1]^+$

4-(4-Benzyloxyphenoxy)-2-chloro-nitrobenzene was prepared as follows:-



4-(4-Hydroxyphenylsulphanyl)-2-amino-nitrobenzene

Using the general method described for 4-(4-hydroxyphenylsulphanyl)-2-amino-nitrobenzene in Example 2, except that one equivalent of NaH was used, 4-(4-benzyloxyphenoxy)-2-amino-nitrobenzene (5.88 g) was prepared from 4-chloro-2-amino-nitrobenzene (4.30 g ; 25 mmol).

Yield : 70%

^{1}H NMR spectrum ($CDCl_3$) : 5.11 (s, 2H) ; 6.25 - 6.30 (m, 2H) ; 7.11 (s, 4H) ; 7.3 - 7.5 (m, 7H) ; 7.98 (d, 1H).

MS-ESI : 337 $[M+H]^+$

4-(4-Benzyloxyphenoxy)-2-chloro-nitrobenzene

Similarly, using the general method described for 4-(4-hydroxyphenylsulphanyl)-2-chloro-nitrobenzene in Example 2, 4-(4-benzyloxyphenoxy)-2-chloro-nitrobenzene (2.09 g) was prepared from 4-(4-benzyloxyphenoxy)-2-amino-nitrobenzene (9.6 g ; 28.5 mmol) after purification by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (10 to 20% EtOAc).

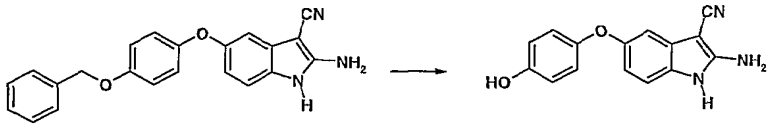
Yield : 20%

^{1}H NMR spectrum (DMSO d_6) : 5.13 (s, 2H) ; 7.01 (dd, 1H) ; 7.15 (m, 4H) ; 7.22 (d, 1H) ; 7.35 (t, 1H) ; 7.41 (t, 2H) ; 7.48 (d, 2H) ; 8.13 (d, 1H).

MS-ESI : 357 $[M+H]^+$

Example 23

5-(4-Hydroxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile



Example 23

Using the general method of hydrogenolysis described in Example 16, 5-(4-hydroxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile (570 mg) was obtained as a white solid from 5-(4-benzyloxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile (Example 22) (1.0 g ; 2.81 mmol) after purification by flash chromatography eluting with EtOAc.

Yield : 76%

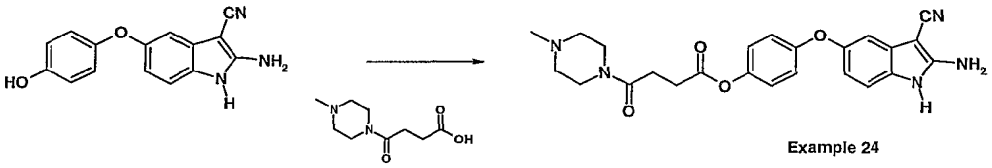
^{1}H NMR spectrum (DMSO d_6) : 6.54 (dd, 1H) ; 6.58 (d, 1H) ; 6.73 (d, 2H) ; 6.75 (s, 2H) ; 6.81 (d, 2H) ; 7.06 (d, 1H) 9.21 (br s , 1H) ; 10.64 (br s, 1H).

LCMS-ESI : 266 $[M+H]^+$

Elemental analysis :	Found	C 67.96	H 4.37	N 15.73
$C_{15}H_{11}N_3O_2$	Requires	C 67.92	H 4.18	N 15.84

Example 24

5-[4-(4-Methylpiperazin-1-yl-4-oxobutanoyloxy)phenoxy]-2-amino-1*H*-indole-3-carbonitrile



Example 24

A solution of 5-(4-hydroxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile (Example 23)(130 mg; 0.5 mmol) and 3-(N-methylpiperazin-1-ylcarbonyl)propanoic acid(128 mg 0.63 mmol) in a mixture of CH_2Cl_2 (5 ml) and CH_3CN (0.5 ml) was treated at room temperature with EDCI (122 mg ; 0.63 mmol) and a catalytic quantity of DMAP (20 mg). The mixture was stirred for overnight and was directly purified by flash chromatography eluting with increasingly polar mixtures of MeOH/CH_2Cl_2 (5 to 10% MeOH). The appropriate

fractions were evaporated to give 5-[4-(4-methylpiperazin-1-yl-4-oxobutanoyloxy)phenoxy]-2-amino-1*H*-indole-3-carbonitrile as a white solid (150 mg).

Yield : 67%

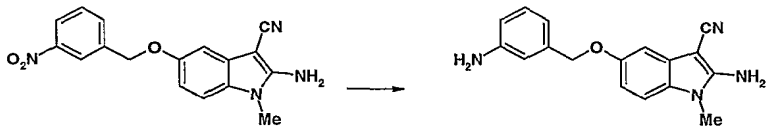
^{1}H NMR spectrum (DMSO d_6) : 2.17 (s, 3H) ; 2.23 (m, 2H) ; 2.30 (m, 2H) ; 2.72 (m, 4H) ; 3.45 (m, 4H) ; 6.61 (dd, 1H) ; 6.73 (d, 1H) ; 6.82 (s, 2H) ; 6.94 (d, 2H); 7.04 (d, 2H) ; 7.13 (d, 1H) ; 10.73 (s, 1H).

MS-ESI : 448 $[M+H]^+$

Elemental analysis :	Found	C 62.56	H 5.98	N 15.02
$C_{24}H_{25}N_5O_4$; 0.8 H_2O	Requires	C 62.41	H 5.80	N 15.16

Example 25

5-(3-Aminobenzyloxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile



Example 25

A solution of 5-(3-nitrobenzyloxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (40 mg ; 0.12 mmol) in MeOH (6 ml) was treated with K_2CO_3 (6 mg) and hydrogenated over PtO_2 (6 mg) at 45 psi at room temperature for 1 hour. After filtration and evaporation to dryness, the residue was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (5 % MeOH) and the appropriate fractions were evaporated to give 5-(3-aminobenzyloxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (32 mg).

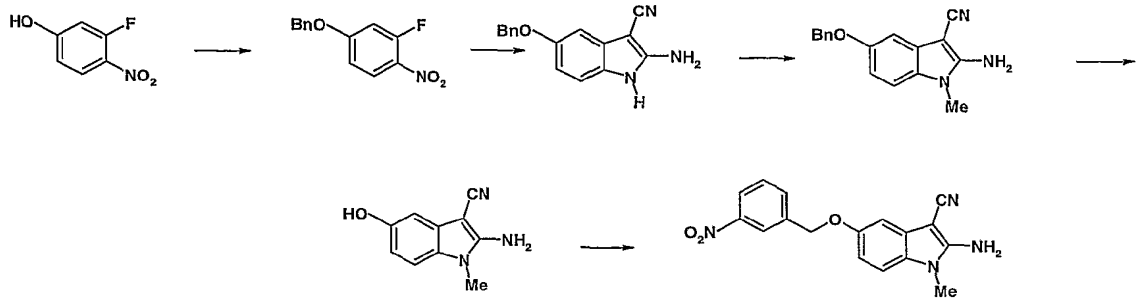
Yield : 91%

^{1}H NMR spectrum (DMSO d_6) : 3.48 (s, 3H) ; 4.94 (s, 2H) ; 5.09 (s, 2H) ; 6.50 (dd, 1H) ; 6.57 (d, 1H) ; 6.63 (m, 2H) ; 6.77 (d, 1H) ; 6.90 (s, 2H) ; 7.01 (t, 1H) ; 7.11 (d, 1H).

LCMS-ESI : 293 $[M+H]^+$

Elemental analysis :	Found	C 64.10	H 5.64	N 16.57
$C_{17}H_{16}N_4O$; 0.75 H_2O 0.1 MeOH 0.2 CH_2Cl_2	Requires	C 63.73	H 5.66	N 17.18

5-(3-Nitrobenzyloxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile was prepared as follows:-



4-Benzyloxy-2-fluoronitrobenzene

A solution of 3-fluoro-4-nitrophenol (25 g ; 0.159 mol) in DMF (600 ml) under argon was treated at room temperature with Na_2CO_3 (33.7 g ; 0.318 mol). The mixture was stirred and treated dropwise with benzyl bromide (32.6 g ; 0.19 mol). Stirring was continued for 3 days when the mixture was poured into water and extracted with Et_2O. The organic phase was washed with water, brine and dried over $MgSO_4$. Evaporation gave 4-benzyloxy-2-fluoronitrobenzene as a yellow solid (38 g).

Yield : 97%

^{1}H NMR spectrum ($CDCl_3$) : 5.15 (s, 2H) ; 6.8 - 6.9 (m, 2H) ; 7.35 - 7.5 (m, 5H) ; 8.1 (t, 1H).

Elemental analysis :	Found	C 63.25	H 4.24	N 5.73
$C_{13}H_{10}FNO_3$	Requires	C 63.16	H 4.08	N 5.67

5-Benzyloxy-2-amino-1*H*-indole-3-carbonitrile

Using the general method described in Example 2, except that two equivalents of aqueous NaOH were employed, 5-benzyloxy-2-amino-1*H*-indole-3-carbonitrile (31.5 g) was obtained as a pale rose solid from 4-benzyloxy-2-fluoronitrobenzene (38 g ; 0.15 mol) after purification by trituration with CH_2Cl_2.

Yield : 80%

^{1}H NMR spectrum (DMSO d_6) : 5.07 (s, 2H) ; 6.58 (dd, 1H) ; 6.66 (s, 2H) ; 6.75 (d, 1H) ; 7.01 (d, 1H) ; 7.25 - 7.5 (m, 5H) ; 10.51 (s, 1H).

LCMS-ESI : 264 $[M+H]^+$

Elemental analysis :	Found	C 70.91	H 4.95	N 15.77
$C_{16}H_{13}N_3O$; 0.4 H_2O	Requires	C 71.04	H 5.14	N 15.53

5-Benzyloxy-2-amino-1-methyl-1*H*-indole-3-carbonitrile

A solution of 5-benzyloxy-2-amino-1*H*-indole-3-carbonitrile (2.96 g ; 11.25 mmol) in DMF (20 ml) under argon was treated at room temperature with Cs_2CO_3 (4.4 g ; 13.5 mmol). The mixture was stirred and treated dropwise with methyl iodide (0.84 ml ; 13.48 mmol). Stirring was continued for 1 hour when the mixture was poured into water. The precipitate was filtered, washed with water and dried to give 5-benzyloxy-2-amino-1-methyl-1*H*-indole-3-carbonitrile as a beige solid (2.77 g).

Yield : 90%

^{1}H NMR (DMSO d_6) : 3.49 (s, 3H) ; 5.11 (s, 3H) ; 6.68 (dd, 1H) ; 6.82 (d, 1H) ; 6.91 (s, 2H) ; 7.13 (d, 1H) ; 7.35 (t, 1H) ; 7.41 (m, 2H) ; 7.47 (d, 2H).

Elemental analysis :	Found	C 72.95	H 5.39	N 15.16
$C_{17}H_{15}N_3O$; 0.2 H_2O	Requires	C 72.68	H 5.53	N 14.96

5-Hydroxy-2-amino-1-methyl-1*H*-indole-3-carbonitrile

Using the general method of hydrogenolysis described in Example16, 5-hydroxy-2-amino-1-methyl-1*H*-indole-3-carbonitrile (1.81 g) was obtained as a white solid from 5-benzyloxy-2-amino-1-methyl-1*H*-indole-3-carbonitrile (2.6 g ; 9.38 mmol) after purification by flash chromatography eluting with EtOAc.

Yield : 100%

^{1}H NMR spectrum (DMSO d_6) : 3.45 (s, 3H) ; 6.43 (dd, 1H) ; 6.56 (d, 1H) ; 6.81 (s, 2H) ; 6.99 (d, 1H) ; 8.83 (s, 1H).

LCMS-ESI : 188 $[M+H]^+$

Elemental analysis :	Found	C 64.05	H 4.92	N 22.20
$C_{10}H_9N_3O$	Requires	C 64.16	H 4.85	N 22.45

5-(3-Nitrobenzyloxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile

A solution of 5-hydroxy-2-amino-1-methyl-1*H*-indole-3-carbonitrile (100 mg ; 0.53 mmol) and 3-nitrobenzyl bromide (130 mg ; 0.6 mmol) in DMF (5 ml) was treated with Cs_2CO_3 (520 mg ; 1.6 mmol) and the mixture was stirred for 2 hours. Water (80 ml) was added and the precipitate was filtered, taken up in methanol, filtered, washed and dried to give 5-(3-nitrobenzyloxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (96 mg).

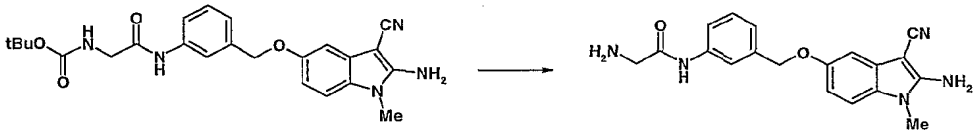
Yield : 56%

^{1}H NMR spectrum (DMSO d_6) : 3.49 (s, 3H) ; 5.28 (s, 2H) ; 6.71 (dd, 1H) ; 6.85 (d, 1H) ; 6.94 (s, 2H) ; 7.15 (d, 1H) ; 7.72 (t, 1H) ; 7.94 (d, 1H) ; 8.20 (d, 1H) ; 8.33 (s, 1H).

LCMS-ESI : 321 $[M-H]^-$

Example 26

5-(3-Glycylbenzyloxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile



Example 26

A solution of 5-[3-(N-*t*-butoxycarbonylglycyl)benzyloxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile (188 mg ; 0.42 mmol) in EtOAc (10 ml) that was saturated with gaseous HCl was stirred at room temperature for 24 hours. An excess of Et_2O was added and the precipitate was filtered and dried to give the hydrochloride of 5-(3-glycylbenzyloxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (170 mg).

Yield : 100%

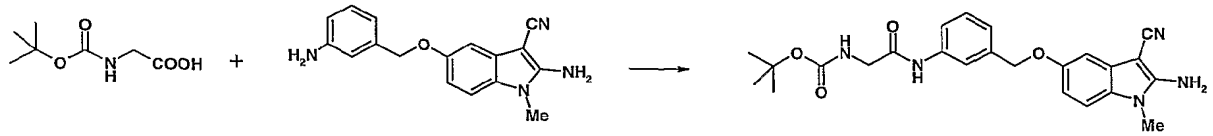
^{1}H NMR spectrum (DMSO d_6) : 3.47 (s, 3H) ; 3.80 (s, 2H) ; 5.10 (s, 2H) ; 6.65 (dd, 1H) ; 6.78 (d, 1H) ; 6.95 (br s, 2H) ; 7.10 (d, 1H) ; 7.18 (d, 1H) ; 7.36 (t, 1H) ; 7.58 (d, 1H) ; 7.68 (s, 1H) ; 8.14 (br s, 3H) ; 10.54 (s, 1H).

LCMS-ESI : 350 $[M+H]^+$

Elemental analysis:	Found	C 52.53	H 5.58	N 15.53
$C_{19}H_{19}N_5O_2$; 0.8 H_2O 0.3 EtOAc 1.9 HCl	Requires	C 52.80	H 5.46	N 15.24

5-[3-(N-*t*-Butyloxycarbonylglycyl)benzyloxyl-2-amino-1-methyl-1*H*-indole-3-carbonitrile

5-[3-(N-*t*-Butoxycarbonylglycyl)benzyloxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile (188 mg)was prepared using the general coupling method described in Example 16



as a white solid from 5-(3-aminobenzyloxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile

(150 mg ; 0.51 mmol) after purification by flash chromatography eluting with EtOAc/CH_2Cl_2 (50/50).

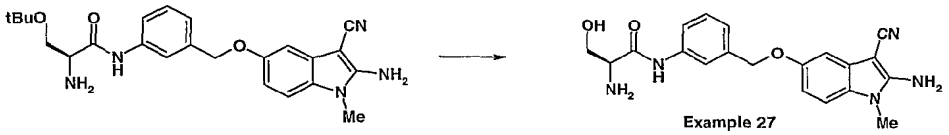
Yield : 80%

^{1}H NMR spectrum (DMSO d_6) : 1.42 (s, 9H) ; 3.50 (s, 3H) ; 3.74 (d, 2H) ; 5.09 (s, 2H) ; 6.67 (dd, 1H) ; 6.82 (d, 1H) ; 6.92 (s, 2H) ; 7.05 (t, 1H) ; 7.14 (m, 2H) ; 7.33 (t, 1H) ; 7.58 (d, 1H) ; 7.69 (s, 1H) ; 9.97 (s, 1H).

LCMS-ESI : 450 $[M+H]^+$

Example 27

5-(3-Serylbenzyloxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile



Example 27

Using the general method of deprotection described in Example 18, 5-(3-serylbenzyloxy)-2-amino-1*H*-indole-3-carbonitrile (177 mg) was obtained as its hydrochloride as a glassy solid from 5-[3-(O-t-butylseryl)benzyloxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile (280 mg ; 0.64 mmol) after purification by reverse phase C18 preparative HPLC eluting with MeOH/H_2O/HCl (80/19/1)

Yield : 70%

^{1}H NMR spectrum (DMSO d_6) : 3.49 (s, 3H) ; 3.7 (s, 1H) ; 3.87 (d, 2H) ; 4.04 (m, 1H) ; 5.11 (s, 2H) ; 6.66 (dd, 1H) ; 6.80 (d, 1H) ; 6.95 (br s, 2H) ; 7.12 (d, 1H) ; 7.20 (d, 1H) ; 7.38 (t, 1H) ; 7.62 (d, 1H) ; 7.75 (s, 1H) ; 8.30 (m, 3H) ; 10.67 (s, 1H).

LCMS-ESI : 380 $[M+H]^+$

Elemental analysis :	Found	C 51.84	H 5.51	N 14.72
$C_{20}H_{21}N_5O_3$; 1.4 HCl 1.8 H_2O	Requires	C 51.69	H 5.65	N 15.07

5-[3-(O-*t*-Butyl-N-FMOC-seryl)benzyloxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile

This was prepared using the general coupling method described in Example 16, 5-[3-(O-*t*-butyl-N-FMOC-seryl)benzyloxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile (730 mg) was obtained as a white solid from 5-(3-aminobenzyloxy)-2-amino-1-methyl-1*H*-

indole-3-carbonitrile (Example 25)(700 mg ; 2.38 mmol) after purification by flash chromatography eluting with EtOAc/CH_2Cl_2 (20% EtOAc).

Yield : 64%

^{1}H NMR spectrum (DMSO d_6) : 1.13 (s, 9H) ; 3.48 (s, 3H) ; 3.55 (m, 2H) ; 4.2 - 4.35 (m, 4H) ; 5.09 (s, 2H) ; 6.66 (dd, 1H) ; 6.81 (d, 1H) ; 6.92 (s, 2H) ; 7.13 (m, 2H) ; 7.33 (m, 3H) ; 7.43 (m, 2H) ; 7.56 (m, 2H) ; 7.76 (m, 3H) ; 7.90 (d, 2H) ; 10.06 (s, 1H).

5-[3-(O-*t*-Butylseryl)benzyloxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile

Using the general FMOC deprotection method described in Example 16, 5-[3-(O-*t*-butylseryl)benzyloxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile (280 mg) was obtained as a white solid from 5-[3-(O-*t*-butyl-N-FMOC-seryl)benzyloxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile (730 mg ; 1.52 mmol) after purification by flash chromatography eluting with increasingly polar mixtures of MeOH/CH_2Cl_2 (2 to 5% MeOH).

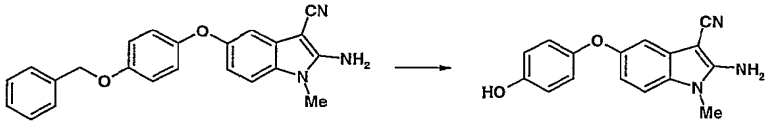
Yield : 42%

^{1}H NMR spectrum (DMSO d_6) : 1.13 (s, 9H) ; 1.93 (br s, 2H) ; 3.4 - 3.5 (m, 3H) ; 3.48 (s, 3H) ; 5.08 (s, 2H) ; 6.66 (dd, 1H) ; 6.80 (d, 1H) ; 6.91 (s, 2H) ; 7.13 (m, 2H) ; 7.32 (t, 1H) ; 7.61 (d, 1H) ; 7.76 (s, 1H) 9.88 (br s, 1H).

MS-ESI : 436 $[M+H]^+$

Example 28

5-(4-Hydroxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile



Example 28

Using the general method of hydrogenolysis described in Example 16 at 18 psi for 15 minutes, 5-(4-hydroxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (1.45 g) was obtained as a white solid from 5-(4-benzyloxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (2.02 g; 5.47 mmol) after purification by flash chromatography eluting with MeOH/CH_2Cl_2 (10 % MeOH).

Yield : 95%

^{1}H NMR spectrum (DMSO d_6) : 3.49 (s, 3H) ; 6.60 (dd, 1H) ; 6.61 (d, 1H) ; 6.74 (d, 2H) ; 6.82 (d, 2H) ; 6.99 (s, 2H) ; 7.16 (d, 1H) ; 9.22 (s, 1H).

LCMS-ESI : 280 $[M+H]^+$

5-(4-benzyloxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile

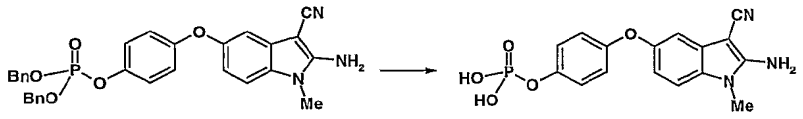
This was prepared using the general method of selective N-alkylation described for 5-benzyloxy-1*H*-indole-3-carbonitrile in Example 25, 5-(4-benzyloxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (1.77 g) was obtained as a white solid from 5-(4-benzyloxyphenloxy)-2-amino-1*H*-indole-3-carbonitrile (2.0 g ; 5.63 mmol) after purification by flash chromatography eluting with increasingly polar mixtures of CH_2Cl_2/EtOAc (10 to 20% EtOAc).

Yield : 85%

^{1}H NMR spectrum (DMSO d_6) : 3.50 (s, 3H) ; 5.07 (s, 2H) ; 6.65 (dd, 1H) ; 6.66 (d, 1H) ; 6.93 (d, 2H) ; 7.00 (d, 2H) ; 7.01 (s, 2H) ; 7.19 (d, 1H) ; 7.33 (t, 1H) ; 7.40 (t, 2H) ; 7.45 (d, 2H).

Example 29

5-(4-Phosponooxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile



Example 29

Using the general method of hydrogenolysis described in Example 16 at 10 psi for 1hour, 5-(4-phosponooxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (920 mg) was obtained as a white solid from 5-[4-(O,O-dibenzylphosponooxy)phenoxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile (1.71 g ; 3.16 mmol) after purification by HP20SS chromatography eluting with MeOH/H_2O (0 to 100 % MeOH).

Yield : 80%

A small sample (300 mg) was repurified by reverse phase C18 preparative HPLC eluting with MeOH/H_2O/AcOH (80/19/1) to give pure 5-(4-phosponooxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (150 mg).

^{1}H NMR spectrum (DMSO d_6 + TFA) : 3.49 (s, 3H) ; 6.69 (dd, 1H) ; 6.76 (d, 1H) ; 6.95 (d, 2H) ; 7.15 (d, 2H) ; 7.23 (d, 1H) ; 12.37 (br s, 2H) ; 12.64 (br s, 2H).

LCMS-ESI : 360 $[M+H]^+$

Elemental analysis :	Found	C 51.45	H 3.96	N 11.12
$C_{16}H_{14}N_3O_5P$; 0.77 H_2O	Requires	C 51.50	H 4.20	N 11.26

5-[4-(O,O-Dibenzylphosponooxy)phenoxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile

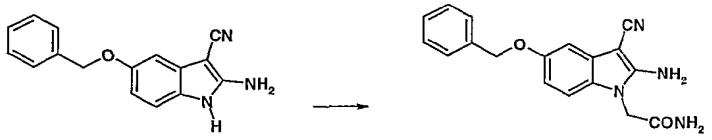
This was prepared as follows:- A solution of 5-(4-hydroxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (1.4 g ; 5 mmol) in acetonitrile (80 ml), CCl_4 (2.44 ml ; 25 mmol) and diisopropylethylamine (1.82 ml ; 10.5 mmol) was treated with a catalytic amount of DMAP (50 mg) and then cooled to 0°C. Dibenzyl phosphite (1.7 ml ; 7.51 mmol) was added and the temperature allowed to rise to room temperature over 30 minutes. The mixture was treated with aqueous KH_2PO_4 (0.5M), the acetonitrile evaporated and the mixture extracted with Et_2O. The organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of CH_2Cl_2/EtOAc (10 to 20% EtOAc) to give 5-[4-(O,O-dibenzylphosponooxy)phenoxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile (1.76 g).

Yield : 65%

^1H NMR spectrum ($CDCl_3$) : 3.52 (s, 3H) ; 5.15 (d, 4H) ; 6.68 (dd, 1H) ; 6.76 (d, 1H) ; 6.91 (d, 2H) ; 7.06 (s, 2H) ; 7.13 (d, 2H) ; 7.23 (d, 1H) ; 7.36 (m, 10H).

Example 30

5-Benzyloxy-1-carbamoylmethyl-2-amino-1*H*-indole-3-carbonitrile



Example 30

Using the general method of selective N-alkylation described for 5-benzyloxy-2-amino-1-methyl-1*H*-indole-3-carbonitrile in Example 25, using iodoacetamide (222 mg ; 1.2 mmol), 5-benzyloxy-1-carbamoylmethyl-2-amino-1*H*-indole-3-carbonitrile (163 mg) was obtained as a white solid from 5-benzyloxy-2-amino-1*H*-indole-3-carbonitrile (263 mg ; 1.0 mmol) after trituration with Et_2O/CH_2Cl_2.

Yield : 51%

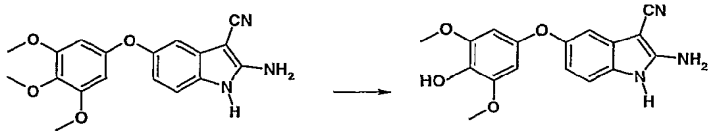
^{1}H NMR spectrum (DMSO d_6) : 4.61 (s, 2H) ; 5.11 (s, 2H) ; 6.65 (dd, 1H) ; 6.81 (d, 1H) ; 6.91 (s, 2H) ; 6.94 (d, 1H) ; 7.30 (s, 1H) ; 7.34 (d, 1H) ; 7.40 (m, 2H) ; 7.47 (m, 2H) ; 7.57 (s, 1H).

LCMS-ESI : 319 $[M-H]^-$

Elemental analysis :	Found	C 65.65	H 5.01	N 17.41
$C_{18}H_{16}N_4O_2$; 0.45 H_2O	Requires	C 65.82	H 5.19	N 17.06

Example 31

5-(3,5-Dimethoxy-4-hydroxy-phenoxy)-2-amino-1*H*-indole-3-carbonitrile



Example 31

A solution of 5-(3,4,5-trimethoxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile (Example 11) (50 mg ; 0.147 mmol) in CH_2Cl_2 (1.0 ml) was treated with trimethyl silyl iodide (30 ul ; 0.2 mmol) and the mixture was stirred at room temperature overnight. The mixture was treated with aqueous $Na_2S_2O_3$ (0.5M), the CH_2Cl_2 evaporated and the mixture extracted with EtOAc. The organic phase was washed with water, brine and dried over $MgSO_4$. Evaporation gave 5-(3,5-dimethoxy-4-hydroxy-phenoxy)-2-amino-1*H*-indole-3-carbonitrile (50 mg).

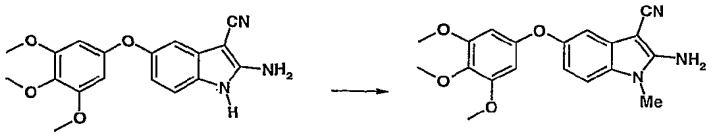
Yield : 100%

^{1}H NMR spectrum (DMSO d_6) : 3.66 (s, 6H) ; 6.26 (s, 2H) ; 6.55 (dd, 1H) ; 6.62 (d, 1H) ; 6.74 (s, 2H) ; 7.05 (d, 1H) ; 8.04 (s, 1H) ; 10.62 (s, 1H).

LCMS-ESI : 326 $[M+H]^+$

Example 32

5-(3,4,5-Trimethoxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile



Example 32

Using the general method of selective N-alkylation described in Example 25, 5-(3,4,5-trimethoxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (77 mg) was obtained as a white solid from 5-(3,4,5-trimethoxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile

(Example 11) (100 mg ; 0.29 mmol) after purification by flash chromatography eluting with CH_2Cl_2/EtOAc (10% EtOAc).

Yield : 75%

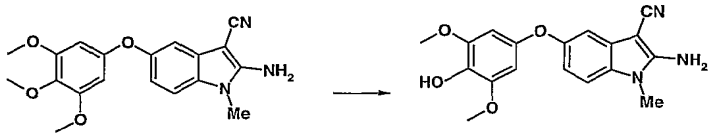
^{1}H NMR spectrum (DMSO d_6) : 3.52 (s, 3H) ; 3.64 (s, 3H) ; 3.69 (s, 6H) ; 6.28 (s, 2H) ; 6.70 (dd, 1H) ; 6.78 (d, 1H) ; 7.05 (s, 2H) ; 7.22 (d, 1H).

LCMS-ESI : 354 $[M+H]^+$

Elemental analysis :	Found	C 64.69	H 5.60	N 11.72
$C_{19}H_{19}N_3O_4$	Requires	C 64.58	H 5.42	N 11.89

Example 33

5-(3,5-Dimethoxy-4-hydroxy-phenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile



Example 33

Using the general method of selective demethylation described for Example 31, 5-(3,5-dimethoxy-4-hydroxy-phenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (50 mg) was obtained as a white solid from 5-(3,4,5-trimethoxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (Example 32) (160 mg ; 0.45 mmol) after purification by flash chromatography eluting with CH_2Cl_2/EtOAc (20% EtOAc).

Yield : 33%

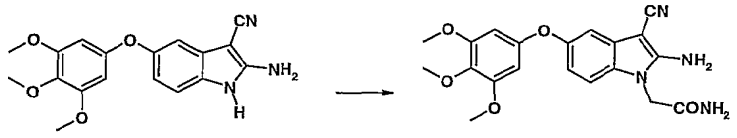
^{1}H NMR spectrum (DMSO d_6) : 3.51 (s, 3H) ; 3.69 (s, 6H) ; 6.30 (s, 2H) ; 6.66 (dd, 1H) ; 6.71 (d, 1H) ; 7.01 (s, 2H) ; 7.19 (d, 1H) ; 8.10 (s, 1H).

LCMS-ESI : 340 $[M+H]^+$

Elemental analysis :	Found	C 63.60	H 5.27	N 12.00
$C_{18}H_{17}N_3O_4$	Requires	C 63.71	H 5.05	N 12.38

Example 34

5-(3,4,5-Trimethoxyphenoxy)-2-amino-1-carbamoylmethyl-1*H*-indole-3-carbonitrile



Example 34

Using the general method of selective N-alkylation described for 5-benzyoxy-2-amino-1-methyl-1*H*-indole-3-carbonitrile in Example 25 using iodoacetamide (350 mg ; 1.88 mmol), 5-(3,4,5-trimethoxyphenoxy)-2-amino-1-carbamoylmethyl-1*H*-indole-3-carbonitrile (192 mg) was obtained as a white solid from 5-(3,4,5-trimethoxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile (Example 11)(320 mg ; 0.94 mmol) after trituration with Et_2O/CH_2Cl_2.

Yield : 52%

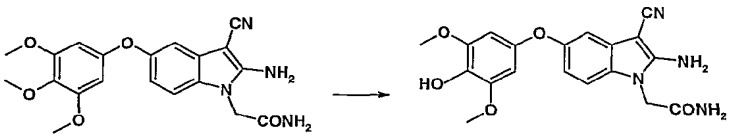
^1H NMR spectrum (DMSO d_6) : 3.64 (s, 3H) ; 3.70 (s, 6H) ; 4.66 (s, 2H) ; 6.31 (s, 2H) ; 6.68 (dd, 1H) ; 6.77 (d, 1H) ; 7.03 (d, 1H) ; 7.04 (s, 2H) ; 7.33 (s, 1H) ; 7.62 (s, 1H).

LCMS-ESI : 397 $[M+H]^+$

Elemental analysis :	Found	C 54.81	H 4.68	N 12.63
$C_{20}H_{20}N_4O_5$; 0.8 H_2O 0.45 CH_2Cl_2	Requires	C 54.70	H 5.05	N 12.48

Example 35

5-(3,5-Dimethoxy-4-hydroxyphenoxy)-2-amino-1-carbamoylmethyl-1*H*-indole-3-carbonitrile



Example 35

Using the general method of selective demethylation described for Example 31 5-(3,5-dimethoxy-4-hydroxyphenoxy)-2-amino-1-carbamoylmethyl-1*H*-indole-3-carbonitrile (95 mg) was obtained as a beige solid from 5-(3,4,5-trimethoxyphenoxy)-2-amino-1-carbamoylmethyl-1*H*-indole-3-carbonitrile (150 mg ; 0.37 mmol) after trituration with Et_2O.

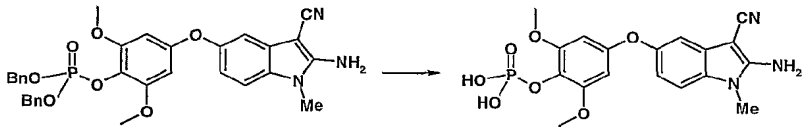
Yield : 67%

^{1}H NMR spectrum (DMSO d_6) : 3.70 (s, 6H) ; 4.64 (s, 2H) ; 6.32 (s, 2H) ; 6.63 (dd, 1H) ; 6.69 (d, 1H) ; 7.00 (d, 1H) ; 7.01 (s, 2H) ; 7.32 (s, 1H) ; 7.61 (s, 1H) ; 8.11 (s, 1H).

LCMS-ESI : 383 $[M+H]^+$

Example 36

5-(3,5-Dimethoxy-4-phosphonooxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile



Example 36

Using the general method of hydrogenolysis described in Example 16 at 2 psi for 2 hours, 5-(3,5-dimethoxy-4-phosphonooxyphenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (37 mg) was obtained as a white solid from 5-[3,5-dimethoxy-4-(O,O-dibenzylphosphonooxy)phenoxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile (88 mg ; 0.14 mmol) after purification by HP20SS chromatography eluting with increasingly polar mixtures of MeOH/H_2O (0 to 50 % MeOH).

Yield : 60%

^{1}H NMR spectrum (DMSO d_6) : 3.49 (s, 3H) ; 3.62 (s, 6H) ; 6.20 (s, 2H) ; 6.68 (dd, 1H) ; 6.78 (d, 1H) ; 7.01 (s, 2H) ; 7.23 (d, 1H).

Elemental analysis :	Found	C 41.45	H 4.11	N 7.69
$C_{18}H_{16}N_3O_7P$; 2.7 H_2O 2.3 Na	Requires	C 41.67	H 4.16	N 8.10

5-[3,5-Dimethoxy-4-(O,O-dibenzylphosphonooxy)phenoxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile

Using the general method of phosphorylation described in Example 29, 5-[3,5-dimethoxy-4-(O,O-dibenzylphosphonooxy)phenoxy]-2-amino-1-methyl-1*H*-indole-3-carbonitrile (88 mg) was obtained as a white solid from 5-(3,5-dimethoxy-4-hydroxy-phenoxy)-2-amino-1-methyl-1*H*-indole-3-carbonitrile (114 mg ; 0.33 mmol) after purification by flash chromatography eluting with CH_2Cl_2/EtOAc (20 % EtOAc).

Yield : 44%

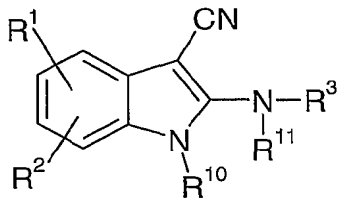
^{1}H NMR spectrum (DMSO d_6) : 3.54 (s, 3H) ; 3.69 (s, 6H) ; 5.22 (d, 4H) ; 6.36 (s, 2H) ; 6.74 (dd, 1H) ; 6.83 (d, 1H) ; 7.07 (s, 2H) ; 7.26 (d, 1H) ; 7.3 - 7.5 (m, 10H).

LCMS-ESI : 599 $[M-H]^-$

5

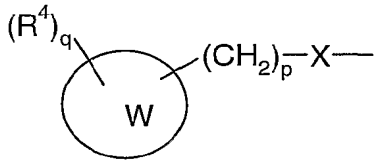
Claims

1. A compound of Formula (I).



Formula (I)

wherein R^1 and R^2 are independently selected from hydrogen, halogen, -CN, a hydrocarbyl group or a group of Formula (II);



Formula (II)

wherein W is aryl or a heterocyclic group,

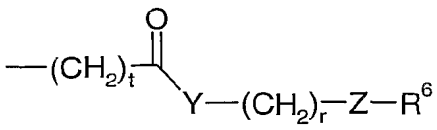
R^4 is independently selected from hydrogen, halogen, -OH, amino, alkanoylamino, —OPO_3H_2, or a hydrocarbyl group, wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified or two R^4 groups together form an optionally substituted cyclic or heterocyclic group;

X is selected from —S—, —O—, —S(O)—, —$S(O_2)$— and —NH—;

p is an integer from 0 to 4; and

q is an integer from 1 to 4;

$R^3$and R^{10} are independently selected from hydrogen, lower alkyl or a group of Formula (IV):



Formula (IV)

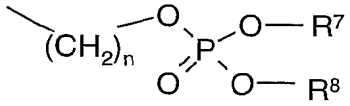
wherein Y is selected from —NH—, —O— or a bond;

Z is selected from —NH—, —O—, —C(O)— or a bond;

r is an integer from 0 to 4;

t is an integer from 0 to 1;

R^6 is hydrogen, a hydrocarbyl group or a group of Formula (V):



Formula (V)

wherein n is an integer of from 1 to 6, and;

R^7 and R^8 are independently selected from hydrogen or a hydrocarbyl group; and

R^{11} is hydrogen or lower alkyl;

or a salt or solvate thereof.

provided that:

iii) when R^1 is an unsubstituted phenylthio group (Ph-S-), R^2 is H, R^{10} is H and R^{11} is H then R^3 is neither H nor $-C(O)-O-CH_2CH_3$; and

iv) R^1, R^2 and R^3 are not all hydrogen.

2. A compound according to claim 1 wherein R^1 is a group of Formula (II).

3. A compound according to claim 2 wherein R^1 is a group of Formula (II) and R^2 is selected from hydrogen, halogen or lower alkyl.

4. A compound according to any one of claims 2 to 3 wherein X is selected from —S—, —O—, —$S(O_2)$— and —NH—.

5. A compound according to any one of claims 2 to 4 wherein R^4 is selected from hydrogen, fluoro, a lower alkanoylamino group, -OH, amino, —OPO_3H_2, or a lower alkoxy group, wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified.

6. A compound according to any one of claims 2 to 5 wherein q is 1 and R^4 is selected from hydrogen, -OH, amino, —OPO_3H_2, methoxy, acetylamino, serylamino, glutamylamino, glycylamino, alanylamino and 4-methylpiperazin-1-ylcarbonylpropanoyloxy.

7. A compound according to any one of claims 2 to 5 wherein q is 2 or 3 and R^4 is independently selected from hydrogen, fluoro, -OH, —OPO_3H_2, or a lower alkoxy group.

8. A compound according to any one of the preceding claims wherein R^3 is hydrogen and R^{10} is independently selected from hydrogen or lower alkyl.

9. A compound selected from

2-phenoxycarbonylamino-5-phenylsulphanyl-1*H*-indole-3-carbonitrile;

5-(4-hydroxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile;

5-(3,6-dimethoxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile;

5-phenylsulphanyl-2-(4-methylpiperazin-1-ylpropoxycarbonylamino)-1*H*-indole-3-carbonitrile;

5-phenylsulphanyl-1-(4-methylpiperazin-1-ylpropoxycarbonyl)-2-amino-1*H*-indole-3-carbonitrile;

6-benzyloxy-2-amino-1*H*-indole-3-carbonitrile;

5-[4-(4-methylpiperazin-1-yl-4-oxobutanoyloxy)phenoxy]-2-amino-1*H*-indole-3-carbonitrile;

5-(4-glycylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(4-alanylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(4-glutamylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(3-glycylbenzyloxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(4-hydroxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(4-phosponooxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(3-serylbenzyloxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(4-acetylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile; and

5-(4-serylaminophenoxy)-2-amino-1*H*-indole-3-carbonitrile;

or salt or solvate thereof.

10. A compound selected from:

5-(4-aminophenoxy)-2-amino-1*H*-indole-3-carbonitrile;

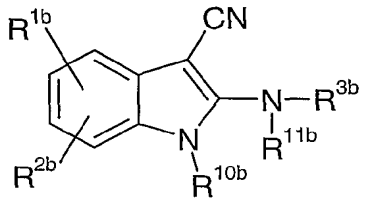
5-(3,4,5-trimethoxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile;

5-(3,4-dimethoxyphenylsulphanyl)-2-amino-1*H*-indole-3-carbonitrile; and

5-(3,4,5-trimethoxyphenoxy)-2-amino-1*H*-indole-3-carbonitrile;

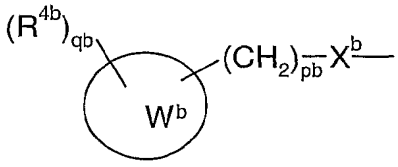
or salt or solvate thereof.

11. The use of a compound of Formula (Ib) as a medicament:



Formula (Ib)

wherein R^{1b} and R^{2b} are independently selected from hydrogen, halogen, -CN, a hydrocarbyl group or a group of Formula (IIb);



Formula (IIb)

wherein W^b is aryl or a heterocyclic group,

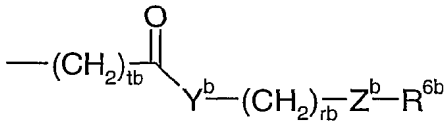
R^{4b} is independently selected from hydrogen, halogen, -OH, amino, alkanoylamino, —OPO_3H_2, or a hydrocarbyl group, wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified or two R^{4b} groups together form an optionally substituted cyclic or heterocyclic group;

X^b is selected from —S—, —O—, —S(O)—, —$S(O_2)$— and —NH—;

pb is an integer from 0 to 4; and

qb is an integer from 1 to 4;

$R^{3b}$and R^{10b} are independently selected from hydrogen, lower alkyl or a group of Formula (IVb):



Formula (IVb)

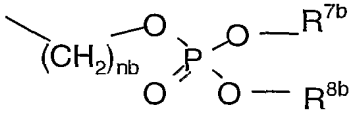
wherein Y^b is selected from —NH—, —O— or a bond;

Z^b is selected from —NH—, —O—, —C(O)— or a bond;

rb is an integer from 0 to 4;

tb is an integer from 0 to 1;

R^{6b} is hydrogen, a hydrocarbyl group or a group of Formula (Vb):



Formula (Vb)

wherein nb is an integer of from 1 to 6, and;

R^{7b} and R^{8b} are independently selected from hydrogen or a hydrocarbyl group; and

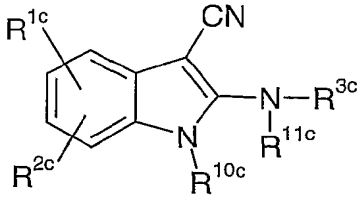
R^{11b} is hydrogen or lower alkyl;

or a salt or solvate thereof;

provided that:

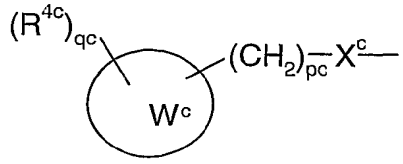
ii) when R^1 is an unsubstituted phenylthio group (Ph-S-), R^2 is H, R^{10} is H and R^{11} is H then R^3 is neither H nor $-C(O)-O-CH_2CH_3$.

12. The use of a compound of Formula (Ic) or a pharmaceutically-acceptable salt or solvate thereof, for the manufacture of a medicament to inhibit and/or reverse and/or alleviate symptoms of angiogenesis and/or any disease state associated with angiogenesis:



Formula (Ic)

wherein R^{1c} and R^{2c} are independently selected from hydrogen, halogen, -CN, a hydrocarbyl group or a group of Formula (IIc);



Formula (IIc)

wherein W^c is aryl or a heterocyclic group,

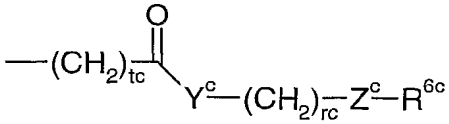
R^{4c} is independently selected from hydrogen, halogen, -OH, amino, alkanoylamino, —OPO_3H_2, or a hydrocarbyl group, wherein the amino group is optionally substituted by an amino acid residue and the hydroxy group is optionally esterified or two R^{4c} groups together form an optionally substituted cyclic or heterocyclic group;

X^c is selected from —S—, —O—, —S(O)—, —$S(O_2)$— and —NH—;

pc is an integer from 0 to 4; and

qc is an integer from 1 to 4;

R^{3c} and R^{10c} are independently selected from hydrogen, lower alkyl or a group of Formula (IVc):



Formula (IVc)

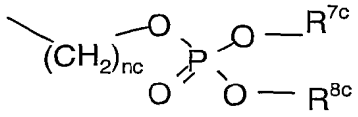
wherein Y^c is selected from —NH—, —O— or a bond;

Z^c is selected from —NH—, —O—, —C(O)— or a bond;

rc is an integer from 0 to 4;

tc is an integer from 0 to 1;

R^{6c} is hydrogen, a hydrocarbyl group or a group of Formula (Vc):



Formula (Vc)

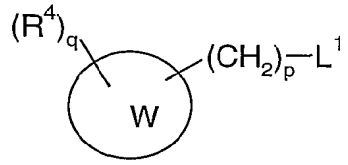
wherein nc is an integer of from 1 to 6, and;

R^{7c} and R^{8c} are independently selected from hydrogen or a hydrocarbyl group; and

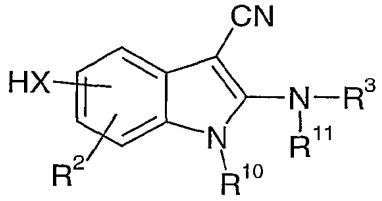
R^{11c} is hydrogen or lower alkyl;

13. A process for preparing a compound of Formula (I), or salt, or solvate thereof, which process (wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, m, n, p, q, r, t, W, X, Y and Z are unless otherwise specified as defined in Formula (I)) comprises:

a) for compounds of Formula (I) wherein R^1 is of the Formula (II) and X is —O—, —S— or —NH—, reacting a compound of Formula (A) with a compound of Formula (B),



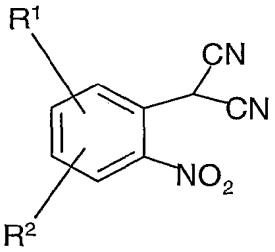
Formula (A)



Formula (B)

wherein L^1 is a leaving group;

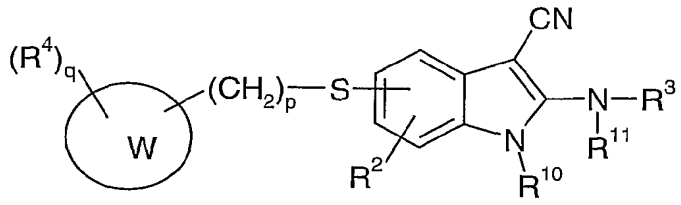
b) for compounds of Formula (I) in which R^3 is hydrogen and R^{11} is hydrogen may be prepared by reduction followed by ring closure of compounds of Formula (C):



Formula (C)

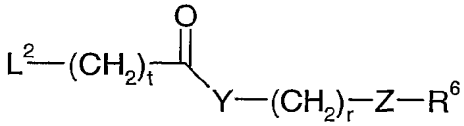
c) for compounds of Formula (I) wherein R^{10} is lower alkyl, reacting a compound of Formula (I) wherein R^{10} is hydrogen with a suitable alkylhalide,

d) for compounds of Formula (I) wherein R^1 is of the Formula (II) and X is —S(O)—, —$S(O_2)$—, oxidising a compound of Formula (D),



Formula (D)

e) for compounds of Formula (I) in which R^3 is a group of Formula (IV) may be prepared by the reaction of compounds of Formula (I) in which R^3 is hydrogen with compounds of Formula (F) below, in which L^2 is a leaving group.:



Formula (F)

and thereafter if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups;

iii) forming a salt, or solvate.

INTERNATIONAL SEARCH REPORT

ational Application No
PCT/GB 01/02335

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/42 A61K31/40 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, CHEM ABS Data, BIOSIS, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 533 672 A (EAKIN MURDOCH A ET AL) 6 August 1985 (1985-08-06) cited in the application claim 1; examples 1,2	1-8,13
A	WO 95 17181 A (PHARMACIA SPA) 29 June 1995 (1995-06-29) page 11, line 2 - line 18; claim 1	1-12
A	WO 99 02166 A (ANGIOGENE PHARM LTD ;DOUGHERTY GRAEME (GB)) 21 January 1999 (1999-01-21) page 12, line 12 - line 23; claim 1	1-12
P,X	WO 00 41669 A (ANGIOGENE PHARM LTD ;DAVIS PETER DAVID (GB)) 20 July 2000 (2000-07-20) page 11, line 9 - line 17; claim 1	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"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
30 July 2001	09/08/2001

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	Usuelli, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

tional Application No
PCT/GB 01/02335

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4533672 A	06-08-1985	AT 26261 T	15-04-1987
		AU 563413 B	09-07-1987
		AU 2054883 A	03-05-1984
		CA 1205078 A	27-05-1986
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		ES 526876 D	01-05-1985
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WO 9902166 A	21-01-1999	AU 8231198 A	08-02-1999
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		TR 9903149 T	21-09-2000
WO 0041669 A	20-07-2000	AU 1995700 A	01-08-2000

Patents JP2017503030

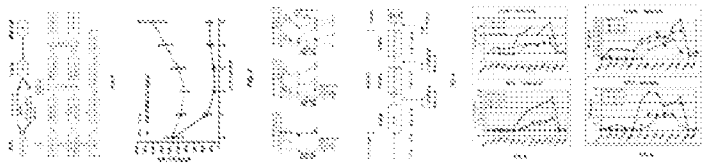
CRF1 receptor antagonist for the treatment of congenital adrenocortical hyperplasia

Abstract

translated from Japanese

CRF1 receptor antagonists directly inhibit ACTH release in patients with CAH, thereby allowing normalization of androgen production while using lower, more physiological doses of hydrocortisone, thus reducing treatment-related side effects. Has the ability to reduce. In one embodiment, a method for treating CAH is provided by administering to a subject in need an effective amount of a CRF1 antagonist, including but not limited to bedtime administration. The

Images (6)



Classifications

A61K31/519 Pyrimidines; Hydrogenated pyrimidines, e.g. trimethoprim ortho- or peri-condensed with heterocyclic rings

View 4 more classifications

JP2017503030A

Japan

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Other languages: Japanese

Inventor: ディミトリィー、グリゴリアディス、,ディミトリィー、グリゴリアディス、

Worldwide applications

2015 CA MX JP WO AU EP NZ CA KR RU HR CN CN RU HR
2016 IL 2018 US 2019 JP 2020 JP AU US 2021 US IL JP

Application JP2016565135A events

2014-01-21 Priority to US201461929941P

2015-01-21 Application filed by ニューロクライン バイオサイエンシーズ、インコーポレイテッド, ニューロクライン バイオサイエンシーズ、インコーポレイテッド

2017-01-26 Publication of JP2017503030A

2018-03-01 Publication of JP2017503030A5

2019-10-02 Application granted

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Status Active

2035-01-21 Anticipated expiration

Show all events

Info: Patent citations (57), Cited by (9), Legal events, Similar documents, Priority and Related Applications

External links: Espacenet, Global Dossier, Discuss

Claims (21)

Hide Dependent

translated from Japanese

A method for treating congenital adrenocortical hyperplasia (CAH) by administering to a subject in need a CRF $_1$ receptor antagonist having a dissociation half-life of greater than 30 minutes. The method of claim 1, wherein the CRF $_1$ receptor antagonist has a dissociation half-life of greater than 40 minutes. The method of claim 1, wherein the CRF $_1$ receptor antagonist has a dissociation half-life of greater than 50 minutes. Said CRF $_1$ receptor antagonist is compound I (NBI-77860; 2,5-dimethyl-3- [2-methyl-4- (methyloxy) phenyl] -N-[(1S) -1- (3-methyl- 1, 2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine). The CRF $_1$ receptor antagonists include NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalalmine (N-butyl-N-ethyl-2,5,6-trimethyl-7- (2,4,6- The method according to claim 1, which is trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine), or DMP904. 6. The method of any one of claims 1-5, wherein the CRF $_1$ receptor antagonist is administered at bedtime. 6. The method of any one of claims 1-5, wherein the CRF $_1$ receptor antagonist is administered during or prior to ACTH release with a predicted circadian rhythm. 8. The method of claim 7, wherein the CRF $_1$ receptor antagonist is administered 3-4 hours prior to ACTH release with a predicted circadian rhythm. A method for reducing the levels of 17-OHP and ACTH in a subject having congenital adrenocortical hyperplasia (CAH) comprising administering to the subject a CRF $_1$ receptor antagonist at bedtime. Including the method. 10. The method of claim 9, wherein the CRF $_1$ receptor antagonist is administered at or prior to ACTH release with a predicted circadian rhythm. 10. The method of claim 9, wherein the CRF $_1$ receptor antagonist is administered 3-4 hours prior to ACTH release with a predicted circadian rhythm. Said CRF $_1$ receptor antagonist is compound I (NBI-77860; 2,5-dimethyl-3- [2-methyl-4- (methyloxy) phenyl] -N-[(1S) -1- (3-methyl- The method according to any one of claims 9 to 11, which is 1,2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine). The CRF $_1$ receptor antagonists include NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalalmine (N-butyl-N-ethyl-2,5,6-trimethyl-7- (2,4,6- The method according to any one of claims 9 to 11, which is (trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine) or DMP904. A CRF $_1$ receptor antagonist for use in treating congenital adrenal hyperplasia (CAH), wherein the CRF $_1$ receptor antagonist has a dissociation half-life greater than 30 minutes, CRF $_1$ receptor antagonist. The CRF $_1$ receptor antagonist has a dissociation half-life greater than 40 minutes, CRF $_1$ receptor antagonist of claim 14. The CRF $_1$ receptor antagonist has a dissociation half-life greater than 50 minutes, CRF $_1$ receptor antagonist of claim 14. Said CRF $_1$ receptor antagonist is compound I (NBI-77860; 2,5-dimethyl-3- [2-methyl-4- (methyloxy) phenyl] -N-[(1S) -1- (3-methyl- The CRF $_1$ receptor antagonist according to claim 14, which is 1,2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine). The CRF $_1$ receptor antagonists include NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalalmine (N-butyl-N-ethyl-2,5,6-trimethyl-7- (2,4,6- The CRF $_1$ receptor antagonist according to claim 14, which is (trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine) or DMP904. The CRF $_1$ receptor antagonist is suitable for administration at bedtime, CRF $_1$ receptor antagonist

according to any one of claims 14 to 18. The CRF $_1$ receptor antagonist is suitable for administration at the time of ACTH release by circadian rhythms predicted or before that, CRF $_1$ receptor antagonist according to any one of claims 14 to 18. The CRF $_1$ receptor antagonist is suitable for administration to 3-4 hours prior to ACTH release by circadian rhythm expected, CRF $_1$ receptor antagonist according to any one of claims 14 to 18.

Description

translated from Japanese

(background)
(Technical field)
Compositions and methods for treating congenital adrenocortical hyperplasia are described herein.

(Description of related technology)
Congenital adrenocortical hyperplasia (CAH) is a group of autosomal recessive genetic disorders that produce little or no cortisol biosynthesis. The most frequent form of the disease is a 21-hydroxylase deficiency caused by mutations in the CYP21A2 gene located on chromosome 6p21, accounting for about 95% of CAH cases (for review see, for example, Speiser et al. , Int. J. Pediatr. Endocrinol. 2010: 494173 (2010)). These mutations can range from a complete loss of enzyme activity required for cortisol synthesis in the adrenal cortex to a range of partial losses resulting in disease severity that is a direct consequence of certain mutations. This continuous form of 21-hydroxylase deficiency is more commonly known as salt-loss and simple maleized forms (grouped as classical CAH) and non-classical CAH (NCCAH) or "late-onset" CAH. It has been broadly classified into a mild form, which is usually diagnosed in late childhood or early adulthood. Nonclassical CAH patients have either homozygous or complex heterozygotes, often with a classical CAH allele. These patients have sufficient enzymatic activity (> 20-50% normal), so that they have no salt loss or cortisol deficiency, have normal external genitals at birth, and many It remains asymptomatic throughout life (Trap et al., Steroids 77 (4): 342-46 (2012)). In the less frequent form of the disease (which accounts for 5% of cases), mutations in the 11β-hydroxylase gene CYP11B1 result in CAH (11β-OH CAH).
Both genetic variations result in congenital adrenocortical hyperplasia, cortisol deficiency and excessive adrenocorticotropic hormone (ACTH) production, along with androgen overproduction. These patients require lifelong management with glucocorticoids and the problems associated with such treatment. Thus, treatment regimens are very necessary to improve health, well-being, quality of life, and to manage associated disorders in patients with CAH.

Speiser et al. , Int. J. et al. Pediatr. Endocrinol. 2010. 494173 (2010) Trapp et al. , Steroids 77 (4). 342-46 (2012)

(Summary)
Corticotropin releasing factor (CRF) activates CRF $_1$ receptor, a class B G protein-coupled receptor (GPCR). CRF $_1$ antagonists directly inhibit ACTH release in patients with CAH, thereby allowing normalization of androgen production while using lower, more physiological doses of hydrocortisone and reducing treatment-related side effects Have

in one embodiment, a method for treating CAH is provided by administering to a subject in need an effective amount of a CRF $_1$ antagonist, including but not limited to bedtime administration. is done.

in a more specific embodiment, the CRF $_1$ antagonist has a dissociation half-life ($t_{1/2}$) greater than 30 minutes, and in another embodiment greater than 40 minutes, and in another embodiment greater than 50 minutes. Have.

Embodiment 1 A method for treating congenital adrenocortical hyperplasia (CAH) by administering to a subject in need a CRF $_1$ receptor antagonist having a dissociation half-life of greater than 30 minutes.

Embodiment 2 The method of embodiment 1, wherein the CRF $_1$ receptor antagonist has a dissociation half-life of greater than 40 minutes.

Embodiment 3 The method of embodiment 1, wherein the CRF $_1$ receptor antagonist has a dissociation half-life of greater than 50 minutes.

Embodiment 4 The CRF $_1$ receptor antagonist is compound I (NBI-77860; 2,5-dimethyl-3- [2-methyl-4- (methyloxy) phenyl] -N-[(1S) -1- (3 -Methyl-1,2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine) according to any one of embodiments 1-3. .

Embodiment 5 The CRF $_1$ receptor antagonist is NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmine (N-butyl-N-ethyl-2,5,6-trimethyl-7- (2,4 , 6-trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine), or DMP904.

Embodiment 6 The method of any one of Embodiments 1 to 5, wherein the CRF $_1$ receptor antagonist is administered at bedtime.

Embodiment 7 The method of any one of Embodiments 1 to 6, wherein the CRF $_1$ receptor antagonist is administered during or prior to ACTH release by a predicted circadian rhythm.

Embodiment 8 The method of embodiment 7, wherein the CRF $_1$ receptor antagonist is administered 3-4 hours before ACTH release with a predicted circadian rhythm.

Embodiment 9 A method for reducing the levels of 17-OHP and ACTH in a subject having congenital adrenocortical hyperplasia (CAH) comprising: subjecting the subject to a CRF $_1$ receptor antagonist at bedtime Administering a step of administering.

Embodiment 10 The method of embodiment 9, wherein the CRF $_1$ receptor antagonist is administered during or prior to ACTH release by a predicted circadian rhythm.

Embodiment 11 The method of embodiment 9 or embodiment 10, wherein the CRF $_1$ receptor antagonist is administered 3-4 hours prior to ACTH release with a predicted circadian rhythm.

Embodiment 12 The CRF $_1$ receptor antagonist is compound I (NBI-77860; 2,5-dimethyl-3- [2-methyl-4- (methyloxy) phenyl] -N-[(1S) -1- (3 -Methyl-1,2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine) according to any one of embodiments 9-11. .

Embodiment 13 The CRF $_1$ receptor antagonist is NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmine (N-butyl-N-ethyl-2,5,6-trimethyl-7- (2,4 , 6-trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine), or DMP904.

A CRF $_1$ receptor antagonist for use in treating an embodiment 14 Congenital adrenal hyperplasia (CAH), wherein the CRF $_1$ receptor antagonist has a dissociation half-life greater than 30 minutes, CRF $_1$ receptors Antagonists.

Embodiment 15 wherein CRF $_1$ receptor antagonist has a dissociation half-life greater than 40 minutes, CRF $_1$ receptor antagonists described 14.

Embodiment 16 wherein CRF $_1$ receptor antagonist has a dissociation half-life greater than 60 minutes, CRF $_1$ receptor antagonist of embodiment 14.

Embodiment 17 The CRF $_1$ receptor antagonist is compound I (NBI-77860; 2,5-dimethyl-3- [2-methyl-4- (methyloxy) phenyl] -N-[(1S) -1- (3 CRF according to any one of embodiments 14 to 16, which is -methyl-1,2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine). $_1$ receptor antagonist.

Embodiment 18 The CRF $_1$ receptor antagonist is NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmine (N-butyl-N-ethyl-2,5,6-trimethyl-7- (2,4 , 6-trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine), or DMP904 CRF $_1$ receptor antagonist according to any one of embodiments 14-16.

CRF $_1$ receptor antagonist of embodiment 19 wherein the CRF $_1$ receptor antagonists, which have any one of embodiments 14 to 18 suitable for administration at bedtime.

Embodiment 20 wherein CRF $_1$ receptor antagonists, CRF $_1$ receptor antagonist according to which has any one of embodiments 14-19 suitable for administration at the time of ACTH release by circadian rhythms predicted or before that .

Embodiment 21 wherein CRF $_1$ receptor antagonists, CRF $_1$ receptor according to which has any one of embodiments 14 to 20 suitable for administration to 3-4 hours prior to ACTH release by circadian rhythms predicted Antagonists.

In other embodiments, the methods and uses described above and herein provide the amount of glucocorticoid or mineralocorticoid to a full grown subject (eg, a human subject) with CAH. At least 10%, 15%, 20%, 30%, 40%, 50% from the recommended daily dose of GC to be administered (eg, hydrocortisone (HC), prednisone, prednisolone, dexamethasone, or fludrocortisone) And a step of reducing by 60%. In other embodiments, the methods and uses described above and herein provide that an amount of glucocorticoid or mineralocorticoid is administered to a growing subject (eg, a human subject) having CAH. Reducing at least 10%, 15%, 20%, 30%, 40%, 50%, 60% from the recommended daily dose of GC (eg, hydrocortisone) or mineral corticoid (eg, fludrocortisone) is further included.

These and other embodiments will be apparent upon reference to the following detailed description. To this end, various references describing in more detail certain background information, procedures, compounds and compositions are set forth herein, each of which is incorporated herein by reference in its entirety. Is done.

Terms not specifically defined herein are intended to be given the meanings given to them by those skilled in the art in view of the present disclosure and context. However, as used herein, unless specified to the contrary, the above terms have the meaning indicated. Throughout this specification, references to "one embodiment" or "an (one) embodiment" include at least one particular feature, structure, or characteristic described in connection with the above embodiment. Means. Thus, the appearances of the phrases "in one embodiment" or "in one (one) embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

Also, as used herein and in the appended claims, the singular forms "a" (one), "an" (one), and "the" (above, this, that) "includes a reference to the plural unless the context clearly indicates otherwise. Thus, for example, reference to "a non-human animal" can refer to one or more non-human animals, or a plurality of such animals, and "a cell" Alternatively, reference to "the cell" includes reference to one or more cells and equivalents thereof (eg, a plurality of cells) known to those of skill in the art, and the like. If a method step is described or claimed and said steps are described to occur in a particular order, the second step "before" (ie, before) the second step occurs (or takes place) The description of the first step has the same meaning when the second step is rewritten to a state that occurs (or is performed) "following" the first step. The term "about" refers to a number or numerical range where the referenced number or numerical range is within experimental variability (or within statistical experimental error). It is an approximation, meaning that its number or numerical range can vary between 1% and 15% of the stated number or numerical range. Note also that the term "or (or or)" is generally used in its sense including "and / or" (and / or) unless the context clearly indicates otherwise. Shall. The term "at least one" has the same meaning and understanding as the term "one or more", for example when referring to at least one compound or at least one composition.

FIG. 1 shows a schematic diagram of a steroid synthesis pathway in the adrenal gland. The most common form of CAH is caused by a 21-hydroxylase (also called 21-α hydroxylase) deficiency, resulting in a decrease in cortisol and an increase in androgens (eg, testosterone and estrogens). A rarer type of classical CAH is 11β-hydroxylase deficiency.

FIG. 2 presents a graph illustrating the effect of Compound I (NBI-77860) on ACTH levels in adrenalectomized rats. Rats were given orally 30 mg / kg Compound I (NBI-77860). Data are expressed as mean plasma concentration of ACTH (± SEM).

FIGS. 3A-C represent graphs illustrating the effect of CRF $_1$ receptor antagonists on ACTH concentrations (distinguished by their dissociation half-life) in adrenalectomized rats.

FIG. 4 is a study design schematic of the clinical trial described in Example 5, designed to evaluate the safety, tolerability and plasma exposure of NBI-77860, and HPA (hypothalamic-pituitary-adrenal).) Represents the effect of this compound on endogenous levels of system hormones.

FIG. 5 represents mean 17-OHP (upper panel) and ACTH levels (lower panel) data during the 24 hour period after administration during the clinical study described in Example 6.

FIG. 6 depicts specific individual subject responses for 17-OHP (upper panel) and ACTH levels (lower panel) over time after administration of 300 mg and 600 mg of NBI-77860 and placebo.

(Detailed explanation)
As described herein, CRF $_1$ receptor antagonists were found to directly inhibit ACTH release in patients with CAH, thereby allowing normalization of androgen production. Administration of a CRF $_1$ receptor antagonist allows the use of lower and more physiological doses of hydrocortisone in subjects with CAH, thus reducing treatment-related side effects.

Newborn screening for CAH is performed by an immunoassay that measures 17-OHP levels in heelstick capillary blood specimens obtained within 72 hours of birth. The blood samples are analyzed for 17-OHP by a commercial dissociation enhanced lanthanide fluorescence immunoassay (DELFIA; PerkinElmer, Waltham Massachets) (White et al., J. Pediatr. 163: 10-12 (2013)).

Nine states in the United States are using the second number of screening tests between 8 and 14 days after birth using biochemical and molecular genetic testing methods, with five more strongly Recommended. Such biochemical methods include immunoassay or liquid chromatography using organic solvent extracts followed by tandem mass spectrometry to determine the steroid ratio of 17-OHP, androstenedione, and 21-deoxycortisol to cortisol. (See, for example, Speiser et al., Int. J. Pediatr. Endocrinol. 2010: 494173, 2010). Genetic screening examines CYP21A2 mutations associated with CAH. Although not widely used in the United States, the addition of a second screen could potentially improve the sensitivity of the entire screening process (here, about 72% for the first screen alone).

Without newborn screening results, young girls with classic CAH are typically identified due to the presence of external genitals with ambiguous gender. Because men have normal external genitals when born, they are not diagnosed unless newborn screening is performed or other medical complications are noticed. Infants who are not initially diagnosed with CAH and experience the salt-losing form of the disease are later diagnosed in the context of insufficient weight gain, vomiting, hyperkalemia and hyponatremia within the first few weeks of life. The

Treatment of CAH is based on normalization of hormone and steroid levels using various drug therapies from diagnosis in childhood to adulthood. Glucocorticoids are currently the standard treatment in CAH and are used to both correct endogenous cortisol deficiency and reduce elevated pituitary ACTH levels (which drive increased androgen production) Is done. Unlike the treatment of Addison's disease (decrease in adrenal function), where cortisol replacement is sufficient, treatment of CAH must also reduce ACTH production and control subsequent androgen excess. Thus, the goal of glucocorticoid treatment is to prevent cortisol supplementation and ACTH suppression in women to prevent masculinization and menstrual disturbances and to inhibit testicular adrenal rest tumor in men. Including. Mineralocorticoid supplementation is required to achieve normal plasma renin activity for maintenance of normal blood pressure, electrolyte balance, and volume state in those patients with a salt-loss form of CAH.

Glucocorticoid treatment regimens support normal physiology and also ensure that sufficient cortisol is available during events that can elicit strong stress responses (eg, comorbidities, exercise, hypotension) Must be secured. Careful monitoring is also necessary to avoid the occurrence of iatrogenic Cushing syndrome due to glucocorticoid overtreatment in an attempt to sufficiently suppress androgen production or Addison syndrome due to inadequate treatment. While overtreatment with mineralocorticoids can cause hypertension, inadequate treatment can lead to hypotension, salt loss, fatigue and increased demand for glucocorticoids Typical laboratory tests to monitor the efficacy of treatment include measurement of 17-OHP, androstenedione, testosterone, renin activity, and electrolyte plasma concentrations.

Adult patients with CAH have an increased prevalence of cardiovascular risk factors including obesity, hypertension, and insulin resistance (eg, Kim et al., Semin Reprod. Med. 27 (4): 316-21 (2009)). From a large cohort study of pediatric and adult CAH patients (n = 244), patients frequently experience inadequate hormonal control and the aforementioned adverse outcomes despite being prescribed various glucocorticoid treatment regimens. (See, for example, Finkelstain et al., J. Clin. Endocrinol Metab. 97 (12): 4429-38 (2012)).

Treatment of CAH involves glucocorticoids (usually hydrocortisone in children but often more potent drugs with a narrow therapeutic index, such as dexamethasone in adults), and mineralocorticoids (if needed for salt loss) This includes attempts to normalize cortisol deficiency (usually fludrocortisone). However, the glucocorticoid dose required to achieve sufficient suppression of excess androgens is usually sufficient for normal physiological doses used only for cortisol replacement, as in patients with Addison's disease. It has exceeded. This increased exposure to glucocorticoids can result in iatrogenic Cushing syndrome, increased cardiovascular risk factors, impaired glucose tolerance, and decreased bone mineral density in CAH patients (eg, Elnecave et al. M., J. Pediatr Endocrinol.Metab.21: 1155-62 (2008); King et al., J.Clin.Endocrinol.Metab.91 (3): 8566-59 (2006); Migeon et al. Metab. Clin. North Am. 30: 193-205 (2001)).

Adrenocorticotropic hormone releasing factor (CRF) was isolated from sheep hypothalamus and identified as a 41 amino acid peptide. CRF has been found to produce significant changes in the functions of the endocrine system, nervous system, and immune system. CRF is the main physiological of basal and stress-induced release of adrenocorticotropic hormone ("ACTH"), β-endorphin, and other proopiomelanocortins ("POMC") (anterior pituitary derived peptides) It is thought to be a regulator (see, eg, Vale et al., Science 213: 1394-1397, 1981). Secretion of CRF causes ACTH release from corticotrophs in the anterior pituitary gland through binding to the CRF $_1$ receptor, a member of the class B family of G protein coupled receptors.

Due to the physiological importance of CRF, the development of biologically active small molecules that have significant CRF $_1$ receptor binding activity and can antagonize the CRF $_1$ receptor is still a desired goal, anxiety, it continues to be the subject of ongoing research and development for the treatment of depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse.

The pituitary hormone ACTH is under the control of the hypothalamic corticotropin releasing factor (CRF) and stimulates cholesterol uptake and drives the synthesis of pregnenolone that initiates steroidogenesis in the adrenal gland (see FIG. 1). about). The adrenal cortex is composed of three zones, which produce distinct classes of hormones, many of which are driven by ACTH, which mobilizes cholesterol through this pathway. Loss of these enzymes as a result of mutation or deletion causes an increase in substrate concentration. The most common form of CAH resulting from mutations or deletions in the 21-hydroxylase gene (CYP21A2) is a potent androgen due to the accumulation of the steroid precursors progesterone and 17-hydroxyprogesterone (17-OHP). is produced by the adrenal glands. Plasma levels of 17-OHP can reach 10 to 1000 times the normal concentration in these cases. These increases result in overproduction of androgens, specifically androstenedione, testosterone, and dihydroxytestosterone, causing masculinization in women. Furthermore, 21-hydroxylase deficiency in CAH causes inadequate biosynthesis of glucocorticoids and mineralocorticoids, specifically cortisol and aldosterone. Cortisol is an important negative feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates inhibition on the hypothalamus and pituitary gland, which increases ACTH levels. Excessive ACTH stimulation causes cord and reticulum hypertrophy, resulting in adrenal hyperplasia.

In one embodiment, the CRF $_1$ receptor antagonist useful for the treatment of CAH is NBI-77860, 2,5-dimethyl-3- [2-methyl-4- (methyloxy) phenyl] -N-[(1S)- 1- (3-methyl-1,2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine (also referred to herein as "Compound I") This has the following structure:

Compound I is a potent CRF $_1$ antagonist with binding pKi = 8.2 (eg Tellew et al., Bioorg. Med. Chem. Lett. 20: 7259, 2010 and International Patent Application Publication No. WO 2006/044958). (Both of which are incorporated herein by reference in their entirety)). As described herein, Compound I has a potent ACTH-lowering effect as shown in adrenalectomized rats.

In another embodiment, CRF $_1$ receptor antagonists useful for treating CAH are US Pat. Nos. 6,586,456, 6,806,282, 6,531,475, 664,261, 6,610,678, WO 98/08846, WO 98/11075, WO 99/10350, WO 2000/059888, WO 2006/044821, WO 2006/102194, WO 2006/107784, WO 2006/116412, WO 2006/126718, WO 2007/066955, WO 2007/069671, WO 2008/036541, WO 2008/036579, WO 2008/051533, WO 2008/082003, WO 2008/083070, WO 200 / 136377, WO 2009/008552, WO 2009/144632, WO 2010/014280, WO 2010/014687, WO 2010/015628, WO 2010/015655, WO 2010/062718, WO 2010/096426, WO 2011/043387, WO 2011 / 092293, WO 2011/095450, WO 2011/092290, and WO 2011/043381.

In yet another embodiment, the CRF $_1$ receptor antagonist is NBI-30775, CP-316, 311, Pexacerfont, emicerfont, SSR-125543 [4- (2-Chloro-4-methoxy-5-methylphenyl).) -N-[(1S) -2-cyclopropyl-1- (3-fluoro-4-methylphenyl) ethyl] -5-methyl-N- (2-propyn-1-yl) -2-thiazolamine] , SSR-126374, ONO-2333, NBI-34041, JNJ-19567470, GSK586529, PF-00572778, CP-376395, antalarmine (N-butyl-N-ethyl-2,5,6-trimethyl-7- (2, 4,6-trimethylphenyl) pyrrolo [3,2- e] pyrimidine-4-amine), and DMP904.

In yet another embodiment, the CRF $_1$ receptor antagonist has a dissociation half-life ($t_{1/2}$) greater than 30 minutes, and in another embodiment greater than 40 minutes, and in another embodiment greater than 50 minutes. Have. The dissociation half-life of a particular CRF $_1$ receptor antagonist is determined by the technique disclosed in Example 3. Representative CRF $_1$ receptor antagonists of these embodiments include Compound I, NBI-30775, NBI-34041, SSR-125543A, antalarmine (N-butyl-N-ethyl-2,5,6-trimethyl-7- (2 , 4,6-trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine), and DMP904

With respect to the compounds described herein, it is also to be understood that when a particular position is designated as hydrogen, such hydrogen (H) can be replaced with deuterium (D). . Incorporation of deuterium instead of hydrogen is known to produce significant effects on the physiological and pharmacological activity of the substituted compound. To this end, it should be understood that deuterium substitution of hydrogen means that the deuterium abundance at that position is substantially greater than the natural deuterium abundance. Thus, in one embodiment, representative compounds include the following.

In another embodiment, any of the aforementioned compounds may incorporate a stable or radioactive isotope. Thus, the use of isotopically-labelled compounds identical to those described herein is also contemplated, wherein one or more atoms are atoms that differ from some atomic mass or mass number normally found in nature. Substituted by an atom having a mass or mass number. Examples of isotopes that can be incorporated into these compounds include hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine isotopes, eg. deuterium (^{2}H) as discussed above, and ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl are included, but are not limited thereto. Certain isotopically-labelled compounds, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are also useful in drug or substrate tissue distribution assays. Tritium hydrogen (^{3}H) and carbon 14 (^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Substitution with heavier isotopes (eg, deuterium (^{2}H)) may provide certain metabolic benefits resulting from greater metabolic stability, eg, increased in vivo half-life or reduced dose requirements, Therefore, it may be preferable in some environments. Isotopically labeled compounds can generally be prepared by performing procedures routinely practiced in the art.
(Effect on plasma ACTH in adrenalectomized rats)

Adrenalectomy eliminates circulating corticosterone (the main glucocorticoid) in rats and eliminates negative feedback control of the HPA system at both the hypothalamic and pituitary (adrenocortical hormone producing cells) levels, and thus plasma ACTH (See, for example, Mims et al., J. Natl. Med. Assoc. 69: 145-47 (1977)) Intravenous injection of peptide CRF $_{1}$ receptor antagonists has been shown to reduce high plasma ACTH levels in adrenalectomized (ADX) rats (see, eg, Rivier et al., J. Med. Chem. 12: 42: 3175). 82 (1999)). These findings were reproduced with the low molecular weight NBI-77860 (Compound I). In adrenalectomized rats, Compound I has a potent capacity for ACTH reduction. The greatest reduction in ACTH correlated with the peak plasma concentration of NBI-77860, however, the duration of the ACTH-lowering effect was beyond drug plasma exposure. Thus, there is a predictable relationship between integrated plasma exposure of NBI-77860 and in vivo efficacy after oral administration in adrenalectomized rats.

The effectiveness of a compound as a CRF receptor antagonist can be determined by various assays The CRF antagonists described herein can inhibit the specific binding of CRF to its receptor and, as a result, can antagonize the activity associated with CRF. A compound can be evaluated for activity as a CRF antagonist by one or more commonly accepted assays, including the assays described in the Examples. CRF antagonists useful in the methods described herein include compounds that exhibit affinity for the CRF receptor.

While not wishing to be bound by theory, in the treatment of CAH, CRF receptor antagonists potentially block ACTH release from pituitary corticotrophic cells, thereby reducing androgen production. Allows for a more sophisticated treatment methodology for cortisol supplementation. Animal and human studies have shown the pharmacological effect of Compound I (NBI-77860) on ACTH release. Standard biomarker assessments used by endocrinologists when monitoring treatment efficacy can be used to monitor the effects of this CRF $_{1}$ receptor antagonist. Plasma levels of 17-OHP, androstenedione, testosterone, cortisol and ACTH, and urinary metabolites of these steroids are easily measured in both children and adults, giving quick and meaningful data regarding the effects of treatment.
(Pharmaceutical compositions and methods for treatment)

The present disclosure relates to a pharmaceutical composition for use in a method for treating CAH comprising any one of the CRF antagonist compounds described herein and a pharmaceutically acceptable excipient. Provide further. Pharmaceutically acceptable excipients are physiologically and pharmaceutically suitable, non-toxic and inert substances or components that do not interfere with the activity of the active ingredient; It can be said. The CRF antagonist compound is used in a pharmaceutical composition for use in a treatment or preventive (or prophylactic) treatment (eg, reducing exacerbation of CAH disease or the occurrence or recurrence of one or more symptoms of the disease). It can be formulated. The methods and excipients described herein are exemplary and are in no way limiting. Pharmaceutically acceptable excipients are well known in the pharmaceutical art and are described, for example, by Rowe et al. , Handbook of Pharmaceutical Excipients: A Comprehensive Guide to Uses, Properties, and Safety, 5 th Ed. , 2006 and Remington: The Science and Practice of Pharmacy (Gennaro, 21 st Ed. Mack Pub. Co., Easton, PA (2005)). Examples of pharmaceutically acceptable excipients include sterile saline and phosphate buffered saline at physiological pH. Preservatives, stabilizers, dyes, buffering agents and the like may be provided in the pharmaceutical compositions. In addition, antioxidants and suspending agents can also be used.

Therapeutic and / or prophylactic benefits include, for example, improved clinical outcome (both therapeutic treatment and prophylactic or preventative measures), where the objective is to reduce undesirable physiological changes or disorders. Preventing, delaying or delaying (reducing), or preventing or delaying or delaying (reducing) the spread or severity of such disorders. As discussed herein, beneficial or desirable clinical results from treating a subject include, but are not limited to: Does it result from a disease, condition or disorder to be treated? Or a reduction, reduction, or alleviation of symptoms associated with them; a decrease in the occurrence of symptoms; an improvement in quality of life; a condition that is free of disease (ie, subject has symptoms (based on which the disease is diagnosed) Decrease the likelihood or tendency to show); decrease the degree of disease; stable (ie, not aggravating) disease; delay or delay in disease progression; improvement or reduction of the disease state As well as detectable or undetectable, regression (whether partial or whole); and / or overall survival. "Treatment" can also mean prolonging survival as compared to expected survival if the subject does not receive treatment. Subjects in need of treatment include those who already have the condition or disorder, as well as subjects who are prone to or at risk of developing the disease, condition or disorder, and the disease or condition. Or people whose disability should be prevented (ie, reducing the likelihood of the disease, disorder or condition occurring). The subject can be a human or non-human mammal (eg, rat, mouse, dog, cat, farm animal, zoo animal).

Optimal dosages can generally be determined using experimental models and / or clinical trials. The optimal dose can depend on the subject's body mass, weight, or blood volume. In general, the amount of a compound described herein present in a dose ranges from about 0.1 mg to about 30 mg / kg subject body weight. In certain embodiments, the single dose is about 50-1000 mg. The use of the minimum dose that is sufficient to provide effective treatment is usually preferred. Subjects can generally be monitored for therapeutic efficacy by clinical assessment and using assays suitable for the condition being treated or prevented. This assay is familiar to those skilled in the art and is described herein. The level of the compound administered to the subject is other biologicals in the biological fluid, eg, blood, blood fraction (eg, serum) and / or urine, and / or derived from the subject. Can be monitored by determining the level of the compound in a laboratory sample. Any method practiced in the art to detect the compound can be used to measure the level of the compound during the course of a treatment regimen.

The dose of the composition for treating CAH or related diseases or disorders comprising at least one of the compounds described herein depends on the condition of the subject, ie the stage of the disease, the disease. The severity of symptoms caused, general health, and age, gender and weight, and other factors apparent to those skilled in the medical arts. Similarly, the dose of the compound can be determined according to parameters understood by those skilled in the medical arts.

The pharmaceutical compositions described herein comprising at least one of the CRF $_{1}$ antagonist compounds described herein are among several routes that efficiently deliver an effective amount of the compound. Any one can be administered to a subject in need. Such administration routes include, for example, oral, parenteral, intestinal, rectal, nasal, buccal, sublingual, intramuscular, and transdermal. Compositions administered by these routes of administration and the like are described in more detail herein.

Administration of the disclosed compounds or compositions includes night administration or administration prior to going to bed (ie, bedtime administration). As used herein, bedtime administration is clinically relevant to the CRF $_1$ antagonist at or before (eg, 2 to 5 hours before) the release of ACTH according to the expected circadian rhythm. Administration that is intended to deliver a concentration. This ACTH release is typically 1-2 am, and most orally administered drugs have a Tmax of several hours, so, for example, 3 to 3 of ACTH release due to the expected circadian rhythm. Administration at 10pm, 4 hours before, is desirable. This same prepulse bedtime administration may be adapted for shift workers (eg, people who work at night and sleep during the day), in which case the administration may not necessarily occur at night . Thus, administration depends on the expected circadian rhythm of ACTH release and can vary depending on the individual's (ie, subject, patient's) specific work and sleep patterns. In certain embodiments, the CRF $_1$ receptor antagonists described herein (eg, NBI-77860, or NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalalmine (N-butyl-N-- Ethyl-2,5,6-trimethyl-7- (2,4,6-trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine), or any one of DMP904) Administered about 2 to 5 hours before (ie, first) the ACTH release due to circadian rhythm. In other embodiments, the CRF $_1$ receptor antagonist is administered to the subject during about 2-4 hours or 3-5 hours prior to ACTH release with the expected circadian rhythm. In a more specific embodiment, the CRF $_1$ receptor antagonist is administered to the subject during about 3-4 hours prior to the release of ACTH according to the expected circadian rhythm.

Also provided herein are methods for reducing 17-OHP and / or ACTH levels in a subject with CAH (ie, patient, individual) by administering a CRF $_1$ receptor antagonist. In certain embodiments, the antagonist is administered at or prior to ACTH release with an expected circadian rhythm. In certain other embodiments, the CRF $_1$ receptor antagonist is administered during about 2-4 hours or about 3-5 hours prior to the expected circadian rhythm ACTH release. In a more specific embodiment, the CRF $_1$ receptor antagonist is administered to the subject during about 3-4 hours prior to ACTH release with the expected circadian rhythm.

Described herein including administering to a female subject in need a CRF $_1$ receptor antagonist in the manner described herein that causes a decrease in the levels of ACTH and 17-OHP in said subject. Methods can result in reduced release of androgens (eg, testosterone and androstenedione. The dose of glucocorticoid can be concomitantly reduced by a clinically significant amount, which in turn reduces side effects. Produce.

The amount of glucocorticoid (GC) and mineralocorticoid (MC) for maintenance therapy in patients with CAH and young growing patients and for maintenance therapy in mature patients is known to those skilled in the art . For example, guidelines can be found in Speiser et al. (J. Clin. Endocrinol. Metab. 95: 4133-60 (2010) (incorporated by reference in its entirety) and shown in Tables 1 and 2 therein, in particular, young growth with CAH. With respect to patients in the art, those skilled in the art will recognize that administration too high with GC can interfere with stature growth in the patient, and thus a book for treating patients with CRF $_1$ receptor antagonists. The methods described herein can include reducing the dose of GC in a clinically significant manner.

In certain embodiments, the method for treating CAH by administering a CRF $_1$ receptor antagonist administers GC at a dose lower than the currently recommended GC dose for treating a subject with CAH. A step can be further included. If the subject is a mature patient, the GC dose (eg, hydrocortisone (HC), prednisone, prednisolone, dexamethasone, or fludrocortisone recommended for maintenance therapy in mature subjects) is: 15-25 mg / day HC, 5-7.5 mg / day Prednisone, 4-6 mg / day Prednisolone; 0.25-0.5 mg / day Dexamethasone, or 0.05-0.2 mg / day Fludrocortisone The dose can be reduced to the extent of about 10%, 15%, 20%, 30%, 40%, 50%, 60% or more. In growing subjects with CAH, the recommended dose of GC (eg, HC) can be reduced from a total recommended dose of 10-15 mg / m ^{2} / day and / or 0.05-0.2 mg. The total dose of fludrocortisone / day is about 10%, 15%, 20%, 30%, 40%, 50%, respectively, in subjects receiving a CRF $_1$ receptor antagonist as described herein. It can be reduced by as much as 60% or more. In one embodiment, a method described herein comprising administering an effective amount of a CRF $_1$ antagonist to a subject in need comprises a clinically significant reduction in ACTH levels compared to placebo. Produce. In a specific embodiment, administering an effective amount of a CRF $_1$ antagonist to a subject in need results in a clinically significant reduction in ACTH levels compared to placebo, wherein the reduction is at least 25%. In another embodiment, administering an effective amount of a CRF $_1$ antagonist to a subject in need results in a clinically significant decrease in ACTH levels compared to placebo, wherein the decrease is at least 50%. For guidelines on the administration of glucocorticoids and mineralocorticoids, see Speiser et al. See (above).

In another embodiment, a method described herein comprising administering an effective amount of a CRF $_1$ antagonist to a subject in need comprises a 17-OHP level clinically compared to a placebo. A significant decrease occurs. In another specific embodiment, administering an effective amount of a CRF $_1$ antagonist to a subject in need results in a clinically significant decrease in 17-OHP levels compared to placebo, wherein The decrease is at least 25%. In yet another embodiment, administering an effective amount of a CRF $_1$ antagonist to a subject in need results in a clinically significant reduction in 17-OHP levels compared to placebo, wherein the reduction is at least 50%.

In one embodiment, a method described herein comprising administering an effective amount of a CRF $_1$ antagonist to a subject in need comprises both ACTH and 17-OHP levels compared to placebo. Produces a clinically significant decrease in In certain embodiments, administering an effective amount of a CRF $_1$ antagonist to a subject in need results in a clinically significant decrease in both ACTH and 17-OHP levels compared to placebo. Where the reduction is at least 25%. In another specific embodiment, administering an effective amount of a CRF $_1$ antagonist to a subject in need results in a clinically significant decrease in both ACTH and 17-OHP levels compared to placebo. Occurs, where the reduction is at least 50%.

The pharmaceutical composition can be in the form of a solution. Alternatively, they can be in the form of a solid (eg, powder, tablet, etc.). A composition comprising any one of the compounds described herein can be formulated for sustained or slow release. Such compositions can generally be prepared using well-known techniques and can be administered, for example, by oral, rectal or subcutaneous implantation, or by implantation at the desired target site. The sustained release formulation may comprise a compound dispersed in a carrier matrix and / or contained within a reservoir surrounded by a rate controlling membrane. Excipients for use within such formulations may be biocompatible and biodegradable; preferably, the formulation provides a relatively constant level of active ingredient release. The amount of active compound contained within the sustained release formulation will depend on the site of implantation, the rate of release and the expected duration, and the nature of the condition to be treated or prevented.

For oral formulations, at least one of the compounds described herein can be used alone or in combination with appropriate additives, eg, conventional additives (eg, lactose, mannitol, Corn starch or potato starch); with binders; with disintegrants; with lubricants; and, if desired, with diluents, buffering agents, wetting agents, preservatives, colorants and flavoring agents, tablets, Powders, granules or capsules can be made. The compounds can be formulated with buffering agents and / or enteric coatings to provide protection of the compounds from the low pH of the stomach environment. The compounds included in the composition can be formulated for oral delivery, for example, with a flavoring agent in a liquid, solid or semi-solid formulation and / or with an enteric coating. Oral formulations can be provided as gelatin capsules that can contain the active compound together with a powdered carrier such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar carriers and diluents can be used to make compressed tablets.

Example 1: CRF receptor binding activity CRF antagonists as used in the methods described herein are described in Grigoriadis et al. (See, eg, Mol. Pharmacol vol 50, pp 679-686, 1996) and Hoare et al. (See, eg, Mol. Pharmacol 63: 751-765, 2003) and can be assessed for binding activity to the CRF receptor by a standard radioligand binding assay as generally described. By utilizing a radiolabeled CRF ligand, the assay can be used to assess the binding activity of the compounds described herein with any CRF receptor subtype.

Briefly, the binding assay involves replacing a radiolabeled CRF ligand with the CRF receptor. More specifically, the binding assay is performed in 96-well assay plates using 1-10 μg cell membranes derived from cells stably transfected with human CRF receptor. Each well contains a compound of interest or a reference ligand (eg, sorbazine, urocortin I, or CRF), 0.05 mL of [^{125}I] tyrosine-sorbazine (final concentration about 150 pM or as determined by Scatchard analysis). K_D) and about 0.05 mL assay buffer (eg Dulbecco's phosphate buffered saline, 10 mM magnesium hydrochloride, 2 mM EGTA) containing 0.1 mL cell membrane suspension containing the CRF receptor. The mixture is incubated for 2 hours at 22 ° C., followed by separation of bound and free radioligand by rapid filtration through glass fiber filters. After three washes, the filter is dried and the radioactivity (^{125}I Auger electrons) is counted using a scintillation counter. All radioligand binding data can be analyzed using the nonlinear least square curve fitting program Prism (GraphPad Software Inc) or XLfit (ID Business Solutions Ltd).
Example 2: CRF $_1$ receptor agonist activity

Fleck et al. (As previously reported in J. Pharmacology and Experimental Therapeutics, 341 (2)" 518-531, 2012) (hereinafter referred to as "Feck et al", incorporated herein by reference in its entirety). Activity of the produced CRF $_1$ receptor antagonists. Such activity is reported as a kinetically derived affinity (K_i) calculated from the association rate constant (k_1) and dissociation rate constant (k_{-1}) by the following equation:

$K_i = k_{-1} / k_1$

See also Fleck et al. In As reported, kinetic K_i of the CRF $_1$ receptor antagonist listed in Table 1 below were reported:

By this same technique, the kinetic Ki of compound I (NBI-77860) was found to be as follows.
Example 3: Dissociation half-life of the CRF $_1$ receptor antagonist ($t_{1/2}$)

The dissociation half-life ($t_{1/2}$) of a CRF $_1$ receptor antagonist as used in the methods described herein is determined by the method of Flek et al. It is evaluated by the technique described in. As described therein, the dissociation rate constant for labeled and unlabeled ligands is expressed as k_{-1} while the drug dissociation half-life of the receptor ($t_{1/2}$) (this is equal to the median residence time) is calculated from the dissociation rate constant (k_{-1}) by the following equation:

$t_{1/2} = 0.693 / k_{-1}$

Fleck et al. As reported in, the dissociation half-life ($t_{1/2}$) of the CRF $_1$ receptor antagonists listed in Table 2 below was reported.

By this same technique, the dissociation half-life of Compound I (NBI-77860) was found to be as follows:

Thus, CRF $_1$ receptor antagonists having a dissociation half-life ($t_{1/2}$) of greater than 30 minutes include antalarmine, NBI-34041, DMP904, NBI-30775, SSR125543A, and NBI-77860 (Compound I) (But is not limited to these). These same compounds also are representative of the CRF $_1$ receptor antagonist having a dissociation half-life greater than 40 minutes ($t_{1/2}$) and dissociation half-life greater than 50 minutes to ($t_{1/2}$).
Example 4: Reduction of ACTH in adrenalectomized rats

Compound I (NBI-77860) (see, for example, Tellew et al., Bioorg. Med. Chem. Lett. 2010, 20: 7259; see WO2006044958) binds pKi 8.2, kinetic Ki 49nM (above, Table 1) and dissociated $t_{1/2}$ 58 min (Table 2 above) are potent CRF $_1$ antagonists.

Intravenous injection of peptide CRF $_1$ receptor antagonists has been shown to reduce high plasma ACTH levels in adrenalectomized (ADX) rats (eg, Rivier et al., J. Med. Chem. 12: 42: 3175). 82 (1999)). These findings were reproduced with the low molecular weight NBI-77860. When administered orally to ADX rats (n = 6 / group), a 30 mg / kg single dose of NBI-77860 significantly reduced plasma ACTH levels for up to 5 hours (see FIG. 2) The duration of efficacy correlated with the peak plasma concentration over time over drug plasma exposure. There is a predictable relationship between NBI-77860 integrated plasma exposure and in vivo efficacy after oral administration in adrenalectomized rats

Fleck et al. Also report the effects of CRF $_1$ receptor antagonists, distinguished by their dissociation half-life on plasma ACTH levels in adrenalectomized rats; ie, NBI 30775, NBI 34041 and NBI 35965. At the highest dose (10 mg / kg), all three ligands drastically reduced ACTH (1 hour after injection, FIGS. 3A-C). After a longer duration, a clear difference emerged between NBI 35965 and the other two ligands. The ACTH level returned to vehicle level by 2 hours for NBI 35965 (FIG. 3C), whereas the response persisted for 4-6 hours for NBI 30775 and NBI 34041 (FIG. 3A). And FIG. 3B).
Example 5: Pharmacodynamic effect of Compound I in humans

In this study, the pharmacodynamic effects of NBI-77860 (Compound I) on human subjects were compared with placebo and a single dose of alprazolam (0.75 mg) by the HPA system produced by metyrapone (0.04 g / kg). Evaluated by observing the effect of a single oral dose on response. Methyrapone blocks cortisol synthesis in the adrenal gland (thus mimicking the cortisol deficiency of CAH) and is associated with a sharp increase in ACTH levels.

Primary analysis was performed by determining ACTH values (AUC (30 minutes to 4 hours)) between 30 minutes and 4 hours after administration. In this analysis, the following observations were made compared to placebo. A significant reduction in ACTH AUC (30 minutes to 4 hours) was observed with alprazolam and NBI-77860, 400 mg treatment. A non-significant decrease in ACTH AUC (30 minutes to 4 hours) was observed with NBI-77860, 50 mg treatment. An increase in AUC (30 minutes to 4 hours) was observed with NBI-77860, 10 mg treatment.

The analysis performed on ACTH values (AUC (2-4 hours)) between 2 and 4 hours post-dose (period when exposure reached C_{max} values) compared to the placebo treatment period , NBI-77860, 400 mg and 50 mg, the ACTH level was significantly reduced during the treatment period; however, the reduction was not observed at the 10 mg dose of NBI-77860.
Example 6: Clinical study

In this study, NBI-77860 (Compound I) was administered with the title "Phase 1, single-blind, placebo-controlled fixation to evaluate the safety and tolerability of NBI-77860 in adult women with congenital adrenocortical hyperplasia. Evaluated in a clinical study called "Phase 1, Single-Blind, Placebo-Controlled, Fixed-Sequence, Single-Dose Study" (IND 117,388). The study was a single-blind, placebo-controlled, single-center, fixed-order, single-dose clinical trial in adult female classic CAH patients. This was designed to evaluate the safety, tolerance, and plasma exposure of NBI-77860, and the effect of this compound on endogenous levels of HPA hormones.

A total of 8 female subjects (aged 19-58 years) medically diagnosed with classic 21-hydroxylase deficient CAH received NBI-77860 300 mg, 600 mg, and 3 different treatment periods. A single bedtime dose (hs) of placebo was administered (see study design schematic in FIG. 4). The subject's usual morning dose of concurrent steroid treatment was delayed until a 16 hour blood sample was collected (ie, up to about 1400 hours).

The PD endpoint for this study is the HPA biomarker of interest in this patient population; namely, 17-hydroxyprogesterone (17-OHP; as the primary PD endpoint), adrenocorticotropic hormone (ACTH), androstenedione, Testosterone and serum cortisol levels were included. The initial analysis of PD variables was a survey of

grouped subject data for each biomarker (mean% from pre-dose levels for the two active dosing conditions compared to placebo conditions) Expressed as a change). Data for average 17-OHP and ACTH levels over the 24 hour period after administration is provided in FIG.

A consistent and clinically significant decrease from pre-dose levels of both 17-OHP and ACTH was observed in these CAH patients throughout the post-dose period after administration of NBI-77860 compared to placebo. In addition to group mean data, individual responses were assessed and treatment "responders" were at least 50 in 17-OHP and ACTH under active NBI-77860 compared to placebo during the morning peak period. Conservatively defined as those subjects with% reduction. This responder analysis resulted in a fairly large responder rate of 50% in the study (none of these patients were responders during the first placebo treatment period). Furthermore, the 300 mg dose produced the same effects on 17-OHP and ACTH as the 600 mg dose. Examples of individual subject responses for these biomarkers are provided in FIG.

The various embodiments described above can be combined to provide further embodiments. All U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications mentioned in this specification and / or listed in the application data sheet are U.S. provisional patent applications. 61,929,941 (filed January 21, 2014); 61,981,033 (filed April 17, 2014); and 62 / 069,155 (October 27, 2014) All of which are hereby incorporated by reference herein. Aspects of the above embodiments can be modified to provide still further embodiments if necessary to use the various patents, applications, and published concepts.

These and other changes can be made to the above embodiments in light of the above detailed description. In general, in the following claims, the terminology used shall be construed to limit the scope of the claims to the specific embodiments disclosed in the specification and the claims. Rather, it is intended to be construed to include all possible embodiments, along with the full scope of equivalents (to which such claims are entitled). Accordingly, the claims are not limited by the above disclosure

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Markopoulou	0	This electronic theses or dissertation has been downloaded from the King's Research Portal at https://kclpure.kcl.ac.uk/portal

Priority And Related Applications

Child Applications (1)

Application	Priority date	Filing date	Relation	Title
JP2019043466A	2014-01-21	2019-03-11	Division	CRF1 receptor antagonist for the treatment of congenital adrenal hyperplasia

Priority Applications (7)

Application	Priority date	Filing date	Title
US201461929941P	2014-01-21	2014-01-21	*US Provisional Application*
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US201461981033P	2014-04-17	2014-04-17	*US Provisional Application*
US61/981,033		2014-04-17	
US201462069155P	2014-10-27	2014-10-27	*US Provisional Application*
US62/069,155		2014-10-27	
PCT/US2015/012315	2014-01-21	2015-01-21	Crf1 receptor antagonists for the treatment of congenital adrenal hyperplasia

Applications Claiming Priority (1)

Application	Filing date	Title
JP2019043466A	2019-03-11	CRF1 receptor antagonist for the treatment of congenital adrenal hyperplasia

Legal Events

Date	Code	Title	Description
2018-01-19	A521	Request for written amendment filed	**Free format text:** JAPANESE INTERMEDIATE CODE: A523 **Effective date:** 20180119
2018-01-19	A621	Written request for application examination	**Free format text:** JAPANESE INTERMEDIATE CODE: A621 **Effective date:** 20180119
2018-12-11	A131	Notification of reasons for refusal	**Free format text:** JAPANESE INTERMEDIATE CODE: A131 **Effective date:** 20181211
2019-03-11	A521	Request for written amendment filed	**Free format text:** JAPANESE INTERMEDIATE CODE: A523 **Effective date:** 20190311
2019-08-02	TRDD	Decision of grant or rejection written	
2019-08-13	A01	Written decision to grant a patent or to grant a registration (utility model)	**Free format text:** JAPANESE INTERMEDIATE CODE: A01 **Effective date:** 20190813

2019-09-12	A61	First payment of annual fees (during grant procedure)	**Free format text:** JAPANESE INTERMEDIATE CODE: A61 **Effective date:** 20190905
2019-09-13	R150	Certificate of patent or registration of utility model	**Ref document number:** 6585625 **Country of ref document:** JP **Free format text:** JAPANESE INTERMEDIATE CODE: R150
2022-08-24	R250	Receipt of annual fees	**Free format text:** JAPANESE INTERMEDIATE CODE: R250

Concepts

machine-extracted

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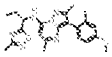
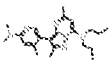
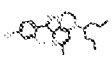
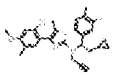
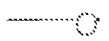
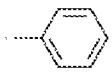
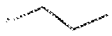
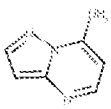
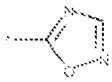
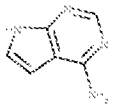
Name	Image	Sections	Count	Query match
receptor antagonist		title,claims,abstract,description	91	0.000
Hyperplasia		title,claims,description	10	0.000
Congenital anomaly		title,claims,description	9	0.000
adrenocortical		title,claims,description	9	0.000
CRHR1		title,abstract	3	0.000
CRHR1		title,abstract	3	0.000
Corticotropin-Releasing Hormone		claims,abstract,description	137	0.000
corticotropin		claims,abstract,description	80	0.000
ACTH and synthetic analog preparations		claims,abstract	8	0.000
compounds		claims,description	60	0.000
3-(4-methoxy-2-methylphenyl)-2,5-dimethyl-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine		claims,description	39	0.000
17α-hydroxyprogesterone		claims,description	26	0.000
Dissociation Half-Life		claims,description	25	0.000
circadian rhythms		claims,description	21	0.000
circadian rhythm		claims,description	18	0.000
3-[6-(dimethylamino)-4-methylpyridin-3-yl]-2,5-dimethyl-N,N-dipropylpyrazolo[1,5-a]pyrimidin-7-amine		claims,description	12	0.000
SSR-126374		claims,description	12	0.000
268545-87-5		claims,description	10	0.000
crinecerfont		claims,description	8	0.000

				
methyloxidanyl		claims,description	3	0.000
phenyl group		claims,description	3	0.000
propyl group		claims,description	3	0.000
pyrazolo[1,5-a]pyrimidin-7-amine		claims,description	3	0.000
Adrenogenital Syndrome		claims,description	2	0.000
Congenital Adrenal Hyperplasia		claims,description	2	0.000
chronic kidney disease		claims	30	0.000
1,2,4-oxadiazol-5-yl group		claims	2	0.000
7H-pyrrolo[2,3-d]pyrimidin-4-amine		claims	1	0.000
Cortisol		abstract,description	30	0.000
hydrocortisone		abstract,description	30	0.000
antagnostic		abstract,description	23	0.000
antagonist		abstract,description	23	0.000
androgen		abstract,description	13	0.000
manufacturing process		abstract,description	8	0.000
normalization		abstract,description	4	0.000
side effect		abstract,description	4	0.000
YNR048W		abstract	1	0.000
crf1		abstract	1	0.000

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(71)出願人　398005054
ニューロクライン　バイオサイエンシーズ，インコーポレイテッド
アメリカ合衆国　カリフォルニア　９２１３０，サン　ディエゴ，エル　カミノ　レアル　１２７９０
(74)代理人　100078282
弁理士　山本　秀策
(74)代理人　100113413
弁理士　森下　夏樹
(72)発明者　グリゴリアディス，　ディミトリ　イー．
アメリカ合衆国　カリフォルニア　９２１３０，　サンディエゴ，　ジンジャーウッド　コーブ　１０６２６

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最終頁に続く

(54)【発明の名称】先天性副腎皮質過形成の処置のためのＣＲＦ１レセプターアンタゴニスト

(57)【要約】
ＣＲＦ$_1$レセプターアンタゴニストは、ＣＡＨを有する患者においてＡＣＴＨ放出を直接阻害し、それによって、ヒドロコルチゾンのより低い、より生理学的な用量を使用しながらアンドロゲン生成の正常化を可能にし、従って、処置関連の副作用を低減する能力を有する。一実施形態において、必要性のある被験体に、有効量のＣＲＦ$_1$アンタゴニストを投与する工程（就寝時投与が挙げられる（が、これらに限定されない））によって、ＣＡＨを処置するための方法が提供される。

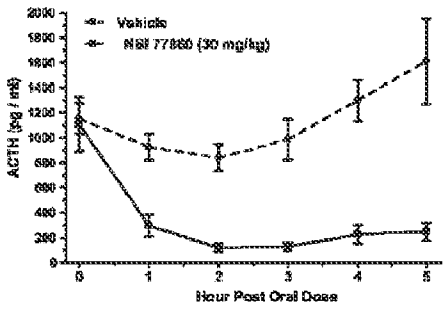


FIG. 2

【特許請求の範囲】
【請求項１】
３０分間を超える解離半減期を有するＣＲＦ$_1$レセプターアンタゴニストを必要性のある被験体に投与する工程によって、先天性副腎皮質過形成（ＣＡＨ）を処置するための方法。
【請求項２】
前記ＣＲＦ$_1$レセプターアンタゴニストは、４０分間を超える解離半減期を有する、請求項１に記載の方法。
【請求項３】
前記ＣＲＦ$_1$レセプターアンタゴニストは、５０分間を超える解離半減期を有する、請求項１に記載の方法。
【請求項４】
前記ＣＲＦ$_1$レセプターアンタゴニストは、化合物Ｉ（ＮＢＩ－７７８６０；　２，５－ジメチル－３－［２－メチル－４－（メチルオキシ）フェニル］－Ｎ－［（１Ｓ）－１－（３－メチル－１，２，４－オキサジアゾール－５－イル）プロピル］ピラゾロ［１，５－ａ］ピリミジン－７－アミン）である、請求項１に記載の方法。
【請求項５】
前記ＣＲＦ$_1$レセプターアンタゴニストは、ＮＢＩ－３０７７５、ＮＢＩ－３４０４１、ＳＳＲ－１２６３７４、ＳＳＲ－１２５５４３、アンタラルミン（Ｎ－ブチル－Ｎ－エチル－２，５，６－トリメチル－７－（２，４，６－トリメチルフェニル）ピロロ［３，２－ｅ］ピリミジン－４－アミン）、もしくはＤＭＰ９０４である、請求項１に記載の方法。
【請求項６】
前記ＣＲＦ$_1$レセプターアンタゴニストは、就寝時に投与される、請求項１～５のいずれか１項に記載の方法。
【請求項７】
前記ＣＲＦ$_1$レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の時にもしくはその前に投与される、請求項１～５のいずれか１項に記載の方法。
【請求項８】
前記ＣＲＦ$_1$レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の３～４時間前に投与される、請求項７に記載の方法。
【請求項９】
先天性副腎皮質過形成（ＣＡＨ）を有する被験体における１７－ＯＨＰおよびＡＣＴＨのレベルを低下させるための方法であって、該方法は、該被験体に、ＣＲＦ$_1$レセプターアンタゴニストを就寝時に投与する工程を包含する、方法。
【請求項１０】
前記ＣＲＦ$_1$レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の時にもしくはその前に投与される、請求項９に記載の方法。
【請求項１１】
前記ＣＲＦ$_1$レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の３～４時間前に投与される、請求項９に記載の方法。
【請求項１２】
前記ＣＲＦ$_1$レセプターアンタゴニストは、化合物Ｉ（ＮＢＩ－７７８６０；　２，５－ジメチル－３－［２－メチル－４－（メチルオキシ）フェニル］－Ｎ－［（１Ｓ）－１－（３－メチル－１，２，４－オキサジアゾール－５－イル）プロピル］ピラゾロ［１，５－ａ］ピリミジン－７－アミン）である、請求項９～１１のいずれか１項に記載の方法。
【請求項１３】
前記ＣＲＦ$_1$レセプターアンタゴニストは、ＮＢＩ－３０７７５、ＮＢＩ－３４０４１、ＳＳＲ－１２６３７４、ＳＳＲ－１２５５４３、アンタラルミン（Ｎ－ブチル－Ｎ－エ

チル－２，５，６－トリメチル－７－（２，４，６－トリメチルフェニル）ピロロ［３，２－ｅ］ピリミジン－４－アミン）、もしくはＤＭＰ９０４である、請求項９～１１のいずれか１項に記載の方法。

【請求項１４】

先天性副腎皮質過形成（ＣＡＨ）を処置するにあたって使用するためのCRF_1レセプターアンタゴニストであって、ここで該CRF_1レセプターアンタゴニストは、３０分間を超える解離半減期を有する、CRF_1レセプターアンタゴニスト。

【請求項１５】

前記CRF_1レセプターアンタゴニストは、４０分間を超える解離半減期を有する、請求項１４に記載のCRF_1レセプターアンタゴニスト。

【請求項１６】

前記CRF_1レセプターアンタゴニストは、５０分間を超える解離半減期を有する、請求項１４に記載のCRF_1レセプターアンタゴニスト。

【請求項１７】

前記CRF_1レセプターアンタゴニストは、化合物Ｉ（ＮＢＩ－７７８６０；　２，５－ジメチル－３－［２－メチル－４－（メチルオキシ）フェニル］－Ｎ－［（１Ｓ）－１－（３－メチル－１，２，４－オキサジアゾール－５－イル）プロピル］ピラゾロ［１，５－ａ］ピリミジン－７－アミン）である、請求項１４に記載のCRF_1レセプターアンタゴニスト。

【請求項１８】

前記CRF_1レセプターアンタゴニストは、ＮＢＩ－３０７７５、ＮＢＩ－３４０４１、ＳＳＲ－１２６３７４、ＳＳＲ－１２５５４３、アンタラルミン（Ｎ－ブチル－Ｎ－エチル－２，５，６－トリメチル－７－（２，４，６－トリメチルフェニル）ピロロ［３，２－ｅ］ピリミジン－４－アミン）、もしくはＤＭＰ９０４である、請求項１４に記載のCRF_1レセプターアンタゴニスト。

【請求項１９】

前記CRF_1レセプターアンタゴニストは、就寝時に投与するために適している、請求項１４～１８のいずれか１項に記載のCRF_1レセプターアンタゴニスト。

【請求項２０】

前記CRF_1レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の時にもしくはその前に投与するために適している、請求項１４～１８のいずれか１項に記載のCRF_1レセプターアンタゴニスト。

【請求項２１】

前記CRF_1レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の３～４時間前に投与するために適している、請求項１４～１８のいずれか１項に記載のCRF_1レセプターアンタゴニスト。

【発明の詳細な説明】

【技術分野】

【０００１】

（背景）

（技術分野）

先天性副腎皮質過形成を処置するための組成物および方法が、本明細書で記載される。

【背景技術】

【０００２】

（関連技術の説明）

先天性副腎皮質過形成（ＣＡＨ）は、コルチゾール生合成をほとんどもしくは全く生じない常染色体劣性遺伝障害の一群である。上記疾患の最も頻度の高い形態は、ＣＡＨ症例のうちの約９５％を占める、染色体６ｐ２１に位置するＣＹＰ２１Ａ２遺伝子における変異によって引き起こされる２１－ヒドロキシラーゼ欠損である（総説に関しては、例えば、Ｓｐｅｉｓｅｒ　ｅｔ　ａｌ．，　Ｉｎｔ．　Ｊ．　Ｐｅｄｉａｔｒ．　Ｅｎｄｏｃｒ

ｉｎｏｌ．　２０１０：４９４１７３　（２０１０）を参照のこと）。これら変異は、特定の変異の直接的結果である疾患重症度を生じる、副腎皮質におけるコルチゾール合成に必要とされる酵素活性の完全な喪失からある範囲の部分的喪失までの範囲に及び得る。２１－ヒドロキシラーゼ欠損のこの連続型は、塩類喪失形態および単純男性化形態（古典的ＣＡＨとしてグループ分けされる）、ならびに非古典的ＣＡＨ（ＮＣＣＡＨ）もしくは「遅発性」ＣＡＨとして公知の、より軽度の形態（これは通常、後期小児期もしくは早期成人期に診断される）へと広く分類されてきた。非古典的ＣＡＨ患者は、ホモ接合性もしくはしばしば、古典的ＣＡＨ対立遺伝子を伴って、複合ヘテロ接合体のいずれかを有する。これら患者は、十分な酵素活性（正常の＞２０～５０％）を有し、その結果、彼らは塩類喪失もしくはコルチゾール欠損を有さず、誕生時に正常な外性器を有し、そして多くは、生涯を通じて無症候性のままである（Ｔｒａｐｐ　ｅｔ　ａｌ．，　Ｓｔｅｒｏｉｄｓ　７７（４）：３４２－４６　（２０１２））。上記疾患の頻度の少ない形態（これは症例のうちの５％を占める）では、１１β－ヒドロキシラーゼ遺伝子ＣＹＰ１１Ｂ１の変異が、ＣＡＨ（１１β－ＯＨ　ＣＡＨ）を生じる。

両方の遺伝的変異は、アンドロゲンの過剰生成とともに、先天性副腎皮質過形成、コルチゾール欠損および過剰な副腎皮質刺激ホルモン（ＡＣＴＨ）生成を生じる。これら患者には、グルココルチコイドでの終生の管理およびこのような処置と関連して付随する問題が要求される。よって、健康状態、幸福、クオリティ・オブ・ライフを改善するために、およびＣＡＨを有する患者における関連障害を管理するために、処置レジメンが非常に必要である。

【先行技術文献】

【非特許文献】

【０００３】

【非特許文献１】Ｓｐｅｉｓｅｒ　ｅｔ　ａｌ．，　Ｉｎｔ．　Ｊ．　Ｐｅｄｉａｔｒ．　Ｅｎｄｏｃｒｉｎｏｌ．　２０１０：４９４１７３　（２０１０）

【非特許文献２】Ｔｒａｐｐ　ｅｔ　ａｌ．，　Ｓｔｅｒｏｉｄｓ　７７（４）：３４２－４６　（２０１２）

【発明の概要】

【課題を解決するための手段】

【０００４】

（要旨）

副腎皮質刺激ホルモン放出因子（ＣＲＦ）は、クラスＢ　Ｇプロテイン共役レセプター（ＧＰＣＲ）であるＣＲＦ$_1$レセプターを活性化する。ＣＲＦ$_1$アンタゴニストは、ＣＡＨを有する患者におけるＡＣＴＨ放出を直接阻害し、それによって、ヒドロコルチゾンのより低い、より生理学的な用量を使用しながらアンドロゲン生成の正常化を可能にし、処置関連副作用を低減する能力を有する。

【０００５】

一実施形態において、必要性のある被験体に、有効量のＣＲＦ$_1$アンタゴニストを投与する工程（就寝時投与が挙げられる（が、これらに限定されない））によって、ＣＡＨを処置するための方法が提供される。

【０００６】

より具体的な実施形態において、上記ＣＲＦ$_1$アンタゴニストは、３０分間を超える、および別の実施形態では４０分間を超える、および別の実施形態では５０分間を超える解離半減期（$t_{1/2}$）を有する。

【０００７】

実施形態１　３０分間を超える解離半減期を有するＣＲＦ$_1$レセプターアンタゴニストを必要性のある被験体に投与する工程によって、先天性副腎皮質過形成（ＣＡＨ）を処置するための方法。

【０００８】

実施形態２　前記ＣＲＦ$_1$レセプターアンタゴニストは、４０分間を超える解離半減期

を有する、実施形態１に記載の方法。

【０００９】

実施形態３　前記ＣＲＦ$_1$レセプターアンタゴニストは、５０分間を超える解離半減期を有する、実施形態１に記載の方法。

【００１０】

実施形態４　前記ＣＲＦ$_1$レセプターアンタゴニストは、化合物Ｉ（ＮＢＩ－７７８６０；　２，５－ジメチル－３－［２－メチル－４－（メチルオキシ）フェニル］－Ｎ－［（１Ｓ）－１－（３－メチル－１，２，４－オキサジアゾール－５－イル）プロピル］ピラゾロ［１，５－ａ］ピリミジン－７－アミン）である、実施形態１～３のいずれか１つに記載の方法。

【００１１】

実施形態５　前記ＣＲＦ$_1$レセプターアンタゴニストは、ＮＢＩ－３０７７５、ＮＢＩ－３４０４１、ＳＳＲ－１２６３７４、ＳＳＲ－１２５５４３、アンタラルミン（Ｎ－ブチル－Ｎ－エチル－２，５，６－トリメチル－７－（２，４，６－トリメチルフェニル）ピロロ［３，２－ｅ］ピリミジン－４－アミン）、もしくはＤＭＰ９０４である、実施形態１～３のいずれか１つに記載の方法。

【００１２】

実施形態６　前記ＣＲＦ$_1$レセプターアンタゴニストは、就寝時に投与される、実施形態１～５のいずれか１つに記載の方法。

【００１３】

実施形態７　前記ＣＲＦ$_1$レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の時にもしくはその前に投与される、実施形態１～６のいずれか１つに記載の方法。

【００１４】

実施形態８　前記ＣＲＦ$_1$レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の３～４時間前に投与される、実施形態７に記載の方法。

【００１５】

実施形態９　先天性副腎皮質過形成（ＣＡＨ）を有する被験体における１７－ＯＨＰおよびＡＣＴＨのレベルを低下させるための方法であって、該方法は、該被験体に、ＣＲＦ$_1$レセプターアンタゴニストを就寝時に投与する工程を包含する、方法。

【００１６】

実施形態１０　前記ＣＲＦ$_1$レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の時にもしくはその前に投与される、実施形態９に記載の方法。

【００１７】

実施形態１１　前記ＣＲＦ$_1$レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の３～４時間前に投与される、実施形態９または実施形態１０に記載の方法。

【００１８】

実施形態１２　前記ＣＲＦ$_1$レセプターアンタゴニストは、化合物Ｉ（ＮＢＩ－７７８６０；　２，５－ジメチル－３－［２－メチル－４－（メチルオキシ）フェニル］－Ｎ－［（１Ｓ）－１－（３－メチル－１，２，４－オキサジアゾール－５－イル）プロピル］ピラゾロ［１，５－ａ］ピリミジン－７－アミン）である、実施形態９～１１のいずれか１つに記載の方法。

【００１９】

実施形態１３　前記ＣＲＦ$_1$レセプターアンタゴニストは、ＮＢＩ－３０７７５、ＮＢＩ－３４０４１、ＳＳＲ－１２６３７４、ＳＳＲ－１２５５４３、アンタラルミン（Ｎ－ブチル－Ｎ－エチル－２，５，６－トリメチル－７－（２，４，６－トリメチルフェニル）ピロロ［３，２－ｅ］ピリミジン－４－アミン）、もしくはＤＭＰ９０４である、実施形態９～１１のいずれか１つに記載の方法。

【００２０】

実施形態１４　先天性副腎皮質過形成（ＣＡＨ）を処置するにあたって使用するためのCRF_1レセプターアンタゴニストであって、ここで該CRF_1レセプターアンタゴニストは、３０分間を超える解離半減期を有する、CRF_1レセプターアンタゴニスト。

【００２１】

実施形態１５　前記CRF_1レセプターアンタゴニストは、４０分間を超える解離半減期を有する、１４に記載のCRF_1レセプターアンタゴニスト。

【００２２】

実施形態１６　前記CRF_1レセプターアンタゴニストは、５０分間を超える解離半減期を有する、実施形態１４に記載のCRF_1レセプターアンタゴニスト。

【００２３】

実施形態１７　前記CRF_1レセプターアンタゴニストは、化合物Ｉ（ＮＢＩ－７７８６０；　２，５－ジメチル－３－［２－メチル－４－（メチルオキシ）フェニル］－Ｎ－［（１Ｓ）－１－（３－メチル－１，２，４－オキサジアゾール－５－イル）プロピル］ピラゾロ［１，５－ａ］ピリミジン－７－アミン）である、実施形態１４～１６のいずれか１つに記載のCRF_1レセプターアンタゴニスト。

【００２４】

実施形態１８　前記CRF_1レセプターアンタゴニストは、ＮＢＩ－３０７７５、ＮＢＩ－３４０４１、ＳＳＲ－１２６３７４、ＳＳＲ－１２５５４３、アンタラルミン（Ｎ－ブチル－Ｎ－エチル－２，５，６－トリメチル－７－（２，４，６－トリメチルフェニル）ピロロ［３，２－ｅ］ピリミジン－４－アミン）、もしくはＤＭＰ９０４である、実施形態１４～１６のいずれか１つに記載のCRF_1レセプターアンタゴニスト。

【００２５】

実施形態１９　前記CRF_1レセプターアンタゴニストは、就寝時に投与するために適している、実施形態１４～１８のいずれか１つに記載のCRF_1レセプターアンタゴニスト。

【００２６】

実施形態２０　前記CRF_1レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の時にもしくはその前に投与するために適している、実施形態１４～１９のいずれか１つに記載のCRF_1レセプターアンタゴニスト。

【００２７】

実施形態２１　前記CRF_1レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の３～４時間前に投与するために適している、実施形態１４～２０のいずれか１つに記載のCRF_1レセプターアンタゴニスト。

【００２８】

他の実施形態において、上記でおよび本明細書で記載される方法および使用は、グルココルチコイドもしくは鉱質コルチコイドの量を、ＣＡＨを有する成熟した（ｆｕｌｌ　ｇｒｏｗｎ）被験体（例えば、ヒト被験体）に投与されるＧＣ（例えば、ヒドロコルチゾン（ＨＣ）、プレドニゾン、プレドニゾロン、デキサメタゾン、もしくはフルドロコルチゾン）の推奨される１日用量から、少なくとも１０％、１５％、２０％、３０％、４０％、５０％、６０％低減する工程をさらに包含する。他の実施形態において、上記でおよび本明細書で記載される方法および使用は、グルココルチコイドもしくは鉱質コルチコイドの量を、ＣＡＨを有する成長中の被験体（例えば、ヒト被験体）に投与されるＧＣ（例えば、ヒドロコルチゾン）もしくは鉱質コルチコイド（例えば、フルドロコルチゾン）の推奨される１日用量から、少なくとも１０％、１５％、２０％、３０％、４０％、５０％、６０％低減する工程をさらに包含する。

【００２９】

これらおよび他の実施形態は、以下の詳細な説明を参照すれば明らかである。この目的に向けて、ある種の背景情報、手順、化合物および組成物をより詳細に記載する種々の参考文献は、本明細書で示され、それらの全体において各々が本明細書に参考として援用される。

【００３０】
本明細書で具体的に定義されない用語は、本開示および状況に鑑みて、当業者によって上記用語に与えられる意味が与えられるものとする。しかし、本明細書で使用される場合、それとは逆に特定されなければ、上記用語は、示される意味を有する。本明細書全体を通じて「一実施形態」もしくは「ある（一）実施形態」への言及は、上記実施形態に関連して記載される特定の特徴、構造もしくは特性が少なくとも一実施形態に含まれることを意味する。従って、本明細書全体を通じて種々の場所における語句「一実施形態において」もしくは「ある（一）実施形態において」との出現は、全てが必ずしも同じ実施形態をいうわけではない。さらに、上記特定の特徴、構造、もしくは特性は、１以上の実施形態において任意の適切な様式で組み合わされ得る。

【００３１】
また、本明細書および添付の特許請求の範囲で使用される場合、単数形「ａ（１つの、ある）」、「ａｎ（１つの、ある）」および「ｔｈｅ（上記、この、その、）」とは、状況が明らかに別のことを指し示さなければ、複数形への言及をも含む。従って、例えば、「ａ　ｎｏｎ－ｈｕｍａｎ　ａｎｉｍａｌ（ある非ヒト動物）」への言及は、１以上の非ヒト動物、もしくは複数のこのような動物に言及し得、「ａ　ｃｅｌｌ（１つの細胞）」もしくは「ｔｈｅ　ｃｅｌｌ（上記細胞）」への言及は、１以上の細胞および当業者に公知のその均等物（例えば、複数の細胞）への言及を含むなど。方法の工程が記載されるかもしくは特許請求され、上記工程が特定の順序で起こると記載される場合、第２の工程「より前に」（すなわち、その前に）起こる（もしくは行われる）第１の工程の記載は、上記第２の工程が上記第１の工程に「引き続いて」起こる（もしくは行われる）という状態に書き換えられる場合には同じ意味を有する。用語「ａｂｏｕｔ（約、およそ）」とは、数もしくは数値範囲に言及する場合、この言及される数もしくは数値範囲が、実験上の変動性の内にある（もしくは統計上の実験誤差の内にある）近似値であり、従って、その数字もしくは数値範囲が、述べられた数もしくは数値範囲の１％～１５％の間で変動し得ることを意味する。用語「ｏｒ（あるいは、または、もしくは）」は一般に、状況が明らかに別のことを指し示さなければ、「ａｎｄ／ｏｒ（および／または）」を含むその意味で使用されることにも注意するものとする。用語「ａｔ　ｌｅａｓｔ　ｏｎｅ（少なくとも１）」とは、例えば、少なくとも１種の化合物もしくは少なくとも１種の組成物に言及する場合、用語「ｏｎｅ　ｏｒ　ｍｏｒｅ（１以上）」と同じ意味および理解を有する。

【図面の簡単な説明】

【００３２】
【図１】図１は、副腎におけるステロイド合成経路の模式図を示す。ＣＡＨの最も一般的な形態は、２１－ヒドロキシラーゼ（２１－αヒドロキシラーゼともいわれる）欠損によって引き起こされ、コルチゾールの減少およびアンドロゲン（例えば、テストステロンおよびエストロゲン）の増大を生じる。古典的ＣＡＨのより希なタイプは、１１β－ヒドロキシラーゼ欠損である。

【００３３】
【図２】図２は、副腎摘出ラットにおけるＡＣＴＨ濃度に対する化合物Ｉ（ＮＢＩ－７７８６０）の効果を図示するグラフを表す。ラットに、３０ｍｇ／ｋｇの化合物Ｉ（ＮＢＩ－７７８６０）を経口的に与えた。データを、ＡＣＴＨの平均血漿濃度（±ＳＥＭ）として表す。

【００３４】
【図３】図３Ａ～Ｃは、CRF_1レセプターアンタゴニストの、副腎摘出ラットにおけるＡＣＴＨ濃度に対する効果（それらの解離半減期によって区別される）を図示するグラフを表す。

【００３５】
【図４】図４は、ＮＢＩ－７７８６０の安全性、寛容性および血漿曝露を評価するために設計された、実施例６に記載される臨床試験の研究デザイン模式図、ならびにＨＰＡ（視床下部－下垂体－副腎）系ホルモンの内因性レベルに対するこの化合物の効果を表す。

【００３６】
【図５】図５は、実施例６に記載される臨床試験の間の、投与後２４時間期間の間中の平均１７－ＯＨＰ（上のパネル）およびＡＣＴＨレベル（下のパネル）のデータを表す。
【００３７】
【図６】図６は、３００ｍｇおよび６００ｍｇのＮＢＩ－７７８６０ならびにプラセボの投与後の経時的な１７－ＯＨＰ（上パネル）およびＡＣＴＨレベル（下パネル）に関する具体的な個々の被験体の応答を表す。
【発明を実施するための形態】
【００３８】
（詳細な説明）
本明細書で記載されるように、CRF_1レセプターアンタゴニストは、ＣＡＨを有する患者におけるＡＣＴＨ放出を直接阻害し、それによって、アンドロゲン生成の正常化を可能にすることが見出された。CRF_1レセプターアンタゴニストの投与は、ＣＡＨを有する被験体においてヒドロコルチゾンのより低い、より生理学的な用量の使用を可能にし、従って、処置関連副作用を低減する。
【００３９】
ＣＡＨの新生児スクリーニングは、生後７２時間以内に得られるヒールスティック毛細管血液標本において１７－ＯＨＰレベルを測定するイムノアッセイによって行われる。上記血液サンプルを、市販の解離増強ランタニド蛍光イムノアッセイ（ＤＥＬＦＩＡ；ＰｅｒｋｉｎＥｌｍｅｒ，Ｗａｌｔｈａｍ Ｍａｓｓａｃｈｕｓｅｔｔｓ）（Ｗｈｉｔｅ ｅｔ ａｌ．，Ｊ．Ｐｅｄｉａｔｒ．１６３：１０－１２（２０１３））によって、１７－ＯＨＰについて分析する。
【００４０】
生化学的試験法および分子遺伝学的試験法を利用して生後８～１４日間の間に行われる二番手のスクリーニング試験は、米国の９つの州が使用しており、さらに５つの州が強く推奨している。上記生化学的方法としては、有機溶媒抽出物を用いたイムノアッセイもしくは液体クロマトグラフィー，続いて、コルチゾールに対する１７－ＯＨＰ、アンドロステンジオン、および２１－デオキシコルチゾールのステロイド比を測定するためのタンデム質量分析法が挙げられる（例えば、Ｓｐｅｉｓｅｒ ｅｔ ａｌ．，Ｉｎｔ．Ｊ．Ｐｅｄｉａｔｒ．Ｅｎｄｏｃｒｉｎｏｌ．２０１０：４９４１７３，２０１０を参照のこと）。遺伝子スクリーニングは、ＣＡＨと関連するＣＹＰ２１Ａ２変異を調べる。米国で広く使用されているわけではないが、第２のスクリーニングを追加することで、スクリーニングプロセス全体の感度（ここで第１のスクリーニングのみでは約７２％である）を潜在的に改善できた。
【００４１】
新生児スクリーニングの結果がなければ、古典的ＣＡＨを有する幼い女児は、代表的には、性別が曖昧な外性器の存在に起因して同定される。男性は、生まれたときに正常な外性器を有するので、新生児スクリーニングが行われなければ、または他の医学的合併症に気づかなければ、診断されない。ＣＡＨと最初に診断されず、この疾患の塩類喪失形態を経験する幼児は、生後数週間以内に体重増大が不十分、嘔吐、高カリウム血症および低ナトリウム血症という状況の中で後に診断される。
【００４２】
ＣＡＨの処置は、幼年期から成人期における診断から種々の薬物療法を使用するホルモンおよびステロイドレベルの正常化に基づく。グルココルチコイドは、ＣＡＨでは現在標準的な処置であり、内因性コルチゾール欠損を矯正する、および下垂体からのＡＣＴＨレベル上昇（これは、アンドロゲン生成増大を駆動する）を低減する、両方のために使用される。コルチゾール補充（ｃｏｒｔｉｓｏｌ ｒｅｐｌａｃｅｍｅｎｔ）が十分であるアジソン病（副腎機能低下）の処置とは異なり、ＣＡＨの処置は、ＡＣＴＨ生成も低減して、その後のアンドロゲン過剰をも制御しなければならない。従って、グルココルチコイド処置の目標は、女性においては男性化および月経障害を防止するために、ならびに男性に

おいては精巣副腎残存腫瘍（ｔｅｓｔｉｃｕｌａｒ　ａｄｒｅｎａｌ　ｒｅｓｔ　ｔｕｍｏｒ）を阻害するために、コルチゾール補充およびＡＣＴＨの抑制を含む。鉱質コルチコイド補充は、ＣＡＨの塩類喪失形態を有するそれら患者において通常血圧、電解質バランス、および容積状態の維持のための正常の血漿レニン活性を達成するために必要とされる。

【００４３】

グルココルチコイド処置のレジメンは、正常な生理機能を支援し、そしてまた、強いストレス応答（例えば、併発疾患、運動、低血圧）を誘発し得る事象の間に十分なコルチゾールが利用可能であることを担保しなければならない。アンドロゲン生成を十分に抑制しようとしてグルココルチコイド過剰処置になることに起因する医原性クッシング症候群、または処置不十分に起因するアジソン症候群の発生を回避するためには、注意深いモニタリングもまた必要である。鉱質コルチコイドでの過剰処置は、高血圧症を引き起こし得る一方で、処置不十分は、低血圧、塩類喪失、疲労およびグルココルチコイドの要求の増大をもたらし得る。処置の効力をモニターするための代表的な実験室での検査としては、１７－ＯＨＰ、アンドロステンジオン、テストステロン、レニン活性、および電解質の血漿濃度の測定が挙げられる。

【００４４】

ＣＡＨを有する成人患者は、肥満、高血圧症、およびインスリン抵抗性を含む心血管疾患のリスク因子の増大した保有率を有する（例えば、Ｋｉｍ　ｅｔ　ａｌ．，　Ｓｅｍｉｎ．　Ｒｅｐｒｏｄ．　Ｍｅｄ．　２７（４）：３１６－２１　（２００９）を参照のこと）。小児および成人のＣＡＨ患者（ｎ＝２４４）の大コホート研究から、患者は、種々のグルココルチコイド処置レジメンを処方されるにも関わらず、不十分なホルモン制御および前述の有害転帰を頻繁に経験していることが示された（例えば、Ｆｉｎｋｉｅｌｓｔａｉｎ　ｅｔ　ａｌ．，　Ｊ．　Ｃｌｉｎ．　Ｅｎｄｏｃｒｉｎｏｌ　Ｍｅｔａｂ．　９７（１２）：４４２９－３８　（２０１２）を参照のこと）。

【００４５】

ＣＡＨの処置は、グルココルチコイド（通常は、小児ではヒドロコルチゾンであるが、成人では、デキサメタゾンのような、しばしば治療指数の狭いより強力な薬剤）、および塩類喪失に必要であれば、鉱質コルチコイド（通常はフルドロコルチゾン）でのコルチゾール欠損を正常化する試みを含む。しかし、過剰なアンドロゲンの十分な抑制を達成するために必要とされるグルココルチコイド用量は、通常は、アジソン病を有する患者におけるように、コルチゾール補充のみに使用される通常の生理学的用量を十分に上回っている。グルココルチコイドへのこの増大した曝露は、ＣＡＨ患者において、医原性クッシング症候群、心血管リスク因子の増大、耐糖能障害、および骨密度（ｂｏｎｅ　ｍｉｎｅｒａｌ　ｄｅｎｓｉｔｙ）の低下をもたらし得る（例えば、Ｅｌｎｅｃａｖｅ　ｅｔ　ａｌ．，　Ｊ．　Ｐｅｄｉａｔｒ．　Ｅｎｄｏｃｒｉｎｏｌ．　Ｍｅｔａｂ．　２１：１１５５－６２　（２００８）；　Ｋｉｎｇ　ｅｔ　ａｌ．，　Ｊ．　Ｃｌｉｎ．　Ｅｎｄｏｃｒｉｎｏｌ．　Ｍｅｔａｂ．　９１（３）：８６５６－５９　（２００６）；　Ｍｉｇｅｏｎ　ｅｔ　ａｌ．，　Ｅｎｄｏｃｒｉｎｏｌ．　Ｍｅｔａｂ．　Ｃｌｉｎ．　Ｎｏｒｔｈ　Ａｍ．　３０：１９３－２０６　（２００１）を参照のこと）。

【００４６】

副腎皮質刺激ホルモン放出因子（ＣＲＦ）を、ヒツジ視床下部から単離し、４１アミノ酸のペプチドとして同定した。ＣＲＦは、内分泌系、神経系、および免疫系の機能において顕著な変化を生じることが見出された。ＣＲＦは、副腎皮質刺激ホルモン（「ＡＣＴＨ」）、β－エンドルフィン、および他のプロオピオメラノコルチン（「ＰＯＭＣ」）（下垂体前葉由来ペプチド）の基底の放出およびストレス誘発性の放出の主要な生理学的調節因子であると考えられる（例えば、Ｖａｌｅ　ｅｔ　ａｌ．，　Ｓｃｉｅｎｃｅ　２１３：１３９４－１３９７，　１９８１を参照のこと）。ＣＲＦの分泌は、Ｇプロテイン共役レセプターのクラスＢファミリーのメンバーであるＣＲＦ$_1$レセプターへの結合を介して、下垂体前葉における副腎皮質刺激ホルモン生成細胞（ｃｏｒｔｉｃｏｔｒｏｐｈ）から

のＡＣＴＨ放出を引き起こす。

【００４７】

ＣＲＦの生理学的重要性に起因して、顕著なＣＲＦ$_1$レセプター結合活性を有しかつ上記ＣＲＦ$_1$レセプターに拮抗できる生物学的に活性な低分子の開発は、未だに望まれる目標であり、不安、鬱病、過敏性腸症候群、心的外傷後ストレス障害、および物質乱用の処置のために進行中の研究および開発の主題であり続けている。

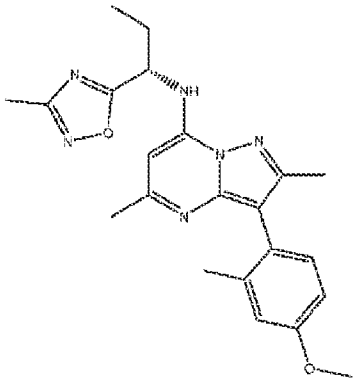
【００４８】

下垂体ホルモンＡＣＴＨは、視床下部の副腎皮質刺激ホルモン放出因子（ＣＲＦ）の制御下にあり、コレステロールの取り込みを刺激し、副腎におけるステロイド生成を開始するプレグネノロンの合成を駆動する（図１を参照のこと）。副腎皮質は、３つのゾーンから構成され、これらは、ホルモンの別個のクラスを生成し、そのうちの多くは、この経路を介してコレステロールを動員させるＡＣＴＨによって駆動される。変異もしくは欠失の結果としてのこれら酵素の欠損は、基質濃度の増大を引き起こす。２１－ヒドロキシラーゼ遺伝子（ＣＹＰ２１Ａ２）における変異もしくは欠失から生じるＣＡＨの最も一般的な形態では、ステロイド前駆体である、プロゲステロンおよび１７－ヒドロキシプロゲステロン（１７－ＯＨＰ）の蓄積が原因で、強力なアンドロゲンが副腎によって生成される。１７－ＯＨＰの血漿レベルは、これら症例において正常濃度の１０～１０００倍にも達し得る。これら増大は、アンドロゲン、具体的には、アンドロステンジオン、テストステロン、およびジヒドロキシテストステロンの過剰生成を生じ、女性において男性化を引き起こす。さらに、ＣＡＨにおける２１－ヒドロキシラーゼ欠損は、グルココルチコイドおよび鉱質コルチコイド、具体的にはコルチゾールおよびアルドステロンの不十分な生合成を引き起こす。コルチゾールは、視床下部のＣＲＦ分泌および下垂体のＡＣＴＨ放出の重要なネガティブフィードバック調節因子である。グルココルチコイド合成および放出の欠如は、視床下部および下垂体に対する抑制を排除し、このことは、ＡＣＴＨレベルを増大させる。過剰なＡＣＴＨ刺激は、束状帯および網状帯の肥大を引き起こし、副腎過形成を生じる。

【００４９】

一実施形態において、ＣＡＨの処置に有用なＣＲＦ$_1$レセプターアンタゴニストは、ＮＢＩ－７７８６０、２，５－ジメチル－３－［２－メチル－４－（メチルオキシ）フェニル］－Ｎ－［（１Ｓ）－１－（３－メチル－１，２，４－オキサジアゾール－５－イル）プロピル］ピラゾロ［１，５－ａ］ピリミジン－７－アミン（本明細書で「化合物Ｉ」ともいわれる）であり、これは、以下の構造を有する。

【化１】



化合物I

【００５０】

化合物Ｉは、結合ｐＫｉ＝８．２を有する強力なＣＲＦ$_1$アンタゴニストである（例えば、Ｔｅｌｌｅｗ ｅｔ ａｌ．，Ｂｉｏｏｒｇ．Ｍｅｄ．Ｃｈｅｍ．Ｌｅｔｔ．２０：７２５９，２０１０および国際特許出願公開番号ＷＯ ２００６／０４４９

５８（これらはともに、それらの全体において本明細書に参考として援用される）を参照のこと）。本明細書で記載されるとおり、化合物Ｉは、副腎摘出ラットにおいて示されるように強力なＡＣＴＨ低下効果を有する。

【００５１】

別の実施形態において、ＣＡＨの処置に有用なCRF_1レセプターアンタゴニストは、米国特許第６，５８６，４５６号、同第６，８０６，２８２号、同第６，５３１，４７５号、同第６，６６４，２６１号、同第６，６１０，６７８号、ＷＯ　９８／０８８４６、ＷＯ　９８／１１０７５、ＷＯ　９９／１０３５０、ＷＯ　２０００／０５９８８８、ＷＯ　２００６／０４４８２１、ＷＯ　２００６／１０２１９４、ＷＯ　２００６／１０７７８４、ＷＯ　２００６／１１６４１２、ＷＯ　２００６／１２６７１８、ＷＯ　２００７／０６９５６５、ＷＯ　２００７／０６９６７１、ＷＯ　２００８／０３６５４１、ＷＯ　２００８／０３６５７９、ＷＯ　２００８／０５１５３３、ＷＯ　２００８／０８２００３、ＷＯ　２００８／０８３０７０、ＷＯ　２００８／１３６３７７、ＷＯ　２００９／００８５５２、ＷＯ　２００９／１４４６３２、ＷＯ　２０１０／０１４２８０、ＷＯ　２０１０／０１４６８７、ＷＯ　２０１０／０１５６２８、ＷＯ　２０１０／０１５６５５、ＷＯ　２０１０／０６２７１８、ＷＯ　２０１０／０９６４２６、ＷＯ　２０１１／０４３３８７、ＷＯ　２０１１／０９２２９３、ＷＯ　２０１１／０９５４５０、ＷＯ　２０１１／０９２２９０、およびＷＯ　２０１１／０４３３８１に記載されるとおりの低分子アンタゴニストである。

【００５２】

さらに別の実施形態において、上記CRF_1レセプターアンタゴニストは、ＮＢＩ－３０７７５、ＣＰ－３１６，３１１、ペキサセルホント、エミセルホント（ｅｍｉｃｅｒｆｏｎｔ）、ＳＳＲ－１２５５４３［４－（２－クロロ－４－メトキシ－５－メチルフェニル）－Ｎ－［（１Ｓ）－２－シクロプロピル－１－（３－フルオロ－４－メチルフェニル）エチル］－５－メチル－Ｎ－（２－プロピン－１－イル）－２－チアゾールアミン］、ＳＳＲ－１２６３７４、ＯＮＯ－２３３３、ＮＢＩ－３４０４１、ＪＮＪ－１９５６７４７０、ＧＳＫ５８６５２９、ＰＦ－００５７２７７８、ＣＰ－３７６３９５、アンタラルミン（Ｎ－ブチル－Ｎ－エチル－２，５，６－トリメチル－７－（２，４，６－トリメチルフェニル）ピロロ［３，２－ｅ］ピリミジン－４－アミン）、およびＤＭＰ９０４である。

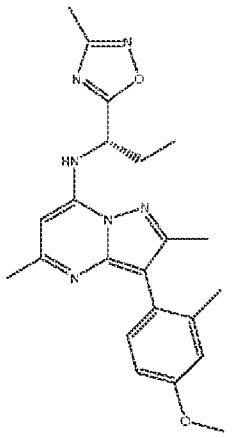
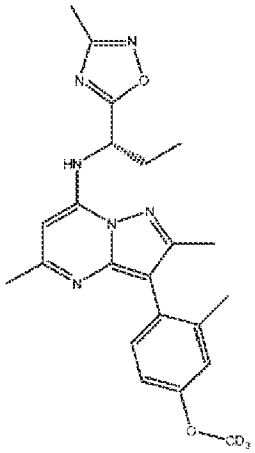
【００５３】

なお別の実施形態において、上記CRF_1レセプターアンタゴニストは、３０分間を超える、および別の実施形態では４０分間を超える、および別の実施形態では５０分間を超える解離半減期（$t_{1/2}$）を有する。特定のCRF_1レセプターアンタゴニストの解離半減期は、実施例３で開示される技術によって決定される。これら実施形態の代表的CRF_1レセプターアンタゴニストとしては、化合物Ｉ、ＮＢＩ－３０７７５、ＮＢＩ－３４０４１、ＳＳＲ－１２５５４３Ａ、アンタラルミン（Ｎ－ブチル－Ｎ－エチル－２，５，６－トリメチル－７－（２，４，６－トリメチルフェニル）ピロロ［３，２－ｅ］ピリミジン－４－アミン）、およびＤＭＰ９０４が挙げられる。

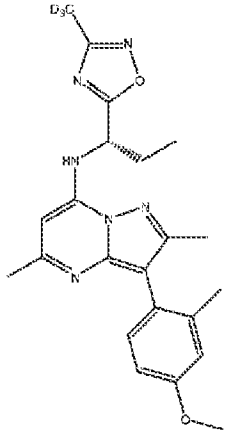
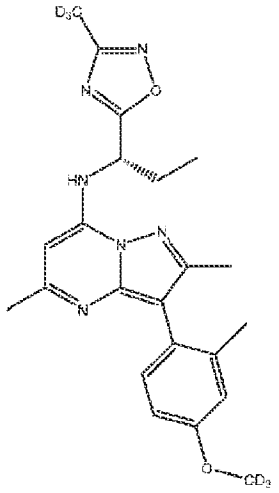
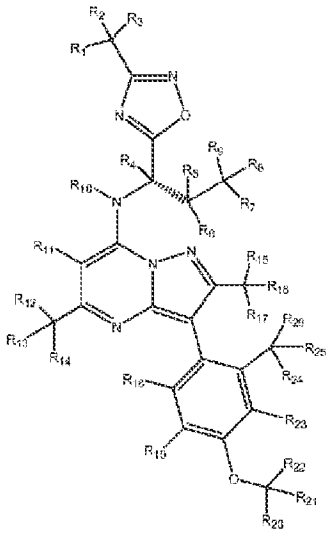
【００５４】

本明細書で記載される化合物に関しては、特定の位置が水素と指定される場合、そのような水素（Ｈ）は、重水素（Ｄ）で置換され得ることもまた、理解されるものとする。水素の代わりに重水素を組み込むことは、その置換された化合物の生理学的活性および薬理学的活性に対して顕著な効果を生じることが公知である。この目的に向けて、水素の重水素置換は、その位置における重水素存在量（ａｂｕｎｄａｎｃｅ）が天然の重水素存在量より実質的に大きいことを意味するということは、理解されるはずである。よって、一実施形態において、代表的化合物としては、以下が挙げられる。

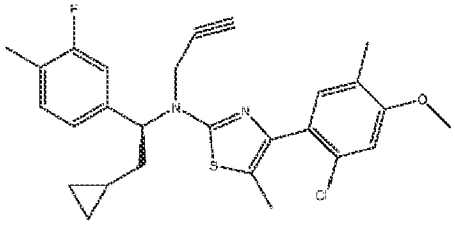
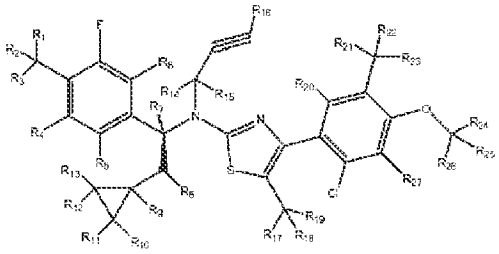
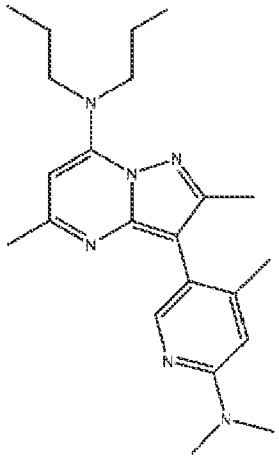
【化２－１】

化合物	構造	化学名
NBI-77860		2,5－ジメチル－3-[2－メチル－4-(メチルオキシ)フェニル]-N-[(1S)-1-(3－メチル－1,2,4－オキサジアゾール－5－イル)プロピル]ピラゾロ[1,5-a]ピリミジン-7-アミン
重水素化 NBI-77860		2,5－ジメチル－3-[2－メチル－4-(d_3-メチルオキシ)フェニル]-N-[(1S)-1-(3－メチル－1,2,4－オキサジアゾール－5－イル)プロピル]ピラゾロ[1,5-a]ピリミジン-7-アミン

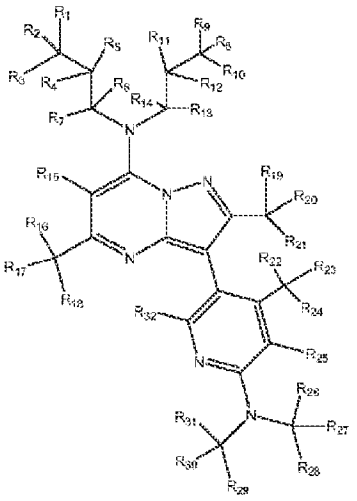
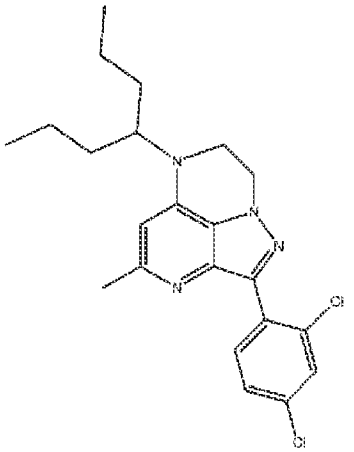
【化２－２】

化合物	構造	化学名
重水素化 NBI-77860		2,5－ジメチル－3-[2－メチル－4-(メチルオキシ)フェニル]-N-[(1S)-1-(3-d_3－メチル－1,2,4－オキサジアゾール－5－イル)プロピル]ピラゾロ[1,5-a]ピリミジン-7-アミン
重水素化 NBI-77860		2,5－ジメチル－3-[2－メチル－4-(d_3-メチルオキシ)フェニル]-N-[(1S)-1-(3-d_3－メチル－1,2,4－オキサジアゾール－5－イル)プロピル]ピラゾロ[1,5-a]ピリミジン-7-アミン
重水素化 NBI-77860		

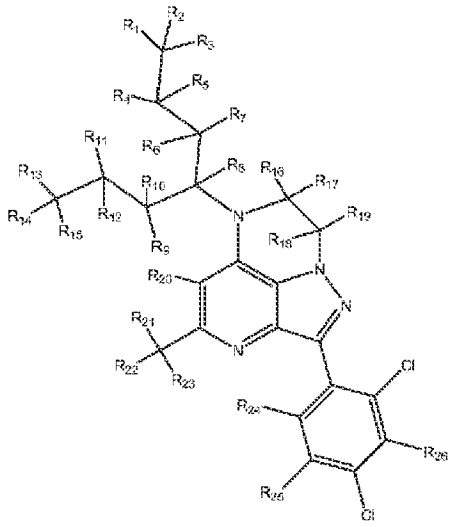
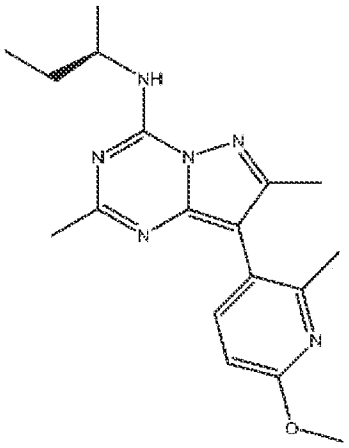
【化２－３】

化合物	構造	化学名
	R_1-R_{26}は、独立してHもしくはD	
SSR-125543		4-(2-クロロ-4-メトキシ-5-メチルフェニル)-*N*-[(1*S*)-2-シクロプロピル-1-(3-フルオロ-4-メチルフェニル)エチル]-5-メチル-*N*-(2-プロピン-1-イル)-2-チアゾールアミン
重水素化 SSR-125543	 R_1-R_{27}は、独立してHもしくはD	
NBI-30775		5-[7-(ジプロピルアミノ)-2,5-ジメチルピラゾロ[1,5-a]ピリミジン-3-イル]-N,N,4-トリメチルピリジン-2-アミン

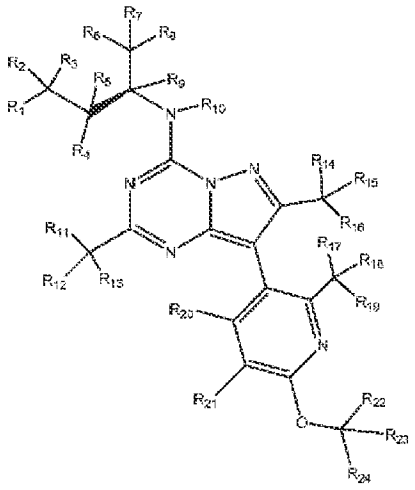
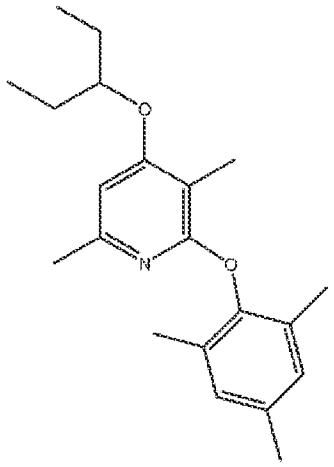
【化２－４】

化合物	構造	化学名
重水素化 NBI-30775	 R_1–R_{32}は、独立してHもしくはD	
NBI-34041		3-(2,4-ジクロロフェニル)-9-(ヘプタン-4-イル)-6-メチル-1,2,5,9-テトラアザトリシクロ[6.3.1.$0^{4,12}$]ドデカ-2,4(12),5,7-テトラエン

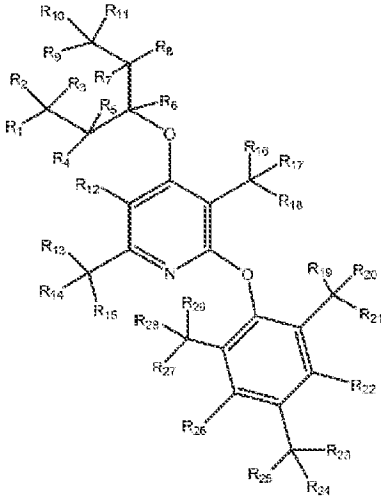
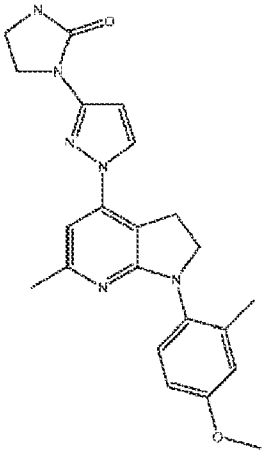
【化２－５】

化合物	構造	化学名
重水素化 NBI-34041	 R_1-R_{26}は、独立してHもしくはD	
ペキサセルホント		N-[(2R)-ブタン-2-イル]-8-(6-メトキシ-2-メチルピリジン-3-イル)-2,7-ジメチルピラゾロ[1,5-a][1,3,5]トリアジン-4-アミン

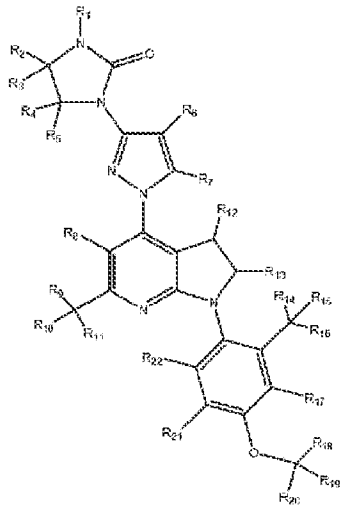
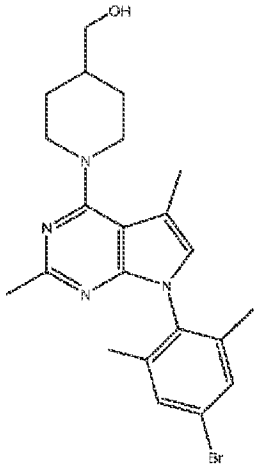
【化２－６】

化合物	構造	化学名
重水素化ペキサセルホント	 R_1-R_{24}は、独立してHもしくはD	
CP-316,311		3,6－ジメチル－4-(ペンタン-3-イルオキシ)-2-(2,4,6-トリメチルフェノキシ)ピリジン

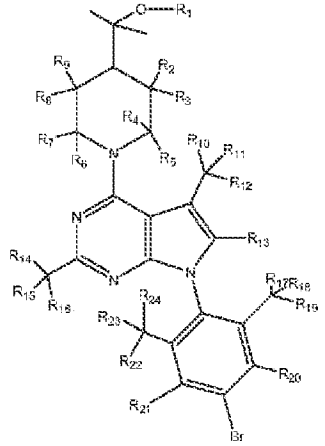
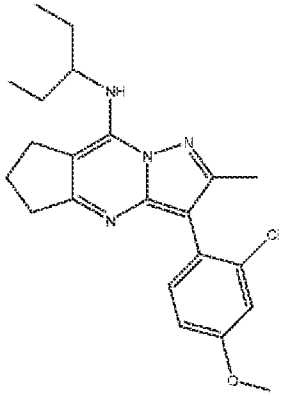
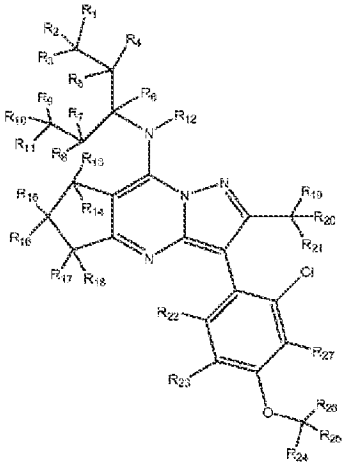
【化２－７】

化合物	構造	化学名
重水素化 CP-316,311	 R_1-R_{29}は、独立してHもしくはD	
GSK876008		

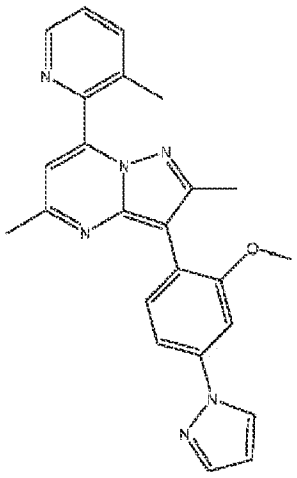
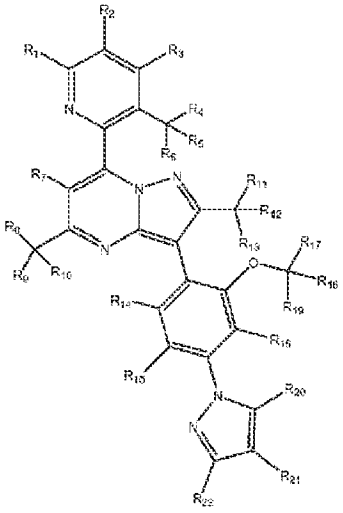
【化２－８】

化合物	構造	化学名
重水素化 GSK876008	 R_1-R_{22}は、独立してHもしくはD	
CRA5626/R3 17573		

【化２－９】

化合物	構造	化学名
重水素化 CRA5626/R3 17573	 R_1-R_{24}は、独立してHもしくはD	
ONO2333Ms		10-(2-クロロ-4-メトキシフェニル)-11-メチル-N-(ペンタン-3-イル)-1,8,12-トリアザトリシクロ[7.3.0.0^{3,7}]ドデカ-2,7,9,11-テトラエン-2-アミン
重水素化 ONO2333	 R_1-R_{27}は、独立してHもしくはD	

