acetate (3.0 equiv, 54.7 g, 558 mmol) and $PdCl_2$(dppf) (0.03 equiv, 4.65 g, 5.58 mmol) in degassed DMF (1 l) was heated at 80°C under nitrogen for 16 h. The DMF was removed under reduced pressure and the resulting dark solid residue was dissolved in CH_2Cl_2 (500 mL). The inorganic residues were removed by filtration through a silica gel pad and the filtrate was purified by column chromatography using a 10% to 15% EtOAc : heptane gradient to afford the product as a yellow viscous oil which crystallized on standing to give *tert-butyl N-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate* (56.5 g, 92 %), ^{1}H NMR (400 MHz, $CDCl_3$) 1.33 (12 H, *s*), 1.53 (9 H, *s*), 6.82 (1H, *br s*), 7.46 (1H, *d*, *J* 11 Hz), 7.55 (1 H, *br d*), and 8.12 (1 H, *br t*), *m/z* 337.2, and RP-HPLC (5 to 100 % CH_3CN in 0.1 N aqueous ammonium acetate over 15 min at 1 mL/min using a Hypersil HyPurity Elite C18, 5m, 200 Å, 250 x 4.6 mm column) t_r= 10.16 min, 90%.

c) tert-Butyl N-4-[4-chloro-7-(1,4-dioxaspiro[4.5]dec-8-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenylcarbamate

A suspension of the 4-chloro-7-(1,4-dioxaspiro[4.5]dec-8-yl)-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (31.18 g, 74.41 mmol), tert-butyl N-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.5 equiv, 37.6 g, 111.6 mmol), sodium carbonate (2.5 equiv, 19.72 g, 186 mmol) and $Pd(PPh_3)_4$ (4 mol%, 3.44 g, 2.98 mmol)in DME (1.2 l) and degassed H_2O (230 mL) was heated at 80°C under nitrogen for 17 h. Additional Pd catalyst (1 mol%, .86 g, 0.74 mmol) was added and the reaction was continued heating at 80°C for a further 24 h. at which point the reaction had proceeded to completion (t.l.c. analysis using 3:7 EtOAc:heptane as the eluent, Rf=0.7). The solvent was removed under reduced pressure and the residue dissolved in EtOAc (500 mL) and the inorganics were removed by filtration through a celite pad. The filtrate was washed with 10% aq. Na_2CO_3 (200 mL) and brine (200 mL), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography purification over silica gel using 1:2 EtOAc:heptane afforded tert-butyl N-4-[4-chloro-7-(1,4-dioxaspiro[4.5]dec-8-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenylcarbamate as an off-white solid (21.0 g, 56%), ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (9 H, s), 1.89 (4 H, m), 2.07 (4 H, m), 4.01 (4 H, s),

4.89 (1 H, m), 6.75 (1 H, br s), 7.23 (1 H, br s), 7.25 (1 H, br s), 7.34 (1 H, br s), 8.14 (1 H, br t), and 8.64 (1 H, s) and RP-HPLC (5 to 100 % CH_3CN in 0.1 N aqueous ammonium acetate over 15 min at 1 mL/min using a Hypersil HyPurity Elite C18, 5μm, 200Å, 250 x 4.6 mm column) t_r= 10.48 min., 100%.

d) 5-(4-Amino-3-fluorophenyl)-7-(1,4-dioxaspiro[4.5]dec-8-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

A cloudy mixture of *tert*-butyl N-4-[4-chloro-7-(1,4-dioxaspiro[4.5]dec-8-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenylcarbamate (10.5 g, 20.92 mmol), aq. ammonium hydroxide (28 - 30 %, 100 mL) and dioxane (100 mL) was placed in a sealed vessel at ambient temperature then heated to 120°C with stirring for 24 h. (t.l.c. analysis using 9:1 EtOAc:heptane as the eluent). The reaction was concentrated *in vacuo*, diluted with EtOAc (300 mL), washed with brine (2x 150 mL), dried (Na_2SO_4) and concentrated under reduced pressure and scrupulously dried to afford *5-(4-Amino-3-fluorophenyl)-7-(1,4-dioxaspiro[4.5]dec-8-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine* as a yellow solid (7.93 g, 99 %), ^{1}H NMR (400 MHz, d_6-DMSO) 1.74 (4 H, *m*), 1.90 (2 H, *m*), 2.06 (2 H, *m*), 3.90 (4 H, m), 4.64 (1 H, *m*), 5.18 (2 H, *br s*), 6.02 (2 H, *br s*), 6.84 (1 H, *t*), 6.97 (1 H, *d*), 7.08 (1 H, *d*), 7.26 (1 H, *s*) and 8.10 (1 H, *s*) and *m/z* 384.2 (MH^+).

e) 4-[4-amino-5-(4-amino-3-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-1-cyclohexanone

5*M* HCl (300 mL) was added slowly to a solution of 5-(4-amino-3-fluorophenyl)-7-(1,4-dioxaspiro[4.5]dec-8-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (18.49 g, 48.28 mmol) in acetone (800 mL) at 0°C the resulting dark orange-brown solution was heated at 60°C for 4 h. (t.l.c. analysis using 10% MeOH in CH_2Cl_2). The acetone was removed under reduced pressure and the acidic layer was basified to approx. pH 8 using sat. aq. Na_2CO_3. The resulting precipitate was collect by filtration and scrupulously dried to afford *4-[4-amino-5-(4-amino-3-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-1-cyclohexanone* as a light brown solid (12.67 g, 77%). A second crop was also obtained from the mother liquor on standing (2.01 g, 12%), ^{1}H NMR (400 MHz, d_6-DMSO) 2.27 (2 H, *m*), 2.30 (4 H, *br d*), 2.73 (2 H, *m*),

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5.14 (1 H, *m*), 5.20 (2 H, *br s*), 6.05 (2 H, *br s*), 6.85 (1 H, *t*), 6.97 (1 H, *dd*), 7.06 (1 H, *dd*), 7.35 (1 H, *s*) and 8.12 (1 H, *s*) and *m/z* 340.1 (MH^+).

cis- and trans- 5-(4-Amino-3-fluorophenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-

Example 304: cis-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide trimaleate

To a solution of 4-[4-amino-5-(4-amino-3-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-1-cyclohexanone (1.0 g, 2.95 mmol), N-methylpiperazine (3 equiv, 0.885 g, 8.85 mmol, 0.98 mL) and glacial acetic acid (3 equiv., 0.51 mL, 8.85 mmol) in dichloroethane (50 mL) under nitrogen was added sodium triacetoxyborohydride (1.3 equiv., 0.81 g, 3.84 mmol). The solution was stirred for 18 hr then additional sodium triacetoxyborohydride (0.40 g, 1.9 mmol) was added and the reaction continued for a further 48 hr. The reaction was concentrated *in vacuo*, partitioned between dichloromethane (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The aqueous layer was further extracted with dichloromethane (4 x 100 mL) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness to give a yellow foam (0.95 g). Purification by column chromatography over silica gel using a dichloromethane:methanol (9:1 to 5:1) gradient afforded *cis-5-(4-amino-3-fluorophenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine*, the higher running component, as a cream solid (400 mg, 32 %) ^{1}H NMR (d_6 DMSO, 400 MHz) 1.56 (3H, br t), 1.68 (2H, br d), 1.99 (5H, m), 2.20 (3H, s), 2.43 (7H, br m), 4.65 (1H, m), 5.20 (2H, s), 6.01 (2H, br s), 6.85 (1H, t, *J*= 9.6 Hz), 6.98 (1H, dd, *J*= 8.0 and 1.6 Hz), 7.10 (1H, dd, *J*=12.4 and 1.6 Hz), 7.12 (1H, s), and 8.10 (1H, s) and RP-HPLC (10 to 90 % CH_3CN in 0.1 N aqueous ammonium acetate over 12 min at 2 mL/min using a Waters Symmetry C18, 250 x 4.6 mm column) tr= 8.619 min., 96%

A mixed fraction was obtained which contained both *cis-* and *trans-*isomers (440 mg, 50:50 mixture), and in addition the lower running fraction contained *trans-5-(4-*

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amino-3-fluorophenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine, as a yellow solid (110 mg, 9%), ^{1}H NMR (d_6 DMSO, 400 MHz) 1.94 (6H, m), 2.17 (3H, s), 2.33 (7H, br m), 2.51 (3H, m), 3.28 (1H, m), 4.51 (1H, m), 5.18 (2H, s), 6.01 (2H, br s), 6.84 (1H, t), 6.96 (1H, dd), 7.04 (1H, dd), 7.30 (1H, s), and 8.08 (1H, s) and RP-HPLC (10 to 40 % CH_3CN in 0.1 N aqueous ammonium acetate over 12 min at 2 mL/min using a Waters Symmetry C18, 250 x 4.6 mm column) t_r= 7.595 min, 97%

Example 305: trans-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide trimaleate

4-Fluorobenzenesulfonyl chloride (45.9 mg, 0.236 mmol) was added to a solution of trans-5-(4-amino-3-fluorophenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (100 mg, 0.236 mmol) in pyridine (2 mL) at 40oC. After 27 hr at 40°C the reaction had reached completion and was concentrated in vacuo. Purification by column chromatography over silica gel using 10% to 50% MeOH in dichloromethane as the gradient afforded as a colurless oil (0.78 mmol). The product was dissolved in ethanol and maleic acid (3 equiv., 27 mg, 0.233 mmol) added. The mixture was heated until homogeneous and *trans-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide trimaleate* crystallised on cooling as a fawn solid (37 mg, 17 %), RP-HPLC (10 to 40 % CH_3CN in 0.1 N aqueous ammonium acetate over 12 min at 2 mL/min using a Waters Symmetry C18, 250 x 4.6 mm column) t_r= 14.528 min., 96% and *m/z* 582.0 (*MH*$^+$).

Example 306: cis-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide

cis-*N1-(4{-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide was prepared*

using the same procedure as detailed for the free base of trans-*N1-(4{-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide except on a 3.36 mmol scale.*

(400 mg, 32%), RP-HPLC (10 to 40 % CH_3CN in 0.1 N aqueous ammonium acetate over 12 min at 2 mL/min using a Waters Symmetry C18, 250 x 4.6 mm column) t_r= 15.232, 94% min. and *m/z* = 582.1 (*MH*$^+$).

Example 307: *5-(4-amino-3-fluorophenyl)-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine*

a) 7-(1-benzyl-4-piperidyl)-4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine

Diethyl diazodicarboxylate (2.0 equiv., 18.19 g, 41.2 mL, 104.8 mmol) was added dropwise over approx. 1 h to a solution of 4-chloro-3-iodopyrrolo[2,3-d]pyrimidine (14.55 g, 52.4 mmol), 1-benzyl-4-hydroxypiperidine (3.0 equiv., 30.06 g, 157.16 mmol) and triphenylphosphine (2.0 equiv., 27.51 g, 104.8 mmol) in THF (730 mL) at room temperature under nitrogen. The reaction reached completion after 72 h (t.l.c. analysis using 1:1 EtOAc:heptane as the eluent, Rf = 0.2). The reaction was concentrated in vacuo and 1:4 ethyl acetate : heptane was added until a precipitate in a clear solution was observed. The precipitate was collected by filtration (Ph3PO) and the filtrate was concentrated, dissolved in ethyl acetate (500 mL) and extracted with aq. HCl (1M, 3 x 200 mL). The combined acidic layers were basified with aq NaOH (4 N) to pH 12 then extracted into ethyl acetate(3 x 300 mL), dried (MgSO4) and concentrated in vacuo. Purification by column chromatography using 5:4 light petroleum (30-60 °C):ethyl acetate over silica gel gave 2 main fractions of which the first fraction contained the product as a pale yellow crystalline solid which was recrystallised from ethyl acetate to give 7-(1-benzyl-4-piperidyl)-4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine as a cream crystalline solid (5.7 g, 24 %); ^{1}H NMR (400 MHz, $CDCl_3$) 2.02 (4H, m), 2.24 (2H, m), 3.06 (2H, br d), 3.58 (2H, s), 4.76 (1H, m), 7.27 (2H, m), 7.32 (3H, m), 7.49 (1H, s) and 8.60 (1H, s) and *m/z* = 452.8 (*MH*$^+$).

b) *tert*-butyl *N*-4-[7-(1-benzyl-4-piperidyl)-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-2-fluorophenylcarbamate

A suspension of 7-(1-benzyl-4-piperidyl)-4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (5.7 g, 12.6 mmol), *tert*-butyl *N*-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.5 equiv, 18.9 g, 6.38 mmol), sodium carbonate (2.5 equiv, 3.34 g, 31.5 mmol) and $Pd(PPh_3)_4$ (4 mol%, 0.58 g, 0.5 mmol) in DME (210 mL) and degassed water (37 mL) was heated at 80°C under nitrogen for 17 h (t.l.c. analysis using 1:1 EtOAc:heptane as the eluent). The reaction mixture was concentrated *in* vacuo, dissolved in ethyl acetate (400 mL) and washed with 10 % aq. Na_2CO_3 (3 x 200 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by column chromatography using 1:1 ethyl acetate:heptane as the eluent to afford *tert*-butyl *N*-4-[7-(1-benzyl-4-piperidyl)-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-2-fluorophenylcarbamate as a white crystalline solid (5.2 g, 9.7 mmol, 77%), ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (9 H, *s*), 2.05 (4H, *m*), 2.24 (2H, *m*), 3.06 (2H, *br d*), 3.60 (2H, *s*), 4.83 (1H, *m*), 7.25 (2H, *m*), 7.29 (1H, *m*), 7.33 (6H, *m*), 8.12 (1H, *br t*) and 8.64 (1H, *s*).

c) *5-(4-amino-3-fluorophenyl)-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine*

A mixture of the *tert*-butyl *N*-4-[7-(1-benzyl-4-piperidyl)-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-2-fluorophenylcarbamate (5.2 g, 9.7 mmol), aq. ammonium hydroxide (28 - 30 %, 100 mL) and 1,4-dioxane (100 mL) was placed in a sealed vessel at ambient temperature then heated to 120 °C with stirring for 16 h. (t.l.c. analysis using EtOAc as the eluent). The reaction was concentrated *in vacuo*, diluted with EtOAc (300 mL), washed with brine (2x 200 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford a brown solid which was triurated with ether (approx. 50 mL) to give *5-(4-amino-3-fluorophenyl)-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine* as a cream solid (3.0 g, 74 %), ^{1}H NMR (400 MHz, $CDCl_3$) 2.06 (4 H, *m*), 2.27 (2 H, *m*), 3.06 (2 H, *m*), 3.59 (2H, *br s*), 3.70 (2 H, *br s*), 4.73 (1H, *m*), 5.12 (2 H, *s*), 6.85 (1 H, *t*), 7.01(1 H, *s*), 7.06 (1 H, *dd*), 7.10 (1 H, *dd*), 7.28 (2 H, *m*), 7.34 (3H, *m*) and 8.31 (1 H, *s*) and m.p. 141-142

°C.

Example 308: N1-4-[4-amino-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide

N1-4-[4-amino-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide (470981) was prepared using the same procedure as detailed for trans-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide tri-maleate except on a 6.96 mmol scale. N1-4-[4-amino-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide was obtained as a cream solid (3.2 g, 80%), m/z 575 (MH^+) and m.p. 265-6 °C.

Example 309: N1-4-[4-amino-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-2,3-dichloro-1-benzenesulfonamide

N1-4-[4-amino-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-2,3-dichloro-1-benzenesulfonamide was prepared in the same manner as detailed above on a 5.04 mmol scale. The resulting *N1-4-[4-amino-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide* was obtained as a brown solid (1.0 g, 32%), m/z 625 (MH^+) and RP-HPLC (5 to 85 % CH_3CN in 0.1 N aqueous ammonium acetate over 20 min at 1 mL/min using a Waters Delta pack 5m C18, 300Å, 150 x 3.9 mm column) t_r= 14.963 min., 95%.

Example 310: N1-4-[4-amino-7-(4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide

A mixture containing N1-4-[4-amino-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide (2.40 g, 4.18 mmol), ammonium formate (10 equiv., 41.8 mmol, 2.62 g), palladium on carbon (10%, 1.2g) and ethanol (100 mL) was heated at reflux with vigorous stirring for 6h., filtered and concentrated *in vacuo*. The solid was partitioned between dichloromethane (50 mL) and water (50 mL). The brown solid which formed at the

phase boundary was collected and analysed for *N1-4-[4-amino-7-(4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide* (0.33 g), *m/z* 485 (MH^+) and m.p. 238-9 °C (dec.).

Example 311: N1-4-[4-amino-7-(1-formyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide

The procedure detailed for the preparation of N1-4-[4-amino-7-(4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide was performed on a smaller scale (0.35 mmol) where the combined organic layers from the work up were isolated, dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a white oil which was purified by preparative HPLC (100% pH 4.5 50mM ammonium acetate to 100% CH_3CN in 8.5 minutes with a 1.5 minute hold at 25 mL/min using a Hypersil 5m BDS C18, 100x 21.2mm column) to yield *N1-4-[4-amino-7-(1-formyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide* as a white solid (50 mg, 27 %), *m/z* = 512.9 (MH^+) and RP-HPLC (5 to 85 % CH_3CN in 0.1 N aqueous ammonium acetate over 20 min at 1 mL/min using a Waters Delta pack 5m C18, 300Å, 150 x 3.9 mm column) t_r= 13.091 min., 95%.

Example 312: N1-[4-(4-amino-7-1-[(1-methyl-1H-4-imidazolyl)sulfonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide dimaleate

1-Methylimidazol-4-yl sulphonyl chloride (1.1 equiv., 0.068 mmol, 12.3 mg) was added to a suspension of 5-(4-amino-3-fluorophenyl)-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (30 mg, 0.062 mmol) and triethylamine (3 equiv., 0.186 mmol, 26 l) in dichloromethane (1 mL) and stirred at ambient temperature for 24 h. The reaction was concentrated *in vacuo*, partitioned between dichloromethane (100 mL) and water (50 mL) and the aqueous layer was further extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. Purification by column chromatography over silica gel using 10 % methanol in dichloromethane yielded a waxy white solid (10 mg). Maleic acid (2 equiv., 4 mg) was added to the product in

hot ethanol and *N1-[4-(4-amino-7-1-[(1-methyl-1H-4-imidazolyl)sulfonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide dimaleate*salt crystallized on cooling (10 mg), RP-HPLC (5 to 85 % CH_3CN in 0.1 N aqueous ammonium acetate over 20 min at 1 mL/min using a Waters Delta pack 5m C18, 300Å, 150 x 3.9 mm column) t_r= 14.186, 100% min. and *m/z* = 629 (*MH*$^+$).

