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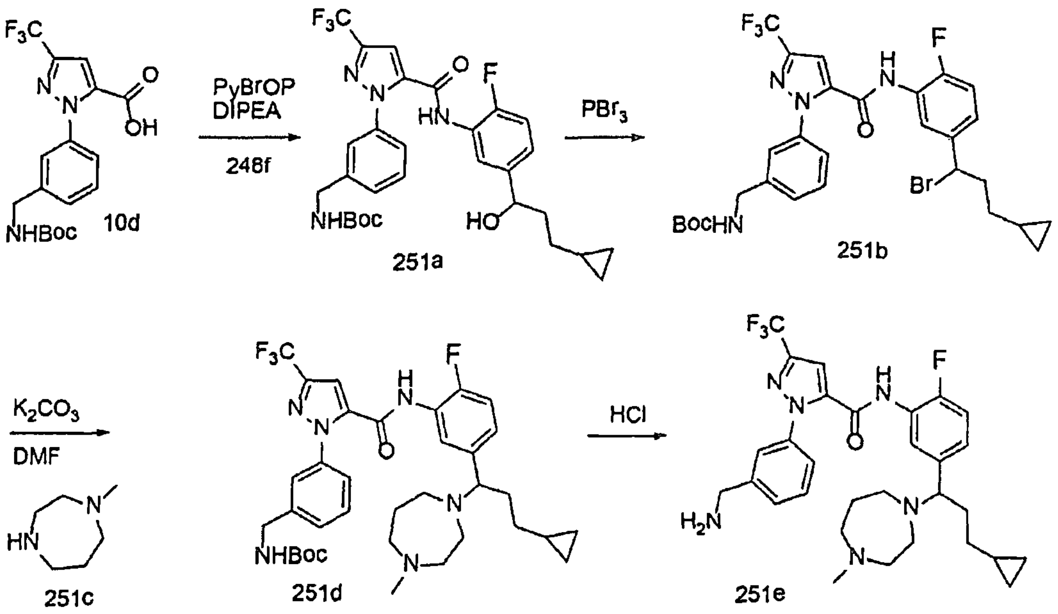
ABSTRACT

Disclosed are compounds of formula (I), as described herein, and pharmaceutically acceptable salts thereof. The compounds are inhibitors of plasma kallikrein. Also provided are pharmaceutical compositions comprising at least one compound of the invention, and methods involving use of the compounds and compositions of the invention in the treatment and prevention of diseases and conditions characterized by unwanted plasma kallikrein activity.

(61 mg, 0.110 mmol, 41.8 % yield) as a light yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.56 (s, 1H), 8.14 – 8.00 (m, 1H), 7.72 – 7.64 (m, 1H), 7.62 (d, J = 7.1 Hz, 1H), 7.55 (d, J = 17.3 Hz, 2H), 7.48 – 7.37 (m, 2H), 7.33 (d, J = 7.1 Hz, 1H), 7.30 – 7.16 (m, 2H), 6.91 (ddd, J = 7.2, 5.0, 0.9 Hz, 1H), 6.84 (dd, J = 8.3, 0.9 Hz, 1H), 6.05 (dd, J = 8.2, 5.4 Hz, 1H), 3.78 (s, 2H), 1.98 (m, 1H), 1.86 (m, 1H), 1.25 (m, 2H), 0.79 – 0.56 (m, 1H), 0.41 – 0.24 (m, 2H), -0.02 – -0.08 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.73, -123.02 ; MS (ES+) 554.3 (M+1), (ES-) 552.3 (M-1).

Scheme 251



Preparation of 1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-(4-methyl-1,4-diazepan-1-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**251e**)

Step-1: Preparation of tert-butyl 3-(5-(5-(3-cyclopropyl-1-hydroxypropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**251a**)

To a solution of 1-(3-((tert-butoxycarbonylamino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**10d**) (4.42 g, 11.47 mmol) in DMF (25 mL) was added 1-(3-amino-4-fluorophenyl)-3-cyclopropylpropan-1-ol (**248f**) (2 g, 9.56 mmol), N-ethyl-N-isopropylpropan-2-amine (8.32 mL, 47.8 mmol) and Bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (4.92 g, 10.51 mmol) at room temperature. The reaction mixture was stirred at room temperature for 48 h under nitrogen atmosphere. The reaction was diluted with ethyl acetate (100 mL) washed with water (2 x 75 mL), brine (75 mL), dried, filtered, and evaporated to dryness. The residue obtained was purified by flash column chromatography [silica gel 40 g, eluting with ethyl acetate in hexanes from 0-25%] to furnish tert-butyl 3-(5-(5-(3-cyclopropyl-1-hydroxypropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**251a**) (4.04 g, 7.01 mmol, 73.3 % yield) as a white foam; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.56 (s, 1H), 7.60 (s, 1H), 7.51 (dd, J = 14.3, 7.0 Hz, 2H), 7.46 – 7.32 (m, 4H), 7.23 – 7.16 (m, 2H), 5.21 (d, J = 4.4 Hz, 1H), 4.51 (q, J = 5.8 Hz, 1H), 4.19 (d, J = 6.2 Hz, 2H), 1.71 – 1.53 (m, 2H), 1.38 (s, 9H), 1.34 – 1.07 (m, 2H), 0.74 – 0.56 (m, 1H), 0.43 – 0.24 (m, 2H), 0.03 – -0.12 (m, 2H); ^{19}F NMR (282 MHz, DMSO) δ -60.80, -124.41; MS (ES+) 599.3 (M+Na); (ES-) 575.2 (M-1).

Step-2: Preparation of tert-butyl 3-(5-(5-(1-bromo-3-cyclopropylpropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**251b**)

To a cold solution (ice-water bath) of tert-butyl 3-(5-(5-(3-cyclopropyl-1-hydroxypropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**251a**) (2.04 g, 3.54 mmol) in THF (20 mL) was added PBr$_3$ (0.112 mL, 1.185 mmol). The resulting mixture was stirred for 40 min at 0 °C and quenched with water (50 mL). The reaction mixture was extracted with ethyl acetate (2 x 25 mL). The organic layers were combined washed with water and brine (50 mL), dried over anhydrous MgSO4, filtered, and evaporated to dryness. The residue obtained was purified by flash column chromatography [silica gel 40 g, eluting with ethyl acetate in hexanes from 0-25%] to furnish tert-butyl 3-(5-(5-(1-bromo-3-cyclopropylpropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**251b**) (1.4 g, 2.189 mmol, 61.9 % yield) as a White solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.64 (s, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.61 (s, 1H), 7.53 – 7.47 (m, 1H), 7.46 – 7.36 (m, 5H), 7.28 (d, J = 9.0 Hz, 1H), 5.32 (t, J = 7.5 Hz, 1H), 4.19 (d, J = 6.2 Hz, 2H), 2.37 – 2.07 (m, 2H), 1.37 (s, 9H), 1.34 – 1.16 (m, 2H), 0.79 – 0.57 (m, 1H), 0.47 – 0.29 (m, 2H), 0.07 – -0.10 (m, 2H); ^{19}F NMR (282 MHz, DMSO) δ -60.82, -121.25; MS (ES+) 661.2, 663.2 (M+Na).

Step-3: Preparation of tert-butyl 3-(5-(5-(3-cyclopropyl-1-(4-methyl-1,4-diazepan-1-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**251d**)

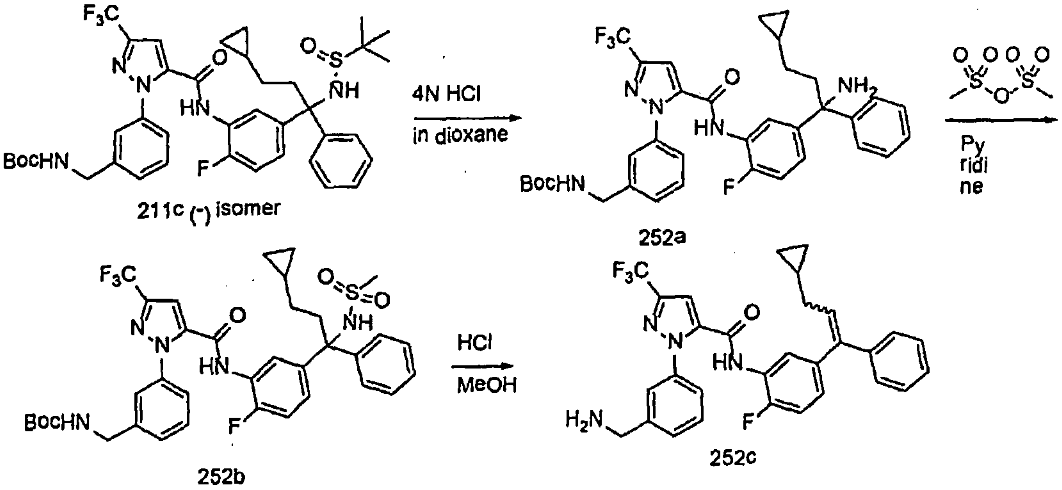
To a solution of tert-butyl 3-(5-(5-(1-bromo-3-cyclopropylpropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**251b**) (200 mg, 0.313 mmol) and *N*-methylhomopiperazine (**251c**) (143 mg, 1.251 mmol) in *N,N*-dimethylformamide (2 mL) was added K_2CO_3 (173 mg, 1.251 mmol). The reaction mixture was stirred at room temperature for 12 h, quenched with water (10mL) and extracted with EtOAc (3x50 mL). The organic layers were combined washed with water (50 mL), brine (25 mL), dried over MgSO4, filtered and concentrated. The residue was purified by flash column chromatography (silica gel 24 g, eluting with 0-90% EtOAc in hexane then 0-40% CMA80 in $CHCl_3$) to furnish tert-butyl 3-(5-(5-(3-cyclopropyl-1-(4-methyl-1,4-diazepan-1-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**251d**) (160 mg, 0.238 mmol, 76 % yield) as white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.56 (s, 1H), 7.60 (s, 1H), 7.54 - 7.29 (m, 6H), 7.26 - 7.10 (m, 2H), 4.19 (d, J = 6.3 Hz, 2H), 3.34 (s, 2H), 2.69 - 2.53 (m, 4H), 2.46 - 2.31 (m, 2H), 2.19 (s, 3H), 1.98 - 1.80 (m, 1H), 1.71 - 1.53 (m, 2H), 1.38 (s, 9H), 1.31 - 1.16 (m, 2H), 1.19 - 0.97 (m, 2H), 0.88 - 0.76 (m, 1H), 0.40 - 0.29 (m, 2H), -0.01 - -0.14 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.80, -124.05.

Step 4: Preparation of 1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-(4-methyl-1,4-diazepan-1-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**251e**)

To a solution of tert-butyl 3-(5-(5-(3-cyclopropyl-1-(4-methyl-1,4-diazepan-1-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**251d**) (156 mg, 0.232 mmol) in MeOH (3 mL) was added HCl (3 N in MeOH, 1.546 mL, 4.64 mmol), stirred at room temperature overnight and concentrated in vacuum . The residue obtained was purified by flash column chromatography (silica gel 12 g, eluting with 0-80% CMA80 in $CHCl_3$), followed by reverse phase column chromatography (C_{18} column 30 g, eluting with 0-50% MeOH in H_2O) to furnish compound **251e** (110 mg, 0.192 mmol, 83 % yield) free base as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.58 (s, 1H), 7.60 (s, 1H), 7.55 (s, 1H), 7.49 - 7.40 (m, 3H), 7.41 - 7.32 (m, 2H), 7.27 - 7.09 (m, 2H), 3.82 (s, 2H), 3.59 (t, J = 7.2 Hz, 1H), 3.33 - 3.03 (m, 2H), 2.68 - 2.54 (m, 3H), 2.18 (s, 3H), 1.95 - 1.81 (m, 1H), 1.76 - 1.47 (m, 4H), 1.33 - 0.92 (m, 5H), 0.70 - 0.57 (m, 1H), 0.41 - 0.22 (m, 2H), -0.01 - -0.14 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.75, -124.00.

To a solution of free base of compound **251e** (89 mg, 0.155 mmol) in MeOH (10 mL) was added HCl (3 N in MeOH, 0.389 mL, 1.554 mmol), stirred at room temperature for 2 h and concentrated in vacuum. The residue was dissolved in H_2O/ACN (10mL, 9.5:0.5, v/v) and freeze-dried to give 1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-(4-methyl-1,4-diazepan-1-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**251e**) (72 mg, 0.126 mmol, 81 % yield) hydrochloride as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.30 - 11.90 (m, 1H), 11.68 - 11.29 (m, 1H), 11.07 - 10.81 (m, 1H), 8.58 (s, 3H), 7.88 (t, J = 6.8 Hz, 1H), 7.82 - 7.70 (m, 3H), 7.69 - 7.50 (m, 4H), 7.52 - 7.36 (m, 1H), 4.54 (s, 1H), 4.12 (d, J = 5.3 Hz, 2H), 3.97 - 3.48 (m, 4H), 3.47 - 3.20 (m, 3H), 2.82 - 2.62 (m, 3H), 2.45 - 2.04 (m, 3H), 1.09 - 0.89 (m, 1H), 0.81 - 0.51 (m, 2H), 0.38-0.27 (m, 2H), -0.04--0.15 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.81, -119.00; MS (ES+): MS (ES+) 573.3 (M+1).

Scheme 252



Preparation of 1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-phenylprop-1-enyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**252c**)

Step-1: Preparation of *tert*-butyl 3-(5-(5-(1-amino-3-cyclopropyl-1-phenylpropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**252a**)

To a stirred solution of *tert*-butyl 3-(5-(5-((-)-3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)-1-phenylpropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**211c**) (1.603 g, 2.118 mmol) in methanol (18 mL) cooled to 0 oC was added 4 N hydrochloric acid in dioxane (1.6 mL, 6.40 mmol) and stirred at 0 oC for 2.5 h. The reaction mixture was quenched with triethylamine (1.100 mL, 7.89 mmol) and concentrated in vacuum to dryness. The residue obtained was purified by flash column chromatography [silica gel, eluting with hexanes/10% methanol in ethyl acetate (1:0 to 1:1)] to furnish *tert*-butyl 3-(5-(5-(1-amino-3-cyclopropyl-1-phenylpropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**252a**) (658 mg, 47.6%) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.52 (s, 1H), 7.62 – 7.07 (m, 12H), 4.19 (d, J = 6.2 Hz, 2H), 2.31 – 2.07 (m, 4H), 1.38 (s, 9H), 1.11 – 0.90 (m, 2H), 0.91 – 0.74 (m, 1H), 0.71 – 0.53 (m, 1H), 0.40 – 0.26 (m, 2H), -0.05 – -0.16 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.79 , -123.62; MS (ES+) 652.4 (M+1), (ES-) 650.4 (M-1).

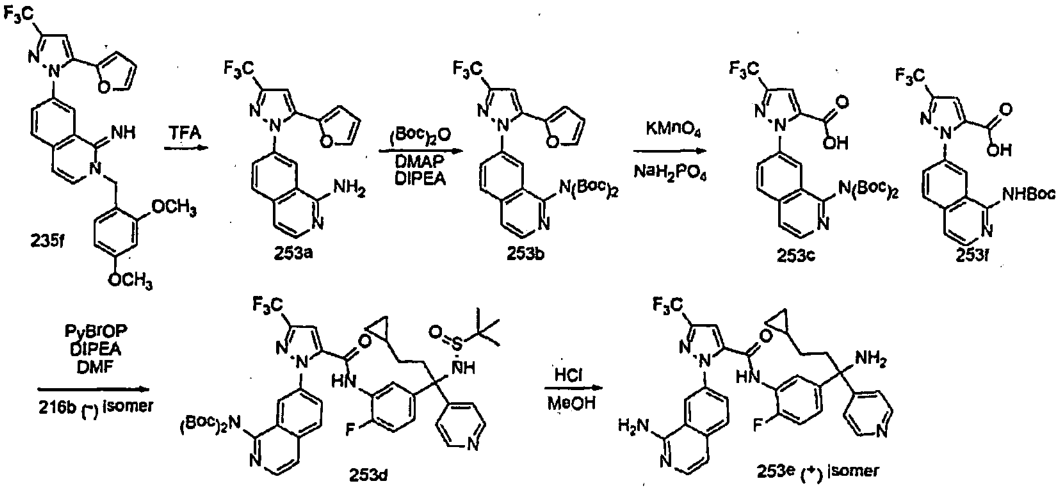
Step-2: Preparation of *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-(methylsulfonamido)-1-phenylpropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**252b**)

To a solution of *tert*-butyl 3-(5-(5-(1-amino-3-cyclopropyl-1-phenylpropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**252a**) (145 mg, 0.222 mmol) in dichloromethane (10 mL) and pyridine (70.4 mg, 0.890 mmol) at 0 °C was added methanesulfonic anhydride (78 mg, 0.445 mmol). The resulting reaction mixture was stirred at room temperature overnight. Additional DIPEA (0.078 mL, 0.445 mmol) and methanesulfonic anhydride (78 mg, 0.445 mmol) was added and the mixture was stirred at room temperature for 2h. The reaction mixture was diluted with water (10 mL) extracted with dichloromethane (3 x 10 mL) The organic layers were combined dried over $MgSO_4$, filtered and concentrated. The residue obtained was purified by flash column chromatography (silica gel, 12 g eluting with EtOAc/hex, 0-50%) to furnish *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-(methylsulfonamido)-1-phenylpropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**252b**) (86 mg) as a white solid; MS (ES+) 752.4 (M+23), (ES-) 728.5 (M-1).

Step-3: Preparation of 1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-phenylprop-1-enyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**252c**)

To a solution of *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-(methylsulfonamido)-1-phenylpropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**252b**) (86 mg, 0.118 mmol) in methanol (20 mL) was added HCl (3 N anhydrous in MeOH, 2mL) and heated at reflux for 30 min. The reaction was concentrated in vacuum and the residue obtained was purified by flash column chromatography (silica gel 12 g, eluting with $CHCl_3$ in CMA-80 0-60%) to furnish compound **252c** (40mg) free base as a white solid. The free base was dissolved in methanol (10 mL) and added HCl (3 N anhydrous in MeOH, 2mL) at room temperature. The Solution was concentrated in vacuum to dryness and the residue was dissolved in water (2 mL) and two drops of acetonitrile, lyophilized to furnish 1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-phenylprop-1-enyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**252c**) (42 mg, 0.079 mmol, 35.3 % yield over 2 steps) hydrochloride salt as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.68 (2s, 1H), 8.38 (bs, 3H), 7.75 – 7.64 (m, 2H), 7.66 – 7.56 (m, 1H), 7.56 – 7.21 (m, 7H), 7.20 – 7.09 (m, 2H), 7.11 – 7.00 (m, 1H), 6.17 (dt, J = 15.1, 7.5 Hz, 1H), 3.36 (s, 2H), 1.94 (q, J = 7.4 Hz, 2H), 0.87 – 0.68 (m, 1H), 0.49 – 0.29 (m, 2H), 0.14 – -0.01 (m, 2H); ^{19}F NMR (282 MHz, DMSO) δ -60.63, -60.64, -122.32, -122.64. (E and Z mixture); MS (ES+): MS (ES+) 535.4 (M+1); 533.3.4 (M-1); Analysis calculated for $C_{30}H_{26}F_4N_4O.HCl.H_2O$: C; 61.17, H; 4.96, N; 9.51; Found: C; 61.39, H; 5.02, N; 9.52.

Scheme 253



Preparation of (+)-N-(5-(1-amino-3-cyclopropyl-1-(pyridin-4-yl)propyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**253e**)

Step-1: Preparation of 7-(5-(furan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-amine (**253a**)

A solution of 2-(2,4-dimethoxybenzyl)-7-(5-(furan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1(2H)-imine (**235f**) (2.88 g, 5.82 mmol) in TFA (10 mL) and anisole (5 mL) was heated to 90 °C for 19 h, cooled to room temperature and concentrated in vacuum. The residue was taken twice in MeOH (50 mL) and evaporated. The pH of the residue was adjusted to 8.0 using saturated aqueous $NaHCO_3$, diluted with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over anhydrous MgSO4, filtered, evaporated to dryness. The residue obtained was purified by flash column chromatography [silica gel 40 g, eluting with ethyl acetate/methanol in hexanes from 0-100%] to furnish 7-(5-(furan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-amine (**253a**) (0.994 g, 49 % yield) as a pale yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (d, *J* = 2.1 Hz, 1H), 7.97 - 7.83 (m, 2H), 7.79 - 7.72 (m, 1H), 7.67 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.34 (s, 1H), 7.03 (d, *J* = 5.8 Hz, 1H), 6.98 (s, 2H, D_2O exchangeable), 6.52 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.20 (dd, *J* = 3.6, 0.8 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.73; MS (ES$^+$): MS (ES+) 345.2 (M+1); MS (ES-) 379.2 (M+Cl).

Step-2: Preparation of di-*tert*-butyl 7-(5-(furan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yliminodicarbonate (**253b**)

To a solution of 7-(5-(furan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-amine (**253a**) (12.177 g, 35.4 mmol) in acetonitrile (150 mL) was added DIPEA (14.83 mL, 85 mmol), $(BOC)_2O$ (61.6 mL, 265 mmol) and DMAP (1.080 g, 8.84 mmol). The mixture was heated at 50 °C overnight, cooled to room temperature and concentrated in vacuum. The residue was treated with brine/water (100 mL/400 mL) and extracted with ethyl acetate (2 x 750 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered, evaporated to dryness. The residue was purified by flash column chromatography (silica gel 120 g, eluting with ethyl acetate in hexanes from 0-80%) to afford di-*tert*-butyl 7-(5-(furan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yliminodicarbonate (**253b**) (13.621 g, 71 % yield) as a brown solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.56 (d, *J* = 5.7 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 1H), 8.10 - 7.99 (m, 2H), 7.91 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.37 (s, 1H), 6.54 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.39 (d, *J* = 3.5 Hz, 1H), 1.27 (s, 18H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.99.

MS (ES$^+$): MS (ES$^+$): 567.2 (M+Na).

Step-3: Preparation of 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253c**) and 1-(1-(*tert*-butoxycarbonylamino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253f**)

To a solution of di-*tert*-butyl 7-(5-(furan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yliminodicarbonate (**253b**) (5.70 g, 10.47 mmol) in *t*-BuOH (220 mL) was added 5% aq. sodium dihydrogenphosphate (2.387 g, 19.90 mmol) in water (50 mL) followed by potassium permanganate (3.31 g, 20.94 mmol). The reaction mixture was stirred at room temperature for 13 h, quenched with 2-propanol (350 mL) and stirred at room temperature overnight. The reaction mixture was filtered through Celite washed with 2-propanol. The filtrate was evaporated to dryness and purified by flash column chromatography (silica gel 80 g, eluting with CMA80 in chloroform from 0-100%) to furnish compound **253c** and **253f**. Each compound were separately acidified with 1N $KHSO_4$ (10 mL), extracted with ethyl acetate (2 x 30 mL), dried over anhydrous $MgSO_4$, filtered, concentrated in vacuum and dried over P_2O_5 to afford:

1. 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253c**) (1.161 g, 2.222 mmol, 21 % yield) as a yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (d, J = 5.7 Hz, 1H), 8.21 (d, J = 8.7 Hz, 1H), 8.09 - 7.97 (m, 3H), 7.59 (s, 1H), 1.29 (s, 18H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.97; MS (ES$^+$): MS (ES+) 545.3 (M+Na); MS (ES-) 521.3 (M-1).
2. 1-(1-(tert-butoxycarbonylamino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253f**) (0.481 g, 11 % yield) as an yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (t, J = 2.8 Hz, 1H), 8.29 (d, J = 3.5 Hz, 1H), 8.10 (dd, J = 8.8, 4.3 Hz, 1H), 7.99 (dd, J = 8.5, 2.1 Hz, 1H), 7.76 - 7.66 (m, 1H), 7.60 (s, 1H), 1.46 (d, J = 1.7 Hz, 9H); MS (ES-) 421.2 (M-1), 843.2 (2M-1).

Step-4: Preparation *di-tert*-butyl 7-(5-(5-(-3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**253d**)

Compound **253d** was prepared from 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253c**) (0.261 g, 0.500 mmol) and (R)-N-((-)-1-(3-amino-4-fluorophenyl)-3-cyclopropyl-1-(pyridin-4-yl)propyl)-2-methylpropane-2-sulfinamide (**216b**) (0.234 g, 0.599 mmol) according to the procedure reported in step-3 of scheme-208 for compound **208c** gave after workup crude **253d** was used as such in the next step; MS (ES$^+$): MS (ES+) 916.6 (M+Na); MS (ES-) 892.6 (M-1).

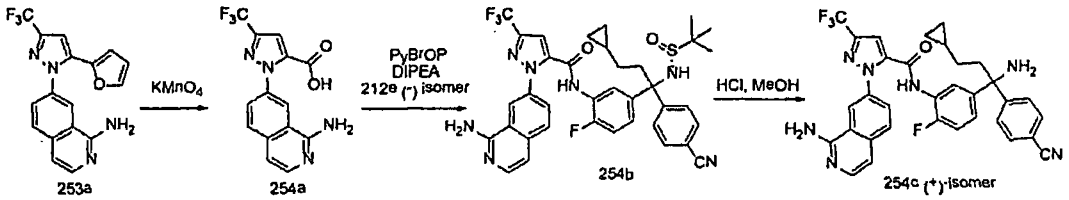
Step-5: Preparation of (+)-N-(5-(1-amino-3-cyclopropyl-1-(pyridin-4-yl)propyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**253e**)

To a stirred solution of *di-tert*-butyl 7-(5-(5-(-3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**253d**) (0.671 g, 0.751 mmol) in methanol (10 mL) was added 3M HCl (in MeOH, 3.75 mL) and heated at reflux for 1 h. The reaction mixture was cooled to room temperature and evaporated to dryness. The residue was dissolved in water (25 mL) washed with MTBE (2 x 50 mL), the aqueous layer was basified with 1N NaOH and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layers were combined dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue obtained was purified by flash chromatography [silica gel 12 g (four separate columns), eluting with CMA80 in chloroform, 0-50%] to afford **253e** (9 mg, 2 % yield) free base as a light brown solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.50 (s, 1H, D_2O exchangeable), 8.50 - 8.34 (m, 3H), 7.88 (d, J = 5.8 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.73 - 7.62 (m, 2H), 7.55 (dd, J = 7.4, 2.4 Hz, 1H), 7.39 - 7.32 (m, 2H), 7.28 (ddd, J = 8.7, 4.8, 2.3 Hz, 1H), 7.16 (dd, J = 10.1, 8.7 Hz, 1H), 7.03 - 6.90 (m, 3H, D_2O exchangeable, 2H), 2.32 (s, 2H), 2.19 (m, 2H), 1.02 (m, 2H), 0.61 (m, 1H), 0.39 - 0.19 (m, 2H), -0.11 (m, 2H); ^{1}H NMR (300 MHz, DMSO-d_6, D_2O) δ 8.38 (td, J = 5.6, 5.1, 1.8 Hz, 3H), 7.90 - 7.75 (m, 2H), 7.71 - 7.59 (m, 2H), 7.49 (dd, J = 7.2, 2.2 Hz, 1H), 7.37 - 7.30 (m, 2H), 7.25 (ddd, J = 9.0, 4.8, 2.4 Hz, 1H), 7.14 (t, J = 9.4 Hz, 1H), 7.00 (d, J = 5.8 Hz, 1H), 2.26 - 2.07 (m, 2H), 0.97 (m, 2H), 0.57 (m, 1H), 0.41 - 0.14 (m, 2H), -0.15 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.71 , -123.61; MS (ES$^+$): MS (ES+): MS (ES+) 590.4 (M+1); (ES-) 588.4 (M-1).

Compound **253e** was treated with methanolic 3 N HCl which afforded on evaporation and lyopholization (+)-N-(5-(1-amino-3-cyclopropyl-1-(pyridin-4-yl)propyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**253e**) hydrochloride salt as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.74 (s, 1H, D_2O exchangeable), 11.02 (s, 1H, D_2O exchangeable), 9.80 (s, 3H, D_2O exchangeable), 9.42 (s, 3H, D_2O exchangeable), 8.95 (s, 1H), 8.87 (m, 2H), 8.13 (d, J = 1.8 Hz, 2H), 7.85 (d, J = 7.0 Hz, 1H), 7.72 (m, 3H), 7.46 (d, J = 7.8 Hz, 2H), 7.37 (d, J = 7.0 Hz, 1H), 2.60 (m, 2H), 1.17 (m, 2H), 0.69 (m, 1H), 0.34 (m, 2H), -0.00 (m, 2H); ^{1}H NMR (300 MHz, DMSO/D_2O-d_6) δ 8.91 (s, 1H), 8.87 – 8.80 (m, 2H), 8.15 (d, J = 1.5 Hz, 2H), 7.89 (s, 1H), 7.82 (d, J = 7.0 Hz, 1H), 7.66 (m, 3H), 7.49 (t, J = 9.4 Hz, 1H), 7.41 (d, J = 7.1 Hz, 1H), 7.35 (m, 1H), 2.56 (m, 2H), 1.14 (m, 2H), 0.73 (m, 1H), 0.38 (m, 2H), 0.12 – -0.09 (m, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -60.89, -119.82; Analysis calculated for

$C_{31}H_{27}F_4N_7O.3HCl.3.5H_2O$: C, 48.86; H, 4.89; Cl, 13.96; N, 12.87; Found; C, 48.62; H, 4.90; Cl, 14.37; N, 12.97; Optical rotation: $[\alpha]_D$ = (+) 19.31 [0.29, MeOH].

Scheme 254



Preparation of (+)-N-(5-(1-amino-1-(4-cyanophenyl)-3-cyclopropylpropyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**254c**)

Step-1: Preparation of 1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**254a**)

Compound **254a** was prepared from 7-(5-(furan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-amine (**253a**) (0.275 g, 0.799 mmol) according to the procedure reported in step-2 of scheme-10 for preparation of compound **9i** gave 1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**254a**) (0.077 g, 0.239 mmol, 29.9 % yield) as a white solid; MS (ES+) 323.2 (M+1), 321.1 (M-1).

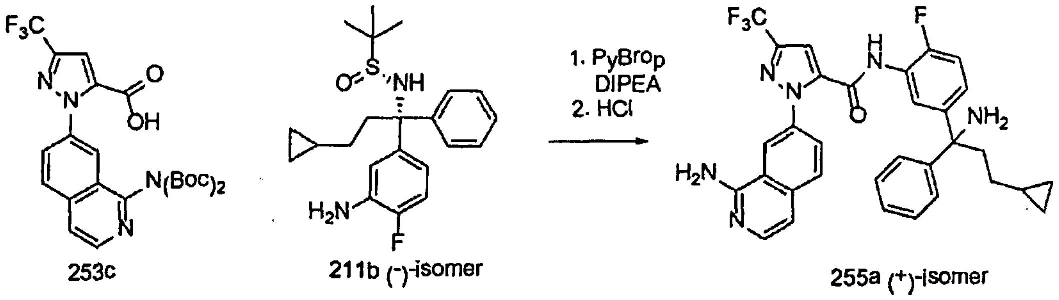
Step-2: Preparation of 1-(1-aminoisoquinolin-7-yl)-N-(5-(1-(4-cyanophenyl)-3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**254b**)

Compound **254b** was prepared from 1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**254a**) [322 mg, 0.999 mmol, which was converted to HCl salt using HCl (3 N in MeOH, 3mL) and concentrating in vacuum to dryness prior to use] and (R)-N-((-)-1-(3-amino-4-fluorophenyl)-1-(4-cyanophenyl)-3-cyclopropylpropyl)-2-methylpropane-2-sulfinamide (**212e**) (248 mg, 0.600 mmol) according to the procedure reported in scheme-237 for preparation of compound **237a** gave after workup crude **254b** which was used as such for next step.

Step-3: Preparation of (+)-N-(5-(1-amino-1-(4-cyanophenyl)-3-cyclopropylpropyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**254c**)

A solution of above crude containing 1-(1-aminoisoquinolin-7-yl)-N-(5-(1-(4-cyanophenyl)-3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**254b**) in dioxane (5mL) was added HCl (4N in dioxane, 2mL) and heated to reflux for 15 min. The solution was concentrated in vacuum and the residue was taken in water washed with EtOAc (50 mL) to remove organic impurities. The aqueous layer was basified with NaOH (1N) and extracted with EtOAc (2 x 50 mL). The organic layer were combined, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography (silica gel 40 g, eluting with 0-40% CMA-80 in chloroform) to furnish (+)-N-(5-(1-amino-1-(4-cyanophenyl)-3-cyclopropylpropyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**254c**) (17 mg, 0.028 mmol, 2.77 % yield) free base as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.45 – 8.38 (m, 1H), 7.88 (d, J = 5.8 Hz, 1H), 7.81 – 7.69 (m, 4H), 7.66 (dd, J = 8.7, 2.0 Hz, 1H), 7.59 – 7.48 (m, 3H), 7.30 – 7.13 (m, 2H), 7.03 – 6.93 (m, 3H), 2.31 – 2.17 (m, 2H), 1.13 – 0.79 (m, 2H), 0.74 – 0.51 (m, 1H), 0.42 – 0.23 (m, 2H), -0.01 – -0.24 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.74, -123.59; IR (KBr) 2230 cm^{-1} ; Optical rotation: $[\alpha]_D$ = (+) 11.61 (0.155, methanol).

Scheme 255

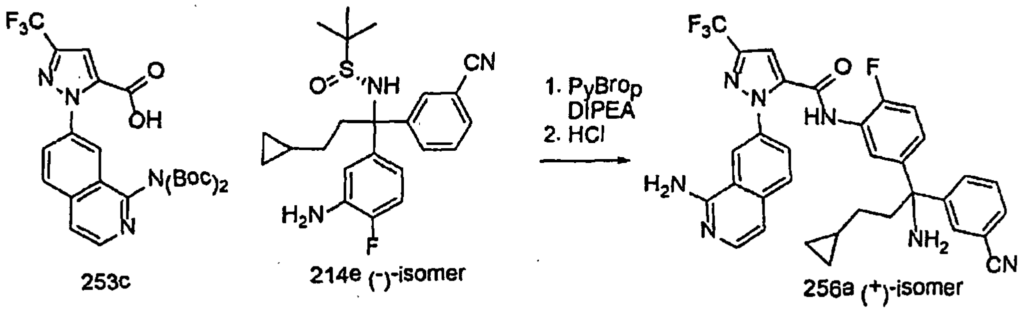


Preparation of (+)-N-(5-(1-amino-3-cyclopropyl-1-phenylpropyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**255a**)

To a solution of 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253c**) (60 mg, 0.115 mmol) in DMF (5 mL) was added (R)-N-((-)-1-(3-amino-4-fluorophenyl)-3-cyclopropyl-1-phenylpropyl)-2-methylpropane-2-sulfinamide (**211b**) (53.5 mg, 0.138 mmol), N-ethyl-N-isopropylpropan-2-amine (30.1 µl, 0.172 mmol) and bromo-tris-pyrrolidino phosphoniumhexafluorophosphate(PyBrop, 64.2 mg, 0.138 mmol) at room temperature.

The reaction mixture was stirred at room temperature for 12 h and diluted with ethyl acetate (100 mL) washed with water (2 x 50 mL). brine (50 mL), dried, filtered, and concentrated in vacuum to dryness to furnish crude residue . The residue was dissolved in anhydrous dioxane (5mL), added HCl (4N in dioxane, 2mL) and heated at 60 °C for 50 min. The reaction mixture was cooled to room temperature and concentrated in vacuum to dryness. The residue was dissolved in water washed EtOAc (50 mL). The aqueous layer was basified with NaOH (1N) and extracted with EtOAc (2 x 50 mL). The organic layer were combined, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography (silica gel 40 g, eluting with 0-40% CMA-80 in chloroform) to furnish compound **255a** as a free base, which was converted in to the HCl salt to furnish (+)-N-(5-(1-amino-3-cyclopropyl-1-phenylpropyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**255a**) (22 mg, 0.037 mmol, 32.5 % yield) hydrochloride salt as a white solid; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 10.84 (s, 1H), 9.22 (s, 4H), 8.86 (s, 1H), 8.07 (s, 2H), 7.87 (s, 1H), 7.80 (d, J = 7.0 Hz, 1H), 7.53 (dd, J = 7.0, 2.0 Hz, 2H), 7.49 – 7.22 (m, 8H), 2.44 (d, J = 8.3 Hz, 2H), 1.17 – 1.00 (m, 2H), 0.72 – 0.53 (m, 1H), 0.38 – 0.23 (m, 2H), -0.03 – -0.09 (m, 2H); ^{19}F NMR (282 MHz, DMSO) δ -60.70, -120.69; MS (ES+): MS (ES+) 589.4 (M+1); 587.4 (M-1); Optical rotation: $[\alpha]_D$ = (+) 8.42 (0.285, methanol); Analysis calculated for: $C_{32}H_{28}F_4N_6O.2HCl.3H_2O$; C, 53.71; H, 5.07; N, 11.74; Found: C, 53.63; H, 4.98; N, 11.65.

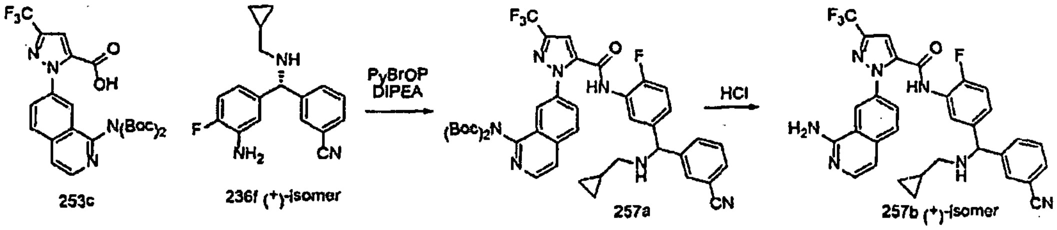
Scheme 256



Preparation of (+)-N-(5-(1-amino-1-(3-cyanophenyl)-3-cyclopropylpropyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**256a**)

To a solution of 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253c**) (40 mg, 0.077 mmol) in DMF (5 mL) was added (R)-N-((-)-1-(3-amino-4-fluorophenyl)-1-(3-cyanophenyl)-3-cyclopropylpropyl)-2-methylpropane-2-sulfinamide (**214e**) (31.7 mg, 0.077 mmol), N-ethyl-N-isopropylpropan-2-amine (13.37 µl, 0.077 mmol) and bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBrop, 35.7 mg, 0.077 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h, diluted with ethyl acetate (100 mL), washed with water (2 x 50 mL), brine (50 mL), dried, filtered, and concentrated in vacuum to dryness to furnish crude residue. The residue was dissolved in anhydrous dioxane (5mL) added HCl (4N in dioxane, 2mL) and heated at 60 °C for 50 min. The reaction mixture was cooled to room temperature and concentrated in vacuum to dryness. The residue obtained was purified by flash column chromatography (silica gel 40 g, eluting with 0-40% CMA-80 in chloroform) to furnish compound **256a** as a free base, which was converted in to the HCl salt to furnish (+)-N-(5-(1-amino-1-(3-cyanophenyl)-3-cyclopropylpropyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**256a**) (7 mg, 0.011 mmol, 14.90 % yield) hydrochloride as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.37 (s, 1H), 10.81 (s, 1H), 9.36 (s, 3H), 9.16 (s, 3H), 8.83 (d, J = 1.5 Hz, 1H), 8.07 (d, J = 1.2 Hz, 2H), 7.92 – 7.81 (m, 3H), 7.79 (d, J = 6.9 Hz, 1H), 7.66 – 7.63 (m, 2H), 7.56 – 7.51 (m, 1H), 7.42 (dd, J = 10.0, 8.7 Hz, 1H), 7.31 (dd, J = 7.4, 4.0 Hz, 2H), 2.61 – 2.38 (m, 2H), 1.07 (m, 2H), 0.65 (m, 1H), 0.31 (m, 2H), -0.06 (m, 2H); ^{19}F NMR (282 MHz, DMSO) δ -60.69, -120.30; MS (ES+): MS (ES+) 614.4 (M+1); 612.4 (M-1); Optical rotation: $[\alpha]_D$ = (+) 15.38 (0.13, methanol).