【化２－１０】

化合物	構造	化学名
NBI76169		
重水素化 NBI76169	 R_1-R_{22}は、独立してHもしくはD	

【００５５】

別の実施形態において、前述の化合物のうちのいずれも、安定なもしくは放射活性な同位体を組み込み得る。よって、本明細書で記載されるものに同一な同位体標識された化合物の使用もまた企図され、ここで１個以上の原子は、天然において通常見出されるある原子質量もしくは質量数とは異なる原子質量もしくは質量数を有する原子によって置換される。これら化合物へと組み込まれ得る同位体の例としては、水素、炭素、窒素、酸素、リン、フッ素および塩素の同位体、例えば、それぞれ、上記で考察されるとおりの重水素（^{2}Ｈ）、ならびに^{3}Ｈ、^{13}Ｃ、^{14}Ｃ、^{15}Ｎ、^{18}Ｏ、^{17}Ｏ、^{31}Ｐ、^{32}Ｐ、^{35}Ｓ、^{18}Ｆ、および^{36}Ｃｌが挙げられるが、それに限定されない。ある種の同位体標識された化合物、例えば、^{3}Ｈおよび^{14}Ｃのような放射活性同位体が組み込まれているものはまた、薬物もしくは基質組織分布アッセイにおいて有用である。トリチウム水素（^{3}Ｈ）および炭素１４（^{14}Ｃ）同位体は、それらの準備および検出可能性の容易さのために特に好ましい。より重い同位体（例えば、重水素（^{2}Ｈ））での置換は、より大きな代謝安定性、例えば、インビボ半減期の増大もしくは用量要求の低下から生じるある種の治療的利点を提供し得、従って、いくつかの環境では好ましい可能性がある。同位体標識

した化合物は一般に、当該分野で慣用的に実施される手順を行うことによって調製され得る。

（副腎摘出ラットにおける血漿ＡＣＴＨに対する効果）

【００５６】

副腎摘出は、ラットにおいて循環コルチコステロン（主なグルココルチコイド）を排除し、視床下部および下垂体（副腎皮質ホルモン生成細胞）両方のレベルにおいてＨＰＡ系のネガティブフィードバック制御を除去し、従って、血漿ＡＣＴＨを慢性的に上昇させる（例えば、Ｍｉｍｓ ｅｔ ａｌ．，Ｊ．Ｎａｔｌ．Ｍｅｄ．Ａｓｓｏｃ．６９：１４５－４７ （１９７７）を参照のこと）。ペプチドＣＲＦ$_1$レセプターアンタゴニストの静脈内注射は、副腎摘出（ＡＤＸ）ラットにおける高い血漿ＡＣＴＨレベルを低下させることが示された（例えば、Ｒｉｖｉｅｒ ｅｔ ａｌ．，Ｊ．Ｍｅｄ．Ｃｈｅｍ．１２：４２：３１７５－８２ （１９９９）を参照のこと）。これら知見は、上記低分子ＮＢＩ－７７８６０（化合物Ｉ）で再現された。副腎摘出ラットにおいて、化合物Ｉは、ＡＣＴＨ低下に関する強力な能力を有する。ＡＣＴＨにおける最大の低減は、ＮＢＩ－７７８６０のピーク血漿濃度と相関した；しかし、ＡＣＴＨ低下効果の持続時間は、薬物血漿曝露を超えていた。従って、副腎摘出ラットにおいて、ＮＢＩ－７７８６０の統合された血漿曝露と経口投与後のインビボ効力との間に推定可能な関係が存在する。

【００５７】

ＣＲＦレセプターアンタゴニストとしての化合物の有効性は、種々のアッセイ法によって決定され得る。本明細書で記載されるＣＲＦアンタゴニストは、ＣＲＦの、そのレセプターへの特異的結合を阻害し得、結果として、ＣＲＦと関連する活性を拮抗し得る。ある化合物は、１種以上の一般に受け入れられているアッセイ（実施例中に記載されるアッセイが挙げられる）によって、ＣＲＦアンタゴニストとしての活性について評価され得る。本明細書で記載される方法に有用なＣＲＦアンタゴニストは、ＣＲＦレセプターに対する親和性を示す化合物を含む。

【００５８】

理論に拘束されることは望まないが、ＣＡＨの処置において、ＣＲＦレセプターアンタゴニストは、下垂体副腎皮質刺激ホルモン生成細胞からのＡＣＴＨ放出を潜在的にブロックし（それによって、アンドロゲンの生成を低下させる）、コルチゾールの補充のためのより洗練された処置方法論を可能にする。動物およびヒトでの研究は、ＡＣＴＨ放出に対する化合物Ｉ（ＮＢＩ－７７８６０）の薬理学的効果を示した。処置効力をモニターする場合に内分泌学者が使用する標準的な生体マーカー評価は、このＣＲＦ$_1$レセプターアンタゴニストの効果をモニターするために使用され得る。１７－ＯＨＰ、アンドロステンジオン、テストステロン、コルチゾールおよびＡＣＴＨの血漿レベル、ならびにこれらステロイドの尿代謝産物は、小児および成人の両方において容易に測定され、処置の影響に関する迅速かつ有意義なデータを与える。

（処置についての薬学的組成物および方法）

【００５９】

本開示は、本明細書で記載されるＣＲＦアンタゴニスト化合物のうちのいずれか１種および薬学的に受容可能な賦形剤を含む、ＣＡＨを処置するための方法において使用するための薬学的組成物をさらに提供する。薬学的に受容可能な賦形剤は、活性成分の活性に干渉しない、生理学的におよび薬学的に適した、非毒性でかつ不活性な物質もしくは成分である；賦形剤はまた、キャリアともいわれ得る。上記ＣＲＦアンタゴニスト化合物は、処置もしくは防止的（もしくは予防的）処置（例えば、ＣＡＨ疾患の増悪、または上記疾患の１以上の症状の発生もしくは再発を低減する）において使用するための薬学的組成物に製剤化され得る。本明細書で記載される方法および賦形剤は例示であり、決して限定ではない。薬学的に受容可能な賦形剤は、薬学分野において周知であり、例えば、Ｒｏｗｅ ｅｔ ａｌ．，Ｈａｎｄｂｏｏｋ ｏｆ Ｐｈａｒｍａｃｅｕｔｉｃａｌ Ｅｘｃｉｐｉｅｎｔｓ：Ａ Ｃｏｍｐｒｅｈｅｎｓｉｖｅ Ｇｕｉｄｅ ｔｏ Ｕｓｅｓ，Ｐｒｏｐｅｒｔｉｅｓ，ａｎｄ Ｓａｆｅｔｙ，５^{ｔｈ} Ｅｄ．，２００６，および

Ｒｅｍｉｎｇｔｏｎ：　Ｔｈｅ　Ｓｃｉｅｎｃｅ　ａｎｄ　Ｐｒａｃｔｉｃｅ　ｏｆ　Ｐｈａｒｍａｃｙ　（Ｇｅｎｎａｒｏ，　２１ｓｔ　Ｅｄ．　Ｍａｃｋ　Ｐｕｂ．　Ｃｏ．，　Ｅａｓｔｏｎ，　ＰＡ　（２００５））に記載される。薬学的に受容可能な賦形剤の例としては、滅菌生理食塩水および生理学的ｐＨのリン酸緩衝化生理食塩水が挙げられる。保存剤、安定化剤、色素、緩衝化剤などは、上記薬学的組成物の中に提供され得る。さらに、抗酸化剤および懸濁剤もまた、使用され得る。

【００６０】

治療的および／もしくは予防的利益としては、例えば、改善された臨床転帰（治療的処置および予防的もしくは防止的手段の両方）が挙げられ、ここでその目的は、望ましくない生理学的変化もしくは障害を防止するもしくは遅らせるもしくは遅延させる（減らす）こと、またはこのような障害の拡大もしくは重篤度を防止するもしくは遅らせるもしくは遅延させる（減らす）ことである。本明細書で考察される場合、被験体を処置することからの有益なもしくは望ましい臨床結果としては、以下が挙げられるが、これらに限定されない：処置される予定の疾患、状態もしくは障害から生じるかもしくはこれらと関連する症状の減退、減少、もしくは緩和；症状の発生の減少；クオリティ・オブ・ライフの改善；疾患がない状態（すなわち、被験体が症状（これに基づいて、疾患の診断が行われる）を示す見込みもしくは傾向を減少させること）が長くなる；疾患の程度の縮小；疾患の安定した（すなわち、悪化していない）状態；疾患進行の遅滞もしくは遅れ；上記疾患状態の改善もしくは軽減；ならびに検出可能であろうと検出不能であろうと、退縮（部分的であろうが全体であろうが）；ならびに／または全生存。「Ｔｒｅａｔｍｅｎｔ（処置）」はまた、被験体が処置を受けなかった場合に予測される生存と比較したときに、生存を長期化することを意味し得る。処置の必要性のある被験体としては、上記状態もしくは障害を既に有している人々、ならびに上記疾患、状態もしくは障害を有する傾向にあるかまたは発生させるリスクのある被験体、ならびに上記疾患、状態もしくは障害が防止される（すなわち、上記疾患、障害もしくは状態の発生の見込みを減少させる）べきである人々が挙げられる。被験体は、ヒトもしくは非ヒト哺乳動物（例えば、ラット、マウス、イヌ、ネコ、家畜、動物園動物）であり得る。

【００６１】

至適用量は、一般に、実験モデルおよび／もしくは臨床試験を使用して決定され得る。上記至適用量は、上記被験体のボディーマス、体重、もしくは血液容積に依存し得る。一般に、ある用量の中に存在する、本明細書で記載される化合物の量は、約０．１ｍｇ～約３０ｍｇ／ｋｇ被験体体重の範囲に及ぶ。ある種の実施形態において、単一用量は、約５０～１０００ｍｇである。有効な治療を提供するために十分である最少用量の使用は、通常好ましい。被験体は、一般に、臨床評価によって、および処置もしくは防止されている状態に適したアッセイを使用して、治療有効性についてモニターされ得る。このアッセイは、当業者が精通しており、本明細書に記載される。被験体に投与される化合物のレベルは、生物学的流体中の、例えば、血液、血液画分（例えば、血清）および／もしくは尿中の、ならびに／または上記被験体に由来する他の生物学的サンプル中の上記化合物のレベルを決定することによってモニターされ得る。上記化合物を検出するために当該分野で実施される任意の方法は、治療レジメンの経過の中で化合物のレベルを測定するために使用され得る。

【００６２】

本明細書で記載される化合物のうちの少なくとも１種を含む、ＣＡＨまたは関連疾患もしくは障害を処置するための組成物の用量は、上記被験体の状態、すなわち、上記疾患のステージ、上記疾患によって引き起こされる症状の重篤度、全身の健康状態、ならびに年齢、性別および体重、ならびに医療分野の当業者に明らかな他の因子に依存し得る。同様に、上記化合物の用量は、医療分野の当業者によって理解されるパラメーターに従って決定され得る。

【００６３】

本明細書で記載されるＣＲＦ$_1$アンタゴニスト化合物のうちの少なくとも１種を含む本

明細書で記載される薬学的組成物は、上記化合物の有効量を効率的に送達するいくつかの経路のうちのいずれか１つによって、必要性のある被験体に投与され得る。このような投与経路としては、例えば、経口、非経口、腸、直腸、鼻内、口内、舌下、筋肉内、および経皮が挙げられる。これら投与経路などによって投与される組成物は、本明細書でより詳細に記載される。

【００６４】

開示される化合物もしくは組成物の投与は、夜間投与もしくは寝る前の投与（すなわち、就寝時投与）を含む。本明細書で使用される場合、就寝時投与とは、予測される概日リズムによるＡＣＴＨ放出の時にもしくはその前に（例えば、２～５時間前）、上記CRF_1アンタゴニストの臨床的に関連する濃度を送達するように意図された投与をいう。このＡＣＴＨ放出は、代表的には午前１～２時であるので、そして大部分の経口投与された薬物は数時間というＴｍａｘを有するので、例えば、予測される概日リズムによるＡＣＴＨ放出の３～４時間前である午後１０時の投与は、望ましい。この同じプレパルス就寝時投与は、シフト労働者（例えば、夜間に働いて日中に睡眠をとる人々）のために適合させられ得、この場合には、投与は、必ずしも夜間に起こらなくてもよい。従って、投与は、予測される概日リズムによるＡＣＴＨ放出に依存し、個体の（すなわち、被験体、患者の）特定の労働および睡眠パターンに依存して変動し得る。ある種の実施形態において、本明細書で記載されるCRF_1レセプターアンタゴニスト（例えば、ＮＢＩ－７７８６０、またはＮＢＩ－３０７７５、ＮＢＩ－３４０４１、ＳＳＲ－１２６３７４、ＳＳＲ－１２５５４３、アンタラルミン（Ｎ－ブチル－Ｎ－エチル－２，５，６－トリメチル－７－（２，４，６－トリメチルフェニル）ピロロ［３，２－ｅ］ピリミジン－４－アミン）、もしくはＤＭＰ９０４のうちのいずれか１種）は、予測される概日リズムによるＡＣＴＨ放出前（すなわち、先に、先だって）の約２～５時間の間に投与される。他の実施形態において、上記CRF_1レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出前の約２～４時間の間もしくは３～５時間の間に、上記被験体に投与される。より具体的な実施形態において、CRF_1レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出前の約３～４時間の間に上記被験体に投与される。

【００６５】

ＣＡＨを有する被験体（すなわち、患者、個体）における１７－ＯＨＰおよび／もしくはＡＣＴＨレベルを、CRF_1レセプターアンタゴニストを投与する工程によって低下させるための方法もまた、本明細書で提供される。ある種の実施形態において、上記アンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の時にもしくはその前に投与される。他のある種の実施形態において、上記CRF_1レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の前の約２～４時間の間もしくは約３～５時間の間に投与される。より具体的な実施形態において、CRF_1レセプターアンタゴニストは、予測される概日リズムによるＡＣＴＨ放出の前の約３～４時間の間に上記被験体に投与される。

【００６６】

CRF_1レセプターアンタゴニストを必要性のある女性被験体に、上記被験体においてＡＣＴＨおよび１７－ＯＨＰのレベルの低下を引き起こす本明細書で記載される様式で投与する工程を包含する本明細書で記載される方法は、アンドロゲン（例えば、テストステロンおよびアンドロステンジオンの放出の低下を生じ得る。グルココルチコイドの用量は、臨床的に有意な量によって付随して低下させられ得、これは、翻って副作用の低下を生じる。

【００６７】

ＣＡＨを有する患者および若く成長中である患者における維持療法のための、ならびに成熟した患者における維持療法のためのグルココルチコイド（ＧＣ）および鉱質コルチコイド（ＭＣ）の量は、当業者に公知である。例えば、ガイドラインは、Ｓｐｅｉｓｅｒ ｅｔ ａｌ．（Ｊ．Ｃｌｉｎ．Ｅｎｄｏｃｒｉｎｏｌ．Ｍｅｔａｂ．９５：４１３３－６０（２０１０）（その全体において参考として援用される）に記載され、そ

の中の表１および表２に示される。特に、ＣＡＨを有する若く成長中である患者に関しては、当業者は、ＧＣでの高すぎる投与が上記患者において身長の成長（ｓｔａｔｕｒａｌ ｇｒｏｗｔｈ）を妨げ得ることを認識する。よって、CRF_1レセプターアンタゴニストで患者を処置するための本明細書で記載される方法は、臨床的に有意な様式でＧＣの用量を低下させる工程を包含し得る。

【００６８】

ある種の実施形態において、CRF_1レセプターアンタゴニストを投与する工程によってＣＡＨを処置するための方法は、ＣＡＨを有する被験体を処置するために現在推奨されるＧＣ用量より低い用量で、ＧＣを投与する工程をさらに包含し得る。上記被験体が成熟した患者である場合、ＧＣの用量（例えば、成熟した被験体における維持療法のために推奨されるヒドロコルチゾン（ＨＣ）、プレドニゾン、プレドニゾロン、デキサメタゾン、もしくはフルドロコルチゾンの用量）は、１５～２５ｍｇ／日　ＨＣ；５～７．５ｍｇ／日　プレドニゾン、４～６　ｍｇ／日　プレドニゾロン；０．２５～０．５ｍｇ／日　デキサメタゾン、もしくは０．０５～０．２ｍｇ／日　フルドロコルチゾンという推奨用量から、約１０％、１５％、２０％、３０％、４０％、５０％、６０％以上の程度、低下させられ得る。ＣＡＨを有する成長中である被験体において、ＧＣ（例えば、ＨＣ）の推奨用量は、１０～１５ｍｇ／m^2／日という合計推奨用量から低下させられ得、そして／または０．０５～０．２ｍｇ／日のフルドロコルチゾンという合計用量は、各々、本明細書で記載されるとおりのCRF_1レセプターアンタゴニストを受ける被験体において約１０％、１５％、２０％、３０％、４０％、５０％、６０％以上の程度低下させられ得る。一実施形態において、必要性のある被験体に有効量のCRF_1アンタゴニストを投与する工程を包含する本明細書で記載される方法は、プラセボと比較して、ＡＣＴＨレベルの臨床的に有意な低下を生じる。具体的実施形態において、必要性のある被験体に有効量のCRF_1アンタゴニストを投与する工程は、プラセボと比較して、ＡＣＴＨレベルの臨床的に有意な低下を生じ、ここでその低下は、少なくとも２５％である。別の実施形態において、必要性のある被験体に有効量のCRF_1アンタゴニストを投与する工程は、プラセボと比較して、ＡＣＴＨレベルの臨床的に有意な低下を生じ、ここでその低下は、少なくとも５０％である。グルココルチコイドおよび鉱質コルチコイドの投与に関するガイドラインについては、Ｓｐｅｉｓｅｒ　ｅｔ　ａｌ．（前出）を参照のこと。

【００６９】

別の実施形態において、必要性のある被験体に有効量のCRF_1アンタゴニストを投与する工程を包含する本明細書で記載される方法は、プラセボと比較して、１７－ＯＨＰレベルの臨床的に有意な低下を生じる。別の具体的実施形態において、必要性のある被験体に有効量のCRF_1アンタゴニストを投与する工程は、プラセボと比較して、１７－ＯＨＰレベルの臨床的に有意な低下を生じ、ここでその低下は、少なくとも２５％である。さらに別の実施形態において、必要性のある被験体に有効量のCRF_1アンタゴニストを投与する工程は、プラセボと比較して、１７－ＯＨＰレベルの臨床的に有意な低下を生じ、ここでその低下は、少なくとも５０％である。

【００７０】

一実施形態において、必要性のある被験体に有効量のCRF_1アンタゴニストを投与する工程を包含する本明細書で記載される方法は、プラセボと比較して、ＡＣＴＨレベルおよび１７－ＯＨＰレベルの両方の臨床的に有意な低下を生じる。ある種の実施形態において、必要性のある被験体に有効量のCRF_1アンタゴニストを投与する工程は、プラセボと比較して、ＡＣＴＨレベルおよび１７－ＯＨＰレベルの両方の臨床的に有意な低下を生じ、ここで上記低下は、少なくとも２５％である。別の具体的実施形態において、必要性のある被験体に有効量のCRF_1アンタゴニストを投与する工程は、プラセボと比較して、ＡＣＴＨレベルおよび１７－ＯＨＰレベルの両方の臨床的に有意な低下を生じ、ここで上記低下は、少なくとも５０％である。

【００７１】

上記薬学的組成物は、液剤の形態にあり得る。あるいは、それらは、固体（例えば、散

剤、錠剤など）の形態にあり得る。本明細書で記載される化合物のうちのいずれか１種を含む組成物は、徐放性もしくは緩慢な放出のために製剤化され得る。このような組成物は、一般に、周知の技術を使用して調製され得、例えば、経口、直腸もしくは皮下移植によって、または所望の標的部位での移植によって、投与され得る。徐放性製剤は、キャリアマトリクスの中に分散された、および／もしくは速度制御膜によって囲まれたレザバ内に含まれた化合物を含み得る。このような製剤内で使用するための賦形剤は、生体適合性であり、生分解性でもあり得る；好ましくは、上記製剤は、活性成分放出の比較的一定なレベルを提供する。徐放性製剤内に含まれる活性化合物の量は、移植部位、放出の速度および予測される持続時間、ならびに処置もしくは防止される予定の状態の性質に依存する。

【００７２】

経口製剤に関しては、本明細書で記載される化合物のうちの少なくとも１種は、単独で使用されるかまたは適切な添加剤と併用されて、例えば、従来の添加剤（例えば、ラクトース、マンニトール、コーンスターチもしくはジャガイモデンプン）とともに；結合剤とともに；崩壊剤とともに；滑沢剤とともに；および望ましい場合には、希釈剤、緩衝化剤、湿潤剤、保存剤、着色剤、および矯味矯臭剤とともに、錠剤、散剤、粒剤もしくはカプセル剤を作製し得る。上記化合物は、胃の環境の低ｐＨからの上記化合物の保護を提供するための緩衝化剤および／もしくは腸溶性コーティングとともに製剤化され得る。上記組成物に含まれる化合物は、例えば、液体、固体もしくは半固体の製剤の中で矯味矯臭剤とともに、および／または腸溶性コーティングとともに、経口送達のために製剤化され得る。経口製剤は、粉末化キャリア（例えば、ラクトース、デンプン、セルロース誘導体、ステアリン酸マグネシウム、ステアリン酸など）とともに上記活性化合物を含み得るゼラチンカプセルとして提供され得る。類似のキャリアおよび希釈剤は、圧縮された錠剤を作製するために使用され得る。

【実施例】

【００７３】

実施例１：ＣＲＦレセプター結合活性

本明細書で記載される方法において使用されるとおりのＣＲＦアンタゴニストは、Ｇｒｉｇｏｒｉａｄｉｓ ｅｔ ａｌ．（例えば、Ｍｏｌ． Ｐｈａｒｍａｃｏｌ ｖｏｌ ５０， ｐｐ ６７９－６８６， １９９６を参照のこと）およびＨｏａｒｅ ｅｔ ａｌ．（例えば、Ｍｏｌ． Ｐｈａｒｍａｃｏｌ ６３： ７５１－７６５， ２００３を参照のこと）によって一般に記載されるとおりの標準的放射性リガンド結合アッセイによって、上記ＣＲＦレセプターへの結合活性について評価され得る。放射性標識したＣＲＦリガンドを利用することによって、上記アッセイは、本明細書で記載される化合物と任意のＣＲＦレセプターサブタイプとの結合活性を評価するために使用され得る。

【００７４】

簡潔には、上記結合アッセイは、放射性標識したＣＲＦリガンドを上記ＣＲＦレセプターから置き換えることを包含する。より具体的には、上記結合アッセイは、ヒトＣＲＦレセプターで安定してトランスフェクトされた細胞に由来する１～１０μｇ 細胞膜を使用して、９６ウェルアッセイプレートの中で行われる。各ウェルは、目的の化合物もしくは参照リガンド（例えば、ソーバジン、ウロコルチンＩ、もしくはＣＲＦ）、０．０５ｍＬの［^{125}Ｉ］チロシン－ソーバジン（終濃度約１５０ｐＭもしくはスキャッチャード分析によって決定される場合のほぼK_D）および上記ＣＲＦレセプターを含む細胞膜懸濁物０．１ｍＬを含む、約０．０５ｍＬ アッセイ緩衝液（例えば、ダルベッコのリン酸緩衝化生理食塩水、１０ｍＭ 塩酸マグネシウム、２ｍＭ ＥＧＴＡ）を受容する。上記混合物を、２時間、２２℃でインキュベートし、続いて、ガラス繊維フィルタでの迅速濾過によって、結合した放射性リガンドと遊離の放射性リガンドとを分離する。３回洗浄した後、上記フィルタを乾燥させ、放射活性（^{125}Ｉのオージェ電子）を、シンチレーションカウンターを使用して計数する。全ての放射性リガンド結合データを、非線形最小自乗曲線フィッティングプログラムＰｒｉｓｍ（ＧｒａｐｈＰａｄ Ｓｏｆｔｗａｒｅ Ｉｎｃ）もしくはＸＬｆｉｔ （ＩＤ Ｂｕｓｉｎｅｓｓ Ｓｏｌｕｔｉｏｎｓ Ｌｔｄ）を使

用して分析し得る。

実施例２：ＣＲＦ$_1$レセプターアゴニスト活性

【００７５】

Ｆｌｅｃｋ ｅｔ ａｌ．（Ｊ．Ｐｈａｒｍａｃｏｌｏｇｙ ａｎｄ Ｅｘｐｅｒｉｍｅｎｔａｌ Ｔｈｅｒａｐｅｕｔｉｃｓ，３４１（２）：５１８－５３１，２０１２）（本明細書中以降「Ｆｌｅｃｋ ｅｔ ａｌ．」、その全体において参考として援用される）に報告されるように、以前同定されたＣＲＦ$_1$レセプターアンタゴニストの活性が示される。このような活性は、以下の式によって、会合速度定数（ｋ$_1$）および解離速度定数（ｋ$_{-1}$）から計算される、速度論的に導出される親和性（Ｋ$_i$）として報告される：

$K_i = k_{-1} / k_1$

【００７６】

また、Ｆｌｅｃｋ ｅｔ ａｌ．で報告されるように、以下の表１に列挙される上記ＣＲＦ$_1$レセプターアンタゴニストの速度論的Ｋ$_i$が報告された：

【表１－１】

表1

代表的CRF$_1$レセプターアンタゴニスト

リガンド	k_1 ($10^6 M^{-1}分^{-1}$)	速度論的 K_i (nM)
NBI-27914	9.4 ± 3	25

【表１－２】

リガンド	k_1 ($10^6 M^{-1}分^{-1}$)	速度論的 K_i (nM)
CP-316,311	13 ± 2	12
NBI-46200	6.2 ± 2	22
DMP696	7.7 ± 2	9.5
ペキサセルホント	2.6 ± 0.1	19
NBI-35965	20 ± 2	2.3
ONO-2333Ms	4.4 ± 2.2	15
アンタラルミン	3.4 ± 0.6	3.9
NBI-34041	8.3 ± 2.0	1.7
DMP904	18 ± 1	0.38
NBI-30775	14 ± 2.0	0.36
SSR125543A	33 ± 5	0.049

【００７７】

この同じ技術によって、化合物Ｉ（ＮＢＩ－７７８６０）の速度論的Ｋｉは、以下のとおりであることが見出された：

【表１－３】

表1(続き)

リガンド	k_1 ($10^6M^{-1}分^{-1}$)	速度論的 K_i (nM)
NBI-77860	0.24±0.05	48±9

実施例３：ＣＲＦ$_1$レセプターアンタゴニストの解離半減期（ｔ$_{1/2}$）

【００７８】

本明細書で記載される方法において使用されるとおりのＣＲＦ$_1$レセプターアンタゴニストの解離半減期（ｔ$_{1/2}$）を、Ｆｌｅｃｋ　ｅｔ　ａｌ．に記載される技術によって評価する。その中で記載されるように、標識されたおよび標識されていないリガンドに関する解離速度定数は、ｋ$_{-1}$と表される一方で、上記レセプターの薬物解離の半減期（ｔ$_{1/2}$）（これは、滞留時間中央値（ｍｅｄｉａｎ　ｒｅｓｉｄｅｎｃｅ　ｔｉｍｅ）に等しい）は、以下の式によって、解離速度定数（ｋ$_{-1}$）から計算される：

$$t_{1/2} = 0.693 / k_{-1}$$

【００７９】

Ｆｌｅｃｋ　ｅｔ　ａｌ．において報告されるように、以下の表２に列挙されるＣＲＦ$_1$レセプターアンタゴニストの解離半減期（ｔ$_{1/2}$）が報告された。

【表２－１】

表2

代表的化合物の解離半減期

リガンド	k_{-1} (分$^{-1}$)	解離 $t_{1/2}$ (分)
NBI 27914	0.27 ± 0.07	2.6
CP-316,311	0.17 ± 0.04	4.1
NBI-46200	0.13 ± 0.002	5.3
DMP696	0.095 ± 0.02	7.3
ベキサセルホント	0.049 ± 0.001	14
NBI-35965	0.048 ± 0.005	16
ONO-2333Ms	0.063 ± 0.029	17
アンタラルミン	0.013 ± 0.002	53
NBI-34041	0.013 ± 0.002	53
DMP904	0.0072 ± 0.002	96
NBI-30775	0.0054 ± 0.0006	130
SSR125543A	0.0016 ± 0.0003	430

【００８０】

この同じ技術によって、化合物Ｉ（ＮＢＩ－７７８６０）の解離半減期は、以下のとおりであることが見出された：

【表２－２】

表2(続き)

リガンド	k_{-1}, 分$^{-1}$	解離 $t_{1/2}$, 分
NBI-77860	0.012 ± 0.0003	58

【００８１】

よって、３０分間を超える解離半減期（$t_{1/2}$）を有するＣＲＦ$_1$レセプターアンタゴニストとしては、アンタラルミン、ＮＢＩ－３４０４１、ＤＭＰ９０４、ＮＢＩ－３０７７５、ＳＳＲ１２５５４３Ａ、およびＮＢＩ－７７８６０（化合物Ｉ）が挙げられる（が、これらに限定されない）。これら同じ化合物はまた、４０分間を超える解離半減期（$t_{1/2}$）および５０分間を超える解離半減期（$t_{1/2}$）を有するＣＲＦ$_1$レセプター

アンタゴニストの代表である。

実施例４：副腎摘出ラットにおけるＡＣＴＨの低下

【００８２】

化合物Ｉ（ＮＢＩ－７７８６０）（例えば、Ｔｅｌｌｅｗ ｅｔ ａｌ．，Ｂｉｏｏｒｇ．Ｍｅｄ．Ｃｈｅｍ．Ｌｅｔｔ．２０１０，２０：７２５９；ＷＯ２００６０４４９５８を参照のこと）は、結合ｐＫｉ ８．２、速度論的Ｋｉ ４９ｎＭ（上記の表１）、および解離$t_{1/2}$ ５８分（上記の表２）を有する強力なCRF_1アンタゴニストである。

【００８３】

ペプチドCRF_1レセプターアンタゴニストの静脈内注射は、副腎摘出（ＡＤＸ）ラットにおいて高い血漿ＡＣＴＨレベルを低下させることが示された（例えば、Ｒｉｖｉｅｒ ｅｔ ａｌ．，Ｊ．Ｍｅｄ．Ｃｈｅｍ．１２：４２：３１７５－８２（１９９９）を参照のこと）。これら知見は、上記低分子ＮＢＩ－７７８６０で再現された。ＡＤＸラット（ｎ＝６／群）に経口投与された場合、ＮＢＩ－７７８６０の３０ｍｇ／ｋｇ単一用量は、最大５時間にわたって血漿ＡＣＴＨレベルを有意に低下させた（図２を参照のこと）。効力の持続時間は、薬物血漿曝露を超える時間経過とともに、ピーク血漿濃度と相関した。副腎摘出ラットにおいて、ＮＢＩ－７７８６０の統合された血漿曝露（ｉｎｔｅｇｒａｔｅｄ ｐｌａｓｍａ ｅｘｐｏｓｕｒｅ）と経口投与後のインビボ効力との間には、推定可能な関係が存在する。

【００８４】

Ｆｌｅｃｋ ｅｔ ａｌ．はまた、副腎摘出ラットにおける血漿ＡＣＴＨレベルに対する、それらの解離半減期によって区別されるCRF_1レセプターアンタゴニスト；すなわち、ＮＢＩ ３０７７５、ＮＢＩ ３４０４１およびＮＢＩ ３５９６５の効果を報告する。最高用量（１０ｍｇ／ｋｇ）では、３種全てのリガンドがＡＣＴＨを急激に低下させた（注射後１時間、図３Ａ～Ｃ）。より長い持続時間の後、明らかな差異が、ＮＢＩ ３５９６５と他の２種のリガンドとの間に出てきた。上記ＡＣＴＨレベルは、ＮＢＩ ３５９６５に関しては２時間までにビヒクルレベルへと戻った（図３Ｃ）のに対して、その応答は、ＮＢＩ ３０７７５およびＮＢＩ ３４０４１に関しては、４～６時間にわたって持続した（図３Ａおよび図３Ｂ）。

実施例５：ヒトにおける化合物Ｉの薬力学的効果

【００８５】

この研究において、ヒト被験体に対するＮＢＩ－７７８６０（化合物Ｉ）の薬力学的効果を、プラセボおよび単一用量のアルプラゾラム（０．７５ｍｇ）に関して、メチラポン（０．０４ｇ／ｋｇ）によって生成されるＨＰＡ系応答に対する単一経口用量の効果を観察することによって評価した。メチラポンは、副腎におけるコルチゾール合成をブロックし（それによって、ＣＡＨのコルチゾール欠損を模倣する）、ＡＣＴＨレベルの急激な反射上昇と関連する。

【００８６】

一次分析を、投与後３０分～４時間の間のＡＣＴＨ値（ＡＵＣ（３０分～４時間））を決定することによって行った。この分析において、プラセボと比較して、以下の観察がなされた。ＡＣＴＨ ＡＵＣ（３０分～４時間）の有意な低下を、アルプラゾラムおよびＮＢＩ－７７８６０、４００ｍｇ処置で観察した。ＡＣＴＨ ＡＵＣ（３０分～４時間）の有意でない低下は、ＮＢＩ－７７８６０、５０ｍｇ処置で認められた。ＡＵＣ（３０分～４時間）の増大は、ＮＢＩ－７７８６０、１０ｍｇ処置で認められた。

【００８７】

投与後２時間～４時間の間のＡＣＴＨ値（ＡＵＣ（２時間～４時間））（曝露がC_{max}値に達した場合の期間）に対して行った分析では、プラセボ処置期間と比較して、ＮＢＩ－７７８６０、４００ｍｇおよび５０ｍｇ処置期間においてＡＣＴＨレベルが有意に低下した；しかし、上記低下は、１０ｍｇ用量のＮＢＩ－７７８６０では認められなかった。

実施例６：臨床研究

【００８８】

この研究において、ＮＢＩ－７７８６０（化合物Ｉ）を、標題「先天性副腎皮質過形成を有する成人女性におけるＮＢＩ－７７８６０の安全性および寛容性を評価するためのフェーズ１、単盲検のプラセボ対照固定順単一用量研究（Ｐｈａｓｅ　１，　Ｓｉｎｇｌｅ－Ｂｌｉｎｄ，　Ｐｌａｃｅｂｏ－Ｃｏｎｔｒｏｌｌｅｄ，　Ｆｉｘｅｄ－Ｓｅｑｕｅｎｃｅ，　Ｓｉｎｇｌｅ－Ｄｏｓｅ　Ｓｔｕｄｙ）」（ＩＮＤ　１１７，３８８）という臨床研究において評価した。上記研究は、成人女性の古典的ＣＡＨ患者における単盲検のプラセボ対照単一施設固定順単一用量臨床試験であった。これを、ＮＢＩ－７７８６０の安全性、寛容性、および血漿曝露、ならびにＨＰＡ系ホルモンの内因性レベルに対するこの化合物の効果を評価するためにデザインした。

【００８９】

古典的な２１－ヒドロキシラーゼ欠損ＣＡＨと医学的に診断された合計８名の女性被験体（年齢１９～５８歳）に、３つの別個の処置期間の間に、ＮＢＩ－７７８６０　３００ｍｇ、６００ｍｇ、およびプラセボの単一就寝時用量（ｈｓ）を投与した（図４の研究デザイン模式図を参照のこと）。投与後１６時間の血液サンプルが集められるまで（すなわち、約１４００時間まで）、上記被験体の、同時のステロイド処置の通常の朝の用量を遅らせた。

【００９０】

この研究に関するＰＤエンドポイントは、この患者集団における目的のＨＰＡ系生体マーカー；すなわち、１７－ヒドロキシプロゲステロン（１７－ＯＨＰ；主要なＰＤエンドポイントとして）、副腎皮質刺激ホルモン（ＡＣＴＨ）、アンドロステンジオン、テストステロン、および血清コルチゾールのレベルを含んだ。ＰＤ変数の初期分析は、各生体マーカーに関するグループ分けされた被験体データの調査であった（プラセボ条件と比較して、上記２種の活性物質（ａｃｔｉｖｅ）投与条件に関する投与前レベルからの平均％変化として表される）。投与後２４時間の期間全体の平均１７－ＯＨＰおよびＡＣＴＨのレベルのデータを、図５に提供する。

【００９１】

１７－ＯＨＰおよびＡＣＴＨの両方の投与前レベルからの一貫したかつ臨床的に有意義な低下を、これらＣＡＨ患者において、プラセボと比較して、ＮＢＩ－７７８６０の投与後の投与後期間全体で観察した。群平均データに加えて、個々の応答を評価し、処置「応答者」を、朝のピーク期間の間にプラセボと比較して、活性なＮＢＩ－７７８６０の下で１７－ＯＨＰおよびＡＣＴＨにおいて少なくとも５０％低下を有するそれら被験体として控えめに定義した。この応答者分析から、上記研究において５０％というかなり大きな応答者割合が得られた（これら患者のうちのいずれも、最初のプラセボ処置期間の間には応答者でなかった）。さらに、上記３００ｍｇ用量は、上記６００ｍｇ用量とほぼ同一の、１７－ＯＨＰおよびＡＣＴＨに対する効果を生じた。これら生体マーカーに関する個々の被験体の応答の例を、図６に提供する。

【００９２】

上記の種々の実施形態は、さらなる実施形態を提供するために組み合わされ得る。本明細書中で言及されるおよび／または出願データシート中に列挙される全ての米国特許、米国特許出願公開、米国特許出願、外国特許、外国特許出願および非特許刊行物は、米国仮特許出願第６１，９２９，９４１号（２０１４年１月２１日出願）；同第６１，９８１，０３３号（２０１４年４月１７日出願）；および同第６２／０６９，１５５号（２０１４年１０月２７日出願）を含め、それらの全体において本明細書に参考として援用される。上記実施形態の局面は、上記種々の特許、出願および公開の概念を使用するために必要であれば、なおさらなる実施形態を提供するために改変され得る。

【００９３】

これらおよび他の変更は、上記の詳細な説明に鑑みて上記実施形態に対して行われ得る。一般に、以下の特許請求の範囲において、使用される用語は、特許請求の範囲を、本明

細書および特許請求の範囲の中で開示される具体的実施形態に限定すると解釈されるものとするのではなく、均等物の全範囲（上記範囲に対して、このような特許請求項の範囲が権利付与される）とともに、全ての考えられる実施形態を含むと解釈されるものとする。よって、特許請求の範囲は、上記開示によって限定されない。

【図１】

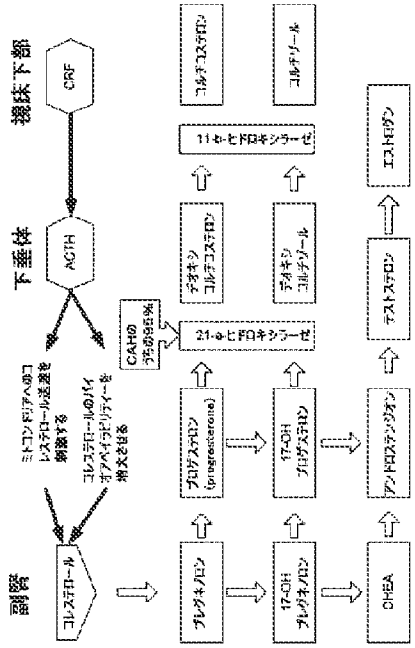


FIG. 1

【図２】

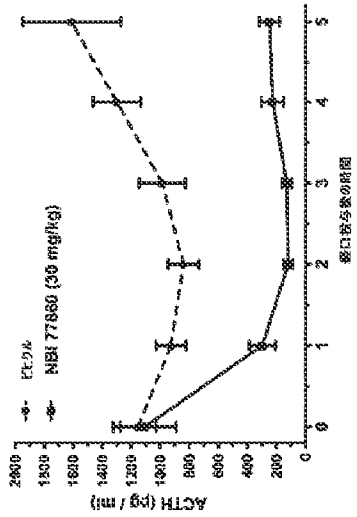


FIG. 2

【図３】

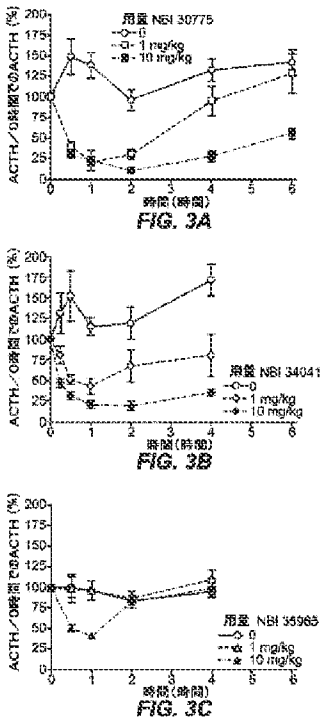


FIG. 3A

FIG. 3B

FIG. 3C

【図４】

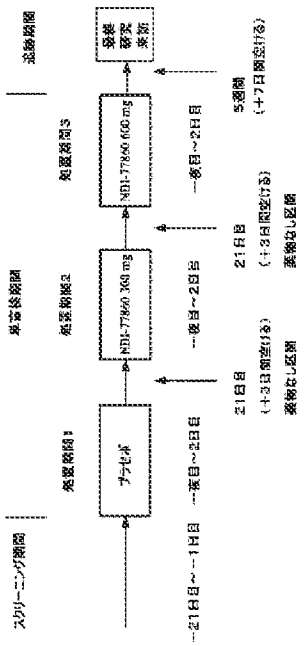


FIG. 4

【図５】

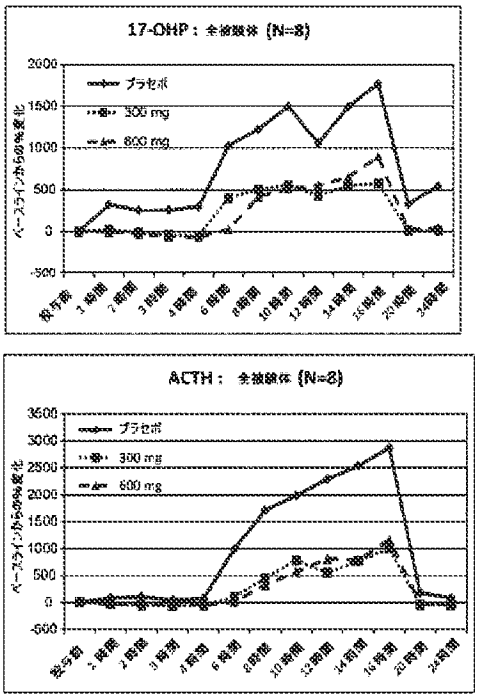


FIG. 5

【図６】

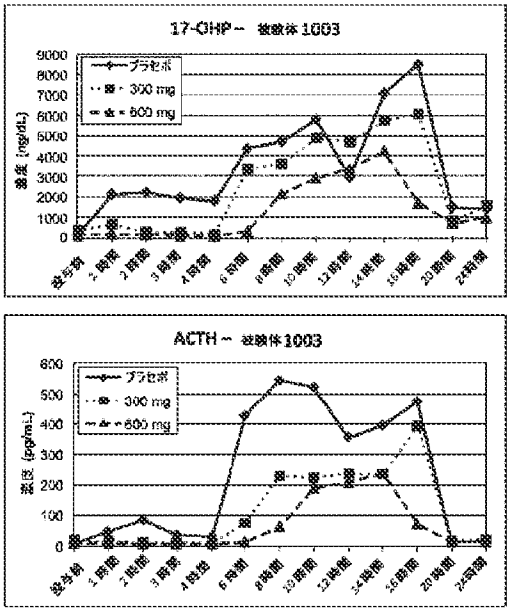


FIG. 6

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/012315

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/427 A61K31/4985 A61K31/519
ADD.

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)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 8 030 304 B2 (CHEN ZHAOGEN [US] ET AL) 4 October 2011 (2011-10-04) cited in the application	1-3, 14-16
Y	column 2, lines 13-46 column 2, line 56	1-21

X	ZOUMAKIS E ET AL: "Corticotropin-releasing hormone receptor antagonists", EUROPEAN JOURNAL OF ENDOCRINOLOGY, vol. 155, no. Suppl. 1, November 2006 (2006-11), pages S85-S91, XP002738177, ISSN: 0804-4643	1-3,5, 14-16,18
Y	page S86, left-hand column, paragraph 3; table 1	1-21

	-/--	

[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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 April 2015	21/04/2015

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, Fax: (+31-70) 340-3016	Engl, Brigitte

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/012315

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KAREN J LOECHNER ET AL: "Alternative Strategies for the Treatment of Classical Congenital Adrenal Hyperplasia: Pitfalls and Promises", INTERNATIONAL JOURNAL OF PEDIATRIC ENDOCRINOLOGY, BIOMED CENTRAL LTD, LONDON, UK, vol. 2010, no. 1, 8 June 2010 (2010-06-08) , page 670960, XP021109266, ISSN: 1687-9856, DOI: 10.1186/1687-9856-2010-670960 page 2, left-hand column, paragraph 1 -----	1-21
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/012315

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/012315

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(71) Applicant: **SPRUCE BIOSCIENCES, INC.** [US/US]; 548 Market Street, Suite 74589, San Francisco, California 94105 (US).

(72) Inventors: **HOWERTON, Alexis**; 548 Market Street, Suite 74589, San Francisco, California 94105 (US). **GERBER, Hal**; 548 Market Street, Suite 74589, San Francisco, California 94105 (US).

(74) Agent: **DELANEY, Simren**; WILSON SONSINI GOODRICH & ROSATI, 650 Page Mill Road, Palo Alto, California 94304 (US).

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(54) Title: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

(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).

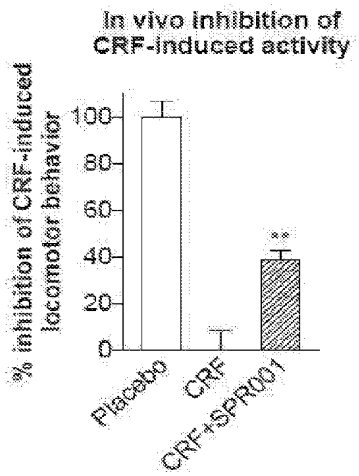

FIG. 11B

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METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/663,951, filed April 27, 2018, and U.S. Provisional Patent Application No. 62/822,815, filed March 23, 2019, which are entirely incorporated herein by reference.

BACKGROUND

[0002] 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).

[0003] 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.

[0004] 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

[0005] 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

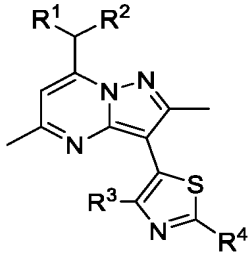
supraphysiologic doses of glucocorticoid (GC), which has adverse effects and fail to suppress 17OHP and A4 in the majority of patients.

[0006] 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.

[0007] 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.

[0008] 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.

[0009] 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):

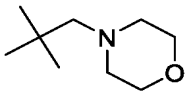
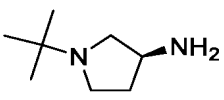
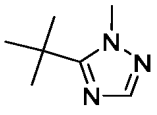
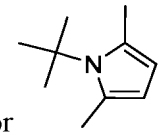


(I), or a pharmaceutically acceptable salt thereof,

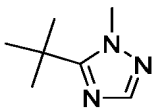
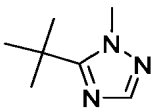
wherein:

R^1 and R^2 are independently ethyl or n-propyl;

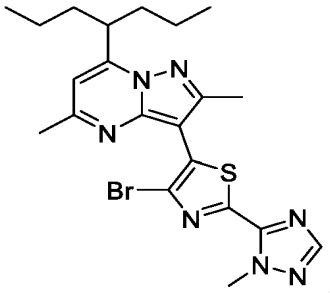
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

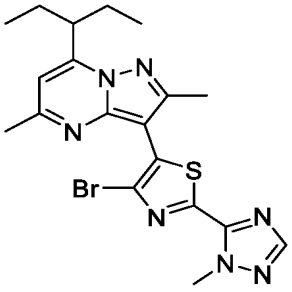
[0010] In some embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is Cl, Br, or methyl. In some embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is morpholin-4-yl or  .

[0011] 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



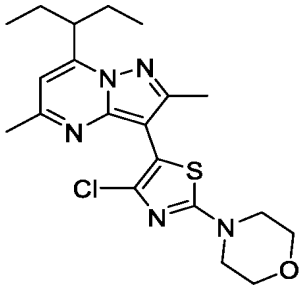
, or a pharmaceutically acceptable salt thereof.

[0012] In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0013] In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0014] 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.

[0015] 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.

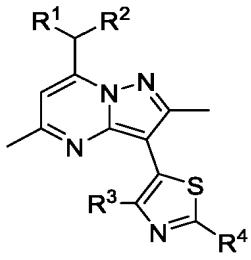
[0016] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is

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.

[0017] 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.

[0018] 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.

[0019] 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:

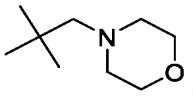
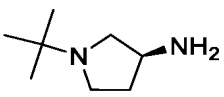
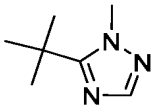
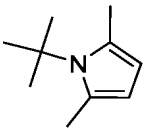


(I), or a pharmaceutically acceptable salt thereof,

wherein:

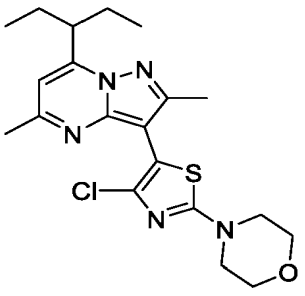
R^1 and R^2 are independently ethyl or n-propyl;

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,  ,  ,  , or  ;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

[0020] In some embodiments, the compound of Formula (I) has the structure:

 , or a pharmaceutically acceptable salt thereof.

[0021] 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.

[0022] 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.

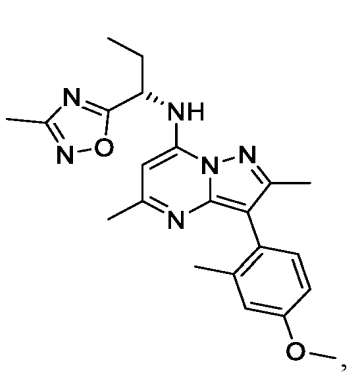
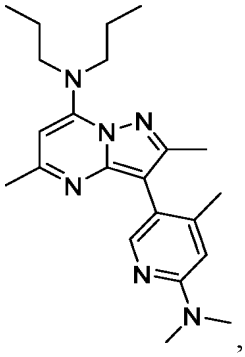
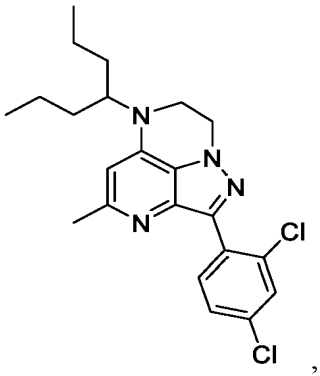
[0023] In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day. In some embodiments, the pharmaceutical composition 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.

[0024] 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.

[0025] 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.

[0026] 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.

[0027] In some embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In some embodiments, the CRF_1 antagonist is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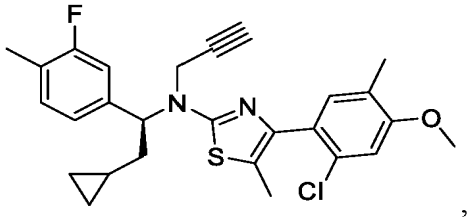
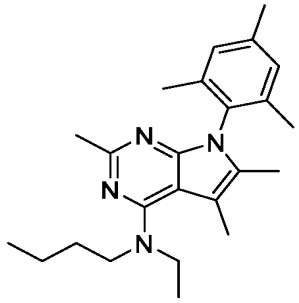
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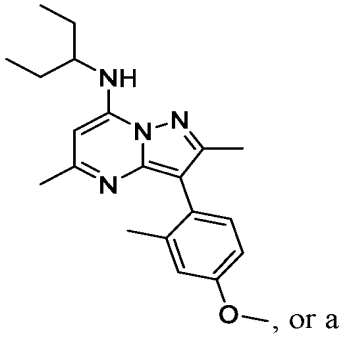
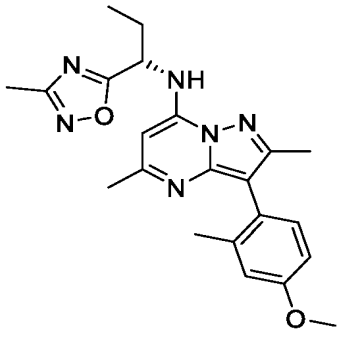

, or a pharmaceutically acceptable salt thereof.

[0028] In some embodiments, the CRF_1 antagonist is


, or a pharmaceutically acceptable salt thereof.

[0029] In some embodiments, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

[0030] 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.

[0031] 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.

[0032] 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.

[0033] 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.

[0034] 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

[0035] 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

[0036] 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:

[0037] FIG. 1A-1B. 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)**.

[0038] 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).

[0039] 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).

[0040] FIG. 4. Graphic representation of patient-level response (measuring ACTH levels) to a CRF_1 antagonist (Compound 1).

[0041] FIG. 5A-5B. Graphic representation of patient-level response of sample responders (measuring ACTH levels) to a CRF_1 antagonist [Subject 003001 **(A)**; Subject 007002 **(B)**].

[0042] FIG. 6. Graphic representation of patient-level response (measuring 17-OHP levels) to a CRF_1 antagonist (Compound 1).

[0043] FIG. 7A-7B. Graphic representation of patient-level response of sample responders (measuring 17-OHP levels) to a CRF_1 antagonist [Subject 003001 **(A)**; Subject 007002 **(B)**].

[0044] FIG. 8. Graphic representation of patient-level response (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1).

[0045] FIG. 9A-9B. Graphic representation of patient-level response of sample responders (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1) [Subject 003001 **(A)**; Subject 007002 **(B)**].

[0046] FIG. 10A-10B. Images of a patient with TART pre-treatment with a CRF_1 antagonist (Compound 1) **(A)** and 6-weeks post-treatment with a CRF_1 antagonist (Compound 1) **(B)**.

[0047] FIG. 11A-11B. 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)**.

[0048] FIG. 12A-12B. Graphic representation of ACTH levels **(A)** and 17-OHP levels **(B)** after treatment with a CRF_1 antagonist (Compound 1).

[0049] FIG. 13. Graphic representation of hormone responses after treatment with a CRF_1 antagonist (Compound 1).

[0050] FIG. 14 depicts the proof of concept and escalating QD dosing at 10 pm.

[0051] FIG. 15A-15D are graphic representations of changes in androstenedione seen in participants in Cohort A and Cohort B.

[0052] FIG. 16A-16D are graphic representations of changes in 17-hydroxyprogesterone seen in participants in Cohort A and Cohort B.

[0053] FIG. 17A-17D are graphic representations of changes in adrenocorticotropic hormone seen in participants in Cohort A and Cohort B.

DETAILED DESCRIPTION

[0054] 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

[0055] 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.

[0056] 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 $-OCH_2-$.

[0057] 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-).

[0058] 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.

[0059] 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).

[0060] 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.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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-

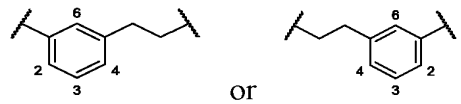
limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, 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.

[0065] 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.

[0066] The symbol "" denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0067] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0068] 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:



[0069] 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.

[0070] 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.

[0071] 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'", $-NR"C(O)_2R'$, -NR-C(NR'R"R'")=NR"", -NR-C(NR'R")=NR'", $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, –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).

[0072] 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$_2$R', –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$_2$R", -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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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 (^{125}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.

[0090] 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.

[0091] "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.

[0092] 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.

[0093] 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^{13C}, R^{13D}, etc., wherein each of R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc. is defined within the scope of the definition of R^{13} and optionally differently.

[0094] 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, radio-labeled 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.

[0095] 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.

[0096] 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.

[0097] 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.

[0098] 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.

[0099] 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.

[0100] 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.

[0101] "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.

[0102] 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.

[0103] 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.

[0104] 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.

[0105] 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.

[0106] "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.

[0107] 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).

[0108] 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.

[0109] 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.

[0110] 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).

[0111] 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.

[0112] 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.

[0113] 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.*).

[0114] 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.

[0115] 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.

[0116] 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.

[0117] "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.

[0118] "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.

[0119] 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.

[0120] 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.

[0121] 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.

[0122] 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, hypernephroid 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.

[0123] 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.

[0124] “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.

[0125] "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.

[0126] 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.

[0127] "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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

[0132] 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.

[0133] 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.

[0134] 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.

[0135] 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.

[0136] 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.

[0137] 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.

[0138] 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.

[0139] 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.

[0140] 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.

[0141] 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.

[0142] 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.

[0143] 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.

[0144] "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., hexamethlymelamine, 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.RTM.), 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; dacliximab; 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; eflornithine; elemene; emitefur; epirubicin; epristeride; 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; lovastatin; 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-1b; 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.TM (i.e. paclitaxel), Taxotere.TM, 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, lnanocine (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 (NCI), 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., diethlystilbestrol, 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.

[0145] "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.

[0146] 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.

[0147] 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).

[0148] 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.

[0149] In a further embodiment, the compounds described herein can be co-administered with 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.

[0150] 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.

[0151] 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.

[0152] 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.

[0153] 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.

[0154] 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.

[0155] 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 eukaroytic 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.

[0156] "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).

[0157] 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.

[0158] 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.

[0159] 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.

[0160] 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.

[0161] The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extra-cellular 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.

[0162] 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.

[0163] 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).

[0164] 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.

[0165] "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).

[0166] 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).

[0167] 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.

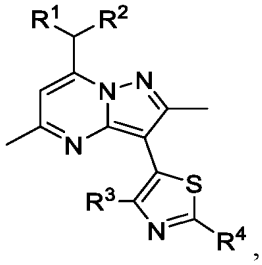
[0168] As used herein, the terms "variants" and "homologs" are used interchangeably to refer to amino acid or nucleic acid sequences that are similar to reference amino acid or nucleic acid sequences, respectively. The term encompasses naturally-occurring variants and non-naturally-occurring variants. 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

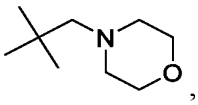
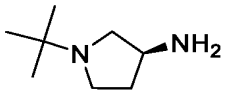
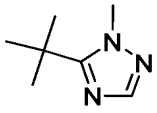
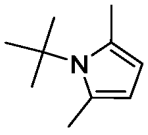
encompass nucleic acid sequences that vary in one or more bases from a naturally-occurring nucleic acid sequence but still translate into an amino acid sequence that corresponds to the naturally-occurring protein due to degeneracy of the genetic code. Non-naturally-occurring variants and homologs include 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.

[0169] 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

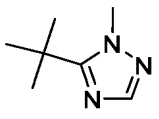
[0170] In an aspect provided herein, is a compound of Formula (I):

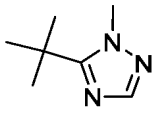


, or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  . R^a and R^b are independently 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.

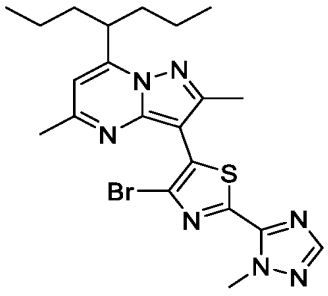
[0171] In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

[0172] In certain embodiments, R^3 is Cl, Br, or methyl.

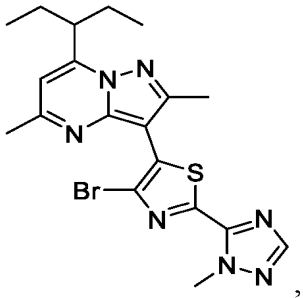
[0173] In certain embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  .

[0174] In certain embodiments, R^4 is morpholin-4-yl or  .

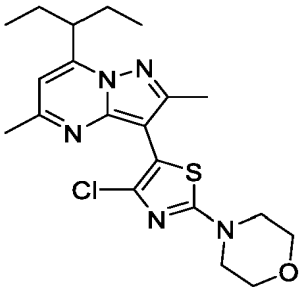
[0175] In certain embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.

[0176] In certain embodiments, the compound is  , or a pharmaceutically acceptable salt thereof.

[0177] In certain embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0178] In certain embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0179] 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.

[0180] 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.

[0181] 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.

[0182] 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

[0183] 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.

[0184] 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.

[0185] 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.

[0186] 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.

[0187] 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.

[0188] 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.

[0189] 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.

[0190] 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, polyvinyl-pyrrolidone, 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.

[0191] 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.

[0192] 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.

[0193] 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.

[0194] 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).

[0195] 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.

[0196] 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.

[0197] 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.

[0198] 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).

[0199] 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.

[0200] 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

[0201] 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.

[0202] 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.

[0203] 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.

[0204] 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.

[0205] 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 rnyelocytic (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 macroglobulinernia; (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, rhabdomyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, aligodendrogliorna, 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, nonserninoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcorna; (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, hypernephroma, 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).

[0206] 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, intracistemal 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.

[0207] 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).

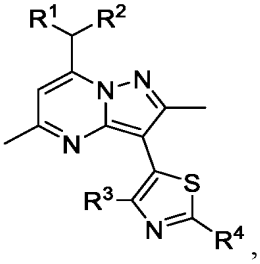
[0208] In one embodiment, provided herein are methods for treating or preventing testicular adrenal rest tumors (TART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

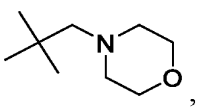
[0209] In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

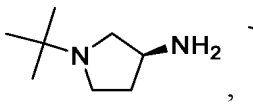
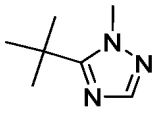
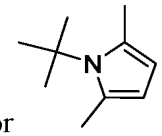
[0210] In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

[0211] 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.

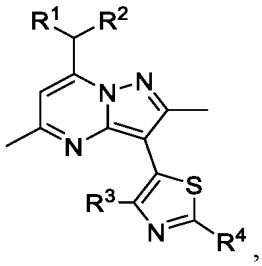
[0212] In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a compound of structural Formula (I):



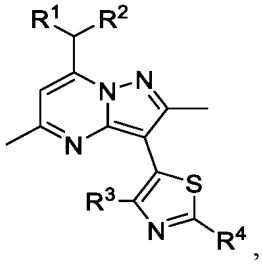
, or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,

 ,  , or  . R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

[0213] 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.

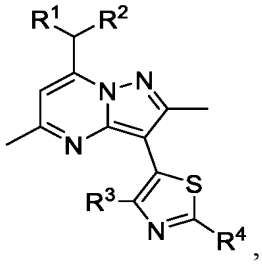
[0214] In an aspect provided herein, is a method of decreasing or reducing adrenocorticotropic hormone (ACTH) levels in a subject in need thereof, comprising administering to the subject contacting the ACTH with a compound of structural Formula (I):

 , 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.

[0215] 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

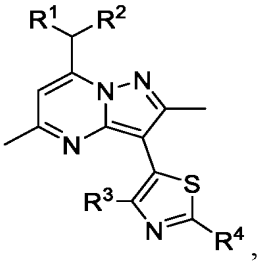
decreased or reduced within about 90 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 2 hours post dosing.

[0216] 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.

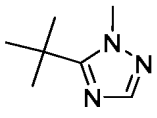
[0217] In an aspect provided herein, is a method of decreasing or reducing androstenedione levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

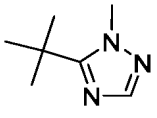


, or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in androstenedione.In certain embodiments, 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.

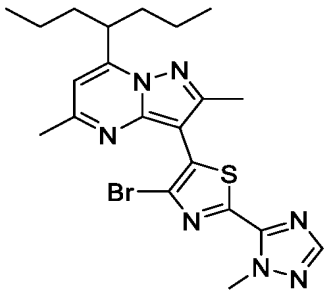
[0218] In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

[0219] In certain embodiments, R^3 is Cl, Br, or methyl.

[0220] In certain embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  .

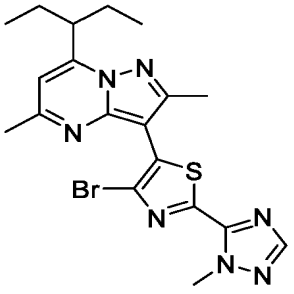
[0221] In certain embodiments, R^4 is morpholin-4-yl or  .

[0222] In certain embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.



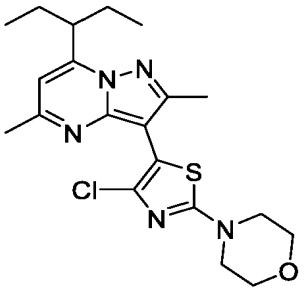
[0223] In certain embodiments, the compound is , or a pharmaceutically acceptable salt thereof.

[0224] In certain embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0225] In certain embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0226] 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.

[0227] 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.

[0228] 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.

[0229] 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.

[0230] 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.

[0231] 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.

[0232] 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.

[0233] 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.

[0234] 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.

[0235] 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.

[0236] 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.

[0237] 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.

[0238] 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.

[0239] 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.

[0240] 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.

[0241] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.

[0242] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet.

[0243] 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.

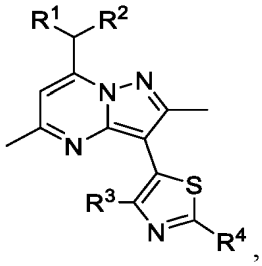
[0244] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, 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.

[0245] 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.

[0246] 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.

[0247] 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.

[0248] 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 excipientcomprising 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.

[0249] 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.

[0250] 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.

[0251] In certain embodiments, the pharmaceutical composition is administered orally.

[0252] 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.

[0253] 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.

[0254] 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.

[0255] 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.

[0256] 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.

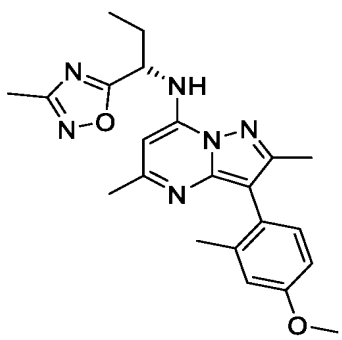
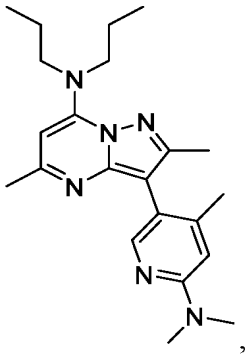
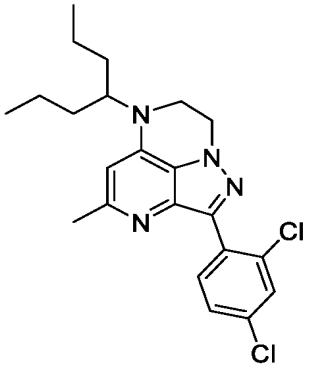
[0257] In certain embodiments, the pharmaceutical composition is administered in the evening. In certain embodiments, the pharmaceutical composition is administered at about 10 pm at night.

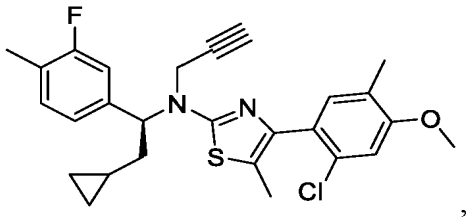
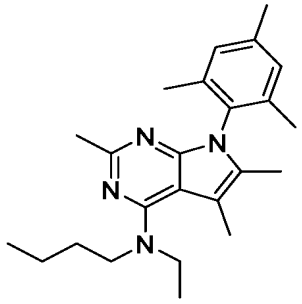
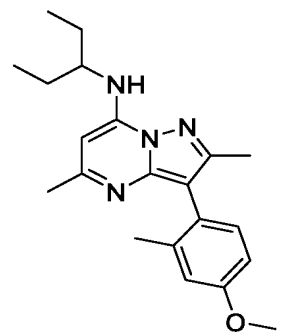
[0258] In certain embodiments, the subject has congenital adrenal hyperplasia (CAH).

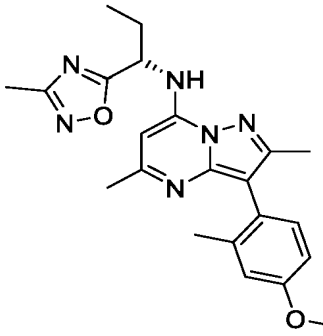
[0259] In certain embodiments, the size and/or number of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced.

[0260] In certain embodiments of the methods disclosed herein, the method further comprises administering to the subject an additional chemotherapeutic agent.

[0261] 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:

 ,  ,  , SSR-126374,

 ,  , or  , or a pharmaceutically acceptable salt thereof. In certain embodiments, the CRF_1 antagonist is

 , or a pharmaceutically acceptable salt thereof.

[0262] 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.

[0263] 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.

[0264] 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.

[0265] 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.

[0266] 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.

[0267] 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).

[0268] 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.

[0269] 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.

[0270] In certain embodiments, the pharmaceutical compositions provided herein further comprise one or more chemotherapeutic agents as defined herein.

A. Oral Administration

[0271] 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.

[0272] 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.

[0273] 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.

[0274] 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.

[0275] 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.

[0276] 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 polyoxyethylene 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.

[0277] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[0278] 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.

[0279] 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.

[0280] 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.

[0281] Coloring and flavoring agents can be used in all of the above dosage forms.

[0282] 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

[0283] 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.

[0284] 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).

[0285] 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.

[0286] 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.

[0287] 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, hydrochloric 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).

[0288] 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.

[0289] 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.

[0290] 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.

[0291] 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.

[0292] 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.

[0293] 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

[0294] 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.

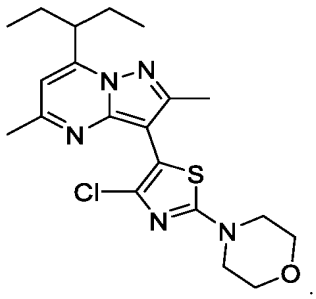
Example 1. A Phase 2, Open-Label Study to Evaluate the Efficacy and Safety of Compound 1 in Subjects with Testicular Adrenal Rest Tumors

[0295] 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.

[0296] 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. 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.

[0297] The structure of Compound 1 is:



[0298] 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.

[0299] 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.

[0300] The specification of study drug dosing at 10pm 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 10pm 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. 1A-1B**).

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

[0301] 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/1.73m^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) >2x upper limit of normal (ULN)
  - Bilirubin >1.5x ULN (isolated bilirubin >1.5x 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

[0302] 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

[0303] 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

[0304] 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 10pm (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack.

[0305] On mornings of study visits with 8am 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 6am and 8am).

[0306] 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

[0307] 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.

[0308] 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. 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

[0309] 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.

[0310] 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.

[0311] 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

[0312] 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.

[0313] 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

[0314] 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.

[0315] 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.

[0316] 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

[0317] 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.

Assessment of Potential Risks and Benefits

[0318] 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.

[0319] 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)

[0320] 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.

[0321] As shown in **FIGS. 4** and **5A-5B**, 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.

[0322] **FIGS. 6** and **7A-7B** 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.

[0323] **FIGS. 8** and **9A-9B** demonstrate attenuation of morning rise in A4 upon treatment with a CRF1 antagonist, indicative of its ability to control excess andreogen 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.

[0324] FIGS. 10A-10B 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.

[0325] FIGS. 11A-11B 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. 11B**).

[0326] FIGS. 12A-12B demonstrate single pill of CRF_1 receptor antagonist improves ACTH and 17-OHP in CAH patients.

[0327] 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

[0328] 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 tolerability of tildacerfont in participants with classic CAH; and to evaluate the pharmacokinetics (PK) of tildacerfont.

ELIGIBILITY CRITERIA

[0329] 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

[0330] 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

[0331] 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

[0332] Table 1 provides a description of the baseline characteristics displayed by Cohort A and Cohort B. In Cohort A, 10 partcipants 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	5M, 5F	1M, 7F
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	2HC, 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

[0333] 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

[0334] Over a wide range of doses (200 to 1000 mg QD), Compound 1exhibited a predictable, dose-dependent PK profile.

EFFICACY

[0335] FIG. 15A-15D 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.

[0336] FIG. 16A-16D show the changes in levels of 17-hydroxyprogesterone (17-OHP) across both cohorts. Levels of 17OHP improved at ≥1 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.

[0337] FIG. 17A-17D show the changes in levels of adrenocorticotropic hormone (ACTH) across both cohorts. Levels of ACTH improved at ≥1 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 fucntional 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

[0338] 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 CAH. Compound 1 exhibited a predictable, dose-dependent PK profile suitable for the target population.

[0339] 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

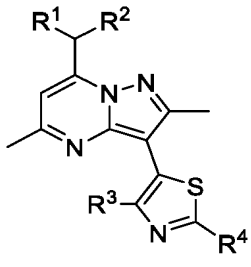
WHAT IS CLAIMED IS:

1. A method of treating 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.

2. The method of claim 1, wherein the subject has congenital adrenal hyperplasia (CAH).

3. The method of claim 1 or 2, wherein the size and/or number of the tumors is decreased or reduced.

4. 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):

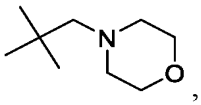
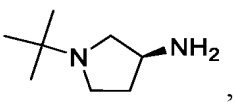
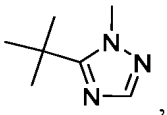
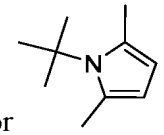


(I), or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 are independently ethyl or n-propyl;

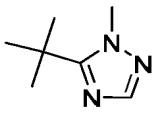
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ;

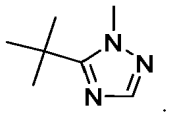
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

5. The method of claim 4, wherein R^3 is Cl, Br, methyl, or trifluoromethyl.

6. The method of claim 4, wherein R^3 is Cl, Br, or methyl.

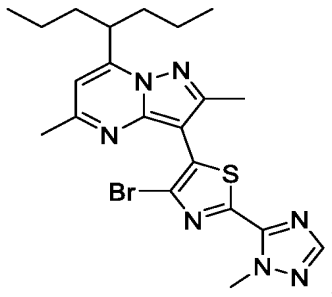
7. The method of claim 4, wherein R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  .

8. The method of claim 4, wherein R^4 is morpholin-4-yl or



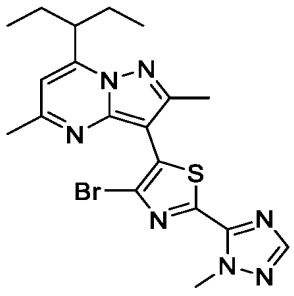
9. The method of claim 4, wherein R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.

10. The method of claim 4, wherein the compound is



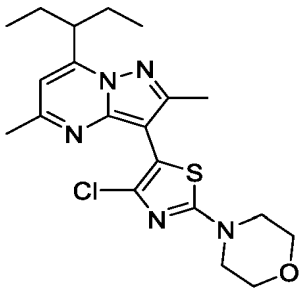
, or a pharmaceutically acceptable salt thereof.

11. The method of claim 4, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

12. The method of claim 4, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

13. The method of claim 4, wherein the subject has congenital adrenal hyperplasia (CAH).

14. The method of claim 4 or 13, wherein the size and/or number of the tumors is decreased or reduced.

15. The method of any one of claims 4-14, wherein 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.

16. The method of any one of claims 4-15, wherein 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.

17. The method of any one of claims 4-15, wherein 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.

18. The method of any one of claims 4-15, wherein 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.

19. The method of any one of claims 4-15, wherein 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.

20. The method of claim 19, wherein 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.

21. The method of claim 19, wherein 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.

22. The method of claim 19, wherein 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.

23. The method of any one of claims 4-22, wherein the compound is administered orally.

24. The method of any one of claims 4-23, wherein the compound is formulated as a capsule or tablet.

25. The method of any one of claims 4-24, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state.

26. The method of any one of claims 4-24, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state.

27. The method of any one of claims 4-26, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day.

28. The method of any one of claims 4-27, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime.

29. The method of any one of claims 4-27, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep.

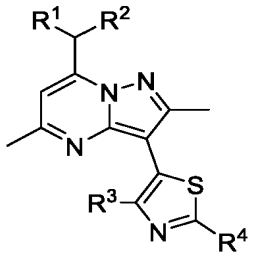
30. The method of any one of claims 4-27, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep.

31. The method of any one of claims 4-27, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep.

32. The method of any one of claims 4-27, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening.

33. The method of any one of claims 4-27, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

34. 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:

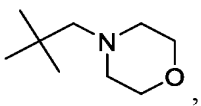
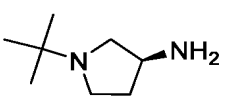
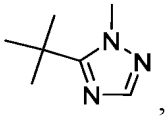
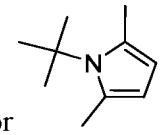


(I), or a pharmaceutically acceptable salt thereof,

wherein:

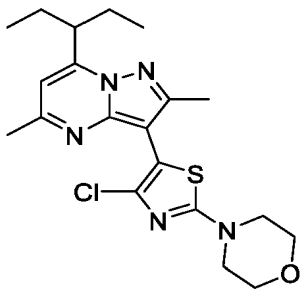
R^1 and R^2 are independently ethyl or n-propyl;

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,  ,  ,  , or  ;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

35. The method of claim 31, wherein the compound of Formula (I) has the structure:



, or a pharmaceutically acceptable salt thereof.

36. The method of claim 31 or 32, wherein the pharmaceutical composition comprises from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

37. The method of any one of claims 34-36, wherein the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

38. The method of any one of claims 34-36, wherein the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

39. The method of any one of claims 34-36, wherein the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

40. The method of any one of claims 34-36, wherein 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.

41. The method of any one of claims 34-36, wherein the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day.

42. The method of claim 41, wherein the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day.

43. The method of claim 41, wherein the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day.

44. The method of claim 41, wherein the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

45. The method of any one of claims 34-44, wherein the pharmaceutical composition is administered orally.

46. The method of any one of claims 34-45, wherein the pharmaceutical composition is formulated as capsule or a tablet.

47. The method of any one of claims 34-46, wherein the pharmaceutical composition is administered in the fed state.

48. The method of any one of claims 34-46, wherein the pharmaceutical composition is administered in the fasted state.

49. The method of any one of claims 34-48, wherein the pharmaceutical composition is administered at least once per day.

50. The method of any one of claims 34-49, wherein the pharmaceutical composition is administered at bedtime.

51. The method of any one of claims 34-50, wherein the pharmaceutical composition is administered less than about 4 hours before sleep.

52. The method of any one of claims 34-51, wherein the pharmaceutical composition is administered less than about 2 hours before sleep.

53. The method of any one of claims 34-52, wherein the pharmaceutical composition is administered less than about 30 minutes before sleep.

54. The method of any one of claims 34-53, wherein the pharmaceutical composition is administered in the evening.

55. The method of any one of claims 34-54, wherein the pharmaceutical composition is administered at about 10 pm at night.

56. The method of any one of claims 1-55, further comprising administering to the subject an additional chemotherapeutic agent.

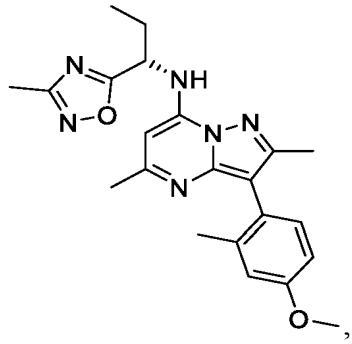
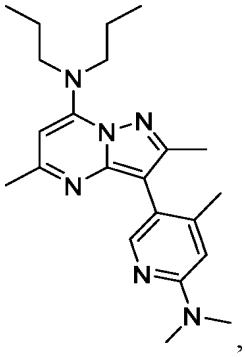
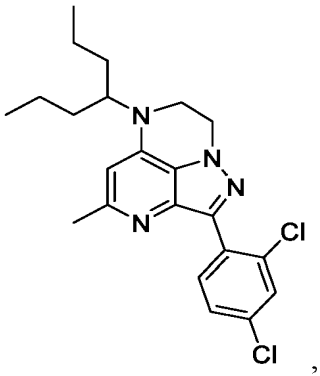
57. The method of claim 56, wherein the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen.

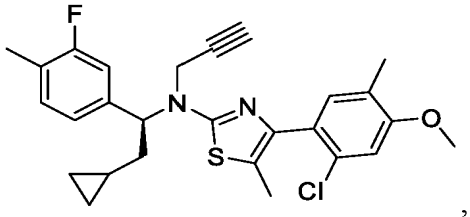
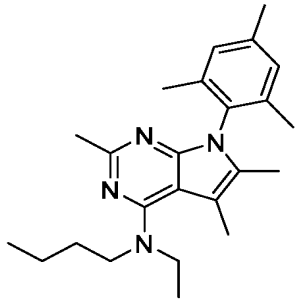
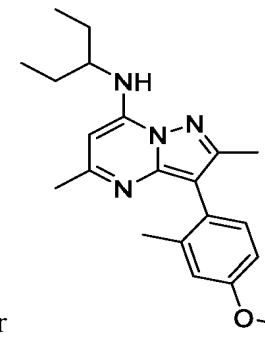
58. The method of claim 57, wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone.

59. The method of claim 57, wherein the mineralocorticoid is fludrocortisone.

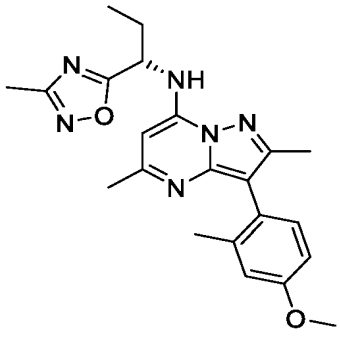
60. The method of claim 56, wherein the additional chemotherapeutic agent is another CRF_1 antagonist.

61. The method of claim 60, wherein the CRF_1 antagonist is

 ,  ,  , SSR-126374,

 ,  , or  , or a pharmaceutically acceptable salt thereof.

62. The method of claim 61, wherein the CRF_1 antagonist is

 , or a pharmaceutically acceptable salt thereof.

63. The method of any one of claims 1-62 further comprising an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

64. The method of claim 63, wherein 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.

65. The method of claim 64, wherein the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

66. The method of claim 65, wherein the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

67. The method of claim 66, wherein the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

68. The method of claim 63, wherein 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.

69. The method of claim 68, wherein 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.

70. The method of claim 68, wherein the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

71. The method of claim 68, wherein the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

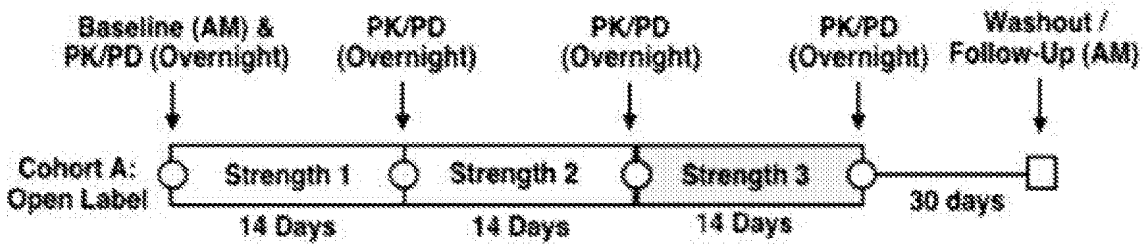

Baseline (AM) & PK/PD (Overnight)
PK/PD (Overnight)
PK/PD (Overnight)
PK/PD (Overnight)
Washout / Follow-Up (AM)
Cohort A: Open Label
Strength 1
Strength 2
Strength 3
30 days
14 Days
14 Days
14 Days

FIG. 1A

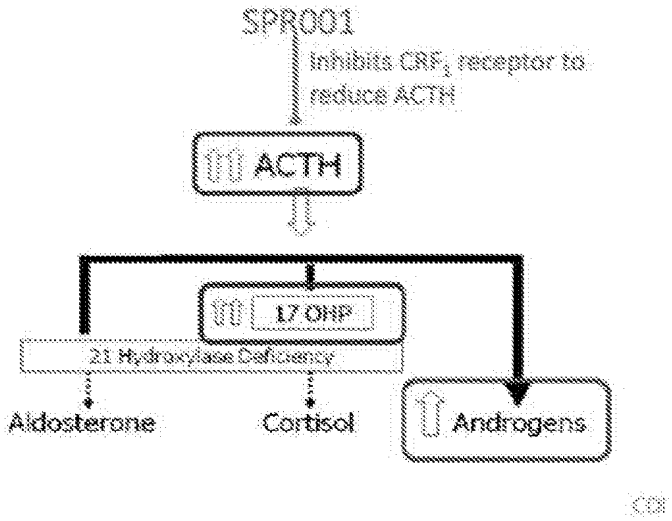

SPR001
Inhibits CRF1 receptor to reduce ACTH
ACTH
17 OHP
21 Hydroxylase Deficiency
Aldosterone
Cortisol
Androgens

FIG. 1B

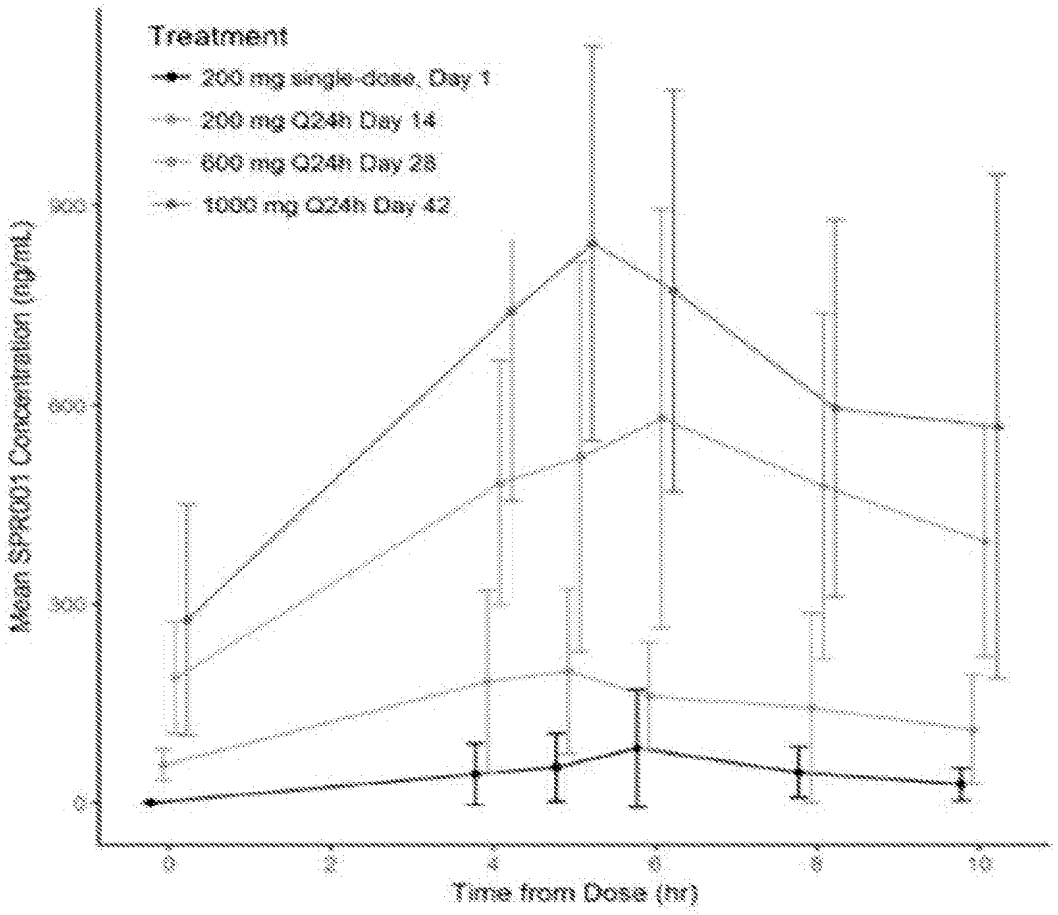

Treatment
200 mg single-dose, Day 1
200 mg Q24h Day 14
600 mg Q24h Day 28
1000 mg Q24h Day 42
Mean SPR001 Concentration (ng/mL)
0
2
4
6
8
10
Time from Dose (hr)

FIG. 2

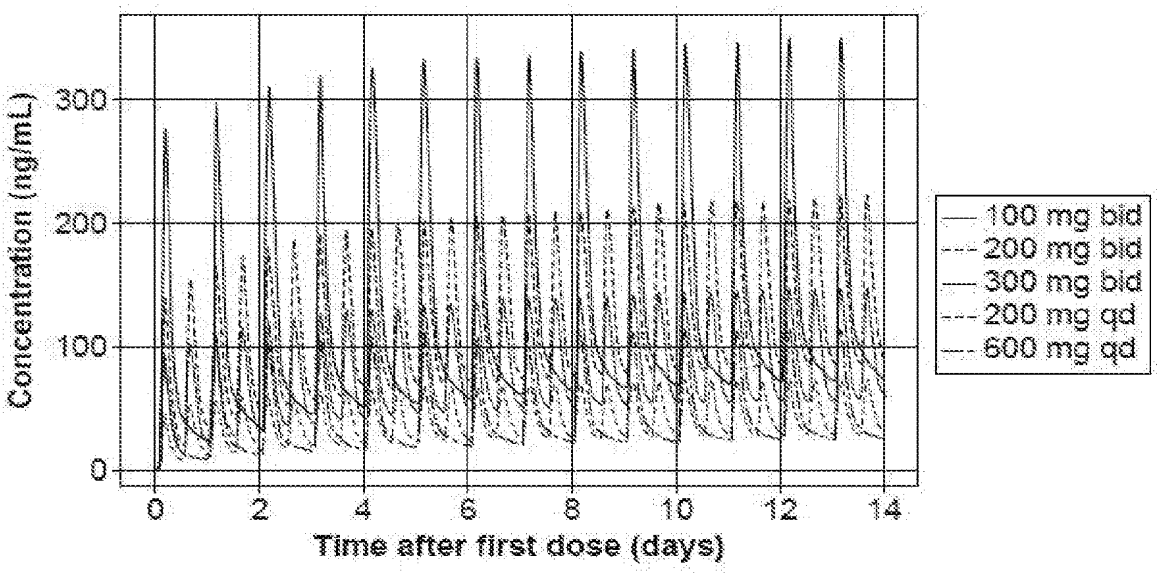

Concentration (ng/mL)
300
200
100
0
0
2
4
6
8
10
12
14
Time after first dose (days)
100 mg bid
200 mg bid
300 mg bid
200 mg qd
600 mg qd

FIG. 3

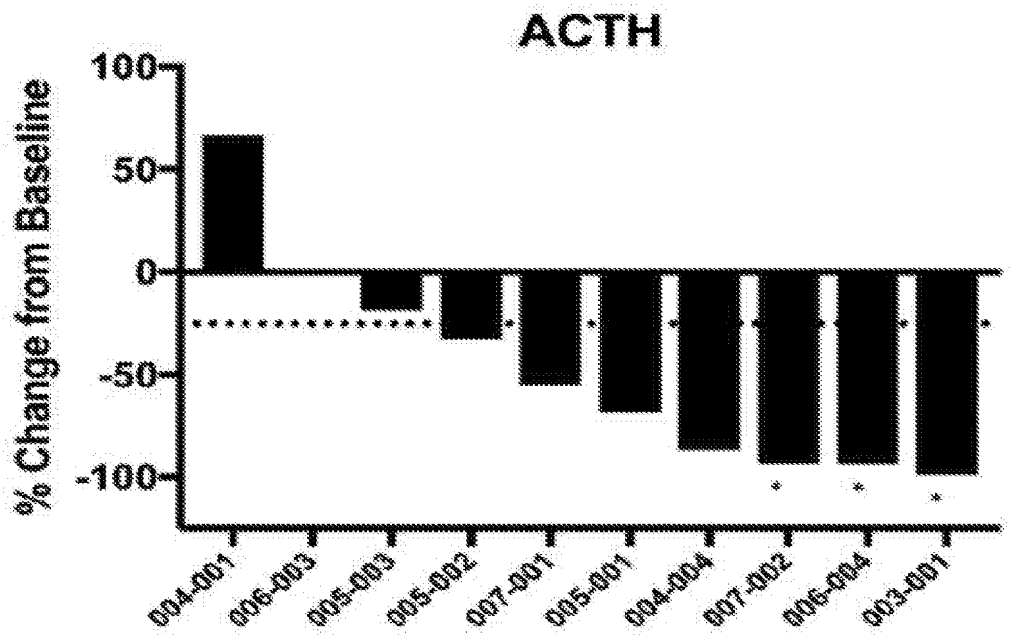

ACTH
% Change from Baseline
100
50
0
-50
-100
*
*
*
004-001
006-003
005-003
005-002
007-001
005-001
004-004
007-002
006-004
003-001

FIG. 4

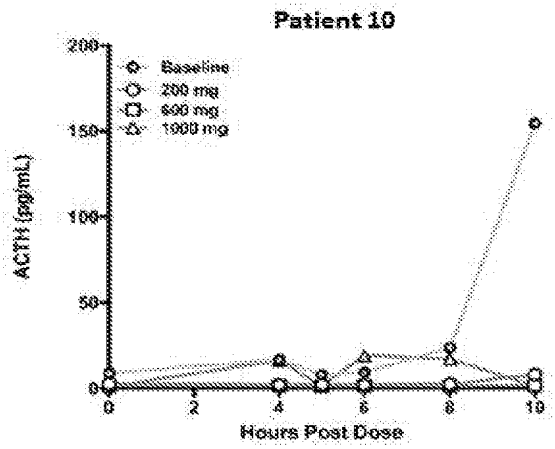


FIG. 5A

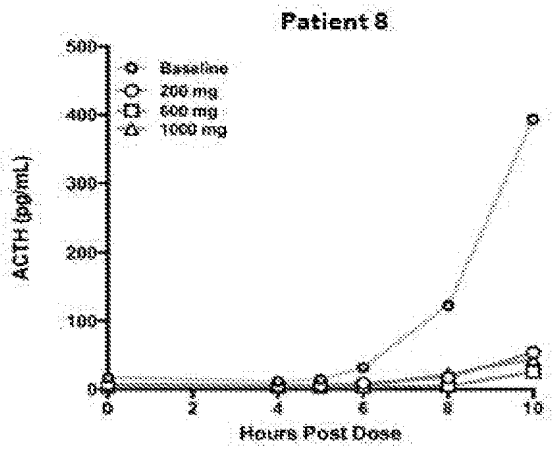


FIG. 5B

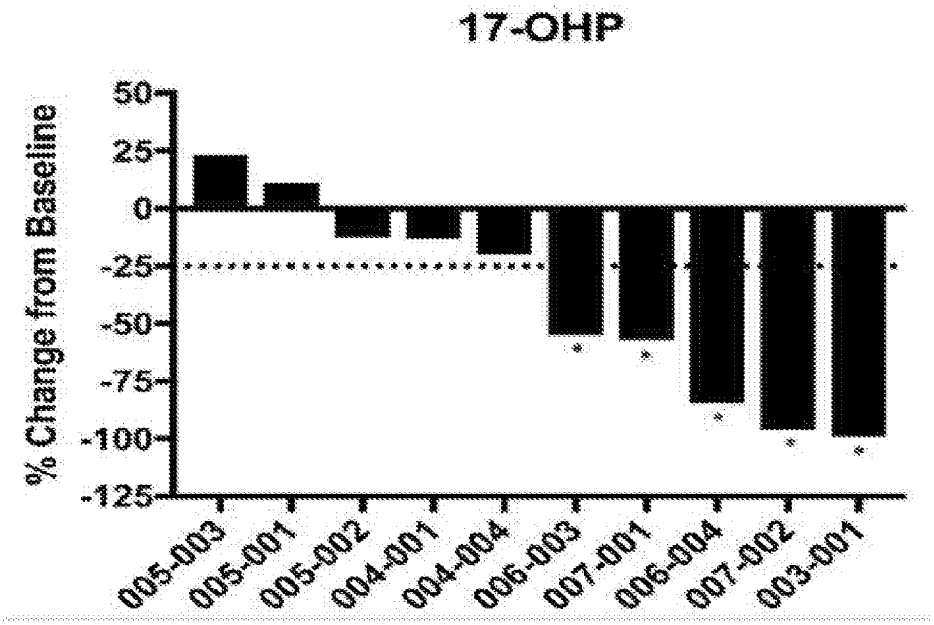


FIG. 6

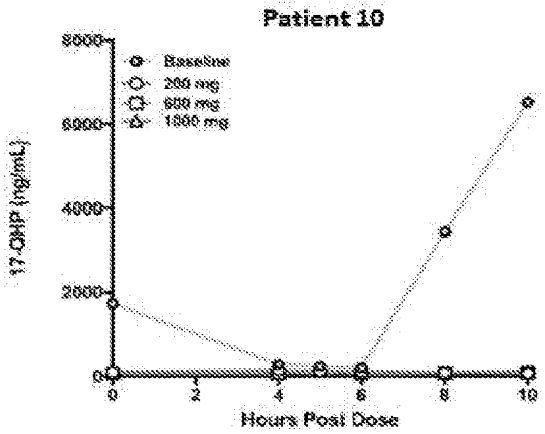


FIG. 7A

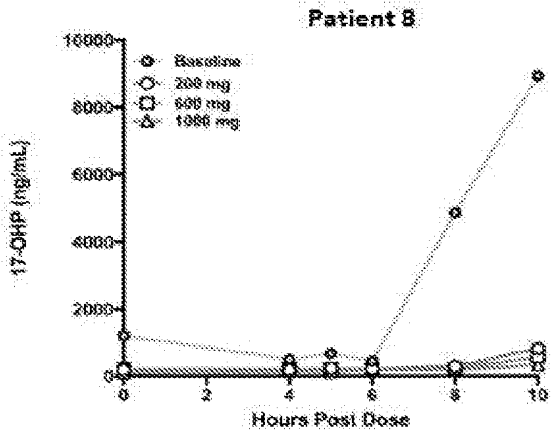


FIG. 7B

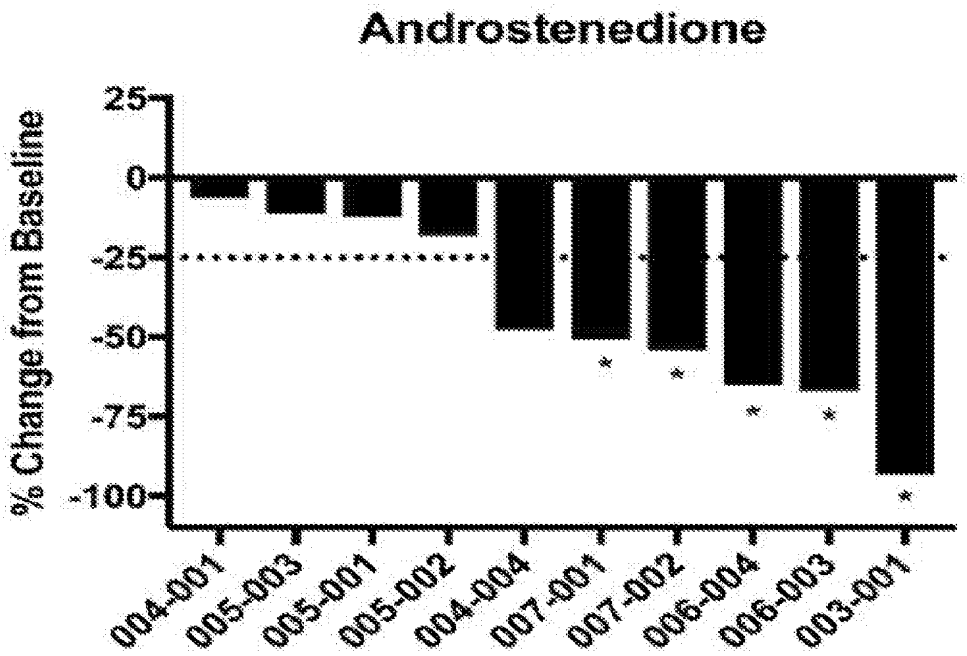


FIG. 8

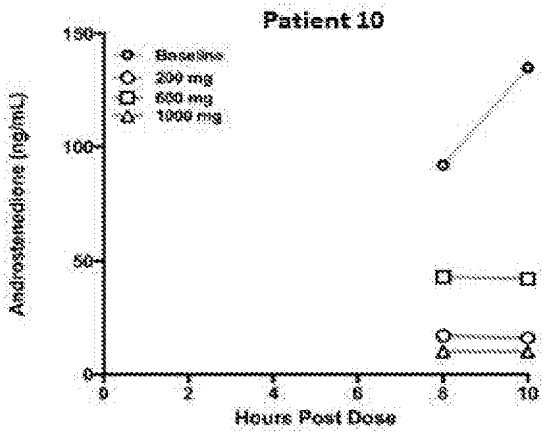


FIG. 9A

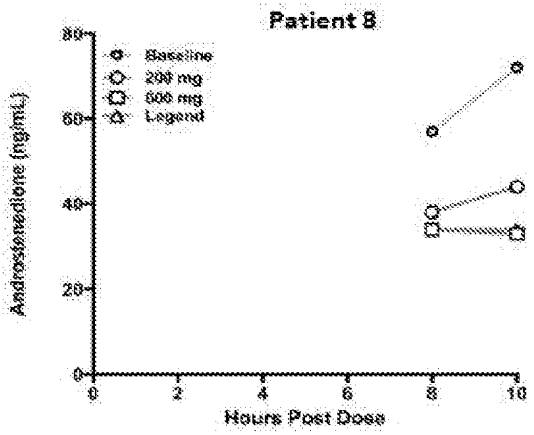


FIG. 9B

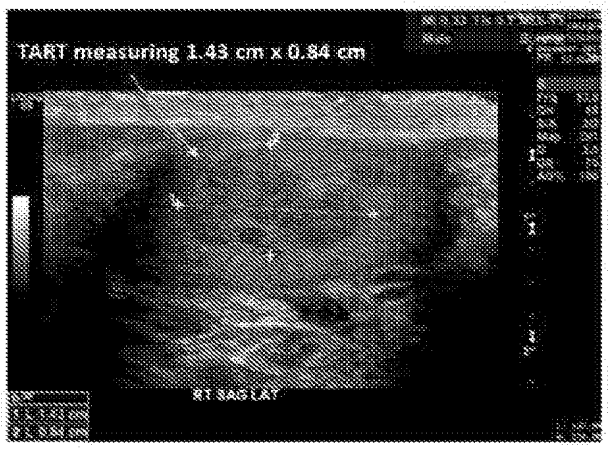


FIG. 10A

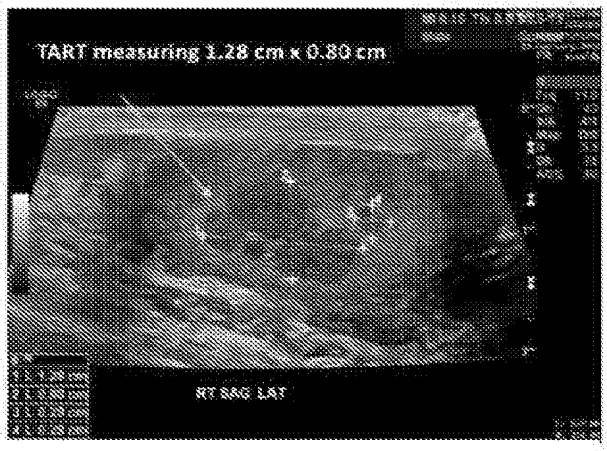


FIG. 10B

In Vitro Binding Assay

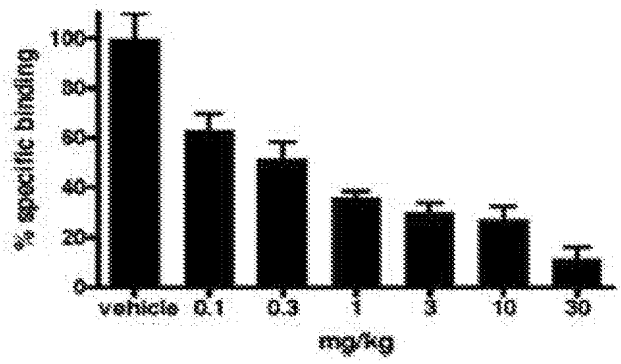


FIG. 11A

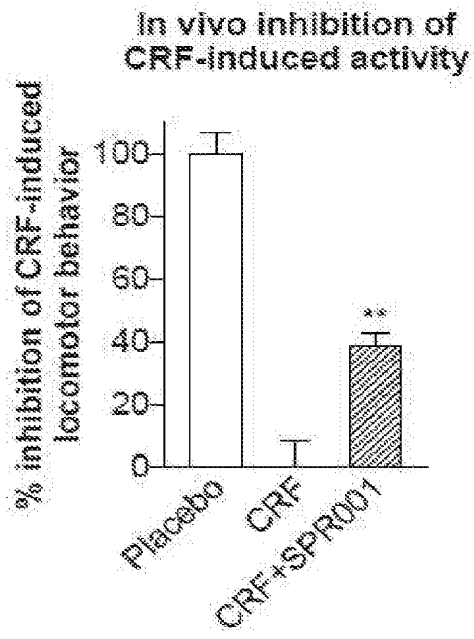


FIG. 11B

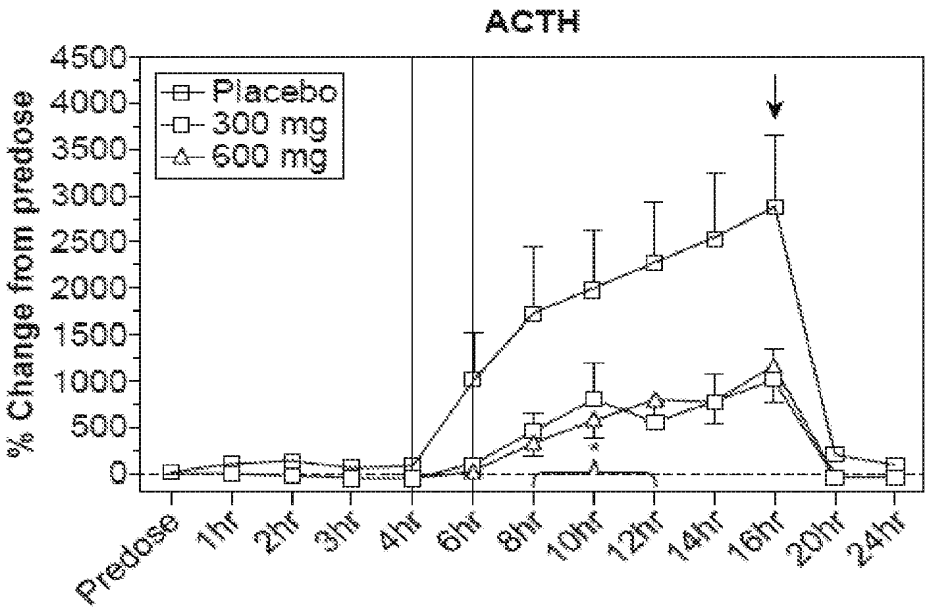


FIG. 12A

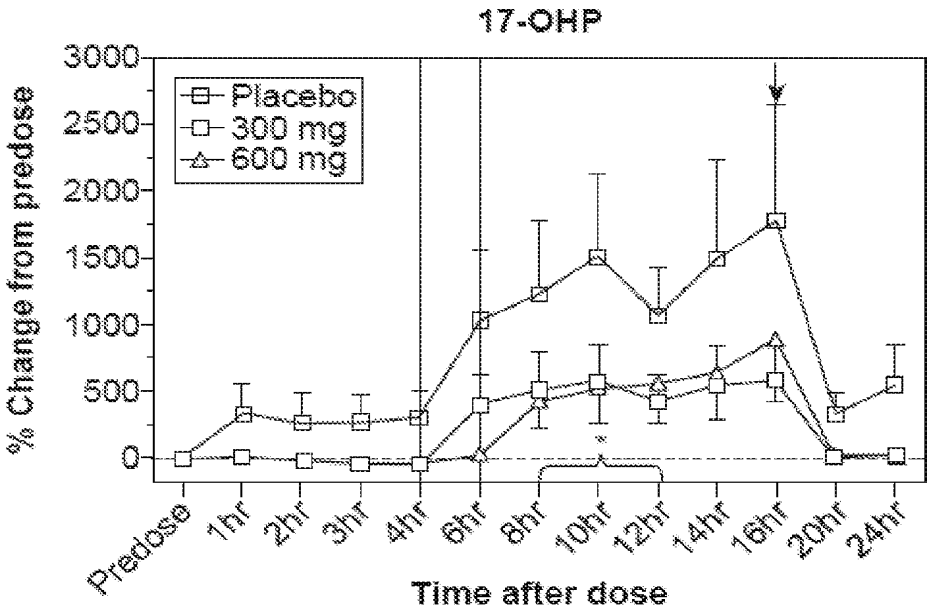


FIG. 12B

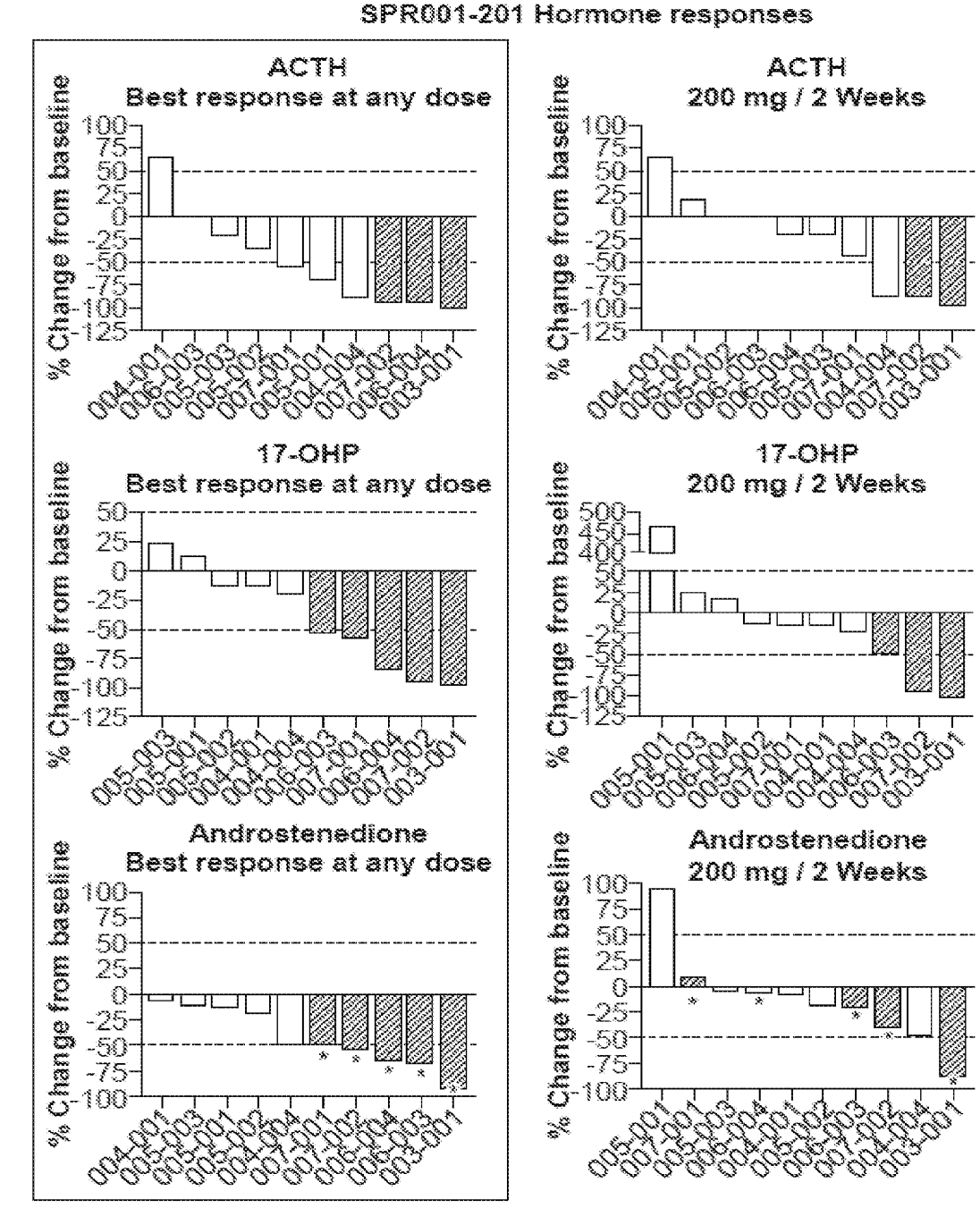


FIG. 13

ACTH: 7.2-63.3 pg/mL 17-OHP: <1200 ng/dL A4: 41-262 ng/dL (M) 27-152 ng/dL (F)

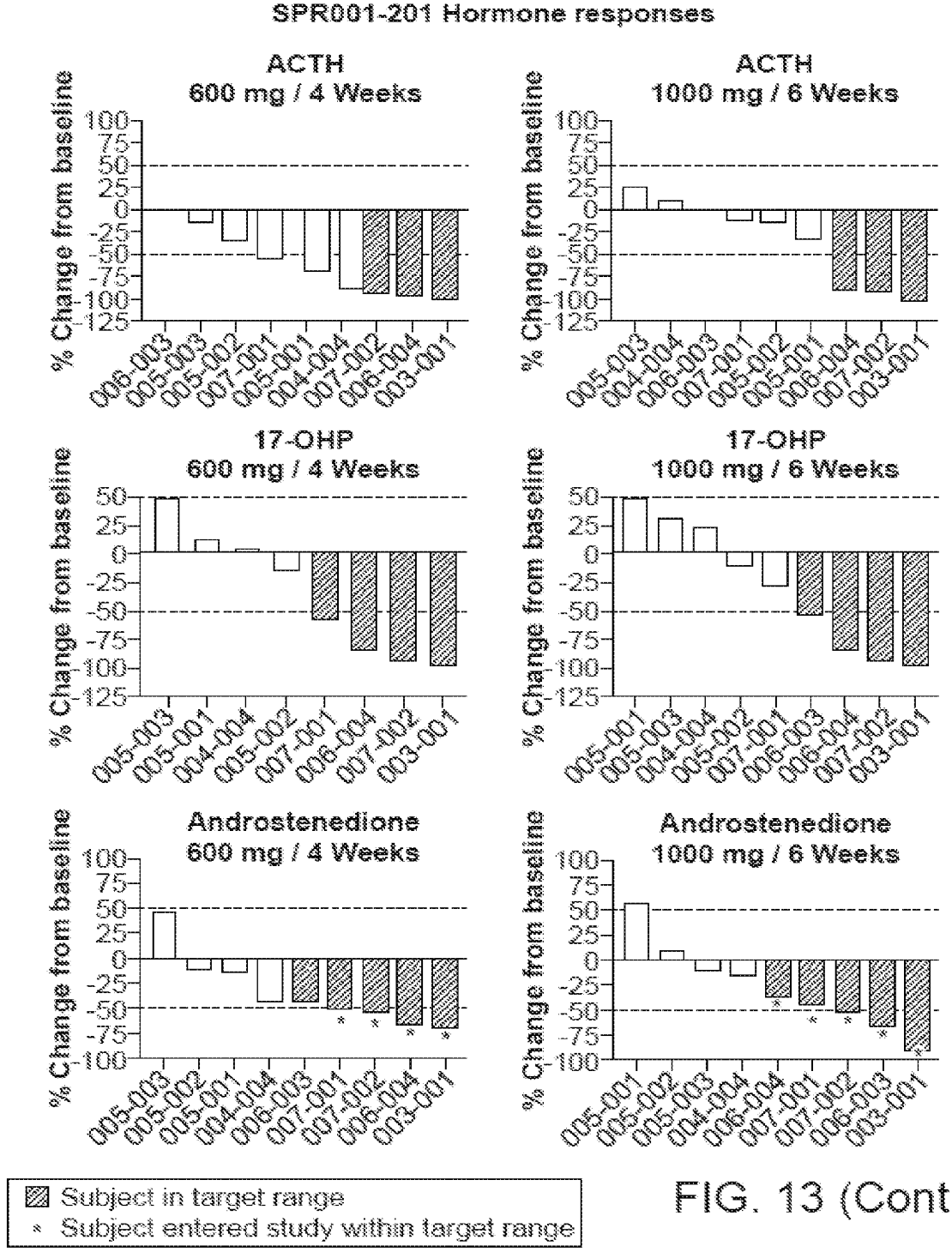


FIG. 13 (Cont.)

ACTH: 7.2-63.3 pg/mL 17-OHP: <1200 ng/dL A4: 41-262 ng/dL (M) 27-152 ng/dL (F)

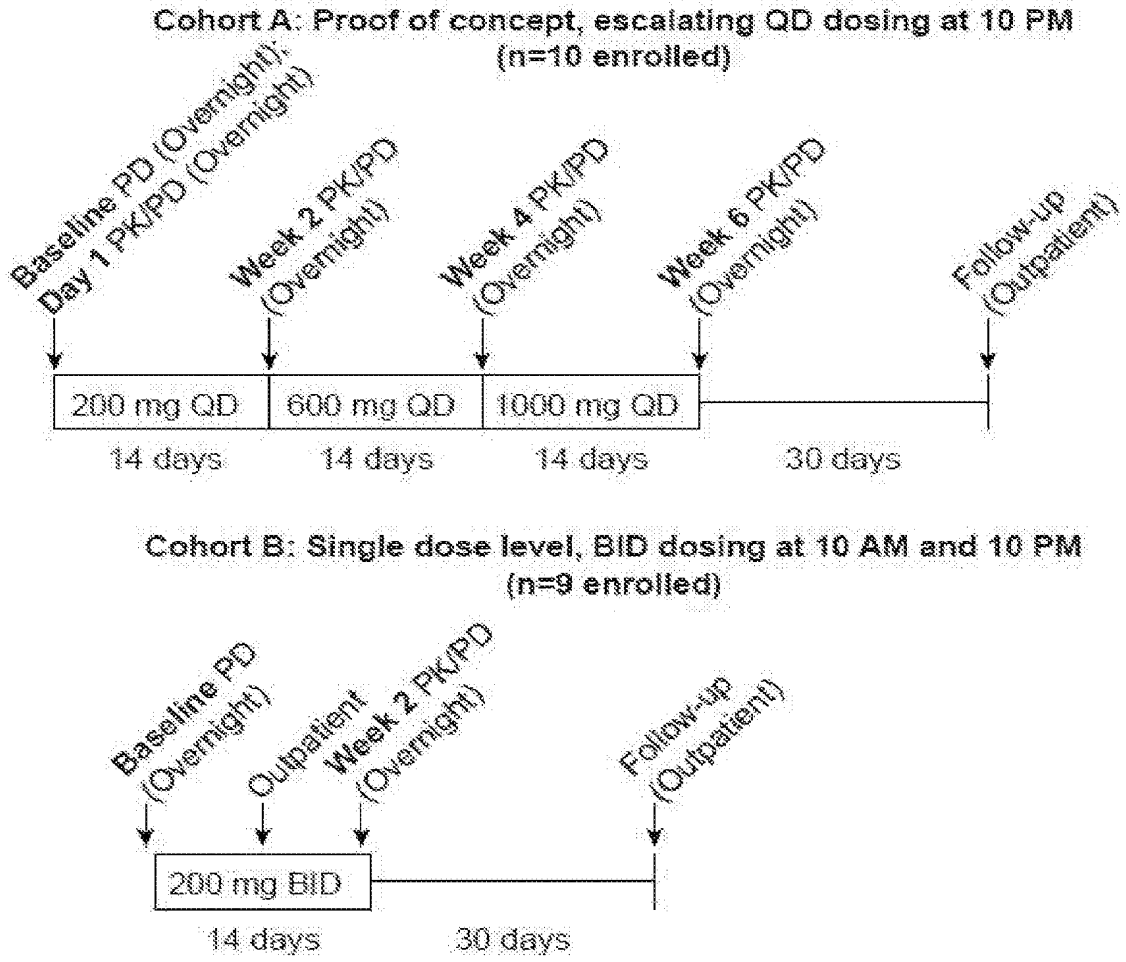

Cohort A: Proof of concept, escalating QD dosing at 10 PM
(n=10 enrolled)
Baseline PD (Overnight);
Day 1 PK/PD (Overnight)
Week 2 PK/PD
(Overnight)
Week 4 PK/PD
(Overnight)
Week 6 PK/PD
(Overnight)
Follow-up
(Outpatient)
200 mg QD
600 mg QD
1000 mg QD
14 days
14 days
14 days
30 days
Cohort B: Single 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

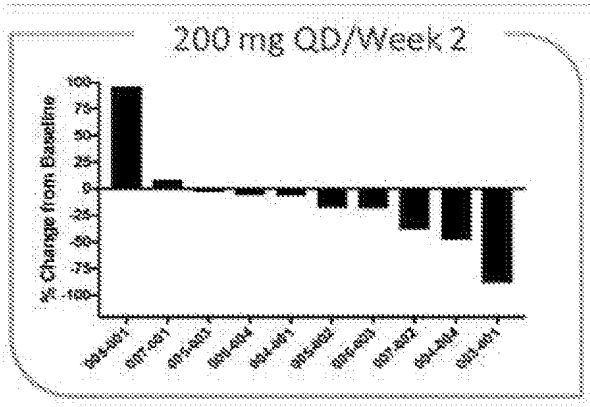


FIG. 15A

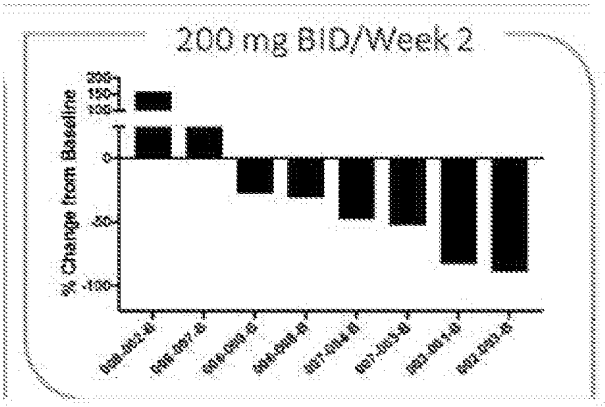


FIG. 15B

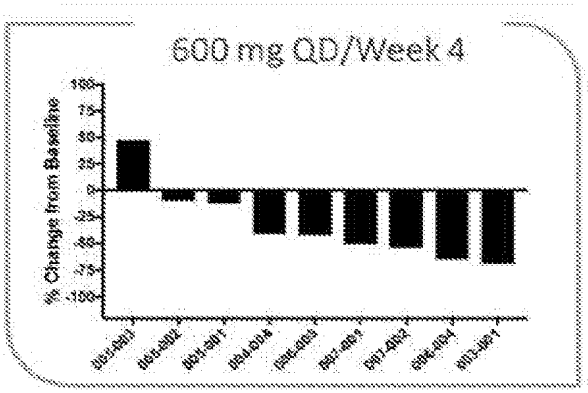


FIG. 15C

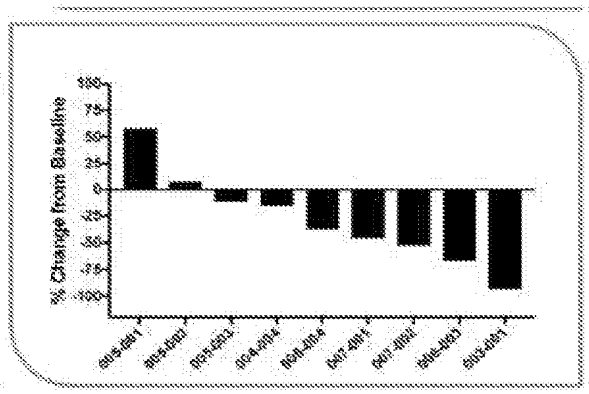


FIG. 15D

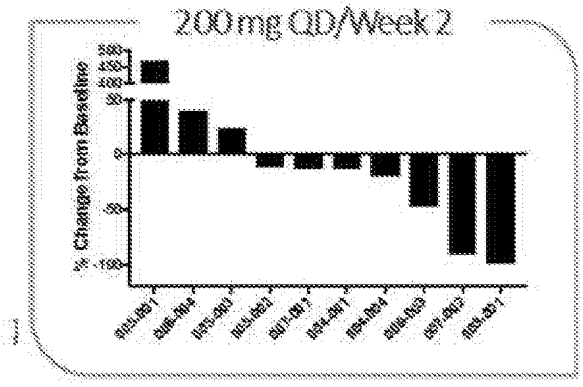


FIG. 16A

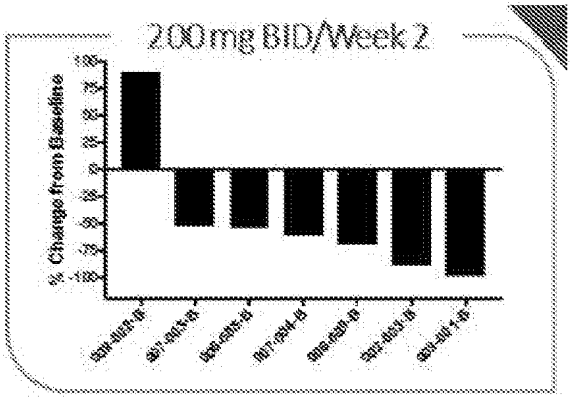


FIG. 16B

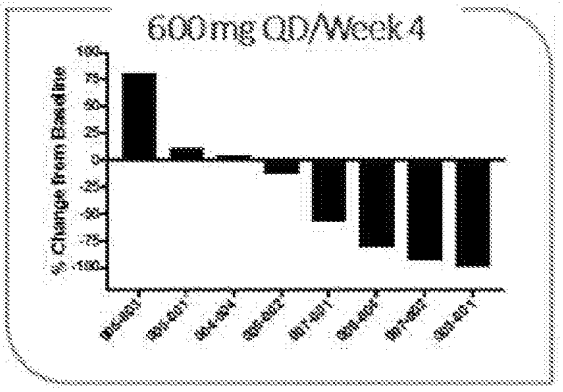


FIG. 16C

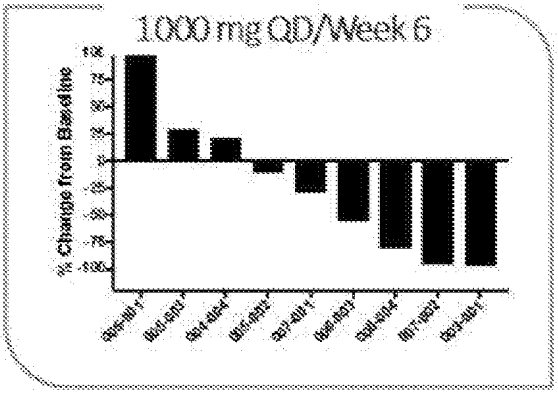


FIG. 16D

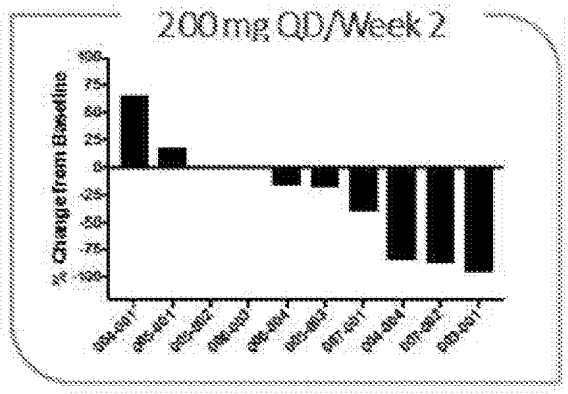


FIG. 17A

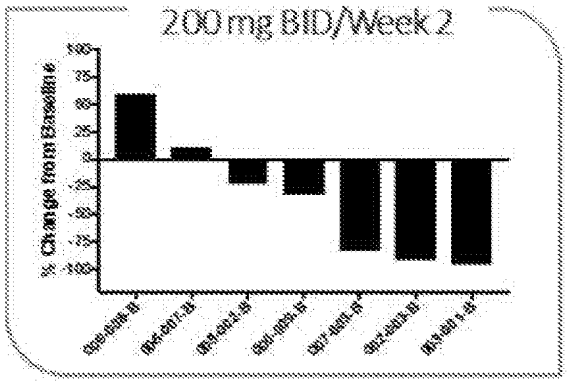


FIG. 17B

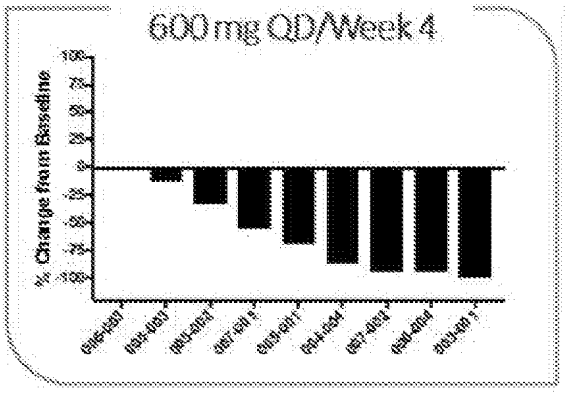


FIG. 17C

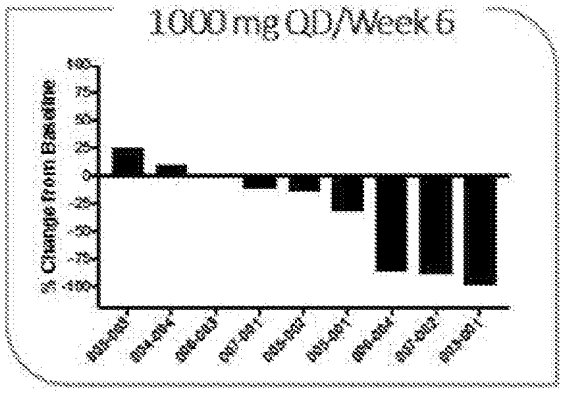


FIG. 17D

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/029486

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/4162; A61K 31/505; A61K 31/519; C07D 231/54; C07D 233/70; C07D 247/02 (2019.01)
CPC - A61K 31/4162; A61K 31/505; A61K 31/519; C07D 231/54; C07D 233/70; C07D 247/02 (2019.05)

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
USPC - 514/228.8; 514/230.2; 514/230.5 (keyword delimited)

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.
Y	US 2017/0020877 A1 (NEUROCRINE BIOSCIENCES, INC.) 26 January 2017 (26.01.2017) entire document	1-4, 9, 13, 14, 34
Y	US 2010/0222339 A1 (CHEN et al) 02 September 2010 (02.09.2010) entire document	1-4, 9, 13, 14, 34
Y	US 2010/0196389 A1 (EVANS-FREKE) 05 August 2010 (05.08.2010) entire document	3, 14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier 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
22 July 2019	12 AUG 2019
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/029486

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.: 15-33, 35-71
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
See extra sheet(s).

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.:
1-4, 9, 13, 14, 34

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/029486

Continued from Box No. III Observations where unity of invention is lacking

Claims 1-4, 9, 13, 14, and 34 have been analyzed subject to the restriction that the claims read on 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 (CRF1) antagonist or a pharmaceutically acceptable salt thereof, wherein the CRF1 antagonist is a compound of structural Formula I or a pharmaceutically acceptable salt thereof, wherein: R1 and R2 are independently ethyl; R3 is hydrogen; and R4 is hydrogen.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-14 and 34 are drawn to methods of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART).

The first invention of Group I+ is restricted to 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 (CRF1) antagonist or a pharmaceutically acceptable salt thereof, wherein the CRF1 antagonist is a compound of structural Formula I or a pharmaceutically acceptable salt thereof, wherein: R1 and R2 are independently ethyl; R3 is hydrogen; R4 is hydrogen; and methods of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART). It is believed that claims 1-4, 9, 13, 14, and 34 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be 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 (CRF1) antagonist or a pharmaceutically acceptable salt thereof, wherein the CRF1 antagonist is a compound of structural Formula I or a pharmaceutically acceptable salt thereof, wherein: R1 and R2 are independently ethyl; R3 is Br; R4 is hydrogen; and methods of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART). Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, R3, R4, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of 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 (CRF1) antagonist or a pharmaceutically acceptable salt thereof; 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):, and 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, these shared technical features do not represent a contribution over the prior art as disclosed by US 2017/0020877 A1 to Neurocrine Biosciences, Inc. and US 2010/0222339 A1 to Chen et al.

US 2017/0020877 A1 to Neurocrine Biosciences, Inc. teaches a method of treating or preventing testicular adrenal rest tumors (TART) (Para. [0044],...glucocorticoid treatment include cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women and to inhibit testicular adrenal rest tumors in men.; Para. [0047], Treatment of CAH includes efforts to normalize the cortisol deficiency with glucocorticoids...; Claim 1, A method for treating Congenital Adrenal Hyperplasia (CAH) by administering to a subject in need thereof a CRF1 receptor antagonist...), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF1) antagonist (Claim 1; Para. [0007]); and a method of treating or preventing testicular adrenal rest tumors (TART) (Paras. [0044] and [0047]; Claim 1), comprising administering to a subject in need thereof a pharmaceutical composition (Paras. [0061] and [0065], The pharmaceutical compositions described herein that comprise at least one of the CRF1 antagonist compounds described herein may be administered to a subject in need by any one of several routes that effectively deliver an effective amount of the compound.; Claim 1).

US 2010/0222339 A1 to Chen et al., in the field of treating congenital adrenal hyperplasia (Para. [0014]), teach a corticotropin-releasing factor type-1 (CRF1) antagonist (Para. [0125], Ex. No. 2, 3-(2,4-Dibromo-thiazol-5-yl)- 7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a] pyrimidine; Para. [0057], The compounds of Formula I are CRF-1 antagonists and, as such, are useful for treating a condition which is treatable by reducing CRF1 receptor tone or stimulation.); a compound of structural Formula (I) wherein , R1 and R2 are independently ethyl; R3 is Br; and R4 is Br (Para. [0125], Ex. No. 2, 3-(2,4-Dibromo-thiazol-5-yl)- 7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a] pyrimidine); and a pharmaceutical composition, comprising a compound of structural Formula (I) (Claim 10, A pharmaceutical composition comprising: a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.; (Para. [0125], Ex. No. 2, 3-(2,4-Dibromo-thiazol-5-yl)- 7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A1

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(71) Applicants *(for all designated States except US)*: ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). ZENECA-PHARMA S.A. [FR/FR]; Zone Industrielle Sud-est, Boîte postale 401, F-51064 Reims Cédex (FR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: LOHMANN, Jean-Jacques, Marcel [FR/FR]; Zeneca-Pharma S.A., Zone Industrielle Sud-est, Boîte postale 401, F-51064 Reims Cédex (FR). HENNEQUIN, Laurent, François, André [FR/FR]; Zeneca-Pharma S.A., Zone Industrielle Sud-est, Boîte postale 401, F-51064 Reims Cédex (FR). THOMAS, Andrew, Peter [GB/GB]; Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: MACK, John, Richard; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

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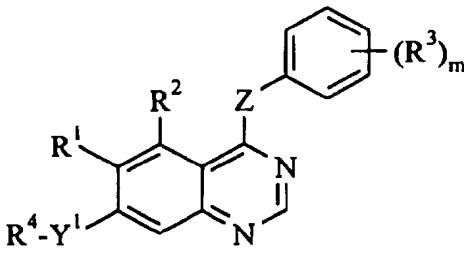
Published
With international search report.

(54) Title: QUINAZOLINE DERIVATIVES

(57) Abstract

The invention relates to quinazoline derivatives of formula (I) [wherein: Y^1 represents -O-, -S-, $-CH_2-$, -SO-, $-SO_2-$, $-NR^5CO-$, $-CONR^6-$, $-SO_2NR^7-$, $-NR^8SO_2-$ or $-NR^9-$ (wherein R^5, R^6, R^7, R^8 and R^9 each independently represents hydrogen, alkyl or alkoxyalkyl); R^1 represents hydrogen, hydroxy, halogeno, nitro, trifluoromethyl, cyano, alkyl, alkoxy, alkylthio, amino or alkylamino. R^2 represents hydrogen, hydroxy, halogeno, alkyl, alkoxy, trifluoromethyl, cyano, amino or nitro; m is an integer from 1 to 5; R^3 represents hydroxy, halogeno, alkyl, alkoxy, alkanoyloxy, trifluoromethyl, cyano, amino or nitro; R^4 represents a group which is or which contains an optionally substituted pyridone, phenyl or aromatic heterocyclic group] and salts thereof; processes for their preparation and pharmaceutical compositions containing a compound of formula (I) or a pharmaceutically acceptable salt thereof as active ingredient. The compounds of formula (I) and the pharmaceutically acceptable salts thereof inhibit the effects of VEGF, a property of value in the treatment of a number of disease states including cancer and rheumatoid arthritis.



(I)

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QUINAZOLINE DERIVATIVES.

The present invention relates to quinazoline derivatives, processes for their preparation, pharmaceutical compositions containing them as active ingredient, methods for the treatment of disease states associated with angiogenesis and/or increased vascular permeability and to their use in the manufacture of medicaments for use in the production of antiangiogenic and/or vascular permeability reducing effects in warm-blooded animals such as humans.

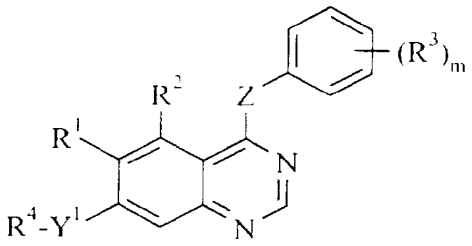
Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with in vitro endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844).

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity

which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the fms-like tyrosine kinase receptor, Flt or Flt1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another fms-like tyrosine kinase receptor, Flt4. Two of these related RTKs, Flt and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

Compounds which have good activity against epidermal growth factor (EGF) receptor tyrosine kinase are disclosed in the European Patent No. 0566226. The present invention is based on the discovery of compounds that surprisingly inhibit the effects of VEGF, a property of value in the treatment of disease states associated with angiogenesis and/or increased vascular permeability such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation and ocular diseases with retinal vessel proliferation. Compounds of the present invention possess higher potency against VEGF receptor tyrosine kinase than against EGF receptor tyrosine kinase. Furthermore, compounds of the present invention, possess substantially higher potency against VEGF receptor tyrosine kinase than against EGF receptor tyrosine kinase or FGF R1 receptor tyrosine kinase. Thus compounds of the invention which have been tested possess activity against VEGF receptor tyrosine kinase such that they may be used in an amount sufficient to inhibit VEGF receptor tyrosine kinase whilst demonstrating no significant activity against EGF receptor tyrosine kinase or FGF R1 receptor tyrosine kinase.

According to one aspect of the present invention there is provided a quinazoline derivative of the formula I:



(I)

[wherein:

Y^1 represents -O-, -S-, $-CH_2-$, -SO-, $-SO_2-$, $-NR^5CO-$, $-CONR^6-$, $-SO_2NR^7-$, $-NR^8SO_2-$ or $-NR^9-$ (wherein R^5, R^6, R^7, R^8 and R^9 each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl);

R^1 represents hydrogen, hydroxy, halogeno, nitro, trifluoromethyl, cyano, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, or $NR^{10}R^{11}$ (wherein R^{10} and R^{11}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl);

R^2 represents hydrogen, hydroxy, halogeno, C_{1-3}alkyl, C_{1-3} alkoxy, trifluoromethyl, cyano, amino or nitro;

m is an integer from 1 to 5;

R^3 represents hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino or nitro;

R^4 is selected from one of the following eight groups:

1) X^1 (wherein X^1 represents a pyridone group, a phenyl group or a 5 or 6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which pyridone, phenyl or heterocyclic group may carry up to 5 substituents selected from halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, $-CONR^{12}R^{13}$ and $-NR^{14}COR^{15}$ (wherein R^{12}, R^{13}, R^{14} and R^{15}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

2) C_{1-5}alkylX^1 (wherein X^1 is as defined hereinbefore);

3) C_{2-5}alkenylX^1 (wherein X^1 is as defined hereinbefore);

4) C_{2-5}alkynylX^1 (wherein X^1 is as defined hereinbefore);

5) C_{1-5}alkylY^2X^1 (wherein Y^2 represents -O-, -S-, -SO-, $-SO_2$-, -OCO-, $-NR^{16}CO$-, $-CONR^{17}$-, $-SO_2NR^{18}$-, $-NR^{19}SO_2$- or $-NR^{20}$- (wherein R^{16}, R^{17}, R^{18}, R^{19} and R^{20} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and X^1 is as defined hereinbefore);

6) C_{2-5}alkenylY^3X^1 (wherein Y^3 represents -O-, -S-, -SO-, $-SO_2$-, -OCO-, $-NR^{21}CO$-, $-CONR^{22}$-, $-SO_2NR^{23}$-, $-NR^{24}SO_2$- or $-NR^{25}$- (wherein R^{21}, R^{22}, R^{23}, R^{24} and R^{25} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and X^1 is as defined hereinbefore);

7) C_{2-5}alkynylY^4X^1 (wherein Y^4 represents -O-, -S-, -SO-, $-SO_2$-, -OCO-, $-NR^{26}CO$-, $-CONR^{27}$-, $-SO_2NR^{28}$-, $-NR^{29}SO_2$- or $-NR^{30}$- (wherein R^{26}, R^{27}, R^{28}, R^{29} and R^{30} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and X^1 is as defined hereinbefore); and

8) C_{1-3}alkylY^5C_{1-3}alkylX^1 (wherein Y^5 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{31}CO$-, $-CONR^{32}$-, $-SO_2NR^{33}$-, $-NR^{34}SO_2$- or $-NR^{35}$- (wherein R^{31}, R^{32}, R^{33}, R^{34} and R^{35} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and X^1 is as defined hereinbefore);

Z represents -NH-, -O-, -S-, or $-CH_2$-; with the proviso that where R^4 is selected from one of the groups 1), 2), and 5) above and X^1 is unsubstituted phenyl or substituted phenyl with 1 to 2 substituents selected from halogeno, C_{1-4}alkyl and C_{1-4}alkoxy, then m is an integer from 3 to 5 and/or Z is -O-, -S-, or $-CH_2$-];

and salts thereof.

Advantageously Y^1 represents -O-, -S-, $-CH_2$-, $-NR^5CO$-, $-NR^8SO_2$- or $-NR^9$- (wherein R^5, R^8 and R^9 each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably Y^1 represents -O-, -S-, $-CH_2$-, $-NR^5CO$-, $-NR^8SO_2$- or -NH- (wherein R^5 and R^8 each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

More preferably Y^1 represents -O-, -S-, $-CH_2$- or -NH-, especially -O-.

In another embodiment of the present invention Y^1 represents -O-, $-NR^5CO$- or $-NR^8SO_2$- (wherein R^5 and R^8 each independently represents hydrogen or C_{1-2}alkyl).

In a further embodiment of the present invention Y^1 is -NHCO-.

In one embodiment of the invention R^1 represents hydrogen, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, or $NR^{10}R^{11}$ (wherein R^{10} and R^{11} are as defined hereinbefore). Conveniently however R^1 is hydrogen, hydroxy, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, C_{1-3}alkoxy or amino.

R^1 is advantageously hydrogen, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy or amino.

R^1 is preferably hydrogen, hydroxy, methyl, ethyl, methoxy or ethoxy, more preferably hydrogen, hydroxy, methyl or methoxy, particularly hydrogen, methyl or methoxy but especially methoxy.

In another embodiment of the present invention R^1 represents hydrogen, hydroxy, cyano, nitro, trifluoromethyl, methyl, ethyl, methoxy or ethoxy.

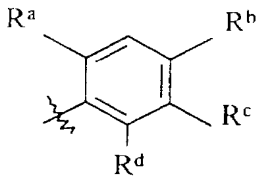
R^2 is advantageously hydrogen, halogeno, amino or nitro.

R^2 is preferably hydrogen, chloro or nitro, but especially hydrogen.

In one embodiment of the present invention R^3 represents hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, cyano, amino or nitro.

Advantageously in another embodiment of the present invention one R^3 substituent is meta-hydroxy and the other one or more are each selected from halogeno and methyl.

In another embodiment of the invention the phenyl group bearing $(R^3)_m$ is of the formula IIa:



(IIa)

(wherein:

R^a represents hydrogen, methyl, fluoro or chloro;

R^b represents hydrogen, methyl, methoxy, bromo, fluoro or chloro;

R^c represents hydrogen or hydroxy;

R^d represents hydrogen, fluoro or chloro, especially hydrogen or fluoro).

In a further embodiment of the invention the phenyl group bearing $(R^3)_m$ is preferably of the formula IIa wherein:

R^a represents hydrogen, fluoro or chloro;

R^b represents hydrogen, methyl, methoxy, bromo, fluoro or chloro, especially hydrogen, methyl or chloro;

R^c represents hydrogen or hydroxy; and

R^d represents hydrogen;

with the proviso that R^a, R^b and R^c do not each represent hydrogen.

Preferably the phenyl group bearing $(R^3)_m$ is the 3-hydroxy-4-methylphenyl group, the 2-fluoro-5-hydroxy-4-methylphenyl group, the 2-fluoro-4-bromophenyl, the 2-fluoro-4-chloro-5-hydroxyphenyl or the 4-chloro-2-fluorophenyl group.

In a particular aspect of the present invention, the phenyl group bearing $(R^3)_m$ is the 3-hydroxy-4-methylphenyl group, but especially the 2-fluoro-5-hydroxy-4-methylphenyl group.

In a further embodiment of the present invention the phenyl group bearing $(R^3)_m$ is the 4-chloro-2-fluorophenyl group.

Advantageously Y^2 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{16}CO$-, $-NR^{19}SO_2$- or $-NR^{20}$- (wherein R^{16}, R^{19} and R^{20} each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably Y^2 represents, -O-, -S-, -SO-, $-SO_2$- or $-NR^{20}$- (wherein R^{20} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

More preferably Y^2 represents -S-, -O- or $-NR^{20}$- (wherein R^{20} represents hydrogen or C_{1-2}alkyl), but most preferably is -O-, or $-NR^{20}$ (wherein R^{20} is as hereinbefore defined).

Advantageously Y^3 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{21}CO$-, $-NR^{24}SO_2$- or $-NR^{25}$- (wherein R^{21}, R^{24} and R^{25} each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably Y^3 represents -O-, -S-, -SO-, $-SO_2$- or $-NR^{25}$- (wherein R^{25} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

More preferably Y^3 represents -O- or $-NR^{25}$- (wherein R^{25} represents hydrogen or C_{1-2}alkyl).

Advantageously Y^4 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{26}CO$-, $-NR^{29}SO_2$- or $-NR^{30}$- (wherein R^{26}, R^{29} and R^{30} each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably Y^4 represents -O-, -S-, -SO-, $-SO_2$- or $-NR^{30}$- (wherein R^{30} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

More preferably Y^4 represents -O- or $-NR^{30}$- (wherein R^{30} represents hydrogen or C_{1-2}alkyl).

Advantageously Y^5 represents -O-, -S-, -SO-, $-SO_2$- or $-NR^{35}$- (wherein R^{35} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably Y^5 represents -O-, -S- or -NR^{35}- (wherein R^{35} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

m is preferably 2 or 3.

Z may for example represent -NH- or -O- but Z is preferably -NH-.

X^1 preferably represents a pyridone group or a 5 or 6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which pyridone group or heterocyclic group may be substituted as hereinbefore defined.

Where X^1 is a 5 or 6-membered aromatic heterocyclic group, it preferably has 1 or 2 heteroatoms, selected from O, N and S, of which more preferably one is N, and may be substituted as hereinbefore defined.

X^1 is particularly a pyridone, pyridyl, imidazolyl, thiazolyl, thienyl, triazolyl or pyridazinyl group which group may be substituted as hereinbefore defined, more particularly a pyridone, pyridyl, imidazolyl, thiazolyl or triazolyl group, especially a pyridone, pyridyl, imidazolyl or triazolyl group which group may be substituted as hereinbefore defined.

Where R^4 is C_{1-5}alkylX^1, C_{2-5}alkenylX^1, C_{2-5}alkynylX^1 or C_{1-3}alkylY^5C_{1-3}alkylX^1, and X^1 is a nitrogen-containing 6-membered aromatic heterocyclic group, said group is advantageously linked to the alkyl, alkenyl or alkynyl moiety via a carbon atom of X^1, said group being such that a nitrogen atom is positioned para- to the carbon atom linked to the alkyl, alkenyl or alkynyl moiety. The C_{1-5}alkyl moiety may if desired be -$(CH_2)_n$-.

Where R^4-Y^1 is X^1-$(CH_2)_n$-Y^1- and n is an integer from 0 to 5, Y^1 is -O-, -NH-, -S- or -CH_2- and X^1 is a nitrogen-containing 6-membered aromatic heterocyclic group, said group is advantageously linked to -$(CH_2)_n$-Y^1- via a carbon atom of X^1, said group being such that a nitrogen atom is positioned para- to the carbon atom linked to -$(CH_2)_n$-Y^1-.

In another example of interest, X^1 is pyrimidine which may be substituted as hereinbefore defined.

In one embodiment of the invention X^1 represents a pyridone, phenyl or 5 or 6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which group may preferably carry up to 2 substituents, more preferably up to one substituent, selected from the group of substituents as hereinbefore defined.

In the definition of X^1, conveniently substituents are selected from halogeno, C_{1-4}alkyl, C_{1-4}alkoxy and cyano, more conveniently substituents are selected from chloro, fluoro, methyl and ethyl.

Conveniently R^4 is selected from one of the following eight groups:

1) X^1 (wherein X^1 is as defined hereinbefore);

2) C_{1-5}alkylX^1 (wherein X^1 is as defined hereinbefore);

3) C_{3-5}alkenylX^1 (wherein X^1 is as defined hereinbefore);

4) C_{3-5}alkynylX^1 (wherein X^1 is as defined hereinbefore);

5) C_{1-5}alkylY^2X^1 (wherein Y^2 and X^1 are as defined hereinbefore);

6) C_{3-5}alkenylY^3X^1 (wherein Y^3 and X^1 are as defined hereinbefore);

7) C_{3-5}alkynylY^4X^1 (wherein Y^4 and X^1 are as defined hereinbefore); and

8) C_{2-3}alkylY^5C_{1-2}alkylX^1 (wherein Y^5 and X^1 are as defined hereinbefore).

Advantageously R^4 is selected from one of the following eight groups:

1) X^1 (wherein X^1 is as defined hereinbefore);

2) C_{1-5}alkylX^1 (wherein X^1 is as defined hereinbefore);

3) 1-X^1prop-1-en-3-yl, 1-X^1but-2-en-4-yl, 1-X^1but-1-en-3-yl, 1-X^1pent-2-en-4-yl or 2-X^1pent-3-en-5-yl (wherein X^1 is as defined hereinbefore with the proviso that when R^4 is 1-X^1prop-1-en-3-yl, X^1 is linked to the alkenyl group via a carbon atom);

4) 1-X^1prop-1-yn-3-yl, 1-X^1but-2-yn-4-yl, 1-X^1but-1-yn-3-yl, 1-X^1pent-2-yn-4-yl or 2-X^1pent-3-yn-5-yl (wherein X^1 is as defined hereinbefore with the proviso that when R^4 is 1-X^1prop-1-yn-3-yl, X^1 is linked to the alkynyl group via a carbon atom);

5) C_{1-5}alkylY^2X^1 (wherein Y^2 and X^1 are as defined hereinbefore);

6) 1-(X^1Y^3)prop-1-en-3-yl, 1-(X^1Y^3)but-2-en-4-yl, 1-(X^1Y^3)but-1-en-3-yl, 1-(X^1Y^3)pent-2-en-4-yl or 2-(X^1Y^3)pent-3-en-5-yl (wherein Y^3 and X^1 are as defined hereinbefore);

7) 1-(X^1Y^4)prop-1-yn-3-yl, 1-(X^1Y^4)but-2-yn-4-yl, 1-(X^1Y^4)but-1-yn-3-yl, 1-(X^1Y^4)pent-2-yn-4-yl or 2-(X^1Y^4)pent-3-yn-5-yl (wherein Y^4 and X^1 are as defined hereinbefore); and

8) C_{2-3}alkylY^5C_{1-2}alkylX^1 (wherein Y^5 and X^1 are as defined hereinbefore).

Preferably R^4 is selected from one of the following eight groups:

1) X^1 (wherein X^1 is as defined hereinbefore);

2) C_{1-5}alkylX^1 (wherein X^1 is as defined hereinbefore);

3) 1-X^1but-2-en-4-yl (wherein X^1 is as defined hereinbefore);

4) 1-X^1but-2-yn-4-yl (wherein X^1 is as defined hereinbefore);

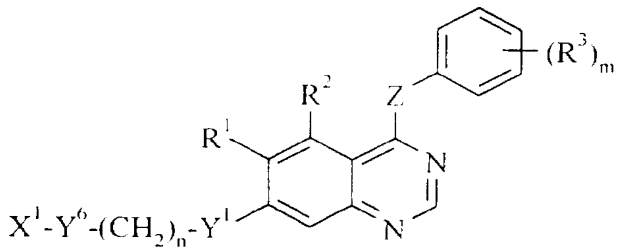
5) C_{1-5}alkylY^2X^1 (wherein Y^2 and X^1 are as defined hereinbefore);

6) 1-(X^1Y^3)but-2-en-4-yl (wherein Y^3 and X^1 are as defined hereinbefore);

7) 1-(X^1Y^4)but-2-yn-4-yl (wherein Y^4 and X^1 are as defined hereinbefore); and

8) ethylY^5methylX^1 (wherein Y^5 and X^1 are as defined hereinbefore).

More preferably the compounds of formula (I) are of the formula (Ia):



(Ia)

(wherein R^1, R^2, R^3, m, X^1, Y^1 and Z are as defined hereinbefore n is an integer from 0 to 5 and Y^6 represents a direct bond, -O-, -S-, -SO-, $-SO_2$-, $-NR^{36}CO$-, $-CONR^{37}$-, $-SO_2NR^{38}$-, $-NR^{39}SO_2$- or $-NR^{40}$- (wherein R^{36}, R^{37}, R^{38}, R^{39} and R^{40} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl)).

Advantageously Y^6 is a direct bond, -O-, -S-, -SO-, $-SO_2$- or $-NR^{40}$- (wherein R^{40} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably Y^6 is a direct bond, -O-, -S- or -NH-.

More preferably Y^6 is a direct bond.

n is advantageously an integer from 0 to 3, preferably 1 to 3.

Therefore, for example, in a particular embodiment of the invention the compounds of formula I are of the formula Ia wherein:

[Y^1 represents -O-, -NH-, -S- or $-CH_2$-;

n is an integer from 0 to 5;

X^1 represents a phenyl group or a 5 or 6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which phenyl or heterocyclic group may carry up to 5

substituents selected from halogeno, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}hydroxyalkoxy, carboxy, cyano, -$CONR^{41}R^{42}$ and -$NR^{43}COR^{44}$ (wherein R^{41}, R^{42}, R^{43} and R^{44}, which may be the same or different, each represents hydrogen or C_{1-4}alkyl);

R^1 represents hydrogen, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, or $NR^{45}R^{46}$ (wherein R^{45} and R^{46}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl);

R^2 represents hydrogen, hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, cyano, amino or nitro;

m is an integer from 1 to 5;

R^3 represents hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino or nitro;

Z represents -NH- or -O-; and

Y^6 is a direct bond;

with the proviso that where X^1 is unsubstituted phenyl or substituted phenyl with 1 to 2 substituents selected from halogeno, C_{1-4}alkyl and C_{1-4}alkoxy, m is an integer from 3 to 5 or Z is -O-];

and salts thereof.

Preferred compounds of the present invention are:-

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(3-pyridylmethoxy)quinazoline

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(3-thienylmethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(2-pyridyloxy)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-[N-methyl-N-(4-pyridyl)]aminoethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-[2-(2-oxo-1,2-dihydro-1-pyridyl)ethoxy]quinazoline

7-(4 cyanobenzyloxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(2-methylimidazol-1-yl)propoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((2-methyl-4-pyridyl)methoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(2-oxo-1,2-dihydro-1-pyridyl)propoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(1-methylimidazol-2-ylthio)propoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(4-pyridyloxy)propoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(4-pyridylthio)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(3-pyridyloxy)ethoxy)quinazoline

7-benzyloxy-4-(2-fluoro-5-hydroxy-4-methylanilino)quinazoline

7-benzyloxy-4-(4-chloro-2-fluoro-5-hydroxyanilino)quinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-((2-methylthiazol-4-yl)methoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((3-thienyl)methoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-methyl-N-(pyridazin-4-yl)amino)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-methyl-N-(6-methylpyrimidin-4-yl)amino)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-7-(2-(3,5-dimethyl-[1,2,4]-triazol-4-yl)ethoxy)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-7-(2-(2,4-dimethylimidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-7-(2-(2,5-dimethylimidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(3-hydroxyanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1,2,4-triazol-4-yl)ethoxy)quinazoline

4-(4-bromo-2-fluoroanilino)-7-(2-([1,2,4]-triazol-1-yl)ethoxy)-6-methoxyquinazoline

and salts thereof, especially hydrochloride salts thereof.

The following compounds of the present invention are especially preferred:-

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyridylmethoxy)quinazoline

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(2-pyridylmethoxy)quinazoline

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(1-methylimidazol-2-ylmethoxy)quinazoline

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(2-methylthiazol-4-ylmethoxy)quinazoline

7-(2-acetamidothiazol-4-ylmethoxy)-4-(3-hydroxy-4-methylanilino)-6-methoxyquinazoline

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyridylpropoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyridylpropoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyridylmethoxy)quinazoline

7-benzyloxy-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(4-pyridyloxy)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-[2-(4-oxo-1,4-dihydro-1-pyridyl)ethoxy]quinazoline

7-benzyloxy-4-(2-fluoro-5-hydroxy-4-methylphenoxy)-6-methoxyquinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-((2-methylthiazol-4-yl)methoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-7-(4-pyridylmethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-((1-methylimidazol-2-yl)methoxy)quinazoline

7-((2-acetamidothiazol-4-yl)methoxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline

7-benzyloxy-4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(4-pyridyl)propoxy)quinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-(3-(4-pyridyl)propoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-(2-(4-pyridyl)ethoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-(3-thienylmethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(4-pyridyl)ethoxy)quinazoline

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-((1-methylbenzimidazol-2-yl)methoxy)quinazoline

7-((2-chloro-6-methyl-4-pyridyl)methoxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline

4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-((4 pyridyl)methoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((4 pyridyl)methoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(2-methylimidazol-1-yl)ethoxy)quinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-((4-pyridyl)methoxy)quinazoline

7-((2-chloro-4-pyridyl)methoxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1-methylimidazol-2-ylthio)ethoxy)quinazoline

7-(3,4-difluorobenzyloxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-((1-methylimidazol-2-yl)methoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-7-((1-methylimidazol-2-yl)methoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-7-(2-(1,2,4-triazol-1-yl)ethoxy)quinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-((3-thienyl)methoxy)quinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-(2-(4-pyridyl)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1,2,4-triazol-1-yl)ethoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-7-((4-pyridyl)carboxamido)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-(4-pyridyl)amino)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1-methylimidazol-2-yl)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-7-((2-cyano-4-pyridyl)methoxy)-6-methoxyquinazoline

and salts thereof, especially hydrochloride salts thereof,

of which the following are particularly preferred:-

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(4-pyridyloxy)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-[2-(4-oxo-1,4-dihydro-1-pyridyl)ethoxy]quinazoline

4-(4-chloro-2-fluoroanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(4-pyridyl)propoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(4-pyridyl)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((4-pyridyl)methoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(2-methylimidazol-1-yl)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1-methylimidazol-2-ylthio)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1,2,4-triazol-1-yl)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-(4-pyridyl)amino)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1-methylimidazol-2-yl)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-7-((2-cyano-4-pyridyl)methoxy)-6-methoxyquinazoline

and salts thereof, especially hydrochloride salts thereof.

Another compound of interest is 4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyrimidinylmethoxy)quinazoline and salts thereof especially hydrochloride salts thereof.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions for that group.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms. Unless otherwise stated the term "alkyl" advantageously refers to chains with 1-6 carbon atoms, preferably 1-4 carbon atoms. The term "alkoxy" as used herein, unless stated otherwise includes "alkyl"-O- groups in which "alkyl" is as hereinbefore defined. The term "aryl" as used herein unless stated otherwise includes reference to a C_{6-10} aryl group which may, if desired, carry one or more substituents selected from halogeno, alkyl, alkoxy, nitro, trifluoromethyl and cyano, (wherein alkyl and alkoxy are as hereinbefore defined). The term "aryloxy" as used herein unless otherwise stated includes "aryl"-O-groups in which "aryl" is as hereinbefore defined. The term "sulphonyloxy" as used herein refers to alkylsulphonyloxy and arylsulphonyloxy groups in which "alkyl" and "aryl" are as hereinbefore defined. The term "alkanoyl" as used herein unless otherwise stated includes alkylC=O groups in which "alkyl" is as defined hereinbefore, for example ethanoyl refers to $CH_3C=O$. In this specification unless stated otherwise the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-butenyl are specific for the straight chain version only. Unless otherwise stated the term "alkenyl" advantageously refers to chains with 2-6 carbon atoms, preferably 4-5 carbon atoms. In this specification unless stated otherwise the term "alkynyl" includes both straight and branched chain alkynyl groups but references to individual alkynyl groups such as 2-butynyl are specific for the straight chain version only. Unless otherwise stated the term "alkynyl" advantageously refers to chains with 2-6 carbon atoms, preferably 4-5 carbon atoms.