Example 313: N1-[4-(4-amino-7-1-[(1,2-dimethyl-1H-4-imidazolyl)sulfonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide

Using the procedure detailed for the synthesis of the free base of N1-[4-(4-amino-7-1-[(1-methyl-1H-4-imidazolyl)sulfonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide dimaleate, *N1-[4-(4-amino-7-1-[(1,2-dimethyl-1H-4-imidazolyl)sulfonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1*-benzenesulfonamide was prepared as a cream solid (9 mg), m.p. 217-8 °C and *m/z* = 643.2 (*MH*$^+$).

Example 314: N1-[4-(4-amino-7-1-[(1,3-dimethyl-1H-5-pyrazolyl)carbonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide

1,3-Dimethylpyrazole-5-carbonyl chloride (1.5 equiv., 14.8 mg, 0.093 mmol) was added to a stirred suspension of 5-(4-amino-3-fluorophenyl)-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (30 mg, 0.062 mmol) and potassium carbonate (2 equiv., 17.1 mg, 0.124 mmol) in N-methylpyrrolidinone (2 mL) and the resulting mixture was stirred at ambient temperature under nitrogen for 16 h. The solvent was removed in vacuo and the mixture purified by column chromatography over silica gel using 5 % methanol in dichloromethane as the eluent to give *N1-[4-(4-amino-7-1-[(1,3-dimethyl-1H-5-pyrazolyl)carbonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide* as a colourless glass (10 mg), RP-HPLC HPLC (100% pH 4.5 50mM ammonium acetate to 100% CH_3CN in 4.5 minutes with a 0.5 minute hold at 3.5 mL/min using a Perkin Elmer

Pecosphere 3m C18 (33 x 4.6mm) column) t_r= 2.98 min., 96% and *m/z* = 629 (*MH*$^+$).

Example 315: N1-(4-{4-amino-7-[1-(2-pyridylcarbonyl)-4-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide

N1-(4-{4-amino-7-[1-(2-pyridylcarbonyl)-4-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide was prepared using the same procedure as detailed for N1-[4-(4-amino-7-1-[(1,3-dimethyl-1H-5-pyrazolyl)carbonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide, (12 mg), RP-HPLC HPLC (100% pH 4.5 50mM ammonium acetate to 100% CH_3CN in 4.5 minutes with a 0.5 minute hold at 3.5 mL/min using a Perkin Elmer Pecosphere 3m C18 (33 x 4.6mm) column) t_r= 2.73 min., 98% and *m/z* = 590.2 (*MH*$^+$).

Example 316: N1-4-(4-amino-7-{4-[1-(1-methylpiperid-4-yl)piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl})-2-fluorophenyl-4-fluoro-1-benzenesulfonamide tri-maleate

Sodium triacetoxyborohydride (28.1 mg, 0.134 mmol) was added to a solution of N1-4-[4-amino-7-(4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide (50 mg, 0.103 mmol) and 1-methylpiperid-4-one (0.92 ml, 0.155 mmol) in glacial acetic acid (0.025 mL) and NMP (3 mL). The reaction was stirred for 20 h at room temperature then additional sodium triacetoxyborohydride (1.3 equiv.)
was added. After a further 24 h the reaction had proceeded to completion and was concentrated *in vacuo*, partitioned between dichloromethane (100 mL) and sat. aq. $NaHCO_3$ (100 mL). The aqueous layer was further extracted with dichloromethane (4 x 100 mL) and the combined organic layers were dried over magnesium sulfate and evaporated to dryness. Purification by column chromatography over silica gel using dichloromethane:methanol:ammonium hydroxide (78:19:3) as the eluent to afford a brown solid. The tri maleate salt was then formed by standard methods to give *N1-4-(4-amino-7-{4-[1-(1-methylpiperid-4-yl)piperidyl]-7H-pyrrolo[2,3-*

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d]pyrimidin-5-yl})-2-fluorophenyl-4-fluoro-1-benzenesulfonamide tri-maleate as a brown solid (45 mg, 75%), m/z 582 (MH^+) and RP-HPLC (5 to 85 % CH_3CN in 0.1 N aqueous ammonium acetate over 20 min at 1 mL/min using a Waters Delta pack 5m C18, 300Å, 150 x 3.9 mm column) t_r= 10.658 min., 95%.

Example 317: N1-4-[4-amino-7-(4-oxocyclohexyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-methoxyphenylbenzamide

a) To a solution of 4-chloro-5-iodo-*7H*-pyrrolo[2,3-d]pyrimidine (25.0 g, 0.09 mol), 1,4-dioxaspiro[4.5]decan-8-ol (35.8 g, 0.0267 mol) and triphenylphosphine (46.7 g, 0.178 mol) in THF (1.2 L) was added diethylazodicarboxylate (30.9 g, 0.178 mol) under nitrogen. The solution was stirred for 20 hr and the majority of solvent was then evaporated (250 mL remaining). EtOAc (450 mL) was then added and the resulting solid was filtered, washed with EtOAc (2 x 50 mL) and dried *in vacuo* to give 4-chloro-7-(1,4-dioxaspiro[4.5]dec-8-yl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (22.5 g, 60%) as a cream solid. ^{1}H NMR (d_6 DMSO, 400 MHz) 8.64 (1H, s), 8.10 (1H, s), 4.74 (1H, m), 3.90 (4H, m), 2.12 (2H, m), 1.91 (2H, m), 1,71-1.83 (4H, m). R_f in 1:4 EtOAc : heptane = 0.12.

b) A solution of *tert*-butyl *N*-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (8.2 g, 23.5 mmol), 4-chloro-7-(1,4-dioxaspiro[4.5]dec-8-yl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (6.57 g, 15.7 mmol), tetrakistriphenylphosphinepalladium (1.1 g, 0.93 mmol), sodium carbonate (4.16 g, 39.2 mmol) in dimethoxyethane (200 mL) and water (100 mL) was heated at 80°C for 20 hr under nitrogen. The resulting solution was cooled to room temperature and partitioned between EtOAc (300 mL) and water (100 mL). The aqueous layer was extracted with EtOAc (3 x 150 mL) and the combined organics were washed with water (1 x 150 mL). The organics were dried (sodium sulphate), filtered and evaporated to leave a solid. On attempting to dissolve in EtOAc/heptane (1:4), a cream solid (2.5 g) crashed out. The filtrate was adsorbed onto silica and purified by flash silica gel column chromatography using 10:1 heptane:EtOAc , 4:1 heptane : EtOAc , 1:1 heptane:EtOAc and 4:1 EtOAc:heptane. The appropriate fractions were

combined to give a white solid which was triturated with heptane/EtOAc (5:1) to give *tert*-butyl *N*-4-[4-chloro-7-(1,4-dioxaspiro[4.5]dec-8-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-2-methoxyphenylcarbamate as a solid (3.2 g), combined yield is 71%.

^{1}H NMR (d_6 DMSO, 400 MHz): 8.66 (1H, s), 7.93 (2H, m), 7.74 (1H, m), 7.19 (1H, s), 7.07 (1H, d), 4.81 (1H, m), 3.93 (4H, m), 3.91 (3H, s), 2.18 (2H, m), 1.99 (2H, m), 1.79 (4H, m), 1. 48 (9H, s). HPLC (conditions: 5 to 95% CH_3CN in 0.1 N aqueous ammonium acetate over 20 min.) t_r = 21.24 min, 100%.

c) *tert*-Butyl *N*-4-[4-chloro-7-(1,4-dioxaspiro[4.5]dec-8-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-2-methoxyphenylcarbamate (5.7 g, 0.011 mol), conc. ammonia solution (100 mL) and dioxan (100 mL) were heated in a pressure vessel for 20 hr at 120°C. The solvent was evaporated and the residue reconstituted in EtOAc/water (250 mL/100 mL). The organic layer was separated , dried (sodium sulphate), filtered and evaporated to give a solid which by HPLC (conditions: 5 to 95% CH_3CN in 0.1 N aqueous ammonium acetate over 20 min.) was observed to be a 2:1 mixture of *tert*-butyl *N*-4-[4-amino-7-(1,4-dioxaspiro[4.5]dec-8-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-2-methoxyphenylcarbamate and 5-(4-amino-3-methoxyphenyl)-7-(1,4-dioxaspiro[4.5]dec-8-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine. The mixture was dissolved in acetone (200 mL) and HCl (5N, 100 mL) was added dropwise over 0.5 hr. The resulting solution was stirred at room temperature overnight and the solvent was then evaporated. The acidic solution was basified with 2N NaOH (ice-cooling) and extracted with EtOAc (3 x 150 mL). The combined organics were washed with water (2 x 100 mL). During the extraction process a solid precipitated. This solid was filtered and triturated in hot EtOAc/MeOH. The insolubles were filtered, the filtrate evaporated and then resulting solid triturated with diethylether/ethyl acetate to give a yellow solid. The organic layers from the original extraction were dried (sodium sulphate), filtered and evaporated. The resulting solid was triturated with diethyl ether/ethyl acetate (5:1) and filtered to give 4-[4-amino-5-(4-amino-3-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-1-cyclohexanone as a yellow solid. (2.3 g, combined yield = 78%). ^{1}H NMR (d_6 DMSO, 400 MHz): 8.17 (1H, s),

Example 148: Ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]propionate

Sodium hydride (120 mg, of a 60% dispersion in mineral oil) was added to a mixture of 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (906 mg) in dry dimethyformamide (30 ml) and the mixture was stirred under nitrogen for 30 minutes at ambient temperature. A solution of ethyl 2-bromopropionate (543 mg) in dry DMF (10 ml) was added dropwise via a syringe over 10 minutes. The mixture was stirred at ambient temperature for 2 hours and then left for 18 hours. The mixture was evaporated under vacuum and the residue was washed with water to give a solid which was triturated with ether and filtered to give ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]propionate, m.p. 139-140°C.

Example 149: N-(2-dimethylaminoethyl)-2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propionamide

A mixture of ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]propionate (425 mg), N,N-dimethylethylenediamine (2 ml) and methanol (20 ml) was boiled under reflux for 18 hours with the exclusion of carbon dioxide. The mixture was cooled and filtered, the filtrate was diluted with water (50 ml) and stirred with ether. The mixture was left standing for 18 hours and the solid which precipitated was collected by filtration, washed with water and then ether and dried to give N-(2-dimethylaminoethyl)-2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propionamide, m.p. 163-164°C.

Example 150: Ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate

A mixture of 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (906 mg), sodium hydride (120 mg, of a 60% dispersion in mineral oil) and dry dimethylformamide (30 ml) was stirred at ambient temperature under nitrogen for 30 minutes. Ethyl bromoacetate (0.5 g) in dimethylformamide (10 ml) was added over 5 minutes at 0-5°C with stirring. The mixture was stirred for 30 minutes at ambient

temperature and then allowed to stand for 18 hours. The mixture was evaporated under vacuum and the residue was triturated with water and ether. The solid obtained was collected by filtration, washed with water and then with ether to give ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate, m.p. 161-161.3°C.

Examples 151-156

General Method

Ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (194 mg) was heated at 62°C and stirred with 10 molar equivalents of the appropriate amine as listed below in methanol (12 ml) for 18 hours to give after work up the following compounds:

Example 151

N-[2-hydroxyethyl-1,1-di(hydroxymethyl)]-2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetamide, m.p. 222-223°C with decomposition, from 2-hydroxyethyl-1,1-di(hydroxymethyl)ethylamine.

Example 152

N-[2-(piperazin-1-yl)ethyl]-2-[4-amino-5-[4-phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidin-7-yl]acetamide, m.p.138-140°C, from 2-(piperazin-1-yl)ethylamine.

Example 153

N-(2-morpholinoethyl)-2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetamide, m.p. 164-165°C, from 2-morpholinoethylamine.

4.74 (1H, m), 3.82 (3H, s), 3.23 (5H, m), 2.78 (3H, s), 2.51 (3H, m), 2.41 (1H, s), 2.09 (4H, m), 1.70 (4H, m). HPLC: (5 to 95% CH_3CN in 0.1 N aqueous ammonium acetate over 20 min.) t_r = 13.30 min , 94%.

F28-45 gave a glassy foam (186 mg) which was dissolved in in ethyl acetate (10 mL) and treated with maleic acid (114 mg) in ethyl acetate (3 mL). The resulting solid was filtered under nitrogen and dried *in vacuo* for 4 hr to give *trans*- benzyl *N*-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methoxyphenyl)carbamate tri-maleate salt (250 mg) as a cream solid. M.pt 146-148°C. HPLC: (5 to 95% CH_3CN in 0.1 N aqueous ammonium acetate over 20 min.) t_r = 13.54 min , 94.6%. ^{1}H NMR (d_6 DMSO, 400 MHz): 8.72 (1H, s), 8.25 (1H, s), 7.77 (1H, d), 7.51 (1H, s), 7.35 (5H, m), 7.10 (1H, s), 7.04 (1H, d), 6.16 (6H, s), 5.17 (2H, s), 4.59 (1H, m), 3.86 (3H, s), 2.70-3.10 (11H, m), 2.50 (3H, s), 1.97 (6H, m), 1.56 (2H, m).

Exxample 320: Trans-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-methoxyphenyl)benzamide

To a solution of *N*1-4-[4-amino-7-(4-oxocyclohexyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-2-methoxyphenylbenzamide (1.2 g, 2.66 mmol), N-methylpiperazine (0.80 g, 7.98 mmol) and glacial acetic acid (0.48 g, 7.98 mmol) in dichloroethane (150 mL) under nitrogen was added sodium triacetoxyborohydride (0.85 g, 3.99 mmol) portionwise. The solution was stirred at room temperature overnight and then quenched by the addition of sodium hydroxide (2 N, 20 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organics were dried (sodium sulphate), filtered and evaporated to leave a solid which was purified by flash silica gel column chromatography using dichloromethane then 5% MeOH/dichloromethane to 20% MeOH/ dichloromethane in 5% increments. F23-36 were combined and evaporated to give a cream solid (0.11 g) which was dissolved in EtOAc (10 mL) and treated with a solution of maleic acid ( ) in EtOAc (5 mL). The resulting fine solid was filtered under a stream of nitrogen to give *trans*-*N*1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methoxyphenyl)benzamide (0.108 g) as a cream solid. ^{1}H NMR (d_6 DMSO,

400 MHz): 9.48 (1H, s), 8.28 (1H, s), 7.97 (3H, m), 7.53-7.63 (4H, m), 7.18 (1H, s), 7.08 (1H, d), 6.85 (1H, bs), 6.16 (6H, s), 4.61 (1H, m), 3,92 (3H, s), 2.70-3.11 (11H, m), 2.01 (7H, m), 1.58 (2H, m). HPLC/MS (Column = Pecosphere 3 C_{18} 3 micron, conditions = 100% 100mM ammonium acetate to 100% acetonitrile over 5 min), t_r = 1.83 min, MH^+ = 540.8

Example 321: Cis-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-methoxyphenyl)-3-phenylpropanamide
and
Trans- N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-methoxyphenyl)-3-phenylpropanamide

a) To a solution of 4-[4-amino-5-(4-amino-3-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-1-cyclohexanone (0.8 g, 2.3 mmol) in pyridine (13 mL) and dichloromethane (32 mL) at 0°C was added hydrocinnamoylchloride (0.57 g, 3.4 mmol) in dichloromethane (5 mL) under nitrogen. The solution was stirred at 0°C for 2 hr, warmed to room temperature and quenched by addition of saturated aqueous citric acid solution (50 mL). The organic layer was washed with saturated aqueous citric acid solution (2 x 50 mL), dried (sodium sulphate), filtered and evaporated to leave *N*1-{4-[4-amino-7-(4-oxocyclohexyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-2-methoxyphenyl}-3-phenylpropanamide (1.0 g, 92% crude) as a brown foam. ^{1}H NMR (d_6 DMSO, 400 MHz):9.17 (1H, s), 8.18 (1H, s), 8.06 (1H, d), 7.51 (1H, s), 7.18-7.29 (6H, m), 7.09 (1H, m), 6.99 (1H, d), 6.21 (2H, bs), 5.18 (1H, m), 3.88 (3H, s), 1.99 – 2.93 (12H, m). HPLC: (5 to 95% CH_3CN in 0.1 N aqueous ammonium acetate over 20 min.) t_r = 14.48 min , 92.2%.

c) To a solution of 92% pure *N*1-{4-[4-amino-7-(4-oxocyclohexyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-2-methoxyphenyl}-3-phenylpropanamide (1.0 g, 2.1 mmol), N-methylpiperazine (0.63 g, 6.3 mmol), acetic acid (0.38 g, 6.3 mmol) in dichloroethane (100 mL) was added sodium triacetoxyborohydride (0.67 g, 3.15 mmol) portionwise under nitrogen. The solution was stirred for 20 hr and then quenched by the addition of saturated aqueous sodium bicarbonate solution (50

mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL), dried (sodium sulphate), filtered and evaporated to leave a sludge which was purified by flash silica gel column chromatography using dichloromethane to 50% MeOH/dichloromethane in 10% increments. F84-96 were combined and evaporated to leave *cis-N*1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methoxyphenyl)-3-phenylpropanamide (0.26 g) as a cream foamy glass. HPLC: (5 to 95% CH_3CN in 0.1 N aqueous ammonium acetate over 20 min.) t_r = 12.65 min , 95.2%.^{1}H NMR (d_6 DMSO, 400 MHz): 9.17 (1H, s), 8.14 (1H, s), 8.05 (1H, d), 7.28 (5H, m), 7.18 (1H, m), 7.10 (1H, s), 6.99 (1H, d), 6.11 (2H, bs), 4.67 (1H, m), 3.88 (3H, s), 2.90 (2H, m), 2.73 (2H, m), 2.50 (7H, m), 2.28 (3H, s), 2.06 (3H, m), 1.71 (2H, m), 1.55 (2H, m). F121-138 were combined and evaporated to leave *trans- N*1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methoxyphenyl)-3-phenylpropanamide (0.11 g) as a white solid. HPLC: (5 to 95% CH_3CN in 0.1 N aqueous ammonium acetate over 20 min.) t_r = 12.61 min , 96.2%. ^{1}H NMR (d_6 DMSO, 400 MHz):9.16 (1H, s), 8.13 (1H, s), 8.04 (1H, d), 7.44 (1H, s), 7.29 (4H, m), 7.18 (1H, m), 7.09 (1H, s), 6.97 (1H, d), 6.11 (2H bs), 4.53 (1H, m), 3.88 (3H, s), 2.93 (2H, m), 2.71 (2H, m), 2.50 (4H, m), 2.30 (5H, m), 2.14 (3H, s), 1.89 (6H, m), 1.46 (2H, m).