Scheme 257



Preparation of (+)-1-(1-aminoisoquinolin-7-yl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**257b**)

Step-1: Preparation of di-*tert*-butyl (7-(5-((5-((3-cyanophenyl)((cyclopropylmethyl)amino)methyl)-2-fluorophenyl)carbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)carbamate (**257a**)

Compound **257a** was prepared from 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253c**) (0.839 g, 1.60 mmol) and (+)-3-((3-amino-4-fluorophenyl)(cyclopropylmethylamino)methyl)benzonitrile (**236f**) (0.569 g, 1.927 mmol) according to the procedure reported in step-3 of scheme-208 for compound **208c** gave after workup crude **257a** which was used as such in the next step; MS (ES+) 800.4 (M+1), 822.4 (M+Na); MS (ES-) 798.4 (M-1).

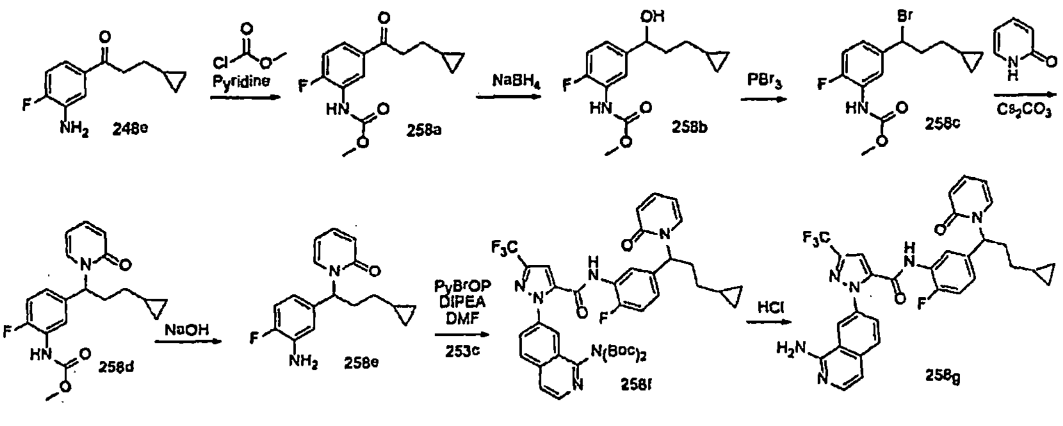
Step-2 : Preparation of (+)-1-(1-aminoisoquinolin-7-yl)-N-(5-((3-cyanophenyl)(cyclopropyl methylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**257b**)

To a stirred solution of di-tert-butyl (7-(5-((5-((3-cyanophenyl)((cyclopropylmethyl) amino)methyl)-2-fluorophenyl)carbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)carbamate (**257a**)(2.58 g, 3.23 mmol) in dioxane (30 mL) was added 4M HCl (dioxane) (4.84 mL, 19.35 mmol) and heated at reflux for 1 h. The reaction was cooled to room temperature and evaporated to dryness. The residue was dissolved in water (10 mL) washed with MTBE (2 x 50 mL), the aqueous layer was basified with 1N NaOH and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layers were combined dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash chromatography [first column; silica gel 24 g, eluting with ethyl acetate/methanol (9:1) in hexanes 0-100%, second column; silica gel 12 g, eluting with ethyl CMA80 in chloroform 0-100%, third column; silica gel 12 g, eluting with CMA80 in chloroform from 0-40%] to afford Compound **257b** (0.10 g, 0.167 mmol, 5.17 % yield) free base as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.52 (s, 1H, D_2O exchangeable), 8.42 (d, *J* = 2.0 Hz, 1H), 7.93 - 7.87 (m, 2H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.75 - 7.63 (m, 4H), 7.59 (dd, *J* = 7.5, 2.2 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.34 (m, 1H), 7.21 (dd, *J* = 10.3, 8.6 Hz, 1H), 6.98 (m, 3H, D_2O exchangeable, 2H), 4.91 (s, 1H), 2.69 (bs, 1H), 2.24 (m, 2H), 0.88 (m, 1H), 0.52 - 0.23 (m, 2H), 0.09 - -0.06 (m, 2H); ^{1}H NMR (300 MHz, DMSO-d_6 D_2O) δ 8.41 (d, *J* = 2.0 Hz, 1H), 7.92 - 7.80 (m, 3H), 7.69 (m, 4H), 7.62 - 7.56 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.35 (ddd, *J* = 8.6, 4.8, 2.2 Hz, 1H), 7.21 (dd, *J* = 10.2, 8.6 Hz, 1H), 7.10 - 7.00 (m, 1H), 4.92 (s, 1H), 2.24 (m, 2H), 0.89 (m, 1H), 0.49 - 0.27 (m, 2H), 0.05 - -0.02 (m, 2H);

^{19}F NMR (282 MHz, DMSO-d_6) δ -60.73, -122.79; MS (ES+): MS (ES+) 600.3 (M+1); MS (ES-) 598.3 (M-1).

To a stirred solution of free base of **257b** (0.093 g, 0.155 mmol) in methanol (10 mL) was added HCl (3M in methanol) (0.517 mL, 1.551 mmol), stirred at room temperature for 1 h, evaporated to dryness, triturated with MTBE (50 mL), filtered, rinsed with MTBE, and dried. The residue was dissolved in water, filtered, lyophilized to dryness afford (+)-1-(1-aminoisoquinolin-7-yl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**257b**) (0.070 g, 0.117 mmol, 75 % yield) hydrochloride salt as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.84 (s, 1H, D_2O exchangeable), 10.24 (s, 2H, D_2O exchangeable), 9.09 (s, 2H, D_2O exchangeable), 8.83 (s, 1H), 8.22 (s, 1H), 8.07 (s, 2H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.92 (dd, *J* = 7.2, 2.3 Hz, 1H), 7.89 - 7.84 (m, 2H), 7.80 (d, *J* = 6.9 Hz, 1H), 7.67 (q, *J* = 7.4 Hz, 2H), 7.42 (dd, *J* = 10.2, 8.6 Hz, 1H), 7.30 (d, *J* = 6.9 Hz, 1H), 5.74 (s, 1H), 2.70 (m, 2H), 1.13 (d, *J* = 11.9 Hz, 1H), 0.63 - 0.47 (m, 2H), 0.29 (h, *J* = 4.1 Hz, 2H); ^{1}H NMR (300 MHz, DMSO-d_6 D_2O) δ 8.81 (d, *J* = 1.3 Hz, 1H), 8.13 (t, *J* = 1.7 Hz, 1H), 8.07 (d, *J* = 1.4 Hz, 2H), 7.98 - 7.82 (m, 4H), 7.78 (d, *J* = 6.9 Hz, 1H), 7.72 - 7.57 (m, 2H), 7.50 - 7.39 (m, 1H), 7.31 (d, *J* = 6.9 Hz, 1H), 5.73 (s, 1H), 2.72 (m, 2H), 1.08 (m, 1H), 0.63 - 0.48 (m, 2H), 0.28 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.88 , -119.84; MS (ES+): MS (ES+) 600.3 (M+1); MS (ES-) 598.3 (M-1), 634.2 (M+Cl); Optical rotation: (+) 0.73 [0.275, MeOH]; Analysis: calculated for $C_{32}H_{25}F_4N_7O.2HCl.2H_2O$: C, 54.24; H, 4.41; Cl, 10.01; N, 13.84; Found: C, 54.37; H, 4.45; Cl, 9.79; N, 13.87.

Scheme 258



Preparation of 1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(2-oxopyridin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**258g**)

Step-1: Preparation of methyl 5-(3-cyclopropylpropanoyl)-2-fluorophenylcarbamate (**258a**)

To a solution of 1-(3-amino-4-fluorophenyl)-3-cyclopropylpropan-1-one (**248e**) (0.207 g, 1.000 mmol) in dichloromethane (4 mL) at 0 °C was added pyridine (0.121 mL, 1.5 mmol) and methyl chloroformate (0.077 mL, 1 mmol). The reaction was slowly warmed to room temperature overnight and evaporated to dryness. The residue was treated with water (25 mL) and extracted with ethyl acetate (2 x 50 mL), combined organics were dried over anhydrous $MgSO_4$, filtered, evaporated to dryness to afford methyl 5-(3-cyclopropylpropanoyl)-2-fluorophenylcarbamate (**258a**) (0.254 g, 96 % yield) as a clear oil; ^1H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H, D_2O exchangeable), 8.30 (dd, J = 7.9, 2.2 Hz, 1H), 7.85 - 7.72 (m, 1H), 7.37 (dd, J = 10.6, 8.6 Hz, 1H), 3.69 (s, 3H), 3.06 (t, J = 7.3 Hz, 2H), 1.51 (q, J = 7.2 Hz, 2H), 0.85 - 0.65 (m, 1H), 0.47 - 0.33 (m, 2H), 0.12 - 0.02 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -117.74; MS (ES+): 266.1 (M+1); MS (ES-) 264.2 (M-1).

Step-2: Preparation of methyl 5-(3-cyclopropyl-1-hydroxypropyl)-2-fluorophenylcarbamate (**258b**)

Compound **258b** was prepared from methyl 5-(3-cyclopropylpropanoyl)-2-fluorophenylcarbamate (**258a**) (2.51 g, 9.46 mmol) according to the procedure reported in step-5 of scheme-248 for preparation of compound **248f** gave after purification by flash column chromatography [silica gel 40 g, eluting with ethyl acetate in hexanes from 0-50%] methyl 5-(3-cyclopropyl-1-hydroxypropyl)-2-fluorophenylcarbamate (**258b**) (2.387 g, 94 % yield) as a colorless oil; ^1H NMR (300 MHz, DMSO-d_6) δ 9.32 (s, 1H, D_2O exchangeable), 7.70 - 7.51 (m, 1H), 7.18 (dd, J = 10.6, 8.4 Hz, 1H), 7.09 (ddd, J = 8.4, 4.9, 2.1 Hz, 1H), 5.21 (d, J = 4.4 Hz, 1H, D2O exchangeable), 4.60 - 4.43 (m, 1H), 3.69 (s, 3H), 1.68 (m, 2H), 1.21 (m, 2H), 0.79 - 0.57 (m, 1H), 0.39 (m, 2H), 0.11 - -0.09 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -127.49; MS (ES+): 290.2 (M+Na); MS (ES-) 266.2 (M-1).

Step-3: Preparation of methyl 5-(1-bromo-3-cyclopropylpropyl)-2-fluorophenylcarbamate (**258c**)

Compound **258c** was prepared from methyl 5-(3-cyclopropyl-1-hydroxypropyl)-2-fluorophenylcarbamate (**258b**) (2.303 g, 8.62 mmol) according to the procedure reported in step-2 of scheme-251 for preparation of compound **251b** gave after purification by flash column chromatography [silica gel 40 g, eluting with ethyl acetate in hexanes from 0-100%] methyl 5-(1-bromo-3-cyclopropylpropyl)-2-fluorophenylcarbamate **(258c)** (1.289 g, 3.90 mmol, 45.3 % yield) as a colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.43 (s, 1H, D_2O exchangeable), 7.78 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.36 - 7.11 (m, 2H), 5.29 (dd, *J* = 8.1, 6.9 Hz, 1H), 3.67 (s, 3H), 2.41 - 2.06 (m, 2H), 1.39 - 1.09 (m, 2H), 0.71 (m, 1H), 0.39 (m, 2H), 0.11 - -0.09 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -124.45; MS (ES-) 328.1 (M-2).

Step-4: Preparation of methyl 5-(3-cyclopropyl-1-(2-oxopyridin-1(2H)-yl)propyl)-2-fluorophenylcarbamate **(258d)**

To a solution of methyl 5-(1-bromo-3-cyclopropylpropyl)-2-fluorophenylcarbamate **(258c)** (1.21 g, 3.66 mmol) in DMF (10 mL) was added pyridin-2(1H)-one (0.418 g, 4.40 mmol) cesium carbonate (1.791 g, 5.50 mmol) and stirred at room temperature overnight. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (2 x 75 mL), combined organics were dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography [silica gel 24 g, eluting with ethyl acetate in hexanes from 0-50%] to furnish of methyl 5-(3-cyclopropyl-1-(2-oxopyridin-1(2H)-yl)propyl)-2-fluorophenylcarbamate **(258d)** (0.606 g, 48.0 % yield) as a colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.37 (s, 1H, D_2O exchangeable), 7.76 - 7.58 (m, 2H), 7.36 (m, 1H), 7.28 - 7.09 (m, 2H), 6.44 - 6.34 (m, 1H), 6.23 (td, *J* = 6.7, 1.5 Hz, 1H), 6.06 (t, *J* = 8.0 Hz, 1H), 3.65 (s, 3H), 2.20 (m, 2H), 1.26 - 0.92 (m, 2H), 0.80 - 0.63 (m, 1H), 0.46 - 0.30 (m, 2H), -0.01 - -0.03 (m, 2H); ^{19}F NMR (282 MHz, DMSO-*d6*) δ -125.28; MS (ES+) 367.3 (M+Na); MS (ES-) 343.3 (M-1).

Step-5: Preparation of 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)pyridin-2(1H)-one **(258e)**

To a solution of methyl 5-(3-cyclopropyl-1-(2-oxopyridin-1(2H)-yl)propyl)-2-fluorophenylcarbamate **(258d)** (0.558 g, 1.620 mmol) in methanol (7 mL) was added 2.5 M NaOH (6.48 mL, 16.20 mmol) and refluxed for 13 h. The reaction mixture was diluted with water and extracted with ethyl acetate (2 x 50 mL), combined organics were dried over anhydrous $MgSO_4$, filtered, evaporated to dryness. The residue was purified by flash column chromatography [silica gel 12 g, eluting with ethyl acetate in hexanes from 0-25%] to furnish of 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)pyridin-2(1H)-one **(258e)** (0.409 g, 88 % yield) as an yellow oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.59 (ddd, *J* = 6.9, 2.1, 0.7 Hz, 1H), 7.35 (ddd, *J* = 8.8, 6.5, 2.0 Hz, 1H), 6.95 (dd, *J* = 11.4, 8.3 Hz, 1H), 6.75 (dd, $J = 8.8, 2.2$ Hz, 1H), 6.53 (ddd, $J = 8.4, 4.3, 2.3$ Hz, 1H), 6.44 - 6.33 (m, 1H), 6.21 (td, $J = 6.7, 1.5$ Hz, 1H), 5.99 (dd, $J = 9.0, 7.0$ Hz, 1H). 5.20 (s, 2H), 2.14 (m, 2H), 1.14 - 1.07 (m, 1H), 1.05 - 0.92 (m, 1H), 0.70 (m, 1H), 0.47 - 0.30 (m, 2H), 0.00 - - 0.10 (m, 2H); MS (ES+): 309.2 (M+Na), MS (ES-) 285.2 (M-1), 321.2 (M+Cl).

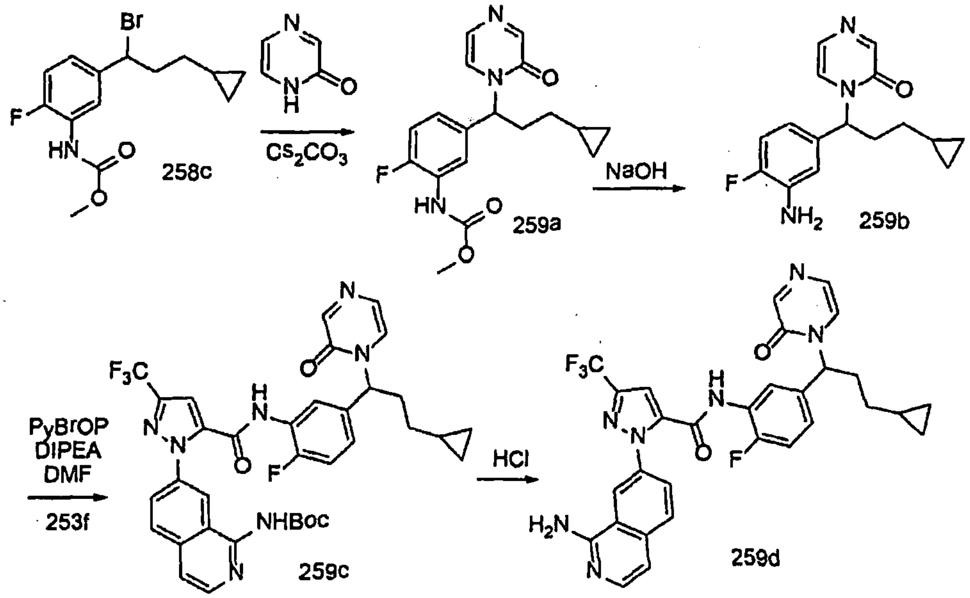
Step-6: Preparation of di-*tert*-butyl 7-(5-(5-(3-cyclopropyl-1-(2-oxopyridin-1(2H)-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**258f**)

Compound **258f** was prepared from 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253c**) (281 mg, 0.538 mmol) and 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)pyridin-2(1H)-one (**258e**) (0.154 g, 0.538 mmol) according to the procedure reported in step-3 of scheme-208 for compound **208c** gave after workup crude di-*tert*-butyl 7-(5-(5-(3-cyclopropyl-1-(2-oxopyridin-1(2H)-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**258f**) as a brown wax which was used as such in next step; MS (ES+): 813.5 (M+1).

Step-7: Preparation of 1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(2-oxopyridin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**258g**)

To a stirred solution of di-*tert*-butyl 7-(5-(5-(3-cyclopropyl-1-(2-oxopyridin-1(2H)-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**258f**) (0.801 g, 1.013 mmol) in methanol (10 mL) was added HCl (3M in methanol) (2.026 mL, 6.08 mmol) and heated at reflux for 1 h. The reaction was cooled to room temperature and evaporated to dryness. The residue was basified with aq. ammonium hydroxide and evaporated to dryness. The residue was purified by flash chromatography [silica gel 12 g, eluting with CMA80 in chloroform from 0-100%]. The sample was dissolved in minimum amount of methanol/1 N HCl, and purified by "reverse phase" flash chromatography [C18 column, eluting with water (0.1%TFA) in methanol from 0-100%]. The compound isolated was triturated with methanolic 3 N HCl, and sonicated and evaporated to dryness. The residue was dissolved in minimum amount of acetonitrile and water, lyophilized to afford 1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(2-oxopyridin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**258g**) (10 mg, 2 % yield) hydrochloride salt as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.38 (s, 1H, D_2O exchangeable), 10.71 (s, 1H, D_2O exchangeable), 9.20 (s, 3H, D_2O exchangeable), 8.84 (s, 1H), 8.09 (s, 2H), 7.85 - 7.75 (m, 2H), 7.70 (dd, J = 7.0, 2.0 Hz, 1H), 7.54 (s, 1H), 7.34 (dd, J = 8.9, 4.8 Hz, 3H), 6.39 (d, J = 9.0 Hz, 1H), 6.23 (t, J = 6.6 Hz, 1H), 6.04 (t, J = 8.0 Hz, 1H), 2.20 (m, 2H), 1.05 (m, 2H), 0.76 - 0.62 (m, 1H), 0.42 - 0.31 (m, 2H), -0.05 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.70, -121.04; MS (ES+): 591.3 (M+1); MS (ES-) 625.3 (M+Cl); Analysis calculated for $C_{31}H_{26}F_4N_6O_2 \cdot 2HCl \cdot 2H_2O$: C, 53.23; H, 4.61; N, 12.01; Found: C, 53.18; H, 4.56; N, 12.38.

Scheme 259



Preparation of 1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(2-oxopyrazin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**259d**)

Step-1: Preparation of methyl 5-(3-cyclopropyl-1-(2-oxopyrazin-1(2H)-yl)propyl)-2-fluorophenylcarbamate (**259a**)

To a solution of methyl 5-(1-bromo-3-cyclopropylpropyl)-2-fluorophenylcarbamate (**258c**) (0.925 g, 2.80 mmol) in DMF (10 mL) was added pyrazin-2(1H)-one (0.323 g, 3.36 mmol) cesium carbonate (0.867 g, 2.66 mmol) and stirred at room temperature overnight. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (2 x 75 mL), combined organics were dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography [silica gel 24 g, eluting with ethyl acetate/methanol (9:1) in hexanes from 0-75%] to furnish methyl 5-(3-

cyclopropyl-1-(2-oxopyrazin-1(2H)-yl)propyl)-2-fluorophenylcarbamate (**259a**) (0.304 g, 31 % yield) as a colorless wax. MS (ES+): 368.3 (M+Na), MS (ES-) 344.2 (M-1).

Step-2: Preparation of 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)pyrazin-2(1H)-one (**259b**)

Compound **259b** was prepared from methyl 5-(3-cyclopropyl-1-(2-oxopyrazin-1(2H)-yl)propyl)-2-fluorophenylcarbamate (**259a**) (301 mg, 0.872 mmol) according to the procedure reported in step-5 of scheme-258 for compound **258e** to afford after purification by flash column chromatography [silica gel 12 g, eluting with ethyl acetate/methanol (9:1) in hexanes from 0-75%) 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)pyrazin-2(1H)-one (**259b**) (61 mg, 24% yield) as a yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (d, J = 1.2 Hz, 1H), 7.65 (d, J = 4.6 Hz, 1H), 7.33 (d, J = 4.5 Hz, 1H), 6.97 (dd, J = 11.4, 8.3 Hz, 1H), 6.76 (dd, J = 8.8, 2.3 Hz, 1H), 6.57 (dt, J = 7.3, 3.4 Hz, 1H), 5.81 (t, J = 8.0 Hz, 1H), 5.22 (s, 2H, D_2O exchangeable), 2.18 (m, 2H), 1.08 (m, 2H), 0.69 (m, 1H), 0.43 - 0.29 (m, 2H), -0.02 (s, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -135.69; MS (ES+): 310.2 (M+Na), MS (ES-) 286.3 (M-1), 322.2 (M+Cl).

Step-3: Preparation of *tert*-butyl 7-(5-(5-(3-cyclopropyl-1-(2-oxopyrazin-1(2H)-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**259c**)

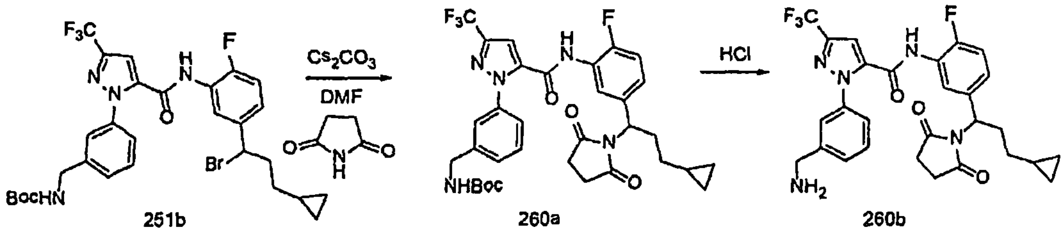
Compound **259c** was prepared from and 1-(1-(tert-butoxycarbonylamino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253f**) (0.102 g, 0.242 mmol) and 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)pyrazin-2(1H)-one (**259b**) (58 mg) according to the procedure reported in step-3 of scheme-208 for compound **208c** gave after workup crude *tert*-butyl 7-(5-(5-(3-cyclopropyl-1-(2-oxopyrazin-1(2H)-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**259c**) (359 mg) as a brown wax which was used as such in next step; MS (ES+) 692.2 (M+1).

Step-4: Preparation of 1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(2-oxopyrazin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**259d**)

To a solution of crude *tert*-butyl 7-(5-(5-(3-cyclopropyl-1-(2-oxopyrazin-1(2H)-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**259c**) (0.338 g, crude reaction mixture) in methanol (10 mL) was added 3 M methanolic HCl (0.977 mL, 2.93 mmol) and heated at reflux for 1.5 h. The reaction was cooled to room temperature and evaporated to dryness. The residue was basified with aq. ammonium hydroxide and evaporated to dryness. The residue was purified by flash chromatography [silica gel 12 g, eluting with CMA80 in chloroform from 0-100%] to afford compound **259d** (12 mg, 4 % yield) free base as a colorless solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.65 (s, 1H, D$_2$O exchangeable), 8.57 - 8.38 (m, 1H), 8.07 (d, J = 1.1 Hz, 1H), 7.94 (d, J = 5.7 Hz, 1H), 7.88 - 7.69 (m, 4H), 7.66 - 7.58 (m, 1H), 7.44 - 7.30 (m, 3H), 7.10 - 6.94 (m, 3H), 5.92 (dd, J = 9.0, 6.9 Hz, 1H), 2.41 - 2.17 (m, 2H), 1.12 (m, 2H), 0.73 (m, 1H), 0.49 - 0.31 (m, 2H), 0.04 - -0.04 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.73, -120.86; MS (ES+) 592.3 (M+1), 614.2 (M+Na); MS (ES-) 590.3(M-1), 626.3 (M+Cl).

Scheme 260



Preparation of 1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-(2,5-dioxopyrrolidin-1-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**260b**)

Step-1: Preparation of *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-(2,5-dioxopyrrolidin-1-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**260a**)

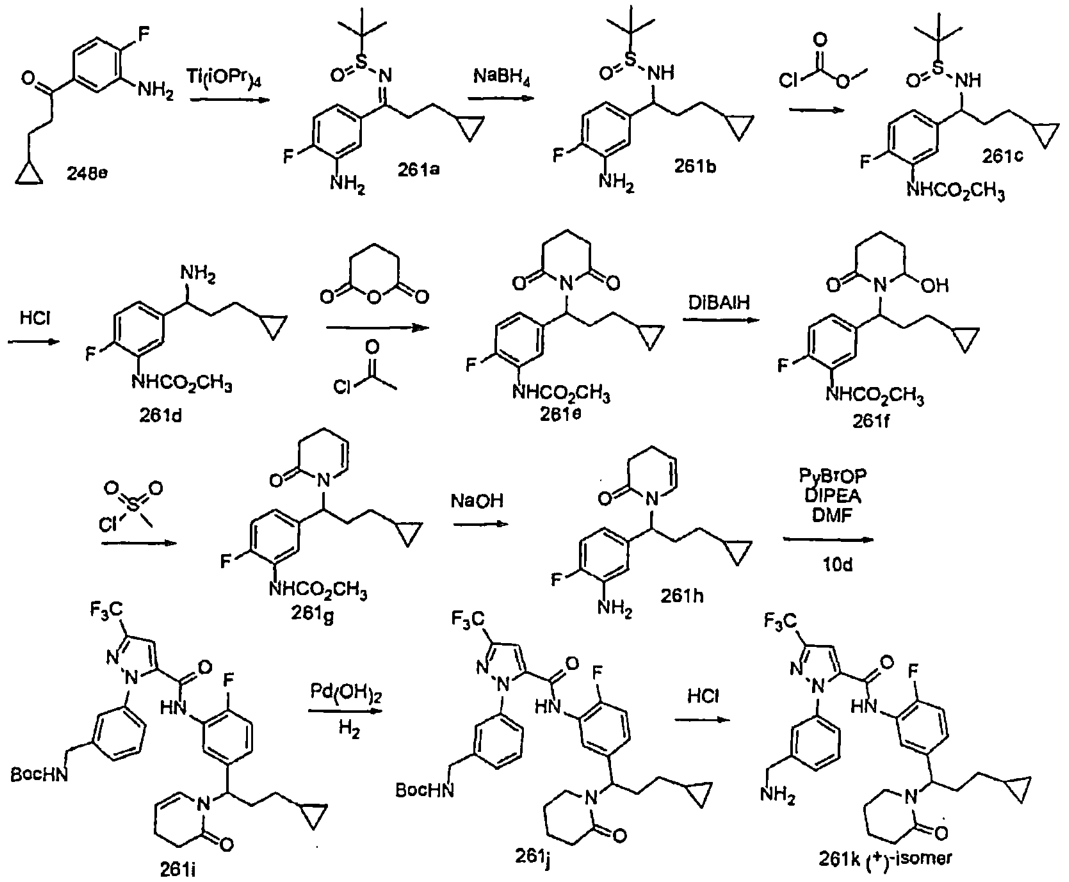
Compound **260a** was prepared from tert-butyl 3-(5-(5-(1-bromo-3-cyclopropylpropyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**251b**) (0.7 g, 1.09 mmol) and pyrrolidine-2,5-dione (0.217 g, 2.19 mmol) according to the procedure reported in step-4 of scheme-258 for preparation of compound **258d** gave after purification by flash column chromatography (silica gel 40 g, eluting with ethyl acetate in hexanes from 0-50%) to *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-(2,5-dioxopyrrolidin-1-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**260a**) (0.19 g, 0.29 mmol, 26.4 % yield) as colorless foam; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.60 (s, 1H), 7.59 (m, 2H), 7.53 – 7.14 (m, 7H), 5.07

(dd, $J = 9.5$, 6.4 Hz, 1H), 4.20 (d, $J = 6.2$ Hz, 2H), 2.70 – 2.57 (m, 4H), 2.47 – 2.31 (m, 1H), 2.16 (m, 1H), 1.37 (s, 11H), 0.66 (s, 1H), 0.37 (m, 2H), -0.01 – -0.12 (m, 2H); ^{19}F NMR (282 MHz, DMSO) δ -60.85, -121.00; MS (ES+) 680.3 (M+Na).

Step-2: Preparation of 1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-(2,5-dioxopyrrolidin-1-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**260b**)

To a solution of *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-(2,5-dioxopyrrolidin-1-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**260a**) (0.15 g, 0.23 mmol) in methanol (5 mL) was added hydrogen chloride in 3 M in methanol (0.76 mL, 2.28 mmol) and stirred at room temperature for 20h. The solution was concentrated in vacuum and resultant residue was partitioned between $NaHCO_3$ solution (40 mL) and EtOAc (30 mL). Layers were separated; aqueous layer was extracted with EtOAc (25 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuum. The residue was purified by flash chromatography (silica gel 12 g, eluting with 0-100% CMA80 in chloroform) to afford 1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-(2,5-dioxopyrrolidin-1-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**260b**) (0.105 g, 0.188 mmol, 83 % yield) as colorless foam; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.32 (s, 1H), 7.71 – 7.14 (m, 9H), 5.07 (dd, $J = 9.5$, 6.4 Hz, 1H), 3.80 (s, 2H), 2.70 – 2.57 (m, 4H), 2.43 (m, 1 H) 2.16 (m, 1H), 1.10 (m, 2H), 0.64 (m, 1H), 0.37 (m, 2H), -0.00 (m, 2H). ^{19}F NMR (282 MHz, DMSO) δ -60.75, -122.08; MS (ES+) 558.3 (M+1).

Scheme 261



Preparation of (+)-1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-(2-oxopiperidin-1-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**261k**)

Step-1: Preparation of N-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropylidene)-2-methylpropane-2-sulfinamide (**261a**)

Compound **261a** was prepared from 1-(3-amino-4-fluorophenyl)-3-cyclopropylpropan-1-one (**248e**) (19.5 g, 94 mmol) and 2-methylpropane-2-sulfinamide (14.83 g, 122 mmol) according to the procedure reported in step-1 of scheme 208 for preparation of compound **208a** (reaction time 62 h) to afford after purification by flash column chromatography [silica gel with hexanes/ethyl acetate (1:0 to 4:1, then 2:1, 1:1)] to give N-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropylidene)-2-methylpropane-2-sulfinamide (**261a**) (14.26 g, 48.9%) as a yellow gum; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.33 (d, J = 8.9 Hz, 1H), 7.10 – 7.03 (m, 2H), 5.39 (s, 2H), 3.32-3.04 (m, 2H), 1.54 – 1.36

(m, 2H), 1.21 (s, 9H), 0.82-0.66 (m, 1H), 0.53 – 0.27 (m, 2H), 0.15 – -0.05 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -129.99; MS (ES+): 333.2 (M+Na).

Step-2: Preparation of N-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)-2-methylpropane-2-sulfinamide (**261b**)

Compound **261b** was prepared from N-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropylidene)-2-methylpropane-2-sulfinamide (**261a**) (4 g, 12.89 mmol) according to the procedure reported in step-5 of scheme 248 for preparation of compound **248f** (reaction temp -78 °C) to afford N-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)-2-methylpropane-2-sulfinamide (**261b**) (4.15 g) as a light yellow gum which was used as such for next step.

Step-3: Preparation of methyl 5-(3-cyclopropyl-1-(1,1-dimethylethylsulfinamido)propyl)-2-fluorophenylcarbamate (**261c**)

To a biphasic solution of N-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)-2-methylpropane-2-sulfinamide (**261b**) (4.5 g, 14.40 mmol) in ethyl acetate (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) was added methyl chloroformate (1.673 mL, 21.60 mmol) and stirred at room temperature for 16 h. Aqueous layers was separated, extracted with ethyl acetate (2x150 mL) and combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography to afford methyl 5-(3-cyclopropyl-1-(1,1-dimethylethylsulfinamido)propyl)-2-fluorophenylcarbamate (**261c**) (4.86 g, 13.12 mmol, 91 % yield) as gummy solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.30 (s, 1H), 7.69 – 7.52 (m, 1H), 7.25 – 6.98 (m, 2H), 5.60 (d, J = 8.2 Hz, 1H), 4.12 (m, 1H), 3.66 (s, 3H), 1.97 – 1.79 (m, 1H), 1.68 (m, 1H), 1.08 (m, 11H), 0.63 (m, 1H), 0.42 – 0.26 (m, 2H), -0.01 – -0.12 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -127.03 (d, J = 44.3 Hz).

Step-4: Preparation of methyl 5-(1-amino-3-cyclopropylpropyl)-2-fluorophenylcarbamate (**261d**)

To a stirred solution of methyl 5-(3-cyclopropyl-1-(1,1-dimethylethylsulfinamido)propyl)-2-fluorophenylcarbamate (**261c**) (4.85 g, 13.09 mmol) in methanol (100 mL) was added hydrochloric acid 4N solution in 1,4-dioxane (16.36 mL, 65.5 mmol) and stirred at room temperature for 30 minutes. The reaction was concentrated in vacuum, residue was dissolved in water (100 mL) basified with saturated sodium bicarbonate solution and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (2 x 50 mL), brine (50 mL), dried, filtered and concentrated in vacuum to afford methyl 5-(1-amino-3-cyclopropylpropyl)-2-fluorophenylcarbamate (**261d**) (3.57 g, 13.41 mmol, 102 % yield) as a thick syrup which was used as such for next step; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.25 (s, 1H), 7.75 – 7.39 (m, 1H), 7.30 – 6.85 (m, 2H), 3.65 (s, 3H), 3.37 (m, 1H), 2.04 (s, 2H), 1.59 (m, 2H), 1.27 – 1.13 (m, 1H), 1.08 – 0.91 (m, 1H), 0.73 – 0.51 (m, 1H), 0.41 – 0.24 (m, 2H), -0.06 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -127.68 .

Step-5: Preparation of methyl 5-(3-cyclopropyl-1-(2,6-dioxopiperidin-1-yl)propyl)-2-fluorophenylcarbamate (**261e**)

To a stirred solution of methyl 5-(1-amino-3-cyclopropylpropyl)-2-fluorophenylcarbamate (**261d**) (3.2 g, 12.02 mmol) in dichloromethane (70 mL) was added dihydro-2H-pyran-2,6(3H)-dione (1.508 g, 13.22 mmol). The reaction was stirred at room temperature for 30 mins added acetyl chloride (17.09 mL, 240 mmol) and heated at reflux for 2 h. The reaction was concentrated in vacuum and purified by flash column chromatography (silica gel, 40 g, eluting with ethyl acetate in hexanes 0 to 100%) to afford methyl 5-(3-cyclopropyl-1-(2,6-dioxopiperidin-1-yl)propyl)-2-fluorophenylcarbamate (**261e**) (4.078 g, 11.25 mmol, 94 % yield) as a colorless solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.28 (s, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.25 – 6.90 (m, 2H), 5.71 (dd, J = 9.2, 6.5 Hz, 1H), 3.65 (s, 3H), 2.62 (m, 4H), 2.37 – 2.12 (m, 2H), 1.88 – 1.75 (m, 2H), 1.20 – 0.99 (m, 2H), 0.68 (m, 1H), 0.47 – 0.32 (m, 2H), 0.05 – 0.00 (m, 1H), -0.01 – -0.07 (m, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -127.01 .

Step-6: Preparation of methyl 5-(3-cyclopropyl-1-(2-hydroxy-6-oxopiperidin-1-yl)propyl)-2-fluorophenylcarbamate (**261f**)

To a stirred solution of methyl 5-(3-cyclopropyl-1-(2,6-dioxopiperidin-1-yl)propyl)-2-fluorophenylcarbamate (**261e**) (3.55 g, 9.80 mmol) in dichloromethane (200 mL) at -78 °C was added diisobutylaluminum hydride (29.4 mL, 29.4 mmol) and stirred at -78 °C for 1 h. Reaction was quenched with methanol (3 mL) and warmed to room temperature. Reaction was diluted with 2 N sodium hydroxide (4 mL) washed with saturated disodium tartarate solution. The layers were separated and aqueous layer was extracted with dichloromethane (2 x 150 mL). the organic layers were combined washed with brine (100 mL), dried, filtered and concentrated to afford methyl 5-(3-cyclopropyl-1-(2-hydroxy-6-oxopiperidin-1-yl)propyl)-2-fluorophenylcarbamate (**261f**) (3.204 g, 8.79 mmol, 90 % yield) which was used as such for next step; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.51 – 9.07 (m, 1H), 7.68 – 7.41 (m, 1H), 7.37 – 6.95 (m, 2H), 5.58 (dd, J = 30.4, 6.5 Hz, 1H), 5.45 (m, 0.5H), 4.96 (m, 0.5H), 4.87 (m, 0.5 H), 4.62 (m, 0.5 H), 3.65 (2s, 3H), 2.35 – 1.99 (m, 4H), 1.81 – 1.59 (m, 2H), 1.59 – 1.36 (m, 2H), 1.27 – 1.06 (m, 2H), 0.70 (m, 1H), 0.45 – 0.25 (m, 2H), 0.05 – -0.18 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -126.93

Step-7: Preparation of methyl 5-(3-cyclopropyl-1-(2-oxo-3,4-dihydropyridin-1(2H)-yl)propyl)-2-fluorophenylcarbamate (**261g**)

To a stirred solution of methyl 5-(3-cyclopropyl-1-(2-hydroxy-6-oxopiperidin-1-yl)propyl)-2-fluorophenylcarbamate (**261f**) (3.2 g, 8.78 mmol) in dichloromethane (100 mL) cooled to 0 °C was added triethylamine (7.34 mL, 52.7 mmol) and methanesulfonyl chloride (1.369 mL, 17.56 mmol). The reaction was allowed to warm to room temperature and stirred for 30 min. The reaction was diluted with dichloromethane (200 mL) and water (50 mL). The aqueous layer was separated and extracted with dichloromethane (2 x 50 mL). The organic layers were combined washed with water (2 x 25 mL), brine (25 mL), dried and concentrated. The crude residue was purified by flash column chromatography (silica gel, 40 g eluting with ethyl acetate in hexanes 0 to 50 to 100%) to afford methyl 5-(3-cyclopropyl-1-(2-oxo-3,4-dihydropyridin-1(2H)-yl)propyl)-2-fluorophenylcarbamate (**261g**) (2.35 g, 6.78 mmol, 77 % yield) as a clear syrup; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.35 (s, 1H), 7.58 (dd, J = 8.0, 2.1 Hz, 1H), 7.18 (dd, J = 10.6, 8.5 Hz, 1H), 7.06 (m, 1H), 6.15 (dt, J = 7.9, 1.6 Hz, 1H), 5.64 (dd, J = 9.9, 6.2 Hz, 1H), 5.17 (dt, J = 8.4, 4.4 Hz, 1H), 3.66 (s, 3H), 2.43 (m, 2H), 2.20 (m, 2H), 2.08 – 1.80 (m, 2H), 1.25 – 1.00 (m, 2H), 0.71 (m, 1H), 0.45 – 0.31 (m, 2H), 0.05 (m, 1H), 0.00 – -0.08 (m, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -126.28 .