In formula I, as hereinbefore defined, hydrogen will be present at positions 2 and 8 of the quinazoline group.

Within the present invention it is to be understood that a quinazoline of the formula I or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits VEGF receptor tyrosine kinase activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

It is also to be understood that certain quinazolines of the formula I and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit VEGF receptor tyrosine kinase activity.

For the avoidance of any doubt, it is to be understood that when Y^1 is, for example, a group of formula $-NR^5CO-$, it is the nitrogen atom bearing the R^5 group which is attached to the quinazoline ring and the carbonyl (CO) group is attached to R^4, whereas when Y^1 is, for example, a group of formula $-CONR^6-$, it is the carbonyl group which is attached to the quinazoline ring and the nitrogen atom bearing the R^6 group is attached to R^4. A similar convention applies to the other two atom Y^1 linking groups such as $-NR^8SO_2-$ and $-SO_2NR^7-$. When Y^1 is $-NR^9-$ it is the nitrogen atom bearing the R^9 group which is linked to the quinazoline ring and to R^4. An analogous convention applies to other groups. It is further to be understood that when Y^1 represents $-NR^9-$ and R^9 is $C_{1-3}alkoxyC_{2-3}alkyl$ it is the $C_{2-3}alkyl$ moiety which is linked to the nitrogen atom of Y^1 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of the formula I when R^4 is, for example, a group of formula $C_{1-5}alkylY^5C_{1-5}alkylX^1$, it is the terminal $C_{1-5}alkyl$ moiety which is bound to Y^1, similarly when R^4 is, for example, a group of formula $C_{2-5}alkenylX^1$ it is the $C_{2-5}alkenyl$ moiety which is bound to Y^1 and an analgous convention applies to other groups. When R^4 is a group $1\text{-}X^1prop\text{-}1\text{-}en\text{-}3\text{-}yl$ it is the first carbon to which the group X^1 is attached and it is the third carbon which is linked to Y^1, similarly when R^4 is a group $2\text{-}X^1pent\text{-}3\text{-}en\text{-}5\text{-}yl$ it is the second carbon to which the group X^1 is attached and it is the fifth carbon which is linked to Y^1, and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when X^1 carries a C_{1-4}aminoalkyl substituent it is the $C_{1-4}alkyl$ moiety which is attached to X^1 whereas when X^1

carries a C_{1-4}alkylamino substituent it is the amino moiety which is attached to X^1 and an analogous convention applies to other groups.

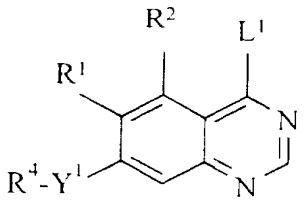
The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula I as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic acids such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid as well as salts with organic acids affording pharmaceutically acceptable anions, such as for example trifluoroacetic, citric or maleic acid. In addition where the compounds of formula I are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic substance or organic base which affords a pharmaceutically acceptable cation. Such salts include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A compound of the formula I, or salt thereof, and other compounds of the invention (as hereinafter defined) may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes include, for example, those illustrated in European Patent Applications Nos. 0520722, 0566226, 0602851 and 0635498. Such processes, are provided as a further feature of the invention and are as described hereinafter. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Thus the following processes (a) to (g) and (i) to (v) constitute further features of the present invention.

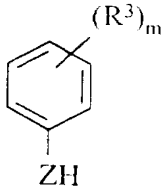
Synthesis of Compounds of Formula I

(a) Compounds of the formula I and salts thereof may be prepared by the reaction of a compound of the formula III:



(III)

(wherein R^1, R^2, R^4 and Y^1 are as defined hereinbefore and L^1 is a displaceable group), with a compound of the formula IV:



(IV)

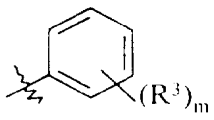
(wherein Z, R^3 and m are as defined hereinbefore) whereby to obtain compounds of the formula I and salts thereof. A convenient displaceable group L^1 is, for example, a halogeno, alkoxy (preferably C_{1-4}alkoxy), aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group.

The reaction is advantageously effected in the presence of either an acid or a base. Such an acid is, for example, an anhydrous inorganic acid such as hydrogen chloride. Such a base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or for example, an alkali metal or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively such a base is, for

example, an alkali metal hydride, for example sodium hydride, or an alkali metal or alkaline earth metal amide, for example sodium amide or sodium bis(trimethylsilyl)amide. The reaction is preferably effected in the presence of an inert solvent or diluent, for example an alkanol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently effected at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 80°C.

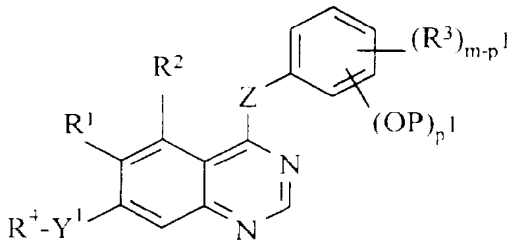
The compound of the invention may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula H-L^1 wherein L^1 has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a base as defined hereinbefore using a conventional procedure.

(b) Where the group of formula IIb:



(IIb)

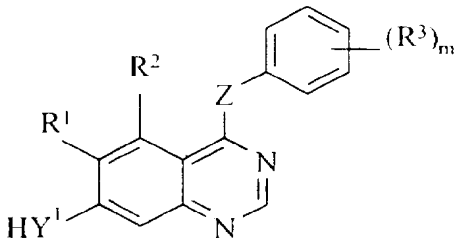
(wherein R^3 and m are as hereinbefore defined) represents a phenyl group carrying one or more hydroxy groups, a compound of the formula I and salts thereof can be prepared by the deprotection of a compound of formula V:



(V)

(wherein Y^1, m, R^1, R^2, R^3, R^4 and Z are as hereinbefore defined, P represents a phenolic hydroxy protecting group and p^1 is an integer from 1 to 5 equal to the number of protected hydroxy groups and such that m-p^1 is equal to the number of R^3 substituents which are not protected hydroxy). The choice of phenolic hydroxy protecting group P is within the standard knowledge of an organic chemist, for example those included in standard texts such as "Protective Groups in Organic Synthesis" T.W. Greene and R.G.M.Wuts, 2nd Ed. Wiley 1991, including ethers (for example, methyl, methoxymethyl, allyl and benzyl), silyl ethers (for example, t-butyldiphenylsilyl and t-butyldimethylsilyl), esters (for example, acetate and benzoate) and carbonates (for example, methyl and benzyl). The removal of such a phenolic hydroxy protecting group may be effected by any of the procedures known for such a transformation, including those reaction conditions indicated in standard texts such as that indicated hereinbefore, or by a related procedure. The reaction conditions preferably being such that the hydroxy derivative is produced without unwanted reactions at other sites within the starting or product compounds. For example, where the protecting group P is acetate, the transformation may conveniently be effected by treatment of the quinazoline derivative with a base as defined hereinbefore and including ammonia, and its mono and di-alkylated derivatives, preferably in the presence of a protic solvent or co-solvent such as water or an alcohol, for example methanol or ethanol. Such a reaction can be effected in the presence of an additional inert solvent or diluent as defined hereinbefore and at a temperature in the range 0 to 50°C, conveniently at or near 20°C.

(c) Production of those compounds of formula I and salts thereof wherein the substituent Y^1 is -O-, -S- or -NR^9- can be achieved by the reaction, conveniently in the presence of a base as defined hereinbefore, of a compound of the formula VI:



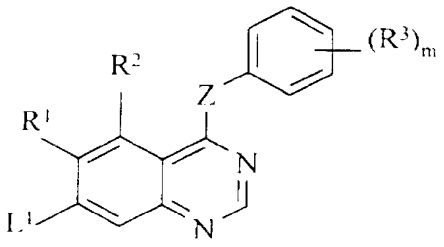
(VI)

(wherein m, Y^1, R^1, R^2, R^3 and Z are as hereinbefore defined) with a compound of formula VII:

$$R^4\text{-}L^1 \qquad \text{(VII)}$$

(wherein R^4 and L^1 are as hereinbefore defined); L^1 is a displaceable group for example a halogeno or sulphonyloxy group such as a bromo or methanesulphonyloxy group. The reaction is preferably effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at or near 50°C.

(d) Compounds of the formula I and salts thereof may be prepared by the reaction of a compound of the formula VIII:



(VIII)

with a compound of the formula IX:

$$R^4\text{-}Y^1\text{-}H \qquad \text{(IX)}$$

(wherein L^1, R^1, R^2, R^3, R^4, Z, m and Y^1 are all as hereinbefore defined). The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at or near 100°C.

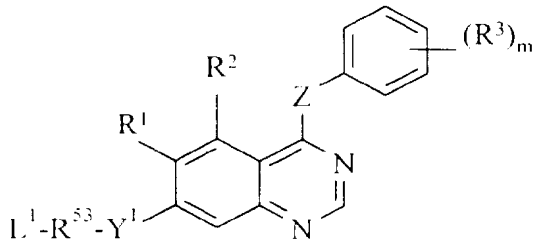
(e) Compounds of the formula I and salts thereof wherein R^4 is C_{1-5}alkylX^2, [wherein X^2 is selected from one of the following three groups:

1) X^1 (wherein X^1 is as defined hereinbefore);

2) Y^7X^1 (wherein Y^7 represents -O-, -S-, $-SO_2-$, $-NR^{47}CO-$, $-NR^{48}SO_2-$ or $-NR^{49}-$ (wherein R^{47}, R^{48} and R^{49} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and X^1 is as defined hereinbefore); and

3) Y^8C_{1-5}alkylY^5X^1 (wherein Y^8 represents -O-, -S-, $-SO_2-$, $-NR^{50}CO-$, $-NR^{51}SO_2-$ or $-NR^{52}-$ (wherein R^{50}, R^{51} and R^{52} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and Y^5 and X^1 are as defined hereinbefore);]

may be prepared by reacting a compound of the formula X:



(X)

(wherein L^1, Y^1, R^1, R^2, R^3, Z and m are as hereinbefore defined and R^{53} is C_{1-3}alkyl) with a compound of the formula XI:

$$X^2\text{-}H \qquad (XI)$$

(wherein X^2 is as defined hereinbefore) to give a compound of the formula I. The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), and at a temperature in the range, for example 0 to 150°C, conveniently at about 50°C.

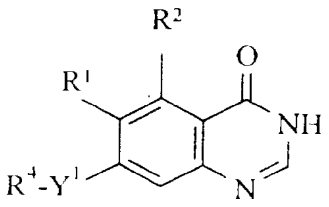
(f) The production of those compounds of the formula I and salts thereof wherein the substituent R^1 is represented by $NR^{10}R^{11}$, where one or both of R^{10} and R^{11} are C_{1-3}alkyl, may be effected by the reaction of compounds of formula I wherein the substituent R^1 is an amino group and an alkylating agent, preferably in the presence of a base as defined hereinbefore. Such alkylating agents are C_{1-3}alkyl moieties bearing a displaceable moiety as defined hereinbefore such as C_{1-3}alkyl halides for example C_{1-3}alkyl chloride, bromide or iodide. The reaction is preferably effected in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)) and at a temperature in the range, for example, 10 to 100°C, conveniently at about ambient temperature.

(g) The production of compounds of formula I and salts thereof wherein one or more of the substituents R^1, R^2 or R^3 is an amino group may be effected by the reduction of a

corresponding compound of formula I wherein the substituent(s) at the corresponding position(s) of the quinazoline and/or phenyl ring is/are a nitro group(s). The reduction may conveniently be effected as described in process (i) hereinafter. The production of a compound of formula I and salts thereof wherein the substituent(s) at the corresponding position(s) of the quinazoline and/or phenyl ring is/are a nitro group(s) may be effected by the processes described hereinbefore and hereinafter in processes (a-e) and (i-v) using a quinazoline compound selected from the compounds of the formulae (I-XXVII) in which the substituent(s) at the corresponding position(s) of the quinazoline and/or phenyl ring is/are a nitro group(s).

Synthesis of Intermediates

(i) The compounds of formula III and salts thereof, constitute a further feature of the present invention. Such compounds in which L^1 is halogeno may for example be prepared by halogenating a compound of the formula XII:

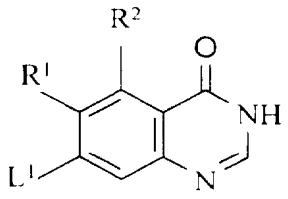


(XII)

(wherein R^1, R^2, R^4 and Y^1 are as hereinbefore defined).

Convenient halogenating agents include inorganic acid halides, for example thionyl chloride, phosphorus(III)chloride, phosphorus(V)oxychloride and phosphorus(V)chloride. The halogenation reaction is conveniently effected in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, or an aromatic hydrocarbon solvent such as benzene or toluene. The reaction is conveniently effected at a temperature in the range, for example 10 to 150°C, preferably in the range 40 to 100°C.

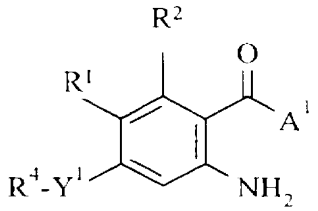
The compounds of formula XII and salts thereof which constitute a further feature of the present invention may for example be prepared by reacting a compound of the formula XIII:



(XIII)

(wherein R^1, R^2 and L^1 are as hereinbefore defined) with a compound of the formula IX as hereinbefore defined. The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at or near 100°C.

The compounds of formula XII and salts thereof may also be prepared by cyclising a compound of the formula XIV:

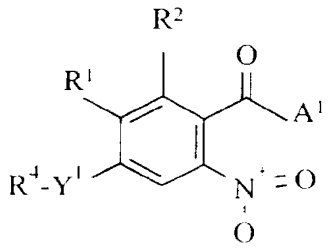


(XIV)

(wherein R^1, R^2, R^4 and Y^1 are as hereinbefore defined, and A^1 is an hydroxy, alkoxy (preferably C_{1-4}alkoxy) or amino group) whereby to form a compound of formula XII or salt thereof. The cyclisation may be effected by reacting a compound of the formula XIV, where

A^1 is an hydroxy or alkoxy group, with formamide or an equivalent thereof effective to cause cyclisation whereby a compound of formula XII or salt thereof is obtained, such as [3-(dimethylamino)-2-azaprop-2-enylidene]dimethylammonium chloride. The cyclisation is conveniently effected in the presence of formamide as solvent or in the presence of an inert solvent or diluent such as an ether for example 1,4-dioxan. The cyclisation is conveniently effected at an elevated temperature, preferably in the range 80 to 200°C. The compounds of formula XII may also be prepared by cyclising a compound of the formula XIV, where A^1 is an amino group, with formic acid or an equivalent thereof effective to cause cyclisation whereby a compound of formula XII or salt thereof is obtained. Equivalents of formic acid effective to cause cyclisation include for example a tri-C_{1-4}alkoxymethane, for example triethoxymethane and trimethoxymethane. The cyclisation is conveniently effected in the presence of a catalytic amount of an anhydrous acid, such as a sulphonic acid for example p-toluenesulphonic acid, and an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, an ether such as diethylether or tetrahydrofuran, or an aromatic hydrocarbon solvent such as toluene. The cyclisation is conveniently effected at a temperature in the range, for example 10 to 100°C, preferably in the range 20 to 50°C.

Compounds of formula XIV and salts thereof, which constitute a further feature of the present invention, may for example be prepared by the reduction of the nitro group in a compound of the formula XV:

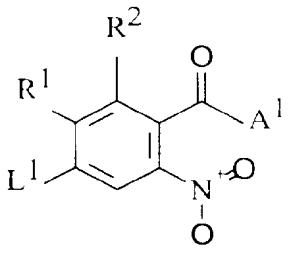


(XV)

(wherein R^1, R^2, R^4, Y^1 and A^1 are as hereinbefore defined) to yield a compound of formula XIV as hereinbefore defined. The reduction of the nitro group may conveniently be effected by any of the procedures known for such a transformation.

The reduction of the nitro group may conveniently be effected by any of the procedures known for such a transformation. The reduction may be carried out, for example, by the hydrogenation of a solution of the nitro compound in the presence of an inert solvent or diluent as defined hereinbefore in the presence of a metal catalyst such as palladium or platinum. A further reducing agent is, for example, an activated metal such as activated iron (produced for example by washing iron powder with a dilute solution of an acid such as hydrochloric acid). Thus, for example, the reduction may be effected by heating a mixture of the nitro compound and the activated metal in the presence of a solvent or diluent such as a mixture of water and alcohol, for example methanol or ethanol, to a temperature in the range, for example 50 to 150°C, conveniently at or near 70°C.

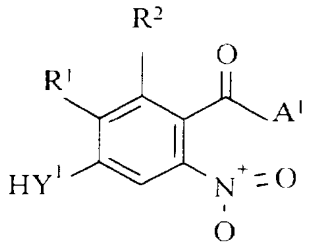
Compounds of the formula XV and salts thereof which constitute a further feature of the present invention, may for example be prepared by the reaction of a compound of the formula XVI:



(XVI)

(wherein R^1, R^2, L^1 and A^1 are as hereinbefore defined) with a compound of the formula IX as hereinbefore defined to give a compound of the formual XV. The reaction of the compounds of formulae XVI and IX is conveniently effected under conditions as described for process (d) hereinbefore.

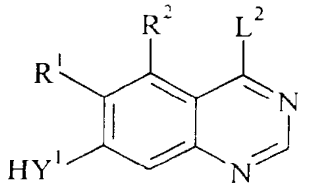
Compounds of formula XV and salts thereof, may for example also be prepared by the reaction of a compound of the formula XVII:



(XVII)

(wherein R^1, R^2, Y^1 and A^1 are as hereinbefore defined with the proviso that Y^1 is not $-CH_2-$) with a compound of the formula VII as hereinbefore defined to yield a compound of formula XV as hereinbefore defined. The reaction of the compounds of formulae XVII and VII is conveniently effected under conditions as described for process (c) hereinbefore.

The compounds of formula III and salts thereof may also be prepared for example by reacting a compound of the formula XVIII:



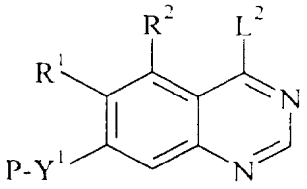
(XVIII)

(wherein R^1, R^2 and Y^1 are as hereinbefore defined with the proviso that Y^1 is not $-CH_2-$ and L^2 represents a displaceable protecting group) with a compound of the formula VII as hereinbefore defined, whereby to obtain a compound of formula III in which L^1 is represented by L^2.

A compound of formula XVIII is conveniently used in which L^2 represents a phenoxy group which may if desired carry up to 5 substituents, preferably up to 2

substituents, selected from halogeno, nitro and cyano. The reaction may be conveniently effected under conditions as described for process (c) hereinbefore.

The compounds of formula XVIII and salts thereof as hereinbefore defined may for example be prepared by deprotecting a compound of the formula XIX:

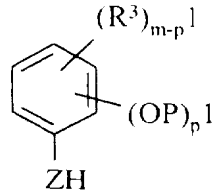


(XIX)

(wherein R^1, R^2, P, Y^1 and L^2 are as hereinbefore defined). Deprotection may be effected by techniques well known in the literature, for example where P represents a benzyl group deprotection may be effected by hydrogenolysis or by treatment with trifluoroacetic acid.

One compound of formula III may if desired be converted into another compound of formula III in which the moiety L^1 is different. Thus for example a compound of formula III in which L^1 is other than halogeno, for example optionally substituted phenoxy, may be converted to a compound of formula III in which L^1 is halogeno by hydrolysis of a compound of formula III (in which L^1 is other than halogeno) to yield a compound of formula XII as hereinbefore defined, followed by introduction of halide to the compound of formula XII, thus obtained as hereinbefore defined, to yield a compound of formula III in which L^1 represents halogen.

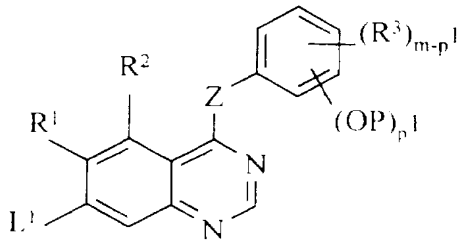
(ii) The compounds of formula V and salts thereof, constitute a further feature of the present invention, and may for example be prepared by the reaction of a compound of formula III as hereinbefore defined with a compound of the formula XX:



(XX)

(wherein R^3, m, p^1, P and Z are as hereinbefore defined). The reaction may for example be effected as described for process (a) hereinbefore.

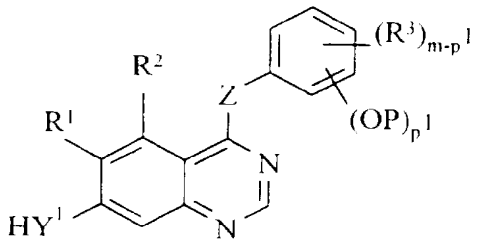
The compounds of formula V and salts thereof may also be prepared by reacting a compound of formula XXI:



(XXI)

(wherein R^1, R^2, L^1, Z, R^3, m, p^1 and P are as hereinbefore defined) with a compound of formula IX as hereinbefore defined. The reaction may for example be effected as described for process (d) above.

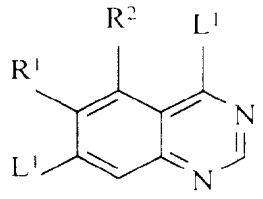
The compounds of formula V and salts thereof may also be prepared by reacting a compound of formula XXII:



(XXII)

(wherein R^1, R^2, R^3, Y^1, Z, P, p^1 and m are as hereinbefore defined with the proviso that Y^1 is not $-CH_2-$) with a compound of the formula VII as hereinbefore defined. The reaction may for example be effected as described for process (c) hereinbefore.

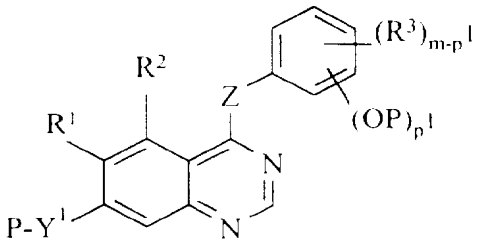
The compounds of formula XXI and salts thereof may for example be prepared by reaction of a compound of formula XXIII:



(XXIII)

(wherein R^1, R^2, and L^1 are as hereinbefore defined, and L^1 in the 4- and 7- positions may be the same or different) with a compound of the formula XX as hereinbefore defined. The reaction may be effected for example by a process as described in (a) above.

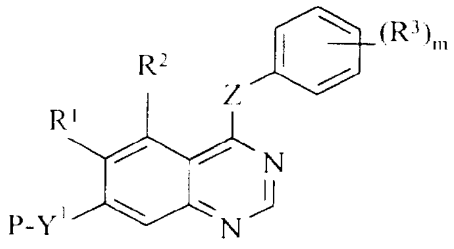
Compounds of the formula XXII and salts thereof may be made by reacting compounds of the formulae XIX and XX as hereinbefore defined, under conditions described in (a) hereinbefore, to give a compound of formula XXIV:



(XXIV)

(wherein R^1, R^2, R^3, P, Z, Y^1, p^1 and m are as hereinbefore defined with the proviso that Y^1 is not $-CH_2-$) and then deprotecting the compound of formula XXIV for example as described in (i) above.

(iii) Compounds of the formula VI and salts thereof, as hereinbefore defined, may be made by deprotecting the compound of formula XXV:



(XXV)

(wherein R^1, R^2, R^3, P, Z, Y^1 and m are as hereinbefore defined) by a process for example as described in (i) above.

Compounds of the formula XXV and salts thereof may be made by reacting compounds of the formulae XIX and IV as hereinbefore defined, under the conditions described in (a) hereinbefore, to give a compound of the formula XXV or salt thereof.

(iv) Compounds of the formula VIII and salts thereof as hereinbefore defined may be made by reacting compounds of the formulae XXIII and IV as hereinbefore defined, the reaction may be effected by a process as described in (a) above.

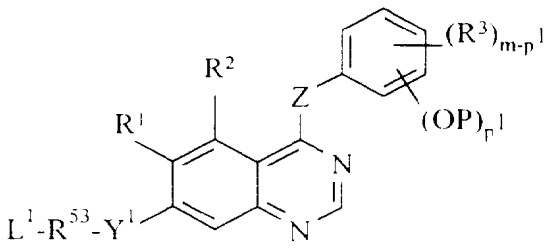
(v) Compounds of the formula X as defined hereinbefore and salts thereof may for example be made by the reaction of a compound of formula VI as defined hereinbefore with a compound of the formula XXVI:

$$L^1\text{-}R^{53}\text{-}L^1$$

(XXVI)

(wherein L^1 and R^{53} are as hereinbefore defined) to give a compound of the formula X. The reaction may be effected for example by a process as described in (c) above.

Compounds of the formula X and salts thereof may also be made for example by deprotecting a compound of the formula XXVII:



(XXVII)

(wherein L^1, R^{53}, Y^1, R^1, R^2, R^3, P, m and p^1 are as defined hereinbefore) by a process for example as described in (b) above.

Compounds of the formula XXVII and salts thereof may be made for example by reacting compounds of the formulae XXII and XXVI as defined hereinbefore, under the conditions described in (c) above.

When a pharmaceutically acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with, for example, an acid using a conventional procedure.

Many of the intermediates defined herein are novel, for example, those of the formulae III, V, XII, XIV and XV and these are provided as a further feature of the invention.

Intermediates of the formulae VIII, X, XXI, XXII, XXIV, XXV and XXVII are also provided as a further feature of the invention.

The identification of compounds which potently inhibit the tyrosine kinase activity associated with the VEGF receptors such as Flt and/or KDR and which inhibit angiogenesis and/or increased vascular permeability is desirable and is the subject of the present invention. These properties may be assessed, for example, using one or more of the procedures set out below:

(a) In Vitro Receptor Tyrosine Kinase Inhibition Test

This assay determines the ability of a test compound to inhibit tyrosine kinase activity. DNA encoding VEGF or epidermal growth factor (EGF) receptor cytoplasmic domains may be obtained by total gene synthesis (Edwards M, International Biotechnology Lab 5(3), 19-25, 1987) or by cloning. These may then be expressed in a suitable expression

system to obtain polypeptide with tyrosine kinase activity. For example VEGF and EGF receptor cytoplasmic domains, which were obtained by expression of recombinant protein in insect cells, were found to display intrinsic tyrosine kinase activity. In the case of the VEGF receptor Flt (Genbank accession number X51602), a 1.7kb DNA fragment encoding most of the cytoplasmic domain, commencing with methionine 783 and including the termination codon, described by Shibuya et al (Oncogene, 1990, 5: 519-524), was isolated from cDNA and cloned into a baculovirus transplacement vector (for example pAcYM1 (see The Baculovirus Expression System: A Laboratory Guide, L.A. King and R. D. Possee, Chapman and Hall, 1992) or pAc360 or pBlueBacHis (available from Invitrogen Corporation)). This recombinant construct was co-transfected into insect cells (for example Spodoptera frugiperda 21(Sf21)) with viral DNA (eg Pharmingen BaculoGold) to prepare recombinant baculovirus. (Details of the methods for the assembly of recombinant DNA molecules and the preparation and use of recombinant baculovirus can be found in standard texts for example Sambrook et al, 1989, Molecular cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press and O'Reilly et al, 1992, Baculovirus Expression Vectors - A Laboratory Manual, W. H. Freeman and Co. New York). For other tyrosine kinases for use in assays, cytoplasmic fragments starting from methionine 806 (KDR, Genbank accession number L04947) and methionine 668 (EGF receptor, Genbank accession number X00588) may be cloned and expressed in a similar manner.

For expression of cFlt tyrosine kinase activity, Sf21 cells were infected with plaque-pure cFlt recombinant virus at a multiplicity of infection of 3 and harvested 48 hours later. Harvested cells were washed with ice cold phosphate buffered saline solution (PBS) (10mM sodium phosphate pH7.4, 138mM NaCl, 2.7mM KCl) then resuspended in ice cold HNTG/PMSF (20mM Hepes pH7.5, 150mM NaCl, 10% v/v glycerol, 1% v/v Triton X100, 1.5mM $MgCl_2$, 1mM ethylene glycol-bis(βaminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA), 1mM PMSF (phenylmethylsulphonyl fluoride); the PMSF is added just before use from a freshly-prepared 100mM solution in methanol) using 1ml HNTG/PMSF per 10 million cells. The suspension was centrifuged for 10 minutes at 13,000 rpm at 4°C, the supernatant (enzyme stock) was removed and stored in aliquots at -70°C. Each new batch of stock enzyme was titrated in the assay by dilution with enzyme diluent (100mM Hepes pH 7.4, 0.2mM Na_3VO_4, 0.1% v/v Triton X100, 0.2mM dithiothreitol). For a typical batch, stock

enzyme is diluted 1 in 2000 with enzyme diluent and 50µl of dilute enzyme is used for each assay well.

A stock of substrate solution was prepared from a random copolymer containing tyrosine, for example Poly (Glu, Ala, Tyr) 6:3:1 (Sigma P3899), stored as 1 mg/ml stock in PBS at -20°C and diluted 1 in 500 with PBS for plate coating.

On the day before the assay 100µl of diluted substrate solution was dispensed into all wells of assay plates (Nunc maxisorp 96-well immunoplates) which were sealed and left overnight at 4°C.

On the day of the assay the substrate solution was discarded and the assay plate wells were washed once with PBST (PBS containing 0.05% v/v Tween 20) and once with 50mM Hepes pH7.4.

Test compounds were diluted with 10% dimethylsulphoxide (DMSO) and 25µl of diluted compound was transferred to wells in the washed assay plates. "Total" control wells contained 10% DMSO instead of compound. Twenty five microlitres of 40mM $MnCl_2$ containing 8µM adenosine-5'-triphosphate (ATP) was added to all test wells except "blank" control wells which contained $MnCl_2$ without ATP. To start the reactions 50µl of freshly diluted enzyme was added to each well and the plates were incubated at room temperature for 20 minutes. The liquid was then discarded and the wells were washed twice with PBST. One hundred microlitres of mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321), diluted 1 in 6000 with PBST containing 0.5% w/v bovine serum albumin (BSA), was added to each well and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One hundred microlitres of horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham product NXA 931), diluted 1 in 500 with PBST containing 0.5% w/v BSA, was added and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One hundred microlitres of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) solution, freshly prepared using one 50mg ABTS tablet (Boehringer 1204 521) in 50ml freshly prepared 50mM phosphate-citrate buffer pH5.0 + 0.03% sodium perborate (made with 1 phosphate citrate buffer with sodium perborate (PCSB) capsule (Sigma P4922) per 100ml distilled water), was added to each well. Plates were then incubated for 20-60 minutes at room temperature until the optical density value of

the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibtion of enzyme activity.

(b) In Vitro HUVEC Proliferation Assay

This assay determines the ability of a test compound to inhibit the growth factor-stimulated proliferation of human umbilical vein endothelial cells (HUVEC).

HUVEC cells were isolated in MCDB 131 (Gibco BRL) + 7.5% v/v foetal calf serum (FCS) and were plated out (at passage 2 to 8), in MCDB 131 + 2% v/v FCS + 3μg/ml heparin + 1μg/ml hydrocortisone, at a concentration of 1000 cells/well in 96 well plates. After a minimum of 4 hours they were dosed with the appropriate growth factor (i.e. VEGF 3ng/ml, EGF 3ng/ml or b-FGF 0.3ng/ml) and compound. The cultures were then incubated for 4 days at 37°C with 7.5% CO_2. On day 4 the cultures were pulsed with 1μCi/well of tritiated-thymidine (Amersham product TRA 61) and incubated for 4 hours. The cells were harvested using a 96-well plate harvester (Tomtek) and then assayed for incorporation of tritium with a Beta plate counter. Incorporation of radioactivity into cells, expressed as cpm, was used to measure inhibition of growth factor-stimulated cell proliferation by compounds.

(c) In Vivo Rat Uterine Oedema Assay

This test measures the capacity of compounds to reduce the acute increase in uterine weight in rats which occurs in the first 4-6 hours following oestrogen stimulation. This early increase in uterine weight has long been known to be due to oedema caused by increased permeability of the uterine vasculature and recently Cullinan-Bove and Koos (Endocrinology, 1993,133:829-837) demonstrated a close temporal relationship with increased expression of VEGF mRNA in the uterus. We have found that prior treatment of the rats with a neutralising monoclonal antibody to VEGF significantly reduces the acute increase in uterine weight, confirming that the increase in weight is substantially mediated by VEGF.

Groups of 20 to 22-day old rats were treated with a single subcutaneous dose of oestradiol benzoate (2.5μg/rat) in a solvent, or solvent only. The latter served as unstimulated controls. Test compounds were orally administered at various times prior to the administration of oestradiol benzoate. Five hours after the administration of oestradiol

benzoate the rats were humanely sacrificed and their uteri were dissected, blotted and weighed. The increase in uterine weight in groups treated with test compound and oestradiol benzoate and with oestradiol benzoate alone was compared using a Student T test. Inhibition of the effect of oestradiol benzoate was considered significant when $p<0.05$.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically acceptable excipient or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intraveous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compositions of the present invention are advantageously presented in unit dosage form. The compound will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square metre body area of the animal, i.e. approximately 0.1-100 mg/kg. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient.

According to a further aspect of the present invention there is provided a compound of the formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have now found that compounds of the present invention inhibit VEGF receptor tyrosine kinase activity and are therefore of interest for their antiangiogenic effects and/or their ability to cause a reduction in vascular permeability.

Thus according to this aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, razoxin, thalidomide);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen,toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example

metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example EGF, FGFs, platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan).

As stated above the compounds defined in the present invention are of interest for their antiangiogenic and/or vascular permeability reducing effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation and ocular diseases with retinal vessel proliferation. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF, especially those tumours which are significantly dependent on VEGF for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

In addition to their use in therapeutic medicine, the compounds of formula I and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of test systems for the evaluation of the effects of inhibitors

of VEGF receptor tyrosine kinase activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

It is to be understood that where the term "ether" is used anywhere in this specification it refers to diethyl ether.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

[(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Koffler hot plate apparatus;

(vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(viii) the following abbreviations have been used:-

DMF N,N-dimethylformamide

DMSO dimethylsulphoxide

NMP 1-methyl-2-pyrrolidinone

THF tetrahydrofuran

TFA trifluoroacetic acid.]

Example 1

To a solution of 4-(3-acetoxy-4-methylanilino)-6-methoxy-7-(4-pyridylmethoxy)quinazoline (93mg, 0.2mmol) in a mixture of methanol (6ml) and methylene chloride (3ml) was added at ambient temperature a 2M aqueous sodium hydroxide solution (0.3ml, 0.6mmol). The mixture was stirred for 10 minutes at ambient temperature, the solvents were partially evaporated, water was added to the residue and the solution was acidified with 0.1M hydrochloric acid to pH6. The precipitate was filtered off, washed with water and dried under vacuum to give **4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyridylmethoxy)quinazoline** hydrochloride (67mg, 87%).

m.p. 249-251°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.13(s, 3H); 4.01(s, 3H); 5.40(s, 2H); 7.05(br s, 2H); 7.24(s, 1H); 7.34(s, 1H); 7.51(d, 2H); 7.92(s, 1H); 8.44(s, 1H); 8.63(d, 2H); 9.34(s, 1H); 9.47(br s, 1H)

MS - ESI: 389 $[MH]^+$

Elemental analysis:	Found	C 61.4	H 5.3	N 12.8
$C_{22}H_{20}N_4O_3$ 1.8H_2O, 0.2HCl	Requires	C 61.7	H 5.6	N 13.1%

The starting material was prepared as follows:

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (10g, 0.04mol), (J. Med. Chem. 1977, vol 20, 146-149), and Gold's reagent (7.4g, 0.05mol) in dioxane (100ml) was stirred and heated at reflux for 24 hours. Sodium acetate (3.02g, 0.037mol) and acetic acid (1.65ml, 0.029mol) were added to the reaction mixture and it was heated for a further 3 hours. The mixture was evaporated, water was added to the residue, the solid was filtered off, washed with water and dried ($MgSO_4$). Recrystallisation from acetic acid gave 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7g, 84%).

A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (2.82g, 0.01mol), thionyl chloride (40ml) and DMF (0.28ml) was stirred and heated at reflux for 1 hour. The mixture was evaporated, the residue was taken up in toluene and evaporated to dryness to give 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (3.45g).

A mixture of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (2.18g, 6.47mmol), 3-acetoxy-4-methylaniline (1.32g, 8mmol) and isopropanol (50ml) was stirred and heated at reflux for 1 hour. The mixture was cooled to ambient temperature. The precipitate was filtered off, washed with isopropanol and ether to give 4-(3-acetoxy-4-methylanilino)-7-benzyloxy-6-methoxyquinazoline hydrochloride (2.69g, 89%).

A mixture of 4-(3-acetoxy-4-methylanilino)-7-benzyloxy-6-methoxyquinazoline hydrochloride (2.68g, 5.75mmol), 10% palladium-on-charcoal catalyst (0.27g) in methanol (50ml), DMF (12ml) and trichloromethane (50ml) was stirred at ambient temperature under an atmosphere of hydrogen (1.5 atmospheres) for 30 minutes. The catalyst was filtered off and the filtrate evaporated. The residual solid was triturated in ether, filtered off and dried under vacuum at 50°C to give 4-(3-acetoxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (2.1g, 100%).

To a solution of 4-(3-acetoxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (375mg, 1mmol) in DMF (16ml) were added at ambient temperature potassium carbonate (415mg, 3mmol) and 4-(bromomethyl)pyridine hydrobromide (J.Org.Chem. 1958, 23, 575, 278mg, 1.1mmol). The reaction mixture was heated at 60°C for 2 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was washed with a saturated aqueous sodium chloride solution, dried ($MgSO_4$) and evaporated. The residue was purified by column flash chromatography, eluting with methylene chloride/methanol (95/5) to give 4-(3-acetoxy-4-methylanilino)-6-methoxy-7-(4-pyridylmethoxy)quinazoline (93mg, 22%).

m.p. 201-202°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.12(s, 3H); 2.34(s, 3H); 4.02(s, 3H); 5.40(s, 2H); 7.27(s, 1H); 7.30(d, 1H); 7.51(d, 2H); 7.62(s, 1H); 7.65(d, 1H); 7.91(s, 1H); 8.47(s, 1H); 8.63(d, 2H); 9.53(s, 1H)

MS - ESI: 453 $[MNa]^+$, 431 $[MH]^+$

Elemental analysis:	Found	C 65.4	H 5.5	N 12.7
$C_{24}H_{22}N_4O_4$ $0.6H_2O$	Requires	C 65.3	H 5.3	N 12.7%

3-Acetoxy-4-methylaniline used as a starting material was prepared as follows:

To a mixture of 2-methyl-5-nitrophenol (2.5g, 16.3mmol) and 1M aqueous sodium hydroxide (24.5ml) was added at ambient temperature acetic anhydride (1.9ml, 20.3mmol). The mixture was stirred for 40 minutes, the solid was filtered off and the filtrate extracted with ethyl acetate. The organic layers were combined, washed with an aqueous saturated sodium chloride solution, dried ($MgSO_4$) and evaporated to yield 2-acetoxy-4-nitrotoluene (3.1g, 100%). A mixture of this material (3.1g, 15.9mmol) and 10% palladium-on-charcoal catalyst (0.12g) in ethyl acetate (50ml) was stirred at ambient temperature under an atmosphere of hydrogen for 2 hours. The catalyst was filtered off and the filtrate evaporated to give 3-acetoxy-4-methylaniline (2.45g, 94%).

Example 2

Using an analogous procedure to that described for the starting material in Example 1, 4-(3-acetoxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (750mg) was reacted with 3-(bromomethyl)pyridine hydrobromide (Can. J. Chem. 1978, 56, 3068) (378mg) to give

4-(3-acetoxy-4-methylanilino)-6-methoxy-7-(3-pyridylmethoxy)quinazoline (293mg, 34%).

m.p. 113-115°C

^1H NMR Spectrum: ($DMSOd_6$) 2.09(s, 3H); 2.30(s, 3H); 3.94(s, 3H); 5.32(s, 2H); 7.27(d, 1H); 7.32(s, 1H); 7.43-7.46(m, 1H); 7.58(s, 1H); 7.59-7.63(m, 1H); 7.85(s, 1H); 7.89-7.92(m, 1H); 8.45(s, 1H); 8.57(dd, 1H); 8.71(d, 1H); 9.48(s, 1H)

MS - ESI: 453 $[MNa]^+$, 431 $[MH]^+$

Elemental analysis:	Found	C 64.4	H 5.7	N 11.7
$C_{24}H_{22}N_4O_4$ $0.85H_2O$	Requires	C 64.7	H 5.4	N 12.6%

Example 3

The compound synthesised in Example 2 was further subjected to basic cleavage of the acetoxy protecting group using an analogous procedure to that described in Example 1 to give **4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(3-pyridylmethoxy)quinazoline** (215mg, 83%).

m.p. 258-259°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.12(s, 3H); 3.94(s, 3H); 5.34(s, 2H); 7.05(s, 2H); 7.32(s, 1H); 7.35(s, 1H); 7.46-7.49(m, 1H); 7.88(s, 1H); 7.93-7.95(m, 1H); 8.43(s, 1H); 8.60(dd, 1H); 8.74(d, 1H); 9.33(s, 1H); 9.35(s, 1H)

MS - ESI: 411 $[MNa]^+$, 389 $[MH]^+$

Elemental analysis:	Found	C 59.2	H 5.5	N 12.6
$C_{22}H_{20}N_4O_3$ $3H_2O$ 0.07HCl	Requires	C 59.4	H 5.9	N 12.6%

Example 4

4-(3-Acetoxy-4-methylanilino)-6-methoxy-7-(2-pyridylmethoxy)quinazoline (170mg, 0.39mmol) was subjected to basic cleavage of the acetoxy protecting group using an analogous procedure to that described in Example 1 to give **4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(2-pyridylmethoxy)quinazoline** hydrochloride (58mg, 38%).

m.p. 236-238°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.30(s, 3H); 3.97(s, 3H); 5.34(s, 2H); 7.02(s, 2H); 7.23(s, 1H); 7.33(s, 1H); 7.36-7.39(m, 1H); 7.56(d, 1H); 7.84-7.88(m, 1H); 7.87(s, 1H); 8.39(s, 1H); 8.91(d, 1H); 9.32(s, 2H)

MS - ESI: 389 $[MH]^+$

Elemental analysis:	Found	C 55.8	H 5.5	N 11.8
$C_{22}H_{20}N_4O_3$ $3H_2O$ 0.75HCl	Requires	C 56.2	H 5.7	N 11.9%

The starting material was prepared as follows:

Using an analogous procedure to that described for the starting material in Example 1, 4-(3-acetoxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (376mg)

was reacted with 2-(chloromethyl)pyridine hydrochloride (328mg) to give 4-(3-acetoxy-4-methylanilino)-6-methoxy-7-(2-pyridylmethoxy)quinazoline (170mg, 40%).

^{1}H NMR Spectrum: (DMSOd_6) 2.12(s, 3H); 2.34(s, 3H); 4.00(s, 3H); 5.37(s, 2H); 7.29(s, 1H); 7.31(s, 1H); 7.39 - 7.42(m, 1H); 7.58 - 7.66(m, 3H); 7.87 - 7.90(m, 1H); 7.91(s, 1H); 8.47(s, 1H); 8.64(d, 1H); 9.52(s, 1H)

Example 5

4-(3-Acetoxy-4-methylanilino)-6-methoxy-7-(pyrimidin-4-ylmethoxy)quinazoline (496mg, 1.15mmol) was subjected to basic cleavage of the acetoxy protecting group using an analogous procedure to that described in Example 1 to give **4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(pyrimidin-4-ylmethoxy)quinazoline** (278mg, 62%).

m.p. 290-291°C

^{1}H NMR Spectrum: (DMSOd_6) 2.13(s, 3H); 4.02(s, 3H); 5.43(s, 2H); 7.05(s, 2H); 7.24(s, 1H); 7.35(s, 1H); 7.67(d, 1H); 7.92(s, 1H); 8.41(s, 1H); 8.89(d, 1H); 9.24(s, 1H); 9.36(s, 1H); 9.38(s, 1H)

MS - ESI: 390 $[MH]^+$

Elemental analysis:	Found	C 58.8	H 5.4	N 16.3
$C_{21}H_{19}N_5O_3.2H_2O$	Requires	C 58.8	H 5.5	N 16.3%

The starting material was prepared as follows:

Using an analogous procedure to that described for the starting material in Example 1, 4-(3-acetoxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (560mg) was reacted in the presence of catalytic potassium iodide with 4-(chloromethyl)pyrimidine (375mg) to give 4-(3-acetoxy-4-methylanilino)-6-methoxy-7-(pyrimidin-4-ylmethoxy)quinazoline (496mg, 74%).

^{1}H NMR Spectrum: (DMSOd_6) 2.13(s, 3H); 2.35(s, 3H); 4.03(s, 3H); 5.44(s, 2H); 7.27(s, 1H); 7.31(d, 1H); 7.62 - 7.68(m, 3H); 7.93(s, 1H); 8.47(s, 1H); 8.89(d, 1H); 9.24(d, 1H); 9.54(s, 1H)

4-(Chloromethyl)pyrimidine was synthesised as follows:

A mixture of 4-methylpyrimidine (2g, 21.2mmol), N-chlorosuccinimide (4.26g, 31.9mmol) and dibenzoylperoxide (500mg) in carbon tetrachloride (100ml) was heated at 80°C for 2 hours. After cooling, the mixture was filtered and the filtrate was evaporated. The resulting oil was purified by flash chromatography using methylene chloride as eluant to give 4-(chloromethyl)pyrimidine as an orange oil (1g, 37%).

Example 6

A solution of 4-(3-acetoxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (400mg, 1.06mmol), (prepared as described for the starting material in Example 1), 2-chloromethyl-1-methylimidazole hydrochloride (354mg, 2.12 mmol), and potassium carbonate (585mg) in DMF (15ml) was heated at 60°C for 15 hours. After cooling to ambient temperature the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was diluted with methanol (20ml) and 2M sodium hydroxide (1ml) was added. After stirring for 1 hour, the reaction mixture was diluted with water (20ml) and 2M hydrochloric acid (3 ml) was added. The resulting solid was filtered off, washed with water and dried under vacuum to give **4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(1-methylimidazol-2-ylmethoxy)quinazoline** hydrochloride (150mg, 29%).

m.p. 257-260°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.17(s, 3H); 3.95(s, 3H); 4.03(s, 3H); 5.68(s, 2H); 7.02(dd, 1H); 7.16(s, 2H); 7.64(s, 1H); 7.72(s, 1H); 7.80(s, 1H); 8.42(s, 1H); 8.8(s, 1H); 9.7(s, 1H); 11.38(s, 1H)

MS - ESI: 392 $[MH]^+$

Elemental analysis:	Found	C 51.7	H 5.5	N 14.2
$C_{21}H_{21}N_5O_3$ 1.65H_2O 1.9HCl	Requires	C 51.4	H 5.4	N 14.3%

Example 7

A solution of 4-(3-acetoxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (400mg, 1.06mmol), (prepared as described for the starting material in Example 1), 4-chloromethyl-2-methylthiazole hydrochloride (390mg, 2.12mmol), potassium carbonate (438mg) and potassium iodide (40mg) in DMF (15ml) was heated at 60°C for 15

hours. After cooling to ambient temperature the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was diluted with methanol (10ml) and 2M sodium hydroxide (2ml) was added. After stirring for 1 hour, the reaction mixture was diluted with water (20ml) and 2M hydrochloric acid (3ml) was added. The resulting solid was filtered off, washed with water and dried under vacuum to give

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(2-methylthiazol-4-ylmethoxy) quinazoline hydrochloride (300mg, 59%).

m.p. 243-245°C

^1H NMR Spectrum: ($DMSOd_6$) 2.17(s, 3H); 2.7(s, 3H); 4.0(s, 3H); 5.35(s, 2H); 7.0(dd, 1H); 7.12(d, 1H); 7.16(d, 1H); 7.58(s, 1H); 7.75(s, 1H); 8.3(s, 1H); 8.8(s, 1H); 9.5-9.8(br s, 1H); 11.3(s, 1H)

MS - ESI: 409 $[MH]^+$

Elemental analysis:	Found	C 51.9	H 5.0	N 11.6	S 6.8	
$C_{21}H_{20}N_4O_3S\ 1H_2O\ 1.7HCl$	Requires	C 51.6	H 4.9	N 11.5	S 6.6%	

Example 8

To a solution of 4-(3-acetoxy-4-methylanilino)-6-methoxy-7-(3-thienylmethoxy)quinazoline (200mg, 0.45mmol) in methylene chloride/methanol (1/1) (20ml) was added, a 2M aqueous sodium hydroxide solution (0.67ml, 1.35mmol). The mixture was stirred for 35 minutes at ambient temperature, the solvents were evaporated, water was added to the residue and the solution was extracted with ethyl acetate. The organic layer was washed with water, brine, then dried ($MgSO_4$) and evaporated to give a white solid. This solid was then dissolved into a saturated solution of hydrochloric acid in methanol (10ml) and stirred for 10 minutes. The solid product was filtered and dried under a vacuum, to give **4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(3-thienylmethoxy)quinazoline** hydrochloride (127mg, 66%).

m.p. 246-248°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15(s, 3H); 3.98(s, 3H); 5.32(s, 2H); 6.98(dd, 1H); 7.10(s, 1H); 7.14(d, 1H); 7.25(d, 1H); 7.40(s, 1H); 7.61(dd, 1H); 7.70(d, 1H); 8.12(s, 1H); 8.74(s, 1H); 9.60(s, 1H)

MS - ESI: 394 $[MH]^+$

Elemental analysis: Found C 58.3 H 4.8 N 9.4 S 7.3 Cl 7.5

$C_{21}H_{19}N_3O_3S$ $0.2H_2O$ 0.95HCl Requires C 58.4 H 4.8 N 9.7 S 7.4 Cl 7.8%

The starting material was prepared as follows:

Using an analogous procedure to that described for the starting material in Example 1, 4-(3-acetoxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (400mg) was reacted in the presence of catalytic potassium iodide with 3-chloromethylthiophene (Journal of the Chemical Society 1958, 4202) (168mg) to give 4-(3-acetoxy-4-methylanilino)-6-methoxy-7-(3-thienylmethoxy)quinazoline (210mg, 46%).

m.p. 201-203°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.11(s, 3H); 2.32(s, 3H); 3.95(s, 3H); 5.27(s, 2H); 7.23(dd, 1H); 7.28(d, 1H); 7.32(s, 1H); 7.58-7.66(m, 4H); 7.85(s, 1H); 8.46(s, 1H); 9.49(s, 1H)

MS - ESI: 436 $[MH]^+$

Elemental analysis: Found C 63.0 H 5.2 N 9.1 S 7.3

$C_{23}H_{21}N_3O_4S$ $0.3H_2O$ Requires C 62.7 H 5.0 N 9.5 S 7.3%

Example 9

7-(2-Acetamidothiazol-4-ylmethoxy)-4-(3-acetoxy-4-methylanilino)-6-methoxyquinazoline (220mg, 0.44mmol) was subjected to basic cleavage of the acetoxy protecting group using an analogous procedure to that described in Example 8 to give, **7-(2-acetamidothiazol-4-ylmethoxy)-4-(3-hydroxy-4-methylanilino)-6-methoxyquinazoline** hydrochloride (41mg, 19%).

m.p. 202-204°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.16(s, 3H); 2.17(s, 3H); 4.01(s, 3H); 5.31(s, 2H); 6.98(dd, 1H); 7.10(d, 1H); 7.17(d, 1H); 7.34(s, 1H); 7.47(s, 1H); 8.22(s, 1H); 8.80(s, 1H); 9.68(br s, 1H)

MS - ESI: 452 $[MH]^+$

Elemental analysis:	Found	C	47.1	H	4.7	N	12.5	S	5.8	Cl 12.2
$C_{22}H_{21}N_5O_4S$ $2H_2O$ 2HCl	Requires	C	47.2	H	4.9	N	12.5	S	5.7	Cl 12.7%

The starting material was prepared as follows:

Using an analogous procedure to that described for the starting material in Example 1, 4-(3-acetoxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (400mg) was reacted in the presence of catalytic potassium iodide with 2-acetamido-4-chloromethylthiazole (252mg) to give 7-(2-acetamidothiazol-4-ylmethoxy)-4-(3-acetoxy-4-methylanilino)-6-methoxyquinazoline (220mg, 42%).

^1H NMR Spectrum: ($DMSOd_6$) 2.13(s, 3H); 2.15(s, 3H); 2.35(s, 3H); 3.97(s, 3H); 5.24(s, 2H); 7.24-7.31(m, 2H); 7.37(s, 1H); 7.63-7.66(m, 2H); 7.87(s, 1H); 8.48(s, 1H); 9.50(s, 1H)

MS - ESI: 494 $[MH]^+$

Example 10

4-(3-Acetoxy-4-methylanilino)-7-(3,5-dimethylisoxazol-4-ylmethoxy)-6-methoxyquinazoline (342mg, 0.76mmol) was subjected to basic cleavage of the acetoxy protecting group using an analogous procedure to that described in Example 8 to give **4-(3-hydroxy-4-methylanilino)-7-(3,5-dimethylisoxazol-4-ylmethoxy)-6-methoxyquinazoline** hydrochloride (209mg, 62%).

m.p. 252-254°C

^1H NMR Spectrum: ($DMSOd_6$) 2.20(s, 3H); 2.29(s, 3H); 2.52(s, 3H); 4.03(s, 3H); 5.23(s, 2H); 7.03(dd, 1H); 7.15(d, 1H); 7.19(d, 1H); 7.44(s, 1H); 8.22(s, 1H); 8.82(s, 1H); 9.67(s, 1H)

MS - ESI: 407 $[MH]^+$

Elemental analysis:	Found	C	59.1	H	5.4	N	12.6	Cl	8.0	
$C_{22}H_{22}N_4O_4$ $0.25H_2O$ 1HCl	Requires	C	59.1	H	5.3	N	12.5	Cl	7.9%	

The starting material was prepared as follows:

Using an analogous procedure to that described for the starting material in Example 1, 4-(3-acetoxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (400mg)

was reacted in the presence of potassium iodide (16mg) with 4-chloromethyl-3,5-dimethylisoxazole (177mg) to give 4-(3-acetoxy-4-methylanilino)-7-(3,5-dimethylisoxazol-4-ylmethoxy)-6-methoxyquinazoline (342mg, 72%).

^{1}H NMR Spectrum: (DMSOd_6) 2.18(s, 3H); 2.33(s, 3H); 2.35(s, 3H); 2.46(s, 3H); 3.98(s, 3H); 4.98(s, 2H); 7.00(s, 1H); 7.15(s, 1H); 7.22-7.25(m, 1H); 7.32(s, 1H); 7.43(dd, 1H); 7.51(s, 1H); 8.66(s, 1H)

Example 11

A solution of 4-(3-acetoxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (400mg, 1.06mmol), (prepared as described for the starting material in Example 1), 4-(3-chloropropyl)pyridyl hydrochloride 410mg, 2.1mmol), potassium carbonate (438mg) and potassium iodide (40mg) in DMF (15ml) was heated at 60°C for 15 hours. After cooling to ambient temperature the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was diluted with methanol (20ml) and 2M sodium hydroxide (2ml) was added. After stirring for 1 hour, the reaction mixture was diluted with water (20ml) and concentrated hydrochloric acid (1ml) was added. The resulting solid was filtered off and was purified by preparative C18 HPLC using a gradient of methanol/water (0% to 80%) as eluant. After evaporation of the methanol, concentrated hydrochloric acid (0.3ml) was added and the solution was evaporated to dryness. After trituration with acetone, the solid was filtered off and dried under vacuum to give **4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyridylpropoxy)quinazoline** hydrochloride (305mg, 59%).

m.p. 278-282°C

^{1}H NMR Spectrum: (DMSO-d_6) 2.15(s, 3H); 2.3(m, 2H); 3.1(m, 2H); 3.96(s, 3H); 4.24(t, 2H); 6.98(dd, 1H); 7.15(m,2H); 7.44(s, 1H); 7.96(d, 2H); 8.31(s, 1H); 8.77(s, 1H); 8.81(d, 2H); 9.7(br s, 1H); 11.34(s, 1H)

MS - ESI: 417 $[MH]^+$

Elemental analysis:	Found	C 57.3	H 5.4	N 11.0
$C_{24}H_{24}N_4O_3$ 0.7H_2O 1.95HCl	Requires	C 57.6	H 5.5	N 11.2%

The starting material was prepared as follows:

Thionyl chloride (1.6ml) was added to a solution of 4-pyridine propanol (2g, 14.5mmol) in trichloromethane (20ml) cooled at 0°C. After stirring for 1 hour at ambient temperature followed by 1 hour at 60°C, the solvent was evaporated and the residue was triturated with ether to give 4-(3-chloropropyl)pyridyl hydrochloride as a white solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15(m, 2H); 3.02(t, 2H); 3.69(t, 2H); 7.96(d, 2H); 8.84(d, 2H)

Example 12

A solution of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (410mg, 1.00mmol), 4-(3-chloropropyl)pyridyl hydrochloride (480mg, 2.5mmol), potassium carbonate (480mg) and potassium iodide (40mg) in DMF (15ml) was heated at 60°C for 15 hours. After cooling to ambient temperature the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was diluted with methanol (10ml) and 2M sodium hydroxide (2ml) was added. After stirring for 1 hour, the reaction mixture was diluted with water (20ml) and concentrated hydrochloric acid (0.5 ml) was added. The resulting solid was filtered off and was purified by preparative C18 HPLC using a gradient of methanol/water (0% to 80%) as eluant. After evaporation of the methanol, concentrated hydrochloric acid (0.3ml) was added and the solution was evaporated to dryness. After trituration with acetone, the solid was filtered off and dried under vacuum to give **4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyridylpropoxy)quinazoline** hydrochloride (243mg, 48%).

m.p. 246-248°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.16(s, 3H); 2.30(m, 2H); 3.09(t, 2H); 3.95(s, 3H); 4.26(t, 2H); 6.90(d, 1H); 7.11(d, 1H); 7.41(s, 1H); 7.94(d, 2H); 8.3(s, 1H); 8.77(s, 1H); 8.80(d, 2H); 9.7(br s, 1H); 11.46(s, 1H)

MS - ESI: 435 $[MH]^+$

Elemental analysis:	Found	C 55.3	H 5.3	N 10.2	Cl 13.0	
$C_{24}H_{23}N_4O_3F$ 0.9H_2O 1.95HCl	Requires	C 55.3	H 5.2	N 10.7	Cl 13.3%	

The starting material was prepared as follows:

A solution of (4-fluoro-2-methyl-5-nitrophenyl) methyl carbonate (3g, 13mmol), (prepared as described in EP 0307777 A2), in ethanol (60ml) containing platinum(IV)oxide (300mg) was stirred under hydrogen at 0.3 atmosphere for 1 hour. After filtration and evaporation of the solvent, 2-fluoro-5-methoxycarbonyloxy-4-methylaniline was isolated as a solid (2.6g, 100%).

^{1}H NMR Spectrum: ($CDCl_3$) 2.07(s, 3H); 3.87(s, 3H); 6.52(d, 1H); 6.80(d, 1H)

A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (800mg, 2.4mmol), (prepared as described for the starting material in Example 1), and 2-fluoro-5-methoxycarbonyloxy-4-methylaniline (570mg, 2.89mmol) in isopropanol (20ml) was refluxed for 2 hours. After cooling to ambient temperature, the solid was filtered, washed with isopropanol and dried under vacuum to give 7-benzyloxy-4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-6-methoxyquinazoline hydrochloride (1.0g, 87%)

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 2.2(s, 3H); 3.85(s, 3H); 4.0(s, 3H); 5.37(s, 2H); 7.3-7.55(m, 8H); 8.13(s, 1H); 8.86(s, 1H)

MS - ESI: 464 $[MH]^+$

A solution of 7-benzyloxy-4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-6-methoxyquinazoline hydrochloride (700mg, 1.45mmol) in DMF (10ml), methanol (10ml) and trichloromethane (10ml) containing 10% palladium-on-charcoal (100mg) was stirred under an atmosphere of hydrogen for 1 hour. After filtration and evaporation of the solvent, the residue was triturated with ether, filtered and dried under vacuum to give 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (570 mg, 98%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.23(s, 3H); 3.87(s, 3H); 4.01(s, 3H); 7.37(s, 1H); 7.45(d, 1H); 7.5(d, 1H); 8.20(s, 1H); 8.77(s, 1H); 11.35(s, 1H); 11.79(s, 1H)

MS - ESI: 374 $[MH]^+$

Example 13

A stirred solution of 4-chloro-6-methoxy-7-(4-pyridylmethoxy)quinazoline (35mg, 0.1mmol) and 2-fluoro-5-hydroxy-4-methylaniline (15mg, 0.1mmol) in a mixture of ethereal

hydrogen chloride (2ml) and isopropanol (5ml) was heated at reflux for 4 hours. The precipitated product was collected by filtration, washed with acetone and dried under vacuum to give **4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyridylmethoxy)quinazoline** hydrochloride (23mg, 47%).

m.p. 257-260°C

^{1}H NMR Spectrum: (DMSOd_6) 2.15(s, 3H); 4.08(s, 3H); 5.60(s, 2H); 6.90(d, 1H); 7.07(d, 1H); 7.47(s, 1 H); 7.93(br d, 2H); 8.74(s, 1H); 8.89(br d, 2 H); 9.62(br s, 1H); 11.46(s, 1H)

MS - ESI: 407 [MH]$^+$

Elemental analysis:	Found	C 52.8	H 4.6	N 10.9
$C_{22}H_{19}N_4O_3F$ $1H_2O$ 2HCl	Requires	C 53.1	H 4.6	N 11.3%

The starting chloroquinazoline was prepared as follows:

Sodium hydride (400mg of an 80% suspension in paraffin oil, 13.3mmol) was added to a solution of phenol (1.26g, 13.3mmol) in dry N-methylpyrrolidone (20ml) and the mixture stirred for 10 minutes.

7-Benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (1.6g, 4.7mmol), (prepared as described for the starting material in Example 1), was then added and the reaction mixture heated at 110°C for 2 hours. The mixture was allowed to cool, water was added and the mixture extracted with ethyl acetate (3x100ml). The combined extracts were then washed with 2M sodium hydroxide solution, water and brine. Removal of the solvent under reduced pressure gave 7-benzyloxy-6-methoxy-4-phenoxyquinazoline (1.6g, 95%) as a yellowish solid.

^{1}H NMR Spectrum: (DMSOd_6) 3.98(s, 3H); 5.37(s, 2H); 7.25-7.6(m, 11H); 7.60(s, 1H); 8.54(s, 1H)

MS - ESI: 359 [MH]$^+$

7-Benzyloxy-6-methoxy-4-phenoxyquinazoline (160mg, 0.44mmol) in TFA (3ml) was heated at reflux for 30 minutes. The solvent was removed by evaporation and the residue treated with aqueous sodium hydrogen carbonate solution. The precipitated product was collected by filtration, washed with water and dried to give 7-hydroxy-6-methoxy-4-phenoxyquinazoline (105mg, 88%).

^{1}H NMR Spectrum: ($DMSOd_6$) 4.00(s, 3H); 7.20(s, 1H); 7.25-7.35(m, 3H); 7.4-7.55(m, 2H); 7.58(s, 1H); 10.73(s, 1 H)

MS - ESI: 269 [MH]$^+$

A mixture of 7-hydroxy-6-methoxy-4-phenoxyquinazoline (95mg, 0.35mmol), 4-chloromethyl pyridine hydrochloride (120mg, 0.74mmol) and potassium carbonate (200mg, 1.4mmol) in DMF (5ml) were heated at 80°C for 2 hours. The reaction mixture was allowed to cool, water was added and the mixture extracted with ethyl acetate (3x50ml). The combined extracts were then washed with water and dried ($MgSO_4$). The solvent was removed by evaporation and the residue trituated with an ethyl acetate/hexane mixture to give 6-methoxy-4-phenoxy-7-(4-pyridylmethoxy)quinazoline (44mg, 35%) as a white solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 4.02(s, 3H); 5.47(s, 2H); 7.25-7.35(m, 3H); 7.45(s, 1H); 7.4-7.55(m, 4H); 7.62(s, 1H); 8.52(s, 1 H); 8.63(dd, 2H)

MS - ESI: 360 [MH]$^+$

A solution of 6-methoxy-4-phenoxy-7-(4-pyridylmethoxy)quinazoline (200mg, 0.56mmol) in 2M hydrochloric acid (15ml) was heated at reflux for 90 minutes. The reaction mixture was allowed to cool and neutralised to pH6-7 with aqueous ammonia. The precipitated product was extracted with methanol/methylene chloride (1:9) and the extract solution dried ($MgSO_4$). Removal of the solvent by evaporation gave 6-methoxy-7-(4-pyridylmethoxy)-3,4-dihydroquinazolin-4-one (90mg, 57%) as a grey solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 3.93(s, 3H); 5.35(s, 2H); 7.18(s, 1H); 7.48(s, 1H); 7.50(m, 2H); 8.04(s, 1 H); 8.62(m, 2H)

MS - ESI: 284 [MH]$^+$

Phosphorus oxytrichloride (0.1ml) was added to a mixture of 6-methoxy-7-(4-pyridylmethoxy)-3,4-dihydroquinazolin-4-one (81mg, 0.29mmol) and N,N-dimethylaniline (0.1ml) in toluene (5ml), and the mixture heated at reflux for 1 hour. The volatiles were removed by evaporation and the residue partitioned between methylene chloride and aqueous ammonia. The organic extract was separated, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by chromatography on silica eluting with ethyl acetate progressing through increasingly polar mixtures to methanol/methylene chloride (1/9) to give 4-chloro-6-methoxy-7-(4-pyridylmethoxy)quinazoline (40mg, 41%).

1H NMR Spectrum: ($DMSOd_6$) 4.04(s, 3H); 5.47(s, 2H); 7.46(s, 1H); 7.50(d, 2H); 7.53(s, 1H); 8.60(d, 2H); 8.85(s, 1 H)

MS - ESI: 302 $[MH]^+$

The starting aniline was prepared as described below:

Methyl chloroformate (6.8ml, 88mmol) was added over 30 minutes to a solution of 4-fluoro-2-methylphenol (10g, 79mmol) in 6% aqueous sodium hydroxide solution at 0°C. The mixture was stirred for 2 hours, then extracted with ethyl acetate (100ml). The ethyl acetate extract was washed with water (100ml) and dried ($MgSO_4$) and the solvent removed by evaporation to give 4-fluoro-2-methylphenyl methyl carbonate (11.4g, 78%) as an oil.

^1H NMR Spectrum: ($DMSOd_6$) 2.14(s, 3H); 3.81(s, 3H); 7.05(m, 1H); 7.1-7.25(m, 2 H)

A mixture of concentrated nitric acid (6ml) and concentrated sulphuric acid (6ml) was added slowly to a solution of 4-fluoro-2-methylphenyl methyl carbonate (11.34g, 62mmol) in concentrated sulphuric acid (6ml) such that the temperature of the reaction mixture was kept below 50°C. The mixture was stirred for 2 hours, then ice/water was added and the precipitated product collected by filtration. The crude product was purified by chromatography on silica eluting with methylene chloride/hexane progressing through increasingly polar mixtures to methanol/methylene chloride (1/19) to give 4-fluoro-2-methyl-5-nitrophenol (2.5g, 22%) as a solid.

^1H NMR Spectrum: ($DMSOd_6$; CD_3COOD) 2.31(s, 3H); 7.38(d, 1H); 7.58(d, 1H)

MS - ESI: 171 $[MH]^+$

A mixture of 4-fluoro-2-methyl-5-nitrophenol (2.1g, 13mmol), iron powder (1g, 18mmol) and iron(II)sulphate (1.5g, 10mmol) in water (40ml) was refluxed for 4 hours. The reaction mixture was allowed to cool, neutralised with 2M aqueous sodium hydroxide and extracted with ethyl acetate (100ml). The ethyl acetate extract was dried ($MgSO_4$) and the solvent removed by evaporation to give 2-fluoro-5-hydroxy-4-methylaniline (0.8g, 47%) as a solid.

^1H NMR Spectrum: ($DMSOd_6$) 1.94(s, 3H); 4.67(s, 2H); 6.22(d, 1H); 6.65(d, 1H); 8.68(s, 1H)

MS - ESI: 142 $[MH]^+$

Example 14

A solution of 7-benzyloxy-4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-6-methoxyquinazoline hydrochloride (259mg, 0.54 mmol), (prepared as described for the starting material in Example 12), in methanol (15ml) containing 1M sodium hydroxide (1.6ml) was stirred at ambient temperature for 1 hour. After addition of water (15ml), concentrated hydrochloric acid (1ml) was added and the mixture was stirred at ambient temperature for 15 minutes. After evaporation of methanol, the precipitate was filtered, washed with water and dried under vacuum to give **7-benzyloxy-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline** hydrochloride (192mg, 80%).

m.p. 294-298°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.2(s, 3H); 4.05(s, 3H); 5.35(s, 2H); 6.9(d, 1H); 7.12(d, 1H); 7.35-7.5(m, 4H); 7.55-7.6(m, 2H); 8.25(s, 1H); 8.8(s, 1H); 9.7(s, 1H); 11.35(s, 1H)

MS - ESI: 406 $[MH]^+$

Elemental analysis:	Found	C 62.3	H 4.9	N 9.3
$C_{23}H_{20}N_3O_3F$ 0.16H_2O 1HCl	Requires	C 62.1	H 4.8	N 9.5%

Example 15

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (200mg, 0.63mmol), 2-(2-chloroethoxy)pyridine hydrochloride (120mg, 0.61mmol) and potassium carbonate (260mg, 1.9mmol) in DMF (25ml) was heated at 90°C for 16 hours. The mixture was diluted with water and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with ethyl acetate/methanol mixtures (100/0 increasing to 90/10) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(2-pyridyloxy)ethoxy)quinazoline** (20mg, 7%) as an off-white solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 3.99(s, 3H); 4.35(t, 2H); 4.42(t, 2H); 6.22(t, 1H); 6.40(d, 1H); 7.42(s, 1H); 7.55(d, 2H); 7.71(d, 1H); 7.85(t, 1H); 8.55(d, 1H); 9.62(s, 1H)

MS - ESI: 441 $[MH]^+$

The starting material was prepared as follows:

A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (1.34g, 4mmol), (prepared as described for the starting material in Example 1), and 4-chloro-2-fluoroaniline (444µl, 4mmol) in isopropanol (40ml) was refluxed for 1.5 hours. After cooling, the precipitate was collected by filtration, washed with isopropanol then ether and dried under vacuum to give 7-benzyloxy-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline hydrochloride (1.13g, 64%).

m.p. 239-242°C

^{1}H NMR Spectrum: ($DMSOd_6$) 4.0(s, 3H); 5.36(s, 2H); 7.39-7.52(m, 9H); 8.1(s, 1H); 8.75(s, 1H)

MS - ESI: 410 $[MH]^+$

Elemental analysis:	Found	C 59.2	H 4.3	N 9.4
$C_{22}H_{17}N_3ClFO_2$ 1HCl	Requires	C 59.2	H 4.1	N 9.41%

A solution of 7-benzyloxy-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline hydrochloride (892mg, 2mmol) in TFA (10ml) was refluxed for 50 minutes. After cooling, the mixture was poured onto ice. The precipitate was collected by filtration, dissolved in methanol (10ml) and basified to pH11 with aqueous ammonia. After concentration by evaporation, the solid product was collected by filtration, washed with water then ether and dried under vacuum to give 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline as a yellow solid (460mg, 72%).

m.p. 141-143°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.95(s, 3H); 7.05(s, 1H); 7.35(d, 1H); 7.54-7.59(m, 2H); 7.78(s, 1H); 8.29(s, 1H)

MS - ESI: 320-322 $[MH]^+$

Thionyl chloride (0.55ml, 7.55mmol) was added to a solution of 2-(2-hydroxyethoxy)pyridine (700mg, 5.04mmol), (J. Org. Chem. 1977, **42**, 1500), in trichloromethane (20ml) at 5°C. The mixture was stirred for 1 hour at 5°C, allowed to warm to ambient temperature and stirred for a further 1 hour. The volatiles were removed by evaporation and by azeotroping with toluene to give 2-(2-chloroethoxy)pyridine hydrochloride (970mg, 99%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.90(t, 2H); 4.20(t, 2H); 6.22(d, 1H); 6.40(d, 1H); 7.44(dd, 1H); 7.64(d, 1H)

MS - ESI: 158 $[MH]^+$

Example 16

Triphenylphosphine (5.5g, 21mmol) followed by 2-[N-methyl-N-(4-pyridyl)]aminoethanol (1.49g, 9.8mmol), (prepared as described in EP 0359389 A1), were added to a stirred solution of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (2.23g, 7mmol), (prepared as described for the starting material in Example 15), in methylene chloride (60ml) under nitrogen. Diethyl azodicarboxylate (3.65g, 21mmol) was then added dropwise and the mixture was stirred at ambient temperature for 2 hours. Ethyl acetate (200ml) was added and the mixture was stirred for a further 2 hours. The solid product was collected by filtration, washed with ethyl acetate, dried under vacuum and finally purified by column chromatography eluting with methylene chloride/methanol (75/25 followed by 60/40 and 50/50) to give a white solid. The purified product was dissolved in methylene chloride/methanol and the insolubles removed by filtration. Ethereal hydrogen chloride (10ml of 3M solution) was added to the filtrate and the volatiles were removed by evaporation. The residue was triturated with ether and the solid product collected by filtration and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-[N-methyl-N-(4-pyridyl)]aminoethoxy)quinazoline** hydrochloride (2.75g, 75%) as a white solid.

m.p. 222-227°C

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 3.29(s, 3H); 3.95(s, 3H); 4.16(t, 2H); 4.48(t, 2H); 7.05(br s, 1H); 7.37(s, 2H); 7.42(d, 1H); 7.58(t, 1H); 7.65(dd, 1H); 8.18(s, 1H); 8.28(br s, 2H); 8.86(s, 1H)

MS - ESI: 454 $[MH]^+$

Elemental Analysis: Found C 51.2 H 4.8 N 12.9

$C_{23}H_{21}N_5O_2ClF$ $0.9H_2O$ 2HCl Requires C 50.9 H 4.6 N 12.9%

Example 17

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (300mg, 0.94mmol), (prepared as described for the starting material in Example 15), 4-(2-

chloroethoxy)pyridine hydrochloride (155mg, 0.79mmol) and potassium carbonate (260mg, 1.9mmol) in NMP (20ml) was heated at 90°C for 2 hours, allowed to cool to ambient temperature and stirred for a further 18 hours. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol mixtures (100/0 increasing to 95/5) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(4-pyridyloxy)ethoxy)quinazoline** (20mg, 7%).

m.p. 200-202°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.90(s, 3H); 4.50(s, 4H); 7.04(d, 2H); 7.26(s, 1H); 7.33(dd, 1H); 7.5-7.6(m, 2H); 7.80(s, 1H); 8.35(s, 1H); 8.39(d, 2H); 9.52(s, 1H)

MS - ESI: 441 $[MH]^+$

The starting material was prepared as follows:

Thionyl chloride (0.75ml, 10mmol) was added to a solution of 4-(2-hydroxyethoxy)pyridine (0.9g, 6.5mmol), (J. Chem. Soc. Perkin II, 1987, 1867), in trichloromethane (20ml) at 5°C. The mixture was stirred for 1 hour at 5°C, allowed to warm to ambient temperature and stirred for a further 2 hours. The volatiles were removed by evaporation and by azeotroping with toluene to give 4-(2-chloroethoxy)pyridine hydrochloride (1.3g, 100%).

^{1}H NMR Spectrum: ($DMSOd_6$) 4.03(t, 2H); 4.62(t, 2H); 7.58(d, 2H); 8.77(d, 2H)

MS - ESI: 158 $[MH]^+$

Example 18

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (300mg, 0.94mmol), (prepared as described for the starting material in Example 15), 1-(2-chloroethyl)-1,2-dihydro-2-pyridone (175mg, 1.11mmol), (J. Am. Chem. Soc. 1951, **73**, 3635), and potassium carbonate (260mg, 1.9mmol) in DMF (30ml) was heated at 80°C for 3 hours, allowed to cool to ambient temperature and stirred for a further 18 hours. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol/triethylamine mixtures (100/0/0

increasing to 70/30/0.5) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-[2-(2-oxo-1,2-dihydro-1-pyridyl)ethoxy]quinazoline** (50mg, 12%).

m.p. 209-211°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.94(s, 3H); 4.35(t, 2H); 4.41(t, 2H); 6.22(dd, 1H); 6.40(d, 1H); 7.14(s, 1H); 7.35(dd, 1H); 7.42(ddd, 1H); 7.5-7.6(m, 2H); 7.70(d, 1H); 7.80(s, 1H); 8.35(s, 1H); 9.53(s, 1H)

MS - ESI: 441 $[MH]^+$

Example 19

1-(3-Hydroxypropyl)-1,4-dihydro-4-pyridone (220mg, 1.44mmol) in methylene chloride (4ml) followed by 1,1'-(Azodicarbonyl)dipiperidine (720mg, 2.86mmol) were added to a stirred solution of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (300mg, 0.94mmol), (prepared as described for the starting material in Example 15), and tributylphosphine (0.69ml, 2.8mmol) in methylene chloride (20ml) under nitrogen at 5°C. The mixture was stirred at 5°C for 3 hours, allowed to warm to ambient temperature and stirred for a further 18 hours. The solvent was removed by evaporation and the residue partitioned between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$), and solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol/triethylamine mixtures (100/0/0 increasing to 70/30/0.5) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-[3-(4-oxo-1,4-dihydro-1-pyridyl)propoxy]quinazoline** (48mg, 11%).

m.p. >250°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.56(m, 2H); 4.00(s, 3H); 3.54(t, 2H); 4.38(t, 2H); 7.42(d, 1H); 7.5-7.65(m, 5H); 8.43(s, 1H); 8.65-8.75(m, 4H)

MS - ESI: 455 $[MH]^+$

The starting material was prepared as follows:

Sodium hydride (946mg of a 50% suspension in mineral oil, 19.7mmol) was added to a solution of 4-hydroxypyridine (1.88g, 19.7mmol) in DMF (50ml) and the mixture stirred for 30 minutes. 2-(3-Bromopropoxy)tetrahydropyran (4.0g, 17.9mmol), (J. Chem. Soc. 1963, 3440), was added and the mixture heated at 100°C for 3 hours. The reaction mixture was

allowed to cool, diluted with water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol mixtures (100/0 increasing to 95/5) to give 1-[3-(tetrahydropyran-2-yloxy)propyl]-1,4-dihydro-4-pyridone (1.5g, 35%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.35-1.75(m, 6H); 1.95(t, 2H); 3.35-3.5(m, 2H); 3.65-3.8(m, 2H); 4.12(t, 2H); 4.57(s, 1H); 6.95(s, 2H); 7.94(s, 2H).

A solution of 1-[3-(tetrahydropyran-2-yloxy)propyl]-1,4-dihydro-4-pyridone (0.75g, 3.16mmol) in acetic acid (8ml), THF (4ml) and water (4ml) was heated at 50°C for 4 hours. The volatiles were removed by evaporation to give 1-(3-hydroxypropyl)-1,4-dihydro-4-pyridone (480mg, 99%) as an off-white solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.9-1.95(m, 2H); 1.97-2.05(m, 2H); 4.0-4.1(m, 2H); 6.91(m, 2H); 8.36(m, 2H)

MS - ESI: 154 $[MH]^+$

Example 20

1-(2-Hydroxyethyl)-1,4-dihydro-4-pyridone (221mg, 1.6mmol) was added to a stirred solution of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (230mg, 0.7mmol), (prepared as described for the starting material in Example 15), and tributylphosphine (0.53ml, 2.1mmol) in methylene chloride (20ml) under nitrogen at 5°C. 1,1'-(Azodicarbonyl)dipiperidine (552mg, 2.2mmol) was added in portions over 10 minutes and the mixture was stirred at 5°C for 2 hours, allowed to warm to ambient temperature and stirred for a further 18 hours. The mixture was diluted with ether, the insolubles removed by filtration and the solvent was removed from the filtrate by evaporation. The residue was partitioned between ethyl acetate and water, the organic phase was separated and dried ($MgSO_4$), and solvent was removed by evaporation. The residue was dissolved in acetone and ethereal hydrogen chloride (1.2ml of a 3M soultion) was added. The mixture was left to stand for 15 minutes and the precipitated product was collected by filtration, washed with ether and dried to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-[2-(4-oxo-1,4-dihydro-1-pyridyl)ethoxy]quinazoline** hydrochloride (54mg, 16%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.98(s, 3H); 4.63(dd, 2H); 4.83(dd, 2H); 7.42(d, 1H); 7.50(s, 1H); 7.56(d, 1H); 7.6-7.65(m, 3H); 8.39(s, 1H); 8.77(s, 1H); 8.80(s, 2H)
MS - ESI: 441 $[MH]^+$

The starting material was prepared as follows:

Sodium hydride (1.27g of a 50% suspension in mineral oil, 26.4mmol) was added to a solution of 4-hydroxypyridine (2.5g, 26mmol) in DMF (50ml) and the mixture stirred for 30 minutes. 2-(2-Bromoethoxy)tetrahydropyran (5.0g, 23.9mmol), (J. Am. Chem. Soc. 1948, **70**, 4187), in DMF (5ml) was added and the mixture heated at 80°C for 3 hours. The reaction mixture was allowed to cool, diluted with water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol mixtures (100/0 increasing to 97/3) to give 1-[2-(tetrahydropyran-2-yloxy)ethyl]-1,4-dihydro-4-pyridone (1.5g, 28%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.39-1.68(m, 6H); 3.39-3.44(m, 1H); 3.64-3.78(m, 2H); 3.86-3.92(m, 1H); 4.20(t, 2H); 4.64(s, 1H); 6.95(d, 2H); 8.36(d, 2H)
MS - ESI: 224 $[MH]^+$

A solution of 1-[2-(tetrahydropyran-2-yloxy)ethyl]-1,4-dihydro-4-pyridone (500mg, 2.23mmol) in acetic acid (4ml), THF (2ml) and water (1ml) was heated at 45°C for 4 hours. The volatiles were removed by evaporation to give 1-(2-hydroxyethyl)-1,4-dihydro-4-pyridone (221mg, 71%) as an off-white solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 3.70(t, 2H); 4.06(t, 2H); 6.95(d, 2H); 8.37(d, 2H)

Example 21

A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (132mg, 0.4mmol), (prepared as described for the starting material in Example 1), and 2-fluoro-5-methoxycarbonyloxy-4-methylphenol (96mg, 0.48mmol) in pyridine (2ml) was heated at reflux for 3 hours. The mixture was allowed to cool, the solvent was removed by evaporation and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/ether

(70/30). The resulting solid was crystallised from methylene chloride and methanol to give **7-benzyloxy-4-(2-fluoro-5-hydroxy-4-methylphenoxy)-6-methoxyquinazoline** (120mg, 64%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15(s, 3H); 3.98(s, 3H); 5.35(s, 2H); 6.75(d, 1H); 7.13(d, 1H); 7.37(d, 1H); 7.45(t, 2H); 7.48-7.56(m, 3H); 7.58(s, 1H); 8.54 (s, 1H); 9.65(br s, 1H)

MS - ESI: 454 $[MH]^+$

Elemental Analysis:	Found	C 67.8	H 4.9	N 6.9
$C_{23}H_{19}N_2O_4F\ 0.1H_2O$	Requires	C 67.7	H 4.7	N 6.9%

The starting material was prepared as follows:

A mixture of (4-fluoro-2-methyl-5-nitrophenyl) methyl carbonate (8g, 35mmol), (EP 0307777 A2), and platinum(IV)oxide (174mg) in ethanol (100ml) and ethyl acetate (70ml) was stirred under hydrogen at 1.3 atmospheres pressure for 1.5 hours. The catalyst was removed by filtration through diatomaceous earth and the solvent removed by evaporation. The residue was purified by column chromatography eluting with petroleum ether/ethyl acetate (7/3) to give 2-fluoro-5-methoxycarbonyloxy-4-methylaniline (6.56g, 94%) as an oil which crystallised.

^{1}H NMR Spectrum ($CDCl_3$): 2.09(s, 3H); 3.66(br s, 2H); 3.90(s, 3H); 6.54(d, 1H); 6.83(d, 1H)

A solution of sodium nitrite (1.63g, 23mmol) in water (19ml) and ice (48g) was added dropwsie to a solution of 2-fluoro-5-methoxycarbonyloxy-4-methylaniline (3.93g, 20mmol) in 35% sulphuric acid (48ml) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes and a solution of copper(II)nitrate trihydrate (467g, 1.93mol) in water (780ml) followed by copper(II)oxide (2.65g, 18mmol) were added. The solution was extracted with ethyl acetate, the organic layer was washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with petroleum ether/ethyl acetate (8/2) to give 2-fluoro-5-methoxycarbonyloxy-4-methylphenol (2.13g, 53%) as a yellow solid.

^{1}H NMR Spectrum ($CDCl_3$): 2.13(s, 3H); 3.91(s, 3H); 5.11(br s, 1H); 6.78(d, 1H); 6.93(d, 1H)

Example 22

A mixture of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (470mg, 1mmol), 4-chloromethyl-2-methylthiazole hydrochloride (368mg, 2mmol), potassium carbonate (414mg, 3mmol) and potassium iodide (40mg) in DMF (15ml) was heated at 60°C for 24 hours. The mixture was allowed to cool and partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was dissolved in methanol (15ml) and 1M sodium hydroxide (2ml) was added and the mixture stirred for 30 minutes. Concentrated hydrochloric acid (0.5ml) was added. The solvent was removed by evaporation. The residue was purified by reverse phase HPLC eluting with a gradient (0-70%) of methanol in water. Concentrated hydrochloric acid (0.3ml) was added to the combined fractions of pure product and the solvent was removed by evaporation. The residue was triturated with acetone, collected by filtration, washed with acetone and dried under vacuum at 55°C to give **4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-((2-methylthiazol-4-yl)methoxy)quinazoline** hydrochloride (225mg, 48%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.17(s, 3H); 2.69(s, 3H); 4.00(s, 3H); 4.7(br s, 1H); 5.34(s, 2H); 6.91(d, 1H); 7.1(d, 1H); 7.60(s, 1H); 7.74(s, 1H); 8.33(s, 1H); 8.79(s, 1H); 11.5(s, 1H)
MS - ESI: 427 $[MH]^+$

The starting material was prepared as follows:

A mixture of (4-fluoro-2-methyl-5-nitrophenyl) methyl carbonate (3g, 13mmol), (EP 0307777 A2), and platinum(IV)oxide (300mg) in ethanol (60ml) was stirred under hydrogen at 0.3 atmosphere for 1 hour. The catalyst was removed by filtration through diatomaceous earth and the solvent removed by evaporation to give 2-fluoro-5-methoxycarbonyloxy-4-methylaniline (2.6g, 100%) as a solid.

^{1}H NMR Spectrum: ($CDCl_3$) 2.07(s, 3H); 3.87(s, 3H); 6.52(d, 1H); 6.80(d, 1H)

A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (800mg, 2.4mmol), (prepared as described for the starting material in Example 1), and 2-fluoro-5-methoxycarbonyloxy-4-methylaniline (570mg, 2.89mmol) in isopropanol (20ml) was heated at reflux for 2 hours. The mixture was allowed to cool to ambient temperature, the precipitated solid was collected by filtration, washed with isopropanol and dried under

vacuum to give 7-benzyloxy-4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-6-methoxyquinazoline hydrochloride (1.0g, 77%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 2.2(s, 3H); 3.85(s, 3H); 4.0(s, 3H); 5.37(s, 2H); 7.3-7.55(m, 8H); 8.13(s, 1H); 8.86(s, 1H)

MS - ESI: 464 [MH]$^+$

A mixture of 7-benzyloxy-4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-6-methoxyquinazoline hydrochloride (700mg, 1.4mmol) and 10% palladium-on-charcoal (100mg) in DMF (10ml), methanol (10ml) and trichloromethane (10ml) was stirred under hydrogen at 1 atmosphere pressure for 1 hour. The catalyst was removed by filtration through diatomaceous earth and the solvent was removed by evaporation. The residue was triturated with ether, collected by filtration and dried under vacuum to give 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (570mg, 98%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.23(s, 3H); 3.87(s, 3H); 4.01(s, 3H); 7.37(s, 1H); 7.45(d, 1H); 7.5(d, 1H); 8.20(s, 1H); 8.77(s, 1H); 11.35(s, 1H); 11.79(s, 1H)

MS - ESI: 374 [MH]$^+$

Example 23

A mixture of 4-chloro-7-(4-pyridylmethoxy)quinazoline hydrochloride (350mg, 1mmol) and 2-fluoro-5-hydroxy-4-methylaniline (155mg, 1.1mmol), (prepared as described for the starting material in Example 13), in isopropanol (15ml) was heated at reflux for 1 hour. The resulting precipitate was collected by filtration and purified by reverse phase HPLC using a gradient (0-75%) of methanol in water. Concentrated hydrochloric acid (0.5ml) was added to the combined fractions of pure product and the solvent was removed by evaporation to give **4-(2-fluoro-5-hydroxy-4-methylanilino)-7-(4-pyridylmethoxy)quinazoline** hydrochloride (140mg, 28%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.16(s, 3H); 5.69(s, 2H); 6.19(d, 1H); 7.1(d, 1H); 7.48(d, 1H); 7.66(dd, 1H); 8.06(d, 2H); 8.84(s, 1H); 8.86(d, 1H); 8.90(d, 2H); 9.7(br s, 1H); 11.71(s, 1H)

MS - ESI: 377 [MH]$^+$

Elemental Analysis: Found C 50.9 H 4.9 N 11.1

$C_{21}H_{17}N_4O_2F$ 2.4H_2O 2HCl Requires C 51.2 H 4.9 N 11.4%

The starting material was prepared as follows:-

Sodium hydride (0.72g of a 60% suspension in mineral oil, 18mmol) was added to a solution of 4-hydroxymethylpyridine (4g, 36mmol) in THF (30ml) and the mixture heated at reflux for 15 minutes. 7-Fluoro-3,4-dihydroquinazolin-4-one (1g, 6mmol), (J. Chem. Soc. section B 1967, 449), was added, the THF was removed by evaporation, and the mixture was heated at 120°C for 30 minutes. The mixture was allowed to cool, diluted with water (40ml) and was adjusted to pH8 with concentrated hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, then ether and dried under vacuum to give 7-(4-pyridylmethoxy)-3,4-dihydroquinazolin-4-one (1.12g, 71%).

^{1}H NMR Spectrum ($DMSOd_6$) 5.35(s, 2H); 7.15-7.22(m, 2H); 7.5(d, 2H); 8.05(d, 1H); 8.07 (s, 1H); 8.6(d,2H).

A mixture of 7-(4-pyridylmethoxy)-3,4-dihydroquinazolin-4-one (320mg, 1.26mmol), DMF (1 drop) and thionyl chloride (10ml) was heated at 60°C for 1 hour. The volatiles were removed by evaporation, the residue was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give 4-chloro-7-(4-pyridylmethoxy)quinazoline hydrochloride (435mg, 98%).

^{1}H NMR Spectrum ($DMSOd_6$) 5.7(s, 2H); 7.32(s, 1H); 7.35(d, 1H); 8.1-8.2(m,3H); 8.62(s,1H); 9.0(d,2H).

MS - ESI: 272 $[MH]^+$

Example 24

A solution of 1,1'-(azodicarbonyl)dipiperidine (378mg, 1.5mmol) in methylene chloride (5ml) was added dropwise to a suspension of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (160mg, 0.5mmol), tributylphosphine (303mg, 1.5mmol) and 2-(imidazol-1-yl)ethanol (67mg, 0.6mmol), (J. Med. Chem. 1993, 25, 4052-4060), in methylene chloride (8ml) and the mixture was stirred for 3 hours at ambient temperature. Acetic acid (60mg, 1mmol) was added and the solvent was removed by evaporation. The solid residue was adsorbed on silica and purified by column chromatography eluting with methylene chloride/methanol (9/1 followed by 8/2). The resulting white solid was dissolved in methylene chloride/methanol and a solution of 5M hydrochloric acid in isopropanol was

added. The solvent was removed by evaporation and the solid was triturated with ether, filtered, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline** hydrochloride (180mg, 74%).

^{1}H NMR Spectrum: ($DMSOd_6$) 4.01(s, 3H); 4.62(t, 2H); 4.76(t, 2H); 7.44(dd, 1H); 7.48(s, 1H); 7.59(t, 1H); 7.66(dd, 1H); 7.72(s, 1H); 7.84(s, 1H); 8.41(s, 1H); 8.78(s, 1H); 9.22(s, 1H)

MS - ESI: 414 $[MH]^+$

Elemental Analysis:	Found	C 48.3	H 4.1	N 14.0
$C_{20}H_{17}N_5O_2ClF$ $0.4H_2O$ 2HCl	Requires	C 48.6	H 4.0	N 14.2%

The starting material was prepared as follows:

A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (1.2g, 3.6mmol), (prepared as described for the starting material in Example 1), and 4-chloro-2-fluoroaniline (444µl, 4mmol) in isopropanol (40ml) was heated at reflux for 1.5 hours. The mixture was allowed to cool, the precipitate was collected by filtration, washed with isopropanol then ether and dried under vacuum to give 7-benzyloxy-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline hydrochloride (1.13g, 71%).

m.p. 239-242°C

^{1}H NMR Spectrum: ($DMSOd_6$) 4.0(s, 3H); 5.36(s, 2H); 7.39-7.52(m, 9H); 8.1(s, 1H); 8.75(s, 1H)

MS - ESI: 410 $[MH]^+$

Elemental analysis:	Found	C 59.2	H 4.3	N 9.4
$C_{22}H_{17}N_3O_2ClF$ HCl	Requires	C 59.2	H 4.1	N 9.4%

A solution of 7-benzyloxy-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline hydrochloride (892mg, 2mmol) in TFA (10ml) was heated at reflux for 50 minutes. The mixture was allowed to cool and then poured on to ice. The precipitate was collected by filtration, dissolved in methanol (10ml) and basified to pH11 with aqueous ammonia. The mixture was concentrated by evaporation, the resulting solid product was collected by filtration, washed with water then ether and dried under vacuum to give 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (460mg, 72%) as a yellow solid.

m.p. 141-143°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.95(s, 3H); 7.05(s, 1H); 7.35(d, 1H); 7.54-7.59(m, 2H); 7.78(s, 1H); 8.29(s, 1H)

MS - ESI: 320 $[MH]^+$

Example 25

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (448mg, 1.4mmol), (prepared as described for the starting material in Example 24), and potassium carbonate (676mg, 4.9mmol) in DMF (10ml) was stirred at ambient temperature for 10 minutes. 4-Chloromethyl-2-methylthiazole hydrochloride (310mg, 1.68mmol) was added and the mixture was heated at 70°C for 3.5 hours. The reaction mixture was allowed to cool and was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and the solvent removed by evaporation. The solid residue was purified by column chromatography eluting with a mixture of methylene chloride/acetonitrile/methanol (50/45/5 followed by 50/40/10). The resulting purified solid was dissolved in methylene chloride/methanol and a solution of 5M hydrogen chloride in isopropanol (1ml) was added. Partial evaporation led to the precipitation of a white solid. This solid was collected by filtration and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((2-methylthiazol-4-yl)methoxy)quinazoline** hydrochloride (240mg, 35%).

m.p. 220-225°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.68(s, 3H); 4.0(s, 3H); 5.36(s, 2H); 7.46(dd, 1H); 7.54(s, 1H); 7.61(t, 1H); 7.7(d, 1H); 7.71(s, 1H); 8.26(s, 1H); 8.83(s, 1H)

MS - ESI: 431 $[MH]^+$

Elemental Analysis:	Found	C 49.3	H 4.0	N 11.3
$C_{20}H_{16}N_4O_2ClFS$ 0.3H_2O 1.5HCl	Requires	C 48.9	H 3.7	N 11.4%

Example 26

Using an analogous procedure to that described in Example 25, 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (224mg, 0.7mmol), (prepared as described for the starting material in Example 24), and 2-chloromethyl-1-methylimidazole

hydrochloride (140mg, 0.8mmol) were combined to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((1-methylimidazol-2-yl)methoxy)quinazoline** hydrochloride (150mg, 44%).

^{1}H NMR Spectrum: (DMSOd_6) 3.94(s, 3H); 4.02(s, 3H); 5.69(s, 2H); 7.44(dd, 1H); 7.6(t, 1H); 7.64(s, 1H); 7.67(dd, 1H); 7.72(d, 1H); 7.81(d, 1H); 8.46(s, 1H); 8.81(s, 1H)

MS - ESI: 414 $[MH]^+$

Elemental Analysis: Found C 48.7 H 4.6 N 13.6

$C_{20}H_{17}N_5O_2ClF$ 0.5H_2O 2HCl Requires C 48.8 H 4.3 N 13.7%

0.25isopropanol

Example 27

A mixture of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (470mg, 1mmol), (prepared as described for the starting material in Example 22), 2-chloromethyl-1-methylimidazole hydrochloride (335mg, 2mmol), potassium carbonate (414mg, 3mmol) and potassium iodide (20mg) in DMF (15ml) was heated at 60°C for 2 hours. The mixture was allowed to cool and partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The crude product was dissolved in methanol (20ml), 2M sodium hydroxide (1ml) was added and the mixture stirred for 15 minutes. Concentrated hydrochloric acid (0.5ml) was added and the solvent was removed by evaporation. The crude product was purified by reverse phase chromatography eluting with methanol/water (1/1). Concentrated hydrochloric acid (0.3ml) was added to the combined fractions containing the pure product and the solvent was removed by evaporation to give **4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-((1-methylimidazol-2-yl)methoxy)quinazoline** hydrochloride (100mg, 21%).

^{1}H NMR Spectrum: (DMSOd_6) 2.17(s, 3H); 3.95(s, 3H); 4.01(s, 3H); 5.70(s, 2H); 6.92(d, 1H); 7.12(d, 1H); 7.63(s, 1H); 7.77(s, 1H); 7.83(s, 1H); 8.43(s, 1H); 8.82(s, 1H); 9.7(br s, 1H); 11.62(br s, 1H)

MS - ESI: 410 $[MH]^+$

Example 28

Using an analogous procedure to that described in Example 27, 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (470mg 1.14mmol), (prepared as described for the starting material in Example 22), and 2-acetamido-4-chloromethylthiazole (381mg, 1.68mmol) were combined to give **7-((2-acetamidothiazol-4-yl)methoxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline** (135mg, 25%).

^{1}H NMR Spectrum: (DMSOd_6; CF_3COOD) 2.16(s, 3H); 2.19(s, 3H); 4.00(s, 3H); 5.33(s, 2H); 6.91(d, 1H); 7.12(d, 1H); 7.33(s, 1H); 7.49(s, 1H); 8.16(s, 1H); 8.82(s, 1H)

MS - ESI: 470 [MH]$^+$

Elemental Analysis:	Found	C 51.5	H 4.5	N 13.8
$C_{22}H_{20}N_5O_4FS$ 0.4H_2O 0.95HCl	Requires	C 51.7	H 4.3	N 13.7%

Example 29

A suspension of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (169mg, 0.5mmol), (prepared as described for the starting material in Example 1), and 4-chloro-2-fluoro-5-hydroxyaniline (97mg, 0.6mmol), (EP 061741 A2), in isopropanol (5ml) was heated at reflux for 2 hours. The resulting precipitate was collected by filtration, washed with isopropanol and ether and dried under vacuum to give **7-benzyloxy-4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxyquinazoline** hydrochloride (197mg, 85%).

^{1}H NMR Spectrum: (DMSOd_6) 4.0(s, 3H); 5.36(s, 2H); 7.15(d, 1H); 7.4-7.5(m, 4H); 7.52(s, 1H); 7.54(d, 2H); 8.23(s, 1H); 8.8(s, 1H); 10.6(s, 1H); 11.39(br s, 1H)

MS - ESI: 426 [MH]$^+$

Elemental Analysis:	Found	C 57.1	H 4.2	N 8.9
$C_{22}H_{17}N_3O_3ClF$ 0.15H_2O 1HCl	Requires	C 56.8	H 4.0	N 9.0%

0.4isopropanol

Example 30

1,1'-(Azodicarbonyl)dipiperidine (1.06g, 4.2mmol) in methylene chloride (15ml) was added dropwise to a solution of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (448mg, 1.4mmol), (prepared as described for the starting material in Example 24), tributylphosphine (848mg, 4.2mmol) and 4-(3-hydroxypropyl)pyridine (322mg,

2.4mmol) in methylene chloride (15ml) and the mixture stirred for 3 hours at ambient remperature. Acetic acid (126mg, 2.1mmol) was added and the solvent was removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5). The purified product was triturated with ether, the resulting solid collected and dissolved in methylene chloride (20ml). 5M Hydrogen chloride in isopropanol solution (0.7ml) was added, the solution was diluted with isopropanol (5ml) and concentrated by evaporation to a total volume of 4ml. Ether was added and the resulting soild was collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(4-pyridyl)propoxy)quinazoline** hydrochloride (520mg, 73%).

^{1}H NMR Spectrum: (DMSOd_6) 2.30(m, 2H); 3.09(t, 2H); 3.97(s, 3H); 4.27(t, 2H); 7.42(s, 1H); 7.44(d, 1H); 7.59(t, 1H); 7.67(dd, 1H); 7.95(d, 2H); 8.34(s, 1H); 8.8(s, 1H); 8.82(d, 2H)
MS - ESI: 439 $[MH]^+$

Elemental Analysis: Found C 53.6 H 4.8 N 10.7
$C_{23}H_{20}N_4O_2ClF$ $0.5H_2O$ 2HCl Requires C 53.1 H 4.6 N 10.6%
0.1isopropanol

Example 31

2M Aqueous sodium hydroxide (1.5ml, 3mmol) was added to a solution of 4-(4-chloro-2-fluoro-5-methoxycarbonyloxyanilino)-6-methoxy-7-(3-(4-pyridyl)propoxy)quinazoline (1.28g, 2.5mmol) in methanol (13ml) and the mixture stirred for 2 hours at ambient temperature. Water was added and the mixture was adjusted to pH7 with 2M hydrochloric acid. The resulting precipitate was collected by filtration, washed with water and dried under vacuum. This solid was dissolved in methylene chloride (30ml) and methanol (5ml) and a solution of 5M hydrogen chloride in isopropanol (2.5ml) was added. The solution was diluted with isopropanol and concentrated under vacuum to a total volume of 10ml. The resulting solid was collected by filtration, washed with isopropanol and then ether and dried under vacuum to give **4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-(3-(4-pyridyl)propoxy)quinazoline** hydrochloride (924mg, 70%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.3(t, 2H); 3.12(t, 2H); 4.0(s, 3H); 4.28(t, 2H); 7.18(d, 1H); 7.4(s, 1H); 7.52(d, 1H); 7.95(d, 2H); 8.32(s, 1H); 8.82(s, 1H); 8.84(d, 2H); 10.65(s, 1H); 11.65(br s, 1H)

MS - ESI: 455 $[MH]^+$

Elemental Analysis:	Found	C 51.9	H 4.5	N 10.7
$C_{23}H_{20}N_4O_5ClF$ 0.55H_2O 1.9HCl	Requires	C 51.5	H 4.7	N 10.5%

The starting material was prepared as follows:

1,1'-(Azodicarbonyl)dipiperidine (2.52g, 10mmol) in methylene chloride (10ml) was added dropwise to a solution of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (1.38g, 3.5mmol), (prepared as described for the starting material in Example 22), tributylphosphine (2g, 10.5mmol) and 4-(3-hydroxypropyl)pyridine (720mg, 5.25mmol) in methylene chloride (25ml) and the mixture stirred for 2.5 hours at ambient temperature. The solvent was removed by evaporation and the residue was triturated with petroleum ether. The solid product was collected by filtration and purified by column chromatography eluting with methylene chloride/methanol (95/5) to give 4-(4-chloro-2-fluoro-5-methoxycarbonyloxyanilino)-6-methoxy-7-(3-(4-pyridyl)propoxy)quinazoline (1.2g, 67%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.18(m, 2H); 2.84(t, 2H); 3.90(s, 3H); 3.97(s, 3H); 4.2(t, 2H); 7.21(s, 1H); 7.3(d, 2H); 7.72-7.82(m, 3H); 8.41(s, 1H); 8.47(d, 2H); 9.67(s, 1H)

MS - ESI: 513 $[MH]^+$

Example 32

2M Aqueous sodium hydroxide (0.3ml, 6mmol) was added to a solution of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline (257mg, 5.5mmol) in methanol (5ml) and the mixture stirred for 1 hour at 40°C. Water and 1M hydrochloric acid (0.6ml) were added and the mixture concentrated to half volume by evaporation. The resulting solid was collected by filtration, dissolved in methylene chloride/methanol and a solution of 7M hydrogen chloride in isopropanol (0.4ml) was added. The volatiles were removed by evaporation, the solid residue was triturated with ether, collected by filtration and dried under vacuum to give **4-(2-fluoro-5-hydroxy-4-**

methylanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline hydrochloride (160mg, 60%).

m.p. 195-220°C

^{1}H NMR Spectrum: (DMSOd_6) 2.16(s, 3H); 4.0(s, 3H); 4.63(t, 2H); 4.76(t, 2H); 6.90(d, 1H); 7.1(d, 1H); 7.44(s, 1H); 7.72(s, 1H); 7.83(s, 1H); 8.31(s, 1H); 8.76(s, 1H); 9.20(s, 1H); 9.7(s, 1H); 11.4(br s, 1H)

MS - ESI: 410 $[MH]^+$

Elemental Analysis:	Found	C 52.3	H 5.1	N 13.7
$C_{21}H_{20}N_5O_3F$ 0.3H_2O 1.9HCl 0.22isopropanol	Requires	C 52.3	H 4.9	N 14.1%

The starting material was prepared as follows:

Diethyl azodicarboxylate (160mg, 1.4mmol) was added to a solution of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (261mg, 0.7mmol), (prepared as described for the starting material in Example 22), triphenylphosphine (367mg, 1.4mmol) and 2-(imidazol-1-yl)ethanol (94mg, 0.84mmol), (J. Med. Chem. 1993, 25, 4052-4060), in methylene chloride (5ml) and the mixture stirred for 1 hour at ambient temperature. Acetic acid (42mg, 0.7mmol) was added and the solvent was removed by evaporation. The residue was triturated with ether, the solid collected by filtration, dried under vacuum and purified by chromatography eluting with methylene chloride/methanol (9/1 followed by 8/2) to give 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline (250mg, 76%).

Example 33

A 1M solution of tetrabutylammonium fluoride in THF (560µl, 0.56mmol) was added to a suspension of 4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline (186mg, 0.28mmol) in THF (5ml) and the mixture stirred at 40°C for 1 hour. Water was added and the organic solvent was removed by evaporation. The resulting precipitate was collected by filtration, washed with water and dried by azeotroping with ethanol. The solid was dissolved in methylene chloride/methanol and a solution of 5M hydrogen chloride in isopropanol (0.5ml) was added. The volatiles were

removed by evaporation and the residue was dissolved in isopropanol (1ml) and ether was added. The resulting precipitate was collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoro-5-hydroxyanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline** hydrochloride (110mg, 78%).

^{1}H NMR Spectrum: (DMSOd_6) 4.01(s, 3H); 4.63(t, 2H); 4.75(t, 2H); 7.17(d, 1H); 7.46(s, 1H); 7.51(d, 1H); 7.72(s, 1H); 7.83(s, 1H); 8.36(s, 1H); 8.79(s, 1H); 9.21(s, 1H); 10.63(br s, 1H); 11.6(br s, 1H)

MS - ESI: 430 [MH]$^+$

Elemental Analysis:	Found	C 45.7	H 3.9	N 12.8	
$C_{20}H_{17}N_5O_3ClF$ $1H_2O$ 2HCl	Requires	C 45.8	H 4.1	N 13.1%	

0.09isopropanol 0.09methylene chloride

The starting material was prepared as follows:

A mixture of 7-benzyloxy-4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxyquinazoline (2.35g, 7mmol), (prepared as described for Example 29), imidazole (1.2g, 17.5mmol), t-butyldiphenylsilylchloride (2.1g, 7.7mmol) and 4-(dimethylamino)pyridine (20mg, 0.16mmol) in DMF (10ml) was stirred for 2 hours at ambient temperature. Water (100ml) and ethyl acetate (30ml) were added, the resulting precipitate was collected by filtration, washed with water and dried under vacuum to give 7-benzyloxy-4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-6-methoxyquinazoline (2g, 43%).

^{1}H NMR spectrum (DMSOd_6) 1.09(s, 9H); 3.86(s, 3H); 5.25(s, 2H); 7.04(d, 1H); 7.23(s, 1H); 7.32-7.5(m, 11H); 7.58(d, 1H); 7.65-7.72(m, 5H); 8.1(s, 1H); 9.25 (br s, 1H)

MS - ESI: 663 [MH]$^+$

A mixture of 7-benzyloxy-4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-6-methoxyquinazoline (2g, 3mmol) and 10% palladium-on-charcoal catalyst (400mg) in DMF (20ml), methanol (20ml) and ethyl acetate (20ml) was stirred under hydrogen at 1.7 atmospheres pressure for 2 hours. The catalyst was removed by filtration and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5 followed by 90/10). The purified product was triturated

with ether, collected by filtration and dried under vacuum to give 4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (1.65g, 95%).

^{1}H NMR spectrum ($DMSOd_6$) 1.09(s, 9H); 3.87(s, 3H); 7.00(s, 1H); 7.07(d, 1H); 7.4-7.5(m, 6H); 7.55(d, 1H); 7.62(s, 1H); 7.7(m, 4H); 8.04(s, 1H); 9.15(br s, 1H); 10.34(br s, 1H)

Diethyl azodicarboxylate (174mg, 1mmol) was added to a solution of 4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (288mg, 0.5mmol), triphenylphosphine (262mg, 1mmol) and 2-(imidazol-1-yl)ethanol (62mg, 0.55mmol), (J. Med. Chem. 1993, 25, 4052-4060), in methylene chloride (5ml) and the mixture stirred for 1 hour at ambient temperature. Acetic acid (30mg, 0.5mmol) was added and the volatiles were removed by evaporation. The residue was triturated with ether, the solid collected by filtration and dried under vacuum to give 4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline (186mg, 55%).

MS - ESI: 668 $[MH]^+$

Example 34

A suspension of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-6-methoxy-7-(2-(4-pyridyl)ethoxy)quinazoline (300mg, 0.63mmol) and 2M aqueous sodium hydroxide (0.38ml, 0.76mmol) in methanol (6ml) was stirred at ambient temperature for 2 hours. Water was added and the mixture adjusted to pH7 with 2M hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried under vacuum. The solid was dissolved in methylene chloride/methanol and a 5M solution of hydrogen chloride in isopropanol (0.5ml) was added. The mixture was diluted with isopropanol, and the methylene chloride and methanol solvents were removed by evaporation. The resulting precipitate was collected by filtration, washed with methylene chloride and dried under vacuum to give **4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-(2-(4-pyridyl)ethoxy)quinazoline** hydrochloride (270mg, 94%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.16(s, 3H); 3.5(t, 2H); 3.99(s, 3H); 4.57(t, 2H); 6.89(d, 1H); 7.12(d, 1H); 7.44(s, 1H); 7.98(d, 2H); 8.24(s, 1H); 8.78(s, 1H); 8.81(d, 2H); 9.7(br s, 1H); 11.38(br s, 1H)

MS - ESI: 421 [MH]$^+$

Elemental Analysis:	Found	C 55.5	H 5.3
$C_{23}H_{21}N_4O_5F$ 0.3H_2O 1HCl 0.3isopropanol	Requires	C 55.6	H 5.1

The starting material was prepared as follow :

Diethyl azodicarboxylate (244mg, 1.4mmol) was added to a suspension of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (261mg, 0.7mmol), (prepared as described for the starting material in Example 22), triphenylphosphine (367mg, 1.4mmol) and 2-(4-pyridyl)ethanol (104mg, 0.84mmol), (Zhur. Obshchei. Khim. 1958, 28, 103-110), in methylene chloride and the mixture stirred for 30 minutes at ambient temperature. The solvent was removed by evaporation. The residue was suspended in ether and the ether then decanted. The resulting crude oil was purified by column chromatography eluting with methylene chloride/methanol (90/10) to give 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-6-methoxy-7-(2-(4-pyridyl)ethoxy)quinazoline (300mg, 90%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.18(s, 3H); 3.16(t, 2H); 3.84(s, 3H); 3.92(s, 3H); 4.44(t, 2H); 7.24(s, 1H); 7.29(d, 1H); 7.40(d, 2H); 7.79(s, 1H); 8.35(s, 1H); 8.49(d, 2H); 9.51(s, 1H)

MS - ESI: 501 [MNa]$^+$

Example 35

Using an analogous procedure to that described in Example 34, 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-6-methoxy-7-(3-thienylmethoxy)quinazoline (220mg, 0.47mmol) was treated with 2M aqueous sodium hydroxide (0.47ml) to give **4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-(3-thienylmethoxy)quinazoline** hydrochloride (180mg, 86%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.17(s, 3H); 3.98(s, 3H); 5.34(s, 2H); 6.89(d, 1H); 7.15(d, 1H); 7.27(d, 1H); 7.47(s, 1H); 7.65(dd, 1H); 7.75(s, 1H); 8.18(s, 1H); 8.77(s, 1H); 9.7(br s, 1H)

MS - ESI: 412 [MH]$^+$

Elemental Analysis:	Found	C 55.5	H 4.5	N 9.0
$C_{21}H_{18}N_3O_5FS$ 0.2H_2O 1HCl 0.09isopropanol	Requires	C 55.9	H 4.4	N 9.2%

The starting material was prepared as follows:

Using an analogous procedure to that described for the starting material in Example 34, 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (261mg, 0.7mmol), (prepared as described for the starting material in Example 22), was combined with 3-thiophenemethanol (96mg, 0.84mmol) to give, after purification by flash chromatography eluting with methylene chloride/methanol (98/2), 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-6-methoxy-7-(3-thienylmethoxy)quinazoline (220mg, 67%).

^{1}H NMR Spectrum: (DMSOd_6) 2.18(s, 3H); 3.85(s, 3H); 3.93(s, 3H); 5.27(s, 2H); 7.23(d, 1H); 7.30(d, 1H); 7.32(s, 1H); 7.40(d, 1H); 7.59(dd, 1H); 7.66(s, 1H); 7.81(s, 1H); 8.35(s, 1H); 9.53(s, 1H)

MS - ESI: 492 [MNa]$^+$

Example 36

A mixture of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (187mg, 0.75mmol), (prepared as described for the starting material in Example 22), 4-bromomethylbenzonitrile (147mg, 0.75mmol) and potassium carbonate (173mg, 1.25mmol) in DMF (5ml) was heated at 50°C for 1 hour. Methanol (5ml) and potassium carbonate (138mg, 1mmol) were added and the mixture stirred at 65°C for 2 hours. The solvent was removed by evaporation, water was added to the residue and the mixture adjusted to pH7 with 2M hydrochloric acid. The resulting precipitate was collected by filtration, washed with water and dried under vacuum. The solid was purified by column chromatography eluting with methylene chloride/methanol (95/5). The purified product was triturated with ether, collected by filtration and dried. The solid was dissolved in methylene chloride/isopropanol and a 5M solution of hydrogen chloride in isopropanol (0.5ml) was added. The mixture was concentrated by evaporation and the resulting precipitate collected by filtration, washed with methylene chloride and dried under vacuum to give 7-

(4-cyanobenzyloxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline hydrochloride (60mg, 25%).

m.p. 265-270°C

^{1}H NMR Spectrum: (DMSOd_6) 2.17(s, 3H); 4.02(s, 3H); 5.47(s, 2H); 6.89(d, 1H); 7.11(d, 1H); 7.38(s, 1H); 7.71(d, 2H); 7.93(d, 2H); 8.23(s, 1H); 8.75(s, 1H); 9.67(s, 1H); 11.24(br s, 1H)

MS - ESI: 431 $[MH]^+$

Elemental Analysis:	Found	C 61.2	H 4.5	N 11.7
$C_{24}H_{19}N_4O_3F$ 0.1H_2O 1HCl	Requires	C 61.5	H 4.3	N 12.0%

Example 37

Diethyl azodicarboxylate (315µl, 2mmol) was added dropwise to a solution of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (319.5mg, 1mmol), (prepared as described for the starting material in Example 24), triphenylphosphine (524mg, 2mmol) and 2-(4-pyridyl)ethanol (160mg, 1.25mmol), (Zhur. Obshchei. Khim. 1958, 28, 103-110), in methylene chloride (7ml). The mixture was stirred for 1 hour at ambient temperature and the solvent was removed by evaporation. The residue was triturated with ether, the solid collected by filtration and purified by column chromatography eluting with methylene chloride/acetonitrile/methanol (85/10/5). The purified solid product was dissolved in a mixture of methylene chloride (50ml) and methanol (50ml) and 5M hydrochloric acid in isopropanol (0.5ml) was added. After diluting with isopropanol (20ml), the mixture was concentrated by evaporation. The precipitated solid was collected by filtration and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(4-pyridyl)ethoxy)quinazoline** hydrochloride (125mg, 25%).

m.p. 189-191°C

^{1}H NMR Spectrum: (DMSOd_6; CF_3COOD) 3.55(t, 2H); 3.99(s, 3H); 4.64(t, 2H); 7.46(s, 1H); 7.48(d, 1H); 7.62(t, 1H); 7.67(dd, 1H); 8.16(d, 2H); 8.17(s, 1H); 8.88(s, 1H); 8.94(d, 1H)

MS - ESI: 425 $[MH]^+$

Elemental Analysis:	Found	C 52.0	H 4.3	N 11.1
$C_{22}H_{18}N_4O_2ClF$ 0.5H_2O 1.95HCl	Requires	C 52.3	H 4.2	N 11.1%

Example 38

3-(Chloromethyl)pyridine hydrochloride (328mg, 2mmol) was added to a mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (319.5mg, 1mmol), (prepared as described for the starting material in Example 24), potassium carbonate (442mg, 3.2mmol) and potassium iodide (33mg, 0.2mmol) in DMF (25ml) at ambient temperature and the reaction mixture then heated at 80°C for 2.5 hours. The mixture was allowed to cool and the volatiles were removed by evaporation. The residue was dissolved in a mixture of ethyl acetate (19ml) and methanol (1ml) and the insolubles removed by filtration. The solvent was removed from the filtrate by evaporation and the residue was purified by column chromatography eluting with methylene chloride/acetonitrile/methanol (50/45/5). The purified product was dissolved in hot methylene chloride and saturated ethereal hydrogen chloride was added. The mixture was concentrated to half volume by evaporation, the resulting precipitate was collected by filtration and dried under vacuum at 70°C to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((3-pyridyl)methoxy)quinazoline** hydrochloride(103mg, 25%).

m.p. 216-221°C

^{1}H NMR Spectrum: (DMSOd_6) 4.03(s, 3H); 5.48(s, 2H); 7.47(d, 1H); 7.54(s, 1H); 7.65(t, 1H); 7.7-7.8(m, 2H); 8.25(d, 1H); 8.35(s, 1H); 8.75(d, 1H); 8.84(s, 1H); 8.90(s, 1H); 11.65(br s, 1H)

MS - ESI: 411 $[MH]^+$

Elemental Analysis:	Found	C 51.9	H 4.2	N 11.4
$C_{21}H_{16}N_4O_2ClF$ 0.8H_2O 1.6HCl	Requires	C 52.2	H 4.0	N 11.6%

Example 39

Using an analogous procedure to that described in Example 38, 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (319.5mg, 1mmol), (prepared as described for the starting material in Example 24), was reacted with 2-(chloromethyl)pyridine hydrochloride (310mg, 1.9mmol) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((2-pyridyl)methoxy)quinazoline** (146mg, 33%).

m.p. 215-218°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.98(s, 3H); 5.4(s, 2H); 7.3(s, 1H); 7.32-7.42(m, 2H); 7.52-7.62(m, 3H); 7.85(s, 1H); 7.90(t, 1H); 8.35(s, 1H); 8.65(d, 1H); 9.6(s, 1H)

MS - ESI: 411 [MH]

Elemental Analysis:	Found	C 59.7	H 3.9	N 13.1
$C_{21}H_{16}N_4O_2ClF\ 0.5H_2O$	Requires	C 60.1	H 4.1	N 13.3%

Example 40

Diethyl azodicarboxylate (128µl, 1.5mmol) was added dropwise to a solution of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (250mg, 0.78mmol), (prepared as described for the starting material in Example 24), triphenylphosphine (410mg, 1.5mmol) and 2-(1-methylimidazol-2-yl)ethanol (147mg, 1.15mmol), (EP 0675112 A1), in methylene chloride (4ml) and the mixture was stirred for 30 minutes at ambient temperature. Further triphenylphosphine (143mg, 0.52mmol) and diethyl azodicarboxylate (85µl, 1mmol) were added and the mixture stirred for 1 hour at ambient temperature. The solid product was collected by filtration and washed with methylene chloride. The solid was dissolved in a mixture of methylene chloride (25ml) and methanol (25ml), and a solution of 2.9M ethereal hydrogen chloride (2ml) was added. The mixture was concentrated by evaporation and the resulting precipitate was collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1-methylimidazol-2-yl)ethoxy)quinazoline** hydrochloride (133mg, 34%).

m.p. 224-229°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.62(t, 2H); 3.94(s, 3H); 4.0(s, 3H); 4.59(t, 2H); 7.43(d, 1H); 7.46(s, 1H); 7.6(t, 1H); 7.6-7.7(m, 3H); 8.41(s, 1H); 8.78(s, 1H); 11.75(br s, 1H)

MS - ESI: 428 [MH]$^+$

Elemental Analysis:	Found	C 48.8	H 4.4	N 13.4
$C_{21}H_{19}N_5O_2ClF\ 1H_2O\ 2HCl$	Requires	C 48.6	H 4.5	N 13.5%

Example 41

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (319.5mg, 1mmol), (prepared as described for the starting material in Example 24), potassium

carbonate (414mg, 3mmol), potassium iodide (16mg, 0.1mmol) and 4-chloromethylpyrimidine (257mg, 2mmol) in DMF (20ml) was heated at 80°C for 2 hours. The solvent was removed by evaporation and the residue was triturated with water. The solid was collected by filtration and dried under vaccum. The solid was purified by column chromatography eluting with methylene chloride/methanol (95/5). The purified white solid was suspended in methanol (25ml) and a solution of 7.5M hydrogen chloride in methanol (20ml) was added. The resulting solid product was collected by filtration, washed with methanol and then pentane and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((pyrimidin-4-yl)methoxy)quinazoline** hydrochloride (172mg, 42%).

m.p. 237-239°C

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 4.07(s, 3H); 5.53(s, 2H); 7.40(s, 1H); 7.46(dd, 1H); 7.65(t, 1H); 7.68-7.72(m, 2H); 8.26(s, 1H); 8.85(s, 1H); 8.91(d, 1H); 9.25(s, 1H)

MS - ESI: 412 $[MH]^+$

Elemental Analysis:	Found	C 49.5	H 3.6	N 14.1
$C_{20}H_{15}N_5O_2ClF$ 0.5H_2O 1.85HCl	Requires	C 49.2	H 3.7	N 14.3%

The starting material was prepared as follows:

A solution of 4-methylpyrimidine (2g, 21.2mmol), N-chlorosuccinimide (4.26g, 31.9mmol) and benzoyl peroxide (500mg, 2.1mmol) in carbon tetrachloride (100ml) was heated at 80°C for 2 hours. The mixture was allowed to cool, the insolubles were removed by filtration and the solvent was removed from the filtrate by evaporation. The residue was purified by column chromatography eluting with methylene chloride to give 4-chloromethylpyrimidine (257mg, 10%).

^{1}H NMR Spectrum: ($DMSOd_6$) 4.81(s, 2H); 7.70(d, 1H); 8.88(d,1H); 9.21(s, 1H)

Example 42

2M Aqueous sodium hydroxide solution (900µl) was added to a solution of 4-(3-acetoxy-4-methylanilino)-6-methoxy-7-((1-methylbenzimidazol-2-yl)methoxy)quinazoline (290mg, 0.6mmol) in methanol (15ml) and methylene chloride (12ml) and the mixture stirred for 25 minutes at ambient temperature. The solvent was

removed by evaporation and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The solid residue was purified by column chromatography eluting with methylene chloride/methanol (97/3 and 95/5). The purified white solid was suspended in methanol (20ml) and a solution of 7.5M hydrochloric acid in methanol (2 equivalents) was added. The solid was collected by filtration, washed with methanol and then pentane and dried under vacuum at 50°C to give **4-(3-hydroxy-4-methylanilino)-6-methoxy-7-((1-methylbenzimidazol-2-yl)methoxy)quinazoline** hydrochloride (106mg, 37%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 2.17(s, 3H); 4.04(s, 3H); 4.15(s, 3H); 6.01(s, 2H); 7.0(dd, 1H); 7.11(d, 1H); 7.18(d, 1H); 7.6-7.75(m, 3H); 7.89(d, 1H); 8.05(d, 1H); 8.27(s, 1H); 8.86(s, 1H)

MS - ESI: 469 $[MNa]^+$

The starting material was prepared as follows:

A solution of 1-methylbenzimidazole (2.5g, 19mmol), (J. Chem. Soc. 1929, 2820-2828), and paraformaldehyde (2g) was heated at 165°C for 30 minutes. Further paraformaldehyde (1g) was added and heating continued for 2 hours. The mixture was allowed to cool and was purified by column chromatography eluting with methylene chloride, followed by methylene chloride/methanol (95/5) to give 2-hydroxymethyl-1-methylbenzimidazole (1.34g, 45%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.84(s, 3H); 4.73(s, 2H); 5.57(br s, 1H); 7.19(t, 1H); 7.25(t, 1H); 7.54(d, 1H); 7.60(d, 1H)

MS - ESI: 185 $[MNa]^+$

A solution of 2-hydroxymethyl-1-methylbenzimidazole (1.1g, 6.7mmol) in thionyl chloride (10ml) was stirred at ambient temperature for 15 minutes and then heated at reflux for 15 minutes. The volatiles were removed by evaporation and the residue purified by column chromatography eluting with methylene chloride/methanol (95/5) to give 2-chloromethyl-1-methylbenzimidazole (506mg, 36%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 4.07(s, 3H); 5.38(s, 2H); 7.6-7.7(m, 2H); 7.9(d, 1H); 8.05(dd, 1H)

MS - ESI: 181 $[MH]^+$

A mixture of 4-(3-acetoxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (240mg, 0.64mmol), (prepared as described for the starting material in Example 1), potassium carbonate (310mg, 2.25mmol), potassium iodide (10mg, 0.064mmol) and 2-chloromethyl-1-methylbenzimidazole (153mg, 0.7mmol) in DMF (12ml) was heated at 65°C for 3 hours. Further 2-chloromethyl-1-methylbenzimidazole (90mg, 0.41mmol) and potassium carbonate (165mg, 1.2mmol) were added and heating continued for 2 hours. The solvent was removed by evaporation and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was triturated with water and the solid product collected by filtration, washed with ether and dried under vacuum to give 4-(3-acetoxy-4-methylanilino)-6-methoxy-7-((1-methylbenzoimidazol-2-yl)methoxy)quinazoline (292mg, 95%).

MS - ESI: 506 $[MNa]^+$

Example 43

2M Aqueous sodium hydroxide solution (700µl, 1.4mmol) was added to a suspension of 7-((2-chloro-6-methyl-4-pyridyl)methoxy)-4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-6-methoxyquinazoline (360mg, 0.7mmol) in methanol (10ml) cooled at 5°C and the mixture was then stirred for 30 minutes at ambient temperature. The solvent was removed by evaporation, the residue diluted with water (10ml) and the mixture adjusted to pH7 with 1M hydrochloric acid. The resulting solid was collected by filtration, washed with water and ether, and dried under vacuum. This solid was dissolved in methanol (5ml) and a 7M solution of hydrogen chloride in methanol (3ml) was added. The precipitate was collected by filtration, washed with methanol and dried under vacuum to give **7-((2-chloro-6-methyl-4-pyridyl)methoxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline** hydrochloride (273mg, 74%).

^1H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 2.18(s, 3H); 2.50(s, 3H); 4.04(s, 3H); 5.42(s, 2H); 6.9(d, 1H); 7.12(d, 1H); 7.35(s, 1H); 7.38(s, 1H); 7.42(s, 1H); 8.21(s, 1H); 8.81(s, 1H)

MS - ESI: 455 $[MH]^+$

Elemental Analysis:	Found	C 49.8	H 4.8	N 10.0
$C_{23}H_{20}N_4O_3ClF\ 1.5H_2O\ 1.9HCl$	Requires	C 50.1	H 4.6	N 10.2%

The starting material was prepared as follows:

A solution of 2-chloro-6-methyl-4-pyridinecarboxylic acid (2g, 12mmol) in ethanol (100ml) and concentrated sulphuric acid (10ml) was heated at reflux for 2 hours. The volatiles were removed by evaporation and the residue was dissolved in methylene chloride. The solution was washed with a saturated aqueous sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (1/9) to give ethyl 2-chloro-6-methyl-4-pyridinecarboxylate (2g, 86%).

^{1}H NMR Spectrum: ($CDCl_3$) 1.41(t, 3H); 2.6(s, 3H); 4.40(q, 2H); 7.63(s, 1H); 7.69(s, 1H)

MS - ESI: 200 $[MH]^+$

Elemental Analysis:	Found	C 54.4	H 5.3	N 7.0
$C_9H_{10}NO_2Cl$	Requires	C 54.1	H 5.0	N 7.0%

Lithium aluminium hydride (350mg, 9.26mmol) was added in portions to a solution of ethyl 2-chloro-6-methyl-4-pyridinecarboxylate (1.85g, 9.26mmol) in THF (40ml) cooled at 0°C. The mixture was stirred for 15 minutes at 0°C and acetic acid (2ml) was added. The mixture was partitioned between ethyl acetate and water and the aqueous layer was adjusted to pH7.5 with 5 % aqueous sodium hydrogen carbonate solution. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (35/65) to give 2-chloro-4-hydroxymethyl-6-methylpyridine (1.28g, 88%).

^{1}H NMR Spectrum: ($CDCl_3$) 1.92(t, 1H); 2.53(s, 3H); 4.70(d, 2H); 7.06(s, 1H); 7.16(s, 1H)

MS - ESI: 157 $[MH]^+$

Elemental Analysis:	Found	C 53.1	H 5.3	N 8.7
C_7H_8NOCl	Requires	C 53.3	H 5.1	N 8.9%

Diethyl azodicarboxylate (296µl, 1.88mmol) was added dropwise to a solution of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (350mg, 0.94mmol), (prepared as described for the starting material in

Example 22), triphenylphosphine (492mg, 1.88mmol) and 2-chloro-4-hydroxymethyl-6-methylpyridine (178mg, 1.12mmol) in methylene chloride (30ml) and the mixture stirred for 30 minutes at ambient temperature. The solvent was removed by evaporation and the residue was purified by column chromatography eluting with ethyl acetate/methylene chloride (75/25). The purified product was triturated with ether, the solid collected by filtration, washed with ether and dried under vacuum to give 7-((2-chloro-6-methyl-4-pyridyl)methoxy)-4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-6-methoxyquinazoline (373mg, 78%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15(s, 3H); 2.5(s, 3H); 3.85(s, 3H); 3.98(s, 3H); 5.35(s, 2H); 7.25(s, 1H); 7.3(d, 1H); 7.35(s, 1H); 7.4(m, 2H); 7.85(s, 1H); 8.35(s, 1H); 9.58(s, 1H)

MS - ESI: 513 $[MH]^+$

Example 44

A mixture of 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (112mg, 0.35mmol), potassium carbonate (138mg, 1mmol) and 4-(chloromethyl)pyridine hydrochloride (59mg, 0.36mmol) in DMF (2ml) was heated at 80°C for 1 hour. The mixture was allowed to cool and partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5) to give **4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-((4-pyridyl)methoxy)quinazoline** (115mg, 80%).

m.p. 197-198°C

^{1}H NMR Spectrum: ($DMSOd_6$) 4.03(s, 3H); 5.46(s, 2H); 7.45(d, 1H); 7.49(s, 1H); 7.5(d, 2H); 7.58(t, 1H); 7.62(s, 1H); 7.72(dd, 1H); 8.58(s, 1H); 8.65(d, 2H)

MS - ESI: 412 $[MH]^+$

Elemental Analysis:	Found	C 59.5	H 3.9	N 9.6
$C_{21}H_{15}N_3O_3ClF\ 0.8H_2O$	Requires	C 59.2	H 3.9	N 9.9%

The starting material was prepared as follows:

4-Chloro-2-fluoro-phenol (264mg, 1.8mmol) was added to a solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (506mg, 1.5mmol), (prepared as described for the starting material in Example 1), in pyridine (8ml) and the mixture heated at

reflux for 45 minutes. The solvent was removed by evaporation and the residue partitioned between ethyl acetate and water. The organic layer was washed with 0.1M hydrochloric acid, water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The solid residue was triturated with petroleum ether and the crude product collected by filtration and purified by flash chromatography eluting with methylene chloride/ether (9/1) to give 7-benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (474mg, 77%) as a cream solid.

m.p. 179-180°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.99(s, 3H); 5.36(s, 3H); 7.35-7.5(m, 4H); 7.55-7.65(m, 5H); 7.72(d, 1H); 8.6(s, 1H)

MS - ESI: 411 $[MH]^+$

Elemental analysis:	Found	C 63.4	H 4.1	N 6.8
$C_{22}H_{16}ClFN_2O_3$ 0.06H_2O 0.05CH_2Cl_2	Requires	C 63.6	H 3.9	N 6.7%

A solution of 7-benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (451mg, 1.1mmol) in TFA (4.5ml) was heated at reflux for 3 hours. The mixture was diluted with toluene and the volatiles removed by evaporation. The residue was triturated with methylene chloride, collected by filtration, washed with ether and dried under vacuum to give 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (320mg, 90%).

^{1}H NMR Spectrum: ($DMSOd_6$) 4.0(s, 3H); 7.27(s, 1H); 7.43(dd, 1H); 7.56(t, 1H); 7.57(s, 1H); 7.72(dd, 1H); 8.5(s, 1H)

MS - ESI: 321 $[MH]^+$

Example 45

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (320mg, 1mmol), (prepared as described for the starting material in Example 24), potassium carbonate (414mg, 3mmol), potassium iodide (40mg) and 4-(chloromethyl)pyridine hydrochloride (250mg, 1.5mmol) in DMF (15ml) was heated at 60°C for 2 hours. The mixture was allowed to cool and partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was suspended in ethanol (20ml) and concentrated hydrochloric acid (0.5ml) was added. The volatiles were removed by evaporation and the solid residue was azeotroped with toluene. The solid product was recrystallised from isopropanol to give **4-(4-**

chloro-2-fluoroanilino)-6-methoxy-7-((4-pyridyl)methoxy)quinazoline hydrochloride (335mg, 70%).

^{1}H NMR Spectrum: ($DMSOd_6$) 4.1(s, 3H); 5.69(s, 2H); 7.46(dd, 1H); 7.52(s, 1H); 7.62(t, 1H); 7.69(dd, 1H); 8.03(d, 2H); 8.55(s, 1H); 8.83(s, 1H); 8.93(d, 2H)

MS - ESI: 411 $[MH]^+$

Elemental Analysis:	Found	C 51.0	H 3.9	N 11.2
$C_{21}H_{16}N_4O_2ClF\ 0.5H_2O\ 1.95HCl$	Requires	C 51.4	H 3.9	N 11.4%

Example 46

Diethyl azodicarboxylate (261mg, 1.5mmol) was added dropwise to a suspension of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (160mg, 0.5mmol), (prepared as described for the starting material in Example 24), triphenylphosphine (393mg, 1.5mmol) and 2-(N-(2,6-dimethyl-4-pyridyl)-N-methylamino)ethanol (125mg, 0.7mmol) in methylene chloride (5ml) and the mixture stirred for 2 hours at ambient temperature. Methanol (10 drops) was added and the mixture was poured on to a column of neutral aluminium oxide and the product was separated by elution with methylene chloride/acetonitrile/methanol (60/35/35). The purified solid product was triturated with ether and collected by filtration. The solid was dissolved in methylene chloride/methanol and a solution of 3M ethereal hydrogen chloride (1ml) was added. The solid was collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-7-(2-(N-(2,6-dimethyl-4-pyridyl)-N-methylamino)ethoxy)-6-methoxyquinazoline** (170mg, 61%).

m.p. 208-212°C

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 2.52(s, 6H); 3.26(s, 3H); 3.98(s, 3H); 4.12(t, 2H); 4.46(t, 2H); 6.8(br s, 1H); 7.1(br s, 1H); 7.38(s, 1H); 7.46(dd, 1H); 7.62(t, 1H); 7.67(dd, 1H); 8.18(s, 1H); 8.89(s, 1H)

MS - ESI: 482 $[MH]^+$

Elemental Analysis:	Found	C 52.2	H 5.2	N 12.2
$C_{25}H_{25}N_5O_2ClF\ 1H_2O\ 2HCl$	Requires	C 52.4	H 5.1	N 12.2%

The starting material was prepared as follows:

A solution of 4-chloro-2,6-dimethylpyridine (849mg, 6mmol), (J. Het. Chem. 1990, 1841), in 2-(methylamino)ethanol (1.35g, 18mmol) and 3M ethereal hydrogen chloride (3 drops) was heated at 140°C for 1 hour. The reaction mixture was allowed to cool and was diluted with water. The insolubles were removed by filtration and the aqueous filtrate was poured onto a suspension of magnesium sulphate (50g) in ethyl acetate (100ml). The insolubles were removed by filtration and the filtrate dried ($MgSO_4$) and the solvent removed by evaporation. The solid residue was triturated with ether, collected by filtration and dried under vacuum at 50°C to give 2-(N-(2,6-dimethyl-4-pyridyl)-N-methylamino)ethanol (960mg, 90%).

m.p. 139-144°C

^{1}H NMR Spectrum: ($CDCl_3$) 2.4(s, 6H); 3.0(s, 3H); 3.51(t, 2H); 3.81(t, 2H); 6.26(s, 2H)

MS - ESI: 181 $[MH]^+$

Example 47

Diethyl azodicarboxylate (261mg, 1.5mmol) was added dropwise to a suspension of of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (160mg, 0.5mmol), (prepared as described for the starting material in Example 24), triphenylphosphine (393mg, 1.5mmol) and 2-(N-(4-pyridyl)amino)ethanol (97mg, 0.7mmol) in methylene chloride (8ml) and the mixture stirred for 2 hours at ambient temperature. The mixture was diluted with ethyl acetate (5ml), the solid product was collected by filtration and purified by chromatography on an aluminium oxide column eluting with methylene chloride/acetonitrile/methanol (60/35/5). The purified solid was triturated with ether and collected by filtration. The solid was dissolved in a mixture of methylene chloride/methanol and 3M ethereal hydrogen chloride (0.5ml) was added. The volatiles were removed by evaporation, the solid residue was suspended in ether, collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-(4-pyridyl)amino)ethoxy)quinazoline** hydrochloride (95mg, 37%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 3.87(t, 2H); 4.00(s, 3H); 4.43(t, 2H); 6.97(dd, 1H); 7.15(dd, 1H); 7.43(s, 1H); 7.46(dd, 1H); 7.66(t, 1H); 7.68(dd, 1H); 8.12(d, 1H); 8.21(s, 1H); 8.34(d, 1H); 8.89(s, 1H)

MS - ESI: 440 $[MH]^+$

Elemental Analysis: Found C 50.0 H 4.3 N 13.2

$C_{22}H_{16}N_5O_2ClF$ $0.8H_2O$ 2HCl Requires C 50.0 H 4.3 N 13.2%

The starting material was prepared as follows:

Using a procedure analogous to that described for the starting material in Example 46, 4-chloropyridine (3g, 20mmol) was treated with aminoethanol (6.1g, 0.1mol) to give 2-(N-(4-pyridyl))aminoethanol (400mg, 25%).

m.p. 110-111°C

^1H NMR Spectrum: ($CDCl_3$) 3.3(m, 2H); 3.81(m, 2H); 4.94(br s, 1H); 6.44(d, 2H); 8.13(d, 2H)

MS - ESI: 138 $[MH]^+$

Example 48

Using a procedure analogous to that described in Example 47, 3-(N-methyl-N-(4-pyridyl)amino)propanol (116mg, 0.7mmol) was treated with 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (160mg, 0.5mmol), (prepared as described for the starting material in Example 24), to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(N-methyl-N-(4-pyridyl)amino)propoxy)quinazoline** hydrochloride (150mg, 55%).

m.p. 243-248°C

^1H NMR Spectrum: ($DMSOd_6$; CD_3COOD) 2.2(t, 2H); 3.21(t, 3H); 3.82(t, 2H); 4.0(s, 3H); 4.31(t, 2H); 6.95(br s, 1H); 7.2(br s, 1H); 7.39(s, 1H); 7.46(dd, 1H); 7.62(t, 1H); 7.68(dd, 1H); 8.2(s, 1H); 8.3(br s, 2H); 8.87(s, 1H)

MS - ESI: 468 $[MH]^+$

Elemental Analysis: Found C 51.4 H 5.1 N 12.9

$C_{24}H_{23}N_5O_2ClF$ $1.2H_2O$ 1.95HCl Requires C 51.4 H 4.9 N 12.5%

The starting material was prepared as follows:

Using a procedure analogous to that described for the starting material in Example 46, 4-chloropyridine (885mg, 59mmol) and 3-(methylamino)propanol (2.1g, 0.23mmol),

(Tetrahedron Lett. 1994, 35, 1545-1548), were heated for 8 hours to give 3-(N-methyl-N-(4-pyridyl)amino)propanol (979mg, 61%).

^{1}H NMR Spectrum: ($CDCl_3$; CD_3COOD) 1.8-1.9(m, 2H); 3.16(s, 3H); 3.6-3.75(m, 4H); 6.8(br s, 2H); 8.30(d, 2H)

MS - ESI: 166 $[MH]^+$

Example 49

Diethyl azodicarboxylate (261mg, 1.5mmol) was added dropwise to a suspension of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (160mg, 0.5mmol), (prepared as described for the starting material in Example 24), triphenylphosphine (393mg, 1.5mmol) and 1-(2-hydroxyethyl)-2-methylimidazole (88mg, 0.7mmol), (Chem.Abs. 1964, 60, 2949), in methylene chloride (8ml) and the mixture stirred for 2 hours at ambient temperature. The mixture was diluted with ether (8ml) and the solid product was collected by filtration. The solid was dissolved in methylene chloride/methanol and a solution of 3M ethereal hydrogen chloride (0.5ml)was added. The resulting precipitate was collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(2-methylimidazol-1-yl)ethoxy)quinazoline** hydrochloride (180mg, 72%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 2.79(s, 3H); 4.02(s, 3H); 4.59(t, 2H); 4.72(t, 2H); 7.40(s, 1H); 7.45(d, 1H); 7.60(s, 1H); 7.62(t, 1H); 7.67(dd, 1H); 7.71(s, 1H); 8.23(s, 1H); 8.89(s, 1H)

MS - ESI: 428 $[MH]^+$

Elemental Analysis:	Found	C 47.9	H 4.7	N 13.3
$C_{21}H_{19}N_4O_2ClF$ 1.4H_2O 2.1HCl	Requires	C 47.6	H 4.6	N 13.2%

Example 50

Diethyl azodicarboxylate (295µl, 1.8mmol) was added dropwise to a solution of 1-(3-hydroxypropyl)imidazole (102mg, 0.81mmol), (EP 0060696 A1), 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (200mg, 0.62mmol), (prepared as described for the starting material in Example 24), and triphenylphosphine (492mg, 1.8mmol) in methylene chloride (4ml) and the mixture stirred for 2 hours at ambient temperature. The solvent was removed by evaporation and the residue was purified by column chromatography

eluting with methylene chloride/acetonitrile/methanol (60/35/5). The purified solid was dissolved in methylene chloride/methanol and 5M ethereal hydrogen chloride (2ml) was added. The volatiles were removed by evaporation, the solid residue was suspended in ether, collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-7-(3-(imidazol-1-yl)propoxy)-6-methoxyquinazoline** hydrochloride (114mg, 36%).

^{1}H NMR Spectrum: (DMSOd_6; CF_3COOD) 2.5(m, 2H); 3.99(s, 3H); 4.32(t, 2H); 4.45(t, 2H); 7.39(s, 1H); 7.45(dd, 1H); 7.61(t, 1H); 7.66(dd, 1H); 7.71(s, 1H); 7.84(s, 1H); 8.19(s, 1H); 8.77(s, 1H); 9.20(s, 1H)

MS - ESI: 428 $[MH]^+$

Elemental Analysis:	Found	C 48.2	H 4.5	N 13.2
$C_{21}H_{19}N_5O_2ClF$ 1.2H_2O 1.9HCl	Requires	C 48.6	H 4.5	N 13.5%

Example 51

7-(2-Bromoethoxy)-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline (98mg, 0.23mmol) was added to a solution of 4-methyl-4H-1,2,4-triazole-3-thiol (40mg, 0.34mmol) and potassium-t-butoxide (36mg, 0.32mmol) in DMF (1ml) and the mixture heated at 40°C for 30 minutes. The reaction mixture was allowed to cool and was partitioned between ammonium chloride and ethyl acetate. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with a gradient of methylene chloride/methanol (95/50 to 80/20). The purified solid product was triturated with ether and collected by filtration. The solid was dissolved in methylene chloride/methanol and 3M ethereal hydrogen chloride (0.5ml) was added. The volatiles were removed by evaporation and the residue was crystallised from methylene chloride and ether. The solid was collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(4-methyl-4H-1,2,4-triazol-3-ylthio)ethoxy)-quinazoline** hydrochloride (90mg, 79%).

^{1}H NMR Spectrum: (DMSOd_6; CF_3COOD) 3.78(s, 3H); 3.81(t, 2H); 3.99(s, 3H); 4.57(t, 2H); 7.40(s, 1H); 7.46(dd, 1H); 7.62(t, 1H); 7.67(dd, 1H); 8.16(s, 1H); 8.89(s, 1H); 9.68(s, 1H)

MS - ESI: 461 $[MH]^+$

Elemental Analysis:	Found	C 43.7	H 3.9	N 14.9
$C_{20}H_{18}N_6O_2ClFS\ 1H_2O\ 2HCl$	Requires	C 43.5	H 4.0	N 15.2%

The starting material was prepared as follows:

1,2-Dibromoethane (725mg, 4mmol) was added by portions of 70µl every 30 minutes to a mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (320mg, 1mmol), (prepared as described for the starting material in Example 24), and potassium carbonate (552mg, 4mmol) in DMF (5ml) heated at 35°C. The mixture was stirred for a further 30 minutes after the completion of the addition and then partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was triturated with petroleum ether/ether, the solid was collected by filtration and dried under vacuum to give 7-(2-bromoethoxy)-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline (200mg, 47%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.89(t, 2H); 3.96(s, 3H); 4.51(t, 2H); 7.23(s, 1H); 7.35(dd, 1H); 7.55(dd, 1H); 7.59(t, 1H); 7.83(s, 1H); 8.36(s, 1H); 9.57(s, 1H)

MS - ESI: 428 $[MH]^+$

Example 52

Using an analogous procedure to that described in Example 51, 7-(2-bromoethoxy)-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline (98mg, 0.23mmol), (prepared as described for the starting material in Example 51), was treated with 5-mercapto-1-methyltetrazole (40mg, 0.35mmol) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1-methyltetrazol-5-ylthio)ethoxy)-quinazoline** hydrochloride (50mg, 44%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 3.8(t, 2H); 3.97(s, 6H); 4.57(t, 2H); 7.35(s, 1H); 7.46(dd, 1H); 7.62(t, 1H); 7.70(dd, 1H); 8.12(s, 1H); 8.87(s, 1H)

MS - ESI: 462 $[MH]^+$

Elemental Analysis:	Found	C 45.1	H 3.7	N 19.3
$C_{19}H_{17}N_7O_2ClFS\ 0.5H_2O\ 1HCl$	Requires	C 45.0	H 3.8	N 19.3%

Example 53

Diethyl azodicarboxylate (295µl, 1.8mmol) was added dropwise to a solution of 2-methyl-1-(3-hydroxypropyl)imidazole (131mg, 0.93mmol), (EP 0060696 A1), triphenylphosphine (492mg, 1.8mmol) and 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (200mg, 0.62mmol), (prepared as described for the starting material in Example 24), in methylene chloride (4ml) and the mixture stirred for 2 hours at ambient temperature. Further 2-methyl-1-(3-hydroxypropyl)imidazole (43mg, 0.31mmol), triphenylphosphine (82mg, 0.31mmol) and diethyl azodicarboxylate (50µl, 0.31mmol) were added and the mixture stirred for a further 3 hours. The volatiles were removed by evaporation and the residue was purified by column chromatography eluting with methylene chloride/methanol (93/7). The purified solid was dissolved in methylene chloride and 3M ethereal hydrogen chloride (2ml) was added. The volatiles were removed by evaporation and the solid residue was suspended in ether, collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(2-methylimidazol-1-yl)propoxy)quinazoline** hydrochloride (104mg, 32%).

^{1}H NMR Spectrum: (DMSOd_6; CF_3COOD) 2.4(t, 2H); 2.60(s, 3H); 4.0(s, 3H); 4.3-4.4(m, 4H); 7.41(s, 1H); 7.46(dd, 1H); 7.58(s, 1H); 7.62(t, 1H); 7.67(dd, 1H); 7.70(s, 1H); 8.21(s, 1H); 8.88(s, 1H)

MS - ESI: 442 $[MH]^+$

Elemental Analysis:	Found	C 49.8	H 5.0	N 12.5
$C_{22}H_{21}N_5O_2ClF$ $1H_2O$ 2HCl 0.23ether	Requires	C 50.1	H 5.0	N 12.7%

Example 54

A solution of 4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(methylaminoethoxy)quinazoline hydrochloride hydrate (135mg, 0.3mmol) and 2-chloropyrimidine (66mg, 0.6mmol) in N,N-diisopropylethylamine (2ml) was heated at reflux for 1 hour. The mixture was allowed to cool and was triturated with ether. The solid product was collected by filtration and purified by column chromatography eluting with methylene chloride/methanol (95/5). The purified oil was crystallised from ether and the solid collected by filtration. The solid was dissolved in methylene chloride/methanol and a solution of 3M ethereal hydrogen chloride (0.5ml) was added. The suspension was diluted with ether, the

solid product collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-methyl-N-(pyrimidin-2-yl)amino)ethoxy)quinazoline** hydrochloride (52mg, 33%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 3.36(s, 3H); 3.9(s, 3H); 4.22(t, 2H); 4.51(t, 2H); 6.94(t, 1H); 7.36(s, 1H); 7.46(d, 1H); 7.63(t, 1H); 7.66(dd, 1H); 8.08(s, 1H); 8.62(d, 2H); 8.9(s, 1H)

MS - ESI: 455 $[MH]^+$

Elemental Analysis:	Found	C 49.8	H 4.4	N 15.9
$C_{22}H_{20}N_6O_2ClF$ 1.1H_2O 1.5HCl	Requires	C 49.9	H 4.5	N 15.9%

The starting material was prepared as follows:

A solution of di-t-butyl dicarbonate (4.52g, 20mmol) in THF (10ml) was added to a solution of 2-(methylamino)ethanol (1.5g, 20mmol) in water (10ml) and THF (10ml) and the mixture was stirred for 18 hours at ambient temperature. The organic solvents was removed by evaporation and the residue was partitioned between water and ether. The organic layer was separated, washed with 0.1M hydrochloric acid and brine, dried ($MgSO_4$) and the solvent removed by evaporation to give 2-(N-methyl-N-t-butoxycarbonylamino)ethanol (3g, 85%) as an oil.

^{1}H NMR Spectrum: ($CDCl_3$) 1.46(s, 9H); 2.92(s, 3H); 3.39(t, 2H); 3.74(t, 2H)

MS - ESI: 176 $[MH]^+$

A solution of 2-(N-methyl-N-t-butoxycarbonylamino)ethanol (116mg, 0.7mmol) in methylene chloride (1ml) was added to a suspension of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (160mg, 0.5mmol), (prepared as described for the starting material in Example 24), and triphenylphosphine (393mg, 1.5mmol) in methylene chloride (5ml). Diethyl azodicarboxylate (261mg, 1.5mmol) was then added dropwise and the mixture was stirred at ambient temperature for 4 hours. The reaction mixture was poured onto a column of silica and eluted with a gradient of methylene chloride/acetonitrile/methanol (70/30/0 to 70/20/10). The partially purified product was further purified by column chromatography eluting with a gradient of methylene chloride/ether/methanol (60/40/0 to 60/10/30). The pure oil was crystallised from ether, collected by filtration and washed with

ether to give 4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-methyl-N-t-butoxycarbonylamino)ethoxy)quinazoline (450mg, 63%).

m.p. 194-196°C

^{1}H NMR Spectrum: ($CDCl_3$) 1.46(s, 9H); 3.05(br s, 3H); 3.72(br s, 2H); 4.02(s, 3H); 4.27(br s, 2H); 7.0(s, 1H); 7.2-7.3(m, 3H); 8.54(t, 1H); 8.69(s, 1H)

MS - ESI: 499 $[MNa]^+$

Elemental Analysis:	Found	C 57.2	H 5.7	N 11.5
$C_{23}H_{26}N_4O_4ClF\ 0.3H_2O$	Requires	C 57.3	H 5.6	N 11.6%

TFA (4ml) was added to a solution of 4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-methyl-N-t-butoxycarbonylamino)ethoxy)quinazoline (390mg, 0.82mmol) in methylene chloride (4ml) and the mixture stirred for 2 hours at ambient temperature. Toluene was added and the volatiles were removed by evaporation. The residue was dissolved in methylene chloride and 3M ethereal hydrogen chloride (1ml) was added. The resulting precipitate was collected by filtration, washed with ether and dried under vacuum to give 4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(methylamino)ethoxy)quinazoline hydrochloride hydrate (290mg; 79%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 2.74(s, 3H); 3.53(t, 2H); 4.05(s, 3H); 4.53(t, 2H); 7.46(d, 1H); 7.47(s, 1H); 7.6-7.7(m, 2H); 8.24(s, 1H); 8.91(s, 1H)

MS - ESI: 377 $[MH]^+$

Elemental Analysis:	Found	C 45.8	H 5.0	N 12.0
$C_{18}H_{18}N_4O_2ClF\ 1.1H_2O\ 2HCl$	Requires	C 46.0	H 4.8	N 11.9%

Example 55

Isonicotinoyl chloride (36mg, 0.2mmol) was added to a suspension of 4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(methylamino)ethoxy)quinazoline hydrochloride hydrate (90mg, 0.1mmol), (prepared as described for the starting material in Example 54), in methylene chloride (3ml) and triethylamine (80mg, 0.8mmol) was then added dropwise. The mixture was stirred for 30 minutes at ambient temperature and the solvent was then removed by evaporation. The residue was partitioned between ethyl acetate and water, the organic layer was separated, washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was dissolved in methylene chloride/methanol and 3M ethereal

hydrogen chloride (0.5ml) was added. The suspension was diluted with ether, the precipitate was collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-methyl-N-(4-pyridylcarbonyl)amino)ethoxy)quinazoline** hydrochloride (75mg, 67%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD; 95°C) 3.1(s, 3H); 3.8-3.9(br s, 2H); 4.1(s, 3H); 4.4-4.6(br s, 2H); 7.4-7.45(m, 2H); 7.55(dd, 1H); 7.65(t, 1H); 7.9-8.0(br s, 2H); 8.28(s, 1H); 8.8(s, 1H); 8.95(s, 2H)

MS - ESI: 482 $[MH]^+$

Elemental Analysis:	Found	C 51.7	H 4.6	N 12.0
$C_{24}H_{21}N_5O_3ClF\ 1H_2O\ 1.7HCl$ 0.1ether	Requires	C 51.5	H 4.6	N 12.3%

Example 56

A mixture of 7-(4-pyridylthio)-3,4-dihydroquinazolin-4-one (100mg, 0.4mmol), thionyl chloride (20ml) and DMF (0.1ml) was heated at reflux for 1.5 hours. The volatiles were removed by evaporation and the residue azeotroped with toluene. A solution of 3-hydroxy-4-methylaniline (53mg, 0.04mmol) in isopropanol (10ml) was added to the solid residue and the mixture was heated at reflux for 2 hours. The mixture was allowed to cool and the precipitated product collected by filtration, washed with isopropanol and dried to give **4-(3-hydroxy-4-methylanilino)-7-(4-pyridylthio)quinazoline** hydrochloride(103mg, 73%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.17(s, 3H); 7.05(dd, 1H); 7.17(d, 1H); 7.19(s, 1H); 7.64(d, 2H); 8.00(d, 1H); 8.20(s, 1H); 8.66(d, 2H); 8.92(s, 1H); 9.05(d, 1H)

MS - ESI: 361 $[MH]^+$

Elemental analysis:	Found	C 53.2	H 4.6	N 11.8
$C_{20}H_{16}N_4OS\ 1H_2O\ 2HCl$	Requires	C 53.2	H 4.4	N 12.4%

The starting material was prepared as follows:

A solution of 2-amino-4-fluorobenzoic acid (3g, 19.3mmol) in formamide (30ml) was heated at 150°C for 6 hours. The reaction mixture was poured onto ice/water 1/1 (250ml). The precipitated solid was collected by filtration, washed with water and dried to give 7-fluoro-3,4-dihydroquinazolin-4-one (2.6g, 82%).

Sodium hydride (3.3g of a 50% suspension in mineral oil, 69mmol) was added to a solution of 4-mercaptopyridine (8.12g, 73mmol) in DMF (100ml) and the mixture stirred for 30 minutes. 7-Fluoro-3,4-dihydroquinazolin-4-one (1.5g, 9mmol) was added and the reaction heated at 100°C for 4 hours. The mixture was allowed to cool, diluted with water and extracted with ethyl acetate. The organic extracts were washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (97/3) to give 7-(4-pyridylthio)-3,4-dihydroquinazolin-4-one (500mg, 6%).

^{1}H NMR Spectrum: ($DMSOd_6$) 7.24(d, 2H); 7.54(dd, 1H); 7.70(d, 1H); 8.10(s, 1H); 8.14(d, 1H); 8.44(d, 2H)

MS - ESI: 256 $[MH]^+$

Example 57

A mixture of 4-chloro-2-fluoro-3-hydroxyaniline (118mg, 0.7mmol), (EP 061741 A2), and 4-chloro-6-methoxy-7-((4-pyridyl)methoxy)quinazoline (200mg, 0.7mmol), (prepared as described for the starting material in Example 13), in isopropanol (10ml) and ethereal hydrogen chloride (5ml) was heated at 80°C for 2 hours and the mixture was allowed to cool. The precipitated product was collected by filtration, washed with isopropanol and dried to give **4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-((4-pyridyl)methoxy)quinazoline** hydrochloride (110mg, 31%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.96(s, 3H); 5.38(s, 2H); 7.14(d, 1H); 7.24(s, 1H); 7.38(d, 1H); 7.48(d, 2H); 7.82(s, 1H); 8.32(s, 1H); 8.58(d, 2H0; 9.48(s, 1H)

MS - ESI: 427 $[MH]^+$

Example 58

A mixture of 7-((2-chloro-4-pyridyl)methoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (150mg, 0.47mmol), phosphoryl chloride (0.2ml) and N,N-dimethylaniline (0.2ml) in toluene (5ml) was heated at reflux for 1 hour. The volatiles were removed by evaporation and the residue was partitioned between ethyl acetate and saturated sodium hydrogen carbonate solution. The organic layer was separated, dried ($MgSO_4$) and the solvent removed by evaporation. A solution of 2-fluoro-5-hydroxy-4-methylaniline (67mg, 0.47mmol), (prepared

as described for the starting material in Example 13), in isopropanol (10ml) was added to the solid residue and the mixture was heated at reflux for 2 hours. The mixture was allowed to cool and the precipitated product collected by filtration, washed with acetone and dried to give **7-((2-chloro-4-pyridyl)methoxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline** hydrochloride (70mg, 30%).

m.p. 245-250°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.30(s, 3H); 4.10(s, 3H); 5.45(s, 2H); 6.90(d, 1H); 7.10(d, 1H); 7.35(s, 1H); 7.50(d, 1H); 7.65(s, 1H); 8.25(s, 1H); 8.45(d, 1H); 8.75(s, 1H); 9.60(br s, 1H); 11.30(s, 1H)

MS - ESI: 441 $[MH]^+$

Elemental analysis:	Found	C 53.7	H 4.0	N 10.9
$C_{22}H_{18}N_4O_3FCl\ 1H_2O\ 1HCl$	Requires	C 53.4	H 4.3	N 11.3%

The starting material was prepared as follows:

Oxalyl chloride (0.3ml) was added to a mixture of 4-(2-chloropyridine)carboxylic acid (950mg, 6mmol) and DMF (0.05ml) in methylene chloride (20ml) and the mixture stirred at ambient temperature for 1 hour. The volatiles were removed by evaporation and ethanol (10ml) was added to the residue and the mixture stirred at ambient temperature for 18 hours. Water was added and the mixture was extracted with ethyl acetate (3x25ml). The extracts were combined, dried ($MgSO_4$) and the solvent removed by evaporation to give ethyl 4-(2-chloropyridine)carboxylate (700mg, 63%) as a brown oil.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.30(t, 3H); 4.37(q, 2H); 7.80(m, 2H); 8.60(d, 1H)

Lithium aluminium hydride (5ml of a 1M solution in ether, 5mmol) was added dropwise to a stirred solution of ethyl 4-(2-chloropyridine)carboxylate (700mg, 3.8mmol) in ether (10ml) at 0°C. The mixture was allowed to warm to ambient temperature, wet ether and 2M sodium hydroxide solution (2ml). The insolubles were removed by filtration, the organic phase was separated and the aqueous layer was extracted with ether (3x25ml). The extracts were combined, dried ($MgSO_4$) and the solvent removed by evaporation to give 2-chloro-4-hydroxymethylpyridine (180mg, 33%) as a brown oil which crystallised on standing.