General Procedure for Substituted Pyrrolopyrimidine Aryl sulfonamides are as follows:

A 0.19 M solution of 5-(4-amino-3-fluorophenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine in pyridine was added one equivalent of substituted aryl sulfonyl chloride. The mixture was heated to 45o C while being shaken in an Incubator Shaker for 24h. The reaction mixture was purified by using mass actuated preparative RP-HPLC (Micromass/Gilson, Hypersil BDS C18, 5u, 100x21.2mm; 100-100% ammonium acetate (0.05 M, pH 4.5)-acetonitrile over 12.5 min, 25 mL/min).

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Compounds synthesized by the above procedure include:

Name	HPLC rt min	m/z
Example 322: Trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-(trifluoromethoxy)-1-benzenesulfonamide trimaleate	3.18	648.39
Example 323: Trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-5-chloro-2-thiophenesulfonamide benzenesulfonamide trimaleate	3.14	604.03
Example 324: Trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-4-fluoro-1-benzenesulfonamide benzenesulfonamide trimaleate	3.07	616.1
Example 325: Trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide trimaleate	3.39	632.12
Example 326: cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-4-fluoro-1-benzenesulfonamide trimaleate	2.82	616.2

Example 327: cis-N-1-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl-2-fluorophenyl)-2,6-difluoro-1-benzenesulfonamide trimaleate	2.66	600.3
Example 328: Trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,6-difluoro-1-benzenesulfonamide trimaleate	2.53	600.3
Example 329: Trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,1,3-benzothiadiazole-4-sulfonamide trimaleate	2.63	622.1
Example 330: Trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3,4-trifluoro-1-benzenesulfonamide trimaleate	2.87	618.1
Example 331: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-nitro-1-benzenesulfonamide trimaleate	3.13	609.1
Example 332: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-fluoro-1-benzenesulfonamide trimaleate	2.89	582.1
Example 333: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,4,6-trichloro-1-benzenesulfonamide trimaleate	3.4	668
Example 334: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,6-dichloro-1-benzenesulfonamide trimaleate	3.04	632.1
Example 335: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-1-benzenesulfonamide trimaleate	2.94	598.1

Example 336: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)- 3-fluoro-1-benzenesulfonamide dimaleate	2.76	582.1
Example 337: cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-5-chloro-2-thiophenesulfonamide dimaleate	3.01	604.3
Example 338: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-bromo-2,5-difluoro-1-benzenesulfonamide trimaleate	3.38	718.3
Example 339: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-chloro-4-fluoro-1-benzenesulfonamide trimaleate	2.98	616.3
Example 340: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl-2-iodo-1-benzenesulfonamide trimaleate	3.02	690.3
Example 341: cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-(trifluoromethoxy)-1-benzenesulfonamide trimaleate	3.22	648.3
Example 342: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide trimaleate	2.97	600.3
Example 343: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-6-methyl-1-benzenesulfonamide trimaleate	3.12	612.3
Example 344: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-4-cyano-1-benzenesulfonamide trimaleate	3.02	623.2
Example 345: Cis-N-1-(4-{4-amino-7-[4-(4-	3.08	618.3

methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3,4-trifluoro-1-benzenesulfonamide trimaleate		
Example 346: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3,4-difluoro-1-benzenesulfonamide trimaleate	2.98	600.3
Example 347: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-bromo-2-fluoro-1-benzenesulfonamide trimaleate	3.13	660.2
Example 348: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-5-bromo-2-thiophenesulfonamide trimaleate	3.16	648.1
Example 349: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,4-dichloro-1-benzenesulfonamide trimaleate	3.09	632.1
Example 350: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3,4-trichloro-1-benzenesulfonamide trimaleate	3.41	668.1
Example 351: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-bromo-5-chloro-2-thiophenesulfonamide trimaleate	3.29	683.9
Example 352: Cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,1,3-benzothiadiazole-4-sulfonamide trimaleate	2.73	622.1
Example 353: cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,1,3-benzoxadiazole-4-sulfonamide trimaleate	2.8	606.1
Example 354: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,5-dichloro-1-	3.18	638

thiophenesulfonamide trimaleate		
Example 355: cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(7-chloro-2,1,3-benzoxadiazole)-4-sulfonamide trimaleate	2.84	640.2
Example 356: Cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(7-methyl-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate	2.89	636.2
Example 357: Cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(5-methyl-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate	2.82	636.2
Example 358: Cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(5-chloro-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate	2.82	656.2
Example 359: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-chloro-2-methyl-1-benzenesulfonamide trimaleate	3.01	612
Example 360: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-bromo-1-benzenesulfonamide trimaleate	2.81	644.2
Example 361: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,5-dibromo-3,6-difluoro-1-benzenesulfonamide trimaleate	3.29	758.1
Example 362: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide trimaleate	2.77	632
Example 363: Cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)- (2-nitrophenyl)methanesulfonamide trimaleate	2.73	623.2

General Synthesis

Method (a)

A mixture of 4-[4-amino-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-yl]-1-cyclohexanone (1.0 g, 2.51 mmol), the appropriate amine (7.54 mmol) and acetic acid (0.45 g, 7.54 mmol) in 1,2-dichloroethane (50 mL) was stirred at ambient temperature under an atmosphere of nitrogen for 30 minutes. Sodium triacetoxyborohydride (0.69 g, 3.26 mmol) was added and the mixture stirred at ambient temperature for 18 hours. Water (20 mL) and sodium bicarbonate (1.26 g, 15.1 mmol) were added to the mixture and stirred for one hour. The mixture was then filtered through a pad of celite and the pad was washed with dichloromethane (75 mL). The organic layer was extracted from the filtrate, dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The cis and trans isomers were purified by flash chromatography on silica gel using a methanol:dichloromethane gradient.

Method (b)

Where appropriate the salts were made as follows.

The above amine (0.909 mmol) was dissolved in warm ethyl acetate (100 mL) then maleic acid (0.32 g, 2.73 mmol) in ethyl acetate (30 mL) was added. The resulting salt formed an oily residue on the bottom and sides of the flask. The supernatant was poured off and the residue was dissolved in water and lyophilized to give the salt

Method (c)

Guanidines were made as follows. The amine (0.536 mmol) was dissolved in DMF (5 mL) and cooled to –5°C and then 1-H pyrazole-1-carbonamide (95 mg, 0.644 mmol) followed by diisopropylethylamine (208 mg, 1.6 mmol) were added. The

reaction mixture was allowed to warm to rt over 16h and then concentrated in vacuo. The reaction was partititoned between water (10 mL) and ethyl acetate (10 mL). The aqueous phase was lyophilized and purified by RP-HPLC.

HPLC protocols:

1. RP-HPLC - Hypersil HyPurity Elite C18, 5 mm, 200A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 15 min, 1ml/min.
2. RP-HPLC - Hypersil HyPurity Elite C18, 5 mm, 200A, 250 x 4.6 mm; 5-100% acetonitrile-0.1 M ammonium acetate over 15 min, 1ml/min.

It should be appreciated that protecting group chemistry is used where approriate.

The following examples were prepared using the methods described above:

Name	Synthetic method	HPLC-RT (Min) (Protocol)	m/z (MH^+)	Additional chemistry
Example 364: Cis-4-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-1-piperazinecarboximidamide	c	14.56 (2)	511.7	
Example 365: Trans-4-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-1-piperazinecarboximidamide	c	14.25 (2)	511.7	
Example 366: Trans-7-(4-{methyl[2-(2-pyridyl)ethyl]amino}cyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine trimaleate	a, b	8.55 (2)	519.6	
Example 367: Cis-3-({4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}amino)propanoic acid	a	10.21 (2)	472.6	Made by hydrolysis of the ester

Example 368: 3-({4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}amino)propanoic acid	a	6.33 (1)	472.6	Made by hydrolysis of the ester
Example 369: Ethyl cis-3-({4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}amino)propanoate dimaleate	a, b	10.42 (1)	500.6	

General Synthesis

Method (d)

To a solution of sodium hydride (22 mg, 0.553 mmol) in THF (2 mL) was added the appropriate phosphonate (0.553 mmol) at 0°C and the resultant mixture was stirred at this temperature for 20 min and then at ambient temperature for 10 min. The reaction mixture was cooled to 0°C and 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimin-7-yl]cyclohexanone (200 mg, 0.503 mmol) added in THF (10 mL) and the resultant mixture allowed to warm to ambient temperature and stirred for 16h. The solvents were removed *in vacuo* and the residue partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous layer was further extracted into ethyl acetate (3 x 5 mL) and the combined organics were washed with water (3 x 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (for intermediates) or RP-HPLC (for final compounds) gave the desired compound.

Method (e)

Hydrogenations were carried out as follows. A mixture of the alkene, (0.068 mmol) and 10% Pd/C (12 mg) in ethanol (18 mL) was stirred under hydrogen (4 atm) for

14h. The solids were removed by filtration and the filtrate concentrated *in vacuo*. Purification by RP-HPLC gave the final compound.

Method (f)

Lithium aluminum hydride reuctions were carried out as follows. A mixture of the substrate (0.19 mmol), lithium aluminum hydride (40 mg, 1.07 mmol) in THF (5 mL) was stirred at room temperature for 16h. Fieser work up followed by purification by RP-HPLC gave the desired compound.

HPLC conditions : RP-HPLC Pecosphere3 C18, 33 x 4.6 mm, 3m column; 0-100% acetonitrile-0.1 M ammonium acetate over 5 min, flow 4ml/min.

It should be appreciated that protecting group chemistry is used where approriate.

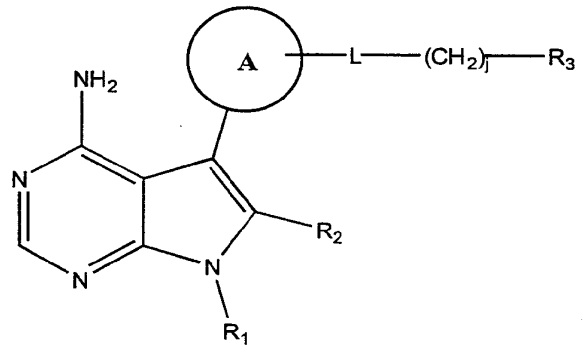
Name	Synthetic Method	HPLC-RT (Min)	m/z (MH^+)	Additional Chemistry
Example 370: {4-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyliden} methyl cyanide	d	3.1	422.5	
Example 371: tert-Butyl 2-[4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyliden}acetate	d	3.97	497.1	
Example 372: Ethyl 2-[4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyliden}acetate	d	3.56	469.0	
Example 373: 2-[4-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyliden}acetate	d	2.69	441.5	Made by hydrolysis of the ethyl ester

Example 374: 7-[4-(2-aminoethyl)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine	f	2.11	428.5	Made by lithium aluminum hydride reduction of the unsaturated cyanide
Example 375: 2-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}acetic acid	e	2.64	443.5	Made by hydrogenation of the unsaturated acid

CLAIMS

We Claim:

1. A compound represented by the following structural formula:



and pharmaceutically acceptable salts thereof, wherein:

Ring A is a six membered aromatic ring or a five or six membered heteroaromatic ring which is optionally substituted with one or more substituents selected from the group consisting of a substituted or unsubstituted aliphatic group, a halogen, a substituted or unsubstituted aromatic group, substituted or unsubstituted heteroaromatic group, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, cyano, nitro, $-NR_4R_5$, $-C(O)_2H$, -OH, a substituted or unsubstituted alkoxycarbonyl, $-C(O)_2$-haloalkyl, a substituted or unsubstituted alkylthio ether, a substituted or unsubstituted alkylsulfoxide, a substituted or unsubstituted alkylsulfone, a substituted or unsubstituted arylthio ether, a substituted or unsubstituted arylsulfoxide, a substituted or unsubstituted arylsulfone, a substituted or unsubstituted alkyl carbonyl, -C(O)-haloalkyl, a substituted or unsubstituted aliphatic ether, a substituted or unsubstituted aromatic ether, carboxamido, tetrazolyl, trifluoromethylsulphonamido, trifluoromethylcarbonylamino, a substituted or unsubstituted alkynyl, a substituted or unsubstituted alkyl amido, a

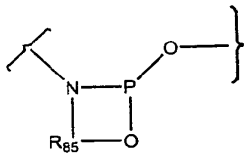
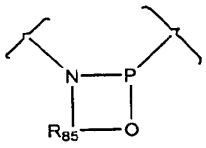
substituted or unsubstituted aryl amido, $-NR_{95}C(O)R_{95}$, a substituted or unsubstituted styryl and a substituted or unsubstituted aralkyl amido, wherein R_{95} is an alipatic group or an aromatic group;

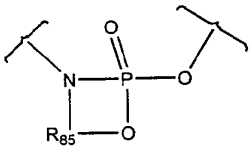
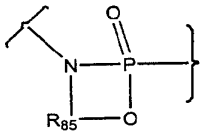
L is -O-; -S-; -S(O)-; $-S(O)_2-$; -N(R)-; -N(C(O)OR)-; -N(C(O)R)-; $-N(SO_2R)$; $-CH_2O-$; $-CH_2S-$; $-CH_2N(R)-$; -CH(NR)-;$-CH_2N(C(O)R))-$; $-CH_2N(C(O)OR)-$;$-CH_2N(SO_2R)-$; -CH(NHR)-; -CH(NHC(O)R)-; $-CH(NHSO_2R)-$; -CH(NHC(O)OR)-;-CH(OC(O)R)-;-CH(OC(O)NHR)-; -CH=CH-; -C(=NOR)-; -C(O)-; -CH(OR)-;-C(O)N(R)-; -N(R)C(O)-; -N(R)S(O)-;-$N(R)S(O)_2-$;-OC(O)N(R)-;-N(R)C(O)N(R)-; -NRC(O)O-;$-S(O)N(R)-$;-$S(O)_2N(R)-$; N(C(O)R)S(O)-; $N(C(O)R)S(O)_2-$; -N(R)S(O)N(R)-; -$N(R)S(O)_2N(R)-$; -C(O)N(R)C(O)-; -S(O)N(R)C(O)-; $-S(O)_2N(R)C(O)-$; -OS(O)N(R)-; $-OS(O)_2N(R)-$; -N(R)S(O)O-; $-N(R)S(O)_2O-$; -N(R)S(O)C(O)-; $-N(R)S(O)_2C(O)-$; -SON(C(O)R)-; $-SO_2N(C(O)R)-$; -N(R)SON(R)-; -$N(R)SO_2N(R)-$; -C(O)O-; -N(R)P(OR')O-; -N(R)P(OR')-; -N(R)P(O)(OR')O-; -N(R)P(O)(OR')-; -N(C(O)R)P(OR')O-; -N(C(O)R)P(OR')-; -N(C(O)R)P(O)(OR')O- or -N(C(O)R)P(OR')-, wherein R and R' are each, independently, -H, an acyl group, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, or a substituted or unsubstituted cycloalkyl group; or

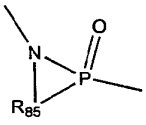
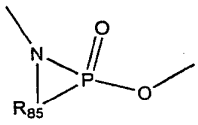
L is $-R_bN(R)S(O)_2-$, $-R_bN(R)P(O)-$, or $-R_bN(R)P(O)O-$, wherein R_b is an alkylene group which when taken together with the sulphonamide, phosphinamide, or phosphonamide group to which it is bound forms a five or six membered ring fused to ring A; or

L is represented by one of the following structural formulas:

254


,

,


,

,


or


wherein R_{85} taken together with the phosphinamide, or phophonamide is a 5-, 6-, or 7-membered, aromatic, heteroaromatic or heterocycloalkyl ring system;

R_1 is a substituted aliphatic group, a substituted cycloalkyl, a substituted bicycloalkyl, a substituted cycloalkenyl, an optionally substituted aromatic group, an optionally substituted heteroaromatic group, an optionally substituted heteroaralkyl, an optionally substituted heterocycloalkyl, an optionally substituted heterobicycloalkyl, an optionally substituted alkylamindo, and optionally substituted arylamido, an optionally substituted

$-S(O)_2$-alkyl or optionally substituted $-S(O)_2$-cycloalkyl, a -C(O)-alkyl or an optionally substituted –C(O)-alkyl, provided that when R_1 is an aliphatic group or cycloalkyl group, R_1 is not exclusively substituted with one or more substitutent selected from the group consisting of hydroxyl and lower alkyl ethers, provided that the heterocycloalkyl is not 2-phenyl-1,3-dioxan-5-yl and provided that an aliphatic group is not substituted exclusively with one or more aliphatic groups, wherein one or more substituent is selected from the group consisting of a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aromatic ether, a substituted or unsubstituted aliphatic ether, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted alkylcarbonyl, a substituted or unsubstituted arylcarbonyl, a substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted aryloxycarbonyl, -OH, a substituted or unsubstituted aminocarbonyl, an oxime, a substituted or unsubstituted azabicycloalkyl, heterocycloalkyl, oxo, aldehyde, a substituted or unsubstituted alkyl sulfonamido group, a substituted or unsubstituted aryl sulfonamido group, a substituted or unsubstituted bicycloalkyl, a substituted or unsubstituted heterobicycloalkyl, cyano, $-NH_2$, an alkylamino, ureido, thioureido and –B-E;

B is a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aromatic, a substituted or unsubstituted heteroaromatic, an alkylene, an aminoalkyl, an alkylenecarbnonyl, or an aminoalkylcarbonyl;

E is a substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted azacycloalkylcarbonyl, a substituted or unsubstituted azacycloalkylsulfonyl, a substituted or unsubstituted azacycloalkylalkyl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted heteroarylcarbonyl, a substituted or unsubstituted heteroarylsulfonyl, a

substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted alkyl sulfonamido, a substituted or unsubstituted aryl sulfonamido, a substituted or unsubstituted bicycloalkyl, a substituted or unsubstituted ureido, a substituted or unsubstituted thioureido or a substituted or unsubstituted aryl;

R_2 is –H, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted cycloalkyl, a halogen, -OH, cyano, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaralkyl, $-NR_4R_5$, or $-C(O)NR_4R_5$;

R_3 is a substituted or unsubstituted aliphatic group, a substituted or unsubstituted alkenyl group, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, or a substituted or unsubstituted heterocycloalkyl;

provided that L is -SN(R)-, $-S(O)N(R)-$, $-S(O)_2N(R)-$, -N(R)S-, -N(R)S(O)-, $-N(R)S(O)_2-$, -N(R)SN(R')-, -N(R)S(O)N(R')-, or -N(R)S(O)$_2$N(R')-when R_3 is a substituted or unsubstituted aliphatic group, a substituted or unsubstituted alkenyl group;

provided that j is 0 when L is –O-, $–CH_2NR-$, -C(O)NR- or –NRC(O)- and R_3 is azacycloalkyl or azaheteroaryl; and

provided that j is 0 when L is –O- and R_3 is phenyl;

R_4, R_5 and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterobicycloalkyl or a substituted or unsubstituted heteroaromatic; or

R_4 and R_5 are each, independently, -H, azabicycloalkyl, heterocycloalkyl, a substituted or unsubstituted alkyl group or Y-Z;

Y is selected from the group consisting of $-(CH_2)_p-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_pO-$, $-(CH_2)_pNH-$, $-(CH_2)_pS-$, $-(CH_2)_pS(O)-$, and $-(CH_2)_pS(O)_2-$;

p is an integer from 0 to 6;

Z is –H, a substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl group; and

j an integer from 0 to 6.