Step-8: Preparation of 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)-3,4-dihydropyridin-2(1H)-one (**261h**)

Compound **261h** was prepared from methyl 5-(3-cyclopropyl-1-(2-oxo-3,4-dihydropyridin-1(2H)-yl)propyl)-2-fluorophenylcarbamate (**261g**) (1.2 g, 3.46 mmol) according to the procedure reported in step-5 of scheme 248 for preparation of compound **258e** to afford 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)-3,4-dihydropyridin-2(1H)-one (**261h**) (0.89 g, 3.09 mmol, 89 % yield) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 6.91 (dd, J = 11.5, 8.4 Hz, 1H), 6.69 (dd, J = 8.8, 2.3 Hz, 1H), 6.44 (m, 1H), 6.09 (dt, J = 7.8, 1.6 Hz, 1H), 5.56 (dd, J = 10.1, 5.9 Hz, 1H), 5.20 – 5.06 (m, 3H), 2.48 – 2.35 (m, 2H), 2.27 – 2.12 (m, 2H), 1.98 – 1.77 (m, 2H), 1.16 – 0.93 (m, 2H), 0.78 – 0.63 (m, 1H), 0.44 – 0.33 (m, 2H), 0.10 – -0.11 (m, 2H); ^{19}F NMR (282 MHz, DMSO) δ -137.03.

Step-9: Preparation of *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-(2-oxo-3,4-dihydropyridin-1(2H)-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**261i**)

Compound **261i** was prepared from 1-(3-((tert-butoxycarbonylamino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**10d**) (0.53 g, 1.38 mmol) and 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)-3,4-dihydropyridin-2(1H)-one (**261h**) (0.4 g, 1.39 mmol) according to the procedure reported in step-3 of scheme 208 for preparation of compound **208c** to afford after purification by flash column chromatography (silica gel 40 g, eluting with ethyl acetate in hexanes from 0-40%) *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-(2-oxo-3,4-dihydropyridin-1(2H)-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**261i**) (0.48 g, 0.73 mmol, 52.8 % yield) as colorless foam; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.60 (s, 1H), 7.60 (s, 1H), 7.44 (ddd, *J* = 26.7, 13.8, 5.9 Hz, 6H), 7.31 – 7.15 (m, 2H), 6.17 (d, *J* = 7.9 Hz, 1H), 5.71 – 5.57 (m, 1H), 5.25 – 5.08 (m, 1H), 4.19 (d, *J* = 6.2 Hz, 2H), 2.49 – 2.35 (m, 2H), 2.27 – 2.12 (m, 2H), 2.05 – 1.88 (m, 2H), 1.37 (s, 9H), 1.27 (m, 1 H), 1.16 – 1.01 (m, 1H), 0.71 (m, 1H), 0.38 (m, 2H), -0.00 (m, 2H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -122.72, -60.80.

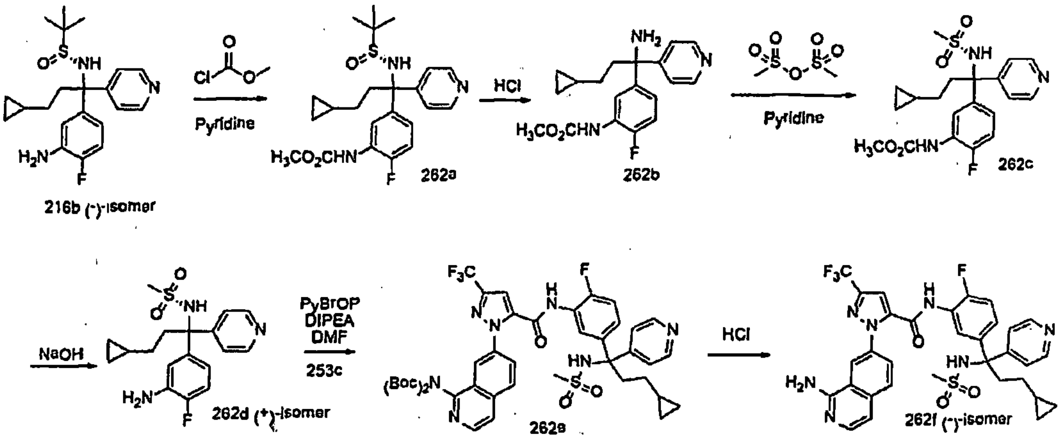
Step-10: Preparation of *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-(2-oxopiperidin-1-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**261j**)

Palladium(II)hydroxide (6.43 mg, 0.023 mmol) was added to a solution of tert-butyl 3-(5-(5-(3-cyclopropyl-1-(2-oxo-3,4-dihydropyridin-1(2H)-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**261i**) (0.15 g, 0.23 mmol) in ethyl acetate (5 mL) and mixture was hydrogenated under H_2 atmosphere for 36 h. Mixture was filtered over celite pad, washed with EtOAc (2x10 mL), concentrated in vacuum and purified by flash column chromatography (silica gel 24 g, eluting with ethyl acetate in hexanes from 0-40%) to afford *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-(2-oxopiperidin-1-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**261j**) (0.09 g, 0.137 mmol, 59.8 % yield) as gummy mass; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.60 (s, 1H), 7.60 (s, 1H), 7.42 (m, 6H), 7.23 (dt, *J* = 13.4, 6.7 Hz, 2H), 5.77 (t, *J* = 8.0 Hz, 1H), 4.19 (d, *J* = 6.3 Hz, 2H), 3.16 – 3.00 (m, 1H), 2.82 – 2.64 (m, 1H), 2.39 – 2.18 (m, 2H), 1.99 (m, 3H), 1.74 – 1.43 (m, 3H), 1.37 (s, 9H), 1.30 (m, 1H), 1.08 (m, 1H), 0.72 (m, 1H), 0.38 (m, 2H), -0.00 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -123.10, -60.81.

Step-11: Preparation of (+)-1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-(2-oxopiperidin-1-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**261k**)

To a solution of *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-(2-oxopiperidin-1-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**261j**) (0.09 g, 0.137 mmol) in methanol (4 mL) was added HCl (0.46 mL, 1.37 mmol, 3 M in methanol), stirred at room temperature for 20 h and concentrated in vacuum. The residue was partitioned between $NaHCO_3$ solution (40 mL) and EtOAc (30 mL). Layers were separated, aqueous layer was extracted with EtOAc (25 mL) and combined organics were washed with brine, dried over $MgSO_4$, filtered concentrated. The residue was purified by flash column chromatography [silica gel 12 g, eluting with CMA80 and chloroform from 0-30%] to afford (+)-1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-(2-oxopiperidin-1-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**261k**) (0.06 g, 0.11 mmol, 79 % yield) as colorless foam; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.59 (s, 1H), 7.58 (s, 1H), 7.54 – 7.38 (m, 4H), 7.38 – 7.10 (m, 3H), 5.76 (t, *J* = 8.0 Hz, 1H), 3.78 (s, 2H), 3.16 – 3.00 (m, 1H), 2.72 (dd, *J* = 12.2, 6.2 Hz, 1H), 2.29 (q, *J* = 6.8 Hz, 2H), 1.95 (dd, *J* = 15.5, 8.1 Hz, 2H), 1.76 – 1.43 (m, 4H), 1.34 – 0.96 (m, 3H), 0.91 – 0.65 (m, 2H), 0.38 (m, 2H), 0.11 – 0.00 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -123.14, -60.74; MS(ES+) 558.3 (M+1); MS(ES-) 556.3 (M-1), 592.3 (M+Cl). Optical rotation: $[\alpha]_D$ = (+) 49.12 [0.285, MeOH].

Scheme 262



Preparation of (-)-1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(methylsulfonamido)-1-(pyridin-4-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**262f**)

Step-1: Preparation of 5-(3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamate (**262a**)

Compound **262a** was prepared from (R)-N-((-)-1-(3-amino-4-fluorophenyl)-3-cyclopropyl-1-(pyridin-4-yl)propyl)-2-methylpropane-2-sulfinamide (**216b**) (0.5 g, 1.284 mmol) according to the procedure reported in step-1 of scheme 258 for preparation of compound **258a** to afford 5-(3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamate (**262a**) (0.573 g, 100 % yield) as a yellow solid which was used as such in next step; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.53 - 8.45 (m, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.34 - 7.28 (m, 2H), 7.21 - 7.08 (m, 2H), 5.51 (s, 1H), 3.64 (s, 3H), 2.71 - 2.40 (m, 2H), 1.15 (s, 9H), 1.10 - 0.85 (m, 2H), 0.73 - 0.55 (m, 1H), 0.43 - 0.29 (m, 2H), -0.02 - -0.11 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -126.83; MS (ES$^+$): MS (ES+) 448.3 (M+1); MS (ES-) 446.3 (M-1), 482.3 (M+Cl).

Step-2: Preparation of methyl 5-(1-amino-3-cyclopropyl-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamate (**262b**)

To a stirred solution of 5-(3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamate (**262a**) (0.551 g, 1.231 mmol) in methanol (12 mL) was added 3M methanolic HCl (2.462 mL, 7.39 mmol) and heated at reflux. The reaction was cooled to room temperature, concentrated in vacuum, basified with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (2 x 30 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, evaporated to dryness to afford methyl 5-(1-amino-3-cyclopropyl-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamate (**262b**) (0.418 g, 1.217 mmol, 99 % yield) as a yellow syrup; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.53 - 8.35 (m, 2H), 7.64 (d, J = 7.6 Hz, 1H), 7.42 - 7.31 (m, 2H), 7.25 - 7.04 (m, 2H), 3.63 (s, 3H), 2.35 (s, 2H), 2.20 (t, J = 8.1 Hz, 2H), 1.12 - 0.91 (m, 2H), 0.73 - 0.56 (m, 1H), 0.41 - 0.29 (m, 2H), -0.03 - -0.10 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -127.63; MS (ES$^+$): MS (ES+) 344.2 (M+1); MS (ES-) 342.2 (M-1).

Step-3: Preparation of methyl 5-(3-cyclopropyl-1-(methylsulfonamido)-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamate (**262c**)

To a stirred solution of methyl 5-(1-amino-3-cyclopropyl-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamate (**262b**) (0.401 g, 1.168 mmol) in dichloromethane (20 mL) at 0 °C was added pyridine (0.471 mL, 5.84 mmol), methanesulfonic anhydride (0.407 g, 2.336 mmol). The resulting mixture was allowed to warm to room temperature overnight. Additional pyridine (0.471 mL, 5.84 mmol) and methanesulfonic anhydride (0.407 g, 2.336 mmol) was added and mixture was stirred for another 3 h at room temperature. Reaction mixture was diluted with brine (20 mL), extracted with dichloromethane (2 x 30 mL), combined organic layers were dried over anhydrous MgSO4, filtered, evaporated to dryness. The residue was purified by flash column chromatography [silica gel 12 g, eluting with CMA80 in chloroform from 0-75%] to afford methyl 5-(3-cyclopropyl-1-(methylsulfonamido)-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamate (**262c**) (0.489 g, 1.160 mmol, 99 % yield) which was used as such in next step; MS (ES$^+$): MS (ES+) 444.2 (M+Na); MS (ES-) 456.2 (M+Cl).

Step-4: Preparation of (+)-N-(1-(3-amino-4-fluorophenyl)-3-cyclopropyl-1-(pyridin-4-yl)propyl)methanesulfonamide (**262d**)

Compound **262d** was prepared from methyl 5-(3-cyclopropyl-1-(methylsulfonamido)-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamate (**262c**) (0.483 g, 1.146 mmol) according to the procedure reported in step-5 of scheme 258 for preparation of compound **258e** to afford (+)-N-(1-(3-amino-4-fluorophenyl)-3-cyclopropyl-1-(pyridin-4-yl)propyl)methanesulfonamide (**262d**) (0.311 g, 0.856 mmol, 74.7 % yield) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 - 8.30 (m, 2H), 7.67 (s, 1H), 7.37 - 7.18 (m, 2H), 6.95 (dd, J = 11.2, 8.5 Hz, 1H), 6.82 (dd, J = 8.9, 2.4 Hz, 1H), 6.50 - 6.36 (m, 1H), 5.21 (s, 2H), 2.66 - 2.54 (m, 1H), 2.35 - 2.24 (m, 1H), 2.21 (s, 3H), 1.15 - 0.97 (m, 1H), 0.87 - 0.67 (m, 1H), 0.64 - 0.47 (m, 1H), 0.40 - 0.20 (m, 2H), -0.02 - -0.20 (m, 2H); MS (ES$^+$): MS (ES-) 362.2 (M-1), 725.3 (2M-1); Optical rotation: [α]D = (+) 21.0 [0.2, MeOH]

Step-5: Preparation of di-*tert*-butyl 7-(5-(5-(3-cyclopropyl-1-(methylsulfonamido)-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**262e**)

Compound 262e was prepared from 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253c**)(0.519 g, 0.994 mmol) and (+)-N-(1-(3-amino-4-fluorophenyl)-3-cyclopropyl-1-(pyridin-4-yl)propyl)methanesulfonamide (**262d**) (0.301 g, 0.828 mmol) according to the procedure reported in step-3 of scheme 208 for preparation of compound **208c** to afford di-*tert*-butyl 7-(5-(5-(3-cyclopropyl-1-(methylsulfonamido)-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate

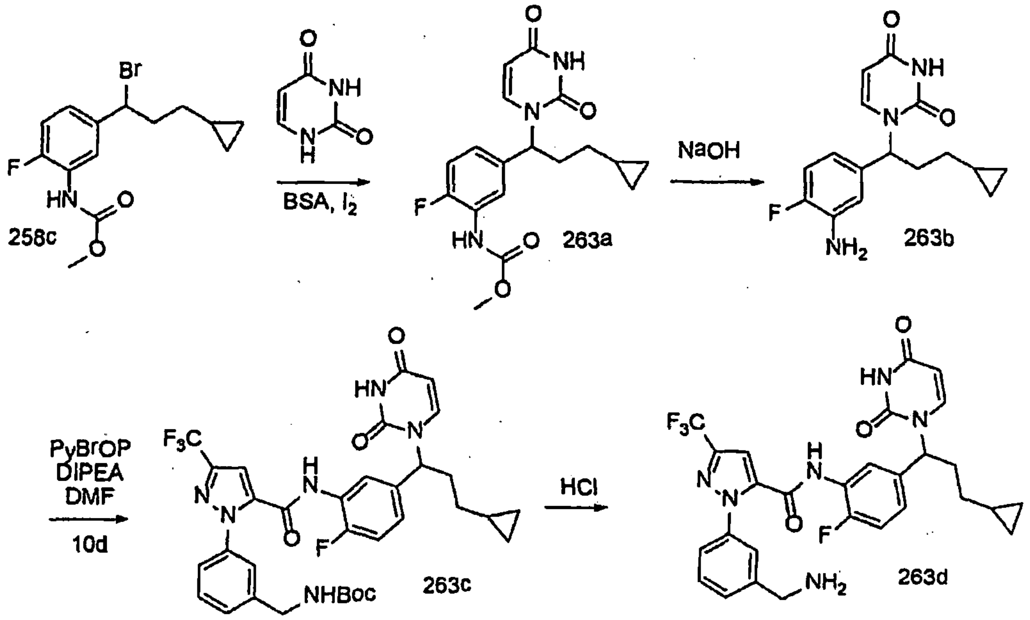
(**262e**), the crude reaction mixture was used as such in the next step; MS (ES+): 868.3 (M+1).

Step-6: Preparation of (-)-1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(methylsulfonamido)-1-(pyridin-4-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**262f**)

Compound **262f** was prepared from di-*tert*-butyl 7-(5-(5-(3-cyclopropyl-1-(methylsulfonamido)-1-(pyridin-4-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**262e**) (1.439 g, 1.658 mmol) according to the procedure reported in step-7 of scheme 258 for preparation of compound **258f** to afford after purification compound **262f** (78 mg, 7 % yield) yellow solid as a free-base; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.69 - 8.45 (m, 2H), 8.43 (s, 1H), 7.98 - 7.51 (m, 6H), 7.40 - 7.14 (m, 3H), 7.10 - 6.84 (m, 3H), 2.31 - 2.22 (m, 2H), 2.27 (s, 3H), 1.21 - 0.93 (m, 2H), 0.90 - 0.71 (m, 1H), 0.65 - 0.48 (m, 1H), 0.38 - 0.20 (m, 2H), -0.05 - -0.21 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.70, -121.52;

To a solution of free base of compound **262f** (0.069 g, 0.103 mmol) in methanol (10 mL) was added HCl (3M in methanol) (0.207 mL, 0.620 mmol), evaporated to dryness, dissolved in minimum amount of water and lyophilized to afford (-)-1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(methylsulfonamido)-1-(pyridin-4-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**262f**) (34 mg, 49 % yield) hydrochloride salt as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.67 (s, 1H, D_2O exchangeable), 10.90 (s, 1H, D_2O exchangeable), 9.33 (s, 2H, D_2O exchangeable), 8.99 - 8.85 (m, 1H), 8.78 (d, *J* = 6.0 Hz, 2H), 8.19 - 8.03 (m, 3H), 7.89 (s, 1H), 7.90 - 7.67 (m, 3H), 7.67 - 7.55 (m, 1H), 7.39 - 7.21 (m, 3H), 2.76 - 2.41 (m, 2H), 2.39 (s, 3H), 1.11 - 0.95 (m, 1H), 0.88 - 0.69 (m, 1H), 0.65 - 0.50 (m, 1H), 0.38 - 0.19 (m, 2H), -0.02 - -0.21 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.90 , -120.70; ^{1}H NMR (300 MHz, DMSO-d_6/D_2O) δ 8.97 (s, 1H), 8.91 - 8.83 (m, 2H), 8.30 - 8.14 (m, 2H), 8.00 - 7.84 (m, 4H), 7.76 (dd, *J* = 7.2, 2.4 Hz, 1H), 7.54 - 6.79 (m, 3H), 2.86 - 2.58 (m, 2H), 2.55 (s, 3H), 1.26 - 1.04 (m, 2H), 1.05 - 0.83 (m, 1H), 0.80 - 0.62 (m, 1H), 0.53 - 0.32 (m, 2H), 0.11 - -0.08 (m, 2H); MS (ES$^+$): MS (ES+) 668.2 (M+1), 702.2 (M+Cl); Optical rotation: $[\alpha]_D$ = (-) 2.0 [0.1, MeOH]; Analysis calculated for : $C_{32}H_{29}F_4N_7O_3S \cdot 2.25HCl \cdot 4.25H_2O$: C, 46.51; H, 4.85; Cl, 9.65; N, 11.87; Found: C, 46.66; H, 4.56; Cl, 9.27; N, 12.03.

Scheme 263



Preparation of 1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**263d**)

Step-1: Preparation of methyl (5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenyl)carbamate (**263a**)

To a suspension of uracil (1 g, 8.92 mmol) in acetonitrile (60 mL) was added N,O-bis trimethylsilyl acetamide (BSA, 4.54 g, 22.30 mmol) and stirred for 30 min. To the reaction mixture was added methyl 5-(1-bromo-3-cyclopropylpropyl)-2-fluorophenylcarbamate (**528c**) (3.54 g, 10.71 mmol), iodine (0.226 g, 0.892 mmol) and heated at reflux until all starting material was consumed. The reaction mixture was cooled to room temperature, concentrated in vacuum, diluted with ethyl acetate (100 mL), and washed with H_2O (50 mL). The organic layer was dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography (silica gel 40 g, eluting with 0-90% EtOAc in hexane) to furnish methyl 5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenylcarbamate (**263a**) (785 mg, 0.498 mmol, 24.4 % yield) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.33 (s, 1H), 9.40 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 6.2 Hz, 1H), 7.29 - 7.16 (m, 1H), 7.19 - 7.09 (m, 1H), 5.58 (t, J = 7.5 Hz, 2H), 3.66 (s, 3H), 2.24 - 2.05 (m, 2H), 1.24 - 1.02 (m, 2H), 0.75 - 0.64 (m, 1H), 0.46 - 0.32 (m, 2H), 0.05 - -0.03 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -125.34; MS (ES+) 362.2 (M+1), 360.2 (M-1).

Step-2: Preparation of 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)pyrimidine-2,4(1H,3H)-dione (**263b**)

Compound **263b** was prepared from methyl 5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenylcarbamate (**263a**) (765 mg, 2.117 mmol) according to the procedure reported in step-5 of scheme 258 for preparation of compound **258e** to afford after purification by flash column chromatography [silica gel 12 g, eluting with 0-60% ethyl acetate in hexanes] 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)pyrimidine-2,4(1H,3H)-dione (**263b**) (450 mg, 1.484 mmol, 70.1 % yield) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.31 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 6.96 (dd, J = 11.2, 8.5 Hz, 1H), 6.71 (d, J = 7.3 Hz, 1H), 6.56 - 6.48 (m, 1H), 5.57 (d, J = 6.3 Hz, 1H), 5.49 (t, J = 7.7 Hz, 1H), 5.21 (s, 2H), 2.21 - 1.97 (m, 2H), 1.21 - 1.00 (m, 2H), 0.76 - 0.59 (m, 1H), 0.42-0.32 (m, 2H), 0.10 - -0.12 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -136.17.

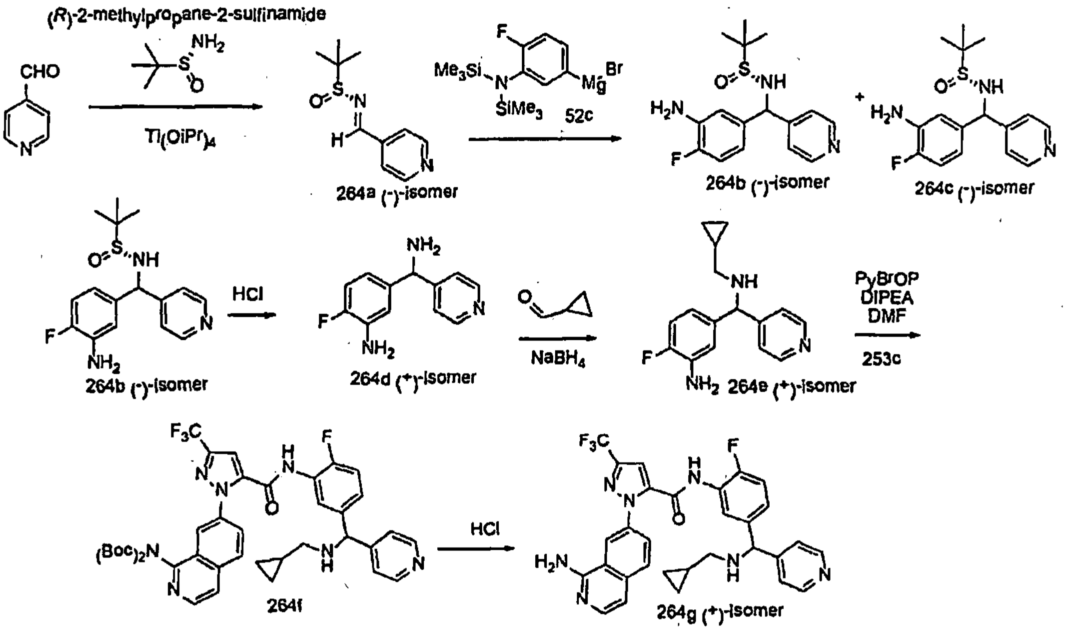
Step-3: Preparation of *tert*-butyl 3-(5-((5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenyl)carbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**263c**)

Compound **263c** was prepared from 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)pyrimidine-2,4(1H,3H)-dione (**263b**) (410 mg, 1.352 mmol) and 1-(3-((tert-butoxycarbonylamino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**10d**) (781 mg, 2.027 mmol) according to the procedure reported in step-3 of scheme 208 for preparation of compound **208c** to afford after purification by flash column chromatography [silica gel 24 g, eluting with 0-90% EtOAc/MeOH (9:1, v/v) in hexane] tert-*butyl* 3-(5-(5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**263c**) (325 mg, 0.485 mmol, 35.9 % yield) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.35 (s, 1H), 10.64 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.64 - 7.25 (m, 9H), 5.59 (d, J = 8.0 Hz, 2H), 4.20 (d, J = 6.1 Hz, 2H), 2.30 - 2.04 (m, 2H), 1.37 (s, 9H), 1.24 - 1.00 (m, 2H), 0.77 - 0.61 (m, 1H), 0.43 - 0.31 (m, 2H), 0.08 - -0.06 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.82, -121.69; MS (ES$^+$), 693.2 (M+Na); (ES$^-$) 669.3 (M-1).

Step-4: Preparation of 1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**263d**)

To a solution of tert-*butyl* 3-(5-(5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**263c**) (300 mg, 0.447 mmol) in MeOH (15 mL) was added HCl (3 N in MeOH) (1.193 mL, 3.58 mmol) and heated at reflux for 40 min. The solution was cooled to room temperature concentrated in vacuum and the residue was purified by flash column chromatography (silica gel 12 g, eluting with 0-60% CMA80 in $CHCl_3$) to furnish 1-(3-(aminomethyl)phenyl)-N-(5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**263d**) (140 mg, 0.245 mmol, 54.9 % yield) as a white solid; ^1H NMR (300 MHz, DMSO-d_6) δ 7.74 (d, J = 8.0 Hz, 1H), 7.63 - 7.48 (m, 3H), 7.48 - 7.39 (m, 2H), 7.38 - 7.25 (m, 3H), 5.60 (m, 2H), 3.78 (s, 2H), 2.26 - 2.05 (m, 2H), 1.22 - 0.98 (m, 2H), 0.77 - 0.62 (m, 1H), 0.45 - 0.32 (m, 2H), 0.00 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.75, -121.72; MS (ES+), 571.3 (M+1), 569.3 (M-1).

Scheme 264



Preparation of (+)-1-(1-aminoisoquinolin-7-yl)-N-(5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**264g**)

Step-1: Preparation of (R)-2-methyl-N-(pyridin-4-ylmethylene)propane-2-sulfinamide (**264a**)

Compound **264a** was prepared from isonicotinaldehyde (11.67 g, 109 mmol) and (R)-2,4,6-triisopropylbenzenesulfinamide (12 g, 99 mmol) according to the procedure reported in step-1 of scheme-222 for the preparation of compound **222a** to afford after purification by flash column chromatography (silica gel 120 g, eluting with ethyl acetate in hexanes from 0-70%) (R)-2-methyl-N-(pyridin-4-ylmethylene)propane-2-sulfinamide (**264a**) (15.60 g, 75 % yield) as a crystalline pale yellow solid; ^{1}H NMR: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.84 - 8.77 (m, 2H), 8.63 (s, 1H), 7.94 - 7.81 (m, 2H), 1.21 (s, 9H); MS (ES$^+$): MS (ES$^+$): 211.2 (M+1); Optical rotation: $[\alpha]_D$ = (-) 99.25 [0.935, MeOH].

Step-2: Preparation of (R)-N-((S)-(3-amino-4-fluorophenyl)(pyridin-4-yl)methyl)-2-methylpropane-2-sulfinamide (**264b**) and (R)-N-((R)-(3-amino-4-fluorophenyl)(pyridin-4-yl)methyl)-2-methylpropane-2-sulfinamide (**264c**)

Compounds **264b** and **264c** was prepared from (R)-2-methyl-N-(pyridin-4-ylmethylene)propane-2-sulfinamide (**264a**) (10.73 g, 51 mmol) and freshly prepared 3-(bis(trimethylsilyl)amino)-4-fluorophenyl)magnesium bromide (**52c**) (107 mL, 81 mmol) according to the procedure reported in step-2 of scheme-222 for the preparation of compound **222b** and **222c** to afford after purification by flash column chromatography [silica gel 120 g, eluting with CMA80 in chloroform, 0-100%] to afford;

1. (R)-N-((S)-(3-amino-4-fluorophenyl)(pyridin-4-yl)methyl)-2-methylpropane-2-sulfinamide (**264b**) (6.979 g, 43% yield) as a light red solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.58 - 8.42 (m, 2H), 7.43 - 7.26 (m, 2H), 6.93 (dd, J = 11.5, 8.3 Hz, 1H), 6.80 - 6.66 (m, 1H), 6.64 - 6.50 (m, 1H), 6.02 (d, J = 6.1 Hz, 1H), 5.40 (d, J = 6.1 Hz, 1H), 5.15 (s, 2H, D_2O exchangeable), 1.14 (s, 9H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -136.78; MS (ES$^+$): MS (ES+) 322.2 (M+1), 344.2 (M+Na); MS (ES-) 320.3 (M-1); Optical rotation: $[\alpha]_D$ = (-) 27.41 [0.54, MeOH].
2. (R)-N-((R)-(3-amino-4-fluorophenyl)(pyridin-4-yl)methyl)-2-methylpropane-2-sulfinamide (**264c**) (5.26 g, 32 % yield) as a yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.59 - 8.44 (m, 2H), 7.48 - 7.31 (m, 2H), 6.92 (dd, J = 11.4, 8.3 Hz, 1H), 6.69 (dd, J = 8.9, 2.2 Hz, 1H), 6.58 - 6.41 (m, 1H), 6.10 (d, J = 6.3 Hz, 1H), 5.36 (d, J = 6.2 Hz, 1H), 5.14 (s, 2H, D_2O exchangeable), 1.14 (s, 9H); ^{19}F NMR

(282 MHz, DMSO-d_6) δ -136.73; MS (ES$^+$): MS (ES+) 322.2 (M+1), 344.2 (M+Na); MS (ES-) 320.3 (M-1), 356.2 (M+Cl); Optical rotation: $[\alpha]_D$ = (-) 77.2 [0.5, MeOH].

Step-3: Preparation of (+)-5-(amino(pyridin-4-yl)methyl)-2-fluoroaniline (**264d**)

Compound **264d** was prepared from (R)-N-((S)-(3-amino-4-fluorophenyl)(pyridin-4-yl)methyl)-2-methylpropane-2-sulfinamide (**264b**) (2.26 g, 7.03 mmol) according to the procedure reported in step-3 of scheme-222 for the preparation of compound **222d** to afford after purification by flash column chromatography [silica gel 40 g, eluting with methanol in chloroform, 0-100%] (+)-5-(amino(pyridin-4-yl)methyl)-2-fluoroaniline (**264d**) (0.344 g, 22% yield) as a yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 - 8.38 (m, 2H), 7.44 - 7.23 (m, 2H), 6.88 (dd, J = 11.5, 8.3 Hz, 1H), 6.74 (dd, J = 8.9, 2.2 Hz, 1H), 6.62 - 6.48 (m, 1H), 5.06 (s, 2H, D_2O exchangeable), 4.92 (s, 1H), 2.26 (s, 2H, D_2O exchangeable); ^{19}F NMR (282 MHz, DMSO-d_6) δ -137.67; MS (ES$^+$): MS (ES+) 218.2 (M+1); MS (ES-) 216.1 (M-1); Optical rotation: $[\alpha]_D$ = (+) 47.55 [0.235, MeOH].

Step-4: Preparation of (+)-5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluoroaniline (**264e**)

Compound **264e** was prepared from (+)-5-(amino(pyridin-4-yl)methyl)-2-fluoroaniline (**264d**) (0.331 g, 1.524 mmol) according to the procedure reported in step-4 of scheme-222 for the preparation of compound **222f** to afford after purification by flash column chromatography (silica gel 12 g , eluting with 0-50% CMA80 in chloroform in hexanes) (+)-5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluoroaniline (**264e**) (0.326 g, 1.201 mmol, 79 % yield) as a yellow oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 - 8.41 (m, 2H), 7.48 - 7.32 (m, 2H), 6.96 - 6.73 (m, 2H), 6.63 - 6.45 (m, 1H), 5.10 (s, 2H, D_2O exchangeable), 4.69 (s, 1H), 2.50 - 2.39 (m, 1H), 2.34 - 2.17 (m, 2H), 0.98 - 0.83 (m, 1H), 0.48 - 0.31 (m, 2H), 0.10 - -0.01 (m, 2H); ^{19}F NMR (282 MHz, DMSO-$d6$) δ -137.28; MS (ES$^+$): MS (ES+) 272.2 (M+1), MS (ES-) 270.2 (M-1); Optical rotation: $[\alpha]_D$ = (+) 41.65 [0.485, MeOH].

Step-5: Preparation of bis-di-*tert*-butyl 7-(5-(5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**264f**)

Compound **264f** was prepared from 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253c**) (0.595 g, 1.139 mmol) and (+)-5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-

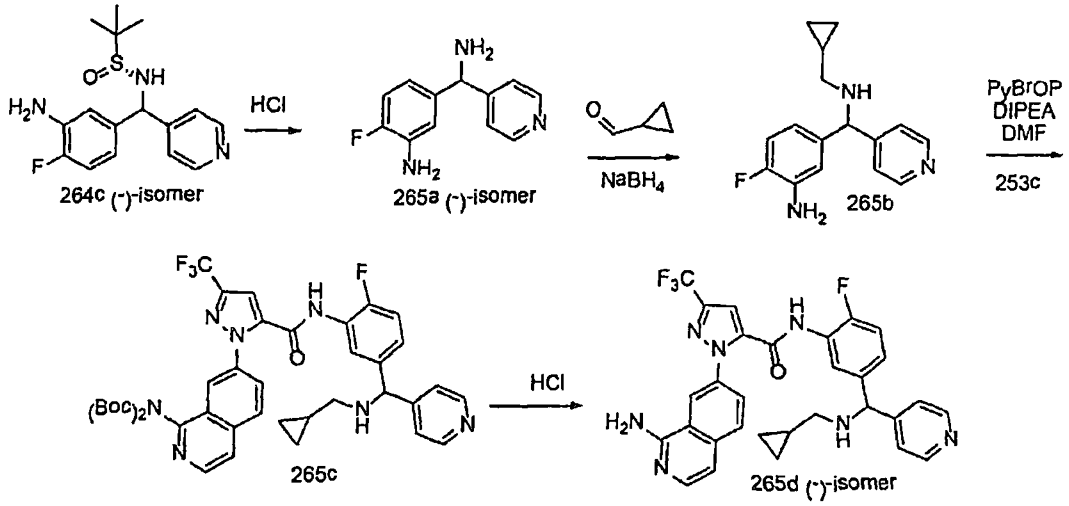
2-fluoroaniline (**264e**) (0.309 g, 1.139 mmol) according to the procedure reported in step-3 of scheme 208 for preparation of compound **208c** to afford bis-di-*tert*-butyl 7-(5-(5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**264f**) as a brown waxy solid which was used as such in next step.

Step-6: (+)-1-(1-aminoisoquinolin-7-yl)-N-(5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**264g**)

Compound **264g** was prepared from bis-di-*tert*-butyl 7-(5-(5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**264f**) (1.4202 g, 1.831 mmol) according to the procedure reported in step-7 of scheme 258 for preparation of compound **258f** to afford after purification compound **264g** as a free-base. The free base was converted to hydrochloride salt to afford after lypholization (+)-1-(1-aminoisoquinolin-7-yl)-N-(5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**264g**) (64 mg, 6 % yield) hydrochloride salt as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.74 (s, 1H, D_2O exchangeable), 10.96 (s, 1H, D_2O exchangeable), 10.76 (s, 1H, D_2O exchangeable), 9.55 – 9.18 (m, 2H, D_2O exchangeable), 8.99 – 8.74 (m, 3H), 8.29 – 8.13 (m, 2H), 8.10 (s, 1H), 8.00 (d, *J* = 6.6 Hz, 1H), 7.93 (s, 1H), 7.88 – 7.66 (m, 2H), 7.42 (t, *J* = 9.4 Hz, 1H), 7.39 – 7.22 (m, 1H), 5.93 (s, 1H), 2.73 (s, 2H), 1.36 – 1.06 (m, 1H), 0.53 (m, 2H), 0.43 – 0.10 (m, 2H); ^{1}H NMR (300 MHz, DMSO/D_2O-d_6) δ 8.92 – 8.74 (m, 3H), 8.10 (s, 2H), 7.94 (d, *J* = 5.6 Hz, 2H), 7.94 – 7.84 (m, 1H), 7.81 (s, 1H), 7.75 (d, *J* = 6.9 Hz, 1H), 7.66 – 7.55 (m, 1H), 7.44 (t, *J* = 9.4 Hz, 1H), 7.36 (d, *J* = 7.1 Hz, 1H), 5.85 (s, 1H), 2.98 – 2.68 (m, 2H), 1.19 – 1.00 (m, 1H), 0.71 – 0.52 (m, 2H), 0.31 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.86, -118.92; MS (ES$^+$): MS (ES+) 576.2 (M+1), 610.2 (M+Cl); HPLC: HPLC (Reverse phase, UV Absorbance 260 nm; Rt = 3.010 min (98.17%)]; Optical rotation: $[\alpha]_D$ = (+) 23.40 [0.265, MeOH]; Analysis calculated for: $C_{30}H_{25}F_4N_7O \cdot 3HCl \cdot 4H_2O$: C, 47.60; H, 4.79; Cl, 14.05; N, 12.95; Found: C, 47.41; H, 4.80; Cl, 13.88; N, 12.87.

Scheme 265



Preparation of (-)-1-(1-aminoisoquinolin-7-yl)-N-(5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**265d**)

Step-1: Preparation of (-)-5-(amino(pyridin-4-yl)methyl)-2-fluoroaniline (**265a**)

Compound **265a** was prepared from (R)-N-((R)-(3-amino-4-fluorophenyl)(pyridin-4-yl)methyl)-2-methylpropane-2-sulfinamide (**264c**) (2.61 g, 8.12 mmol) according to the procedure reported in step-3 of scheme-222 for the preparation of compound **222d** to afford after purification by flash column chromatography [silica gel 40 g, eluting with methanol in chloroform, 0-100%] (-)-5-(amino(pyridin-4-yl)methyl)-2-fluoroaniline (**265a**) (1.736 g, 98 % yield) as a reddish yellow oil which was used as such in the next step; MS (ES$^+$): MS (ES+) 218.2 (M+1); MS (ES-) 216.1 (M-1); Optical rotation: $[\alpha]_D$ = (-) 62.35 [0.51, MeOH].

Step-2: Preparation of (-)-5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluoroaniline (**265b**)

Compound **265b** was prepared from (-)-5-(amino(pyridin-4-yl)methyl)-2-fluoroaniline (**265a**) (1.79 g, 8.24 mmol) according to the procedure reported in step-4 of scheme-222 for the preparation of compound **222f** to afford after purification by flash column chromatography (silica gel 40 g, eluting with 0-100% CMA80 in chloroform) (-)-5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluoroaniline (**265b**) (0.089 g, 4 % yield) as a yellow oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 - 8.35 (m, 2H), 7.52 - 7.28 (m, 2H), 6.99 - 6.74 (m, 2H), 6.64 - 6.44 (m, 1H), 5.09 (s, 2H), 4.68 (s, 1H), 2.51 - 2.36 (m, 1H), 2.37 - 2.18 (m, 2H), 1.00 - 0.81 (m, 1H), 0.48 - 0.32 (m, 2H), 0.11 - 0.00 (m, 2H); ^{19}F

NMR (282 MHz, DMSO-d_6) δ -137.26; MS (ES$^+$): MS (ES+) 272.3 (M+1); MS (ES-) 270.3 (M-1).