^{1}H NMR Spectrum: ($DMSOd_6$) 4.55(s, 2H); 5.50(br s, 1H); 7.32(d, 1H); 7.20(s, 1H); 8.30(d, 1H)

A mixture of 2-chloro-4-hydroxymethylpyridine (180mg, 1.25mmol), thionyl chloride (0.2ml) in toluene (10ml) was stirred at ambient tempertaure for 1 hour. The volatiles were removed by evaporation to give 2-chloro-4-chloromethylpyridine hydrochloride (180mg, 0.9mmol). A mixture of 7-hydroxy-6-methoxy-4-phenoxyquinazoline (268mg, 1mmol), (prepared as described for the starting material in Example 13), potassium carbonate (680mg, 5mmol) and DMF (10ml) was added to this crude product and the mixture was heated at 90°C for 1 hour. The mixture was allowed to cool, diluted with water and extracted with ethyl acetate (3x70ml). The extracts were combined, washed with water (x3) and brine, dried ($MgSO_4$) and the solvent removed by evaporation to give 7-((2-chloro-4-pyridyl)methoxy)-6-methoxy-4-phenoxyquinazoline (260mg, 66%) as a solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 4.00(s, 3H); 5.45(s, 2H); 7.30(m, 3H); 7.42(s, 1H); 7.4-7.5(m, 3H); 7.60(s, 1H); 7.62(s, 1H); 8.44(d, 1H); 8.52(s, 1H)

MS - ESI: 394 $[MH]^+$

A mixture of 7-((2-chloro-4-pyridyl)methoxy)-6-methoxy-4-phenoxyquinazoline (260mg, 0.7mmol) and 2M hydrochloric acid (15ml) was heated at 85°C for 2 hours. The mixture was allowed to cool and adjusted to pH6-7 with sodium hydrogen carbonate solution. The resulting precipitate was collected by filtration and dried to give 7-((2-chloro-4-pyridyl)methoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (160mg, 76%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.90(s, 3H); 5.36(s, 2H); 7.18(s, 1H); 7.45(m, 2H); 7.46(s, 1H); 7.59(s, 1H); 8.42(d, 1H)

MS - ESI: 318 $[MH]^+$

Example 59

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (950mg, 3mmol), (prepared as described for the starting material in Example 24), 2-bromo-4-bromomethylpyridine (765mg, 3mmol) and potassium carbonate (2.38g 17mmol) in DMF (10ml) was heated at 80°C for 2 hours. The mixture was allowed to cool, poured into water and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and the solvent removed by evaporation and azeotroped with toluene. The residue was triturated with ethyl acetate/hexane and the solid product collected by filtration, washed with ethyl acetate/hexane

and dried to give **7-((2-bromo-4-pyridyl)methoxy)-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline** (647mg, 44%).

m.p. 210-212°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.98(s, 3H); 5.40(s, 2H); 7.25(s, 1H); 7.30(d, 1H); 7.50(s, 1H); 7.50(d, 1H); 7.55(m, 2H); 7.74(s, 1H); 7.86(s, 1H); 8.35(br s, 1H); 8.42(d, 1H); 9.56(s, 1H)

MS - ESI: 489 $[MH]^+$

Elemental analysis:	Found	C 52.0	H 3.2	N 11.2
$C_{21}H_{15}N_4O_2BrClF$	Requires	C 51.5	H 3.1	N 11.4%

The starting material was prepared as follows:

A mixture of 2-bromo-4-methylpyridine (12.2g), N-bromosuccinimide (30g) and 2,2`-azobis(2-methylpropionitrile) (100mg) in carbon tetrachloride (200ml) was heated at reflux for 2.5 hours. The mixture was allowed to cool and the insoluble material removed by filtration. The solvent was removed from the filtrate by evaporation and the residue was purified by filtration through a silica pad eluting with ethyl acetate/hexane (10/1) to give 2-bromo-4-bromomethylpyridine.

^{1}H NMR Spectrum: ($DMSOd_6$) 4.65(s, 2H); 7.50(d, 1H); 7.42(s, 1H); 7.70(s, 1H); 8.35(d, 1H)

MS - ESI: 250 $[MH]^+$

Example 60

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (600mg, 2mmol), (prepared as described for the starting material in Example 24), 4-chloromethyl-2-cyanopyridine hydrochloride (620mg, 3mmol) and potassium carbonate (1.0g 7mmol) in DMF (8ml) was heated at 80°C for 30 minutes. The mixture was allowed to cool, poured into water and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and the solvent removed by evaporation and azeotroped with toluene. The residue was triturated with ethyl acetate/hexane, the solid product collected by filtration and purified by column chromatography eluting with ethyl acetate and further chromatography eluting with methylene chloride/methanol (99/1). The purified product was recrystallised from ethyl

acetate/hexane to give **4-(4-chloro-2-fluoroanilino)-7-((2-cyano-4-pyridyl)methoxy)-6-methoxyquinazoline** (35mg, 4%).

m.p. 209-213°C

^{1}H NMR Spectrum: (DMSOd_6) 3.98(s, 3H); 5.44(s, 2H); 7.26(s, 1H); 7.34(dd, 1H); 7.53(dd, 1H); 7.58(d, 1H); 7.80(d, 1H); 7.85(s, 1H); 8.27(s, 1H); 8.35(s, 1H); 8.80(d, 1H); 9.60(s, 1H)

MS - ESI: 436 [MH]$^+$

Elemental analysis:	Found	C 60.3	H 3.4	N 16.1
$C_{22}H_{15}N_5O_2ClF$	Requires	C 60.6	H 3.5	N 16.1%

The starting material was prepared as follows:

Tetrabutyl ammonium fluoride (9ml of a 1M solution in THF, 9mmol) was added to a solution of 2-cyano-4-dimethyl-t-butylsilyloxymethylpyridine (1.4g, 5.6mmol), (J.Het. Chem. 1993, **30**, 631), in THF (15ml) and the mixture was stirred for 2 hours at ambient temperature. Water was added and the volatiles were removed by evaporation. The residue was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and the solvent removed by evaporation to give 2-cyano-4-hydroxymethylpyridine (0.55g, 73%).

^{1}H NMR Spectrum: (DMSOd_6) 4.65(s, 2H); 5.70(t, 1H); 7.70(d, 1H); 7.95(s, 1H); 8.75(d, 1H)

A mixture of 2-cyano-4-hydroxymethylpyridine (0.51g, 3.8mmol) and thionyl chloride (0.6ml) in toluene (20ml) was stirred at room temperature for 1 hour. The volatiles were removed by evaporation and the residue azeotroped with toluene to give 4-chloromethyl-2-cyanopyridine hydrochloride (620mg, 86%).

^{1}H NMR Spectrum: (DMSOd_6) 4.75(s, 2H); 7.75(dd, 1H); 8.05(s, 1H); 8.34(d, 1H)

Example 61

A mixture of 7-((6-chloro-2-oxo-1,2-dihydropyrid-4-yl)methoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (190mg, 0.4mmol), thionyl chloride (5ml) and DMF (0.1ml) was heated at reflux for 2 hours. The volatiles were removed by evaporation and the residue azeotroped with toluene. A solution of 4-chloro-2-fluoroaniline (1ml) in isopropanol (15ml) was added to the solid residue and the mixture was heated at reflux for 3 hours. The mixture was allowed to cool and the precipitated product collected by filtration, washed with

isopropanol and dried to give **4-(4-chloro-2-fluoroanilino)-7-((6-chloro-2-oxo-1,2-dihydropyrid-4-yl)methoxy)-6-methoxyquinazoline** hydrochloride (110mg, 41%).
m.p. 271-273°C (decomp.)
^{1}H NMR Spectrum: (DMSOd_6) 4.08(s, 3H); 5.35(s, 2H); 6.70(s, 1H); 7.00(s, 1H); 7.30(s, 1H); 7.40(d, 1H); 7.60(m, 2H); 8.30(s, 1H); 8.75(s, 1H)
MS - ESI: 461 [MH]$^+$

The starting material was prepared as follows:

A mixture of 2,6-dichloro-4-hydroxymethylpyridine (1.72g, 16mmol) and 40% aqueous sodium hydroxide solution (5ml) in methanol (50ml) was heated at reflux for 24 hours. The mixture was allowed to cool and the volatiles removed by evaporation. The residue was extracted with ethyl acetate and the solvent removed from the extracts by evaporation. The residue was recrystallised from ethyl acetate/hexane to give 2-chloro-4-hydroxymethyl-6-methoxypyridine (490mg, 28%).
^{1}H NMR Spectrum: (DMSOd_6) 3.80(s, 3H); 4.45(d, 2H); 5.45(t, 1H); 6.70(s, 1H); 6.98(s, 1H)

Thionyl chloride (1.0ml) was added to a solution of 2-chloro-4-hydroxymethyl-6-methoxypyridine (0.9g, 5.2mmol) in toluene (10ml) and the mixture stirred at ambient temperature for 1 hour. The volatiles were removed by evaporation, the residue was azeotroped with toluene and dried under vacuum to give 2-chloro-4-chloromethyl-6-methoxypyridine hydrochloride (0.88g, 74%).
^{1}H NMR Spectrum: (DMSOd_6) 3.85(s, 3H); 4.70(s, 2H); 6.90(s, 1H); 7.15(s, 1H)

A mixture of 7-hydroxy-6-methoxy-4-phenoxyquinazoline (1.1g, 4.1mmol), (prepared as described for the starting material in Example 13), 2-chloro-4-chloromethyl-6-methoxypyridine hydrochloride (0.88g, 3.9mmol) and potassium carbonate (2.0g, 14mmol) in DMF (20ml) was heated at 80°C for 1 hour. The mixture was allowed to cool, diluted with water and the precipitated product collected by filtration, washed with water and dried to give 7-((2-chloro-6-methoxy-4-pyridyl)methoxy)-6-methoxy-4-phenoxyquinazoline (1.38g, 79%).
^{1}H NMR Spectrum: (CDCl_3) 3.95(s, 3H); 4.04(s, 3H); 5.20(s, 2H); 6.70(s, 1H); 6.95(s, 1H); 7.18(m, 3H); 7.30(t, 1H); 7.40(t, 2H); 7.58(s, 1H); 8.52(s, 1H)
MS - ESI: 424 [MH]$^+$

A mixture of 7-((2-chloro-6-methoxy-4-pyridyl)methoxy)-6-methoxy-4-phenoxyquinazoline (400mg, 0.95mmol) and 2M hydrochloric acid (20ml) was heated at reflux for 3 hours. The mixture was allowed to cool and adjusted to pH6-7 with aqueous ammonia solution. The resulting precipitate was collected by filtration washed with water and dried to give crude 7-((6-chloro-2-oxo-1,2-dihydropyrid-4-yl)methoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (190mg, 60%).

Example 62

Thionyl chloride (0.6ml) was added to a solution of 4-hydroxymethyl-2-methoxypyridine (0.59g, 4.2mmol) in toluene (10ml) and the mixture stirred at ambient temperature for 1.5 hours. The volatiles were removed by evaporation and the residue was azeotroped with toluene and dried under vacuum to give crude 4-chloromethyl-2-methoxypyridine hydrochloride (0.50g, 2.6mmol) which was used directly. This product was then added to a mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (420mg, 1.3mmol), (prepared as described for the starting material in Example 24), and potassium carbonate (1.0g 7mmol) in DMF (8ml) and the resulting mixture was heated at 75°C for 2 hours. The mixture was allowed to cool, diluted with water and the precipitated solid collected by filtration, washed with water and dried to give **4-(4-chloro-2-fluoroanilino)-7-((2-methoxy-4-pyridyl)methoxy)-6-methoxyquinazoline** (140mg, 25%).

m.p. 202-204°C

^{1}H NMR Spectrum: (DMSOd_6) 3.85(s, 3H); 3.98(s, 3H); 5.35(s, 2H); 6.88(s, 1H); 7.05(d, 1H); 7.24(s, 1H); 7.35(dd, 1H); 7.54(dd, 1H); 7.58(t, 1H); 7.84(s, 1H); 8.11(d, 1H); 8.35(s, 1H); 9.58(br s, 1H)

MS - ESI: 441 $[MH]^+$

Elemental analysis:	Found	C 59.9	H 4.1	N 12.4
$C_{22}H_{18}N_4O_3ClF$	Requires	C 59.9	H 4.1	N 12.7%

The starting material was prepared as follows:

A mixture of ethyl 2-hydroxy-pyridine-4-carboxylate (1.0g, 6mmol), (Chem. Abs. 1957, 8740c), methyl iodide (1ml) and silver(I)carbonate (1.64g) in toluene (20ml) was heated at reflux for 2 hours. The mixture was allowed to cool and the insolubles removed by

filtration through diatomaceous earth and the pad was washed through with ethyl acetate. The filtrate was washed with water, dried ($MgSO_4$) and the solvent removed by evaporation to give ethyl 2-methoxy-pyridine-4-carboxylate (0.93g, 86%) as a yellow oil.

^{1}H NMR Spectrum: ($CDCl_3$) 1.30(t, 3H); 3.90(s, 3H); 4.30(q, 2H); 7.24(s, 1H); 7.35(d, 1H); 8.20(d, 1H)

MS - ESI: 182 [MH]$^+$

A solution of ethyl 2-methoxy-pyridine-4-carboxylate (0.93g, 5mmol) in ether (5ml) was added to lithium aluminium hydride (0.3g, 8mmol) in ether (10ml) cooled to 5°C and the mixture stirred for 2 hours. Water was added, the mixture was filtered through diatomaceous earth and the pad was washed through with ethyl acetate. The filtrate was extracted with ethyl acetate and the combined extracts were washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation to give 4-hydroxymethyl-2-methoxypyridine (0.64g, 89%) as a yellow oil.

^{1}H NMR Spectrum: ($CDCl_3$) 3.86(s, 3H); 4.62(s, 2H); 6.65(s, 1H); 6.76(d, 1H); 8.05(d, 1H)

MS - ESI: 140 [MH]$^+$

Example 63

Thionyl chloride (0.3ml) was added to a solution of 4-hydroxymethyl-2-methylpyridine (240mg, 1.9mmol) in toluene (10ml) and the mixture stirred at ambient temperature for 2 hours. The volatiles were removed by evaporation, the residue azeotroped with toluene and dried under vacuum to give crude 4-chloromethyl-2-methylpyridine hydrochloride which was used directly. This product was then added to a mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (510mg, 1.6mmol), (prepared as described for the starting material in Example 24), and potassium carbonate (1.4g 10mmol) in DMF (8ml) for 90 hours. The mixture was diluted with water and the precipitated solid collected by filtration, washed with water and dried to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((2-methyl-4-pyridyl)methoxy)quinazoline** (290mg, 43%), a sample was recrystallised from ethyl acetate/hexane.

m.p. 221-224°C

^{1}H NMR Spectrum: ($CDCl_3$) 2.50(s, 3H); 4.00(s, 3H); 5.20(s, 2H); 6.98(s, 1H); 7.15(d, 1H); 7.2(m, 4H); 8.45(m, 2H); 8.60(s, 1H)

Elemental analysis:	Found	C 61.7	H 4.2	N 13.2
$C_{22}H_{18}N_4O_2ClF$	Requires	C 62.2	H 4.3	N 13.2%

The starting material was prepared as follows:

Oxalyl chloride (1.9g, 15mmol) was added to 2-chloro-6-methyl-pyridine-4-carboxylic acid (1.7g, 10mmol) in methylene chloride (30ml) and the mixture stirred for 2 hours. The volatiles were removed by evaporation and methanol (20ml) added to the residue. The mixture was stirred for 1 hour and the volatiles removed by evaporation to give methyl 2-chloro-6-methyl-pyridine-4-carboxylate (1.85g, 100%) as an off-white solid.

^{1}H NMR Spectrum: ($CDCl_3$) 2.55(s, 3H); 3.90(s, 3H); 7.55(s, 1H); 7.60(s, 1H);
MS - ESI: 186 $[MH]^+$

A mixture of methyl 2-chloro-6-methyl-pyridine-4-carboxylate (1.8g, 10mmol) and 10% palladium-on-charcoal catalyst (200mg) in methanol (100ml) was stirred under hydrogen at 5 atmospheres pressure. The catalyst was removed by filtration and the volatiles removed from the filtrate by evaporation. The residue was treated with 10% aqueous sodium hydroxide solution and extracted with ether (3x30ml). The combined extracts were dried ($MgSO_4$) and the solvent removed by evaporation to give methyl 2-methyl-pyridine-4-carboxylate (800mg, 53%) as an oil.

A solution of methyl 2-methyl-pyridine-4-carboxylate (800mg, 6mmol) in ether (5ml) was added to lithium aluminium hydride (340mg, 9mmol) in ether (10ml) cooled to 5°C and the mixture stirred for 2 hours. Water was added, the mixture was filtered through diatomaceous earth and the pad was washed through with ethyl acetate. The filtrate was extracted with ethyl acetate and the combined extracts were washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation to give 4-hydroxymethyl-2-methylpyridine (240mg, 38%) as a yellow oil.

^{1}H NMR Spectrum: ($CDCl_3$) 2.48(s, 3H); 5.44(s, 2H); 7.00(d, 1H); 7.10(s, 1H); 8.40(d, 1H)
MS - ESI: 124 $[MH]^+$

Example 64

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (350mg, 0.9mmol), (prepared as described for the starting material in Example 24), 2-(2-

chloroethylthio)-1-methylimidazole hydrochloride (203mg, 0.95mmol) and potassium carbonate (303mg 2.2mmol) in NMP (20ml) was heated at 90°C for 2 hours. The mixture was allowed to cool, diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (100/0 increasing to 90/10) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1-methylimidazol-2-ylthio)ethoxy)quinazoline** (75mg, 17%) as a solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 3.46(s, 3H); 3.93(s, 3H); 4.39-4.44(m, 4H); 7.13(dd, 2H); 7.23(s, 1H); 7.31(dd, 1H); 7.49-7.60(m, 2H); 7.79(s, 1H); 8.37(s, 1H); 9.51(s, 1H)

MS - ESI: 460 $[MH]^+$

Elemental analysis:	Found	C 52.8	H 4.0	N 14.3
$C_{21}H_{19}N_4O_2ClFS\ 1H_2O$	Requires	C 52.8	H 4.4	N 14.7%

The starting material was prepared as follows:

2-Chloroethanol (3g, 37mmol) was added to a solution of 2-mercapto-1-methylimidazole (3.45g, 30mmol) in 2M aqueous sodium hydroxide solution (30ml) and the mixture heated at 100°C for 2 hours. The mixture was allowed to cool and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and the solvent removed by evaporation to give 2-(2-hydroxyethylthio)-1-methylimidazole (3.9g, 82%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.04(t, 2H); 3.30(s, 3H); 3.54(t, 2H); 5.00(s, 1H); 6.87(s, 1H); 7.20(s, 1H)

Thionyl chloride (1.41ml, 19mmol) was slowly added to a solution of 2-(2-hydroxyethylthio)-1-methylimidazole (1.81g, 11mmol) in trichloromethane (20ml) at 5°C. The mixture was stirred for 1 hour at 5°C and then for 3 hours at ambient temperature. The volatiles were removed by evaporation and the residue azeotroped with toluene to give 2-(2-chloroethylthio)-1-methylimidazole hydrochloride (1.5g, 77%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.58 (t, 2H); 3.78(s, 3H); 3.80(t, 2H); 7.78(d, 1H); 7.83(d, 1H)

Example 65

Thionyl chloride (0.55ml, 7.5mmol) was added to a solution of 1-(3-hydroxypropyl)-1.2dihyro-2-pyridone (770mg, 5mmol) in trichloromethane (15ml) at 5°C. The mixture was

stirred at 5°C for 1 hour and then at ambient temperature for 2 hours. The volatiles were removed by evaporation, the residue azeotroped with toluene and dried under vacuum to give crude 1-(3-chloropropyl)-1,2-dihydro-2-pyridone (500mg) which was used directly. Part of this product (206mg, 1.2mmol) was then added to a mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (350mg, 1.0mmol), (prepared as described for the starting material in Example 24), and potassium carbonate (303mg, 2.2mmol) in NMP (20ml) and the reaction mixture was heated at 90°C for 2 hours. The mixture was allowed to cool, diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol mixtures (100/0 increasing to 95/5) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(2-oxo-1,2-dihydro-1-pyridyl)propoxy)quinazoline** (194mg, 50%).

m.p. 216-218°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.18(m, 2H); 3.90(s, 3H); 4.06(t, 2H); 4.15(t, 2H); 6.18(t, 1H); 6.38(d, 1H); 7.15(s, 1H); 7.30-7.42(m, 2H); 7.50-7.64(m, 3H); 7.79(s, 1H); 8.34(s, 1H); 9.50(s, 1H)

MS - ESI: 455 $[MH]^+$

Elemental analysis:	Found	C 59.4	H 4.6	N 12.1
$C_{23}H_{20}N_4O_3ClF\ 0.5H_2O$	Requires	C 59.6	H 4.6	N 12.1%

The starting material was prepared as follows:

Sodium hydride (1.31g of a 50% suspension in mineral oil, 27mmol) was added to a solution of 2-hydroxypyridine (2.35g, 24mmol) in DMF (50ml) and the mixture stirred for 30 minutes. 2-(3-Bromopropoxy)tetrahydropyran (5.0g, 22.5mmol), (J. Chem. Soc. 1963, 3440), was added and the mixture heated at 100°C for 3 hours and then stirred at ambient temperature for 18 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol mixtures (100/0 increasing to 97/3) to give:

1-(3-(2-tetrahydropyranyloxy)propyl)-1,2-dihydro-2-pyridone (1.6g, 30%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.39-1.75(m, 6H); 1.85(m, 2H); 3.24-3.42(m, 3H); 3.58-3.74(m, 2H); 3.90(t, 2H); 4.52(s, 1H); 6.18(t, 1H); 6.35(d, 1H); 7.38(dd, 1H); 7.60(dd,1H)
MS - ESI: 238 $[MH]^+$
and
2-(3-(2-tetrahydropyranyloxy)propyloxy)pyridine (1.43g, 27%).
^{1}H NMR Spectrum: ($DMSOd_6$) 1.38-1.70(m, 6H); 1.90(m, 2H); 3.30(m, 3H); 3.34-3.50(m, 2H); 3.62-3.80(m, 2H); 4.30(t, 2H); 4.52(s, 1H); 6.78(d, 1H); 6.92(dd, 1H); 7.64(m, 1H); 8.15(dd,1H)
MS - ESI: 238 $[MH]^+$

A solution of 1-(3-(2-tetrahydropyranyloxy)propyl)-1,2-dihydro-2-pyridone (1.0g, 4.5mmol) in acetic acid (8ml), THF (4ml) and water (2ml) was heated at 50°C for 4 hours. The volatiles were removed by evaporation and the residue azeotroped with toluene to give 1-(3-hydroxypropyl)-1,2-dihydro-2-pyridone (680mg, 99%) as an off-white solid.
^{1}H NMR Spectrum: ($DMSOd_6$) 1.74(m, 2H); 3.38(m, 2H); 3.90(t, 2H); 4.58(s, 1H); 6.18(dd, 1H); 6.38(d, 1H); 7.38(m, 1H); 7.60(dd, 1H)

Example 66

Thionyl chloride (0.80ml, 11mmol) was added to a solution of 2-(3-hydroxypropylthio)-1-methylimidazole (1.25g, 7.3mmol) in trichloromethane (25ml) at 5°C. The mixture was stirred at 5°C for 1 hour and then at ambient temperature for 2 hours. The volatiles were removed by evaporation, the residue azeotroped with toluene and dried under vacuum to give crude 2-(3-chloropropylthio)-1-methylimidazole hydrochloride (1.0g) which was used directly. Part of this product (226mg, 1.0mmol) was added to a mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (350mg, 1.0mmol), (prepared as described for the starting material in Example 24), and potassium carbonate (303mg 2.2mmol) in NMP (20ml) and the mixture was heated at 90°C for 2 hours. The mixture was allowed to cool, diluted with water and extracted with ethyl acetate. The combined extracts were wahed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (100/0 increasing to 95/5) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(1-methylimidazol-2-ylthio)propoxy)quinazoline** (29mg, 6%).

m.p. 199-201°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.22(m, 2H); 3.44(s, 3H); 3.94(s, 3H); 4.10(m, 4H); 7.10(d, 2H); 7.30(dd, 1H); 7.50-7.60(m, 2H); 7.79(s, 1H); 8.34(s, 1H); 9.50(s, 1H)

MS - ESI: 474 [MH]$^+$

Elemental analysis:	Found	C 50.9	H 4.8	N 13.2
$C_{22}H_{21}N_5O_2ClFS\ 2.5H_2O$	Requires	C 50.9	H 5.1	N 13.5%

The starting material was prepared as follows:

Sodium hydride (0.95g of a 50% suspension in mineral oil, 20mmol) was added to a solution of 2-mercapto-1-methylimidazole (2.26g, 19mmol) in DMF (100ml) and the mixture stirred for 30 minutes. 2-(3-Bromopropoxy)tetrahydropyran (5.0g, 22.5mmol), (J. Chem. Soc. 1963, 3440), was added and the mixture heated at 100°C for 3 hours and then stirred at ambient temperature for 18 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol mixtures (100/0 increasing to 97/3) to give 1-methyl-2-(3-(2-tetrahydropyranyloxy)propylthio)imidazole (2.5g, 55%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.38-1.72(m, 6H); 1.80(m, 2H); 3.0(t, 2H); 3.36-343(m, 2H); 3.58(s, 3H); 3.62-3.78(m, 2H); 4.50(s, 1H); 6.90(s, 1H); 7.21(s, 1H)

A solution of 1-methyl-2-(3-(2-tetrahydropyranyloxy)propylthio)imidazole (2.0g, 7.8mmol) in acetic acid (8ml), THF (4ml) and water (2ml) was heated at 50°C for 4 hours. The volatiles were removed by evaporation and the residue azeotroped with toluene to give 2-(3-hydroxypropylthio)-1-methylimidazole (1.3g, 100%) as an off-white solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.68(m, 2H); 2.98(t, 2H); 3.42(t, 2H); 3.57(s, 3H); 4.10(s, 1H); 6.90(d, 1H); 7.20(d, 1H)

Example 67

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (350mg, 1.0mmol), (prepared as described for the starting material in Example 24), 4-(3-chloropropoxy)pyridine hydrochloride (206mg, 1.0mmol) and potassium carbonate (303mg, 2.2mmol) in NMP (20ml) was heated at 90°C for 2 hours. The mixture was allowed to cool.

diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol mixtures (100/0 increasing to 95/5) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(4-pyridyloxy)propoxy)quinazoline** (257mg, 56%).

m.p. 138-140°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.25(m, 2H); 3.92(s, 3H); 4.24(t, 2H); 4.30(t, 2H); 6.98(dd, 2H); 7.20(s, 1H); 7.31(dd, 1H); 7.55(dd, 2H); 7.79(s, 1H); 8.32-8.38(m, 3H); 9.50(s, 1H)

MS - ESI: 455 $[MH]^+$

Elemental analysis:	Found	C 58.4	H 4.7	N 11.8
$C_{23}H_{20}N_4O_3ClF\ 1H_2O$	Requires	C 58.4	H 4.7	N 11.8%

The starting material was prepared as follows:

A mixture of 4-chloropyridine (7g, 47mmol), ethylene glycol (17.9g, 235mmol) and sodium hydroxide (4.67g, 195mmol) in DMSO (80ml) was heated at 100°C for 24 hours. Most of the solvent was removed by evaporation and the residue was diluted with ice water. The aqueous mixture was extracted with ethyl acetate, the extracts combined, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol mixtures (100/0 increasing to 97/3) to give 4-(3-hydroxypropoxy)pyridine (3.2g, 45%).

Thionyl chloride (2.2ml, 30mmol) was added slowly to a solution of 4-(3-hydroxypropoxy)pyridine (3.1g, 20mmol) in trichloromethane (40ml) at 5°C. The mixture was stirred at 5°C for 1 hour and then at ambient temperature for 2 hours. The volatiles were removed by evaporation, the residue azeotroped with toluene and dried under vacuum to give 4-(3-chloropropoxy)pyridine hydrochloride (3.81g, 91%) as a solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.22(m, 2H); 3.80(t, 2H); 4.42(t, 2H); 7.55(d, 2H); 8.72(d, 2H)

MS - ESI: 172 $[MH]^+$

Example 68

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (350mg, 1.0mmol), (prepared as described for the starting material in Example 24), 4-(2-chloroethylthio)pyridine hydrochloride (252mg, 1.2mmol) and potassium carbonate (454mg, 3.3mmol) in NMP (30ml) was heated at 90°C for 2 hours. The mixture was allowed to cool, diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with ethyl acetate/methanol mixtures (100/0 increasing to 75/25) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(4-pyridylthio)ethoxy)quinazoline** (13mg, 3%).

m.p. 182-186°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.58(t, 2H); 3.90(s, 3H); 4.40(t, 2H); 7.20(s, 1H); 7.32(d, 1H); 7.40(d, 2H); 7.50-7.60(m, 2H); 7.80(s, 1H); 8.32(s, 1H); 8.38(d, 2H); 9.57(s, 1H)

MS - ESI: 457 $[MH]^+$

The starting material was prepared as follows:

Sodium hydride (890mg of a 50% suspension in mineral oil, 19mmol) was added to a solution of 4-mercaptopyridine (2.34g, 21mmol) in DMF (75ml) and the mixture stirred for 30 minutes. 2-(2-Bromoethoxy)tetrahydropyran (4.0g, 19mmol), (J. Am. Chem. Soc. 1948, **70**, 4187), was added and the mixture heated at 100°C for 3 hours and then stirred at ambient temperature for 18 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol mixtures (100/0 increasing to 97/3) to give 4-(2-(tetrahydropyran-2-yloxy)ethylthio)pyridine (2.8g, 56%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.35-1.64(m, 6H); 3.35-3.42(m, 1H); 3.58-3.82(m, 3H); 4.60(s, 1H); 7.30(dd, 2H); 8.33(dd, 2H)

A solution of 4-(2-(tetrahydropyran-2-yloxy)ethylthio)pyridine (2.73g, 11mmol) in acetic acid (8ml), THF (4ml) and water (2ml) was heated at 50°C for 4 hours. The volatiles were removed by evaporation and the residue azeotroped with toluene to give 4-(2-hydroxyethylthio)pyridine (1.39g, 79%) as an off-white solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 3.10(t, 2H); 3.60(q, 2H); 5.00(t, 1H); 7.22(d, 2H); 8.30(d, 2H)

Thionyl chloride (0.98ml, 13.5mmol) was added slowly to a solution of 4-(2-hydroxyethylthio)pyridine (1.39g, 9.0mmol) in trichloromethane (25ml) at 5°C. The mixture was stirred at 5°C for 1 hour and then at ambient temperature for 2 hours. The volatiles were removed by evaporation, the residue azeotroped with toluene and dried under vacuum to give 4-(2-chloroethylthio)pyridine hydrochloride (500mg, 26%) as a solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 3.65(t, 2H); 3.90(t, 2H); 7.90(d, 2H); 8.60(d, 2H)

MS - ESI: 174 $[MH]^+$

Example 69

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (350mg, 1.0mmol), (prepared as described for the starting material in Example 24), 3-(2-chloroethoxy)pyridine hydrochloride (234mg, 1.2mmol) and potassium carbonate (456mg, 3.3mmol) in NMP (20ml) was heated at 90°C for 2 hours. The mixture was allowed to cool, diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol mixtures (100/0 increasing to 95/5) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(3-pyridyloxy)ethoxy)quinazoline** (95mg, 20%).

m.p. 188-190°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.90(s, 3H); 4.45(m, 4H); 7.24(s, 1H); 7.18(dd, 1H); 7.42-7.60(m, 3H); 7.80(s, 1H); 8.20(d, 1H); 8.35(s, 2H); 9.50(s, 1H)

MS - ESI: 441 $[MH]^+$

Elemental analysis:	Found	C 55.0	H 3.9	N 11.8	
$C_{22}H_{18}N_4O_3ClF\ 2H_2O$	Requires	C 55.4	H 4.6	N 11.7%	

The starting material was prepared as follows:

Sodium hydride (1.02g of a 50% suspension in mineral oil, 42mmol) was added to a solution of 3-hydroxypyridine (2.01g, 21mmol) in DMF (50ml) and the mixture stirred for 30 minutes. 2-(2-Bromoethoxy)tetrahydropyran (4.0g, 19mmol), (J. Am. Chem. Soc. 1948, **70**, 4187), was added and the mixture heated at 100°C for 3 hours and then stirred at ambient

temperature for 18 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol mixtures (100/0 increasing to 97/3) to give 3-(2-(tetrahydropyran-2-yloxy)ethoxy)pyridine (2.28g, 48%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.38-1.65(m, 6H); 3.40(m, 1H); 3.65-3.79(m, 2H); 3.85-3.95(m, 1H); 4.20(t, 2H); 4.62(s, 1H); 7.30(dd, 1H); 7.39(dd, 1H); 8.15(d, 1H); 8.28(d, 1H)

MS - ESI: 224 $[MH]^+$

A solution of 3-(2-(tetrahydropyran-2-yloxy)ethoxy)pyridine (1.54g, 7mmol) in acetic acid (8ml), THF (4ml) and water (2ml) was heated at 50°C for 4 hours. The volatiles were removed by evaporation and the residue azeotroped with toluene to give 3-(2-hydroxyethoxy)pyridine (820mg, 86%) as an off-white solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 3.70(t, 2H); 4.05(t, 2H); 4.85(s, 1H); 7.25(dd, 1H); 7.37(dd, 1H); 8.10(d, 1H); 8.24(d, 1H)

MS - ESI: 140 $[MH]^+$

Thionyl chloride (0.89ml, 12mmol) was added slowly to a solution of 3-(2-hydroxyethoxy)pyridine (1.13g, 8mmol) in trichloromethane (20ml) at 5°C. The mixture was stirred at 5°C for 1 hour and then at ambient temperature for 2 hours. The volatiles were removed by evaporation, the residue azeotroped with toluene and dried under vacuum to give 3-(2-chloroethoxy)pyridine hydrochloride (300mg, 19%) as a solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 3.99(t, 2H); 4.42(t, 2H); 7.82(dd, 1H); 8.05(dd, 1H); 8.42(d, 1H); 8.62(s, 1H)

Example 70

2-Fluoro-5-hydroxy-4-methylaniline (170mg, 1.2mmol), (prepared as described for the starting material in Example 13), was added to a solution of 7-benzyloxy-4-chloroquinazoline hydrochloride (307mg, 1mmol) in 2-pentanol (5ml) and the mixture stirred at 120°C for 2 hours. The mixture was allowed to cool and the resulting precipitate was collected by filtration, washed with isopropanol and then ether and dried under vacuum at 70°C to give **7-benzyloxy-4-(2-fluoro-5-hydroxy-4-methylanilino)quinazoline** hydrochloride (331mg, 80%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.16(s, 3H); 5.36(s, 2H); 6.88(d, 1H); 7.12(d, 1H); 7.3-7.65(m, 7H); 8.68(d, 1H); 8.82(s, 1H); 9.68(s, 1H); 11.4(s, 1H)

MS - ESI: 376 $[MH]^+$

Elemental analysis:	Found	C 63.7	H 4.8	N 10.0	
$C_{22}H_{18}N_3O_2F$ 1HCl	Requires	C 64.2	H 4.7	N 10.2%	

The starting material was prepared as follows:

Sodium (368mg, 16mmol) was added to benzyl alcohol (10ml, 96mmol) and the mixture was heated at 148°C for 30 minutes. 7-Fluoro-3,4-dihydroquinazolin-4-one (656mg, 4mmol), (J. Chem. Soc. section B 1967, 449), was added and the mixture maintained at 148°C for 24 hours. The reaction mixture was allowed to cool, the solution was poured on to water (170ml) and the aqueous mixture adjusted to pH3 with concentrated hydrochloric acid. The precipitate was collected by filtration, washed with water, ether and dried under vacuum to give 7-benzyloxy-3,4-dihydroquinazolin-4-one (890mg, 89%) as a white solid.

m.p. 267-269°C

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 5.32(s, 2H); 7.25(d, 1H); 7.32-7.52(m, 6H); 8.12(d, 1H); 8.99(s, 1H)

MS - ESI: 252 $[MH]^+$

Elemental analysis:	Found	C 71.4	H 4.9	N 10.7	
$C_{15}H_{12}N_2O_2$ 0.04H_2O	Requires	C 71.2	H 4.8	N 11.1%	

A mixture of 7-benzyloxy-3,4-dihydroquinazolin-4-one (800mg, 3.17mmol) and DMF (100µl) in thionyl chloride (20ml, 0.27mmol) was heated at reflux for 3 hours. Excess thionyl chloride was removed by evaporation and the residue azeotroped with toluene and dried under vacuum to give 7-benzyloxy-4-chloroquinazoline hydrochloride (835mg, 86%) as a cream solid.

m.p. 131-132°C

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 5.32(s, 2H); 7.29(d, 1H); 7.34-7.52(m, 6H); 8.12(d, 1H); 9.03(s, 1H)

MS - ESI: 270 $[MH]^+$

Example 71

Using an analogous procedure to that described in Example 70, 7-benzyloxy-4-chloroquinazoline hydrochloride (307mg, 1mmol), (prepared as described for the starting material in Example 70), was treated with 4-chloro-2-fluoro-5-hydroxyaniline (193mg, 1.2mmol), (EP 061741 A2), to give **7-benzyloxy-4-(4-chloro-2-fluoro-5-hydroxyanilino)quinazoline** hydrochloride (407mg, 94%).

m.p. 253-257°C

^{1}H NMR Spectrum: (DMSOd_6) 5.37(s, 2H); 7.16(d, 1H); 7.32-7.5(m, 4H); 7.54(s, 1H); 7.56(d, 2H); 7.59(dd, 1H); 8.73(d, 1H); 8.86(s, 1H); 10.63(br s, 1H); 11.6(br s, 1H)

MS - ESI: 396 [MH]$^+$

Elemental analysis:	Found	C 57.8	H 3.8	N 9.7
$C_{21}H_{15}N_3O_2ClF$ 0.3H_2O 1HCl Requires		C 57.6	H 3.8	N 9.6%

Example 72

Using an analogous procedure to that described in Example 36, 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (224mg, 0.6mmol), (prepared as described for the starting material in Example 22), was treated with 4-bromomethyl-1,2-difluorobenzene (149mg, 0.72mmol) to give **7-(3,4-difluorobenzyloxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline** hydrochloride (90mg, 31%).

^{1}H NMR Spectrum: (DMSOd_6) 2.17(s, 3H); 4.0(s, 3H); 5.33(s, 2H); 6.88(d, 1H); 7.11(d,1H); 7.38(s, 1H); 7.41(m, 1H); 7.55(m, 1H); 7.62(m, 1H); 8.17(s, 1H); 8.75(s, 1H); 9.68(s, 1H); 11.15(s, 1H)

MS - ESI: 442 [MH]$^+$

Elemental analysis:	Found	C 58.0	H 4.3	N 8.7
$C_{23}H_{18}N_3O_3F_3$ 0.9HCl 0.08 isopropanol	Requires	C 58.3	H 4.1	N 8.8

Example 73

Tetrabutylammonium fluoride (563µl of a 1M solution in THF, 0.62mmol) was added to a solution of 4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-6-methoxy-7-((1-methylimidazol-2-yl)methoxy)quinazoline (207mg, 0.31mmol) in THF (5ml) cooled at

5°C and the mixture was then stirred for 1 hour at ambient temperature. Water was added and the volatiles were removed by evaporation. The solid residue was dissolved in methylene chloride/methanol and a 5M solution of hydrogen chloride in isopropanol (0.3ml) was added. The solvent was removed by evaporation, the solid residue was resuspended in ether, collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-((1-methylimidazol-2-yl)methoxy)quinazoline** hydrochloride (99mg, 63%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.93(s, 3H); 4.01(s, 3H); 5.67(s, 2H); 7.16(d, 1H); 7.52(d, 1H); 7.58(s, 1H); 7.70(s, 1H); 7.78(s, 1H); 8.31(s, 1H); 8.8(s, 1H); 10.58(s, 1H); 11.35(br s, 1H)

MS - ESI: 430 $[MH]^+$

Elemental analysis: Found C 45.8 H 4.3 N 12.9

$C_{20}H_{17}N_5O_3ClF$ $1.4H_2O$ 2HCl Requires C 45.5 H 4.2 N 13.3%

The starting material was prepared as follows:

Diethyl azodicarboxylate (219µl, 1.4mmol) was added dropwise to a solution of 4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (400mg, 0.7mmol), (prepared as described for the starting material in Example 33), 2-hydroxymethyl-1-methylimidazole (82mg, 0.83mmol), (J. Chem. Soc. 1927, 3128-3136), and triphenylphosphine (365mg, 1.4mmol) in methylene chloride (12ml) cooled at 0°C. The mixture was stirred for 1 hour at ambient temperature and further 2-hydroxymethyl-1-methylimidazole (68mg, 0.69mmol), triphenylphosphine (91mg, 0.34mmol) and diethyl azodicarboxylate (54µl, 0.34mmol) were added. The mixture was stirred for 1 hour at ambient temperature and the solvent was removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (94/6) to give 4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-6-methoxy-7-((1-methylimidazol-2-yl)methoxy)quinazoline (116mg, 25%).

^{1}H NMR Spectrum: ($CDCl_3$) 1.16(s, 9H); 3.75(s, 3H); 3.93(s, 3H); 5.28(s, 2H); 6.84(s, 1H); 6.91(s, 1H); 7.02(s, 1H); 7.17(d, 1H); 7.32-7.48(m, 8H); 7.78(2d, 4H); 8.08(s, 1H); 8.18(d, 1H)

Example 74

A mixture of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxyquinazoline hydrochloride (400mg, 0.98mmol), 2-chloromethyl-1-methylimidazole hydrochloride (210mg, 1.25mmol), potassium carbonate (580mg, 4.2mmol) and potassium iodide (17mg, 0.1mmol) in DMF (20ml) was stirred at 65°C for 4.5 hours followed by 17 hours at ambient temperature. The solvent was removed by evaporation and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and the solvent removed by evaporation. The solid residue was purified by column chromatography eluting with methylene chloride/methanol (97/3) to give a yellow solid (258mg). This solid was dissolved in methanol (5ml) and a 1M aqueous sodium hydroxide solution (660µl, 0.66mmol) was added. The mixture was stirred for 15 minutes, then water was added and the mixture adjusted to pH7 with concentrated hydrochloric acid. The aqueous mixture was extracted with ethyl acetate and the combined organic extract was washed with water, brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by flash chromatography eluting with methylene chloride/methanol (95/5). The purified solid product was dissolved in methanol and methanolic hydrogen chloride (1.5ml of a 7.5M solution) was added. The volatiles were removed by evaporation, the solid residue was suspended in pentane, collected by filtration, washed with pentane and dried under vacuum to give **4-(2-fluoro-5-hydroxy-4-methylanilino)-7-((1-methylimidazol-2-yl)methoxy)quinazoline** hydrochloride (105mg, 44%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.16(s, 3H); 3.92(s, 3H); 5.71(s, 2H); 6.90(d, 1H); 7.1(d, 1H); 7.52(d, 1H); 7.64(d, 1H); 7.71(s, 1H); 7.78(s, 1H); 8.77(d, 1H); 8.82(s, 1H); 9.7(br s, 1H); 11.45(br s, 1H)

MS - ESI: 380 $[MH]^+$

Elemental analysis:	Found	C 52.2	H 5.0	N 15.1
$C_{20}H_{18}N_5O_2F$ 0.9H_2O 1.8HCl	Requires	C 52.1	H 4.7	N 15.2%

The starting material was prepared as follows :-

Sodium (368mg, 16mmol) was added to benzyl alcohol (10ml, 96mmol) and the mixture was heated at 148°C for 30 minutes. 7-fluoro-3,4-dihydroquinazolin-4-one (656mg,

4mmol), (J. Chem. Soc. section B 1967, 449), was added and the mixture maintained at 148°C for 24 hours. The reaction mixture was allowed to cool, the solution was poured on to water (170ml) and the aqueous mixture adjusted to pH3 with concentrated hydrochloric acid. The precipitate was collected by filtration, washed with water, then ether and dried under vacuum to give 7-benzyloxy-3,4-dihydroquinazolin-4-one (890mg, 89%) as a white solid.

m.p. 267-269°C

^{1}H NMR Spectrum: (DMSOd_6; CF_3COOD) 5.32(s, 2H); 7.25(d, 1H); 7.32-7.52(m, 6H); 8.12(d, 1H); 8.99(s, 1H)

MS - ESI: 252 $[MH]^+$

Elemental analysis:	Found	C 71.4	H 4.9	N 10.7
$C_{15}H_{12}N_2O_2$ 0.04H_2O	Requires	C 71.2	H 4.8	N 11.1%

A mixture of 7-benzyloxy-3,4-dihydroquinazolin-4-one (800mg, 3.17mmol) and DMF (100µl) in thionyl chloride (20ml, 0.27mmol) was heated at reflux for 3 hours. Excess thionyl chloride was removed by evaporation and the residue azeotroped with toluene and dried under vacuum to give 7-benzyloxy-4-chloroquinazoline hydrochloride (835mg, 86%) as a cream solid.

m.p. 131-132°C

^{1}H NMR Spectrum: (DMSOd_6; CF_3COOD) 5.32(s, 2H); 7.29(d, 1H); 7.34-7.52(m, 6H); 8.12(d, 1H); 9.03(s, 1H)

MS - ESI: 270 $[MH]^+$

2-Fluoro-5-methoxycarbonyloxy-4-methylaniline (883mg, 4.4mmol), (prepared as described for the starting material in Example 12), was added to a solution of 7-benzyloxy-4-chloroquinazoline hydrochloride(1g, 3.7mmol) in 2-pentanol (15ml) at 120°C and the mixture was then heated at reflux for 4 hours. The mixture was allowed to cool and the precipitate was collected by filtration, washed with isopropanol followed by ether and dried under vacuum to give 7-benzyloxy-4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)quinazoline hydrochloride (1.65g, 97%) as a cream solid.

m.p. 219-220°C

^{1}H NMR Spectrum: (DMSOd_6) 2.22(s, 3H); 3.86(s, 3H); 5.37(s, 2H); 7.30-7.60(m, 9H); 8.60(d, 1H); 8.80(s, 1H); 11.2(s, 1H)

MS - ESI: 434 $[MH]^+$

Elemental analysis:	Found	C 60.1	H 4.9	N 8.5
$C_{24}H_{20}N_3O_4F$ 1HCl $0.5H_2O$	Requires	C 60.2	H 4.6	N 8.8%

7-Benzyloxy-4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)quinazoline hydrochloride (1.53g, 3.25mmol) and 10% palladium-on-charcoal catalyst (180mg) in a mixture of methanol (75ml), DMF (6ml) and trichloromethane (30ml) was stirred under hydrogen at 1.5 atmospheres pressure for 45 minutes. The catalyst was removed by filtration through diatomaceous earth and the solvent removed from the filtrate by evaporation. The residue was triturated with ether, the resulting solid was collected by filtration and dried under vacuum to give 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxyquinazoline hydrochloride (1.23g, 84%) as an orange solid.

m.p. 205-210°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.22(s, 3H); 3.85(s, 3H); 7.24(d, 1H); 7.35(dd, 1H); 7.42(d, 1H); 7.45(d, 1H); 8.58(d, 1H); 8.81(s, 1H); 11.40(s, 1H); 11.76(s, 1H)

MS - ESI: 344 $[MH]^+$

Example 75

Diethyl azodicarboxylate (244mg, 1.4mmol) was added dropwise to a suspension of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-hydroxy-6-methoxyquinazoline hydrochloride (261mg, 0.7mmol), (prepared as described for the starting material in Example 22), triphenylphosphine (367mg, 1.4mmol) and 2-(1,2,4-triazol-1-yl)ethanol (95mg, 0.84mmol), (Ann. Pharm. Fr. 1977, 35, 503-508), in methylene chloride (5ml). The mixture was stirred for 1 hour at ambient temperature and further triphenylphosphine (184mg, 0.7mmol), 2-(1,2,4-triazol-1-yl)ethanol (63mg, 0.56mmol) and diethyl azodicarboxylate (122mg, 0.7mmol) were added. The mixture was stirred for a further 2.5 hours and the solvent was removed by evaporation. The residue was dissolved in methanol (5ml) and 2M aqueous sodium hydroxide solution (2ml) was added. The mixture was stirred for 20 minutes and the mixture was partitioned between ether and water. The aqueous layer was acidified to pH7 with 2M hydrochloric acid and the resulting precipitate was collected by filtration, washed with water, and dried under vacuum. The resulting solid was dissolved in methylene chloride/methanol and a 5M solution of hydrogen chloride in isopropanol (0.5ml) was added.

The volatiles were removed by evaporation, the solid was resuspended in ether, collected by filtration, washed with ether and dried under vacuum to give **4-(2-fluoro-5-hydroxy-4-methylanilino)-7-(2-(1,2,4-triazol-1-yl)ethoxy)quinazoline** hydrochloride (180mg, 56%).

^{1}H NMR Spectrum: (DMSOd_6) 2.16(s, 3H); 3.97(s, 3H); 4.59(t, 2H); 4.74(t, 2H); 6.9(d, 1H); 7.10(d, 1H); 7.37(s, 1H); 8.03(s, 1H); 8.23(s, 1H); 8.62(s, 1H); 8.79(s, 1H); 9.7(br s, 1H); 11.4(s, 1H)

MS - ESI: 411 $[MH]^+$

Elemental analysis:	Found	C 53.2 H 4.8 N 18.4
$C_{20}H_{19}N_6O_3F$ 0.1H_2O 1.2HCl	Requires	C 52.7 H 4.5 N 18.4%

Example 76

Tetrabutylammonium fluoride (608µl of a 1M solution in THF, 0.67mmol) was added to a solution of 4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-6-methoxy-7-((3-thienyl)methoxy)quinazoline (224mg, 0.33mmol) in THF (5ml) cooled at 5°C. After stirring for 1 hour at ambient temperature, water was added. The THF was removed by evaporation. The precipitate was collected by filtration and dried by azeotroping with ethanol. The solid was dissolved in methylene chloride/methanol and a solution of 5M hydrochloric acid in isopropanol was added. The volatiles were removed by evaporation. The residue was suspended in ether, collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-((3-thienyl)methoxy)quinazoline** hydrochloride (132mg, 85%).

m.p. 277-281°C

^{1}H NMR Spectrum: (DMSOd_6) 3.99(s, 3H); 5.34(s, 2H); 7.15(d, 1H); 7.26(d, 1H); 7.49(s, 1H); 7.53(d, 1H); 7.61(m, 1H); 7.75(s, 1H); 8.22(s, 1H); 8.8(s, 1H); 10.59(s, 1H); 11.38(br s, 1H)

MS - ESI: 432 $[MH]^+$

Elemental analysis:	Found	C 51.0 H 3.5 N 8.9
$C_{20}H_{15}N_3O_3ClFS$ 0.1H_2O 1HCl	Requires	C 51.1 H 3.5 N 8.9%

The starting material was prepared as follows:

Diethyl azodicarboxylate (274µl, 1.7mmol) was added dropwise to a solution of 4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (400mg, 0.7mmol), (prepared as described for the starting material in Example 33), 3-thiophenemethanol (119mg, 1mmol) triphenylphosphine (456mg, 1.7mmol) in methylene chloride (12ml) cooled at 0°C. The mixture was stirred for 2 hours at ambient temperature, the solvent was removed by evaporation and the residue was purified by column chromatography eluting with methylene chloride/ether (95/5). The purified product was triturated with petroleum ether/ethyl acetate (8/2) and the solid product was collected by filtration, washed with ether and dried under vacuum to give 4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-6-methoxy-7-((3-thienyl)methoxy)quinazoline (223mg, 47%). ^{1}H NMR Spectrum: (DMSOd_6) 1.09(s, 9H); 3.85(s, 3H); 5.23(s, 2H); 7.04(d, 1H); 7.21(d, 1H); 7.25(s, 1H); 7.4-7.5(m, 6H); 7.58(m, 2H); 7.62-7.75(m, 6H); 8.1(s, 1H); 9.22(br s, 1H)

Example 77

Diethyl azodicarboxylate (274µl, 1.7mmol) was added dropwise to a solution of 4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (400mg, 0.7mmol), (prepared as described for the starting material in Example 33), triphenylphosphine (456ml, 1.7mmol), 2-(4-pyridyl)ethanol (128mg, 1mmol), (Zhur. Obshchei. Khim. 1958, 28, 103-110), in methylene chloride (12ml) cooled at 0°C. The mixture was stirred for 2 hours at ambient temperature and the solvent was removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (97/3) to give a white solid (416mg). A portion of this solid (390mg) was dissolved in THF (6ml), the solution was cooled to 0°C and tetrabutylammonium fluoride (1.1ml of a 1M solution in THF, 1.1 mmol) was added and the mixture was stirred for 2 hours at ambient temperature. Water was added, the organic solvent was removed by evaporation and the resulting precipitate was collected by filtration. The solid was dissolved in methylene chloride/methanol and a 5M solution of hydrogen chloride in isopropanol (0.5ml) was added. The volatiles were removed by evaporation and the solid was resuspended in isopropanol and collected by filtration, washed with isopropanol and ether and dried under vacuum to give **4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-(2-(4-pyridyl)ethoxy)quinazoline** hydrochloride (123mg, 42%).

^{1}H NMR Spectrum: (DMSOd_6; CD_3COOD) 3.49(t, 2H); 3.99(s, 3H); 4.6(t, 2H); 7.16(d, 1H); 7.41(s, 1H); 7.51(d, 1H); 8.05(br s, 2H); 8.19(s, 1H); 8.84(s, 1H); 8.86(br s, 2H)

MS - ESI: 441 $[MH]^+$

Elemental analysis:	Found	C 50.4	H 4.7	N 10.0
$C_{22}H_{18}N_4O_3ClF$ 1.1H_2O 1.8HCl 0.23isopropanol	Requires	C 50.5	H 4.5	N 10.4%

Example 78

Using an analogous procedure to that described in Example 77, 4-(4-chloro-5-diphenyl-t-butylsilyloxy-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (300mg, 0.52mmol), (prepared as described for the starting material in Example 33), was treated with 4-hydroxymethyl-2-methylthiazole (100mg, 0.87mmol) to give **4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-((2-methylthiazol-4-yl)methoxy)quinazoline** hydrochloride (132mg, 52%).

^{1}H NMR Spectrum: (DMSOd_6) 2.68(s, 3H); 4.00(s, 3H); 5.35(s, 2H); 7.17(d, 1H); 7.52(d, 1H); 7.56(s, 1H); 7.72(s, 1H); 8.29(s, 1H); 8.83(s, 1H); 10.63(br s, 1H); 11.58(s, 1H)

MS - ESI: 447 $[MH]^+$

Elemental analysis:	Found	C 48.2	H 3.7	N 11.2
$C_{20}H_{16}N_4O_3ClFS$ 0.6H_2O 1.2HCl	Requires	C 47.9	H 3.7	N 11.2%

The starting material was prepared as follows :-

A solution of 4-chloromethyl-2-methylthiazole (1.84g, 10mmol) in water (9ml) and concentrated hydrochloric acid (2ml) was heated at reflux for 20 hours. The mixture was allowed to cool and was adjusted to pH5 with 2M aqueous sodium hydroxide solution and the mixture was extracted with ethyl acetate. The organic extract was washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (97/3) to give 4-hydroxymethyl-2-methylthiazole (800mg, 54%).

^{1}H NMR Spectrum ($CDCl_3$) 2.72(s, 3H); 2.92(br s, 1H); 4.73(s, 2H); 7.03(s, 1H)

Example 79

Diethyl azodicarboxylate (197µl, 1.2mmol) was added dropwise to a solution of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (200mg, 0.6mmol), (prepared as described for the starting material in Example 24), 3-thiophenemethanol (107mg, 0.93mmol) and triphenylphosphine (328mg, 1.2mmol) in methylene chloride (6ml) cooled at 0°C. The mixture was stirred for 2 hours at ambient temperature and further triphenylphosphine (157mg, 0.57mmol), 3-thiophenemethanol (107mg, 0.93mmol) and diethyl azodicarboxylate (98.5µl, 0.59mmol) were added. The mixture was stirred for 2 hours at ambient temperature and the solvent was removed by evaporation. The residue was dissolved in ethyl acetate and the solution was washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/ethyl acetate (4/6). The resulting oil was dissolved in ether and a 5M solution of hydrogen chloride in isopropanol (1ml) was added. The resulting precipitate was collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((3-thienyl)methoxy)quinazoline** hydrochloride (59mg, 20%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.99(s, 3H); 5.34(s, 2H); 7.25(d, 1H); 7.43(d, 1H); 7.45(s, 1H); 7.58-7.63(m, 2H); 7.7(dd, 1H); 7.72(dd, 1H); 8.17(s, 1H); 8.78(s, 1H)

MS - ESI: 416 $[MH]^+$

Elemental analysis:	Found	C 53.5	H 3.7	N 9.0
$C_{20}H_{15}N_3O_2ClFS$ 0.95HCl	Requires	C 53.3	H 3.6	N 9.3%

Example 80

A mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (250mg, 0.78mmol), (prepared as described for the starting material in Example 24), 2-acetamido-4-chloromethylthiazole (164mg, 0.86mmol) and potassium carbonate (216mg, 1.5mmol) in DMF (5ml)was stirred at 40°C for 7 hours. The mixture was partitioned between ethyl acetate and water and the aqueous layer was adjusted to pH7 with 2M hydrochloric acid. The organic phase was washed with water, brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5). The purified solid was dissolved in a mixture of methylene chloride and methanol and a 5M solution of hydrogen chloride in isopropanol (1.0ml) was added. The

volatiles were removed by evaporation to give a solid, which was triturated with ether, collected by filtration and dried under vacuum to give **7-((2-acetamidothiazol-4-yl)methoxy)-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline** hydrochloride (96mg, 24%).

m.p. 194-202°C

^{1}H NMR Spectrum: ($DMSOd_6$) 2.14(s, 3H); 4.0(s, 3H); 5.31(s, 2H); 7.34(s, 1H); 7.45(dd, 1H); 7.52(s, 1H); 7.60(t, 1H); 7.68(dd, 1H); 8.30(s, 1H); 8.81(s, 1H)

MS - ESI: 474 $[MH]^+$

Elemental analysis:	Found	C 46.9	H 3.8 N 13.2
$C_{21}H_{17}N_5O_3ClFS$ $1.1H_2O$ 1.1HCl	Requires	C 47.3	H 3.8 N 13.1%

Example 81

Diethyl azodicarboxylate (295µl, 1.8mmol) was added dropwise to a solution of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (300mg, 0.93mmol), (prepared as described for the starting material in Example 24), 2-(1,2,4-triazol-1-yl)ethanol (159mg, 1.4mmol), (Ann. Pharm. Fr. 1977, 35, 503-508), and triphenylphosphine (492mg, 1.8mmol) in methylene chloride (10ml). The mixture was stirred for 2 hours at ambient temperature and further triphenylphosphine (246mg, 0.9mmol) and diethyl azodicarboxylate (147µl, 0.9mmol) were added. The mixture was stirred for 1 hour at ambient temperature and the resulting precipitate was collected by filtration, washed with methylene chloride and ether and dried under vacuum. This solid was suspended in methylene chloride/methanol and a 5M solution of hydrogen chloride in isopropanol (1.0ml) was added. The volatiles were removed by evaporation, the residue was triturated with ether. The resulting solid was collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1,2,4-triazol-1-yl)ethoxy)quinazoline** hydrochloride (219mg, 52%).

m.p. 169-174°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.99(s, 3H); 4.60(t, 2H); 4.74(t, 2H); 7.43(d, 1H); 7.45(s, 1H); 7.59(t, 1H); 7.67(dd, 1H); 8.06(s, 1H); 8.41(s, 1H); 8.68(s, 1H); 8.83(s, 1H)

MS - ESI: 415 $[MH]^+$

Elemental analysis:	Found	C 47.0	H 4.3 N 16.5

$C_{19}H_{16}N_6O_2ClF$ 1.6 $1H_2O$ 1HCl 0.35isopropanol Requires C 47.0 H 4.4 N 16.4%

Example 82

Diethyl azodicarboxylate (295µl, 1.8mmol) was added dropwise to a solution of 1-(3-hydroxypropyl)-[1,2,4]-triazole (119mg, 0.93mmol), (EP0060696 A1), 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (200mg, 0.62mmol), (prepared as described for the starting material in Example 24), and triphenylphosphine (492g, 1.8mmol) in methylene chloride (4ml) and the mixture stirred for 3 hours at ambient temperature. The mixture was purified by column chromatography eluting with methylene chloride/acetonitrile/methanol (60/32/8). The purified product was triturated with a mixture of pentane and ether, collected by filtration and dried under vacuum to give a white solid. This solid was dissolved in methylene chloride/methanol and ethereal hydrogen chloride (1ml of a 5M solution) was added. The volatiles were removed by evaporation. The solid residue was suspended in ether, collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(1,2,4-triazol-1-yl)propoxy)quinazoline** hydrochloride (121mg, 39%).

^1H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 2.44(t, 2H); 4.0(s, 3H); 4.3(t, 2H); 4.5(t, 2H); 7.32(s, 1H); 7.47(dd, 1H); 7.62(t, 1H); 7.70(dd, 1H); 8.08(s, 1H); 8.41(s, 1H); 8.87(s, 1H); 9.10(s, 1H)

MS - ESI: 429 $[MH]^+$

Elemental analysis: Found C 47.8 H 4.2 N 16.6

$C_{20}H_{18}N_6O_2ClF$ 0.2H_2O 2HCl Requires C 47.5 H 4.1 N 16.6%

Example 83

Diethyl azodicarboxylate (209mg, 1.2mmol) was added dropwise to a suspension of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (128mg, 0.4mmol), (prepared as described for the starting material in Example 24), triphenylphosphine (314mg, 1.2 mmol) and 2-(N-methyl-N-(pyridazin-4-yl)amino)ethanol (80mg, 0.52mmol) in methylene chloride (5ml) and the mixture stirred for 2 hours at ambient temperature. The solvent was removed by evaporation, the residue was triturated with ether and the resulting solid was collected by

filtration. The solid was purified by column chromatography eluting with methylene chloride/methanol (9/1 followed by 8/2) to give a white solid. This solid was dissolved in methylene chloride/methanol and ethereal hydrogen chloride (0.5ml of a 4M solution) was added. The volatiles were removed by evaporation, the residue was triturated with ether, collected by filtration and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-methyl-N-(pyridazin-4-yl)amino)ethoxy)quinazoline** hydrochloride (110mg, 60%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.11(s, 3H); 3.89(s, 3H); 3.94(t, 2H); 4.37(t, 2H); 6.85(dd, 1H); 7.21(s, 1H); 7.35(dd, 1H); 7.55(dd, 1H); 7.59(t, 1H); 7.8(s, 1H); 8.36(s, 1H); 8.59(d, 1H); 8.90(d, 1H); 9.57(s, 1H)

Elemental analysis:	Found	C 47.2	H 4.6	N 14.7
$C_{22}H_{20}N_6O_2ClF$ 1.5H_2O 2.15HCl	Requires	C 47.2	H 4.5	N 15.0%

The starting material was prepared as follows:

A solution of 4-bromo-3,6-dichloro-pyridazine (1.11g, 5mmol), (J.Chem. Soc., Perkin Trans I, 1974, 696), and 2-(methylamino)ethanol (0.75g, 10mmol) in isopropanol (10ml) was heated at reflux for 30 minutes. The solvent was removed by evaporation, the residue was partitioned between methylene chloride and water and the aqueous layer was adjusted to pH9 with solid potassium carbonate. The organic layer was separated, washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was triturated with ether, collected by filtration and dried under vacuum to give 2-(N-(3,6-dichloropyridazin-4-yl)-N-methylamino)ethanol (1g, 90%).

^{1}H NMR Spectrum: ($CDCl_3$) 2.1(br s, 1H); 3.09(s, 3H); 3.71(t, 2H); 3.93(t, 2H); 6.8(s, 1H)

MS - ESI: 221 $[MH]^+$

A mixture of 2-(N-(3,6-dichloropyridazin-4-yl)-N-methylamino)ethanol (444mg, 2mmol) and 10% palladium-on-charcoal catalyst (150mg) in ethanol (15ml), methanol (5ml) and aqueous ammonia (15ml) was stirred under hydrogen at 3 atmospheres pressure for 4 hours. The catalyst was removed by filtration and the solvent removed from the filtrate by evaporation. The residue was dissolved in methylene chloride, the insoluble material was removed by filtration and the solvent was removed from the filtrate by evaporation. The residue was purified by column chromatography on neutral aluminum oxide eluting with

methylene chloride/methanol (95/5 followed by 90/10). The purified product was triturated with petroleum ether, the solid product was collected by filtration and dried under vacuum to give 2-(N-methyl-N-(pyridazin-4-yl)amino)ethanol (275mg, 91%).

^{1}H NMR Spectrum: ($CDCl_3$) 3.06(s, 3H); 3.57(t, 2H); 3.89(t, 2H); 6.52(dd, 1H); 8.48(d, 1H); 8.54 (d, 1H)

MS - ESI: 153 $[MH]^+$

Example 84

2M Aqueous sodium hydroxide solution (560µl, 1.1mmol) was added to a solution of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-((4-pyridyl)carboxamido)quinazoline (250mg, 0.56mmol) in methanol (7ml) cooled at 0°C and the mixture then stirred for 1 hour at ambient temperature. The mixture was diluted with water and the mixture adjusted to pH6 with 2M hydrochloric acid. The resulting solid was collected by filtration, washed with water and dried under vacuum. The solid was dissolved in methylene chloride/methanol and isopropanolic hydrogen chloride (0.7ml of a 5M solution) was added. The volatiles were removed by evaporation, the solid residue was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give **4-(2-fluoro-5-hydroxy-4-methylanilino)-7-((4-pyridyl)carboxamido)quinazoline** hydrochloride (241mg, 93%).

MS - ESI: 390 $[MH]^+$

^{1}H NMR Spectrum: ($DMSOd_6$; CFCOOD) 2.2(s, 3H); 6.94(d, 1H); 7.13(d, 1H); 8.18(d, 1H); 8.53(d, 2H); 8.68(s, 1H); 8.77(d, 1H); 8.94(s, 1H); 9.20(d, 2H)

Elemental analysis:	Found	C 52.0	H 4.3	N 14.3
$C_{21}H_{16}N_5O_2F$ 1.2H_2O 1.95HCl	Requires	C 52.3	H 4.3	N 14.5%

The starting material was prepared as follows:

A mixture of 7-nitro-3,4-dihydroquinazolin-4-one (J. Chem. Soc. 1950, 1104-1111) (5g, 26mmol) in thionyl chloride (50ml) and DMF (1ml) was heated at reflux for 1.5 hours. Excess thionyl chloride was removed by evaporation and the residue azeotroped with toluene. The residue was suspended in ether, collected by filtration and dried under vacuum to give 4-chloro-7-nitroquinazoline hydrochloride (6.4g, 100%).

^{1}H NMR Spectrum: ($DMSOd_6$) 8.26(dd, 1H); 8.36(d, 1H); 8.40(s, 1H); 8.42(dd, 1H)
MS - ESI: 209 [MH]$^+$

A solution of 4-chloro-7-nitroquinazoline hydrochloride (2.46g, 10mmol) and 2-fluoro-5-methoxycarbonyloxy-4-methylaniline (2.2g, 11mmol), (prepared as described for the starting material in Example 12), in isopropanol (25ml) was heated at 50°C for 1 hour. The mixture was allowed to cool, the precipitated solid was collected by filtration recrystallised from methylene chloride/methanol/isopropanol to give 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-nitroquinazoline hydrochloride (1.8g, 45%) as a yellow solid.
^{1}H NMR Spectrum: ($DMSOd_6$) 2.21(s, 3H); 3.86(s, 3H); 7.40(d, 1H); 7.46(d, 1H); 8.49(dd, 1H); 8.63(s, 1H); 8.84(s, 1H); 8.89(d, 1H)
MS - ESI: 373 [MH]$^+$

Elemental analysis:	Found	C 50.0	H 3.6	N 13.8
$C_{17}H_{13}N_4O_5F$ 1HCl	Requires	C 50.0	H 3.5	N 13.7%

A mixture of 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-nitroquinazoline hydrochloride (5.3g, 13mmol) and 10% palladium-on-charcoal catalyst (1g) in ethanol (100ml), ethanolic hydrogen chloride (1.8ml of a 7M solution) and methanol (20ml) was stirred under hydrogen at 1.7 atmospheres pressure for 75 minutes. The catalyst was removed by filtration through diatomaceous earth and the filter pad thoroughly washed with methylene chloride, methanol and ether and the solvent was removed from the filtrate by evaporation to give 7-amino-4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)quinazoline hydrochloride (4.8g, 97%) as a yellow solid.
^{1}H NMR Spectrum: ($DMSOd_6$) 2.22(s, 3H); 3.87(s, 3H); 6.77(s, 1H); 7.08(dd, 1H); 7.15(m, 2H); 7.41(m, 2H); 8.35(d, 1H); 8.63(s, 1H); 11.03(s, 1H)
MS - ESI: 343 [MH]$^+$

A solution of 7-amino-4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)quinazoline hydrochloride (0.45g, 1.2mmol) and isonicotinoyl chloride hydrochloride (296mg, 1.66mmol) in pyridine (15ml) was stirred for 2 hours at ambient temperature, followed by 1 hour at 40°C. Further isonicotinoyl chloride hydrochloride (84mg, 0.46mmol) was added and the mixture was stirred at 40°C for 2 hours. The volatiles were removed by evaporation, the mixture was diluted with water. The aqueous mixture was adjusted to pH7 and extracted with ethyl acetate. The combined extracts were washed with

brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by flash chromatography eluting with methylene chloride/methanol (95/5 followed by 92/8). The purified solid was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give 4-(2-fluoro-5-methoxycarbonyloxy-4-methylanilino)-7-((4-pyridyl)carboxamido)quinazoline (264mg, 49%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.19(s, 3H); 3.86(s, 3H); 7.31(d, 1H); 7.45(d, 1H); 7.92(d, 2H); 7.98(d, 1H); 8.31(s, 1H); 8.43(d, 1H); 8.47(s, 1H); 8.83(d, 2H); 9.78(br s, 1H); 10.89(br s, 1H)

Example 85

4-Chloro-2-fluoroaniline (77mg, 0.53mmol) was added to a solution of 4-chloro-6-methoxy-7-(2-(N-methyl-N-(6-methylpyrimidin-4-yl)amino)ethoxy)quinazoline hydrochloride (140mg, 0.35mmol) in isopropanol (5ml) and the mixture heated at reflux for 1 hour. The solvent was removed by evaporation and the residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate solution. The organic layer was separated, washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by flash chromatography eluting with methylene chloride/methanol (95/5). The purified solid was dissolved in methylene chloride/methanol and ethereal hydrogen chloride (1ml of a 5M solution) was added. The volatiles were removed by evaporation, the residue was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-methyl-N-(6-methylpyrimidin-4-yl)amino)ethoxy)quinazoline** hydrochloride (75mg, 39%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 2.46 and 2.47(2s, 3H); 3.35 and 3.42(2s, 3H); 3.97 and 3.98 (2s, 3H); 4.2(br s, 1H); 4.3(br s, 1H); 4.5(br s, 2H); 7.05 and 7.3(2s, 1H); 7.4 and 7.5(m, 2H); 7.62(t, 1H); 7.7(d, 1H); 8.25(br s, 1H); 8.8 and 8.9(2s, 2H)

MS - ESI: 469 $[MH]^+$

The starting material was prepared as follows:

Sodium hydride (1.44g of a 60% suspension in mineral oil, 36mmol) was added in portions over 20 minutes to a solution of 7-benzyloxy-3,4-dihydroquinazolin-4-one (8.46g, 30mmol), (prepared as described for the starting material in Example 70), in DMF (70ml) and

the mixture stirred for 1.5 hours. Chloromethyl pivalate (5.65g, 37.5mmol) was added dropwise and the mixture stirred 2 hours at ambient temperature. The mixture was diluted with ethyl acetate (100ml) and poured onto ice/water (400ml) and 2M hydrochloric acid (4ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate, the combined extracts were washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was triturated with a mixture of ether and petroleum ether, the solid was collected by filtration and dried under vacuum to give 7-benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (10g, 84%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.11(s, 9H); 3.89(s, 3H); 5.3(s, 2H); 5.9(s, 2H); 7.27(s, 1H); 7.35(m, 1H); 7.47(t, 2H); 7.49(d, 2H); 7.51(s, 1H); 8.34(s, 1H)

A mixture of 7-benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (7g, 17.7mmol) and 10% palladium-on-charcoal catalyst (700mg) in ethyl acetate (250ml), DMF (50ml), methanol (50ml) and acetic acid (0.7ml) was stirred under hydrogen at atmospheric pressure for 40 minutes. The catalyst was removed by filtration and the solvent removed from the filtrate by evaporation. The residue was triturated with ether, collected by filtration and dried under vacuum to give 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (4.36g, 80%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.1(s, 9H); 3.89(s, 3H); 5.89(s, 2H); 7.0(s, 1H); 7.48(s, 1H); 8.5(s, 1H)

Diethyl azodicarboxylate (679mg, 3.9mmol) was added dropwise to a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (918mg, 3mmol), triphenylphosphine (1g, 3.9mmol) and 2-(N-methyl-N-(t-butylcarbonyl)amino)ethanol (682mg, 3.9mmol), prepared as described below, in methylene chloride (20ml) and the mixture stirred for 1 hour at ambient temperature. Further 2-(N-methyl-N-(t-butylcarbonyl)amino)ethanol (105mg, 0.6mmol), triphenylphosphine (786mg, 3mmol) and diethyl azodicarboxylate (522mg, 3mmol) were added and the mixture stirred for 30 minutes at ambient temperature. The mixture was concentrated to half volume by evaporation and purified by column chromatography eluting with methylene chloride/ether (7/3 increasing to 1/1) to give 6-methoxy-7-(2-(N-methyl-N-(t-butylcarbonyl)amino)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.3g, 98%).

^{1}H NMR Spectrum: ($CDCl_3$) 1.2(s, 9H); 1.45(s, 9H); 3.05(br s, 3H); 3.72(br s, 2H); 3.98(s, 3H); 4.25(br s, 2H); 5.95(s, 2H); 7.1(br s, 1H); 7.6(s, 1H); 8.2(s, 1H)

A solution of 6-methoxy-7-(2-(N-methyl-N-(t-butylcarbonyl)amino)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.39g, 3mmol) in methylene chloride (4ml) and TFA (4ml) was stirred at ambient temperature for 1 hour. Toluene was added, and the volatiles were removed by evaporation. The residue was triturated with ether and the resulting solid was collected by filtration. The solid was dissolved in water, sodium hydrogen carbonate was added and the aqueous mixture was extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and the solvent removed by evaporation. The residue was triturated with ether and the solid was collected by filtration to give 6-methoxy-7-(2-(methylamino)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (800mg, 73%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 1.13(s, 9H); 2.72(s, 3H); 3.45(br s, 2H); 3.95(s, 3H); 4.5(t, 2H); 5.94(s, 2H); 7.31(s, 1H); 7.6(s, 1H); 8.47(s, 1H)

MS - ESI: 364 $[MH]^+$

A solution of 6-methoxy-7-(2-(methylamino)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (363mg, 1mmol) and 4-chloro-6-methylpyrimidine (257mg, 2mmol), (J. Het. Chem., 1969, 6, 879), in N,N-diisopropylethylamine (2ml) was heated at reflux for 30 minutes. The volatiles were removed by evaporation and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5) to give 6-methoxy-7-(2-(N-methyl-N-(6-methylpyrimidin-4-yl)amino)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (365mg, 80%).

^{1}H NMR Spectrum: ($CDCl_3$) 1.19(s, 9H); 2.36(s, 3H); 3.18(s, 3H); 3.95(s, 3H); 4.09(t, 2H); 4.34(t, 2H); 5.9(s, 2H); 6.3(s, 1H); 7.14(s, 1H); 7.63(s, 1H); 8.17(s, 1H); 8.5(s, 1H)

MS - ESI: 456 $[MH]^+$

A solution of 6-methoxy-7-(2-(N-methyl-N-(6-methylpyrimidin-4-yl)amino)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (365mg, 0.8mmol) in methanolic ammonia (30ml of a 3M solution) was stirred at ambient temperature for 16 hours. The volatiles were removed by evaporation, the residue was triturated with ether, the solid was collected by filtration, washed with ether and dried under vacuum to give 6-methoxy-7-

(2-(N-methyl-N-(6-methylpyrimidin-4-yl)amino)ethoxy)-3,4-dihydroquinazolin-4-one (250mg, 92%).

^{1}H NMR Spectrum: (DMSOd_6; CF_3COOD) 2.44(s, 3H); 3.32 and 3.39(2s, 3H); 3.86 and 3.87(2s, 3H); 4.12(t, 1H); 4.25(t, 1H); 4.42(m, 2H); 7.02 and 7.23(2s, 1H); 7.24(t, 1H); 7.50(s, 1H); 8.55 and 8.8(2m, 1H); 8.78 and 8.80(2s, 1H)

MS - ESI: 342 $[MH]^+$

A mixture of 6-methoxy-7-(2-(N-methyl-N-(6-methylpyrimidin-4-yl)amino)ethoxy)-3,4-dihydroquinazolin-4-one (250mg, 0.73mmol) in thionyl chloride (5ml) and DMF (0.1ml) was heated at reflux for 1 hour. The mixture was diluted with toluene and the volatiles were removed by evaporation. The residue was triturated with methylene chloride/ether, the solid was collected by filtration and dried under vacuum to give 4-chloro-6-methoxy-7-(2-(N-methyl-N-(6-methylpyrimidin-4-yl)amino)ethoxy)quinazoline hydrochloride (260mg, 90%).

2-(N-methyl-N-(t-butylcarbonyl)amino)ethanol was prepared as follows :-

A solution of di-t-butyldicarbonate (4.52g, 20mmol) in THF (10ml) was added to a solution of 2-(N-methylamino)ethanol (1.5g, 20mmol) in a mixture of water (10ml) and THF (10ml). The mixture was stirred at ambient temperature for 18 hours, the THF was removed by evaporation and the aqueous residue was partitioned between ether and water. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated to give 2-(N-methyl-N-(t-butylcarbonyl)amino)ethanol (3g, 85%).

^{1}H NMR Spectrum ($CDCl_3$) 1.46(s, 9H); 2.92(s, 3H); 3.39 (t, 2H); 3.75(t, 2H).

MS - ES: 176 $[MH]^+$

Example 86

Diethyl azodicarboxylate (295µl, 1.8mmol) was added dropwise to a suspension of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (200mg, 0.62mmol), (prepared as described for the starting material in Example 24), 2-(3,5-dimethyl-[1,2,4]-triazol-4-yl)ethanol (114mg, 0.81mmol), (EP 0329357 A1), and triphenylphosphine (492mg, 1.8mmol) in methylene chloride (4ml) and the mixture stirred for 1 hour at ambient temperature. The precipitated solid was collected by filtration, washed with ether and dried under vacuum. The solid was dissolved in methylene chloride/methanol and ethereal hydrogen chloride (2ml of 4.5M solution) was added. The volatiles were removed by evaporation, the residue was

suspended in ether, collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-7-(2-(3,5-dimethyl-[1,2,4]-triazol-4-yl)ethoxy)-6-methoxyquinazoline** hydrochloride (184mg, 54%).

^{1}H NMR Spectrum: (DMSOd_6; CF_3COOD) 2.78(s, 6H); 4.03(s, 3H); 4.57(t, 2H); 4.75(t, 2H); 7.37(s, 1H); 7.46(d, 1H); 7.64(t, 1H); 7.66(d, 1H); 8.31(s, 1H); 8.87(s, 1H)

MS - ESI: 443 $[MH]^+$

Elemental Analysis:	Found	C 48.0	H 4.6	N 16.1
$C_{21}H_{20}N_6O_2ClF\ 1H_2O\ 1.85HCl$	Requires	C 47.7	H 4.6	N 15.9%

Example 87

Diethyl azodicarboxylate (295µl, 1.8mmol) was added dropwise to a solution of the 75/25 mixture of 2-(2,4-dimethylimidazol-1-yl)ethanol and 2-(2,5-dimethylimidazol-1-yl)ethanol (114mg, 0.81mmol), 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (200mg, 0.62mmol), (prepared as described for the starting material in Example 24), and triphenylphosphine (492mg, 1.8mmol) in methylene chloride (4 ml) and the mixture stirred for 4 hours at ambient temperature. Further triphenylphosphine (49mg, 0.18mmol), mixture of imidazolylethanols (26mg, 0.18mmol) and diethyl azodicarboxylate (29µl, 0.18mmol) were added and the mixture stirred for 1 hour. The precipitated solid was collected by filtration, washed with methylene chloride, and dried under vacuum. The solid was dissolved in methylene chloride/methanol and ethereal hydrogen chloride (1.5ml of a 4.5M solution) was added. The volatiles were removed by evaporation, the solid residue was suspended in ether, collected by filtration, washed with ether and dried under vacuum to give a 75/25 mixture of **4-(4-chloro-2-fluoroanilino)-7-(2-(2,4-dimethylimidazol-1-yl)ethoxy)-6-methoxyquinazoline** hydrochloride and **4-(4-chloro-2-fluoroanilino)-7-(2-(2,5-dimethylimidazol-1-yl)ethoxy)-6-methoxyquinazoline** hydrochloride (159mg, 48%).

^{1}H NMR Spectrum: (DMSOd_6; CF_3COOD) 2.23 and 2.43(2s, 3H); 2.73 and 2.76(2s, 3H); 4.02(s, 3H); 4.6(br s, 2H); 4.6 and 4.75(m, 2H); 7.3-7.5(m, 3H); 7.61(t, 1H); 7.68(d, 1H); 8.24(s, 1H); 8.88(s, 1H)

MS - ESI: 442 $[MH]^+$

Elemental analysis:	Found	C 49.9	H 4.6	N 13.3

$C_{22}H_{21}N_5O_3ClF\ 1.1H_2O\ 1.85HCl$ Requires C 50.1 H 4.8 N 13.3%

The starting material was prepared as follows:

2,4-Dimethylimidazole (1.5g, 15.6mmol) was added in portions to a suspension of sodium hydride (936mg of a 60% suspension in mineral oil, 23mmol) in DMF (8ml) and the mixture was stirred for 30 minutes at ambient temperature. 2-Bromoethanol (1.66ml, 23mmol) was added and the mixture stirred at 100°C for 16 hours. The solvent was removed by evaporation and concentrated hydrochloric acid (1ml) was added to the residue. The resulting solid was triturated with methylene chloride, collected by filtration and dried under vacuum. The solid was purified by column chromatography on neutral alumina eluting with methylene chloride/methanol (97/3) and then column chromatography eluting with methylene chloride/methanol (93/7 followed by 90/10) to give a 75/25 mixture of 2-(2,4-dimethylimidazol-1-yl)ethanol and 2-(2,5-dimethylimidazol-1-yl)ethanol (650mg, 29%).
MS - ESI: 140 $[MH]^+$

Example 88

Diethyl azodicarboxylate (236µl, 1.5mmol) was added dropwise to a suspension of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (160mg, 0.5mmol), (prepared as described for the starting material in Example 24), triphenylphosphine (393mg, 1.5mmol) and 2-(3-pyridyl)ethanol (86mg, 0.7mmol), (J.Heterocycl. Chem. 1992, **29**, 1663), in methylene chloride (6ml) and the mixture stirred for 4 hours at ambient temperature. The mixture was poured directly on to a silica column and eluted with methylene chloride/acetonitrile/methanol (60/35/5). The purified solid was dissolved in methylene chloride/methanol and ethereal hydrogen chloride (1.5ml of a 4.5M solution) was added. The volatiles were removed by evaporation, the solid residue was suspended in ether, collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(3-pyridyl)ethoxy)quinazoline** hydrochloride (154mg, 52%).
^1H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 3.45(t, 2H); 4.01(s, 3H); 4.56(t, 2H); 7.44(s, 1H); 7.46(d, 1H); 7.61(t, 1H); 7.67(d, 1H); 8.13(t, 1H); 8.19(s, 1H); 8.71(d, 1H); 8.88(s, 1H); 8.9(d, 1H); 9.01(s, 1H)

MS - ESI: 425 $[MH]^+$

Elemental analysis: Found C 52.7 H 4.3

$C_{22}H_{18}N_4O_2ClF$ $0.8H_2O$ 1.8HCl Requires C 52.3 H 4.3%

Example 89

Diethyl azodicarboxylate (236µl, 1.5mmol) was added dropwise to a suspension of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (160mg, 0.5mmol), (prepared as described for the starting material in Example 24), triphenylphosphine (393mg, 1.5mmol) and 2-(6-methyl-2-pyridyl)ethanol (96mg, 0.7mmol), (J. Chem. Soc. A, 1971, 388), in methylene chloride (6ml) and the mixture stirred for 16 hours at ambient temperature. The mixture was poured directly on to a silica column and eluted with methylene chloride/methanol (95/5). The purified solid was dissolved in methylene chloride/methanol and ethereal hydrogen chloride (1.5ml of a 4.5M solution) was added. The mixture was diluted with ether and the resulting precipitate was collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(6-methyl-2-pyridyl)ethoxy)quinazoline** hydrochloride (97mg, 34%).

^1H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 2.78(s, 3H); 3.64(t, 2H); 3.98(s, 3H); 4.67(t, 2H); 7.46(s, 1H); 7.48(br s, 1H); 7.62(t, 1H); 7.68(dd, 1H); 7.85(d, 1H); 7.94(d, 1H); 8.19(s, 1H); 8.48(t, 1H); 8.88(s, 1H)

MS - ESI: 439 $[MH]^+$

Elemental Analysis: Found C 52.7 H 4.5 N 10.7

$C_{23}H_{20}N_4O_2ClF$ $1H_2O$ 1.8HCl Requires C 52.9 H 4.6 N 10.7%

Example 90

A mixture of 4-chloro-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline (49mg, 0.16mmol) and 3-hydroxyaniline (21mg, 0.19mmol) in isopropanol (3ml) and isopropanolic hydrogen chloride (0.2ml of a 5M solution) was stirred at 80°C for 1 hour. The precipitated solid was collected by filtration, washed with isopropanol and ether and dried under vacuum to give **4-(3-hydroxyanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline** hydrochloride (56mg, 93%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 4.01(s, 3H); 4.64(t, 2H); 4.78(t, 2H); 6.71(d, 1H); 7.1(m, 2H); 7.28(t, 1H); 7.41(s, 1H); 7.74(s, 1H); 7.83(s, 1H); 8.21(s, 1H); 8.87(s, 1H); 9.22(s, 1H)

MS - ESI: 378 [MH]$^+$

Elemental Analysis: Found C 52.7 H 4.9 N 15.1

$C_{20}H_{19}N_5O_3$ $0.6H_2O$ 1.85HCl Requires C 52.7 H 4.9 N 15.4%

The starting material was prepared as follows:

Diethyl azodicarboxylate (435mg, 2.5mmol) was added dropwise to a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (612mg, 2mmol), (prepared as described for the starting material in Example 85), 2-(imidazol-1-yl)ethanol (280mg, 2.5mmol), (J. Med. Chem. 1993, **25** 4052-4060), and triphenylphosphine (655mg, 2.5mmol) in methylene chloride (10ml) at 5°C. The mixture was stirred for 10 minutes at 5°C and then 1 hour at ambient temperature. The mixture was poured directly on to a silica column and eluted with methylene chloride/methanol (95/5) to give 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (640mg, 80%).

^{1}H NMR Spectrum: ($CDCl_3$) 1.19(s, 9H); 3.98(s, 3H); 4.34(m, 2H); 4.45(m, 2H); 5.94(s, 2H); 7.02(s, 1H); 7.07(s, 1H); 7.11(s, 1H); 7.64(s, 1H); 7.67(s, 1H); 8.17(s, 1H)

MS - ESI: 423 [MNa]$^+$

Elemental Analysis: Found C 58.3 H 6.4 N 13.9

$C_{20}H_{24}N_4O_5$ $0.7H_2O$ Requires C 58.2 H 6.2 N 13.6%

A solution of 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (640mg, 1.6mmol) in saturated methanolic ammonia (10ml) was stirred for 15 hours at ambient temperature. The volatiles were removed by evaporation, the solid was triturated with ether, collected by filtration and dried under vacuum to give 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (412mg, 90%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.89(s, 3H); 4.4-4.5(m, 4H); 6.9(s, 1H); 7.16(s, 1H); 7.28(s, 1H); 7.47(s, 1H); 7.7(s, 1H); 7.99(s, 1H)

MS - ESI: 287 [MH]$^+$

Elemental Analysis: Found C 57.8 H 5.2 N 19.3

$C_{14}H_{14}N_4O_3.0.3H_2O$ Requires C 57.7 H 5.1 N 19.2%

A mixture of 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (412mg, 1.44mmol), thionyl chloride (5 ml) and DMF (0.2ml) was heated at reflux for 1 hour. The mixture was diluted with toluene and the volatiles were removed by evaporation. The residue was suspended in methylene chloride, cooled to 0°C and aqueous sodium hydrogen carbonate solution was added. The resulting precipitate was collected by filtration and dried under vacuum to give 4-chloro-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline (258mg, 59%).

^{1}H NMR Spectrum: ($DMSOd_6$) 4.01(s, 3H); 4.47(m, 2H); 4.53(m, 2H); 6.89(s, 1H); 7.27(s, 1H); 7.41(s, 1H); 7.49(s, 1H); 7.70(s, 1H); 8.88(s, 1H)

MS - ESI: 327 $[MNa]^+$

Example 91

Diethyl azodicarboxylate (220µl, 1.4mmol) was added dropwise to a solution of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (150mg, 0.47mmol), (prepared as described for the starting material in Example 24), 2-(1,2,4-triazol-4-yl)ethanol (64mg, 0.56mmol) and triphenylphosphine (369mg, 1.4mmol) in methylene chloride (5ml) and the mixture stirred for 30 minutes at ambient temperature. Further 2-(1,2,4-triazol-4-yl)ethanol (16mg, 0.14mmol), triphenylphosphine (37mg, 0.14mmol) and diethyl azodicarboxylate (22µl, 0.14mmol) was added and the mixture stirred for 1 hour at ambient temperature. The precipitated solid was collected by filtration, washed with methylene chloride and methanol and dried under vacuum. The solid was dissolved in methylene chloride/methanol and ethereal hydrogen chloride (1.5ml of a 2.2M solution) was added. The volatiles were removed by evaporation, the solid residue was suspended in ether, collected by filtration, washed with ether and dried under vacuum to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1,2,4-triazol-4-yl)ethoxy)quinazoline** hydrochloride (93mg, 40%).

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 4.02(s, 3H); 4.66(t, 2H); 4.85(t, 2H); 7.41(s, 1H); 7.46(dd, 1H); 7.62(t, 1H); 7.69(dd, 1H); 8.11(s, 1H); 8.89(s, 1H); 9.55 (s, 2H)

MS - ESI: 415 $[MH]^+$

Elemental analysis: Found C 45.9 H 3.7 N 17.1

$C_{19}H_{16}N_6O_2ClF$ $0.5H_2O$ 2HCl Requires C 45.9 H 3.9 N 16.9%

The starting material was prepared as follows:

A solution of N,N-dimethylformamide azine (1g, 7mmol), (J. Chem. Soc. C, 1967, 1664), p-toluene sulphonic acid (45mg) and ethanolamine (4.3g, 70mmol) in benzene (15ml) was heated at reflux for 8 hours. The mixture was allowed to cool, the solvent was removed by evaporation and the residue was purified by column chromatography eluting with methylene chloride/methanol (90/10 followed by 85/15) to give 2-(1,2,4-triazol-4-yl)ethanol (328mg, 41%).

^{1}H NMR Spectrum: ($CDCl_3$) 3.97(t, 2H); 4.11(t, 2H); 4.9(br s, 1H); 8.06(s, 2H)
MS - ESI: 113 $[MH]^+$

Example 92

1,1'-(azodicarbonyl)dipiperidine (480mg, 1.9mmol) was added in portions to a mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (200mg, 0.63mmol), 3-benzyloxypropanol (150µl, 0.95mmol) and tributylphosphine (459µl, 1.86mmol) in methylene chloride (20ml) at 5°C. The reaction was stirred for 1 hour at 5°C and then for 18 hours at ambient temperature. The mixture was diluted with ether and stirred for 15 minutes. The insolubles were removed by filtration and the volatiles were removed from the filtrate by evaporation. The residue was partitioned between ethyl acetate and water, and the organic layer was separated, dried ($MgSO_4$) and the solvent removed by evaporation. A 1M solution of ethereal hydrogen chloride was added to the residue, the resulting solution was reduced in volume by evaporation and the resulting precipitate was collected by filtration and dried to give **7-(3-benzyloxypropoxy)-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline** hydrochloride (90mg, 31%).

^{1}H NMR Spectrum ($CDCl_3$) 2.12(t, 2H); 3.62(t, 2H); 4.00(t, 3H); 4.28(t, 2H); 4.45(s, 2H); 7.21-7.38(m, 6H); 7.42(d 1H); 7.60(t, 1H); 7.64(dd, 1H); 8.22(s, 1H); 8.80(s, 1H)
MS - ESI: 468 $[MH]^+$

Example 93

1,1`-(azodicarbonyl)dipiperidine (840mg, 3mmol) was added in portions to a mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (315mg, 1mmol), ethyl 4-hydroxymethyl-2-pyridinecarboxylate (250mg, 1.4mmol), (J. Het. Chem. 1993, 30, 631-635) and tributylphosphine (800µl, 3mmol) in methylene chloride (50ml) at 0°C. The mixture was allowed to warm to ambient temperature over 2 hours, the insolubles were removed by filtration and the filtrate was washed with water and brine, dried (Na_2SO_4) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (10:0 increasing to 9:1). The purified product was recrystallised from methylene chloride/hexane to give **4-(4-chloro-2-fluoroanilino)-7-(2-ethoxycarbonylpyrid-4-yl)methoxy-6-methoxyquinazoline** (285mg, 60%).

m.p. 212-214°C

^{1}H NMR Spectrum ($DMSOd_6$) 1.30(t, 3H); 3.96(s, 3H); 4.35(q, 2H); 5.45(s, 2H); 7.14(s, 1H); 7.35(dd, 1H); 7.5-7.6(m, 2H); 7.85(s, 1H); 8.15(s, 1H); 8.35(s, 1H); 8.75(d, 1H); 9.55(s, 1H)

Elemental analysis:	Found	C 58.9	H 4.4	N 12.0	
$C_{24}H_{20}ClFN_4O_4$ 0.5 H_2O	Requires	C 58.7	H 4.4	N 11.5%	

Example 94

1,1`-(azodicarbonyl)dipiperidine (1.68g, 6mmol) was added in portions to a mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (640mg, 2mmol), 4-hydroxymethyl-2-(methylamino)pyridine (385mg, 2.8mmol) and tributylphosphine (1.6ml, 6mmol) in methylene chloride (50ml) at 0°C. The mixture was allowed to warm to ambient temperature over 2 hours, the insolubles were removed by filtration and the filtrate was washed with water and brine, dried (Na_2SO_4) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (10:0 increasing to 9:1). The purified product was dissolved in acetone/methanol and a 1M solution of ethereal hydrogen chloride was added. The resulting precipitate was collected by filtration and dried to give **4-(4-chloro-2-fluoroanilino)-7-(2-(methylamino)pyrid-4-yl)methoxy-6-methoxyquinazoline** hydrochloride (395mg, 45%).

^{1}H NMR Spectrum ($DMSOd_6$) 2.95(d, 3H); 4.05(s, 3H); 5.42(s, 2H); 6.90(d, 1H); 7.15(s, 1H); 7.40(d, 1H); 7.44(s, 1H); 7.58(t, 1H); 7.62(dd, 1H); 7.95(d, 1H); 8.46(s, 1H); 8.75(s, 1H); 9.06(br s, 1H); 11.83(br s, 1H)

MS - ESI: 440 [MH]$^+$

The starting material was prepared as follows :-

A mixture of 2-chloro-4-hydroxymethylpyridine (1.0g, 7mmol), (prepared as described for the starting material in Example 58), and methylamine (30ml of a 30% solution in ethanol) was heated in a Carius tube for 16 hours at 200°C. The mixture was allowed to cool and the mixture partitioned between saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer was separated, dried ($MgSO_4$) and the volatiles removed by evaporation. The residue was purified by column chromatography eluting with ethyl acetate to give 4-hydroxymethyl-2-(methylamino)pyridine (440mg, 46%) as a yellow oil.

^{1}H NMR Spectrum ($DMSOd_6$) 2.72(d, 3H); 4.35(d, 2H); 5.15(t, 1H); 6.30(br d, 1H); 6.35(d, 1H); 6.38(s, 1H); 7.85(d, 1H)

Example 95

1,1'-(azodicarbonyl)dipiperidine (1.68g, 6mmol) was added in portions to a mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (640mg, 2mmol), 4-hydroxymethyl-2-(dimethylamino)pyridine (426mg, 2.8mmol) and tributylphosphine (1.6ml, 6mmol) in methylene chloride (50ml) at 0°C. The mixture was allowed to warm to ambient temperature over 2 hours, the insolubles were removed by filtration and the filtrate was washed with water and brine, dried (Na_2SO_4) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (100:0 increasing to 95:5). The purified product was dissolved in acetone/methanol and a 1M solution of ethereal hydrogen chloride was added. The resulting precipitate was collected by filtration and dried to give **4-(4-chloro-2-fluoroanilino)-7-(2-(dimethylamino)pyrid-4-yl)methoxy-6-methoxyquinazoline** hydrochloride (305mg, 30%).

m.p. 290°C

^{1}H NMR Spectrum ($DMSOd_6$) 3.05(s, 6H); 4.05(s, 3H); 5.45(s, 2H); 6.95(d, 1H); 7.35(s, 1H); 7.42(dd, 1H); 7.56(t, 2H); 7.62(dd, 1H); 8.00(d, 1H); 8.55(s, 1H); 9.80(s, 1H); 11.95(br s, 1H)

MS - ESI: 454 [MH]$^+$

Elemental analysis: Found C 47.2 H 4.9 N 12.1

$C_{33}H_{31}ClFN_5O_3$ 3 HCl H_2O Requires C 47.6 H 4.5 N 12.1%

The starting material was prepared as follows :-

A mixture of 2-chloro-4-hydroxymethylpyridine (1.0g, 7mmol), (prepared as described for the starting material in Example 58), and dimethylamine (30ml of a 30% solution in ethanol) was heated in a Carius tube for 16 hours at 200°C. The mixture was allowed to cool and the mixture partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried ($MgSO_4$) and the volatiles removed by evaporation. The residue was purified by column chromatography eluting with ethyl acetate to give 4-hydroxymethyl-2-(dimethylamino)pyridine (1g, 94%) as a yellow oil.

^{1}H NMR Spectrum ($DMSOd_6$) 3.00(s, 6H); 4.40(d, 2H); 5.20(t, 1H); 6.45(d, 1H); 6.55(s, 1H); 7.96(d, 1H)

MS - ESI: 153 $[MH]^+$

Example 96

A mixture of 4-(3-hydroxyprop-2-en-1-yl)pyridine (180mg, 1.3mmol) and thionyl chloride (0.3ml) in toluene (10ml) was stirred at room temperature for 2 hours. The volatiles were removed by evaporation to give crude 4-(3-chloroprop-2-en-1-yl)pyridine hydrochloride (180mg, 0.94mmol)) This product was added to a mixture of 4-(4-chloro-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (500mg, 1.6mmol) and potassium carbonate (500mg, 4.9mmol) in DMF (20 ml) and the mixture stirred at 100°C for 1 hour. The reaction mixture was allowed to cool and partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (100/0 increasing to 95/5) and then by reverse phase (C18) HPLC eluting with methanol/water (30/70 increasing to 50/50) to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(pyrid-4-yl)prop-2-en-1-yloxy)quinazoline** (15mg, 4%).

^{1}H NMR Spectrum ($DMSOd_6$) 4.00(s, 3H); 5.05(d, 2H); 6.93(d, 1H); 7.11(dt, 1H); 7.40(s, 1H); 7.40-7.43(m, 2H); 7.60(t, 1H); 7.65(d, 1H); 7.80(m, 2H); 8.05(s, 1H); 8.70(br s, 2H)

MS - ESI: 437 $[MH]^+$

The starting material was prepared as follows :-

n-Butyllithium (25ml of a 1.6M solution in hexane, 40mmol) was added dropwise to a stirred suspension of 2-hydroxyethyltriphenylphosphonium bromide (7.74g, 20mmol) in THF (50ml) at -70°C and the mixture allowed to warm to -30°C and stirred for 2 hours. 4-Pyridinecarboxaldehyde (2.16g, 20mmol) was added to the resulting red solution, and the mixture stirred for 1 hour at -30°C and then cooled to -70°C. n-Butyllithium (12.5ml of a 1.6M solution in hexane, 20mmol) was added and the reaction mixture stirred at -70°C for 1 hour. The mixture was quenched with isopropanol and allowed to warm to ambient temperature. Saturated aqueous ammonium chloride solution was added, the organic layer separated and the aqueous layer extracted with ethyl acetate (3x50ml). The combined extracts were washed with brine and dried ($MgSO_4$) and the volatiles removed by evaporation. The residue was purified by column chromatography eluting with ethyl acetate to give 4-(3-hydroxyprop-2-en-1-yl)pyridine

MS - ESI: 136 $[MH]^+$

Example 97

A suspension of 4-chloro-7-(2-(1,2,4-triazol-1-yl)ethoxy)-6-methoxyquinazoline (214mg, 0.7mmol), 4-bromo-2-fluoroaniline (160mg, 0.84mmol) in isopropanolic hydrogen chloride (1ml of a 5M solution) and isopropanol (5ml) was heated at 80°C for 1 hour. The mixture was allowed to cool, the precipitate was collected by filtration, washed with isopropanol and then ether and dried under vacuum at 70°C to give **4-(4-bromo-2-fluoroanilino)-7-(2-(1,2,4-triazol-1-yl)ethoxy)-6-methoxyquinazoline** hydrochloride (55mg, 15%).

^1H NMR Spectrum ($DMSOd_6$) 3.99(s, 3H); 4.62(t, 2H); 4.75(t, 2H); 7.37(s, 1H); 7.5-7.7(m, 2H); 7.81(d, 1H); 8.04(s, 1H); 8.24(s, 1H); 8.63(s, 1H); 8.84(s, 1H); 11.52(s, 1H)

MS - ESI: 459 $[MH]^+$

Elemental analysis	Found	C 41.8	H 3.4	N 15.6	
$C_{19}H_{16}BrFN_6O_2$ 0.8 H_2O 1.9 HCl	Requires	C 42.0	H 3.6	N 15.5%	

The starting material was prepared as follows :-

Diethyl azodicarboxylate (1.1ml, 7mmol) was added dropwise to a solution of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.7 g, 5.55mmol), 2-(1,2,4-triazol-1-yl)ethanol (791mg, 7mmol), (Ann. Pharm. Fr. 1977,35,503-508) and triphenylphosphine (1.8g, 7mmol) cooled at 5°C. The mixture was allowed to warm to ambient temperature and stirred for 1 hour. The mixture was poured directly on to a column of silica and eluted with methylene chloride/methanol (95/5) to give 6-methoxy-3-((pivaloyloxy)methyl)-7-(2-(1,2,4-triazol-1-yl)ethoxy)-3,4-dihydroquinazolin-4-one (1.64g, 74%).

^{1}H NMR Spectrum (DMSOd_6, CF_3COOD) 1.12(s, 9H); 3.87(s, 3H); 4.57(t, 2H); 4.74(t, 2H); 5.92(s, 2H); 7.24(s, 1H); 7.51(s, 1H); 8.36(d, 1H); 8.41(s, 1H); 9.02(d, 1H)

MS - ESI: 424 $[MNa]^+$

Elemental analysis	Found	C 56.5	H 6.0	N 17.6
$C_{19}H_{23}N_5O_5$	Requires	C 56.9	H 5.8	N 17.%

A solution of 6-methoxy-3-((pivaloyloxy)methyl)-7-(2-(1,2,4-triazol-1-yl)ethoxy)-3,4-dihydroquinazolin-4-one (1.6g, 4mmol) in saturated methanolic ammonia (25ml) was stirred at ambient temperature for 2 days. The volatiles were removed by evaporation, the solid residue was triturated with ether, collected by filtration and dried under vacuum to give 6-methoxy-7-(2-(1,2,4-triazol-1-yl)ethoxy)-3,4-dihydroquinazolin-4-one (1.11g, 98%)

^{1}H NMR Spectrum (DMSO d_6) 3.84(s, 3H); 4.51(t, 2H); 4.65(t, 2H); 7.16(s, 1H); 7.44(s, 1H); 7.89(s, 1H); 7.99(s, 1H); 8.55(s, 1H)

MS - EI: 287 $[M]^+$

Elemental analysis	Found	C 53.9	H 4.6	N 24.6
$C_{13}H_{13}N_5O_3$	Requires	C 54.4	H 4.6	N 24.4

A solution of 6-methoxy-7-(2-(1,2,4-triazol-1-yl)ethoxy)-3,4-dihydroquinazolin-4-one (1.11g, 3.86mmol) and DMF (0.6 ml) in thionyl chloride (15ml) was heated at reflux for 1 hour. The mixture was allowed to cool, toluene was added and the volatiles were removed by evaporation. The residue was partitioned between methylene chloride and water and the aqueous layer was adjusted to pH8.5 with saturated aqueous sodium hydrogen carbonate solution. The organic layer was separated, washed with brine, dried ($MgSO_4$), and the solvent removed by evaporation. The residue was purified by column chromatography eluting with

methylene chloride/methanol (95/5). The purified solid was triturated with ether, collected by filtration, washed with water and then ether, and dried under vacuum to give 4-chloro-6-methoxy-7-(2-(1,2,4-triazol-1-yl)ethoxy)quinazoline (756mg, 65%).

^{1}H NMR Spectrum (DMSO d_6) 3.97(s, 3H); 4.65(dd, 2H); 4.70(dd, 2H); 7.39(s, 1H); 7.52(s, 1H); 7.99(s, 1H); 8.57(s, 1H); 8.89(s, 1H)

MS - ESI: 306 $[MH]^+$

Example 98

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)	Tablet I	mg/tablet
	Compound X	100
	Lactose Ph.Eur	182.75
	Croscarmellose sodium	12.0
	Maize starch paste (5% w/v paste)	2.25
	Magnesium stearate	3.0

(b)	Tablet II	mg/tablet
	Compound X	50
	Lactose Ph.Eur	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0
	Polyvinylpyrrolidone (5% w/v paste)	2.25
	Magnesium stearate	3.0

(c)	Tablet III	mg/tablet
	Compound X	1.0
	Lactose Ph.Eur	93.25

Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d) Capsule — mg/capsule

Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e) Injection I — (50 mg/ml)

Compound X	5.0% w/v
1N Sodium hydroxide solution	15.0% v/v
0.1N Hydrochloric acid (to adjust pH to 7.6)	
Polyethylene glycol 400	4.5% w/v
Water for injection to 100%	

(f) Injection II — (10 mg/ml)

Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1N Sodium hydroxide solution	15.0% v/v
Water for injection to 100%	

(g) Injection III — (1mg/ml,buffered to pH6)

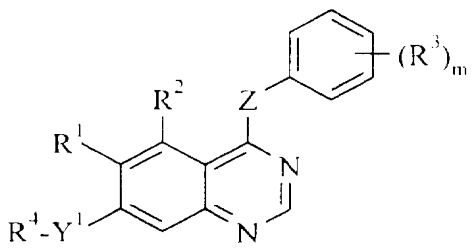
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection to 100%	

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIMS

1. A quinazoline derivative of the formula I:



(I)

[wherein:

Y^1 represents -O-, -S-, $-CH_2-$, -SO-, $-SO_2-$, $-NR^5CO-$, $-CONR^6-$, $-SO_2NR^7-$, $-NR^8SO_2-$ or $-NR^9-$ (wherein R^5, R^6, R^7, R^8 and R^9 each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl);

R^1 represents hydrogen, hydroxy, halogeno, nitro, trifluoromethyl, cyano, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, or $NR^{10}R^{11}$ (wherein R^{10} and R^{11}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl);

R^2 represents hydrogen, hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, cyano, amino or nitro;

m is an integer from 1 to 5;

R^3 represents hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino or nitro;

R^4 is selected from one of the following eight groups:

1) X^1 (wherein X^1 represents a pyridone group, a phenyl group or a 5 or 6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which pyridone, phenyl or heterocyclic group may carry up to 5 substituents selected from halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, $-CONR^{12}R^{13}$ and $-NR^{14}COR^{15}$ (wherein R^{12}, R^{13}, R^{14} and R^{15}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

2) C_{1-5}alkylX^1 (wherein X^1 is as defined hereinbefore);

3) C_{2-5}alkenylX^1 (wherein X^1 is as defined hereinbefore);

4) C_{2-5}alkynylX^1 (wherein X^1 is as defined hereinbefore);

5) C_{1-5}alkylY^2X^1 (wherein Y^2 represents -O-, -S-, -SO-, $-SO_2-$, -OCO-, $-NR^{16}CO-$, $-CONR^{17}-$, $-SO_2NR^{18}-$, $-NR^{19}SO_2-$ or $-NR^{20}-$ (wherein R^{16}, R^{17}, R^{18}, R^{19} and R^{20} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and X^1 is as defined hereinbefore)

6) C_{2-5}alkenylY^3X^1 (wherein Y^3 represents -O-, -S-, -SO-, $-SO_2-$, -OCO-, $-NR^{21}CO-$, $-CONR^{22}-$, $-SO_2NR^{23}-$, $-NR^{24}SO_2-$ or $-NR^{25}-$ (wherein R^{21}, R^{22}, R^{23}, R^{24} and R^{25} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and X^1 is as defined hereinbefore);

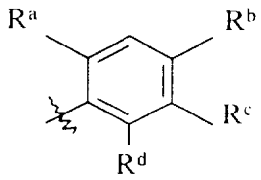
7) C_{2-5}alkynylY^4X^1 (wherein Y^4 represents -O-, -S-, -SO-, $-SO_2-$, -OCO-, $-NR^{26}CO-$, $-CONR^{27}-$, $-SO_2NR^{28}-$, $-NR^{29}SO_2-$ or $-NR^{30}-$ (wherein R^{26}, R^{27}, R^{28}, R^{29} and R^{30} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and X^1 is as defined hereinbefore); and

8) C_{1-3}alkylY^5C_{1-3}alkylX^1 (wherein Y^5 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{31}CO-$, $-CONR^{32}-$, $-SO_2NR^{33}-$, $-NR^{34}SO_2-$ or $-NR^{35}-$ (wherein R^{31}, R^{32}, R^{33}, R^{34} and R^{35} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and X^1 is as defined hereinbefore); Z represents -NH-, -O-, -S-, or $-CH_2-$; with the proviso that where R^4 is selected from one of the groups 1), 2), and 5) above and X^1 is unsubstituted phenyl or substituted phenyl with 1 to 2 substituents selected from halogeno, C_{1-4}alkyl and C_{1-4}alkoxy, then m is an integer from 3 to 5 and/or Z is -O-, -S-, or $-CH_2-$];and salts thereof.

2. A quinazoline derivative as claimed in claim 1 wherein R^1 represents hydrogen, hydroxy, methyl, ethyl, methoxy or ethoxy.

3. A quinazoline derivative as claimed in claim 1 or claim 2 wherein R^2 is hydrogen.

4. A quinazoline derivative as claimed in any one of the preceding claims wherein the phenyl group bearing $(R^3)_m$ is of the formula:-



(IIa)

(wherein:

R^a represents hydrogen, methyl, fluoro or chloro;

R^b represents hydrogen, methyl, methoxy, bromo, fluoro or chloro;

R^c represents hydrogen or hydroxy; and

R^d represents hydrogen, fluoro or chloro.

5. A quinazoline derivative as claimed in any one of the preceding claims wherein Z is NH.

6. A qunazoline derivative as claimed in any one of the preceding claims wherein Y^1 represents -O-, -S-, $-CH_2-$, $-NR^5CO-$, NR^8SO_2- or -NH- (wherein R^5 and R^8 each independently represent hydrogen, C_{1-2} alkyl or C_{1-2} alkoxyethyl).

7. A quinazoline derivative as claimed in any one of the preceding claims wherein the moiety X^1 in the group R^4 represents a pyridone group or a 5 or 6- membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which pyridone or heterocyclic group may, if desired, be substituted as defined in claim 1.

8. A quinazoline derivative as claimed in claim 7 wherein the moiety X^1 represents a pyridone, pyridyl, imidazolyl, thiazolyl, thienyl, triazolyl or pyridazinyl group which may, if desired, be substituted as defined in claim 1.

9. A quinazoline derivative as claimed in any one of the preceding claims wherein R^4 represents the group $X^1-Y^6-(CH_2)_n-$ in which Y^6 is a direct bond -O-, -S- or -NH-, n is an integer from 1 to 3 and X^1 is as defined in any one of claims 1, 7 and 8.

10. A quinazoline derivative as claimed in claim 1 selected from :-

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(4-pyridyloxy)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-[2-(4-oxo-1,4-dihydro-1-pyridyl)ethoxy]quinazoline

4-(4-chloro-2-fluoroanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(4-pyridyl)propoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(4-pyridyl)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((4-pyridyl)methoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(2-methylimidazol-1-yl)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1-methylimidazol-2-ylthio)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1,2,4-triazol-1-yl)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-(4-pyridyl)amino)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1-methylimidazol-2-yl)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-7-((2-cyano-4-pyridyl)methoxy)-6-methoxyquinazoline

and salts thereof.

11. A quinazoline derivative as claimed in claim 1 selected from:-

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyridylmethoxy)quinazoline

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(2-pyridylmethoxy)quinazoline

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(1-methylimidazol-2-ylmethoxy)quinazoline

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(2-methylthiazol-4-ylmethoxy)quinazoline

7-(2-acetamidothiazol-4-ylmethoxy)-4-(3-hydroxy-4-methylanilino)-6-methoxyquinazoline

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyridylpropoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyridylpropoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-(4-pyridylmethoxy)quinazoline

7-benzyloxy-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline

7-benzyloxy-4-(2-fluoro-5-hydroxy-4-methylphenoxy)-6-methoxyquinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-((2-methylthiazol-4-yl)methoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-7-(4-pyridylmethoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-((1-methylimidazol-2-yl)methoxy)quinazoline

7-((2-acetamidothiazol-4-yl)methoxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline

7-benzyloxy-4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxyquinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-(3-(4-pyridyl)propoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-(2-(4-pyridyl)ethoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxy-7-(3-thienylmethoxy)quinazoline

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-((1-methylbenzimidazol-2-yl)methoxy)quinazoline

7-((2-chloro-6-methyl-4-pyridyl)methoxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline

4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-((4 pyridyl)methoxy)quinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-((4-pyridyl)methoxy)quinazoline

7-((2-chloro-4-pyridyl)methoxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline

7-(3,4-difluorobenzyloxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-((1-methylimidazol-2-yl)methoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-7-((1-methylimidazol-2-yl)methoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-7-(2-(1,2,4-triazol-1-yl)ethoxy)quinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-((3-thienyl)methoxy)quinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-(2-(4-pyridyl)ethoxy)quinazoline

4-(2-fluoro-5-hydroxy-4-methylanilino)-7-((4-pyridyl)carboxamido)quinazoline

and salts thereof.

12. A quinazoline derivative as claimed in claim 1 selected from:-

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(3-pyridylmethoxy)quinazoline

4-(3-hydroxy-4-methylanilino)-6-methoxy-7-(3-thienylmethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(2-pyridyloxy)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-[N-methyl-N-(4-pyridyl)]aminoethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-[2-(2-oxo-1,2-dihydro-1-pyridyl)ethoxy]quinazoline

7-(4 cyanobenzyloxy)-4-(2-fluoro-5-hydroxy-4-methylanilino)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(2-methylimidazol-1-yl)propoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((2-methyl-4-pyridyl)methoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(2-oxo-1,2-dihydro-1-pyridyl)propoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(1-methylimidazol-2-ylthio)propoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(3-(4-pyridyloxy)propoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(4-pyridylthio)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(3-pyridyloxy)ethoxy)quinazoline

7-benzyloxy-4-(2-fluoro-5-hydroxy-4-methylanilino)quinazoline

7-benzyloxy-4-(4-chloro-2-fluoro-5-hydroxyanilino)quinazoline

4-(4-chloro-2-fluoro-5-hydroxyanilino)-6-methoxy-7-((2-methylthiazol-4-yl)methoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-((3-thienyl)methoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-methyl-N-(pyridazin-4-yl)amino)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(N-methyl-N-(6-methylpyrimidin-4-yl)amino)ethoxy)quinazoline

4-(4-chloro-2-fluoroanilino)-7-(2-(3,5-dimethyl-[1,2,4]-triazol-4-yl)ethoxy)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-7-(2-(2,4-dimethylimidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-7-(2-(2,5-dimethylimidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(3-hydroxyanilino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(2-(1,2,4-triazol-4-yl)ethoxy)quinazoline

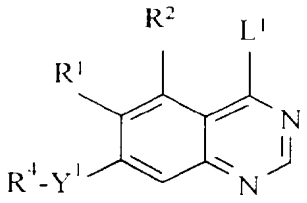
4-(4-bromo-2-fluoroanilino)-7-(2-([1,2,4]-triazol-1-yl)ethoxy)-6-methoxyquinazoline

and salts thereof.

13. A quinazoline derivative as claimed in any one of the preceding claims in the form of a pharmaceutically acceptable salt.

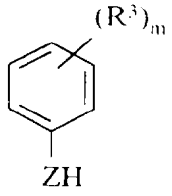
14. A process for the preparation of a quinazoline derivative of formula I or salt thereof (as defined in claim 1) which comprises:-

(a) the reaction of a compound of the formula III:



(III)

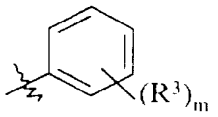
(wherein R^1, R^2, R^4 and Y^1 are as defined in claim 1 and L^1 is a displaceable group), with a compound of the formula IV:



(IV)

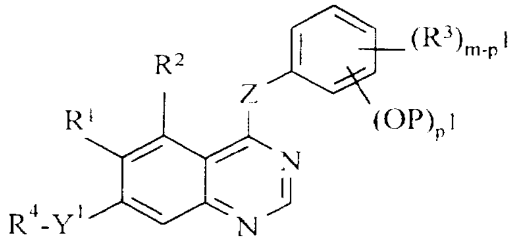
(wherein Z, R^3 and m are as defined in claim 1) whereby to obtain compounds of the formula I and salts thereof;

(b) for the preparation of compounds of formula I and salts thereof in which the group of formula IIb:-



(IIb)

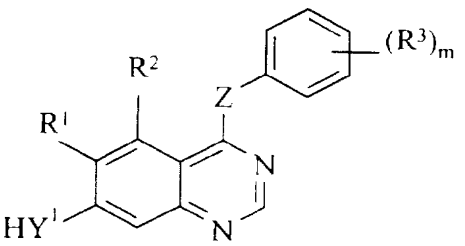
(wherein R^3 and m are as defined in claim 1) represents a phenyl group carrying one or more hydroxy groups, the deprotection of a compound of formula V:



(V)

(wherein Y^1, m, R^1, R^2, R^3, R^4 and Z are as defined in claim 1, P represents a phenolic hydroxy protecting group and p^1 is an integer from 1 to 5 equal to the number of protected hydroxy groups and such that $m-p^1$ is equal to the number of R^3 substituents which are not protected hydroxy).

(c) for the preparation of those compounds of formula I and salts thereof wherein the substituent Y^1 is -O-, -S- or $-NR^9-$, the reaction, of a compound of the formula VI:



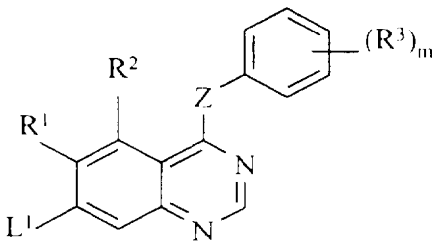
(VI)

(wherein m, Y^1, R^1, R^2, R^3 and Z are as defined in claim 1) with a compound of formula VII:

$$R^4\text{-}L^1 \qquad \text{(VII)}$$

(wherein R^4 is as defined in claim 1 and L^1 is as herein defined);

(d) the reaction of a compound of the formula VIII:



(VIII)

(wherein R^1, R^2, R^3, Z and m are as defined in claim 1 and L^1 is as herein defined) with a compound of the formula IX:

$$R^4\text{-}Y^1\text{-}H \qquad \text{(IX)}$$

(wherein R^4 and Y^1 are as defined in claim 1);

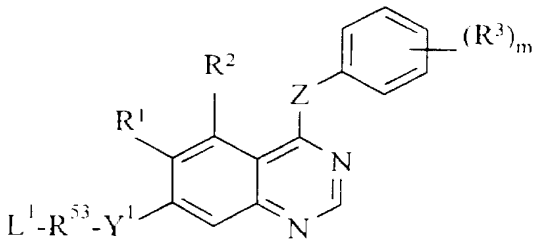
(e) for the preparation of compounds of formula I and salts thereof wherein R^4 is C_{1-5}alkylX^2, [wherein X^2 is selected from one of the following three groups:

1) X^1 (wherein X^1 is as defined in claim 1);

2) Y^7X^1 (wherein Y^7 represents -O-, -S-, -SO_2-, -NR^{47}CO-, -$NR^{48}SO_2$- or -NR^{49}- (wherein R^{47}, R^{48} and R^{49} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and X^1 is as defined in claim 1); and

3) Y^8C_{1-5}alkylY^5X^1 (wherein Y^8 represents -O-, -S-, -SO_2-, -NR^{50}CO-, -$NR^{51}SO_2$- or -NR^{52}- (wherein R^{50}, R^{51} and R^{52} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and Y^5 and X^1 are as defined in claim 1);]

the reaction of a compound of the formula X:



(X)

(wherein Y^1, R^1, R^2, R^3, Z and m are as defined in claim 1, L^1 is as defined herein and R^{53} is C_{1-5}alkyl) with a compound of the formula XI:

$$X^2\text{-}H \qquad \text{(XI)}$$

(wherein X^2 is as defined herein) to give a compound of the formula I;

(f) for the preparation of those compounds of formula I and salts thereof wherein the substituent R^1 is represented by $NR^{10}R^{11}$, where one or both of R^{10} and R^{11} are C_{1-5}alkyl, the reaction of compounds of formula I wherein the substituent R^1 is an amino group with an alkylating agent;

(g) for the preparation of those compounds of formula I and salts thereof wherein one or more of the substituents R^1, R^2 or R^3 is an amino group, the reduction of a corresponding compound of formula I wherein the substituent(s) at the corresponding position(s) of the quinazoline and/or phenyl ring is/are a nitro group(s); and when a pharmaceutically acceptable salt of a quinazoline derivative of formula I is required, reaction of the compound obtained with an acid or base whereby to obtain the desired pharmaceutically acceptable salt.

15. A pharmaceutical composition which comprises as active ingredient a quinazoline derivative of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient or carrier.

16. A method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined in claim 1.

INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/GB 96/03075

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/94 C07D239/88 C07D401/12 C07D403/12 C07D409/12
C07D413/12 C07D417/12 A61K31/505

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.
A	EP 0 566 226 A (ZENECA LTD.) 20 October 1993 cited in the application see claims 1,11	1,5,15
A	EP 0 635 498 A (ZENECA LTD.) 25 January 1995 cited in the application see claims 1,11	1,5,15
A	EP 0 520 722 A (I.C.I. PLC) 30 December 1992 cited in the application see claims 1,2	1,5,15
A,P	WO 96 30347 A (PFIZER INC.) 3 October 1996 see claims 1,24; examples 38,39,56	

-/--

[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

Date of the actual completion of the international search	Date of mailing of the international search report
1 April 1997	11.04.97

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	Hass, C

Form PCT ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB 96/03075

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 96 15118 A (ZENECA LTD.) 23 May 1996 see claims 1,11	1,5,15
A,P	WO 96 09294 A (THE WELLCOME FOUNDATION LTD.) 28 March 1996 see claims 1,7,9,20	1,5,15
A	WO 95 21613 A (SUGEN INC. ET AL.) 17 August 1995 see abstract; claims 2,8	1,5,15
A	EP 0 326 307 A (KYOWA HAKKO KOGYO CO., LTD.) 2 August 1989 see claims 1,5; page 23, compound 45 (example 48)	1,5,15

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 96/03075

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 16 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 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 searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/GB 96/03075

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 566226 A	20-10-93	AT 130000 T	15-11-95
		AU 661533 B	27-07-95
		AU 3101093 A	22-07-93
		CA 2086968 A	21-07-93
		DE 69300754 D	14-12-95
		DE 69300754 T	28-03-96
		ES 2078798 T	16-12-95
		HU 9500185 A	28-07-95
		NZ 245662 A	26-09-95
		SK 1693 A	09-09-93
		US 5457105 A	10-10-95
		ZA 9300015 A	20-07-93
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		WO 9503283 A	02-02-95
		JP 9500636 T	21-01-97
		US 5475001 A	12-12-95
		ZA 9405156 A	19-01-95
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		AU 651215 B	14-07-94
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		NO 180105 B	11-11-96
		NZ 243082 A	24-02-95
		SK 182792 A	09-08-95
WO 9630347 A	03-10-96	AU 5040696 A	10-10-96
		CN 1137037 A	04-12-96
		NO 961299 A	01-10-96
		PL 313541 A	14-10-96
WO 9615118 A	23-05-96	AU 3813095 A	06-06-96
		ZA 9509572 A	13-05-96
WO 9609294 A	28-03-96	AU 3482495 A	09-04-96

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. nal Application No
PCT/GB 96/03075

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9521613 A	17-08-95	AU 1842395 A	29-08-95
		CA 2182949 A	17-08-95
		EP 0748219 A	18-12-96
EP 326307 A	02-08-89	AT 110071 T	15-09-94
		DE 68917485 D	22-09-94
		DE 68917485 T	09-02-95
		JP 2022274 A	25-01-90
		US 5063227 A	05-11-91

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	
Serial Number:	19/043,275	Examiner:	Not Yet Assigned
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**5486**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: February 5, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☒ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a

patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☒ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☒ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $200.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (50535-710.304).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: February 5, 2025

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79641

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

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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	19/043,275
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	
				Examiner Name	Not Yet Assigned
Sheet	1	of	9	Attorney Docket Number	50535-710.304

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-4328245	05-04-1982	YU; Cheng-Der et al.	
	002	US-4409239	10-11-1983	YU; Cheng-Der	
	003	US-4410545	10-18-1983	YU; Cheng-Der et al.	
	004	US-4861760	08-29-1989	MAZUEL; Claude et al.	
	005	US-4911920	03-27-1990	JANI; Rajni et al.	
	006	US-5212162	05-18-1993	MISSEL; Paul J. T. et al.	
	007	US-5403841	04-04-1995	LANG; John C. et al.	
	008	US-10849908	12-01-2020	HOWERTON; Alexis et al.	
	009	US-11007201	05-18-2021	HOWERTON; Alexis et al.	
	010	US-11304950	04-19-2022	HOWERTON et al.	
	011	US-11311549	04-26-2022	HOWERTON; Alexis et al.	
	012	US-11344557	05-31-2022	HOWERTON; Alexis et al.	
	013	US-11351177	06-07-2022	HOWERTON; Alexis et al.	
	014	US-12115166	10-15-2024	HOWERTON; Alexis et al.	
	015	US-20100196389	08-05-2010	EVANS-FREKE; Stephen	
	016	US-20100222339	09-02-2010	CHEN; Zhaogen et al.	
	017	US-20170020877	01-26-2017	GRIGORIADIS; Dimitri E.	
	018	US-20220143037	05-12-2022	HOWERTON; Alexis et al.	
	019	US-20220211711	07-07-2022	HOWERTON; Alexis et al.	

Examiner Signature		Date Considered	

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				Examiner Name	Not Yet Assigned
Sheet	2	of	9	Attorney Docket Number	50535-710.304

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[2]–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-101516887-A	08-26-2009	LILLY CO ELI [US]	Abstract:	☒
	002	CN-106102740-A	11-09-2016	NEUROCRINE BIOSCIENCES INC.	Abstract:	☒
	003	JP-2010504344-A	02-12-2010	ELI LILLY AND CO.	Machine Translation:	☒
	004	JP-2017503030-A	01-26-2017	NEUROCRINE BIOSCIENCES, INC.	Machine Translation:	☒
	005	JP-H0971528-A	03-18-1997	HAYASHIBARA BIOCHEM LAB [JP]	Abstract:	☒
	006	WO-0040529-A1	07-13-2000	ANGIOGENE PHARM LTD [GB], et al.		☐
	007	WO-0041669-A2	07-20-2000	ANGIOGENE PHARM LTD [GB], et al.		☐
	008	WO-0192224-A1	12-06-2001	ASTRAZENECA AB [SE], et al.		☐
	009	WO-0204434-A1	01-17-2002	ANGIOGENE PHARM LTD [GB], et al.		☐
	010	WO-0208213-A1	01-31-2002	ANGIOGENE PHARM LTD [GB], et al.		☐

Examiner Signature		Date Considered	

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				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	
				Examiner Name	Not Yet Assigned
Sheet	3	of	9	Attorney Docket Number	50535-710.304

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	011	WO-2007109853-A1	10-04-2007	VELACOR THERAPEUTICS PTY LTD [AU], et al.		☐
	012	WO-2008036579-A1	03-27-2008	LILLY CO ELI [US], et al.		☐
	013	WO-2015112642-A1	07-30-2015	NEUROCRINE BIOSCIENCES INC [US]		☐
	014	WO-2019036472-A1	02-21-2019	SPRUCE BIOSCIENCES INC [US]		☐
	015	WO-2019036503-A1	02-21-2019	SPRUCE BIOSCIENCES INC [US]		☐
	016	WO-2019210266-A1	10-31-2019	SPRUCE BIOSCIENCES INC [US]		☐
	017	WO-9722596-A1	06-26-1997	ZENECA LTD [GB], et al.		☐
	018	WO-9730035-A1	08-21-1997	ZENECA LTD [GB], et al.		☐
	019	WO-9732856-A1	09-12-1997	ZENECA LTD [GB], et al.		☐
	020	WO-9813354-A1	04-02-1998	ZENECA LTD [GB], et al.		☐
	021	WO-9902166-A1	01-21-1999	ANGIOGENE PHARM LTD [GB], et al.		☐

Examiner Signature		Date Considered	

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				First Named Inventor	HOWERTON; Alexis
				Art Unit	
				Examiner Name	Not Yet Assigned
Sheet	4	of	9	Attorney Docket Number	50535-710.304

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	AL-MUHAMMED, J. et al. In-vivo studies on dexamethasone sodium phosphate liposomes. Journal of microencapsulation 13(3):293-306 (1996).	☐
	002	BERGE, Stephen M. et al. Pharmaceutical Salts. Journal of Pharmaceutical Sciences 66(1):1-19 (1977).	☐
	003	CHEN, Hua-dong. et al. Ovarian adrenal rest tumors undetected by imaging studies and identified at surgery in three females with congenital adrenal hyperplasia unresponsive to increased hormone therapy dosage. Endocrine pathology 28(2):146-151 (2017).	☐
	004	CHONN, Archadio et al. Recent Advances in Liposomal Drug-delivery Systems. Current Opinion in Biotechnology 6(6):698-708 (1995).	☐
	005	Co-pending U.S. Application No. 18/941,832, inventors HOWERTON; Alexis et al., filed on November 08, 2024.	☐
	006	Co-pending U.S. Application No. 19/043,264, inventors HOWERTON; Alexis et al., filed on January 31, 2025.	☐
	007	Co-pending U.S. Application No. 19/043,303, inventors HOWERTON; Alexis et al., filed on January 31, 2025.	☐
	008	EYLES et al. Oral delivery and fate of poly(lactic acid) microsphere-encapsulated interferon in rats. J Pharm Pharmacol. 49(7):669-74 (1997).	☐
	009	GAO, Zhi-Hui. et al. Controlled Release of a Contraceptive Steroid From Biodegradable and Injectable Gel Formulations: in Vitro Evaluation. Pharmaceutical research 12(6):857-863 (1995).	☐
	010	JIN et al. Testicular adrenal rest tumors in a patient with untreated congenital adrenal hyperplasia. Korean J Pediatr 2011;54(3):137-140.	☐

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				First Named Inventor	HOWERTON; Alexis
				Art Unit	
				Examiner Name	Not Yet Assigned
Sheet	5	of	9	Attorney Docket Number	50535-710.304

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	011	KAPRARA, et al. The corticotropin releasing factor system in cancer: expression and pathophysiological implications. Cellular and molecular life sciences 67(8):1293-1306 (2010).	☐
	012	MENDES-DOS-SANTOS et al. Prevalence of Testicular Adrenal Rest Tumor and Factors Associated with Its Development in Congenital Adrenal Hyperplasia. Hormone Res. In Paed. 90:161-168 (2018).	☐
	013	MUNSON, Peter et al. Ligand: a Versatile Computerized Approach for Characterization of Ligand-binding Systems. Analytical Biochemistry 107(1):220-239 (1980).	☐
	014	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Granting Institution of Post-Grant Review of U.S. Patent No. 11,007,201 dated December 1, 2023 (pp. 1-38) (PGR2022-00025).	☐
	015	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Final Written Decision of Post-Grant Review of U.S. Patent No. 10,849,908 dated November 26, 2024 (pp. 1-62) (PGR2021-00088).	☐
	016	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Final Written Decision of Post-Grant Review of U.S. Patent No. 11,007,201 dated November 27, 2024 (pp. 1-60) (PGR2022-00025).	☐
	017	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petition for Post Grant Review of U.S. Patent No. 10,849,908 dated May 28, 2021 (pp. 1-90) (PGR2021-00088).	☐
	018	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petition for Post Grant Review of U.S. Patent No. 11,007,201 dated February 18, 2022 (pp 1-92) (PGR2022-00025).	☐

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	019	OSTRO, Mark J. et al. Use of Liposomes as Injectable-drug Delivery Systems. American Journal of Hospital Pharmacy 46(8):1576-1587 (1989).	☐
	020	PCT/US2019/029486 International Invitation to Pay Additional Fees dated June 4, 2019.	☐
	021	PCT/US2019/029486 International Search Report and Written Opinion dated August 12, 2019.	☐
	022	RAO. Recent developments of collagen-based materials for medical applications and drug delivery systems. J Biomater Sci Polym Ed. 7(7):623-45 (1995).	☐
	023	REICHMAN et al. Fertility in Patients with Congenital Adrenal Hyperplasia. Fertility and Sterility, Vol. 101, No. 2, 2014. 301-309.	☐
	024	REISCH et al. Testicular adrenal rest tumors develop independently of long-term disease control: a longitudinal analysis of 50 adult men with congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency. J. Clin. Endocrinol. Metab. 98(11):E1820-E1826 (2013).	☐
	025	SMEETS et. al. Molecular characterization of testicular adrenal rest tumors in congenital adrenal hyperplasia: lesions with both adrenocortical and Leydig cell features. JCEM 100(3):E524-E530 (2015).	☐
	026	TIOSANO et al. Ovarian adrenal rest tumor in a congenital adrenal hyperplasia patient with adrenocorticotropin hypersecretion following adrenalectomy. Hormone Res. in Paediatrics 74:223-228 (2010).	☐
	027	U.S. Serial No. 17/081,694 Office Action dated February 26, 2021.	☐
	028	U.S. Serial No. 17/081,694 Office Action dated June 11, 2021.	☐
	029	U.S. Serial No. 17/667,285 Office Action dated December 29, 2023.	☐

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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	19/043,275
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	
				Examiner Name	Not Yet Assigned
Sheet	7	of	9	Attorney Docket Number	50535-710.304

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]
	030	U.S. Serial No. 17/667,285 Office Action dated June 10, 2024.	☐
	031	ZAAROUR et al. Bilateral Ovary Adrenal Rest Tumor in a Congenital Adrenal Hyperplasia Following Adrenalectomy. Endocrinol. Pract. 20(4):e69-e74 (2014).	☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. Applicant's unique citation designation number (optional). See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. Applicant is to place a check mark here if English language Translation is attached. 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 CFR 1.14. This collection is estimated to take 2 hours 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, 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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Sheet	8	of	9	Attorney Docket Number	50535-710.304

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).

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☐ 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.

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Please see 37CFR 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):

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☒ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

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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)	**2025-02-05**
Name/Print	Victoria Cheng	Registration Number	79641

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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 CFR 1.14. 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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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.

Bibliographic data

Title:	Thiazole pyrazolopyrimidines as crf1 receptor antagonists
Pub/Pat no:	CN101516887A
Pub/Issue Date:	2009-08-26
Inventor(s):	ZHAOGEN CHEN[US]| HAMDOUCHI HAMDOUCHI CHAFIQ [US]| JAMES HEMBRE ERIK[US]| ARTHUR HIPSKIND PHILIP[US]| KENNETH MYERS JASON[US]| TAKAKO TAKAKUWA[US]| LEE TOTH JAMES[US] |CHEN ZHAOGEN |HAMDOUCHI CHAFIQ HAMDOUCHI |HEMBRE ERIK JAMES |HIPSKIND PHILIP ARTHUR |MYERS JASON KENNETH |TAKAKUWA TAKAKO |TOTH JAMES LEE
Applicant(s):	LILLY CO ELI[US]
Classification:	A61K31/505AI; A61P25/22AI; A61P25/24AI; A61P25/30AI; A61P29/00AI; C07D487/04AI
Application number:	CN20078035145 2007-09-17
Priority number:	WO2007US78605 20070917; US20060826264P 20060920;

Abstract of CN101516887A

The present invention relates to compounds of Formula (I), pharmaceutical compositions thereof, and use thereof as corticotropin releasing factor 1 (CRF1) receptor antagonists in the treatment of psychiatric and neuroendocrine disorders, neurological diseases, and metabolic syndrome.