2. The compound of Claim 1, wherein R_3 is selected from the group consisting of a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, a substituted or unsubstituted pyridyl, a substituted or unsubstituted thienyl, a substituted or unsubstituted benzotriazole, a substituted or unsubstituted tetrahydropyranyl, a substituted or unsubstituted tetrahydrofuranyl, a substituted or unsubstituted dioxane, a substituted or unsubstituted dioxolane, a substituted or unsubstituted quinoline, a substituted or unsubstituted thiazole, substituted or unsubstituted isoxazole, substituted or unsubstituted cyclopentanyl, a substituted or unsubstituted bezofuran, substituted or unsubstituted benzothiophene, substituted or unsubstituted benzisoxazole, substituted or unsubstituted benzisothiazole, substituted or unsubstituted benzothiazole, substituted or unsubstituted bezoxazole, substituted or unsubstituted benzoxazole, substituted or unsubstituted bezimidazole, substituted or unsubstituted benzoxadiazole, substituted or unsubstituted benzothiadiazole, substituted or unsubstituted isoquinoline, substituted or unsubstituted quinoxaline, substituted or unsubstituted indole and substituted or unsubstituted pyrazole.

3. The compound of Claim 2 wherein R_3 is substituted with one or more substituent selected from the group consisting of F, Cl, Br, I, CH_3, NO_2, OCF_3, OCH_3, CN, CO_2CH_3, CF_3, t-butyl, pyridyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted benzyl, substituted or unsubstituted benzenesulfonyl, substituted or unsubstituted phenoxy, substituted or unsubstituted phenyl, substituted or unsubstituted amino, carboxyl, substituted or unsubstituted tetrazolyl, styryl, -S-(substituted or unsubstituted aryl), -S-(substituted or unsubstituted heteroaryl), substituted or

unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -NR_fR_g, alkynyl, -$C(O)NR_fR_g$, R_c and CH_2OR_c;

R_f, R_g and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterobicycloalkyl or a substituted or unsubstituted heteroaromatic; or

R_f and R_g are each, independently, -H, a substituted or unsubstituted aliphatic group, or a substituted or unsubstituted aromatic group; and

R_c is hydrogen, or substituted or unsubstituted alkyl or substituted or unsubstituted aryl, -W-$(CH_2)_t$-NR_dR_e, -W-$(CH_2)_t$-O-alkyl, , -W-$(CH_2)_t$-S-alkyl, -W-$(CH_2)_t$-OH; or -W-$(CH_2)_t$-OR_f;

t is an integer from 0 to 6;

W is a bond or –O-, -S-, -S(O)-, -$S(O)_2$-, or –NR_k-;

R_k is -H or alkyl; and

R_d, R_e and the nitrogen atom to which they are attached together form a 3, 4, 5, 6 or 7-membered substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterobicyclic group; or

R_d and R_e are each, independently, -H, alkyl, alkanoyl or –K-D;

K is -$S(O)_2$-, -C(O)-, -C(O)NH-, -$C(O)_2$-, or a direct bond;

D is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaromatic group, a substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aminoalkyl, a substituted or unsubstituted aminocycloalkyl, $COOR_i$, or substituted or unsubstituted alkyl; and

R_i is a substituted or unsubstituted aliphatic group or a substituted or unsubstituted aromatic group.

4. The compound of claim 3, wherein R_3 is a substituted or unsubstituted phenyl.

5. The compound of Claim 1, wherein ring A is selected from the group consisting of a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, a substituted or unsubstituted pyridyl, and a substituted or unsubstituted indole.

6. The compound of Claim 5 wherein ring A is substituted with one or more substituent selected from the group consisting of F, Cl, Br, I, CH_3, NO_2, OCF_3, OCH_3, CN, CO_2CH_3, CF_3, t-butyl, pyridyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted benzyl, substituted or unsubstituted benzenesulfonyl, substituted or unsubstituted phenoxy, substituted or unsubstituted phenyl, substituted or unsubstituted amino, carboxyl, substituted or unsubstituted tetrazolyl, styryl, -S-(substituted or unsubstituted aryl), -S-(substituted or unsubstituted heteroaryl), substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -NR_fR_g, alkynyl, -$C(O)NR_fR_g$, R_c and CH_2OR_c;

R_f, R_g and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterobicycloalkyl or a substituted or unsubstituted heteroaromatic; or

R_f and R_g are each, independently, -H, a substituted or unsubstituted aliphatic group or a substituted or unsubstituted aromatic group; and

R_c is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -W-$(CH_2)_t$-NR_dR_e, -W-$(CH_2)_t$-O-alkyl, , -W-$(CH_2)_t$-S-alkyl, -W-$(CH_2)_t$-OH; or -W-$(CH_2)_t$-OR_f;

t is an integer from 0 to 6;

W is a bond or –O-, -S-, -S(O)-, -$S(O)_2$-, or –NR_k-;

R_k is -H or alkyl; and

R_d, R_e and the nitrogen atom to which they are attached together form a 3, 4, 5, 6 or 7-membered substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterobicycloalkyl or a substituted or

unsubstituted heteroaromatic; or

R_d and R_e are each, independently, -H, alkyl, alkanoyl or –K-D;

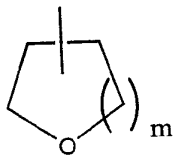
K is $-S(O)_2-$, -C(O)-, -C(O)NH-, $-C(O)_2-$, or a direct bond;

D is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaromatic group, a substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aminoalkyl, a substituted or unsubstituted aminocycloalkyl, $COOR_i$, or a substituted or unsubstituted alkyl; and

R_i is a substituted or unsubstituted aliphatic group or a substituted or unsubstituted aromatic group.

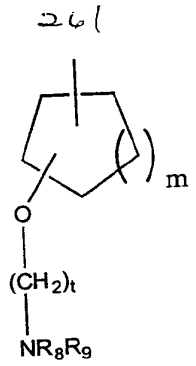
7. The compound of Claim 6, wherein ring A is a substituted or unsubstituted phenyl.

8. The compound of Claim 1 wherein R_1 is of the formula



wherein m is an integer from 0 to 3.

9. The compound of Claim 1 wherein R_1 is of the formula



wherein:

m is an integer from 0 to 3;

t is an integer from 1 to 6; and

R_8, R_9 and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heteroaromatic or substituted or unsubstituted heterobicyclicalkyl group; or

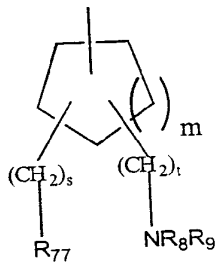
R_8 and R_9 are each, independently, -H, azabicycloalkyl, heterocycloalkyl or Y_2-Z_2;

Y_2 is selected from the group consisting of -C(O)-, -$(CH_2)_q$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_q$O-, -$(CH_2)_q$NH-, -$(CH_2)_q$S-, -$(CH_2)_q$S(O)-, and -$(CH_2)_q$S$(O)_2$-;

q is an integer from 0 to 6; and

Z_2 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl group.

10. The compound of Claim 1 wherein R_1 is of the formula



wherein:

m is an integer from 1 to 3;

s and t are each, independently, an integer from 0 to 6; and

R_8, R_9 and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocycloalkyl group, substituted or unsubstituted heteroaryl group, or a substituted heterobicyclicalkyl group; or

R_8 and R_9 are each, independently, -H, azabicycloalkyl, heterocycloalkyl or $-Y_2-Z_2$;

Y_2 is selected from the group consisting of -C(O)-, $-(CH_2)_q-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_qO-$, $-(CH_2)_qNH-$, $-(CH_2)_qS-$, $-(CH_2)_qS(O)-$ and-$(CH_2)_qS(O)_2-$;

q is an integer from 0 to 6;

Z_2 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl;

R_{77} is $-OR_{78}$, or $-NR_{79}R_{80}$;

R_{78} is –H or a substituted or unsubstituted aliphatic group;

R_{79}, R_{80} and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocycloalkyl group, substituted or unsubstituted heteroaryl group, or a substituted heterobicyclicalkyl group; or

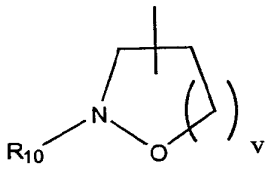
R_{79} and R_{80} are each, independently, -H, azabicycloalkyl, heterocycloalkyl or $-Y_3-Z_3$;

Y_3 is selected from the group consisting of -C(O)-, $-(CH_2)_q-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_qO-$, $-(CH_2)_qNH-$, $-(CH_2)_qS-$, $-(CH_2)_qS(O)-$ and-$(CH_2)_qS(O)_2-$;

q is an integer from 0 to 6;

Z_3 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl.

11. The compound of Claim 1 wherein R_1 is of the formula



wherein:

v is an integer from 1 to 3; and

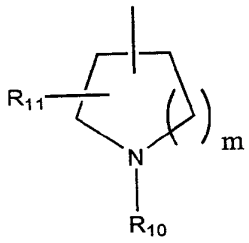
R_{10} is -H, azabicycloalkyl, heterocycloalkyl or Y_2-Z_2;

Y_2 is selected from the group consisting of -C(O)-, -$(CH_2)_q$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_q$O-, -$(CH_2)_q$NH-, -$(CH_2)_q$S-, -$(CH_2)_q$S(O)-, and -$(CH_2)_q$S$(O)_2$-;

q is an integer from 0 to 6; and

Z_2 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl.

12. The compound of Claim 1 wherein R_1 is of the formula



wherein:

m is an integer from 0 to 3;

R_{10} is -H, azabicycloalkyl, heterocycloalkyl or Y_2-Z_2;

Y_2 is selected from the group consisting of -C(O)-, -$(CH_2)_p$-,-$S(O)_2$-, C(O)O-, -SO_2NH-, -CONH-, -$(CH_2)_q$O-, -$(CH_2)_q$NH-, -$(CH_2)_q$S-, -$(CH_2)_q$S(O)-, and -$(CH_2)_q$S$(O)_2$-;

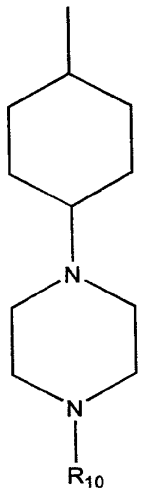
q is an integer from 0 to 6; and

Z_2 is –H, a substituted or unsubstituted alkyl, a substituted or

unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl; and

R_{11} represents one or more substituents independently selected from the group consisting of hydrogen, hydroxy, oxo, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted alkoxyalkyl, a substituted or unsubstituted aminocarbonyl, a substituted or unsubstituted alkylcarbonyl, a substituted or unsubstituted arylcarbonyl, a substituted or unsubstituted heteroarylcarbonyl, a substituted or unsubstituted aminoalkyl and a substituted or unsubstituted aralkyl groups, provided that the carbon atoms adjacent to the nitrogen atom are not substituted by a hydroxy group.

13. The compound of Claim 1 wherein R_1 is of the formula



wherein:

R_{10} is H, azabicycloalkyl, heterocycloalkyl or Y_2-Z_2;

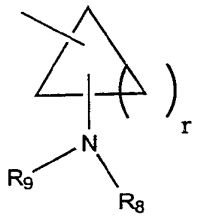
Y_2 is selected from the group consisting of -C(O)-, $-(CH_2)_q$-,$-S(O)_2$-, -C(O)O-, $-SO_2NH$-, -CONH-, $(CH_2)_qO$-, $-(CH_2)_qNH$-, $-(CH_2)_qS$-, $-(CH_2)_qS(O)$-, and $-(CH_2)_qS(O)_2$-;

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q is an integer from 0 to 6; and

Z_2 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl.

14. The compound of Claim 1 wherein R_1 is of the formula



wherein:

r is an integer from 1 to 6; and

R_8, R_9 and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocycloalkyl group, substituted or unsubstituted heteroaryl group, or a substituted heterobicyclicalkyl group; or

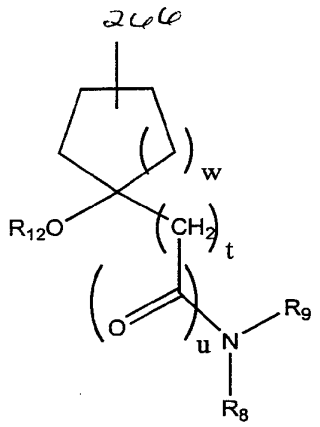
R_8 and R_9 are each, independently, -H, azabicycloalkyl, heterocycloalkyl or Y_2-Z_2;

Y_2 is selected from the group consisting of -C(O)-, $-(CH_2)_q$-,$-S(O)_2$-, -C(O)O-, $-SO_2NH$-, -CONH-, $(CH_2)_qO$-, $-(CH_2)_qNH$-, $-(CH_2)_qS$-, $-(CH_2)_qS(O)$-, and-$(CH_2)_qS(O)_2$-;

q is an integer from 0 to 6; and

Z_2 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl group.

15. The compound of Claim 1 wherein R_1 is of the formula



wherein:

w is an integer from 0 to 4;

t is an integer from 0 to 6;

u is 0 or 1;

R_{12} is hydrogen or a substituted or unsubstituted alkyl group;

R_8, R_9 and the nitrogen atom together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heteroaromatic, or a substituted or unsubstituted heterobicycloalkyl; or

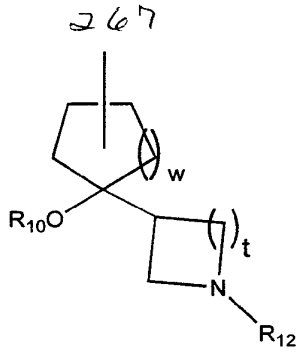
R_8 and R_9 are each, independently, -H, azabicycloalkyl, heterocycloalkyl or Y_2-Z_2;

Y_2 is selected from the group consisting of -C(O)-, $-(CH_2)_q$-,$-S(O)_2$-, -C(O)O-, $-SO_2NH$-, -CONH-, $(CH_2)_qO$-, $-(CH_2)_qNH$-, $-(CH_2)_qS$-, $-(CH_2)_qS(O)$-, and $-(CH_2)_qS(O)_2$-;

q is an integer from 0 to 6; and

Z_2 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl.

16. The compound of Claim 1 wherein R_1 is of the formula



wherein:

w is an integer from 0 to 4;

t is an integer from 0 to 6;

R_{10} is hydrogen or a substituted or unsubstituted alkyl group;

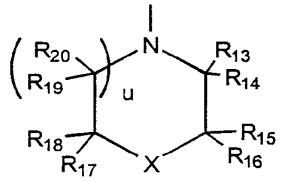
R_{12} is -H, azabicycloalkyl, heteocycloalkyl or Y_2-Z_2;

Y_2 is selected from the group consisting of -C(O)-, -$(CH_2)_q$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_q$O-, -$(CH_2)_q$NH-, -$(CH_2)_q$S-, -$(CH_2)_q$S(O)-, and -$(CH_2)_q$S$(O)_2$-;

q is an integer from 0 to 6; and

Z_2 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl.

17. The compound of Claim 14 wherein R_8, R_9 and the nitrogen atom together form a heterocycloalkyl group; of the formula



wherein:

R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19} and R_{20} are each, independently, lower alkyl or hydrogen; or

at least one pair of substituents R_{13} and R_{14}; R_{15} and R_{16}; R_{17} and R_{18}; or R_{19} and R_{20} together are an oxygen atom; or

at least one of R_{13} and R_{15} is cyano, $CONHR_{21}$, $COOR_{21}$, CH_2OR_{21} or $CH_2NR_{21}(R_{22})$;

R_{21}, R_{22} and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocycloalkyl group, substituted or unsubstituted heteroaryl group, or a substituted heterobicyclicalkyl group; or

R_{21} and R_{22} are each, independently, -H, azabicycloalkyl, heterocycloalkyl or Y_3-Z_3;

Y_3 is selected from the group consisting of -C(O)-, $-(CH_2)_q$-,$-S(O)_2$-, -C(O)O-, $-SO_2NH$-, -CONH-, $(CH_2)_qO$-, $-(CH_2)_qNH$-, $-(CH_2)_qS$-, $-(CH_2)_qS(O)$-; and $-(CH_2)_qS(O)_2$-;

q is an integer from 0 to 6; and

Z_3 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl;

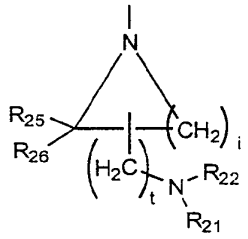
X is –O-, -S-, -SO-, $-SO_2$-, $-CH_2$-, $-CH(OR_{23})$- or NR_{23};

R_{23} is -H, substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, $-C(NH)NH_2$, $-C(O)R_{24}$, or $-C(O)OR_{24}$;

R_{24} is hydrogen, substituted or unsubstituted alkyl, a substituted or unsubstituted aryl or a substituted or unsubstituted aralkyl; and

u is 0 or 1.

18. The compound of Claim 14 wherein R_8, R_9 and the nitrogen atom together form a heterocycloalkyl of the formula



wherein:

R_{25} and R_{26} are each, independently, hydrogen or lower alkyl; or

R_{25} and R_{26} together are an oxygen atom; and

R_{21}, R_{22} and the nitrogen atom together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocycloalkyl group; or

R_{21} and R_{22} are each, independently, -H, azabicycloalkyl, heterocycloalkyl or Y_3-Z_3;

Y_3 is –H, selected from the group consisting of -C(O)-, -$(CH_2)_s$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_s$O-, -$(CH_2)_s$NH-, -$(CH_2)_s$S-, -$(CH_2)_s$S(O)-, and -$(CH_2)_s$S$(O)_2$-;

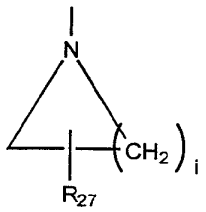
s is an integer from 0 to 6; and

Z_3 is a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl;

i is an integer from 1 to 6; and

t is an integer from 0 to 6.