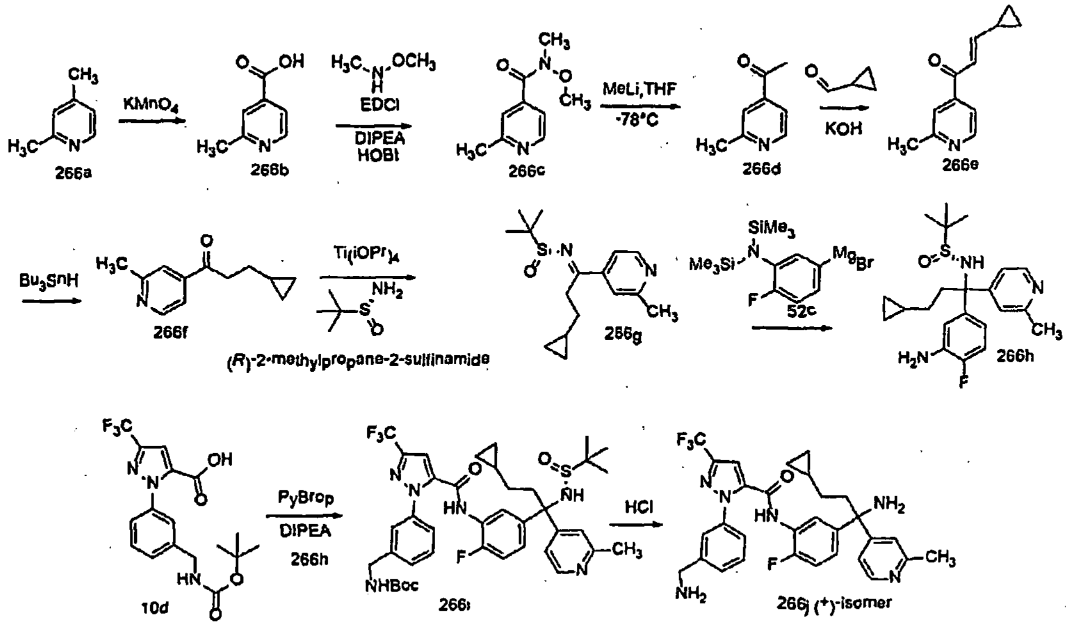
Step-3: Preparation of bis-di-*tert*-butyl 7-(5-(5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**265c**)

Compound **265c** was prepared from 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253c**) (81 mg, 0.155 mmol) and (-)-5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluoroaniline (**265b**) (50 mg, 0.186 mmol) according to the procedure reported in step-3 of scheme 208 for preparation of compound **208c** to afford crude bis-di-*tert*-butyl 7-(5-(5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**265c**) which was used as such in next step.

Step-4: Preparation of (-)-1-(1-aminoisoquinolin-7-yl)-N-(5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**265d**)

To a solution of crude bis-di-*tert*-butyl 7-(5-(5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-ylcarbamate (**265c**) from above step in anhydrous dioxane (5 mL) was added HCl (4N in dioxane, 2mL) and heated at 60 °C for 50min. The reaction mixture was cooled to room temperature and concentrated in vacuum to dryness. The residue obtained was purified by flash column chromatography (silica gel 40 g, eluting with 0-40% CMA-80 in chloroform) to furnish compound **265d** as a free base, which was converted to the HCl salt to afford (-)-1-(1-aminoisoquinolin-7-yl)-N-(5-((cyclopropylmethylamino)(pyridin-4-yl)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**265d**) (25 mg, 0.043 mmol, 28.0 % yield) hydrochloride as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.50 (s, 1H), 10.87 (s, 1H), 10.48 (s, 2H), 9.26 (s, 2H), 8.76 – 8.69 (m, 2H), 8.09 (m, 2H), 8.01 – 7.84 (m, 5H), 7.80 (d, J = 7.0 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.42 (dd, J = 10.3, 8.6 Hz, 1H), 7.33 (d, J = 7.0 Hz, 1H), 5.80 (d, J = 7.2 Hz, 1H), 2.83 – 2.62 (m, 2H), 1.26 – 1.05 (m, 1H), 0.65 – 0.44 (m, 2H), 0.42 – 0.21 (m, 2H); MS (ES+) 576.4 (M+1); 574.4 (M-1); Optical rotation: $[\alpha]_D$ = (-) 16 [0.25, MeOH]; Analysis calculated for $C_{30}H_{25}F_4N_7O.3HCl.3.5H_2O$: C, 48.17; H, 4.72; N, 13.11; Found: C, 48.29; H, 4.70; N, 12.88.

Scheme 266



Preparation of (+)-N-(5-(1-amino-3-cyclopropyl-1-(2-methylpyridin-4-yl)propyl)-2-fluorophenyl)-1-(3-(aminomethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**266j**)

Step-1: Preparation of 2-methyl-isonicotinic acid (**266b**)

To a solution of 2, 4-dimethyl-pyridine (**266a**) (100 g, 933.245 mmol) in water (1000 mL) was added potassium permanganate (294.97 g, 1866.489 mmol) portion-wise over a period of 2 h. The resulting reaction mixture was heated at 80°C for 12 h. The reaction mixture was cooled to room temperature, filtered through celite bed and filtrate was concentrated under reduced pressure to a volume of 250 mL at 50°C. The obtained solution was cooled to 0°C and pH was adjusted to 3 using 1 N HCl (temperature between 0°C to 5°C). The solid obtained was collected by filtration washed with chilled water and dried to afford 2-methylisonicotinic acid (**266b**) (22.3 g, yield: 17.42%); ^{1}H NMR (D_2O) δ 8.52 (s, 1H), 7.94-7.90 (m, 2H), 2.69 (s, 3H); MS (+) 138.1 (M+1).

Step-2: Preparation of N-methoxy-N,2-dimethylisonicotinamide (**266c**)

To a stirred solution of 2-methylisonicotinic acid (**266b**) (17.8 g, 129.798 mmol) in N,N-dimethylformamide (180 mL) was added N,N-diisopropylethylamine (67.105 g, 519.192 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 40.299 g, 259.596 mmol) and hydroxybenzotriazole (HOBt, 39.753 g, 259.596 mmol) at room temperature. The resulting reaction mixture was stirred for 0.5 h at room temperature followed by the addition of N, O dimethyl hydroxyl amine hydrochloride (13.8 g, 141.479 mmol). The reaction mixture was stirred at room temperature for 12 h, quenched with water (500 mL), extracted with ethyl acetate (5 x 500 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue obtained was purified by column chromatography to afford N-methoxy-N,2-dimethylisonicotinamide (**266c**) (23 g, 98.4% yield) as a reddish thick solid; ^{1}H NMR ($CDCl_3$) δ 8.29-8.27 (d, 1H), 7.08 (s, 1H), 7.02-7.01 (d, 1H), 3.27 (s, 3H), 3.07 (s, 3H), 2.32 (s, 3H); MS (ES+) 181.1 (M+1).

Step-3: Preparation of 1-(2-methylpyridin-4-yl)ethanone (**266d**)

To a stirred solution of N-methoxy-N,2-dimethylisonicotinamide (**266c**) (26 g, 144.281mmol) in THF (520 mL) was added MeLi (6.342 g, 288.562 mmol, 1 M solution in THF) under nitrogen atmosphere at -78°C. The reaction mixture was warmed to room temperature over a period of 1 h, quenched with saturated NH_4Cl solution at 0°C. The resulting reaction mixture was extracted with ethyl acetate and the organic layer was washed with water and brine, dried over sodium sulfate, filtered and concentrated. The residue obtained was purified by column chromatography to afford 1-(2-methylpyridin-4-yl)ethanone (**266d**) (11 g, 56.4% yield) as a reddish thick liquid; ^{1}H NMR ($CDCl_3$) δ 8.61-8.59 (d, 1H), 7.51-7.45 (d, 1H), 7.45-7.44 (m, 1H), 2.56 (s, 3H), 2.53 (s, 3H); MS (ES+) 136.1(M+1).

Step-4: Preparation of 3-cyclopropyl-1-(2-methylpyridin-4-yl)prop-2-en-1-one (**266e**)

To a solution of 1-(2-methylpyridin-4-yl)ethanone (**266d**) (11.g, 81.383 mmol) in methanol (110 mL) at 0 °C was added cyclopropane carboxaldehyde (10.039 g, 143.234 mmol), aqueous potassium hydroxide (1N, 0.911 g, 16.276 mmol) and stirred at room temperature for 12 h. The reaction mixture was cooled to 0°C, added 1N Hydrochloric acid (20.5 mL) and concentrated to remove methanol. The obtained residue was partitioned with ethyl acetate and water (75:75 mL). Aqueous layer was separated and extracted with ethyl acetate (2 x 75 mL). The combined organic layer were washed with water (100 mL), brine (100 mL), dried over sodium sulfate, filtered and concentrated. The residue obtained was purified by column chromatography to afford 3-cyclopropyl-1-(2-methylpyridin-4-yl)prop-2-en-1-one (**266e**) (4.5 g, 29.5% yield) as a reddish liquid; MS (ES+) 188.1 (M+1).

Step-5: Preparation of 3-cyclopropyl-1-(2-methylpyridin-4-yl)propan-1-one (**266f**)

Compound **266f** was prepared from 3-cyclopropyl-1-pyridin-4-yl-propenone (**266e**) (8 g, 42.726 mmol) according to the procedure reported in step-2 of scheme 212 as described for preparation of compound **212c** gave after purification by column chromatography 3-cyclopropyl-1-(2-methylpyridin-4-yl)propan-1-one (**266f**) (5.5 g 68.1% yield) as yellow liquid; ^{1}H NMR (CDCl$_3$) δ 8.61-8.59 (d, 1H), 7.53 (s, 1H), 7.47-7.46 (dd, 1H), 3.02-2.97 (m, 2H), 2.58 (s, 3H), 1.60-1.53 (m, 2H), 0.71-0.66 (m, 1H), 0.41-0.37 (m, 2H), 0.05-0.01 (m, 2H); MS (ES+) 190.2 (M+1).

Step-6: Preparation of (R)-N-(3-cyclopropyl-1-(2-methylpyridin-4-yl)propylidene)-2-methylpropane-2-sulfinamide (**266g**)

Compound **266g** was prepared from 3-cyclopropyl-1-(2-methylpyridin-4-yl)propan-1-one (**266f**) (5.5 g, 29.062 mmol) and R-2-methyl propane-2-sulfinamide (4.209g, 34.729 mmol) according to the procedure reported in step-1 of scheme 208 as described for preparation of compound **208a** gave after purification by column chromatography (R)-N-(3-cyclopropyl-1-(2-methylpyridin-4-yl)propylidene)-2-methylpropane-2-sulfinamide (**266g**) (7 g, 82.44% yield) as a yellow liquid; ^{1}H (CDCl$_3$) δ 8.51-8.49 (d, 1H), 7.51-7.33 (m, 2H), 3.35-3.05 (m, 2H), 2.54 (s, 3H), 1.54-1.49 (m, 2H), 1.24 (s, 9H), 0.75-0.61(m, 1H), 0.41-0.31 (m, 2H), 0.05-0.01 (m, 2H); MS (ES+) 293.2 (M+1).

Step-7: Preparation of (R)-N-(1-(3-amino-4-fluorophenyl)-3-cyclopropyl-1-(2-methylpyridin-4-yl)propyl)-2-methylpropane-2-sulfinamide (**266h**)

Compound **266h** was prepared from (R)-N-(3-cyclopropyl-1-(2-methylpyridin-4-yl)propylidene)-2-methylpropane-2-sulfinamide (**266g**) (5.5 g, 29.062 mmol) and R-2-methyl propane-2-sulfinamide (2 g, 6.839 mmol) and freshly prepared (3-(bis(trimethylsilyl)amino)-4-fluorophenyl)magnesium bromide (**52c**) (19.10 mL, 15.28 mmol) according to the procedure reported in step-2 of scheme 208 as described for preparation of compound **208b** gave after purification by column chromatography (R)-N-(1-(3-amino-4-fluorophenyl)-3-cyclopropyl-1-(2-methylpyridin-4-yl)propyl)-2-methylpropane-2-sulfinamide (**266h**) (0.8 g, 29.0% yield) as a reddish thick liquid; ^{1}H NMR (DMSO-d$_6$) δ 8.36-8.34 (d, 1H), 7.24 (s, 1H), 7.12-7.10 (d, 1H), 6.95-6.91 (m, 1H), 6.76-6.72 (m.1H),6.59-6.50 (m, 1H), 5.38-5.32 (m, 1H), 5.11 (s, 2H), 2.49 (s, 3H), 2.05-2.01 (m, 2H), 1.55-1.51 (m, 2H), 1.16 (s, 9H), 0.9-0.85 (m, 1H), 0.39-0.37 (m, 2H), 0.03-0.09 (m, 2H); MS (ES+) 404.3 (M+1).

Step-8: Preparation of *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)-1-(2-methylpyridin-4-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**266i**)

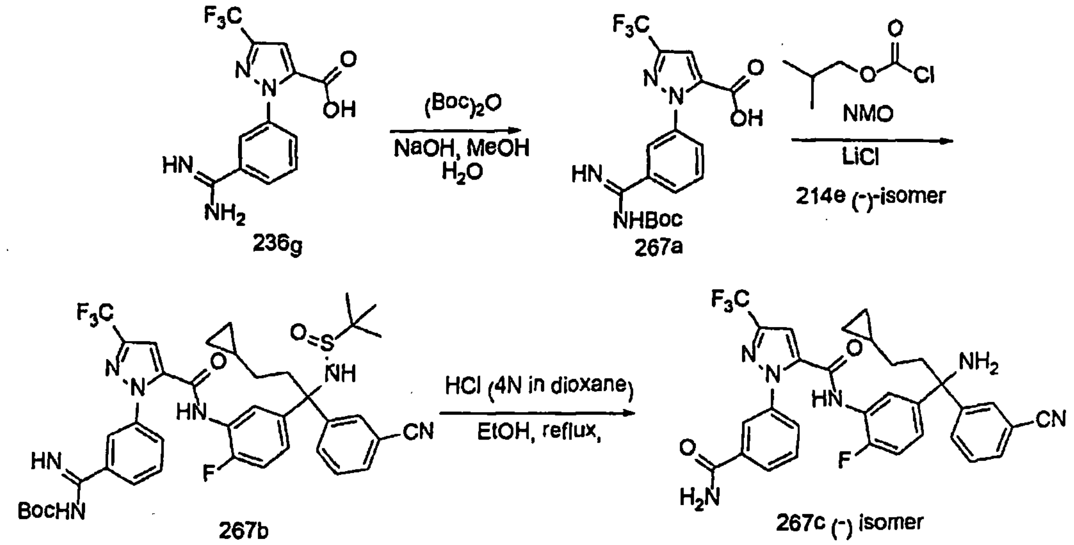
Compound **266i** was prepared from (R)-N-(1-(3-amino-4-fluorophenyl)-3-cyclopropyl-1-(2-methylpyridin-4-yl)propyl)-2-methylpropane-2-sulfinamide (**266h**) (0.5 g, 1.238 mmol) and 1-(3-((*tert*-butoxycarbonylamino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**10d**) (0.573 g, 1.2 mmol) according to the procedure reported in step-3 of scheme 208 as described for preparation of compound **208c** gave after purification by column chromatography of *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)-1-(2-methylpyridin-4-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**266i**) (0.25 g, 26.2% yield) as a reddish thick liquid; ^{1}H NMR (DMSO-d_6) δ 10.66 (s, 1H), 8.42-8.40 (d, 1H), 7.65-7.49 (m, 2H), 7.48-7.28(m, 8H), 7.14(s, 1H), 5.54(s,1H),4.27-4.25 (d, 2H), 2.58 (s, 3H), 1.47-1.45 (m, 2H), 1.5 (s, 9H),1.34-1.31 (m, 2H) 1.2(s, 9H), 0.85-0.71(m, 1H), 0.45-0.35 (m, 2H), 0.03-0.01 (m, 2H); MS (ES+) 771.4 (M+1).

Step-9: Preparation of (+)-N-(5-(1-amino-3-cyclopropyl-1-(2-methylpyridin-4-yl)propyl)-2-fluorophenyl)-1-(3-(aminomethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**266j**)

To a stirred solution of *tert*-butyl 3-(5-(5-(3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)-1-(2-methylpyridin-4-yl)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzylcarbamate (**266i**) (0.25 g, 0.324 mmol) in ethanol (5 mL) was added HCl (4N in MeOH, 20 mL) at room temperature. The resulting reaction mixture was heated to reflux for 1 hour, cooled to room temperature and concentrated in vacuum. The residue obtained was purified twice by flash chromatography (silica, 12g, eluting with 0-100% CMA80 in $CHCl_3$) to (+)-N-(5-(1-amino-3-cyclopropyl-1-(2-methylpyridin-4-yl)propyl)-2-fluorophenyl)-1-(3-(aminomethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**266j**) (65 mg, 35.5% yield) free base as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.29 (d, J = 5.3 Hz, 1H), 7.57 (m, 2H), 7.50 (m, 1H), 7.42 (m, 2H), 7.29 (m, 3H), 7.19 (d, J = 9.6 Hz, 1H), 7.12 (d, J = 6.6 Hz, 1H), 3.77 (s, 2H), 2.40 (s, 3H), 2.31 – 2.08 (m, 4H), 1.09 – 0.78 (m, 2H), 0.70 – 0.52 (m, 1H), 0.40 – 0.27 (m, 2H), 0.03 – -0.14 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.73, -124.10; MS (ES+) 567.3 (M+1); 565.3 (M-1); Optical Rotation $[\alpha]_D$ = (+) 12.38 [0.21, MeOH]. To a solution of free base of compound (**266j**) (50 mg, 0.088 mmol) in MeOH (3 mL) was added HCl (3 N in MeOH) (0.588 mL, 1.765 mmol), stirred for 3h at room temperature and concentrated in vacuum to dryness. The residue was taken up with water/ACN freeze dried to give (+)-N-(5-(1-amino-3-cyclopropyl-1-(2-methylpyridin-4-

yl)propyl)-2-fluorophenyl)-1-(3-(aminomethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**266j**) (56mg, 94% yield) hydrochloride salt as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.93 (s, 1H), 9.78 (s, 3H), 8.77 (d, J = 5.9 Hz, 1H), 8.52 (s, 3H), 7.83 – 7.77 (m, 1H), 7.74 (m, 2H), 7.71 – 7.58 (m, 3H), 7.58 – 7.47 (m, 2H), 7.40 (dd, J = 7.0, 1.5 Hz, 2H), 4.11 (d, J = 5.8 Hz, 2H), 2.65 (s, 3H), 2.63 – 2.50 (m, 2H), 1.32 – 0.94 (m, 2H), 0.67 (m, 1H), 0.48 – 0.24 (m, 2H), 0.01 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.82, -119.73. MS (ES+) 567.3 (M+1), (ES-) 565.4 (M-1).

Scheme 267



Preparation of (-)-N-(5-(1-amino-1-(3-cyanophenyl)-3-cyclopropylpropyl)-2-fluorophenyl)-1-(3-carbamoylphenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**267c**)

Step-1: Preparation of 1-(3-(N-(*tert*-butoxycarbonyl)carbamimidoyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**267a**)

To a solution of 1-(3-carbamimidoylphenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**236g**) (1.2 g, 4.02 mmol) in MeOH-H_2O (50 mL, Ratio: 1:2) was added $(Boc)_2O$ (1.121 g, 4.83 mmol) and sodium hydroxide (0.322 g, 8.05 mmol). The resulting mixture was stirred at room temperature for 12 h. Additional $(Boc)_2O$ (0.878 g, 4.02 mmol) was added and the resulting mixture was stirred for 8 h, diluted with water (100mL) and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried, filtered, and concentrated in vacuum to dryness. The residue obtained was purified by flash column chromatography (silica gel 40 g, eluting with 0-100% CMA-80 in chloroform) to afford 1-(3-(N-(*tert*-butoxycarbonyl)carbamimidoyl)phenyl)-3-(trifluoromethyl)-1Hpyrazole-5-carboxylic acid (**267a**) (205 mg, 0.515 mmol, 12.79 % yield) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.12 – 7.94 (m, 2H), 7.77 – 7.65 (m, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.13 (s, 1H), 1.45 (s, 9H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.45; MS (ES+): 399.4 (M+1), (ES-) 397.3 (M-1).

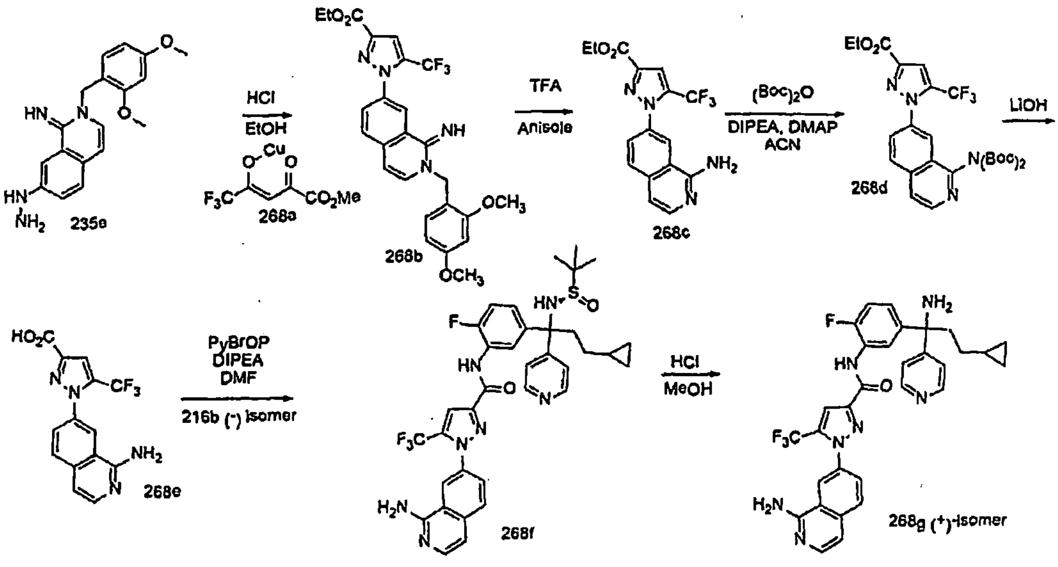
Step-2: Preparation of *tert*-butyl (3-(5-(5-(1-(3-cyanophenyl)-3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)(imino)methylcarbamate (**267b**)

To a solution of 1-(3-(N-(tert-butoxycarbonyl)carbamimidoyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**267a**) (150 mg, 0.377 mmol) in THF (20 mL) at 0 °C was added NMO (44.1 mg, 0.377 mmol), isobutylchloroformate (153 mg, 1.125 mmol) and stirred at 0 °C for 1h. To the reaction mixture was added (R)-N-((-)-1-(3-amino-4-fluorophenyl)-1-(3-cyanophenyl)-3-cyclopropylpropyl)-2-methylpropane-2-sulfinamide (**214e**) (156 mg, 0.377 mmol), lithium chloride (23.95 mg, 0.565 mmol), stirred at 0 °C for 2 h, quenched with water (10 mL) and extracted with ethyl acetate (3 x 20mL). The organic layers were combined, dried, filtered, and concentrated in vacuum to dryness. The residue obtained was purified by flash column chromatography (silica gel 12g, eluting with 0-100% EtOAc in hexane) to *tert*-butyl (3-(5-(5-(1-(3-cyanophenyl)-3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)(imino)methylcarbamate (**267b**) (88 mg, 0.111 mmol, 29.4 % yield) as a white solid; ^{1}H NMR (300 MHz, Chloroform-d) δ 8.09 (m, 1H), 7.90 (s, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.55 (d, J = 7.9 Hz, 2H), 7.47 (m, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.20 (m, 1H), 7.04 (m, 1H), 6.99 – 6.92 (m, 1H), 2.58 (m, 2H), 1.49 (s, 9H), 1.19 (s, 9H), 0.97 – 0.85 (m, 2H), 0.59 (m, 1H), 0.36 (m, 2H), -0.12 (m, 2H); MS (ES+): 794.6 (M+1); IR (KBr) 2232cm^{-1}

Step-3: Preparation of (-)-N-(5-(1-amino-1-(3-cyanophenyl)-3-cyclopropylpropyl)-2-fluorophenyl)-1-(3-carbamoylphenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**267c**)

To a solution of to *tert*-butyl (3-(5-(5-(1-(3-cyanophenyl)-3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)propyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)(imino)methylcarbamate (**267b**) (70 mg, 0.088 mmol) in EtOH (10 mL) was added HCl (4N in dioxane) (0.220 mL, 0.882 mmol) and heated at reflux for 10 min. The solution was concentrated under vacuum to dryness and the residue obtained was purified by flash column chromatography (silica gel, eluting with 0-100% CMA80 in chloroform) to furnish compound **267c** (17 mg, 0.029 mmol) free base as a white solid. The free base was converted into HCl salt by using HCl (4N in dioxane, 0.1 mL) and freeze dried to afford (-)-N-(5-(1-amino-1-(3-cyanophenyl)-3-cyclopropylpropyl)-2-fluorophenyl)-1-(3-carbamoylphenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**267c**), 17 mg, 0.027 mmol, 30.7 % yield) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.73 (s, 1H), 9.26 (s, 3H), 8.16 (s, 1H), 8.04 – 7.98 (m, 2H), 7.89 (dt, J = 7.3, 1.4 Hz, 1H), 7.83 (s, 1H), 7.71 – 7.54 (m, 7H), 7.42 (dd, J = 10.1, 8.8 Hz, 1H), 7.29 – 7.19 (m, 1H), 2.50 (dp, J = 39.9, 1.8 Hz, 2H), 1.06 (tt, J = 12.3, 5.3 Hz, 2H), 0.77 – 0.59 (m, 1H), 0.48 – 0.29 (m, 1H), -0.02 (s, 2H); ^{19}F NMR (282 MHz, MeOH-d_4) δ -64.55, -128.38; MS (ES+) 613.5 (M+Na); IR (KBr) 2235cm^{-1}; Analysis calculated for $C_{31}H_{26}F_4N_6O_2.HCl.2.75H_2O$; C, 55.03; H, 4.84; N, 12.42; Found: C, 55.30; H, 4.81; N, 12.00; Optical rotation: $[\alpha]_D$ = (-) 3.2 [0.125, MeOH].

Scheme 268



Preparation of (+)-N-(5-(1-amino-3-cyclopropyl-1-(pyridin-4-yl)propyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxamide (**268g**)

Step-1: Preparation of ethyl 1-(2-(2,4-dimethoxybenzyl)-1-imino-1,2-dihydroisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (**268b**)

To a solution of 2-(2,4-dimethoxybenzyl)-7-hydrazinylisoquinolin-1(2H)-imine hydrochloride (**235e**) (13.434 g, 41.4 mmol) in ethanol (50 mL) was added the copper complex (**268a**) (prepared according to *Russian Chemical Bulletin*, **1990**, 1273-1277) (10.79 g, 41.4 mmol). The resulting mixture was cooled to 0 °C, added conc. HCl (15.10 g, 414 mmol) and stirred at room temperature overnight. Additional HCl (7.02 g, 193 mmol) was added and reaction mixture was heated at reflux overnight, cooled to room temperature and concentrated in vacuum. The residue was purified by flash column chromatography (silica gel, eluting with CMA80 in chloroform 0-70%) to afford ethyl 1-(1-aminoisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (**268c**) (1.90 g, 5.42 mmol, 13.10 % yield) and ethyl 1-(2-(2,4-dimethoxybenzyl)-1-imino-1,2-dihydroisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (**268b**) (4.1 g, 8.19 mmol, 19.78 % yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.76 – 7.55 (m, 3H), 7.27 (d, J = 7.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 2.3 Hz, 1H), 6.48 (dd, J = 8.4, 2.3 Hz, 1H), 6.21 (d, J = 7.4 Hz, 1H), 4.97 (s, 2H), 4.35 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{19}F NMR (282 MHz, DMSO) δ -56.85.

Step-2: Preparation of ethyl 1-(1-aminoisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (**268c**)

Compound **268c** was prepared from ethyl 1-(2-(2,4-dimethoxybenzyl)-1-imino-1,2-dihydroisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (**268b**) (4.1 g, 8.19 mmol) according to the procedure reported for the preparation of compound **253a**, step-1 scheme-253 gave after purification by column chromatography (silica gel, eluting with CMA80 in chloroform 0-40%) ethyl 1-(1-aminoisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (**268c**) (2.4 g, 6.85 mmol, 84 % yield) as an off white solid; ^{1}H NMR (300 MHz, Chloroform-d) δ 8.49 (s, 1H), 7.86 (q, J = 8.6 Hz, 2H), 7.52 (d, J = 6.5 Hz, 1H), 7.36 (s, 1H), 7.02 (d, J = 6.1 Hz, 1H), 4.38 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H).

Step-3: Preparation of ethyl 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (**268d**)

To a solution of ethyl 1-(1-aminoisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (**268c**) (1.90 g, 5.42 mmol) in acetonitrile (75 mL) was added DIPEA (4.74 mL, 27.1 mmol), Boc anhydride (3.55 g, 16.27 mmol), DMAP (0.066 g, 0.542 mmol) and stirred at room temperature overnight. Additional Boc anhydride (2.368 g, 10.85 mmol) were added, and the reaction mixture was heated at 60 °C for 4 h. The reaction mixture was cooled to room temperature, added Boc anhydride (1.776 g, 8.14 mmol) and heated at 50 °C overnight. The reaction mixture was evaporated to dryness, treated with brine (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organics were dried over $MgSO_4$, filtered, evaporated to dryness and the residue obtained was purified by flash column chromatography (silica gel 40 g, eluting with 0-40% ethyl acetate in hexane) to afford ethyl 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (**268d**) (647 mg, 1.175 mmol, 21.67 % yield) as a white semi-solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.57 (d, *J* = 5.7 Hz, 1H), 8.16 (s, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.87 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.78 (d, *J* = 5.7 Hz, 1H), 7.42 (s, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.32 (s, 18H).

Step-4: Preparation of 1-(1-aminoisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid (**268e**)

To a solution of ethyl 1-(1-(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (**268d**) (544 mg, 0.988 mmol) in THF/H_2O (30 mL, Ratio: 3:1) at room temperature was added lithium hydroxide monohydrate (415 mg, 9.88 mmol) and heated at 67 °C overnight. The reaction mixture was diluted with EtOAc (35 mL), organic layer was separated and the aqueous layer was acidified with conc. HCl to pH 2. The white precipitate obtained was collected by filtration, washed with water (2 x 5 mL), dried in vacuum to furnish 1-(1-aminoisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid (**268e**) (295 mg, 93%) as a white solid. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.52 (s, 1H), 7.98 – 7.86 (m, 2H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.61 (s, 1H), 7.25 (s, 2H), 7.06 (d, *J* = 5.7 Hz, 1H); ^{19}F NMR (282 MHz, DMSO) δ -56.71; MS (ES+) 323 (M+1), (ES-) 321 (M-1).

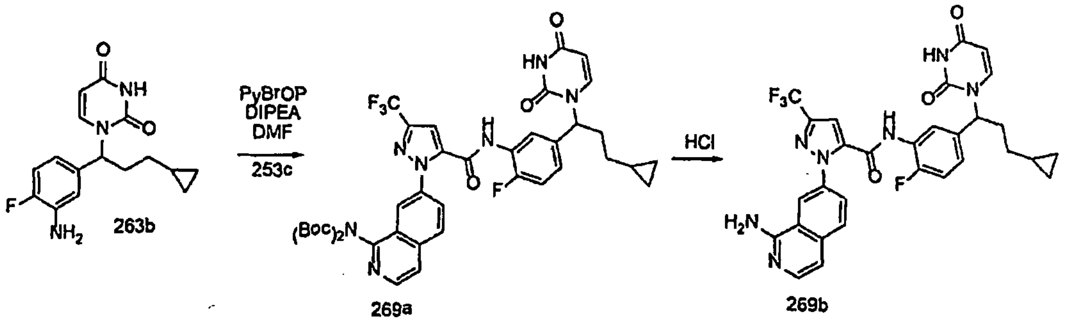
Step-5: Preparation of 1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)-1-(pyridin-4-yl)propyl)-2-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxamide (**2368f**)

Compound **268f** was prepared from 1-(1-aminoisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid (**268e**) (100 mg, 0.310 mmol) and (R)-N-((-)-1-(3-amino-4-fluorophenyl)-3-cyclopropyl-1-(pyridin-4-yl)propyl)-2-methylpropane-2-sulfinamide (**216b**) (121 mg, 0.310 mmol) using procedure reported in step-3 of scheme-208 to furnish after purification by column chromatography (silica gel, eluting with 0-40% CMA80 in $CHCl_3$) 1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)-1-(pyridin-4-yl)propyl)-2-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxamide (**268f**) (120 mgs) which was used as such without further purification.

Step-6: (+)-N-(5-(1-amino-3-cyclopropyl-1-(pyridin-4-yl)propyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxamide (**268g**)

To a solution of 1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-((R)-1,1-dimethylethylsulfinamido)-1-(pyridin-4-yl)propyl)-2-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxamide (**268f**) (120 mg, 0.173 mmol) in ethanol (10 mL) was added HCl (32mg, 0.865 mmol) and heated at reflux for 3 h. The reaction mixture was cooled to room temperature, concentrated in vacuum and purified by flash column chromatography (silica gel, eluting with chloroform in CMA80 0-40%) to give (+)-N-(5-(1-amino-3-cyclopropyl-1-(pyridin-4-yl)propyl)-2-fluorophenyl)-1-(1-aminoisoquinolin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxamide (**268g**) (7 mg, 0.012 mmol, 6.86 % yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.54 (d, J = 2.3 Hz, 1H), 8.49 - 8.41 (m, 2H), 7.96 - 7.89 (m, 2H), 7.86 - 7.76 (m, 1H), 7.68 (s, 1H), 7.63 (dd, J = 7.5, 2.4 Hz, 1H), 7.43 - 7.38 (m, 2H), 7.32 (m, 1H), 7.19 (dd, J = 10.2, 8.6 Hz, 1H), 7.03 (d, J = 5.1 Hz, 3H), 2.34 (s, 2H), 2.23 (m, 2H), 1.06 (m, 2H), 0.64 (m, 1H), 0.44 - 0.31 (m, 2H), -0.01 - -0.15 (m, 2H); ^{19}F NMR (282 MHz, DMSO) δ -56.82, -124.34; MS (ES+) 590.3 (M+1); (ES-) 588.3 (M-1); Optical rotation: $[\alpha]_D$ = (+) 10.67 [0.225, MeOH].

Scheme 269



Preparation of 1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**269b**)

Step-1: Preparation of 1-(1-bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**269a**)

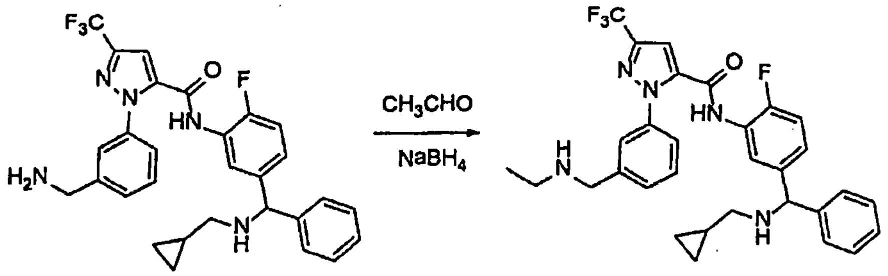
Compound **269a** was prepared from 1-(1-(3-amino-4-fluorophenyl)-3-cyclopropylpropyl)pyrimidine-2,4(1H,3H)-dione (**263b**) (163 mg, 0.537 mmol) and 1-(1-

(bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**253c**) (337 mg, 0.645 mmol) according to the procedure reported in step-3 of scheme 208 for preparation of compound **208c** to afford after purification by flash column chromatography [silica gel 40 g, eluting with 0-90% EtOAc/MeOH (9:1, v/v) in hexane] 1-(1-bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**269a**) (55 mg, 0.068 mmol, 12.7 % yield) as a white solid; MS (ES^+), 830.4 (M+Na); (ES^-) 806.4 (M-1).

Step-2: Preparation of 1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**269b**)

To a solution of 1-(1-bis(*tert*-butoxycarbonyl)amino)isoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**269a**) (55 mg, 0.068 mmol) in MeOH (15 mL) was added HCl (3 N in MeOH) (0.45 mL, 1.36 mmol) and stirred at room temperature overnight. The reaction was concentrated in vacuum and the residue obtained was purified by flash column chromatography (silica gel 24 g, eluting with 0-40% CMA80 in $CHCl_3$) to furnish 1-(1-aminoisoquinolin-7-yl)-N-(5-(3-cyclopropyl-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**269b**) (9.0 mg, 0.015 mmol, 41.4% yield) as a white solid; ^1H NMR (300 MHz, DMSO-d_6) δ 11.36 (s, 1H), 10.60 (s, 1H), 8.42 (s, 1H), 7.88 (d, J = 5.7 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.74 – 7.63 (m, 3H), 7.52 (d, J = 7.2 Hz, 1H), 7.29 (d, J = 7.9 Hz, 2H), 6.98 (m, 3H), 5.57 (m, 2H), 2.31 – 1.98 (m, 2H), 1.32 – 0.95 (m, 2H), 0.78 – 0.57 (m, 1H), 0.47 – 0.29 (m, 2H), 0.13 – -0.12 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.73, -121.27.

Scheme 270



42b (-)-isomer

270a (-)-isomer

Preparation of (-)-N-(5-((cyclopropylmethylamino)(phenyl)methyl)-2-fluorophenyl)-1-(3-((ethylamino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**270a**)

To a solution of (-)-1-(3-(aminomethyl)phenyl)-N-(5-((cyclopropylmethylamino)(phenyl)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**42b**) (0.25 g, 0.46 mmol) in MeOH (10 mL) was added acetaldehyde (0.16 mL, 2.8 mmol) and stirred at room temperature for 10 mins. To the reaction mixture was added sodium borohydride (0.035 g, 0.93 mmol) and continued stirring at room temperature for 6 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuum. The residue obtained was purified by flash chromatography [silica gel 24 g, eluting with 0 to 30% CMA80 in chloroform) to afford compound **270a** (0.11 g, 0.194 mmol, 41.8 % yield) free base as a white solid; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 10.53 (s, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.56 (s, 1H), 7.50 - 7.24 (m, 9H), 7.22 - 7.14 (m, 2H), 4.83 (s, 1H), 3.73 (s, 2H), 2.45 (m, 2H), 2.26 (d, J = 6.6 Hz, 2H), 0.96 (m, 4H), 0.43 - 0.30 (m, 2H), 0.04 (m, 2H); 19F NMR (282 MHz, DMSO-d6) δ -60.54, -123.79; MS (ES+) 566.4 (M+1); MS (ES-) 564.4 (M-1), 600.3 (M+Cl); The free base (0.7 g) was converted to HCl salt using 3 N HCl (5 eq) to obtain (-)-N-(5-((cyclopropylmethylamino)(phenyl)methyl)-2-fluorophenyl)-1-(3-((ethylamino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (**270a**) hydrochloride as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.16 (s, 2H), 9.20 (s, 2H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.80 – 7.11 (m, 12H), 5.75 – 5.57 (m, 1H), 4.21 (t, *J* = 5.8 Hz, 2H), 3.05 – 2.83 (m, 2H), 2.70 (m, 2H), 1.18 (m, 4H), 0.60 – 0.50 (m, 2H), 0.29 (m, 2H); Optical rotation: $[\alpha]_D$ = (-) 3.57 [0.28, MeOH].

Example 271

Plasma kallikrein activity assay. The effect of compounds of the invention on human plasma kallikrein activity was determined using the chromogenic substrates (DiaPharma Group, Inc., West Chester, OH, USA). In these experiments, 2 nM kallikrein (Enzyme Research Laboratories, South Bend, IN, USA) was incubated with 80 μM S2302 (H-D-Pro-Phe-Arg-p-nitroaniline) in the absence or presence of increasing concentrations of compounds of the invention in a final volume of 200 μL Tris-HCl buffer (200 mM NaCl; 2.5 mM $CaCl_2$; 50 mM Tris-HCl, pH 7.8).