[19] 中华人民共和国国家知识产权局

[12] 发明专利申请公布说明书

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A61P 25/24 (2006.01)
A61P 29/00 (2006.01)
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[71] 申请人 伊莱利利公司
地址 美国印第安纳州
[72] 发明人 Z·陈 C·H·哈姆杜迟
E·J·亨布雷
P·A·希普斯金德
J·K·迈尔斯 高赤贵子
J·L·托特

[74] 专利代理机构 北京市中咨律师事务所
代理人 黄革生 贾士聪

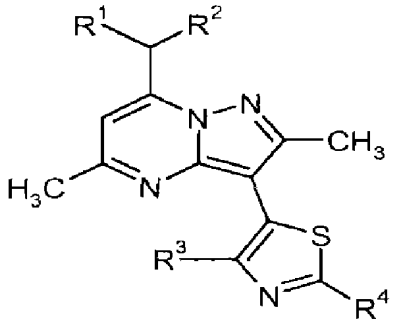
权利要求书 3 页 说明书 49 页

[54] 发明名称

作为 CRF1 受体拮抗剂的噻唑吡唑并嘧啶类

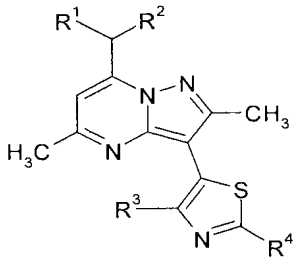
[57] 摘要

本发明涉及式(I)化合物、其药学上可接受的盐以及其作为促肾上腺皮质激素释放因子 1(CRF1)受体拮抗剂在治疗精神病学和神经内分泌障碍、神经病学疾病和代谢综合征中的用途。



I

1. 式 I 化合物或其药学上可接受的盐:

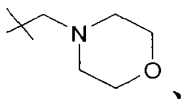
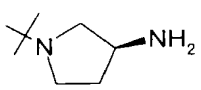
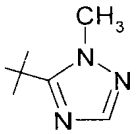
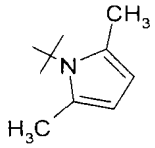


式 I

其中:

R^1 和 R^2 独立地是乙基或正丙基;

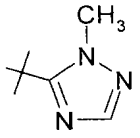
R^3 是氢、Cl、Br、甲基、三氟甲基或甲氧基;

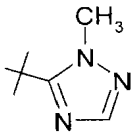
R^4 是氢、Br、R^aR^bN-、甲氧基甲基、正丁基、乙酰氨基、吡啶-4-基、吗啉-4-基、  、  、  或  ;

R^a 和 R^b 独立地是氢、C_1-C_3 烷基、$H_2NCH_2CH_2$-、$(CH_3)_3COC(O)NHCH_2CH_2$-或 $CH_3CH_2CH_2NHCH_2CH_2$-。

2. 根据权利要求 1 所述的化合物或其药学上可接受的盐,其中 R^3 是 Cl、Br、甲基或三氟甲基。

3. 根据权利要求 1 或 2 所述的化合物或其药学上可接受的盐,其中 R^3 是 Cl 或 Br。

4. 根据权利要求 1 至 3 中任意一项所述的化合物或其药学上可接受的盐,其中 R^4 是 R^aR^bN-、吡啶-4-基、吗啉-4-基或  。

5. 根据权利要求 1 至 4 中任意一项所述的化合物或其药学上可接受的盐,其中 R^4 是吗啉-4-基或  。

6. 根据权利要求 1 至 4 中任意一项所述的化合物或其药学上可接受的盐，其中 R^4 是 R^aR^bN-，R^a 和 R^b 独立地是 C_1-C_3 烷基。

7. 根据权利要求 1 所述的化合物或其药学上可接受的盐，其是 3-[4-溴-2-(2-甲基-2*H*-[1,2,4]三唑-3-基)-噻唑-5-基]-2,5-二甲基-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶。

8. 根据权利要求 1 所述的化合物或其药学上可接受的盐，其是 3-(4-溴-2-(2-甲基-2H-[1,2,4]三唑-3-基)-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶。

9. 根据权利要求 1 所述的化合物或其药学上可接受的盐，其是 3-(4-氯-2-吗啉-4-基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶。

10. 一种药物组合物，其包含：权利要求 1 至 9 中任意一项所述的化合物或其药学上可接受的盐和药学上可接受的赋形剂。

11. 一种治疗患者的抑郁、焦虑、酒精或物质滥用、肥胖、高血压、代谢综合征、肠易激惹综合征、癫痫、中风、睡眠障碍、变态反应、偏头痛、经前期综合征、不孕、性功能障碍、先天性肾上腺增生、库欣病、早产、应激诱导的胃溃疡、炎性障碍、垂体肿瘤或异位垂体源肿瘤、慢性疲劳综合征、纤维肌痛、内脏痛或多发性硬化的方法，其包括：给需要其的患者施用治疗有效量的权利要求 1 至 9 中任意一项所述的化合物或其药学上可接受的盐。

12. 一种治疗患者的焦虑或抑郁的方法，其包括：给需要其的患者施用治疗有效量的权利要求 1 至 9 中任意一项所述的化合物或其药学上可接受的盐。

13. 一种治疗患者的酒精或物质滥用的方法，其包括：给需要其的患者施用治疗有效量的权利要求 1 至 9 中任意一项所述的化合物或其药学上可接受的盐。

14. 根据权利要求 1 至 9 中任意一项所述的化合物或其药学上可接受的盐，其用在治疗中。

15. 根据权利要求 1 至 9 中任意一项所述的化合物或其药学上可接受

的盐，其用于治疗抑郁、焦虑、酒精或物质滥用、肥胖、高血压、代谢综合征、肠易激惹综合征、癫痫、中风、睡眠障碍、变态反应、偏头痛、经前期综合征、不孕、性功能障碍、先天性肾上腺增生、库欣病、早产、应激诱导的胃溃疡、炎性障碍、垂体肿瘤或异位垂体源肿瘤、慢性疲劳综合征、纤维肌痛、内脏痛或多发性硬化。

16. 根据权利要求 **1** 至 **9** 中任意一项所述的化合物或其药学上可接受的盐，其用于治疗焦虑或抑郁。

17. 根据权利要求 **1** 至 **9** 中任意一项所述的化合物或其药学上可接受的盐，其用于治疗酒精或物质滥用。

作为 CRF1 受体拮抗剂的噻唑吡唑并嘧啶类

技术领域

本发明涉及新的噻唑吡唑并嘧啶化合物、其药物组合物以及其作为 CRF1 受体拮抗剂在治疗精神病学和神经内分泌障碍、神经病学疾病和代谢综合征中的用途。

背景技术

促肾上腺皮质激素释放因子(CRF)是一种 41 个氨基酸的肽，其是垂体前叶分泌阿黑皮素原(POMC)衍生肽的主要生理调节物。除其对垂体的内分泌作用外，CRF 的免疫组织化学定位还证明，该激素在中枢神经组织中具有广泛的下丘脑外(extrahypothalamic)分布并且产生与其在脑中的神经递质或神经调节物作用相一致的广谱自律、电生理和行为作用。还有迹象表明，CRF 在整合免疫系统对生理学、心理学和免疫学应激物的响应方面具有重要作用。

已经表明在精神病学障碍和包括抑郁和焦虑在内的神经病学疾病以及下面的疾病中涉及 CRF：阿尔茨海默病、亨廷顿舞蹈病、进行性核上性麻痹、肌萎缩性侧索硬化、帕金森病、癫痫、偏头痛、酒精和物质滥用以及相关的戒断症状、肥胖、代谢综合征、先天性肾上腺增生、库欣病、高血压、中风、肠易激惹综合征、应激诱导的胃溃疡、经前期综合征、性功能障碍、早产、炎性障碍、变态反应、多发性硬化、内脏痛、睡眠障碍、垂体肿瘤或异位垂体源肿瘤(ectopic pituitary-derived tumors)、慢性疲劳综合征和纤维肌痛。

已经鉴定了 CRF 受体亚型 CRF1 和 CRF2，其在脑中的分布不均，从而表明可能的功能多样性。例如，广泛分布的脑 CRF1 受体强烈参与与环境应激物接触时伴随的情绪性。显然是 CRF1 而不是 CRF2 受体介导选择

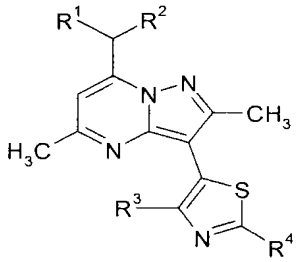
致焦虑样(select anxiogenic like)行为。更离散的间隔/下丘脑(hypothalmic)分布和供替代选择的内源性配体的可用性表明 CRF2 受体具有不同的功能。例如，据报道，一种相对于 CRF1 受体而言对 CRF2 具有优先亲合性的新 CRF-族神经肽在不产生用选择性 CRF1 激动作用所观察到的行为活化特性的情况下抑制食欲。在另一些情况中，CRF2 激动作用产生与 CRF1 拮抗剂或 CRF1 基因缺失所报道的那些作用相似的作用。例如，虽然已经提出用 CRF2 激动剂作为抗肥胖药，但是 CRF1 拮抗剂对肥胖而言也可能是一种重要的治疗。

在 WO 94/13676、WO 97/29109、WO 98/08847 和 WO 98/03510 中描述了可用作 CRF 拮抗剂的某些吡咯并[2,3-*d*]嘧啶类、吡咯并[3,2-*d*]嘧啶类、吡唑并[1,5-*a*]嘧啶类、1,2,3-三唑并[4,5-*b*]吡啶类和吡唑并[1,5-*a*]-1,3,5-三嗪类。

本发明提供了可用作 CRF1 受体拮抗剂的新的噻唑吡唑并嘧啶类。由于上述原因，希望发现对于精神病学和神经内分泌障碍、神经病学疾病和代谢综合征的治疗而言为可能有价值的治疗剂的新的有效的选择性 CRF1 拮抗剂。此外，由于大多数可商购获得的 CNS 和心血管药物表现出不良的生物利用度和药动学性质，还希望发现相对于已知 CRF 拮抗剂如 CP154526 和 NBI30775 而言具有良好生物利用度和药动学性质的新化合物。

发明概述

在一个实施方案中，本发明提供了式 I 化合物或其药学上可接受的盐，

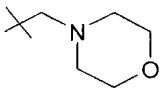
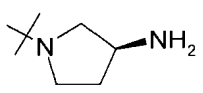
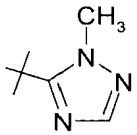
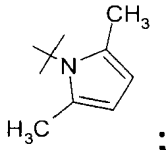


式 I

其中：

R^1和R^2独立地是乙基或正丙基;

R^3是氢、Cl、Br、甲基、三氟甲基或甲氧基;

R^4是氢、Br、R^aR^bN-、甲氧基甲基、正丁基、乙酰氨基、吡啶-4-基、吗啉-4-基、  、  、  或  ;

R^a和R^b独立地是氢、C_1-C_3烷基、$H_2NCH_2CH_2$-、$(CH_3)_3COC(O)NHCH_2CH_2$-或$CH_3CH_2CH_2NHCH_2CH_2$-。

在另一个实施方案中，本发明提供了一种药物组合物，其包含：式I化合物或其药学上可接受的盐和药学上可接受的赋形剂。

在另一个实施方案中，本发明涉及一种治疗患者的抑郁、焦虑、酒精或物质滥用、肥胖、高血压、代谢综合征、肠易激惹综合征、癫痫、中风、睡眠障碍、变态反应、偏头痛、经前期综合征、不孕、性功能障碍、先天性肾上腺增生、库欣病、早产、应激诱导的胃溃疡、炎性障碍、垂体肿瘤或异位垂体源肿瘤、慢性疲劳综合征、纤维肌痛、内脏痛或多发性硬化的方法，其包括：给需要其的患者施用治疗有效量的式I化合物或其药学上可接受的盐。

在另一个实施方案中，本发明涉及式I化合物或其药学上可接受的盐在制备药物中的用途，所述药物用于治疗抑郁、焦虑、酒精或物质滥用、肥胖、高血压、代谢综合征、肠易激惹综合征、癫痫、中风、睡眠障碍、变态反应、偏头痛、经前期综合征、不孕、性功能障碍、先天性肾上腺增生、库欣病、早产、应激诱导的胃溃疡、炎性障碍、垂体肿瘤或异位垂体源肿瘤、慢性疲劳综合征、纤维肌痛、内脏痛或多发性硬化。

在另一个实施方案中，本发明涉及用于治疗抑郁、焦虑、酒精或物质滥用、肥胖、高血压、代谢综合征、肠易激惹综合征、癫痫、中风、睡眠障碍、变态反应、偏头痛、经前期综合征、不孕、性功能障碍、先天性肾上腺增生、库欣病、早产、应激诱导的胃溃疡、炎性障碍、垂体肿瘤或异位垂体源肿瘤、慢性疲劳综合征、纤维肌痛、内脏痛或多发性硬化的式I

化合物或其药学上可接受的盐。

在另一个实施方案中，本发明涉及用于治疗的式 I 化合物或其药学上可接受的盐。

发明详述

如上文和整个本申请的说明书中所用的那样，除非另有说明，否则下面的术语应被理解为具有下列含义:

“烷基”是指在链中具有 1 至 5 个碳原子的饱和脂族烃基，其可以是直链的或支链的。

“药学上可接受的赋形剂”是指用于增进制剂特性的药学上可接受的配制载体、溶液或添加剂。该类赋形剂必需与制剂中的其它成分相容并且对其接受者无害，它们是本领域技术人员所众所周知的(参见例如 ***Remingtons Pharmaceutical Sciences***, 第 19 版, **Mack Publishing Company, 1995**)。

“药学上可接受的盐”是指本发明的化合物相对无毒的无机和有机酸加成盐和碱加成盐。这些盐可以在化合物的最后分离和纯化中原位制备。具体而言，酸加成盐可通过分别将纯化的游离碱形式的化合物与适宜的有机酸或无机酸反应并分离由此形成的盐来制备(参见例如 ***Remingtons Pharmaceutical Sciences***, 第 19 版, **Mack Publishing Company, 1995**)。

“治疗有效量”或“有效量”是指将在组织、系统、动物或人中引起研究者、兽医、医生或其它临床医师所寻求的生物学或医学响应或者所需的治疗作用的本发明式 I 化合物或包含本发明式 I 化合物的药物组合物的量。

术语“治疗”等包括减缓和逆转障碍的进展。这些术语还包括即使障碍或病症实际上未被消除和即使障碍或病症的进展本身未被减缓或逆转但是缓解、改善、减弱、消除或减轻了障碍或病症的一种或多种症状。术语“治疗”以及类似术语还包括防止性(例如，预防性)治疗和姑息性治疗。疾病的预防表现为疾病的发作被拖延或延迟。

分子结构中的符号“——”表示该特定取代基的连接位置。

当任何变量在任何组分或在式 I 中出现一次以上时，其定义在每次出

现时都是彼此独立的。而且，只有当取代基和/或变量的组合产生稳定的化合物时，该类组合才是允许的。在选择本发明的化合物时，本领域普通技术人员将意识到各种取代基、即 R^1、R^2 等是根据化学结构连接性的众所周知的原则来进行选择的。

按照本公开物中所用的标准命名法，首先描述指定侧链的末端部分，然后描述朝向连接点的毗邻官能团。例如，芳基羰基氨基烷基取代基与芳基-C(O)-NH-烷基-等同。

本发明包括下列实施方案，它们可以被进一步组合：

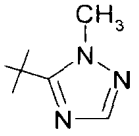
(a) 式 I 化合物，其中 R^1 和 R^2 是乙基；

(b) 式 I 化合物，其中 R^1 和 R^2 是正丙基；

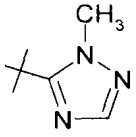
(c) 式 I 化合物，其中 R^3 是 Cl、Br、甲基或三氟甲基；

(d) 式 I 化合物，其中 R^3 是 Cl；

(e) 式 I 化合物，其中 R^3 是 Br；

(f) 式 I 化合物，其中 R^4 是 R^aR^bN-、吡啶-4-基、吗啉-4-基或  ；

(g) 式 I 化合物，其中 R^4 是吗啉-4-基；

(h) 式 I 化合物，其中 R^4 是  ；

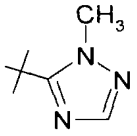
(i) 式 I 化合物，其中 R^a 和 R^b 独立地是 C_1-C_3 烷基；

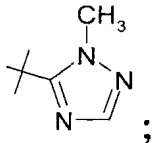
(j) 式 I 化合物，其中 R^1 和 R^2 是乙基，R^3 是 Cl，R^4 是吗啉-4-基；

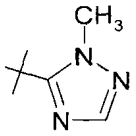
(k) 式 I 化合物，其中 R^1 和 R^2 是正丙基，R^3 是 Cl，R^4 是吗啉-4-基；

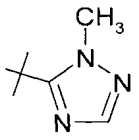
(l) 式 I 化合物，其中 R^1 和 R^2 是乙基，R^3 是 Br，R^4 是吗啉-4-基；

(m) 式 I 化合物，其中 R^1 和 R^2 是正丙基，R^3 是 Br，R^4 是吗啉-4-基；

(n) 式 I 化合物，其中 R^1 和 R^2 是乙基，R^3 是 Cl，R^4 是  ；

(o) 式 I 化合物，其中 R^1 和 R^2 是正丙基，R^3 是 Cl，R^4 是  ；

(p) 式 I 化合物，其中 R^1 和 R^2 是乙基，R^3 是 Br，R^4 是  ；

(q) 式 I 化合物，其中 R^1 和 R^2 是正丙基，R^3 是 Br，R^4 是  ；

(r) 式 I 化合物或其药学上可接受的盐用于治疗抑郁或焦虑的用途;

(s) 式 I 化合物或其药学上可接受的盐用于治疗酒精或物质滥用的用途;

(t) 式 I 化合物或其药学上可接受的盐用于治疗酒精或物质滥用以及相关的戒断症状的用途;

(u) 式 I 化合物或其药学上可接受的盐，对于 CRF1 结合而言，其表现出≤ 500 nM 的 Ki 值;

(v) 式 I 化合物或其药学上可接受的盐，对于 CRF1 结合而言，其表现出≤ 50 nM 的 Ki 值;

(w) 式 I 化合物或其药学上可接受的盐，对于 CRF1 结合而言，其表现出≤ 5 nM 的 Ki 值;

(x) 式 I 化合物或其药学上可接受的盐，对于 CRF1 结合而言，其表现出≤ 500 nM 的 Ki 值，并且相对于 CRF2 而言选择性与 CRF1 结合(即，更低的 Ki);

(y) 式 I 化合物或其药学上可接受的盐，对于 CRF1 结合而言，其表现出≤ 50 nM 的 Ki 值，并且相对于 CRF2 而言选择性与 CRF1 结合(即，更低的 Ki);

(z) 式 I 化合物或其药学上可接受的盐，对于 CRF1 结合而言，其表现出≤ 5 nM 的 Ki 值，并且相对于 CRF2 而言选择性与 CRF1 结合(即，更低的 Ki); 和/或

(aa) 相对于一些已知的 CRF 拮抗剂(例如，CP154526 和 NBI30775)

而言，具有优良的生物利用度和药动学性质的具体例举的化合物，如实施例 15。

本发明的化合物优选被配制为通过各种途径施用的药物组合物的形式。该类组合物优选用于口服施用。该类药物组合物和制备该类药物组合物的方法在本领域中是众所周知的(参见例如 ***Remington: The Science and Practice of Pharmacy***, A. Gennaro 等人编辑，第 19 版, Mack Publishing Co., 1995)。

式 I 化合物一般在宽的剂量范围内都有效。例如，每天的剂量通常落在约 0.0001 至约 30 mg/kg 体重范围内。在一些情况中，低于上述范围下限的剂量水平可能就远远足够了，而在另一些情况中，可以使用更大的剂量而不会导致任何有害的副作用，因此，上述剂量范围并非旨在以任何方式对本发明的范围进行限制。应当清楚的是，实际施用的化合物的量将由医师根据相关的情况来确定，所述情况包括所治疗的病症、所选择的施用途径、被施用的实际化合物或化合物组合、各患者的年龄、体重和响应情况以及患者的症状的严重程度。

式 I 化合物是 CRF-1 拮抗剂并且因此可用于治疗能通过降低 CRF1 受体的品质(tone)或兴奋性(stimulation)来治疗的病症。已经表明促肾上腺皮质激素释放因子(CRF)(一种 41 个氨基酸的肽，其是垂体前叶分泌阿黑皮素原(POMC)衍生肽的主要生理调节物)[J. Rivier 等人, ***Proc. Natl. Acad. Sci (USA)*** 80:4851 (1983); W. Vale 等人, ***Science*** 213:1394 (1981)]与许多医学病症有关。例如，除其对垂体的内分泌作用外，CRF 的免疫组织化学定位还证明，该激素在中枢神经组织中具有广泛的下丘脑外分布并且产生与其在脑中的神经递质或神经调节物作用相一致的广谱自律、电生理和行为作用[W. Vale 等人, ***Rec. Prog. Horm. Res.*** 39:245 (1983); G. F. Koob, ***Persp. Behav. Med.*** 2:39 (1985); E. B. De Souza 等人, ***J. Neurosci.*** 5:3189 (1985)]。还有迹象表明，CRF 在整合免疫系统对生理学、心理学和免疫学应激物的响应方面具有重要作用[参见例如 J. E. Blalock, ***Physiological Reviews*** 69:1 (1989); J. E. Morley, ***Life Sci.*** 41:527 (1987)]。

已经表明在精神病学障碍和包括抑郁和焦虑在内的神经病学疾病中涉及 CRF[D. M. Nielsen, *Life Sci.* 78:909-919; H. E. Kunzel 等人, *J. Psychiatr. Res.* 37:525-533; D. R. Gehlert 等人, *Eur. J. Pharmacol.* 509:145-153]。认为 CRF 还参与下列疾病的病因学和病理生理学：阿尔茨海默病、亨廷顿舞蹈病、进行性核上性麻痹和肌萎缩性侧索硬化，因为这些疾病涉及中枢神经系统中 CRF 神经元功能障碍[关于综述，参见：E. B. De Souze, *Hosp. Practice* 23:59 (1988)]。已经表明长期施用 CRF 产生多巴胺系统损害，这表明其在帕金森病中起作用[E. Izzo 等人, *Pharmacol. Biochem. Behav.* 81:701-708 (2005)]。其中有 CRF 参与的其它神经病学障碍包括癫痫[T. Z. Baram 等人, *Brain Res.* 770:89-95 (1997)]和偏头痛[T. C. Theoharides 等人, *Endocrinology* 136:5745-5750(1995)]。已经表明 CRF 参与酒精和物质滥用以及相关的戒断症状[D. H. Overstreet 等人, *Pharmacol. Biochem. Behav.* 77:405-413; Y. Shaham 等人, *Psychopharmacology (Berl)* 137: 184-190]。此外，有迹象表明 CRF 在各种内分泌障碍和心血管疾病如肥胖[E. Timofeeva 和 D. Richard, *Neuroendocrinology* 66:327-340 (1997)]、代谢综合征[A. M. Ward 等人, *Metabolism* 53:720-726(2004)]、先天性肾上腺增生[D. P. Merke 和 G. B. Cutler Jr., *Endocrinol. Metab. Clin. North Am.* 30:121-135(2001)]、库欣病[M. Labeur 等人, *Curr. Drug Targets Immune Endocr. Metabol. Disord.* 4:335-342(2004)]，高血压[R. J. Briscoe 等人，*Brain Res.* 881:204-207(2000)]和中风[S. L. Stevens 等人, *J. Cereb. Blood Flow Metab.* 23:1151-1159(2003)]中起作用。已经表明胃紊乱如肠易激惹综合征[Y. Tache 等人, *Eur J. Surg.* Suppl:16-22(2002)]和应激诱导的胃溃疡[K. E. Gabry 等人, *Mol. Psychiatry* 7:474-483, 433(2002)]与 CRF 有关。此外，还表明 CRF 在女性健康的各个领域例如经前期综合征[F. Facchinetti 等人, *Psychosom. Med.* 56:418-422(1994)]、不孕[L. Ghizzoni 等人，*Endocrinology* 138:4806-4811(1997)]、性功能障碍[J. E. Jones 等人, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 283:R591-597(2002)]和早产[P. D. Wadhwa 等人, *Am. J. Obstet. Gynecol.* 191:1063-1069(2004)]中起作用。还有迹象表明 CRF 在

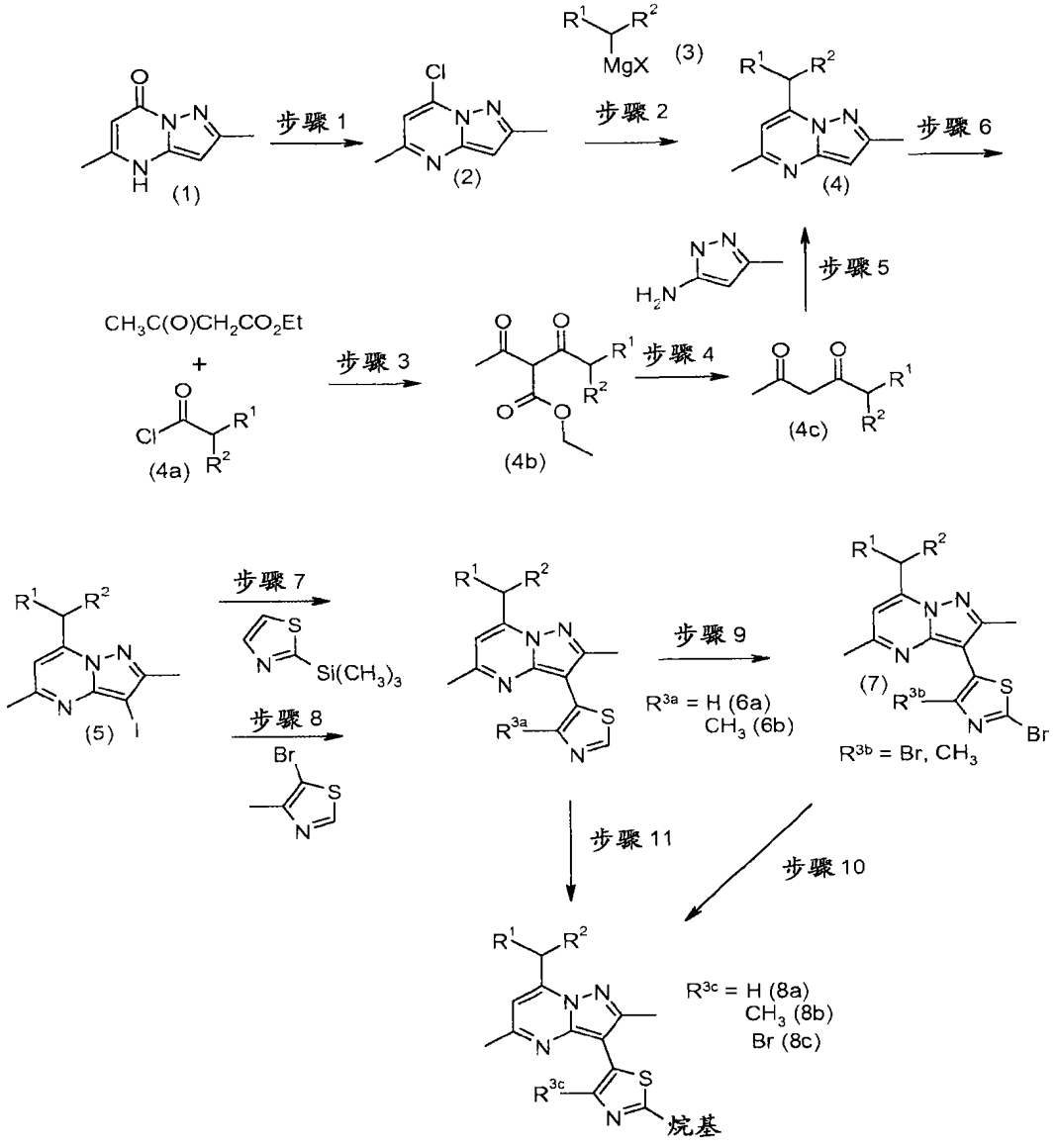
免疫系统中具有重要作用，表明其有治疗炎性障碍[A. Gravanis 和 A. N. Margioris, *Curr. Med. Chem.* 12:1503-1512(2005)]、变态反应[L. K. Singh 等人, *Brain Behav. Immun.* 13:225-239(1999)]、多发性硬化和其它自身免疫性障碍[C. Benou 等人, *J. Immunol.* 174:5407-5413(2005)]的潜能。除前述疾病外，还表明在内脏痛[M. Nijsen 等人，*Neurogastroenterol. Motil.* 17:423-432(2005)]、睡眠障碍[T. M. Buckley 和 A. F. Schatzberg, *J. Clin. Endocrinol. Metab.* 90:3106-3114(2005)]、垂体肿瘤或异位垂体源肿瘤[K. D. Dieterich 等人, *J. Clin. Endocrinol. Metab.* 83: 3327-3331 (1998)]、慢性疲劳综合征和纤维肌痛[G. Neeck 和 L. J. Crofford, *Rheum. Dis. Clin. North Am.* 26:989-1002(2000)]中也涉及 CRF。

已经鉴定了 CRF 受体亚型 CRF1 和 CRF2，其在脑中的分布不均[D. T. Chalmers 等人, *TIPS* 17:166-72(1996)]，从而表明其可能的功能多样性[S. C. Heinrichs 等人, *Regul. Peptides* 71:15(1997)]。例如，广泛分布的脑 CRF1 受体强烈参与与环境应激物接触时伴随的情绪性[G. Liebsch 等人, *Regul. Peptides* 59: 229-39(1995); D. W. Schulz, *PNAS* 93: 10477-82(1996)]。显然，是 CRF1 而不是 CRF2 受体介导选择致焦虑样行为[Heinrichs 等人, 1997]。更离散的间隔/下丘脑分布[D. T. Chalmers 等人, *J. Neurosci.* 15(10): 6340-50 (1995)]和供替代选择的内源性配体的可用性[J. Vaughan 等人, *Nature* 378: 287-92(1995)]表明 CRF2 受体具有不同的功能角色[Heinrichs 等人, 1997]。例如，据报道，一种相对于 CRF1 受体而言对 CRF2 具有优先亲合性的新 CRF-族神经肽在不产生用选择性 CRF1 激动作用所观察到的行为活化特性的情况下抑制食欲(H. Tezval 等人, *PNAS* 101(25): 9468-9473 (2004)]。在一些情况中，CRF2 激动作用产生与 CRF1 拮抗剂或 CRF1 基因缺失所报道的那些作用相似的作用[S. C. Heinrichs, *Trends in Pharmacological Sciences* 20(8):311-5(1999)]。例如，虽然已经提出用 CRF2 激动剂作为抗肥胖药，但是 CRF1 拮抗剂对肥胖而言也可能是一种重要的治疗[C. Contoreggi 等人, *Neuroendocrinology* 80(2):111-23(2004)]。

制备本发明的化合物

本发明的所有化合物都可以化学制备，例如，通过按照下面所述的合成途径来制备。但是，下面的讨论并非旨在以任何方式对本发明的范围进行限制。例如，所述各途径的特定合成步骤可以以不同方式组合，或者与来自不同流程图的步骤联合，从而制备另外的式 I 化合物。各步骤的产物可以用常规方法来回收，所述方法包括萃取、蒸发、沉淀、色谱法、过滤、研磨、结晶等。在下面的流程图中，除非另有说明，否则所有取代基均如前面所定义，适宜的试剂在本领域中是众所周知和可理解的。

流程图 1



可以按照流程图 1 中所述的反应来形成式(6a,b)、(7)或 8(a-c)的化合物。一种适宜的式(6a,b)、(7)或(8a-c)的化合物是其中基团定义如下的化合物：R^1 和 R^2 如式 I 中所定义，R^{3a} = H 或 CH_3，R^{3b} = Br 或 CH_3，R^{3c} = H、CH_3 或 Br。

在流程图 1 的步骤 1 中，用氯氧化磷(phosphorous oxychloride)和二甲基苯胺在惰性溶剂如甲苯中在溶剂的回流温度下将式(1)的吡唑并[1,5-a]嘧啶-7-酮转化成 7-氯-2,5-二甲基-吡唑并[1,5-a]嘧啶。

在步骤 2 中，使式(3)的格氏试剂(X = Cl 或 Br)与式(2)的氯化物在惰性溶剂如甲苯中在回流温度下反应，得到式(4)的 7-烷基吡唑并嘧啶。

或者，可以如步骤 3、4 和 5 中所示的那样获得式(4)的 7-烷基吡唑并嘧啶。在步骤 3 中，将乙酰乙酸乙酯用式(4a)的酰卤在存在氯化镁的情况下进行酰化，得到式(4b)的二酮基-酯。将式(4b)的二酮基-酯在 Krapcho 条件下脱羧，得到式(4c)的二酮。例如，将(4b)在二甲基亚砜中在约 130 至 170℃的温度下加热以进行脱羧。在步骤 5 中，将式(4c)的二酮与 3-氨基-5-甲基吡唑在质子溶剂如甲醇、乙醇或乙酸中环化，得到式(4)的 7-烷基吡唑并嘧啶。优选的条件在约 0 至 60℃的温度下使用乙酸。

在步骤 6 中，用过量的 N-碘琥珀酰亚胺在乙腈中将式(4)的吡唑并嘧啶官能化成式(5)的碘代吡唑并嘧啶。

在流程图 1 的步骤 7 或 8 中，使式(5)的碘代吡唑并嘧啶与噻唑卤化锌在 Negishi 交叉偶联反应中反应，得到式(6a)或(6b)的噻唑基吡唑并嘧啶(Jensen, J.; Skjaerbaek, N.; Vedso, P. *Synthesis* 2001, 128)。所述噻唑卤化锌是用本领域技术人员众所周知的方法产生的。例如，在步骤 7 中，将 2-三甲基硅烷基噻唑用正丁基锂、仲丁基锂或叔丁基锂处理，然后用 $ZnCl_2$ 进行锂-锌交换。将有机锌试剂与式(5)的碘代吡唑并嘧啶在存在钯催化剂例如二氯[1,1'-双(二苯基-膦基)二茂铁]钯(II)二氯甲烷的情况下在惰性溶剂如 THF 中在回流温度下偶联约 12 至 36 小时，得到式(6a)的噻唑吡唑并嘧啶。

或者，在步骤 8 中，用 5-溴-4-甲基噻唑和锌金属产生噻唑溴化锌并基本如步骤 7 中所述的那样将其用于 Negishi 交叉偶联中，得到式(6b)的噻唑

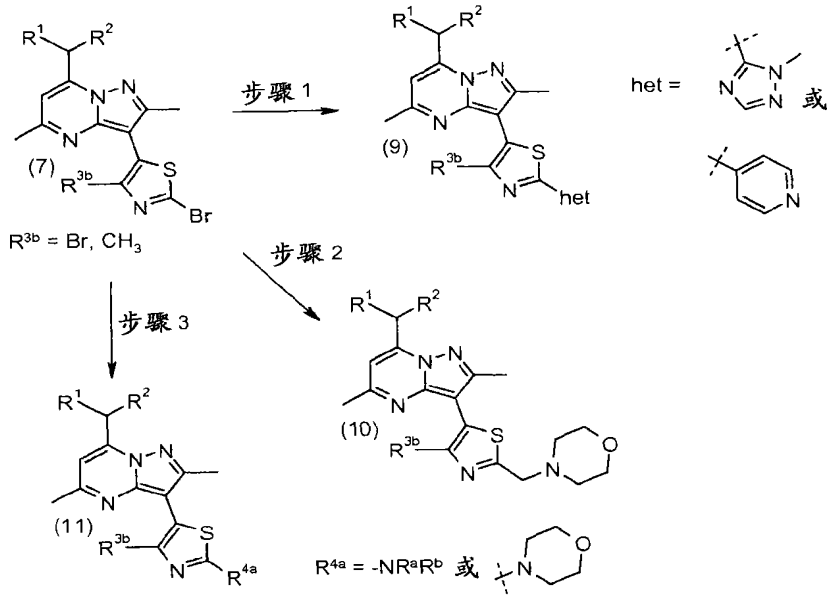
吡唑并嘧啶。

在流程图 1 的步骤 9 中，将式(6a,b)的噻唑溴化，得到式(7)的溴代或二溴代噻唑，其中 R^{3b} = Br 或 CH_3。根据 R^{3a} 是 CH_3 还是 H，将噻唑分别用 1 或 2 eq N-溴琥珀酰亚胺溴化。

式(8a-c)的烷基噻唑是在步骤 11 中由式(6a,b)的噻唑获得的或者在步骤 10 中由式(7)的溴代噻唑获得的。在步骤 10 中，用正丁基锂、仲丁基锂或叔丁基锂进行卤素-锂交换，得到噻唑锂试剂，随后使其与亲电子试剂如烷基卤如碘甲基甲基醚或碘丁烷反应。在步骤 11 中，通过用正丁基锂、仲丁基锂或叔丁基锂去质子化和随后与亲电子试剂如碘甲基甲基醚或碘丁烷反应来形成噻唑锂试剂。

本领域技术人员应当意识到，可以容易地对噻唑环系进行官能化，可以容易地制备噻唑中间体如 2-三甲基硅烷基-噻唑(Dondoni, A.等人 *J. Org. Chem.* 1988, *53*, 1748)。5-溴-4-甲基噻唑是通过用溴在乙酸中对 4-甲基噻唑进行溴化来获得的(Collins, I. J.等人, WO2003093252, 2003 年 11 月 13 日)。通过使乙酰乙酸乙酯与 5-甲基-2*H*-吡唑-3-基胺在回流的乙酸中进行缩合可容易地制得 2,5-二甲基-4*H*-吡唑并[1,5-a]嘧啶-7-酮(1)。

流程图 2



可以按照流程图 2 中所述的反应来形成式(9)、(10)或(11)的化合物。一

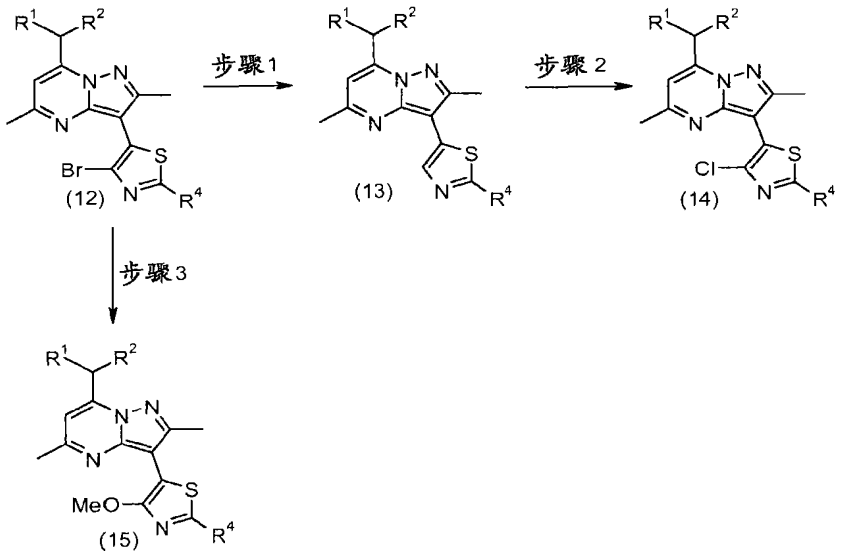
种适宜的式(9)、(10)或(11)的化合物是其中基团定义如下的化合物：R^1、R^2、R^a和R^b如式I中所定义，R^{3b} = Br或CH_3，R^{4a} = $-NR^aR^b$或-N-吗啉基，“het”具有所述的定义。

在步骤1中，使式(7)的溴代噻唑与杂环锌试剂在Negishi交叉偶联反应中偶联，得到式(9)的噻唑杂环。例如，将1-甲基-1,2,4-三唑在约-80至-65℃下用正丁基锂、仲丁基锂或叔丁基锂处理、然后用氯化锌处理，并且在原位与式(7)的溴代噻唑反应。该反应优先在惰性溶剂如THF中在存在钯催化剂如二氯[1,1'-双(二苯基-膦基)二茂铁]钯(II)二氯甲烷或四(三苯基膦)钯(0)的情况下进行。将反应温热至回流温度。或者，杂环锌试剂由卤代杂环如4-碘吡啶和锌金属形成。

在流程图2的步骤2中，中间体2-甲酰基噻唑是通过用正丁基锂、仲丁基锂或叔丁基锂进行卤素-锂交换、然后与N-甲酰基吗啉反应来形成的。使甲酰基噻唑在存在有机胺如吗啉的情况下进行还原胺化，得到式(10)的吗啉基甲基噻唑。还原胺化在本领域中是众所周知的，通常使用无机硼氢化物试剂如硼氢化钠或氰基硼氢化钠。优选的条件在惰性溶剂如二氯甲烷或THF中使用三乙酰氧基硼氢化钠。

在步骤3中，用式$-NR^aR^b$的胺或用吗啉使式(7)的溴代噻唑进行置换反应，得到式(11)的氨基噻唑。该反应在惰性溶剂如THF或二噁烷中用无机碱如碳酸铯在70至110℃下进行。

流程图3

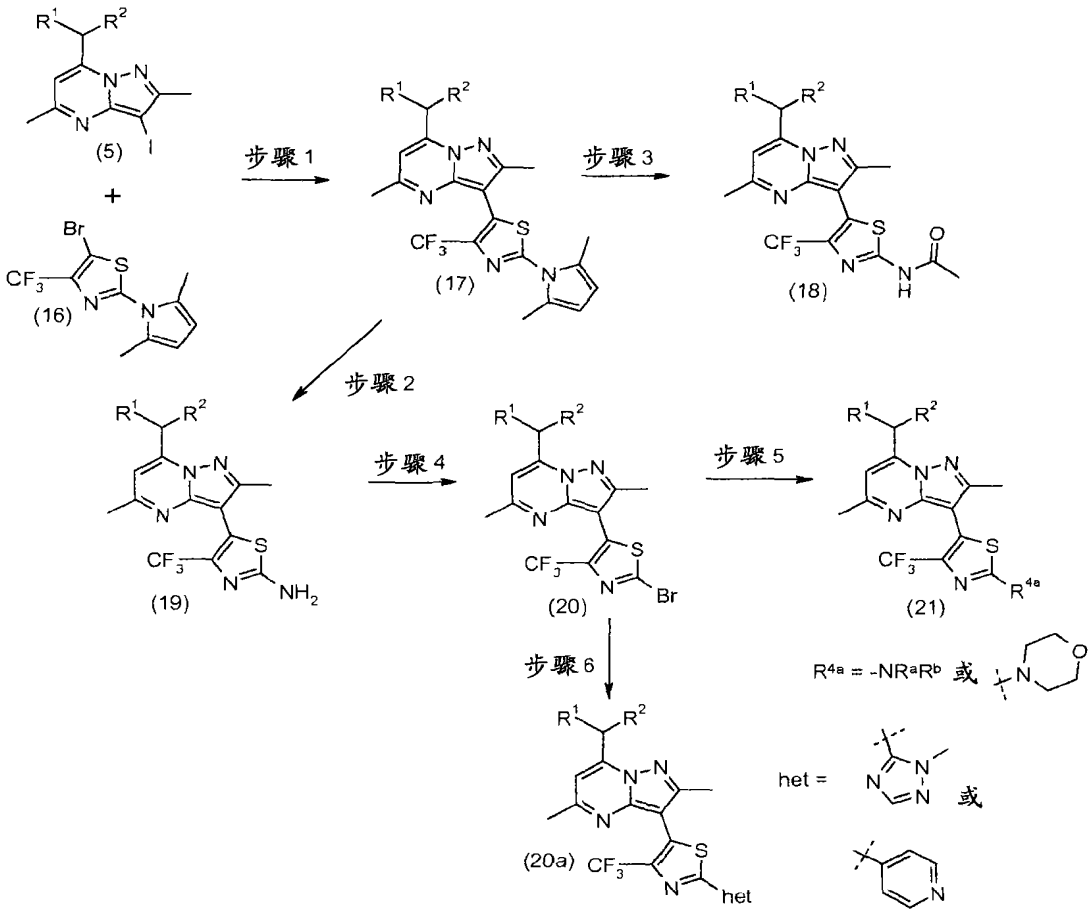


可以按照流程图 3 中所述的反应来形成式(13)、(14)或(15)的化合物。一种适宜的式(13)、(14)或(15)的化合物是其中 R^1、R^2 和 R^4 如式 I 中所定义的化合物。

本领域技术人员应当意识到，可以容易地将 4-溴噻唑如式(12)的 4-溴噻唑处理成具有其它官能团。例如，在步骤 1 中，可以用氯化亚铜将该溴化物脱卤素化，得到式(13)的噻唑，随后用 N-氯琥珀酰亚胺将其氯化，得到式(14)的 4-氯噻唑。

在流程图 3 的步骤 3 中，在存在处于甲醇中的碘化亚铜(I)的情况下在约 100 至 120℃下在惰性溶剂如二甲基甲酰胺中用甲醇钠对式(12)的 4-溴噻唑进行置换，得到式(15)的 4-甲氧基噻唑。

流程图 4



可以按照流程图 4 中所述的反应来形成式(17)、(18)、(19)、(20)、(20a)或(21)的化合物。一种适宜的式(17)、(18)、(19)、(20)、(20a)或(21)的化合物是其中基团定义如下的化合物：R^1、R^2、R^a和R^b如式 I 中所定义，R^{4a}是-NR^aR^b或-N-吗啉基，“het”具有所述的定义。

在流程图 4 的步骤 1 中，使式(5)的碘代吡唑并嘧啶和式(6)的 5-溴噻唑进行 Negishi 交叉偶联，形成式(17)的二甲基吡咯基噻唑。例如，将式(16)的 5-溴噻唑在约-80 至-65℃下用正丁基锂、仲丁基锂或叔丁基锂处理、然后用氯化锌处理。将有机锌试剂在原位与式(5)的碘代吡唑并嘧啶反应。该偶联反应优先在惰性溶剂如 THF 中在回流温度下在存在钯催化剂如双(三-叔丁基膦)钯(0)的情况下进行。

在步骤 2 中，将式(17)的二甲基吡咯基噻唑去保护，得到式(19)的氨基噻唑。将二甲基吡咯用羟胺在乙酸中在约 60 至 100℃的温度下处理约 4 至

8 小时，优选约 6 小时。在步骤 3 中，为了形成式(18)的噻唑乙酰胺，使用与步骤 2 中所用条件相同的条件，不同的是反应持续约 72 小时。

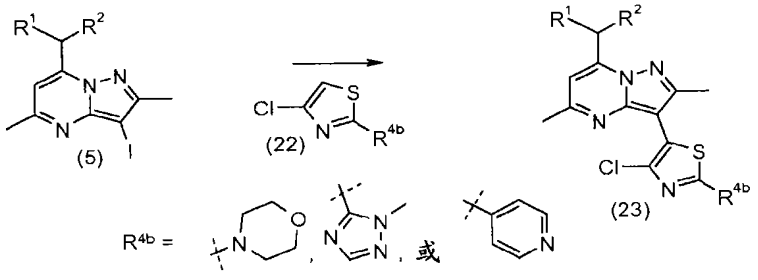
在流程图 4 的步骤 4 中，用改进的 Sandmeyer 反应将式(19)的 2-氨基噻唑转化成式(20)的 2-溴噻唑。优选的条件在约 60 至 80℃的温度下在乙腈中使用亚硝酸烷基酯如亚硝酸叔丁酯和溴化铜(II)。

在步骤 5 中，用式-NR^aR^b 的胺或用吗啉使式(20)的 2-溴噻唑进行置换反应，得到式(21)的氨基噻唑。该反应在惰性溶剂如甲醇、THF 或二噁烷中进行，或者在不使用溶剂的情况下进行，使用过量的胺，反应温度为约 70 至 110℃。或者，用反应胺和过量的三乙胺或无机碱如碳酸铯进行该反应。在式(21)的氨基噻唑的合成中，也考虑各种去保护步骤，如除去氨基甲酸叔丁酯(BOC)，因为在-NR^aR^b 携带式 I 中所定义的其它胺官能团的情况下，为了进行上述反应，这样的步骤可能是需要的或有益的。适宜的保护基团的选择和使用在本领域中是众所周知的和可理解的(参见例如 ***Protecting Groups in Organic Synthesis***, Theodora Greene (Wiley-Interscience))。

在流程图 4 的步骤 6 中，以与流程图 2 的步骤 1 中所述方式相似的方式使式(20)的 2-溴噻唑与杂环锌试剂在 Negishi 交叉偶联反应中偶联，得到式(20a)的噻唑杂环。

本领域技术人员应当意识到，式(16)的官能化的噻唑可用本领域中已知的方式来制备。例如，将硫脲与溴代酮如 3-溴-1,1,1-三氟丙-2-酮环化，得到 4-三氟甲基-噻唑-2-基胺。随后用己烷-2,5-二酮对该胺进行溴化和保护，得到(16)。

流程图 5

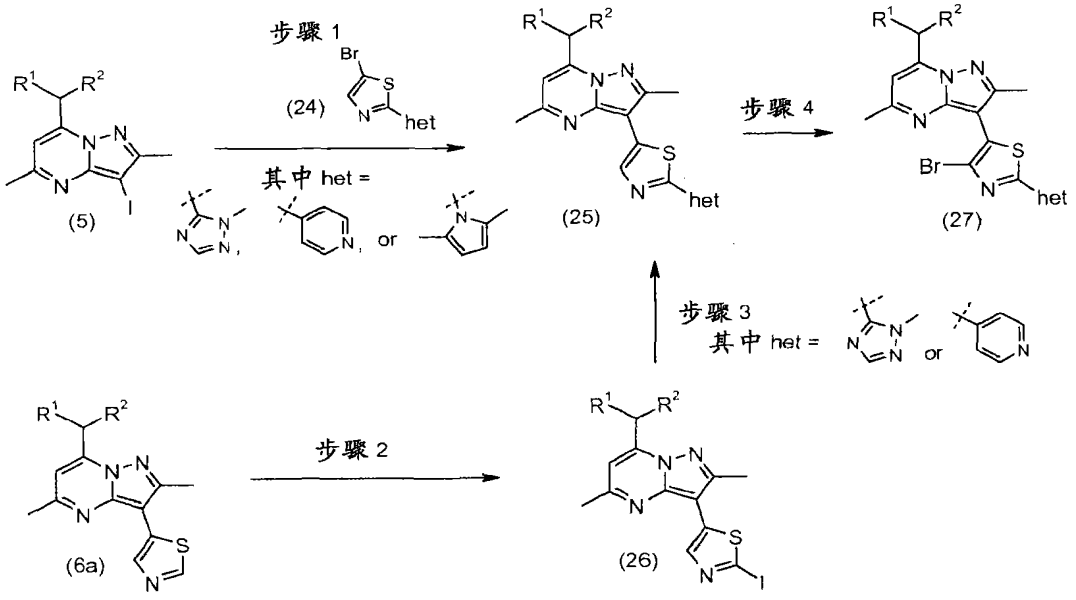


可以按照流程图 5 中所述的反应来形成式(23)的化合物。一种适宜的式(23)的化合物是其中基团定义如下的化合物：R^1 和 R^2 如式 I 中所定义，R^{4b} 具有所述定义。

使式(5)的碘代吡唑并嘧啶与例如式(22)的 4-氯-2-吗啉代-噻唑进行交叉偶联，形成式(23)的吡唑并嘧啶噻唑。例如，将所述反应物在存在碘化铜、醋酸钯和三苯基膦的情况下用碱如碳酸铯偶联。该偶联反应优先在惰性溶剂如 DMF 中在约 100 - 150℃下进行 4-24 小时。

本领域技术人员应当意识到，式(22)的官能化的噻唑可用本领域中已知的方式来制备。例如，可以使 2,4-二氯噻唑与吗啉反应，得到式(22)的 2-吗啉代-噻唑。也可以将 2,4-二氯噻唑耗竭性溴化，得到 2,5-二溴-4-氯噻唑。随后用正丁基锂在 THF 中在-90℃下进行溴-锂交换并用水淬灭，得到 2-溴-4-氯噻唑[*J. Chem. Soc. Perkin Trans I: Org Bioorg. Chem. (*1972-1999), (2):215-219(1992)]。可以用杂环锌试剂使 2-溴-4-氯噻唑进行 Negishi 交叉偶联反应，得到噻唑-2-基三唑或吡啶。

流程图 6



可以按照流程图 6 中所述的反应来形成式(27)的化合物。一种适宜的式(27)的化合物是其中基团定义如下的化合物：R^1 和 R^2 如式 I 中所定义，"het"分别具有步骤 1 或步骤 3 中所述的定义。

在流程图 6 的步骤 1 中，通过使式(5)的碘代吡唑并嘧啶与式(24)的溴代噻唑反应获得杂环噻唑，例如式(25)的杂环噻唑。该反应在存在溴化 N-丁基铵和碱如醋酸钾的情况下用钯催化剂如具有三(2,4-二-叔丁基-苯基)-磷烷(phosphane)的醋酸钯在惰性溶剂如 N-甲基吡咯烷酮中在约 100-150℃的温度下进行。

或者，在步骤 2 中，将式(6a)的噻唑基吡唑并嘧啶碘化，得到式(26)的 2-碘噻唑。将该噻唑用二异丙基氨基锂在-70 至-80℃的温度下处理约 1 小时，然后用 N-碘琥珀酰亚胺在大约相同的温度下在惰性溶剂如 THF 中处理。然后进行步骤 3，在该步骤中，用与流程图 2 的步骤 1 中所述条件相似的 Negishi 交叉偶联条件形成式(25)的三唑基或 4-吡啶基噻唑。

在流程图 6 的步骤 4 中，将式(25)的噻唑基吡唑并嘧啶溴化，得到式(27)的溴代噻唑。该溴化是用 N-溴琥珀酰亚胺在存在少量乙酸的情况下在惰性溶剂如乙腈中进行的。

可以如流程图 4 的步骤 2、3、4 和 5 中所述的那样进一步对其中 het = 2,5-二甲基-吡咯-1-基的式(27)的化合物进行修饰，从而获得本发明的化合物。

本领域技术人员应当意识到，可以用本领域中已知的方法容易地制备式(24)的杂环噻唑类。例如，可以用 1,1-二甲氧基-N,N-二甲基-甲胺将噻唑-2-甲酰胺环化成三唑，然后用 N-甲基-肼处理，获得三唑基噻唑，随后可以用 N-溴琥珀酰亚胺将其溴化。根据文献操作可得到 4-噻唑-2-基-吡啶，可将其溴化，得到 4-(5-溴-噻唑-2-基)-吡啶。5-溴-2-(2,5-二甲基-吡咯-1-基)-噻唑可以通过使 2-氨基-5-溴噻唑与己烷-2,5-二酮反应来容易地获得。

本文所用的“TLC”是指薄层色谱；“HPLC”是指高效液相色谱；“LC/MS”是指液相色谱/质谱；“GC/MS”是指气相色谱/质谱”；“HR-ToF’是指高分辨率的飞行时间(high resolution time-of-flight)；“APCI”是指大气压化学电离；“δ”是指从四甲基硅烷向低磁场的百万分数；“THF”是指四氢呋喃；“EtOAc”是指乙酸乙酯；“MeOH”是指甲醇；“EtOH”是指乙醇；“DMF”是指二甲基甲酰胺。

实施例

无需进一步加工，认为本领域技术人员可以用前面的描述来充分实施本发明。用下面的制备例和实施例来对本发明进行进一步详细说明。它们旨在进行举例说明，而不是要以任何方式对本发明进行限制。其中的试剂和起始材料可容易地获得或者可被本领域普通技术人员容易地合成。实施例 1-35 提供了代表性的化合物并说明了其制备。实施例 A-D 说明了可用于测定本发明化合物的生物学性质的各种生物学测定法。本领域技术人员将迅速意识到实施例中所述的操作的适宜变型。本发明的化合物的名称是用 ChemDraw Ultra® 7.0.1 版提供的。盐是以游离碱加共轭酸的形式来进行命名的。

制备例 1

2,5-二甲基-4H-吡唑并[1,5-*a*]嘧啶-7-酮

将乙酰乙酸乙酯(128 g, 0.98 mol)滴加到 5-甲基-2*H*-吡唑-3-基胺(100 g, 0.95 mol 的乙酸溶液(500 mL)中，同时保持其温度为 25-28℃。将混合物在回流下加热 10 小时，然后将其冷却至室温。将反应加入到被冷却至 5℃的叔-丁基甲基醚(5 L)中，同时保持其温度低于 10℃。将其在 5℃下搅拌 1 小时，过滤。将所得物质真空干燥过夜，得到白色固体(158 g, 96%)。

制备例 2

7-氯-2,5-二甲基-吡唑并[1,5-*a*]嘧啶

向 2,5-二甲基-4*H*-吡唑并[1,5-*a*]嘧啶-7-酮(10.0 g, 61.3 mmol)在甲苯(150 mL)中的混悬液中加入 *N*,*N*-二甲基苯胺(9.7 mL, 76.7 mmol)。向这种白色混悬液中滴加三氯氧化磷(phosphorus oxychloride)(11.2 mL, 122.6 mmol)。将其在惰性气氛下回流 3 小时，冷却至室温并将反应减压浓缩成棕色油状物。将该油状物溶解于乙酸乙酯(250 mL)中并用 1.0 N NaOH 碱化。分离出有机相，用乙酸乙酯对碱性水相进行萃取(2 × 100 mL)。将有机相合并，用无水硫酸镁干燥，过滤，减压浓缩，得到棕色固体。将该物质

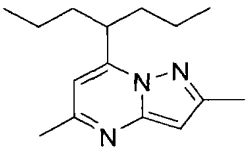
用快速色谱进行纯化，用 80%己烷/20%(30% THF/己烷)至 0%己烷/100%(30% THF/己烷)以 20%的增量逐步梯度洗脱，得到浅绿色固体(6.65 g, 59%)。ES/MS m/z (^{35}Cl) 182.3 $(M+1)^+$。

另一种操作:

将 2,5-二甲基吡唑并[1,5-*a*]嘧啶-7-酮(20 g, 122 mmol)加入到 1,4-二噁烷(60 mL)中。将混合物在 22℃下搅拌 10 分钟，然后加入 N,N-二乙基苯胺(20.8 mL, 128 mmol)。将其再搅拌 5 分钟，然后历经 15 分钟加入三氯氧化磷(11.7 mL, 126 mmol)。将混合物在 22℃下搅拌 15 分钟，然后历经 35 分钟加热至 80-85℃并将反应在这一温度下保持 1.5 小时。将被冷却的反应混合物缓慢加入到被冷却至 0-5℃的磷酸氢二钾(106.7 g, 612.82 mmol)在水(325 mL)中的溶液中，在加入期间保持温度低于 5℃。将混合物在 22℃下进行搅拌，然后加入甲基-叔-丁基醚(150 mL)。分离有机层，用甲基-叔-丁基醚对水层进行萃取(2 × 100 mL)。将有机部分合并，用硫酸钠干燥，过滤，蒸发掉溶剂。用硅胶色谱进行纯化，用己烷/乙酸乙酯(2/1)进行洗脱，得到黄色固体形式的标题化合物(20.7 g, 88%)。ES/MS m/z (^{35}Cl) 182 $(M+1)^+$。

制备例 3

7-(1-丙基-丁基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶



向一个配有回流冷凝器的烘箱干燥的烧瓶中加入无水 THF(40 mL)、碘(催化量)、镁条(1.92 g, 78.9 mmol)和 4-溴庚烷(9.4 mL, 52 mmol)。将反应在油浴中加热至回流。当格氏反应开始时，反应温度迅速升高。将反应在 90℃下再搅拌 4 小时，冷却至室温。使镁金属沉降(也可以进行离心)，在正氩气压下通过套管将格氏试剂加入到装有 7-氯-2,5-二甲基吡唑并[1,5-*a*]嘧啶(4.80 g, 26.3 mmol)(位于无水甲苯(20 mL)中)的烧瓶中。将反应

在惰性气氛下回流过夜。将反应冷却至室温并用水淬灭。用乙酸乙酯(150 mL)稀释，然后加入水(100 mL)和饱和氯化铵(50 mL)。将水相分离出来并用二氯甲烷(75 mL)萃取。将有机相合并，用无水硫酸镁干燥，过滤，减压浓缩。将所得残余物用快速色谱进行纯化，用 80%己烷/20%(20%乙酸乙酯/己烷)至 0%己烷/100%(20%乙酸乙酯/己烷)以 20%的增量逐步梯度洗脱，得到黄色晶体(3.08 g, 48%)。ES/MS m/z 246.3 $(M+1)^+$。

另一种操作:

将镁屑(3.5 g, 144 mmol)和催化量的碘(100 mg)在 THF(100 mL)中的混合物在氮气气氛下加热至 65℃。加入几滴纯 4-溴庚烷并将混合物加热至反应开始。然后，历经在 2 小时加入 4-溴庚烷(17.6 mL, 94.9 mmol)在 THF(42 mL)中的溶液，同时保持温度为 65-70℃。将混合物再回流 1 小时，然后将反应冷却至 22℃。在氮气气氛下，将制得的格氏试剂加入到被冷却至 0℃的 7-氯-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(10.2 g; 53.3 mmol)在 THF(60 mL)中的溶液中。历经 45 分钟，通过套管加入镁试剂溶剂，同时保持温度低于 10℃。然后将混合物在 5℃下再搅拌 30 分钟。向这种混合物中加入 10%氯化铵水溶液(wt/wt)(125 mL)并将其在 22℃下搅拌 30 分钟。分离有机层并用乙酸乙酯对水层进行萃取(2 × 25 mL)。将有机层合并并用硫酸钠干燥。对混合物进行过滤并蒸发掉溶剂。用硅胶快速色谱对该粗品物质进行纯化，用己烷/乙酸乙酯(5/1)进行洗脱，得到标题化合物(8 g, 62%)。ES/MS m/z 246 $(M+1)^+$。

制备例 3a

7-(1-丙基-丁基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶

另一种路径

步骤 1: 3-乙酰基-3-氧代-4-丙基-庚酸乙酯

将氯化镁(14.63 g, 153.70 mmol)加入到二氯甲烷(500 mL)中，然后一次性加入乙酰乙酸乙酯(19.55 mL, 20.00 g, 153.79 mmol)并将其在室温下搅拌 1 小时。将混合物在冰水浴中冷却并滴加吡啶(24.86 mL, 24.32 g, 307.39 mmol)。在 0℃下在氮气下向该白色浆液中滴加二-正丙基乙酰氯(25.00 g,

153.70 mmoles)。在完全加入后，除去冷却浴，温热至环境温度并将其搅拌 16 小时。将反应用 1 N HCl(400 mL)淬灭并分离出底层。将有机部分用硫酸镁干燥，过滤，真空浓缩，得到黄色油状物(34 g, 86%)。将该物质不进行进一步纯化地直接用于下一步。

步骤 2: 5-丙基-辛烷-2,4-二酮

将 3-乙酰基-3-氧代-4-丙基-庚酸乙酯(32.4 g, 126.39 mmol)溶解于二甲基亚砜(100 mL)和水(5 mL)中。将该溶液在 150℃下加热 6 至 8 小时或者用 GC/MS 对反应进行追踪。将反应冷却，用庚烷萃取(3 × 100 mL)。将合并的有机部分用水(100 mL)和盐水(100 mL)洗涤。在 50℃下真空浓缩以除去大部分庚烷。得到 23.29g 油状物并将其直接用于下一步。

步骤 3: 7-(1-丙基-丁基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶

将 5-丙基-辛烷-2,4-二酮(15 g, 81.40 mmol)混合到乙酸(15 mL)中并将其在冰浴上进行冷却。分批加入 5-氨基-3-甲基吡唑(7.91 g, 81.40 mmol)并在环境温度下进行搅拌。在 3 小时后，用 GC/MS 检查是否反应完全。GC 表明与真实样品相比存在正确的区域异构体。蒸馏掉过量的乙酸。加入水(50 mL)并用庚烷(50 mL)萃取。用盐水(50 mL)对庚烷部分进行洗涤。将有机层用 $MgSO_4$ 干燥，过滤，真空浓缩，得到粗品油状物(15.8 g, 79%)。^1H NMR ($CDCl_3$): 6.39(s, 1H); 6.31(s, 1H); 3.75(m, 1H); 2.55(s, 3H); 2.45(s, 3H); 1.71(q, 4H); 1.23(m, 4H); 0.85(t, 6H)。

基本如制备例 3 中所述的那样用任何一种操作制备下面的化合物。用 3-溴戊烷来制备格氏试剂。

制备例号	化学名	物理数据
4	7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶	ES/MS m/z 218.1 $(M+1)^+$

制备例 5

7-(1-丙基-丁基)-3-碘-2,5-二甲基-吡唑并[1,5-*a*]嘧啶

将 7-(1-丙基-丁基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(3.08 g, 12.5 mmol)溶

解于无水乙腈(25 mL)中并以 10 分钟的时间间隔加入 6 份(每份 0.70 g) N-碘琥珀酰亚胺(4.2 g, 18.7 mmol)。在室温下搅拌过周末。除去乙腈，用二氯甲烷(100 mL)对剩下的油状物进行稀释。用饱和氯化铵溶液(2 × 50 mL)洗涤。收集有机相，用无水硫酸镁干燥，过滤，减压浓缩，得到深红色的油状物。用快速色谱对该油状物进行纯化，用 100%己烷/0%(20%乙酸乙酯/己烷)至 0%己烷/100%(20%乙酸乙酯/己烷)以 50%的增量逐步进行梯度洗脱，得到橙色油状物(10.97 g, 87%)。^{1}H NMR (400 MHz, $CDCl_3$): 6.42(s, 1H), 3.74-3.70(m, 1H), 2.58(s, 3H), 2.46(s, 3H), 1.74-1.68(m, 4H), 1.28-1.14(m, 4H), 0.84(t, J = 7.0 Hz, 6H)。

基本如制备例 5 所述的那样制备下面的化合物。

制备例号	化学名	物理数据
6	7-(1-乙基-丙基)-3-碘-2,5-二甲基-吡唑并[1,5-*a*]嘧啶	1H NMR(400 MHz, $CDCl_3$): 6.44(s, 1H), 3.59(m, 1H), 2.61(s, 3H), 2.49(s, 3H), 1.86-1.76(m, 4H), 0.85(t, J = 7.5 Hz, 6H)。

制备例 6 的另一种操作:

将乙酸(1 mL)和 N-碘琥珀酰亚胺(6.7 g, 29.9 mmol)一次性加入到 7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(6 g, 27.5 mmol)在乙腈(60 mL)中的溶液中。将混合物在 22℃下搅拌 2 小时。蒸发掉溶剂，将残余物吸收于水(50 mL)和甲基-叔丁基醚(100 mL)中。将有机部分分离出来，用硫酸钠干燥，过滤，蒸发掉溶剂，得到标题化合物(9.2 g, 96%)。ES/MS m/z 344 $(M+1)^+$。

制备例 7

2-三甲基硅烷基-噻唑

将正丁基锂(20.4 mL, 51.0 mmol, 2.5 M 的己烷溶液)与乙醚(50 mL)在一个配有滴液漏斗和温度计的三颈烧瓶中混合到一起。冷却至-78℃，滴加

噻唑(4.25 g, 50.0 mmol)在乙醚(50 mL)中的溶液。在完全加入后，将反应混合物在-78℃下搅拌 30 分钟，然后加入三甲基氯硅烷(5.4 g, 50 .0 mmol)。在-78℃下搅拌 1 小时，然后温热至室温。通过加入饱和碳酸氢钠来将反应淬灭。用乙醚萃取水层。用盐水洗涤合并的有机部分，用硫酸钠干燥。过滤并减压浓缩，得到残余物。通过蒸馏进行纯化，得到 8.33 g (52-56℃/ 15 mm Hg)标题化合物。^{1}H NMR (400 MHz, $CDCl_3$) 8.13(d, 1H, J=2.6 Hz), 7.54(d, 1H, J = 2.6 Hz), 0.43(s, 9H)。

制备例 8

5-溴-4-甲基噻唑

在 0℃下，向 4-甲基噻唑(15.0 g, 152 mmol)在乙酸(30 mL)中的溶液中加入溴(9.27 mL, 182 mmol)。将反应混合物缓慢温热至室温并搅拌过夜。用二氯甲烷稀释并用 1 N NaOH 和盐水洗涤。将有机层用硫酸钠干燥，过滤，真空浓缩。用硅胶柱色谱对粗产物进行纯化，用己烷/乙酸乙酯(5/1)进行洗脱，得到标题化合物(9.94 g, 37%)。^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69(s, 1H), 2.43(s, 3H)。

制备例 9

噻唑-2-甲酸乙酯

历经 15 分钟，向 2-三甲基硅烷基噻唑(135 g, 858.1 mmol)在甲苯(1350 mL)中的混合物中加入氯甲酸乙酯(98.4 mL, 1.03 mol)在甲苯(1350 mL)中的溶液。将反应在 22℃下搅拌 2 小时。将该溶液加到 25%(wt/wt)碳酸钠水溶液(5 L)上并搅拌 30 分钟。分离有机层，用二氯甲烷(2 × 1 L)反萃取水层。将有机层合并并蒸发掉溶剂，得到标题化合物(134 g, 99%)。ES/MS m/z 158 $(M+1)^+$。

制备例 10

噻唑-2-甲酰胺

将噻唑-2-甲酸乙酯(150 g, 0.9 mol)加入到甲醇(75 mL)和 30%氢氧化铵水溶液(750 mL)的混合物中，将混合物在回流下加热 1 小时。然后冷却至 22℃，在真空下蒸发掉甲醇。将混合物在室温下搅拌 30 分钟，滤出固体。将分离出来的固体真空干燥，得到标题化合物(98 g, 85%)。ES/MS m/z 129 $(M+1)^+$。

制备例 11

1-甲基-5-噻唑-2-基-1H-[1,2,4]三唑

将 1,1-二甲氧基-*N*,*N*-二甲基-甲胺(240 mL)冷却至 10℃并分三份加入噻唑-2-甲酰胺(60 g, 421 mmol)。将混合物在 10℃下搅拌 30 分钟。然后将混合物在 45 分钟内逐渐加热至回流。蒸馏掉所形成的甲醇，然后将反应加热至 100℃达 1.5 小时。将混合物冷却至 60℃并通过真空蒸馏除去过量的 1,1-二甲氧基-N,N-二甲基-甲胺。将残余物冷却至 22℃，加入己烷(200 mL)。将混合物研磨 15 分钟，过滤，将固体干燥至恒重，然后用于下一步。

将上面分离出来的固体(68 g)加入到乙酸(680 mL)中并将混合物冷却至 10℃。以保持温度低于 15℃的速度加入 *N*-甲基-肼(27 mL, 509 mmol)。将混合物在 30 分钟内温热至 20℃，然后逐渐加热至 90℃。在 90℃下搅拌 30 分钟，然后冷却至 22℃。通过真空蒸馏除去乙酸。将残余物加到水上，通过加入 25%氢氧化钠水溶液调至 pH = 8。用甲基-叔丁基醚对水层进行萃取(3 × 600 mL)。将有机层合并，蒸发掉溶剂。用硅胶色谱对所得的残余物进行纯化，用己烷/异丙醇(9/1)进行洗脱，得到标题化合物(49 g, 70%)。ES/MS m/z 167 $(M+1)^+$。

制备例 12

5-(5-溴-噻唑-2-基)-1-甲基-1*H*-[1,2,4]三唑

历经 1 小时分三批向甲基-5-噻唑-2-基-1H-[1,2,4]三唑(6.55 g; 39.4 mmol)和二甲基甲酰胺(32 mL)的混合物中加入 N-溴琥珀酰亚胺(14 g, 78.8 mmol)。将混合物在 22℃下搅拌 18 小时，然后加入到被冷却至 0-5℃的水

(300 mL)中。分离出水层，用甲基-叔丁基醚(2 × 200 mL)萃取。将有机层合并，用 7%碳酸氢钠水溶液(100 mL)洗涤，然后用硫酸钠干燥。过滤并蒸发掉溶剂，得到标题化合物(9.5 g, 93%)。ES/MS m/z (^{79}Br/^{81}Br) 245/247 $(M+1)^+$。

制备例 13

2,5-二甲基-3-[2-(2-甲基-2*H*-[1,2,4]三唑-3-基)-噻唑-5-基]-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶

将 5-(5-溴-噻唑-2-基)-1-甲基-1H-[1,2,4]三唑(6.5 g, 23.8 mmol)和 2,5-二甲基-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶(6 g, 24.5 mmol)合并到 N-甲基吡咯烷酮(58 mL)中并将其在氮气下搅拌至完全形成溶液。然后，加入溴化四-N-丁基铵(5.47 g, 16.7 mmol)和醋酸钾(11.8 g, 119 mmol)并将混合物在氮气气氛下加热至 100℃。通过用真空/氮气清洁三个循环对该热混合物进行脱气。然后加入醋酸钯(216 mg, 0.94 mmol)和三(2,4-二-叔丁基-苯基)-磷烷(787 mg, 1.2 mmol)。将混合物在 125℃下在氮气下加热 4 小时。将混合物冷却至 22℃并加入到水(750 mL)中。用甲基-叔丁基醚(3 × 200 mL)对水层进行萃取，将有机部分合并，蒸发。通过用硅胶垫过滤纯化残余物，用己烷/乙酸乙酯(4/1)进行洗脱。将包含产物的级分合并，蒸发掉溶剂，得到标题化合物(7 g, 72%)。ES/MS m/z 410$(M+1)^+$。

制备例 14

2,5-二甲基-7-(1-丙基-丁基)-3-噻唑-5-基-吡唑并[1,5-*a*]嘧啶

向一个烘箱干燥的烧瓶中加入被溶解于无水 THF(30 mL)中的 2-三甲基硅烷基噻唑(1.765 g, 11.24 mmol)并将其在惰性气氛下冷却至-78℃。缓慢加入正丁基锂(2.5 M 己烷溶液, 4.5 mL, 11.24 mmol)并在-78℃下搅拌 30 分钟。一次性加入无水氯化锌(2.26 g, 16.58 mmol)并在-78℃下搅拌 30 分钟。使反应升至室温，搅拌 30 分钟，加入 7-(1-丙基-丁基)-3-碘-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(1.624 g, 5.18 mmol)和二氯[1,1'-双(二苯基膦基)二茂铁]钯

(II)二氯甲烷(0.423 g, 0.518 mmol)。在油浴(90℃)中在惰性气氛下回流过夜。将反应冷却至室温，用饱和碳酸氢钠淬灭，用乙酸乙酯(150 mL)稀释。将水相分离出来并用乙酸乙酯(75 mL)萃取。将有机相合并，用无水硫酸镁干燥，过滤，减压浓缩。将所得残余物用快速色谱进行纯化，用 100%己烷/0%(30% THF/己烷)至 0%己烷/100%(30% THF/己烷)以 10%的增量逐步进行梯度洗脱，得到白色固体(0.720 g, 42%)。ES/MS m/z 329.0$(M+1)^+$。

基本如制备例 14 中所述的那样来制备下面的化合物。

制备例号	化学名	物理数据
15	7-(1-乙基-丙基)-2,5-二甲基-3-噻唑-5-基-吡唑并[1,5-*a*]嘧啶	1H NMR(400 MHz, $CDCl_3$): d 8.75(s, 1H), 8.75(s, 1H), 8.28(s, 1H), 6.47(s, 1H), 3.62-3.55(m, 1H), 2.65(s, 3H), 2.61(s, 3H), 1.89-1.75(m, 4H), 0.85(t, 6H, *J* = 7.5 Hz), 0.85(t, 6H, *J* = 7.5 Hz)。

制备例 15 的另一种操作:

在-78℃下，在氮气下，将正丁基锂(76.5 mL, 191 mmol, 2.5 M 的己烷溶液)加入到 2-三甲基硅烷基噻唑(30 g, 191 mmol)在 THF(450 mL)中的溶液中，在加入期间保持温度低于-74℃。将该混合物在-78℃下搅拌 30 分钟，然后一次性加入氯化锌干粉(39.9 g, 286 mmol)并将混合物历经 1 小时温热至 22℃。加入 7-(1-乙基-丙基)-3-碘-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(30 g, 87 mmol)和 1,1'-双(二苯基膦基)二茂铁氯化钯(II)(6.5 g, 8 mmol)并将混合物在氮气下加热至回流达 8 小时。将混合物冷却至 22℃并加入 10%氯化铵水溶液(450 mL)。分离有机层并用甲基-叔丁基醚对水层进行洗涤(2 × 100 mL)。将有机部分合并，用硫酸钠干燥，过滤，蒸发掉溶剂，得到标题化合物(20.4 g, 78%)。ES/MS m/z 301$(M+1)^+$。

制备例 16

7-(1-乙基-丙基)-3-(2-碘-噻唑-5-基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶

在-78℃下，在氮气气氛下，将新制备的二-异丙基氨基锂溶液(150 ml; 62.4 mmol, 0.6 M 的 THF 溶液)加入到 7-(1-乙基-丙基)-2,5-二甲基-3-噻唑-5-基-吡唑并[1,5-*a*]嘧啶(17.8 g, 62.4 mmol)在 THF(100 mL)中的混合物中，在加入期间保持温度低于-74℃。将该混合物在-78℃下搅拌 1 小时，然后加入 N-碘琥珀酰亚胺(15 g, 63 mmol)在 THF(100 mL)中的溶液，同时保持温度低于-74℃。将反应逐渐温热至 22℃，然后加入 10%氯化铵水溶液(300 mL)。分离有机层，用甲基-叔丁基醚对水层进行洗涤(2 × 200 mL)。将有机层合并，用硫酸钠干燥，过滤并蒸发掉溶剂。用硅胶色谱对所得的残余物进行纯化，用己烷/丙酮(5/1)进行洗脱，得到标题化合物(15 g, 60%)。ES/MS m/z 427 $(M+1)^+$。

实施例 1

7-(1-乙基-丙基)-2,5-二甲基-3-(4-甲基-噻唑-5-基)-吡唑并[1,5-*a*]嘧啶

将 Rieke®锌(10 g，位于 100 mL THF 中, 13.2 mL, 18.48 mmol)加入到 5-溴-4-甲基噻唑(2.13 g, 18.48 mmol)中并在回流下加热 2 小时。将混合物冷却至室温，通过离心使锌沉降。向位于干燥四氢呋喃(10 mL)中的 7-(1-乙基-丙基)-3-碘-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(900 mg, 2.62 mmol)中用氮气鼓泡，加入有机溴化锌溶液，然后加入[1,1'-双(二苯基膦基)二茂铁]-二氯钯(II)(106 mg, 0.13 mmol)。将反应混合物在回流下搅拌过夜，然后冷却至室温。向反应混合物中加入氯化铵溶液并用二氯甲烷萃取。将有机部分用硫酸钠干燥，过滤，真空除去溶剂。用硅胶柱色谱对粗产物进行纯化，用己烷/乙酸乙酯(3/1)进行洗脱，得到标题化合物(652 mg, 79%)。^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80(s, 1H), 6.48(s, 1H), 3.63(m, 1H), 2.57(s, 3H), 2.43 (s, 3H), 2.40(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J = 7.3Hz)。ES/MS m/z 315 $(M+1)^+$。

制备例 17

3-(2,4-二溴-噻唑-5-基)-2,5-二甲基-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶

将 2,5-二甲基-7-(1-丙基-丁基)-3-噻唑-5-基-吡唑并[1,5-*a*]嘧啶(3.15 g, 9.59 mmol)溶解于乙腈(100 mL)中并一次性加入 N-溴琥珀酰亚胺(4.27 g, 24.0 mmol)。在惰性气氛下搅拌过夜并用 TLC 证实反应进行完全。减压浓缩，用二氯甲烷(150 mL)稀释油状物，用水(75 mL)洗涤。将有机相用无水硫酸镁干燥，过滤，减压浓缩。将所得的油状物用快速色谱进行纯化，用 100%己烷/0%(30% THF/己烷)至 0%己烷/100%(30% THF/己烷)逐步梯度洗脱(0-10-15-20-25-30-35-40-45-50-100%的 30%THF/己烷)，得到黄色晶体(3.70 g, 79%)。ES/MS m/z ($^{79}Br^{81}Br$) 486.7 $(M+1)^+$。

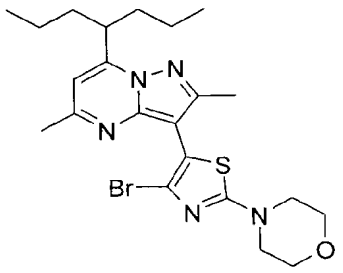
基本如制备 17 中所述的那样制备下面的化合物，不同的是用二氯甲烷作为溶剂。

实施例编号	化学名	物理数据
2	3-(2,4-二溴-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶	MS (APCI) m/z ($^{79}Br^{81}Br$) 459.1 $(M+1)^+$
3*	3-(2-溴-4-甲基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶	ES/MS m/z (^{79}Br) 393 $(M+1)^+$

*使用 1.1 eq NBS，搅拌 3 天。

实施例 4

3-(4-溴-2-吗啉-4-基-噻唑-5-基)-2,5-二甲基-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶



向一个烘箱干燥的烧瓶中加入 3-(2,4-二溴噻唑-5-基)-2,5-二甲基-7-(1-

丙基-丁基)-吡唑并[1,5-*a*]嘧啶(0.973 g, 2.00 mmol)、无水二噁烷(20 mL)、吗啉(0.872 g, 10.0 mmol)和碳酸铯(1.95 g, 6.00 mmol)。在油浴(105℃)中在惰性气氛下回流过夜。用 LC/MS 证实反应完全。用乙酸乙酯(100 mL)稀释，用水(50 mL)洗涤，用乙酸乙酯(50 mL)反萃取水相。将有机相合并，用硫酸镁干燥，过滤，减压浓缩。将所得残余物用快速色谱进行纯化，用100%己烷/0%(40%二氯甲烷/20%乙酸乙酯/2% 7 N 氨的甲醇溶液/38%己烷)至 0%己烷/100%(40%二氯甲烷/20%乙酸乙酯/2% 7 N 氨的甲醇溶液/38%己烷)以 10%的增量逐步梯度洗脱，得到灰白色固体(0.878 g, 89%)。ES/MS m/z (^{79}Br) 491.7$(M+1)^+$。

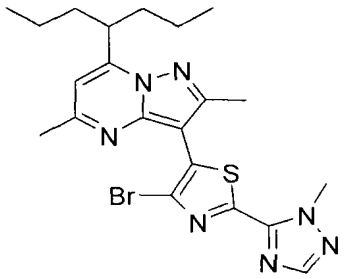
基本如实施例 4 中所述的那样用 2.0 二甲基胺/THF 或吗啉作为胺、用 THF 或二噁烷作为溶剂制备下面的实施例。这些反应是在密封的容器或 Schlenk 管中进行的。

实施例号	化学名	物理数据
5*	{4-溴-5-[2,5-二甲基-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶-3-基]-噻唑-2-基}-二甲基胺	ES/MS (^{79}Br) 449.8 $(M+1)^+$。
6	3-(4-溴-2-吗啉-4-基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶	MS (APCI) m/z (^{81}Br) 466.5 $(M+1)^+$
7	{4-溴-5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-噻唑-2-基}-二甲基-胺	MS (APCI) m/z (^{81}Br) 424.4 $(M+1)^+$
8	{5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-4-甲基-噻唑-2-基}-二甲基-胺	ES/MS m/z 358 $(M+1)^+$
9	7-(1-乙基-丙基)-2,5-二甲基-3-(4-甲基-2-吗啉-4-基-噻唑-5-基)-吡唑并[1,5-*a*]嘧啶	ES/MS m/z 400 $(M+1)^+$

*使用 6 eq 碳酸铯。

实施例 10

3-[4-溴-2-(2-甲基-2*H*-[1,2,4]三唑-3-基)-噻唑-5-基]-2,5-二甲基-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶



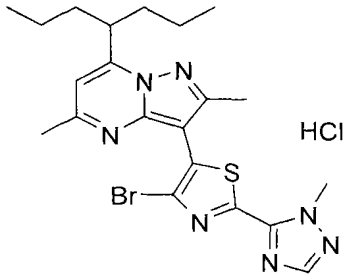
向一个烘箱干燥的烧瓶中加入 1-甲基-1,2,4-三唑(0.498, 6.00 mmol)和无水 THF(20 mL)，在惰性气氛下冷却至-78℃。缓慢加入正丁基锂(2.5M 己烷溶液, 2.4 mL, 6.0 mmol)并搅拌 30 分钟。一次性加入无水氯化锌(1.36 g, 10.0 mmol)并在-78℃下搅拌 30 分钟。使反应温热至室温，搅拌 30 分钟，加入 3-(2,4-二溴噻唑-5-基)-2,5-二甲基-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶(0.973 g, 2.00 mmol)和二氯[1,1'-双(二苯基膦基)二茂铁]钯(II)二氯甲烷(0.163 g, 0.200 mmol)。将反应在油浴(90℃)中在惰性气氛下回流过夜。将反应冷却至室温，用水淬灭，用乙酸乙酯(100 mL)稀释。分离出含水部分，用二氯甲烷(50 mL)萃取。将有机相合并，用无水硫酸镁干燥，过滤，减压浓缩。将所得残余物用快速色谱进行纯化，用 100%己烷/0%(10%乙腈/40% THF/50%己烷)至 0%己烷/100%(10%乙腈/40% THF/50%己烷)以 10%的增量逐步梯度洗脱，得到白色固体(0.090 g, 9%)。ES/MS m/z (^{79}Br) 487.7 $(M+1)^+$。

另一种制备方法：

向 2,5-二甲基-3-[2-(2-甲基-2H-[1,2,4]三唑-3-基)-噻唑-5-基]-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶(6 g, 14.65 mmol)在乙腈(60 mL)中的溶液中一次性加入 N-溴琥珀酰亚胺(2.74 g, 15.4 mmol)并在 22℃下搅拌 10 小时。蒸发掉溶剂，将残余物溶解于水(50 mL)和甲基-叔丁基醚(100 mL)的混合物中。分离有机层，用另外的甲基-叔丁基醚对水层进行萃取(2 × 50 mL)。将有机部分合并，蒸发掉溶剂。通过用硅胶垫过滤来对所得物质进行纯化，用己烷/乙酸乙酯(3/1)进行洗脱。将包含产物的级分合并，蒸发掉溶剂。加入庚烷(25 mL)并对固体进行研磨。将固体滤出，真空干燥，得到标题化合物(5.5 g, 77%)。ES/MS m/z (^{79}Br/^{81}Br) 488/490$(M+1)^+$。

实施例 10a

3-[4-溴-2-(2-甲基-2*H*-[1,2,4]三唑-3-基)-噻唑-5-基]-2,5-二甲基-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶，盐酸盐



将 3-[4-溴-2-(2-甲基-2*H*-[1,2,4]三唑-3-基)-噻唑-5-基]-2,5-二甲基-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶(750 mg, 1.54 mmol)溶解于丙酮(5 mL)中并加入 1 M HCl 的乙醚溶液(1.84 mL, 1.84 mmol)。将混合物在室温下搅拌 3 小时并真空浓缩。将残余物溶解于乙醚/己烷= 1/1(5 mL)中，使所需的 HCl 盐结晶(526 mg, 65%)。ES/MS m/z (^{81}Br) 490 $(M+1)^+$; ^{1}H-NMR ($CDCl_3$): 8.20(s, 1H), 6.82(s, 1H), 4.21(s, 3H), 3.64(m, 1H), 2.49(m, 3H), 2.44(s, 3H), 1.75(m, 4H), 1.96(m, 4H), 0.81(m, 6H)。

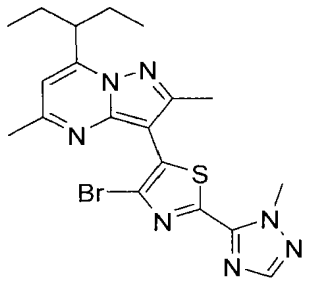
基本如实施例 10 中所述的那样来制备下面的化合物。

实施例编号	化学名	物理数据
11*	7-(1-乙基-丙基)-2,5-二甲基-3-[4-甲基-2-(2-甲基-2H-[1,2,4]三唑-3-基)-噻唑-5-基]-吡唑并[1,5-*a*]嘧啶	ES/MS m/z 396 $(M+1)^+$

* 用 0.5 M 位于 THF 中的氯化锌代替无水氯化锌。在 80℃下加热 3 天。

实施例 12

3-(4-溴-2-(2-甲基-2H-[1,2,4]三唑-3-基)-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶



在-78℃下，在氮气气氛下，将正丁基锂(2.5M 己烷溶液, 0.6 mL, 1.5 mmol)加入到 1-甲基-1,2,4-三唑(124.5 mg, 1.5 mmol)在 THF(3 mL)中的溶液中并搅拌 30 分钟。加入无水氯化锌(409 mg, 3.0 mmol)，继续搅拌 30 分钟，温热至室温并搅拌 2 小时。加入 3-(2,4-二溴-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(229 mg, 0.5 mmol)，然后加入四(三苯基膦)钯(58 mg, 0.05 mmol)并回流过夜。冷却至室温，用乙酸乙酯稀释，用饱和氯化铵洗涤。将有机部分用硫酸钠干燥，过滤，浓缩，获得残余物。用快速色谱对粗品物质进行纯化，用己烷:乙酸乙酯(10:2.5)进行洗脱，得到黄色泡沫形式的标题化合物(77 mg)。MS (APCI) m/z (^{79}Br) 460.4 $(M+1)^+$。

从实施例 21 开始的另一种制备方法:

将乙酸(1 mL)和 N-溴琥珀酰亚胺(4.1 g, 22 mmol)加入到 7-(1-乙基-丙基)-2,5-二甲基-3-[2-(2-甲基-2H-[1,2,4]三唑-3-基)-噻唑-5-基]-吡唑并[1,5-*a*]嘧啶(8 g, 21 mmol)在乙腈(80 mL)中的溶液中。将混合物在 22℃下搅拌 2 小时。然后蒸发掉溶剂，向所得的残余物中加入水(50 mL)和甲基-叔丁基醚(100 mL)。将有机部分分离出来，用硫酸钠干燥，过滤，蒸发掉溶剂。将所得的残余物用异丙醇重结晶，得到标题化合物(8.7 g, 90%)。ES/MS (m/z): (^{79}Br/^{81}Br) 460/462 $(M+1)^+$。

实施例 12a

3-(4-溴-2-(2-甲基-2H-[1,2,4]三唑-3-基)-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶, 对-甲苯磺酸

将 3-(4-溴-2-(2-甲基-2H-[1,2,4]三唑-3-基)-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(50 mg, 0.109 mmol)溶解于丙酮(3 mL)

中。加入 0.25 M 对-甲苯磺酸水溶液(434.4 μL, 0.109 mmol)，将所得混合物蒸发至干。加入乙酸乙酯(12 mL)以使固体部分溶解。加入甲醇(1 mL)以获得澄清溶液。通过缓慢蒸发来对该溶液进行浓缩，直至观察到晶体。通过过滤分离出晶体并在 25℃下真空干燥，得到约 50 mg 标题化合物。

用使用下列 HPLC 条件的离子色谱测定该盐的化学计量：柱：Phenomenex Phenosphere SAX, 4.6 × 150 mm，30℃；流动相：50%乙腈/50% 0.025 M 磷酸钠缓冲液, pH = 4.5；流速= 1.5 mL/min；检测：UV, 205 nm；进样体积= 5 μL；运行时间= 3 分钟。理论量计算值：27.2%甲苯磺酸根；实测值：28.4%甲苯磺酸根(三次 HPLC 运行的均值)。

实施例 13

{4-氯-5-[2,5-二甲基-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶-3-基]-噻唑-2-基}-二甲基胺

向一个烘箱干燥的烧瓶中加入{4-溴-5-[2,5-二甲基-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶-3-基]-噻唑-2-基-二甲基胺(0.20, 0.44 mmol)和无水 THF (3.0 mL)并在惰性气氛下冷却至-78℃。缓慢加入正丁基锂(1.6 M 己烷溶液, 0.42 mL, 0.67 mmol)并搅拌 30 分钟。一次性加入 N-氯琥珀酰亚胺(0.120 g, 0.889 mmol)并在-78℃下搅拌 30 分钟。使反应温热至室温，搅拌 5 小时，用 LC/MS 检查反应进程。用乙酸乙酯(100 mL)稀释，用饱和氯化铵(50 mL)洗涤，用二氯甲烷(50 mL)反萃取水相。将有机相合并，用无水硫酸镁干燥，过滤，减压浓缩。将所得残余物用快速色谱进行纯化，用 100%己烷/0%(25% THF/己烷)至 0%己烷/100%(25% THF/己烷)以 10%的增量逐步梯度洗脱，得到白色固体(0.087 g, 48%)。ES/MS m/z (^{35}Cl) 406.0 $(M+1)^+$。

基本如实施例 13 所述的那样用上面制得的适宜溴代噻唑来制备下面的实施例。

实施例号	化学名	物理数据
14	3-(4-氯-2-吗啉-4-基-噻唑-5-基)-2,5-二甲基-7-(1-丙基-丁基)-吡唑并[1,5-*a*]嘧啶	ES/MS m/z (^{35}Cl) 448.0 $(M+1)^+$
15	{4-氯-5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-噻唑-2-基}-二甲基-胺	MS (APCI) m/z (^{35}Cl) 378.0 $(M+1)^+$

制备例 18

2,4-二氯噻唑

将噻唑烷-2,4-二酮(50 g, 0.43 mol)在三氯氧化磷(240 mL)中的混合物冷却至5℃，历经15分钟加入吡啶(34 mL, 0.43 mol)。将混合物加热至125℃达4小时，然后冷却至22℃。通过真空蒸馏除去过量的三氯氧化磷并将残余物加入到被冷却至5℃的水(1 L)中。将混合物用二氯甲烷(3 × 400 mL)萃取。将有机部分合并，蒸发掉溶剂，得到标题化合物(50 g, 76%)。EI/MS m/z: (^{35}Cl^{35}Cl/^{35}Cl^{37}Cl/^{37}Cl^{37}Cl) 153/155/157 $(M+1)^+$。

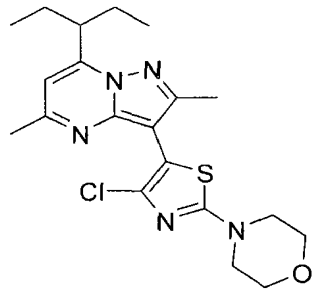
制备例 19

4-氯-2-吗啉代-噻唑

向2,4-二氯噻唑(34 g, 0.22 mol)在乙腈(425 mL)中的混合物中加入碳酸钾(60.9 g, 0.44 mol)，然后历经30分钟滴加吗啉(21.2 mL, 0.225 mol)。将混合物在40℃下回流，然后冷却至22℃。对混合物过滤并蒸发滤液。将残余物用异丙醇(60 mL)在22℃下研磨1小时。将固体滤出并真空干燥至恒重，得到标题化合物(34.5 g, 76%)。ES/MS m/z (^{35}Cl) 205 $(M+1)^+$。

实施例 16

3-(4-氯-2-吗啉-4-基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶



在氮气气氛下，将 3-(4-溴-2-吗啉-4-基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(116 mg, 0.25 mmol)溶解于 THF(1.5 mL)中并冷却至-78℃。加入正丁基锂(0.1 mL. 2.5 M 己烷溶液, 0.25 mmol)并在-78℃下搅拌 30 分钟。加入 N-氯琥珀酰亚胺(33.4 mg, 0.25 mmol)并再搅拌 30 分钟，同时缓慢温热至室温。在搅拌过夜后，通过加入饱和氯化铵溶液将反应淬灭，用乙酸乙酯萃取。用盐水洗涤有机层，用硫酸钠干燥，过滤，浓缩，获得残余物。用快速色谱对该粗品物质进行纯化，用己烷:二氯甲烷:乙酸乙酯(5:5:2)洗脱，得到标题化合物(54 mg)。MS (APCI) m/z (^{35}Cl) 420.6 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$): 6.44(s, 1H), 3.79(t, 4H, *J*=4.8 Hz), 3.63-3.56(m, 1H), 3.47(t, 4H, *J*=4.8 Hz), 2.55(s, 3H), 2.45(s, 3H), 1.88-1.75(m, 4H), 0.87(t, 6H, *J*=7.5 Hz)。

从制备例 6 开始的另一种制备方法:

将 7-(1-乙基-丙基)-3-碘-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(9 g, 26.2 mmol)和 4-氯-2-吗啉代-噻唑(7.5 g, 36.7 mmol)合并到之前用氮气进行了脱气的二甲基甲酰胺(90 mL)中。加入碳酸铯(17.8 g, 55 mmol)、碘化亚铜(250 mg, 1.31 mmol)、三苯基膦(550 mg, 2.09 mmol)和醋酸钯(117 mg, 0.52 mmol)。将混合物加热至 125℃达 16 小时，然后冷却至 22℃。加入水(900 mL)并用甲基-叔丁基醚(3 × 200 mL)萃取。将有机部分合并，蒸发掉溶剂。用硅胶色谱进行纯化，用己烷/乙酸乙酯(4/1)进行洗脱，得到标题化合物(6.4 g, 62%)。ES/MS m/z (^{35}Cl) 420 $(M+1)^+$。

实施例 16a

3-(4-氯-2-吗啉-4-基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-

吡唑并[1,5-*a*]嘧啶，盐酸盐

在 50℃下，将 3-(4-氯-2-吗啉-4-基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(1.40 g, 3.33 mmol)溶解于丙酮(10 mL)中并冷却至室温。加入氯化氢(2M 乙醚溶液, 2.0 mL, 4.0 mmol)并在超声波仪中充分搅拌。将溶液浓缩少量，加入最低限度的乙醚以使 HCl 盐结晶。将混合物在冷藏器中冷却过夜。加入另外的氯化氢(2M 乙醚溶液, 2.0 mL, 4.0 mmol)，在冷藏器中冷却。将结晶性物质滤出，干燥，得到标题化合物(1.15 g, 75%)。ES/MS m/z (^{35}Cl) 420 $(M+1)^+$; ^{1}H NMR (CDCl3): 9.18(br, 1H), 6.86(s, 1H), 3.72(m, 4H), 3.49(m, 1H), 3.39(m, 4H), 2.48(s, 3H), 2.38(s, 3H), 1.79(m, 4H), 0.79(m, 6H)。

实施例 17

3-(4-溴-2-丁基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶

在-78℃下，在氮气气氛下，将正丁基锂(2.5M 己烷溶液, 0.2 mL, 0.5 mmol)加入到 3-(2,4-二溴-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(230 mg, 0.5 mmol)在 THF(3 mL)中的溶液中。在 30 分钟后，加入 1-碘丁烷(138 mg, 0.75 mmol)并继续搅拌 1 小时。温热至室温并搅拌 1 小时。通过加入饱和氯化铵溶液来将反应淬灭并用乙酸乙酯萃取。将有机部分用硫酸钠干燥，过滤，浓缩，获得残余物。用快速色谱对该粗品物质进行纯化，用己烷/乙酸乙酯(10/1.5)进行洗脱，得到橙色泡沫形式的标题化合物(78 mg)。ES/MS m/z (^{81}Br) 437.4 $(M+1)^+$。

基本如实施例 17 所述的那样制备下面的实施例。

实施例号	化学名	物理数据
18	3-(4-溴-2-甲氧基甲基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶	MS (APCI) m/z (^{81}Br) 424.6 $(M+1)^+$

实施例 19

7-(1-乙基-丙基)-3-(2-甲氧基甲基-噻唑-5-基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶

在-78℃下，在氮气气氛下，将正丁基锂(2.5M 己烷溶液，0.4 mL，1.0 mmol)加入到 7-(1-乙基-丙基)-2,5-二甲基-3-噻唑-5-基-吡唑并[1,5-a]嘧啶(300 mg, 1.0 mmol)在 THF(3 mL)中的溶液中。搅拌 30 分钟，加入 1-碘甲基甲基醚(205 mg, 1.2 mmol)。继续搅拌 1 小时，然后缓慢温热至室温并搅拌过夜。通过加入饱和氯化铵溶液来将反应淬灭，用乙酸乙酯萃取。将有机层用盐水洗涤，用硫酸钠干燥，过滤，真空浓缩，获得残余物。用快速色谱对该粗品物质进行纯化，用己烷/乙酸乙酯(10/2)进行洗脱，得到黄色泡沫形式的标题化合物(184 mg)。MS (APCI) m/z 345.3 $(M+1)^+$。

实施例 20

3-(4-氯-2-甲氧基甲基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶

在-78 °C 下，将正丁基锂(2.5 M 己烷溶液, 174 mL, 0.43 mmol)加入到进行着搅拌的 7-(1-乙基-丙基)-3-(2-甲氧基甲基-噻唑-5-基)-2,5-二甲基-吡唑并[1,5-a]嘧啶(150 mg, 0.43 mmol)在 THF(3 mL)中的溶液中。搅拌 30 分钟并加入 N-氯琥珀酰亚胺(87 mg, 0.653 mmol)。搅拌 30 分钟，然后将反应缓慢温热至室温，使反应继续进行过夜。通过加入饱和氯化铵溶液来将反应淬灭，用乙酸乙酯萃取，用硫酸钠干燥，过滤，浓缩，获得残余物。用快速色谱进行纯化，用己烷/乙酸乙酯(10/2)进行洗脱，得到标题化合物(7 mg)。MS (APCI) m/z (^{35}Cl) 379.3 $(M+1)^+$。

实施例 21

7-(1-乙基-丙基)-2,5-二甲基-3-[2-(2-甲基-2H-[1,2,4]三唑-3-基)-噻唑-5-基)-吡唑并[1,5-*a*]嘧啶

将 3-(4-溴-2-(2-甲基-2H-[1,2,4]三唑-3-基)-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(175 mg, 0.38 mmol)和氯化亚铜(I)(132

mg, 1.33 mmol)在 DMF(5 mL)中进行混合并加热至 120℃达 24 小时。冷却至室温，用乙酸乙酯稀释并用盐水洗涤。将有机层用硫酸钠干燥，过滤，真空浓缩，得到残余物。用快速色谱进行纯化，用己烷、然后用己烷/EtOAc (10/1.8)进行洗脱，得到黄色-橙色固体(45 mg)。ES/MS m/z 382.0$(M+1)^+$。

另一种制备方法：

在-78℃下，在氮气气氛下，将正丁基锂(2.5 M 己烷溶液, 57.6 mL, 144 mmol)加入到 *N*-甲基三唑(11.95 g, 144 mmol)在 THF(600 mL)中的溶液中，在加入期间保持温度低于-74℃。然后一次性加入氯化锌干粉(26 g, 192 mmol)并将混合物在 1 小时内温热至 22℃。一次性加入 7-(1-乙基-丙基)-3-(2-碘-噻唑-5-基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(12.5 g, 29 mmol)和四(三苯基)膦钯催化剂(1.15 g, 0.01 mol)，将混合物在氮气下加热至回流达 8 小时。将混合物冷却至 22℃并加入水(300 mL)。分离有机层并用甲基-叔丁基醚萃取水层(2 × 200 mL)。将有机部分合并，用硫酸钠干燥，过滤，蒸发掉溶剂。通过硅胶垫来进行纯化，用己烷/乙酸乙酯(4/1)进行洗脱，得到标题化合物(8 g, 72%)。ES/MS m/z 382 $(M+1)^+$。

实施例 22

3-(4-氯-2-(2-甲基-2H-[1,2,4]三唑-3-基)-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶

将 7-(1-乙基-丙基)-2,5-二甲基-3-[2-(2-甲基-2H-[1,2,4]三唑-3-基)-噻唑-5-基)-吡唑并[1,5-*a*]嘧啶(20 mg, 0.052 mmol)和 N-氯琥珀酰亚胺(7.6 mg, 0.0569 mmol)在二氯甲烷(0.5 mL)和乙腈(0.5 mL)中的混合物在室温下在一个小瓶中搅拌过夜。浓缩，获得残余物。用快速色谱进行纯化，用己烷、然后用己烷/乙酸乙酯(10/1.5)洗脱，得到标题化合物(16 mg)。ES/MS m/z (^{35}Cl) 416.0 $(M+1)^+$。

实施例 23

7-(1-乙基-丙基)-3-(4-甲氧基-2-吗啉-4-基-噻唑-5-基)-2,5-二甲基-

吡唑并[1,5-*a*]嘧啶

将 3-(4-溴-2-吗啉-4-基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(162 mg, 0.35 mmol)、甲醇钠(57 mg, 1.05 mmol)和碘化亚铜(I)(67 mg, 0.35 mmol)在甲醇(3 mL)中的混合物在一个密封的 4-mL 小瓶中在 120℃下搅拌 15 小时。冷却至室温，通过过滤除去固体，将滤液真空浓缩。用快速色谱对残余物进行纯化，用己烷/THF(10/2)进行洗脱。用甲醇将该物质重结晶，得到标题化合物(20 mg)。ES/MS m/z 416.0 $(M+1)^+$。

制备例 20

4-溴-5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-噻唑-2-甲醛

在-78℃下，在氮气气氛下，将正丁基锂(1.6 M 己烷溶液, 0.312 mL, 0.50 mmol)加入到 3-(2,4-二溴-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(230 mg, 0.50 mmol)的 THF 溶液(2.5 mL)中并搅拌 30 分钟。加入 N-甲酰基吗啉(58 mg, 0.50 mmol)的 THF(0.5 mL)溶液。搅拌 1 小时，然后将反应在-20℃下储存过夜。将反应温热至室温，用醚稀释，通过加入 4 N HCl (4 mL)将其淬灭。将有机相分离出来并用 4 N HCl (2 × 4 mL)萃取。将含水部分合并，用碳酸氢钠固体处理至 pH = 8 至 9，然后用乙醚萃取。将所有的有机层合并，用盐水洗涤，用硫酸钠干燥，过滤，浓缩，获得残余物。用快速色谱对该粗品物质进行纯化，用己烷/二氯甲烷/乙酸乙酯(5/5/1)洗脱，得到标题化合物(154 mg)。MS (APCI) m/z (^{81}Br) 409.0 $(M+1)^+$。

实施例 24

3-(4-溴-2-吗啉-4-基-甲基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶

将 4-溴-5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-噻唑-2-甲醛(150 mg, 0.368 mmol)、吗啉(35 mg, 0.405 mmol)和三乙酰氧基硼氢化钠(97 mg, 0.46 mmol)合并到二氯甲烷(3 mL)和甲醇(0.5 mL)中。搅拌过夜，再加入一些吗啉(35 mg, 0.405 mmol)和三乙酰氧基硼氢化钠(97 mg,

0.46 mmol)，再搅拌 4 小时。真空除去溶剂，用二氯甲烷稀释，用盐水洗涤。将有机相用硫酸钠干燥，过滤并真空浓缩。将所得的物质用快速色谱进行纯化，用二氯甲烷:2 M 氨的甲醇溶液(10:1)洗脱，得到一种混合物。用反相柱对混合物进行纯化，用水/乙腈(80/20)至水/乙腈(10/90)洗脱，得到标题化合物(20 mg)。ES/MS m/z (^{81}Br) 480.0 $(M+1)^+$。

实施例 25

3-(4-溴-2-吡啶-4-基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-a]嘧啶

在-78℃下，在氮气气氛下，将正丁基锂(1.6 M 己烷溶液, 0.312 mL, 0.5 mmol)加入到 3-(2,4-二溴-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(229 mg, 0.5 mmol)在 THF(4 mL)中的溶液中。搅拌 30 分钟后，加入无水氯化锌(264 mg, 1.5 mmol)，继续搅拌 30 分钟。将反应温热至室温并搅拌 1 小时。加入 4-碘吡啶(103 mg, 0.5 mmol)，然后加入 1,1'-双(二苯基膦基)二茂铁氯化钯(II)(二氯甲烷加合物)(0.40.8 mg, 0.05 mmol)。将反应加热至回流过夜。冷却至室温，用乙酸乙酯稀释，用水和盐水洗涤。将有机层用硫酸钠干燥，过滤，浓缩，获得残余物。用快速色谱对该粗品物质进行纯化，用二氯甲烷:2 N 氨的甲醇溶液(10:0.75)洗脱，得到一种混合物。用反相柱对混合物进行纯化，用水:乙腈= 80:20 至水:乙腈= 10:90 进行洗脱，得到标题化合物(19 mg)。ES/MS m/z (^{79}Br) 456.0 $(M+1)^+$。

制备例 21

4-三氟甲基-噻唑-2-基胺

将硫脲(4.0 g, 52.3 mmol)和 3-溴-1,1,1-三氟丙-2-酮(5.5 mL, 10 g, 52.3 mmol)加入到乙醇(100 mL)中并在 50℃下加热 2 小时。冷却至室温，浓缩至干。将残余物溶解于水中并用 2M NaOH 将 pH 调至>12。用乙醚萃取(4×)。将合并的有机萃取物用硫酸钠干燥，过滤并真空浓缩。用硅胶色谱对所得材料进行纯化(CH_2Cl_2)，得到标题化合物(6.9 g, 79%)。ES/MS m/z

169 $(M+1)^+$。

制备例 22

5-溴-4-三氟甲基-噻唑-2-基胺，氢溴酸盐

将溴(2.0 mL, 6.28 g, 39.3 mmol)滴加到冰浴冷却的 4-三氟甲基-噻唑-2-基胺(6.0 g, 35.7 mmol)在乙醚(60 mL)中的溶液中。在完全加入后搅拌 1 小时，然后温热至室温。通过过滤收集固体并用乙醚洗涤，得到标题化合物(10.5 g, 90%)。ES/MS m/z ($^{79}Br/^{81}Br$) 247/249 $(M+1)^+$。

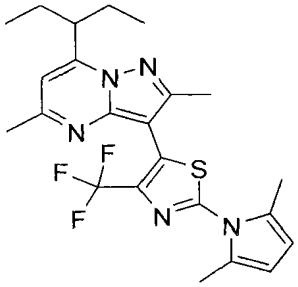
制备例 23

5-溴-2-(2,5-二甲基-吡咯-1-基)-4-三氟甲基-噻唑

将己烷-2,5-二酮(3.5 mL, 3.4 g, 30.2 mmol)加入到 5-溴-4-三氟甲基-噻唑-2-基胺氢溴酸盐(9.0 g, 27.4 mmol)在甲醇(60 mL)中的溶液中。在室温下搅拌过夜。加入磷酸盐缓冲液(50 mL, pH = 7)。通过过滤收集沉淀，用水洗涤。将滤饼溶解于 CH_2Cl_2 中，用硫酸钠干燥。过滤并真空浓缩，得到标题化合物(8.2 g, 92%)。^1H NMR (400 MHz, $CDCl_3$) δ 5.91(s, 2H), 2.27(s, 6H)。

实施例 26

3-[2-(2,5-二甲基-吡咯-1-基)-4-三氟甲基-噻唑-5-基]-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶



将 5-溴-2-(2,5-二甲基-吡咯-1-基)-4-三氟甲基-噻唑(2.2 g, 6.6 mmol)在 THF(25 mL)中的溶液在干冰浴中进行冷却。滴加叔丁基锂(1.7 M 的戊烷溶

液, 8.5 mL, 14.5 mmol)。搅拌 45 分钟，然后滴加氯化锌(0.5 M 的 THF 溶液, 14.6 mL, 7.3 mmol)。搅拌 5 分钟并除去冷却浴。搅拌 30 分钟，然后加入 7-(1-乙基-丙基)-3-碘-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(1.5 g, 4.4 mmol)和双(三-叔丁基膦)钯(0)(450 mg, 0.9 mmol)。回流 24 小时。将反应冷却，将混合物倾倒到乙醚中，用水(2×)洗涤。将合并的水层用乙醚洗涤。将合并的有机部分用硫酸钠干燥，过滤，真空浓缩至干。用硅胶色谱对所得的残余物进行纯化(75-100% CH_2Cl_2 的己烷溶液)，得到标题化合物(1.47 g, 72%)。HR-ToF-MS m/z $C_{23}H_{26}F_3N_5S+H^+$的计算值：462.1939，实测值：462.1915。

实施例 27

5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-4-三氟甲基-噻唑-2-基胺

将羟胺(2 mL, 50%的水溶液)加入到 3-[2-(2,5-二甲基-吡咯-1-基)-4-三氟甲基-噻唑-5-基]-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(1.1 g, 2.3 mmol)在乙酸(10 mL)中的溶液中。将反应加热至 80℃达 6 小时。冷却至室温。倾倒到乙醚中，用 2 M NaOH 洗涤 2 次，然后用水洗涤一次。将有机部分用硫酸钠干燥，过滤，浓缩，真空浓缩至干。用硅胶色谱对所得的残余物进行纯化(40%乙酸乙酯的己烷溶液)，得到标题化合物(0.76 g, 87%)。ES/MS m/z 384 $(M+1)^+$。

制备例 24

3-(2-溴-4-三氟甲基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶

将溴化铜(II)(540 mg, 2.4 mmol)和亚硝酸叔丁酯(0.36 mL, 310 mg, 3.0 mmol)在乙腈(20 mL)中的混合物加热至 60℃。加入固体形式的 5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-a]嘧啶-3-基]-4-三氟甲基-噻唑-2-基胺(755 mg, 2.0 mmol)。将反应加热至 80℃达 2 小时。将反应冷却，倾倒到乙醚中，

用水萃取(3×)。将有机层用硫酸钠干燥，过滤，浓缩，真空浓缩至干。用硅胶色谱对所得的残余物进行纯化(CH_2Cl_2)，得到标题化合物(0.77 g, 87%)。ES/MS m/z ($^{79}Br/^{81}Br$) 447, 449 $(M+1)^+$。

实施例 28

{5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-4-三氟甲基-噻唑-2-基}-二甲基-胺

将一个包含位于甲醇(4 mL)中的 3-(2-溴-4-三氟甲基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(313 mg, 0.7 mmol)和二甲胺(2 M 的 THF 溶液, 4 mL, 8 mmol)的密封管加热至 80℃达 2 小时。将反应冷却并真空浓缩。用硅胶色谱对所得的残余物进行纯化，用 0-30%乙酸乙酯的 CH_2Cl_2 溶液洗涤，得到标题化合物(0.28 g, 97%)。HR-ToF-MS m/z $C_{19}H_{24}F_3N_5S+H^+$的计算值: 412.1770, 实测值: 412.1783。

基本如实施例 28 中所述的那样制备下面的实施例，不同的是将反应回流 8 小时。

实施例号	化学名	物理数据
29	7-(1-乙基-丙基)-2,5-二甲基-3-(2-吗啉-4-基-4-三氟甲基-噻唑-5-基)-吡唑并[1,5-*a*]嘧啶	HR-ToF-MS m/z $C_{21}H_{26}F_3N_5OS+H^+$ 的计算值: 454.1873, 实测值: 454.1888

实施例 30

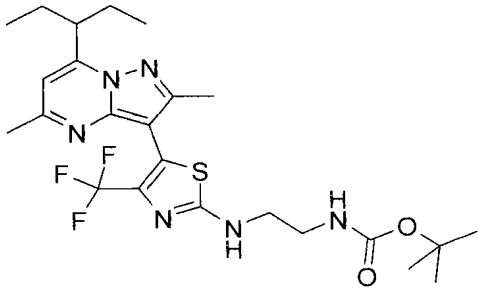
N-{5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-4-三氟甲基-噻唑-2-基}-乙酰胺

将羟胺(50%的水溶液, 5 mL)加入到 3-[2-(2,5-二甲基-吡咯-1-基)-4-三氟甲基-噻唑-5-基]-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(2.4 g, 5.2 mmol)在乙酸(25 mL)中的溶液中。将反应加热至 80℃达 72 小时。将反应冷却至室温，倾倒到乙醚中，用 2 M NaOH(2×)洗涤，然后用水洗涤一次。

将有机部分用硫酸钠干燥，过滤并浓缩至干。用柱色谱对所得残余物进行纯化，用 40%乙酸乙酯的己烷溶液洗脱，得到标题化合物(0.28 g, 13%)。HR-ToF-MS m/z $C_{19}H_{22}F_3N_5OS+H^+$ 的计算值：426.1575，实测值：426.1565。

实施例 31

(2-{5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-4-三氟甲基-噻唑-2-基氨基}-乙基)-氨基甲酸叔丁酯



将(2-氨基-乙基)-氨基甲酸叔丁酯(0.5 mL, 506 mg, 3.2 mmol)加入到3-(2-溴-4-三氟甲基-噻唑-5-基)-7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶(100 mg, 0.22 mmol)和三乙胺(0.3 mL, 222 mg, 2.2 mmol)在甲醇(1 mL)中的溶液中。蒸发掉甲醇并加热至 80℃过夜。将反应冷却至室温并真空浓缩。用柱色谱对所得残余物进行纯化，用 10-50%乙酸乙酯的 CH_2Cl_2 溶液洗脱，得到标题化合物(0.11 g, 97%)。ES/MS m/z 527.2 $(M+1)^+$。

用适宜的胺基本如实施例 31 中所述的那样制备下面的化合物。

制备例或实施例号	化学名	物理数据
制备例 25*	[2-({5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-4-三氟甲基-噻唑-2-基}-丙基-氨基)-乙基]-氨基甲酸叔丁酯	ES/MS m/z 569.3$(M+1)^+$
制备例 26**	(S)-(1-{5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-4-三氟甲基-噻唑-2-基}-吡咯烷-3-基)-氨基甲酸叔丁酯	ES/MS m/z 553.3$(M+1)^+$

实施例 32***	*N*-{5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-4-三氟甲基-噻唑-2-基}-*N*,*N*'-二丙基-乙烷-1,2-二胺，盐酸盐	ES/MS m/z 511.2(M+1)$^+$

* 在 EtOH 中在回流下加热过夜。蒸发掉 EtOH，在 110℃下加热 24 小时。

** 在 EtOH 中在 80℃下加热过夜。

*** 制备该 HCl 盐，用 EtOAc/己烷重结晶。

实施例 33

N^1-{5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-4-三氟甲基-噻唑-2-基}-乙烷-1,2-二胺，盐酸盐

将(2-{5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-4-三氟甲基-噻唑-2-基氨基}-乙基)-氨基甲酸叔丁酯(101 mg,0.192 mmol)加入到 1 M HCl 的甲醇溶液(1 mL)中。将反应在 70℃下加热过夜。将反应冷却并由甲醇/乙酸乙酯真空浓缩。用乙酸乙酯对所得的残余物进行研磨，得到标题化合物(64 mg, 78%)。ES/MS m/z 427.0 (M+1)$^+$。

基本如实施例 33 中所述的那样制备下面的实施例。

实施例号	化学名	物理数据
34	N^1-{5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-*a*]嘧啶-3-基]-4-三氟甲基-噻唑-2-基}-N^1-丙基-乙烷-1,2-二胺，盐酸盐	ES/MS m/z 469.2(M+1)$^+$
35	(*S*)-1-{5-[7-(1-乙基-丙基)-2,5-二甲基-吡唑并[1,5-a]嘧啶-3-基]-4-三氟甲基-噻唑-2-基}-吡咯烷-3-基胺，盐酸盐	ES/MS m/z 453.0(M+1)$^+$

实施例 A

用离体结合进行的体内效力评估

为了评估体内效力，用离体结合对本发明的化合物进行评价。使用 D.

R. Gehlert 等人, *EJP* 509: 145-153(2005)中所提供的操作，通过口服途径将化合物施用于大鼠。然后如 Gehlert 等人所述的那样对 ^{125}I-蛙皮降压肽与小脑的离体结合进行评估。例如，实施例 15 在 10 mg/kg 下提供 65%的抑制。

实施例 B

CRF1 滤膜结合测定法

在产生具有足够受体密度以开展结合测定法的重组细胞系方面，通过使用由 Stanford 许可的 Phoenix 逆转录病毒表达系统克服了以质粒为基础的人 CRF1 表达的限制。用稳定的 HEK-hCRF1 细胞系制备膜，如下建立结合反应(200 μL): 50 μL ^{125}I-蛙皮降压肽(终浓度为 0.2 nM)、50 μL 化合物和 100 μL CRF1 膜(25 μg/反应)。将反应在室温下孵育 2 小时，然后通过用预处理的 FB 微孔玻璃纤维滤板(96 孔)过滤来终止反应。将板用冰冷的测定缓冲液(50 mM tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2)洗涤两次，风干过夜，用 100 μL Microscint 40 在 MicroBeta 计数器中进行计数。在存在 0.5 μM 未标记的蛙皮降压肽的情况下测定非特异性结合(NSB)。通常一式三份地进行测定，用 Graph Pad Prism 对中值数据点作图。

用这种测定法，本发明具体给出的化合物以低于 1 μM 的 Ki(抑制常数)抑制滚动(roller)/粘附细胞中 ^{125}I-蛙皮降压肽(4 nM)的结合。例如，实施例 15 表现出 6.2 nM 的 Ki。

实施例 C

CRF2 滤膜结合测定法

在产生具有足够受体密度以开展结合测定法的重组细胞系方面，通过使用由 Stanford 许可的 Phoenix 逆转录病毒表达系统克服了以质粒为基础的人 CRF2 表达的限制。用稳定的 HEK-hCRF2 细胞系制备膜，如下建立结合反应(200 μL): 50 μL ^{125}I-蛙皮降压肽(终浓度为 0.2 nM)、50 μL 化合物和 100 μL CRF2 膜(25 μg/反应)。将反应在室温下孵育 2 小时，然后通过用预处理的 FB 微孔玻璃纤维滤板(96 孔)过滤来终止反应。将板用冰冷的

测定缓冲液(50 mM tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2)洗涤两次，风干过夜，用 100 μL Microscint 40 在 MicroBeta 计数器中进行计数。在存在 0.5 μM 未标记的蛙皮降压肽的情况下测定非特异性结合(NSB)。或者，用闪烁亲近测定法来对化合物进行评价。如下建立该测定法：50 μL ^{125}I-蛙皮降压肽(终浓度为 0.2 nM)、50 μL 化合物或未标记的蛙皮降压肽(NSB)和 100 μL 含 250 μg 麦胚凝集素(WGA)的 SPA 小珠和 CRF2 膜(1.5 μg/反应)。将板在室温下孵育 4-5 小时，然后在 200 X g 下离心 10 分钟。用 Wallac Trilux 闪烁计数器来对结合的放射性进行评估。通常使用一式三份的测定来对结合进行评估，用 Graph Pad Prism 对中值数据点作图。首先在固定浓度下对化合物进行筛选，如果注意到足够的活性，则随后产生浓度-响应曲线。

在所述 CRF2 结合测定法中对本发明的具体给出的化合物进行了试验，它们对 CRF2 受体表现出弱亲合性。例如，实施例 15 在 50 μM 的浓度下表现出 11%的抑制。这一结果表明本发明的化合物对 CRF1 受体具有选择性(相对于 CRF2 而言)。

实施例 D

生物利用度和药动学性质

分布容积(Vdist)是指药物在机体中的量与药物在血液或血浆中的浓度之比。分布容积指的是在与血液或血浆中的浓度相同的浓度下，包含机体中的全部药物量所需的体液体积：Vdist = 机体中的药物量/血液或血浆中的药物浓度(Goodman and Gillman's)。对于 10 mg 的剂量和 10 mg/L 的血浆浓度而言，分布容积将为 1 升。分布容积反映了药物在血管外组织中的存在程度。大的分布容积反映了与血浆蛋白结合相比化合物倾向于与组织组分结合。在临床情况中，可以用 Vdist 来确定获得稳态浓度的负荷剂量。

为了测定分布容积，给雄性 Sprague Dawley 大鼠(N=3)施用 1 mg/kg 的化合物静脉内单剂量。在给药后 0.08 至 24 小时，在一些时间点收集多个血浆样品。用 LC/MS/MS 对血浆样品进行分析以测定血浆浓度。进行血浆药动学计算以确定包括 Vdist 和血浆清除率(Clp)在内的药动学参数。

本发明的化合物优选具有良好的生物利用度。例如，大部分可商购的CNS和心血管药物表现出<10 L/Kg的人Vdist。与CRF拮抗剂CP154526(Schulz等人, *Proc. Natl. Acad. Sci. (USA)*, 93:10477 (1996))和NBI30775(Chen等人, *Drug Development Research*, 65:216 (2005))相比(当单独进行分析时，CP154526和NBI30775分别表现出114 L/Kg和76 L/Kg的大鼠Vdist)，当单独进行分析时，本发明的实施例15在给予1 mg/kg的静脉内单剂量后仅表现出7.2 L/Kg的大鼠Vdist。

此外，血浆清除率(CLp)是药物由机体除去速率的量度。按照静脉内剂量和一级动力学，可以用下列方程确定血浆清除率：CLp = 剂量/AUC，其中AUC是描述血浆药物浓度与从0至无穷大时间的函数关系的曲线下总面积。当单独进行分析时，在单次静脉内剂量后，参比物CRF拮抗剂CP154526和NBI37582分别表现出83和306 mL/min/kg的大鼠清除率(CLp)，而当单独进行分析时，本发明的实施例15仅表现出23.6 mL/min/kg的大鼠CLp。

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 19/043,275

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	350
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	770
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	880
TOTAL CLAIMS (37 CFR 1.16(i))	21 minus 20 =	* 1			OR	x 200 =	200
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x =	0
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2200

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
19/043,275	01/31/2025		2800	50535-710.304	21	1

CONFIRMATION NO. 5486

21971
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650 PAGE MILL ROAD
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FILING RECEIPT

OC000000084761469

Date Mailed: 02/24/2025

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Alexis HOWERTON, San Francisco, CA;
Hal GERBER, San Francisco, CA;

Applicant(s)

Spruce Biosciences, Inc., South San Francisco, CA;

Power of Attorney: None

Domestic Applications for which benefit is claimed

This application is a CON of 18/941,832 11/08/2024
which is a CON of 17/667,285 02/08/2022 ABN
which is a CON of 17/081,694 10/27/2020 PAT 11,304,950
which is a CON of PCT/US2019/029486 04/26/2019
which claims benefit of 62/822,815 03/23/2019
and claims benefit of 62/663,951 04/27/2018

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) **- None.**
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

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Permission to Access Search Results: Yes

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If Required, Foreign Filing License Granted: 02/21/2025

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 19/043,275**

Projected Publication Date: 06/05/2025

Non-Publication Request: No

Early Publication Request: No

Title

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
19/043,275	01/31/2025	Alexis HOWERTON	50535-710.304

CONFIRMATION NO. 5486

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INFORMAL NOTICE

OC00000084761532

Date Mailed: 02/24/2025

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):

  Alexis HOWERTON
  Hal GERBER

  An inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to each inventor must be submitted no later than the date on which the issue fee is paid in response to a notice requiring such fee. See 37 CFR 1.53(f).

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,275	01/31/2025	Alexis HOWERTON	50535-710.304	5486

21971 7590 04/04/2025

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EXAMINER
CENTRAL, DOCKET

ART UNIT	PAPER NUMBER
OPAP	

NOTIFICATION DATE	DELIVERY MODE
04/04/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 19/043,275	**Applicant(s)** HOWERTON et al.	
	Examiner IRVIN DINGLE	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 31 January 2025 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to IRVIN DINGLE at (571)272-3210. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/IRVIN DINGLE/ Lead Paralegal Specialist, OPET	

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,275	01/31/2025	Alexis HOWERTON	50535-710.304	5486

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WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
PIHONAK, SARAH	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
05/30/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Office Action Summary	Application No. 19/043,275	Applicant(s) HOWERTON et al.	
	Examiner SARAH PIHONAK	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 1/31/25.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ 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.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-21 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-21 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, 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.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 1/31/25 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ 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)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

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.

Priority

This application, filed 01/31/2025 is a Continuation of 18941832, filed 11/08/2024

18941832 is a Continuation of 17667285, filed 02/08/2022, now abandoned

17667285 is a Continuation of 17081694, filed 10/27/2020, now U.S. Patent # 11304950.

17081694 is a Continuation of PCT/US2019/029486, filed 04/26/2019.

PCT/US2019/029486 Claims Priority from Provisional Application 62822815, filed 03/23/2019; and Priority from Provisional Application 62663951, filed 04/27/2018.

Status of Claims

1. Claims 1-21 are currently pending. A track one status has been granted.

2. Claims 1-21 were examined and are rejected.

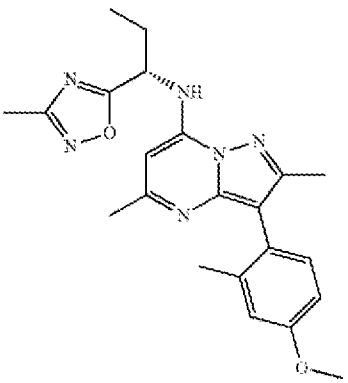
Claim Rejections-35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

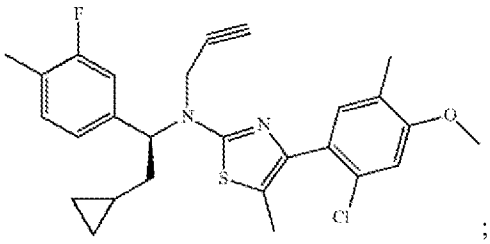
> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

Claim(s) 1, 3, 5-8, 10-12, 15-16, and 20-21 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Grigoridadis, US 20170020877 A1, publ. 1/26/2017 (cited in an IDS), as evidenced by El-Maouche et. al., Lancet, vol. 309, pp. 2194-2210, publ. 2017.

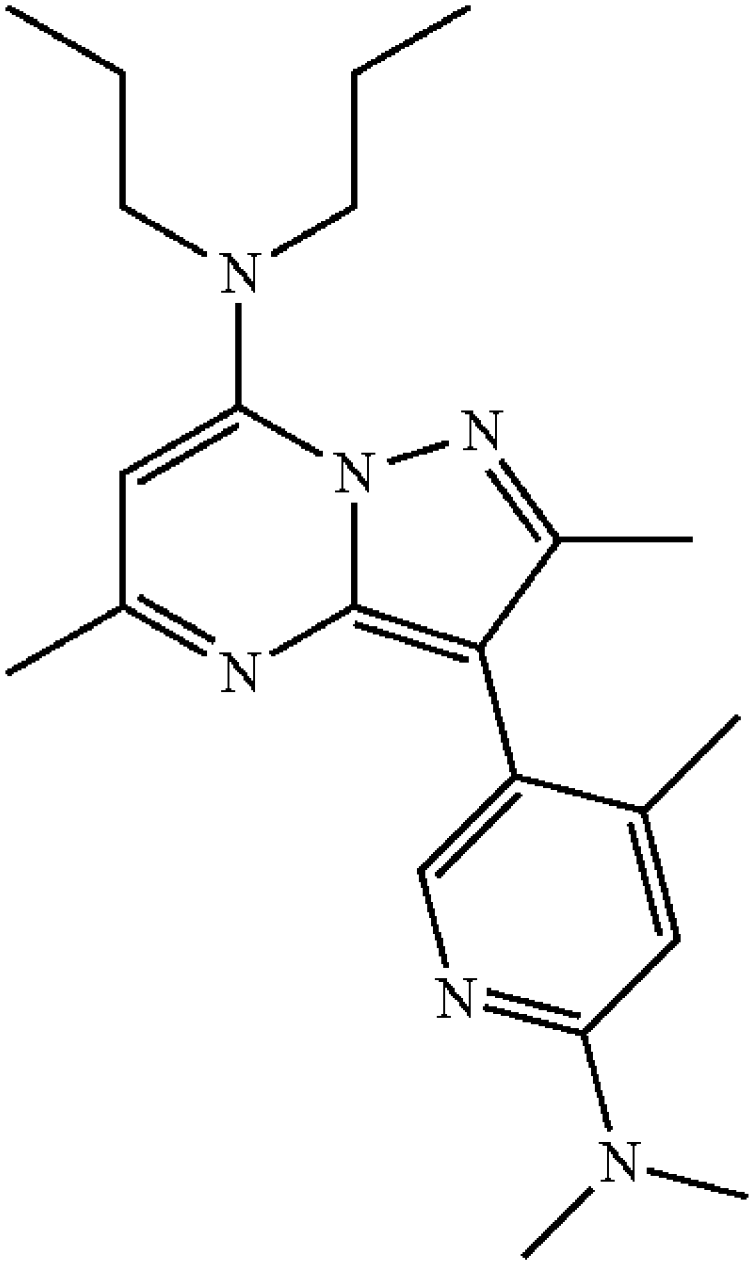
Grigoriadis discloses the treatment of congenital adrenal hyperplasia (CAH) in patients by administering a CRF1 antagonist to normalize androgen production while using lower doses of hydrocortisone, reducing treatment associated side effects (title & abstract; para [0006-0007], [0040]). Coadministration of a CRF1 antagonist with hydrocortisone or another glucocorticoid for the treatment of CAH is disclosed (para [0070]). Grigoriadis discloses treatment of CAH by administering the CRF1 antagonist, NBI-77860 (para [0020], [0051]):



. Grigoriadis discloses CAH as a group of autosomal recessive genetic disorders resulting in little or no cortisol biosynthesis (para [0004]); CAH is an endocrine disorder, as evidenced by El-Maouche et. al. (p. 2194, 4th para of Introduction). Grigoriadis also discloses the following compounds as CRF1 antagonists for treatment of CAH (para [0026]; p. 6, see SSR-125543; p. 7, NBI-30775):



;



; and SSR-126374.

Oral administration is disclosed in the form of tablets or capsules (para [0074]); Grigoriadis further discloses oral administration of a single dose of CRF1 antagonist compound of 50 mg.

and 400 mg. (para [0087-0089]), and treatment of adult females by administration of a single 300 mg. dose (para [0091]). Grigoriadis therefore anticipates the claims.

Claim Rejections-35 USC § 103

4. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date

of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claim(s) 9 and 13-14 is/are rejected under 35 U.S.C. 103 as being unpatentable over Grigoridadis, US 20170020877 A1 as evidenced by El-Maouche et. al., Lancet, vol. 309, pp. 2194-2210, publ. 2017, as applied to claims 1, 3, 5-8, 10-12, 15-16, and 20-21.

The disclosure of Grigoriadis as discussed previously is incorporated herein. Furthermore, Grigoriadis teaches treatment of CAH patients who are fully grown, as well as those who are actively growing (para [0030], [0069-0070]). Thus, it would have been prima facie obvious to have treated the endocrine disorder, CAH, in a subject in need thereof comprising administering a CRF1 antagonist as disclosed previously in a therapeutically effective amount, wherein the subject is an adolescent, and have had a reasonable expectation of success.

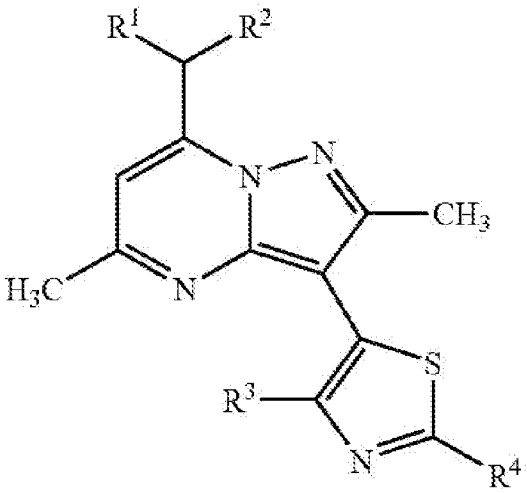
Regarding the dose amounts in claims 13-14, Grigoriadis further teaches a single dose of CRF1 antagonist can range from about 50-1000 mg. (para [0063]). As such, one of ordinary skill in the art would have found it prima facie obvious before the effective filing date of the claims to have administered a CRF1 antagonist to a subject having the endocrine disorder, CAH, at a dose of about 100 mg., or about 200 mg., based on the teachings of Grigoriadis.

5. Claim(s) 1-2, 10-16, and 20 is/are rejected under 35 U.S.C. 103 as being unpatentable over Chen et. al., US 20100222339 A1, publ. 9/2/2010 (cited in an IDS).

Chen teaches compounds having activity as corticotropin releasing factor-1 antagonists, and pharmaceutical compositions comprising these compounds, for the treatment of

psychiatric, neuroendocrine, and neurological diseases, as well as metabolic syndrome (title & abstract; para [0001]). Chen teaches CRF1 antagonists, or a pharmaceutically acceptable salt thereof having the following structural formula (para [0008-0012]):

Formula I

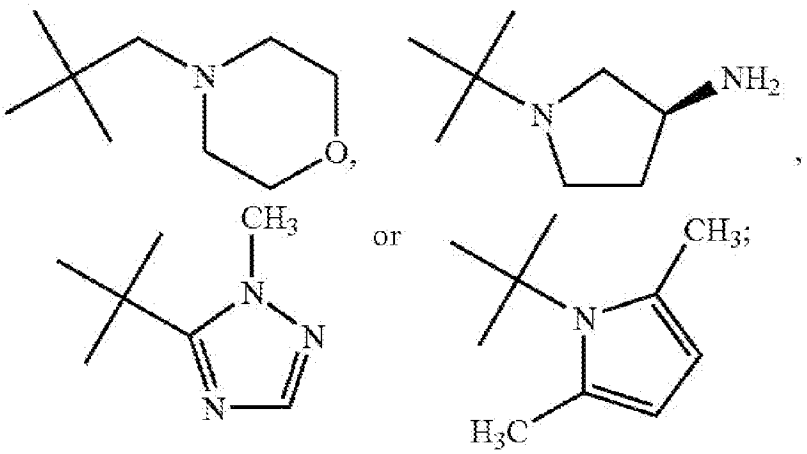


wherein:

[0009] R^1 and R^2 are independently ethyl or n-propyl;

[0010] R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl or methoxy;

[0011] R^4 is hydrogen, Br, R^aR^bN—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



[0012] R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—;

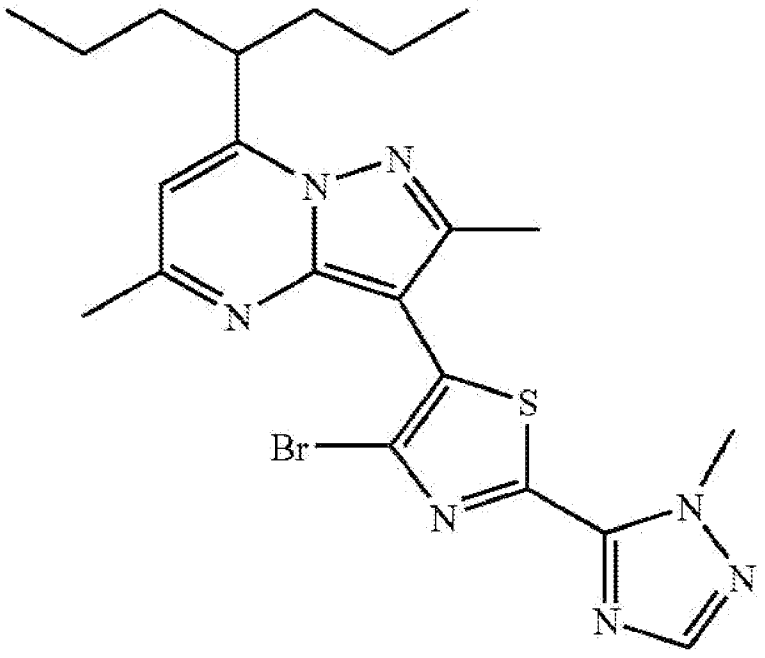
or a pharmaceutically acceptable salt thereof

Additionally, Chen teaches administering a CRF1 antagonist in a therapeutically effective amount to a patient in need thereof, wherein the patient has a condition including congenital adrenal hyperplasia (para [0014], [0016]). Chen exemplifies the following compounds as CRF1 antagonists (para [0129], [0135], [0144]):

Example 10

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

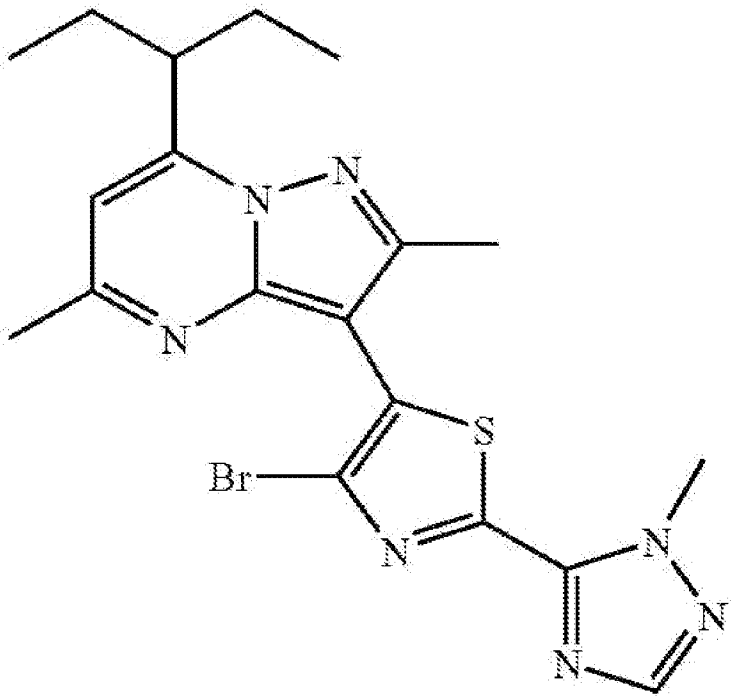
[0129]



Example 12

3-(4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

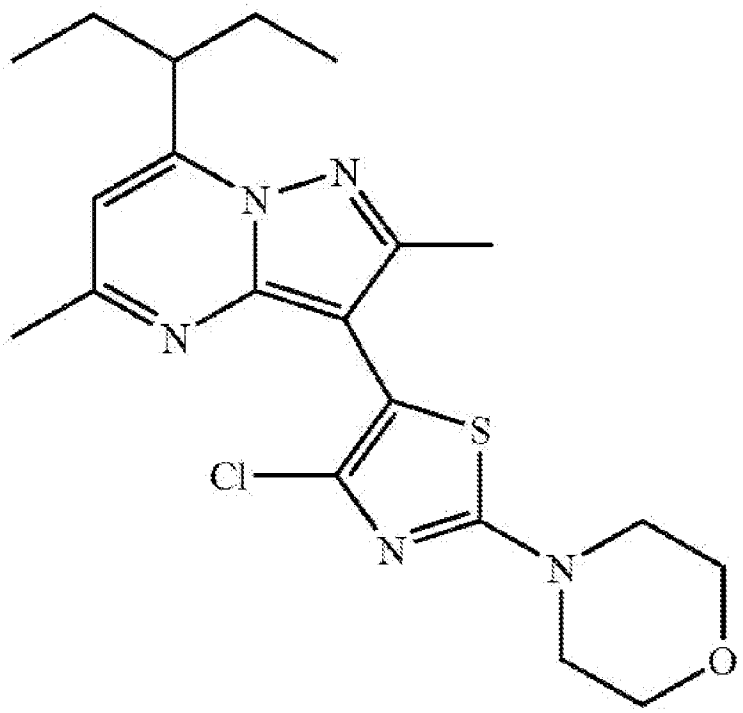
[0135]



Example 16

3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

[0144]



. Chen exemplifies a 10 mg. dose of compound (para [0179]), and further teaches dosages to range from about 0.0001-30 mg/kg body weight, as well as that the amount will be further determined based on route of administration and characteristics of the patient (para [0056]). As such, it would have been prima facie obvious to one of ordinary skill in the art, before the effective filing date of the claims to have treated a neuroendocrine disorder, which falls within the group of endocrine disorders recited by the claims, comprising administering an effective

amount of one of the CRF1 antagonists shown above to a patient in need thereof, including a patient having congenital adrenal hyperplasia, and have had a reasonable expectation of success. Although Chen doesn't explicitly teach the doses recited by claims 12-15, Chen does teach the dose of agent will be determined based on route of administration and characteristics of the patient. As such, it would have been prima facie obvious to one of ordinary skill in the art to have arrived at the doses recited by instant claims 12-15 by routine experimentation, in the absence of evidence indicating the criticality of these dose amounts. See MPEP 2144.05(II)A: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Claim Rejections-Nonstatutory Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*,

11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or

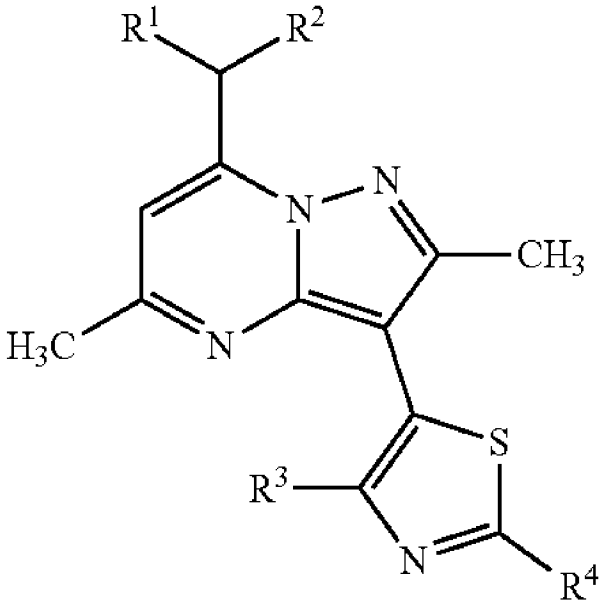
PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about e Terminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

Claims 1-17 and 20-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 11304950 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass treating a subject having testicular adrenal rest tumors or ovarian adrenal rest tumors, particularly in a subject having congenital adrenal hyperplasia (CAH) by administering a CRF1 antagonist; see patented claims 1-2 and instant claims 1, 4, and 5. Additionally, both sets of claims recite overlapping doses of the CRF1 antagonist administered (see 1-400 mg/day of patented claim 13 & instant claim 11); oral administration (see patented claim 14); wherein the CRF1 antagonist is formulated as a capsule or tablet (patented claim 15 & instant claim 21); and wherein the subject is further administered a glucocorticoid selected from beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone (see patented claims 16-18 & instant claims 6-7). As such, the claims are not patentably distinct.

7. Claims 1-3, 6-7, 9-17, and 20-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 and 20-21 of U.S. Patent No. 11858932 B2 in view of Markopoulos et. al., J. Clin. Endocrinol. Metab., vol. 96(3), pp. 623-631, publ. 2011. Although the instant and patented claims are not identical, both sets of claims are drawn to a

method of treatment by administering to a subject a therapeutically effective amount of a CRF1 antagonist. The difference between the claims is that the instant claims are drawn broadly to treating an endocrine disorder, while the patented claims are drawn to treatment of polycystic functional adrenal hyperandrogenism (PCOS-FAH). Markopoulos teaches about 20-60% of PCOS patients have FAH (p. 624, left col., 1st 3 para). As such, PCOS-FAH meets the limitation of an endocrine disorder. Furthermore, both sets of claims recite administering CRF1 antagonists that overlap structurally; the patented claims recite administering a CRF1 antagonist of Formula (I):

Formula (I)



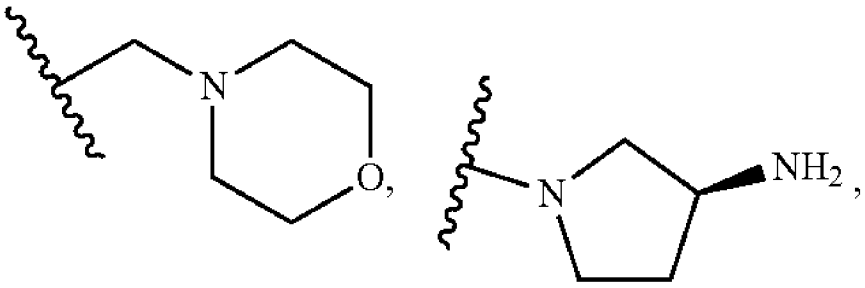
or a pharmaceutically acceptable salt thereof, wherein:

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,



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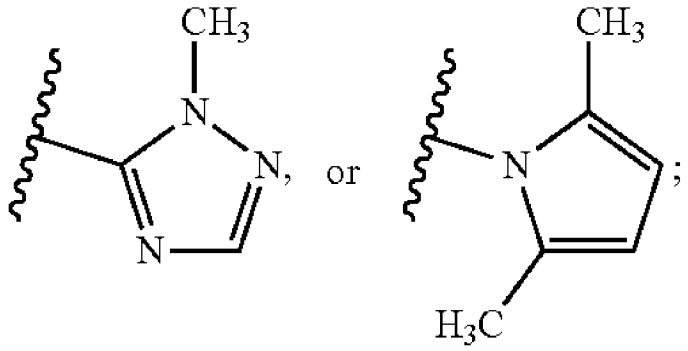


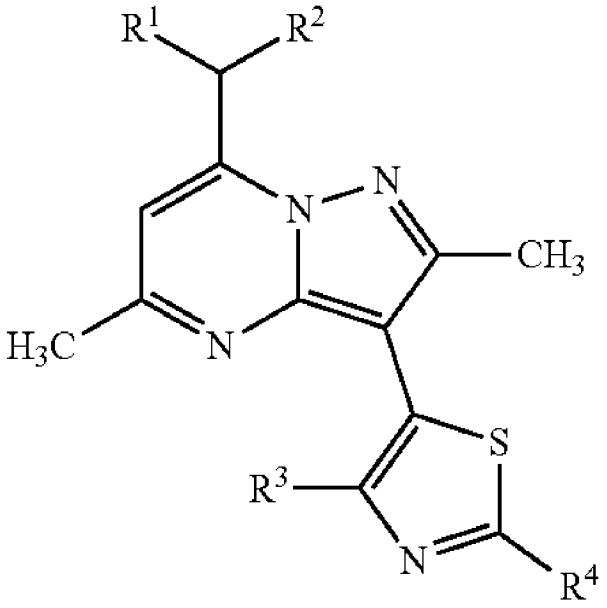
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $—CH_2CH_2NH_2$, $—CH_2CH_2NHC(O)OC(CH_3)_3$, or $—CH_2CH_2NHCH_2CH_2CH_3$.

. Both sets of claims also recite administering the CRF1 antagonist in overlapping doses (see patented claim 3 for about 5-400 mg/day, and instant claim 11, for about 10-400 mg/day); wherein the CRF1 antagonist is administered as a tablet or capsule (see patented claim 20 & instant claim 21); and wherein the subject is an adult or non-adult (see patented claim 21 & instant claims 9-10). For these reasons, the instant and patented claims are obvious variants of each other and are not patentably distinct.

8. Claims 1-3, 6-7, 9-17, and 20-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 and 20-21 of U.S. Patent No. 12098152 B2 in view of Markopoulos et. al., J. Clin. Endocrinol. Metab., vol. 96(3), pp. 623-631, publ. 2011. Although the instant and patented claims are not identical, both sets of claims are drawn to a method of treatment by administering to a subject a therapeutically effective amount of a CRF1 antagonist. The difference between the claims is that the instant claims are drawn broadly to

treating an endocrine disorder, while the patented claims are drawn to treatment of polycystic functional adrenal hyperandrogenism (PCOS-FAH). Markopoulos teaches about 20-60% of PCOS patients have FAH (p. 624, left col., 1st 3 para). As such, PCOS-FAH meets the limitation of an endocrine disorder. Furthermore, both sets of claims recite administering CRF1 antagonists that overlap structurally; the patented claims recite administering a CRF1 antagonist of Formula (I):

Formula (I)

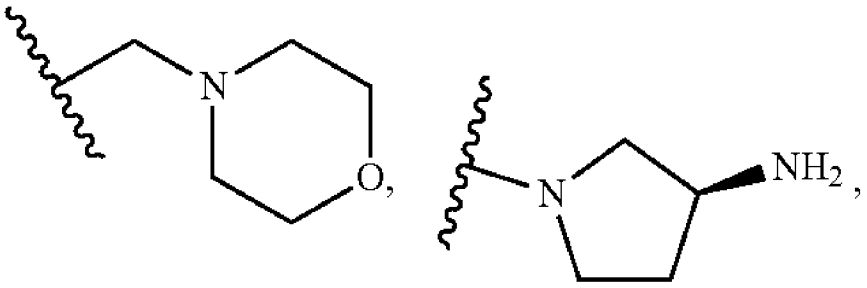


or a pharmaceutically acceptable salt thereof, wherein:

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,



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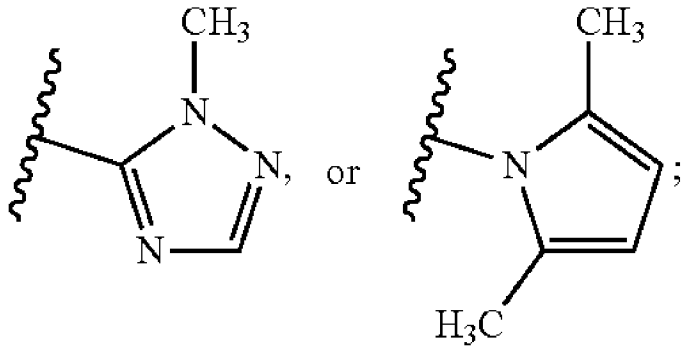
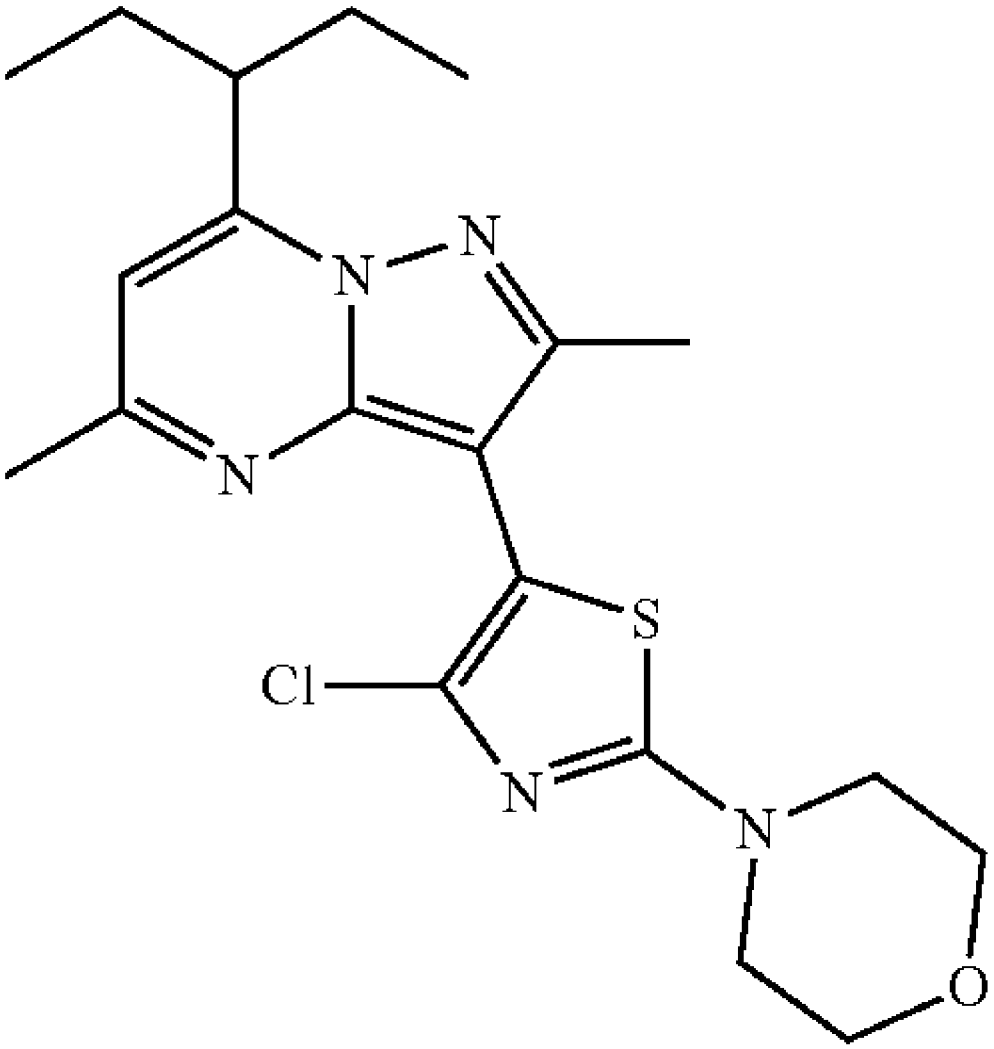


R^a and R^b are independently hydrogen, C_1-C_3alkyl, —$CH_2CH_2NH_2$, —$CH_2CH_2NHC(O)OC(CH_3)_3$, or —$CH_2CH_2NHCH_2CH_2CH_3$.

. Both sets of claims also recite administering the CRF1 antagonist in overlapping doses (see patented claim 3 for about 5-400 mg/day, and instant claim 11, for about 10-400 mg/day); wherein the CRF1 antagonist is administered as a tablet or capsule (see patented claim 20 & instant claim 21); and wherein the subject is an adult or non-adult (see patented claim 21 & instant claims 9-10). For these reasons, the instant and patented claims are obvious variants of each other and are not patentably distinct.

9. Claims 1-2, 5-17, and 20-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4, 7-9, 11-17, and 20-21 of U.S. Patent No. 11311549 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass treating the endocrine disorder, CAH, by administering the CRF1 antagonist shown below:



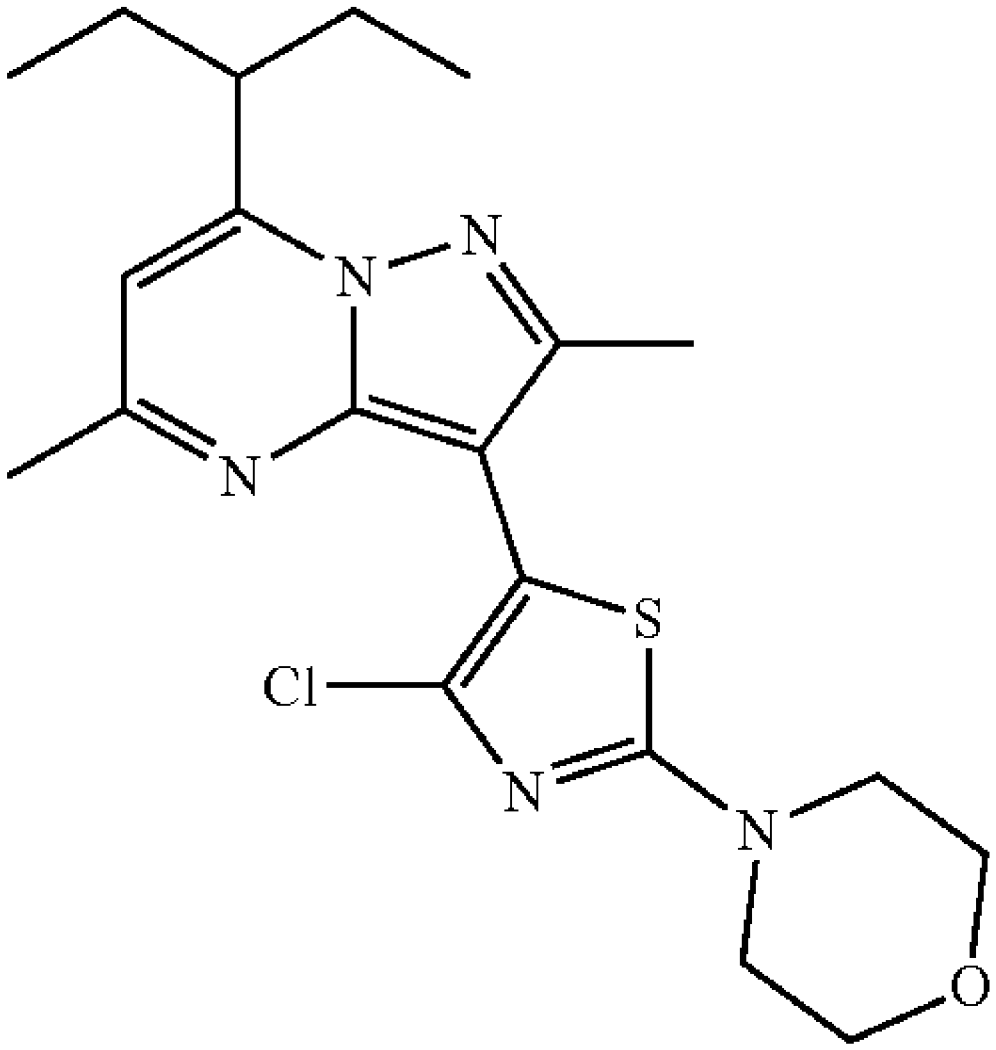
(see instant claims 1 & 5).

Furthermore, both sets of claims recite administering the CRF1 antagonist in overlapping doses (see between about 50-1600 mg/day for patented claim 2 & instant claim 11); wherein the CRF1 antagonist is in the form of a tablet or capsule (see patented claim 8 & instant claim 21); and wherein the subject is further administered a glucocorticoid selected from beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone,

methylprednisolone, prednisolone, prednisone, or triamcinolone (see patented claims 17 & 20, & instant claims 6-7). For these reasons, the claims are not patentably distinct.

10. Claims 1-2, 5-17, and 20-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4, 7-9, 11-17, 19-24, and 26-27 of U.S. Patent No. 11344557 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass treating the endocrine disorder, CAH, by administering a CRF1 antagonist (see instant claims 1 and 5). Furthermore, both sets of claims recite administering the CRF1 antagonist in overlapping doses (see between about 50-1600 mg/day for patented claim 2 & instant claim 11); wherein the CRF1 antagonist is in the form of a tablet or capsule (see patented claim 8 & instant claim 21); and wherein the subject is further administered a glucocorticoid selected from beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone (see patented claims 17 & 26, & instant claims 6-7). For these reasons, the claims are not patentably distinct.

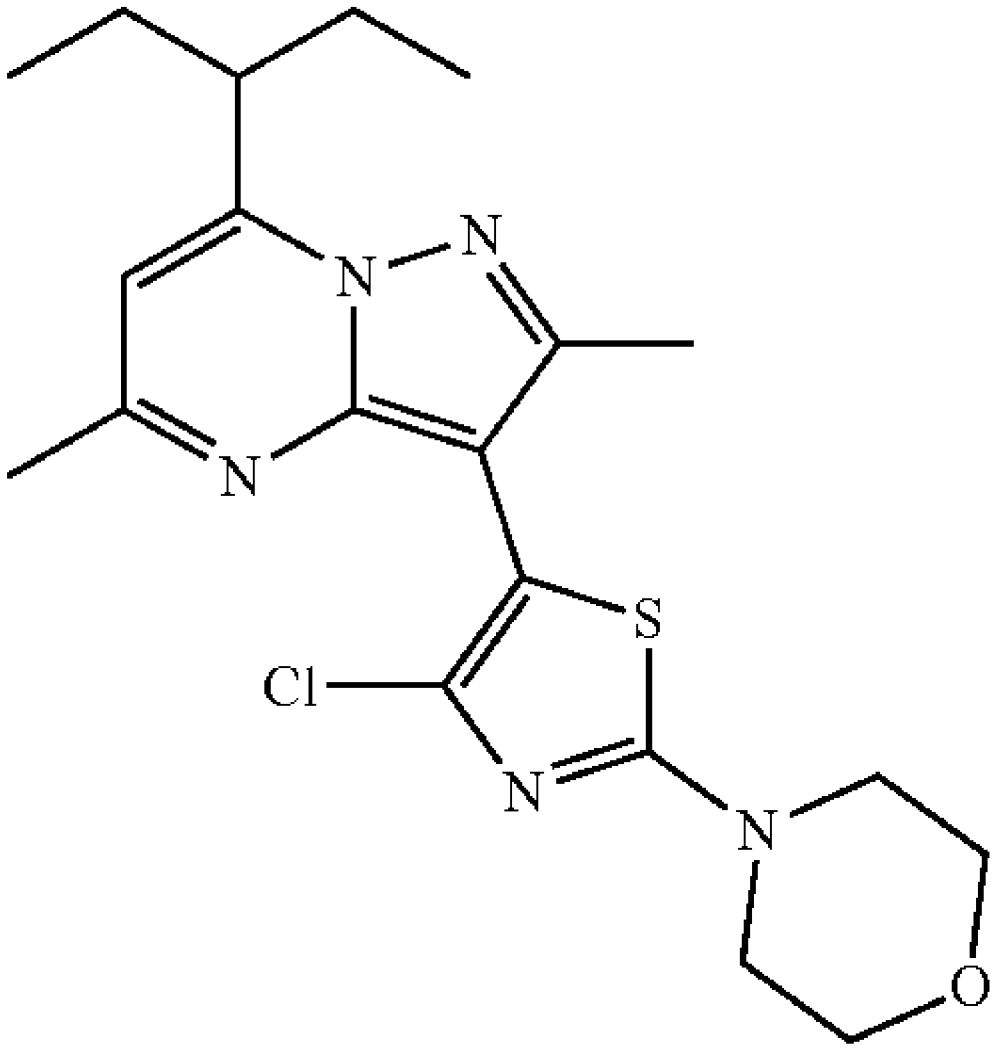
11. Claims 1-2, 5-17, and 20-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4, 7-9, 11, and 14-21 of U.S. Patent No. 11351177 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass treating the endocrine disorder, CAH, by administering the CRF1 antagonist shown below:



(see instant claims 1 and 5). Furthermore, both sets of claims recite administering the CRF1 antagonist in overlapping doses (see between about 50-1600 mg/day for patented claim 2 & instant claim 11); wherein the CRF1 antagonist is in the form of a tablet or capsule (see patented claim 8 & instant claim 21); and wherein the subject is further administered a glucocorticoid selected from beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or

triamcinolone (see patented claims 11 & 20, & instant claims 6-7). For these reasons, the claims are not patentably distinct.

12. Claims 1-2 and 5-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 181-188, 194-195, 198-199, 202, and 204 of copending application 18078649. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass treating the endocrine disorder, CAH, by administering the CRF1 antagonist shown below:



(see instant claims 1 and 5). Furthermore, both sets of claims recite administering the CRF1 antagonist in overlapping doses (see between about 50-800 mg/day for copending claim 181 & instant claim 11); wherein the subject is in a fed state (see copending claim 181 and instant claims 18-19); wherein the CRF1 antagonist is administered once daily (see copending claim 187 & instant claim 16); wherein the CRF1 antagonist is administered twice per day (copending claim 204 and instant claim 17); and wherein the subject is further administered a glucocorticoid selected from beclomethasone, betamethasone, budesonide, cortisone,

dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone (see copending claims 189 and 194, & instant claims 6-7). For these reasons, the claims are not patentably distinct.

13. Claims 1-5, 9-15, and 17-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 72-91 of copending application 18941832. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass administering a CRF1 antagonist small molecule drug, wherein the drugs are identical structurally (see instant claim 1 & copending claim 72). The copending claims recite treating a benign tumor, while the instant claims recite treating an endocrine disorder, however, the copending claims recite the benign tumor to be a testicular adrenal rest tumor or an ovarian adrenal rest tumor (see copending claim 75), which is also a condition recited for treatment by instant claim 4. Both sets of claims further recite treating CAH (see instant claim 5 & copending claim 76); wherein the doses of the CRF1 antagonist are overlapping (from about 5-800 mg as recited by copending claim 78, compared to from about 10-400 mg. for instant claim 11); wherein the subject is in a fed state (copending claim 84 & instant claims 18-19); wherein the CRF1 antagonist is administered twice per day (copending claim 83 & instant claim 17); wherein the CRF1 antagonist is administered orally (instant claim 20 & copending claim 85); and wherein the CRF1 antagonist is administered as a tablet or capsule (copending claim 91 & instant claim 21). The instant and copending claims are therefore not distinct.

14. Claims 1-5, 9-17, and 20-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of copending application 19043303. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass administering a CRF1 antagonist small molecule drug, wherein the drugs are identical structurally (see instant claim 1 & copending claim 1). The copending claims recite changing a metabolic parameter in a subject having an ovarian adrenal rest tumor or a testicular adrenal rest tumor, while the instant claims recite treating an endocrine disorder, however, treatment of OART or TART are also recited for treatment by instant claim 4. Both sets of claims further recite treating CAH (see instant claim 5 & copending claim 5); wherein the doses of the CRF1 antagonist are the same (from about 10-400 mg. for instant claim 11 & copending claim 8); wherein the CRF1 antagonist is administered once per day (instant claim 16 & copending claim 13); twice per day (copending claim 14 & instant claim 17); wherein the CRF1 antagonist is administered orally (instant claim 20 & copending claim 15); and wherein the CRF1 antagonist is administered as a tablet or capsule (copending claim 16 & instant claim 21). The instant and copending claims are therefore not distinct.

15. Claims 1-3, 5, and 9-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-21 of copending application 19043264. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass administering a CRF1 antagonist small molecule drug, wherein the drugs are identical structurally (see instant claim 1 & copending claim 1). The copending

claims recite treating menstrual irregularity, while the instant claims recite treating an endocrine disorder, however, both sets of claims recite treatment of a patient with congenital adrenal hyperplasia (see copending and instant claim 5). Both sets of claims further recite wherein the doses of the CRF1 antagonist are the same (from about 10-400 mg. for instant claim 11 & copending claim 8); wherein the CRF1 antagonist is administered once per day (instant claim 16 & copending claim 13); twice per day (copending claim 14 & instant claim 17); wherein the subject is in a fed state (see copending claims 15-16 & instant claims 18-19); wherein the CRF1 antagonist is administered orally (instant claim 20 & copending claim 17); and wherein the CRF1 antagonist is administered as a tablet or capsule (copending claim 18 & instant claim 21). The instant and copending claims are therefore not distinct.

Information Disclosure Statement

16. The IDS filed on 2/5/25 has been considered.

Conclusion

17. Claims 1-21 are rejected.

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.

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SARAH . PIHONAK
Primary Examiner
Art Unit 1627

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

Notice of References Cited	Application/Control No. 19/043,275	Applicant(s)/Patent Under Reexamination HOWERTON et al.	
	Examiner SARAH PIHONAK	Art Unit 1627	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title, Date, Publisher, Edition or Volume, Pertinent Pages
	U	Markopoulos et. al., J. Clin. Endocrinol. Metab., vol. 96(3), pp. 623-631, publ. 2011 (Year: 2011)
	V	El-Maouche et. al., Lancet, vol. 309, pp. 2194-2210, publ. 2017 (Year: 2017)
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in YYYY-MM-DD format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,275	HOWERTON et al.
	Examiner	Art Unit
	SARAH PIHONAK	1627

CPC - Searched*		
Symbol	Date	Examiner
a61k31/519; a61p5/06,08	05/28/2025	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.

Search Notes		
Search Notes	Date	Examiner
a61k31/519; a61p5/06,08	05/28/2025	s.p.
inventor & applicant search in PE2E, patent data portal	05/28/2025	s.p.
invention & claims search in stn, PE2E	05/28/2025	s.p.

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/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	2025/05/16 04:02 PM
L2	390	(a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND ((administer* OR administration* OR provid* OR deliver* OR treat*) WITH (fed OR fasted OR fasting OR food*))	(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	2025/05/28 08:58 AM
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L4	31	((("Spruce") near3	(US-PGPUB; USPAT)	OR	ON	ON	2025/05/28

		("Biosciences") near3 ("Inc"))).AS,AANM.					09:26 AM
L5	21	((("HOWERTON") near3 ("Alexis"))).INV.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/05/28 09:26 AM
L6	21	((("GERBER") near3 ("Hal"))).INV.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/05/28 09:27 AM
L7	8	(a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND ((endocrine OR hormone OR hormonal) WITH (disease* OR disorder* OR condition* OR syndrome*)) AND (L4 OR L5 OR L6)	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/05/28 09:27 AM
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			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)				

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

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    US 20250064812       A1   Alive           20250306
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS   MARPAT 171:505981; CASFORMULTNS 2019:2064514

LINK INFORMATION
 PUBLICATIONS        APPLICATIONS          REGISTER
 ------------------- --------------------- ----------------------
 AU 2019260793 A1    AU 2019-260793        Register
 AU 2019260793 B2    AU 2019-260793        Register
 AU 2023203095 A1    AU 2023-203095        Register
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 EP 3784233 A1       EP 2019-793181        Register|Federated Reg.
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 JP 2021522340 T     JP 2021-509725        Register|Global Dossier
 JP 7427655 B2       JP 2021-509725        Register|Global Dossier
 MX 2020011344 A     MX 2020-11344         Register
 US 11304950 B2      US 2020-17081694      Register|Global Dossier
 US 20210038604 A1   US 2020-17081694      Register|Global Dossier
 US 20220211711 A1   US 2022-17667285      Register|Global Dossier
 US 20250064812 A1   US 2024-18941832      Register|Global Dossier
 WO 2019210266 A1    WO 2019-US29486       Register|Global Dossier

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L1          2357 S E18-E25
               E "ENDOCRINE DISORDERS"/CT
               E E28+ALL/CT
L2          6374 S E39
L3             4 S L1 AND L2
               E "CONGENITAL ADRENAL HYPERPLASIA"/CT
L4          1475 S E42
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L8             3 S L7 AND (PY<=2018 OR AY<=2018 OR PRY<=2018)

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L18               STRUCTURE UPLOADED
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L20           36 S L18 SSS FULL

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L27      200485 S E54
                E "BIOAVAILABILITY (PHARMACOKINETICS)"/CT
                E E66+ALL/CT
L28       72552 S E77
L29           0 S L26 AND (L27 OR L28)
L30          23 S L1 AND (L27 OR L28)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 9

Complete if Known	
Application Number	19/043,275
Filing Date	01-31-2025
First Named Inventor	HOWERTON; Alexis
Art Unit	
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-710.304

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-4328245	05-04-1982	YU; Cheng-Der et al.	
	002	US-4409239	10-11-1983	YU; Cheng-Der	
	003	US-4410545	10-18-1983	YU; Cheng-Der et al.	
	004	US-4861760	08-29-1989	MAZUEL; Claude et al.	
	005	US-4911920	03-27-1990	JANI; Rajni et al.	
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	007	US-5403841	04-04-1995	LANG; John C. et al.	
	008	US-10849908	12-01-2020	HOWERTON; Alexis et al.	
	009	US-11007201	05-18-2021	HOWERTON; Alexis et al.	
	010	US-11304950	04-19-2022	HOWERTON et al.	
	011	US-11311549	04-26-2022	HOWERTON; Alexis et al.	
	012	US-11344557	05-31-2022	HOWERTON; Alexis et al.	
	013	US-11351177	06-07-2022	HOWERTON; Alexis et al.	
	014	US-12115166	10-15-2024	HOWERTON; Alexis et al.	
	015	US-20100196389	08-05-2010	EVANS-FREKE; Stephen	
	016	US-20100222339	09-02-2010	CHEN; Zhaogen et al.	
	017	US-20170020877	01-26-2017	GRIGORIADIS; Dimitri E.	
	018	US-20220143037	05-12-2022	HOWERTON; Alexis et al.	
	019	US-20220211711	07-07-2022	HOWERTON; Alexis et al.	

Examiner Signature	/SARAH PIHONAK/	Date Considered	05/16/2025

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. Applicant's unique citation designation number (optional). See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. Applicant is to place a check mark here if English language Translation is attached. 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 CFR 1.14. This collection is estimated to take 2 hours 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, 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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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

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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	19/043,275
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	
				Examiner Name	Not Yet Assigned
Sheet	2	of	9	Attorney Docket Number	50535-710.304

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[2]-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-101516887-A	08-26-2009	LILLY CO ELI [US]	Abstract:	☒
	002	CN-106102740-A	11-09-2016	NEUROCRINE BIOSCIENCES INC.	Abstract:	☒
	003	JP-2010504344-A	02-12-2010	ELI LILLY AND CO.	Machine Translation:	☒
	004	JP-2017503030-A	01-26-2017	NEUROCRINE BIOSCIENCES, INC.	Machine Translation:	☒
	005	JP-H0971528-A	03-18-1997	HAYASHIBARA BIOCHEM LAB [JP]	Abstract:	☒
	006	WO-0040529-A1	07-13-2000	ANGIOGENE PHARM LTD [GB], et al.		☐
	007	WO-0041669-A2	07-20-2000	ANGIOGENE PHARM LTD [GB], et al.		☐
	008	WO-0192224-A1	12-06-2001	ASTRAZENECA AB [SE], et al.		☐
	009	WO-0204434-A1	01-17-2002	ANGIOGENE PHARM LTD [GB], et al.		☐
	010	WO-0208213-A1	01-31-2002	ANGIOGENE PHARM LTD [GB], et al.		☐

Examiner Signature	/SARAH PIHONAK/	Date Considered	05/16/2025

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 9

Complete if Known	
Application Number	19/043,275
Filing Date	01-31-2025
First Named Inventor	HOWERTON; Alexis
Art Unit	
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-710.304

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]
	011	WO-2007109853-A1	10-04-2007	VELACOR THERAPEUTICS PTY LTD [AU], et al.		☐
	012	WO-2008036579-A1	03-27-2008	LILLY CO ELI [US], et al.		☐
	013	WO-2015112642-A1	07-30-2015	NEUROCRINE BIOSCIENCES INC [US]		☐
	014	WO-2019036472-A1	02-21-2019	SPRUCE BIOSCIENCES INC [US]		☐
	015	WO-2019036503-A1	02-21-2019	SPRUCE BIOSCIENCES INC [US]		☐
	016	WO-2019210266-A1	10-31-2019	SPRUCE BIOSCIENCES INC [US]		☐
	017	WO-9722596-A1	06-26-1997	ZENECA LTD [GB], et al.		☐
	018	WO-9730035-A1	08-21-1997	ZENECA LTD [GB], et al.		☐
	019	WO-9732856-A1	09-12-1997	ZENECA LTD [GB], et al.		☐
	020	WO-9813354-A1	04-02-1998	ZENECA LTD [GB], et al.		☐
	021	WO-9902166-A1	01-21-1999	ANGIOGENE PHARM LTD [GB], et al.		☐

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				First Named Inventor	HOWERTON; Alexis
				Art Unit	
				Examiner Name	Not Yet Assigned
Sheet	4	of	9	Attorney Docket Number	50535-710.304

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	AL-MUHAMMED, J. et al. In-vivo studies on dexamethasone sodium phosphate liposomes. Journal of microencapsulation 13(3):293-306 (1996).	☐
	002	BERGE, Stephen M. et al. Pharmaceutical Salts. Journal of Pharmaceutical Sciences 66(1):1-19 (1977).	☐
	003	CHEN, Hua-dong. et al. Ovarian adrenal rest tumors undetected by imaging studies and identified at surgery in three females with congenital adrenal hyperplasia unresponsive to increased hormone therapy dosage. Endocrine pathology 28(2):146-151 (2017).	☐
	004	CHONN, Archadio et al. Recent Advances in Liposomal Drug-delivery Systems. Current Opinion in Biotechnology 6(6):698-708 (1995).	☐
	005	Co-pending U.S. Application No. 18/941,832, inventors HOWERTON; Alexis et al., filed on November 08, 2024.	☐
	006	Co-pending U.S. Application No. 19/043,264, inventors HOWERTON; Alexis et al., filed on January 31, 2025.	☐
	007	Co-pending U.S. Application No. 19/043,303, inventors HOWERTON; Alexis et al., filed on January 31, 2025.	☐
	008	EYLES et al. Oral delivery and fate of poly(lactic acid) microsphere-encapsulated interferon in rats. J Pharm Pharmacol. 49(7):669-74 (1997).	☐
	009	GAO, Zhi-Hui. et al. Controlled Release of a Contraceptive Steroid From Biodegradable and Injectable Gel Formulations: in Vitro Evaluation. Pharmaceutical research 12(6):857-863 (1995).	☐
	010	JIN et al. Testicular adrenal rest tumors in a patient with untreated congenital adrenal hyperplasia. Korean J Pediatr 2011;54(3):137-140.	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 5 of 9

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First Named Inventor	HOWERTON; Alexis
Art Unit	
Examiner Name	Not Yet Assigned
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	011	KAPRARA, et al. The corticotropin releasing factor system in cancer: expression and pathophysiological implications. Cellular and molecular life sciences 67(8):1293-1306 (2010).	☐
	012	MENDES-DOS-SANTOS et al. Prevalence of Testicular Adrenal Rest Tumor and Factors Associated with Its Development in Congenital Adrenal Hyperplasia. Hormone Res. In Paed. 90:161-168 (2018).	☐
	013	MUNSON, Peter et al. Ligand: a Versatile Computerized Approach for Characterization of Ligand-binding Systems. Analytical Biochemistry 107(1):220-239 (1980).	☐
	014	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Granting Institution of Post-Grant Review of U.S. Patent No. 11,007,201 dated December 1, 2023 (pp. 1-38) (PGR2022-00025).	☐
	015	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Final Written Decision of Post-Grant Review of U.S. Patent No. 10,849,908 dated November 26, 2024 (pp. 1-62) (PGR2021-00088).	☐
	016	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Final Written Decision of Post-Grant Review of U.S. Patent No. 11,007,201 dated November 27, 2024 (pp. 1-60) (PGR2022-00025).	☐
	017	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petition for Post Grant Review of U.S. Patent No. 10,849,908 dated May 28, 2021 (pp. 1-90) (PGR2021-00088).	☐
	018	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petition for Post Grant Review of U.S. Patent No. 11,007,201 dated February 18, 2022 (pp 1-92) (PGR2022-00025).	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 6 of 9

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Application Number	19/043,275
Filing Date	01-31-2025
First Named Inventor	HOWERTON; Alexis
Art Unit	
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-710.304

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	019	OSTRO, Mark J. et al. Use of Liposomes as Injectable-drug Delivery Systems. American Journal of Hospital Pharmacy 46(8):1576-1587 (1989).	☐
	020	PCT/US2019/029486 International Invitation to Pay Additional Fees dated June 4, 2019.	☐
	021	PCT/US2019/029486 International Search Report and Written Opinion dated August 12, 2019.	☐
	022	RAO. Recent developments of collagen-based materials for medical applications and drug delivery systems. J Biomater Sci Polym Ed. 7(7):623-45 (1995).	☐
	023	REICHMAN et al. Fertility in Patients with Congenital Adrenal Hyperplasia. Fertility and Sterility, Vol. 101, No. 2, 2014. 301-309.	☐
	024	REISCH et al. Testicular adrenal rest tumors develop independently of long-term disease control: a longitudinal analysis of 50 adult men with congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency. J. Clin. Endocrinol. Metab. 98(11):E1820-E1826 (2013).	☐
	025	SMEETS et. al. Molecular characterization of testicular adrenal rest tumors in congenital adrenal hyperplasia: lesions with both adrenocortical and Leydig cell features. JCEM 100(3):E524-E530 (2015).	☐
	026	TIOSANO et al. Ovarian adrenal rest tumor in a congenital adrenal hyperplasia patient with adrenocorticotropin hypersecretion following adrenalectomy. Hormone Res. in Paediatrics 74:223-228 (2010).	☐
	027	U.S. Serial No. 17/081,694 Office Action dated February 26, 2021.	☐
	028	U.S. Serial No. 17/081,694 Office Action dated June 11, 2021.	☐
	029	U.S. Serial No. 17/667,285 Office Action dated December 29, 2023.	☐

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				Application Number	19/043,275
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	
				Examiner Name	Not Yet Assigned
Sheet	7	of	9	Attorney Docket Number	50535-710.304

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	030	U.S. Serial No. 17/667,285 Office Action dated June 10, 2024.	☐
	031	ZAAROUR et al. Bilateral Ovary Adrenal Rest Tumor in a Congenital Adrenal Hyperplasia Following Adrenalectomy. Endocrinol. Pract. 20(4):e69-e74 (2014).	☐

Examiner Signature	/SARAH PIHONAK/	Date Considered	05/16/2025

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				First Named Inventor	HOWERTON; Alexis
				Art Unit	
				Examiner Name	Not Yet Assigned
Sheet	8	of	9	Attorney Docket Number	50535-710.304

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 37CFR 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)	**2025-02-05**
Name/Print	Victoria Cheng	Registration Number	79641

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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.
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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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BIB DATA SHEET

CONFIRMATION NO. 5486

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
19/043,275	01/31/2025 RULE	514	1627	50535-710.304

APPLICANTS
Spruce Biosciences, Inc., South San Francisco, CA;

INVENTORS
Alexis HOWERTON, San Francisco, CA;
Hal GERBER, San Francisco, CA;

**** CONTINUING DATA ***************************
This application is a CON of 18/941,832 11/08/2024
which is a CON of 17/667,285 02/08/2022 ABN
which is a CON of 17/081,694 10/27/2020 PAT 11304950
which is a CON of PCT/US2019/029486 04/26/2019
which claims benefit of 62/822,815 03/23/2019
and claims benefit of 62/663,951 04/27/2018

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
02/21/2025

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged		STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ Yes ☑ No	☐ Yes ☑ No	/SARAH PIHONAK/ Examiner's Signature	☐ Met after Allowance SP Initials	CA	14	21	1

ADDRESS
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050
UNITED STATES

TITLE
METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

FILING FEE RECEIVED		
0.00	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
19/043,275	01/31/2025	Alexis HOWERTON	50535-710.304

CONFIRMATION NO. 5486

21971
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

PUBLICATION NOTICE

Date Mailed: 06/05/2025

Title:METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Publication No.US-2025-0177404-A1
Publication Date:06/05/2025

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be viewed using the USPTO's publicly available Searchable Databases via the Patent Public Search tool at www.uspto.gov. The direct link to access the Patent Public Search tool is currently https://ppubs.uspto.gov/pubwebapp/static/pages/ppubsbasic.html.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through Patent Center, the USPTO's electronic patent application filing and management system. The direct link to access this status information is currently https://patentcenter.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of Patent Center.