19. The compound of Claim 14 wherein R_8, R_9 and the nitrogen atom together form a heterocycloalkyl group; of the formula



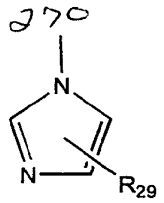
wherein:

i is an integer from 1 to 6; and

R_{27} is CH_2OH, $C(O)NR_{24}R_{28}$ or $COOR_{24}$;

R_{24} and R_{28} are each, independently, hydrogen or a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl or a substituted or unsubstituted aralkyl group.

20. The compound of Claim 14 wherein R_8, R_9 and the nitrogen atom together form a heteroaromatic group of the formula



wherein:

R_{29} is a –Cl, substituted or unsubstituted alkyl, a substituted or unsubstituted aryl or a substituted or unsubstituted aralkyl group, carboxylic acid, cyano, $C(O)OR_{30}$, CH_2OR_{30}, $CH_2NR_{21}R_{22}$ or $C(O)NR_{21}R_{22}$;

R_{30} is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heterocycloalkyl or heterocycloaryl group; and

R_{21}, R_{22} and the nitrogen atom together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocycloalkyl group, a substituted or unsubstituted heteroaromatic or a substitutituted or unsubstituted heterobicycloalkyl; or

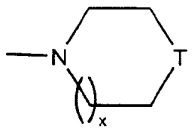
R_{21} and R_{22} are each, independently, H, azabicycloalkyl, heterocycloalkyl or Y_3-Z_3;

Y_3 is selected from the group consisting of -C(O)-, $-(CH_2)_t$-,$-S(O)_2$-, -C(O)O-, $-SO_2NH$-, -CONH-, $(CH_2)_tO$-, $-(CH_2)_tNH$-, $-(CH_2)_tS$-, $-(CH_2)_tS(O)$-, and $-(CH_2)_tS(O)_2$-;

t is an integer from 0 to 6; and

Z_3 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl.

21. The compound of Claim 14 wherein at least one of R_8 and R_9 is of the formula Y_3-D, wherein D is of the formula



wherein:

Y_3 is selected from the group consisting of -C(O)-, $-(CH_2)_t-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_tO-$, $-(CH_2)_tNH-$, $-(CH_2)_tS-$, $-(CH_2)_tS(O)-$, and $-(CH_2)_tS(O)_2-$;

t is an integer from 0 to 6;

T is –O-, -C(O)-, -S-, -SO-, $-SO_2-$, $-CH_2-$, $-CH(OR_{24})-$ or $-N(R_{24})-$;

R_{24} is hydrogen or a substituted or unsubstituted alkyl, aryl or aralkyl group; and

x is 0, 1 or 2.

22. The compound of Claim 14 wherein at least one of R_8 and R_9 is of the formula $Y_3-N(R_{31})R_{32}$, wherein:

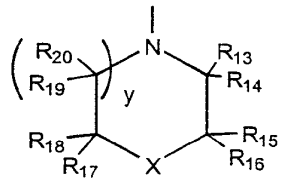
Y_3 is selected from the group consisting of -C(O)-, $-(CH_2)_t-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_tO-$, $-(CH_2)_tNH-$, $-(CH_2)_tS-$, $-(CH_2)_tS(O)-$, and $-(CH_2)_tS(O)_2-$;

t is an interger from 0 to 6;

R_{31} and R_{32} are each, independently, substituted or unsubstituted carboxyalkyl, a substituted or unsubstituted alkoxycarbonylalkyl, a substituted or unsubstituted hydroxyalkyl, a substituted or unsubstituted alkylsulfonyl, a substituted or unsubstituted alkylcarbonyl or a substituted or unsubstituted cyanoalkyl; or

R_{31} and R_{32}, together with the nitrogen atom, form a five- or six-membered heterocycloalkyl group, a substituted or unsubstituted heteroaromatic or a substitutituted or unsubstituted heterobicycloalkyl.

23. The compound of Claim 15 wherein R_8, R_9 and the nitrogen atom together form a heterocycloalkyl of the formula



wherein

R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19} and R_{20} are each, independently, lower alkyl or hydrogen; or

at least one pair of substituents R_{13} and R_{14}; R_{15} and R_{16}; R_{17} and R_{18}; or R_{19} and R_{20} together are an oxygen atom; or

at least one of R_{13} and R_{15} is cyano, $CONHR_{21}$, $COOR_{21}$, CH_2OR_{21} or $CH_2NR_{21}(R_{22})$;

R_{21}, R_{22} and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocycloalkyl group, substituted or unsubstituted heteroaryl group, or a substituted heterobicyclicalkyl group; or

R_{21} and R_{22} are each, independently, -H, azabicycloalkyl, heterocycloalkyl or Y_3-Z_3;

Y_3 is selected from the group consisting of -C(O)-, $-(CH_2)_s$-,$-S(O)_2$-, -C(O)O-, $-SO_2NH$-, -CONH-, $(CH_2)_sO$-, $-(CH_2)_sNH$-, $-(CH_2)_sS$-, $-(CH_2)_sS(O)$- and $-(CH_2)_sS(O)_2$-;

s is an integer from 0 to 6; and

Z_3 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl;

X is –O-, -S-, -SO-, $-SO_2$-, $-CH_2$-, $-CH(OR_{23})$- or NR_{23};

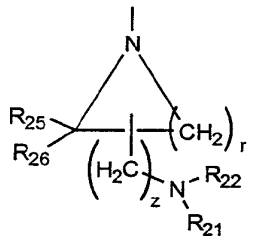
R_{23} is hydrogen, substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, $-C(NH)NH_2$, $-C(O)R_{24}$, or $-C(O)OR_{24}$;

R_{24} is hydrogen, substituted or unsubstituted alkyl, a substituted or unsubstituted aryl or a substituted or unsubstituted aralkyl; and

y is 0 or 1.

24. The compound of Claim 15 wherein R_8, R_9 and the nitrogen atom together form a heterocycloalkyl of the formula

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wherein

R_{25} and R_{26} are each, independently, hydrogen or lower alkyl; or

R_{25} and R_{26} together are an oxygen atom;

R_{21}, R_{22} and the nitrogen atom together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocycloalkyl group, a substituted or unsubstituted heteroaromatic or a substitutituted or unsubstituted heterobicycloalkyl; or

R_{21} and R_{22} are each, independently, -H, azabicycloalkyl, heterocycloalkyl or Y_3-Z_3;

Y_3 is selected from the group consisting of -C(O)-, -$(CH_2)_s$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_s$O-, -$(CH_2)_s$NH-, -$(CH_2)_s$S-, -$(CH_2)_s$S(O)-, and -$(CH_2)_s$$S(O)_2$-;

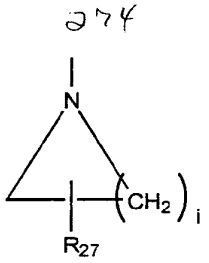
s is an integer from 0 to 6; and

Z_3 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl group; or

r is an integer from 1 to 6; and

z is an integer from 0 to 6.

25. The compound of Claim 15 wherein R_8, R_9 and the nitrogen atom together form a heterocycloalkyl group of the formula



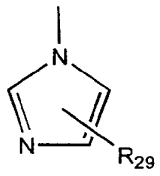
wherein

i is an integer from 1 to 6; and

R_{27} is CH_2OH $C(O)NR_{24}R_{28}$ or $COOR_{24}$;

R_{24} and R_{28} are each, independently, hydrogen or a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl or a substituted or unsubstituted aralkyl group.

26. The compound of Claim 15 wherein R_8, R_9 and the nitrogen atom together form a heteroaromatic group of the formula



wherein:

R_{29} is a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl or a substituted or unsubstituted aralkyl group, carboxyl, cyano, $C(O)OR_{30}$, CH_2OR_{30}, $CH_2NR_{21}R_{22}$ or $C(O)NR_{21}R_{22}$;

R_{30} is a –H, substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heterocycloalkyl or a substituted or unsubstituted heterocycloaryl group;

R_{21}, R_{22} and the nitrogen atom together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocycloalkyl group, a substituted or unsubstituted heteroaromatic or a substitutituted or unsubstituted heterobicycloalkyl; or

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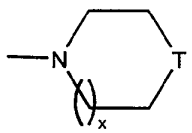
R_{21} and R_{22} are each, independently, -H, azabicycloalkyl, heterocycloalkyl or Y_3-Z_3;

Y_3 is selected from the group consisting of -C(O)-, -$(CH_2)_s$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_s$O-, -$(CH_2)_s$NH-, -$(CH_2)_s$S-, -$(CH_2)_s$S(O)-, and -$(CH_2)_s$$S(O)_2$-;

s is an integer from 0 to 6; and

Z_3 is –H, a substituted or unsubstituted alkyl group, a substituted or unsubstituted amino, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group or a substituted or unsubstituted heterocycloalkyl group.

27. The compound of Claim 15 wherein at least one of R_8 and R_9 is of the formula Y_3-D, wherein D is of the formula



wherein:

Y_3 is selected from the group consisting of -C(O)-, -$(CH_2)_s$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_s$O-, -$(CH_2)_s$NH-, -$(CH_2)_s$S-, -$(CH_2)_s$S(O)-, and -$(CH_2)_s$$S(O)_2$-;

s is an integer from 0 to 6;

T is –O-, -C(O)-, -S-, -SO-, -SO_2-, -CH_2-, -$CH(OR_{33})$- or –NR_{33}-;

R_{33} is hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, -$C(NH)NH_2$, -$C(O)R_{34}$, or -$C(O)OR_{34}$;

R_{34} is hydrogen, substituted or unsubstituted alkyl, aryl or aralkyl,; and

x is 0, 1 or 2.

28. The compound of Claim 15 wherein at least one of R_8 and R_9 is of the formula Y_3-$N(R_{31})R_{32}$, wherein:

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Y_3 is selected from the group consisting of -C(O)-, -$(CH_2)_s$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_s$O-, -$(CH_2)_s$NH-, -$(CH_2)_s$S-, -$(CH_2)_s$S(O)-, and -$(CH_2)_s$$S(O)_2$-;

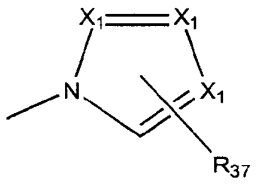
s is an integer from 0 to 6;

R_{31} and R_{32} are each, independently, substituted or unsubstituted carboxyalkyl, a substituted or unsubstituted alkoxycarbonylalkyl, a substituted or unsubstituted hydroxyalkyl, a substituted or unsubstituted alkylsulfonyl, a substituted or unsubstituted alkylcarbonyl or a substituted or unsubstituted cyanoalkyl; or

R_{31} and R_{32}, together with the nitrogen atom, form a five- or six-membered heterocycloalkyl group, a substituted or unsubstituted heteroaromatic or a substitutituted or unsubstituted heterobicycloalkyl.

29. The compound of Claim 12 wherein Z_2 is of the formula $N(R_{35})R_{36}$, wherein R_{35} and R_{36} are each, independently, hydrogen, alkyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl, aminocarbonyl, cyano, alkylcarbonyl or aralkyl.

30. The compound of Claim 12 wherein Z_2 is of the formula

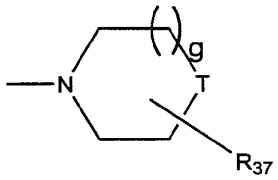


wherein:

each X_1 is, independently, CH or N; and

R_{37} is hydrogen, cyano or a substituted or unsubstituted alkyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted alkoxyalkyl, a substituted or unsubstituted hydroxyalkyl, a substituted or unsubstituted aminocarbonyl, a substituted or unsubstituted alkylcarbonyl or a substituted or unsubstituted aralkyl group.

31. The compound of Claim 12 wherein Z_2 is of the formula



wherein

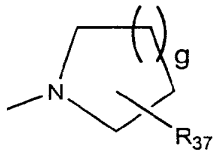
g is an integer from 0 to 3;

T is –O-, -C(O)-, -S-, -SO-, -SO_2-, -CH_2-, -$CH(OR_{34})$- or –$N(R_{34})$-;

R_{34} is hydrogen, substituted or unsubstituted alkyl, a substituted or unsubstituted aryl or a substituted or unsubstituted aralkyl; and

R_{37} is hydrogen, cyano or a substituted or unsubstituted alkyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted alkoxyalkyl, a substituted or unsubstituted hydroxyalkyl, a substituted or unsubstituted aminocarbonyl, a substituted or unsubstituted alkylcarbonyl or a substituted or unsubstituted aralkyl group.

32. The compound of Claim 12 wherein Z_2 is of the formula



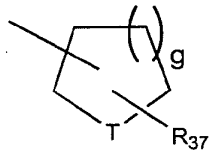
wherein:

g is an integer from 0 to 3; and

R_{37} is hydrogen, cyano or a substituted or unsubstituted alkyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted

alkoxyalkyl, a substituted or unsubstituted hydroxyalkyl, a substituted or unsubstituted aminocarbonyl, a substituted or unsubstituted alkylcarbonyl or a substituted or unsubstituted aralkyl group.

33. The compound of Claim 12 wherein Z_2 is of the formula



wherein:

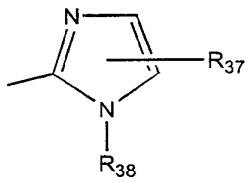
T is –O-, -C(O)-, -S-, -SO-, -SO_2-, -CH_2-, -$CH(OR_{34})$- or –$N(R_{34})$-;

R_{34} is hydrogen, substituted or unsubstituted alkyl, a substituted or unsubstituted aryl or a substituted or unsubstituted aralkyl; and

g is an integer from 0 to 3; and

R_{37} is hydrogen, cyano or a substituted or unsubstituted alkyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted alkoxyalkyl, a substituted or unsubstituted hydroxyalkyl, a substituted or unsubstituted aminocarbonyl, a substituted or unsubstituted alkylcarbonyl or a substituted or unsubstituted aralkyl.

34. The compound of Claim 12 wherein Z_2 is of the formula

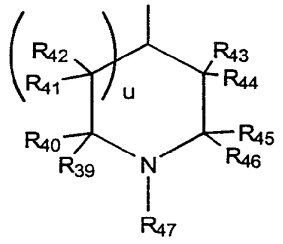


wherein:

R_{37} is hydrogen, cyano, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted alkoxyalkyl, a substituted or unsubstituted hydroxyalkyl, a substituted or unsubstituted aminocarbonyl, a substituted or unsubstituted alkylcarbonyl , a substituted or unsubstituted thioalkoxy or a substituted or unsubstituted aralkyl; and

R_{38} is hydrogen, substituted or unsubstituted alkyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted alkoxyalkyl, a substituted or unsubstituted aminocarbonyl, perhaloalkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkylcarbonyl or a substituted or unsubstituted aralkyl.

35. The compound of Claim 1 wherein R_1 is of the formula



wherein:

u is 0 or 1;

R_{39}, R_{40}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45} and R_{46} are each, independently, methyl or hydrogen; or

at least one pair of substituents R_{39} and R_{40}; R_{41} and R_{42}; R_{43} and R_{44}; or R_{45} and R_{46} together are an oxygen atom; and

R_{47} is H, azabicycloalkyl, heterocycloalkyl or Y_2-Z_2;

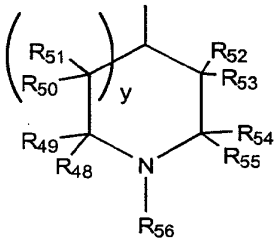
Y_2 is selected from the group consisting of -C(O)-, -$(CH_2)_q$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_q$O-, -$(CH_2)_q$NH-, -$(CH_2)_q$S-, -$(CH_2)_q$S(O)-, and -$(CH_2)_q S(O)_2$-;

q is an integer from 0 to 6; and

Z_2 is –H, a substituted or unsubstituted alkyl, a substituted or

unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl group; or

R_{47} is of the formula



wherein:

y is 0 or 1;

R_{48}, R_{49}, R_{50}, R_{51}, R_{52}, R_{53}, R_{54} and R_{55} are each, independently, methyl or hydrogen; or

at least one pair of substituents R_{48} and R_{49}; R_{50} and R_{51}; R_{52} and R_{53}; or R_{54} and R_{55} together are an oxygen atom; and

R_{56} is -H, azabicycloalkyl, heterocycloalkyl or Y_3-Z_3,

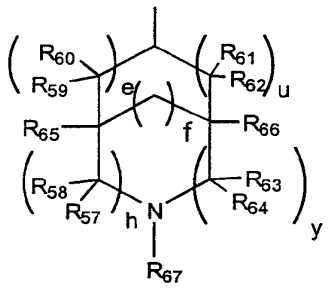
Y_3 is selected from the group consisting of -C(O)-, -$(CH_2)_t$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_t$O-, -$(CH_2)_t$NH-, -$(CH_2)_t$S-, -$(CH_2)_t$S(O)-; and -$(CH_2)_t$S$(O)_2$-;

t is an integer from 0 to 6; and

Z_3 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl.

36. The compound of Claim 1 wherein R_1 is of the formula

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wherein:

e, f, h, u and y are independently 0 or 1;

R_{57}, R_{58}, R_{59}, R_{60}, R_{61}, R_{62}, R_{63}, R_{64}, R_{65} and R_{66} are each, independently, methyl or hydrogen; or

at least one pair of substituents R_{57} and R_{58}; R_{59} and R_{60}; R_{61} and R_{62}; or R_{63} and R_{64} together are an oxygen atom; and

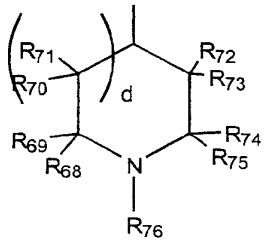
R_{67} is H, azabicycloalkyl, heterocycloalkyl or Y_2-Z_2;

Y_2 is selected from the group consisting of -C(O)-, $-(CH_2)_q$-,$-S(O)_2$-, -C(O)O-, $-SO_2NH$-, -CONH-, $(CH_2)_qO$-, $-(CH_2)_qNH$-, $-(CH_2)_qS$-, $-(CH_2)_qS(O)$-, and $-(CH_2)_qS(O)_2$-;

p is an integer from 0 to 6; and

Z_2 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl; or

R_{67} is of the formula



wherein:

d is 0 or 1;

R_{68}, R_{69}, R_{70}, R_{71}, R_{72}, R_{73}, R_{74} and R_{75} are each, independently, lower alkyl or hydrogen; or

at least one pair of substituents R_{68} and R_{69}; R_{70} and R_{71}; R_{72} and R_{73}; and R_{74} and R_{75} together are an oxygen atom; and

R_{76} is -H, azabicycloalkyl, heterocycloalkyl or Y_3-Z_3;

Y_3 is selected from the group consisting of -C(O)-, -$(CH_2)_t$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_t$O-, -$(CH_2)_t$NH-, -$(CH_2)_t$S-, -$(CH_2)_t$S(O)-, and -$(CH_2)_t$$S(O)_2$-;

p is an integer from 0 to 6;

Z_3 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl group.