After incubation at 30 °C, the activity of kallikrein was measured as a change in absorbance at OD 405 nm using BioTek PowerWave X340 Microplate Reader (Winooski, VT, USA). Data were analyzed using SigmaPlot software (Systat Software, Inc., San Jose, CA, USA) (Four Parameter Logistic Curve). Ki values for the inhibitors were determined using the Cheng–Prusoff equation (*Biochem. Pharmacol.* 1973, 22, 3099).

The compounds disclosed in this application have Ki values less than 1 micromolar (μM) for the plasma kallikrein enzyme. See **Table 1.**

Table 1. Measured Ki values for compounds.

Compound	Ki (nM)
161e	>100
162c	>100
163g	>100
17d	>100
18f	>100
19d	>100
20d	>100
18g	>50-100
22b	>100
23c	>100
24c	>100
25b	>50-100
25c	>100
26f	>100
18i	>50-100
18h	>50-100
21e	>100
18j	>100
18k	0.1-50
27f	>50-100

Compound	Ki (nM)
28f	>100
29e	0.1-50
30g	>100
31f	>100
32f	>50-100
33e	>100
33f	>100
34d	>100
35g	>50-100
34c	0.1-50
18e	>100
81c	>100
39e	>100
40b	>100
41e	0.1-50
74a	0.1-50
75a	>50-100
38d	0.1-50
76h	>100
36d	0.1-50

Compound	Ki (nM)
77e	0.1-50
43f	0.1-50
44c	0.1-50
78d	0.1-50
79f	0.1-50
80h	0.1-50
87f	0.1-50
88b	0.1-50
82f	0.1-50
83c	0.1-50
46g	0.1-50
205f	>100
89g	0.1-50
91a	0.1-50
86g	0.1-50
45g	0.1-50
47f	0.1-50
92g	0.1-50
84h	0.1-50
85c	0.1-50

Compound	Ki (nM)
93b	>100
94b	0.1-50
95i	0.1-50
96f	0.1-50
48f	0.1-50
164e	0.1-50
97f	>100
98b	0.1-50
99g	0.1-50
100e	0.1-50
101e	0.1-50
102b	0.1-50
103b	0.1-50
104f	0.1-50
105g	0.1-50
49h	0.1-50
106a	0.1-50
50f	0.1-50
107f	0.1-50
108e	0.1-50

Compound	Ki (nM)
109f	0.1-50
110f	0.1-50
111f	0.1-50
112g	0.1-50
113f	0.1-50
114f	0.1-50
115e	>50-100
116e	0.1-50
117e	0.1-50
118f	0.1-50
119e	0.1-50
120e	0.1-50
122g	0.1-50
121f	0.1-50
123g	0.1-50
124f	0.1-50
51f	0.1-50
125g	0.1-50
126g	0.1-50
127f	0.1-50

Compound	Ki (nM)
128g	0.1-50
129f	0.1-50
130g	0.1-50
131b	0.1-50
132f	0.1-50
133g	0.1-50
134f	0.1-50
135c	0.1-50
136a	>100
137a	0.1-50
137b	>100
138f	0.1-50
52h	0.1-50
139b	0.1-50
140e	0.1-50
167f	>100
141e	0.1-50
142f	0.1-50
143l	0.1-50
144d	0.1-50

Compound	Ki (nM)
145c	>100
146g	0.1-50
147e	0.1-50
148b	0.1-50
149b	0.1-50
53f	0.1-50
150f	0.1-50
153b	0.1-50
151g	0.1-50
152d	0.1-50
154e	0.1-50
155c	0.1-50
156c	0.1-50
54e	0.1-50
55b	0.1-50
58c	0.1-50
56c	0.1-50
68c	0.1-50
61e	0.1-50
59c	0.1-50

Compound	Ki (nM)
57e	0.1-50
60e	0.1-50
71a	0.1-50
71b	0.1-50
65a	0.1-50
65b	0.1-50
192f	0.1-50
168b	0.1-50
169b	>100
170b	>100
171b	>100
172b	>100
173b	>100
174b	>100
175b	>100
176b	>100
177b	>100
178b	>100
179b	>100
180b	>100

Compound	Ki (nM)
181b	>100
182b	>100
183b	>100
184b	>100
185b	>100
186b	>100
187b	>100
188b	0.1-50
189b	>100
190b	>100
193f	0.1-50
191b	>100
195f	0.1-50
196f	0.1-50
197f	0.1-50
198f	0.1-50
194f	0.1-50
199f	0.1-50
200f	0.1-50
201f	0.1-50

Compound	Ki (nM)
202f	0.1-50
203f	>100
157a	>100
158a	>100
159a	>100
160a	>100
207j	0.1-50
247c	0.1-50
247e	0.1-50
248j	0.1-50
249b	0.1-50
250c	0.1-50
252c	0.1-50
251e	>50-100
260b	0.1-50
262f	0.1-50
263d	0.1-50
15g	>100
16b	>100
90f	>100

Compound	Ki (nM)
166e	0.1-50
165e	0.1-50
50g	0.1-50
50h	0.1-50
43g	0.1-50
43h	0.1-50
44d	0.1-50
44e	0.1-50
47g	0.1-50
47h	0.1-50
46h	0.1-50
46i	0.1-50
48g	0.1-50
48h	0.1-50
51g	0.1-50
51h	0.1-50
64a	0.1-50
64b	0.1-50
49i	0.1-50
49j	0.1-50

Compound	Ki (nM)
42b	0.1-50
42a	0.1-50
67a	0.1-50
67b	0.1-50
70a	0.1-50
70b	0.1-50
69a	0.1-50
69b	0.1-50
68d	0.1-50
68e	0.1-50
63a	0.1-50
63b	0.1-50
73a	0.1-50
73b	0.1-50
72c	0.1-50
72d	0.1-50
66a	0.1-50
66b	0.1-50
37b	0.1-50
37a	0.1-50

Compound	Ki (nM)
206d	0.1-50
205d	0.1-50
205e	0.1-50
208d	0.1-50
209d	0.1-50
210d	0.1-50
211d	0.1-50
212g	0.1-50
214g	0.1-50
213d	0.1-50
222k	>100
223f	>100
220f	0.1-50
224b	>100
225a	0.1-50
226a	>100
227d	0.1-50
228a	0.1-50
229i	0.1-50
230a	>100

Compound	Ki (nM)
231d	0.1-50
232a	>100
246f	0.1-50
234d	>100
235g	0.1-50
218c	0.1-50
219c	0.1-50
239d	>100
267c	>100
240b	0.1-50
236h	0.1-50
237a	0.1-50
238c	0.1-50
241a	0.1-50
215d	>100
238d	0.1-50
221i	0.1-50
216d	0.1-50
243a	0.1-50
217d	>50-100

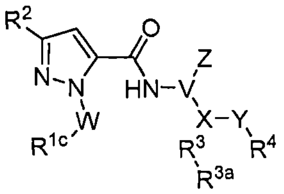
Compound	Ki (nM)
244g	0.1-50
244h	0.1-50
244i	0.1-50
244j	0.1-50
244k	0.1-50
253e	0.1-50
245c	0.1-50
257b	0.1-50
254c	0.1-50
255a	0.1-50
265d	0.1-50
256a	0.1-50
268g	>50-100
258g	0.1-50
248l	0.1-50
248k	0.1-50
264g	0.1-50
261k	0.1-50
259d	0.1-50
266j	0.1-50
269b	0.1-50
270a	>50-100

EQUIVALENTS

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention.

We Claim:

1. A compound, or a pharmaceutically acceptable salt thereof, represented by formula I:



(I)

wherein:

V is optionally substituted aryl or heteroaryl;

W is optionally substituted aryl or heteroaryl;

X represents CH, C(OH), C(O(C$_1$-C$_6$)alkyl), -C(NH$_2$), -C(NR^{a}R^b), -C(N$_3$), -C(CN), -C(NO$_2$), -C(S(O)$_n$R^a), -C[-C(=O)R^c], -C[-C(=O)R^c], -C[-C(=O)NR^{c}R^d], -C[-C(=O)SR^c], -C[-S(O)R^c], -C[-S(O)$_2$R^c], -C[S(O)(OR^c)], -C[-S(O)$_2$(OR^c)], -C[-SO$_2$NR^{c}R^d], -C(halogen), -C[(C$_1$-C$_8$)alkyl], -C[(C$_4$-C$_8$)carbocyclylalkyl], -C[(C$_1$-C$_8$)substituted alkyl], -C[(C$_2$-C$_8$)alkenyl], -C[(C$_2$-C$_8$)substituted alkenyl], -C[(C$_2$-C$_8$)alkynyl], -C[(C$_2$-C$_8$)substituted alkynyl], -C[aryl(C$_1$-C$_8$)alkyl], C(O)N, CH$_2$N, N , C(O), P(O), -O-, S(O)N, or S(O)$_2$N; provided that:

if X represents CH, then -Y-R^4 represents -H or -OH, or both Y and R^4 are present;

if X represents C(OH), C(O(C$_1$-C$_6$)alkyl), -C(NH$_2$), -C(NR^{a}R^b), -C(N$_3$), -C(CN), -C(NO$_2$), -C(S(O)$_n$R^a), -C[-C(=O)R^c], -C[-C(=O)R^c], -C[-C(=O)NR^{c}R^d], -C[-C(=O)SR^c], -C[-S(O)R^c], -C[-S(O)$_2$R^c], -C[S(O)(OR^c)], -C[-S(O)$_2$(OR^c)], -C[-SO$_2$NR^{c}R^d], -C(halogen), -C[(C$_1$-C$_8$)alkyl], -C[(C$_4$-C$_8$)carbocyclylalkyl], -C[(C$_1$-C$_8$)substituted alkyl], -C[(C$_2$-C$_8$)alkenyl], -C[(C$_2$-C$_8$)substituted alkenyl], -C[(C$_2$-C$_8$)alkynyl], -C[(C$_2$-C$_8$)substituted alkynyl], or -C[aryl(C$_1$-C$_8$)alkyl], then -Y-R^4 is present;

if X represents C(O)N, then -Y-R^4 represents H; or -Y-R^4 represents H, and -R^3-R^{3a} represents H;

if X represents CH$_2$N, then -Y-R^4 represents (C$_1$-C$_6$)alkyl;

if X represents N, then -Y-R^4 represents H, or both Y and R^4 are present; and if X represents C(O) or -O-, then -Y-R^4 is absent;

-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -$CH_2C(O)$-R^4, -CH_2NH-R^4, -CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl]R^4, -heterocyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

Z is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2NH_2, (C_3-C_8)cycloalkyl, $(CH_2)_rOR^a$, NO_2, $(CH_2)_r NR^aR^b$, $(CH_2)_rC(O)R^a$, $NR^aC(O)R^b$, $C(O)NR^cR^d$, $NR^aC(O)NR^cR^d$, -$C(=NR^a)NR^cR^d$, $NHC(=NR^a)NR^cR^d$, NR^aR^b, $SO_2NR^cR^d$, $NR^aSO_2NR^cR^d$, NR^aSO_2-(C_1-C_6)alkyl, $NR^aSO_2R^a$, $S(O)_pR^a$, $(CF_2)_rCF_3$, $NHCH_2R^a$, OCH_2R^a, SCH_2R^a, $NH(CH_2)_2(CH_2)_rR^a$, $O(CH_2)_2(CH_2)_rR^a$, and $S(CH_2)_2(CH_2)_rR^a$; or alternatively Z is a 5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of N, O, and S;

R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, -C(=NH)NH_2, -$CONR^aR^b$, -(C_1-C_6)alkyl$CONR^aR^b$, -SO_2CH_3, formyl, acyl, -NH_2, -C(=NH)NH(OH), -C(=NH)NH(C(O)O-(C_1-C_6)alkyl), -C(=NH)NH(C(O)O-(C_1-C_6)haloalkyl), -C(=NH)NH(C(O)S-(C_1-C_6)alkyl), -C(=NH)NH(C(O)(OCH(C_1-C_6)alkyl)OC(O)(C_1-C_6)alkyl), optionally substituted aryl, or optionally substituted heteroaryl;

R^2 represents halo, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_1-C_6)fluoroalkyl, -OCH_3, -Si$(CH_3)_3$, -$CONH_2$, -C(O)OH, cyano, or phenyl;

R^3, when present, represents -NH-, -O-, optionally substituted aryl, heteroaryl, phenyl, carbocyclyl, or heterocyclyl;

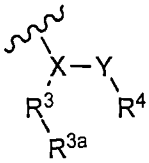
R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2NH_2, (C_3-C_8)cycloalkyl, $(CH_2)_rOR^a$, NO_2, $(CH_2)_r NR^aR^b$, $(CH_2)_rC(O)R^a$,

$NR^aC(O)R^b$, $C(O)NR^cR^d$, $NR^aC(O)NR^cR^d$, $-C(=NR^a)NR^cR^d$, $NHC(=NR^a)NR^cR^d$, NR^aR^b, $SO_2NR^cR^d$, $NR^aSO_2NR^cR^d$, NR^aSO_2-(C_1-C_6)alkyl, $NR^aSO_2R^a$, $S(O)_pR^a$, $(CF_2)_rCF_3$, $NHCH_2R^a$, OCH_2R^a, SCH_2R^a, $NH(CH_2)_2(CH_2)_rR^a$, $O(CH_2)_2(CH_2)_rR^a$, or $S(CH_2)_2(CH_2)_rR^a$; or alternatively R^{3a} is a 5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of N, O, and S;

R^4 represents hydrogen, hydroxy, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, $-CH_2OH$, $-CH((C_1$-$C_6)alkyl)OH$, $-CH(NH_2)CH((C_1$-$C_6)alkyl)_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl, optionally substituted heteroaryl(C_1-C_6)alkyl, $-CH_2S(C_1$-$C_6)alkyl$, amino, or cyano; or $-(CR^aR^b)_r(CR^aR^b)_p-$ fused to the 4-position of the ring bearing Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent $-NR^a-$ fused to the position *ortho* to X on that phenyl;

each R^a and R^b is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, aryl(C_1-C_8)alkyl, (C_3-C_8)carbocyclylalkyl, $-C(=O)R^c$, $-C(=O)OR^c$, $-C(=O)NR^cR^d$, $-C(=O)SR^c$, $-S(O)R^c$, $-S(O)_2R^c$, $-S(O)(OR^c)$, or $-SO_2NR^cR^d$;

each R^c and R^d is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_4-C_8) carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1$-$C_8)alkyl$, $-S(O)_n(C_1$-$C_8)alkyl$, or aryl(C_1-C_8)alkyl; or when R^c and R^d are bonded to a common nitrogen atom, then they may form a 3- to 7-membered heterocyclic ring wherein optionally a carbon atom of said heterocyclic ring may be replaced with -O-, -S- or $-NR^a-$;



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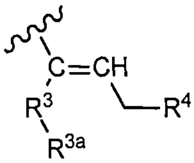

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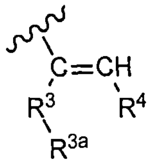

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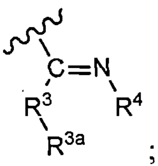


;

n is 2 or 3;

r is independently for each occurrence 0, 1, 2, or 3;

p is independently for each occurrence 0, 1, or 2; and

the stereochemical configuration at any chiral center is *R*, *S*, or a mixture of *R* and *S*.

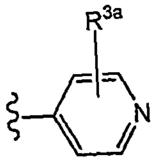
2. The compound of claim 1, wherein X represents CH, and both Y and R^4 are present.

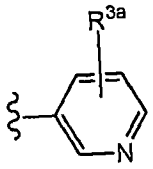
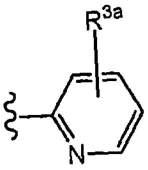
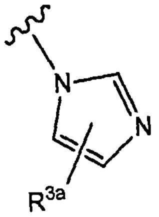
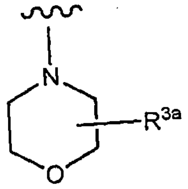
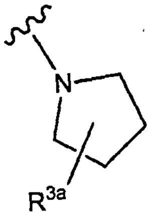
3. The compound of claim 1, wherein -X-Y- represents $-CHNHCH_2-$.

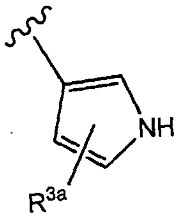
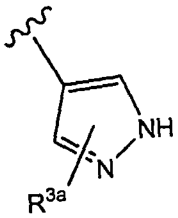
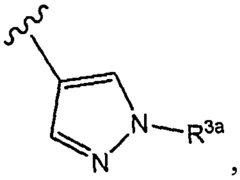
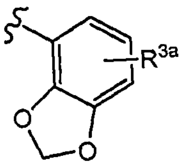
4. The compound of claim 1, wherein -X-Y- represents $-C(OH)CH_2CH_2-$.

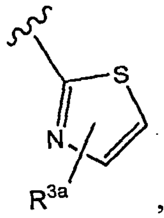
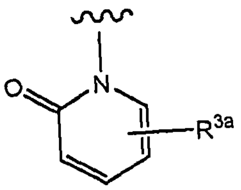
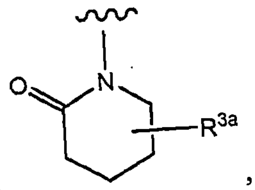
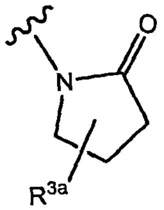
5. The compound of claim 1, wherein -X-Y- represents $-CHOCH_2-$.

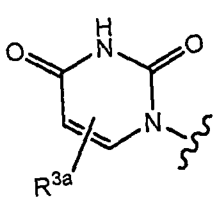
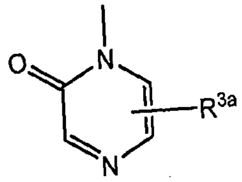
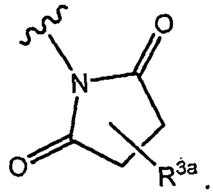
6. The compound of claim 1, wherein R^3 represents phenylene-R^{3a}.

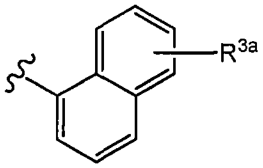
7. The compound of claim 1, wherein $-R^3-R^{3a}$ represents ,

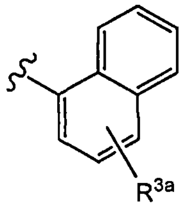
, , , , ,

, , , ,

, , , ,

, , or .

8. The compound of claim 1, wherein $-R^3-R^{3a}$ represents 

or 

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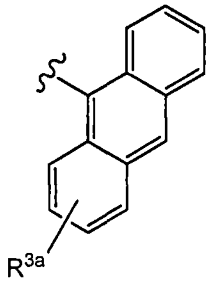
9. The compound of claim 1, wherein $-R^3-R^{3a}$ represents 

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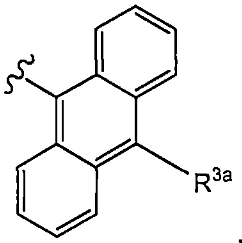
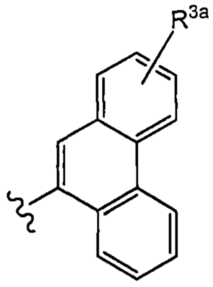
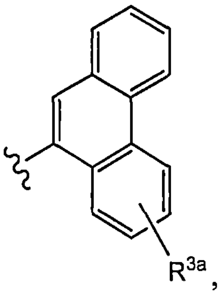
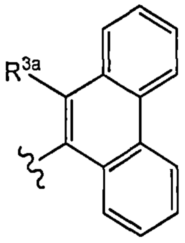


, 

, 

, or 

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10. The compound of claim 1, wherein R^{3a} is absent.

11. The compound of claim 1, wherein R^4 is cyclopropyl.

12. The compound of claim 1, wherein R^3 is phenyl, and R^{3a} is *ortho*, *meta*, or *para* -OH.

13. The compound of claim 1, wherein R^3 is phenyl, and R^{3a} is *ortho*, *meta*, or *para* $-NH_2$.

14. The compound of claim 1, wherein R^3 is phenyl, and R^{3a} is *ortho*, *meta*, or *para* -CN.

15. The compound of claim 1, wherein Z is absent.

16. The compound of claim 1, wherein Z represents fluoro.

17. The compound of claim 1, wherein Z represents chloro.

18. The compound of claim 1, wherein Z represents 2-F, 4-F, 5-F, 6-F, 6-Cl, or 5-(C_3-C_8)cycloalkyl.

19. The compound of claim 1, wherein Z represents 6-F.

20. The compound of claim 1, wherein R^{1c} represents aminomethyl.

21. The compound of claim 1, wherein R^{1c} represents cyano.

22. The compound of claim 1, wherein R^{1c} represents $-SO_2CH_3$.

23. The compound of any one of claims 1-22, wherein R^2 is $-CH_3$ or $-CF_3$.

24. The compound of any one of claims 1-22, wherein R^2 is $-CF_3$.

25. The compound of any one of claims 1-22, wherein R^2 is *tert*-butyl.

26. The compound of any one of claims 1-22, wherein R^2 is cyclopropyl.

27. The compound of any one of claims 1-22, wherein R^2 is $-OCH_3$.

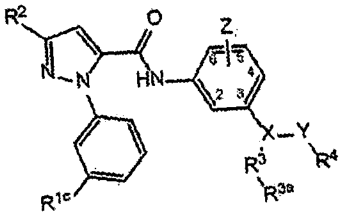
28. The compound of any one of claims 1-22, wherein R^2 is $-Si(CH_3)_3$.

29. The compound of any one of claims 1-22, wherein R^2 is $-CONH_2$.

30. The compound of any one of claims 1-22, wherein R^2 is cyano.

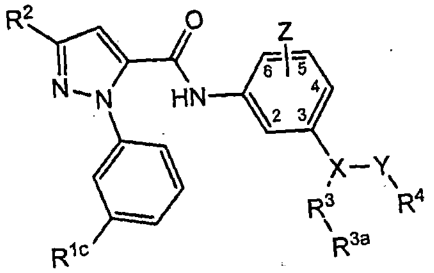
31. The compound of any one of claims 1-22, wherein R^2 is phenyl.

32. The compound of claim 1, or a pharmaceutically acceptable salt thereof represented by formula II:



(II).

33. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula III:



(III)

wherein:

X represents CH, C(OH), C(O(C_1-C_6)alkyl), C(O)N, CH_2N, N, C(O), or -O-;

-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -CH_2C(O)-R^4, -CH_2NH-R^4, -CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl]R^4, -heterocyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

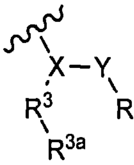
Z is absent or represents halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2NH_2, or (C_3-C_8)cycloalkyl;

R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, -SO_2CH_3, formyl, acyl, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3,

$(C_1\text{-}C_6)$alkoxy, aryl, aryloxy, amino, amino$(C_1\text{-}C_6)$alkyl, $-C(O)NH_2$, cyano, $-NHC(O)(C_1\text{-}C_6)$alkyl, $-SO_2(C_1\text{-}C_6)$alkyl, and $-SO_2NH_2$;

R^4 represents hydrogen, hydroxy, optionally substituted $(C_1\text{-}C_6)$alkyl, optionally substituted $(C_3\text{-}C_8)$cycloalkyl, heterocyclyl$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $-CH_2OH$, $-CH((C_1\text{-}C_6)alkyl)OH$, $-CH(NH_2)CH((C_1\text{-}C_6)alkyl)_2$, optionally substituted aryl, optionally substituted aryl$(C_1\text{-}C_6)$alkyl, heteroaryl, optionally substituted heteroaryl$(C_1\text{-}C_6)$alkyl, $-CH_2S(C_1\text{-}C_6)$alkyl, amino, or cyano ; or $-CH_2-$ fused to the 4-position of the ring bearing Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent -NH- fused to the position *ortho* to X on that phenyl; and



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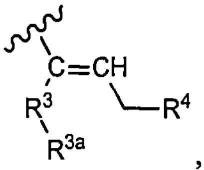

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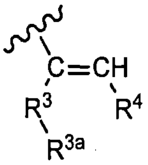

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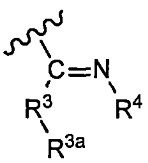

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34. The compound of claim 33, wherein X represents CH, and both Y and R^4 are present.

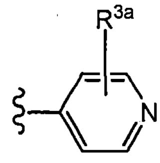
35. The compound of claim 33, wherein -X-Y- represents $-CHNHCH_2-$.

36. The compound of claim 33, wherein -X-Y- represents $-C(OH)CH_2CH_2-$.

37. The compound of claim 33, wherein -X-Y- represents $-CHOCH_2-$.

38. The compound of claim 33, wherein R^3 represents phenylene-R^{3a}.

39. The compound of claim 33, wherein $-R^3-R^{3a}$ represents



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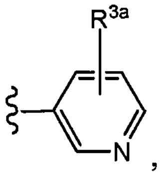

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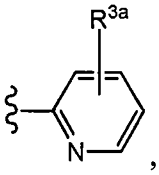

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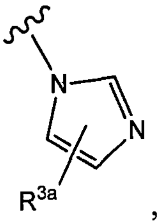

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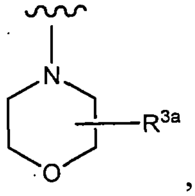

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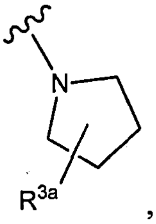

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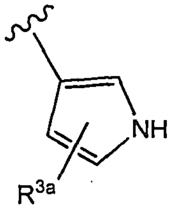
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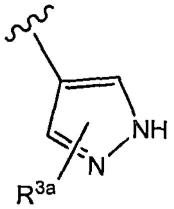
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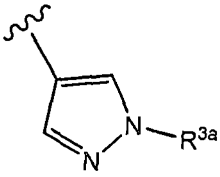
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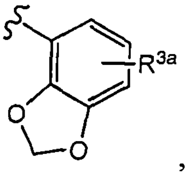
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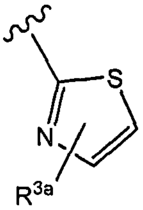
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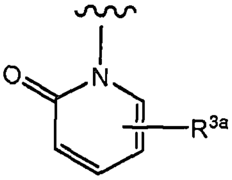
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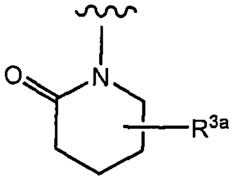
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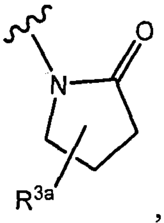
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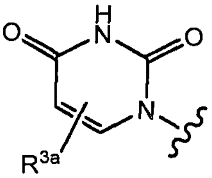
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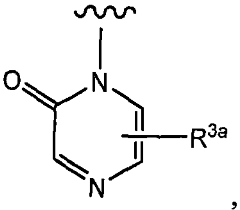
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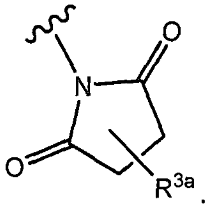
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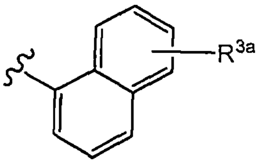
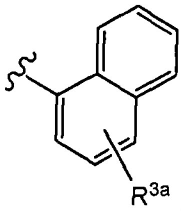
40. The compound of claim 33, wherein $-R^3-R^{3a}$ represents 

or 
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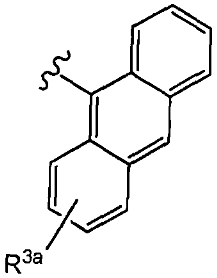
41. The compound of claim 33, wherein $-R^3-R^{3a}$ represents 
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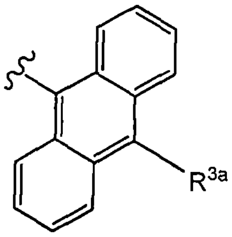
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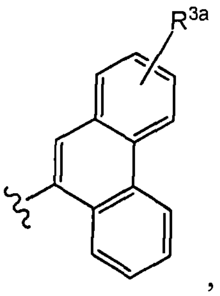
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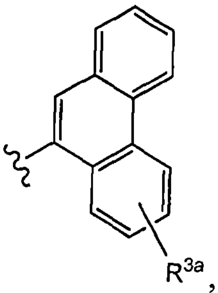
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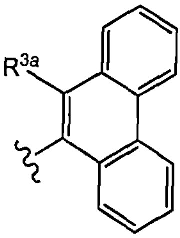

.

42. The compound of claim 33, wherein R^{3a} is absent.

43. The compound of claim 33, wherein R^4 is cyclopropyl.

44. The compound of claim 33, wherein R^3 is phenyl, and R^{3a} is *ortho*, *meta*, or *para* -OH.

45. The compound of claim 33, wherein R^3 is phenyl, and R^{3a} is *meta* or *para* -NH_2.

46. The compound of claim 33, wherein R^3 is phenyl, and R^{3a} is *meta* or *para* -CN.

47. The compound of claim 33, wherein Z is absent.

48. The compound of claim 33, wherein Z represents fluoro.

49. The compound of claim 33, wherein Z represents chloro.

50. The compound of claim 33, wherein Z represents 2-F, 4-F, 5-F, 6-F, 6-Cl, or 5-(C_3-C_8)cycloalkyl.

51. The compound of claim 33, wherein Z represents 6-F.

52. The compound of claim 33, wherein R^{1c} represents aminomethyl.

53. The compound of claim 33, wherein R^{1c} represents cyano.

54. The compound of claim 33, wherein R^{1c} represents -SO_2CH_3.

55. The compound of any one of claims 33-54, wherein R^2 is -CH_3 or -CF_3.

56. The compound of any one of claims 33-54, wherein R^2 is -CF_3.

57. The compound of any one of claims 33-54, wherein R^2 is *tert*-butyl.

58. The compound of any one of claims 33-54, wherein R^2 is cyclopropyl.

59. The compound of any one of claims 33-54, wherein R^2 is -OCH_3.

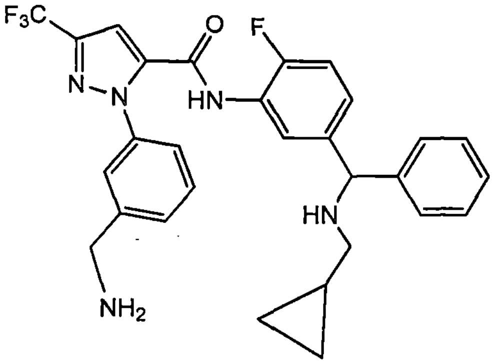
60. The compound of any one of claims 33-54, wherein R^2 is -$Si(CH_3)_3$.

61. The compound of any one of claims 33-54, wherein R^2 is -$CONH_2$.

62. The compound of any one of claims 33-54, wherein R^2 is cyano.

63. The compound of any one of claims 33-54, wherein R^2 is phenyl.

64. The compound of claim 33, wherein said compound is selected from the group consisting of:



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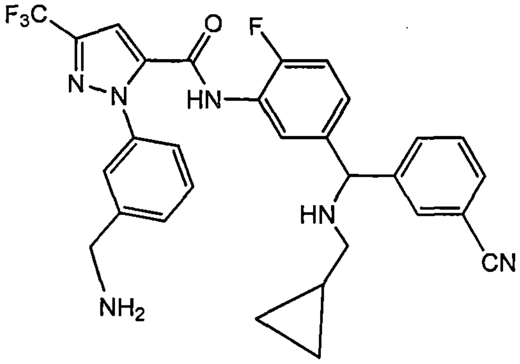

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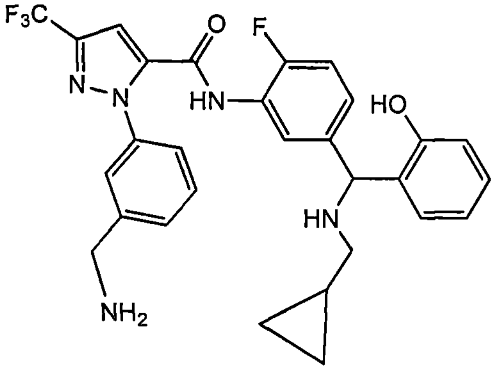

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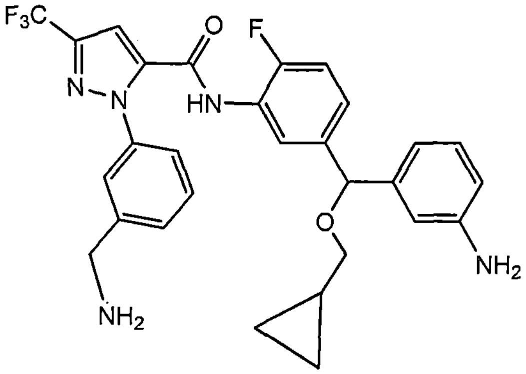

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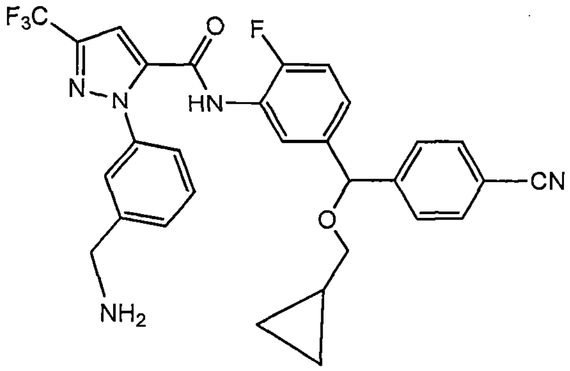

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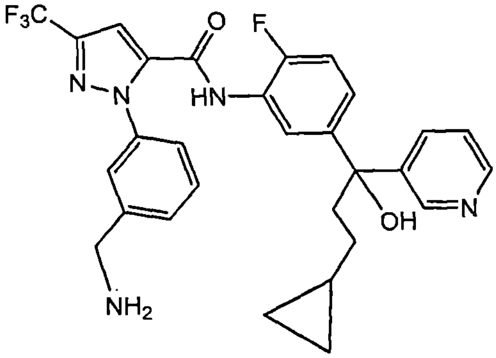

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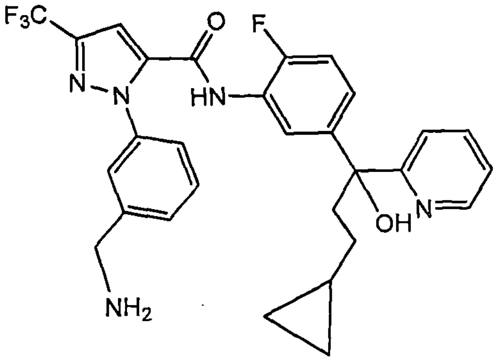

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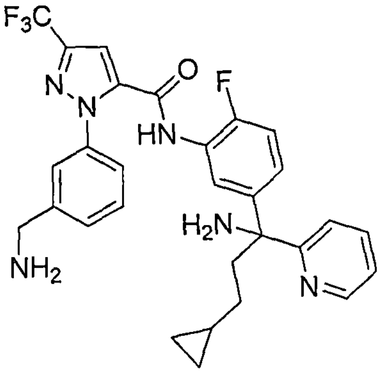
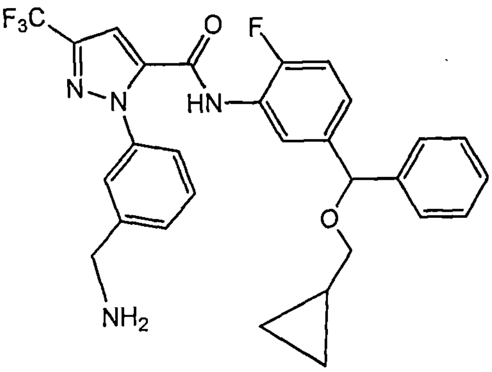


.