Further assistance in electronically accessing the publication, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

USPTO Automated Interview Request (AIR)

Jul 30 2025

This paper requesting to schedule and/or conduct an interview is appropriate because:

This submission is requested to be accepted as an authorization for this interview to communicate via the internet. Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned concerning scheduling of the interview via video conference, instant messaging, or electronic mail, and to conduct the interview in accordance with office practice including video conferencing.

Name(s):
Victoria Cheng, Kaia Parenti (Reg. No. 81050)

S-signature:
/Victoria Cheng/

Registration Number:
79641

U.S. Application Number:
19043275

Confirmation Number:
5486

E-mail Address:
vcheng@wsgr.com

Phone Number:
+1 8583502240

Proposed Time of Interview:
8-6-2025 1:00 PM ET

Alternative Proposed Time(s) of Interview:
8-7-2025 1:00 PM ET

Alternative Proposed Time(s) of Interview:
8-7-2025 1:30 PM ET

Prefered Interview Type:
Video Conference

I am the applicant or applicant's representative for this application.

Topic for Discussion:

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,275	**08/08/2025 03:01:00 PM Z ET**	**50535-710.304**

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 #	5486	FILED BY	Colleen Mensching
PATENT CENTER #	71766393	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710.304 - Internet Comms Auth.pdf	2	Internet Communications Authorization	209 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Spruce 50535-710.304 - Internet Comms Auth.pdf	38FD092E6BF701BFD7A09D6D6E51D5797F7E0B4779C8FD1249D9C9AC14B0A3515CC7F57BB5C57623F5341B2BE449A5DBBAD77724AB532AC31003DF9D3713A631

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Doc Code: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorization/Internet Communications Authorization Withdrawal

PTO/SB/439 (11-15)

AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS		
	Application No.	19/043,275
	Filing Date	01/31/2025
	First Named Inventor	Alexis HOWERTON
	Art Unit	1627
	Examiner Name	Sarah PIHONAK
	Practitioner Docket No.	50535-710.304

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I. To authorize permission for Internet Communications.

☒ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

II. To withdraw authorization for Internet Communications.

☐ The authorization given on _____, to the USPTO to communicate with the undersigned and any practitioner in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via Internet communications such as video conferencing, instant messaging, or electronic mail is hereby withdrawn. I understand that the withdrawal is effective when approved rather than when received.

I am the

☐ applicant.

☐ attorney or agent of record. Registration number _____.

☒ attorney or agent acting under 37 CFR 1.34. Registration number 79,641.

/Victoria Cheng/ — Signature

August 8, 2025 — Date

Victoria CHENG — Typed or printed name

(832) 605-2488 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Juristic entities must be represented by a patent practitioner (see 37 CFR 1.31, which is applicable to any paper filed on or after September 16, 2012, that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below*.

☒ * Total of 1 forms are submitted.

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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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,275	01/31/2025	Alexis HOWERTON	50535-710.304	5486

21971 7590 08/08/2025

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER
PIHONAK, SARAH

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
08/08/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Applicant-Initiated Interview Summary	**Application No.** 19/043,275	**Applicant(s)** HOWERTON et al.		
	Examiner SARAH PIHONAK	**Art Unit** 1627	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
SARAH PIHONAK	Primary Examiner	Video Conference
Victoria Cheng	Attorney of Record	
Kaia Parenti	Attorney	

Date of Interview: 06 August 2025

Issues Discussed:

Proposed Amendment(s)

Attys. Cheng and Parenti discussed a proposed amendment to claim 1 to incorporate the limitations of claims 17 and 19. The examiner agreed this proposed amendment would overcome the 102 and 103 rejections of record. Applicant intends to submit a response to the non-final action with proposed amendments to the claims. The examiner will also review the nonstatutory double patenting rejections of record upon receipt of Applicant's response.

/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,275	**08/11/2025 03:05:22 PM Z ET**	**50535-710.304**

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 #	5486	FILED BY	Colleen Mensching
PATENT CENTER #	71798435	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710.304 - POA.pdf	2	Power of Attorney	355 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Spruce 50535-710.304 - POA.pdf	CFF9D4DF2A729B9ACE930CF2B345DEFB54CB6F31722C5581CD437CD3188FAC1055095A38BE3718E27FB2F6D767670AA1A08519DD59AC277B7B580B65C06F2F95

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New Applications Under 35 U.S.C. 111

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

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Document Description: Power of Attorney

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Application Number	19/043,275
Filing Date	01/31/2025
First Named Inventor	Alexis HOWERTON
Title	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS
Art Unit	1627
Examiner Name	Sarah PIHONAK
Attorney Docket Number	50535-710.304

SIGNATURE of Applicant or Patent Practitioner

Signature	/Victoria Cheng/	Date (Optional)	08/11/2025
Name	Victoria Cheng	Registration Number	79,641
Title (if Applicant is a juristic entity)	Patent Practitioner		
Applicant Name (if Applicant is a juristic entity)	Spruce Biosciences, Inc.		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of 1 forms are submitted.

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Docusign Envelope ID: 46A528D5-8B52-454C-9DFF-B47E6DF8077D

Document Description: Power of Attorney

PTO/AIA/82B (07-13)
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 21971

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Spruce Biosciences, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	Signed by: Samir Ghanta A8EFEB34D8F9452...	Date (Optional)	11-Aug-2025
Name	Samir Ghanta		
Title	President and CFO		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of 1 forms are submitted.

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0035. Public burden for this form is estimated to average 3 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.** If filing this completed form by mail, send to: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,275	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**5486**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: August 13, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☒ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.304).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: August 13, 2025

By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81050

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,275
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	21	Attorney Docket Number	50535-710.304

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		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	2	of	21	Attorney Docket Number	50535-710.304

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	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-20220143037	05-12-2022	HOWERTON; Alexis et al.	
	029	US-20230159533	05-25-2023	REDDY; Dasharatha et al.	
	030	US-20230321112	10-12-2023	HOWERTON; Alexis et al.	
	031	US-20230414627	12-28-2023	HOWERTON; Alexis et al.	
	032	US-20240043432	02-08-2024	REDDY; Dasharatha et al.	
	033	US-20240261300	08-08-2024	GHOSH; Sangita et al.	

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	034	US-20240293421	09-05-2024	REDDY; Dasharatha et al.	
	035	US-20250064812	02-27-2025	HOWERTON; Alexis et al.	
	036	US-20250177403	06-05-2025	HOWERTON; Alexis et al.	
	037	US-20250195527	06-19-2025	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	EP-2094709-B1	09-15-2010	LILLY CO ELI [US]		☐
	003	EP-3784233-B1	06-05-2024	SPRUCE BIOSCIENCES INC [US]		☐
	004	EP-3984523-A1	04-20-2022	NEUROCRINE BIOSCIENCES INC [US], et al.		☐
	005	JP-2000302693-A	10-31-2000	PFIZER PROD INC.	Abstract:	☒

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	006	WO-0059908-A2	10-12-2000	DU PONT PHARM CO [US]		☐
	007	WO-0123388-A2	04-05-2001	NEUROGEN CORP [US], et al.		☐
	008	WO-02072202-A1	09-19-2002	BRISTOL MYERS SQUIBB PHARMA CO [US]		☐
	009	WO-2005020910-A2	03-10-2005	PHARMACIA CORP [US], et al.		☐
	010	WO-2005063755-A1	07-14-2005	SB PHARMCO INC [US], et al.		☐
	011	WO-2005079868-A2	09-01-2005	SB PHARMCO INC [US], et al.		☐
	012	WO-2006102194-A1	09-28-2006	LILLY CO ELI [US], et al.		☐
	013	WO-2010039678-A1	04-08-2010	LILLY CO ELI [US], et al.		☐
	014	WO-2013160317-A2	10-31-2013	HOLSBOERMASCHMEYER NEUROCHEMIE GMBH [DE]		☐
	015	WO-2020115555-A2	06-11-2020	NEUROCRINE BIOSCIENCES INC [US], et al.		☐

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	016	WO-2021016208-A1	01-28-2021	SPRUCE BIOSCIENCES INC [US]		☐
	017	WO-2022036123-A1	02-17-2022	SPRUCE BIOSCIENCES INC [US]		☐
	018	WO-2023091684-A1	05-25-2023	SPRUCE BIOSCIENCES INC [US]		☐
	019	WO-9413676-A1	06-23-1994	PFIZER [US], et al.		☐
	020	WO-9729109-A1	08-14-1997	JANSSEN PHARMACEUTICA NV [BE], et al.		☐
	021	WO-9803510-A1	01-29-1998	DU PONT MERCK PHARMA [US]		☐
	022	WO-9808847-A1	03-05-1998	PFIZER [US], et al.		☐

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	6	of	21	Attorney Docket Number	50535-710.304

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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Sheet	7	of	21	Attorney Docket Number	50535-710.304

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]
	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.	☐
	015	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).	☐

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	016	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).	☐
	017	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).	☐
	018	DO, Hien-Quang et al. Copper-catalyzed arylation of C-H bonds; Abstracts of Papers, 236th ACS National Meeting, New Orleans, LA, Apr. 6-10, 2008, Accession No. 2008:390596.	☐
	019	DO, Hien-Quang et al. Copper-Catalyzed Arylation of Heterocycle C-H Bonds. J Am Chem Soc. 129(41):12404-12405 (2007).	☐
	020	ENGELS, Manon et al. Testicular adrenal rest tumors: current insights on prevalence, characteristics, origin, and treatment. Endocrine Reviews 40(4):973-987 (2019).	☐
	021	EP19793181.9 Brief Communication - Opposition Proceedings dated August 5, 2025.	☐
	022	EP19793181.9 Reply from the opponent to submission of proprietor dated July 18, 2025.	☐
	023	EP19793181.9 Reply of the Patent Proprietor to the notice(s) of opposition dated June 18, 2025.	☐
	024	EP19793181.9 Letter from the Opponent - Opposition Proceedings dated March 6, 2025.	☐
	025	ESCOBAR-MORREALE, HF., Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 14(5):270-284 (2018).	☐
	026	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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				Examiner Name	PIHONAK, SARAH
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	027	FLECK, Beth A. et al. Binding Kinetics Redefine the Antagonist Pharmacology of the Corticotropin-releasing Factor Type 1 Receptor. The Journal of Pharmacology and Experimental Therapeutics 341(2):518-531 (2012).	☐
	028	FUQUA et al. Duration of suppression of adrenal steroids after glucocorticoid administration. Int J Pediatr Endocrinol 2010:712549 (2010).	☐
	029	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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	031	HE, Liqi et al. 4-(1,3-Dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)pyrazolo[1,5-a]-1,3,5-triazine: A Potent, Orally Bioavailable CRF1 Receptor Antagonist. J Med Chem 43:449-456 (2000).	☐
	032	HODGETTS et al. Discovery of N-(1-ethylpropyl)-[3-methoxy-5-(2-methoxy-4-trifluoromethoxyphenyl)-6-methyl-pyrazin-2-yl]amine 59 (NGD 98-2): an orally active corticotropin releasing factor-1 (CRF-1) receptor antagonist. J Med Chem 54:4187-4206 (2011).	☐
	033	JOSEPH, Dana N., and Shannon Whirledge. Stress and the HPA axis: balancing homeostasis and fertility. International journal of molecular sciences 18(10):2224, 1-15 (2017).	☐
	034	KHADILKAR et al., Can polycystic ovarian syndrome be cured? Unfolding the concept of secondary polycystic ovarian syndrome. J Obstet Gynaecol India 69(4):297-302 (2019).	☐

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	035	LEE et al. Attenuated Forms of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency. J Clin Endocrinol Metab. 55(5):866-871 (1982).	☐
	036	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).	☐
	037	MAJO et al. Facile Palladium-Catalyzed Synthesis of 3-Arylpyrazolo-[1,5-a]pyrimidines. Adv. Synth. Catal. 345(5):620-624 (2003).	☐
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	041	MORABBI, Mohammad-Javad et al., Pexacerfont as a CRF1 Antagonist for the Treatment of Withdrawal Symptoms in Men With Heroin/Methamphetamine Dependence: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. International Clinical Psychopharmacology 1-9 (2017).	☐
	042	NELLA et al. A Phase 2 Study of Continuous Subcutaneous Hydrocortisone Infusion in Adults With Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab. 101(12):4690-4698 (2016).	☐

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	043	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Defence dated March 13, 2025 (Claim No. HP-2025-000005) (pp. 1-3).	☐
	044	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Grounds of Invalidity dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	045	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Particulars of Claim dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	046	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).	☐
	047	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).	☐
	048	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).	☐
	049	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).	☐
	050	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).	☐

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	051	Neurocrine Biosciences, Inc. (Plaintiff) v. Spruce Biosciences, Inc. (Defendant). Memorandum dated June 9, 2025 (Case No. 1:25-cv-00059-JDW (pp. 1-10).	☐
	052	NISSEN, Trygve et al. The clinical case report: a review of its merits and limitations. BMC Research Notes 7:264, 1-7 (2014).	☐
	053	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).	☐
	054	PCT/US2007/078605 International Search Report and Written Opinion dated January 31, 2008.	☐
	055	PCT/US2009/058722 International Search Report and Written opinion dated January 25, 2010.	☐
	056	PCT/US2018/046707 International Search Report and Written Opinion dated October 24, 2018.	☐
	057	PCT/US2018/046760 International Search Report and Written Opinion dated October 24, 2018.	☐
	058	PCT/US2020/042820 International Search Report and Written Opinion dated November 25, 2020.	☐
	059	PCT/US2021/045780 International Search Report and Written Opinion dated December 17, 2021.	☐
	060	PCT/US2022/050436 International Search Report and Written Opinion dated November 18, 2022.	☐
	061	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).	☐

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	062	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).	☐
	063	SARAFOGLOU et al. SUN-LB064 A Phase 2, Dose-Escalation, Safety and Efficacy Study of Tildacerfont (SPR001) for the Treatment of Patients with Classic Congenital Adrenal Hyperplasia. Journal of the Endocrine Society 3(Supplement_1):SUN-LB064 (2017).	☐
	064	SARAFOGLOU, Kyriakie et al. Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies. The Journal of Clinical Endocrinology and Metabolism 106(11):e4666-e4679 (2021).	☐
	065	SPEISER, Phyllis W. et al. Congenital Adrenal Hyperplasia Due to Steroid 21-hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology and Metabolism 95(9):4133-4160 (2010).	☐
	066	Spruce Biosciences announces topline results from CAHMELIA-203 in adult classic CAH and CAHPTAIN-205 in pediatric classic CAH. Spruce Biosciences :1-7 (2024).	☐
	067	Spruce Biosciences announces topline results from CAHMELIA-204 in adult CAH and CAHPTAIN-205 in adult and pediatric CAH. Spruce Biosciences :1-4 (2024).	☐
	068	SPRUCE BIOSCIENCES, INC. Study of SPR001 in Adults with Classic Congenital Adrenal Hyperplasia. 2017. Pages 1-7.	☐
	069	SPRUCE BIOSCIENCES, INC. Study to Evaluate the Safety and Efficacy of SPR001 in Subjects with Classic Congenital Adrenal Hyperplasia. 2018. Pages 1-7.	☐

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	070	STIKKELBROECK, Nike M. M. L. et al. High prevalence of testicular adrenal rest tumors, impaired spermatogenesis, and Leydig cell failure in adolescent and adult males with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology and Metabolism 86(12):5721-5728 (2001).	☐
	071	STIKKELBROECK, Nike M. M. L. et. al. Monitoring of menstrual cycles, ovulation, and adrenal suppression by saliva sampling in female patients with 21- hydroxylase deficiency. Fertility & sterility 80(4):1030-1036 (2003).	☐
	072	THAKRAL, Naveen K. et al. Salt Disproportionation in the Solid State: Role of Solubility and Counterion Volatility. Molecular pharmaceutics 13(12):4141-4151 (2016).	☐
	073	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.	☐
	074	TRAPP et al. Congenital adrenal hyperplasia: an update in children. Curr Opin Endocrinol Diabetes Obes. 18(3):166-70 (2011).	☐
	075	TURCU, Adina F. and Richard J. Auchus. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinology and Metabolism Clinics 44(2):275-296 (2015).	☐
	076	TURCU, Adina F., and Richard J. Auchus. Novel treatment strategies in congenital adrenal hyperplasia. Current Opinion in Endocrinology, Diabetes and Obesity 23(3):225-232 (2016).	☐
	077	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).	☐

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	078	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).	☐
	079	U.S. Provisional Application No. 62/822,815 filed on March 23, 2019.	☐
	080	U.S. Serial No. 17/586,228 Office Action dated June 10, 2022.	☐
	081	U.S. Serial No. 13/063,226 Office Action dated January 24, 2013.	☐
	082	U.S. Serial No. 16/388,620 Office Action dated July 15, 2019.	☐
	083	U.S. Serial No. 16/388,620 Office Action dated November 25, 2019.	☐
	084	U.S. Serial No. 16/639,540 Office Action dated July 11, 2022.	☐
	085	U.S. Serial No. 16/639,540 Office Action dated March 28, 2024.	☐
	086	U.S. Serial No. 16/639,540 Office Action dated May 25, 2023.	☐
	087	U.S. Serial No. 16/639,540 Office Action dated November 16, 2021.	☐
	088	U.S. Serial No. 16/639,540 Office Action dated September 28, 2023.	☐
	089	U.S. Serial No. 16/639,541 Office Action dated April 4, 2022.	☐
	090	U.S. Serial No. 17/063,592 Office Action dated December 7, 2021.	☐

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	091	U.S. Serial No. 17/078,054 Office Action dated December 14, 2020.	☐
	092	U.S. Serial No. 17/359,411 Office Action dated January 6, 2022.	☐
	093	U.S. Serial No. 17/359,414 Office Action dated November 16, 2021.	☐
	094	U.S. Serial No. 17/586,228 Office Action dated March 30, 2022.	☐
	095	U.S. Serial No. 17/720,074 Office Action dated August 26, 2022.	☐
	096	U.S. Serial No. 18/078,649 Office Action dated March 21,2024.	☐
	097	U.S. Serial No. 18/078,649 Office Action dated October 9, 2024.	☐
	098	U.S. Serial No. 18/078,649 Office Action dated September 8, 2023.	☐
	099	U.S. Serial No. 18/307,718 Office Action dated October 12, 2023.	☐
	100	U.S. Serial No. 18/310,463 Office Action dated October 31, 2024.	☐
	101	U.S. Serial No. 19/043,264 Office Action dated April 25, 2025.	☐
	102	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.	☐

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				Examiner Name	PIHONAK, SARAH
Sheet	17	of	21	Attorney Docket Number	50535-710.304

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]
	103	WALDRON, James. Spruce saws off only drug after 2nd hyperplasia fail, leaving biotech's direction in doubt. Fierce Biotech :1-2 (2024).	☐
	104	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).	☐
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	108	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.	☐
	109	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).	☐
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	111	ZORRILLA, Eric P. et al., Progress in Corticotropin-Releasing Factor-1 Antagonist Development. Drug Discov Today 15(9-10):371-383 (2010).	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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				Application Number	19/043,275
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	18	of	21	Attorney Docket Number	50535-710.304

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	112	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		Date Considered	

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	19	of	21	Attorney Docket Number	50535-710.304

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).

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TIMING FEE

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COPIES

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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:	/Kaia R. Parenti/	Date (YYYY-MM-DD)	2025-08-13
Name/Print	Kaia R. Parenti	Registration Number	81050

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Sheet	20	of	21	Attorney Docket Number	50535-710.304

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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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,275	**08/13/2025 06:45:30 PM Z ET**	**50535-710.304**

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 #	5486	FILED BY	Jennifer Vail
PATENT CENTER #	71845068	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kaia Parenti

Documents

TOTAL DOCUMENTS: 36

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
NPL_US16639540_OA_16NOV2021.pdf	4	Non Patent Literature	160 KB
NPL_US16388620_OA_15July2019.pdf	8	Non Patent Literature	262 KB
NPL_US13063226-OA-01-24-2013.pdf	12	Non Patent Literature	416 KB
NPL_US16388620_OA_25Nov2019.pdf	9	Non Patent Literature	316 KB
NPL_US16639540_OA_28March2024_.pdf	11	Non Patent Literature	652 KB
NPL_US16639540-OA-07-11-2022.pdf	9	Non Patent Literature	508 KB

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Digest

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NPL_US18307718_OA_12OCT2023.pdf	60895E71BE9C2E41F11F7D19AE2F8490EB94F296469A5DB68687FF2CCDB7F135B326FC96A8676EB2E87EDE7839404DFB7907AE5E236B157E15AB532677AE55CE
NPL_ZORRILLA_Therapeutic_potential_799_828_2004.pdf	A3B551A1857E6E694BCE52581D96A0DFD63CD292005F520730978C80DF712D3E6A64E8063EEFBA9EF3C20CF69CDE969D38DB9A351D1F3E161787EE4F64B7B22E
Spruce 50535-710_304_IDS.pdf	BF780FC6C6848890A78B910D46F16E73477B54ACB5AA880F2C26C9A1AF4972A993D7150DF72FE4D329B2D146E2F4D24AFCFC7866015EFD28ECD3E26B58BB9BB1
Spruce 50535-710_304_IDS-TRAN.LET.pdf	6FBD498A3E0D81C212E3C14CCEA38E84041E06FC6AFE98309A1BB8169F35AE2D00FF4E4A6923970A441E6D959F98058751718EA25F53064D66B4248DC94B12A9
Spruce 50535-710_304_IDS-IDS.pdf	03C67B0FC8264B55E0280597803457A93814012968134BCEDB3E17E0328F30C84E892EF20417E88677A7FA1E9ECAFA0F3CA47077F8DBA17AEC61B9D91705F19B

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,275	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**5486**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: August 13, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☒ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.304).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: August 13, 2025

By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81050

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,275
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	21	Attorney Docket Number	50535-710.304

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		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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				Examiner Name	PIHONAK, SARAH
Sheet	2	of	21	Attorney Docket Number	50535-710.304

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-20220143037	05-12-2022	HOWERTON; Alexis et al.	
	029	US-20230159533	05-25-2023	REDDY; Dasharatha et al.	
	030	US-20230321112	10-12-2023	HOWERTON; Alexis et al.	
	031	US-20230414627	12-28-2023	HOWERTON; Alexis et al.	
	032	US-20240043432	02-08-2024	REDDY; Dasharatha et al.	
	033	US-20240261300	08-08-2024	GHOSH; Sangita et al.	

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Sheet	3	of	21	Attorney Docket Number	50535-710.304

U. S. PATENT DOCUMENTS

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	034	US-20240293421	09-05-2024	REDDY; Dasharatha et al.	
	035	US-20250064812	02-27-2025	HOWERTON; Alexis et al.	
	036	US-20250177403	06-05-2025	HOWERTON; Alexis et al.	
	037	US-20250195527	06-19-2025	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	EP-2094709-B1	09-15-2010	LILLY CO ELI [US]		☐
	003	EP-3784233-B1	06-05-2024	SPRUCE BIOSCIENCES INC [US]		☐
	004	EP-3984523-A1	04-20-2022	NEUROCRINE BIOSCIENCES INC [US], et al.		☐
	005	JP-2000302693-A	10-31-2000	PFIZER PROD INC.	Abstract:	☒

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	4	of	21	Attorney Docket Number	50535-710.304

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]
	006	WO-0059908-A2	10-12-2000	DU PONT PHARM CO [US]		☐
	007	WO-0123388-A2	04-05-2001	NEUROGEN CORP [US], et al.		☐
	008	WO-02072202-A1	09-19-2002	BRISTOL MYERS SQUIBB PHARMA CO [US]		☐
	009	WO-2005020910-A2	03-10-2005	PHARMACIA CORP [US], et al.		☐
	010	WO-2005063755-A1	07-14-2005	SB PHARMCO INC [US], et al.		☐
	011	WO-2005079868-A2	09-01-2005	SB PHARMCO INC [US], et al.		☐
	012	WO-2006102194-A1	09-28-2006	LILLY CO ELI [US], et al.		☐
	013	WO-2010039678-A1	04-08-2010	LILLY CO ELI [US], et al.		☐
	014	WO-2013160317-A2	10-31-2013	HOLSBOERMASCHMEYER NEUROCHEMIE GMBH [DE]		☐
	015	WO-2020115555-A2	06-11-2020	NEUROCRINE BIOSCIENCES INC [US], et al.		☐

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	016	WO-2021016208-A1	01-28-2021	SPRUCE BIOSCIENCES INC [US]		☐
	017	WO-2022036123-A1	02-17-2022	SPRUCE BIOSCIENCES INC [US]		☐
	018	WO-2023091684-A1	05-25-2023	SPRUCE BIOSCIENCES INC [US]		☐
	019	WO-9413676-A1	06-23-1994	PFIZER [US], et al.		☐
	020	WO-9729109-A1	08-14-1997	JANSSEN PHARMACEUTICA NV [BE], et al.		☐
	021	WO-9803510-A1	01-29-1998	DU PONT MERCK PHARMA [US]		☐
	022	WO-9808847-A1	03-05-1998	PFIZER [US], et al.		☐

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	6	of	21	Attorney Docket Number	50535-710.304

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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Sheet	7	of	21	Attorney Docket Number	50535-710.304

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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.	☐
	015	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).	☐

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
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	016	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).	☐
	017	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).	☐
	018	DO, Hien-Quang et al. Copper-catalyzed arylation of C-H bonds; Abstracts of Papers, 236th ACS National Meeting, New Orleans, LA, Apr. 6-10, 2008, Accession No. 2008:390596.	☐
	019	DO, Hien-Quang et al. Copper-Catalyzed Arylation of Heterocycle C-H Bonds. J Am Chem Soc. 129(41):12404-12405 (2007).	☐
	020	ENGELS, Manon et al. Testicular adrenal rest tumors: current insights on prevalence, characteristics, origin, and treatment. Endocrine Reviews 40(4):973-987 (2019).	☐
	021	EP19793181.9 Brief Communication - Opposition Proceedings dated August 5, 2025.	☐
	022	EP19793181.9 Reply from the opponent to submission of proprietor dated July 18, 2025.	☐
	023	EP19793181.9 Reply of the Patent Proprietor to the notice(s) of opposition dated June 18, 2025.	☐
	024	EP19793181.9 Letter from the Opponent - Opposition Proceedings dated March 6, 2025.	☐
	025	ESCOBAR-MORREALE, HF., Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 14(5):270-284 (2018).	☐
	026	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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	027	FLECK, Beth A. et al. Binding Kinetics Redefine the Antagonist Pharmacology of the Corticotropin-releasing Factor Type 1 Receptor. The Journal of Pharmacology and Experimental Therapeutics 341(2):518-531 (2012).	☐
	028	FUQUA et al. Duration of suppression of adrenal steroids after glucocorticoid administration. Int J Pediatr Endocrinol 2010:712549 (2010).	☐
	029	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).	☐
	030	GILLIGAN P. et al., The Discovery of 4-(3-Pentylamino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-pyrazolo-[1,5-alpha]-pyrimidine: A corticotrophin-Releasing Factor (hCRF1)Antagonist. Bioorganic & Medicinal Chemistry 8(1):181-189 (2000).	☐
	031	HE, Liqi et al. 4-(1,3-Dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)pyrazolo[1,5-a]-1,3,5-triazine: A Potent, Orally Bioavailable CRF1 Receptor Antagonist. J Med Chem 43:449-456 (2000).	☐
	032	HODGETTS et al. Discovery of N-(1-ethylpropyl)-[3-methoxy-5-(2-methoxy-4-trifluoromethoxyphenyl)-6-methyl-pyrazin-2-yl]amine 59 (NGD 98-2): an orally active corticotropin releasing factor-1 (CRF-1) receptor antagonist. J Med Chem 54:4187-4206 (2011).	☐
	033	JOSEPH, Dana N., and Shannon Whirledge. Stress and the HPA axis: balancing homeostasis and fertility. International journal of molecular sciences 18(10):2224, 1-15 (2017).	☐
	034	KHADILKAR et al., Can polycystic ovarian syndrome be cured? Unfolding the concept of secondary polycystic ovarian syndrome. J Obstet Gynaecol India 69(4):297-302 (2019).	☐

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	035	LEE et al. Attenuated Forms of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency. J Clin Endocrinol Metab. 55(5):866-871 (1982).	☐
	036	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).	☐
	037	MAJO et al. Facile Palladium-Catalyzed Synthesis of 3-Arylpyrazolo-[1,5-a]pyrimidines. Adv. Synth. Catal. 345(5):620-624 (2003).	☐
	038	Malvern Instruments Worldwide. A Basic Guide to Particle Characterization. Inform - White Paper (pp 1-26) (2012).	☐
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	040	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).	☐
	041	MORABBI, Mohammad-Javad et al., Pexacerfont as a CRF1 Antagonist for the Treatment of Withdrawal Symptoms in Men With Heroin/Methamphetamine Dependence: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. International Clinical Psychopharmacology 1-9 (2017).	☐
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	043	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Defence dated March 13, 2025 (Claim No. HP-2025-000005) (pp. 1-3).	☐
	044	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Grounds of Invalidity dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	045	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Particulars of Claim dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	046	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).	☐
	047	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).	☐
	048	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).	☐
	049	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).	☐
	050	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).	☐

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	051	Neurocrine Biosciences, Inc. (Plaintiff) v. Spruce Biosciences, Inc. (Defendant). Memorandum dated June 9, 2025 (Case No. 1:25-cv-00059-JDW (pp. 1-10).	☐
	052	NISSEN, Trygve et al. The clinical case report: a review of its merits and limitations. BMC Research Notes 7:264, 1-7 (2014).	☐
	053	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).	☐
	054	PCT/US2007/078605 International Search Report and Written Opinion dated January 31, 2008.	☐
	055	PCT/US2009/058722 International Search Report and Written opinion dated January 25, 2010.	☐
	056	PCT/US2018/046707 International Search Report and Written Opinion dated October 24, 2018.	☐
	057	PCT/US2018/046760 International Search Report and Written Opinion dated October 24, 2018.	☐
	058	PCT/US2020/042820 International Search Report and Written Opinion dated November 25, 2020.	☐
	059	PCT/US2021/045780 International Search Report and Written Opinion dated December 17, 2021.	☐
	060	PCT/US2022/050436 International Search Report and Written Opinion dated November 18, 2022.	☐
	061	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).	☐

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	062	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).	☐
	063	SARAFOGLOU et al. SUN-LB064 A Phase 2, Dose-Escalation, Safety and Efficacy Study of Tildacerfont (SPR001) for the Treatment of Patients with Classic Congenital Adrenal Hyperplasia. Journal of the Endocrine Society 3(Supplement_1):SUN-LB064 (2017).	☐
	064	SARAFOGLOU, Kyriakie et al. Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies. The Journal of Clinical Endocrinology and Metabolism 106(11):e4666-e4679 (2021).	☐
	065	SPEISER, Phyllis W. et al. Congenital Adrenal Hyperplasia Due to Steroid 21-hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology and Metabolism 95(9):4133-4160 (2010).	☐
	066	Spruce Biosciences announces topline results from CAHMELIA-203 in adult classic CAH and CAHPTAIN-205 in pediatric classic CAH. Spruce Biosciences :1-7 (2024).	☐
	067	Spruce Biosciences announces topline results from CAHMELIA-204 in adult CAH and CAHPTAIN-205 in adult and pediatric CAH. Spruce Biosciences :1-4 (2024).	☐
	068	SPRUCE BIOSCIENCES, INC. Study of SPR001 in Adults with Classic Congenital Adrenal Hyperplasia. 2017. Pages 1-7.	☐
	069	SPRUCE BIOSCIENCES, INC. Study to Evaluate the Safety and Efficacy of SPR001 in Subjects with Classic Congenital Adrenal Hyperplasia. 2018. Pages 1-7.	☐

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	070	STIKKELBROECK, Nike M. M. L. et al. High prevalence of testicular adrenal rest tumors, impaired spermatogenesis, and Leydig cell failure in adolescent and adult males with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology and Metabolism 86(12):5721-5728 (2001).	☐
	071	STIKKELBROECK, Nike M. M. L. et. al. Monitoring of menstrual cycles, ovulation, and adrenal suppression by saliva sampling in female patients with 21- hydroxylase deficiency. Fertility & sterility 80(4):1030-1036 (2003).	☐
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	074	TRAPP et al. Congenital adrenal hyperplasia: an update in children. Curr Opin Endocrinol Diabetes Obes. 18(3):166-70 (2011).	☐
	075	TURCU, Adina F. and Richard J. Auchus. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinology and Metabolism Clinics 44(2):275-296 (2015).	☐
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	077	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).	☐

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	079	U.S. Provisional Application No. 62/822,815 filed on March 23, 2019.	☐
	080	U.S. Serial No. 17/586,228 Office Action dated June 10, 2022.	☐
	081	U.S. Serial No. 13/063,226 Office Action dated January 24, 2013.	☐
	082	U.S. Serial No. 16/388,620 Office Action dated July 15, 2019.	☐
	083	U.S. Serial No. 16/388,620 Office Action dated November 25, 2019.	☐
	084	U.S. Serial No. 16/639,540 Office Action dated July 11, 2022.	☐
	085	U.S. Serial No. 16/639,540 Office Action dated March 28, 2024.	☐
	086	U.S. Serial No. 16/639,540 Office Action dated May 25, 2023.	☐
	087	U.S. Serial No. 16/639,540 Office Action dated November 16, 2021.	☐
	088	U.S. Serial No. 16/639,540 Office Action dated September 28, 2023.	☐
	089	U.S. Serial No. 16/639,541 Office Action dated April 4, 2022.	☐
	090	U.S. Serial No. 17/063,592 Office Action dated December 7, 2021.	☐

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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	19/043,275
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	16	of	21	Attorney Docket Number	50535-710.304

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. 17/078,054 Office Action dated December 14, 2020.	☐
	092	U.S. Serial No. 17/359,411 Office Action dated January 6, 2022.	☐
	093	U.S. Serial No. 17/359,414 Office Action dated November 16, 2021.	☐
	094	U.S. Serial No. 17/586,228 Office Action dated March 30, 2022.	☐
	095	U.S. Serial No. 17/720,074 Office Action dated August 26, 2022.	☐
	096	U.S. Serial No. 18/078,649 Office Action dated March 21,2024.	☐
	097	U.S. Serial No. 18/078,649 Office Action dated October 9, 2024.	☐
	098	U.S. Serial No. 18/078,649 Office Action dated September 8, 2023.	☐
	099	U.S. Serial No. 18/307,718 Office Action dated October 12, 2023.	☐
	100	U.S. Serial No. 18/310,463 Office Action dated October 31, 2024.	☐
	101	U.S. Serial No. 19/043,264 Office Action dated April 25, 2025.	☐
	102	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.	☐

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	103	WALDRON, James. Spruce saws off only drug after 2nd hyperplasia fail, leaving biotech's direction in doubt. Fierce Biotech :1-2 (2024).	☐
	104	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).	☐
	105	WILLIAMS, John P. Corticotropin-releasing factor 1 receptor antagonists: a patent review. Expert Opin Ther Pat 23(8):1057-68 (2013).	☐
	106	World Health Organization Drug Information, 32(2):369-370 (2018).	☐
	107	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).	☐
	108	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.	☐
	109	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).	☐
	110	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).	☐
	111	ZORRILLA, Eric P. et al., Progress in Corticotropin-Releasing Factor-1 Antagonist Development. Drug Discov Today 15(9-10):371-383 (2010).	☐

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Sheet	18	of	21	Attorney Docket Number	50535-710.304

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	112	ZORRILLA, Eric P. et al. The therapeutic potential of CRF1 antagonists for anxiety. Expert opinion on investigational drugs 13(7):799-828 (2004).	☐

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Signature:	/Kaia R. Parenti/	Date (YYYY-MM-DD)	2025-08-13
Name/Print	Kaia R. Parenti	Registration Number	81050

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,275	**08/13/2025 06:45:30 PM Z ET**	**50535-710.304**

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 #	5486	FILED BY	Jennifer Vail
PATENT CENTER #	71845068	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
DA / 232415	**E20258CI46208710**	**Jennifer Vail**

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(51) International Patent Classification 6 :
C07D 487/04, 471/04, A61K 31/505, 31/435 // (C07D 487/04, 239:00, 231:00) (C07D 471/04, 249:00, 221:00) (C07D 487/04, 239:00, 209:00)

A1

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60/025,039 28 August 1996 (28.08.96) US

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: CHEN, Yuhpyng, Liang [US/US]; 8 Waterview Drive, Waterford, CT 06385 (US).

(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

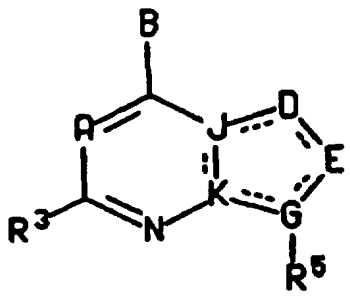
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), 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: SUBSTITUTED 6,5-HETERO-BICYCLIC DERIVATIVES

(57) Abstract

This invention relates to compounds of formula (I), wherein the dashed lines represent optional double bonds; A is nitrogen or CR^7; B is $-NR^1R^2$, $-CR^1R^2R^{10}-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$; J and K are each independently nitrogen or carbon and both J and K are not nitrogens; D and E are each selected, independently, from nitrogen, CR^4, C=O, C=S, sulfur, oxygen, CR^4R^6 and NR^8; G is nitrogen or carbon; and their use for the prevention or inhibition of a disorder that can be treated by antagonizing CRF.



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SUBSTITUTED 6,5- HETERO-BICYCLIC DERIVATIVES

Background of the invention

This invention relates to certain pharmaceutically active substituted 6,5-hetero-bicyclic derivatives, pharmaceutical compositions containing them and methods of administering them to subjects in need of their corticotropin releasing factor antagonist activity.

The substituted heterocyclic derivatives claimed in this case exhibit activity as corticotropin releasing factor (hormone) CRF (CRH) antagonists.

CRF antagonists are mentioned in U.S. Patents 4,605,642 and 5,063,245 referring to peptides and pyrazolinones, respectively. They are also referred to in the following: PCT Patent Application PCT/IB95/00439, which designates the United States and was filed on June 6, 1995 and published on December 14, 1995; PCT Patent Application PCT/IB95/00373, which designates the United States and was filed on May 18, 1995 and published on December 21, 1995; U.S. Patent Application 08/448,539, which was filed in the PCT on Nov. 12, 1993 and entered the U.S. national phase on June 14, 1995; PCT Patent Application WO 95/10506, which was filed on October 12, 1993 and published on April 20, 1995, and U.S. Patent Application 08/481,413, which was filed in the PCT on November 26, 1993 and entered the U.S. national phase on July 24, 1995; U.S. Patent Application 08/254,820, which was filed on April 19, 1995; Provisional U.S. Patent Application 60/008,396, which was filed on December 8, 1995; and Provisional U.S. Patent Application 60/006,333, which was filed on November 8, 1995. All the foregoing patent applications are incorporated herein by reference in their entireties.

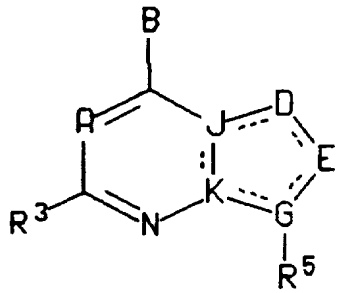
The importance of CRF antagonists is set out in the literature, e.g., P. Black, Scientific American SCIENCE & MEDICINE, 1995, p. 16-25; T. Lovenberg et al., Current Pharmaceutical Design, 1995, 1, 305-316; and United States Patent 5,063,245, which is referred to above. A recent outline of the different activities possessed by CRF antagonists is found in M. J. Owens et al., Pharm. Rev., Vol. 43, pages 425 to 473 (1991), also incorporated herein by reference. Based on the research described in these two and other references, CRF antagonists are effective in the treatment of a wide range of stress-related illnesses, mood disorders such as depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced depression, postpartum depression, dysthemia, bipolar disorders and cyclothymia;

chronic fatigue syndrome; eating disorders such as anorexia and bulimia nervosa; generalized anxiety disorder; panic disorder; phobias; obsessive-compulsive disorder, post-traumatic stress disorder, pain perception such as fibromyalgia; headache; gastrointestinal diseases; hemorrhagic stress; ulcers; stress-induced psychotic episodes; fever; diarrhea; post-operative ileus, colonic hypersensitivity; irritable bowel syndrome; Crohn's disease; spastic colon; inflammatory disorders such as rheumatoid arthritis and osteoarthritis; pain; asthma; psoriasis; allergies; osteoporosis; premature birth; hypertension, congestive heart failure; sleep disorders; neurodegenerative diseases such as Alzheimer's disease, senile dementia of the Alzheimer's type, multiinfarct dementia, Parkinson's disease, and Huntington's disease; head trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; spinal cord trauma; psychosocial dwarfism; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone; obesity; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; infertility, cancer; infertility; muscular spasms; urinary incontinence; hypoglycemia and immune dysfunctions including stress induced immune dysfunctions, immune suppression and human immunodeficiency virus infections; and stress-induced infections in humans and animals.

The compounds of this invention are also believed to be inhibitors of CRH binding protein and therefore useful in the treatment of disorders the treatment of which can be effected or facilitated by inhibiting such protein. Examples of such disorders are Alzheimer's disease and obesity.

Summary of the Invention

The present invention relates to compounds of the formula



I

or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

J and K are each independently nitrogen or carbon and both J and K are not nitrogens ;

D and E are each selected, independently, from nitrogen, CR^4, C=O, C=S, sulfur, oxygen, CR^4R^6 and NR^8 ;

G is nitrogen or carbon;

the ring containing D, E, G, K, and J in formula I may be a saturated or unsaturated 5-membered ring and may optionally contain one or two double bonds and may optionally contain from one to three heteroatoms in the ring and may optionally have one or two C=O or C=S groups;

R^1 is C_1-C_6 alkyl optionally substituted with one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, -O-(C_1-C_4 alkyl), CF_3, -C(=O)O-(C_1-C_4alkyl), -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, $-NO_2$, -SO(C_1-C_4 alkyl), $-SO_2$(C_1-C_4 alkyl), $-SO_2$NH(C_1-C_4 alkyl) and $-SO_2$N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl),

-COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl);

-NR^1R^2 or -$CR^1R^2R^{10}$ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, (C_1-C_2 alkylene)-O-(C_1-C_2 alkyl), (C_1-C_2 alkylene)-OH, or -S(C_1-C_4 alkyl);

each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, (C_1-C_2 alkylene)-OH, CF_3, CH_2SCH_3, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl);

R^6 is hydrogen, methyl or ethyl;

R^8 is hydrogen or C_1-C_4 alkyl;

R^5 is phenyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl and wherein each of the foregoing R^5 groups is substituted with from one to four substituents R^{13} wherein one to three of said substituents may be selected, independently, from fluoro, chloro, C_1-C_6 alkyl and -O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, OH, (C_1-C_4 alkylene)-OH, (C_1-C_4alkylene)-O-(C_1-C_2 alkyl), -CN, -CF_3, -NO_2, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -OCO(C_1-C_4 alkyl), (C_1-C_4 alkylene)-O-(C_1-C_4 alkyl), -S(C_1-C_6 alkyl), (C_1-C_4 alkylene)-S-(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally have one or two double bonds;

R^7 is hydrogen, C_1-C_4 alkyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, -O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), -OCF_3, -CF_3, -CH_2OH or -CH_2O(C_1-C_2 alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1-C_4 alkyl; and

with the proviso that: a) when both J and K are carbon and D is CR^4 and E is nitrogen, then G can not be nitrogen; (b) when both J and K are carbons and D and G are nitrogens, then E can not be CR^4 or C=O or C=S; (c) when both J and K are carbons and D and E are carbons, then G can not be nitrogen; (d) when G is carbon, it must be double bonded to E; and (e) in the ring containing J, K, D, E and G, there can not be two double bonds adjacent to each other.

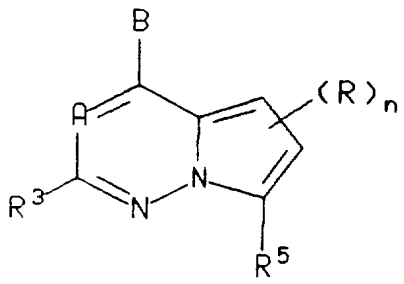
and the pharmaceutically acceptable salts of such compounds.

When the ring containing D, E, G, K and J is a 5-membered heteroaromatic ring, it may be, e.g., pyrazolo, imidazolo, thieno, furano, thiazolo, oxazolo, triazolo or thiadiazolo.

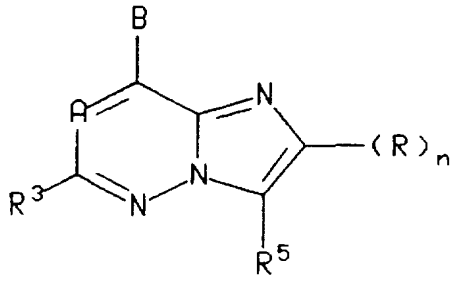
The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, unless otherwise indicated, means -O-alkyl, where "alkyl" is defined as above.

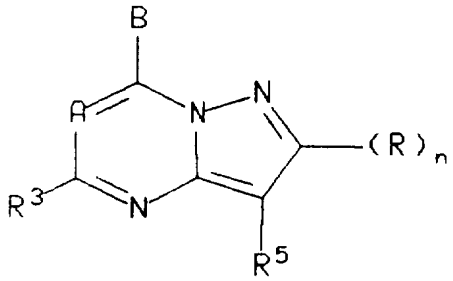
Examples of more specific embodiments of formula I are the following, wherein $(R)_n$ represents from zero to two substituents, wherein such substitutents are as defined above in the definition of formula I.



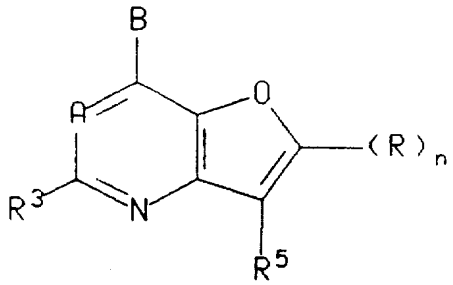
I-A



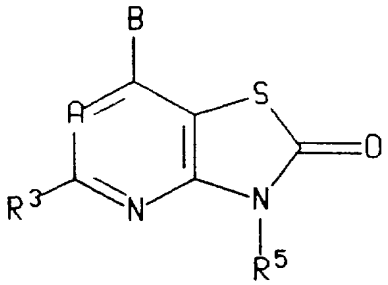
I-B



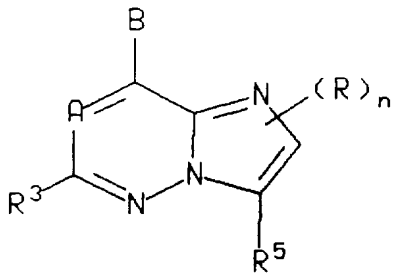
I-E



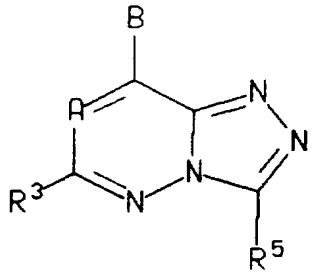
I-J



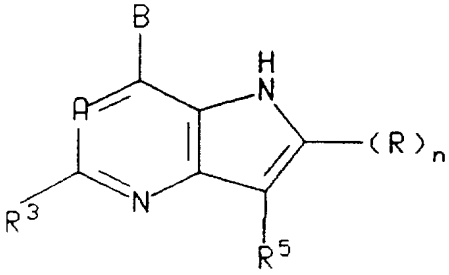
I-K



I-C



I-D



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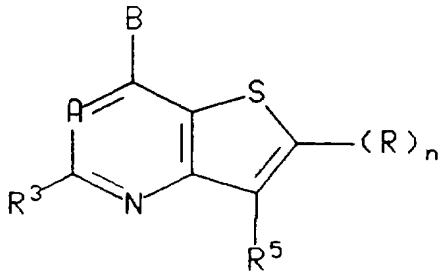
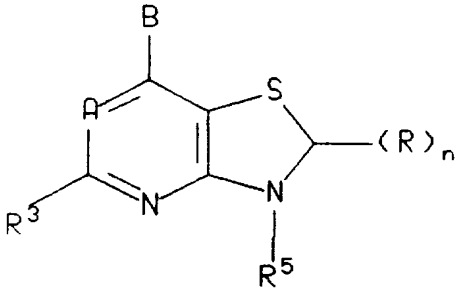
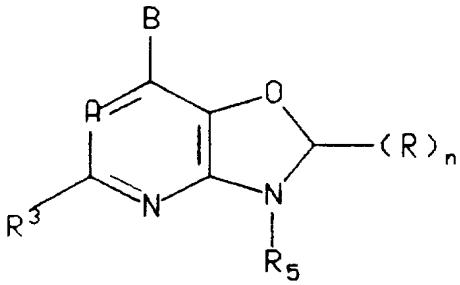


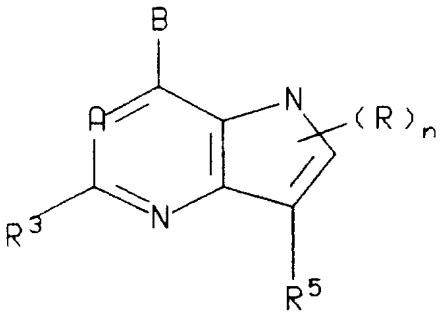
I-H



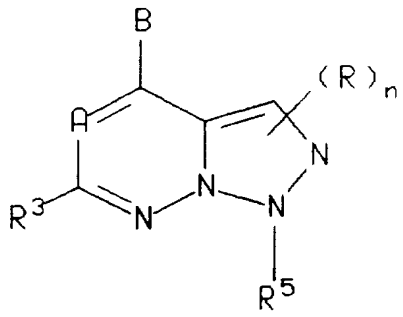
I-L



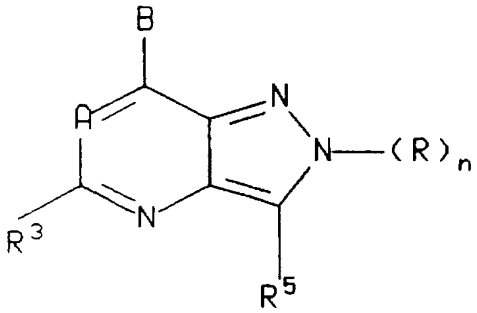
I-M



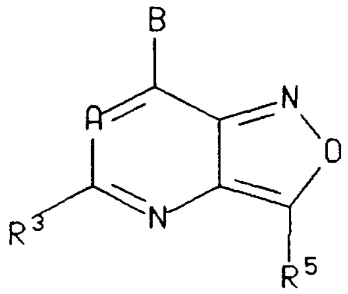
I-N



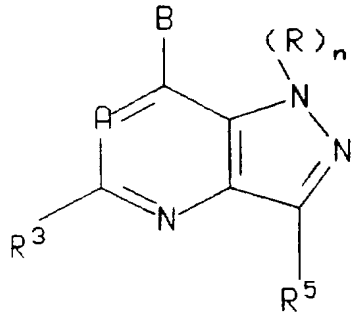
I-O



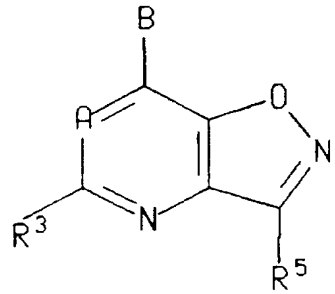
I-R



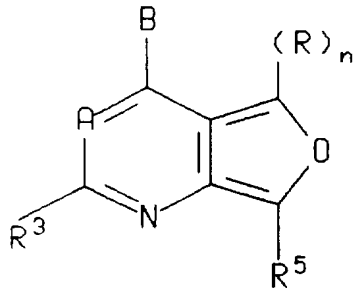
I-S



I-V



I-W



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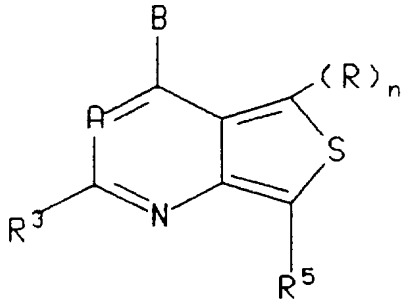

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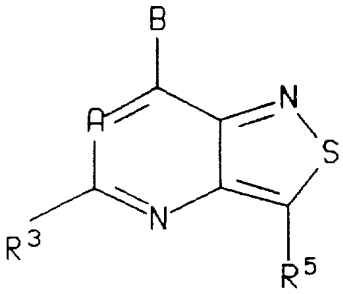
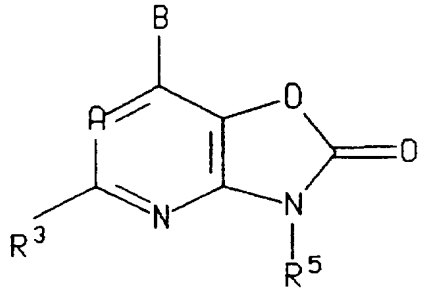


I-T



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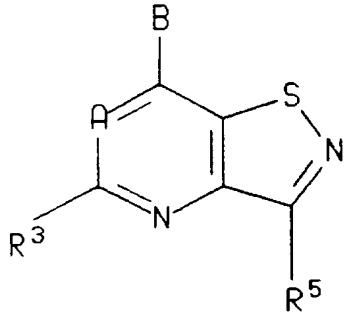
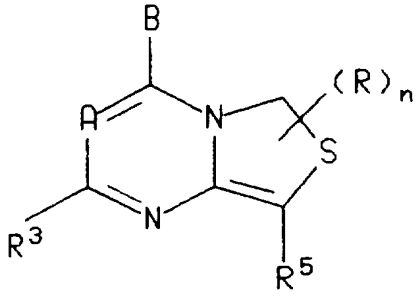
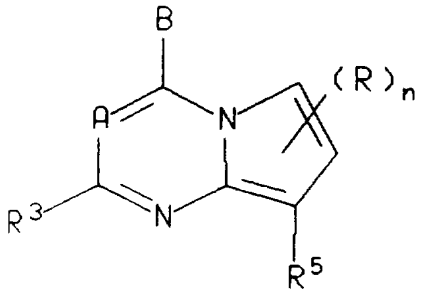


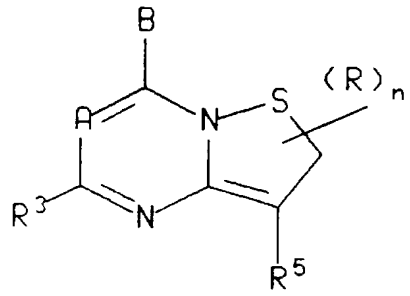
I-X



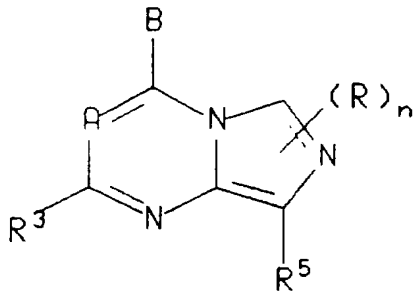
I-B′



I-Y



I-Z



I-A'

More specific embodiments of this invention include compounds of the above formula I wherein B is $-CHR^1R^2$, $-NR^1R^2$, $-NHCHR^1R^2$, $-OCHR^1R^2$ or $-SCHR^1R^2$, and R^1 is C_1-C_6 alkyl, which may optionally be substituted with one hydroxy, fluoro, CF_3 or C_1-C_4 alkoxy group and which may optionally contain one double or triple bond; and R^2 is benzyl or C_1-C_6 alkyl, which may optionally contain one double or triple bond, wherein said C_1-C_6 alkyl and the phenyl moiety of said benzyl may optionally be substituted with one fluoro, CF_3, C_1-C_2 alkyl, C_1-C_2 alkoxy or chloro group.

Other more specific embodiments of this invention include compounds of formula I wherein R^3 is methyl, ethyl, chloro or methoxy; R^4 and R^6 are selected from hydrogen, methyl and ethyl; R^5 is di- or tri-substituted phenyl, pyridyl, or pyrimidyl, in which the two or three substitutents on said phenyl, pyridyl or pyrimidyl are selected, independently, from C_1-C_4 alkyl, -O-(C_1-C_4 alkyl), (C_1-C_2 alkyl)-O-(C_1-C_4 alkyl), $-CF_3$, $-OCF_3$, -CHO, -(C_1-C_4 alkyl)-OH, cyano, chloro, fluoro, bromo and iodo, wherein each of the forgoing C_1-C_4 alkyl groups may optionally contain one double or triple bond;

Other more specific embodiments of this invention include compounds of the formula I wherein B is or contains an NR^1R^2 or $CR^1R^2R^{10}$ moiety which forms a saturated or unsaturated 5-membered carbocyclic ring wherein one of the ring carbons may optionally be replaced by a sulfur or oxygen atom.

Other more specific embodiments of this invention include compounds of the formula I wherein A is nitrogen or CR^7 and R^7 is hydrogen or methyl.

Other more specific embodiments of this invention include compounds of the formula I wherein B is $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$.

Other more specific embodiments of this invention include compounds of the formula I wherein A is CH, J and K are carbon and D, E, and G are nitrogen;

Other more specific embodiments of this invention include compounds of the formula I wherein J and D are nitrogen, K and G are carbon, and E is CH, CCH_3, or CC_2H_5.

Other more specific embodiments of this invention include compounds of the formula I wherein B contains a $-NR^1R^2$ or $-CR^1R^2R^{10}$ moiety that is a saturated or unsaturated three to five membered ring.

Other more specific embodiments of this invention include compounds of the formula I wherein J and K are carbon, and D--E--G is O-$C(CH_3)$=C, O-CH=C,

S-C(CH_3)=C, S-CH=C, N(CH_3)-C(CH_3)=C, N(CH_3)-CH=C, O-N=C, S-N=C, N(CH_3)-N=C, O-CH_2N, S-CH_2N, or NH-C(C_1-C_2alkyl)=C.

Examples of preferred compounds of the formula I:

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethyl-propyl-amine;

[6-bromo-5-bromomethyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]-pyridin-7-yl]-(1-ethyl-propyl)-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]-pyridin-7-yl]-amine;

[6-bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-methyl-amine; and

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]-pyridine.

Other compounds of formula I include the following:

4-(1-ethyl-propoxy)-2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]-pyrimidine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

[3-(4-bromo-2,6-dimethyl-phenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;

butyl-ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

3-(4-bromo-2,6-dimethyl-phenyl)-7-(1-ethyl-propoxy)-5-methyl-pyrazolo[1,5-a]-pyrimidine;

[2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-diethyl-amine;

[2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-ethyl-propyl-

amine;

[8-(4-chloro-2,6-dimethyl-phenyl)-2,7-dimethyl-pyrrolo[1,2-a]pyrimidin-4-yl]-ethyl-propyl-amine;

[8-(4-chloro-2,6-dimethyl-phenyl)-2,7-dimethyl-pyrrolo[1,2-a]pyrimidin-4-yl]-diethyl-amine;

[8-(4-chloro-2,6-dimethyl-phenyl)-2,6-dimethyl-pyrrolo[1,2-a]pyrimidin-4-yl]-diethyl-amine;

[2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-diethyl-amine;

[2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-ethyl-propyl-amine;

butyl-[2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-ethyl-amine;

[2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-(1-ethyl-propyl)-amine;

[8-(4-chloro-2,6-dimethyl-phenyl)-2,6-dimethyl-pyrrolo[1,2-a]pyrimidin-4-yl]-(1-ethyl-propyl)-amine;

8-(4-chloro-2,6-dimethyl-phenyl)-4-(1-ethyl-propoxy)-2,6-dimethyl-pyrrolo[1,2-a]-pyrimidine;

4-(1-ethyl-propoxy)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]-pyrimidine;

4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidine;

(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-amine;

butyl-ethyl-[2-methyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-amine;

butyl-ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-2H-isothiazolo[2,3-a]-pyrimidin-7-yl]-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-2H-isothiazolo[2,3-a]-pyrimidin-7-yl]-amine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-2H-isothiazolo[2,3-a]-pyrimidine;

4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-imidazo[1,5-a]-

pyrimidine;

(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-imidazo[1,5-a]pyrimidin-4-yl]-amine;

[2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-imidazo[1,5-a]pyrimidin-4-yl]-(1-ethyl-propyl)-amine;

4-(1-ethyl-propoxy)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-imidazo[1,5-a]-pyrimidine;

4-(1-ethyl-propoxy)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-6,7-dihydro-imidazo [1,5-a]pyrimidine;

4-(1-ethyl-propoxy)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-thiazolo[3,4-a]-pyrimidine;

4-(1-ethyl-propoxy)-2-methyl-7-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-b]pyridazine;

4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-b]-pyridazine;

4-(1-ethyl-propoxy)-2,6-dimethyl-7-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-b]; pyridazine;

4-(1-ethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-b]-pyridazine;

[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-b]pyridazin-4-yl]-(1-ethyl-propyl)-amine;

(1-ethyl-propyl)-[2-methyl-7-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-b]pyridazin-4-yl]-amine;

[2,6-dimethyl-3-(2,4,6-trimethyl-phenyl)-imidazo[1,2-b]pyridazin-8-yl]-(1-ethyl-propyl)-amine;

8-(1-ethyl-propoxy)-2,6-dimethyl-3-(2,4,6-trimethyl-phenyl)-imidazo[1,2-b]-pyridazine;

8-(1-ethyl-propoxy)-6-methyl-3-(2,4,6-trimethyl-phenyl)-imidazo[1,2-b]pyridazine;

(1-ethyl-propyl)-[6-methyl-3-(2,4,6-trimethyl-phenyl)-imidazo[1,2-b]pyridazin-8-yl]-amine;

(1-ethyl-propyl)-[2-methyl-7-(2,4,6-trimethyl-phenyl)-imidazo[1,5-b]pyridazin-4-yl]-amine;

[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-imidazo[1,5-b]pyridazin-4-yl]-(1-ethyl-propyl)-amine;

4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-imidazo[1,5-b]-pyridazine-b]pyridazine;

butyl-[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-imidazo[1,5-b]pyridazin-4-yl]-ethyl-amine;

[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-imidazo[1,5-b]pyridazin-4-yl]-ethyl-propyl-amine;

[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-imidazo[1,5-b]pyridazin-4-yl]-diethyl-amine;

diethyl-[6-methyl-3-(2,4,6-trimethyl-phenyl)-[1,2,4]triazolo[4,3-b]pyridazin-8-yl]-amine;

ethyl-[6-methyl-3-(2,4,6-trimethyl-phenyl)-[1,2,4]triazolo[4,3-b]pyridazin-8-yl]-propyl-amine;

butyl-ethyl-[6-methyl-3-(2,4,6-trimethyl-phenyl)-[1,2,4]triazolo[4,3-b]pyridazin-8-yl]-amine;

(1-ethyl-propyl)-[6-methyl-3-(2,4,6-trimethyl-phenyl)-[1,2,4]triazolo[4,3-b]-pyridazin-8-yl]-amine;

8-(1-ethyl-propoxy)-6-methyl-3-(2,4,6-trimethyl-phenyl)-[1,2,4]triazolo[4,3-b]-pyridazine;

7-(1-ethyl-propoxy)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]-pyridine;

7-(1-ethyl-propoxy)-1,2,5-trimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]-pyridine;

(1-ethyl-propyl)-[1,2,5-trimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]-pyridin-7-yl]-amine;

[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

butyl-[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-ethyl-amine;

[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-ethyl-propyl-amine;

[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-diethyl-amine;

ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-

propyl-amine;

butyl-ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-amine;

diethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-amine;

[3-(4-bromo-2,6-dimethyl-phenyl)-5-methyl-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

[3-(4-chloro-2,6-dimethyl-phenyl)-5-methyl-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

3-(4-chloro-2,6-dimethyl-phenyl)-7-(1-ethyl-propoxy)-5-methyl-3H-[1,2,3]triazolo[4,5-b]pyridine;

3-(4-bromo-2,6-dimethyl-phenyl)-7-(1-ethyl-propoxy)-5-methyl-3H-[1,2,3]triazolo[4,5-b]pyridine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[4,5-b]pyridine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[4,5-b]pyridin-7-yl]-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-isoxazolo[4,5-b]pyridin-7-yl]-amine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-isoxazolo[4,5-b]pyridine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-thieno[3,2-b]pyridine;

7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-thieno[3,2-b]pyridine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-thieno[3,2-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-thieno[3,2-b]pyridin-7-yl]-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-furo[3,2-b]pyridin-7-yl]-amine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-furo[3,2-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-furo[3,2-b]pyridine;

7-(1-ethyl-propoxy)- 5-methyl-3-(2,4,6-trimethyl-phenyl)-furo[3,2-b]pyridine;

4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-6H-pyrrolo[3,4-b]-pyridine;

4-(1-ethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-6H-pyrrolo[3,4-b]-

pyridine;

(1-ethyl-propyl)-[2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-6H-pyrrolo[3,4-b]pyridin-4-yl]-amine;

[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-2-thia-4-aza-inden-7-yl]-(1-ethyl-propyl)-amine;

7-(1-ethyl-propoxy)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-2-thia-4-aza-indene;

4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-furo[3,4-b]pyridine;

[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-furo[3,4-b]pyridin-4-yl]-(1-ethyl-propyl)-amine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-2H-pyrazolo[4,3-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-2H-pyrazolo[4,3-b]-pyridine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[4,3-b]pyridine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[4,3-b]pyridin-7-yl]-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]-pyrimidin-7-yl]-amine;

diethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl]-amine;

ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl]-propyl-amine;

butyl-ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]-pyrimidin-7-yl]-amine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-diethyl-amine;

butyl-[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethyl-amine;

butyl-ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-propyl-amine;

diethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

[3-(4-chloro-2,6-dimethyl-phenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;

[3-(4-chloro-2,6-dimethyl-phenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;

3-(4-chloro-2,6-dimethyl-phenyl)-7-(1-ethyl-propoxy)-5-methyl-pyrazolo[1,5-a]-pyrimidine;

8-(4-chloro-2,6-dimethyl-phenyl)-4-(1-ethyl-propoxy)-2-methyl-pyrazolo[1,5-a]-[1,3,5]triazine;

(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-amine;

4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a][1,3,5]-triazine;

4-(1-ethyl-propoxy)-2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a][1,3,5]-triazine;

[2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-(1-ethyl-propyl)-amine;

[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrazolo[4,3-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

7-(1-ethyl-propoxy)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrazolo[4,3-b]-pyridine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[4,5-b]-pyridine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[4,5-b]pyridin-7-yl]-amine;

1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-7-(1-ethyl-propoxy)-1H-pyrrolo[3,2-b]pyridine;

1,5-dimethyl-3-(2,6-dimethyl-4-chloro-phenyl)-7-(1-ethyl-propoxy)-1H-pyrrolo[3,2-b]pyridine;

2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-7-(1-ethyl-propoxy)-1H-pyrrolo[3,2-b]pyridine;

2,5-dimethyl-3-(2,6-dimethyl-4-chloro-phenyl)-7-(1-ethyl-propoxy)-1H-pyrrolo[3,2-b]pyridine;

7-(1-cyclopropylmethyl-propoxy)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine;

7-(1-cyclopropylmethyl-propoxy)-1,5-dimethyl-3-(2,6-dimethyl-4-chloro-phenyl)-1H-pyrrolo[3,2-b]pyridine;

1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-7-(tetrahydro-furan-3-yloxy)-1H-pyrrolo[3,2-b]pyridine;

1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-7-(S)-(tetrahydro-furan-3-yloxy)-1H-pyrrolo[3,2-b]pyridine;

1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-7-(1-propyl-butoxy)-1H-pyrrolo[3,2-b]pyridine;

7-sec-butylsulfanyl-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine;

cyclopropylmethyl-[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-b]pyrimidin-4-yl]-propyl-amine;

2-[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-ylamino]-butan-1-ol;

1,5-dimethyl-7-thiazolidin-3-yl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine;

[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-ethyl-(2,2,2-trifluoro-ethyl)-amine;

cyclopropylmethyl-[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-propyl-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-isoxazolo[4,5-b]pyridin-7-yl]-amine; and

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-isoxazolo[4,5-b]-pyridine.

This invention also relates to a pharmaceutical composition for the treatment, prevention or inhibition of (a) 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, or (b) 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, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions (e.g., dependencies on alcohol, nicotine, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; 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; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., 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; multiinfract dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; and hypoglycemia in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in the treatment of such disorder, and a pharmaceutically acceptable carrier.

The invention also relates to a method for the treatment, prevention or inhibition of (a) a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitator by CRF, or (b) 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, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders;

cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome; Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; 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; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., 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, nicotine, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; and hypoglycemia in a mammal, including a human, comprising administering to a subject in need of said treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder.

This invention also relates to a method of treating or preventing a disorder or condition, the treatment or prevention of which can be effected or facilitated by inhibiting CRH binding protein, in a mammal, including a human, comprising administering to said mammal a CRH binding protein inhibiting amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

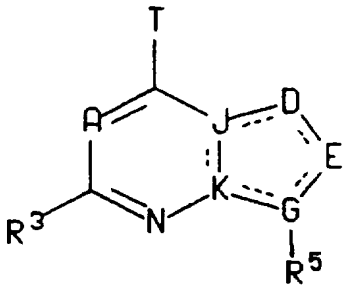
This invention also relates to a pharmaceutical composition for treating or preventing a disorder or conditon, the treatment or prevention of which can be effected or facilitated by inhibiting CRH binding protein in a mammal, including a human, comprising a CRH binding protein inhibiting amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

This invention includes all optical isomers and other stereoisomers of compounds of the formula I. When such compounds contain one or more chiral

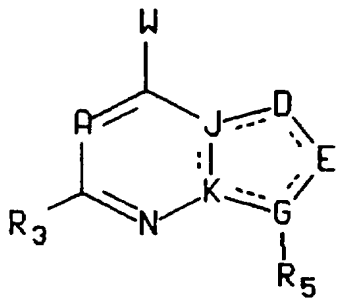
centers, it is understood that the invention includes the racemic mixtures as well as all individual enantiomers and diastereomers of such compounds, and mixtures thereof.

Detailed Description of the Invention

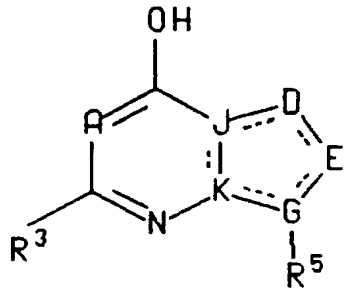
The following compounds having the formulas II, III, IV and V are useful as intermediates in the synthesis of compounds of the formula I.



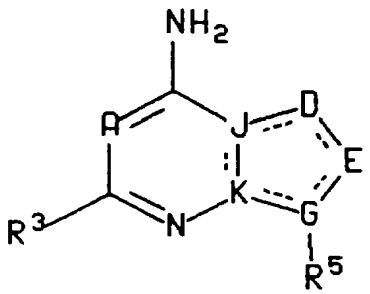
II



III



IV

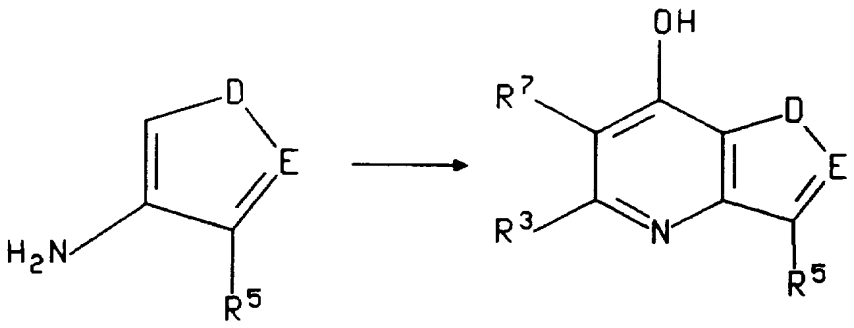


V

wherein T is chloro, bromo, iodo or $-OSO_2CF_3$; W is cyano, formyl, or $-COO(C_0-C_4$ alkyl) and A, J, K, D, E, G, R^3, and R^5 are as defined above with reference to formula I.

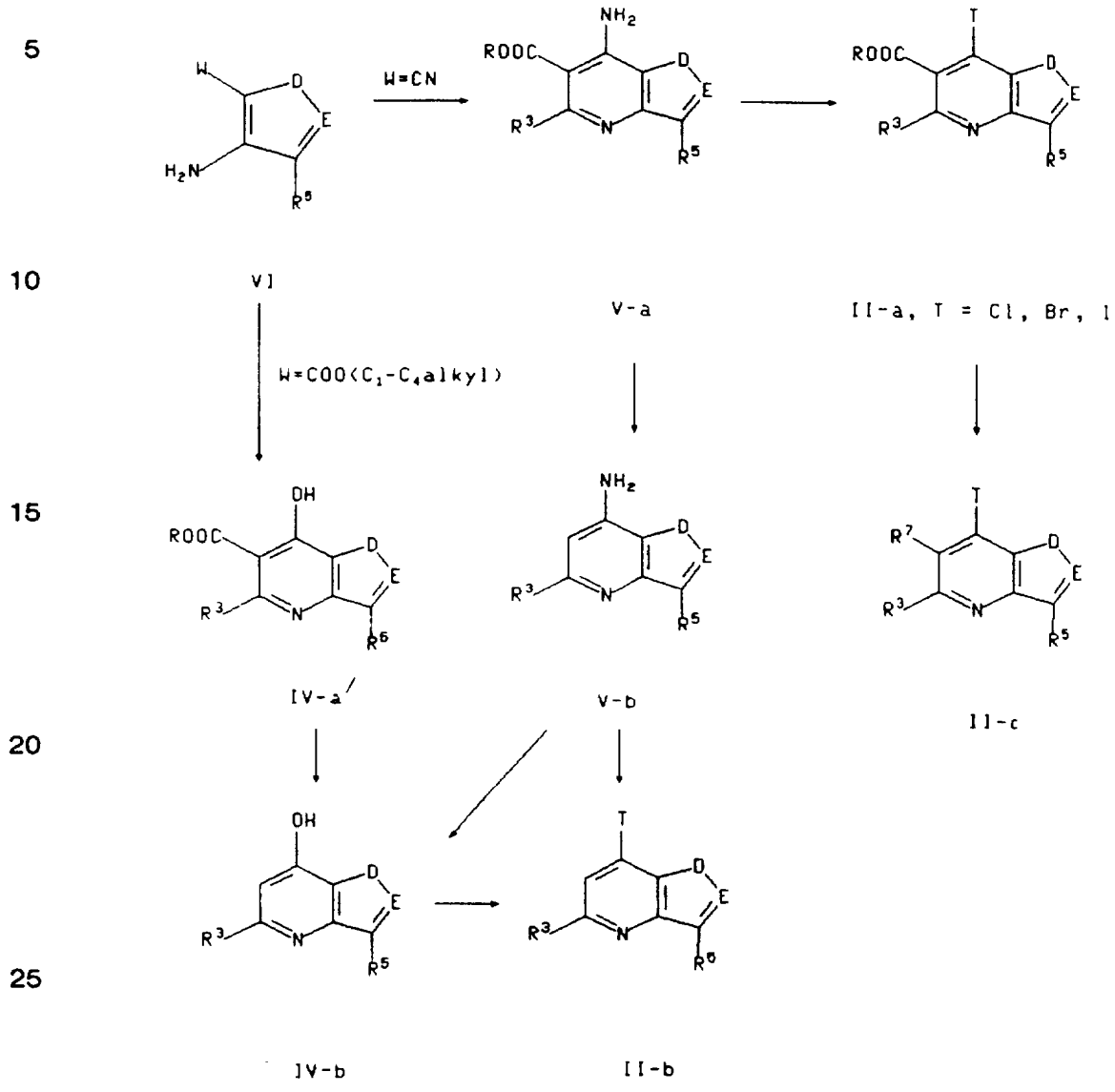
Compounds of the formula I may be prepared as described below. In the reaction schemes and discussion that follow, A, B, D, E, G, J, K, R^3, R^5 and structural formulae I, II, III, IV, and V are defined as above.

SCHEME 1

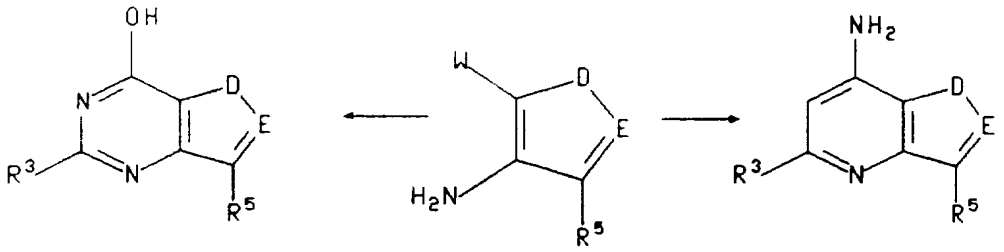


VI-a IV-a

SCHEME 2

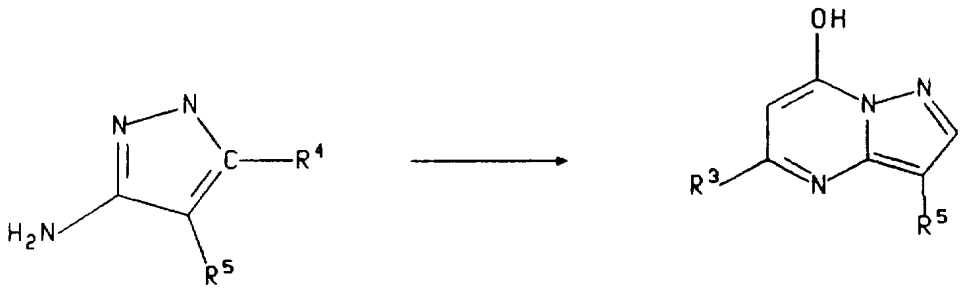


SCHEME 3



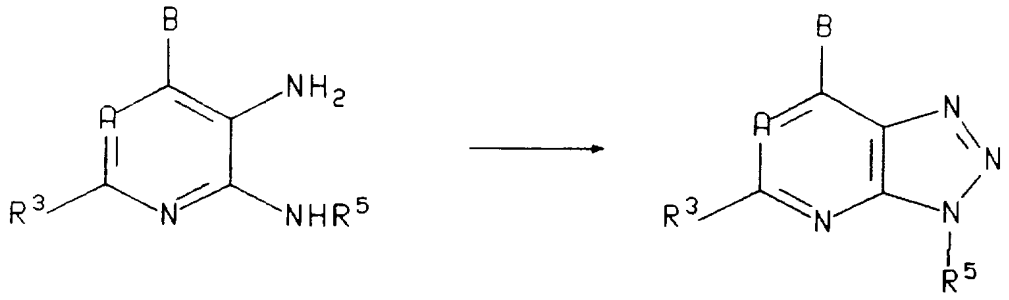
IV-c VI (W=CN, -COO(C_1-C_4 alkyl), -$CONH_2$) V-b

SCHEME 4



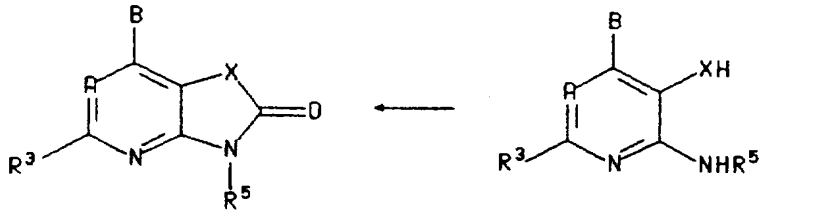
IX IV-d

SCHEME 5



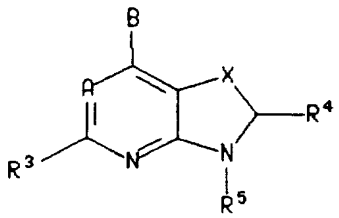
X I-N

SCHEME 6



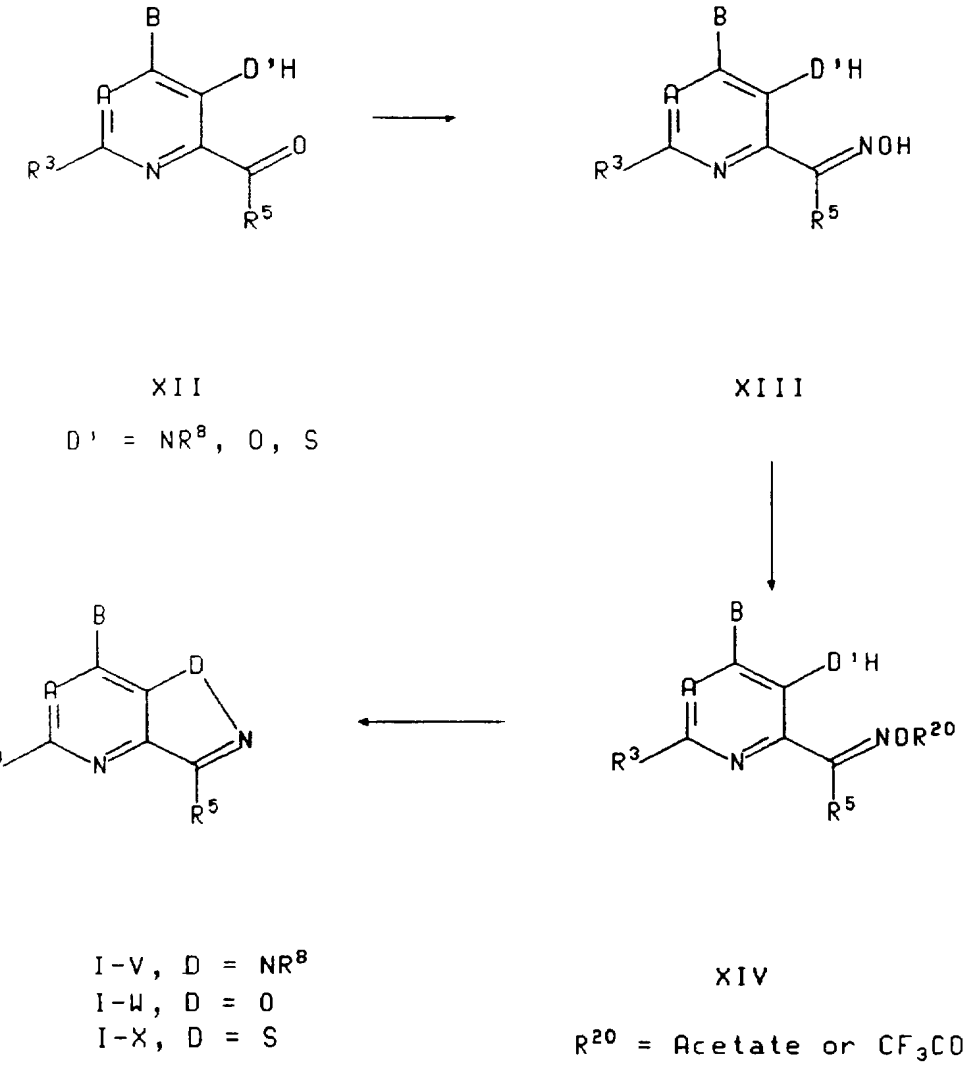
I-K, X=S or O, Y=O
I-U, X=S or O, Y=S

XI



I-L, X=S
I-M, X=O

SCHEME 7



XII

D' = NR^8, O, S

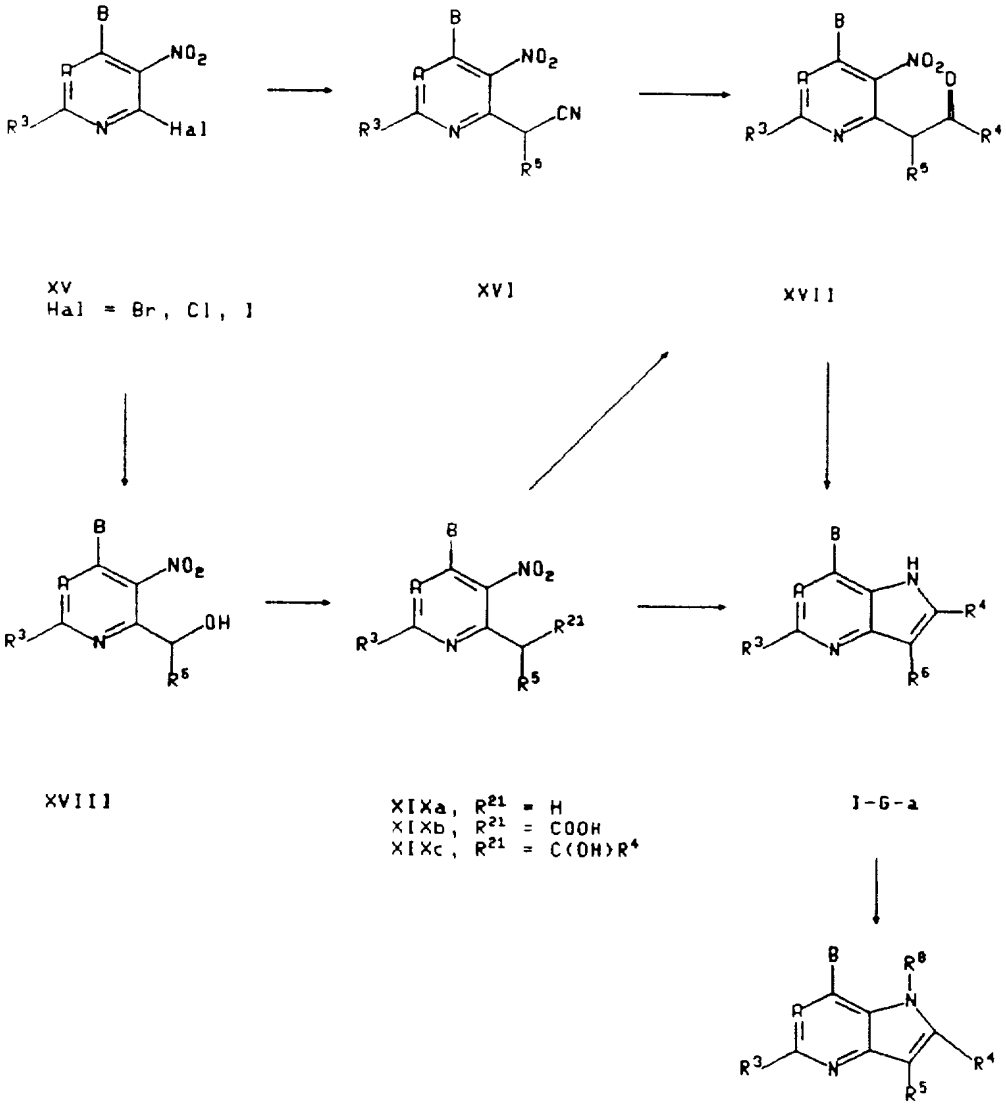
XIII

XIV

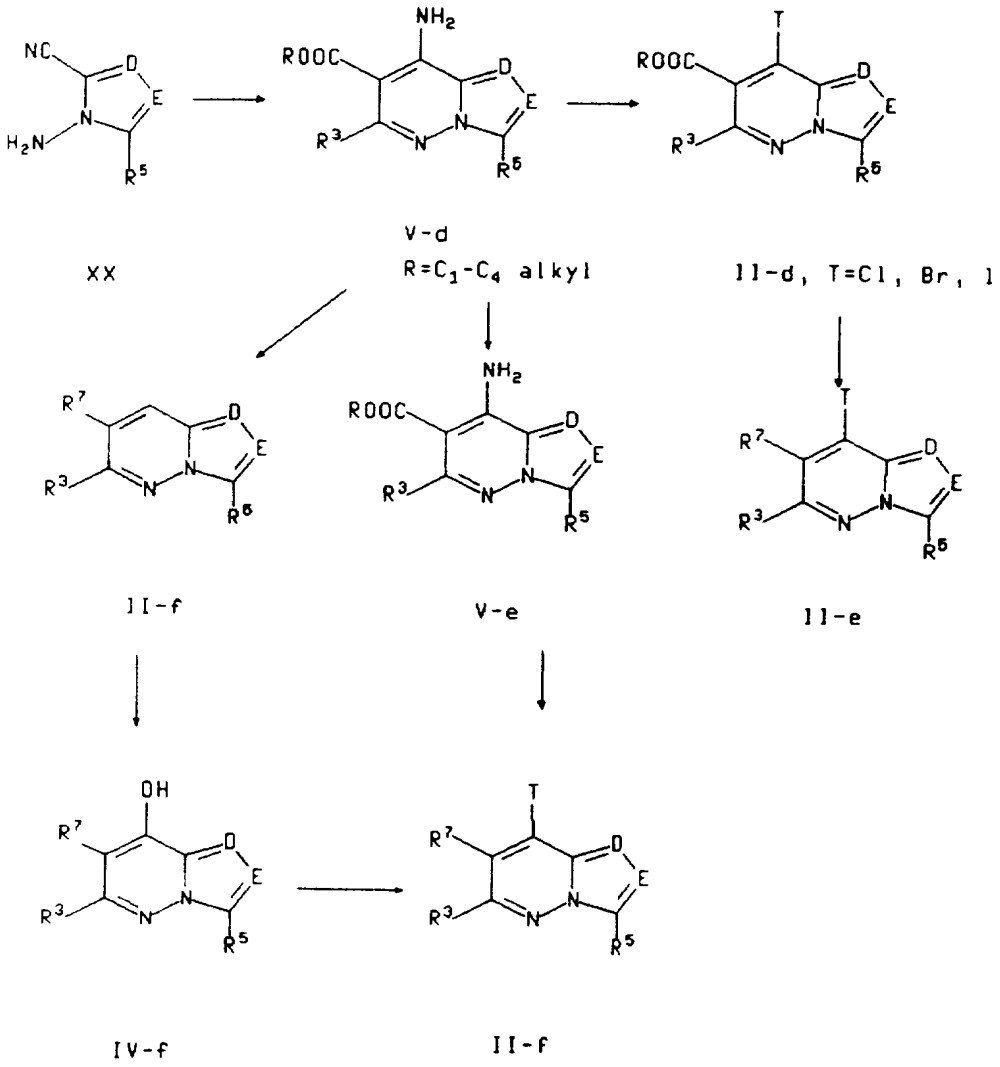
R^{20} = Acetate or CF_3CO

I-V, D = NR^8
I-W, D = O
I-X, D = S

SCHEME 8


XV
Hal = Br, Cl, I
XVI
XVII
XVIII
XIXa, R21 = H
XIXb, R21 = COOH
XIXc, R21 = C(OH)R4
I-G-a
I-6

SCHEME 9


NC
D
E
H_2N
N
R^5
XX
NH_2
ROOC
R^3
V-d
R=C_1-C_4 alkyl
T
II-d, T=Cl, Br, I
R^7
II-f
V-e
II-e
OH
IV-f

Compounds of the formula I wherein B is $-NR^1R^2$ or $-NHCR^1R^2R^{11}$ may be prepared by reacting a compound of the formula II wherein T is chloro, bromo, or iodo with a compound of the formula BH, in the presence of a base, with or without an organometallic compound such as Cu(I)X, wherein X is chloro, bromo or iodo, or an acid (such as p-TsOH (Ts=Tosyl) or another sterically hindered phenol) or an equivalent agent known to those of skill in the art. Suitable solvents for this reaction include DMSO, NMP, dimethylacetamide and THF. An excess of BH may be used as both the reagent and the base. Other bases such as potassium or sodium carbonate, a trialkylamine, a potassium or sodium (C_1-C_4 alkoxide) and sodium hydride may also be used. When R^7 is an electron withdrawing group such as -COO(C_1-C_4alkyl) or CN, the reaction generally is carried out at a temperature between about room temperature and about 100°C. When R^7 is a non-electron withdrawing group, the reaction temperature can generally range from about 50°C to about 270°C and the pressure can generally range from about 4 psi to about 300 psi. A pressure reactor may be used.

Alternatively, the compounds of formula I may be prepared by reacting a compound of the formula II wherein T is bromo or iodo with 1 equivalent or an excess of BH and a base such as sodium or potassium carbonate or a sodium or potassium (C_1-C_4 alkoxide), in the presence of a palladium (II) or a palladium (0) catalyst such as $Pd(OAc)_2$ or $Pd(PPh_3)_4$, together with a racemic or chiral phosphino agent such as 2,2-bis(diphenylphosphino)-1,1-binaphthyl (BINAP). Alternatively, premade Pd(II)(BINAP) may be used in an appropriate inert (i.e., inert with respect to the reaction at hand) solvent such as toluene, xylene, dioxane or sulfolane, at a temperature from about room temperature to about 180°C, preferably at about reflux temperature.

Compounds of the formula I wherein B is $-OCR^1R^2R^{11}$, $-SCR^1R^2R^{11}$, or $-NHCR^1R^2R^{11}$ may be prepared by reacting compounds in the formula II wherein T is chloro, bromo or iodo with a compound of the formula BH in the presence of a base which is capable of deprotonation of BH (e.g., sodium or potassium hydride, or an organometallic base such as sodium diisopropylamide, sodium bis(trimethylsilyl)amide, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, a sodium C_1-C_4 alkoxide or n-butyllithium), in an inert organic solvent such as tetrahydrofuran, acetonitrile, dimethylsulfoxide, acetone, a C_2-C_5 alcohol, chloroform, benzene, xylene, toluene, N,N-dimethylformamide (DMF), methylene chloride, 1-methyl-2-pyrrolidinone or a mixture of

two or more of the above solvents (e.g., DMSO and THF), at a temperature from about 0°C to about 180°C, preferably from about 50°C to about 180°C.

Compounds of the formula I wherein B is $-CR^1R^2R^{11}$, $-C(C=CR^2R^{12})R^1$, $-CR^2R^{11}NHR^1$, $-CR^2R^{11}OR^1$, $-CR^2R^{11}SR^1$, or $-C(O)R^2$ may be prepared from compounds of the formula III wherein W is cyano, formyl or carboxy, as described below.

Reacting compounds of formula III wherein W is cyano with a Grignard reagent containing the group R^2 in an inert solvent such as THF, glyme, ether or dioxane, will yield corresponding compounds of formula I wherein B is $-COR^2$. Further reaction of the compounds of formula I wherein B is COR^2 with a Grignard reagent containing R^1, using a solvent such as those referred to above, will yield the corresponding the compounds of formula I wherein B is $-CR^1R^2OH$. Reacting compounds of formula III wherein W is formyl with a Grignard reagent containing the group R^2, in an ethereal solvent such as those referred to above, will yield the corresponding compounds of formula I wherein B is $-CHR^2OH$.

Compounds of formula I wherein B is $-CR^1R^2R^{11}$ or $-C(C=CR^2R^{11})R^1$ may be prepared by conventional methods. Thus, reaction of a compound of the formula I wherein B is $-CR^{1'}R^{2'}OH$, (wherein $R^{1'}$ and $R^{2'}$ are defined as R^1 and R^2, respectively, except that $R^{1'}$ may not be R^1 and $R^{2'}$ may not be R^2), with an acid such as concentrated sulfuric acid in acetic acid, or a Burgess inner salt such as (carboxysulfamoyl)triethylammonium hydroxide methyl ester, will yield a compound of the formula I wherein B is $-C(=CR^2R^{11})R^1$. Hydrogenation of a compound of formula I wherein B is $-C(=CR^2R^{11})R^1$ using palladium on carbon (Pd/C) or a platinum dioxide catalyst in a (C_1-C_4)alkanol solvent will yield a compound of the formula I wherein B is $-CHR^1R^2$. Reaction of a compound of the formula I wherein B is $-CR^1R^2OH$ with diethylaminosulfur trifluoride or triphenylphosphine/carbon tetrachloride in an inert solvent such as carbon tetrachloride will afford a compound of the formula I wherein B is $-CR^1R^2F$ or $-CR^1R^2Cl$, respectively.

Reduction of a compound of formula I wherein B is $-COR^2$ with sodium borohydride, in an inert solvent such as a (C_1-C_4)alkanol, will yield a compound of the formula I wherein B is $-CHR^2OH$. Alkylation of a compound of the formula I wherein B is $-CHR^2OH$ with an alkyl halide (such as alkyl iodide) in the presence of a base such as sodium hydride (NaH) at room temperature, in an inert solvent such as toluene, THF,

dioxane or ether, will yield the corresponding compound of the formula I wherein B is $-CHR^2OR^1$.

Compounds of the formula I wherein B is $-CR^2R^{10}NHR^1$ may be prepared by conventional methods such as reductive amination of the corresponding compounds of the formula I wherein B is $-C(O)R^2$ with an appropriate amine and reducing agent (such as sodium cyanoborohydride, sodium triacetoxyborohydride, or lithium aluminum tetrahydride) in an appropriate inert solvent such as a C_1-C_4 alkanol or acetic acid.

Conversion of compounds in formula I wherein B is $-C(O)R^2$ into compounds in formula I wherein B is $-C(S)R^2$ can be accomplished using standard methods well known in the art (e.g., using Lawesson's Reagent or diphosphorus pentasulfide (P_2S_5)). Reduction of compounds of the formula I wherein B is $-C(S)R^2$ with a reducing agent such as sodium borohydride or lithium aluminum tetrahydride gives the corresponding compounds of the formula I wherein B is $-CHR^2SH$. Alkylation of compounds of the formula I wherein B is $-CHR^2SH$ with alkyl halide (such as alkyl iodide) in the presence of a base such as sodium hydride in an inert solvent such as THF, DMF or toluene at about room temperature will afford the corresponding compounds of the formula I wherein B is $-CHR^2SR^1$.

Compounds in formula II may be prepared from compounds of the formula IV or V as described below.

Compounds of formula II wherein T is chloro, bromo or iodo can be prepared by reacting compounds of the formula IV with from one equivalent to an excess of POT_3 (wherein T is chloro, bromo or iodo) in the presence or absence of a di(C_1-C_4 alkyl)aniline, preferably diethylaniline, with or without a solvent (such as dichloroethane, DMF, dimethylsulfoxide (DMSO) or acetamide), at a temperature from about room temperature to about 180°C, preferably from about 100°C to about 150°C. Alternatively, compounds of formula II wherein T is chloro, bromo or iodo can be prepared by reacting the corresponding compounds of formula II wherein T is $-O-SO_2CF_3$ with a sodium or potassium halide, in an appropriate inert solvent such as THF, sulfolane, DMSO, DMF or acetonitrile, at a temperature from about 60°C to about 180°C. Compounds of formula II wherein T is $-OSO_2CF_3$ can be prepared by reacting compounds of formula IV with Tf_2O in the presence of a base such as triethylamine or pyridine, in an appropriate inert solvent such as THF, methylene chloride, dioxane,

ether or toluene, at an temperature from about 0°C to about 50°C, preferably from about 0°C to about room temperature.

Alternatively, compounds of formula II wherein T is chloro, bromo or iodo may be prepared by reacting compounds of formula V with a (C_1-C_7 alkyl)-nitrite and Cu(I)T_2 (wherein T is chloro, bromo or iodo) in an appropriate inert solvent such as acetonitrile, acetone, methylene chloride, THF, dioxane, benzene, toluene, dichloroethane, DMF, DMSO or N-methylpyrrolidinone (NMP) at a temperature from about room temperature to about 150°C, preferably from about 40°C to about 100°C.

Compounds of the formula IV may be prepared by reacting the appropriate compounds of formula V with sodium nitrite ($NaNO_2$) in an aqueous acid such as sulfuric acid, acetic acid or phosporic acid, with or without an organic solvent, preferably in acetonitrite (CH_3CN) or acetone.

Compounds of formula III wherein W is cyano can be prepared by reacting the corresponding compounds of formula II wherein T is chloro, bromo or iodo with potassium cyanide, copper cyanide, sodium cyanide or a di(C_1-C_4alkyl)aluminum cyanide in an appropriate inert solvent such as dimethylsulfoxide, DMF, toluene or xylene, at temperature from about room temperature to about 180°C, preferably from about 60°C to about 150°C, with or without Pd(II)OAc or Pd(0)(PPh_3)$_4$.

Compounds of formula III wherein W is -CHO or -COOH may be prepared by reacting compounds in formula II wherein T is bromo or iodo with an organolithium reagent such as t-BuLi, s-BuLi, or n-BuLi in an appropriate inert solvent such as THF, dioxane, ether, benzene or methylene chloride, at temperature from about -120°C to about room temperature, preferably from about -110°C to about -60°C, followed by quenching with an appropriate electrophile such as DMF or CO_2 (gas or dry ice), to give compounds of formula III wherein W is -CHO and -COOH, respectively.

It is understood that the general organic chemistry knowledge can be applied to change the steps of the reaction sequences described herein depending on the feasibility of the reaction. For example, a protecting group may be used at any stage of the various syntheses described above at which it is workable, or an ester group may be reduced to the corresponding C_1-C_4 alkyl group at any convenient stage. Compounds of formulas I - XVIII, wherein R^3 is chloro, bromo, -COO(C_1-C_4 alkyl) or -COOH, can be converted to the corresponding compounds wherein R^3 is (C_1-C_4 alkyl), -O(C_1-C_4 alkyl), fluoro, -S(C_1-C_4 alkyl) at any convenient stage, as appropriate, in the

syntheses referred to above using methods described in the literature. Compounds of formula I - XVIII, wherein R^3 is -O(C_1-C_4 alkyl) or -S(C_1-C_4 alkyl) can be prepared by reacting the corresponding compounds wherein R^3 is chloro, bromo or iodo, with a nucleophile such as a C_1-C_4 alkanol or a C_1-C_4 alkanethiol, in the presence of an organic or inorganic base. Suitable bases for such a reaction include sodium and sodium hydride. Compounds of formulas I - XVIII wherein R^3 is fluoro can be prepared by reacting the corresponding compounds wherein R^3 is chloro with tetrabutylammonium fluoride in a suitable inert solvent such as DMSO, methylene chloride, or tetrahydrofuran. Tetrahydrofuran is preferred.

Reduction of an ester or carboxylic acid using lithium aluminum tetrahydride/aluminum trichloride ($LiAlH_4/AlCl_3$) in an appropriate inert solvent such as THF, ether, or dioxane, at temperature from about 100°C to about room temperature, will afford the corresponding compound wherein R^3 is CH_3. Conversion of compounds wherein B is -COOH to the corresponding compounds wherein B is -CO(C_1-C_3 alkyl) may be accomplished using standard alkylation methods well known in art. Reduction of compounds wherein B is -CO(C_1-C_3 alkyl) using standard methods well known in the art will afford the corresponding compounds wherein R^3 is one of various (C_1-C_4 alkyl) derivatives.

Compounds of the formula IV-a wherein A is CR^7 and G, J, and K are carbon may be prepared by heating compounds of formula VI-a with an appropriate compound of the formula $R^3C(O)CR^7COO(C_1$-C_4 alkyl) under acid or Lewis acid conditions with or without a solvent, as shown in Scheme 1. Examples of such reaction conditions are: a) heating in polyphosphoric acid; b) heating in toluene, benzene or xylene in the presence of acid catalyst (such as p-TsOH, sulfuric acid or HCl(g)) using a Dean-Stark trap; or c) heating in an appropriate solvent such as dichloroethane, diphenylether (Ph_2O) or Dowtherm A in the presence of a Lewis acid such as $SnCl_4$, $ZnCl_2$/HCl or $AlCl_3$.

Compounds of formula VI-a may be prepared using methods described in the scientific literature. (See Gazz. Chim. Ital.; 111, p167-172(1981); Chem. Pharm. Bull.; 24, 3001-3010 (1976); J. Org. Chem., 38, 1777-1780 (1973); Chem. Abstr. 68, 68982f (1968); Aust. J. Chem.; 22, 563-572(1969); J. Chem. Soc. Perkin Trans.2, p1954, p1957 (1972); J. Heterocycl. Chem.; FR, 19, 443-445(1982); J. Heterocycl. Chem., 22,

1496-1502 (1985); Tetrahedron, 47, 4639-4644 (1991); J. Heterocycl. Chem., 28, 2053-2055 (1991); J. Heterocycl. Chem., 29, 251-153 (1992).

Compounds of formula V-a and IV-a', wherein R is C_1-C_4alkyl can be prepared by heating compounds of formula VI wherein W is -CN and -COO(C_1-C_4 alkyl), respectively, with an appropriate $R^3C(O)CH_2COO(C_1$-C_4 alkyl) in the presence of a Lewis acid such as $SnCl_4$, $AlCl_3$, $TiCl_3$ or $ZnCl_2$, in a inert solvent such as dichloroethane, at about the reflux temperature, as shown in Scheme 2. Base hydrolysis of a compound of the formula V-a or IV-a' with sodium hydroxide in H_2O/(C_1-C_4 alcohol) at reflux, or with lithium hydroxide in water/THF or water/dioxane at temperature from about room temperature to about the reflux temperature, followed by decarboxylation by heating in a oil bath at a temperature from about 140-180°C will give a compound of formula V-b or IV-b, respectively. Compounds of the formulas V-a and IV-a' may be converted into compounds of the formula II-a, and compounds of the formulas V-b and IV-b may be converted into compounds of the formula II-b by the procedures described above. The conversion of compounds of the formula II-a into those of the formula II-c can be accomplished using procedures analogous to those described above for converting compounds wherein R^3 is -COO(C_1-C_4 alkyl) into those wherein R^3 is C_1-C_4 alkyl.

Compounds of formula VI may be prepared using methods described in the literature. (See Liebigs Ann Chem., 1534-1546, 1979; Gazz. Chim. Ital., 97, 25-33, 1967; Gazz. Chim. Ital., 120, 725-730, 1990; Eur. J. Med. Chem. Chim. Ther., 26, 143-158, 1991; J. Heterocycl. Che., Fr. 19, 443-445, 1982; J. Heterocycl. Chem., 22, 1496-1502, 1985; J. Heterocycl. Chem., 31, 305-312, 1994; J. Heterocycl. Chem., 24, 243-245, 1987; J. Org. Chem. 57, 3713-3716, 1992; Liebigs Ann Chem., 1702-1710, 1984; Chem. Pharm. Bull., 34, 701-702, 1986; Pharmazie, 48, 849-853, 1993; Bull. Soc. Chim. Belg., 103, 181-184, 1994; and Indian. J. Chem. Sect. B, 33, 436-440, 1994).

Compounds of formula IV-c wherein A is N and G, J, and K are carbon may be prepared, as shown in Scheme 3, by reacting compounds of formula VI with $(R^3CO)_2O$, R^3COOH or $R^3CO(OC_1$-C_2 alkyl)$_3$, in acetic acid or an appropriate inert organic solvent such as toluene, dioxane, acetonitrile, methylene chloride or chloroform, at a temperature from about 25°C to about 150°C, preferably at about the reflux temperature, followed by heating in 85% phosphoric acid or an aqueous acid such as acetic acid, hydrochloric acid or sulfuric acid, preferably in 50-85% phosphoric acid. Compounds of formula V-b may be prepared, as shown in Scheme 3, by heating the

corresponding compounds of formula VI with excess of the appropriate compound of the formula R^3CONH_2.

Compounds of formula IV-d may be prepared, as shown in Scheme 4, by reacting compounds of formula IX with an appropriate reagent having the formula $R^3C(O)CHR^7COO(C_1\text{-}C_4alkyl)$ in an R^3COOH solvent at temperature from about 60°C to about 180°C, preferably at about the reflux temperature.

Compounds of formula I-N may be prepared, as shown in Scheme 5, by reacting the corresponding compounds of formula X with a ($C_1\text{-}C_7$ alkyl)nitrite, with or without $CuBr_2$, $CuCl_2$, or CuI_2, in an appropriate inert solvent such as acetonitrile, acetone, methylene chloride, chloroform, benzene or toluene, preferably acetonitrile at a temperature from about 25°C to about 150°C, preferably from about 60°C to 100°C.

Compounds of formula I-L and I-M may be prepared, as shown in Scheme 6, by reacting compounds of formula XI wherein X is S or O with a compound of the formula R^4CHO or $R^4CH(OC_1\text{-}C_2$ alkyl)$_2$ and an acid catalyst such as p-TsOH, HCl, HBr, H_2SO_4, or HCl, in toluene, xylene or benzene, preferably toluene, with from one to ten equivalents of water, at temperature from about 70°C to about 160°C, using a Dean-Stark trap or in the presence of anhydrous sodium sulfate.

Compounds of formula I-K and I-U may be prepared by reacting the corresponding compounds of formula XI with triphosgene and thiophosgene, respectively, and a base such as triethylamine or pyridine in an appropriate inert solvent such as methylene chloride, THF, dioxane, ether, benzene or chloroform, preferably methylene chloride or dry THF, at temperature from about 0°C to about 25°C.

Compounds of formula I-V, I-W, and I-X may be prepared, as illustrated in Scheme 7, starting from compounds of formula XII. Compounds of formula XIII may be prepared by reacting the corresponding compounds of formula XII with hydroxylamine in acidic (e.g., in trifluoroacetic acid) or basic (e.g., in NaOAc or NaOH and hydroxylamine hydrochloride in a $C_1\text{-}C_4$ alcohol/water mixture) conditions at temperatures from about 25°C to about 150°C, preferably at about the reflux temperature. Compounds of formula XIV can be prepared by heating the corresponding compounds of formula XIII in acetic anhydride, trifluoroacetic anhydride or Tf_2O, with or without a solvent such as acetic acid or methylene chloride, in the presence of an appropriate amine base such as triethylamine or pyridine. Compounds of formula I-V, I-W and I-X may be prepared by heating the corresponding compounds

of formula XIV and pyridine in an inert solvent such as DMF, DMSO, NMP, sulfolane or acetamide at a temperature from about 80°C to about 180°C.

Compounds of formula I-G may be prepared, as illustrated in Scheme 8, by reducing the corresponding compounds of formula XVII. This reduction can be performed using standard methods known in literature for reduction of a nitro group to an amino group. Such methods include hydrogenation or reduction by iron in acetic acid. Cyclization may occur upon reduction or heating in an appropriate solvent such as a C_1-C_4 alcohol, acetonitrile, toluene, THF, methylene chloride or acetic acid.

The conversion of compounds of formula XVI into those of formula XVII can be accomplished using methods analogous to those described above for the conversion of compounds of formula V wherein W is cyano into compounds of formula I wherein B is a group having a carbon atom directly attached to the bicyclic ring. The best method for conversion of a cyano group to a -COOH group is acid hydrolysis, for example, heating the cyano compound in 50-85% phosphoric acid or 50-90% acetic acid, preferably phosphoric acid. The best method for converting a cyano group into a -CO(C_1-C_4 alkyl) is reacting the cyano compound with a Grignard reagent at a temperature from about 0°C to about 25°C in ether, THF or dioxane. The best method for converting a cyano group into a -CHO group is a diisobutylaluminum hydride reduction in THF, dioxane, or ether at a temperature from about -78°C to about 25°C, preferably from about -78°C to about -40°C.

Compounds of the formula XVI may be prepared by reacting compounds of formula XV, wherein Hal is chloro, bromo or iodo, with a sodium, potassium, or lithium salt of R^5CH_2CN in an appropriate inert solvent such as toluene, benzene, a C_1-C_5 alcohol, THF, DMSO, dioxane, or pyridine, with or without a Pd(II) or Pd(0) catalyst, at a temperature from about -78°C to about 130°C.

Alternatively, compounds of formula XVII may be prepared by subjecting compounds of the formula XV to halogen-metal exchange (e.g., using an organo lithium agent such as tBuLi, s-BuLi or BuLi at -78°C in ether, THF, or dioxane), followed by quenching with an electorphile such as R^5CHO, to give compounds of formula XVIII. Compounds of formula XIX-a may be prepared by reacting the corresponding compounds of formula XVIII with thionyl chloride, followed by reduction. Reacting compounds of formula XIX-a with a base (such as organolithium agent (e.g., lithium diisopropylamide or BuLi), followed by quenching with an electrophile (such as carbon

dioxide) will yield the corresponding compounds of formula XIX-b wherein R^{21} is -COOH. Compounds of formula XIX-c wherein R^{21} is -C(OH)R^4 may be prepared in a similar fashion by quenching the appropriate compound of formula XIX-a with an electrophile of the formula C_1-C_3 alkyl-CHO. Compounds of formula XVII can be prepared by reacting compounds of formula XIX-c with PCC (pyridinium chlorochromate) using standard PCC oxidation methods that are well known in the art.

Compounds of formula II-d, II-e and II-f, wherein T is chloro, bromo or iodo and D, E, R^3, R^5 and R^7 are as defined to those in formula I may be prepared, as shown in Scheme 9, by methods analogous to those described in Scheme 2. Alternatively, Compounds of formula II-d to II-f may be prepared using procedures analogous to those described in the literature (See: Pharm. Bull, 5, 229-231, 1957; Monatsh Chem, 100, 671-678, 1969; J. Heterocycl. Chem., 3, 218-220, 1966, Chem. Pharm. Bull,. 23, 2891-2895, 1975; J. Heterocycl. Chem., 8, 1-6, 1971; Justus Liebigs Ann. Chem, 735, 35-44, 1970; Tetrahedron Lett, 1479, 1968; and Chem. Abstr., 1939, 4988.)

The acid addition salts of compounds of the formula can be prepared in a conventional manner by treating a solution or suspension of the corresponding free base with one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration or crystallization techniques can be employed to isolate the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, and related acids.

The compounds of formula I and their pharmaceutically acceptable salts (hereinafter referred to, collectively, as "the active compounds of this invention") may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions, oils (e.g., sesame oil, peanut oil) and various organic solvents. The pharmaceutical compositions formed by combining the novel compounds of formula I and pharmaceutically acceptable carriers can then be readily administered in a variety of dosage forms such as tablets, oil gel, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients

such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, methylcellulose, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions containing an active compound of this invention or a pharmaceutically acceptable salt thereof in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The effective dosages for the active compounds of this invention will depend on the intended route of administration and factors such as the age and weight of the patient, as generally known to a physician. The dosages will also depend on the particular illness to be treated. For instance, the daily dosage for stress-induced illnesses, inflammatory disorders, Alzheimer's disease, gastro-intestinal diseases, anorexia nervosa, hemorrhagic stress and drug and alcohol withdrawal symptoms will generally range from about 0.1 to about 50 mg/kg body weight of the patient to be treated.

Methods that may be used to determine the CRF antagonist activity of the active compounds of this invention and their pharmaceutically acceptable salts are described in Endocrinology, 116, 1653-1659 (1985) and Peptides, 10, 179-188 (1985). The binding activities for compounds of the formula I, expressed as IC_{50} values, generally range from about 0.5 nanomolar to about 10 micromolar. Methods that can be used

to determine the CRF binding protein inhibiting activity of compounds of the formula I are described in Brain Research, (1997), 745 (1,2),248-255.

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples. Melting points are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) and C^{13} nuclear magnetic resonance spectra (C^{13} NMR) were measured for solutions in deuterochloroform ($CDCl_3$) and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

The following abbreviations are used in the Examples: Ph=phenyl; iPr=isopropyl.

EXAMPLE 1

7-(1-Ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine

A solution of 3-pentanol (140 mg, 1.5 mmol) in 1 ml of dry THF was treated with 60% sodium hydride in oil (28 mg, 0.7 mmol) and stirred at room temperature for 10 min. A solution of 7-chloro-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine (75 mg, 0.262 mmol) in 1 ml of dry THF was added and the resulting mixture was heated at reflux for 5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give the crude material. The residue was purified through silica gel column chromatography using 3:7 chcloroform:hexane as eluent to give 75mg (88%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 7.97(s,1H), 6.97(s,2H), 6.03(s,1H), 4.56(m,1H), 2.53(s,3H), 2.32(s,3H), 2.13(s,6H), 2.10(m,4H), 1.09(t,6H) ppm.

EXAMPLE 2

[2,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine

A mixture of 7-Chloro-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a] pyrimidine (60 mg, 0.2 mmol) and 1-ethylpropylamine (4 ml) in 1ml of N-methylpyrrolidinone was heated at 125°C oil bath for 15 hrs. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated and purified through silica gel column chromatography using 20% ethyl acetate in hexane as eluent to give 35 mg of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$) δ

6.96(s,2H), 6.00(d,1H), 5.77(s,1H), 3.47 (m,1H), 2.43(s,3H), 2.32(s,3H), 2.22(s,3H), 2.05(s,6H), 1.5-1.9(m,4H), 1.04(t,6H) ppm.

EXAMPLE 3

(1-Ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine

A mixture of 7-chloro-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a] pyrimidine (190 mg, 0.63 mmol) and 1-ethylpropylamine (4 ml) in 1ml of N-methylpyrrolidinone was heated at 125°C oil bath for 15 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated and purified through silica gel column chromatography using chloroform to 2% methanol in chloroform as eluent to give 195 mg (87%) of the title compound as a green solid. ^{1}H NMR ($CDCl_3$) δ 7.87(s,1H), 6.97(s,2H), 6.12(d,1H), 5.85(s,1H), 3.52(m,1H), 2.48(s,3H), 2.09(s,3H), 2.16(s,6H), 1.6-1.9(m,4H), 1.05(t,6H)ppm.

EXAMPLE 4

7-(1-Ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo [1,5-a]pyrimidine

To a suspension of 60% Sodium hydride in oil (160 mg) in 4 ml of DMSO was added 3-pentanol (853 mg), and then 7-chloro-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl) -pyrazolo[1,5-a]pyrimidine (580 mg) at room temperature. The mixture was heated at 88°C overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated and purified through silica gel column chromatography using 10% hexane in chloroform as eluent to give the title compound as an orange oil. ^{1}H NMR ($CDCl_3$) δ 6.96(s,2H), 5.95(s,1H), 4.52(m,1H), 2.48(s,3H), 2.33(s,3H), 2.27(s,3H), 2.03(s,6H), 1.75-2.00(m,4H), 1.08(t,6H)ppm.

EXAMPLE 5

[2,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethyl-propyl-amine

A mixture of 7-chloro-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a] pyrimidine (200 mg, 0.66 mmol) and N-propylethylamine (2 ml) in 1ml of N-methylpyrrolidinone was heated at 135°C oil bath for 4 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated and purified through silica gel column chromatography using hexane to 10% ethyl acetate in hexane as eluent to give 150 mg of the title compound as a clear

green oil. ^{1}H NMR ($CDCl_3$) δ 6.95(s,2H), 5.80(s,1H), 3.85(q,2H), 3.67(dd,2H), 2.41(s,3H), 2.32(s,3H), 2.21(s,3H), 2.03(s,6H), 1.76(m,2H), 1.29(t,3H), 0.98(t,3H) ppm.

EXAMPLE 6

[6-Bromo-5-bromomethyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b] pyridin-7-yl]-(1-ethyl-propyl)-amine

To a solution of butyl nitrite (119 mg, 1.15 mmol) and CuBr2 (205 mg, 0.919 mmol) in 16 ml of acetonitrile was added N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine (250 mg, 0.766 mmol). The resulting mixture was heated at 65°C for 1.5 hrs. The mixture was cooled to room temperature and 2N HCl (16 ml) was added. The mixture was neutralized with 2N NaOH and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give a brown oil. The oil residue was purified through silica gel column chromatography using 1:1 hexane :ethyl acetate as eluent to give 61mg of [6-bromo-5-bromomethyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b] pyridin-7-yl]-(1-ethyl-propyl)-amine as white crystals. Mp 123-125°C. ^{1}H NMR ($CDCl_3$) δ 7.06(s,2H), 5.53(d,1H), 5.22(m,1H), 4.67(s,2H), 2.39(s,3H), 1.96(s,6H), 1.6-1.9(m,4H), 1.06(t,6H)ppm and 103 mg of [6-bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine as white solid. Mp 115-117°C. ^{1}H NMR ($CDCl_3$) δ 7.04(s,2H), 5.36(d,1H), 5.21(m,1H), 2.64(s,3H), 2.38(s,3H), 1.95(s,6H), 1.6-1.9(m,4H), 1.05(t,6H)ppm.

EXAMPLE 7

(1-Ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b] pyridin-7-yl]-amine

A mixture of butyl nitrite (119 mg, 1.15 mmol) and N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine (250 mg, 0.766 mmol) in anhydrous acetonitrile (16 ml) was heated at 65°C for 2 hours. The mixture was cooled to room temperature and 2N HCl (16 ml) was added. The mixture was neutralized with 2N NaOH and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 250 mg of the crude product as a brown oil. The oil residue was purified through silica gel column using chloroform as eluent to give 201 mg of the title compound as golden yellow solid. Mp 131-133°C. ^{1}H NMR ($CDCl_3$) δ 7.022(s,2H), 6.20(s,1H), 5.44(d,1H), 3.65(m,1H), 2.50(s,3H), 2.36(s,3H), 1.96(s,6H), 1.5-1.8(m,4H), 1.03(t,6H)ppm.

EXAMPLE 8

[6-Bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-methyl-amine

To a solution of [6-bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo [4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine (50 mg, 0.12 mmol) in dry THF)1.5 ml) was added 2.5 M n-BuLi in hexane (0.14 ml) at -78°C. After stirring at -78°C for 10 min, 0.5 ml of methyl iodide was added at that temperature then allowed to warmed to room temperature and stirred for 15 min for 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 46 mg of brown oil. The residue was purified through silica gel coliumn chromatography using 1:1 chloroform:hexane as eluent to give the title compound as a golden oil. ^{1}H NMR ($CDCl_3$) δ 7.04(s,2H), 4.35(m,1H), 3.32(s,3H), 2.70(s,3H), 2.38(s,3H), 1.94(s,6H), 1.7-2.0(m,4H), 1.01(t,6H)ppm.

EXAMPLE 9

7-(1-Ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3] triazolo[4,5-b]pyridine

A mixture of 4-(1-Ethyl-propoxy)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3-diamine (50 mg, 0.153 mmol) and butyl nitrite (24 mg, 0.229 mmol) in 4 ml acetonitrile was heated at 65°C for 2 hours. An additional 0.13 ml of butyl nitrite was added and the resulting mixture was heated at 65°C for 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 58 mg of brown oil. The oil was purified through silica gel column chromatography using 5% ethyl acetate in hexane as eluent to give 46 mg (88%) of the title compound as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.04(s,2H), 6.60(s,1H), 5.26(m,1H), 2.57(s,3H), 2.38(s,3H), 1.94(s,6H), 1.8-2.0(m, 4H), 1.07(t,6H) ppm.

EXAMPLE 10

4-(1-Ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine

To a solution of 3-pentanol (0.09 ml, 0.883 mmol) in dry THF was added 60% NaH in oil (20 mg, 0.500 mmol) and stirred for 5 min. A solution of 4-chloro-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine (50 mg, 0.166 mmol) in dry THF was added to the reaction mixture and the resulting mixture was heated at reflux for 2 hr. The mixture was quenched with water, extracted with ethyl acetate. The

organic layer was washed with brine, separated, dried and concentrated to dryness to give the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 6.92(s,3H), 5.43(m,1H), 4.02(s,3H), 2.56(s,3H), 2.29(s,3H), 2.08(s,6H), 1.80(m,4H), 0.99(t,6H).

The title compounds of Examples 11-14 were prepared by the method analogous to that described in Example 10 starting from of 4-chloro-2-methyl-5-substituted-7-(substituted-phenyl)-5H-pyrrolo[3,2-d]pyrimidine or 7-chloro-5-methyl-1-substituted-3-(substituted-phenyl)-1H-pyrrolo[3,2-b]pyridine and an appropriate alcohol or thiol and a base.

EXAMPLE 11

(+)-2,5-Dimethyl-4-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine.

^{1}H NMR ($CDCl_3$) δ 6.95(s,1H), 6.92(s,2H), 5.88(m,1H), 3.9-4.08(m,4H), 4.01(s,3H), 2.56(s,3H), 2.29(s,3H), 2.2-2.4(m,2H), 2.07(s,6H) ppm.

EXAMPLE 12

2,5-Dimethyl-4-(S)-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine.

^{1}H NMR ($CDCl_3$) δ 6.95(s,1H), 6.92(s,2H), 5.88(m,1H), 3.9-4.08(m,4H), 4.01(s,3H), 2.56(s,3H), 2.29(s,3H), 2.2-2.4(m,2H), 2.07(s,6H) ppm.

EXAMPLE 13

2,5-Dimethyl-4-(1-propyl-butoxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine.

^{1}H NMR ($CDCl_3$) δ 6.93(s,2H), 6.92(s,1H), 5.58(m,1H), 4.02(s,3H), 2.56(s,3H), 2.29(s,3H), 2.09(s,6H), 1.6-1.8(m,4H), 1.4-1.6(m,4H), 0.96(t,6H)ppm.

EXAMPLE 14

4-sec-Butylsulfanyl-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine.

^{1}H NMR ($CDCl_3$) δ 6.97(s,1H), 6.94(s,2H), 4.34(m,1H), 4.13(s,3H), 2.63(s,3H), 2.30(s,3H), 2.07(s,6H), 1.7-1.9(m,2H), 1.48(d,3H), 1.09(t,3H) ppm.

The title compounds of Examples 15-18 were prepared using the following procedure.

PROCEDURE FOR EXAMPLES. 15 - 18

A mixture of 4-chloro-2-methyl-5-substituted-7-(substituted-phenyl)-5H-pyrrolo[3,2-d]pyrimidine or 7-bromo-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-

pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester (1 mmol) and an appropriate amine in DMSO (2 ml) was heated in 130°C oil bath until all the starting material was consumed. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness to give the corresponding 4-alkylamino-2-methyl-5-substituted-7-(substituted-phenyl)-5H-pyrrolo[3,2-d]pyrimidineor 7-alkylamino-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester derivative. Silica gel column chromatography may be used for purification.

EXAMPLE 15

[2,5-Dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]-(1-ethyl-propyl)-amine

^{1}H NMR ($CDCl_3$) δ 6.91(s,2H), 6.76(s,1H), 4.61(d,1H,NH), 4.33(m,1H), 4.04(s,3H), 2.49(s,3H), 2.28(s,3H), 2.09(s,6H), 1.72(m,2H), 1.60(m,2H), 0.98(t,6H)ppm.

EXAMPLE 16

Butyl-[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]-ethyl-amine

^{1}H NMR ($CDCl_3$) δ 6.96(s,1H), 6.92(s,2H), 3.93(s,3H), 3.44(q,2H), 3.40(m,2H), 2.57(s,3H), 2.29(s,3H), 2.09(s,6H), 1.57(m,2H), 1.30(m,2H), 1.14(t,3H), 0.88(t,3H)ppm.

EXAMPLE 17

2,5-Dimethyl-4-thiazolidin-3-yl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine

^{1}H NMR ($CDCl_3$) δ 7.03(s,1H), 6.92(s,2H), 4.78(s,2H), 4.02(s,3H), 3.96(m,2H), 3.18(m,2H), 2.56(s,3H), 2.29(,3H), 2.06(s,6H) ppm.

EXAMPLE 18

7-(1-Ethyl-propylamino)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester

^{1}H NMR ($CDCl_3$) δ 6.98(s,1H), 6.93(s,2H), 5.40(d,1H), 3.97(s,3H), 3.91(s,3H), 3.35(m,1H), 2.57(s,3H), 2.30(s,3H), 2.09(s,6H), 1.52(m,4H), 0.87(t,6H) ppm.

EXAMPLE 19

7-(1-Ethyl-propylamino)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]-pyridine-6-carboxylic acid

A mixture of 7-(1-ethyl-propylamino)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester and NaOH in a 1:1 mixture of

MeOH/water was heated at reflux over night. The resulting mixture was acidified with 2N HCl to a pH of 4-5, and extracted with chloroform. The organic layer was dried and concentrated to give the title compound.

^{1}H NMR ($CDCl_3$) δ 7.02(s,1H), 6.82(s,2H), 3.98(s,3H), 3.78(m,1H), 2.59(s,3H), 2.07(s,3H), 2.00(s,6H), 1.64(m,4H), 0.90(t,6H) ppm.

EXAMPLE 20

[1,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-(1-ethyl-propyl)-amine

A mixture of 7-(1-ethyl-propylamino)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid was heated in 150-160°C oil bath until all the starting material was consumed. ^{1}H NMR ($CDCl_3$) δ 6.94(s,2H), 6.87(s,1H), 6.15(s,1H), 6.10(d,1H), 4.24(s,3H), 3.50(m,1H), 2.64(s,3H), 2.30(s,3H), 2.05(s,6H), 1.77(m,4H), 1.02(t,6H)ppm.

PREPARATION A

4-(2,4,6-Trimethyl-phenyl)-2H-pyrazol-3-ylamine

A mixture of 3-oxo-2-(2,4,6-trimethyl-phenyl)-propionitrile (2.300 g, 12.3 mmol), hydrazine hydrate (0.93 g) and glacial acetic acid (1.55 ml) in 20 ml benzene was heated at reflux for 4.5 hours. Reaction mixture was cooled to room temperature and 50 ml of 18.5% HCl in water was added. The benzene layer was separated and reextracted with 18.5% HCl. The aqueous layer were combined and neutralized with ammonium hydroxide and stirred at rt. overnight. Precipitate formed and was filtered to yield the title compound (0.256 g) as a yellow solid. The benzene layer was concentrated and purified through silica gel column using 5% methanol in chloroform as eluent to give an additional 1.450 g of the title compound; ^{1}H NMR ($CDCl_3$) δ 7.24(s,1H), 6.95(s,2H), 4.75(brs,2H), 2.32(s,3H),2.13(s,6H) ppm.

PREPARATION B

5-Methyl-4-(2,4,6-trimethyl-phenyl)-2H-pyrazol-3-ylamine

The title compound was prepared as white solid by the method analogous to that described in preparation A starting from 3-oxo-2-(2,4,6-trimethyl-phenyl)-butyronitrile. ^{1}H NMR ($CDCl_3$) δ 7.7(brs,1H), 6.96(s,2H), 2.32(s,3H), 2.13(s,3H), 2.06(s,6H) ppm.

PREPARATION C

2,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-4H-pyrazolo[1,5-a]pyrimidin-7-one

Methyl acetoacetate (0.38 ml) was added to a solution of 5-methyl-4-(2,4,6-trimethyl-phenyl)-2H-pyrazol-3-ylamine (641 mg, 2.98 mmol) in 4 ml of acetic acid. The reaction mixture was heated at reflux for overnight. The mixture was concentrated to dryness and the residue was purified through silica gel column chromatography using 5% methanol in chloroform as eluent to give 560 mg (65.5%) of the title compound as a white solid; ^{1}H NMR (DMSO-d_6) δ 11.7(s,1H), 6.98(s,2H), 5.52(s,1H), 2.29(s,3H), 2.20(s,3H), 1.97(s,3H), 1.95(s,6H) ppm.

PREPARATION D

5-Methyl-3-(2,4,6-trimethyl-phenyl)-4H-pyrazolo[1,5-a]pyrimidin-7-one

Methyl acetoacetate (0.7 ml) was added to a solution of 4-(2,4,6-Trimethyl-phenyl)-2H-pyrazol-3-ylamine (1.120 g, 5.57 mmol) in 5 ml of acetic acid and the resulting mixture was heated at reflux for two days. Reaction mixture cooled and a white solid formed. Ethanol (6 ml) was added and stirred at room temperature overnight, filtered to give white solid which was recrystallized from ethanol to give 673 mg(45.2%) of the title compound as white crystals. ^{1}H NMR (DMSO-d_6) δ 11.9(s,1H), 7.7(s,1H), 6.95(s,2H), 5.55(s,1H), 2.25(s,3H), 2.20(s,3H), 2.0(s,6H)ppm.

PREPARATION E

7-Chloro-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine

A suspension of 5-methyl-3-(2,4,6-trimethyl-phenyl)-4H-pyrazolo[1,5-a]pyrimidin -7-one (590 mg, 2.2 mmol) in 9 ml of $POCl_3$ was treated with diethylaniline (0.7 ml) and the resulting mixture was stirred at reflux for 15 hours. The reaction mixture was concentrated to dryness. The residue was treated with ice water and stirred for 20 min, then extracted with chloroform. The organic layer was dried and concentrated to yield an orange oil which crystallized upon standing. The material was purified through silica gel column chromatography using chloroform as eluent to give 590 mg (94%) of the title compound as a yellow solid; ^{1}H NMR ($CDCl_3$) δ 8.08(s,1H), 6.98(s,2H), 6.86(s,1H), 2.56(s,3H), 2.33(s,3H), 2.09(s,6H) ppm.

PREPARATION F

7-Chloro-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine

The title compound was prepared as an oil by the method analogous to that described in preparation E starting from 2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-4H-pyrazolo[1,5-a]pyrimidin-7-one. ^{1}H NMR ($CDCl_3$) δ 6.98(s,2H), 6.77(s,1H), 2.51(s,3H), 2.33(s,3H), 2.31(s,3H), 1.99(s,6H) ppm.

PREPARATION G

2,5-Dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol

A mixture of 3-amino-1-methyl-4-(2,4,6-trimethylphenyl)-1H-pyrrole-2-carbonitrile (0.4 mmol) and acetic anhydride (0.043 ml) in acetic acid (0.01 ml) was heated at reflux untill all the starting material was consumed. The reaction mixture was concentrated to dryness. The residue was quenched with water and extracted with ethyl acetate. The organic extracts was washed with brine and concentrated to dryness. The residue was suspended in 0.5 ml of 85% phosphoric acid and heated at 130°C for 1 hour. The mixture was cooled and poured into ice-water, stirred until solid formed. The solid was filtered to give 2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol. The alternative way for the work up is via extraction technique. The ice water was extracted with chloroform. The organic layer was dried and concentrated to dryness to give the desired product.

^{1}H NMR δ ($CDCl_3$) 6.92(s,2H), 6.88(s,1H), 4.14(s,3H), 2.43(s,3H), 2.29(s,3H), 2.09(s,6H).

The following compounds can be prepared in a similar manner:

2,5-Dimethyl-7-(2,6-dimethyl-4-chloro-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol;

2,5-Dimethyl-7-(2,6-dimethyl-4-bromo-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol;

2-Methyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol;

2-Methyl-7-(2,6-dimethyl-4-chloro-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol;

2-Methyl-7-(2, 6-drimethyl-4-bromo-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol; and

2-Methyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol;

PREPARATION H

4-Chloro-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine

A mixture of 2, 5-dimethyl-7-(2,4,6-trimethylphenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol (1 mmol) in $POCl_3$ (1.3 ml) was heated at reflux until all the starting material were

consumed (about 1-3 hours). The mixture was concentrated to dryness. The residue was porued into ice-water and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness to give the title compound.

^{1}H NMR ($CDCl_3$) δ 7.18(s,1H), 6.95(s,2H), 4.16(s,3H), 2.69(s,3H), 2.31(s,3H), 2.05(s,6H) ppm.

PREPARATION I

7-Amino-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester

A mixture of 3-amino-1-methyl-4-(2,4,6-trimethylphenyl)-1H-pyrrole-2-carbonitrile (2 mmol), methyl acetoacetate (4 mmol) and $SnCl_4$ (4 mmol) in 1, 2-dichloroethane was heated at reflux for about six hours until all the starting material were consumed. The mixture was quenched with acetone, basified with saturated $NaHCO_3$, then filtered through Celite®. The filtrate was concentrated to dryness. The residue was quenched with water and extracted with chloroform. The chloroform layer was washed with brine, dried and concentrated to dryness to give 7-amino-1,5-dimethyl -3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester. The product may be purified by trituration.

^{1}H NMR ($CDCl_3$) δ 6.91(s,2H), 6.85(s,1H), 6.28(brs,2H), 4.10(s,3H), 3.89(s,3H), 2.62(s,3H), 2.28(s,3H), 2.09(s,6H) ppm.

PREPARATION J

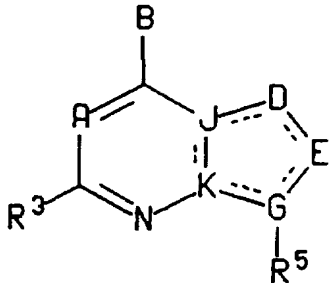
7-Bromo-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester

A mixture 7-amino-1, 5-dimethyl-3-(2, 4, 6-trimethylphenyl)-1H-pyrrolo[3, 2-b]pyridine-6-carboxylic acid methyl ester (1 mmol), n-butylnitrite (BuONO) (1.5 mmol) and $CuBr_2$ in acetonitrile was heated at 60-70°C until all starting material was consumed. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness to give the title compound.

^{1}H NMR ($CDCl_3$) δ 7.09(s,1H), 6.94(s,2H), 4.16(s,3H), 3.98(s,3H), 2.52(s,3H), 2.30(s,3H), 2.04(s,6H) ppm. 2,7-dibromo-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl) -1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester was also produced as a minor component. ^{1}H NMR ($CDCl_3$) δ 7.00(s,2H), 4.45(s,3H), 4.03(s,3H), 2.51(s,3H), 2.34(s,3H), 2.12(s,6H) ppm.

CLAIMS

1. A compound of the formula



I

or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$ $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

J and K are each independently nitrogen or carbon and both J and K are not nitrogens ;

D and E are each selected, independently, from nitrogen, CR^4, C=O, C=S, sulfur, oxygen, CR^4R^6 and NR^8 ;

G is nitrogen or carbon;

the ring containing D, E, G, K, and J in formula I may be a saturated or unsaturated 5-membered ring and may optionally contain one or two double bonds and may optionally contain from one to three heteroatoms in the ring and may optionally have one or two C=O or C=S groups;

R^1 is C_1-C_6 alkyl optionally substituted with one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, -O-(C_1-C_4 alkyl), CF_3, -C(=O)O-(C_1-C_4alkyl), -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, $-NO_2$, -SO(C_1-C_4 alkyl), $-SO_2$(C_1-C_4 alkyl), $-SO_2$NH(C_1-C_4 alkyl) and $-SO_2$N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1-C_4

alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl);

-NR^1R^2 or $CR^1R^2R^{10}$ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, (C_1-C_2 alkylene)-O-(C_1-C_2 alkyl), (C_1-C_2 alkylene)-OH, or -S(C_1-C_4 alkyl);

each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, (C_1-C_2 alkylene)-OH, CF_3, CH_2SCH_3, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl);

R^6 is hydrogen, methyl or ethyl;

R^8 is hydrogen or C_1-C_4 alkyl;

R^5 is phenyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl and wherein each of the foregoing R^5 groups is substituted with from one to four substituents R^{13} wherein one to three of said substituents may be selected, independently, from fluoro, chloro, C_1-C_6 alkyl and -O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, OH, (C_1-C_4 alkylene)-OH, (C_1-C_4alkylene)-O-(C_1-C_2 alkyl), -CN, -CF_3, -NO_2,

$-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_2$ alkyl)$(C_1-C_6$ alkyl), $-OCO(C_1-C_4$ alkyl), $(C_1-C_4$ alkylene)$-O-(C_1-C_4$ alkyl), $-S(C_1-C_6$ alkyl), $(C_1-C_4$ alkylene$)-S-(C_1-C_4$ alkyl), $-C(=O)O(C_1-C_4$ alkyl), $-C(=O)(C_1-C_4$ alkyl), -COOH, $-SO_2NH(C_1-C_4$ alkyl), $-SO_2N(C_1-C_2$ alkyl$)(C_1-C_4$ alkyl), $-SO_2NH_2$, $-NHSO_2(C_1-C_4$ alkyl), $-S(C_1-C_6$ alkyl) and $-SO_2(C_1-C_6$ alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally have one or two double bonds;

R^7 is hydrogen, C_1-C_4 alkyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, $-O(C_1-C_4$ alkyl), $-C(=O)(C_1-C_4$ alkyl), $-C(=O)O(C_1-C_4$ alkyl), $-OCF_3$, $-CF_3$, $-CH_2OH$ or $-CH_2O(C_1-C_2$ alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1-C_4 alkyl; and

with the proviso that: a) when both J and K are carbons and D is CR^4 and E is nitrogen, then G can not be nitrogen; (b) when both J and K are carbons and D and G are nitrogens, then E can not be CR^4 or C=O or C=S; (c) when both J and K are carbons and D and E are carbons, then G can not be nitrogen; (d) when G is carbon, it must be double banded to E; and (e) in the ring containing J, K, D, E and G, there can not be two double bonds adjacent to each other;

and the pharmaceutically acceptable salts of such compounds.

2. Compounds according to claim 1 wherein B is $-NR^1R^2$, $-NHCHR^1R^2$, $-OCHR^1R^2$ and R^1 is C_1-C_6 alkyl, which may optionally be substituted with one fluoro, or C_1-C_4 alkoxy group and which may optionally contain one double or triple bond; and R^2 is C_1-C_4 alkyl or $(C_1-C_2$ alkyl$)$-CO-$(C_1-C_2$ alkyl) which may optionally contain one double or triple bond.

3. Compounds according to claim 1, wherein B is $-CHR^1R^2$, $-NR^1R^2$, $-NHCHR^1R^2$, $-OCHR^1R^2$, $-SCHR^1R^2$; and R^1 is C_1-C_6 alkyl, which may optionally be substituted with one hydroxy, fluoro, CF_3, cyclopropyl or C_1-C_4 alkoxy group and which may optionally contain one double or triple bond; and R^2 is benzyl or C_1-C_6 alkyl, which may optionally contain one double or triple bond, wherein said C_1-C_6 alkyl and the phenyl moiety of said benzyl may optionally be substituted with one fluoro, hydroxy, CF_3, cyclopropyl, C_1-C_2 alkyl, C_1-C_2 alkoxy or chloro group.

4. Compounds according to claim 1 wherein R^3 is methyl.

5. Compounds according to claim 1 wherein R^4, R^6, R^8, R^9, and R^{12} are hydrogen or methyl.

6. Compounds according to claim 1 wherein R^5 is di- or tri-substituted phenyl in which the two or three substitutents are independently selected from C_1-C_4 alkyl, O-(C_1-C_4 alkyl), (C_1-C_4 alkylene)-O-(C_1-C_4alkyl), CF_3, OCF_3, CHO, (C_1-C_4alkylene)-OH, cyano, chloro, fluoro, bromo and iodo, wherein each of the forgoing (C_1-C_4) alkyl groups may optionally contain one double or triple bond.

7. Compounds 1 wherein R^3 is methyl, ethyl, chloro or methoxy; and each of R^4, R^6, R^8, R^9, and R^{12} is, independently, hydrogen, methyl or ethyl.

8. Compounds wherein R^5 is di- or tri-substituted pyridyl, or pyrimidyl in which the two or three substitutents are independently selected from C_1-C_4 alkyl, O-(C_1-C_4 alkyl), (C_1-C_4 alkylene)-O-(C_1-C_4 alkyl), CF_3, OCF_3, CHO, (C_1-C_4 alkylene)-OH, cyano, chloro, fluoro, bromo and iodo, wherein each of the forgoing (C_1-C_4) alkyl groups may optionally contain one double or triple bond.

9. Compounds according to claim 1 wherein A is N, CH or CCH_3.

10. Compounds according to claim 1 wherein A is CH, J and K are carbon and D, E, and G are nitrogen.

11. Compounds according to claim 1 wherein J and D are nitrogen, and K and G are carbon, and E is CH, CCH_3 or CC_2H_5.

12. Compounds according to claim 1 wherein J and K are carbon, and D--EG is O-$C(CH_3)$=C, O-CH=C, S-$C(CH_3)$=C, S-CH=C, N(CH_3)-$C(CH_3)$=C, NHC(CH_3)=C, NHC(CH_3CH_2)=C, N(CH_3)-CH=C, O-N=C, S-N=C, N(CH_3)-N=C, O-CH_2N or S-CH_2N.

13. A compound according to claim 1 wherein B is -CHR^1R^2, -$NCHR^1R^2$ or -$OCHR^1R^2$, and the CHR^1R^2 group of B is a cyclopentane ring, a tetrahydrofuran ring or a tetrahydrothienyl ring.

14. A compound according to claim 1 wherein the NR^1R^2 group of B is a five membered saturated or unsaturated heterocyclic ring.

15. A compound according to claim 14 wherein the NR^1R^2 is a pyrrolo ring, a pyrrolidino ring, a thiazolidino ring or a morpholino ring.

16. A pharmaceutical composition for the treatment, prevention or inhibition of (a) 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, or (b) 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, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer;diarrhea; stress-induced fever; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; 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; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., 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; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; and hypoglycemia in a mammal, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder, and a pharmaceutically acceptable carrier.

17. A method for the treatment, prevention or inhibition of (a) 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, or (b) 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 premenstrual syndrome, and

postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; 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; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., 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; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; and hypoglycemia in a mammal, comprising administering to a subject in need of said treatment an amount of a compound according to claim 1, that is effective in treating such disorder.

18. A method of treating or preventing a disorder or condition, the treatment or prevention of which can be effected or facilitated by inhibiting CRH binding protein in a mammal, comprising administering to said mammal a CRH binding protein inhibiting amount of a compound according to claim 1.

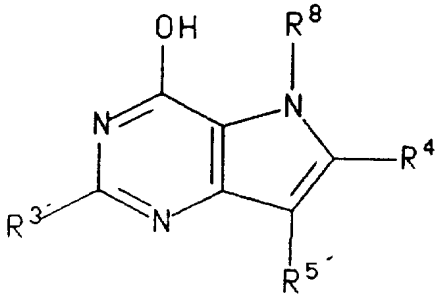
19. A pharmaceutical composition for treating or preventing a disorder or condition, the treatment or prevention of which can be effected or facilitated by inhibiting CRH binding protein in a mammal, comprising a CRH binding protein inhibiting amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

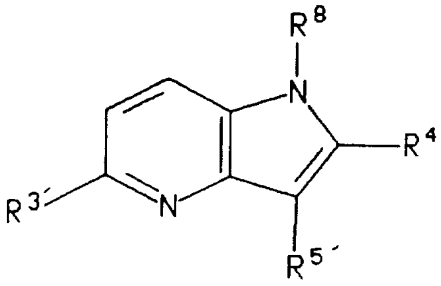
20. A compound according to claim 11 or 12 wherein A is N or CH, R^3 is methyl and each R^4, R^6, R^8, R^9 and R^{12} is, independently, hydrogen or methyl.

21. A compound according to claim 20, wherein R^5 is di- or tri-substituted phenyl, wherein the two or three substitutents are independently selected from C_1-C_4

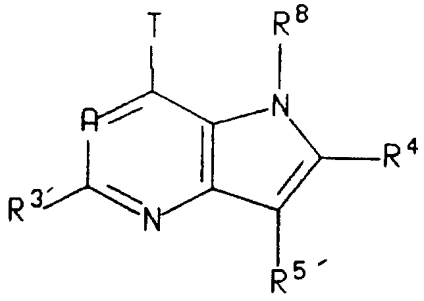
alkyl, O-(C_1-C_4 alkyl), (C_1-C_4 alkylene)-O-(C_1-C_4alkyl), CF_3, OCF_3, CHO, (C_1-C_4alkylene)-OH, cyano, chloro, fluoro, bromo and iodo, wherein each of the forgoing (C_1-C_4) alkyl groups may optionally contain one double or triple bond.

22. A compound of the formula





or



wherein $R^{3'}$ is C_1-C_4 alkyl, $R^{7'}$ is hydrogen, methyl, chloro, bromo, -COOH or -COO(C_1-C_4 alkyl), T is chloro, bromo, iodo or triflate, R^8 is hydrogen or C_1-C_4 alkyl and R^4 is hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, (C_1-C_2 alkylene)-OH, CF_3, CH_2SCH_3, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl);

23. A compound according to claim 1 wherein said compound is:

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;

[2,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;

(1-Ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

7-(1-Ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;

[2,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethyl-propyl-amine;

[6-Bromo-5-bromomethyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

(1-Ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-amine;

[6-Bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-methyl-amine;

7-(1-Ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridine;

4-(1-Ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;

(±)-2,5-Dimethyl-4-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo-[3,2-d]pyrimidine;

2,5-Dimethyl-4-(S)-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo-[3,2-d]pyrimidine;

2,5-Dimethyl-4-(1-propyl-butoxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine; or

4-sec-Butylsulfanyl-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;

or a pharmaceutically acceptable salt of such compound.

INTERNATIONAL SEARCH REPORT

Intern. ial Application No
PCT/IB 97/00922

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 C07D471/04 A61K31/505 A61K31/435
//(C07D487/04,239:00,231:00),(C07D471/04,249:00,221:00),
(C07D487/04,239:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 33750 A (PFIZER) 14 December 1995 see claims 1,13 ---	1,16
P,X	WO 96 35689 A (NEUROGEN) 14 November 1996 see page 3, line 18 - line 25; claim 1; examples IE,II,ID -----	1,16,22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 1997	04. 11. 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	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ational application No.
PCT/IB 97/00922

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 17 and 18
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr. ial Application No
PCT/IB 97/00922

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9533750 A	14-12-95	AU 2453095 A	04-01-96
		BR 9502708 A	30-04-96
		EP 0764166 A	26-03-97
		FI 964894 A	05-12-96
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		CA 2194756 A	14-11-96
		EP 0770080 A	02-05-97

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(71) Applicants *(for all designated States except US)*: JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). NEUROCRINE BIOSCIENCES INC. [US/US]; 3050 Science Park Road, San Diego, CA 92121-1102 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CHEN, Chen [CN/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). WEBB, Thomas, R. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). McCARTHY, James, R. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). MORAN, Terence, J. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). WILCOXEN, Keith, M. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US).

(74) Agent: WANTE, Dirk; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).

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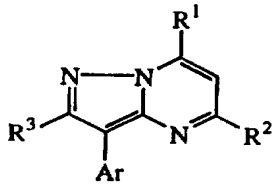
(54) Title: PYRAZOLOPYRIMIDINES AS CRF RECEPTOR ANTAGONISTS

(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).

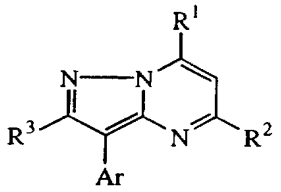
Accordingly, clinical data suggest that CRF receptor antagonists may represent novel antidepressant and/or anxiolytic drugs that may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF.

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.

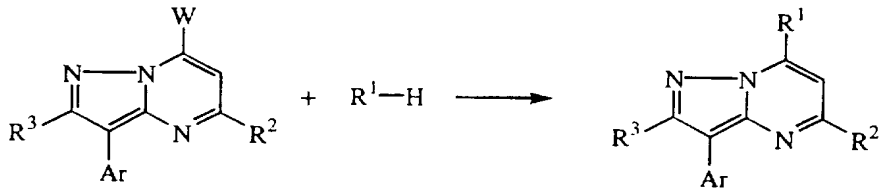
Preferred compounds are those compounds of formula (I) wherein R^1 is NR^4R^5 and R^4 is C_{3-4}alkyl or allyl, preferably propyl; R^5 is C_{2-4}alkyl, allyl or cyclopropylmethyl, preferably propyl; R^2 is methyl; R^3 is hydrogen, methyl or methylthio, preferably

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.

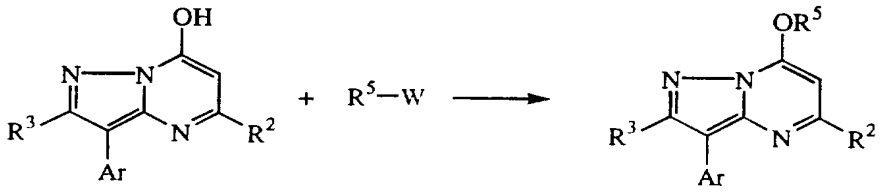
The compounds of the present invention can generally be prepared by alkylating a pyrazolopyrimidine of formula (II) with an intermediate of formula (III). In intermediate (II), W is an appropriate leaving group such as halo, e.g. chloro, bromo, or a sulfonyloxy group, e.g. a mesyloxy or a tosyloxy group.



(II) (III) (I)

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.

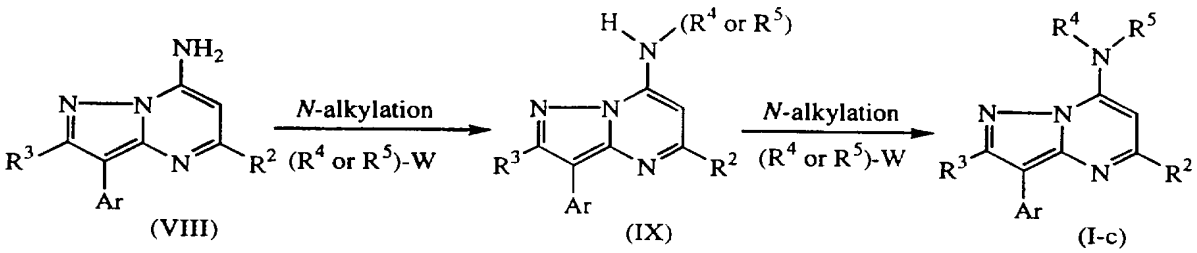
Also, compounds of formula (I) wherein R^1 is OR^5 , said compounds being represented by formula (I-a), may be prepared by *O*-alkylating an intermediate of formula (VI) with an intermediate of formula (VII), wherein W is as defined above.



(VI) (VII) (I-a)

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.



(VIII) (IX) (I-c)

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.

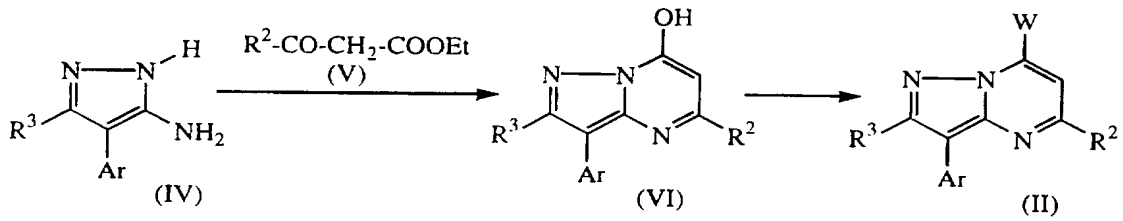
The compounds of formula (I) wherein R^3 is C_{1-6}alkylthio can be converted into compounds of formula (I) wherein R^3 is C_{1-6}alkylsulfonyl or C_{1-6}alkylsulfoxy by an oxidation reaction, e.g. treatment with a peroxide such as 3-chloroperbenzoic acid in a reaction-inert solvent, e.g. dichloromethane. 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.

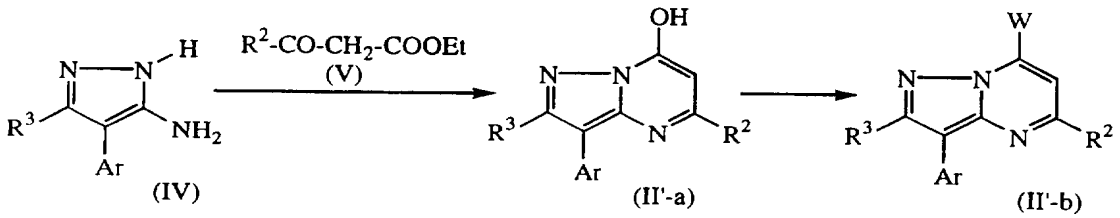
Intermediates of formula (II) can be prepared according to the procedure as described in Robins et al., *J. Heterocyclic Chem.* 22:601-634, 1985.



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).

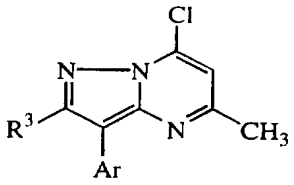
b) A mixture of intermediate 7 and hydrazine hydrobromide (100 mmol) was dissolved in ethanol/water (9:1, total 100 ml) and refluxed for 1 hour. The reaction mixture was concentrated and the residue was partitioned between ethyl acetate and sodium bicarbonate solution. The combined extracts were dried 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

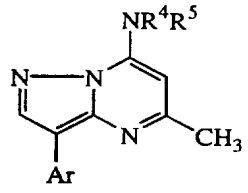
To a solution of compound 56 (100 mg) in a mixture of concentrated HCl (1 ml) and water (1 ml), cooled in an ice bath, was added a solution of sodium nitrite (21 mg) in water (1 ml). The solution was added to a mixture of copper(I)chloride (281 mg) in concentrated HCl with stirring in an ice bath. A 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.

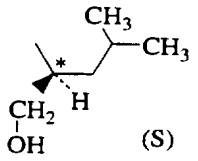
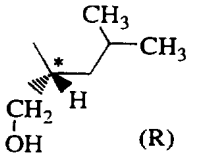
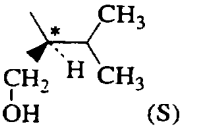
Example B.10

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.

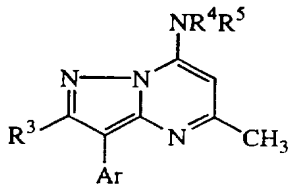
Table 2 :



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 :



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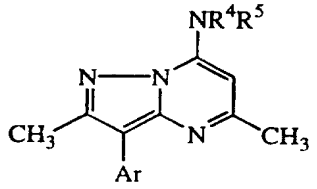
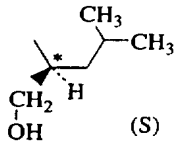
Co. No.	Ex. No.	R^3	R^4	R^5	Ar
30	B.1	CH_3S	hydrogen	n-propyl	2,4-dichlorophenyl
31	B.1	CH_3S	hydrogen	2-propyl	2,4-dichlorophenyl

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

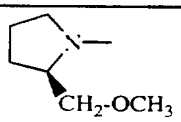
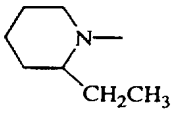
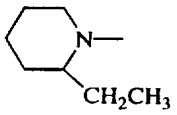
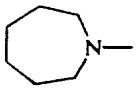
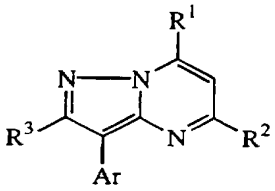
Co. No.	Ex. No.	R^4 and R^5 taken together	Ar
128	B.1		4-chlorophenyl
129	B.1		4-chlorophenyl
130	B.1		6-dimethylamino-4-methyl-3-pyridinyl
131	B.1		6-dimethylamino-4-methyl-3-pyridinyl

Table 5 :



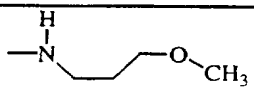
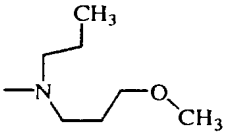
Co. No.	Ex. No.	R^1	R^2	R^3	Ar
46	B.4		n-C_4H_9	H	2,4-dichlorophenyl
47	B.4		n-C_4H_9	H	2,4-dichlorophenyl
50	B.3	CH_3CH_2O-	CH_3	CH_3-S-	2,4-dichlorophenyl

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

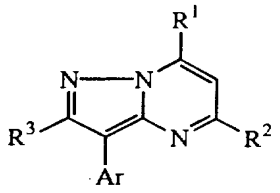
1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I. The solution was cooled to room temperature and supplemented 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;

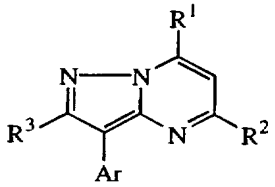
the stereochemically isomeric forms, or the pharmaceutically acceptable acid addition salts thereof.