37. The compound of Claim1, wherein R_2 is –H.

38. The compound of Claim 1, wherein L is –O-, -$NHSO_2$R-, -NC(O)O-, or NHC(O)-.

39. A method of inhibiting protein kinase activity comprising administering a compound of Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof.

40. The method of Claim 39 wherein said protein kinase is selected from the group consisting of KDR, FGFR-1, PDGFRβ, PDGFRα, IGF-1R, c-Met, Flt-1, TIE-2, Lck, Src, fyn, Lyn, Blk, and yes.

41. The method of Claim 39 wherein the activity of said protein kinase affects hyperproliferative disorders.

42. The method of Claim 39 wherein the activity of said protein kinase affects angiogenesis, vascular permeability, immune response or inflammation.

43. A method of treating a patient having a condition which is mediated by protein kinase activity, said method comprising the step of administering to the patient a therapeutically effective amount of a compound of Formula I as defined in Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolite thereof.

44. The method of Claim 43 wherein said protein kinase is selected from the group consisting of KDR, Flt-1, PDGFRβ, PDGFRα, IGF-1R, c-Met, TIE-2, Lck, Src, fyn, Lyn, Blk, and yes.

45. The method of Claim 43 wherein the condition mediated by protein kinase activity is a hyperproliferative disorder.

46. The method of Claim 43 wherein the activity of said protein kinase affects angiogenesis, vascular permeability, an immulogic response or an imflammatory response.

47. The method of Claim 43 wherein the protein kinase is a protein serine/threonine kinase or a protein tyrosine kinase.

48. The method of Claim 43 wherein the condition mediated by protein kinase activity is one or more ulcers.

49. The method of Claim 48 wherein the ulcer or ulcers are caused by a bacterial or fungal infection; or the ulcer or ulcers are Mooren ulcers; or the ulcer or ulcers are a symptom of ulcerative colitis.

50. The method of Claim 43 wherein the condition mediated by protein kinase activity is Lyme disease, sepsis or infection by Herpes simplex, Herpes Zoster, human immunodeficiency virus, parapoxvirus, protozoa or toxoplasmosis.

51. The method of Claim 43 wherein the condition mediated by protein kinase activity is von Hippel Lindau disease, pemphigoid, psoriasis, Paget's disease or polycystic kidney disease.

52. The method of Claim 43 wherein the condition mediated by protein kinase activity is fibrosis, sarcoidosis, cirrhosis, thyroiditis, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic occlusive pulmonary disease, asthma, exudtaes, ascites, pleural effusions, pulmonary edema, cerebral edema or edema following burns, trauma, radiation, stroke, hypoxia or ischemia.

53. The method of Claim 43 wherein the condition mediated by protein kinase activity is ovarian hyperstimulation syndrome, preeclampsia, menometrorrhagia, or endometriosis.

54. The method of Claim 43 wherein the condition mediated by protein kinase activity is chronic inflammation, systemic lupus, glomerulonephritis, synovitis, inflammatory bowel disease, Crohn's disease, glomerulonephritis, rheumatoid arthritis and osteoarthritis, multiple sclerosis or graft rejection.

55. The method of Claim 43 wherein the condition mediated by protein kinase activity is sickle cell anaemia.

56. The method of Claim 43 wherein the condition mediated by protein kinase activity is an ocular condition.

57. The method of Claim 56 wherein the ocular condition is ocular or macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser treatment complications, conjunctivitis, Stargardt's disease, Eales disease, retinopathy

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or macular degeneration.

58. The method of Claim 43 wherein the condition mediated by protein kinase activity is a cardiovascular condition.

59. The method of Claim 58 wherein the condition mediated by protein kinase acitivity is atherosclerosis, restenosis, ischemia/reperfusion injury, vascular occlusion, venous malformation or carotid obstructive disease.

60. The method of Claim 43 wherein the condition mediated by protein kinase activity is cancer.

61. The method of Claim 60 wherein the cancer is a solid tumor, a sarcoma, fibrosarcoma, osteoma, melanoma, retinoblastoma, a rhabdomyosarcoma, glioblastoma, neuroblastoma, teratocarcinoma, an hematopoietic malignancy and malignant ascites.

62. The method of Claim 61 wherein the cancer is Kaposi's sarcoma, Hodgkin's disease, lymphoma, myeloma or leukemia.

63. The method of Claim 43 wherein the condition mediated by protein kinase actitivity is Crow-Fukase (POEMS) syndrome or a diabetic condition.

64. The method of Claim 63 wherein the diabetic condition is insulin-dependent diabetes mellitus glaucoma, diabetic retinopathy or microangiopathy.

65. A method of decreasing fertility in a patient, said method comprising the step of administering to the patient an effective amount of a compound of Formula I as defined in Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolite thereof.

66. The method of Claim 43 wherein the compound of Formula I or a physiologically acceptable salt, prodrug or biologically active metabolite thereof is administered in an amount effective to promote angiogenesis or vasculogenesis.

67. The method of Claim 66 wherein the protein kinase is Tie-2.

68. The method of Claim 66 wherein the compound of Formula I, or physiologically acceptable salt, prodrug or biologically active metabolite thereof, is administered in combination with a pro-angiogenic growth factor.

69. The method of Claim 68 wherein the pro-angiogenic growth factor is selected from the group consisiting of VEGF, VEGF-B, VEGF-C, VEGF-D, VEGF-E, HGF, FGF-1, FGF-2, derivatives thereof and antiiodotypic antibodies.

70. The method of Claim 66 wherein the protein kinase-mediated condition is anemia, ischemia, infarct, transplant rejection, a wound, gangrene or necrosis.

71. The method of Claim 43 wherein the protein kinase activity is involved in T cell activation, B cell activation, mast cell degranulation, monocyte activation, the potentiation of an inflammatory response or a combination thereof.

72. A compound selected from the group consisting of:

Cis-5-(4-phenoxyphenyl)-7-(4-pyrrolidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine,
Trans-5-(4-phenoxyphenyl)-7-(4-pyrrolidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine ,
Cis-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohex-1-yl)-7H-pyrrolo[2,3-

d]pyrimidin-4-ylamine hydrochloride,

Trans-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine,

Trans-7-(4-dimethylaminocyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo [2,3-d]pyrimidin-4-ylamine,

Cis-7-(4-dimethylaminocyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine,

5-(4-phenoxyphenyl)-7-(4-piperidyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylamine dihydrochlorid,

5-(4-phenoxyphenyl)-7-(3-pyrrolidinyl) -7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylamine dihydrochloride,

Cis-7-[4-(4-isopropylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,

Trans-7-[4-(4-isopropylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,

Cis-7-{4-[4-(2-methoxyethyl)piperazino]cyclohexyl}-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,

Trans-7-{4-[4-(2-methoxyethyl)piperazino]cyclohexyl}-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,

Cis-7-[-4-(4-ethylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,

trans-7-[4-(4-ethylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,

Cis-7-[4-(4-isopropylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tris maleate,

Trans-7-[4-(4-isopropylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tris maleate,

Cis-7-{4-[4-(2-methoxyethyl)piperazino]cyclohexyl}-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tris maleate,

Trans-7-{4-[4-(2-methoxyethyl)piperazino]cyclohexyl}-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tris maleate,

Cis-7-(4-{[3-(1*H*-1-imidazolyl)propyl]amino}cyclohexyl)-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine trimaleate salt,

Trans-7-(4-{[3-(1*H*-1-imidazolyl)propyl]amino}cyclohexyl)-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dimaleate salt,

Cis-7-[4-(dimethylamino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dimaleate salt,

Trans-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohexyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dimaleate salt,

Trans-5-(4-phenoxyphenyl)-7-(4-tetrahydro-1*H*-1-pyrrolylcyclohexyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dimaleate salt,

Cis-5-(4-phenoxyphenyl)-7-(4-piperazinocyclohexyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine trimaleate salt,

Trans-5-(4-phenoxyphenyl)-7-(4-piperazinocyclohexyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine trimaleate salt,

7-[3-(4-methylpiperazino)cyclopentyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-maleate,

Trans-7-[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,

Trans-7-[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-maleate,

trans-7-[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-hydrochloride,

cis-7 -[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-maleate salt,

cis-7 -[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-hydrochloride,

Trans-5-(2-methyl-4-phenoxyphenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine trimaleate,

Cis- benzyl N-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}2-methoxyphenyl)carbamate tri-maleate,

Trans- benzyl N-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-

pyrrolo[2,3-d]pyrimidin-5-yl}-2-methoxyphenyl)carbamate tri-maleate,
Trans-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-methoxyphenyl)benzamide,
Trans-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-methoxyphenyl)benzamide tri-maleate,
Cis-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-methoxyphenyl)-3-phenylpropanamide,
Trans- N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-methoxyphenyl)-3-phenylpropanamide,
cis- *N*1-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl-2-methoxyphenyl)-3-phenylpropanamide trimaleate salt,
trans-*N*1-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl-2-methoxyphenyl)-3-phenylpropanamide tri-maleate,
cis-2-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)-6-[(3-methoxypropyl)amino]benzonitrile tri-maleate,
trans-2-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)-6-[(3-methoxypropyl)amino]benzonitrile tri-maleate,
is-2-amino-6-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)benzonitrile tri-maleate,
trans-2-amino-6-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)benzonitrile tri-maleate,
cis-2-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)-6-[(4-methylphenyl)sulfanyl]benzonitrile tri-maleate,
trans-2-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)-6-[(4-methylphenyl)sulfanyl]benzonitrile tri-maleate,
cis-2-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)-6-(2-pyridylsulfanyl)benzonitrile tri-maleate,

trans-2-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)-6-(2-pyridylsulfanyl)benzonitrile tri-maleate,
cis-5-(2-methyl-4-phenoxyphenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-maleate,
trans-5-(2-methyl-4-phenoxyphenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-maleate,
cis-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide tri-maleate,
trans-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide tri-maleate,
N1-4-[4-amino-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide,
N1-4-[4-amino-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-2,3-dichloro-1-benzenesulfonamide,
N1-4-[4-amino-7-(4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide,
N1-4-[4-amino-7-(1-formyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide,
N1-[4-(4-amino-7-1-[(1-methyl-1H-4-imidazolyl)sulfonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide dimaleate,
N1-[4-(4-amino-7-1-[(1,2-dimethyl-1H-4-imidazolyl)sulfonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide,
N1-[4-(4-amino-7-1-[(1,3-dimethyl-1H-5-pyrazolyl)carbonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide,
N1-(4-{4-amino-7-[1-(2-pyridylcarbonyl)-4-piperidyl]-7H-pyrrolo[2,3-

d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide,

N1-4-(4-amino-7-{4-[1-(1-methylpiperid-4-yl)piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl})-2-fluorophenyl-4-fluoro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-(trifluoromethoxy)-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-5-chloro-2-thiophenesulfonamide benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-4-fluoro-1-benzenesulfonamide benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-4-fluoro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl-2-fluorophenyl)-2,5-difluoro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,6-difluoro-1-benzenesulfonamide trimaleate,

trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,1,3-benzothiadiazole-4-sulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3,4-trifluoro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-nitro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-fluoro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,4,6-trichloro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,6-dichloro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)- 3-fluoro-1-benzenesulfonamide dimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-5-chloro-2-thiophenesulfonamide dimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-bromo-2,6-difluoro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-chloro-4-fluoro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl-2-iodo-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-(trifluoromethoxy)-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-6-methyl-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-4-cyano-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3,4-trifluoro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3,4-difluoro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-bromo-2-fluoro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-5-bromo-2-thiophenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,4-dichloro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3,4-trichloro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-bromo-5-chloro-2-thiophenesulfonamide trimaleate,

cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,1,3-benzothiadiazole-4-sulfonamide trimaleate,

cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,1,3-benzoxadiazole-4-sulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-

d]pyrimidin-5-yl}-2-fluorophenyl)-2,5-dichloro-1-thiophenesulfonamide trimaleate,

cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(7-chloro-2,1,3-benzoxadiazole)-4-sulfonamide trimaleate,

cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(7-methyl-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate,

cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(5-methyl-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate,
cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(5-chloro-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate,
cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-chloro-2-methyl-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-bromo-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,5-dibromo-3,6-difluoro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide trimaleate,

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)- (2-nitrophenyl)methanesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-nitro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-fluoro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,4,6-trichloro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,6-dichloro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)- 3-fluoro-1-benzenesulfonamide dimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-bromo-2,5-difluoro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-

d]pyrimidin-5-yl}-2-fluorophenyl)-3-chloro-4-fluoro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl-2-iodo-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-6-methyl-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-4-cyano-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3,4-difluoro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-bromo-2-fluoro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-5-bromo-2-thiophenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,4-dichloro-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3,4-trichloro-1-benzenesulfonamide

trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-bromo-5-chloro-2-thiophenesulfonamide trimaleate,

trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,1,3-benzoxadiazole-4-sulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,5-dichloro-1-thiophenesulfonamide trimaleate,

trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(7-chloro-2,1,3-benzoxadiazole)-4-sulfonamide trimaleate,

trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(7-methyl-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate,

trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(5-methyl-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate,

trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(5-chloro-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-chloro-2-methyl-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-bromo-1-benzenesulfonamide trimaleate,

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,5-dibromo-3,6-difluoro-1-benzenesulfonamide trimaleate, or

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)- (2-nitrophenyl)methanesulfonamide trimaleate.

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PCT/US 99/21560

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 28161 A (NOVARTIS AG) 7 August 1997 (1997-08-07) claims 1-11	1-7
X	WO 97 32879 A (NOVARTIS AG) 12 September 1997 (1997-09-12) claims 1-13	1-7
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P,X	WO 98 41525 A (KNOLL AG) 24 September 1998 (1998-09-24) claims 1-30	1-7
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

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16 December 1999	11/01/2000

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Inter nal Application No
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INTERNATIONAL SEARCH REPORT

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(74) Agents: **GARRETT, Artur, S.** et al.; Finnegan, Henderson, Farabow, Garrett & Dunner, L., L.P., 1300 I Street, N.W., Washington, DC20005-3315 (US).

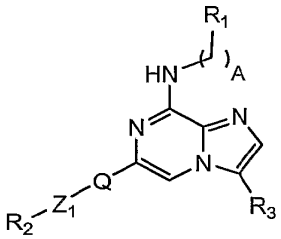
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(54) Title: IMIDAZO[1,2-A]PYRAZIN-8-YLAMINES AND METHOD OF INHIBITION OF BRUTON'S TYROSINE KINASE BY SUCH COMPOUNDS



(I)

(57) Abstract: Compounds of Formula (I-a) and all pharmaceutically-acceptable forms thereof, are described herein. The variables R_1, R_2, R_3, Z_1, Q, and A shown in Formula I-a are defined herein. Pharmaceutical compositions containing one or more compounds of Formula (I-a), or a pharmaceutically acceptable form of such compounds, and one or more pharmaceutically acceptable carriers, excipients, or diluents are provided herein. Methods of treating patients suffering from certain diseases responsive to inhibition of tyrosine kinase activity are also given. In certain embodiments the diseases are responsive to inhibition of Btk activity and/or B-cell proliferation. Such methods comprise administering to such patients an amount of a compound of Formula (I-a) effective to reduce signs or symptoms of the disease. These diseases include cancer, an autoimmune and/or inflammatory disease, or an acute inflammatory reaction. Thus methods of treatment include administering a sufficient amount of a compound or salt as provided herein to decrease the symptoms or slow the progression of these diseases. Other embodiments include methods of treating other animals, including livestock and domesticated companion animals, suffering from a disease responsive to inhibition of kinase activity. Methods of treatment include administering a compound of Formula (I-a) as a single active agent or administering a compound of Formula (I-a) in combination with one or more other therapeutic agent. A method for determining the presence of Btk in a sample, comprising contacting the sample with a compound or form thereof of Formula (I-a) under conditions that permit detection of Btk activity, detecting a level of Btk activity in the sample, and therefrom determining the presence or absence of Btk in the sample.

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IMIDAZO'1,2-A!PYRAZIN-8-YLAMINES AND METHOD OF INHIBITION OF BRUTON'S TYROSINE KINASE BY SUCH COMPOUNDS

FIELD OF INVENTION

[0001] Certain imidazo[1,2-a]pyrazin-8-ylamine and related compounds, which when appropriately substituted are inhibitors of tyrosine kinase activity, including Bruton's tyrosine kinase (Btk) activity, are provided herein. Certa in compounds provided herein are highly active and/ or specific inhibitors of Btk activity. Pharmaceutical compositions comprising such compounds, and methods of using certain imidazo[1,2-a]pyrazin-8-ylamine and related compounds to treat a variety of diseases responsive to inhibition of Btk activity and/ or inhibition of B-cell proliferation, are also disclosed. Additionally, methods for using such compounds as probes for the detection and/ or localization of Btk in biological samples are given.

BACKGROUND

[0002] Protein kinases, the largest family of human enzymes, encompass well over 500 proteins. Kinases play critical roles in signaling pathways controlling fundamental cellular processes such as proliferation, differentiation, and death (apoptosis). Abnormal kinase activity has been implicated in a wide range of diseases, including multiple cancers and autoimmune and inflammatory diseases. The multifaceted role of kinases in key cell signaling pathways provides a significant opportunity to identify novel drugs targeting kinases and signaling pathways. Diseases mediated by receptor kinase activity include, but are not limited to, diseases characterized in part by abnormal levels of cell proliferation (i.e. tumor growth), programmed cell death (apoptosis), cell migration and invasion, and angiogenesis associated with tumor growth.

[0003] Because kinases are key regulators they are ideal drug design targets. Inhibitors of kinases are among the most important classes of pharmaceutical compounds known. Highly specific, cell-permeable inhibitors of one or more individual kinases are

useful for the treatment of various kinase-implicated diseases. Kinase inhibiting compounds are additionally useful for the systematic investigation of the cellular function of one or more kinases, and thus, provide valuable tools for the identification of various kinases of therapeutic interest.

[0004] Bruton's Tyrosine Kinase (Btk) is a member of the Tec family of tyrosine kinases, and is a critical regulator of early B-cell development as well as mature B-cell activation, signaling and survival.

[0005] B-cell signaling through the B-cell receptor (BCR) leads to a wide range of biological outputs, which in turn depend on the developmental stage of the B-cell. The magnitude and duration of BCR signals must be precisely regulated. Aberrant BCR-mediated signaling can cause disregulated B-cell proliferation and/or the formation of pathogenic auto-antibodies leading to multiple autoimmune and/or inflammatory diseases. Mutation of Btk in humans results in X-linked agammaglobulinaemia (XLA). This disease is associated with the impaired maturation of B-cells, diminished immunoglobulin production, comprised T-cell-independent immune responses and marked attenuation of the sustained calcium sign upon BCR stimulation.