65. The compound of claim 33, wherein said compound is selected from the group consisting of:



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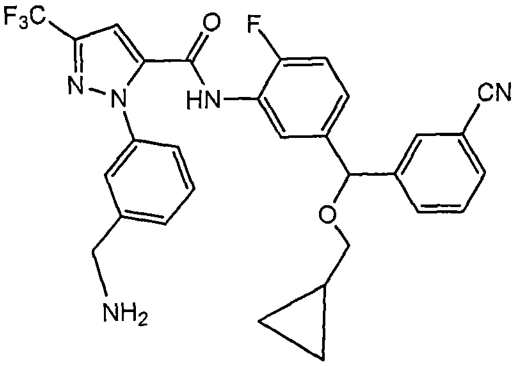

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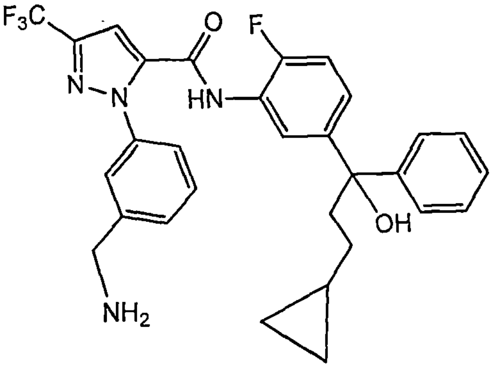

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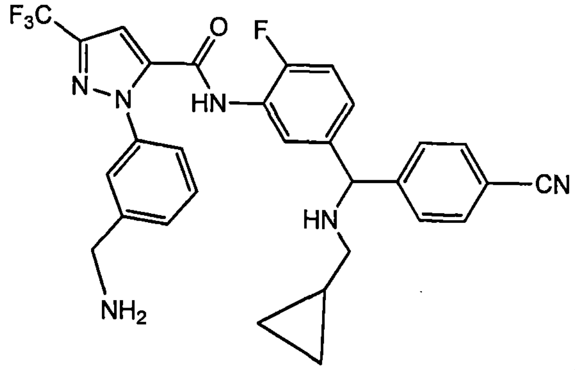
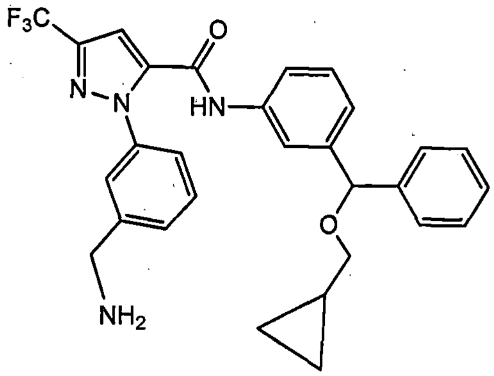
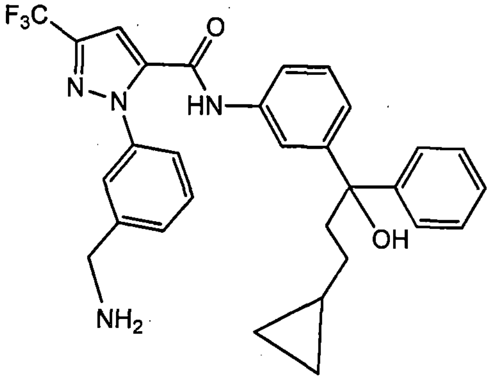

F3C
O
F
N
N
HN
CN
HN
NH2

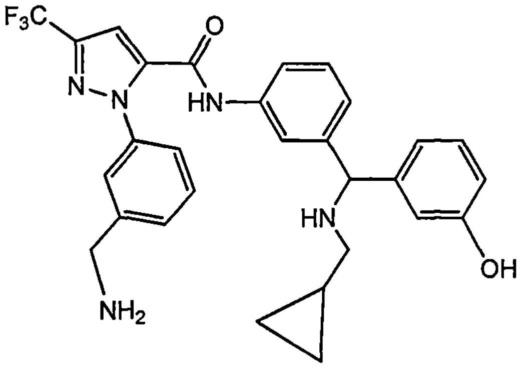
,


F3C
O
N
N
HN
O
NH2

,


F3C
O
N
N
HN
OH
NH2

,



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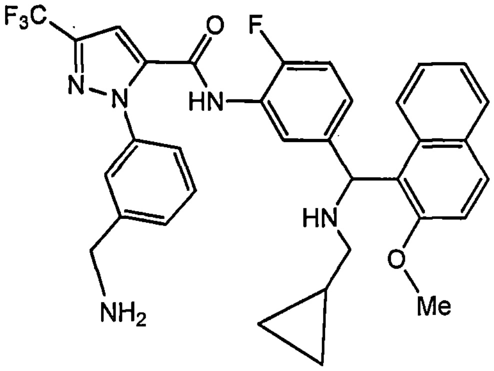
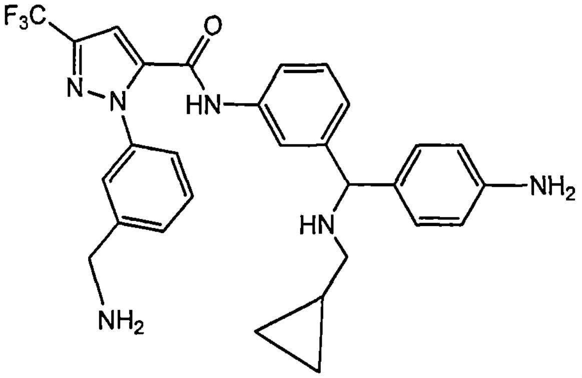


66. The compound of claim 33, wherein said compound is selected from the group consisting of:



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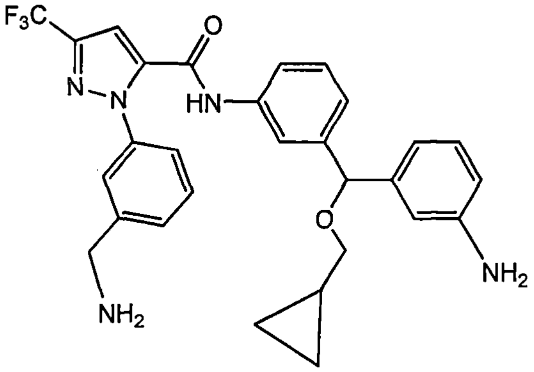

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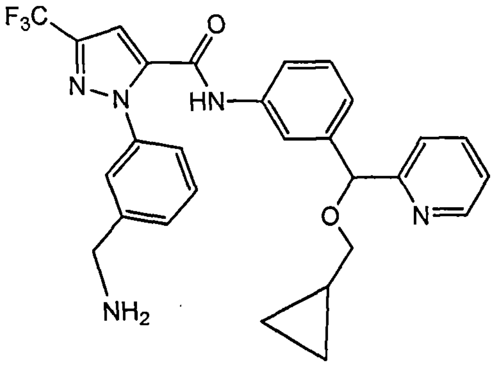
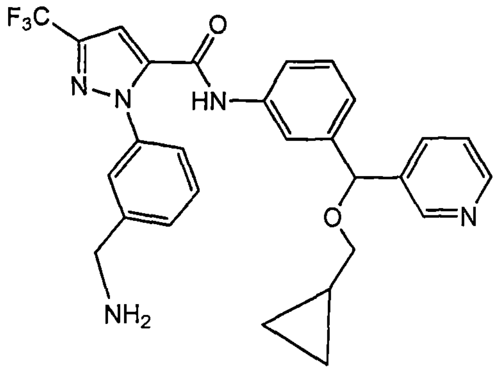

F3C
O
N
N
HN
N
O
NH2

,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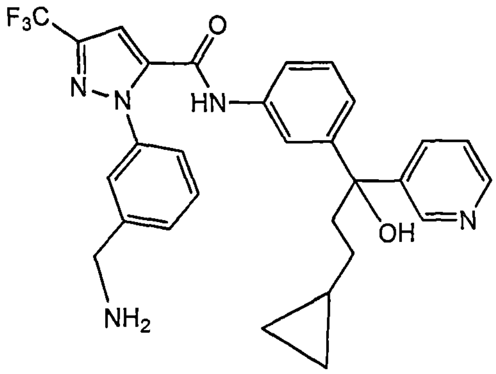
N
N
HN
O
N
NH2

,


F3C
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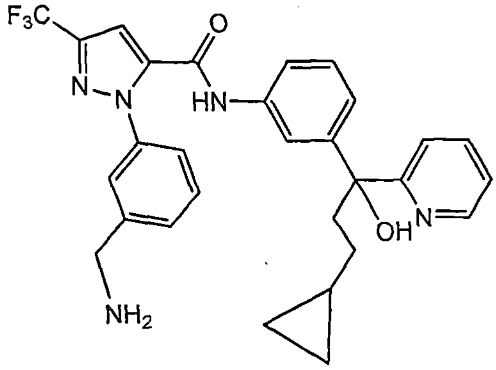
N
HN
OH
N
NH2

,


F3C
O
N
N
HN
OH
N
NH2

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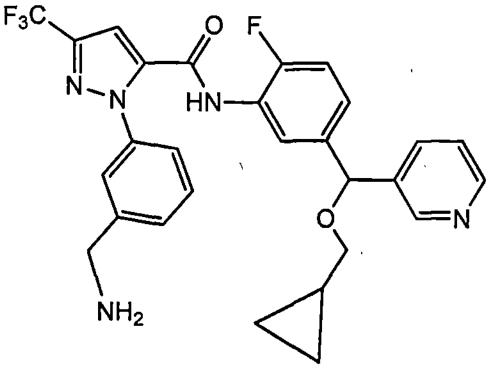

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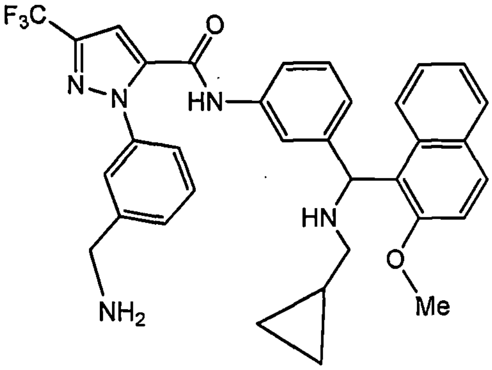

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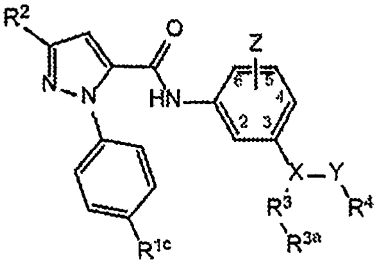
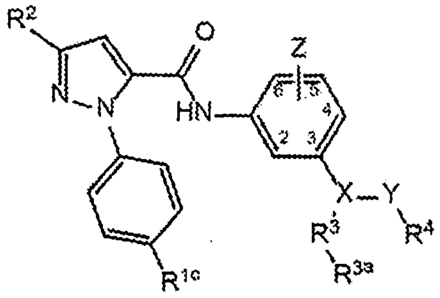
67. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula IV:



(IV).

68. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula V:



(V)

wherein;

X represents CH, C(OH), C(O(C_1-C_6)alkyl), C(O)N, CH_2N, N, C(O), or -O-;

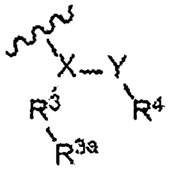
-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -$CH_2C(O)$-R^4, -CH_2NH-R^4, -CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl]R^4, -heterocyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

Z is absent or represents halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl , -SO_2(C_1-C_6)alkyl, -SO_2NH_2, or (C_3-C_8)cycloalkyl ;

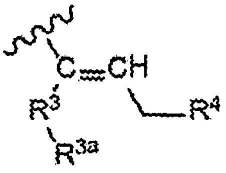
R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, -SO_2CH_3, formyl, acyl, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6)alkyl, -CF_3 , -OCF_3 , (C_1-C_6)alkoxy- aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl and -SO_2NH_2;

R_4 represents hydrogen, hydroxy, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, - CH_2OH, -CH((C_1-C_6)alkyl)OH, -CH(NH_2)CH((C_1-C_6)alkyl)$_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl, optionally substituted heteroaryl(C_1- C_6)alkyl, -CH_2S(C_1-C_6)alkyl, amino, or cyano; or -CH_2- fused to the 4-position of the ring bearing Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or, when R3 is phenyl, can represent -NH - fused to the position *ortho* to X on that phenyl; and



can represent



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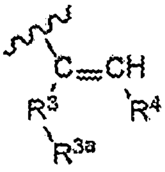

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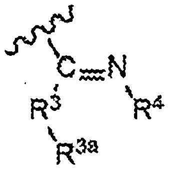

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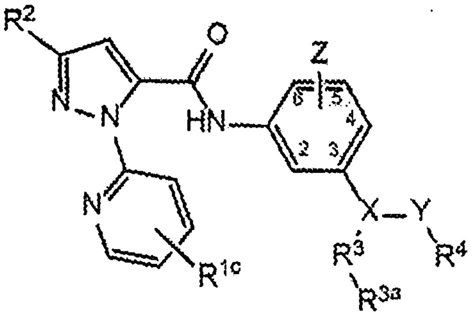
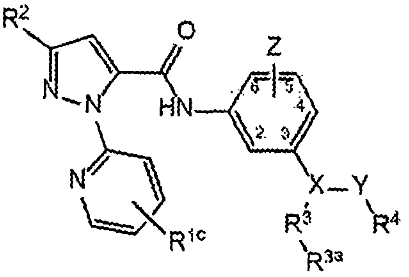
69. The compound of claim 1, or a pharmaceutically acceptable salt thereof represented by formula VI:



(VI).

70. The compound of claim 1, or a pharmaceutically acceptable salt thereof represented by formula VII:



(VII)

wherein:

X represents CH, C(OH), C(O(C_1-C_6)alkyl), C(O)N, CH_2N, N, C(O), or -O-;

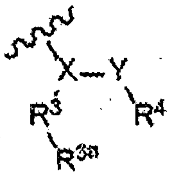
-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -CH_2C(O)-R^4, -CH_2NH-R^4,-CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl)-R^4, -heteroeyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

Z is absent or represents halo, hydroxy, (C$_1$-C$_6$)alkyl, -CF$_3$, -OCF$_3$, (C$_1$-C$_6$)alkoxy, aryl, aryloxy, amino, amino(C$_1$-C$_6$)alkyl, -C(O)NH$_2$, cyano, -NHC(O)(C$_1$-C$_6$)alkyl, -SO$_2$(C$_1$- C$_6$)alkyl, -SO$_2$NH$_2$, or (C$_3$-C$_8$)cycloalkyl;

R^{1c} represents halo, amino(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxy, cyano, -SO$_2$CH$_3$, formyl, acyl, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C$_1$-C$_6$)alkyl, -CF$_3$, -OCF$_3$, (C$_1$-C$_6$)alkoxy, aryl, aryloxy, amino, amino(C$_1$-C$_6$)alkyl, -C(O)NH$_2$, cyano, -NHC(O)(C$_1$-C$_6$)alkyl, -SO$_2$(C$_1$- C$_6$)alkyl, and -SO$_2$NH$_2$;

R^4 represents hydrogen, hydroxy, optionally substituted(C$_1$-C$_6$)alkyl, optionally substituted (C$_3$-C$_8$)cycloalkyl, heterocyclyl(C$_1$-C$_6$)alkyl, (C$_3$-C$_8$)cycloalkyl(C$_1$-C$_6$)alkyl, - CH$_2$OH, -CH((C$_1$-C$_6$)alkyl)OH, -CH(NH$_2$)CH((C$_1$-C$_6$)alkyl)$_2$, optionally substituted aryl, optionally substituted aryl(C$_1$-C$_6$)alkyl, heteroaryl, optionally substituted heteroaryl(C$_1$- C$_6$)alkyl, -CH$_2$S(C$_1$-C$_6$)alky!, amino, or cyano; or -CH$_2$- fused to the 4-position of the ring hearing Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent -NH- fused to the position *ortho* to X on that phenyl; and



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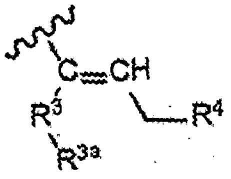

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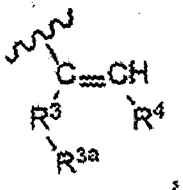

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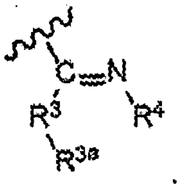

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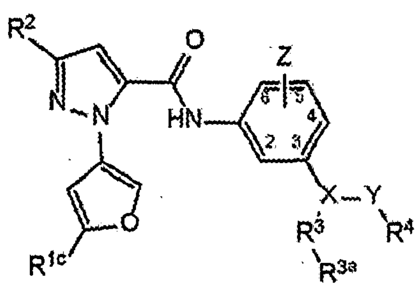
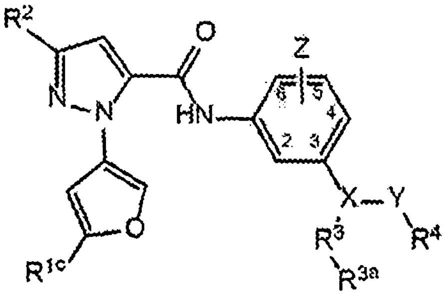
71. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula VIII:



(VIII).

72. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula IX:



(IX)

wherein:

X represents CH, C(OH), C(O(C_1-C_6)alkyl), C(O)N, CH_2N, N, C(O), or -O-;

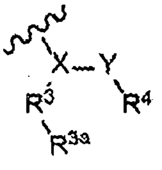
-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -$CH_2C(O)$-R^4, -CH_2NH-R^4, -CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4; -N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4 -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl]R^4, -heterocyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

Z is absent or represents halo, hydroxy, (C_1-C_6)alkyl -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2NH_2, or (C_3-C_8)cycloalkyl;

R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, -SO_2CH_3, formyl, acyl, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3 , (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1- C_6)alkyl and -SO_2NH_2;

R^4 represents hydrogen, hydroxy, optionally substituted (C_1-C_6)alkyl optionally substituted (C_1-C_6)cycloalkyl, heterocyclyl(C_1-C_6)alkyl, (C_3-C_8) cycloalkyl(C_1-C_6)alkyl, -CH_2OH, -CH((C_1-C_6)alkyl)OH, -CH (NH_2)CH((C_1-C_6)alkyl)$_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl, optionally substituted heteroaryl(C_1-C_6)alkyl, CH_2S(C_1-C_6)alkyl, amino, or cyano; or -CH_2- fused to the 4-position of the ring bearing Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent -NH- fused to the position *ortho* to X on that phenyl; and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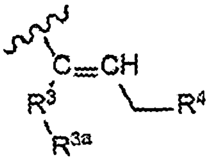
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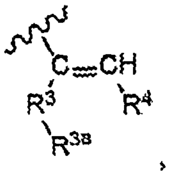
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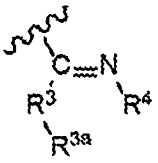
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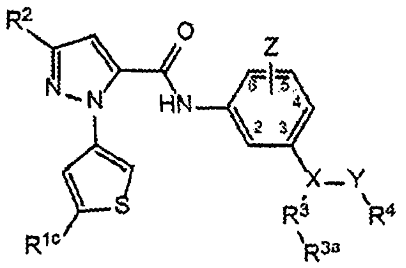
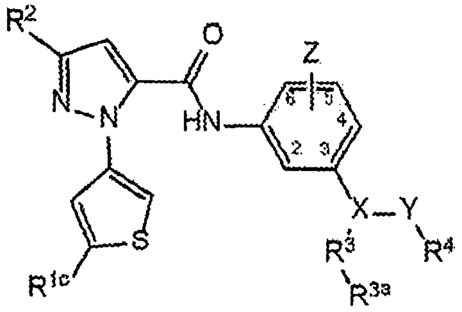
73. The compound of claim 1, or a pharmaceutically acceptable salt thereof represented by formula X:



(X)

74. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XI:



(XI)

wherein:

X represents CH, C(OH), C(O(C_1-C_6)alkyl), C(O)N, CH_2N, N, C(O), or -O-;

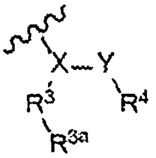
-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -CH_2C(O)-R^4, -CH_2NH-R^4, -CH_2N((C_1-C_6)alkyl)-R^4, -C$R^a$$R^b$-$R^4$, -NH-$R^4$, -NHC$H^2$-$R^4$, -NHC(O)-$R^4$ -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl]R^4, -heteroeyciyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)N$R^a$$R^b$, -S$CH_2$$R^4$, or -S$R^4$, wherein the ($C_1$-$C_6$)alkyl moiety of -(($C_1$-$C_6$)alkyl)-$R^4$ is optionally substituted;

Z is absent or represents halo, hydroxy, (C_1-C_6)alkyl, $-CF_3$, $-OCF_3$, (C_1-C_6)alkoxy, aryl aryloxy, amino, amino(C_1-C_6)alkyl, $-C(O)NH_2$, cyano, $-NHC(O)(C_1-C_6)$alkyl, $-SO_2(C_1- C_6)$alkyl, $-SO_2NH_2$, or (C_3-C_8)cycloalkyl;

R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, $-SO_2CH_3$, formyl, acyl, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C1-C6)alkyl, -CF3, -OCF3, (C1-C6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, $-C(O)NH_2$, cyano, $-NHC(O)(C_1-C_6)$alkyl, $-SO_2(C_1- C_6)$alkyl, and $-SO_2NH_2$;

R^4 represents hydrogen, hydroxy, optionally substituted(C_1-C_6)alkyl, optionally substituted (C_1-C_6)cycloalkyl. heterocyclyl(C_1-C_6)alkyl, (C_1-C_6)cycloalkyl(C_1-C_6)alkyl, $- CH_2OH$, $-CH((C_1-C_6)alkyl)OH$, $-CH(NH_2)CH((C_1-C_6)alkyl)_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl, optionally substituted heteroaryl$(C_1- C_6)$alkyl, $-CH_2S(C_1-C_6)$alkyl, amino, or cyano; or $-CH_2-$ fused to the 4-position of the ring hearing Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent -NH- fused to the position *ortho* to X on that phenyl; and



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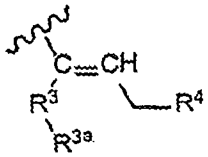

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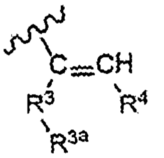

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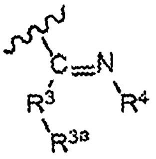

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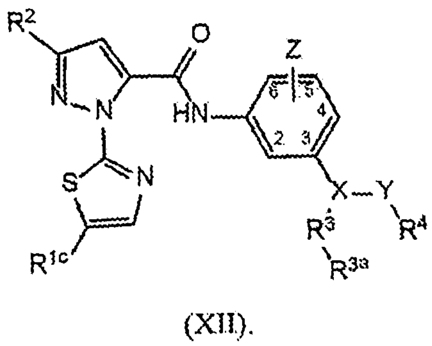
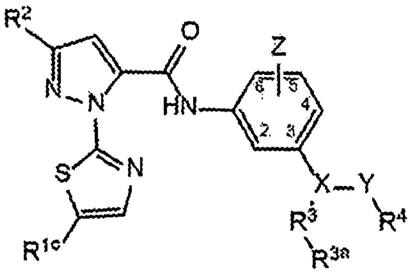
75. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XII:



(XII).

76. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XIII:



(XIII)

wherein

X represents CH, C(OH), C(O(C_1-C_6)alkyl), C(O)N, CH_2N, N, C(O), or -O-;

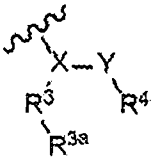
-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -$CH_2C(O)$-R^4, -CH_2NH-R^4, -CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alkyl)CH_2-R^4, -N(($CH_2)_2OH$)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl)-R^4, -heterocyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

Z is absent or represents halo, hydroxy, (C_1-C_6)alkyl -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2NH_2, or (C_3-C_8)cycloalkyl;

R^{1c} represents halo, amino(C_1-C_6) alkyl, (C_1-C_6)alkoxy, cyano, -SO_2CH_3, formyl, acyl, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6) alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1- C_6)alkyl, and -SO_2NH_2;

R^4 represents hydrogen, hydroxy, optionally substituted (C_1-C_6)alkyl optionally substituted (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, -CH_2OH, -CH((C_1-C_6)alkyl)OH, CH(NH_2)CH((C_1-C_6)alkyl$)_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl, optionally substituted heteroaryl(C_1-C_6) alkyl, -CH_2S(C_1-C_6)alkyl, amino, or cyano; or -CH_2- fused to the 4-position of the ring bearing Z to form a 5- to 7-me inhered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent -NH- fused to the position *ortho* to X on that phenyl; and



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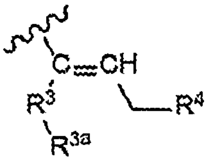

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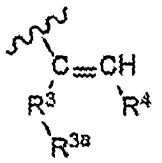

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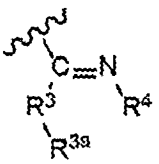

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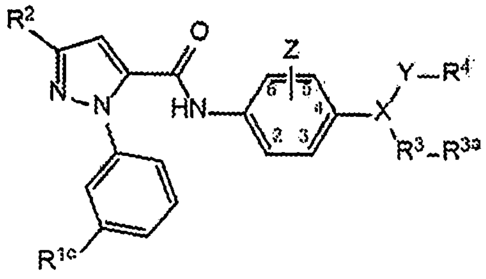
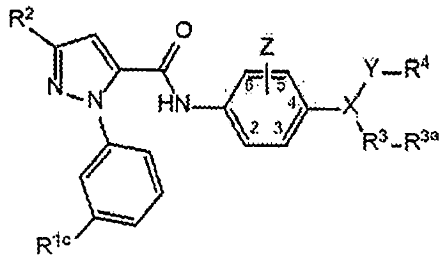
77. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XIV:



(XIV).

78. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XV:



(XV)

wherein:

X represents CH, C(OH), C(O(C_1-C_6)alkyl), C(O)N, CH_2N, N, C(O), or -O-;

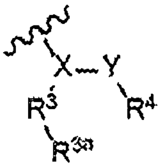
-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -$CH_2C(O)$-R^4, -CH_2NH-R^4,-CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl]R^4, -heterocyelyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

Z is absent or represents halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3 (C_1-C_6)alkoxy, aryl aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1- C_6)alkyl, -SO_2NH_2, or (C_3-C_8)cycloalkyl;

R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, -SO_2CH_3, formyl, acyl, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1- C_6)alkyl, and -SO_2NH_2;

R^4 represents hydrogen, hydroxy, optionally substituted(C_1-C_6)alkyl, optionally substituted (C_3-C_8)cycloalkyl. heterocyclyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, - CH_2OH, -CH((C_1-C_6)alkyl)OH, -CH(NH_2)CH((C_1-C_6)alkyl$)_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl, optionally substituted heteroaryl(C_1- C_6)alkyl , -CH_2S(C_1-C_6)alkyl, amino, or cyano; or -CH_2- fused to the 4-position of the ring hearing Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent -NH- fused to the position *ortho* to X on that phenyl; and



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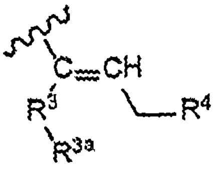

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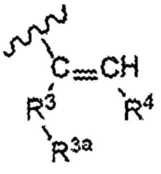

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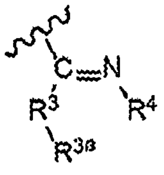

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79. The compound of claim 78, wherein X represents CH, and both Y and R^4 are present.

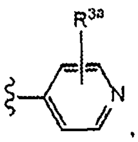
80. The compound of claim 78, wherein -X-Y- represents -$CHNHCH_2$-.

81. The compound of claim 78, wherein -X-Y- represents -C(OH)CH_2CH_2-.

82. The compound of claim 78, wherein -X-Y- represents -$CHOCH_2$-,

83. The compound of claim 78, wherein R^3 represents phenylene-R^{3a}.

84. The compound of claim 78, wherein -R^3-R^{3a} represents



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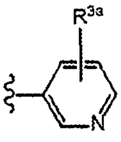

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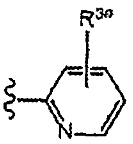
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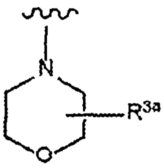
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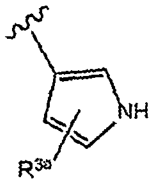
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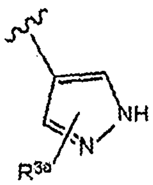
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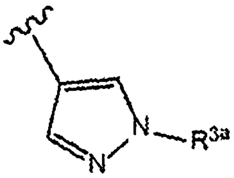
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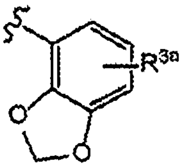
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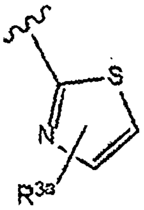
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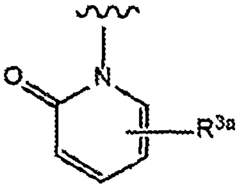
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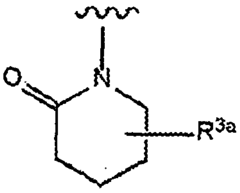
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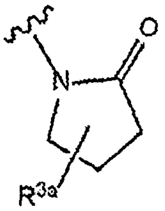
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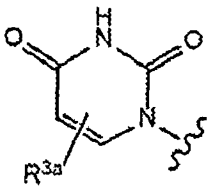
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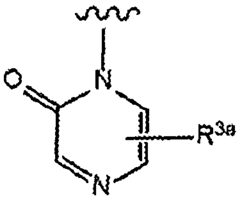
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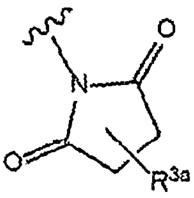
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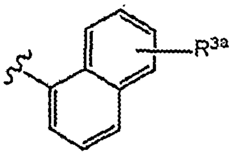
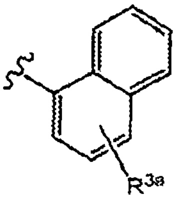
85. The compound of claim 78, wherein -R^3-R^{3a} represents



or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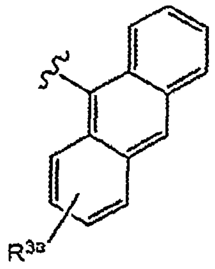
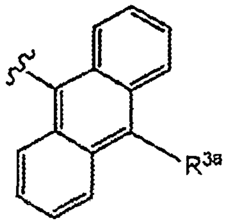
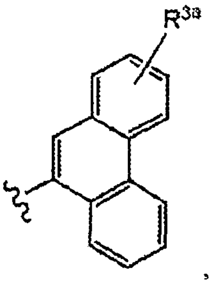
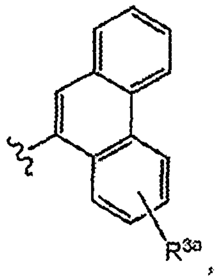
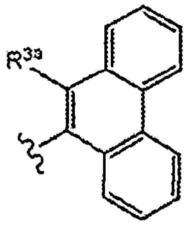
86. The compound of claim 78, wherein $-R^3-R^{3a}$ represents ,

,
,
, or
.

87. The compound of claim 78, wherein R^{3a} is absent.

88. The compound of claim 78, wherein R^4 is cyclopropyl.

89. The compound of claim 78, wherein R^3 is phenyl, and R^{3a} is *ortho*, *meta*, or *para* -OH.

90. The compound of claim 78, wherein R^3 is phenyl, and R^{3a} is *ortho*, *meta*, or *para* $-NH_2$.

91. The compound, of claim 78, wherein R^3 is phenyl, and R^{3a} is *ortho*, *meta*, or *para* -CN.

92. The compound of claim 78, wherein Z is absent.

93. The compound of claim 78, wherein Z represents fluoro.

94. The compound of claim 78, wherein Z represents chloro.

95. The compound of claim 78, wherein Z represents 2-F, 3-F, 5-F, 6-F, 6-Cl, or 5-(C_3-C_8)cycloalkyl.

96. The compound of claim 78, wherein Z represents 6-F.

97. The compound of claim 78, wherein R^{1c} represents aminomethyl.

98. The compound of claim 78, wherein R^{1c} represents cyano.

99. The compound of claim 78, wherein R^{1c} represents $-SO_2CH_3$,

100. The compound of any one of claims 78-99, wherein R^2 is $-CH_3$ or $-CF_3$.

101. The compound of any one of claims 78-99, wherein R^2 is $-CF_3$.

102. The compound of any one of claims 78-99, wherein R^2 is *tert*-butyl.

103. The compound of any one of claims 78-99, wherein R^2 is cyclopropyl.

104. The compound of any one of claims 78-99, wherein R^2 is $-OCH_3$.

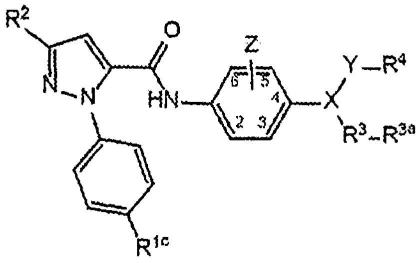
105. The compound of any one of claims 78-99, wherein R^2 is $-Si(CH_3)_3$.

106. The compound of any one of claims 78-99, wherein R^2 is $-CONH_2$.

107. The compound of any one of claims 76-99, wherein R^2 is cyano.

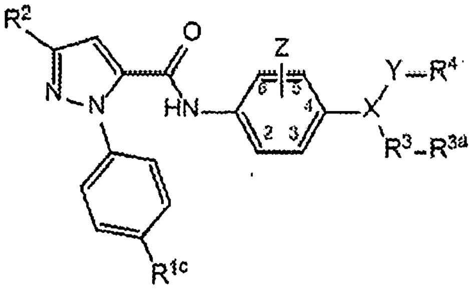
108. The compound of any one of claims 78-99, wherein R^2 is phenyl.

109. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XVI:



(XVI)

110. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XVII:



(XVII)

wherein:

X represents CH, C(OH), C(O(C_1-C_6)alkyl), C(O)N, CH_2N, N, C(O), or -O-;

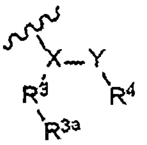
-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -$CH_2C(O)$-R^4, -CH_2NH-R^4, -CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl)-R^4, -heterocyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

Z is absent or represents halo, hydroxy, (C_1-C_6)alkyl, -CF_3 -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1- C_6)alkyl, -SO_2NH_2, or (C_3-C_8)cycloalkyl ;

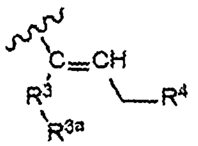
R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, -SO_2CH_3, formyl, acyl, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1- C_6)alkyl, and -SO_2NH_2;

R^4 represents hydrogen, hydroxy, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)cycloalkyl, heterocyclyl(C_1-C_6)alkyl, (C_1-C_6)cycloalkyl(C_1-C_6)alkyl - CH_2OH, -CH((C_1-C_6)alkyl)OH, -CH(NH_2)CH((C_1-C_6)alkyl)$_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl, optionally substituted heteroaryl(C_1- C_6)alkyl, -CH_2S(C_1-C_6)alkyl, amino, or cyano; or -CH_2- fused to the 4-position of the ring bearing Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent -NH- fused to the position *ortho* to X on that phenyl; and



can represent



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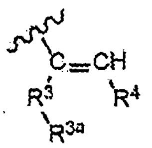

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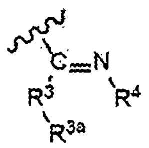

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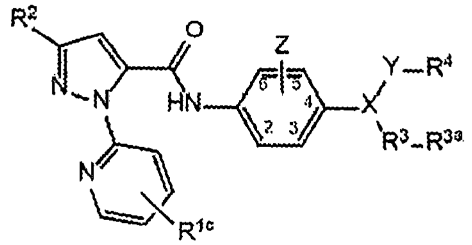
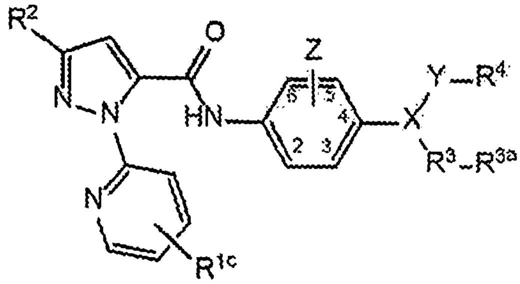
111. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XVIII:



(XVIII)

112. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XIX:



(XIX)

wherein:

X represents CH, C(OH), C(O(C_1-C_6)alkyl), C(O)N, CH_2N, N, C(O), or -O-;

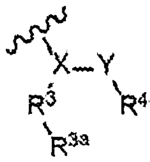
-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -$CH_2C(O)$-R^4, -CH_2NH-R^4, -CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4 -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl]R^4, -heterocyelyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

Z is absent or represents halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1-C_6) alkyl, -SO_2NH_2, or (C_3-C_8)cycloalkyl;

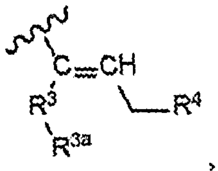
R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, -SO_2CH_3, formyl, acyl, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, and -SO_2NH_2;

R^4 represents hydrogen, hydroxy, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, -CH_2OH, -CH((C_1-C_6)alkyl)OH, -CH(NH_2)CH((C_1-C_6)alkyl)$_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl optionally substituted heteroaryl(C_1-C_6)alkyl, -CH_2S(C_1-C_6)alkyl, amino, or cyano; or -CH_2- fused to the 4-position of the ring bearing Z to form a 5- to 7-merabered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent -NH- fused to the position *ortho* to X on that phenyl; and



can represent



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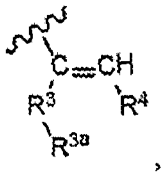

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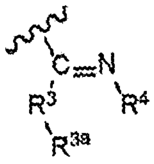

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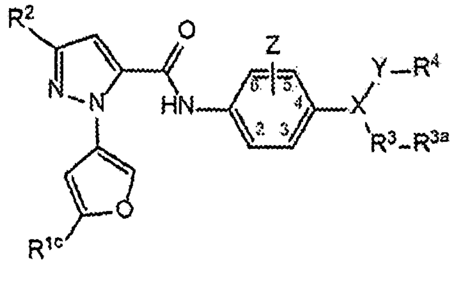
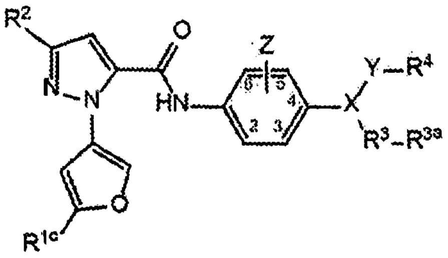
113. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XX:



(XX)

114. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XXI:



(XXI)

wherein:

X represents CH, C(OH), C(O(C_1-C_6)alkyl), C(O)N, CH_2N, N, C(O), or -O-;

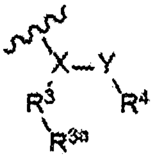
-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -$CH_2C(O)$-R^4, -CH_2NH-R^4, -CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl]R^4, -heterocyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4- is optionally substituted;

Z is absent or represents halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1- C_6)alkyl, -SO_2NH_2, or (C_3-C_8)cycloalkyl;

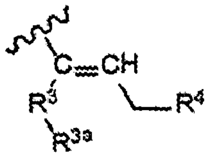
R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, -SO_2CH_3, formyl, acyl, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1- C_6)alkyl, and -SO_2NH_2;

R^4 represents hydrogen, hydroxy, optionally substituted(C_1-C_6)alkyl, optionally substituted (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, - CH_2OH, -CH((C_1-C_6)alky)OH , -CH(NH_2)CH((C_1-C_6)alkyl)$_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl, optionally substituted heteroaryl(C_1- C_6)alkyl, -CH_2S(C_1-C_6)alkyl, amino, or cyano; or -CH_2- fused to the 4-position of the ring hearing Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent -NH- fused to the position *ortho* to X on that phenyl; and



can represent



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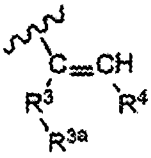

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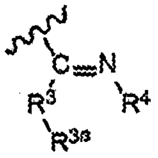

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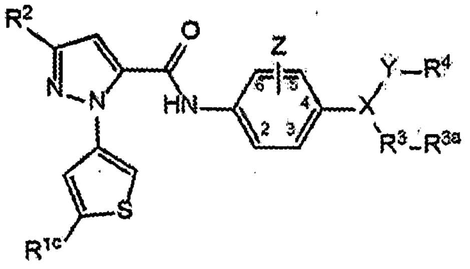
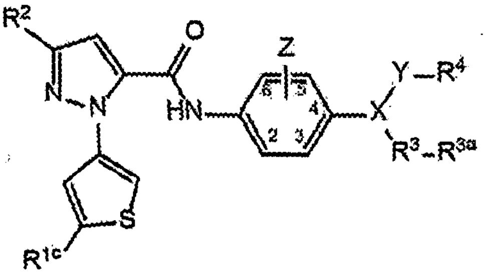
115. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XXII:



(XXII)

116. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XXIII:



(XXIII)

wherein:

X represents CH, C(OH), C(O(C_1-C_6)alkyl), C(O)N, CH_2N, N, C(O), or -O-;

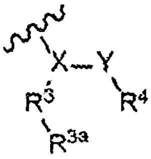
-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -$CH_2C(O)$-R^4, -CH_2NH-R^4, -CH_2N(C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alky])CH_2-R^4, -N((CH_2)$_2$OH)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl]R^4, -heterocyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

Z is absent or represents halo, hydroxy, (C_1-C_6)alkyl, $-CF_3$, $-OCF_3$, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, $-C(O)NH_2$, cyano, $-NHC(O)(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$alkyl, $-SO_2NH_2$, or (C_3-C_8)cycloalkyl;

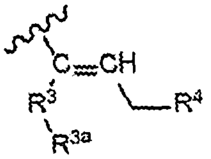
R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, $-SO_2CH_3$, formyl, acyl, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6)alkyl, $-CF_3$, $-OCF_3$, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, $-C(O)NH_2$, cyano, $-NHC(O)(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$alkyl, and $-SO_2NH_2$;

R^4 represents hydrogen, hydroxy, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, $-CH_2OH$, $-CH((C_1-C_6)alkyl)OH$, $-CH(NH_2)CH((C_1-C_6)alkyl)_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl, optionally substituted heteroaryl(C_1-C_6)alkyl, $-CH_2S(C_1-C_6)$alkyl, amino, or cyano; or $-CH_2-$ fused to the 4-position of the ring beating Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent -NH- fused to the position *ortho* to X on that phenyl; and



can represent



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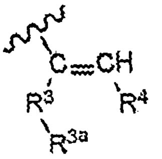

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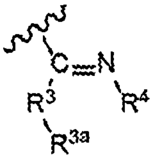

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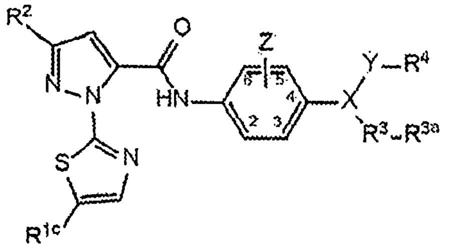
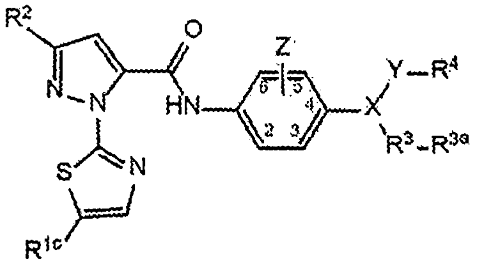
117. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XXIV:



(XXIV)

118. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XXV:



(XXV)

wherein:

X represents CH, C(OH), C(O(C_1-C_6)alkyl), C(O)N, CH_2N, N, C(O), or -O-;

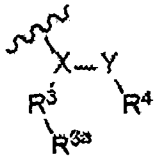
-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -$CH_2C(O)$-R^4, -CH_2NH-R^4, -CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4,-N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6) alkyl]R^4, -heterocyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

Z is absent or represents halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2NH_2, or (C_3-C_8)cycloalkyl;

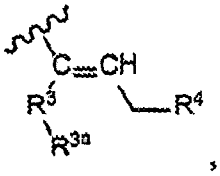
R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, -SO_2CH_3, formyl, acyl, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1- C_6)alkyl, and -SO_2NH_2;

R^4 represents hydrogen, hydroxy, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, -CH_2OH, -CH((C_1-C_6)alkyl)OH, -CH(NH_2)CH((C_1-C_6)alkyl)$_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl, optionally substituted heteroaryl(C_1- C_6)alkyl, -CH_2S(C_1-C_6)alkyl, amino, or cyano; or -CH_2- fused to the 4-position of the ring hearing Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent -NH- fused to the position *ortho* to X on that phenyl; and



can represent



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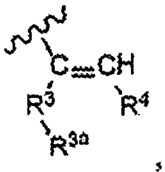

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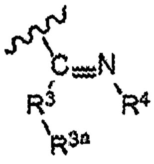

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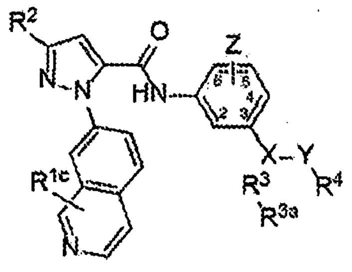
119. The compound of claim 1, or a pharmaceutically acceptable salt thereof, represented by formula XXVI:



(XXVI)

wherein:

X represents CH, C(OH), -C(NH_2), or -C(NR^aR^b);

-Y-R^4, when present, represents -((C_1-C_6)alkyl)-R^4, -$CH_2C(O)$-R^4 -CH_2NH-R^4, -CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl]R^4, -heterocyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -OC(O)NR^aR^b, -SCH_2R^4, or -SR^4, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

Z is absent or represents halo, hydroxy, ((C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1- C_6)alkyl, -SO_2NH_2, or (C_3-C_8)cycloalkyl;

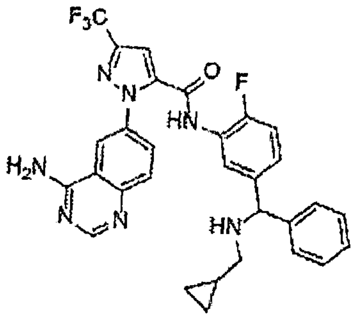
R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, -SO_2CH_3, formyl, acyl, - NH_2, or optionally substituted aryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C1-C6)alkyl, -CFS, -OCF3, (C1-C6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1- C_6)alkyl, and -SO_2NH_2; and

R^4 represents hydrogen, hydroxy, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_1-

C_6)alkyl, CH_2OH, -CH((C_1-C_6)alkyl)OH, -CH(NH_2)CH((C_1-C_6)alkyl$)_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl, optionally substituted heteroaryl(C_1- C_6)alkyl, -CH_2S(C_1-C_6)alkyl, amino, or cyano; or -CH_2- fused to the 4-position of the ring bearing Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or, when R^3 is phenyl, can represent -NH- fused to the position *ortho* to X on that phenyl.