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.

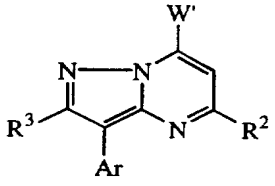
10. The use of compounds of formula



(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).

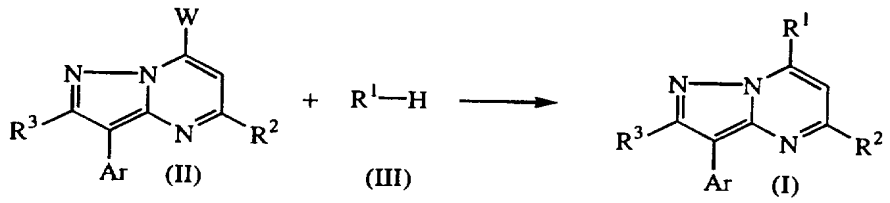
11. A compound of formula (II') wherein the radicals R^2, R^3 and Ar are as defined in any of claims 1 to 5 and radical W' is hydroxy, halo, mesyloxy or tosyloxy; a stereoisomeric form or an acid addition salt form thereof, with the proviso that compounds wherein Ar is unsubstituted phenyl are not included.



(II')

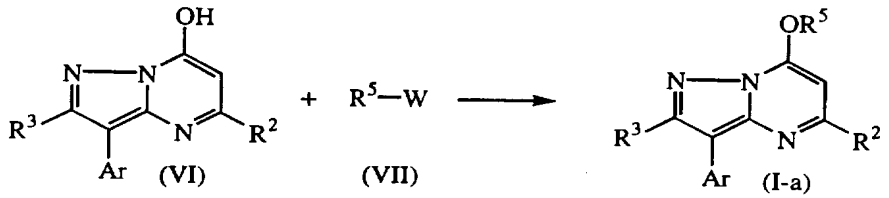
12. A process of preparing a compound as claimed in claim 1, characterized by

a) reacting an intermediate of formula (II) with an intermediate of formula (III) in a reaction-inert solvent,



(II) (III) (I)

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,



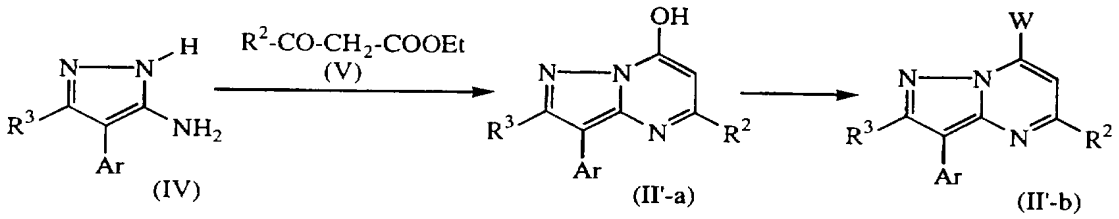
(VI) (VII) (I-a)

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 Applicaton No
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A. CLASSIFICATION OF SUBJECT MATTER
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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)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 61 057 587 A (SHIONOGI AND CO., LTD., JAPAN) 1986 cited in the application & CHEMICAL ABSTRACTS, vol. 105, no. 25, 22 December 1986 Columbus, Ohio, US; abstract no. 226617e, see abstract ---	1
X	JP 42 011 753 A (SHIONOGI AND CO., LTD.) 1967 cited in the application see the whole document & CHEMICAL ABSTRACTS, vol. 67, no. 23, 4 December 1967 Columbus, Ohio, US; abstract no. 108663r, see abstract --- -/--	1

[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

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" 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
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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

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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		CA 2150709 A	23-06-94
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(71) Applicants *(for all designated States except US)*: **SB PHARMCO PUERTO RICO INC** [US/US]; The Prentice Hall Corp. System of PR Inc, c/o FGR Corporate Services Inc, BBV Tower 8th Floor, 254 Munoz Rivera Avenue, San Juan, PUERTO RICO 009 (US). **NEUROCRINE BIOSCIENCES INC** [US/US]; 12790 El Camino Real, San Diego, California 92130 (US).

(71) Applicant *(for MG only)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SLEE, Deborah** [US/US]; Neurocrine Biosciences Inc, 12790 El Camino Real, San Diego, California 92130 (US). **GRIGORIADIS, Dimitri** [CA/US]; Neurocrine Biosciences Inc, 12790 El Camino Real, San Diego, CA 92130 (US). **WILLIAMS, John** [US/US]; Neurocrine Biosciences Inc, 12790 El Camino Real, San Diego, CA 92130 (US).

(74) Agent: **DOLTON, Peter**; GlaxoSmithKline, CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

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(54) Title: CRF RECEPTOR ANTAGONISTS, THEIR PREPARATIONS, THEIR PHARMACEUTICAL COMPOSITION AND THEIR USES

(57) Abstract: CRF receptor antagonists are disclosed which have utility in the treatment of a variety of disorders, including the treatment of disorders manifesting hypersecretion of CRF in a warm-blooded animals. CRF receptor antagonists which are labeled with a positron emitting isotope for use in PET are also disclosed.

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CRF RECEPTOR ANTAGONISTS, THEIR PREPARATION, THEIR PHARMACEUTICAL COMPOSITION AND THEIR USES

TECHNICAL FIELD

This invention relates generally to CRF receptor antagonists their preparation, their pharmaceutical composition and their uses. CRF receptor antagonists are disclosed which have utility in the treatment of a variety of disorders, including the treatment of disorders manifesting hypersecretion of CRF in a warm-blooded animals. CRF receptor antagonists which are labeled with a positron emitting isotope for use in PET are also disclosed.

BACKGROUND OF THE INVENTION

Positron Emission Tomography (PET) is a non-invasive imaging technology where a compound labeled with a positron-emitting isotope is administered to provide an in-situ image of the binding of the positron-emitting compound. The image can be used to determine localization and quantification of specific areas where the labeled compound binds providing diagnostic and drug discovery applications. Positron emitting isotopes generally used for PET include ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{76}Br and ^{124}I. The ^{13}N and ^{15}O isotopes have very short half lives limiting their usefulness. ^{76}Br and ^{124}I have half lives of 16.3 hours and 4.2 days respectively which would allow easy production of labeled CRF antagonists but the addition of the large halogen group changes the activity of the compound and adds unwanted lipophilicity. ^{11}C has a relatively short 20.5 minute half life but ease of incorporating ^{11}C into a PET compound makes this a useful isotope. ^{18}F has a half life of 110 minutes which allows sufficient time for incorporation of the isotope into a tracer, purification and administration into a subject.

The incorporation of a positron emitting isotope into a Corticotropin-releasing factor (CRF) antagonist may allow for the use of PET imaging in determining the binding of labeled antagonists to CRF receptors. CRF is a 41 amino acid peptide which has been found to produce profound alterations in endocrine, nervous and immune

system function. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotropic hormone ("ACTH"), ß-endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (Vale et al., *Science 213*:1394-1397, 1981). The CRF receptor is coupled to a GTP-binding protein (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. 278*:332, 1983), stimulation of the sympathoadrenomedullary pathway (Brown et al., *Endocrinology 110*:928, 1982), an increase of heart rate and blood pressure (Fisher et al., *Endocrinology 110*:2222, 1982), an increase in oxygen consumption (Brown et al., *Life Sciences 30*:207, 1982), alteration of gastrointestinal activity (Williams et al., *Am. J. Physiol. 253*:G582, 1987), suppression of food consumption (Levine et al., *Neuropharmacology 22*:337, 1983), modification of sexual behavior (Sirinathsinghji et al., *Nature 305*:232, 1983), and immune function compromise (Irwin et al., *Am. J. Physiol. 255*:R744, 1988). Furthermore, clinical data suggests that CRF may be hypersecreted in the brain in depression, anxiety-related disorders, and anorexia nervosa. (DeSouza, *Ann. Reports in Med. Chem. 25*:215-223, 1990). Accordingly, clinical data suggests that CRF receptor antagonists may represent

novel antidepressant and/or anxiolytic drugs that may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF.

The administration of CRF antagonist which has been labeled with a positron emitting isotope may permit the use of PET imaging to provide an in situ evaluation of the labeled antagonist's binding characteristics in the brain. The antagonist should possess several characteristics such as specific binding to CRF receptors, high brain penetration and the ability to be labeled with a positron emitting isotope as the ultimate step in the synthesis.

U.S. Patent Nos. 6,514,982, 6,531,475, 6,664,261 and PCT application WO98/03510 describe CRF antagonists for use in treating various CRF mediated diseases. The synthesis of certain pyrrolopyrimidines as PET ligands for the CRF receptor has also been described. (L. Martarello et al., *Nuclear Medicine and Biology*, **28** (2001) 187-195).

While significant strides have been made toward achieving CRF regulation through administration of CRF receptor antagonists, there remains a need in the art for effective small molecule CRF receptor antagonists. There is also a need for pharmaceutical compositions containing such CRF receptor antagonists, as well as methods relating to the use thereof to treat, for example, stress-related disorders. The used of CRF antagonists bearing a Positron emitting isotope as diagnostic and drug discovery tools is also addressed. The present invention fulfills these needs, and provides other related advantages.

SUMMARY OF THE INVENTION

In brief, this invention is generally directed to CRF receptor antagonists 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(S)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-{2-fluoroethyl}amino)pyrazolo[2,3-a]pyrimidine and 6-(cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-(S)-ethyl-7,8-dihydro-4-methyl-6H-

1,3,6,8a-tetraazaacenaphthylene, including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof.

The CRF receptor antagonists of this invention may be radiolabeled and have utility as diagnostic agents, research agents and agents useful in drug development and evaluation. These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain procedures, compounds and/or compositions, and are hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to compounds useful as corticotropin-releasing factor (CRF) receptor antagonists and as PET ligands.

In a first embodiment, the CRF receptor antagonists of this invention are taken from 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(S)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-{2-fluoroethyl}amino)pyrazolo[2,3-a]pyrimidine and 6-(cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-(S)-ethyl-7,8-dihydro-4-methyl-6H-1,3,6,8a-tetraazaacenaphthylene.

In another embodiment, the CRF antagonist is labeled with a positron emitting isotope to allow for imaging of the antagonist by PET. The isotope is generally taken from ^{11}C and ^{18}F as these isotopes may generally be added as the last step of a synthesis, may be purified quickly and may be administered to a subject, generally in intravenous form.

The compounds of the present invention may generally be utilized as the free base. Alternatively, the compounds of this invention may be used in the form of acid addition salts. Acid addition salts of the free base amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic,

ascorbic, succinic, methanesulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Thus, the term "pharmaceutically acceptable salt" of structure (I) is intended to encompass any and all acceptable salt forms.

In general, the compounds of the present invention may be made according to the organic synthesis techniques known to those skilled in this field, as well as by the representative methods set forth in the Examples.

The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention are capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of the present invention may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (*J. Neuroscience 7*:88, 1987) and Battaglia et al. (*Synapse 1*:572, 1987). As mentioned above, suitable CRF antagonists include compounds which demonstrate CRF receptor affinity. CRF receptor affinity may be determined by binding studies that measure the ability of a compound to inhibit the binding of a radiolabeled CRF (*e.g.*, [^{125}I]tyrosine-CFR) to its receptor (*e.g.*, receptors prepared from rat cerebral cortex membranes). The radioligand binding assay described by DeSouza et al. (*supra*, 1987) provides an assay for determining a compound's affinity for the CRF receptor. Such activity is typically calculated from the 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)).

The CRF receptor antagonists of the present invention demonstrate activity at the CRF receptor site, and may be used as therapeutic agents for the treatment of a wide range of disorders or illnesses including endocrine, psychiatric, and neurological disorders or illnesses. More specifically, the CRF receptor antagonists of 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), pain, Cushing's disease, infantile spasms, epilepsy and other seizures in both infants and adults, and various substance abuse and withdrawal (including alcoholism).

Additional uses of the PET labeled CRF receptor antagonists of the present invention include use in clinical research and diagnosis of various disease states involving the CRF receptor. The labeled CRF receptor antagonists may also useful in the study of pharmacology, drug pharmacokinetics, pharmacodynamics, biodistribution and metabolism (Victor Pike, *Drug Information Journal*, **31** (1997), 997-1013).

In another embodiment of the invention, pharmaceutical compositions containing one or more CRF receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a CRF receptor antagonist of the present invention (*i.e.*, a compound of structure (I)) and a pharmaceutically acceptable carrier and/or diluent. The CRF receptor antagonist is present in the composition in an amount which is effective to treat a particular disorder--that is, in an amount sufficient to achieve CRF receptor antagonist activity, and preferably with acceptable toxicity to the patient. Preferably, the pharmaceutical compositions of the present invention may include a CRF receptor antagonist in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more preferably from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a CRF receptor antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the CRF receptor antagonist in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, PA 1990.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (I) in

vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound.

In another embodiment, the present invention provides a method for treating a variety of disorders or illnesses, including endocrine, psychiatric and neurological disorders or illnesses. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the disorder or illness. Such methods include systemic administration of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of CRF receptor antagonists include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention 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, pain, Cushing's disease, infantile spasms, epilepsy, and substance abuse or withdrawal.

The following examples are provided for purposes of illustration, not limitation.

EXAMPLES

The CRF receptor antagonists of this invention may be prepared by the methods disclosed in Examples 1 to 4. Example 5 presents a method for determining the receptor binding affinity.

Analytical HPLC-MS (LC-MS)

HP 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (electrospray);

HPLC column: YMC ODS AQ, S-5, 5μ, 2.0 x50 mm cartridge;

HPLC gradients: 1.5 mL/minute, from 10 % acetonitrile in water to 90 % acetonitrile in water in 2.5 minutes, maintaining 90 % for 1 minute.

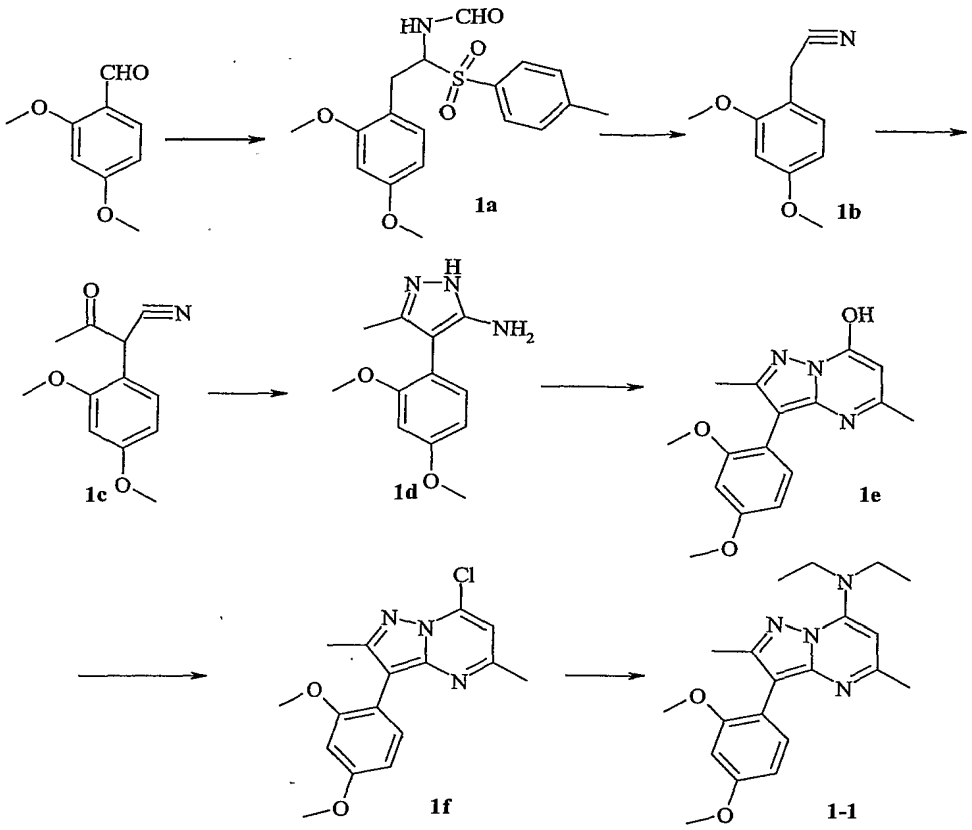
Prep. HPLC-MS

Gilson HPLC-MS equipped with Gilson 215 auto-sampler/fraction collector, an UV detector and a ThermoFinnigan AQA Single QUAD Mass detector (electrospray);

HPLC column: BHK ODS-O/B, 5 μ, 30x75 mm

HPLC gradients: 35 mL/minute, 10 % acetonitrile in water to 100 % acetonitrile in 7 minutes, maintaining 100 % acetonitrile for 3 minutes.

EXAMPLE 1



Step 1A:

A suspension of potassium t-butyloxide (7.3 g, 65 mmol, 1.4 eq) in 1,2-dimethoxyethane (DME, 40 mL) was chilled to –50 °C under nitrogen. Tosylmethyl isocyanide (9.1 g, 46.5 mmol, 1 eq) in 40 mL DME was added dropwise while the temperature was kept below –50 °C. 2,4-Dimethoxybenzaldehyde (7.7 g, 46.5 mmol, 1 eq) was added dropwise and the reaction mixture was stirred for 30 minutes to give compound **1a**. MeOH (100mL) was added and the mixture was refluxed for 30 minutes. Most of the DME and MeOH were removed, the residue was resuspended in water (100 mL) and ethyl acetate (100 mL). Following neutralization with acetic acid, the organic layer was washed with brine and dried under sodium sulfate, concentrated and purified by silica gel column using 25% ethyl acetate in hexane to yield 5.5g of **1b** as a white solid.

Step 1B:

To 2, 4-dimethoxyphenylacetonitrile **1b** (36.0 g, 204 mmol, 1 equiv.) in dry THF (300 mL) was added 12 g (510 mmol, 2.5 equiv) of 60% NaH portionwise. A few drops of EtOAc were added and the reaction was heated gently to initiate the reaction. The remaining EtOAc (150 mL) was then added dropwise. After 2 hours the reaction was poured into ice water and was washed with ether. The aqueous layer was acidified to pH = 6 and was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated in vacuo to give 44.2 g of **1c**.

Step 1C:

A mixture of **1c** (8.17 g, 37.3 mmol) and hydrazine monohydrobromide (15.3 g, 135.4 mmol) was refluxed in EtOH/H_2O (6:1) for 5 h. After evaporation of EtOH, the residue was extracted with EtOAc and water. The organic phase was dried and evaporated to dryness to give **1d**.

Step 1D:

A mixture of the compound **1d** (6.5 g, 27.9 mmol) was refluxed with ethyl acetoacetate (5.0 mL) in acetic acid (100 mL) for 3 h. After evaporation of AcOH, ethyl ether was added and **1e** (10.4 g) was obtained after filtration through a medium fritted funnel. In place of the acetic acid solvent, the reaction may be refluxed in dioxane (50 mL) overnight followed by addition of ether to precipitate the product.

Step 1E:

To a suspension of compound **1e** (1.9 g, 6.3 mmol) in acetonitrile was added $POCl_3$ (2.2 mL, 24.1 mmol). The suspension was heat to reflux for 5 h. The resulting orange solution was cooled to room temperature and poured onto ice-water. After extraction with EtOAc, compound **1f** was obtained by column chromatography purification (1.70 g, 85%).

Step 1F:

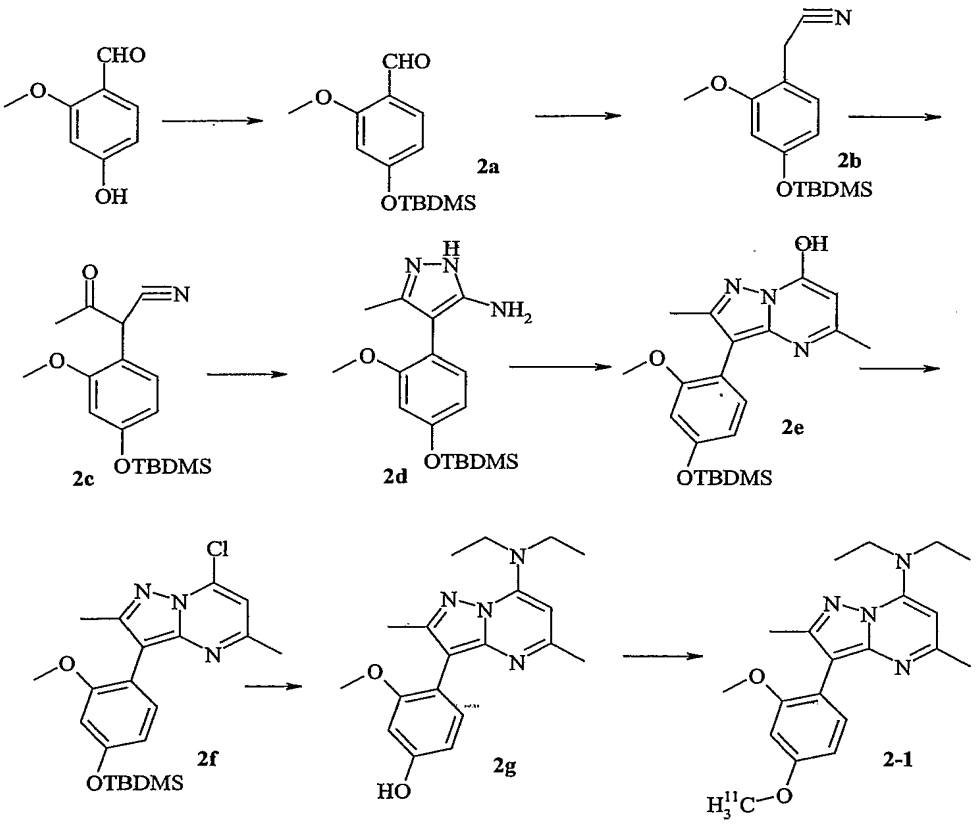
Compound **1f** (30 mg) and excess diethylamine in acetonitrile (0.8 mL) were heated at 160 °C with a microwave for 16 min. Purification with a Sciex2 prep LC-MS system

gave 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine **1-1**. LCMS 355 (MH^+), FW = 354.45

Following the same general procedure the following compounds were also synthesized: 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine. LCMS 385 (MH^+), FW = 384.48;

2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(S)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine. LCMS 396 (MH^+), FW = 396.49.

EXAMPLE 2

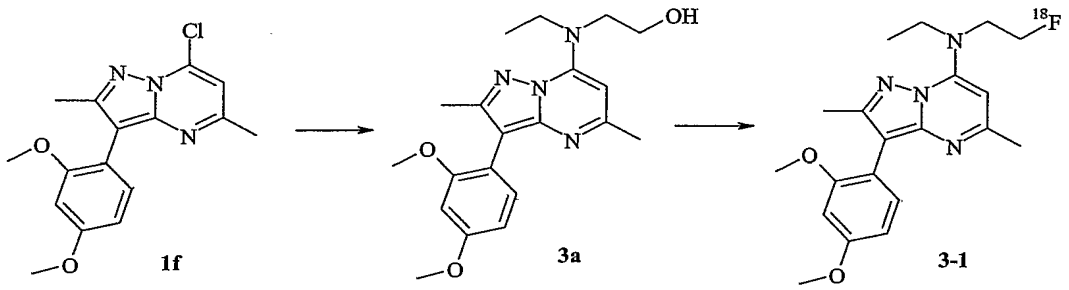


Step 2A:

2-Hydroxy-4-methoxybenzaldehyde is protected by reaction with tert-butyldimethylsilyl chloride (TBDMSCl) and imidazole in DMF to give the tert-

butyldimethylsilyl ether **2a**. Using **2a** and following the procedure as outlined in steps 1A to 1E, compound **2f** is realized. **2f** and diethylamine following the procedure of Step 1F followed by deprotection of the tert-butyldimethylsilyl group with tetrabutylammonium fluoride or acid under standard conditions gives **2g**. Alkylation of the hydroxy group of **2g** with ^{11}C methyl iodide and sodium hydride in solvent such as DMF or acetonitrile gives **2-1**.

EXAMPLE 3



Step 3A:

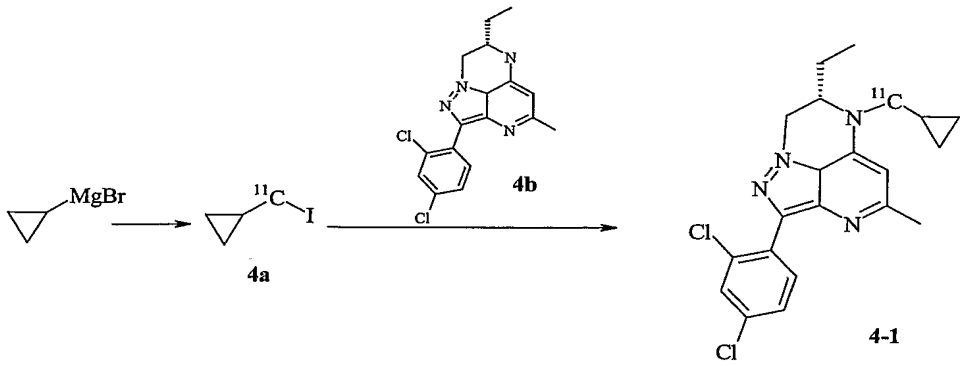
Compound **1f** and ethylaminoethanol following the procedure of Step 1F gives **3a**.

Step 3B:

Compound **3a** is converted to the sulfonate ester such as mesylate, tosylate or triflate followed by reaction with ^{18}F ion to give **3-1** (L. Martarello et al., Nuclear Medicine and Biology **28** (2001) 187-195). Compound **3a** and methanesulfonyl chloride in pyridine yields a mesylate which undergoes a nucleophilic substitution with $K^{18}F$ to give **3-1** which is purified by HPLC.

EXAMPLE 4

6-(CYCLOPROPYLMETHYL)-2-(2,4-DICHLOROPHENYL)-7-(S)-ETHYL-7,8-DIHYDRO-4-METHYL-6H-1,3,6,8A-TETRAAZAACENAPHTHYLENE



Step 4A:

According to the general procedure of Ishiwata et al., *Appl. Radiat. Isot.*, **46**, 10: 1009-1013, cyclopropyl-[^{11}C]-methyliodide is prepared. [^{11}C]CO_2 is transferred into a solution of cyclopropyl magnesium bromide in THF at 0 – 5 °C, followed by immediate reduction with lithium aluminum hydride. Hydroiodic acid is added, the mixture is heated to give **4a** after purification.

Step 4B:

Compound **4b** (synthesized according to various procedures in U.S. Patent No. 6,531,475) is alkylated with compound **4a** using standard conditions such as sodium hydride, sodium methoxide or cesium carbonate in a solvent such as DMF followed by purification by HPLC to give **4-1**.

EXAMPLE 5

CRF RECEPTOR BINDING ACTIVITY

The compounds of this invention may be evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by

Grigoriadis et al. (*Mol. Pharmacol* vol50, pp679-686, 1996) and Hoare et al. (*Mol. Pharmacol* vol63 pp751-765, 2003.) By utilizing radiolabeled CRF ligands, the assay may be used to evaluate the binding activity of the compounds of the present invention with any CRF receptor subtype.

Briefly, the binding assay involves the displacement of a radiolabeled CRF ligand from the CRF receptor. More specifically, the binding assay is performed in 96-well assay plates using 1-10μg cell membranes from cells stably transfected with human CRF receptors. Each well receives about 0.05 ml assay buffer (*e.g.*, Dulbecco's phosphate buffered saline, 10 mM magnesium chloride, 2mM EGTA) containing compound of interest or a reference ligand (for example, sauvagine, urocortin I or CRF), 0.05 ml of [^{125}I] tyrosine - sauvagine (final concentration ~150 pM or approximately the K_D as determined by Scatchard analysis) and 0.1 ml of a cell membrane suspension containing the CRF receptor. The mixture is incubated for 2 hours at 22 °C followed by separation of the bound and free radioligand by rapid filtration over glass fiber filters. Following three washes, the filters are dried and radioactivity (Auger electrons from ^{125}I) is counted using a scintillation counter. All radioligand binding data may be analyzed using the non-linear least-squares curve-fitting programs Prism (GraphPad Software Inc) or XL*fit* (ID Business Solutions Ltd).

It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

1. A compound taken from 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(S)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine, and 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-{2-fluoroethyl}amino)pyrazolo[2,3-a]pyrimidine.
2. A compound taken from 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(S)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-{2-fluoroethyl}amino)pyrazolo[2,3-a]pyrimidine and 6-(cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-(S)-ethyl-7,8-dihydro-4-methyl-6H-1,3,6,8a-tetraazaacenaphthylene for use as PET ligands.
3. A composition comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier or diluent.
4. A method for treating a disorder manifesting hypersecretion of CRF in a warm-blooded animal comprising administering to the animal an effective amount of the pharmaceutical composition of claim 3.
5. The method of claim 4 wherein the disorder is depression.
6. The method of claim 4 wherein the disorder is an anxiety-related disorder.
7. The method of claim 4 wherein the disorder is irritable bowel syndrome.
8. A composition comprising a compound of claim 2 in combination with a pharmaceutically acceptable carrier or diluent.

Bibliographic data

Title:	CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR PREVENTING SUDDEN DEATH
Pub/Pat no:	JP2000302693A
Pub/Issue Date:	2000-10-31
Inventor(s):	FOSSA ANTHONY ANDREA|FOSSA ANTHONY ANDREA
Applicant(s):	PFIZER PROD INC
Classification:	A61K31/41AI; A61K31/437AI; A61K31/44AI; A61K31/4409AI; A61K31/4418AI; A61K31/455AI; A61K31/505AI; A61K31/506AI; A61K31/519AI; A61K31/52AI; A61K31/522AI; A61K45/00AI; A61P43/00AI; C07D213/69AI; C07D213/70AI; C07D213/74AI; C07D239/34AI; C07D239/47AI; C07D239/48AI; C07D239/50AI; C07D471/04AI; C07D473/34AI
Application number:	JP20000100606 2000-04-03
Priority number:	US19990127659P 19990402;

Abstract of JP2000302693A

PROBLEM TO BE SOLVED: To obtain a medicine having low side effect, effective for preventing the sudden death of animal and useful for the treatment of cardiac diseases, hypertension, osteoporosis, anxiety, diabetes, or the like, by including a therapeutically effective amount of a corticotropin releasing factor antagonist. SOLUTION: The objective medicine contains a therapeutically effective amount of a corticotropin releasing factor antagonist such as a compound (salt) expressed by formula I or II [the dotted line is optionally existing double bond; A is N or CR7 (R7 is H, a 1-4C alkyl, or the like); B is NR1R2, CR1R2R11 (R1 is H or a 1-6C alkyl; R2 is a 1-6C alkyl, an aryl, or the like; R11 is H, hydroxy, or the like), or the like; D is N, CR10 (R10 is H, a 1-6C alkyl, or the like), or the like; E is N, CR4 (R4 is H, a 1-6C alkyl, or the like), or the like; Z is NH, O, S, or the like; R3 is H, a halogen, a 1-6C alkyl, or the like; R5 is phenyl, naphthyl, or the like], e.g. 4-(1-ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethyl- benzyl)-pyrimidine. The daily administration rate of the compound is preferably 1.0-20 mg/kg body-weight.

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(33)優先権主張国　米国（ＵＳ）

(71)出願人　39706/152
ファイザー・プロダクツ・インク
アメリカ合衆国コネチカット州グロトン市
イースタン・ポイント・ロード
(72)発明者　アンソニー・アンドレア・フォッサ
アメリカ合衆国コネチカット州06340，グロトン，イースタン・ポイント・ロード，ファイザー・インク
(74)代理人　100089705
弁理士　社本　一夫　（外５名）

(54)【発明の名称】　突然死予防のためのコルチコトロピン放出因子アンタゴニスト

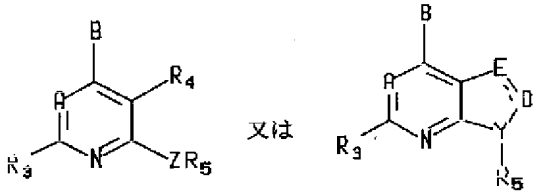
(57)【要約】
コルチコトロピン放出因子アンタゴニストの治療上有効量を動物に投与する。本発明の方法は、心臓疾患、高血圧、頻脈、うっ血性心不全、脳卒中，骨粗鬆症、早産、心理的萎縮、ストレス性発熱、潰瘍、下痢、術後腸閉塞、精神的不安及びストレスに関連する腸の過敏、糖尿病、神経性疾患、脳障害、ギランバレー症候群、小児突然死症候群、先天性過換気症候群又は尿毒症性神経障害の患者に特に有用である。

【特許請求の範囲】

【請求項１】　動物における突然死の予防のための、治療上有効量のコルチコトロピン放出因子アンタゴニストを含む、薬剤。

【請求項２】　コルチコトロピン放出因子アンタゴニストが、式I又はII：

【化１】



I　　II

［式中、点線は所望により存在する二重結合を表し、
Aは－CR_7又はNであり、
Bは－NR_1R_2、－$CR_1R_2R_{11}$、－C（＝CR_1R_{12}）R_2、－NHC$R_{11}R_1R_2$、－O$CR_{11}R_1R_2$、－S$CR_{11}R_1R_2$、－$CR_{11}R_2OR_1$、－C$R_{11}R_2SR_1$、－C（S）R_2、－$NHNR_1R_2$、－$CR_2R_{11}NHR_1$又は－C（O）R_2であり；DはEとDとが二重結合で結合し、及びEが－CR_4であるとき、N又は－CR_{10}であり；EとDとが二重結合で結合し、及びEがNであるとき、－CR_{10}であり；又はEとDとが単結合で結合しているとき、－CR_8R_9、－CHR_{10}、－C＝O、－C＝S、－C＝NH又は－C＝NCH_3であり；EはEとDとが二重結合で結合しているとき、－CR_4又はNであり；又はEとDとが単結合で結合しているとき、－CR_4R_6又は－NR_6であり；YはN又は－CHであり；ZはNH、O、S、－N（C_1～C_2アルキル）又は－$CR_{12}R_{13}$であり、このときR_{12}及びR_{13}は各々独立に水素、トリフルオロメチル若しくはメチルであるか、又はR_{12}及びR_{13}の一方がシアノ、他方が水素若しくはメチルであり；R_1は水素又はC_1～C_6アルキルであり、このとき前記C_1～C_6アルキルはヒドロキシ、シアノ、ニトロ、フルオロ、クロロ、ブロモ、ヨード、CF_3、C_1～C_4アルコキシ、－O－CO－（C_1～C_4アルキル）、－O－CO－NH（C_1～C_4アルキル）、－O－CO－N（C_1～C_4アルキル）（C_1～C_2アルキル）、－NH（C_1～C_4アルキル）、－N（C_1～C_2アルキル）（C_1～C_4アルキル）、－S（C_1～C_4アルキル）、－N（C_1～C_4アルキル）CO（C_1～C_4アルキル）、－NHCO（C_1～C_4アルキル）、－CO_2（C_1～C_4アルキル）、－CONH（C_1～C_4アルキル）、－CON（C_1～C_4アルキル）（C_1～C_2アルキル）、（C_1～C_4アルキル）スルフィニル、（C_1～C_4アルキル）スルホニル及び（C_1～C_4アルキル）スルファニルから独立して選択される2個以下の置換基で置換されていてもよく、このとき前述のR_1基中の前記C_1～C_6アルキル、C_1～C_4アルコキシ及びC_1～C_4アルキル部分は、1個の二重結合又は三重結合を含んでもよく；R_2はC_1～C_6アルキル、ヘテロアリール、アリール、ヘテロアリール（C_1～C_4アルキル）又はアリール（C_1～C_4アルキル）であり、このとき前記アリール及び前記（アリール）C_1～C_4アルキルのアリール部分はフェニル及びナフチルから選択され、及び前記ヘテロアリール及び前記（ヘテロアリール）C_1～C_4アルキルのヘテロアリール部分はチエニル、ベンゾチエニル、ピリジル、チアゾリル、キノリル、ピラジニル、ピリミジル、イミダゾリル、フラニル、ベンゾフラニル、ベンゾチアゾリル、イソチアゾリル、ベンズイソチアゾリル、ベンズイソキサゾリル、ベンズイミダゾリル、インドリル及びベンゾキサゾリルから選択されるか；又はR_2はC_3～C_8シクロアルキル又は（C_3～C_8シクロアルキル）C_1～C_6アルキルであり、このとき少なくとも4個の環員を有する前記シクロアルキル及び少なくとも4個の環員を有する前記（C_3～C_8シクロアルキル）C_1～C_6アルキルのシクロアルキル部分の環員炭素の1又は2個は、酸素若しくは硫黄によって、又は－NR_{14}（このときR_{14}は水素又はC_1～C_4アルキルである）によって置換されていてもよく；及び前述のR_2基の各々は、クロロ、フルオロ及びC_1～C_4アルキルから独立して選択される3個以下の置換基によって、又はブロモ、ヨード、シアノ、ニトロ、C_1～C_6アルコキシ、－O－CO－（C_1～C_4アルキル）、－O－CO－N（C_1～C_4アルキル）（C_1～C_2アルキル）、－CO_2（C_1～C_4アルキル）、（C_1～C_4アルキル）スルファニル、（C_1～C_4アルキル）スルフィニル及び（C_1～C_4アルキル）スルホニルから選択される1個の置換基によって置換されていてもよく、このとき前記C_1～C_4アルキル及び前述のR_2基のC_1～C_6アルキル部分は、1個の炭素－炭素二重結合又は三重結合を含んでもよく；又は前記－NR_1R_2及び前記－$CR_1R_2R_{11}$のR_1及びR_2は一緒に飽和若しくは部分飽和の5～8員環を形成し、このとき前記環は1又は2個の炭素－炭素二重結合を含んでもよく、及びこのとき環員炭素の1又は2個はO、S及びNから選択されるヘテロ原子により置き換えられていてもよく；R_3は水素、C_1～C_6アルキル、フルオロ、クロロ、ブロモ、ヨード、ヒドロキシ、アミノ、SH、－NH（C_1～C_4アルキル）、－N（C_1～C_4アルキル）（C_1～C_2アルキル）、－CH_2OH、－CH_2OCH_3、－O（C_1～C_4アルキル）、（C_1～C_4アルキル）スルファニル、（C_1～C_4アルキル）スルホニル又は（C_1～C_4アルキル）スルフィニルであり、このとき前記C_1～C_6アルキル及び前述のR_3基のC_1～C_4アルキル部分は1個の二重結合又は三重結合を含んでもよく、及びヒドロキシ、アミノ、C_1～C_3アルコキシ、－NH（C_1～C_2アルキル）、－N（C_1～C_2アルキル）$_2$、－$NHCOCH_3$、フルオロ、クロロ及びC_1～C_3チオアルキルから独立して選択される1～3個の置換基によって置換されていてもよく；R_4は水素、C_1～C_6アルキル、フルオロ、クロロ、ブロモ、ヨード、C_1～C_6アルコキシ、ホルミル、トリフルオロメトキシ、－CH_2OCH_3、－$CH_2OCH_2CH_3$、－$CH_2CH_2OCH_3$、－CH_2CF_3、CF_3、アミノ、ニトロ、－NH（C_1～C_4アルキル）、－N（CH_3）$_2$、－$NHCOCH_3$、－$NHCONHCH_3$、（C_1～C_4アルキル）スルファニル、（C_1～C_4アルキル）スルフィニル、（C_1～C_4アルキル）

スルホニル、シアノ、ヒドロキシ、－CO（C_1～C_4アルキル）、－CHO又は－CO_2（C_1～C_4アルキル）であり、このとき前述のR_4基の前記C_1～C_6アルキル、C_1～C_6アルコキシ及びC_1～C_4アルキル部分は、1個の二重結合又は三重結合を含んでもよく、及びヒドロキシ、アミノ、－NHCOCH_3、－NH（C_1～C_2アルキル）、－N（C_1～C_2アルキル）$_2$、－CO_2（C_1～C_4アルキル）、－CO（C_1～C_4アルキル）、C_1～C_3アルコキシ、（C_1～C_3アルキル）スルファニル、フルオロ、クロロ、シアノ及びニトロから選択される1個の置換基で置換されていてもよく；R_5はフェニル、ナフチル、チエニル、ベンゾチエニル、ピリジル、キノリル、ピラジノリル、ピリミジル、イミダゾリル、フラニル、ベンゾフラニル、ベンゾチアゾリル、イソチアゾリル、ベンゾイソチアゾリル、チアゾリル、イソキサゾリル、ベンズイソキサゾリル、ベンズイミダゾリル、トリアゾリル、ピラゾリル、ピロリル、インドリル、アザインドリル、ベンズオキサゾリル、オキサゾリル、ピロジニリル、チアゾリジニル、モルホリニル、ピリジニル、テトラゾリル又は3～8員シクロアルキル環又は9～12員ビシクロアルキル環システムであり、このとき前記シクロアルキル環及び前記ビシクロアルキル環システムは、1又は2個のO、S又は－N－G（このときGは水素、C_1～C_4アルキル、C_1～C_4アルカノイル、フェニル又はベンジルである）であり、このとき前述のR_5基の各々は、フルオロ、クロロ、C_1～C_6アルキル、C_1～C_6アルコキシ及びトリフルオロメチルから独立して選択される3個以下の置換基によって、又はブロモ、ヨード、シアノ、ニトロ、アミノ、－NH（C_1～C_4アルキル）、－N（C_1～C_4アルキル）（C_1～C_2アルキル）、－CO_2（C_1～C_4アルキル）、－CO（C_1～C_4アルキル）、－SO_2NH（C_1～C_4アルキル）、－SO_2N（C_1～C_4アルキル）（C_1～C_2アルキル）、－SO_2NH_2、－$NHSO_2$（C_1～C_4アルキル）、－S（C_1～C_4アルキル）及び－SO_2（C_1～C_4アルキル）から選択される1個の置換基によって置換されていてもよく、このとき前述のR_5基の前記C_1～C_4アルキル及びC_1～C_6アルキル部分は、1個の二重結合又は三重結合を含んでもよく、及びフルオロ、クロロ、ヒドロキシ、アミノ、メチルアミノ、ジメチルアミノ及びアセチルから独立して選択される1又は2個の置換基によって置換されていてもよく；R_6は水素又はC_1～C_6アルキルであり、このとき前記C_1～C_6アルキルは1個のヒドロキシ、メトキシ、エトキシ又はフルオロ基により置換されていてもよく；R_7は水素、C_1～C_4アルキル、フルオロ、クロロ、ブロモ、ヨード、シアノ、ヒドロキシ、C_1～C_4アルコキシ、－CO（C_1～C_4アルキル）、－CO_2（C_1～C_4アルキル）、－OCF_3、CF_3、－CH_2OH、－CH_2OCH_3又は－$CH_2OCH_2CH_3$であり；R_8及びR_9は各々独立して水素、ヒドロキシ、メチル、エチル、メトキシ又はエトキシであるか；又はR_8及びR_9は一緒にオキソ（＝O）基を形成し；R_{10}は水素、C_1～C_6アルキル、フルオロ、クロロ、ブロモ、ヨード、C_1～C_6アルコキシ、ホルミル、アミノ、－NH（C_1～C_4アルキル）、－N（C_1～C_4アルキル）（C_1～C_2アルキル）、シアノ、カルボキシ、アミド又は－SO_n（C_1～C_4アルキル）（このときnは0、1又は2である）であり、このとき前述のR_{10}基の前記C_1～C_6アルキル及びC_1～C_4アルキル部分は1個のヒドロキシ、トリフルオロメチル、アミノ、カルボキシ、アミド、－NHCO（C_1～C_4アルキル）、－NH（C_1～C_4アルキル）、－N（C_1～C_4アルキル）（C_1～C_2アルキル）、－CO_2（C_1～C_4アルキル）、C_1～C_3アルコキシ、C_1～C_3チオアルキル、フルオロ、ブロモ、クロロ、ヨード、シアノ又はニトロによって置換されていてもよく；並びにR_{11}は水素、ヒドロキシ、フルオロ又はメトキシである］の化合物、又はその医薬として許容できる塩である、請求項1記載の薬剤。

【請求項３】　Bが－NR_1R_2、－$NHCHR_1R_2$、－$CR_1R_2R_{11}$、－$SCHR_1R_2$又は－$OCHR_1R_2$であり；R_1が、１個のヒドロキシ、フルオロ又はC_1～C_2アルコキシ基で置換されていてもよく、及び1個の炭素－炭素二重結合又は三重結合を含んでもよい、C_1～C_6アルキルであり；R_2がベンジル又は1個の炭素－炭素二重結合又は三重結合を含んでもよいC_1～C_6アルキルであり、このとき前記C_1～C_6アルキル及び前記ベンジルのフェニル部分がフルオロ、C_1～C_2アルキル又はC_1～C_2アルコキシにより置換されていてもよく；並びにR_{11}が水素又はフルオロである、請求項2記載の薬剤。

【請求項４】　R_2が（アリール）C_1～C_4アルキル又は（ヘテロアリール）C_1～C_4アルキルであり、このとき前記アリール部分がフェニル、フラニル又はベンゾフラニルであり、及び前記ヘテロアリール部分がチエニル、ベンゾチエニル、チアゾリル、ピリジル又はベンゾチアゾリルである、請求項2記載の薬剤。

【請求項５】　BがNR_1R_2又はCHR_1R_2であり、このときR_1及びR_2がN又はCHと一緒になって5又は6員環を形成し、このとき前記環が硫黄、酸素、又はBがNR_1R_2であるときはさらに窒素を有してもよい、請求項2記載の薬剤。

【請求項６】　Bが－$NHCHR_1R_2$又は－$OCHR_1R_2$であり、このときCHR_1R_2部分が1個の酸素又は硫黄を含んでもよい5又は6員環である、請求項2記載の薬剤。

【請求項７】　R_3がメチル、クロロ又はメトキシであり；R_4がメチル、－CH_2OH、シアノ、トリフルオロメトキシ、メトキシ、トリフルオロメチル、クロロ、－CO_2CH_3、－CH_2OCH_3、－CH_2Cl、－CH_2F、アミノ又はニトロであり；R_6が水素、メチルスルフィニル、メチルスルファニル、メチルスルホニル又はエチルであり；並びにR_5がフェニル又はピリジルであり、このとき前記フェニル又はピリジルがフルオロ、クロロ、ブロモ、ヨード、C_1～C_4アルコキシ、トリフルオロメチル、C_1～C_3ヒドロキシアルキル、－CO_2（C_1～C_2アルキル）、C_1～C_2アルキルアミノ、－CO（C_1～C_4アルキル）及びC_1～C_6アルキルから独立して選択される1個の置換基によって置換され、

このとき前記C_1～C_6アルキル及び前記C_1～C_4アルキルが、１個のヒドロキシ又はフルオロ基によって置換されていてもよく、及び1個の炭素－炭素二重結合又は三重結合を含んでもよい；請求項2記載の薬剤。

【請求項８】　式I又はIIの化合物が、以下から選択される、請求項2記載の薬剤：4－（1－エチル－プロポキシ）－2，5－ジメチル－6－（2，4，6－トリメチル－ベンジル）－ピリミジン；2－（4－ブロモ－2，6－ジメチル－フェノキシ）－4－（1－エチル－プロポキシ）－3，6－ジメチル－ピリジン；2－（4－エチル－2，6－ジメチル－フェノキシ）－4－（1－エチル－プロポキシ）－3，6－ジメチル－ピリジン；3－エチル－4－（1－エチル－プロポキシ）－6－メチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン；2－（2，6－ジメチル－4－プロピル－フェノキシ）－4－（1－エチル－プロポキシ）－3，6－ジメチル－ピリジン；4－（1－エチル－プロポキシ）－2－（4－メトキシ－2，6－ジメチル－フェノキシ）－3，6－ジメチル－ピリジン；2－（4－エトキシ－2，6－ジメチル－フェノキシ）－4－（1－エチル－プロポキシ）－3，6－ジメチル－ピリジン；2－（4－クロロ－2，6－ジメチル－フェノキシ）－4－（1－エチル－プロポキシ）－3，6－ジメチル－ピリジン；4－（1－メトキシメチル－プロポキシ）－3，6－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン；［3，6－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－ジエチル－アミン；［3，6－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－エチル－プロピル－アミン；［2，5－ジメチル－6－（2，4，6－トリメチル－フェノキシ）－ピリミジン－4－イル］（1－エチル－プロピル）アミン；ブチル－［3，6－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－エチル－アミン；4－（1－エチル－プロポキシ）－3，6－ジメチル－2－（2，4，6－トリメチル－フェニルスルファニル）－ピリジン；ブチル－［2－（4－クロロ－2，6－ジメチル－フェノキシ）－3，6－ジメチル－ピリジン－4－イル］－エチル－アミン；4－（1－エチル－プロピルアミノ）－6－メチル－2－（2，4，6－トリメチル－フェノキシ）－ニコチン酸メチルエステル；［3，6－ジメチル－2－（2，4，6－トリメチル－フェニルスルファニル）－ピリジン－4－イル］－エチル－プロピル－アミン；［4－（1－エチル－プロピルアミノ）－6－メチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－3－イル］－メタノール；［2－（4－クロロ－2，6－ジメチル－フェノキシ）－3，6－ジメチル－ピリジン－4－イル］－エチル－プロピル－アミン；1－（エチル－プロピル）－［6－メチル－3－ニトロ－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－アミン；N4－（1－エチル－プロピル）－6－メチル－3－ニトロ－N2－（2，4，6－トリメチル－フェニル）－ピリジン－2，4－ジアミン；N4－（1－エチル－プロピル）－6－メチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－3，4－ジアミン；N4－（1－エチル－プロピル）－6－メチル－N2－（2，4，6－トリメチル－フェニル）－ピリジン－2，3，4－トリアミン；［3，6－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－エチル－（2，2，2－トリフルオロ－エチル）－アミン；［3－クロロメチル－6－メチル－2－（2，4，6－トリメチル－フェノキシ）ピリジン－4－イル］－（1－エチル－プロピル）－アミン；［3，6－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－（1－エチル－プロピル）－アミン；（1－エチル－プロピル）－［2－メチル－5－ニトロ－6－（2，4，6－トリメチル－ピリジン－3－イルオキシ）－ピリミジン－4－イル］－アミン；（1－エチル－プロピル）－［3－メトキシメチル－6－メチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－アミン；N－（1－エチル－プロピル）－2－メチル－5－ニトロ－N－（2，4，6－トリメチル－ピリジン－3－イル）－ピリミジン－4，6－ジアミン；［2－（4－クロロ－2，6－ジメチル－フェノキシ）－3，6－ジメチル－ピリジン－4－イル］－ジエチル－アミン；4－（1－エチル－プロポキシ）－3，6－ジメチル－2－（2，4，6－トリメチルフェノキシ）－ピリジン；ブチル－［2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－6，7－ジヒドロ－5H－ピロロ［2，3－d］ピリミジン－4－イル］－エチル－アミン；4－（ブチル－エチルアミノ）－2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－5，7－ジヒドロ－ピロロ［2，3－d］ピリミジン－6－オン；4－（1－エチルプロポキシ）－2，5－ジメチル－6－（2，4，6－トリメチルフェノキシ）－ピリミジン；N－ブチル－N－エチル－2，5－ジメチル－N－（2，4，6－トリメチルフェニル）－ピリミジン－4，6－ジアミン；（1－エチル－プロピル）－［5－メチル－3－（2，4，6－トリメチル－フェニル）－3H－イミダゾ［4，5－b］ピリジン－7－イル］－アミン；［2，5－ジメチル－3－（2，4，6－トリメチル－フェニル）－3H－イミダゾ［4，5－b］ピリジン－7－イル］－（1－エチル－プロピル）－アミン；N4－（1－エチル－プロピル）－6，N3－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－3，4－ジアミン；N4－（1－エチル－プロピル）－6，N3，N3－トリメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－3，4－ジアミン；6－（1－エチル－プロポキシ）－2－メチル－N4－（2，4，6－トリメチル－フェニル）－ピリミジン－4，5－ジアミン；［4－（1－エチル－プロポキシ）－3，6－ジメチル－ピリジン－2－イル］－（2，4，6－トリメチルフェニル）－アミン；及び6－（エチル－プロピル－アミノ）－2，7－ジメチル－9－（2，4，6－トリメチルフェニル）－7，9－

ジヒドロープリン－8－オン。
【請求項９】　化合物が、以下から選択される、請求項2記載の方法：ブチル－［3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1H－ピラゾロ［3，4－b］ピリジン－4－イル］－エチルアミン；3，6－ジメチル－4－（テトラヒドロフラン－3－イルオキシ）－1－（2，4，6－トリメチルフェニル）－1H－ピラゾロ［3，4－b］ピリジン；［3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1H－ピラゾロ［3，4－b］ピリジン－4－イル］－（1－メトキシメチルプロピル）－アミン；4－（1－メトキシメチルプロポキシ）－3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1H－ピラゾロ［3，4－b］ピリジン；（1－エチルプロピル）－［3，5，6－トリメチル－1－（2，4，6－トリメチルフェニル）－1H－ピラゾロ［3，4－b］ピリジン－4－イル］－アミン；4－（1－エチルプロポキシ）－2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－b］ピリジン；4－（1－エチルプロポキシ）－2，5，6－トリメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－b］ピリジン；4－（1－エチルプロポキシ）－2，5－ジメチル－7－（2，6－ジメチル－4－ブロモフェニル）－7H－ピロロ［2，3－b］ピリジン；3－｛（4－メチル－ベンジル）－［3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1H－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミノ｝－プロパン－1－オール；ジエチル－［6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1H－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；2－｛ブチル－［6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1H－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミノ｝－エタノール；ジブチル－｛6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1H－ピラゾロ［3，4－d］ピリミジン－4－イル｝－アミン；ブチル－エチル－［6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1H－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；ブチル－シクロプロピルメチル－［6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1H－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；ジ－1－プロピル－［6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1H－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；ジアリル－［6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1H－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；ブチル－エチル－［6－クロロ－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1H－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；ブチル－エチル－［6－メトキシ－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1H－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；プロピル－エチル－［3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1H－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；4－（1－エチル－プロピル）－6－メチル－3－メチルスルファニル－1－（2，4，6－トリメチルフェニル）－1H－ピラゾロ［3，4－d］ピリミジン；2－［3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1H－ピラゾロ［3，4－d］ピリミジン－4－イルアミン］－ブタン－1－オール；［3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1H－ピラゾロ－［3，4－d］ピリミジン－4－イル］－（1－メチルプロピル）アミン；4－（1－メトキシメチルプロポキシ）－3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－１H－ピラゾロ［3，4－d］ピリミジン；n－ブチル－エチル－［2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン－4－イル］アミン；ジ－n－プロピル－［2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン－4－イル］アミン；エチル－n－プロピル－［2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン－4－イル］アミン；ジエチル－2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン－4－イル］アミン；n－ブチル－エチル－［2，5，6－トリメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン－4－イル］アミン；2－｛N－n－ブチル－N－［2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン－4－イル］アミノ｝－エタノール；4－（1－エチル－プロピル）－2，5，6－トリメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン；n－ブチル－エチル－［2，5－ジメチル－7－（2，4－ジメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン－4－イル］アミン；2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジル－4－イル］－（1－エチル－プロピル）アミン；2－［7－（4－ブロモ－2，6－ジメチルフェニル）－2，5－ジメチル－7H－ピロロ［2，3－d］ピリミジン－4－イルアミノ］－ブタン－1－オール；2－（S）－［7－（4－ブロモ－2，6－ジメチルフェニル）－2，5－ジメチル－7H－ピロロ［2，3－d］ピリミジン－4－イルアミノ］－ブタン－1－オール；4－（1－エチル－プロポキシ）－2，5，6－トリメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン；4－（1－メトキシメチルプロポキシ）－3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3

-d]ピリミジン;4-(1-エチル-ブチル)-2,5,6-トリメチル-7-(2,4,6-トリメチルフェニル)-7H-ピロロ-[2,3-d]ピリミジン;[7-(4-ブロモ-2,6-ジメチル-フェニル)-2,5-ジメチル-7H-ピロロ[2,3-d]ピリミジン-4-イル]-(1-メトキシメチル-プロピル)-アミン;2-[7-(2-ブロモ-4,6-ジメチル-フェニル)-2,5-ジメチル-7H-ピロロ[2,3-d]ピリミジン-4-イルアミノ]-ブタン-1-オール;2-[7-(4-エチル-2,6-ジメチル-フェニル)-2,5-ジメチル-7H-ピロロ[2,3-d]ピリミジン-4-イルアミノ]-ブタン-1-オール;2-[7-(2-エチル-4,6-ジメチルフェニル)-2,5-ジメチル-7H-ピロロ[2,3-d]ピリミジン-4-イルアミノ]-ブタン-1-オール;及び2-[7-(2-フルオロメチル-4,6-ジメチルフェニル)-2,5-ジメチル-7H-ピロロ[2,3-d]ピリミジン-4-イルアミノ]-ブタン-1-オール。

【請求項10】 突然死のリスクが、動物における疾患状態の存在に関連し、このとき前記疾患状態が、心臓疾患、高血圧、頻脈、うっ血性心不全、脳卒中,骨粗鬆症、早産、心理的萎縮、ストレス性発熱、潰瘍、下痢、術後腸閉塞、精神的不安及びストレスに関連する腸の過敏、糖尿病、神経性疾患、脳障害、ギランバレー症候群、小児突然死症候群、先天性過換気症候群又は尿毒症性神経障害である、請求項1記載の薬剤。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、臨床上有効な量のコルチコトロピン放出因子(CRF)アンタゴニストを投与することによる、特定の患者における突然死の発生を減じる方法に関する。CRFアンタゴニストは、QT分散(dispersion)及び心拍変動(heart ratevariability)を改善することによって、患者における突然死の発生を減じると考えられる。

【0002】

【従来技術】突然の予期しない死が、中程度の心疾患にかかっていた患者の50%、重篤な心疾患を経験している患者の25%に起こっている(Barrら、Lancet、343(8893):327-29(1994))。心室再分極(ventricular repolarization)における局所変化は、不整脈の電気神経学的基質を示すものであるが、QTインターバル(分散)の内部誘導(interlead)変動によって検出されうる。QTインターバル分散は、急性心筋梗塞の後の心室不整脈(ventricular tachyarrhythmias)、長期のQT症候群、慢性心疾患及び肥大性心筋症にかかった患者に見られる(例えば、Potratzら、Eur. Heart J.、14:254(1993);Dayら、Br. Heart J.、63:342-44(1990);及びBujaら、Am. J. Cardiol、72:973-976(1993)を参照せよ。)。

【0003】本明細書に記載されたような式I及びIIの化合物及びそれらの医薬として許容できる塩、並びにそのような化合物の塩の製造方法は、欧州特許出願EP0773023A1、並びに、より詳細にはPCT国際特許出願PCT/IB95/00373(公開番号WO95/34563)、PCT/IB95/00439(公開番号WO95/33750)、PCT/US93/11333(公開番号WO94/13677)及び PCT/US93/10715(公開番号WO94/13676)中に開示されている。上記のこれらの欧州特許出願及びPCT国際特許出願の内容はすべて、引用により本明細書中に取り込まれる。

【0004】前述のPCT国際特許出願は、CRFにより引き起こされ又は促進される病気の治療における、また、不安、鬱、倦怠症候群(fatigue syndrome)、胃腸疾患、頭痛、痛み、ガン、免疫機能不全、出血性ストレス(hemorrhagic stress)、薬物中毒、薬物及びアルコールの中断症状、不妊(fertility problems)、ストレスに起因する精神病性挿間(stress-induced psychotic episodes)、アルツハイマー病のような神経変性性疾患、クローン病、痙攣性結腸及び過敏結腸のような過敏腸症候群(irritable bowel syndrome)、食欲不振(anorexia nervosa)のような摂食疾患、関節炎のような炎症性疾患、喘息及びアレルギー等の治療における、式I及びIIの化合物の使用についても言及している。

【0005】本発明の方法において列記されている疾患の治療のために用いることのできる他のCRFアンタゴニストは、PCT国際特許出願PCT/IB95/00318(国際公開番号WO95/33727)、PCT/IB97/00918(国際公開番号WO98/05661)、PCT/IB97/00904(国際公開番号WO98/08846)及びPCT/IB97/00922(国際公開番号WO98/08847)、PCT/EP98/02267(国際公開番号WO98/47874)、PCT/EP98/02268(国際公開番号WO98/47903)、PCT/US98/09861(国際公開番号WO98/51312)、PCT/US98/13840(国際公開番号WO99/01439)、PCT/US98/13913(国際公開番号WO99/01454)並びに米国特許5,063,245、5,109,111、5,132,111、5,245,009、5,464,847、5,493,006、5,510,458、5,605,642、5,644,057、5,663,292、5,668,145、5,705,646及び5,712,303に記載されている。ここで引用したPCT国際特許出願及び米国特許は、それらの全体を本明細書に援用する。

【0006】CRFアンタゴニストの重要性は文献、例えば米国特許5,063,245に論じられている。この内容はすべて、引用により本明細書中に取り込まれる。CRFアンタゴニストによって示される異なる活性の最近のアウトラインを、M. J. Owensら、Pharm. Rev.、43:425-73(1991)に見ることができる。この内容もすべて、引用により本明細書中に取り込まれる。。

【0007】PCT国際特許出願PCT/US98/07831(国際公開番号WO98/47899)は、炎症性疾患の治療における置換ピロロピリジンの有効性を開示する。開示された化合物は、特定の炎症性サイトカイン、即ちTNF-αI及び

L-1βの産生を阻害する。掲げられている炎症性サイトカインに関連した炎症性疾患の一つは、うっ血性心疾患である。しかしながら、QT分散又は心拍変動については言及されていない。

【０００８】

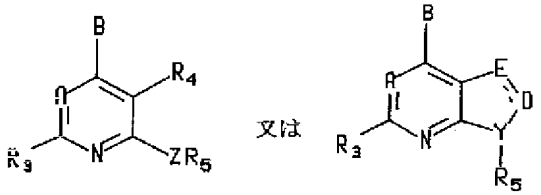
【課題を解決するための手段】本発明は、動物における突然死を予防する方法であって、前記動物、好ましくはヒトに、臨床上有効量のコルチコロトピン放出因子アンタゴニストを投与することを含む前記方法を提供する。

【０００９】本発明の方法は、特定の患者、詳細には、心臓血管又は心臓に関連した疾患、例えば、高血圧（hypertension）、頻脈（tachycardia）、うっ血性心不全（congestive heart failure）等に苦しむ患者における突然死を予防する際に最も有用である。また、他の疾患、例えば、脳卒中（stroke）、骨粗鬆症（osteoporosis）、早産（premature birth）、心理的萎縮（psychosocial dwarfism）、ストレス性発熱（stress-induced fever）、潰瘍（ulcer）、下痢（diarrhea）、術後腸閉塞（post-operative ileus）、精神的不安及びストレスに関連する腸の過敏（colonic hypersensitivity associated with psychopathological disturbance and stress）等の患者においても同様に有用である。本発明の方法はまた、糖尿病患者における突然死を予防する際にも有用である。また、多くの神経疾患（neurological disorders）、例えば、脳障害（brain damage）、ギランバレー症候群（Guillain-Barre syndrome）、小児突然死症候群（sudden infant death syndrome）、先天性過換気症候群（congenital hypoventilation syndrome）又は尿毒症性神経障害（uremic neuropathy）等の患者においても同様に有用である。

【００１０】好ましい実施態様において、本発明は式I又はIIの化合物を用いる。

【００１１】

【化２】



I　　II

【００１２】式中、点線は所望により存在する二重結合を表し、Aは$-CR_7$又はNであり、Bは$-NR_1R_2$、$-CR_1R_2R_{11}$、$-C(=CR_1R_{12})R_2$、$-NHCR_{11}R_1R_2$、$-OCR_{11}R_1R_2$、$-SCR_{11}R_1R_2$、$-CR_{11}R_2OR_1$、$-CR_{11}R_2SR_1$、$-C(S)R_2$、$-NHNR_1R_2$、$-CR_2R_{11}NHR_1$又は$-C(O)R_2$であり；DはEとDとが二重結合で結合し、及びEが$-CR_4$であるとき、N又は$-CR_{10}$であり；EとDとが二重結合で結合し、及びEがNであるとき、$-CR_{10}$であり；又はEとDとが単結合で結合しているとき、$-CR_8R_9$、$-CHR_{10}$、-C=O、-C=S、-C=NH又は$-C=NCH_3$であり；EはEとDとが二重結合で結合しているとき、$-CR_4$又はNであり；又はEとDとが単結合で結合しているとき、$-CR_4R_6$又は$-NR_6$であり；YはN又は-CHであり；ZはNH、O、S、-N（C_1～C_2アルキル）又は$-CR_{12}R_{13}$であり、このときR_{12}及びR_{13}は各々独立に水素、トリフルオロメチル若しくはメチルであるか、又はR_{12}及びR_{13}の一方がシアノ、他方が水素若しくはメチルであり；R_1は水素又はC_1～C_6アルキルであり、このとき前記C_1～C_6アルキルはヒドロキシ、シアノ、ニトロ、フルオロ、クロロ、ブロモ、ヨード、CF_3、C_1～C_4アルコキシ、-O-CO-（C_1～C_4アルキル）、-O-CO-NH（C_1～C_4アルキル）、-O-CO-N（C_1～C_4アルキル）（C_1～C_2アルキル）、-NH（C_1～C_4アルキル）、-N（C_1～C_2アルキル）（C_1～C_4アルキル）、-S（C_1～C_4アルキル）、-N（C_1～C_4アルキル）CO（C_1～C_4アルキル）、-NHCO（C_1～C_4アルキル）、$-CO_2$（C_1～C_4アルキル）、-CONH（C_1～C_4アルキル）、-CON（C_1～C_4アルキル）（C_1～C_2アルキル）、（C_1～C_4アルキル）スルフィニル、（C_1～C_4アルキル）スルホニル及び（C_1～C_4アルキル）スルファニルから独立して選択される2個以下の置換基で置換されていてもよく、このとき前述のR_1基中の前記C_1～C_6アルキル、C_1～C_4アルコキシ及びC_1～C_4アルキル部分は、1個の二重結合又は三重結合を含んでもよく；R_2はC_1～C_6アルキル、ヘテロアリール、アリール、ヘテロアリール（C_1～C_4アルキル）又はアリール（C_1～C_4アルキル）であり、このとき前記アリール及び前記（アリール）C_1～C_4アルキルのアリール部分はフェニル及びナフチルから選択され、及び前記ヘテロアリール及び前記（ヘテロアリール）C_1～C_4アルキルのヘテロアリール部分はチエニル、ベンゾチエニル、ピリジル、チアゾリル、キノリル、ピラジニル、ピリミジル、イミダゾリル、フラニル、ベンゾフラニル、ベンゾチアゾリル、イソチアゾリル、ベンズイソチアゾリル、ベンズイソキサゾリル、ベンズイミダゾリル、インドリル及びベンゾキサゾリルから選択されるか；又はR_2はC_3～C_8シクロアルキル又は（C_3～C_8シクロアルキル）C_1～C_6アルキルであり、このとき少なくとも4つの環員を有する前記シクロアルキル及び少なくとも4個の環員を有する前記（C_3～C_8シクロアルキル）C_1～C_6アルキルのシクロアルキル部分の環炭素の1又は2個は、酸素若しくは硫黄によって、又は$-NR_{14}$（このときR_{14}は水素又はC_1～C_4アルキルである）によって置換されていてもよく；及び前述のR_2基は、クロロ、フルオロ及びC_1～C_4アルキルから独立して選択される3個以下の置換基によって、又はブロモ、ヨード、シアノ、ニトロ、C_1～C_6アルコキシ、-O-CO-（C_1～C_4アルキル）、-O-CO-N（C_1～C_4アルキル）（C_1～C_2アルキル）、$-CO_2$（C_1～C_4アルキル）、（C_1～C_4アルキル）スルファニル、（C_1～C_4アルキル）スルフィニル及び（C_1～C_4アルキル）スルホニルから選択される1個の置換基によって

置換されていてもよく、このとき前記C_1～C_4アルキル及び前述のR_2基のC_1～C_6アルキル部分は、1個の炭素－炭素二重結合又は三重結合を含んでもよく；又は前記－NR_1R_2及び前記－$CR_1R_2R_{11}$のR_1及びR_2は、一緒になって飽和若しくは部分飽和の5～8員環を形成し、このとき前記環は1又は2個の炭素－炭素二重結合又は三重結合を含んでもよく、及びこのとき環員炭素の1又は2個は、O、S及びNから選択されるヘテロ原子により置き換えられていてもよく；R_3は水素、C_1～C_6アルキル、フルオロ、クロロ、ブロモ、ヨード、ヒドロキシ、アミノ、SH、－NH（C_1～C_4アルキル）、－N（C_1～C_4アルキル）（C_1～C_2アルキル）、－CH_2OH、－CH_2OCH_3、－O（C_1～C_4アルキル）、（C_1～C_4アルキル）スルファニル、（C_1～C_4アルキル）スルホニル又は（C_1～C_4アルキル）スルフィニルであり、このとき前記C_1～C_6アルキル及び前述のR_3基のC_1～C_4アルキル部分は1個の二重結合又は三重結合を含んでもよく、及びヒドロキシ、アミノ、C_1～C_3アルコキシ、－NH（C_1～C_2アルキル）、－N（C_1～C_2アルキル）$_2$、－$NHCOCH_3$、フルオロ、クロロ及びC_1～C_3チオアルキルから独立して選択される1～3個の置換基によって置換されていてもよく；R_4は水素、C_1～C_6アルキル、フルオロ、クロロ、ブロモ、ヨード、C_1～C_6アルコキシ、ホルミル、トリフルオロメトキシ、－CH_2OCH_3、－$CH_2OCH_2CH_3$、－$CH_2CH_2OCH_3$、－CH_2CF_3、CF_3、アミノ、ニトロ、－NH（C_1～C_4アルキル）、－N（CH_3）$_2$、－$NHCOCH_3$、－$NHCONHCH_3$、（C_1～C_4アルキル）スルファニル、（C_1～C_4アルキル）スルフィニル、（C_1～C_4アルキル）スルホニル、シアノ、ヒドロキシ、－CO（C_1～C_4アルキル）、－CHO又は－CO_2（C_1～C_4アルキル）であり、このとき前述のR_4基の前記C_1～C_6アルキル、C_1～C_6アルコキシ及びC_1～C_4アルキル部分は、1個の二重結合又は三重結合を含んでもよく、及びヒドロキシ、アミノ、－$NHCOCH_3$、－NH（C_1－C_2アルキル）、－N（C_1～C_2アルキル）$_2$、－CO_2（C_1～C_4アルキル）、－CO（C_1～C_4アルキル）、C_1～C_3アルコキシ、（C_1～C_3アルキル）スルファニル、フルオロ、クロロ、シアノ及びニトロから選択される1個の置換基で置換されていてもよく；R_5はフェニル、ナフチル、チエニル、ベンゾチエニル、ピリジル、キノリル、ピラジノリル、ピリミジル、イミダゾリル、フラニル、ベンゾフラニル、ベンゾチアゾリル、イソチアゾリル、ベンゾイソチアゾリル、チアゾリル、イソキサゾリル、ベンズイソキサゾリル、ベンズイミダゾリル、トリアゾリル、ピラゾリル、ピロリル、インドリル、アザインドリル、ベンズオキサゾリル、オキサゾリル、ピロジニリル、チアゾリジニル、モルホリニル、ピリジニル、テトラゾリル又は3～8員シクロアルキル環若しくは9～12員ビシクロアルキル環システムであり、このとき前記シクロアルキル環及び前記ビシクロアルキル環システムは、1又は2個のO、S又は－N－G（このときGは水素、C_1～C_4アルキル、C_1～C_4アルカノイル、フェニル又はベンジルである）であり、このとき前述のR_5基の各々は、フルオロ、クロロ、C_1～C_6アルキル、C_1～C_6アルコキシ及びトリフルオロメチルから独立して選択される3個以下の置換基によって、又はブロモ、ヨード、シアノ、ニトロ、アミノ、－NH（C_1～C_4アルキル）、－N（C_1～C_4アルキル）（C_1～C_2アルキル）、－CO_2（C_1～C_4アルキル）、－CO（C_1～C_4アルキル）、－SO_2NH（C_1～C_4アルキル）、－SO_2N（C_1～C_4アルキル）（C_1～C_2アルキル）、－SO_2NH_2、－$NHSO_2$（C_1～C_4アルキル）、－S（C_1～C_4アルキル）及び－SO_2（C_1～C_4アルキル）から選択される1個の置換基によって置換されていてもよく、このとき前述のR_5基の前記C_1～C_4アルキル及びC_1～C_6アルキル部分は、1個の二重結合又は三重結合を含んでもよく、及びフルオロ、クロロ、ヒドロキシ、アミノ、メチルアミノ、ジメチルアミノ及びアセチルから独立して選択される1又は2個の置換基によって置換されていてもよく；R_6は水素又はC_1～C_6アルキルであり、このとき前記C_1～C_6アルキルは1個のヒドロキシ、メトキシ、エトキシ又はフルオロ基により置換されていてもよく；R_7は水素、C_1～C_4アルキル、フルオロ、クロロ、ブロモ、ヨード、シアノ、ヒドロキシ、C_1～C_4アルコキシ、－CO（C_1～C_4アルキル）、－CO_2（C_1～C_4アルキル）、－OCF_3、CF_3、－CH_2OH、－CH_2OCH_3又は－$CH_2OCH_2CH_3$であり；R_8及びR_9は各々独立して水素、ヒドロキシ、メチル、エチル、メトキシ又はエトキシであるか；又はR_8及びR_9は一緒にオキソ（＝O）基を形成し；R_{10}は水素、C_1～C_6アルキル、フルオロ、クロロ、ブロモ、ヨード、C_1～C_6アルコキシ、ホルミル、アミノ、－NH（C_1～C_4アルキル）、－N（C_1～C_4アルキル）（C_1～C_2アルキル）、シアノ、カルボキシ、アミド又は－SO_n（C_1～C_4アルキル）（このときnは0、1又は2である）であり、このとき前述のR_{10}基の前記C_1～C_6アルキル及びC_1～C_4アルキル部分は1個のヒドロキシ、トリフルオロメチル、アミノ、カルボキシ、アミド、－NHCO（C_1～C_4アルキル）、－NH（C_1～C_4アルキル）、－N（C_1～C_4アルキル）（C_1～C_2アルキル）、－CO_2（C_1～C_4アルキル）、C_1～C_3アルコキシ、C_1～C_3チオアルキル、フルオロ、ブロモ、クロロ、ヨード、シアノ又はニトロによって置換されていてもよく；並びにR_{11}は水素、ヒドロキシ、フルオロ又はメトキシである。

【００１３】好ましくは、Bが－NR_1R_2、－$NHCHR_1R_2$、－$CR_1R_2R_{11}$、－$SCHR_1R_2$又は－$OCHR_1R_2$であり；R_1が、１個のヒドロキシ、フルオロ又はC_1～C_2アルコキシ基で置換されていてもよく、及び1個の炭素－炭素二重結合又は三重結合を含んでもよいC_1～C_6アルキルであり；R_2がベンジル又は1個の炭素－炭素二重結合又は三重結合を含んでもよいC_1～C_6アルキルであり、このとき前記C_1～C_6アルキル及び前記ベンジルのフェニル部分がフルオロ、C_1～C_2アルキル又はC_1～C_2アルコキシにより置換されていてもよく；並びにR_{11}が水素又はフルオロである。

【００１４】また好ましくは、R_2が（アリール）C_1～C_4アルキル又は（ヘテロアリール）C_1～C_4アルキルであり、このとき前記アリール部分がフェニル、フラニル又はベンゾフラニルであり、及び前記ヘテロアリール部分がチエニル、ベンゾチエニル、チアゾリル、ピリジル又はベンゾチアゾリルである。

【００１５】また好ましくは、BがNR_1R_2又はCHR_1R_2であり、このときR_1及びR_2がN又はCHと一緒になって5又は6員環を形成し、このとき前記環が硫黄、酸素、又はBがNR_1R_2であるときはさらに窒素を有してもよい。

【００１６】また好ましくは、Bが－$NHCHR_1R_2$又は－$OCHR_1R_2$であり、このときCHR_1R_2部分が1個の酸素又は硫黄を含んでもよい5又は6員環である。

【００１７】また好ましくは、R_3がメチル、クロロ又はメトキシであり；R_4がメチル、－CH_2OH、シアノ、トリフルオロメトキシ、メトキシ、トリフルオロメチル、クロロ、－CO_2CH_3、－CH_2OCH_3、－CH_2Cl、－CH_2F、アミノ又はニトロであり；R_6が水素、メチルスルフィニル、メチルスルファニル、メチルスルホニル又はエチルであり；並びにR_5がフェニル又はピリジルであり、このとき前記フェニル又はピリジルがフルオロ、クロロ、ブロモ、ヨード、C_1～C_4アルコキシ、トリフルオロメチル、C_1～C_3ヒドロキシアルキル、－CO_2（C_1～C_2アルキル）、C_1～C_2アルキルアミノ、－CO（C_1～C_4アルキル）及びC_1～C_6アルキルから独立して選択される1個の置換基によって置換され、このとき前記C_1～C_6アルキル及び前記C_1～C_4アルキルは１個のヒドロキシ又はフルオロ基によって置換されていてもよく、及び1個の炭素－炭素二重結合又は三重結合を含んでもよい。

【００１８】式I又はIIの化合物は、以下の化合物を含む：4－（1－エチル－プロポキシ）－2，5－ジメチル－6－（2，4，6－トリメチル－ベンジル）－ピリミジン；2－（4－ブロモ－2，6－ジメチル－フェノキシ）－4－（1－エチル－プロポキシ）－3，6－ジメチル－ピリジン；2－（4－エチル－2，6－ジメチル－フェノキシ）－4－（1－エチル－プロポキシ）－3，6－ジメチル－ピリジン；3－エチル－4－（1－エチル－プロポキシ）－6－メチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン；2－（2，6－ジメチル－4－プロピル－フェノキシ）－4－（1－エチル－プロポキシ）－3，6－ジメチル－ピリジン；4－（1－エチル－プロポキシ）－2－（4－メトキシ－2，6－ジメチル－フェノキシ）－3，6－ジメチル－ピリジン；2－（4－エトキシ－2，6－ジメチル－フェノキシ）－4－（1－エチル－プロポキシ）－3，6－ジメチル－ピリジン；2－（4－クロロ－2，6－ジメチル－フェノキシ）－4－（1－エチル－プロポキシ）－3，6－ジメチル－ピリジン；4－（1－メトキシメチル－プロポキシ）－3，6－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン；［3，6－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－ジエチル－アミン；［3，6－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－エチル－プロピル－アミン；［2，5－ジメチル－6－（2，4，6－トリメチル－フェノキシ）－ピリミジン－4－イル］（1－エチル－プロピル）アミン；ブチル－［3，6－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－エチル－アミン；4－（1－エチル－プロポキシ）－3，6－ジメチル－2－（2，4，6－トリメチル－フェニルスルファニル）－ピリジン；ブチル－［2－（4－クロロ－2，6－ジメチル－フェノキシ）－3，6－ジメチル－ピリジン－4－イル］－エチル－アミン；4－（1－エチル－プロピルアミノ）－6－メチル－2－（2，4，6－トリメチル－フェノキシ）－ニコチン酸メチルエステル；［3，6－ジメチル－2－（2，4，6－トリメチル－フェニルスルファニル）－ピリジン－4－イル］－エチル－プロピル－アミン；［4－（1－エチル－プロピルアミノ）－6－メチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－3－イル］－メタノール；［2－（4－クロロ－2，6－ジメチル－フェノキシ）－3，6－ジメチル－ピリジン－4－イル］－エチル－プロピル－アミン；1－（エチル－プロピル）－［6－メチル－3－ニトロ－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－アミン；N4－（1－エチル－プロピル）－6－メチル－3－ニトロ－N2－（2，4，6－トリメチル－フェニル）－ピリジン－2，4－ジアミン；N4－（1－エチル－プロピル）－6－メチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－3，4－ジアミン；N4－（1－エチル－プロピル）－6－メチル－N2－（2，4，6－トリメチル－フェニル）－ピリジン－2，3，4－トリアミン；［3，6－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－エチル－（2，2，2－トリフルオロ－エチル）－アミン；［3－クロロメチル－6－メチル－2－（2，4，6－トリメチル－フェノキシ）ピリジン－4－イル］－（1－エチル－プロピル）－アミン；［3，6－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－（1－エチル－プロピル）－アミン；（1－エチル－プロピル）－［2－メチル－5－ニトロ－6－（2，4，6－トリメチル－ピリジン－3－イルオキシ）－ピリミジン－4－イル］－アミン；（1－エチル－プロピル）－［3－メトキシメチル－6－メチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－4－イル］－アミン；N－（1－エチル－プロピル）－2－メチル－5－ニトロ－N－（2，4，6－トリメチル－ピリジン－3－イル）－ピリミジン－4，6－ジアミン；［2－（4－クロロ－2，6－ジメチル－フェノキシ）－3，6－ジメチル－ピリジン－4－イル］－ジエチル－アミン；4－（1－エチル－プロポキシ）－3，6－ジメチル－2－（2，4，6－トリメチルフェノキシ）－ピリジン；ブチル－［2，5－ジメチル－7－（2，4，6－トリメチル

フェニル）－6，7－ジヒドロ－5Ｈ－ピロロ［2，3－d］ピリミジン－4－イル］－エチル－アミン；4－（ブチル－エチルアミノ）－2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－5，7－ジヒドロ－ピロロ［2，3－d］ピリミジン－6－オン；4－（1－エチルプロポキシ）－2，5－ジメチル－6－（2，4，6－トリメチルフェノキシ）－ピリミジン；N－ブチル－N－エチル－2，5－ジメチル－N－（2，4，6－トリメチルフェニル）－ピリミジン－4，6－ジアミン；（1－エチル－プロピル）－［5－メチル－3－（2，4，6－トリメチル－フェニル）－3Ｈ－イミダゾ［4，5－b］ピリジン－7－イル］－アミン；［2，5－ジメチル－3－（2，4，6－トリメチル－フェニル）－3Ｈ－イミダゾ［4，5－b］ピリジン－7－イル］－（1－エチル－プロピル）－アミン；N4－（1－エチル－プロピル）－6，N3－ジメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－3，4－ジアミン；N4－（1－エチル－プロピル）－6，N3，N3－トリメチル－2－（2，4，6－トリメチル－フェノキシ）－ピリジン－3，4－ジアミン；6－（1－エチル－プロポキシ）－2－メチル－N4－（2，4，6－トリメチル－フェニル）－ピリミジン－4，5－ジアミン；［4－（1－エチル－プロポキシ）－3，6－ジメチル－ピリジン－2－イル］－（2，4，6－トリメチルフェニル）－アミン；及び6－（エチル－プロピル－アミノ）－2，7－ジメチル－9－（2，4，6－トリメチルフェニル）－7，9－ジヒドロ－プリン－8－オン。

【００１９】式I又はIIの化合物は、さらに以下の化合物を含む：ブチル－［3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1Ｈ－ピラゾロ［3，4－b］ピリジン－4－イル］－エチルアミン；3，6－ジメチル－4－（テトラヒドロフラン－3－イルオキシ）－1－（2，4，6－トリメチルフェニル）－1Ｈ－ピラゾロ［3，4－b］ピリジン；［3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1Ｈ－ピラゾロ［3，4－b］ピリジン－4－イル］－（1－メトキシメチルプロピル）－アミン；4－（1－メトキシメチルプロポキシ）－3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1Ｈ－ピラゾロ［3，4－b］ピリジン；（1－エチルプロピル）－［3，5，6－トリメチル－1－（2，4，6－トリメチルフェニル）－1Ｈ－ピラゾロ［3，4－b］ピリジン－4－イル］－アミン；4－（1－エチルプロポキシ）－2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7Ｈ－ピロロ［2，3－b］ピリジン；4－（1－エチルプロポキシ）－2，5，6－トリメチル－7－（2，4，6－トリメチルフェニル）－7Ｈ－ピロロ［2，3－b］ピリジン；4－（1－エチルプロポキシ）－2，5－ジメチル－7－（2，6－ジメチル－4－ブロモフェニル）－7Ｈ－ピロロ［2，3－b］ピリジン；3－｛（4－メチル－ベンジル）－［3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミノ｝－プロパン－1－オール；ジエチル－［6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；2－｛ブチル－［6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミノ｝－エタノール；ジブチル－｛6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イル｝－アミン；ブチル－エチル－［6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；ブチル－エチル－［6－メチル－3－メチルスルホニル－1－（2，4，6－トリクロロフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；ブチル－シクロプロピルメチル－［6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；ジ－1－プロピル－［6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；ジアリル－［6－メチル－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；ブチル－エチル－［6－クロロ－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；ブチル－エチル－［6－メトキシ－3－メチルスルファニル－1－（2，4，6－トリクロロフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；プロピル－エチル－［3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イル］－アミン；4－（1－エチル－プロピル）－6－メチル－3－メチルスルファニル－1－（2，4，6－トリメチルフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン；2－［3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1Ｈ－ピラゾロ［3，4－d］ピリミジン－4－イルアミン］－ブタン－1－オール；［3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－1Ｈ－ピラゾロ－［3，4－d］ピリミジン－4－イル］－（1－メチルプロピル）アミン；4－（1－メトキシメチルプロポキシ）－3，6－ジメチル－1－（2，4，6－トリメチルフェニル）－１Ｈ－ピラゾロ［3，4－d］ピリミジン；n－ブチル－エチル－［2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7Ｈ－ピロロ［2，3－d］ピリミジン－4－イル］アミン；ジ－n－プロピル－［2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7Ｈ－ピロロ［2，3－d］ピリミジン－4－イル］アミン；エチル－n－プロピル－［2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7Ｈ－ピロロ［2，3－d］ピリミジン－4－イル］アミン；ジエチル－2，5－

ジメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン－4－イル］アミン；n－ブチル－エチル－［2，5，6－トリメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン－4－イル］アミン；2－｛N－n－ブチル－N－［2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン－4－イル］アミノ｝－エタノール；4－（1－エチル－プロピル）－2，5，6－トリメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン；n－ブチル－エチル－［2，5－ジメチル－7－（2，4－ジメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン－4－イル］アミン；2，5－ジメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジル－4－イル］－（1－エチル－プロピル）アミン；2－［7－（4－ブロモ－2，6－ジメチルフェニル）－2，5－ジメチル－7H－ピロロ［2，3－d］ピリミジン－4－イルアミノ］－ブタン－1－オール；2－（S）－［7－（4－ブロモ－2，6－ジメチルフェニル）－2，5－ジメチル－7H－ピロロ［2，3－d］ピリミジン－4－イルアミノ］－ブタン－1－オール；4－（1－エチル－プロポキシ）－2，5，6－トリメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン；4－（1－メトキシメチルプロポキシ）－2，5，6－トリメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ［2，3－d］ピリミジン；4－（1－エチル－ブチル）－2，5，6－トリメチル－7－（2，4，6－トリメチルフェニル）－7H－ピロロ－［2，3－d］ピリミジン；［7－（4－ブロモ－2，6－ジメチル－フェニル）－2，5－ジメチル－7H－ピロロ［2，3－d］ピリミジン－4－イル］－（1－メトキシメチル－プロピル）－アミン；2－［7－（2－ブロモ－4，6－ジメチル－フェニル）－2，5－ジメチル－7H－ピロロ［2，3－d］ピリミジン－4－イルアミノ］－ブタン－1－オール；2－［7－（4－エチル－2，6－ジメチル－フェニル）－2，5－ジメチル－7H－ピロロ［2，3－d］ピリミジン－4－イルアミノ］－ブタン－1－オール；2－［7－（2－エチル－4，6－ジメチルフェニル）－2，5－ジメチル－7H－ピロロ［2，3－d］ピリミジン－4－イルアミノ］－ブタン－1－オール；及び2－［7－（2－フルオロメチル－4，6－ジメチルフェニル）－2，5－ジメチル－7H－ピロロ［2，3－d］ピリミジン－4－イルアミノ］－ブタン－1－オール。

【００２０】CRFアンタゴニストによる、心臓での副交感神経及び交感神経の電気的作用の正常化によるQT分散における改善は、致命的な心室不整脈の発生を減少させる結果になり、そして死亡率の低減の結果になると考えられる。同様に、CRFアンタゴニストは同じメカニズムを介して、心拍変動の改善により死亡率を低減すると考えられる。心拍変動は中間心拍の周囲の揺動（fluctuations around the mean heart rate）であり、心臓性呼吸のコントロール系（cardiorespiratorycontrol system）の相関として用いることができる。低い心拍の変動、即ち副交感神経又は交感神経の何れかの支配は、糖尿病、心疾患及び骨折後（post－infarction）の患者における、並びに多くの神経障害（例えば、脳障害、ギランバレー症候群、小児突然死症候群、先天性過換気症候群）又は尿毒症性神経障害等における突然の心臓死に関係する（例えば、Malpasら、Diabetes、39：1177－1181（1990）；Wooら、J. Am. Coll. Cardfol. 、23：565－569（1994）；Biggerら、Circulation、85：164－171（1992）；及びvan Ravenswaaij－ArtsらのAnnals of Intemal Medicine、118：436－447（1993））を参照せよ。）。

【００２１】CRFアンタゴニストは、多くの疾患において、心臓及び呼吸器系への中枢神経の拍出（neural outflow）のバランスをとることによって突然死の発生を減じる。リスクのある患者は、心電図QT分散及び心拍変動という手段で、容易かつ安価にモニターされて、そのような治療が有効であるかどうかを決定することができる。

【００２２】疾患の状態に加えて、他の症状を緩和するために患者に投与されるある薬物は、QT分散及び／又は心拍変動を引き起こすか、又はそのような結果になりうる。このような薬物の例として、フェノチアジン及び非特異的抗精神病薬（例えば、クロルプロマジン、レスピラドン）、クラス1A及びクラスIII不整脈薬（例えば、キニジン及びソトロール）、並びに麻酔薬（例えば、エンフルラン、イソフルラン）等を挙げることができる。このような場合もまた、心臓における副交感神経及び交感神経の電気的作用を正常化し、患者のQT分散及び心拍変動を改善するために、CRFアンタゴニストを投与することが有効であると考えられる。

【００２３】CRFアンタゴニストは単独で、特定の患者における突然死を減じる一方で、CRFアンタゴニストを他の薬物と組み合わせることも好ましいと考えられる。例えば、心臓及び／又は呼吸器系への神経の拍出のバランスをとることができる他の薬物は、CRFアンタゴニストの有効性を相互作用によって改善しうる。

【００２４】本発明の方法において使用するための好ましい式I及びIIの化合物、並びにそれらの医薬として許容できる塩は、容易に製造することができる。式IIの化合物（A、D、及びYはNであり、二重結合でEとDとが結合し、Eが－CR_4である）は、上記のPCT公開WO94／13677に記載された１又はそれ以上の合成方法によって製造できる。式IIの化合物（A及びYはNであり、二重結合でEとDとが結合し、Eが－CR_4であり、Dが－CR_{10}である）は、上記のPCT公開WO94／13676に記載された１又はそれ以上の合成方法によって製造できる。式IIの化合物（Aが－CR_7であり、二重結合でEとDとが結合し、Eが－CR_4であり、D及びNが－CR_{10}であり、YがNである）は、上記のPC

T公開WO95／34563に記載された1又はそれ以上の合成方法によって製造できる。式IIの他の化合物及び式Iの化合物は、上記のPCT公開WO95／33750に記載された1又はそれ以上の合成方法によって製造できる。好ましい化合物のあるものの製造に関する更なる有用な情報は、PCT／IB95／00437（公開番号WO96／39388）中に与えられている。これは特定の中間体の生産を記載するものである。

【００２５】式I又はIIの化合物の医薬として許容できる塩は、酸性又は塩基性の基の塩を含む。例えば、医薬として許容できる塩は、R_{10}置換基がカルボキシである場合のような酸性の基の、ナトリウム、カルシウム又はカリウム塩を含む。そのような塩は、一般的には式I又はIIの化合物の1を、適当な溶媒中で、1モル等量のNaOH又はKOHと組み合わせることにより製造される。アミノ基のような塩基性の基の医薬として許容できる酸付加塩は、式I又はIIの化合物の塩基形態のものと適当な酸を反応させることにより形成される。塩基性の基の医薬として許容できる塩は、塩酸塩、シュウ酸塩、硫酸塩、リン酸塩、リン酸水素塩、リン酸二水素塩、酢酸塩、コハク酸塩、クエン酸塩、酒石酸塩、乳酸塩、マンデル酸塩、メタンスルホン酸（メシラート；mesylate）塩及びp－トルエンスルホン酸（トシラート；tosylate）塩等を含む。1価の酸の塩（例えば、塩酸塩、シュウ酸塩、p－トルエンスルホン酸塩、酢酸塩）の場合、少なくとも1モル等量、そして通常はモル過剰の酸を用いる。しかし、そのような塩が、硫酸塩、ヘミコハク酸塩（hemisuccinate）、リン酸水素塩又はリン酸塩として所望される場合、一般的には適切かつ正確な化学等量の酸が用いられる。

【００２６】フリーの塩基及び酸は、通常、所望の塩の沈殿が期待できる共溶媒中で組み合わされ、そうでなければ濃縮するか又は非溶媒を添加することによって単離される。

【００２７】本明細書において3～8員のシクロアルキル環、又は9～12員のビシクロアルキル環システムに言及するときは、それらの各々は所望により1又は2個のO、S、又はN－Gを有してもよく、シクロアルキル環又はビシクロアルキル環システムにおいては酸素及び硫黄原子が互いに結合しないことが理解される。シクロアルキル環が3員であるとき、１個のO、S又はN－Gを含んでもよい。例えば、O及びNHを有する6員のシクロアルキル環は、モルホリニルである。R_2又はR_5がヘテロサイクリック基である場合、基は、１個の炭素原子を介して連結することができる。

【００２８】上記の式I及びIIには、表される群類に含まれるすべての化合物のラセミ体及びすべての立体異性体（例えば、すべての幾何異性体、及びすべての光学異性体）が含まれることが意図されている。

【００２９】本発明の方法においては、式I及びIIの化合物、並びにそれらの医薬として許容できる塩は、単独で又は医薬として許容できるキャリヤと組み合わされて、単回又は複数回の何れかで投与されうる。好ましい医薬として許容できるキャリヤは、不活性固体希釈剤又は充填剤、滅菌水性溶液、及び種々の有機溶媒を含む。そして、活性化合物及び医薬として許容できるキャリヤとの組み合わせにより形成された医薬組成物は、種々の投与型、例えば、錠剤、粉末剤、トローチ剤（lozenge）、シロップ剤、注射用液剤等で容易に投与される。これらの医薬組成物は、適切であれば、芳香剤、結合剤、賦形剤等を含みうる。そして、経口投与の目的のためには、錠剤は、クエン酸ナトリウム、炭酸カルシウム及びリン酸カルシウムのような種々の賦形剤を含むことができ、でんぷん、アルギン酸及び特定の複合ケイ酸塩のような種々の崩壊剤と、ポリビニルピロリドン、ショ糖、ゼラチン及びアラビアゴムのような結合剤とを一緒に含んでもよい。加えて、ステアリン酸マグネシウム、ラウリル硫酸ナトリウム及びタルクのような滑剤は、錠剤化の目的のためにしばしば有用である。同一タイプの固体組成物はまた、軟質及び硬質ゼラチンカプセル中に充填物として用いることができる。これは、好ましくはラクトース（乳糖）及び高分子量のポリエチレングリコールを含む。水性懸濁剤又はエリキシル剤が経口投与のために求められるときは、水、エタノール、プロピレングリコール、グリセリン及びそれらの組み合わせのような希釈剤とともに、その剤の中の本質的な活性成分は、種々の甘味剤又は芳香剤、着色料又は染料及び、望ましければ、乳化剤又は懸濁化剤と組み合わせることができる。一般的には経口投与が好ましい。しかし、患者が嚥下することができないとき、又はそれ以外の理由で経口投与に支障があるときは、直腸、腸管外（parenteral）又は局所投与のような他の投与経路が適するであろう。

【００３０】腸管外投与のためには、ゴマ油若しくは落花生油、水溶性プロピレングリコール又は滅菌水溶液中に溶解した活性成分の液剤を用いることができる。そのような液剤は、必要であれば緩衝化することが好ましく、また、そのような液体は最初に充分な塩類又はグルコースで等張化する。このような特別の液剤は、静脈中、筋中、皮下又は腹腔内に投与するのに特に好ましい。用いられる滅菌水性溶媒は当業者に知られた標準的な技術によって得ることができる。

【００３１】経皮的（例えば局所）投与の目的のためには、希釈され、滅菌された水性又は部分的に水性の液剤（通常約0．1％～5％濃度）、そうでなければ上記の腸管外投与用液剤と同様のものを用いることができる。

【００３２】ある量の活性成分を有する種々の医薬組成物の製造方法は、当業者に知られており、又は本明細書の開示により明らかである。他には、例えば、Remington'sPharmaceutical Sciences、Mack Publishing社、Easton、Pa.、第15版（1975）を参照せよ。

【００３３】本発明の方法において、式I及びIIの化合物並びにそれらの医薬として許容できる塩の効果的な投与量は、医者には一般的に知られているように、意図する投与経路及び他の要素（例えば、患者の年齢及び体重）に依存する。一般的には、一日あたりの投与量は、約0．1mg／kg～約50mg／kg（治療されるべき患者の体重）が好ましい。より好ましくは、一日あたりの投与量は、約1．0mg／kg～約20mg／kg（体重）である。この一日あたりの投与量は、単回又は分割投与により与えることができる。

【００３４】式I及びIIの化合物並びにそれらの医薬として許容できる塩の、CRFアンタゴニスト活性の検定方法は、Wynnら、Endocrinology、116：1653－1659（1985）及びGrigoriadisら、Peptides、10：179－188（1989）に記載されている。これらの方法は、試験されるされる化合物のCRF受容体に対する結合親和性（CRFアンタゴニストとして期待される活性に非常に関係がある）を測定するものである。IC_{50}値として表現される活性化合物の結合親和性は、概して、約0．2ナノモル濃度～約10マイクロモル濃度である。

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(71) Applicants *(for all designated States except US)*: **NEUROGEN CORPORATION** [US/US]; 35 Northeast Industrial Road, Branford, CT 06405 (US). **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DARROW, James, W.** [US/US]; 4 Dinatale Drive, Wallingford, CT 06492 (US). **DE LOMBAERT, Stephane** [US/US]; 37 Concord Drive, Madison, CT 06443 (US). **BLUM, Charles** [US/US]; 785 West Pond Meadow Rd., Westbrook, CT 06498 (US). **TRAN, Jennifer** [US/US]; 56 Barker Hill drive, Guilford, CT 06437 (US). **GIANGIORDANO, Mark** [US/US]; Building 2-14, 45 Jefferson Road, Branford, CT 06405 (US). **GRIFFITH, David, Andrew** [US/US]; 10 Barley Hill Road, Old Saybrook, CT 06475 (US). **CARPINO, Philip, Albert** [US/US]; 50 Meridian St., Groton, CT 06340 (US).

(74) Agents: **RICHARDS, John**; Ladas & Parry, 26 West 61st Sreet, New York, NY 10023 et al. (US).

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(54) Title: AMINO SUBSTITUTED PYRAZOLO[1,5,-a]-1,5-PYRIMIDINES AND PYRAZOLO[1,5-a]-1,3,5-TRIAZINES

(57) Abstract: Disclosed are compounds of the formula: (I), where R^1, R^2, R^3, R^4, R^5, R^6, and X are defined herein. These compounds are selective modulators of NPY1 receptors. These compounds are useful in the treatment of a number of CNS disorders, metabolic disorders, and peripheral disorders, particularly eating disorders and hypertension. Methods of treatment of such disorders as well as packaged pharmaceutical compositions are also provided. Compounds of the invention are also useful as probes for the localization of NPY1 receptors and as standards in assays for NPY1 receptor binding. Methods of using the compounds in receptor localization studies are given.

APPLICATION FOR UNITED STATES LETTERS PATENT IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

(Case No. U-012956-1)

(FORMERLY PROVISIONAL U012425-2)

Title: Amino Substituted Pyrazolo[1,5,-a]-1,5-Pyrimidines and Pyrazolo [1,5-a]-1,3,5-Triazines

Amino Substituted Pyrazolo[1,5,-a]-1,5-Pyrimidines and Pyrazolo[1,5-a]-1,3,5-Triazines

Related Application

This application claims priority from provisional application 60/156868 filed on September 30, 1999, which is incorporated herein by reference.

Field of the Invention

This invention relates to certain amino substituted pyrazolo[1,5,-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines, preferably those which selectively and/or potently bind mammalian neuropeptide Y (NPY) receptors. This invention also relates to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds in treating physiological disorders associated with an excess of neuropeptide Y, especially feeding disorders, some psychiatric disorders, and certain cardiovascular diseases.

Background of the Invention

Neuropeptide Y (NPY) is a 36 amino acid peptide first isolated in 1982 and subsequently found to be largely conserved across species. It belongs to a large family of peptides that includes, among others, peptide YY (PYY) and pancreatic peptide (PP). NPY is believed to be the most abundant peptide in the mammalian brain. It is also found in sympathetic neurons, and NPY-containing fibers have been found in peripheral tissues, such as around the arteries in the heart, the respiratory tract, the gastrointestinal tract, and the genitourinary tract. Central injection of NPY elicits a multitude of physiological responses, such as stimulation of feeding, increase in fat storage, elevation of blood sugar and insulin, anxiolytic behaviors, reduction in locomotor activity, hormone release, increase in blood pressure, reduction in body temperature, and catalepsy. In the cardiovascular system, NPY is believed to be involved in the regulation of coronary tone, while in the gastrointestinal tract, PYY is reported to cause inhibition of gastric acid secretion, pancreatic exocrine secretion, and gastroinestinal motility. These effects appear to be selectively mediated by various NPY receptors which currently include the Y_1, Y_2, Y_3, Y_4, Y_5, and Y_6 subtypes, in addition to the hypothetical Y_1-like subtype. Selective peptidic agonists and

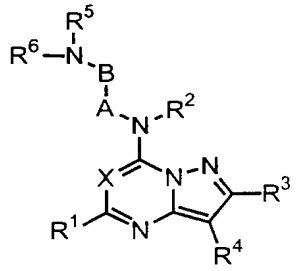
antagonists have been identified for most of the subtypes, but few selective non-peptidic antagonists have been reported. The Y_1 and Y_5 receptor subtypes appear to be involved in appetite regulation, but their relative contribution to the modulation of food intake and energy expenditure remains unclear. The discovery of non-peptidic antagonists of the Y_1 and/or Y_5 receptor provides novel therapeutic agents, that are less prone to the shortcomings of the peptide antagonists, namely, for example, poor metabolic stability, low oral bioavailability, and poor brain permeability, for the treatment of obesity and cardiovascular diseases. Recently, a few of such agents have been reported, some of which having demonstrated pharmacological efficacy in pre-clinical animal models. The present invention provides a novel class of potent non-peptidic antagonists of the NPY receptors, in particular, the Y_1 receptor.

Insofar as is known, aminoalkyl substituted pyrazolo[1,5,-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines have not been previously reported as NPY receptor antagonists useful in the treatment of feeding and cardiovascular disorders. However, this general class of compounds has been described for other uses by virtue of different mechanisms of action, e.g., as antagonists of the corticotropin releasing factor (CRF_1). For example International Patent Publication WO 98/03510 describes certain pyraazolotriazines and pyrazolopyrimidines as being of use as corticotropin releasing factors.

Summary of the Invention

Compounds that interact with the Y_1 receptor and inhibit the activity of neuropeptide Y at those receptors are useful in treating physiological disorders associated with an excess of neuropeptide Y, including eating disorders, such as, for example, obesity and bulimia, and certain cardiovascular diseases, for example, hypertension.

This invention relates to a method of treating a physiological disorder associated with an excess of neuropeptide Y, which method comprises administering to a mammal in need of said treatment an effective amount of an amino substituted pyrazolo[1,5,-a]-1,5-pyrimidine or a pyrazolo[1,5-a]-1,3,5-triazine of the formula I:



Formula I

or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, and

X is N or CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with

R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2 –C_6-alkenyl, C_2 –C_6-alkynyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl,

or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that for SO_2R^7, R^7 cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN.

Preferred compounds of Formula I exhibit a 20-fold or more greater affinity for the NPY_1 receptor than for the CRF_1 receptor. Preferred compounds of Formula I also do not exhibit high affinity for the CRF_1 receptor.

This invention also encompasses, in additional embodiments, the novel compounds of formula I, and the salts and solvates thereof, as well as pharmaceutical formulations comprising a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers, excipients, or diluents thereof.

This invention also encompasses methods to treat physiological disorders associated with an excess of neuropeptide Y, such as eating and cardiovascular disorders, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of the formula I.

This invention also encompasses methods of selectively inhibiting binding of NPY to NPY_1 receptors, which comprises contacting a compound of formula I with neuronal cells, wherein the compound is present in an amount effective to produce a concentration sufficient to inhibit binding of NPY to NPY_1 receptors in vitro.

Detailed Description of the Invention

The current invention includes a novel group of aminoalkyl substituted 4-amino pyrazolopyrimidines and 7-amino pyrazolo triazines, those of formula I. Preferred aminoalkyl substituted 4-amino pyrazolopyrimidines and 7-amino pyrazolo triazines bind with high affinity to the NPY_1 receptor and more preferably act as antagonists of NPY binding to the NPY_1 receptor. Preferred compounds of the invention bind with high selectivity to the NPY_1 receptor, particulary such compounds do not bind with high affinity to CRF_1 receptors. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of Formula I with the NPY1 receptor results in the pharmaceutical utility of these compounds.

The invention further comprises methods of treating patients in need of such treatment with an amount of a compound of the invention sufficient to alter the symptoms of a eating disorder or cardiovascular disorder.

The present invention also pertains to methods of inhibiting the binding of NPY receptor ligands, such as NPY or PYY, to the NPY_1 receptors which methods involve contacting a compound of the invention with cells expressing NPY_1 receptors, wherein the compound is present at a concentration sufficient to inhibit the binding of NPY receptor Ligands to NPY_1 receptors *in vitro*. This method includes inhibiting the binding of NPY receptor ligands to NPY_1 receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of NPY receptor ligands to NPY receptors *in vitro*. The amount of a compound that would be sufficient to inhibit the binding of a NPY receptor ligand to the NPY_1 receptor may be readily determined via an NPY_1 receptor binding assay, such as the assay described in Example 94A. The NPY_1 receptors used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of rat brain or from cells expressing cloned human NPY_1 receptors.

The present invention also pertains to methods for altering the signal-transducing activity of NPY1 nreceptors, said method comprising exposing cells expressing such receptors to an effective amount of a compound of the invention. This method includes altering the signal-transducing activity of NPY1 receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to alter the signal-transducing activity of NPY1 receptors *in vitro*. The amount of a compound that would be sufficient to alter the signal-transducing activity of NPY1 receptors may be determined via a NPY1 receptor signal transduction assay, such as the assay described in Example 93B.

The NPY1 receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the NPY1 receptor.

Radiolabeled derivatives the NPY1 receptor ligands provided by this invention are also useful for mapping the location of NPY1 receptors (e.g., in tissue sections via autoradiography) and as radiotracers for positron emission tomography (PET) imaging, single photon emission computerized tomography (SPECT), and the like, to characterize such receptors in living subjects.

In addition to compounds of Formula I, the invention also provides as preferred compounds, compounds of Formula I wherein

X is N or CH; and

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl. Such compounds will be referred to as compounds of **Formula Ia**.

Other preferred compounds of Formula I are those compounds wherein

X is N or CH; R^1 is C_1-C_6 alkyl; R^2 is H or C_1-C_6 alkyl; and

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl. Such compounds will be referred to as compounds of **Formula Ib**.

In another embodiment the invention provides compounds of Formula I, wherein

X is N or CH; R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; R^2 is H or C_1-C_6 alkyl; R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and R^5 is H. Such compounds will be referred to as compounds of **Formula Ic**.

Further provided are compounds wherein:

X is N or CH; R^1 is C_1-C_6 alkyl; R^2 is H or C_1-C_6 alkyl; R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; R^4 is phenyl, mono-, di-, or tri-substituted C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and R^7, R^8, and R^9 are as defined for Formula I. Such compounds will be referred to as compounds of **Formula Id**.

In yet another embodiment the invention provides compounds of Formula I wherein X is N or CH; R^1 is C_1-C_6 alkyl; R^2 is H or C_1-C_6 alkyl; R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and R^4 is phenyl, mono-, di-, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$,

C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; R^5 is H; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl. Such compounds will be referred to as compounds of **Formula Ie**.

Additionally the invention provides compounds of Formula I wherein X is N or CH; R^1 is C_1-C_6 alkyl; R^2 is H or C_1-C_6 alkyl; R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and R^4 is phenyl, mono-, di-, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl. Such compounds will be referred to as compounds of **Formula If.**

Particularly preferred are compounds of Formula I wherein R^5 is H, and R^6 is cycloalkyl or (cycloalkyl)alkyl.(Compounds of **Formula Ig**)

For each of Formula Ia-Ig compounds that exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding are preferred. Also preferred are compounds of Formula I, and Formula Ia-Ig that do not exhibit a Ki or IC_{50} of 5 micromolar or less, or more preferably that do not exhibit a Ki or IC_{50} of 1 micromolar or less, for the CRF1 receptor in an assay of CRF1 receptor binding. An assay of CRF receptor binding is given in Example 94.

In certain situations, the compounds of formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by

conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

Representative compounds of the present invention, which are encompassed by formula I, include, but are not limited to the compounds in Examples 1-87 and their pharmaceutically acceptable acid addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-(CH_2)n-COOH where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the acylated prodrugs of the compounds of formula I. "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 the invention 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. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by formula I.

Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers. The invention includes all tautomeric forms of a compound.

By "heteroatom" in the present invention is meant oxygen or sulfur, or a nitrogen atom optionally substituted by C_1-C_6 lower alkyl, C_1-C_6 arylalkyl, C_1-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_8 alkanoyl, C_1-C_6 sulfonyl.

By "alkyl", "lower alkyl", or "C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "cycloalkyl", or "C_3-C_{10} cycloalkyl" in the present invention is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi-, or polycyclic ring system, such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like.

By "(cycloalkyl)alkyl", "lower (cycloalkyl)alkyl", or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl in the present invention is meant a straight or branched alkyl substituent formed of 1 to 6 carbon atoms attached to a mono-, bi, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, and the like.

The term "C_2-C_6 alkenyl" in the present invention means hydrocarbon chains having 2 to 6 carbons in a straight or branched arrangement and containing one or more unsaturated carbon-carbon double bonds which may occur in any stable point along the chain, such as, for example, ethenyl, allyl, isopropenyl, and the like.

By "cycloalkenyl" or "C_3-C_{10} cycloalkenyl" in the present invention is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi, or polycyclic ring system having 3-10 carbon atoms and containing one or more carbon-carbon double bonds which may occur in any stable point in the ring, such as, for example, cyclopentenyl, cyclohexenyl, or cycloheptenyl.

The term "C_2-C_6 alkynyl" in the present invention means hydrocarbon chains having 2 to 6 carbons in a straight or branched arrangement and containing one or more unsaturated carbon-carbon triple bonds which may occur in any stable point along the chain, such as, for example, ethynyl, propargyl, and the like.

The term "aryl" in the present invention means a monocyclic or bicyclic aromatic group having preferably 6 to 10 carbon atoms, such as, for example, phenyl or naphthyl.

The term "heteroaryl" in the present invention means an aryl group in which one or more of the ring(s) carbon atoms have been replaced with a heteroatom. Such groups preferably have

4 to 10 carbon atoms and 1 to 4 heteroatoms, such as, for example, pyridyl, pyrimidinyl, triazinyl, imidazolyl, oxazolyl, isoxazolyl, indolyl, pyrrolyl, pyrazolyl, quinolinyl, isoquinolinyl, thiazolyl, benzothiadiazolyl, triazolyl, triazinyl, pyrazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, tetrazolyl.

The term "heterocyclyl", "heterocycle"or "heterocycloalkyl" in the present invention means a saturated or partially saturated heteroaryl group.

By "C_1-C_6 arylalkyl" or "C_1-C_6 heteroarylalkyl" in the present invention is meant a branched or straight-chain alkyl group having 1-6 carbon atoms and substituted on one of the carbon atoms by an optionally substituted aryl or heteroaryl ring, such as, for example, benzyl, phenethyl, methylpyridyl, ethylpyridyl, and the like.

By "C_5-C_8 arylcycloalkyl" in the present invention is meant cycloalkyl groups having 5-8 carbon atoms and fused to an aryl group, such as, for example, 1,2,3,4 tetrahydronaphthalenyl, 2,3-dihydrobenzothienyl, or 2,3-dihydobenzofuranyl.

By "C_5-C_8 heteroarylcycloalkyl" in the present invention is meant cycloalkyl groups having 5-8 carbon atoms fused to a heteroaryl group, such as, for example, 1,2,3,4 tetrahydroquinolyl, 2,3-dihydrobenzothienyl, 2,3-dihydobenzofuranyl, or indolinyl.

By "alkoxy", "C_1-C_6 alkoxy", or "C_1-C_6 alkyloxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By "cycloalkoxy", "C_3-C_{10} cycloalkoxy", or "C_3-C_{10} cycloalkyloxy" in the present invention is meant a group formed by an oxygen atom attached to a mono-, bi, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, or cycloheptoxy.

By "(cycloalkyl)alkyloxy", "(C_3-C_{10} cycloalkyl) C_1-C_6 alkoxy", or "(C_3-C_{10} cycloalkyl) C_1-C_6 alkyloxy" in the present invention is meant a group formed by an oxygen atom attached to a 1-6 carbon chain linked to a mono-, bi, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropylmethyloxy, cyclobutylmethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, cycloheptylmethyloxy, and the like.

By "C_3-C_6 aminocarbocycle" is meant a cyclic amino group formed by a nitrogen contained in a ring having 3 to 6 carbon atoms, such as, for example, azetidino, pyrrolidino, piperidino, perhydroazepino.

By "C_2-C_5 aminoheterocycle" is meant a cyclic amino group formed by a nitrogen contained in a ring having 2 to 5 carbon atoms and one other heteroatom, such as, for example, morpholino, thiomorpholino, piperazino.

By the terms "halo" or "halogen" in the present invention is meant fluoro, chloro, bromo, and iodo.

"Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms substituted with 1 or more halogens.

The term "C_2-C_8 alkanoyl" means an acyl group with 2 to 8 carbon atoms in a linear, branched, or C_3-C_{10} cycloalkyl arrangement, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, trifluoromethyl, OR^7, NR^8R^9, $CONR^8R^9$, $COOR^7$, or CN.

The term "C_1-C_6 alkyl sulfonyl" means an alkylsulfonyl group containing 1 to 6 carbon atoms in a linear, branched, or C_3-C_7 cycloalkyl arrangement.

The term "substituted" means that one or more hydrogen on the designated atom is replaced by the specified group, provided that the valence on the designated atom is not exceeded, and that a chemically stable compound results from the substitution.

A stable compound is defined herein as one that can be isolated, characterized, and tested for biological activity.

The term "oxo" (i.e. =O) indicates that two geminal hydrogen atoms are replaced by a double-bond oxygen group.

The term "hydroximino" (i.e. =N-OH)) indicates that two geminal hydrogen atoms are replaced by a double-bond nitrogen atom substituted with a hydroxyl group.

The term "C_1-C_6 alkoximino" (i.e. =N-O-Alkyl) indicates that two geminal hydrogen atoms are replaced by a double-bond nitrogen atom substituted with a C_1-C_2 alkoxy group, such as, for example, methoximino (=N-OMe).

In the present invention, the term "potent" in the context of NPY1 receptor antagonists qualifies a binding affinity with a Ki of less than 10 micromolar, preferably less than 1 micromolar, and more preferably less than 100 nanomolar in the human NPY1 binding assay.

In the present invention, the term "selective" in the context of NPY1 receptor antagonists qualifies a binding affinity with a Ki in the human NPY1 binding assay that is 10-fold or 20-fold, preferably 100-fold, and more preferably 1000-fold, less than the Ki of the same compound measured in another receptor binding assay, in particular the NPY_5 and $CRF1_1$ receptor binding assays. Binding assays for the NPY_5 and $CRF1_1$ receptors have been described, for example, in *J. Clin. Invest.*, 102, 2136 (**1998**) and in *Endocrinology* 116, 1653 (**1985**), respectively. A CRF1 receptor binding assay is also given in Example 94.

As the compounds of formula I are selective antagonists of the Y1 receptor, they are of value in the treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of neuropeptide Y. Thus, the invention provides methods for the treatment or prevention of a physiological disorder associated with an excess of neuropeptide Y, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof. The term "physiological disorder associated with an excess of neuropeptide Y" encompasses those disorders associated with an inappropriate stimulation of neuropeptide Y receptors, regardless of the actual amount of neuropeptide Y present locally. These physiological disorders may include: disorders or diseases pertaining to the heart, blood vessels or the renal system, such as vasospasm, heart failure, shock, cardiac hypertrophy increased blood pressure, angina, myocardial infarction, sudden cardiac death, arrhythmia, peripheral vascular disease, and abnormal renal conditions such as impaired flow of fluid, abnormal mass transport, or renal failure; conditions related to increased sympathetic nerve activity for example, during or after coronary artery surgery, and operations and surgery in the gastrointestinal tract; cerebral diseases and diseases related to the central nervous system, such as cerebral infarction, neurodegeneration, epilepsy, stroke, and conditions related to stroke, cerebral vasospasm and hemorrhage, depression, anxiety, schizophrenia, and dementia; conditions related to pain or nociception; diseases related to abnormal gastrointestinal motility and secretion, such as different forms of ileus, urinary incontinence, and Crohn's disease; abnormal drink and food intake disorders, such as obesity, anorexia, bulimia, and metabolic disorders; diseases related to sexual dysfunction and reproductive disorders; conditions or disorders associated with inflammation; respiratory diseases, such as asthma and conditions related to asthma and

bronchoconstriction; and diseases related to abnormal hormone release, such as leutinizing hormone, growth hormone, insulin, and prolactin.

Pharmaceutical Preparations

The compounds of general 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 term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. 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.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert 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 may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

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 or kaolin, 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 of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachid 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 palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

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, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachid 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 and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said

partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. 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. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions 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 are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 50 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 3 g per patient per day), although higher amounts , for example up to 140 mg./kg/day may be appropriate in some circumstances. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most eating disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of stress and depression a dosage regimen of 1 or 2 times daily is particularly preferred.

It will be understood, however, that the specific dose level 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 undergoing therapy.

Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to oral bioavailability, low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.

Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (*Journal of Chromatography B* **1996,** *677*, 1-27).

Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (*Drug Metabolism and Disposition* **1998,** *26*, 1120-1127).

As discussed above, preferred compounds of the invention exhibit good activity in standard *in vitro* NPY receptor binding assays, specifically the assay as specified in Example 93A, which follows. References herein to "standard *in vitro* NPY receptor binding assay" are intended to refer to that protocol as defined in Example 93A which follows. Generally preferred compounds of the invention exhibit a K_i of about 1 micromolar or less, still more preferably and K_i of about 100 nanomolar or less even more preferably an K_i of about 10 nanomolar or less or even 1 nanomolar or less in such a defined standard *in vitro* NPY receptor binding assay as exemplified by Example 93A which follows.

In appropriate case, the compounds of the invention may be employed in combination with other active agents. The invention therefore also provides pharmaceutical combination compositions comprising a therapeutically effective amount of a composition comprising: (a) first compound, said first compound being a compound as described above a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle or diluent. . To this end therefore the invention also provides a kit comprising: (a) first compound, said first compound being a compound as described above, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; and (c) means for containing said first and second unit dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

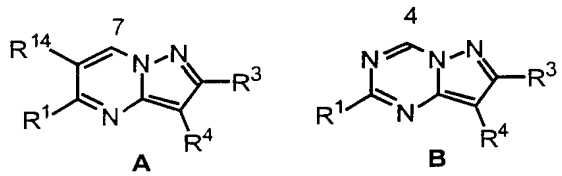
Synthetic Schemes

Preparation of Amino Substituted Pyrazolo[1,5,-a]-1,5-Pyrimidines and Pyrazolo[1,5-a]-1,3,5-Triazines Derivatives

An illustration of preparation methods of compounds of the present invention is given in the Schemes below. In particular displacement of a leaving group Z, as in formula **10** (Scheme 1) by the appropriate substituted amine provides a method to convert the heterocyclic cores of the present invention, i.e. aryl or heteroaryl substituted pyrazolo[1,5,-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines, into compounds that potently interact with the NPY1 receptor. Such transformations may require several consecutive chemical steps. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention. The disclosures of all articles and references mentioned in this application, including patents, are incorporated herein by reference.

Unless otherwise specified the variable R^1, R^2, R^3, R^4, R^5, R^6, and X are as defined for Formula I.

One general approach is to convert a heterocyclic core **A** and or a heterocyclic core **B**



A B

to a compound that exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, wherein

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN;

by substituting the 7-position of the heterocyclic core **A** or the 4-position of the heterocyclic core **B** with a diamine group $-N[R^2]-A-B-N[R^6]-R^5$

wherein:

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with

R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl,
or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that for SO_2R^7, R^7 cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

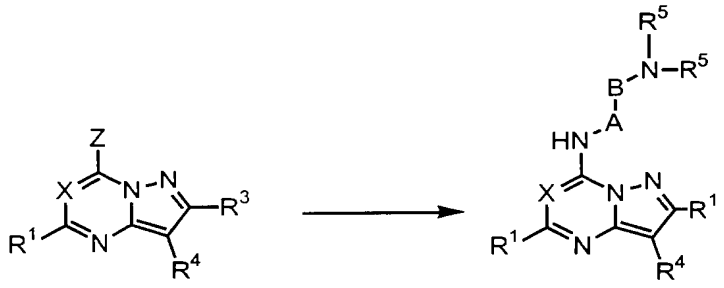
R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle; and

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H.

More specifically the following schemes may be used.

SCHEME 1



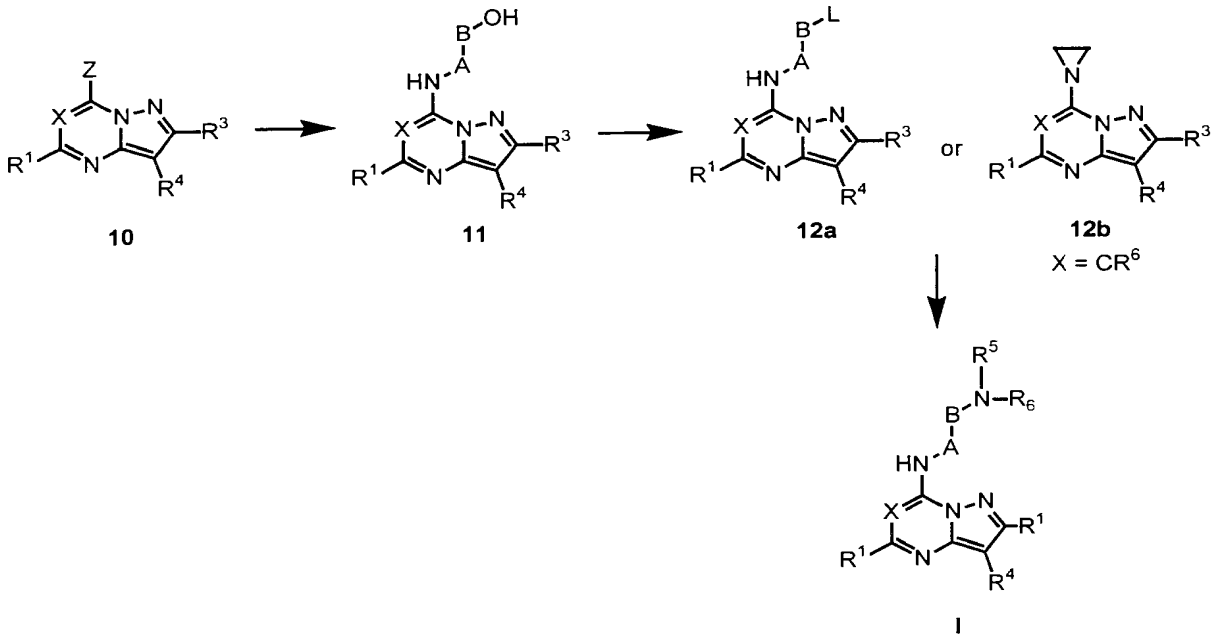
10 I

As illustrated in Scheme 1, compounds of formula I can be prepared from intermediate compounds of formula **10**, where Z is halogen (preferably chloro or bromo), alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy, and X, R^1, R^3 and R^4 are defined above, using the procedures outlined below.

Compounds of formula **10** react with an amine of formula H_2N-A-B-N[R^6]-R^5, where A,B, R^5 and R^6 are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C 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 (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or

toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

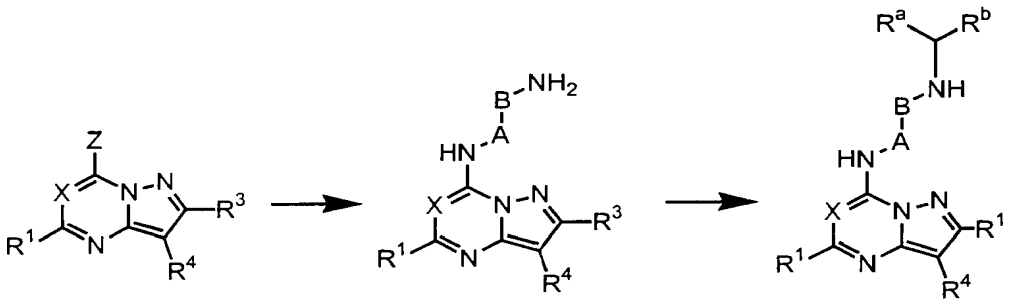
SCHEME 2



Alternatively, as shown in Scheme 2, compounds of formula I can be obtained by first reacting a compound of formula **10** with an amino alcohol of formula H_2N-A-B-OH, where A and B are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250°C to generate intermediates of formula **11**. Reacting a compound of formula **11** with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from –78°C to 250C°C to afford products of formula **12a** (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy) or **12b** when A and B are both CH_2 and X is CR^{14}. Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3, PBr_5., CCl_4/PPh_3. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl

aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from –20°C to 100C°C. Compounds of formula **12a** or **12b** can then be reacted with an amine of formula $HN[R^6]$-R^5, where R^5 and R^6 are defined as above, to give a compound of formula I. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

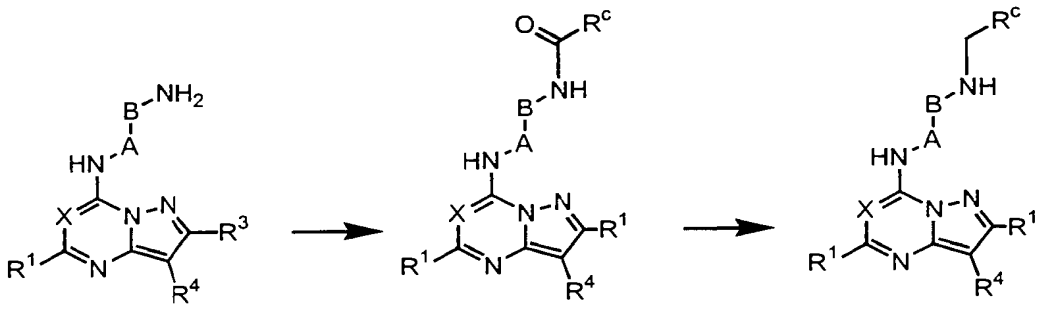
SCHEME 3



10 **13** **Ia**

A subset of compounds of formula I, described under formula Ia, can be obtained by first reacting a compound of formula **10** with a diamine of formula H_2N-A-B-NH_2, where A and B are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250°C to generate intermediates of formula **13**. Reaction of a compound of formula **13** with an aldehyde or ketone of Formula R^a-C=O-R^b in the presence of a reducing agent provides a compound of formula Ia, where the grouping R^a-CH-R^b corresponds to R^5 in formula I, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -78C°C to 100°C.

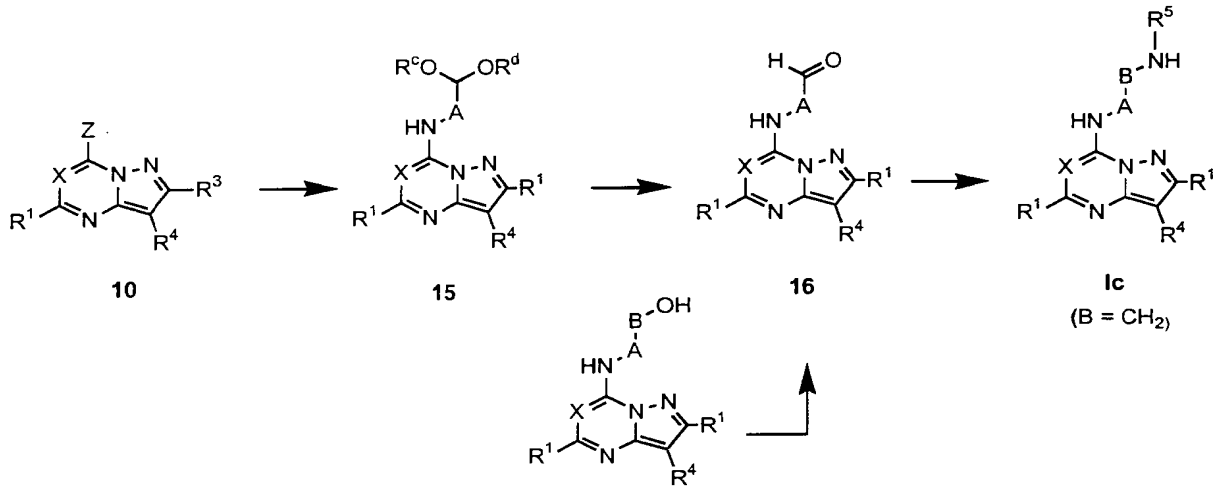
SCHEME 4



13 14 Ib

Alternatively, a subset of compounds of formula I, described under formula Ib, can be obtained by first reacting a compound of formula 13 with an activated acid of formula R^c-C=O-Z, where Z is halo (preferably chloro), O-acyl (preferably O-C=O-R^c), in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78 °Cto 250C°C to generate an amide intermediate of formula 14. Reaction of a compound of formula 14 with a reducing agent provides a compound of formula Ib, where the grouping R^c-CH_2 corresponds to R^5 in formula I, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -78°C to 100°C.

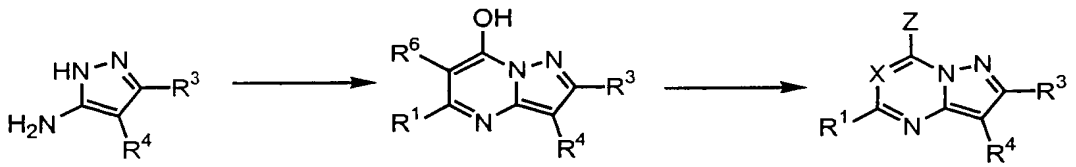
SCHEME 5



Alternatively, a subset of compounds of formula I, described under formula Ic, can be obtained by first reacting a compound of formula **10** with an amine of formula H_2N-A-CH(OR^c)(OR^d), where A is defined above, and R^c and R^d are C_1-C_6 lower alkyls or, taken together, complete a ketal group, such as, for example a dioxane or dioxolane group, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250C°C to generate compounds of formula **15**. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or

toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Compounds of formula **15** react with a protic acid in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250°C, followed by aqueous work-up to generate compounds of formula **16**. Inert solvents may include, but are not limited to dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Protic acids include, but are not limited to, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, methane sulfonic acid. Alternatively, compounds of formula **16** can be obtained by oxidation of compounds of formula **11** where B= CH_2. Oxidizing agents include, but are not limited to, transition metal oxides, such as CrO_3 or MnO_2, pyridine-chromium complexes, such as $CrO_3.C_5H_5N$, pyridinium dichromate or pyridinium chlorochromate, or an oxalyl chloride-DMSO-triethylamine reagent (Swern oxidation). Compounds of formula **16** react with amines of formula $H_2N\text{-}R^5$, where R^5 is defined above, in the presence of a reducing agent in the presence or absence of an inert solvent in the presence or absence of a protic acid at temperatures ranging from –78°C to 100°C, to give compounds of formula **Ic**. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene).

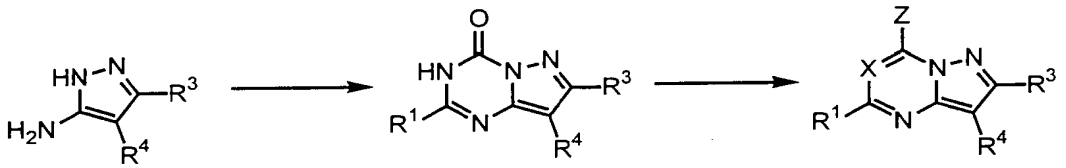
SCHEME 6



When X is CR^{14}, as defined above, compounds of formula **10** may be obtained from compounds of formula **22**. Compounds of formula **22** can be reacted with compounds of formula R^1-C=O-CH(R^{14})-C=O-R^c, where R^1 and R^{14} are defined above, and R^c is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence or absence of a base in an inert solvent at reaction temperatures ranging from –50C°C to 250C°C to afford compounds of formula **23a**. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Compounds of formula **23a** can then be reacted with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from –78C°C to 250°C to afford products of formula **10** (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy and X is CR^{14}). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3, or PBr_5. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or

anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

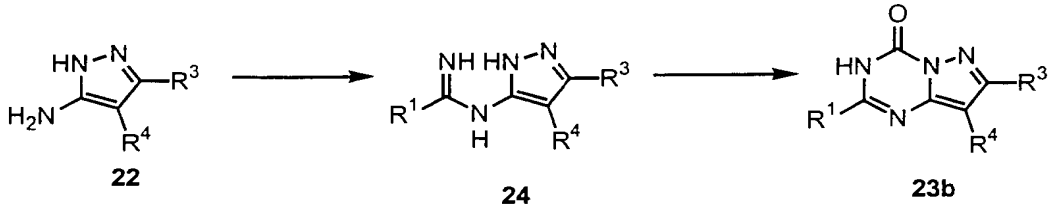
SCHEME 7



When X is N, compounds of formula **22** can be reacted with compounds of formula R^1-C=N($COOR^g$)-OR^f, where R^1 is defined above, and R^g is lower alkyl (1-6 carbons), and R^f is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence or absence of a base in an inert solvent at reaction temperatures ranging from –50°C to 250°C to afford compounds of formula **23b**. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably

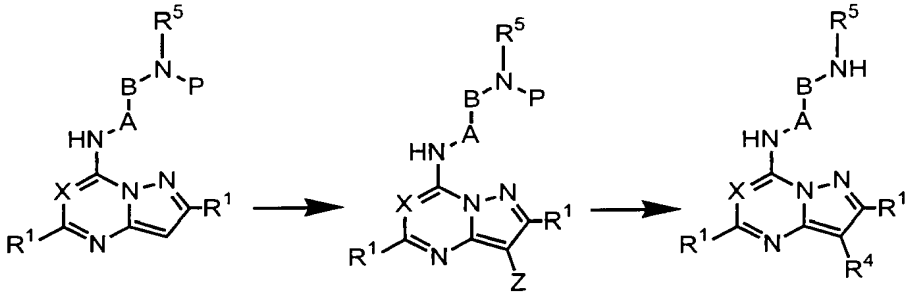
acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), heteroaromatic hydrocarbons (preferably pyridine). Compounds of formula **23b** can then be reacted with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from –78C to 250C to afford products of formula **10** (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy and X is N). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3, or PBr_5. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

SCHEME 8



Alternatively, compounds of formula **23b** can be obtained by first reacting compounds of formula **22** with compounds of the formula R^1-(C=NH)-OR^h, where R^1 is defined above and R^g is a lower alkyl group (preferably methyl or ethyl), in the presence or absence of an acid in an inert solvent to give an intermediate of formula **24**. Compounds of formula **24** react with a compound of formula R^i-C=O-R^j, where R^i and R^j are each or independently lower alkoxy (preferably methoxy or ethoxy), 1-imidazolyl, halo, aryloxy (preferably 4-nitrophenoxy) in the presence or absence of an inert solvent to afford compounds of formula **23b**. Bases may include, but are not limited to, alkali metals (preferably sodium), alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

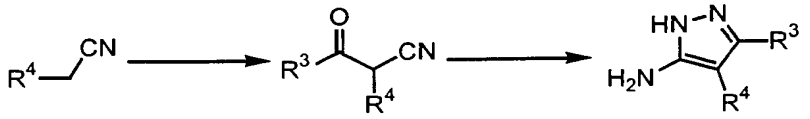
SCHEME 9



17 18 I

Compounds of formula I can also be prepared from compounds of formula **17** (prepared using the methods applicable to the synthesis of compounds of formula I), where P is H or an appropriate amino protecting group. Such groups, known in the art of organic synthesis for the protection of amines, include those listed in "Protective Groups in Organic Synthesis", by Greene and Wuts [John Wiley & Sons, NY, **1991**]. Examples of amine protecting groups include, but are not limited to, acyl types (such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl), carbamate types (such as benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenymethyloxycarbonyl, allyloxycarbonyl, and 2,2,2-trichloroethyloxycarbonyl), alkyl types (such as benzyl and triphenylmethyl). Reacting compounds of formula **17** with a halogenating agent provides compounds of formula **18** where X is Br, Cl, or I. Compounds of formula **18** react with a compound of formula R^4M (where M is alkali metal, ZnCl, ZnBr, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$, copper halides, $B(OH)_2$, B(O-lower alkyl)$_2$, or Sn(lower alkyl)$_3$) in the presence or absence of an organometallic catalyst in the presence or absence of a base in an inert solvent at temperatures ranging from −100°C to 200°C to give compounds of formula I (or their N-protected forms which can then be deprotected). Similar conditions have been described in WO 98/54093. Those skilled in the art will recognize that the reagents R^4M may be generated in situ. Organometallic catalysts include but are not limited to, palladium phosphine complexes (such as $Pd(PPh_3)_4$), palladium halides or alkanoates (such as $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$), or nickel complexes (such as $NiCl_2(PPh_3)_2$). Bases may include, but are not limited to, alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkali metal carbonates or bicarbonates, alkali metal hydroxides, alkali metal phosphates, or trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 10

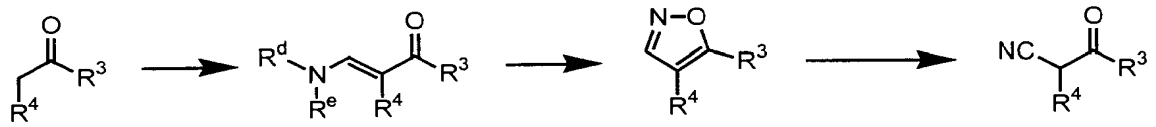


20 **21** **22**

Compounds of formula **22** may be obtained from compounds of formula **20**, where R^4 is defined as above. Compounds of formula **20** are reacted with compounds of formula R^3-C=O-R^c, where R^3 is defined above and R^c is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence of a base in an inert solvent at reaction temperatures ranging from –78°C to 200°C to afford compounds of formula **21**. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Alternatively, compounds of formula **20** may be reacted with a solvent of formula R^3-C=O-R^c, where R^3 is defined above and R^c is lower alkoxy (1-6 carbons), in the presence of an alkali metal (preferably sodium) at reaction temperatures ranging from –78°C to 200°C to afford compounds of formula **21**. Compounds of formula **21** may be reacted with hydrazine (hydrate or hydrochloride salt) in an inert solvent, at reaction temperatures ranging from 0°C to 200°C, preferably 70°C to 150°C, to afford compounds of formula **22**. Inert solvents may include, but are not limited to, water, lower alkanoic acids (preferably formic, acetic, or trifluoro acetic acid), alkyl alcohols (1-8 carbons) (preferably methanol or ethanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), cyclic ethers

(preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 11



24 **25** **26** **21**

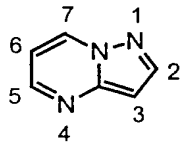
Alternatively, compounds of formula **21** can be obtained by first reacting compounds of formula **24** with dialkyl formamide dialkyl acetal of formula $(R^dR^e)N\text{-}CH(OR^f)_2$ where R^d, R^e, and R^f are each or independently C_1-C_6 lower alkyl (preferably methyl) in the presence or absence of an inert solvent at reaction temperatures ranging from 0°C to 250°C, preferably between 70C°C and 150°C to provide compounds of formula **25**. Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Compounds of formula 25 can be reacted with hydroxylamine salt (preferably hydrochloride) in the presence or absence of an inert solvent at reaction temperatures ranging from 0°C to 250°C, preferably between 70C°C and 200°C to provide oxazoles of formula **26**. Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Oxazole intermediates of formula **26**

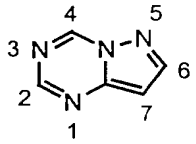
can be reacted with a base in the presence or absence of an inert solvent at reaction temperatures ranging from 0C°C to 200°C. Bases may include, but are not limited to, alkali hydroxides (preferably sodium or potassium hydroxide), alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

EXAMPLES

The following examples listed in the TABLE are provided to describe the invention in further details. These examples can be prepared by one or more of the above-mentioned method and are intended to illustrate and not to limit the invention.

The numbering system used to describe the compounds of the present invention is as follows:





Commercial reagents were used without further purification. THF refers to tetrahydrofuran. LDA refers to lithium diisopropylamide and DBU refers to 1,8-diazabicyclo[5.4.0]undec-7-ene. Room or ambient temperature refers to 20°C to 25°C. Concentration implies the use of a rotary evaporator. TLC refers to thin layer chromatography.

Mass spectral data were obtained either by CI or APCI methods. Other commonly used abbreviations are: Ph is phenyl, Me is methyl, Et is ethyl, Pr is n-propyl, iPr is isopropyl, Bu is butyl, iBu is isobutyl (CH_2-$CHMe_2$), tBu is tert-butyl, cBu is cyclobutyl, Pent is n-pentyl, cPent is cyclopentyl, cHex is cyclohexyl, Py is pyridyl, MeOH means methanol, EtOH means ethanol, EtOAc means ethyl acetate, Et_2O means diethyl ether, CH_2Cl_2 means methylene chloride, DMSO means dimethyl sulfoxide, NMP means N-methyl pyrrolidone, THF means tetrahydrofuran, DMF means dimethyl formamide, EX means example,

EXAMPLE 1

Preparation of 7-(2-(cyclohexylamino)ethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine

(formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R3 is CH_3, R^4 is 2,6-dimethyl-4-chlorophenyl, R^5 is cyclohexyl)

A. 4-Bromo-3,5-dimethyl chlorobenzene

Slurry 2,6-dimethyl-4-chloroaniline hydrochloride (23g, 193.11 g/mol) in CH_2Cl_2 (100 ml) and wash with saturated $NaHCO_3$ to generate the free base. Dry over Na_2SO_4, filter and evaporate down to a violet oil. Slurry up in 120 mL 6.0 N H_2SO_4 and stir vigorously at ambient temperature to break up larger pieces of solid. Cool to 0°C in an ice/water bath, then portionwise over 15 min add a clear colorless solution of $NaNO_2$ in 50 mL H_2O. Maintain temperature 15°C over course of addition, stirring under dry N_2. After 1 hour, carefully pour the cold reaction solution (solution A) into a second solution (solution B) containing 31.7 g CuBr in 33 mL aqueous HBr (48%) at ambient temperature. Let stand at ambient temperature until gas evolution ceases, then heat to 110°C under N_2 while stirring. Stir for 3 h, then cool to rt. Extract the aqueous layer with a (2:1) mixture of hexanes and Et_20 (2 x 500 mL), then dry the combined organic layers over Na_2SO_4, filter and evaporate down to a brown oil. Triturate the oil with hexanes (100 mL), filter out the remaining solids and wash with copious amounts of hexanes.

Evaporate the hexane layers to concentrate then flush through a pad of silica to remove baseline material, using hexanes as eluent. Evaporate to a clear colorless oil (13.5g).

B. 4-Chloro-2,6-dimethyl benzaldehyde

Dissolve 4-bromo-3,5-dimethyl chlorobenzene (6.5 g) in 50 mL anhydrous THF and cool to –78°C (dry ice/acetone) under N_2. Dropwise over 5 min add a solution of butyllithium (12.50 mL, 2.5M in hexanes) to the stirring solution of aryl bromide at –78°C. After 2 h, dropwise add anhydrous DMF (5.0 mL) to the orange/red reaction solution and allow to warm to ambient temperature overnight while stirring under N_2. Evaporate the yellow solution down to a yellow oil and partition between H_2O (100 mL) and CH_2Cl_2 (100 mL). Extract the aqueous layer once with CH_2Cl_2, then pool the organic layers and dry over Na_2SO_4, filter and evaporate down to 5.0 g of yellow oil. Use without further purification. LCMS = 169.6 (MH^+)

C. 4-Chloro-2,6-dimethyl benzyl alcohol

Dissolve 4-chloro-2,6-dimethyl benzaldehyde (5.0 g, 168.64 g/mol) in 100 mL dry MeOH. Cool to 0°C while stirring under N_2. Portionwise add powdered $NaBH_4$ (0.76g, 37.85 g/mol) over 5 min. Stir at 0°C for 2 h, monitoring by TLC until aldehyde consumed, then evaporate to a yellow oil. Add H_2O (50 mL) and bring to pH 7.0 by addition of saturated NH_4Cl. Extract the neutral aqueous layer with CH_2Cl_2 (3 x 75 mL) and dry the pooled organic layers over Na_2SO_4. Filter and concentrate to a yellow oil. Flush through a pad of silica to remove baseline material, then evaporate to a yellow solid (3.0 g) which can be used without further purification. LCMS = 171.6 (MH^+), 169.6 (M^-)

D. 4-Chloro-2,6-dimethyl phenyl acetonitrile

Dissolve 4-chloro-2,6-dimethyl benzyl alcohol (2.8g, 170.66 g/mol) in CH_2Cl_2 (25 mL) and cool to 0°C under N_2. Dropwise add thionyl chloride (2.4 mL, 3.90 g, 118.9 g/mol) in 10 mL CH_2Cl_2 while stirring under N_2. After 2 h, monitoring by TLC (alcohol Rf=0.35, chloride Rf=1.0; using 20% EtOAc / 80% hexanes as eluent), quench the reaction carefully by addition of

saturated $NaHCO_3$ (100 mL) and stir until gas evolution ceases. Separate layers, then extract the aqueous layer with CH_2Cl_2 (100 mL). Pool the organic layers, dry over Na_2SO_4, filter and evaporate to a pale yellow oil. Take up in DMSO (25 mL), add solid NaCN (1.25 g, 49.011 g/mol) and heat to 60°C while stirring under N_2. Stir 2 h until chloride consumed (TLC; chloride Rf=1.0, nitrile Rf=0.6; using 20% EtOAc / 80% hexanes as eluent), then cool to rt. Add 2.0 N NaOH (150 mL) and stir until orange precipitate forms, then filter and wash solid with H_2O. Dissolve solid in CH_2Cl_2, wash with H_2O, the dry over Na_2SO_4. Filter the organic layer and evaporate to an orange oil which crystallizes upon standing at ambient temperature. (2.3 g). LCMS = 180.2 (MH^+), 178.2 (M^-).

E. 2-(4-Chloro-2,6-dimethylphenyl)-3-oxobutanenitrile

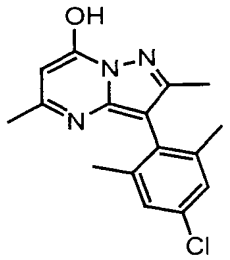
Dissolve 4-chloro-2,6-dimethyl phenyl acetonitrile (2.3 g, 179.2 g/mol) in 15 mL EtOAc and add sodium metal (0.35 g, pea-sized fragments). Heat to reflux (90°C bath temperature) under N_2 overnight. Evaporate down to solid and slurry up in Et_2O (100 mL); stir vigorously to break up fragments. Filter and wash solid with copious amounts of Et_2O. Dissolve solid in H_2O to form a clear yellow solution, and add 1.0 N HCl (100 mL) to pH 1. Extract the resulting cloudy solution with CH_2Cl_2 (3 x 100 mL) until aqueous layer is clear. Pool and dry the organic layers over Na_2SO_4, filter and evaporate to yellow oil (1.8g). TLC: Rf=0.2 using 20% EtOAc / 80% hexanes as eluent. LCMS = 222.3 (MH^+); 220.2 (M^-)

F. 5-Amino-4-(4-chloro-2,6-dimethylphenyl)-3-methylpyrazole

Dissolve anhydrous hydrazine (0.91g, 0.90 mL) in 20 mL toluene. Add glacial acetic acid (2.25 mL) and allow to stand at ambient temperature for 10 min until solution becomes cloudy white. Add a solution of 2-(4-chloro-2,6-dimethylphenyl)-3-oxobutanenitrile in 10 mL toluene, rinsing out the ketonitrile flask with an additional 5 mL toluene. Heat to reflux under N_2 (130°C) with Dean-Stark trap attached. Water will begin to accumulate after 10 min or so. After 2 h, evaporate down and partition between 1.0 N NaOH (100 mL) and EtOAc (100 mL). Extract aqueous layer with EtOAc (2 x 100 mL), then pool the organic layers and dry over Na_2SO_4.

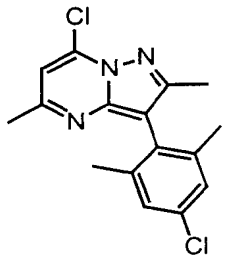
Filter and evaporate to yellow oil (1.75 g). Use without further purification. LCMS = 236.5 (MH^+); 234.5 (M^-).

G. 7-Hydroxy-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a]pyrimidine



Dissolve 5-amino-4-(4-chloro-2,6-dimethylphenyl)-3-methylpyrazole in 20 mL glacial acetic acid at ambient temperature, and add ethyl acetoacetate (2.0 mL, 1.99 g). Heat to reflux (130°C) under N_2 overnight. Evaporate down to concentrate and add 200 mL Et2O to precipitate out product. Stir at ambient temperature for 1 hour, then filter and wash the resulting white solid (1.25 g) with copious amounts of Et_2O. LCMS = 302.2 (MH^+); 300.2 (M^-).

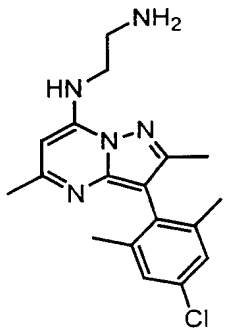
H. 7-Chloro-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a]pyrimidine



Slurry 7-hydroxy-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine in 10 mL $POCl_3$ and reflux at 130°C under N_2. After 2 h, monitoring by TLC (alcohol Rf=0.5, chloride Rf=1.0; EtOAc as eluent), quench the reaction carefully at ambient temperature by diluting with 50 mL CH_2Cl_2 and pouring slowly into non-stirring saturated $NaHCO_3$. Adjust stirring speed to control rate of quenching of residual $POCl_3$ and stir until gas evolution ceases. Separate the layers and extract the aqueous layer with CH_2Cl_2 (2 x 50 mL).

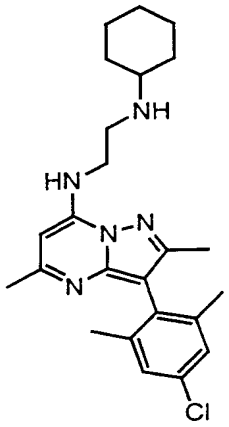
Pool the organic layers and dry over Na_2SO_4. Filter and evaporate to yellow oil, which is used directly without further purification.

I. 7-(2-aminoethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine



Dissolve 7-chloro-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine in 25 mL CH_3CN, then add excess ethylenediamine (5 mL) and heat to 80°C for 3-6 h under N_2 with attached reflux condenser. (TLC; product diamine Rf=0.5, aryl chloride Rf=1.0; [10% (2.0M NH_3 in MeOH) / 90% CH_2Cl_2] as eluent). Cool to ambient temperature and evaporate to yellow oil. Partition between CH_2Cl_2 (50 mL) and 1.0 N NaOH (50 mL), and extract aqueous layer 2 x 30 mL CH_2Cl_2. Pool organic layers, dry over Na_2SO_4, filter and evaporate to yellow-white foam (1.25 g). Use without further purification. LCMS = 344.4 (MH^+); 342.3 (M^-).

J. 7-(2-(Cyclohexylamino)ethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine



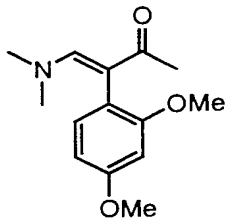
Dissolve 7-(2-aminoethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo [1,5-a] pyrimidine (0.183g, 5.4 x 10^{-4} mol, 339.2 g/mol) in dichloroethane (5 mL) and add cyclohexanone (100.12 g/mol) and sodium triacetoxyborohydride (0.172 g, 211.94 g/mol). To the resultant slurry, add glacial acetic acid (0.032 mL, 5.4 x 10^{-4} mol) and stir at ambient temperature under N_2 for 3 h. Partition between CH_2Cl_2 (3 mL) and 1.0 N NaOH (10 mL), then separate the layers and chromatograph the CH_2Cl_2 layer using [10% (2.0M NH_3 in MeOH) / 90% CH_2Cl_2] as eluent. Obtained 0.16 g white solid-foam upon evaporation.

EXAMPLE 2

Preparation of 7-(2-cyclopentylamino)ethylamino)-3-(2,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

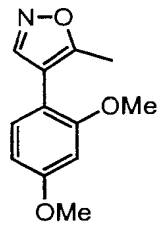
(formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,4-dimethoxyphenyl, R^5 is cyclopentyl)

A. (3E)-3-(2,4-dimethoxyphenyl)-4-(dimethylamino)but-3-en-2-one



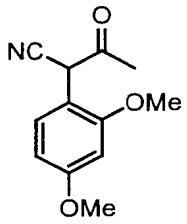
Dissolve 1-(2,4-dimethoxyphenyl)acetone (1.0 g, 5.15 mmol, 194.23 g/mol) in DMF-diethyl acetal (4.5 mL, 25.7 mmol, 147.22 g/mol) and stir under N_2 at 100°C overnight. TLC using 20% EtOAc / 80% hexanes; (ketone Rf = 0.25, product Rf = 0.0). Evaporate to thick oil, dissolve in EtOAc (25 mL) and wash with H_2O (3 x 25 mL). Extract pooled H_2O layers with EtOAc. Dry pooled organic layers over Na_2SO_4, filter and evaporate to thick oil which solidifies upon standing at ambient temperature (0.98 g). Use without further purification. LCMS = 250.2 (MH^+); 248.2 (M^-).

B. 4-(2,4-Dimethoxyphenyl)-5-methyl-isoxazole



Dissolve (3E)-3-(2,4-dimethoxyphenyl)-4-(dimethylamino)but-3-en-2-one (5.1 g, 20.6 mmol) in EtOH (50 mL) and add NH_2OH•HCl (3.05 g, 44.0 mmol). Heat to reflux under N_2 for 20 min. Cool and evaporate to red-brown oil. Dissolve in CH_2Cl_2, dry over Na_2SO_4, filter and concentrate to red-brown oil (4.4 g). Use without further purification. LCMS = 220.2 (MH^+); 218.2 (M^-).

C. 2-(2,4-Dimethoxyphenyl)-3-oxobutanenitrile.



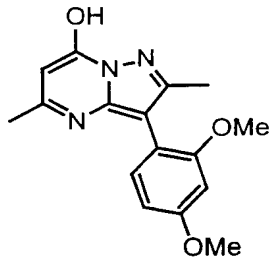
Slurry 4-(2,4-dimethoxyphenyl)-5-methyl-isoxazole (4.4 g) in 1.0 N NaOH (35 mL) and add 35 mL MeOH to dissolve. Heat at 60°C under N_2 for 1 hour, then cool to clear brown solution. Add 1.0 N HCl to acidify to pH 1, then filter the resulting white solid precipitate.

Dissolve solid in EtOAc, dry over Na_2SO_4, filter and concentrate to red oil. Use without further purification. LCMS = 220.2 (MH^+); 218.2 (M^-).

D. 5-Amino-4-(2,4-dimethoxylphenyl)-3-methylpyrazole

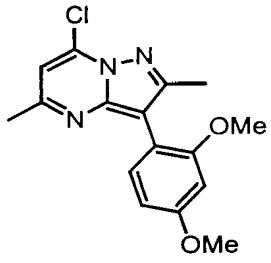
This compound was prepared as described in Example 1F.

E. 7-Hydroxy-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine



This compound was prepared as described in Example 1G.

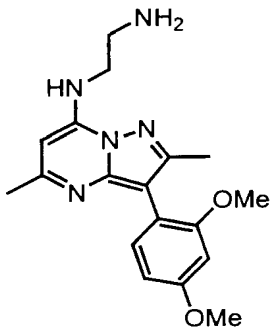
F. 7-Chloro-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine



Slurry 7-hydroxy-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a] pyrimidine in 10 mL $POCl_3$ and reflux at 130°C under N_2. After 2 h, monitoring by TLC (alcohol Rf=0.5, chloride Rf=1.0; EtOAc as eluent), quench the reaction carefully at ambient temperature by diluting with 50 mL CH_2Cl_2 and pouring slowly into non-stirring saturated $NaHCO_3$. Adjust stirring speed to control rate of quenching of residual $POCl_3$ and stir until gas evolution ceases. Separate the layers and extract the aqueous layer with CH_2Cl_2 (2 x 50 mL). Pool the organic

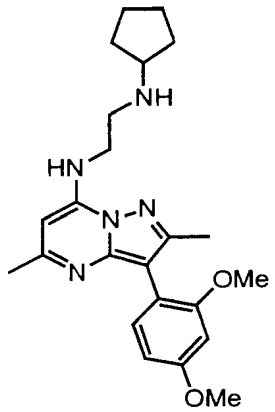
layers and dry over Na_2SO_4. Filter and evaporate to yellow oil, which is used directly without further purification.

G. 7-(2-aminoethylamino)-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a] pyrimidine



Dissolve 7-chloro-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a] pyrimidine in 25 mL CH_3CN, then add excess ethylenediamine (5 mL) and heat to 80°C for 3-6 h under N_2 with attached reflux condenser. (TLC: [10% (2.0M NH_3 in MeOH) / 90% CH_2Cl_2] as eluent). Cool to ambient temperature and evaporate to yellow oil. Partition between CH_2Cl_2 (50 mL) and 1.0 N NaOH (50 mL), and extract aqueous layer 2 x 30 mL CH_2Cl_2. Pool organic layers, dry over Na_2SO_4, filter and evaporate to yellow-white foam. Use without further purification.

H. 7-(2-cyclopentylamino)ethylamino)-3-(2,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine.



This compound was prepared as described in Example 1J.

EXAMPLE 3

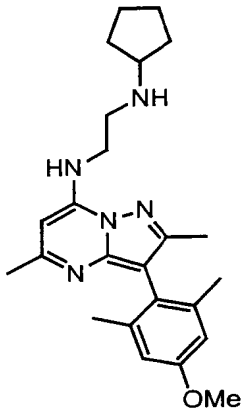
Preparation of 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine

(formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,4-dimethyl-4-methoxyphenyl, R^5 is cyclopentyl)

A. 4-Methoxy-2,6-dimethyl phenyl acetonitrile

Dropwise add a solution of chlorotrimethylsilane (20 mL) in CH_2Cl_2 (40 mL) to a stirred solution cooled to 0°C of 4-methoxy-2,6-dimethyl benzyl alcohol (approx. 74 mmol) in 300 mL CH_2Cl_2. Solution changes color from colorless to yellow and then to purple over the course of the reaction. After 2 h, monitoring by TLC (alcohol Rf=0.25, chloride Rf=0.95; using 20% EtOAc / 80% hexanes as eluent), evaporate down to a yellow oil. Dissolve in dry DMF (50 mL) and cool to 0°C under N_2. Add freshly ground NaCN (7.0 g) portionwise over 5 minute (exothermic) to the stirring reaction, forming a yellow/white slurry. Stir for 5-8 h at 0°C until no starting material remains, as determined by TLC (nitrile Rf=0.5; using 20% EtOAc / 80% hexanes as eluent). Partition the reaction solution between EtOAc (100 mL) and 0.1 N NaOH (300 mL). Dry the EtOAc layer over Na2SO4, filter and evaporate to yellow oil. Chromatograph in 10% EtOAC / 90% hexanes on silica to remove residual chloride and evaporate to 2.1 g yellow solid; clean by TLC. LCMS = 176.5 (MH^+), 174.4 (M^-).