[0006] Evidence for the role of Btk in autoimmune and/or inflammatory disease has been established in Btk-deficient mouse models. For example, in standard murine preclinical models of systemic lupus erythematosus (SLE), Btk deficiency has been shown to result in a marked amelioration of disease progression. Moreover, Btk deficient mice are also resistant to developing collagen-induced arthritis and are less susceptible to Staphylococcus-induced arthritis.

[0007] A large body of evidence supports the role of B-cells and the humoral immune system in the pathogenesis of autoimmune and/or inflammatory diseases. Protein-based therapeutics (such as Rituxan) developed to deplete B-cells, represent an important approach to the treatment of a number of autoimmune and/or inflammatory diseases. Because of Btk's role in B-cell activation, inhibitors of Btk are useful as inhibitors of B-cell mediated pathogenic activity (such as autoantibody production).

[0008] Btk is also expressed in mast cells and monocytes and has been shown to be important for the function of these cells. For example, Btk deficiency in mice is associated with impaired IgE-mediated mast cell activation (marked diminution of TNFα and other

inflammatory cytokine release), and greatly reduced TNFα production by activated monocytes.

[0009] Thus, inhibition of Btk activity is useful for the treatment of autoimmune and/or inflammatory diseases such as: SLE, rheumatoid arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, and asthma. In addition, Btk has been reported to play a role in apoptosis, thus inhibition of Btk activity is useful for the treatment of B-cell lymphoma and leukemia.

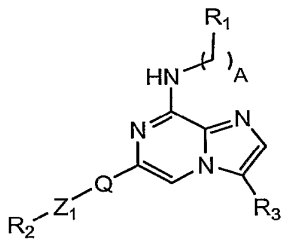
[0010] Agents capable of inhibiting Btk kinase activity, are highly desirable for the treatment of a variety of diseases, including cancer, an autoimmune and/or inflammatory disease, or an acute inflammatory reaction. Specific, cell-penetrating, small molecule, non-peptide antagonists of Btk are of particular value for such therapies. Such compounds are also useful for the systematic investigation of the cellular function of Btk, and thus, are valuable research tools for the identification of cell signalling proteins of therapeutic interest.

[0011] The present invention fulfills this need, and provides further related advantages.

SUMMARY

[0012] Inhibitors of kinase activity, which may generally be described as imidazo[1,2-a]pyrazin-8-ylamines and related compounds, are disclosed herein. Certain compounds provided herein are highly active and/ or specific inhibitors of Btk (Bruton's tyrosine kinase) activity.

[0013] One embodiment provides a compound of Formula I-a



Formula I-a

or a pharmaceutically acceptable form thereof.

Within Formula I-a:

A is 0 or 1.

R_1 is phenyl or heteroaryl, each of which is optionally substituted with one of

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

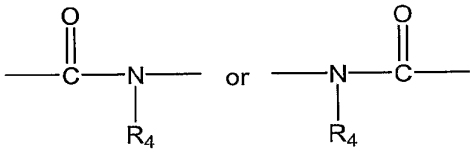
(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl.

Each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl.

And, R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

R_2 is C_1-C_7 alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, (heterocycloalkyl)C_0-C_2alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, or R_2 is (phenyl)C_0-C_2alkyl, (phenoxy)C_0-C_2alkyl, or (heteroaryl)C_0-C_2alkyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, -SO_2NH_2, oxo, -COOH, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_2-C_6alkanoyl, C_1-C_6hydroxyalkyl, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6alkyl, mono- and di- C_1-C_6alkylamino, mono- and di-C_1-C_6alkylcarboxamide, C_1-C_6alkoxycarbonyl, phenyl, and heteroaryl, and –(C=O)R_{13} wherein R_{13} is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, C_1-C_3haloalkyl, heterocycloalkyl, phenyl, or heteroaryl.

Z_1 is



wherein R_4 is hydrogen, or R_4 is C_1-C_6alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each of which is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6 alkyl, mono- and di-C_1-C_6 alkylamino, and -C(O)R_{14} wherein R_{14} is C_1-C_6 alkyl, C_1-C_3haloalkyl, or phenyl.

Q is phenyl or pyridyl.

R_3 is hydrogen, C_1-C_7 alkyl, or halogen, or

R_3 is heterocycloalkyl, C_3-C_7cycloalkyl, or heteroaryl, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, -SO_2NH_2, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3halooalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6-alkoxy)C_1-C_6 alkoxy, mono- and di-C_1-C_6alkylamino, aminoC_1-C_6 alkyl, and -C(O)R_{14}.

[0014] In certain embodiments compounds of Formula I-a, which exhibit an IC_{50} of 1 micromolar or less, 100 nanomolar or less, or 10 nanomolar or less in standard biochemical assay for Btk activity, such as the biochemical assay described in Example 6, are provided herein. Preferred compounds described herein are highly active inhibitors of B-cell

proliferation. For example certain compounds described herein exhibit an IC_{50} value less than or equal to 10 micromolar, or an IC_{50} value less than or equal to 1 micromolar, or an IC_{50} value less than or equal to 500 nM in the tritiated thymidine incorporation assay for B-cell proliferation described in Example 8. Preferred compounds described herein are specific inhibitors of B-cell proliferation, exhibiting an IC_{50} value that is at least 3-fold, preferably 5-fold, and more preferably 10-fold greater for T-cell proliferation than the IC_{50} for B-cell proliferation. The IC_{50} for T-cell proliferation may be determined via a standard assay for T-cell proliferation such as the thymidine incorporation assay of Example 9.

[0015] A method for determining the presence of Btk in a sample, comprising contacting the sample with a compound or form thereof of Formula I-a under conditions that permit detection of Btk activity, detecting a level of Btk activity in the sample, and therefrom determining the presence or absence of Btk in the sample, is also provided herein.

[0016] Pharmaceutical compositions, comprising one or more compounds of Formula I-a, or any pharmaceutically acceptable form thereof, together with at least one pharmaceutically acceptable carrier or excipient, are provided herein.

[0017] Other embodiments pertain to packaged pharmaceutical compositions which comprise a pharmaceutical composition, comprising one or more compounds of Formula I-a or any pharmaceutically acceptable form thereof, together with at least one pharmaceutically acceptable carrier or excipient in a container and with instructions for using the pharmaceutical composition to treat a patient. Preferably the instructions are for using the pharmaceutical composition to treat a patient suffering from a disease responsive to inhibition of Btk activity.

[0018] Still other embodiments pertain to a method of inhibiting Btk kinase. In certain embodiments the method comprises contacting a cell or cells expressing Btk, either *in vivo* or *in vitro*, with a compound of Formula I-a or form thereof in an amount sufficient to detectably inhibit Btk activity *in vitro*.

[0019] Inhibiting Btk activity can effectively inhibit B-cell proliferation. Small molecule (less than 600 amu) Btk inhibitors that are orally bioavailable, such as certain compounds and forms of Formula I-a, are particularly desirable for this purpose. Thus a method of inhibiting B-cell proliferation, by contacting cells expressing Btk, either *in vivo* or *in vitro* with a compound having a molecular weight less than 600 amu in an amount

sufficient to detectably inhibit the activity of Btk *in vitro* is provided herein. In certain embodiments the compound will be a heterocyclic compound, such as a heterocyclic compound having a bicyclic heterocyclic group. In certain embodiments the compound is a compound of Formula I-a.

[0020] A method of treating a mammal suffering from at least one disease responsive to inhibition of Btk activity, by administering to the mammal an effective amount of a compound that is a highly active Btk inhibitor in an *in vitro* assay of Btk activity is included herein. Preferably the compound is also a specific inhibitor of B-cell proliferation, exhibiting an IC_{50} value that is at least 3-fold, preferably 5-fold, and more preferably 10-fold greater for T-cell proliferation than the IC_{50} value for B-cell proliferation.

[0021] Methods for treating a patient having a disease responsive to inhibition of Btk activity and/ or responsive to inhibition of B-cell proliferation, are provided herein. Such methods comprise administering to the patient an effective amount of a compound or form thereof of Formula I-a. The patient may be a mammal. Preferably the patient is a human patient, however methods of treating non-human patients are included herein. For example in some embodiments the patient is a companion animal, such as a cat or dog, or the patient is a livestock animal, such as a horse, cow, or pig. Particularly included herein are methods in which the disease responsive to Btk inhibition is cancer, an autoimmune and/or inflammatory disease, or an acute inflammatory reaction.

[0022] Methods of treatment include administering a compound of Formula I-a as a single active agent or administering a compound of Formula I-a in combination with one or more other active agents.

DETAILED DESCRIPTION

[0023] Certain terms to be used herein are provided prior to setting forth the invention in detail. Compounds of the present invention are described using standard nomenclature. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

CHEMICAL DESCRIPTION AND TERMINOLOGY

[0024] Formula I-a includes all subformulae thereof. For example Formula I-a includes compounds of Formulas 1 to 9.

[0025] Certain compounds are described herein using a general formula that includes variables, e.g. R_1, R_2, R_3, Q, Z_1, and A. Unless otherwise specified, each variable within such a formula is defined independently of other variables. When any variable occurs more than one time in Formula I-a, its definition on each occurrence is independent of its definition at every other occurrence.

[0026] In accordance with the usual meaning of "a" and "the" in patents, reference to "a" kinase or "the" kinase is inclusive of one or more kinases. Unless otherwise specified the term "compounds" includes all pharmaceutically acceptable forms of the disclosed structures.

[0027] In certain situations, the compounds of Formula I-a may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g. asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers. For compounds having asymmetric centers, it should be understood that all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included in the present invention. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

[0028] Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers, but rather includes all tautomeric forms.

[0029] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example, and without limitation, isotopes of hydrogen include tritium and deuterium and isotopes of carbon include ^{11}C, ^{13}C, and ^{14}C.

[0030] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When the substituent is oxo (i.e., =O), then 2 hydrogens on the atom are replaced. When aromatic moieties are substituted by an oxo group, the aromatic ring is replaced by the corresponding partially unsaturated ring. For example a pyridyl group substituted by oxo is a pyridone. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture, and subsequent formulation into an effective therapeutic agent.

[0031] Suitable groups that may be present on a "substituted" position include, but are not limited to, e.g., halogen; cyano; hydroxyl; nitro; azido; alkanoyl (such as a C_2-C_6 alkanoyl group such as acyl or the like); carboxamido; alkyl groups (typically having 1 to about 8 carbon atoms, or 1 to about 6 carbon atoms); cycloalkyl groups, alkenyl and alkynyl groups (including groups having one or more unsaturated linkages and from 2 to about 8, or 2 to about 6 carbon atoms); alkoxy groups having one or more oxygen linkages and from 1 to about 8, or from 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those having one or more thioether linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; alkylsulfinyl groups including those having one or more sulfinyl linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; alkylsulfonyl groups including those having one or more sulfonyl linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; aminoalkyl groups including groups having one or more N atoms and from 1 to about 8, or from 1 to about 6 carbon atoms; aryl having 6 or more carbons and one or more rings, (e.g., phenyl, biphenyl, naphthyl, or the like, each ring either substituted or unsubstituted aromatic); arylalkyl having 1 to 3 separate or fused rings and from 6 to about 18 ring carbon atoms, with benzyl being an exemplary arylalkyl group; arylalkoxy having 1 to 3 separate or fused rings and from 6 to about 18 ring carbon atoms, with benzyloxy being an exemplary arylalkoxy group; or a saturated, unsaturated, or aromatic heterocyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O, or S atoms, e.g. coumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, pyridyl, pyrazinyl, pyrimidinyl, furanyl, pyrrolyl,

thienyl, thiazolyl, triazinyl, oxazolyl, isoxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl, and pyrrolidinyl. Such heterocyclic groups may be further substituted, e.g. with hydroxy, alkyl, alkoxy, halogen or amino.

[0032] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CHO is attached through carbon of the carbonyl (C=O) group.

[0033] As used herein, "alkyl" includes both branched and straight chain saturated aliphatic hydrocarbon groups, having the specified number of carbon atoms, generally from 1 to about 12 carbon atoms. The term C_1-C_7alkyl as used herein indicates an alkyl group having from 1 to 7 carbon atoms. When C_0-$C_n$alkyl is used herein in conjunction with another group, for example, (heterocycloalkyl)C_0-C_2alkyl, the indicated group, in this case heterocycloalkyl, is either directly bound by a single covalent bond (C_0), or attached by an alkyl chain having the specified number of carbon atoms, in this case from 1 to 2 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, 3-methylbutyl, t-butyl, n-pentyl, and sec-pentyl. Alkyl groups described herein typically have from 1 to about 12 carbons atoms. Preferred alkyl groups are lower alkyl groups, those alkyl groups having from 1 to about 8 carbon atoms, from 1 to about 6 carbon atoms, or from 1 to about 4 carbons atoms e.g. C_1-C_8, C_1-C_6, and C_1-C_4alkyl groups.

[0034] "Alkenyl" as used herein, indicates a straight or branched hydrocarbon chain comprising one or more unsaturated carbon-carbon bonds, which may occur in any stable point along the chain. Alkenyl groups described herein typically have from 2 to about 12 carbons atoms. Preferred alkenyl groups are lower alkenyl groups, those alkenyl groups having from 2 to about 8 carbon atoms, e.g. C_2-C_8, C_2-C_6, and C_2-C_4 alkenyl groups. Examples of alkenyl groups include ethenyl, propenyl, and butenyl groups.

[0035] "Alkynyl" as used herein, indicates a straight or branched hydrocarbon chain comprising one or more triple carbon-carbon bonds that may occur in any stable point along the chain, such as ethynyl and propynyl. Alkynyl groups described herein typically have from 2 to about 12 carbons atoms. Preferred alkynyl groups are lower alkynyl groups; those alkynyl groups having from 2 to about 8 carbon atoms, e.g. C_2-C_8, C_2-C_6, and C_2-C_4 alkynyl groups.

[0036] "Alkoxy" indicates an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge (-O-). Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n- propoxy, i- propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3- pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3- methylpentoxy.

[0037] In the term "(Alkoxy)alkyl" alkoxy and alkyl are as defined above and the point of attachment is on the alkyl group. For example (C_1-C_6alkoxy)C_1-C_6alkyl indicates an alkoxy group having from 1 to about 6 carbon atom attached through its oxygen atom to an alkyl group having from 1 to about 6 carbon atoms and further attached to the core molecule through a carbon atom in the C_1-C_6alkyl portion.

[0038] In the term "(Alkoxy)alkoxy" alkoxy is as defined above and the point of attachment is on the oxygen of the second listed alkoxy group. For example (C_1-C_6alkoxy)C_1-C_4alkoxy indicates an alkoxy group have from 1 to about 6 carbon atom attached through its oxygen atom to an second alkoxy group, this one having, for example, from 1 to about 4 carbon atoms, and further attached to the core molecule through an oxygen bridge. Similarly the term "(alkoxy)(alkoxy)alkoxy" refers to two such alkoxy groups attached to a third alkoxy, which is further attached to the core molecule through an oxygen bridge.

[0039] "Alkanoyl" indicates an alkyl group as defined above, attached through a keto (-(C=O)-) bridge. Alkanoyl groups have the indicated number of carbon atoms, with the carbon of the keto group being included in the numbered carbon atoms. For example a C_2alkanoyl group is an acetyl group having the formula $CH_3(C=O)$-.

[0040] As used herein, "alkylthio" means alkyl-S-, where the alkyl group is an alkyl group as defined above having the defined number of carbon atoms. An exemplary alkylthio group is methylthio.

[0041] As used herein the term "alkoxycarbonyl" indicates an alkoxy group, as defined above, having the indicated number of carbon atoms, attached through a keto (-(C=O)-) bridge. The alkoxy moiety of the alkoxycarbonyl group has the indicated number of carbon atoms. The carbon of the keto bridge is not included in this number. C_3alkoxycarbonyl indicates for example, groups of the formula $CH_3(CH_2)_2$-O-(C=O)- or $(CH_3)_2(CH)$-O-(C=O)-.

[0042] As used herein "aminoalkyl" is an alkyl group as defined herein, having the indicated number of carbon atoms, and substituted with at least one amino substituent ($-NH_2$). When indicated, aminoalkyl groups, like other groups described herein, may be additionally substituted.

[0043] As used herein, the term "mono- and/ or di-alkylamino" indicates secondary or tertiary alkyl amino groups, wherein the alkyl groups are as defined above and have the indicated number of carbon atoms. The point of attachment of the alkylamino group is on the nitrogen. The alkyl groups are independently chosen. Examples of mono- and/ or di-alkylamino groups include ethylamino, dimethylamino, and methyl-propyl-amino. "Mono- and/or di- alkylaminoalkyl" groups are mono- and/ or di-alkylamino groups attached through an alkyl linker having the specified number of carbon atoms, for example a di-methylaminoethyl group. Tertiary amino substituents may by designated by nomenclature of the form *N*-R-*N*-R', indicating that the groups R and R' are both attached to a single nitrogen atom.

[0044] As used herein, the term "mono- and/ or di-(alkylamino)alkyl" indicates a mono- and/ or di-alkylamino group as defined attached through an alkyl linker having the specified number of carbon atoms. Similarly "mono- and/ or di-(alkylamino)alkoxy" indicates a mono- and/ or di-alkylamino group as defined attached through an alkoxy linker having the specified number of carbon atoms.

[0045] As used herein the term "mono- and/ or di-alkylcarboxamide" refers to groups of formula ($alkyl_1$)-NH-(C=O)- and ($alkyl_1$)($alkyl_2$)-N-(C=O)- in which the $alkyl_1$ and $alkyl_2$ groups are independently chosen alkyl groups as defined above having the indicated number of carbon atoms. "Carboxamide" is a group of the formula $-(C=O)NH_2$.

[0046] As used herein, the term "aryl" indicates aromatic groups containing only carbon in the aromatic ring or rings. Such aromatic groups may be further substituted with carbon or non-carbon atoms or groups. Typical aryl groups contain 1 or 2 separate, fused, or pendant rings and from 6 to about 12 ring atoms, without heteroatoms as ring members. Where indicated, aryl groups may be substituted. Such substitution may include fusion to a 5 to 7-membered saturated cyclic group that optionally contains 1 or 2 heteroatoms independently chosen from N, O, and S, to form, for example, a 3,4-methylenedioxy-phenyl

group. Aryl groups include, for example, phenyl, naphthyl, including 1- naphthyl and 2-naphthyl, and bi-phenyl.