120. The compound of claim 119, wherein said compound is selected from the group consisting of:



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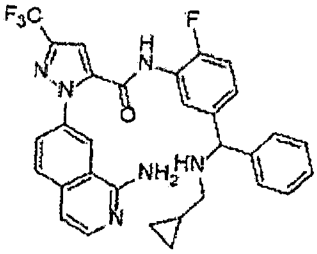

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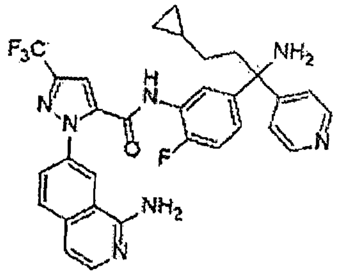

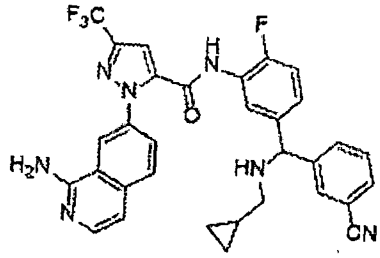

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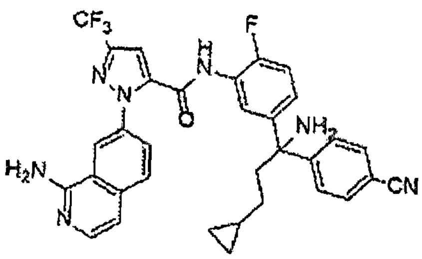

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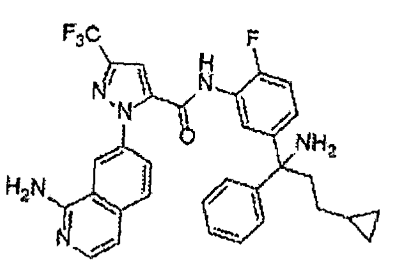

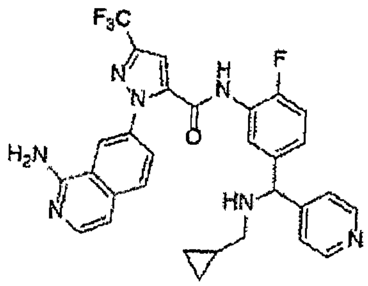

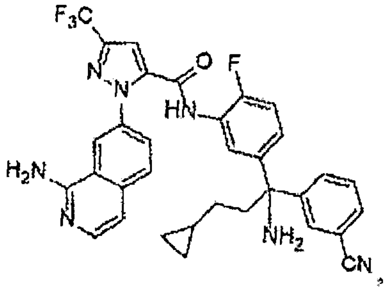

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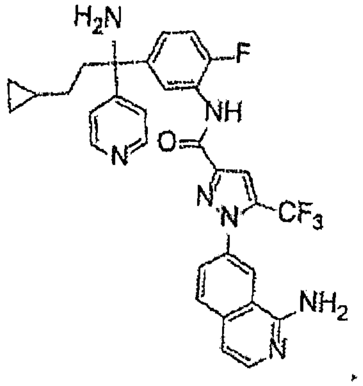

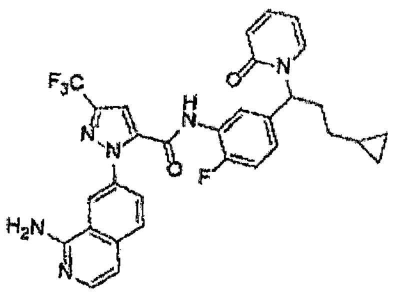

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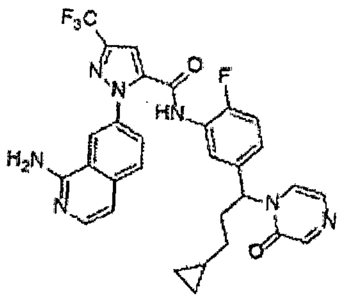

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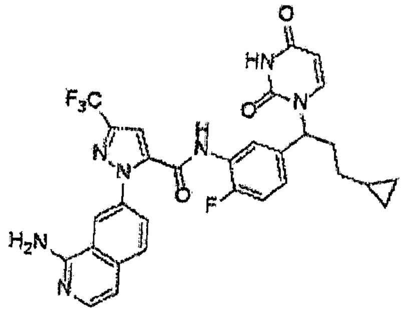

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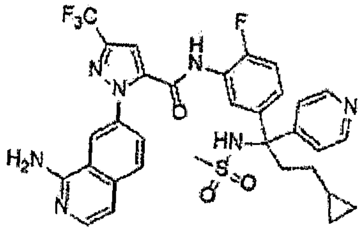

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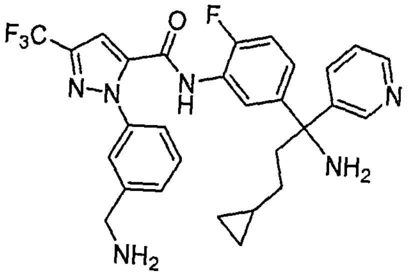
121. The compound of claim 1, wherein said compound is selected from the group consisting of:



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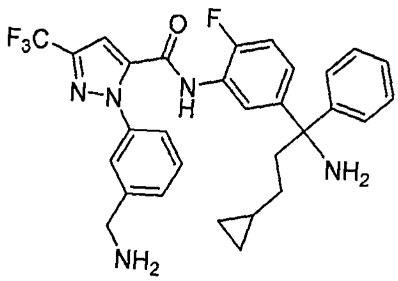

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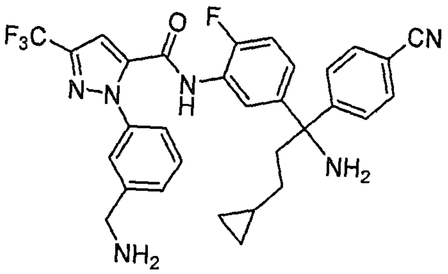

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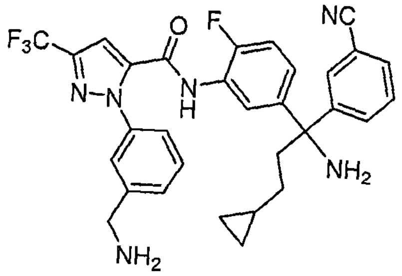

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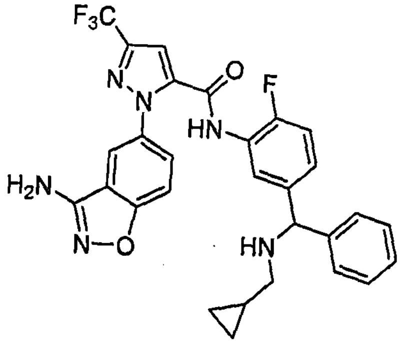

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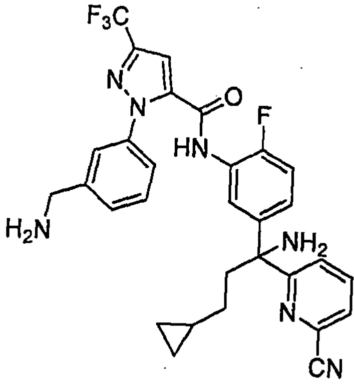

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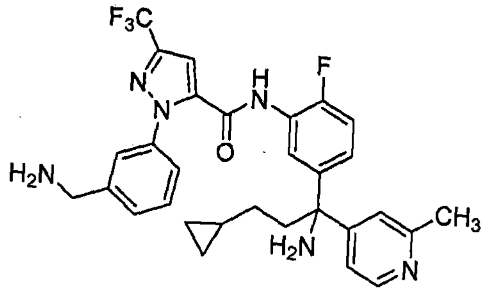

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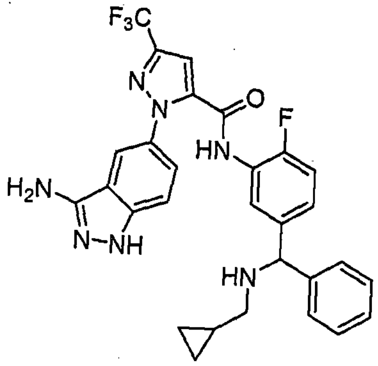

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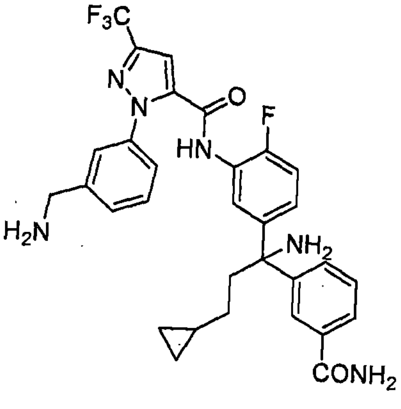

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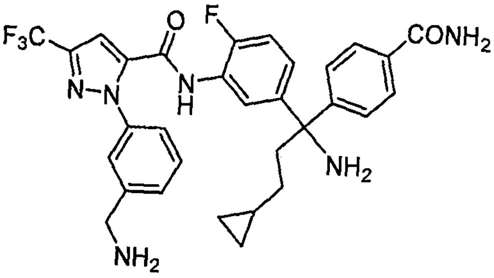

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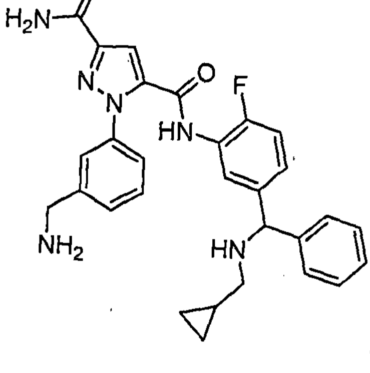

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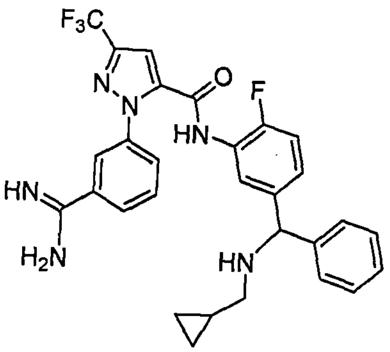
122. The compound of claim 1, wherein said compound is selected from the group consisting of:



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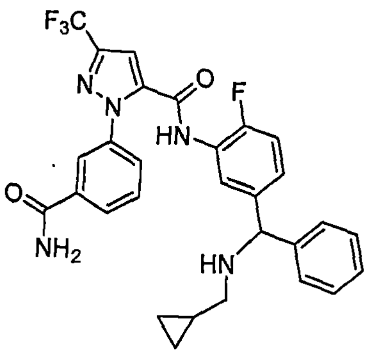

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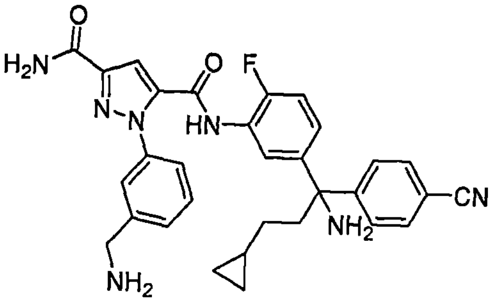

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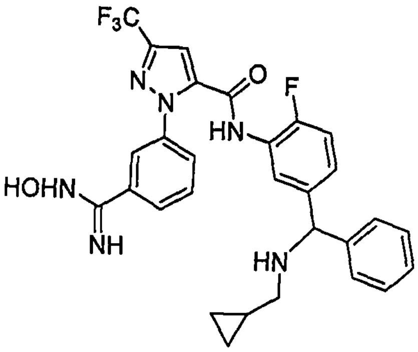

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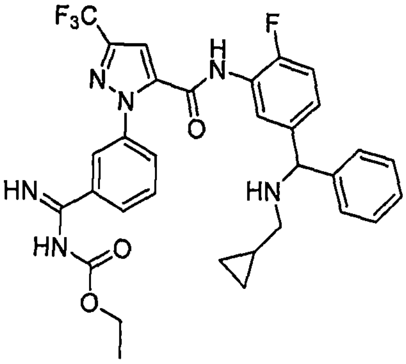

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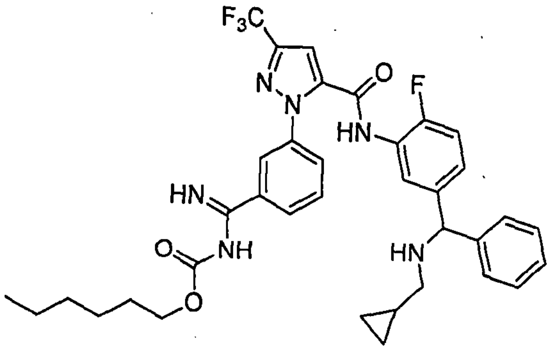

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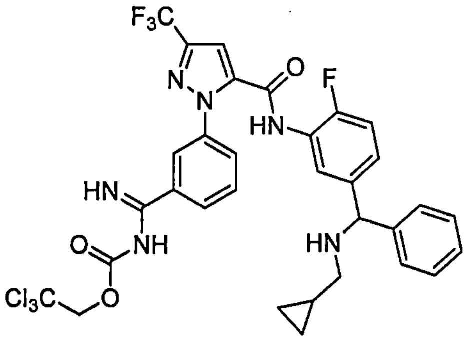

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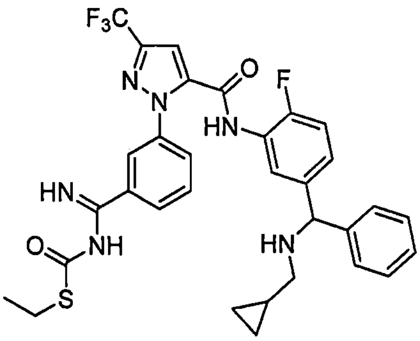

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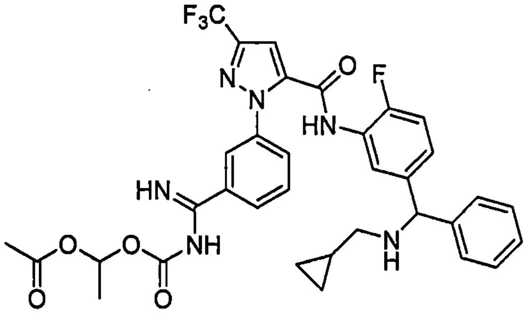

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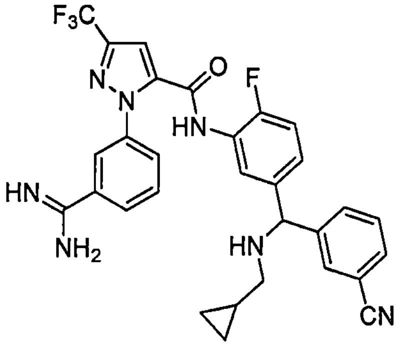

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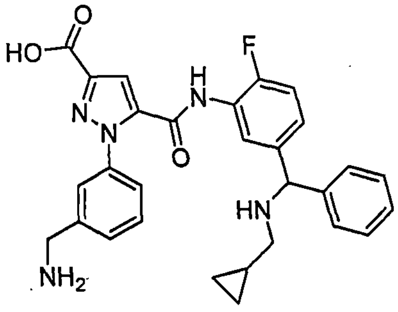
123. The compound of claim 1, wherein said compound is selected from the group consisting of: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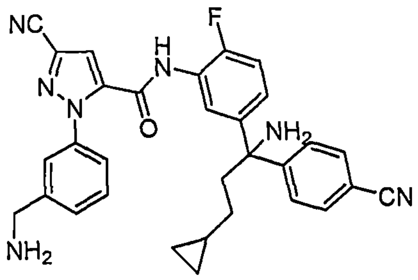
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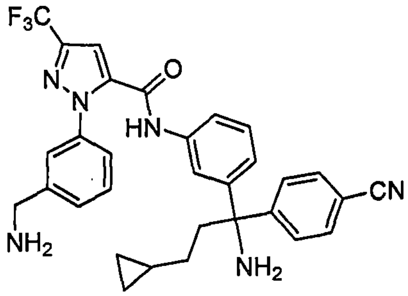
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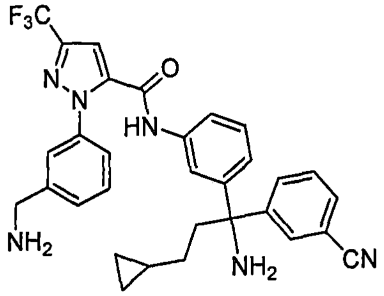
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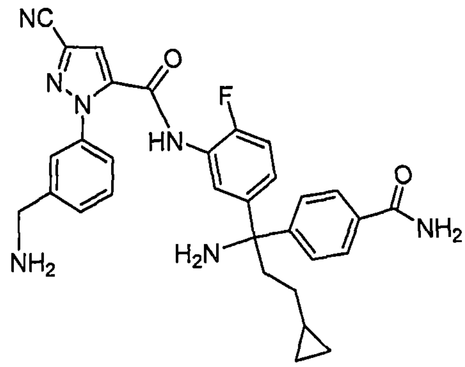
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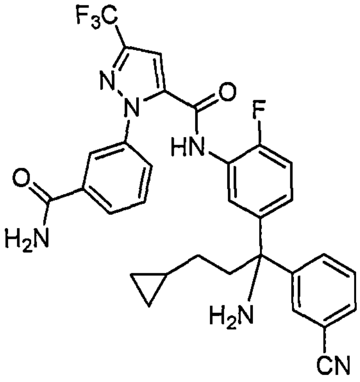
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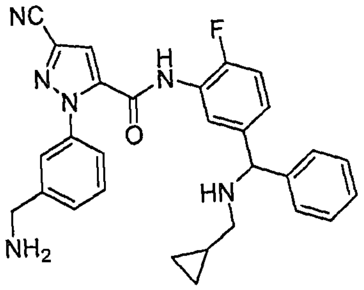

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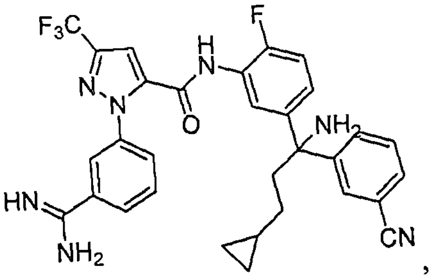

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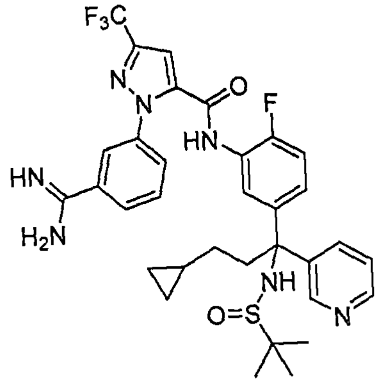

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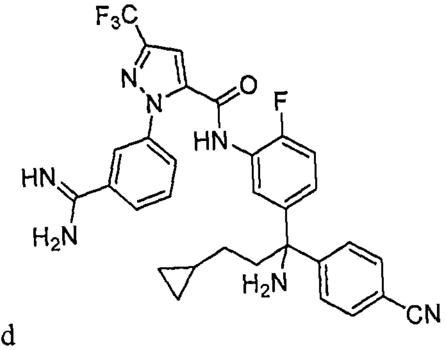

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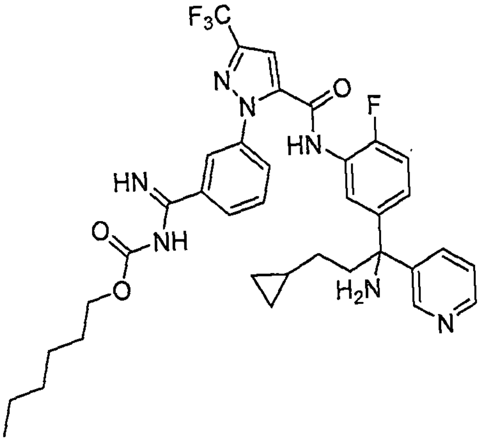
124. The compound of claim 1, wherein said compound is selected from the group consisting of:



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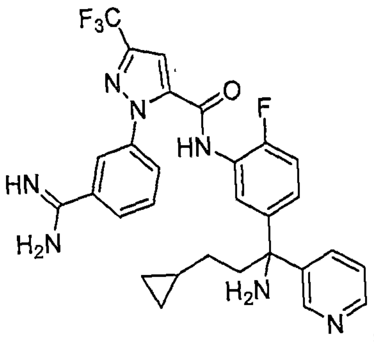

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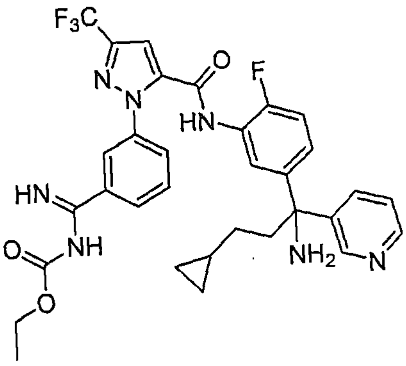

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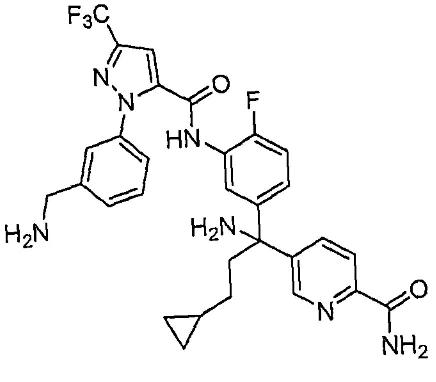

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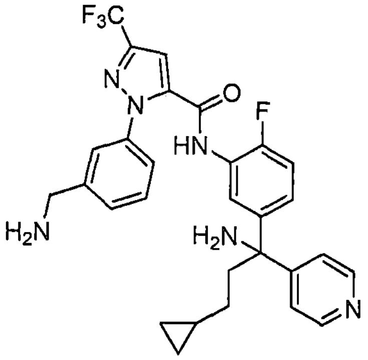

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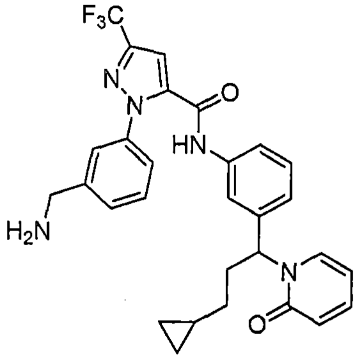

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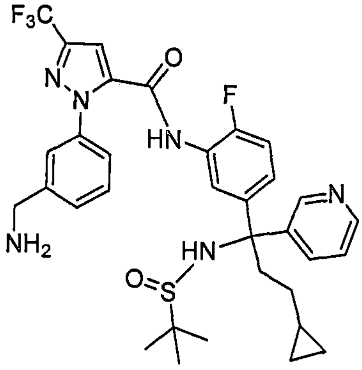

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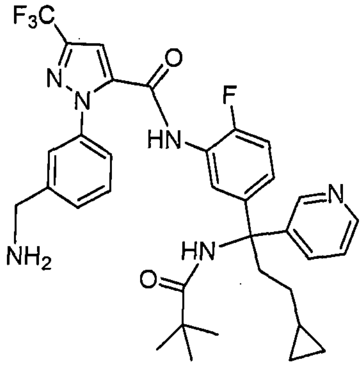

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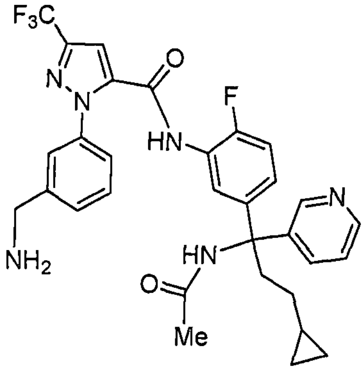
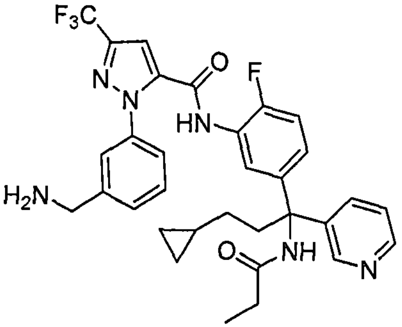


, and



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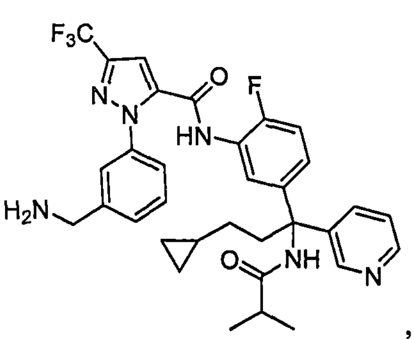
125. The compound of claim 1, wherein said compound is selected from the group consisting of: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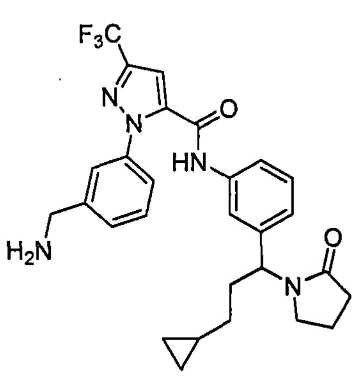
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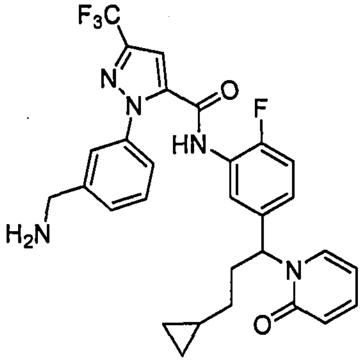
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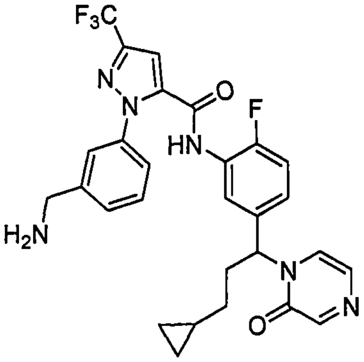
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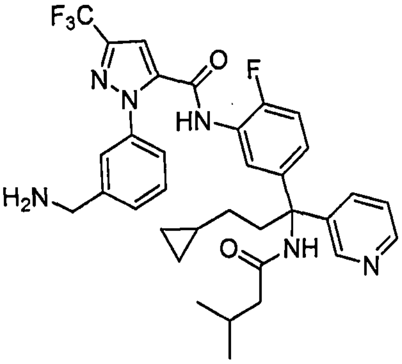
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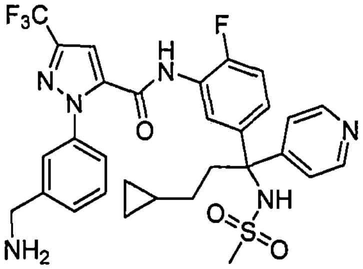
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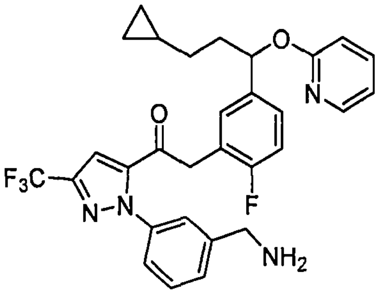
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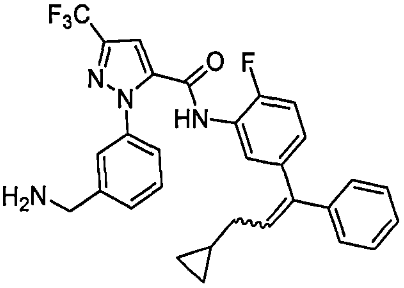
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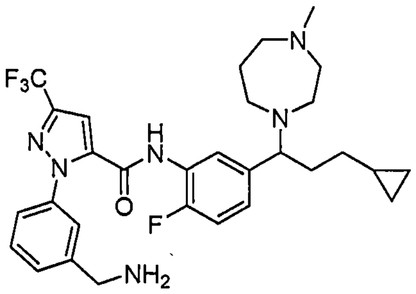

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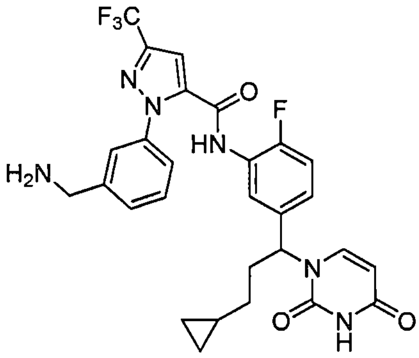

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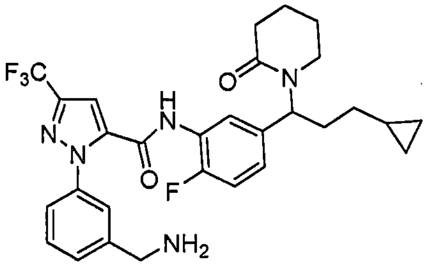

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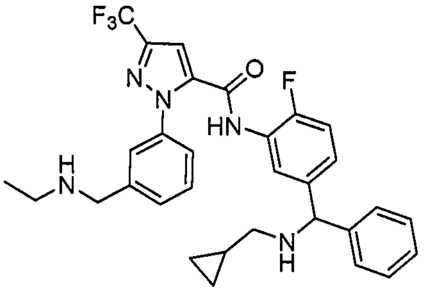
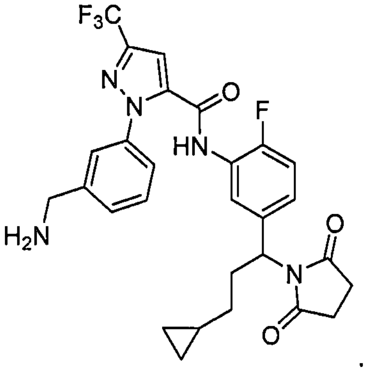


,

and



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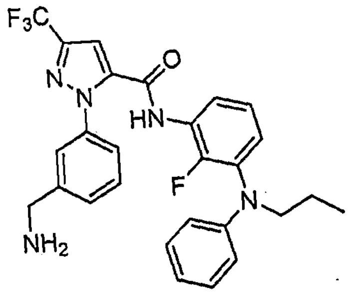
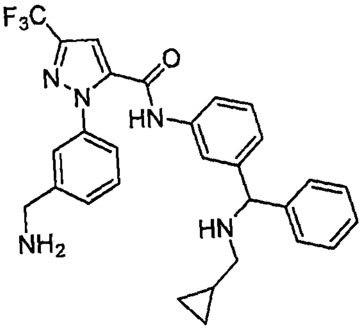
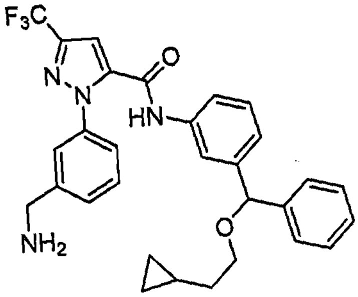
126. The compound of claim 1, wherein said compound is selected from the group consisting of:


F3C
N
N
O
HN
F
N
NH2

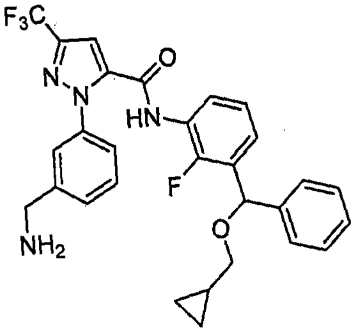
,


F3C
N
N
O
HN
NH2
HN

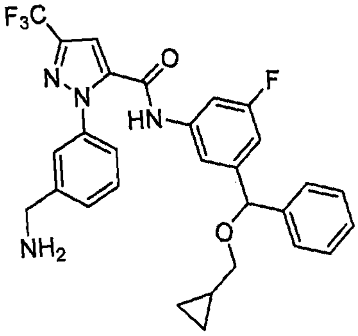
,


F3C
N
N
O
HN
O
NH2

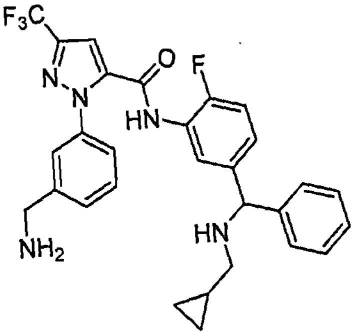
,


F3C
N
N
O
HN
F
O
NH2

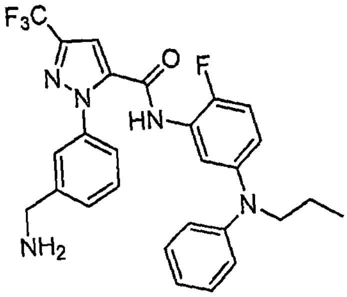
,


F3C
N
N
O
HN
F
O
NH2

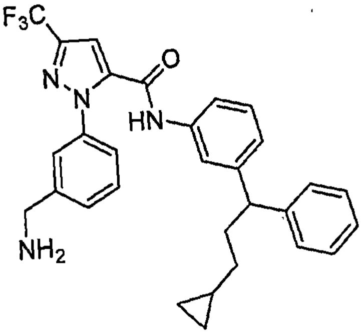
,


F3C
N
N
O
F
HN
HN
NH2

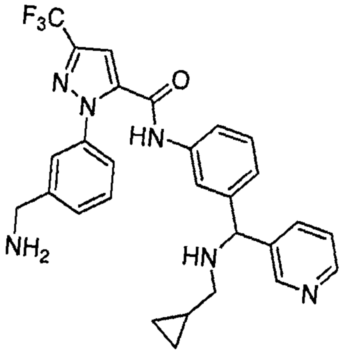
,


F3C
N
N
O
F
HN
N
NH2

,


F3C
N
N
O
HN
NH2

,



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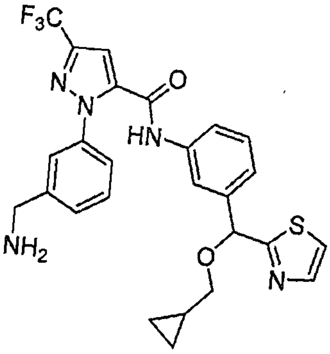

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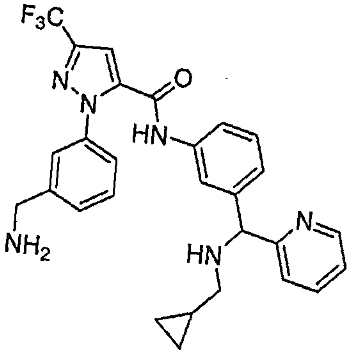

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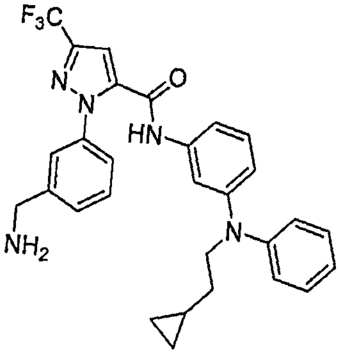

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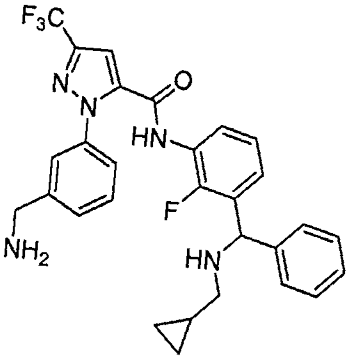

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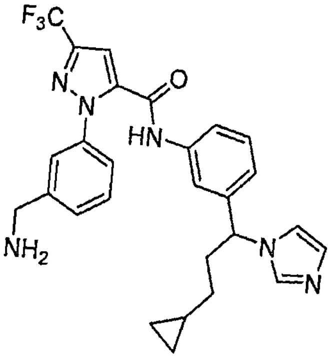
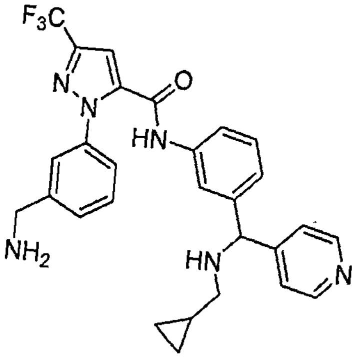


, and



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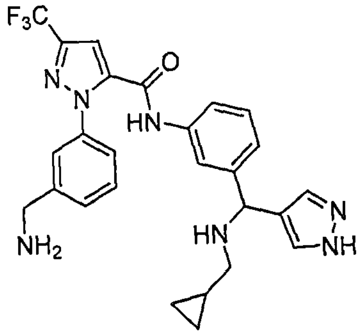
127. The compound of claim 1, wherein said compound is selected from the group consisting of:



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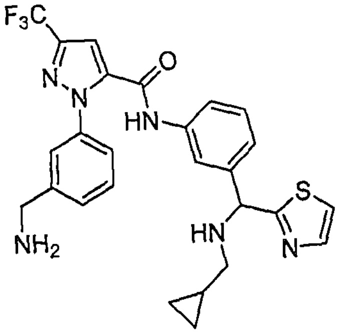

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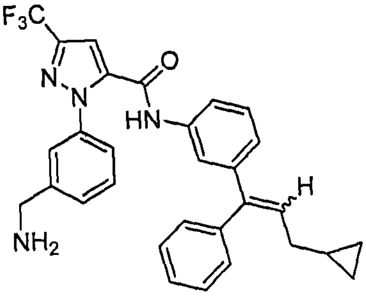

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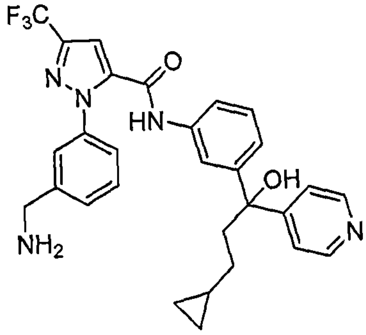

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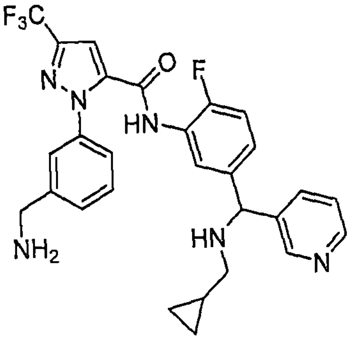

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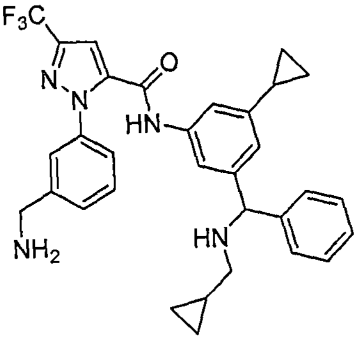

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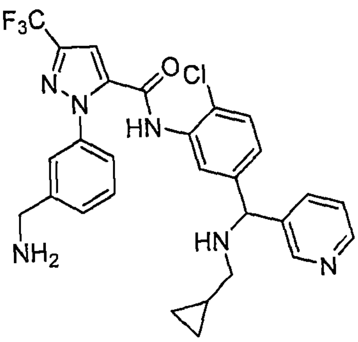

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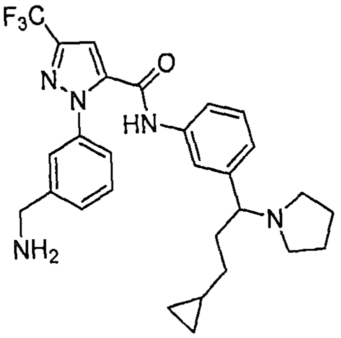

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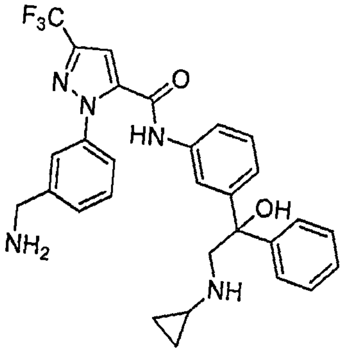
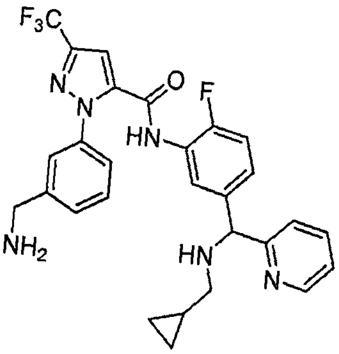


,



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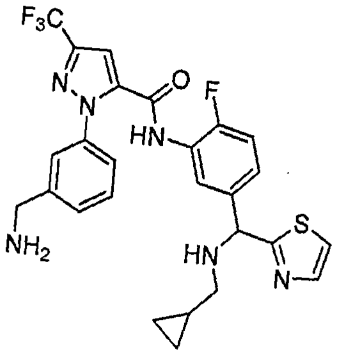

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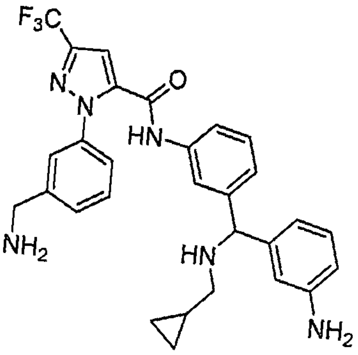

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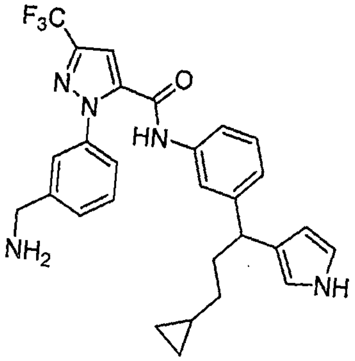

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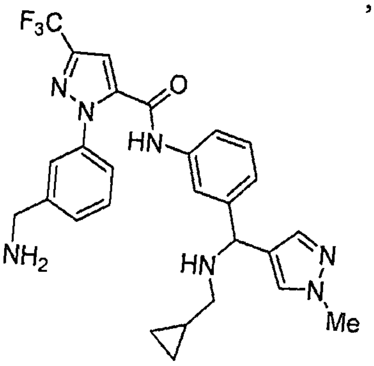
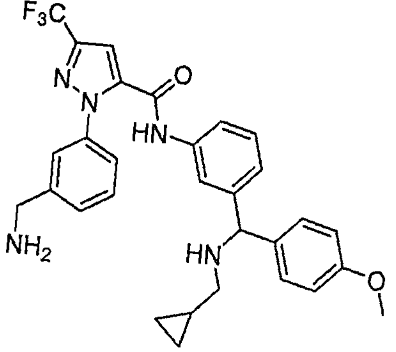


,

and



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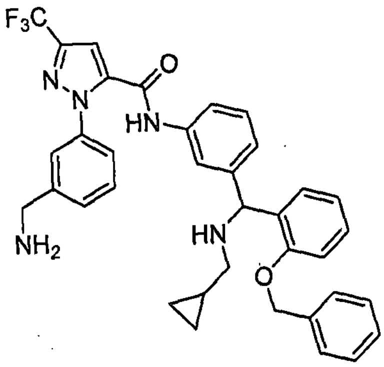
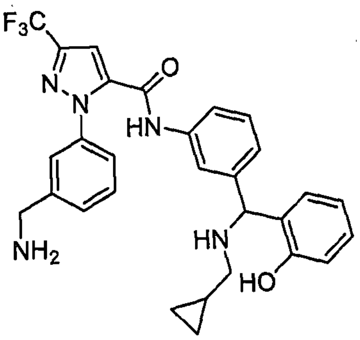
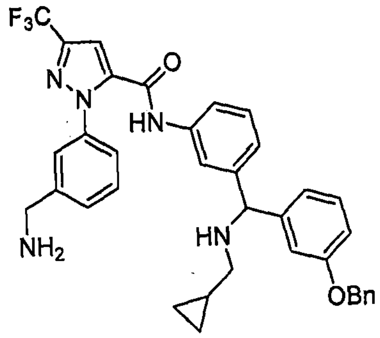
128. The compound of claim 1, wherein said compound is selected from the group consisting of:


F3C
N
N
O
HN
NH2
HN
O

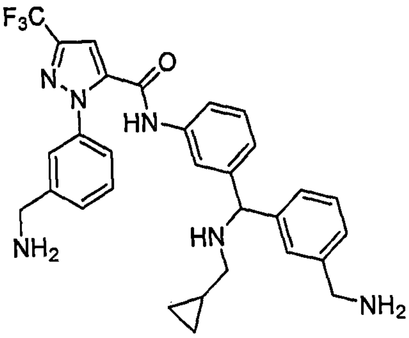
,


F3C
N
N
O
HN
NH2
HN
HO

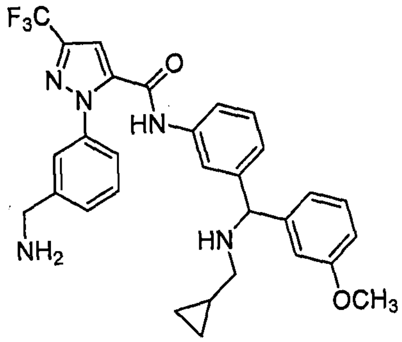
,


F3C
N
N
O
HN
NH2
HN
OBn

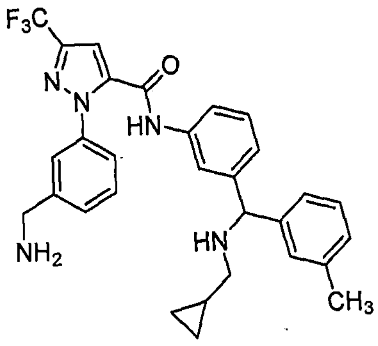
,


F3C
N
N
O
HN
NH2
HN
NH2

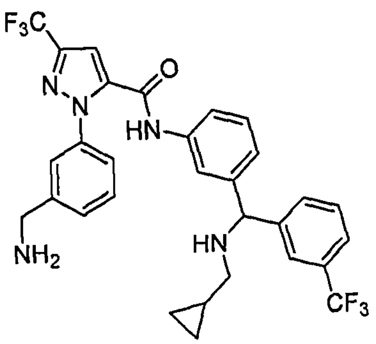
,


F3C
N
N
O
HN
NH2
HN
OCH3

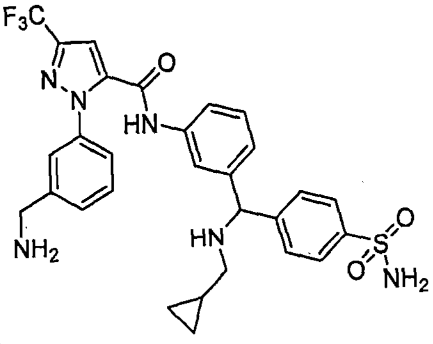
,


F3C
N
N
O
HN
NH2
HN
CH3

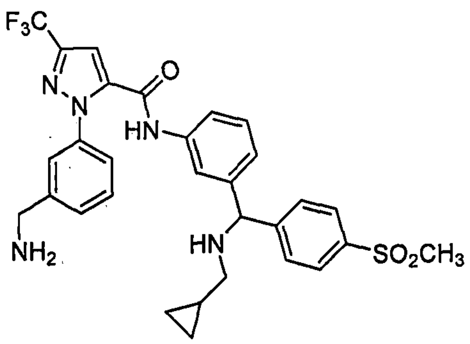
,


F3C
N
N
O
HN
NH2
HN
CF3

,


F3C
N
N
O
HN
NH2
HN
O
S
O
NH2

,



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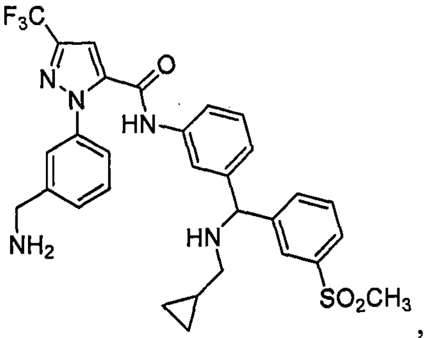

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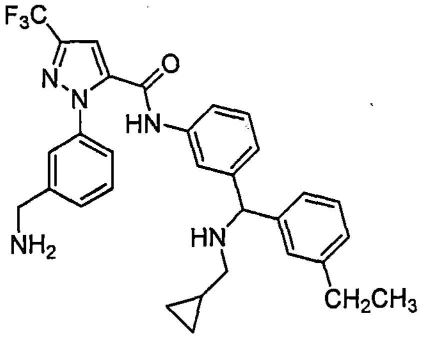

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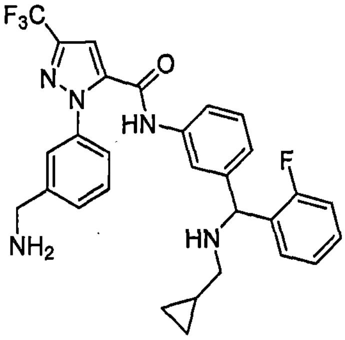

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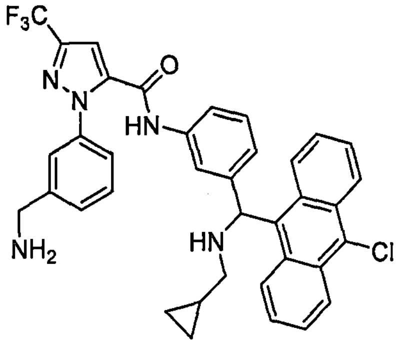

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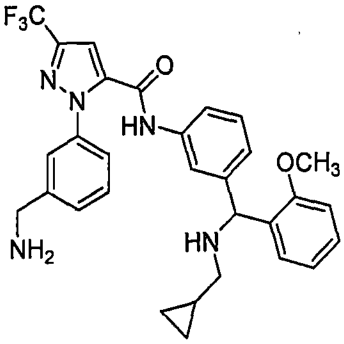
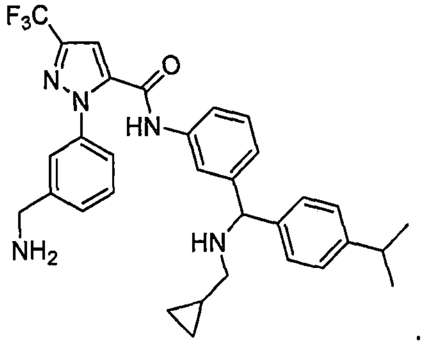


, and



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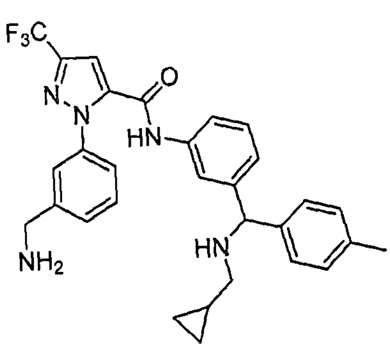
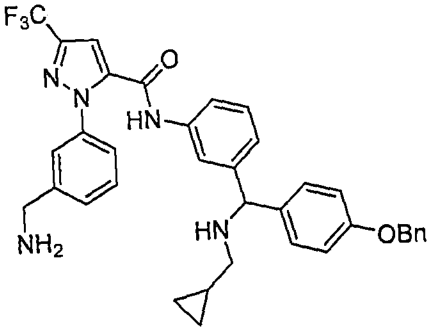
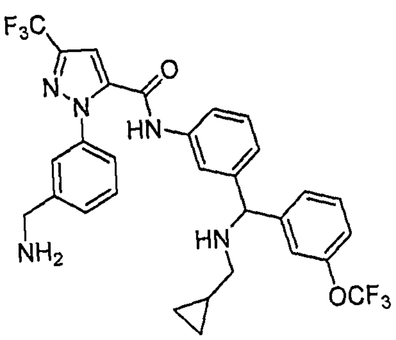
129. The compound of claim 1, wherein said compound is selected from the group consisting of:


F3C
N
N
O
HN
NH2
HN

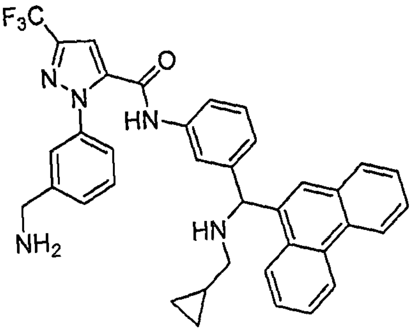
,


F3C
N
N
O
HN
NH2
HN
OBn

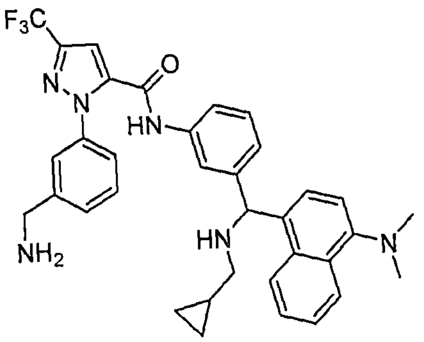
,


F3C
N
N
O
HN
NH2
HN
OCF3

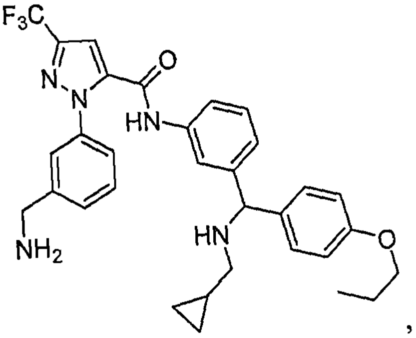
,


F3C
N
N
O
HN
NH2
HN

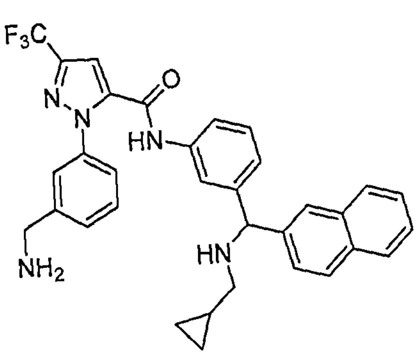
,


F3C
N
N
O
HN
NH2
HN
N

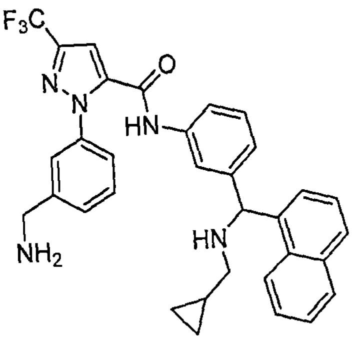
,


F3C
N
N
O
HN
NH2
HN
O

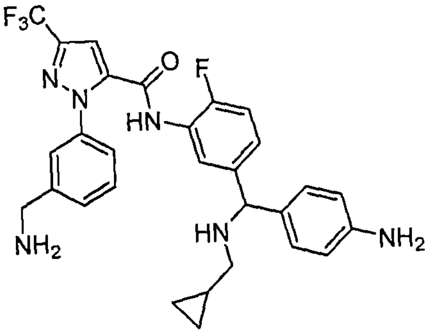
,


F3C
N
N
O
HN
NH2
HN

,


F3C
N
N
O
HN
NH2
HN

,



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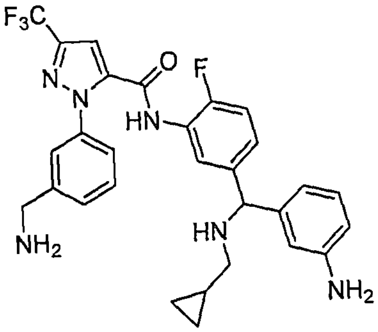

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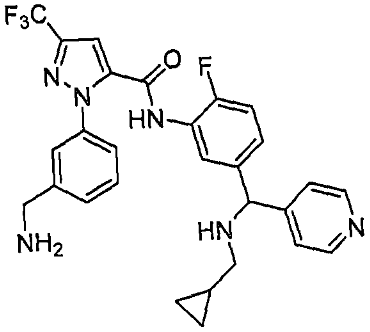

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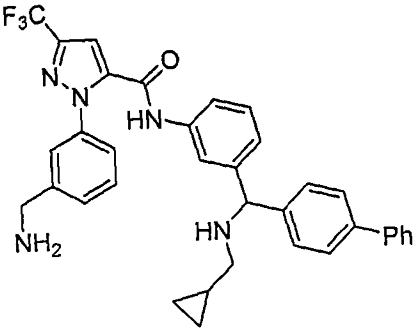

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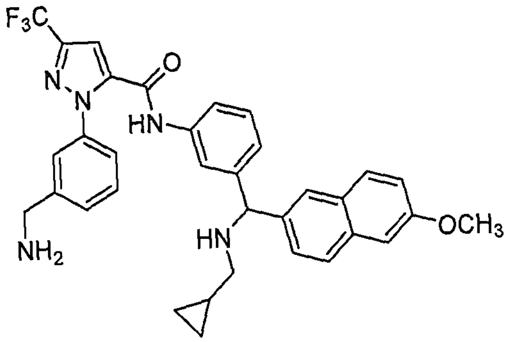
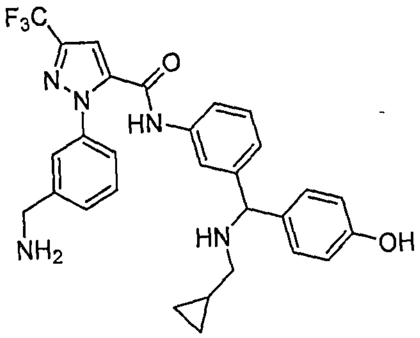
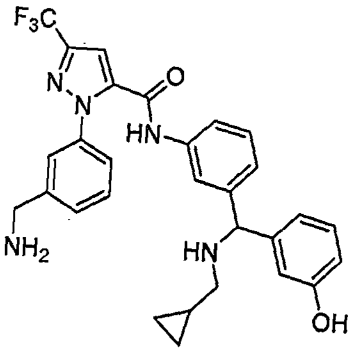


, and



.

130. The compound of claim 1, wherein said compound is selected from the group consisting of:



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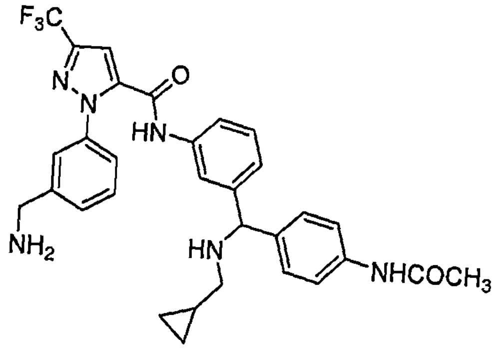

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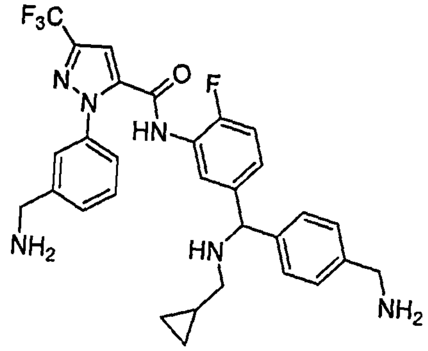

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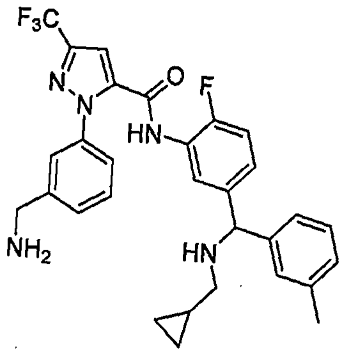

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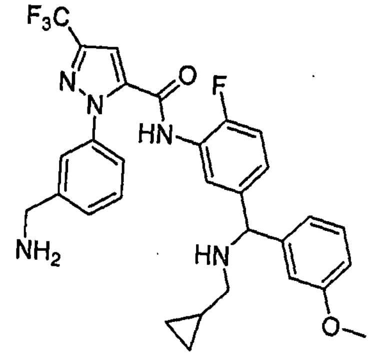

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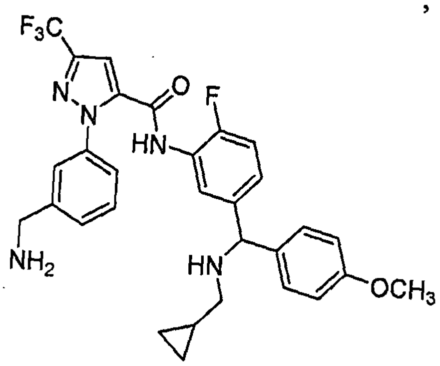

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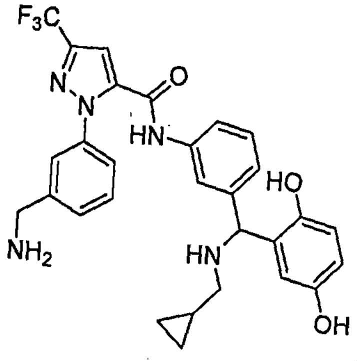
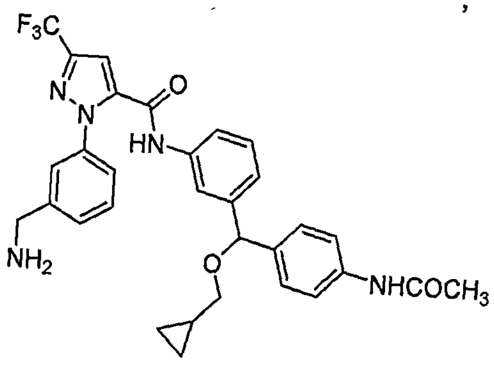
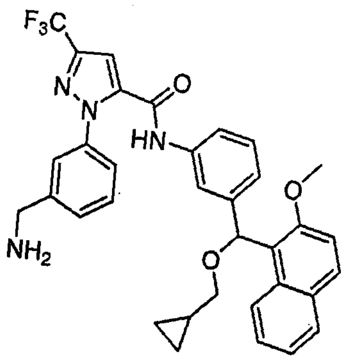


,



,



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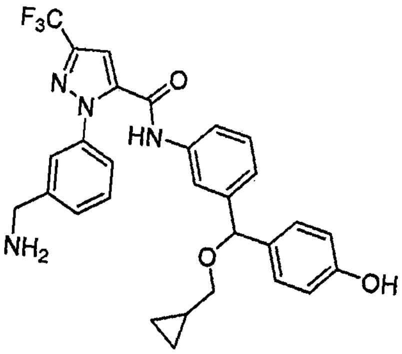

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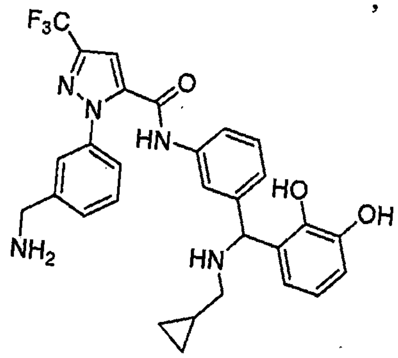
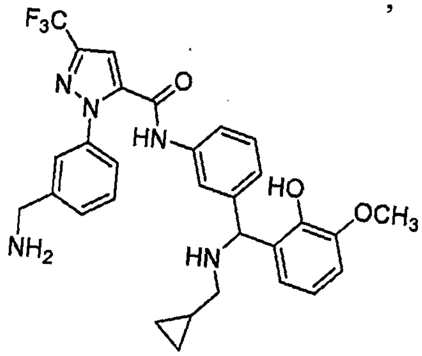
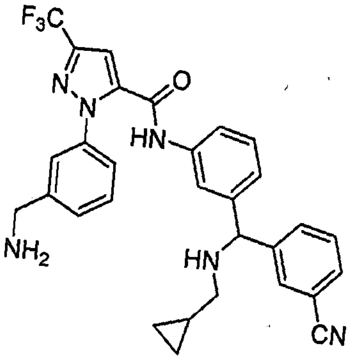


,

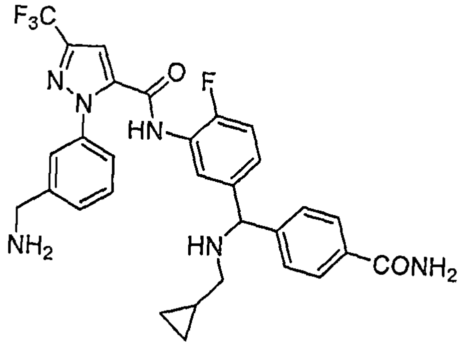


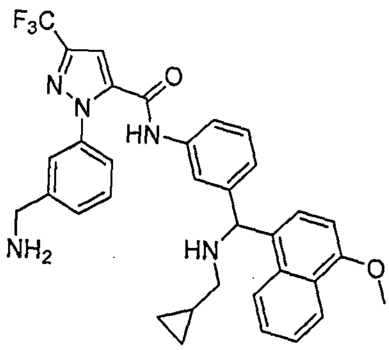
, and

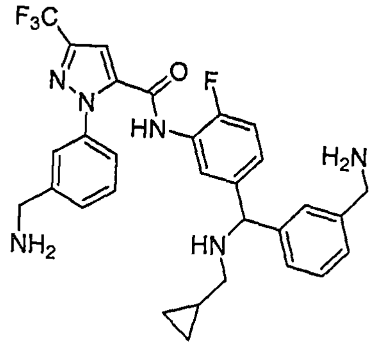


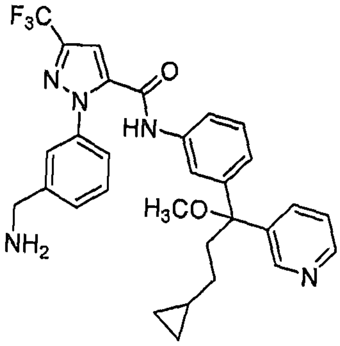
.

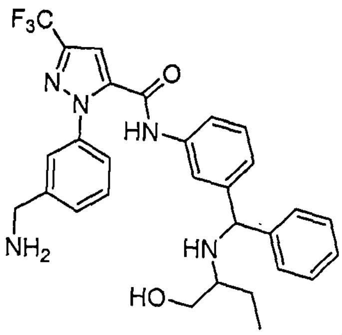
131. The compound of claim 1, wherein said compound is selected from the group consisting of:

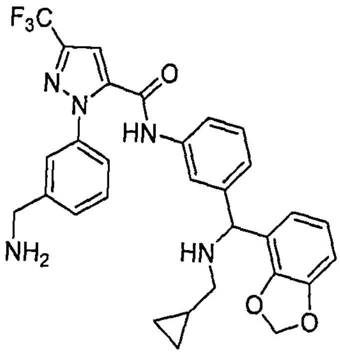

F3C
N
N
O
F
HN
NH2
HN
CONH2
,

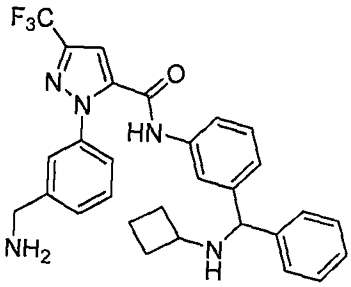

F3C
N
N
O
HN
NH2
HN
O
,

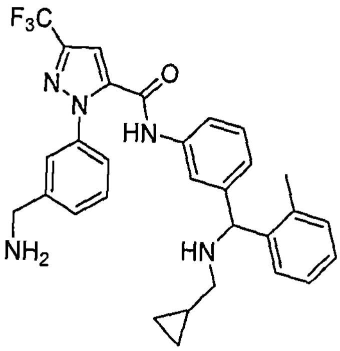

F3C
N
N
O
F
HN
H2N
NH2
HN
,

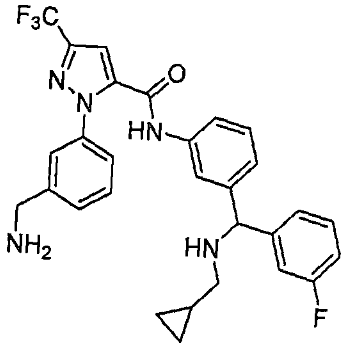

F3C
N
N
O
HN
NH2
H3CO
N
,


F3C
N
N
O
HN
NH2
HN
HO
,


F3C
N
N
O
HN
NH2
HN
O
O
,


F3C
N
N
O
HN
NH2
N
H
,


F3C
N
N
O
HN
NH2
HN
,



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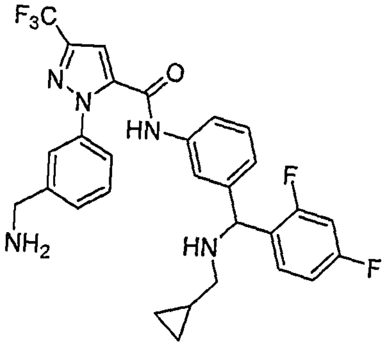
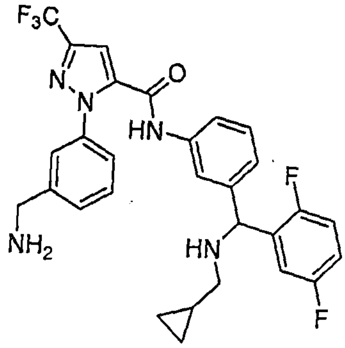


,



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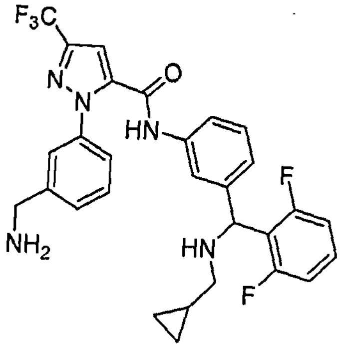
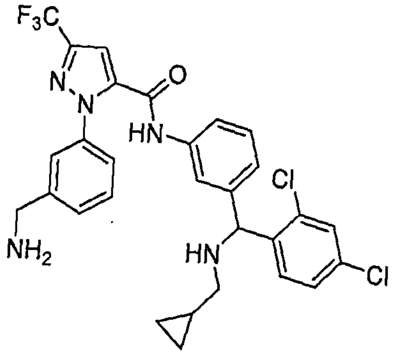
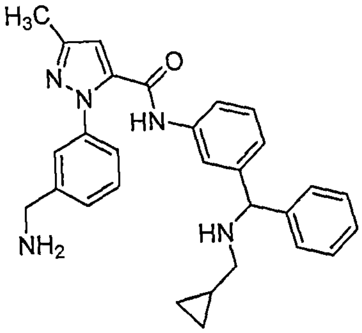


, and

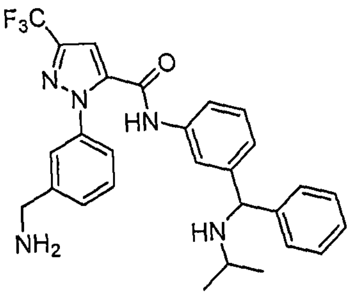


.

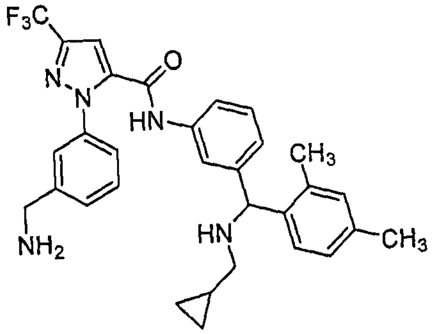
132. The compound of claim 1, wherein said compound is selected from the group consisting of:


H3C
N
N
O
HN
NH2
HN

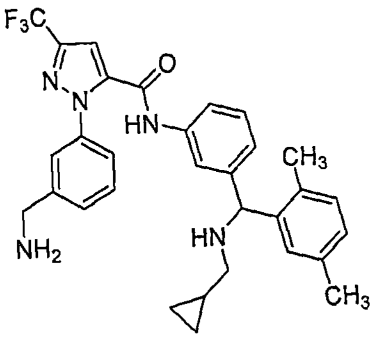
,


F3C
N
N
O
HN
NH2
HN

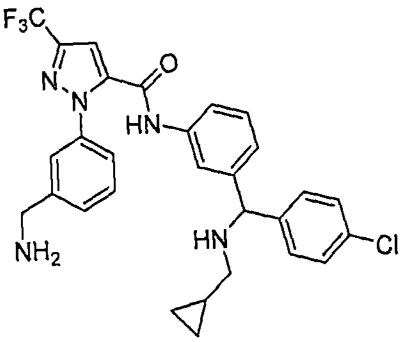
,


F3C
N
N
O
HN
CH3
NH2
HN
CH3

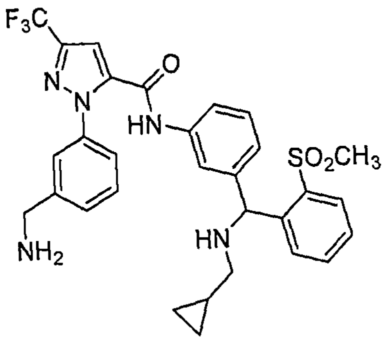
,


F3C
N
N
O
HN
CH3
NH2
HN
CH3

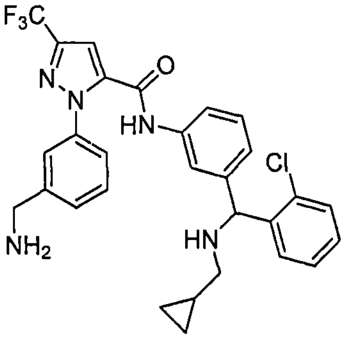
,


F3C
N
N
O
HN
NH2
HN
Cl

,


F3C
N
N
O
HN
SO2CH3
NH2
HN

,



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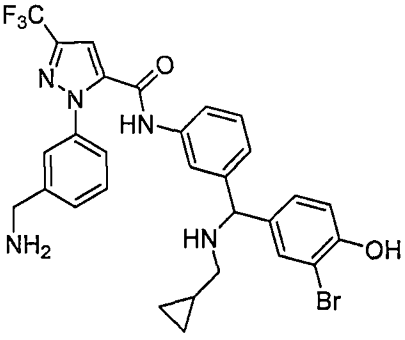
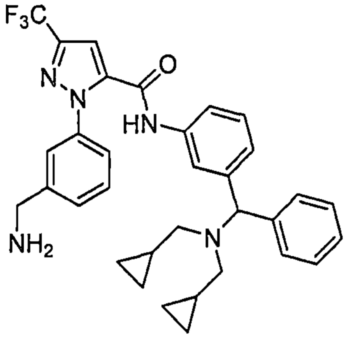


, and



.

133. A pharmaceutical composition, comprising a compound of any one of claims 1-132; and a pharmaceutically acceptable carrier.

134. The pharmaceutical composition of claim 133, wherein the pharmaceutical composition is formulated for parenteral administration.

135. The pharmaceutical composition of claim 133, wherein the pharmaceutical composition is formulated for oral administration.

136. The pharmaceutical composition of claim 133, wherein the pharmaceutical composition is formulated for the prophylactic or therapeutic treatment of a disease or condition characterized by unwanted plasma kallikrein activity.

137. A method of treating or preventing a disease or condition characterized by unwanted plasma kallikrein activity, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-132.

138. The method of claim 137, wherein the disease or condition characterized by unwanted plasma kallikrein activity is selected from the group consisting of stroke, inflammation, reperfusion injury, acute myocardial infarction, deep vein thrombosis, post fibrinolytic treatment condition, angina, edema,

angioedema, hereditary angioedema, sepsis, arthritis, hemorrhage, blood loss during cardiopulmonary bypass, inflammatory bowel disease, diabetes mellitus, retinopathy, diabetic retinopathy, diabetic macular edema, diabetic macular degeneration, age-related macular edema, age-related macular degeneration, proliferative retinopathy, neuropathy, hypertension, brain edema, increased albumin excretion, macroalbuminuria, and nephropathy.

139. The method of claim 137, wherein the disease or condition characterized by unwanted plasma kallikrein activity is angioedema.

140. The method of claim 137, wherein the disease or condition characterized by unwanted plasma kallikrein activity is hereditary angioedema.

141. The method of claim 137, wherein the disease or condition characterized by unwanted plasma kallikrein activity is stroke.

142. The method of claim 137, wherein the disease or condition characterized by unwanted plasma kallikrein activity is reperfusion injury.

143. The method of claim 137, wherein the disease or condition characterized by unwanted plasma kallikrein activity is acute myocardial infarction.

144. The method of claim 137, wherein the disease or condition characterized by unwanted plasma kallikrein activity is hemorrhage.

145. The method of claim 137, wherein the disease or condition characterized by unwanted plasma kallikrein activity is blood loss during cardiopulmonary bypass.

146. The method of claim 137, wherein the disease or condition characterized by unwanted plasma kallikrein activity is selected from the group consisting of retinopathy, diabetic retinopathy, diabetic macular edema, diabetic macular degeneration, age-related macular edema, age-related macular degeneration, and proliferative retinopathy.