B. 7-(2-(Cyclopentylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine



7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine is obtained from 4-methoxy-2,6-dimethyl phenyl acetonitrile using the procedures described in EXAMPLE 1 E, F, G, H, I, and J.

EXAMPLE 4

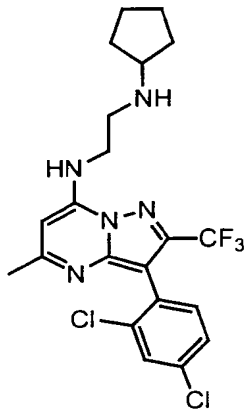
Preparation of 7-(2-(cyclopentylamino)ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine

(formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CF_3, R^4 is 2,4-dichlorophenyl, R^5 is cyclopentyl)

A. 2-(2,4-Dichlorophenyl)-4,4,4-trifluoro-3-oxobutanenitrile

Slurry 2,4-dichlorophenylacetonitrile (I) (5.0 g, 26.9 mmol, 186.04 g/mol) in ethyl trifluoroacetate (6.4 mL, 7.6 g, 142.08 g/mol) and add 20 mL anhydrous THF. Portionwise at ambient temperature add NaH (1.88g, 47.1 mmol, 60% in mineral oil) over 5 min. Heat reaction to reflux (90°C bath temperature) overnight. Evaporate to thick red-brown oil and partition between Et_2O (100 mL) and H_2O (60 mL). Separate layers and extract H_2O with Et_2O (2 x 75 mL). Acidify the aqueous layer with 1.0 N HCl to pH 1 (becomes cloudy white suspension) and extract aqueous layer with CH_2Cl_2 (3 x 100 mL). Dry pooled CH_2Cl_2 layers over Na_2SO_4, filter and concentrate to yellow oil (7.5 g, 26.5 mmol). Use without further purification. LCMS = 281.9 (MH^+); 279.8 (M^-)

B. 7-(2-(Cyclopentylamino)ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine



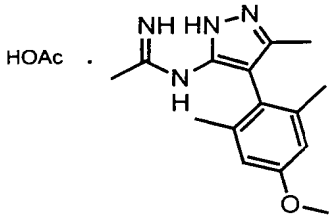
7-(2-(Cyclopentylamino)ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine is obtained from 2-(2,4-dichlorophenyl)-4,4,4-trifluoro-3-oxobutanenitrile using the procedures described in EXAMPLE 1 F, G, H, I, and J.

EXAMPLE 5

Preparation of 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-methoxy-2,6-dimethylphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

(formula I where X is N, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,6-dimethyl-4-methoxyphenyl, R^5 is cyclopentyl)

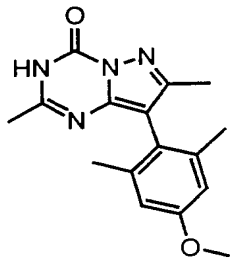
A. (Iminoethyl)[4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazol-5-yl]amine acetate salt.



To a solution of 5-amino-4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazole (1.89 g) in acetonitrile (30 mL) add ethylacetimidate (free base, 1.8 mL) followed by acetic acid (0.47

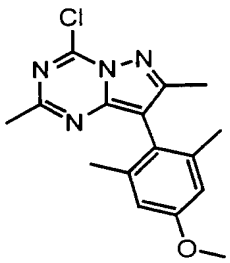
mL). Collect the precipitate that formed upon stirring overnight by filtration. Wash the solid with dry ether and dry to afford 2.61 g of (iminoethyl)[4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazol-5-yl]amine acetate salt as a white powder.

B. 2,6-Dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one.



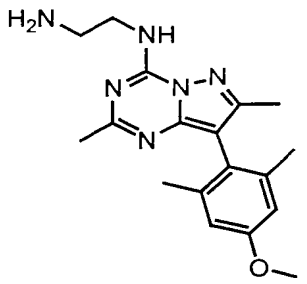
Add sodium pieces (1.81 g) to a flask containing anhydrous ethanol and equipped with a reflux condenser. Allow the mixture to stir until all the sodium is consumed and then add the amidine (2.61 g as the acetate salt) from step A in one portion. Add diethyl carbonate (7.6 mL) and reflux the mixture overnight. Concentrate the mixture under reduced pressure, dissolve the residue in water (75 mL) and adjust the pH to 5 with 3N HCl. Extract the aqueous mixture with EtOAc and wash the extracts with brine, dry over anhydrous sodium sulfate, and concentrate in vacuo to obtain a foam. Stir the residue with hexanes for 20 min and collect the solid by filtration, then wash with hexanes to obtain 2.01 g of 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one as a yellow powder: MS 299 (M+H).

C. 4-Chloro-2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine.



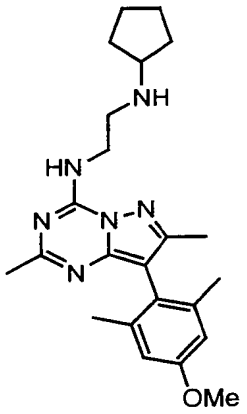
Dissolve 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one from step B (1 g) in $POCl_3$ (50 mL) and add N,N-dimethylaniline (0.55 mL). Reflux the reaction mixture under a dry nitrogen atmosphere for 18h at which time concentrate the mixture under reduced pressure. Dissolve the residue in EtOAc and wash with a saturated aqueous $NaHCO_3$ solution, then with brine. Dry the organic layer over anhydrous sodium sulfate, filter and concentrate under reduced pressure to obtain 4-chloro-2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine as a dark oil. MS 317 (M+H).

D. 2,6-Dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-aminoethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine.



Dissolve 4-chloro-2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine in dry toluene (10 mL) to form a stock solution of the chloride (~0.34 M). Add a portion of this solution (8 mL) dropwise into a stirring solution of ethylenediamine (3.6 mL) in acetonitrile (50 mL) which is heated to 60°C. After 3h at 60°C, cool the solution, concentrate under reduced pressure, dilute with 10% NaOH and extract with EtOAc. Wash the combined extracts with brine, dry over anhydrous sodium sulfate and concentrate under reduced pressure to obtain a yellow residue. Triturate the residue with 20% EtOAc/hexanes and collect the resulting solid by filtration to obtain 0.72 g of 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-aminoethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine as a yellow solid: MS 341 (M+H).

E. 7-(2-(Cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-methoxy-2,6-dimethylphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.



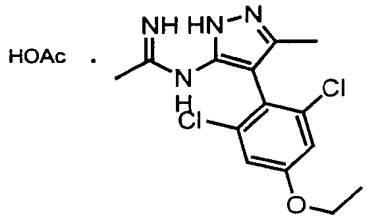
Dissolve 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-aminoethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine from step D (0.211 g) in dry dichloroethane (15 mL) and add cyclopentanone (1 equiv). Add acetic acid (35 μL) followed by sodium triacetoxyborohydride (0.184 g) and stir the resulting homogeneous mixture overnight at ambient temperature. Dilute the reaction mixture with 4 volumes of CH_2Cl_2, wash with brine, dry over anhydrous sodium sulfate, and concentrate under reduced pressure to obtain a yellow solid. Purify using preparative thin-layer chromatography [10% MeOH(2N NH_3)/CH_2Cl_2] to obtain 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-methoxy-2,6-dimethylphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

EXAMPLE 6

Preparation of 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-ethoxy-2,6-dichlorophenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

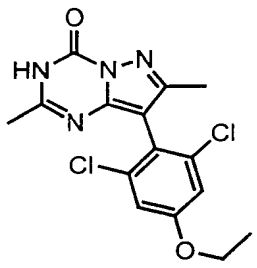
formula I where X is N, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,6-dichloro-4-ethoxyphenyl, R^5 is cyclopentyl.

A. (Iminoethyl)[4-(4-ethoxy-2,6-dichlorophenyl)-3-methylpyrazol-5-yl]amine acetate salt.



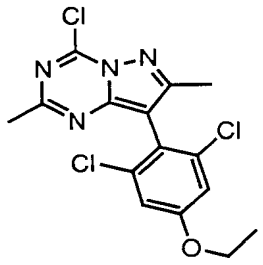
To a solution of 5-amino-4-(4-ethoxy-2,6-dichlorophenyl)-3-methylpyrazole (4.8 g) in acetonitrile (50 mL) add ethylacetimidate (free base, 2.3 mL) followed by acetic acid (0.96 mL). Collect the precipitate that formed upon stirring overnight by filtration. Wash the solid with dry ether and dry to afford 5.02 g of (iminoethyl)[4-(4-ethoxy-2,6-dichlorophenyl)-3-methylpyrazol-5-yl]amine acetate salt as a white powder.

B. 2,6-Dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one.



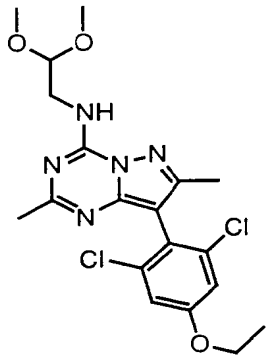
Add sodium pieces (2.98 g) to a flask containing anhydrous ethanol and equipped with a reflux condenser. Allow the mixture to stir until all the sodium is consumed and then add the amidine (5.02 g as the acetate salt) from step A in one portion. Add diethyl carbonate (12.6 mL) and reflux the mixture for four h. Concentrate the mixture under reduced pressure, dissolve the residue in water (75 mL) and adjust the pH to 5 with 3N HCl. Extract the aqueous mixture with EtOAc and wash the extracts with brine, dry over anhydrous sodium sulfate, and concentrate in vacuo to obtain a foam. Stir the residue with hexanes for 20 min and collect the solid by filtration, then wash with hexanes to obtain 4.41 g of 2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one as a beige solid: MS 353 (M+H).

C. 4-Chloro-2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine.



Dissolve 2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one from step B (1.05 g) in $POCl_3$ (50 mL) and add 2,6-lutidine (0.45 mL). Reflux the reaction mixture under a dry nitrogen atmosphere for 48h and then concentrate the mixture under reduced pressure. Dissolve the residue in EtOAc and wash with a saturated aqueous $NaHCO_3$ solution, then with brine. Dry the organic layer over anhydrous sodium sulfate, filter and concentrate under reduced pressure to obtain an oil which crystallizes upon standing. Wash the solid with hexanes to remove residual 2,6-lutidine and collect the solid on a sintered glass funnel yielding 4-chloro-2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine. MS 372 (M+H).

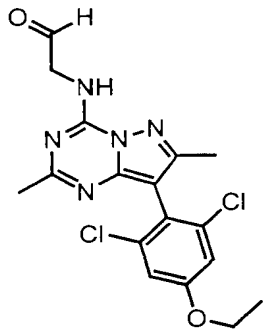
D. 2,6-Dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-4-(2,2-dimethoxyethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine.



Dissolve the product from step C in dry acetonitrile and then add 2.1 equivalents of aminoacetaldehyde dimethyl acetal. Heat the solution to 60°C and stir under a dry nitrogen

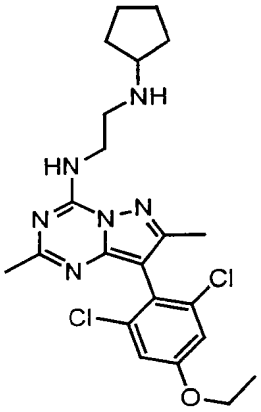
atmosphere for 2-6 h. Remove the solvent under reduced pressure, dilute with 10% NaOH and extract with EtOAc. Wash the combined extracts with brine, dry over anhydrous sodium sulfate and concentrate under reduced pressure to obtain a yellow oil which crystallizes upon standing. The product, 2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-4-(2,2-dimethoxyethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine, is used without further purification. MS (M+H).

E. 2-{[7-(2,6-dichloro-4-ethoxyphenyl)-2,5,6-trimethyl-3-pyrazolino[2,3-a]1,3,5-triazin-4-yl]amino}ethanal.



Dissolve the product obtained from step D in neat trifluoroacetic acid (25mL). After allowing the mixture to stand at ambient temperature for 0.5h, concentrate the mixture under reduced pressure. Add saturated aqueous sodium bicarbonate and stir the resulting heterogeneous mixture for 0.5h. Extract the aqueous solution with EtOAc, wash the EtOAc extracts with brine and then dry over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure yields the aldehyde as an off-white foam. ^{1}H NMR (CDCl3): δ 9.79 (s, 1H, CHO).

F. 7-(2-(Cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-ethoxy-2,6-dichlorophenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.



Dissolve the aldehyde (62 mg, 0.16 mmol) obtained from step E in dry dichloroethane (4 mL). Add 1.1 equivalents of cyclopentylamine followed by 1 equivalent of acetic acid. After the addition of sodium triacetoxyborohydride (1.4 eq), stir the solution at ambient temperature for several h. Dilute the reaction mixture with 4 volumes of CH_2Cl_2 then wash the mixture with brine (1x), dry over anhydrous Na2SO4. Concentrate under reduced pressure. Preparative thin layer chromatography [10% MeOH(2N NH_3)/CH_2Cl_2)] of the oily residue yields7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-ethoxy-2,6-dichlorophenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

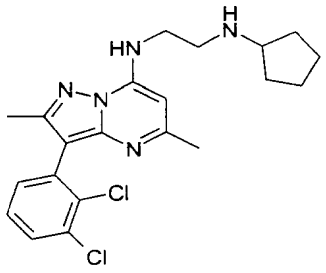
The preparation of the compounds of the present invention by the above-mentioned methods is illustrated further by the following examples, delineated in the TABLE which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them. Commonly used abbreviations are: Ph is phenyl, Me is methyl, Et is ethyl, Pr is n-propyl, iPr is isopropyl, cPr is cyclopropyl, Bu is butyl, iBu is isobutyl (CH_2-$CHMe_2$), tBu is tert-butyl, cBu is cyclobutyl, Pent is n-pentyl, cPent is cyclopentyl, cHex is cyclohexyl, Py is pyridyl, Bn is benzyl (CH_2Ph), Ac is acetyl (CH_3-(C=O)), tBOC is tert-butyloxycarbonyl (tBuO-(C=O)). EX means example.

By way of further exemplification, details of the preparation used in Example 14 which is included in the Table are as follows:

EXAMPLE 14

Preparation of N-cyclopentyl-N'-[3-(2,3-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine hydrochloride salt

formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,3-dichloro-4-ethoxyphenyl, R^5 is cyclopentyl, R^6 is H.



A. 7-Chloro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

2,5-Dimethyl-4H-pyrazolo[1,5-a]pyrimidin-7-one (3.5 g, 21 mmol) in phosphorus oxychloride (20 mL) was stirred at reflux. After 3 hours the dark purple reaction was cooled and then extracted from ice water with ethyl acetate. The combined organic layers were washed with water and saturated aqueous sodium bicarbonate, dried (Na_2SO_4) and then concentrated under reduced pressure to give the title compound (3.0 g, 77%) as a brown solid: +APcI MS $(M+1)^+$ 182; ^{1}H NMR ($CDCl_3$) δ: 6.74 (s, 1H), 6.42 (s, 1H), 2.55 (s, 3H), 2.53 (s, 3H).

B. N-(2,5-Dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-ethane-1,2-diamine

To a stirred solution of 7-chloro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (3.0 g, 16.5 mmol) in ethanol (60 mL) was added ethylene diamine (4 mL, 60 mmol). After refluxing 18 hours the reaction was cooled, poured into saturated aqueous sodium bicarbonate, and then washed with ethyl acetate. The aqueous layer was then extracted with 3:7 isopropyl alcohol/chloroform, the combined extracts were dried (Na_2SO_4) and then concentrated under reduced pressure to give the title compound as an amorphous brown solid (3.2 g, 94%): +APcI MS $(M+1)^+$ 206; ^{1}H NMR (methanol-d_4) δ: 6.05 (s, 1H), 6.00 (s, 1H), 3.45 (m, 2H), 2.91 (m, 2H).

C. N-Cyclopentyl-N'-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-ethane-1,2-diamine

To a stirred solution of N-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-ethane-1,2-diamine (3.2 g, 16 mmol) and cyclopentanone (2.7 mL, 30 mmol) in methanol (30 mL)/acetic acid (3 mL) was added sodium cyanoborohydride (0.94 g, 15 mmol), portionwise. After stirring 1 hour the reaction was concentrated under reduced pressure and then extracted from saturated aqueous sodium bicarbonate with ethyl acetate. The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure to give the crude product as a brown oil (5.6 g): +APcI MS $(M+1)^+$ 274; ^1H NMR ($CDCl_3$) δ: 6.11 (s, 1H), 6.76 (s, 1H), 3.21 (t, 2H), 3.21 (m, 1H), 3.04 (t, 1H), 2.42 (s, 3H), 2.40 (s, 3H).

D. Cyclopentyl-[2-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino)-ethyl]-carbamic acid tert-butyl ester

To a stirred solution of the crude N-cyclopentyl-N'-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-ethane-1,2-diamine (5.6 g) in methylene chloride (24 mL)/methanol (2 mL) was added di-tert-butyl dicarbonate (5.1 g, 23 mmol) and then 4- dimethylaminopyridine (0.6 g, 4.9 mmol). After stirring 5 hours the reaction was concentrated under reduced pressure and then chromatographed (1:1 ethyl acetate/hexanes) to afford the title compound as an orange glass (2.3 g, 39% from B)): +APcI MS $(M+1)^+$ 374; ^1H NMR ($CDCl_3$) δ: 6.16 (s, 1H), 5.78 (s, 1H), 4.25-4.15 (br s, 1H), 3.47 (m, 4H), 2.47 (s, 3H), 2.41 (s, 3H), 1.51 (s, 9H).

E. Cyclopentyl-[2-(3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino)-ethyl]-carbamic acid tert-butyl ester

To a 0 °C stirred solution of cyclopentyl-[2-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino)-ethyl]-carbamic acid tert-butyl ester (89 mg, 0.24 mmol) in chloroform (5 mL) was added N-iodosuccinimide (54 mg, 0.24 mmol). After stirring 30 minutes the reaction was extracted from saturated aqueous sodium thiosulfate with chloroform. The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure to give the product as a slightly yellowed glass

(102 mg, 85%): +APcI MS $(M+1)^+$ 500; ^{1}H NMR ($CDCl_3$) δ: 5.82 (s, 1H), 4.25-4.10 (br s, 1H), 3.46 (s, 4H), 2.51 (s, 3H), 2.41 (s, 3H), 1.50 (s, 9H).

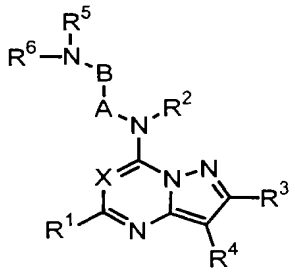
F. Cyclopentyl-{2-[3-(2,3-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-carbamic acid tert-butyl ester

A suspension of cyclopentyl-[2-(3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino)-ethyl]-carbamic acid tert-butyl ester (38 mg, 0.076 mmol) and 2,3-dichlorobenzeneboronic acid in toluene (0.5 mL)/ethanol (0.5 mL)/2 M aqueous sodium carbonate (0.22 mL) was degassed (3X) by alternately pulling a vacuum followed by repressurization with nitrogen. Tetrakis(triphenylphosphine)palladium (10 mg, 0.009 mmol) was added, and the mixture was degassed (3X) again. The mixture was stirred for 2.5 hours at 100 °C, concentrated under reduced pressure, and then chromatographed (4:1 hexanes/ethyl acetate) to give the product as colorless oil (24 mg, 60%): +APcI MS $(M+1)^+$ 518; ^{1}H NMR ($CDCl_3$) δ: 7.42 (dd, 1H), 7.30 (dd, 1H), 7.22 (t, 1H), 5.84 (s, 1H), 4.25-4.10 (br s, 1H), 3.49 (s, 4H), 2.44 (s, 3H), 2.32 (s, 3H), 1.52 (s, 9H).

G. N-Cyclopentyl-N'-[3-(2,3-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine hydrochloride salt

The cyclopentyl-{2-[3-(2,3-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-carbamic acid tert-butyl ester (21mg, 0.040 mmol) was stirred for 1 hour in 2:1 ethanol/concentrated aqueous hydrochloric acid (1.5 mL), concentrated under reduced pressure, and then concentrated 2 additional times from ethanol to give the title compound (17 mg, 94%): +APcI MS $(M+1)^+$ 418; ^{1}H NMR (methanol-d_4) δ: 7.69 (d, 1H), 7.50-7.40 (m, 2H), 6.78 (s, 1H), 4.06 (br s, 2H), 3.63 (br m, 1H), 3.42 (br s, 2H), 2.60 (s, 3H), 2.34 (s, 3H).

Table of Examples



EX	X	R^1	R^2	R^3	R^4	A-B-N[R^6]-R^5	MW
7.	CH	Me	H	Me	2-Cl-4-F-Ph	(CH2)2-NH-cHex	415.93
8.	CH	Me	H	Me	2-Cl-4-F-Ph	(CH2)2-NH-cPent	401.92
9.	CH	Me	H	Me	2-Cl-4-OEt-Ph	(CH2)2-NH-cPent	427.98
10.	CH	Me	H	Me	2-Cl-6-F-Ph	(CH2)2-NH-cPent	401.91
11.	CH	Me	H	Me	2-Cl-Ph	(CH2)2-NH-cPent	383.93
12.	CH	Me	H	Me	2-F-4-Br-Ph	(CH2)2-NH-cPent	482.83
13.	CH	Me	H	Me	2-F-Ph	(CH2)2-NH-cPent	367.47
14.	CH	Me	H	Me	2,3-diCl-Ph	(CH2)2-NH-cPent	418.37
15.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH2)2-NH-cPent	448.4
16.	CH	Me	H	Me	2,4-diCl-Ph	(CH2)2-NH-cBu	404.24
17.	CH	Me	H	Me	2,4-diCl-Ph	(CH2)2-NH-CH2-cPr	404.34
18.	CH	Me	H	Me	2,4-diCl-Ph	(CH2)2-NH-cHex	432.39
19.	N	Me	H	Me	2,4-diCl-Ph	(CH2)2-NH-cHex	433.4
20.	CH	Me	H	Me	2,4-diCl-Ph	(CH2)2-NH-cPent	418.36
21.	N	Me	H	Me	2,4-diCl-Ph	(CH2)2-NH-cPent	419.4
22.	CH	Me	H	Me	2,4-diF-6-OEt-Ph	(CH2)2-NH-cPent	465.98
23.	CH	Me	H	Me	2,4-diF-Ph	(CH2)2-NH-cHex	399.48
24.	CH	Me	H	Me	2,4-diF-Ph	(CH2)2-NH-cPent	385.45
25.	CH	Me	H	Me	2,4-diOMe-6Cl-Ph	(CH2)2-NH-cPent	443.98
26.	CH	Me	H	Me	2,4-diOMe-6Cl-Ph	(CH2)2-NH2	375.9
27.	CH	Me	H	Me	2,4-diOMe-Ph	(CH2)2-NH-cHex	423.55
28.	CH	Me	H	Me	2,4,6-triF-Ph	(CH2)2-NH-cPent	439.91
29.	CH	Me	H	Me	2,4,6-triMe-Ph	CH2-(2-Me-piperidin-6-yl)	391.6
30.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cBu	377.53
31.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-CH2-cPr	377.53

32.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cHex	405.59
33.	CH	Et	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cHex	419.61
34.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cPent	391.55
35.	CH	Me	H	CF3	2,4,6-triMe-Ph	(CH2)2-NH-cPent	445.52
36.	N	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cPent	392.5
37.	CH	Et	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cPent	405.59
38.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-iBu	379.55
39.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-iPr	365.52
40.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-tBu	379.54
41.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)3-NH-cPent	405.59
42.	CH	Me	H	Me	2,5-diCl-Ph	(CH2)2-NH-cPent	418.37
43.	CH	Me	H	Me	2,5-diF-Ph	(CH2)2-NH-cHex	385.46
44.	N	Me	H	Me	2,5-diMe-4-OMe-Ph	(CH2)2-NH-cHex	422.6
45.	CH	Me	H	Me	2,5-diMe-4-OMe-Ph	(CH2)2-NH-cHex	421.59
46.	N	Me	H	Me	2,5-diMe-4-OMe-Ph	(CH2)2-NH-cPent	408.5
47.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH2)2-NH-(CH2)2-NH2	394.31
48.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH2)2-NH-CH2-CMe2-NH2	422.36
49.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH2)2-NH2	395.3
50.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	CH2-CHMe-NH2	408.33
51.	CH	Me	H	Me	2,6-diCl-4-OH-Ph	(CH2)2-NH-cPent	434.37
52.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	4-NH2-cHex	434.37
53.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	4-NH2-cHex	434.37
54.	CH	iPr	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-CHEt-NH2	450.4
55.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH2-(2-Me-piperidin-6-yl)	448.4
56.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-N(CH2-cPr)2	488.46
57.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(3-NH2-cHex)	434.37
58.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(cis-2-NH2-cHex)	434.37
59.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(trans-2-NH2-cHex)	434.37
60.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-cPr	434.37
61.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-Et	436.39
62.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cPent	448.4
63.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-Et	408.33
64.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH2	380.28
65.	CH	iPr	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH2	408.33
66.	CH	tBu	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH2	422.4
67.	CH	nPr	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH2	408.3
68.	CH	CF3	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH2	434.3

69.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)3-NH-Et	422.36
70.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)3-NH2	394.31
71.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH2-(piperidin-2-yl)	434.3
72.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH2-CHMe-NH2	394.3
73.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	CH2-CHMe-NH2	408.33
74.	CH	iPr	H	Me	2,6-diCl-4-OMe-Ph	CH2-CHMe-NH2	422.36
75.	CH	nPr	H	Me	2,6-diCl-4-OMe-Ph	CH2-CHMe-NH2	422.36
76.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH2-CMe2-CH2-NH2	422.36
77.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH2-CMe2-CH2-NH2	477.44
78.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH2-CMe2-NH2	408.33
79.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CHMe-CHMe-NH2	408.33
80.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	CHMe-CHMe-NH2	422.4
81.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	pyrrolidin-3-yl	406.3
82.	CH	Me	H	Me	2,6-diCl-Ph	(CH2)2-NH-cPent	418.37
83.	N	Me	H	Me	2,6-diCl-Ph	(CH2)2-NH-cPent	419.4
84.	CH	Me	H	Me	2,6-diCl-Ph	(CH2)2-NH-Et	378.30
85.	CH	Me	H	Me	2,6-diF-4-OEt-Ph	(CH2)2-NH-cPent	465.98
86.	CH	Me	H	Me	2,6-diF-Ph	(CH2)2-NH-cPent	385.46
87.	CH	Me	H	Me	2,6-diMe-4-OCF3-Ph	(CH2)2-NH-cPent	461.52
88.	N	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH2)2-NH2	340.4
89.	CH	Me	H	Me	2,6-diMe-4-tBu-Ph	(CH2)2-NH-cPent	433.65
90.	N	Me	H	Me	2Cl-4F-Ph	(CH2)2-NH-cHex	416.9
91.	N	Me	H	Me	2Cl-4F-Ph	(CH2)2-NH-cPent	402.9

EXAMPLE 92

Cyclopentyl-{1-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-piperidin-3-yl}-amine (MW 488.5)

EXAMPLE 93

7-piperazino-2,5-dimethyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine (MW 376.28)

EXAMPLE 94

Characterization of NPY receptor interactions and in vivo function

A. Assay for Human NPY_1 Receptor Binding Activity: Compounds are assayed for activity using the following method: A cDNA encoding human NPY1 (SEQ ID NO:1) is ligated in the appropriate orientation for expression into the commercial expression vector pBacPAK9 (Clontech, Palo Alto, CA) for expression in SF9 cells. Each Baculoviral expression vector is co-transfected along with BACULOGOLD DNA (BD PharMingen, San Diego, CA) into S*f*9 cells. The S*f*9 cell culture supernatant is harvested three days post-transfection. The recombinant virus-containing supernatant is serially diluted in Hink's TNM-FH insect medium (JRH Biosciences, Kansas City) supplemented Grace's salts and with 4.1mM L-Gln, 3.3 g/L LAH, 3.3 g/L ultrafiltered yeastolate and 10% heat-inactivated fetal bovine serum (hereinafter "insect medium") and plaque assayed for recombinant plaques. After four days, recombinant plaques are selected and harvested into 1 ml of insect medium for amplification. Each 1 ml volume of recombinant baculovirus (at passage 0) is used to infect a separate T25 flask containing 2 x 10^6 S*f*9 cells in 5 mls of insect medium. After five days of incubation at 27°C, supernatant medium is harvested from each of the T25 infections for use as passage 1 inoculum. Recombinant baculoviral clones are then subjected to a second round of amplification, using 1 ml of passage 1 stock to infect 1 x 10^8 cells in 100 ml of insect medium divided into 2 T175 flasks. Forty-eight hours post infection, passage 2 medium is harvested from each 100ml prep and plaque assayed for titer. The cell pellets from the second round of amplification are assayed for affinity binding of radiolabeled ligand (see below) to verify recombinant receptor expression. A third round of amplification is then initiated using an M.O.I. of 0.1 to infect a liter of S*f*9 cells. Forty hours post-infection the supernatant medium is harvested to yield passage 3 baculoviral stock and the cell pellet assayed for affinity binding. Titer of the passage 3 baculoviral stock is determined by plaque assay and an M.O.I. and Incubation Time Course experiment is carried out to determine conditions for optimal receptor expression.

Log-phase S*f*9 cells are infected with stocks of recombinant baculovirus encoding the proteins of interest (e.g., human NPY1 and three g-proteins), followed by culturing in insect medium at 27°C. 72 hours post-infection, a sample of cell suspension is analyzed for viability by

trypan blue dye exclusion, and the remaining S*f*9 cells are harvested via centrifugation (3000 rpm/ 10 min/ 4°C).

Preparation of purified membranes: S*f*9 cell pellets are resuspended in homogenization buffer (10 mM HEPES, 250 mM sucrose, 0.5 □g/ml leupeptin, 2 □g/ml Aprotinin, 200 □M PMSF, and 2.5 mM EDTA, pH 7.4) and homogenized using a POLYTRON homogenizer (setting 5 for 30 seconds). The homogenate is centrifuged (536 x g/ 10 min/ 4°C) to pellet the nuclei. The supernatant containing isolated membranes is decanted to a clean centrifuge tube, centrifuged (48,000 X g/ 30 min, 4°C) and resuspended in 30 ml, or preferably 20 ml of homogenization buffer. This centrifugation and resuspension step is repeated twice. The final pellet is resuspended in ice cold Dulbecco's PBS containing 5 mM EDTA and stored in frozen aliquots until needed at -80°C. The protein concentration of the resulting membrane preparation is measured using the Bradford protein assay (Bio-Rad Laboratories, Hercules, CA). By this measure, a 1-liter culture of cells typically yields 50-100 mg of total membrane protein.

CO-infection for GTPγ^{35}S binding assay: Four baculoviral expression vector stocks are used to infect a culture of *Sf*9 cells with an MOI of 1:1:1:1. These four consisted of one vector encoding the human NPY1 receptor and a different commercially obtained baculoviral expression vector stock encoding each of the three subunits of a heterotrimeric G-protein, in particular, the G-protein-encoding virus stocks are obtained from BIOSIGNAL Inc., Montreal, and are **1)** a Gα G-protein subunit-encoding virus stock (either the rat Gα_{i2} G-protein-encoding virus stock BIOSIGNAL #V5J008 or the rat Gα_O G-protein-encoding virus stock BIOSIGNAL #V5H010), **2)** a bovine β1 G-protein-encoding virus stock (BIOSIGNAL #V5H012), and **3)** a human γ2 G-protein-encoding virus stock (BIOSIGNAL #V6B003). Agonist-stimulated GTPγ^{35}S binding on purified membranes is assessed using hNPY 1-36 (American Peptide Co., Sunnyvale, CA) as agonist in order to ascertain functional activity as measured by GTPγ^{35}S binding.

B. GTPγ^{35}S binding assay: Purified S*f*9 cell membranes are resuspended by Dounce homogenization (tight pestle) in GTPγ^{35}S binding assay buffer (50 mM Tris pH 7.0, 120 mM NaCl, 2 mM MgCl2, 2 mM EGTA, 0.1% BSA, 0.1 mM bacitracin, 100KIU/mL Aprotinin, 5 µM GDP) and added to reaction tubes at a concentration of 30 µg/reaction tube. After adding increasing doses of the agonist hNPY 1-36 (American Peptide Co., Sunnyvale, CA), reactions

are initiated by the addition of 100 pM GTPγ^{35}S. Following a 30-minute incubation at ambient temperature, the reactions are terminated by vacuum filtration over GF/C filters (pre-soaked in wash buffer, 0.1% BSA) followed by washing with ice-cold wash buffer (50 mM Tris pH 7.0, 120mM NaCl).

Bound GTPγ^{35}S is determined by liquid scintillation spectrometry of the washed filters. Non-specific binding is determined using 10 mM GTPγS. Data are generally expressed as % maximal response and are derived by determining the maximal agonist stimulated % above basal stimulation. Computer analysis may be conveniently used to calculate estimated EC_{50}, IC_{50} and K_i values from GTPγ^{35}S binding experiment data, e.g., using SigmaPlot software. The binding affinity for the preferred compounds of the invention, expressed as K_i values, ranges from about 0.1 nanomolar to about 5 micromolar. Particularly preferred compounds yield a K_i value of less than 100 nanomolar, most preferably less than 10 nanomolar .

Assay for affinity binding of radiolabeled ligand: Purified membranes are washed with PBS and re-suspended by gentle pipetting in binding buffer (50 mM Tris(HCl), 5 mM KCl, 120 mM NaCl, 2 mM CaCl2, 1 mM MgCl2, 0.1% bovine serum albumin (BSA), pH 7.4). Membranes (5μg) are added to siliconized (Sigmacote, Sigma) polypropylene tubes in addition to 0.050 nM [125I]NPY (porcine, New England Nuclear Corp., Boston, MA) for competition analysis or 0.010-0.500 nM [125I]NPY (porcine) for saturation analysis. For evaluation of guanine nucleotide effects on receptor affinity, GTP is added at a final concentration of 100 μM. Cold displacers are added at concentrations ranging from 10-12 M to 10-6 M to yield a final volume of 0.250 mL. Nonspecific binding is determined in the presence of 1 μM NPY (human, American Peptide Co., Sunnyvale, CA) and accounts for less than 10% of total binding. Following a 2-hour incubation at ambient temperature, the reaction is terminated by rapid vacuum filtration. Samples are filtered over presoaked GF/C Whatman filters (1.0% polyethyleneimine for 2 hours) and rinsed 2 times with 5 mL cold binding buffer lacking BSA. Remaining bound radioactivity is measured by gamma counting. To estimate the Bmax, Kd and Ki, the results of binding experiments are analyzed using SigmaPlot software (SPSS Science, Chicago, IL). The binding affinity for the compounds of the invention, expressed as a Ki value, ranges from about 0.1 nanomolar to about 10 micromolar. The most preferred compounds of the

invention have a Ki of less than 100 nanomolar and a binding selectivity of >100-fold relative to other G-protein coupled receptors, including NPY_5 and $CRF1_1$ receptors.

C. *In vivo* analysis - Food Deprivation

Subjects. Experimentally naive and experienced male Sprague-Dawley rats (Sasco, St. Louis, MO) weighing 210-300g at the beginning of the experiment are used. Animals are triple-housed in stainless steel hanging cages in a temperature (22 C ± 2) and humidity (40-70% RH) controlled animal facility with a 12:12 hour light-dark cycle. Food (Standard Rat Chow, PMI Feeds Inc., #5012) and water are available ad libitum.

Apparatus. Consumption data is collected while the animals are housed in Nalgene Metabolic cages (Model #650-0100). Each cage is comprised of subassemblies made of clear polymethlypentene (PMP), polycarbonate (PC), or stainless steel (SS). All parts disassemble for quick and accurate data collection and for cleaning. The entire cylinder-shaped plastic and SS cage rests on a SS stand and houses one animal.

The animal is contained in the round Upper Chamber (PC) assembly (12cm high and 20cm in diameter) and rests on a SS floor. Two subassemblies are attached to the Upper Chamber. The first assembly consists of a SS feeding chamber (10cm long, 5cm high and 5cm wide) with a PC feeding drawer attached to the bottom. The feeding drawer has two compartments: a food storage compartment with the capacity for approximately 50g of pulverized rat chow, and a food spillage compartment. The animal is allowed access to the pulverized chow by an opening in the SS floor of the feeding chamber. The floor of the feeding chamber does not allow access to the food dropped into the spillage compartment.
The second assembly includes a water bottle support, a PC water bottle (100ml capacity) and a graduated water spillage collection tube. The water bottle support funnels any spilled water into the water spillage collection tube.

The lower chamber consists of a PMP separating cone, PMP collection funnel, PMP fluid (urine) collection tube, and a PMP solid (feces) collection tube. The separating cone is attached to the

top of the collection funnel, which in turn is attached to the bottom of the Upper Chamber. The urine runs off the separating cone onto the walls of the collection funnel and into the urine collection tube. The separating cone also separates the feces and funnels it into the feces collection tube.

Food consumption, water consumption, and body weight may be measured with an Ohaus Portable Advanced scale (±0.1g accuracy).

Procedure. Prior to the day of testing, animals are habituated to the testing apparatus by placing each animal in a Metabolic cage for 1 hour. On the day of the experiment, animals that have been food deprived the previous night are weighed and assigned to treatment groups. Assignments are made using a quasi-random method utilizing the body weights to assure that the treatment groups had similar average body weight. Animals are then administered either vehicle (0.5% methyl cellulose) or drug (a compound of the invention). At that time, the feeding drawer is filled with pulverized chow, the filled water bottle, and the empty urine and feces collection tubes are weighed. Two hours after drug treatment, each animal is weighed and placed in a Metabolic Cage. Following a one-hour test session, animals are removed and body weight obtained. The food and water containers are then weighed and the food and water consumption data recorded.

Drugs. Drug suspended in vehicle, or vehicle alone as a control, is administered orally (PO) using a gavage tube connected to a 3 or 5ml syringe at a volume of 10ml/kg. Drug is made into a homogenous suspension by stirring and ultrasonicating for at least 1 hour prior to dosing.

Statistical Analyses. The means and standard errors of the mean (SEM) for food consumption, water consumption, and body weight change are obtained. One-way analysis of variance using Systat (5.2.1) is used to test for group differences. A significant effect is defined as having a p value of $<.05$.

The following parameters are defined: Body weight change is the difference between the body weight of the animal immediately prior to placement in the metabolic cage and its body weight at

the end of the one hour test session. Food consumption is the difference in the weight of the food drawer prior to testing and the weight following the 1-hour test session. Water consumption is the difference in the weight of the water bottle prior to testing and the weight following the 1-hour test session. Preferred compounds of the invention reduce food intake and body weight gain, preferably to a statistically significant degree as determined by standard parametric analysis such as a student's T-test.

Example 95

Assay for CRF Receptor Binding Activity

As discussed above, the following assay is defined herein as a standard in vitro CRF receptor binding assay. The assay may be used to demonstrate CRF1 receptor-binding activity. The CRF receptor binding is performed using a modified version of the assay described by Grigoriadis and De Souza (*Methods in Neurosciences,* Vol. 5, 1991). IMR-32 human neuroblastoma cells, a cell-line that naturally expresses the CRF1 receptor, are grown to confluency in DMEM containing FBS.

To prepare receptor-containing membranes, cells are homogenized in wash buffer (50 mM Tris HCl, 10 mM $MgCl_2$, 2 mM EGTA, pH 7.4) and centrifuged at 48,000g for 10 min at 4°C. The pellet is re-suspended in wash buffer and the homogenization and centrifugation steps are performed two additional times.

Membrane pellets containing CRF receptors are re-suspended in 50 mM Tris buffer pH 7.7 containing 10 mM $MgCl_2$ and 2 mM EDTA and centrifuged for 10 min at 48000 x g. Membranes are washed again and brought to a final concentration of 1500 mg/ml in binding buffer (Tris buffer above with 0.1 % BSA, 15 mM bacitracin and 0.01 mg/ml aprotinin.). For the binding assay, 100 ml of the membrane preparation are added to 96 well microtube plates containing 100 ml of ^{125}I-CRF (SA 2200 Ci/mmol, final concentration of 100 pM) and 50 ml of test compound. Binding is carried out at ambient temperature for 2 h. Plates are then harvested on a Brandel 96 well cell harvester and filters are counted for gamma emissions on a Wallac 1205 Betaplate liquid scintillation counter. Non specific binding is defined by 1 mM cold CRF. IC_{50} values are calculated with the non-linear curve fitting program RS/1 (BBN Software Products Corp., Cambridge, MA). The binding affinity for a compound of Formula I expressed as an IC_{50} value generally ranges from about 0.5 nanomolar to about 10 micromolar.

Example 96

Preparation of radiolabeled probe compounds of the invention

The compounds of the invention are prepared as radiolabeled probes 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, IL; Cambridge Isotope Laboratories, Inc. Andover, MA; SRI International, Menlo Park, CA; Wizard Laboratories, West Sacramento, CA; ChemSyn Laboratories, Lexena, KS;

Example 97

Preparation of radiolabeled probe compounds of the invention

The compounds of the invention are prepared as radiolabeled probes 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, IL; Cambridge Isotope Laboratories, Inc. Andover, MA; SRI International, Menlo Park, CA; Wizard Laboratories, West Sacramento, CA; ChemSyn Laboratories, Lexena, KS; American Radiolabeled Chemicals, Inc., St. Louis, MO; and Moravek Biochemicals Inc., Brea, CA.

Tritium labeled probe compounds are also conveniently 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.

Example 98

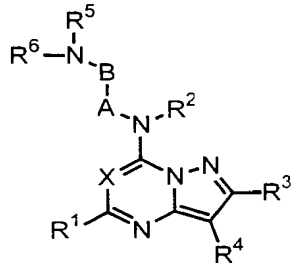
Receptor autoradiography

Receptor autoradiography (receptor mapping) is 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 prepared as described in the preceding Example.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

WHAT IS CLAIMED IS:

1. A compound of the formula



I

or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, and

X is N or CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with

R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that for SO_2R^7, R^7 cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN.

2. A compound according to Claim 1, wherein X is N.

3. A compound according to Claim 1, wherein

X is N; and

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

4. A compound according to Claim 1, wherein

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl; and

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl.

5. A compound according to Claim 1, wherein

X is N;

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^5 is H.

6. A compound according to Claim 1, wherein;

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl;

R^4 is phenyl, mono-, di-, or tri-substituted C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and

R^7, R^8, and R^9 are as defined in Claim 1.

7. A compound according to Claim 1, wherein:

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^4 is phenyl, mono-, di-, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 is H; and

R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

8. A compound according to Claim 1, wherein:

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^4 is phenyl, mono-, di-, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and

R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

9. A compound according to Claim 1, wherein X is CH.

10. A compound according to Claim 1, wherein

X is CH; and

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

11. A compound according to Claim 1, wherein

X is CH;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl; and

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl.

12. A compound according to Claim 1, wherein

X is N;

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^5 is H.

13. A compound according to Claim 1, wherein;

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl;

R^4 is phenyl, mono-, di-, or tri-substituted C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and

R^7, R^8, and R^9 are as defined in Claim 1.

14. A compound according to Claim 1, wherein:

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^4 is phenyl, mono-, di-, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 is H; and

R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

15. A compound according to Claim 1, wherein:

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^4 is phenyl, mono-, di-, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and

R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

16. A compound according to Claim 1 wherein the compound exhibits a 20-fold greater affinity for the NPY1 receptor in a assay of NPY1 receptor binding than for the CRF1 receptor in an assay of CRF1 receptor binding.

17. A compound according to Claim 1 wherein the compound exhibits a 100-fold greater affinity for the NPY1 receptor in a assay of NPY1 receptor binding than for the CRF1 receptor in an assay of CRF1 receptor binding.

18. A method for treating eating disorders and cardiovascular disorders comprising administering to a patient suffering from an eating disorder or cardiovascular disorder a compound according to Claim 1.

19. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.

20. A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 19 in a container and comprising instructions for using the composition to treat a patient suffering from an eating disorder or hypertension.

21. A method for localizing NPY receptors in tissue section samples comprising: contacting with a sample of tissue a detectably-labeled compound of Claim 1 under conditions that permit binding of the compound to the sample of tissue; washing the tissue sample to remove unbound compound; and detecting the bound compound.

22. The method of Claim 21, wherein the compound is radiolabeled.

23. A method of inhibiting the binding of NPY to the NPY1 receptor, which method comprises contacting, in the presence of NPY, a solution comprising a compound of Claim 1 with cells expressing the NPY1 receptor, wherein the compound is present in the solution at a

concentration sufficient to reduce levels of NPY binding to cells expressing the NPY1 receptor in vitro.

24. A method for altering the signal-transducing activity of a cell surface NPY1 receptor, said method comprising contacting cells expressing such a receptor with a solution comprising a compound according to Claim 1, wherein the compound is present in the solution at a concentration sufficient to reduce levels of NPY binding to cells expressing the NPY1 receptor in vitro.

25. A compound according to any one of Claim 1 wherein in an assay of NPY binding the compound exhibits an K_i of 1 micromolar or less.

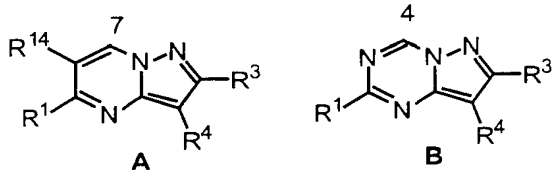
26. A compound according to any one of Claim 1 wherein in an assay of NPY binding the compound exhibits an K_i of 100 nanomolar or less.

27. A compound according to any one of Claim 1 wherein in an assay of NPY binding the compound exhibits an K_i of 100 nanomolar 10 nanomolar or less.

28. A method for treating obesity or bulimia nervosa which comprises administering an effective amount of a compound according to Claim 1 to a patient in need thereof.

29. A method for treating hypertension which comprises administering an effective amount of a compound according to Claim 1 to a patient in need thereof.

30. A method of converting a heterocyclic cores **A** and or a heterocyclic core **B**



to a compound that exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding,

wherein

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN;

by substituted the 7-position of the heterocyclic core **A** or the 4-position of the heterocyclic core **B** with a diamine group $-N[R^2]$-A-B-$N[R^6]$-R^5

wherein:

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with

R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl,

or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6

alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that for SO_2R^7, R^7 cannot be H;

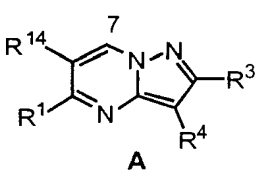
R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

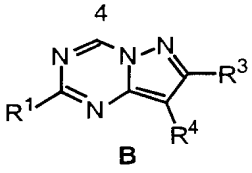
R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle; and

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H.

31. A method of converting a heterocyclic cores **A** and or a heterocyclic core **B**



A

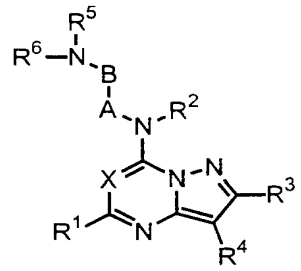


B

to a compound that exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, and

exhibits a 20-fold greater affinity for the NPY1 receptor in a assay of NPY1 receptor binding than for the CRF1 receptor in an assay of CRF1 receptor binding.

32. A compound of the formula



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or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, and

X is N or CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with

R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-

C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1 – C_6, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 is H;

R^6 and C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that for SO_2R^{13}, R^{13} cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

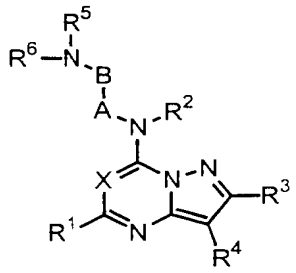
R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN.

33. A compound of the formula



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or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, and

X is N or CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with

R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7,

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, halogen, C_1-C_6 haloalkyl, CN, alkylsulfonyl, OR^7, NR^8R^9, $CONR^8R^9$, $COOR^7$, $SO_2NR^8R^9$, COR^7, SO_2R^7.

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents

independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

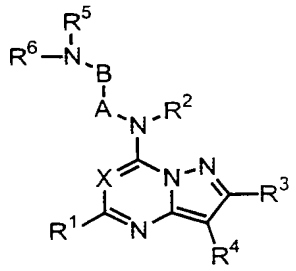
R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN.

34. A compound of formula



I

or a pharmaceutically acceptable salt, hydrate, or prodrug wherein:

X is N or CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^2 is H,
C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with
R^7,
C_3-C_{10} cycloalkyl, or
(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or
R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or
A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each substituted with aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), heterocycloalkyl, cyclopentenyl, cyclohexenyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl , trifluoromethylsulfonyl, C_1-C_6 alkyl-NR^8R^9, C_1-C_6 alkyl-CN , C_1-C_6 alkyl-$CONR^8R^9$, (C_1-C_4)alkyl-OR^7, C_1-C_6 alkyl-$COOR^7$and optionally substituted with 1 to 4 substituents independently selected at each occurrence from C_1-C_6 alkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7.

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl,

or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN.

35. A compound according to Claim 33, wherein

X is N, CH.

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl

R^2 is H

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl.

R^4 is phenyl, mono-, di-, or tri-substituted C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, OR^7

R^5 is H

R^7 is methyl, ethyl, isopropyl, propyl.

36 A compound of claim 35 wherein the compound has the structure N-cyclohexyl-N'-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-Cyclohexyl-N'-[8-(2,6-dichloro-4-methoxy-phenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine; N-cyclohexyl-N'-[2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine; N-cyclohexyl-N'-[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cCyclopentyl-N'-[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cyclopentyl-N'-[2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine; N-cyclopentyl-N'-[8-(2,6-dichloro-4-methoxy-phenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine; N-cyclopentyl-N'-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine.

37 A compound according to Claim 34, wherein R^{14} is H, C_1-C_4 alkyl.

38 A compound according to claim 37 wherein

R^2 is H; R^6 is H;

X is N, CH;

A is CH_2, optionally substituted with one or two of the following: F, CF_3, or methyl, ethyl, isopropyl;

B is CH_2, optionally substituted with one or two of the following: F, CF_3, or methyl, ethyl, isopropyl.

39 A compound according to claim 38 wherein

R^5 is C_1-C_7 alkyl, C_1-C_6 cycloalkyl, or C_1-C_6 cycloalkyl C_1-C_2 alkyl;

A, B is CH_2.

40 A compound according to claim 38 wherein
R^4 is selected from aryl or heteroaryl, each substituted with aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), heterocycloalkyl, cyclopentenyl, cyclohexenyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl , trifluoromethylsulfonyl, C_1-C_6 alkyl-NR^8R^9, C_1-C_6 alkyl-CN , C_1-C_6 alkyl-$CONR^8R^9$, (C_1-C_4)alkyl-OR^7, C_1-C_6 alkyl-$COOR^7$and optionally substituted with 1 to 4 substituents independently selected at each occurrence from C_1-C_6 alkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl.

41 A compound of claim 40 wherein
R^4 is phenyl substituted with acetylene, cyclopentenyl, cyclohexenyl, (C_1-C_4)alkyl-OR^7, C_1-C_3 alkenyl, and optionally substituted with 1 to 2 substituents independently selected at each occurrence from methyl, F, Cl, CF_3, OR^7;
R^7 is H, methyl, ethyl.

42 A compound of claim 41 where the structure is N-cyclohexyl-N'-[3-(2,6-dichloro-4-ethynyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cyclopentyl-N'-[3-(2,6-dichloro-4-ethynyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cyclopentyl-N'-[3-(2,6-dichloro-4-cyclopent-1-enyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cyclohexyl-N'-[3-(2,6-dichloro-4-cyclopent-1-enyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-Cyclohexyl-N'-[8-(2,6-dichloro-4-cyclopent-1-enyl-phenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine; N-cyclohexyl-N'-[8-(2,6-dichloro-4-propenyl-phenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine.

43 A compound according to Claim 33 wherein the compound exhibits a 20-fold greater affinity for the NPY1 receptor in a assay of NPY1 receptor binding than for the CRF receptor in an assay of CRF receptor binding.

44 A compound according to Claim 33 wherein the compound exhibits a 100-fold greater affinity for the NPY1 receptor in a assay of NPY1 receptor binding than for the CRF receptor in an assay of CRF receptor binding.

45 A method for treating eating disorders and cardiovascular disorders comprising administering to a patient suffering from an eating disorder or cardiovascular disorder a compound according to Claim 33.

46 A pharmaceutical composition comprising a compound according to Claim 33 and a pharmaceutically acceptable carrier.

47 A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 33 in a container and comprising instructions for using the composition to treat a patient suffering from an eating disorder or hypertension.

48 A method for localizing NPY receptors in tissue section samples comprising: contacting with a sample of tissue a detectably-labeled compound of Claim 33 under conditions that permit binding of the compound to the sample of tissue; washing the tissue sample to remove unbound compound; and detecting the bound compound.

49 The method of Claim 48, wherein the compound is radiolabeled.

50 A method of inhibiting the binding of NPY to the NPY1 receptor, which method comprises contacting, in the presence of NPY, a solution comprising a compound of Claim 33 with cells expressing the NPY1 receptor, wherein the compound is present in the solution at a concentration sufficient to reduce levels of NPY binding to cells expressing the NPY1 receptor in vitro.

51 A method for altering the signal-transducing activity of a cell surface NPY1 receptor, said method comprising contacting cells expressing such a receptor with a solution comprising a compound according to Claim 33, wherein the compound is present in the solution at a

concentration sufficient to reduce levels of NPY binding to cells expressing the NPY1 receptor in vitro.

52 A compound according to Claim 33 wherein in an assay of NPY binding the compound exhibits an K_i of 1 micromolar or less.

53 A compound according to any one of Claim 33 wherein in an assay of NPY binding the compound exhibits an K_i of 1 micromolar or less.

54 A compound according to any one of Claim 33 wherein in an assay of NPY binding the compound exhibits an K_i of 100 nanomolar or less.

55 A method for treating obesity or bulimia nervosa which comprises administering an effective amount of a compound according to Claim 33 to a patient in need thereof.

56 A method for treating hypertension which comprises administering an effective amount of a compound according to Claim 33 to a patient in need thereof.

57 A method of converting core heterocyles of formula A and B to a compound that exhibits a Ki of 5 micromolar or less in an assay of NPY receptor binding.

58 A method of treating obesity comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula as defined in claim 34 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug.

59 A method as recited in claim 58 wherein the amount of the compound in FormulaI as defined in claim 34 is about 0.01 mg/kg/day to about 50 mg/kg/day.

60 A method as recited in claim 59 wherein the mammal is female or male human.

61 A pharmaceutical composition which comprises a therapeutically effective amount of compound of claim 34 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

62 A pharmaceutical composition for the treatment of obesity which comprises a therapeutically effective amount of compound of claim 34 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

63 A pharmaceutical combination composition comprising a therapeutically effective amount of a composition comprising: (a) first compound, said first compound being a compound of claim 34, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent.

64 A method of treating obesity comprising administering to a mammal in need of such treatment: (a) first compound, said first compound being a compound of claim 34, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; (and (c) wherein the amounts of the first and second compounds result in a therapeutic effect.

65 A kit comprising: (a) first compound, said first compound being a compound of claim 34, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; and (c) means for containing said first and second unit dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

66 A pharmaceutical combination composition comprising a therapeutically effective amount of a composition comprising (a) first compound, said first compound being a compound of claim 34, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, insulin, metformin, acarbose, a thiazolidinedione, a glitazone, rezulin, trogitalazone, a sulfonylurea, glipazide, glyburide, or chlorpropamide; (c) a pharmaceutical carrier, vehicle, or diluent.

67 A pharmaceutical composition comprising a compound as defined in claim 34 for the treatment of disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, diabetes, dislipidemia, hypertension, memory loss, epileptic seizures, migraine, sleep disorders, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea.

68 A method of selectively inhibiting binding of NPY_1 receptors, which comprises contacting a compound of claim 33 with neuronal cells, wherein the compound is present in an amount effective to produce a concentration sufficient to selectively inhibit binding of NPY peptides to NPY_1 receptors in vitro.

SEQUENCE LISTING

<110> Darrow, James W.
Horvath, Raymond F.
Blum, Charles
Tran, Jennifer
De Lombaert, Stephane
Hodgetts, Kevin J.
Carpino, Philip A.

<120> Amino Substituted Pyrazolo [1,5,-a]-1,5-Pyrimidines and Pyrazolo [1,5-a]-1,3,5-Triazines

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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.

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[71] 申请人 俄亥俄州立大学研究基金会
地址 美国俄亥俄州
共同申请人 田纳西大学研究基金会
[72] 发明人 J·T·多尔顿 D·D·米勒
I·拉科夫 C·博尔
M·L·莫勒

[74] 专利代理机构 永新专利商标代理有限公司
代理人 张晓威

权利要求书 32 页 说明书 162 页 附图 19 页

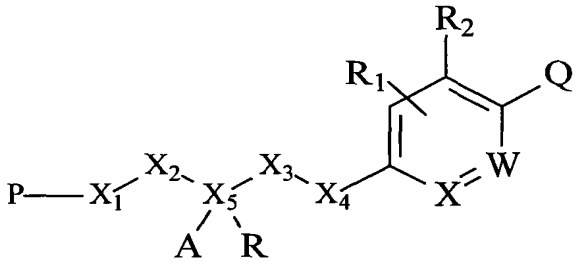
[54] 发明名称

选择性雄激素受体调节剂、它们的类似物和衍生物以及它们的用途

[57] 摘要

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

1. 化合物，其由式 I 的结构表示：



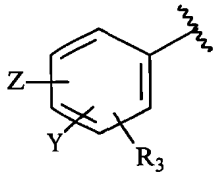
I

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；

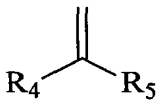
X_3 是 C_{1-4} 亚烷基、NH、N、CH(OH)、键；或者 X_1 和 X_3 与 X_1 和 X_3 所连接的 X_2 和 X_5 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X_3 和 X_5 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_3 和 X_4 一起形成双键或一起形成饱和的或不饱和

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

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

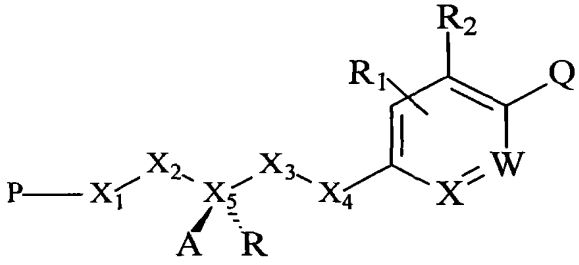
如果 P 是 H，X 是 C，X_1 是 NH，X_2 是 C(O)，R 是 OH，A 是烷基，X_3 是键或 CH_2 并且 X_4 是键或 CH_2，R_1 和 R_2 是 H，那么 Q 不是 H 或卤素；

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

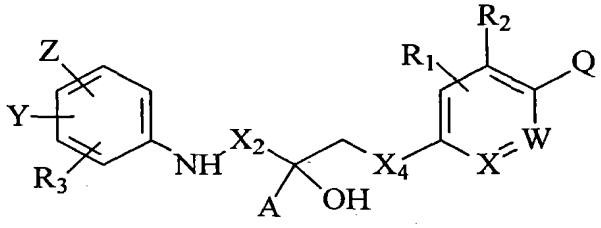
X_2 一起形成噁唑烷二酮，R 是烷基，X_3 是 CH_2 并且 X_4 是 O、NH、S、SO_2 或 CH_2，那么 Q 不是卤化物。

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；

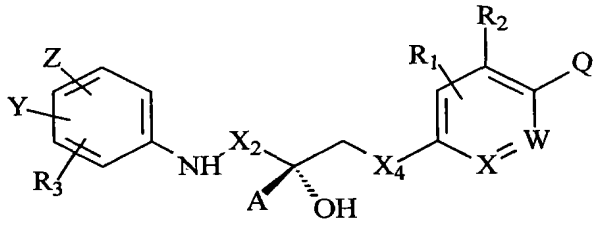
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

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

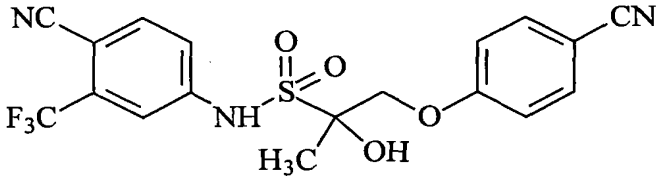
R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

4. 权利要求 3 的化合物，其由以下结构表示：



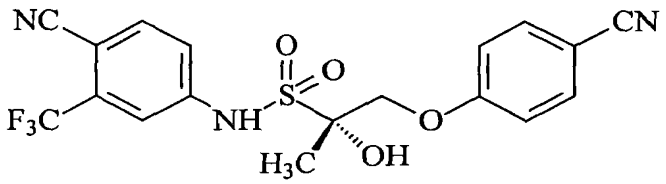
。

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：



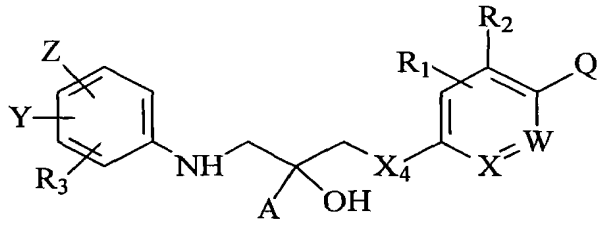
V 。

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)[=$CHCH_2N(CH_3)_2$]、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；

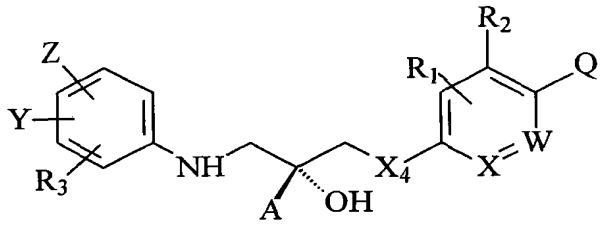
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

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。

8. 权利要求 7 的化合物，其由以下结构表示：



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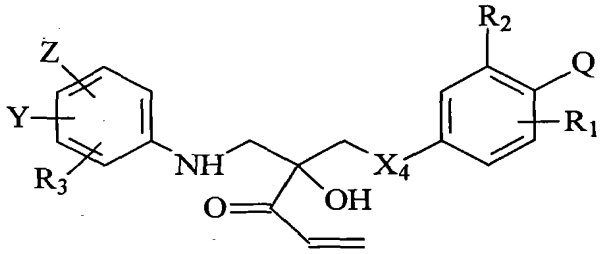
9. 权利要求 7 的化合物，其中所述化合物由式 VII 的结构表示：



VII

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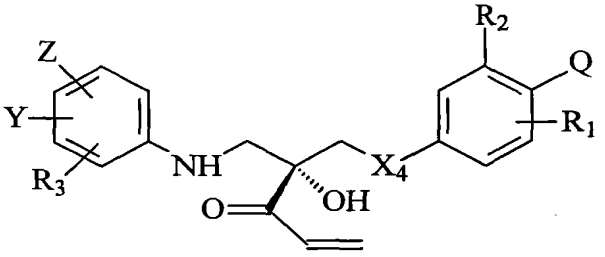
10. 权利要求 9 的化合物，其由以下结构表示：



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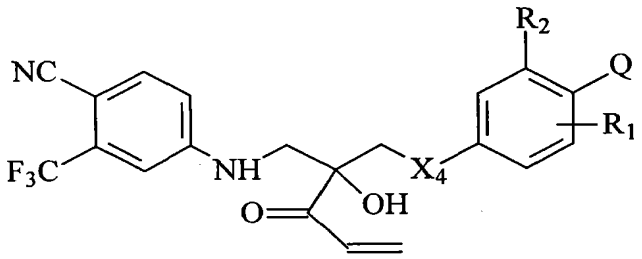
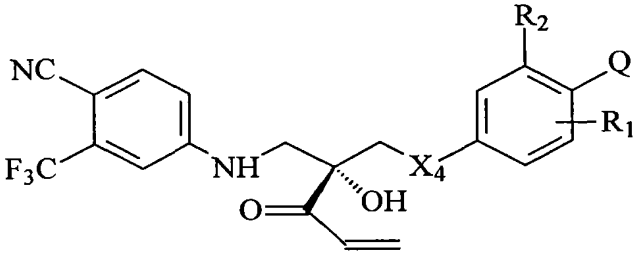
11. 权利要求 9 的化合物，其中所述化合物由式 X 的结构表示：



VIII 。

12. 权利要求 11 的化合物，其由以下结构表示：



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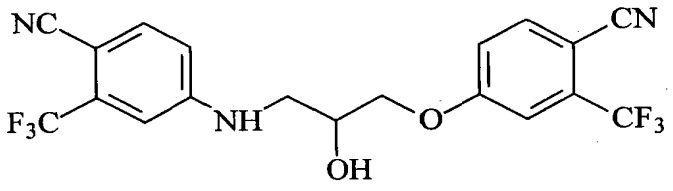
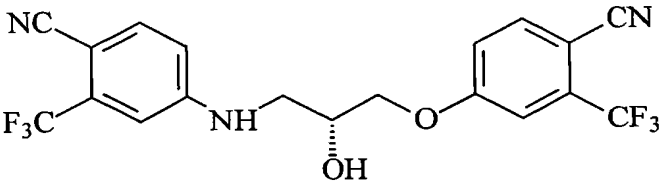
13. 权利要求 7 的化合物，其中所述化合物由式 IX 的结构表示：



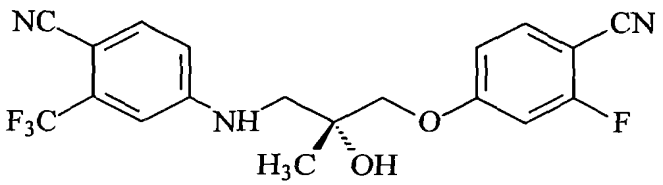
IX 。

14. 权利要求 13 的化合物，其由以下结构表示：



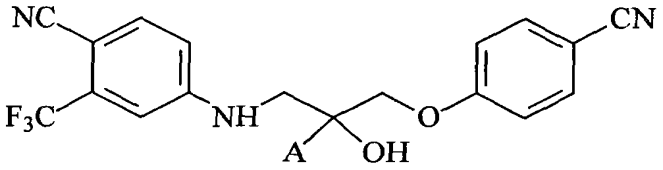
。

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：



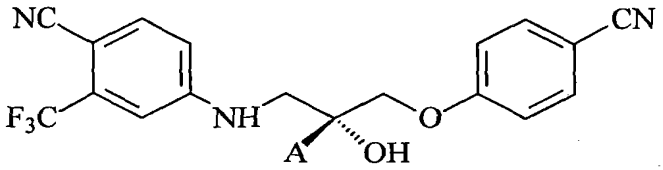
X 。

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：



。

18. 权利要求 15 的化合物，其中 A 是 CH_2OH。

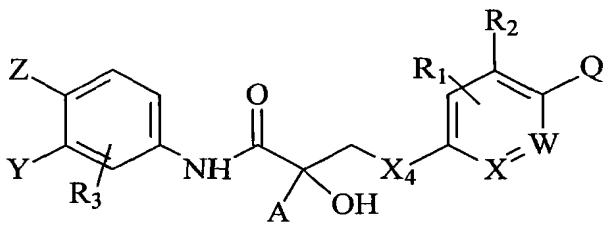
19. 权利要求 17 的化合物，其中 A 是 CH_2OMe。

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。

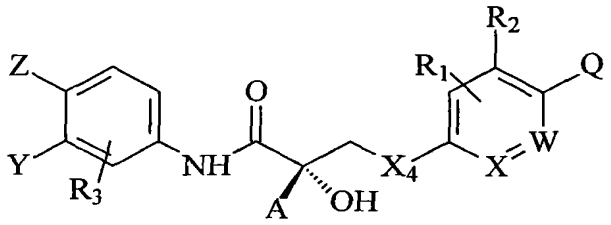
25. 权利要求 24 的化合物，其中 A 是 CH$_2$OH。

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。

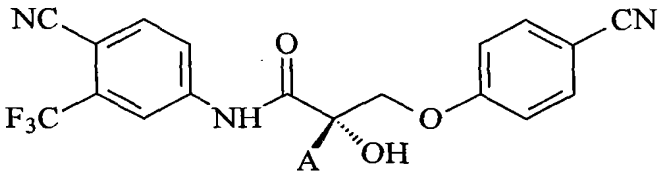
28. 权利要求 23 的化合物，其中 Q 是 CN，Z 是 CN，Y 是 CF_3，并且 R_1、R_2 和 R_3 是 H。

29. 权利要求 23 的化合物，其由以下结构表示：



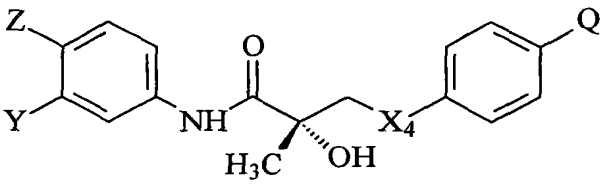
。

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。

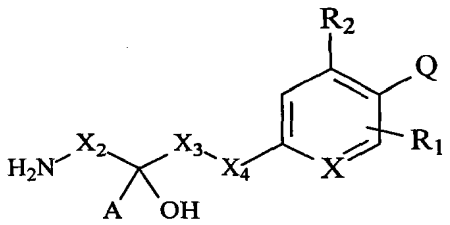
32. 权利要求 31 的化合物，其中 Q 是 F。

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。

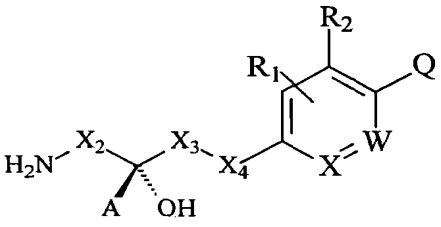
37. 权利要求 36 的化合物，其中X_2是CH_2。

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：

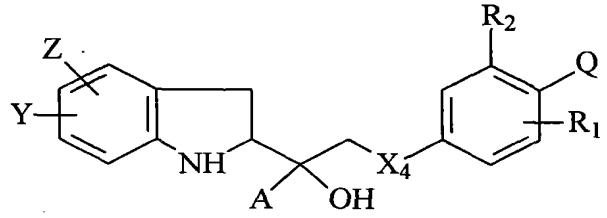


。

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。

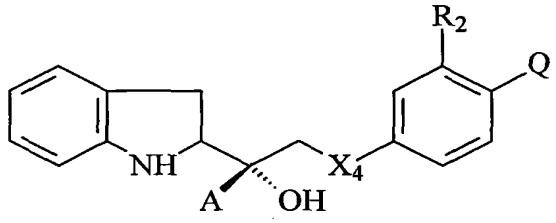
47. 权利要求 44 的化合物，其中 Q 是 CN。

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。

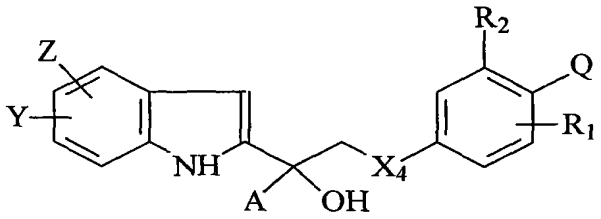
50. 权利要求 44 的化合物，其中 A 是 CH_3，X_4 是 O，Z 是 CN，Q 是 CN，R_1 和 R_2 是 H，并且 Y 是 CF_3。

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。

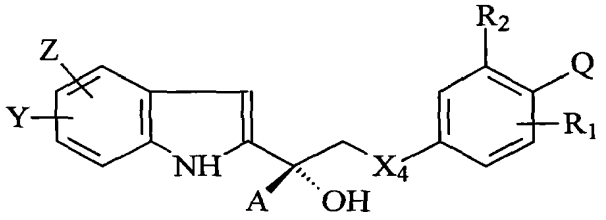
54. 权利要求 52 的化合物，其中 X_4 是 O。

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。

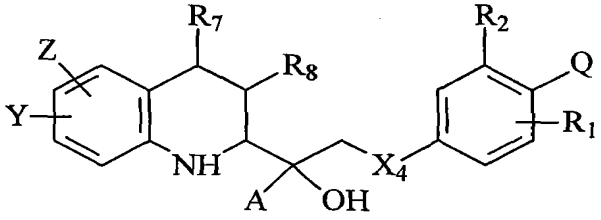
57. 权利要求 52 的化合物，其中 A 是 CH_3，X_4 是 O，Z 是 CN，Q 是 CN，R_1 和 R_2 是 H，并且 Y 是 CF_3。

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。

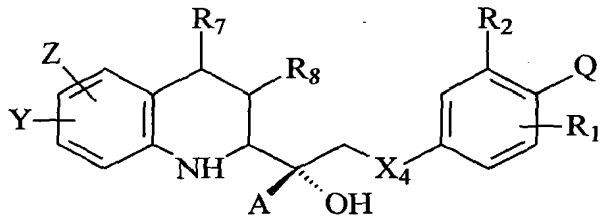
63. 权利要求 58 的化合物，其中 R_7 是=CH_2 且 R_8 是氧代。

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：



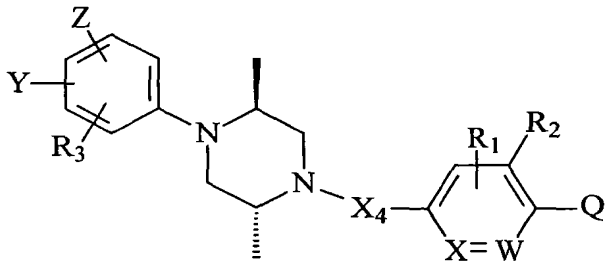
。

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。

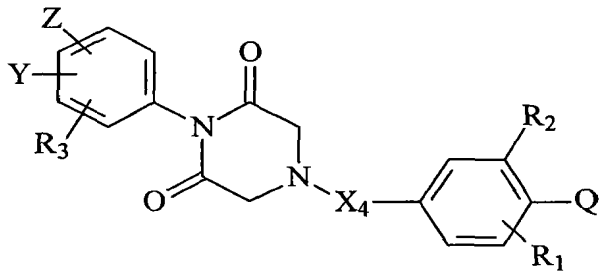
71. 权利要求 70 的化合物，其中 X_4 是 O。

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。

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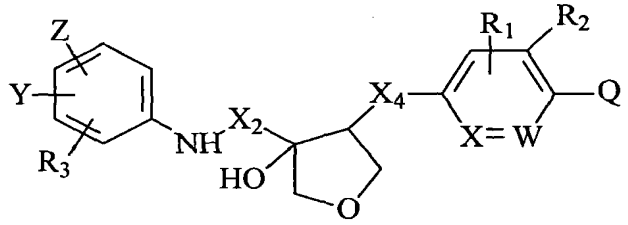
82. 权利要求80的化合物，其中所述化合物由式XXXIV的结构表示：



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。

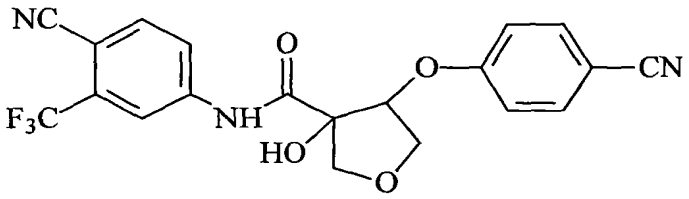
84. 权利要求82的化合物，其中Q是CN。

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)。

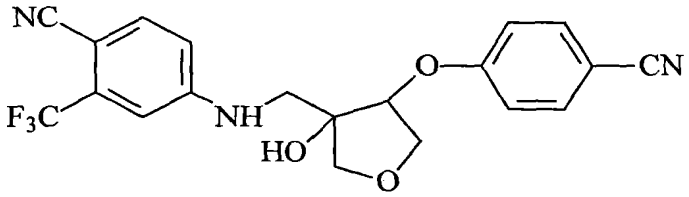
87. 权利要求 82 的化合物，其中 Z 是 CN 且 Y 是 CF_3。

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：



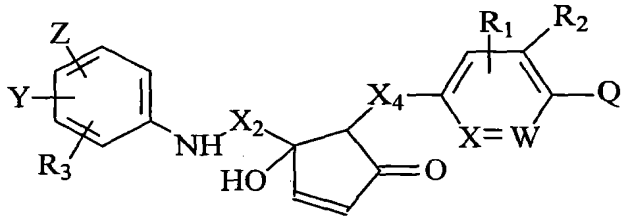
XXXV 。

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。

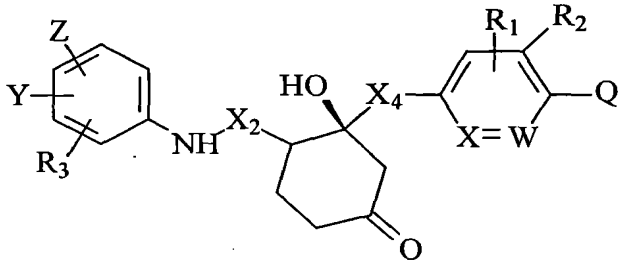
92. 权利要求 90 的化合物，其中 X_2 是 C(O)。

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；

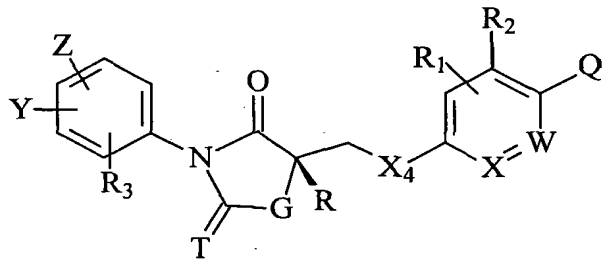
其中

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、$C(O)CH_2NH_2$、

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$C(O)NH(C_{1-4}$ 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；

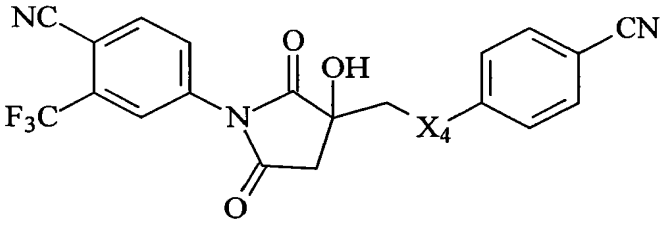
R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2；

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：

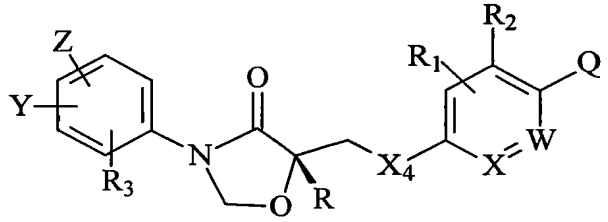


XLV

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

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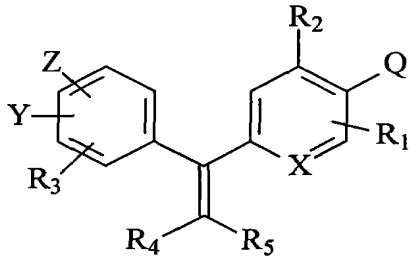
其中：

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；

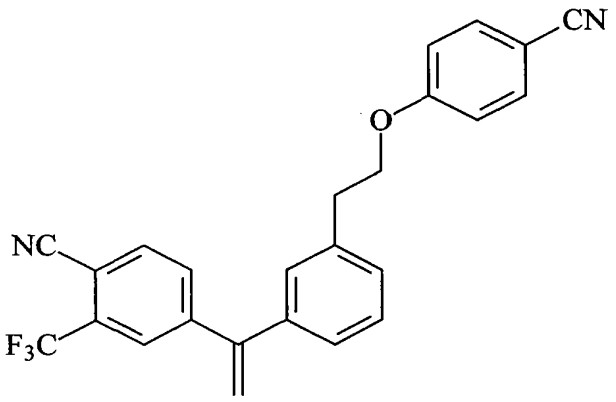
R_2 是由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

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

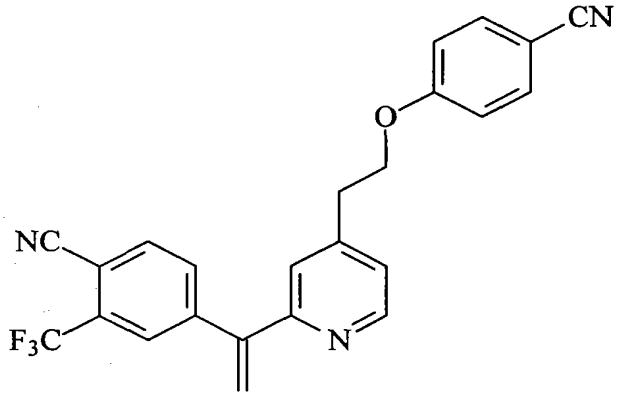
R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

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：



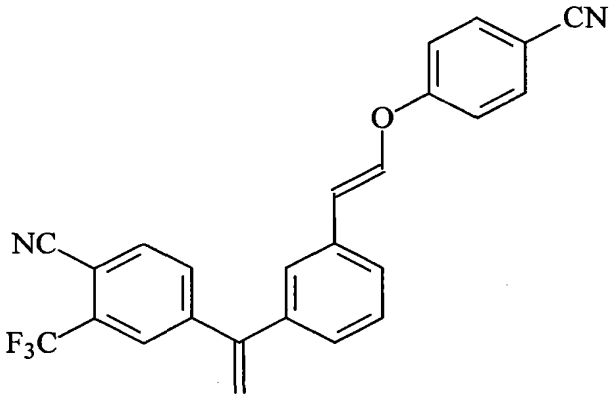
XLVIII 。

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：



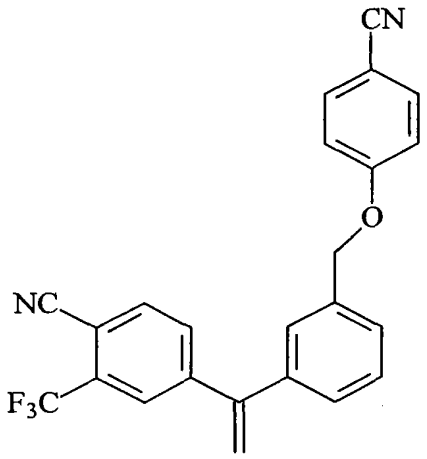
XLIX 。

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：



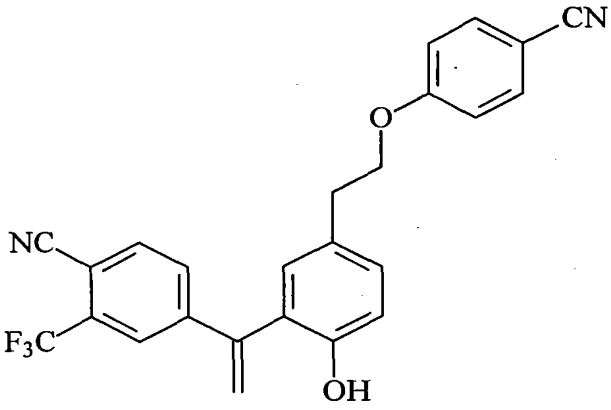
L 。

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。

2205

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。

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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。

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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

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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。

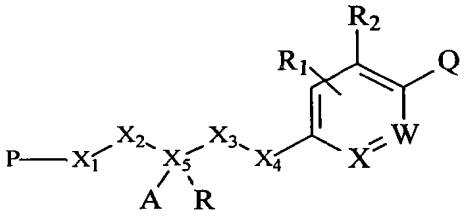
脊髓损伤（SCI）可能会导致改变中枢神经递质的分泌和产生，这继而可能造成下丘脑-垂体-肾上腺轴功能障碍，导致睾酮和其它激素水平的下降。SCI 或其它急性疾病或创伤在特征上包括分解代谢增强伴随合成代谢活动减弱，引发易于损失瘦身体组织的病症。只要分解代谢过程不中断，那么紊乱的营养利用将继续下去。损失瘦体重的影响包括伤口扩展和愈合机制受损。由于营养不良和蛋白缺乏加上固定，脊髓损伤的患者处于高度的患褥疮的风险中。

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：



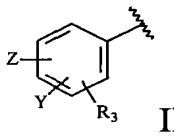
I

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；

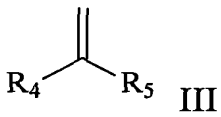
X_2 是 C_{1-4} 亚烷基、SO_2、C(O)、CH-[CH_2-(C_{4-8} 环)]、CH(C_{1-4} 烷基)、CH(NH_2)、CH(OH)、CH(C_{1-4} 卤代烷基)、键；或者 X_2 和 R_3 与 X_2 所连接的 X_1 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X_2 和 X_5 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；

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；

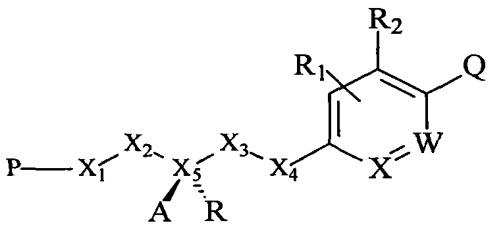
或者

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

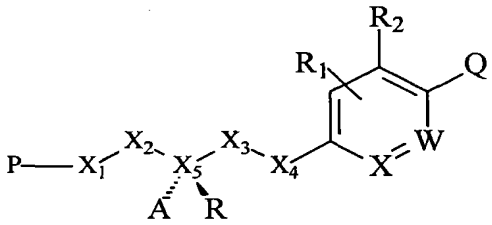
或者

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。

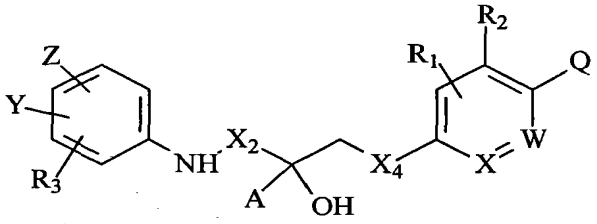
在另一个实施方案中，式 I 的化合物由以下结构表示：



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)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 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；

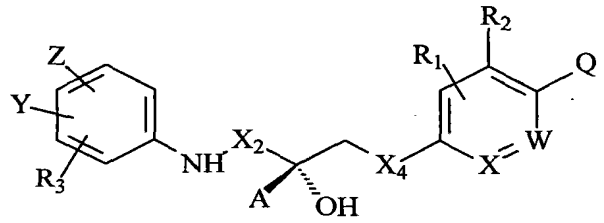
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2；

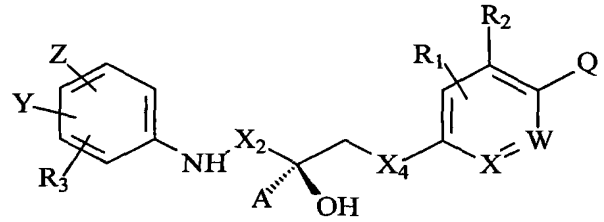
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

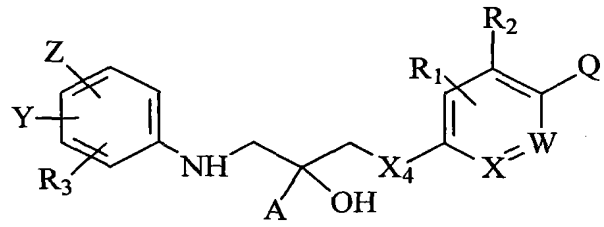
在另一个实施方案中，式 IV 的化合物由以下结构表示：



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；

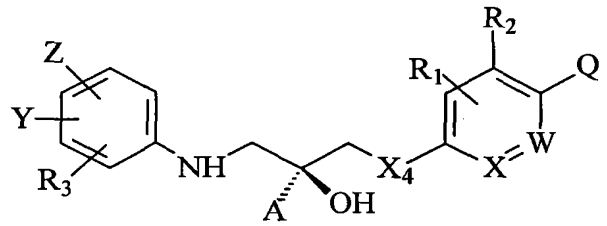
R_2是H、由R_6取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或CH=CH-O-对氰基苯基；

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

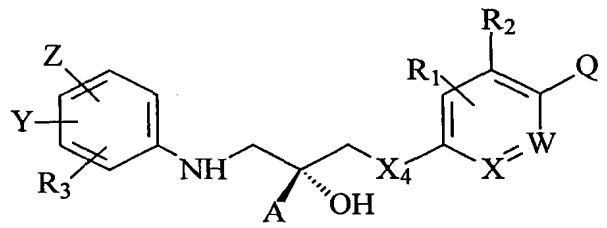
R_6是CN、NO_2、$NHC(O)CH_3$或卤化物。

在另一个实施方案中，式VI的化合物由以下结构表示：

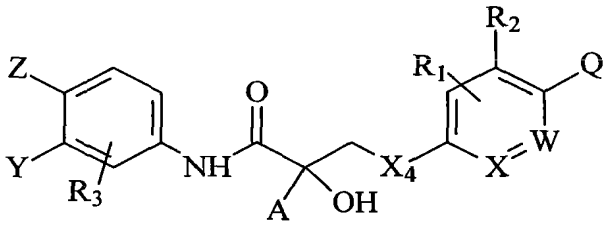


在一个实施方案中，式VI的化合物由以下结构表示：

2222



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-[$CH_2CH_2N(CH_3)_2$]；

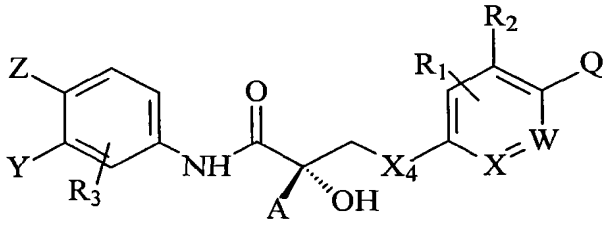
R_1 是 H、OH、F、Cl、Br 或 I；

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；

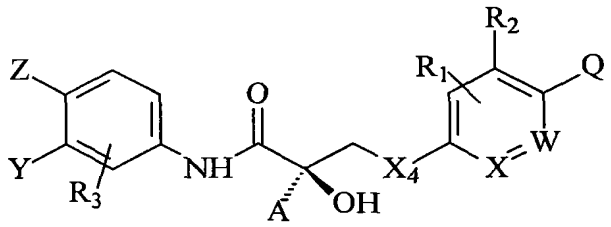
R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2；

R'是 NH_2、OH 或 CH_3；并且

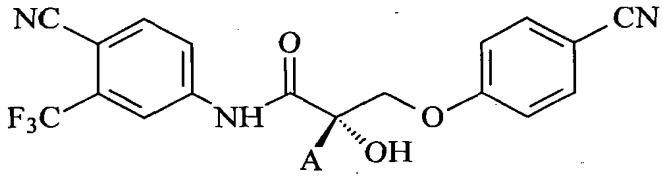
R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。在另一个实施方案中，式 XII 的化合物由以下结构表示：



在另一个实施方案中，式 XII 的化合物由以下结构表示：



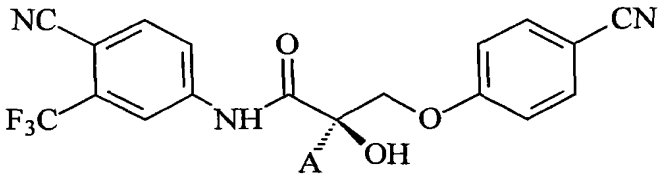
在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：



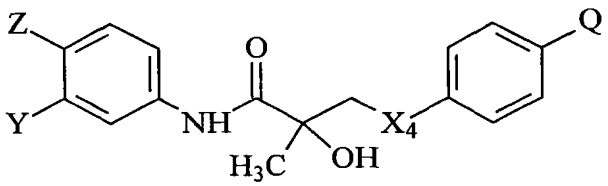
XIII

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

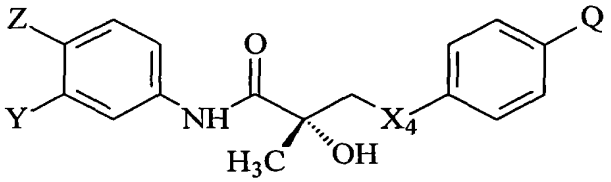
C[=CHCH$_2$N(CH$_3$)$_2$]、PO(C$_{1-4}$烷基)、N[CH$_2$CH$_2$N(CH$_3$)$_2$]、NO[CH$_2$CH$_2$N(CH$_3$)$_2$]；

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

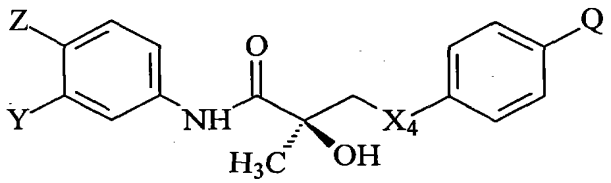
Y是H、C$_{1-4}$烷基、CF$_3$、CN、NO$_2$、F、Cl、I或Br。

在另一个实施方案中，式XVII的化合物由以下结构表示：

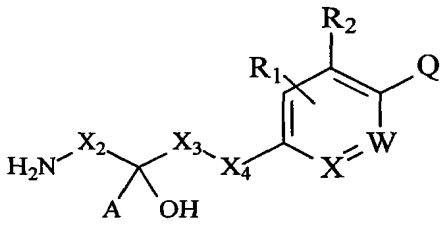


XVII

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；

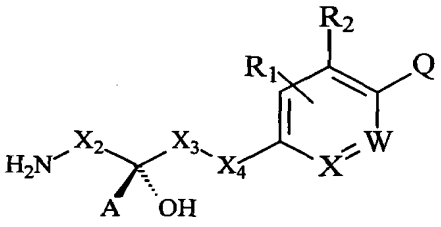
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物；

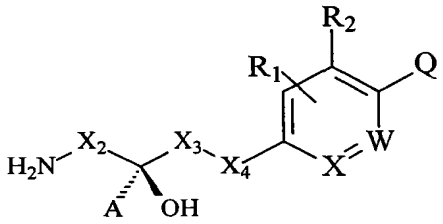
其中

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。

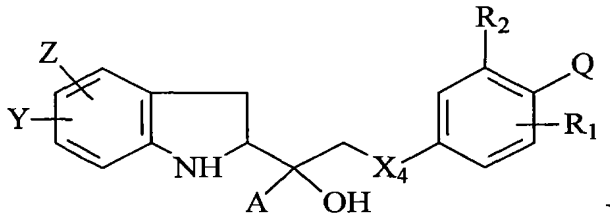
在另一个实施方案中，式 XIX 的化合物由以下结构表示：



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$_2$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、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$_3$)$_2$]；

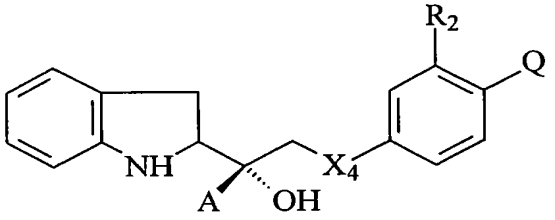
R_1 是 H、OH、F、Cl、Br 或 I；

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；

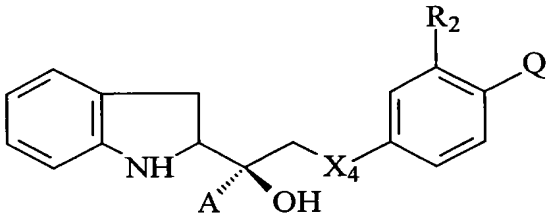
R'是 NH$_2$、OH 或 CH$_3$；并且

R_6 是 CN、NO$_2$、NHC(O)CH$_3$ 或卤化物。

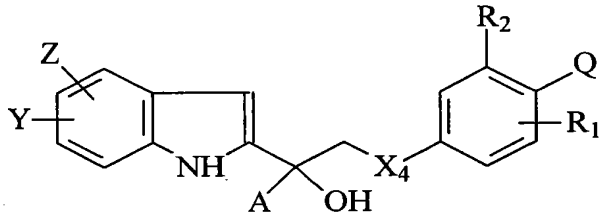
在另一个实施方案中，式 I 的化合物由以下结构表示：



或在另一个实施方案中，



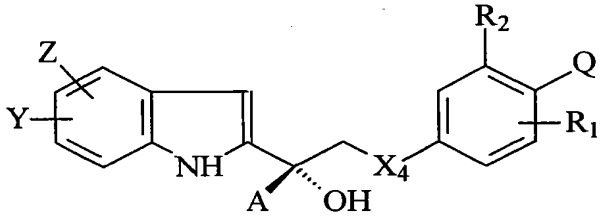
在一个实施方案中，本发明提供由式 XXI 的结构表示的化合物：



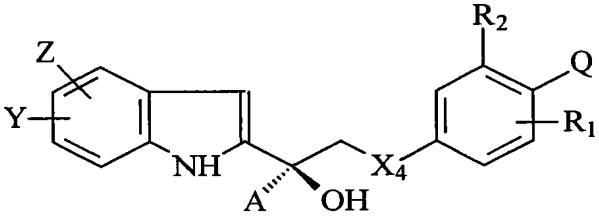
XXI

其中 A、Z、Y、X_4、Q、R_1 和 R_2 如在化合物 XX 中所述。

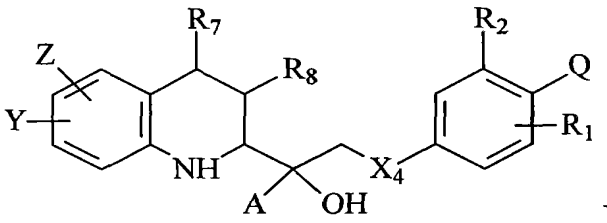
在另一个实施方案中，式 XXI 的化合物由以下结构表示：



或在另一个实施方案中，



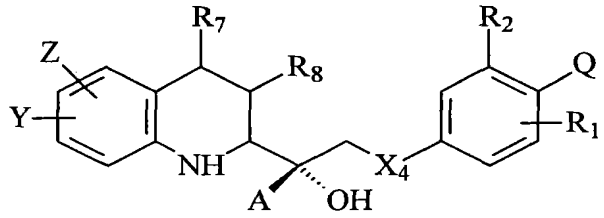
在一个实施方案中，本发明提供由式 XXII 的结构表示的化合物：



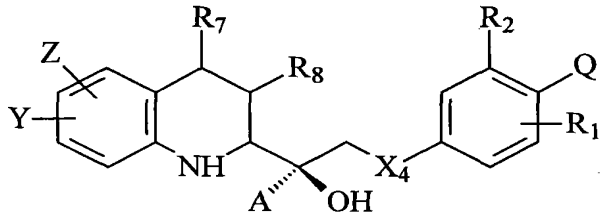
XXII

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。

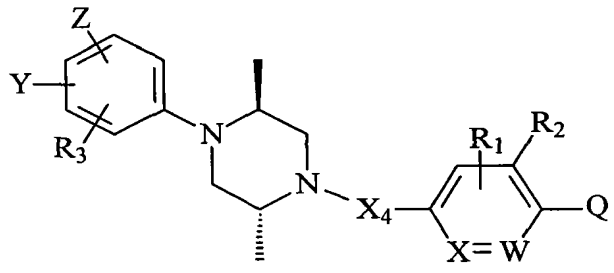
在另一个实施方案中，式 XXII 的化合物由以下结构表示：



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；

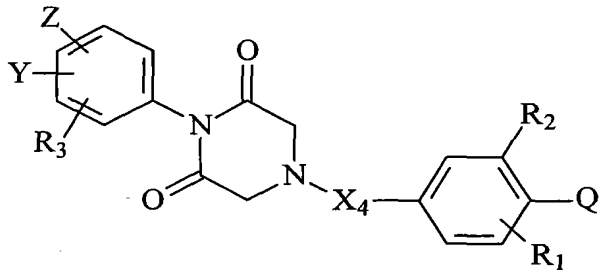
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

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。

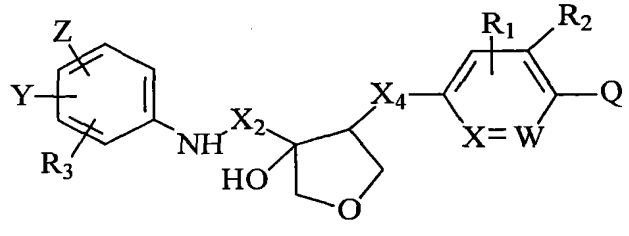
在一个实施方案中，本发明提供由式 XXXIII 的结构表示的化合物：



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-[$CH_2CH_2N(CH_3)_2$]；

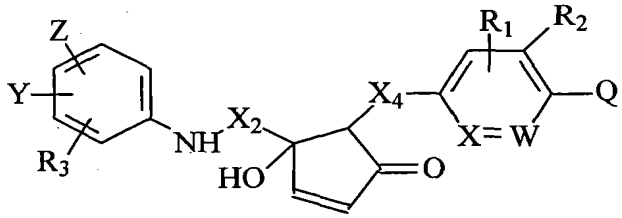
R_1是H、OH、F、Cl、Br或I；

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：

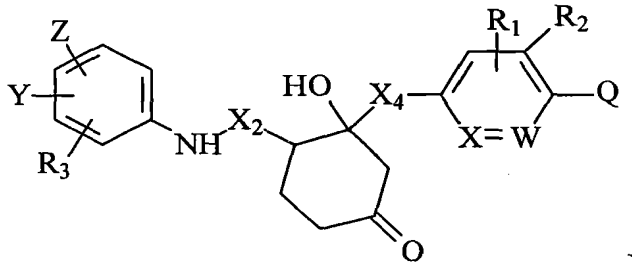


XXXVII

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。

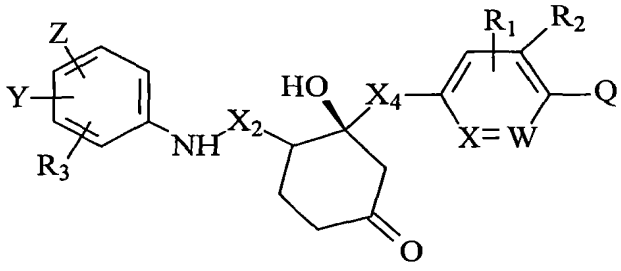
在一个实施方案中，本发明提供由式XXXVIII的结构表示的化合物：



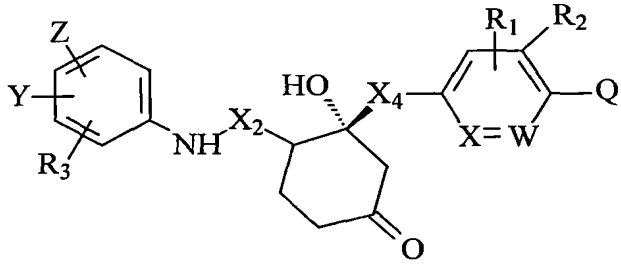
XXXVIII

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。

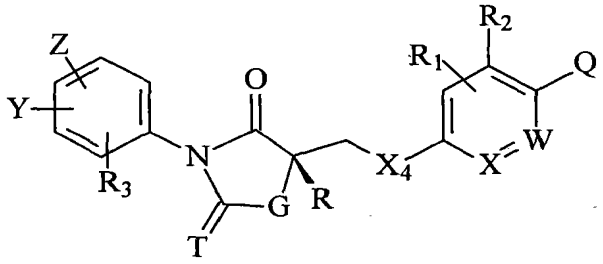
在另一个实施方案中，式XXXVIII的化合物由以下结构表示：



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；

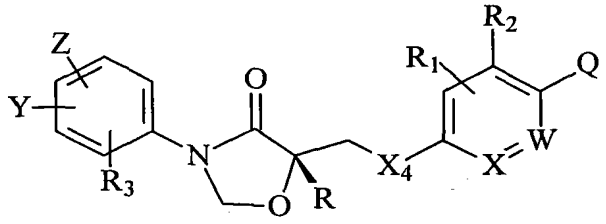
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

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。

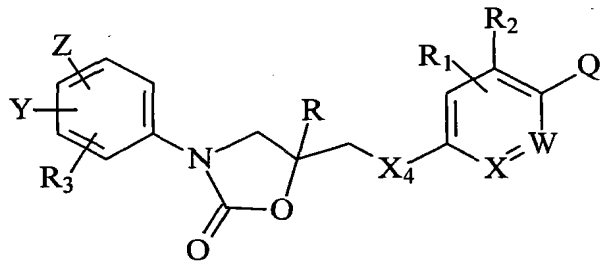
在一个实施方案中，本发明提供式 XLII 的化合物：



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

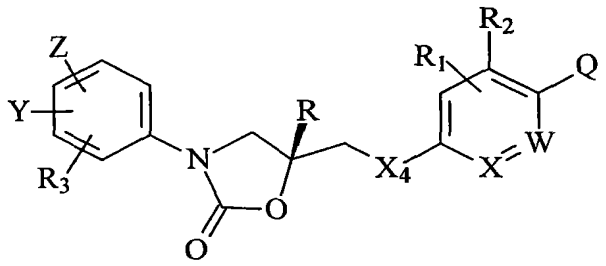
其中：

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；

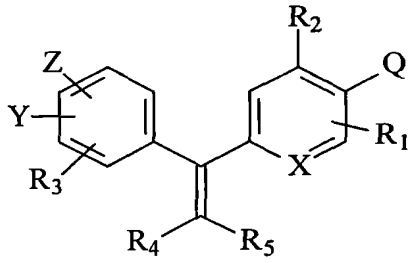
其中

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）。

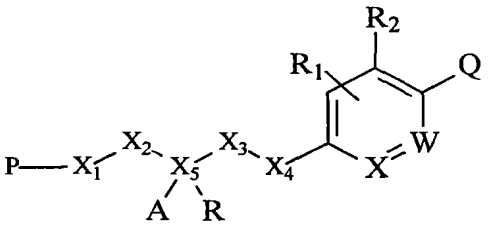
图14描绘了与*R*-比卡鲁胺结合的突变型W741L雄激素受体配体结合域。图14A显示与*R*-比卡鲁胺结合的AR LBD(W741L)的总体结构的侧视图。AF2区（螺旋3、4和12）以绿色突出显示。保守的电荷-发夹（charge-clamp）残基是H3中的K720和H12中的E897。图14B显示与DHT结合的野生型AR LBD的AF2区的结构细节。W741侧链显示在充满原子的空间中。

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

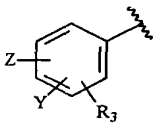
其中

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；

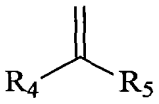
X_3 是 C_{1-4} 亚烷基、NH、N、CH(OH)、键；或者 X_1 和 X_3 与 X_1 和 X_3 所连接的 X_2 和 X_5 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X_3 和 X_5 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_3 和 X_4 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

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)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 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；

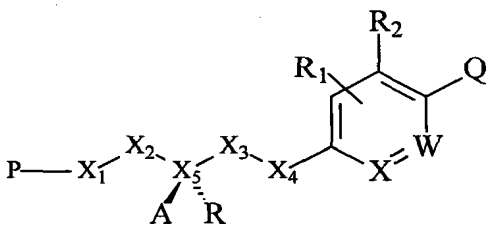
或者

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；

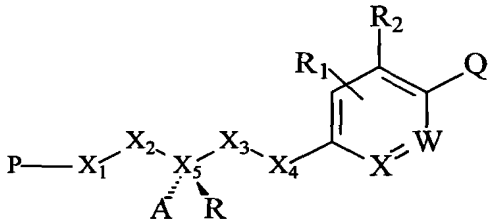
或者

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。

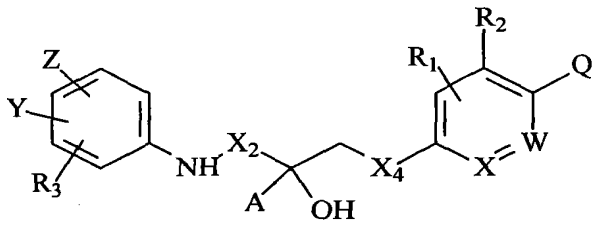
在另一个实施方案中，式 I 的化合物由以下结构表示：



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；

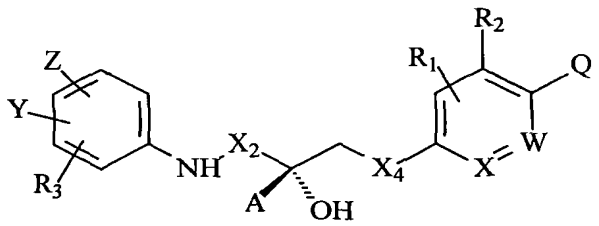
R_2 是 H、R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2；

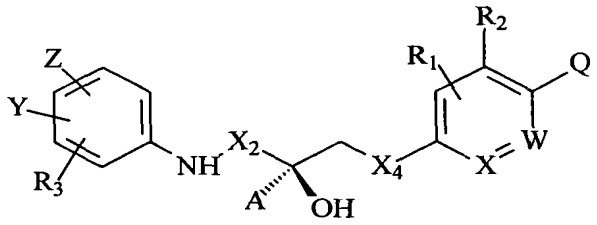
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

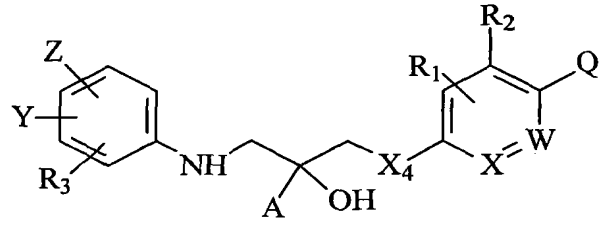
在另一个实施方案中，式 IV 的化合物由以下结构表示：



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;

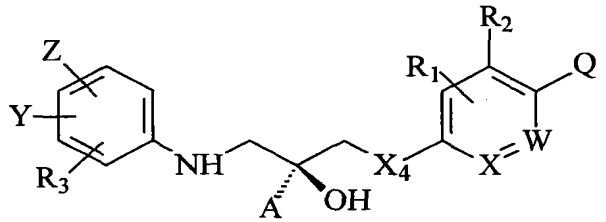
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基;

R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2;

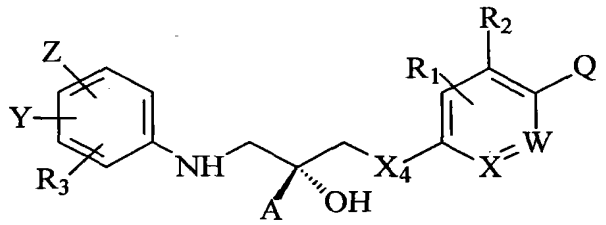
R'是 NH_2、OH 或 CH_3;并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

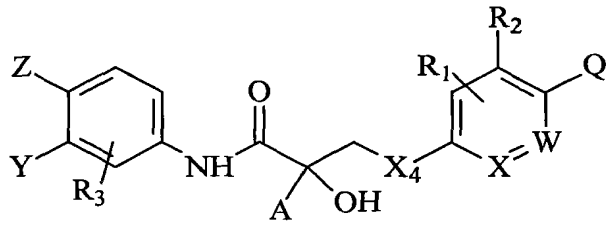
在另一个实施方案中,式 VI 的化合物由以下结构表示:



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；

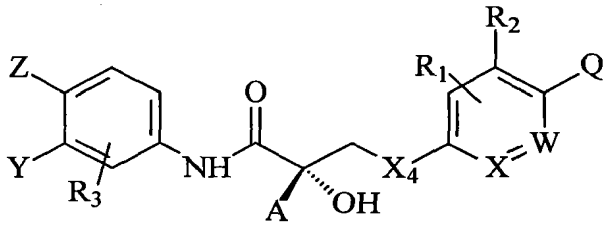
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

R_3 是 H、C_{1-4}烷基、卤化物、CN 或 NO_2；

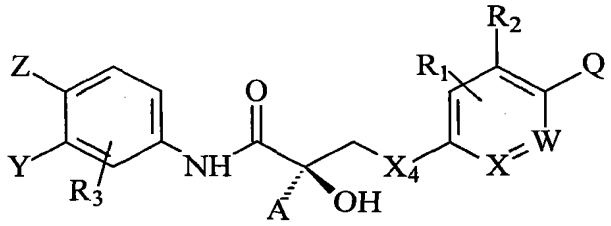
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

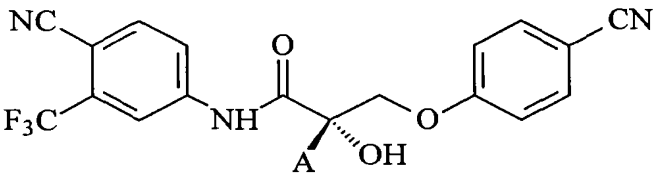
在另一个实施方案中，式 XII 的化合物由以下结构表示：



在另一个实施方案中，式 XII 的化合物由以下结构表示：



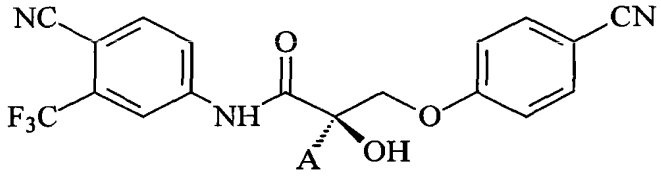
在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：



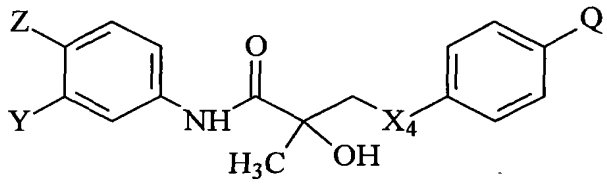
XIII

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

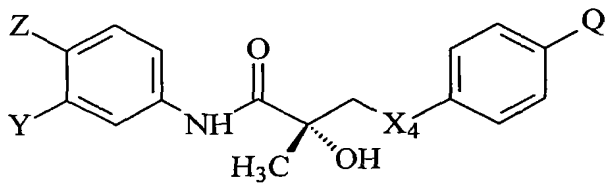
X_4 是 $S(O)[=CHCH_2N(CH_3)_2]$、$C(OH)[CH_2CH_2N(CH_3)_2]$、$C[=CHCH_2N(CH_3)_2]$、$PO(C_{1-4}$ 烷基)、$N[CH_2CH_2N(CH_3)_2]$、$NO[CH_2CH_2N(CH_3)_2]$；

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)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 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

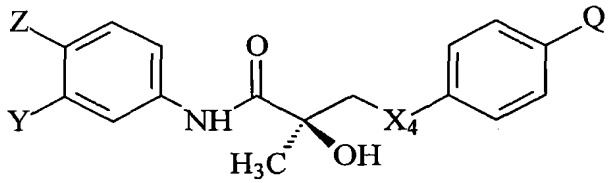
Y 是 H、C_{1-4} 烷基、CF_3、CN、NO_2、F、Cl、I 或 Br。

在另一个实施方案中，式 XVII 的化合物由以下结构表示：

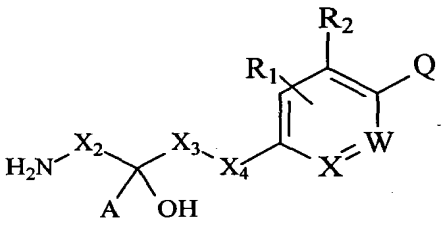


XVII

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)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 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；

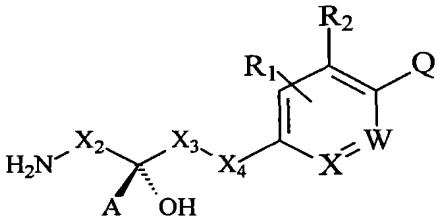
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物；

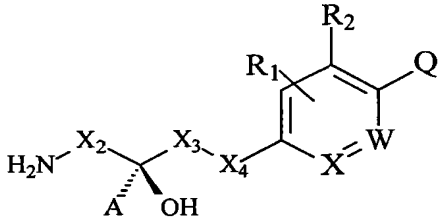
其中

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，R1 和 R_2 是 H，那么 Q 不是 H 或卤素。

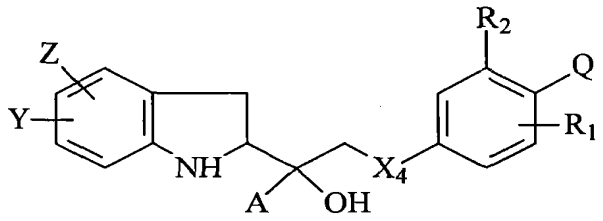
在另一个实施方案中，式 XIX 的化合物由以下结构表示：



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-[$CH_2CH_2N(CH_3)_2$]；

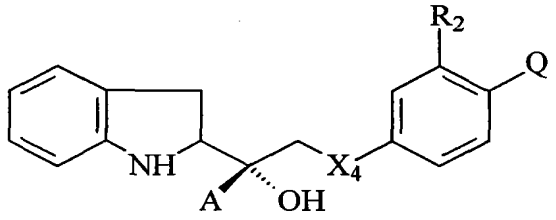
R_1 是 H、OH、F、Cl、Br 或 I；

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；

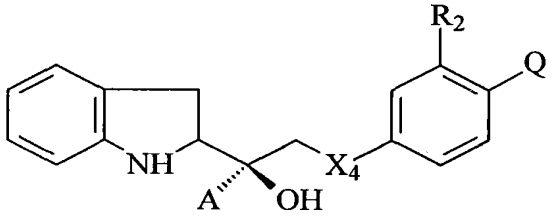
R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

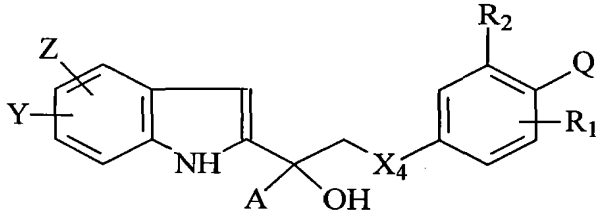
在另一个实施方案中，式 I 的化合物由以下结构表示：



或在另一个实施方案中，



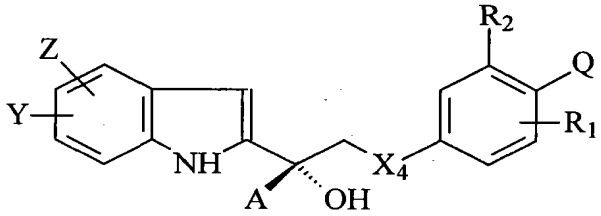
在一个实施方案中，本发明提供由式 XXI 的结构表示的化合物：



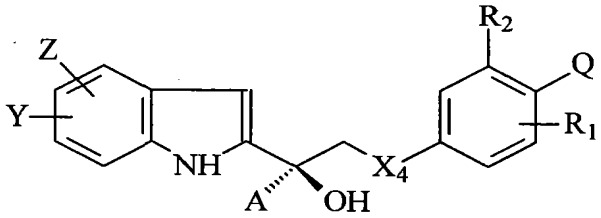
XXI

其中 A、Z、Y、X_4、Q、R_1 和 R_2 如在化合物 XX 中所述。

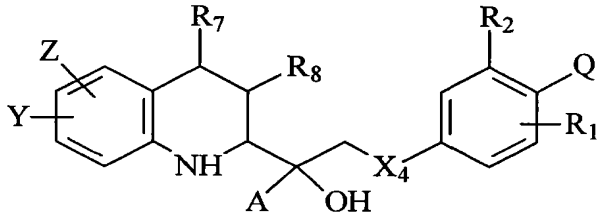
在另一个实施方案中，式 XXI 的化合物由以下结构表示：



或在另一个实施方案中，



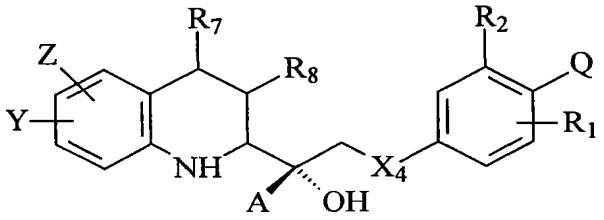
在一个实施方案中，本发明提供由式 XXII 的结构表示的化合物：



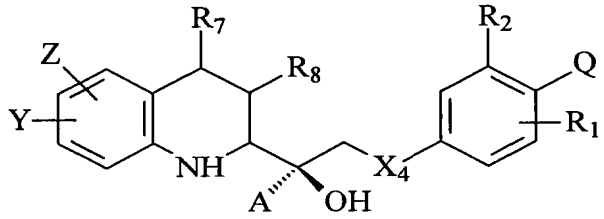
XXII

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。

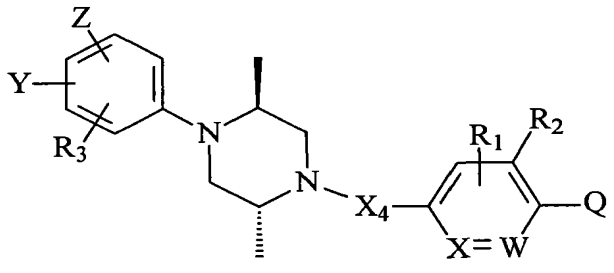
在另一个实施方案中，式 XXII 的化合物由以下结构表示：



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

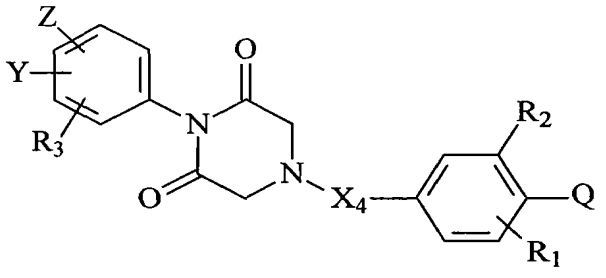
或 CH=CH-O-对氰基苯基；

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。

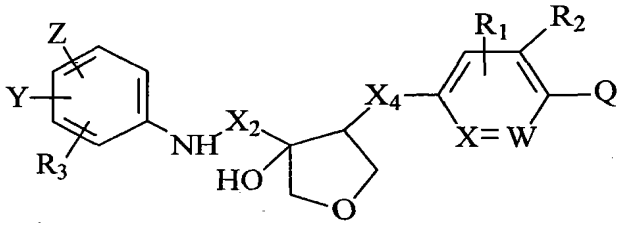
在一个实施方案中，本发明提供由式 XXXIII 的结构表示的化合物：



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-[$CH_2CH_2N(CH_3)_2$]；

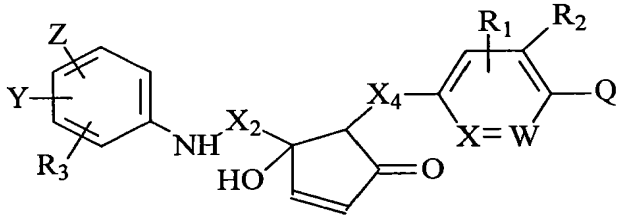
R_1是 H、OH、F、Cl、Br 或 I；

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：

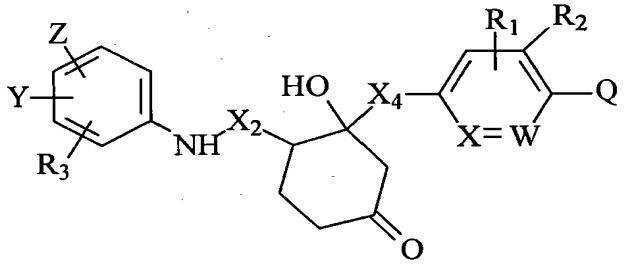


XXXVII

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。

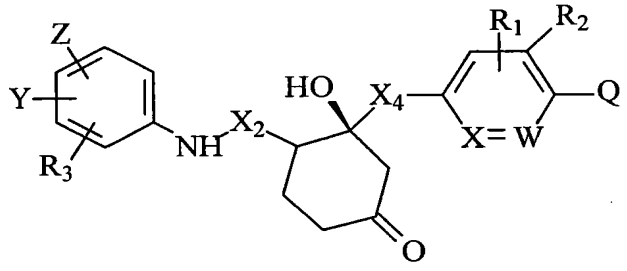
在一个实施方案中，本发明提供由式 XXXVIII 的结构表示的化合物：



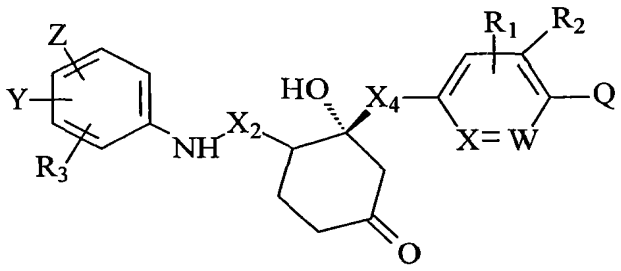
XXXVIII

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

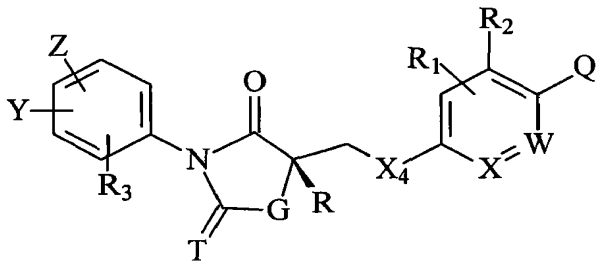
如果 P 是式 II，X 是 C，X_3 是 CH_2，X_4 是 O 或 NH，R_1、R_2 和 R_3 是 H，并且 X_5 和 X_1 形成 5 元环噁唑烷-2-酮，那么 Q 不是卤素或 H；

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；

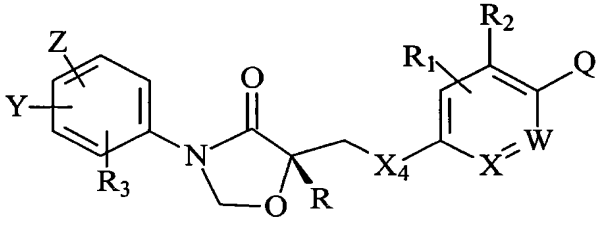
R'是 NH_2、OH 或 CH_3；并且

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。

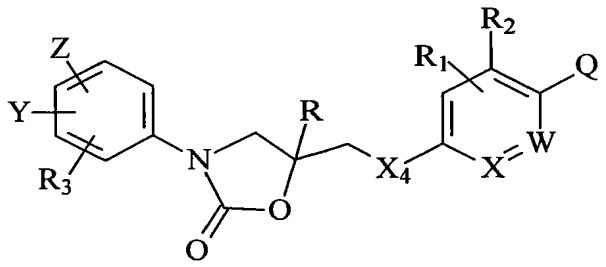
在一个实施方案中，本发明提供式 XLII 的化合物：



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

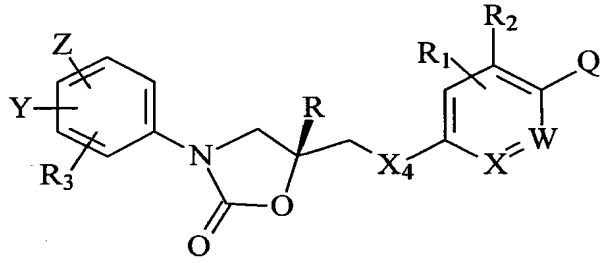
其中：

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；

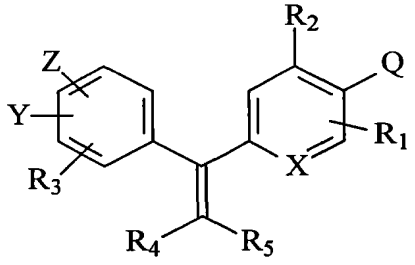
其中

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：

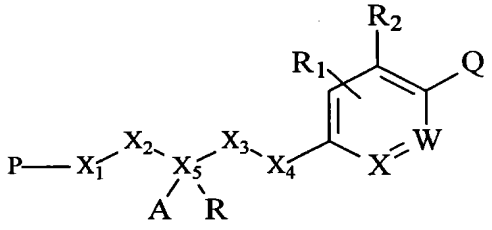


在一个实施方案中，本发明提供由式 XLVII 的结构表示的化合物：



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：



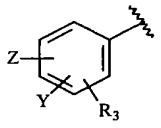
I

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；

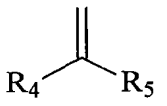
X_3 是 C_{1-4} 亚烷基、NH、N、CH(OH)、键；或者 X_1 和 X_3 与 X_1 和 X_3 所连接的 X_2 和 X_5 一起形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环；或者 X_3 和 X_5 形成饱和的或不饱和的、取代的或未取代的 5-或 6-元环，且 A 不存在；或者 X_3 和 X_4 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环；

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；

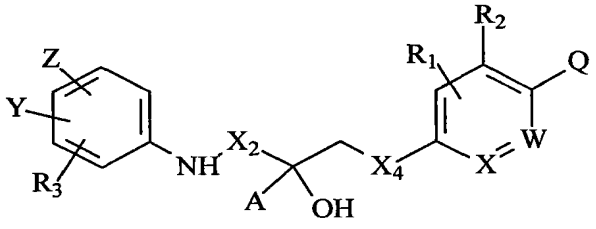
或者

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$_2$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_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；

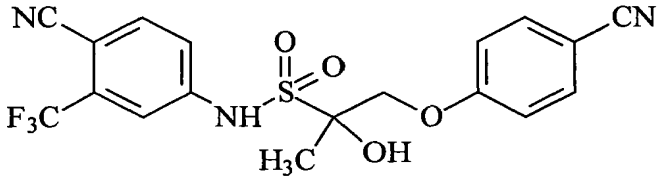
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

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

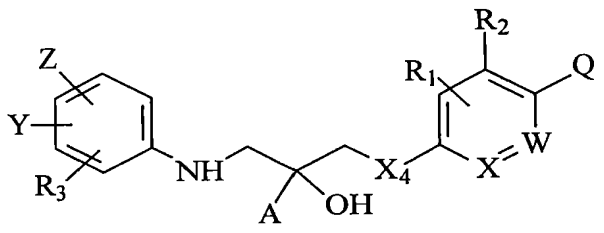
R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

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；

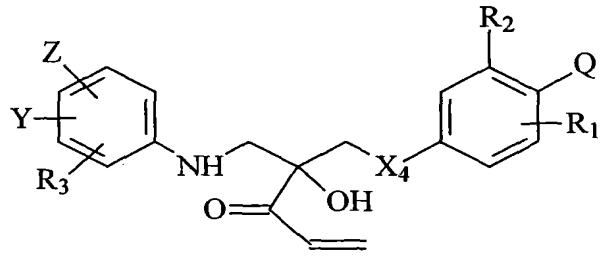
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

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。

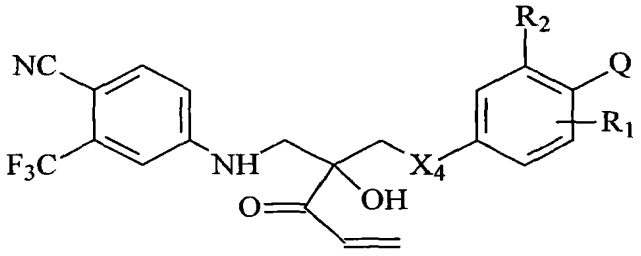
在一个实施方案中，本发明提供由式 VII 的结构表示的化合物：



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。

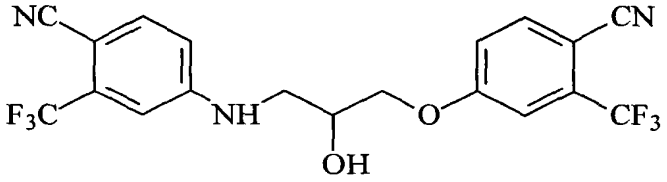
在另一个实施方案中，本发明提供由式 VIII 的结构表示的化合物：



VIII

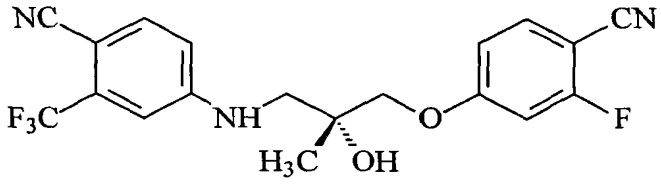
其中 R_1、R_2、Q 和 X_4 如以上在化合物 VI 中所述。

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：



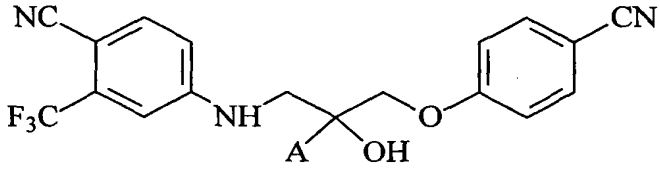
IX **8**

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：



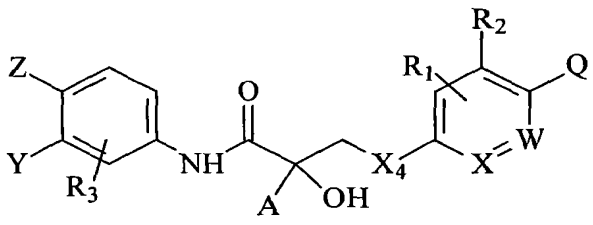
XI

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；

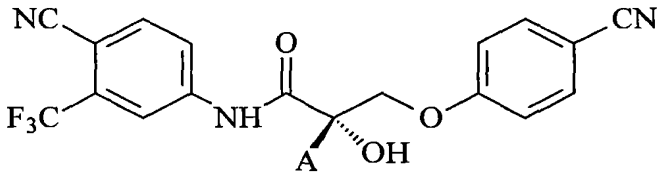
R'是 NH_2、OH 或 CH_3；并且

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。

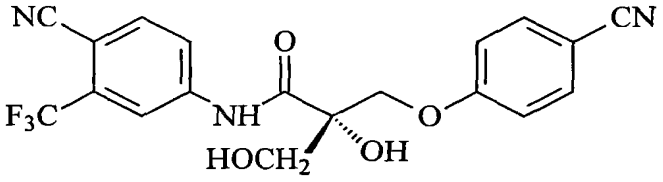
在一个实施方案中，本发明提供由式 XIII 的结构表示的化合物：



XIII

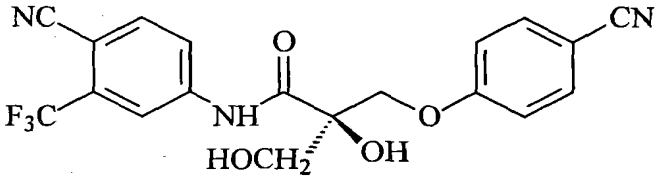
其中 A 如以上在化合物 XII 中所述。

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：

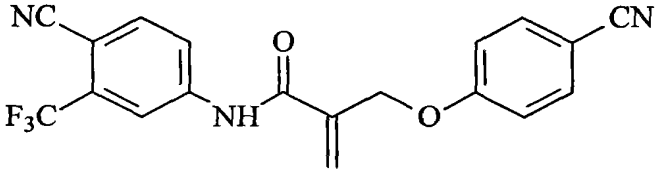


XIV

或在另一个实施方案中，

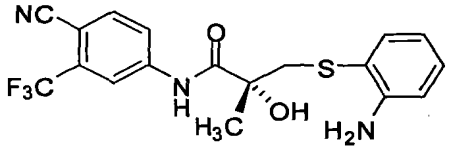


在一个实施方案中，本发明提供由式 XV 的结构表示的化合物：



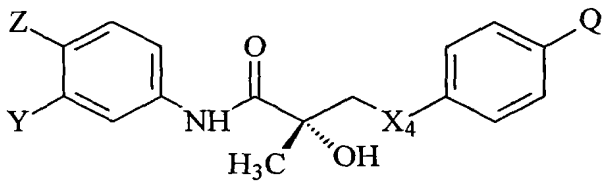
XV

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

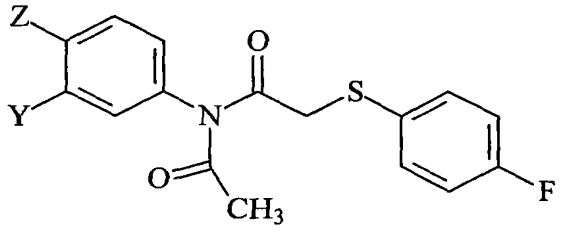
Q 是 H、CN、OH、NO_2、CF_3、卤化物、C_{2-6} 烯基、C_{2-6} 炔基、$C(O)CH_2NH_2$、$C(O)NH(C_{1-4}$ 烷基)、$C(O)N(C_{1-4}$ 烷基$)_2$、$C(O)NH_2$、$NH(C_{1-4}$ 烷基)、$NHC(O)NH(C_{1-4}$ 烷基)、$CH_2C(O)NH_2$、$NHC(O)NH_2$、$NHCO(C_{1-4}$ 烷基)、$NHSO_2(C_{1-4}$ 烷基)、$O-[CH_2CH_2CH(CH_3)_2]$、$O-[CH_2CH_2(C_{4-8}$ 环烷基)]、$O-[CH_2CH_2(C_{4-8}$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



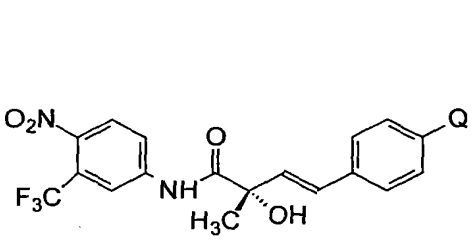
XVIII

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：

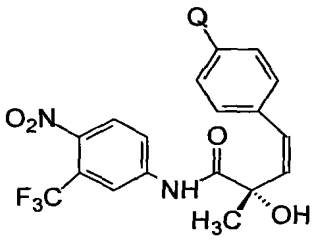
在一个实施方案中，本发明提供式 I 的化合物，其中 X_3 和 X_4 一起形成双键或一起形成饱和的或不饱和的、取代的或未取代的 3-6 元环。在另一个实施方案中，所述 3-6 元环是环丙基、环丁基、环戊基、环己基、环丁烯基、环戊烯基、环己烯基、苯、哌啶、吡咯、四氢呋喃、吡咯烷、琥珀

酰亚胺、噁唑烷、噁唑烷二酮或噁唑烷酮。

在另一个实施方案中，本发明提供由式 LIII 的结构表示的化合物：

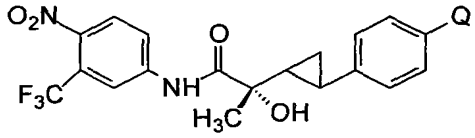


或

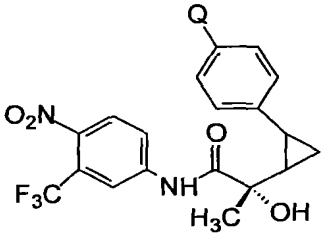


LIII-反式　　LIII-顺式

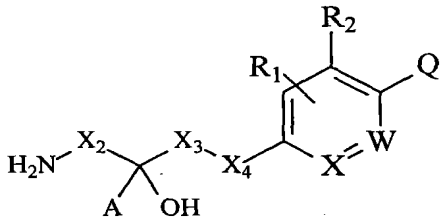
在另一个实施方案中，本发明提供由式 LIV 的结构表示的化合物：



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；

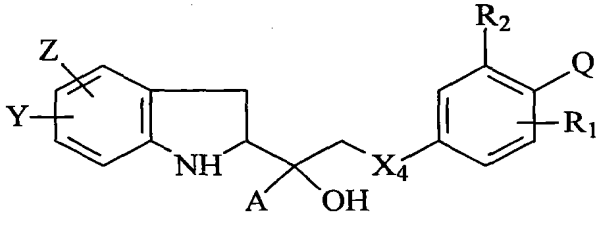
其中

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；

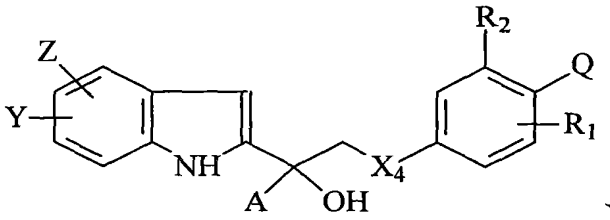
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

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：

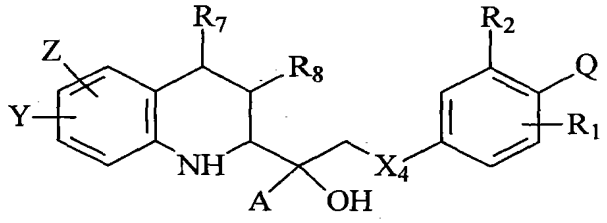


XXI

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

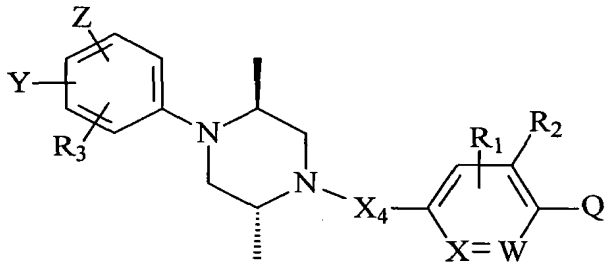
其中 A、Z、Y、X_4、Q、R_1 和 R_2 如在化合物 XX 中所述，R_7 是 H 或氧代，R_8 是 H 或=CH_2。

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；

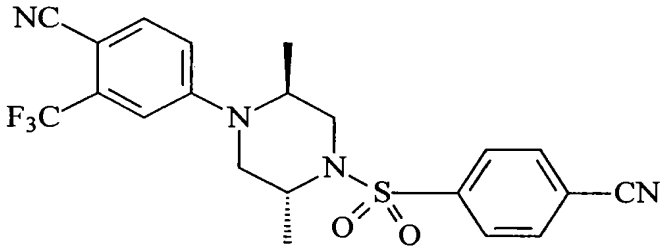
R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2；

R'是 NH_2、OH 或 CH_3；并且

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

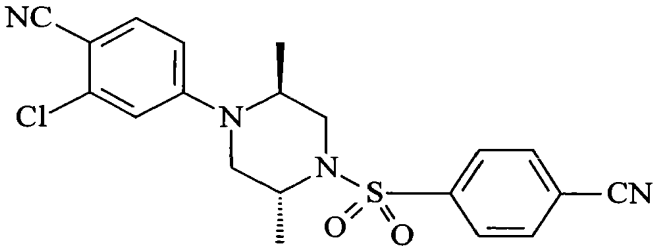
在另一个实施方案中，化合物 XXIII 的 X_4 是 O。在另一个实施方案中，化合物 XXIII 的 Q 是 CN。在另一个实施方案中，化合物 XXIII 的 Z 是 CN，并且 Y 是 CF_3。在另一个实施方案中，化合物 XXIII 的 X_4 是 O，Z 是 CN，Q 是 CN，R_1、R_2 和 R_3 是 H，并且 Y 是 CF_3。

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：



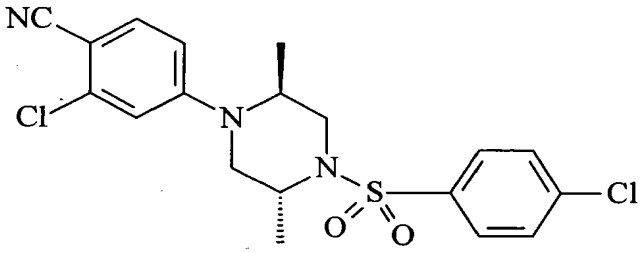
XXIV

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：



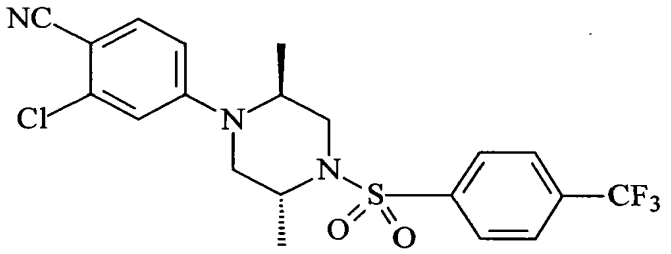
XXV

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：



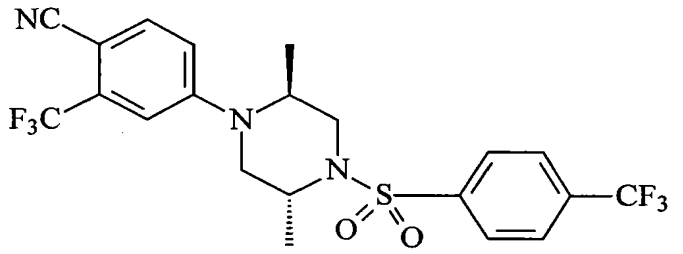
XXVI

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：



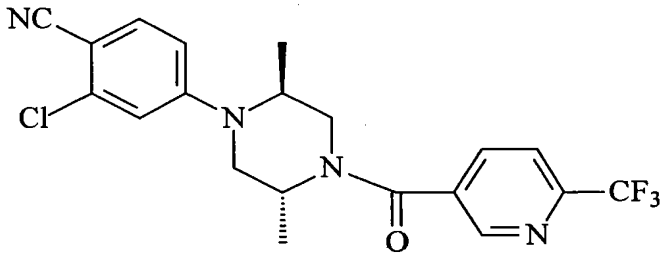
XXVII

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：



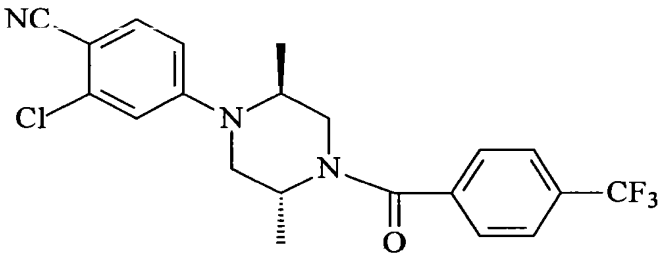
XXVIII

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：



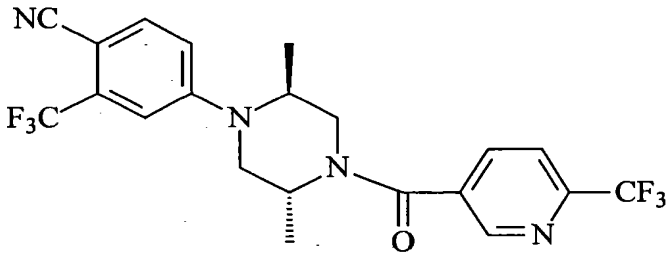
XXIX

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：



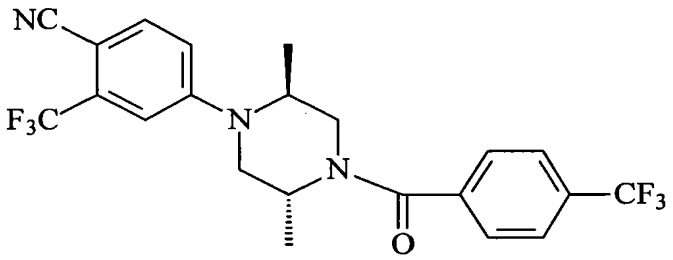
XXX

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：



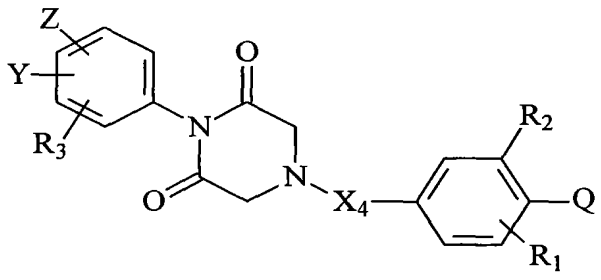
XXXI

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：



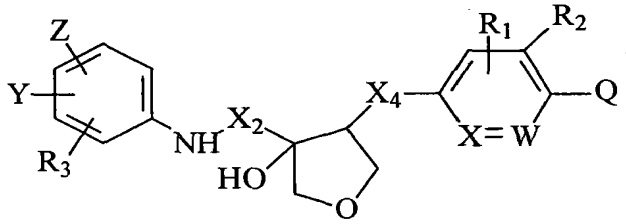
XXXIII

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；

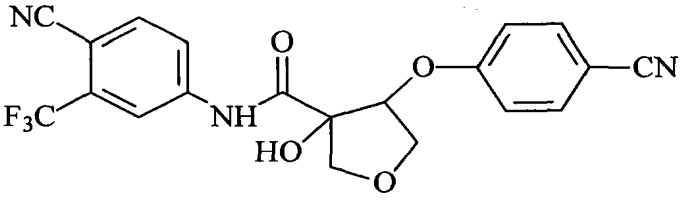
R_3 是 H、C_{1-4}烷基、卤化物、CN 或 NO_2；

R'是 NH_2、OH 或 CH_3；和

R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

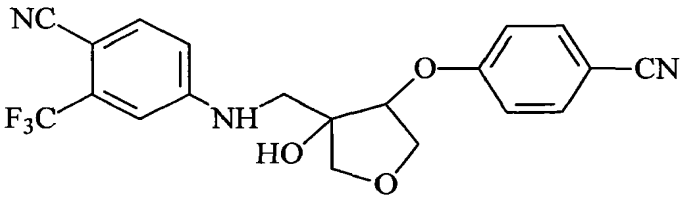
在另一个实施方案中，化合物 XXXIV 的 X_4 是 O。在另一个实施方案中，化合物 XXXIV 的 Q 是 CN。在另一个实施方案中，化合物 XXXIV 的 X_2 是 CH_2。在另一个实施方案中，化合物 XXXIV 的 X_2 是 C(O)。在另一个实施方案中，化合物 XXXIV 的 Z 是 CN，并且 Y 是 CF_3。在另一个实施方案中，化合物 XXXIV 的 X_4 是 O，Z 是 CN，Q 是 CN，R_1、R_2 和 R_3 是 H，并且 Y 是 CF_3。

在另一个实施方案中，本发明提供式 XXXV 的化合物：



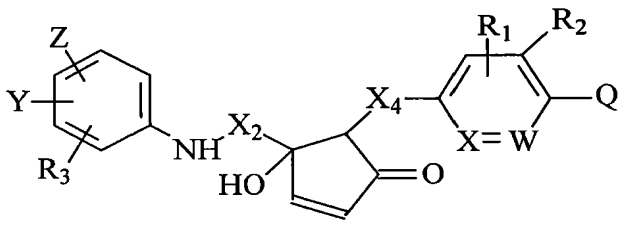
XXXV

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

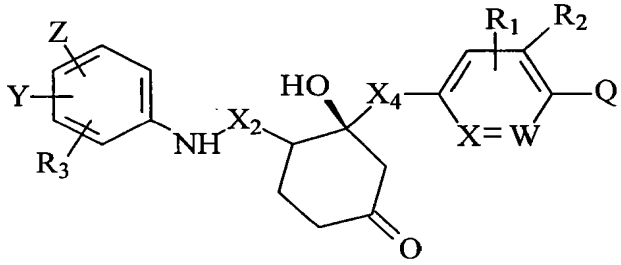
XXXVII

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

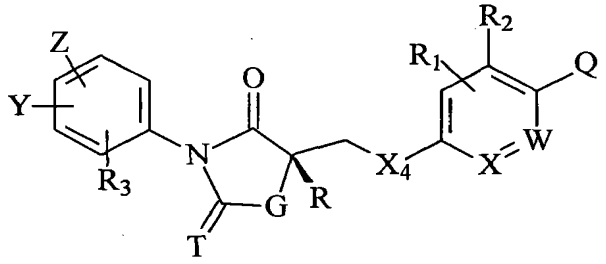
如果 P 是式 II，X 是 C，X_3 是 CH_2，X_4 是 O 或 NH，R_1、R_2 和 R_3 是 H，并且 X_5 和 X_1 形成 5 元环噁唑烷-2-酮，那么 Q 不是卤素或 H；

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；

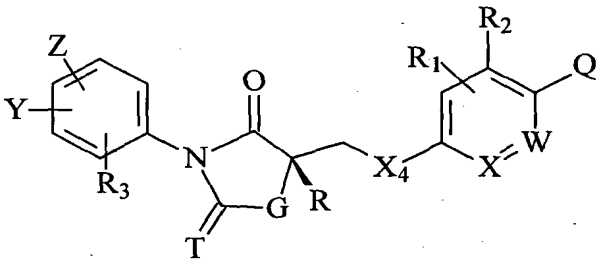
R_2 是 H、由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

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)、$O\text{-}[CH_2CH_2CH(CH_3)_2]$、$O\text{-}[CH_2CH_2(C_{4-8}$ 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、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;

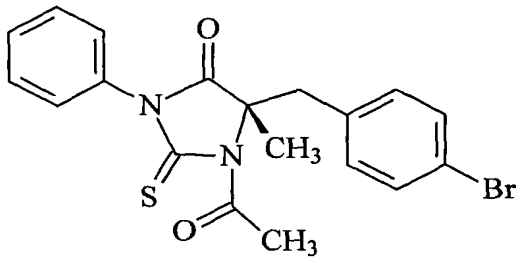
R_3 是 H、C_{1-4} 烷基、卤化物、CN 或 NO_2;

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

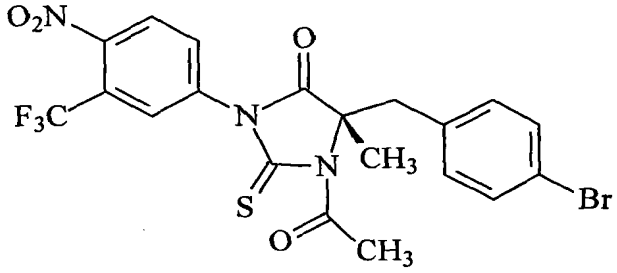
如果 R_3 是 H,X 和 W 是 C,G 是 O,T 是 O,R 是烷基,X_3 是 CH_2,并且 X_4 是 O、NH、S、SO_2 或 CH_2,那么 Q 不是卤化物。

在一个实施方案中,本发明提供式 XL 的化合物:



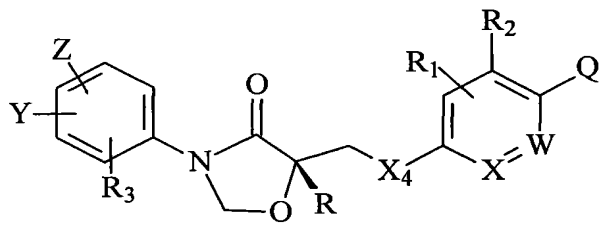
XL

在一个实施方案中,本发明提供式 XLI 的化合物:



XLI

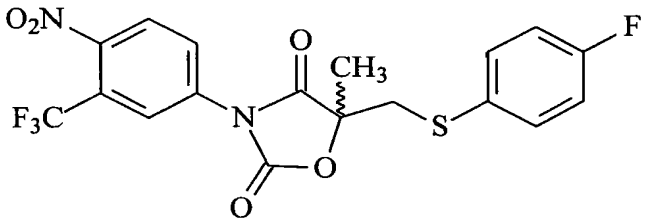
在一个实施方案中,本发明提供式 XLII 的化合物:



XLII

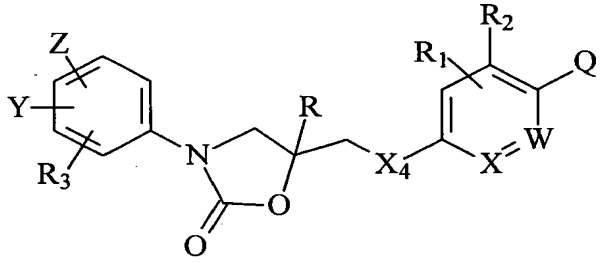
其中 X、X_4、Z、Y、Q、R_1、R_2 和 R_3 如以上在化合物 XXXIX 中所述。

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

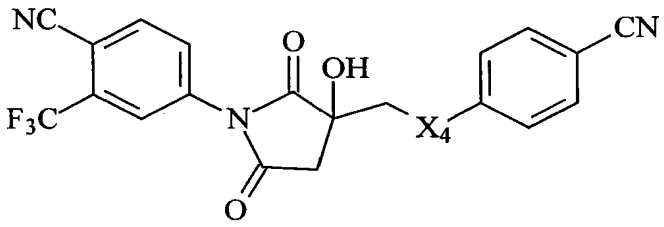
其中：

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。

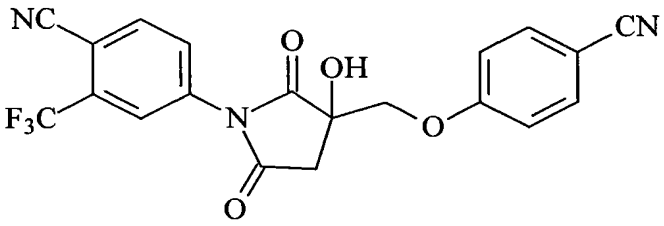
在一个实施方案中，本发明提供由式 XLV 的结构表示的化合物：



XLV

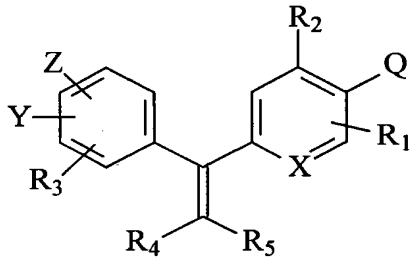
其中 X_4 如以上在化合物 XXXIX 中所述。

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；

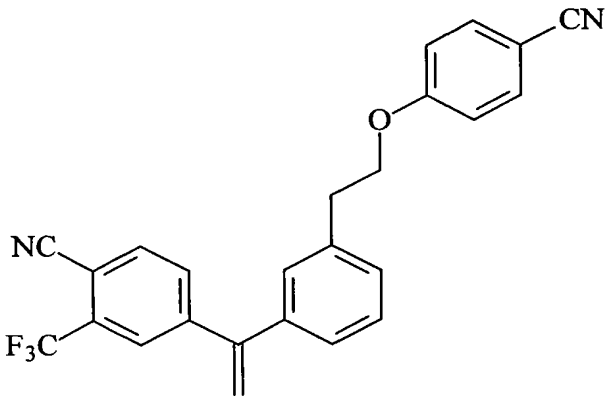
R_2 是由 R_6 取代的苄基、$(CH_2)_2$-O-对氰基苯基、CH_2-O-对氰基苯基或 CH=CH-O-对氰基苯基；

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

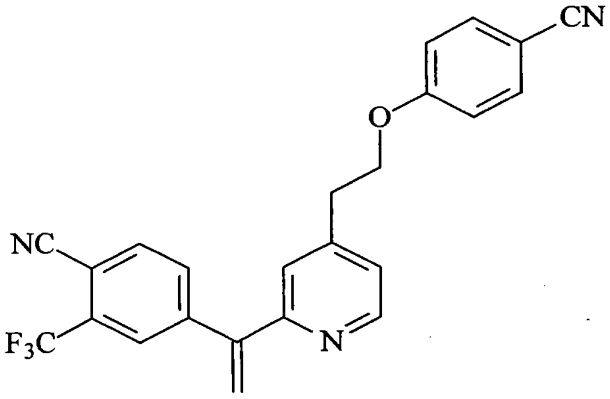
R_6 是 CN、NO_2、$NHC(O)CH_3$ 或卤化物。

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：



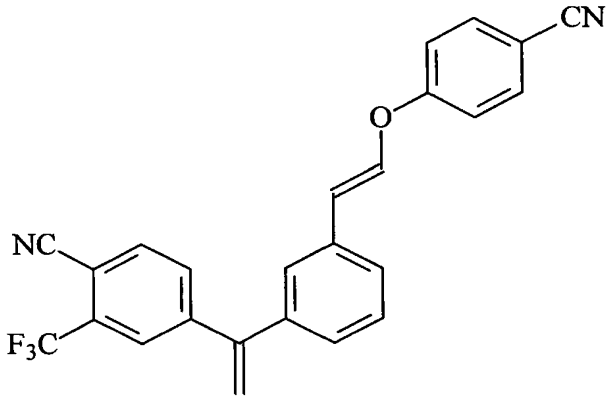
XLVIII

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：



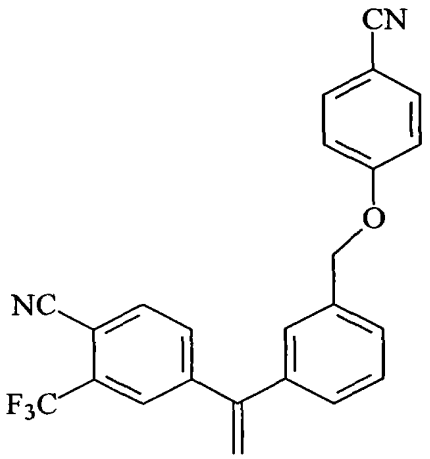
XLIX

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：



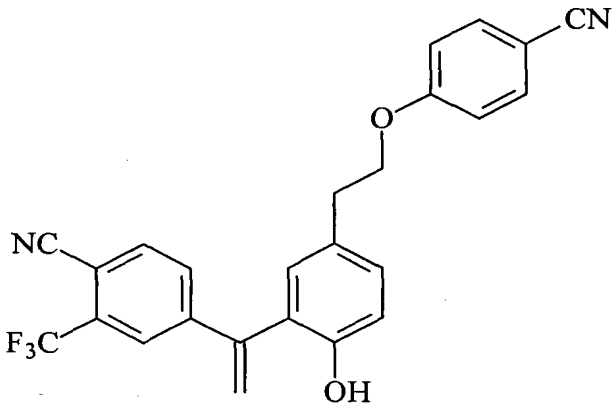
L

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、已基间苯二酚盐（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