[0047] "Cycloalkyl" as used herein, indicates a monocyclic or multicyclic saturated hydrocarbon ring group, having the specified number of carbon atoms, usually from 3 to about 10 ring carbon atoms. Monocyclic cycloalkyl groups typically have from 3 to about 8 carbon ring atoms or from 3 to about 7 carbon ring atoms. Multicyclic cycloalkyl groups may have 2 or 3 fused cycloalkyl rings or contain bridged or caged cycloalkyl groups. Cycloalkyl substituents may be pendant to the substituted nitrogen or carbon atom, or where a substituted carbon atom may have two substituents a cycloalkyl group may be attached as a spiro group. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl as well as bridged or caged saturated ring groups such as norbornane or adamantane.

[0048] As used herein "(cycloalkyl)C_0-C_2alkyl indicates a cycloalkyl groups as defined above either directly attached via a single covalent bond or attached through an ethylene (-CH_2CH_2-) or methylene (-CH_2-) linker.

[0049] As used herein "haloalkyl" indicates both branched and straight-chain alkyl groups having the specified number of carbon atoms, substituted with 1 or more halogen atoms, generally up to the maximum allowable number of halogen atoms. Examples of haloalkyl include, but are not limited to, trifluoromethyl, difluoromethyl, 2-fluoroethyl, and penta-fluoroethyl.

[0050] "Haloalkoxy" indicates a haloalkyl group as defined above attached through an oxygen bridge.

[0051] "Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and/ or iodo.

As used herein, "heteroaryl" indicates a stable 5- to 7-membered monocyclic aromatic ring which contains from 1 to 4, or preferably from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a stable bicyclic or tricyclic system containing at least one 5 to 7 membered aromatic ring which contains from 1 to 4, or preferably from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon. When the total number of S and O atoms in the heteroaryl group exceeds 1, these heteroatoms are not adjacent to one another. It is preferred that the total number of S

and O atoms in the heteroaryl group is not more than 2. It is particularly preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, oxazolyl, pyranyl, pyrazinyl, pyrazolopyrimidinyl, pyrazolyl, pyridizinyl, pyridyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienylpyrazolyl, thiophenyl, triazolyl, benzo[*d*]oxazolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxadiazolyl, dihydrobenzodioxynyl, furanyl, imidazolyl, indolyl, and isoxazolyl.

[0052] The term "heterocycloalkyl" indicates a saturated monocyclic group containing from 1 to about 3 heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a saturated bicyclic ring system having at least one N, O, or S ring atom with remaining atoms being carbon. Monocyclic heterocycloalkyl groups have from 4 to about 8 ring atoms, and more typically have from 5 to 7 ring atoms. Bicyclic heterocycloalkyl groups typically have from about five to about 12 ring atoms. Preferred heterocycloalkyl groups include monocyclic heterocycloalkyl groups that contain from 5 to 7 ring atoms and 1 or 2 heteroatoms independently chosen from N, O, and S. Examples of heterocycloalkyl groups include morpholinyl, piperazinyl, piperidinyl, and pyrrolidinyl groups.

[0053] In the term "(heterocycloalkyl)alkyl" the groups heterocycloalkyl and alkyl are as defined above and the point of attachment to the core structure is on the alkyl group.

[0054] As used herein "hydroxyalkyl" is an alkyl group as defined herein, having the indicated number of carbon atoms, and substituted with at least one hydroxyl substituent (-OH). When indicated, hydroxyalkyl groups, like other groups described herein, may be additionally substituted. Similarly the term "hydroxyalkoxy" indicates an alkoxy group as defined herein, having the indicated number of carbon atoms, and substituted with at least one hydroxyl substituent (-OH).

[0055] "Pharmaceutically acceptable forms" of the compounds recited herein include pharmaceutically acceptable salts, hydrates, solvates, crystal forms, polymorphs, chelates, non-covalent complexes, esters, clathrates, prodrugs, and mixtures of such compounds. Pharmaceutically acceptable salts are a preferred pharmaceutically acceptable form.

[0056] "Pharmaceutically acceptable salts" include derivatives of the disclosed compounds wherein the parent compound is modified by making non-toxic acid or base salts

thereof, and further refers to pharmaceutically acceptable solvates of such compounds and such salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, conventional non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred, where practicable. Lists of additional suitable salts may be found, e.g., in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, Pa., p. 1418 (1985).

[0057] The term "prodrugs" includes any compounds that become compounds of Formula I-a when administered to a mammalian subject, e.g., upon metabolic processing of the prodrug. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate and like derivatives of functional groups (such as alcohol or amine groups) in the compounds of Formula I-a.

[0058] The term "active agent" is used to indicate a compound, including any pharmaceutically form thereof, or natural product, which has biological activity. Preferably an "active agent" is a compound having pharmaceutical utility. For example an active agent

may be a compound of Formula I-a, or an anti-cancer or anti-inflammatory therapeutic, which is not a compound of Formula I-a.

[0059] The term "effective amount" of a compound of this invention means an amount effective, when administered to a human or non-human patient, to provide a therapeutic benefit such as amelioration of symptoms, slowing of disease progression, or prevention of disease e.g., an effective amount may be an amount sufficient to decrease the symptoms of a disease responsive to Btk inhibition, and preferably is an amount sufficient to reduce cancer symptoms, the symptoms of an autoimmune and/or inflammatory disease, or the symptoms of an acute inflammatory reaction. In some embodiments an effective amount of a compound described herein is an amount sufficient to decrease the number of detectable cancerous cells in an organism, detectably slow or stop the growth of a cancerous tumor, or more preferably an amount sufficient to shrink a cancerous tumor. In certain circumstances a patient suffering from cancer may not present symptoms of being affected. Thus, a therapeutically effective amount of a compound is also an amount sufficient to prevent a significant increase or significantly reduce the detectable level of cancerous cells or cancer markers in the patient's blood, serum, or tissues. In methods described herein for treating autoimmune and/or inflammatory diseases or acute inflammatory reactions, an effective amount may also be an amount sufficient, when administered to a patient, to detectably slow progression of the disease, or prevent the patient to whom the compound is given from presenting symptoms of the autoimmune and/ or inflammatory disease, or acute inflammatory response. In certain methods described herein for treating autoimmune and/or inflammatory diseases or acute inflammatory reactions, an effective amount may also be an amount sufficient to produce a detectable decrease in the amount of a marker protein or cell type in the patient's blood or serum. For example, in some embodiments an effective amount is an amount of a compound described herein sufficient to significantly decrease the number of B-cells. In another example, in some embodiments an effective amount is an amount of a compound described herein sufficient to decrease the level of anti-acetylcholine receptor antibody in a patient's blood with the disease myasthenia gravis,.

[0060] The term "inhibition" indicates a significant decrease in the baseline activity of a biological activity or process. "Inhibition of Btk activity" refers to a decrease in Btk activity as a direct or indirect response to the presence of a compound of Formula I-a, relative

to the activity of Btk in the absence of the compound. The decrease in activity may be due to the direct interaction of the compound with Btk, or due to the interaction of the compound with one or more other factors that in turn affect Btk activity. For example, the presence of the compound may decrease Btk activity by directly binding to the Btk, by causing (directly or indirectly) another factor to decrease Btk activity, or by (directly or indirectly) decreasing the amount of Btk present in the cell or organism.

[0061] Inhibition of Btk activity also refers to observable inhibition of Btk activity in a standard biochemical assay for Btk activity, such as the ATP hydrolysis assay of Example 6. Preferred inhibitors of Btk activity have an IC_{50} value less than or equal to 1 micromolar, more preferably less than or equal to less than 100 nanomolar, and still more preferably less than or equal to 10 nanomolar.

[0062] Without wishing to be bound to any particular theory it is believed that the inhibition of Btk activity causes an inhibition of B-cell proliferation. "Inhibition of B-cell proliferation" refers to inhibition of proliferation of abnormal B-cells, such as cancerous B-cells, e.g. lymphoma B-cells and/ or inhibition of normal, non-diseased B-cells. The term "inhibition of B-cell proliferation" indicates any significant decrease in the number of B-cells, either *in vitro* or *in vivo*. Thus *in vitro* an inhibition of B-cell proliferation would be any significant decrease in the number of B-cells in an *in vitro* sample contacted with a compound of Formula I-a as compared to a matched sample not contacted with a compound of Formula I-a.

[0063] Inhibition of B-cell proliferation also refers to observable inhibition of B-cell proliferation in a standard thymidine incorporation assay for B-cell proliferation, such as the assay of Example 8. Preferred inhibitors of B-cell proliferation have an IC_{50} value less than or equal to 10 micromolar, more preferably less than or equal to less than 1 micromolar, and still more preferably less than or equal to 500 nanomolar.

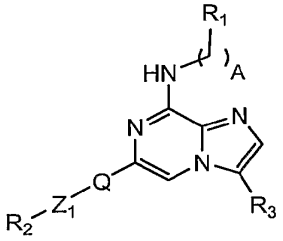
[0064] By "significant" is meant any detectable change that is statistically significant in a standard parametric test of statistical significance such as Student's T-test, where $p < 0.05$.

[0065] A "disease responsive to Btk inhibition" is a disease in which inhibiting Btk kinase provides a therapeutic benefit such as an amelioration of symptoms, decrease in

disease progression, prevention or delay of disease onset, or inhibition of aberrant activity of certain cell-types (monocytes, B-cells, and mast cells).

IMIDAZO[1,2-*a*]PYRAZINE COMPOUNDS

[0066] In addition to compounds of Formula I-a (above), compounds of Formula 1



(Formula 1)

and the pharmaceutically acceptable form thereof, are also disclosed.

Within Formula 1:

A is 0 or 1.

R_1 is phenyl or heteroaryl, each of which is substituted with one of

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl.

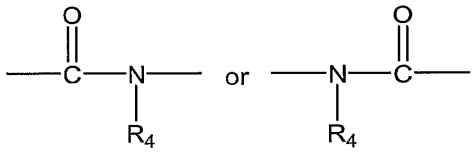
Each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl.

And, R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-

C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

R_2 is C_1-C_7 alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, (heterocycloalkyl)C_0-C_2alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, or R_2 is (phenyl)C_0-C_2alkyl, (phenoxy)C_0-C_2alkyl, or (heteroaryl)C_0-C_2alkyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, -SO_2NH_2, oxo, -COOH, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_2-C_6alkanoyl, C_1-C_6hydroxyalkyl, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6alkyl, mono- and di- C_1-C_6alkylamino, mono- and di-C_1-C_6alkylcarboxamide, C_1-C_6alkoxycarbonyl, phenyl, heteroaryl, and –(C=O)R_{13} wherein R_{13} is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, C_1-C_3haloalkyl, heterocycloalkyl, phenyl, or heteroaryl.

Z_1 is



wherein R_4 is hydrogen, or R_4 is C_1-C_6alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each of which is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6 alkyl, mono- and di-C_1-C_6 alkylamino, and -C(O)R_{14} wherein R_{14} is C_1-C_6 alkyl, C_1-C_3haloalkyl, or phenyl.

Q is phenyl or pyridyl.

R_3 is hydrogen, halogen, or C_1-C_7 alkyl, or

R_3 is heterocycloalkyl, C_3-C_7cycloalkyl, or heteroaryl, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, -SO_2NH_2, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3halooalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6-alkoxy)C_1-C_6 alkoxy, mono- and di-C_1-C_6alkylamino, aminoC_1-C_6 alkyl, and -C(O)R_{14}.

The Variable A

[0067] Also included herein are compounds of Formula 1 wherein A is 0 and compounds of Formula 1 wherein A is 1.

The Variable R_1

[0068] Further provided herein are compounds of Formula 1 and pharmaceutically acceptable forms thereof, wherein the variable R_1 satisfies one or more of the following conditions set forth in A. to O.

[0069] A. R_1 is phenyl or pyridyl, each of which is substituted with one of

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$, where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl.

Each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl.

And, R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

[0070] B. R_1 is phenyl or pyridyl, each of which is substituted with one of oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH, and R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl,

(C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

[0071] C. R_1 is phenyl or pyridyl, each of which is substituted with one of oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH, and R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

[0072] D. R_1 is phenyl or pyridyl, each of which is substituted with one of oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH, and R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0073] E. R_1 is phenyl or pyridyl, each of which is substituted with one of (ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl.

Each of which (ii) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl.

And, R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

[0074] F. R_1 is phenyl or pyridyl, each of which is substituted with one of C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, or (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide.

And, R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

[0075] G. R_1 is phenyl or pyridyl, each of which is substituted with one of C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, or (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy.

And, R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0076] H. R_1 is phenyl or pyridyl, each of which is substituted with one of pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, [1,4]diazepanyl, phenyl, imidazolyl, or 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazine, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide.

And, R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

[0077] I. R_1 is phenyl or pyridyl, each of which is substituted with one of pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, [1,4]diazepanyl, phenyl, imidazolyl, or 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazine, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide.

And, R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0078] J. R_1 is phenyl or pyridyl, each of which is substituted with one of (iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_7cycloalkyl, or heterocycloalkyl. Each of which (iii) is substituted with 0 to 3 substituents

independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl.

And, R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

[0079] K. R_1 is phenyl or pyridyl, each of which is substituted with one of -C_1-C_4alkyl(C=O)OR_{10}, -C_0-C_4alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_4alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_4alkylNR_{10}(C=O)R_{11}, -C_0-C_4alkyl(SO_2)R_{10}, or -C_0-C_4alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, or [1,4]diazepanyl, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide.

And, R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0080] L. R_1 is phenyl or pyridyl, each of which is substituted with one of (iv) – L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl, each of which (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl.

And, R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

[0081] M. R_1 is phenyl or pyridyl, each of which is substituted with one of –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, [1,4]diazepanyl, phenyl, imidazolyl, or 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazine, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide.

And, R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

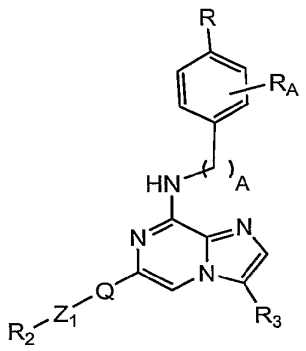
[0082] N. R_1 is phenyl or pyridyl, each of which is substituted with one of –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, [1,4]diazepanyl, phenyl, imidazolyl, or 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazine, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide.

And, R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0083] O. L is phenyl or pyridyl, each of which is substituted with one of –CH_2-, -(C=O)-, or -(CH_2)(C=O)-, and G is pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, or [1,4]diazepanyl, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, -COOH, -$CONH_2$, C_1-C_2alkyl, C_1-C_2alkoxy, C_2-C_2alkanoyl, C_1-C_2alkoxycarbonyl, mono- and di-C_1-C_2alkylamino, and mono- and di-C_1-C_2alkylcarboxamide.

And, R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0084] Also disclosed herein are compounds and pharmaceutically acceptable forms of Formula 2:



Formula 2

[0085] Within Formula 2

A, R_2, Z_1, Q, and R_3 carry any of the definitions set forth herein for these variables. For example R_2 may have the definition set forth for this variable in Formula I-a, R_2 may have the definition set forth for this variable in Formula 1, R_2 may have any of the values set forth for this variable in the claims, or in the subsection titled "the R_2 variable."

R is

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

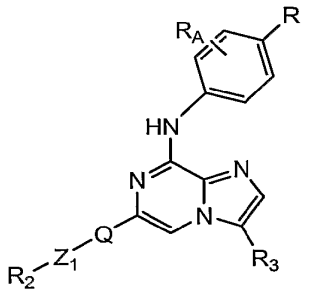
(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl. Each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo,

-COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl.

R_A is 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-

C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

[0086] Another embodiment includes compounds and pharmaceutically acceptable forms in which R_1 is a phenyl substituted at the para position by R, and substituted at any other position by R_A i.e. the invention provides compounds and pharmaceutically acceptable forms of Formula 3



Formula 3.

[0087] Within Formula 3

R_2, Z_1, Q, and R_3 carry any of the definitions set forth herein for these variables and R and R_A carry the definitions set forth for these variables for Formula 2.

The R_2 Variable

[0088] Further provided herein are compounds of Formula 1 and pharmaceutically acceptable forms thereof, wherein the variable R_2 satisfies one or more of the following conditions.

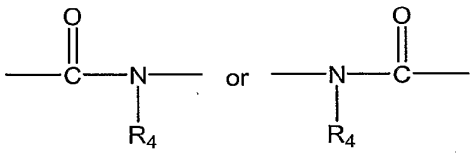
[0089] A. R_2 is (phenyl)C_0-C_2alkyl, (phenoxy)C_0-C_2alkyl, or (pyridyl)C_0-C_2alkyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, -SO_2NH_2, oxo, -COOH, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_2-C_6alkanoyl, C_1-C_6hydroxyalkyl, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6alkyl, mono- and di-C_1-C_6 alkylamino, mono- and di-C_1-C_6alkylcarboxamide, C_1-C_6alkoxycarbonyl, phenyl, heteroaryl, and –(C=O)R_{13} wherein R_{13} is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, C_1-C_3haloalkyl, heterocycloalkyl, phenyl, or heteroaryl.

[0090] B. R_2 is (phenyl)C_0-C_2alkyl, (phenoxy)C_0-C_2alkyl, or (pyridyl)C_0-C_2alkyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy,

cyano, amino, halogen, $-SO_2NH_2$, oxo, -COOH, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_4alkanoyl, C_1-C_4hydroxyalkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, mono- and di-C_1-C_6alkylamino, mono- and di-C_1-C_6alkylcarboxamide, C_1-C_4alkoxycarbonyl, phenyl, and imidazolyl.

The Z_1 Variable

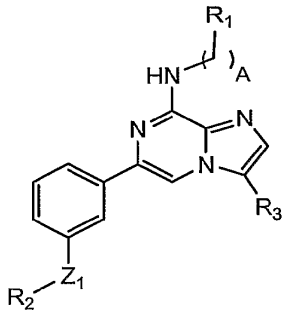
[0091] Within certain embodiments Z_1 is



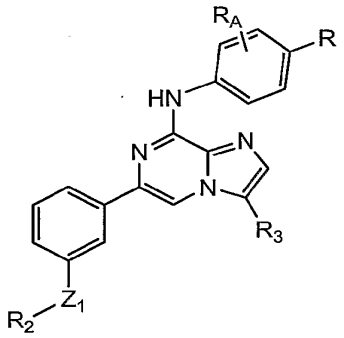
wherein R_4 is hydrogen, C_1-C_6alkyl, or C_3-C_7cycloalkyl. In some of these embodiments R_4 is hydrogen or methyl.

The Q Variable

[0092] Additional embodiments, pertain to compounds and pharmaceutically acceptable forms of Formula 4 and Formula 5



Formula 4



Formula 5

[0093] Within Formula 4 and 5:

A, R. R_A, R_1, R_2, Z_1, and R_3 carry any of the definitions set forth herein for these variables.

In certain embodiments of Formula 5, R is

(i) oxo, -CHO, –COOH, $-CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl$(SO_2)R_{10}$, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl.

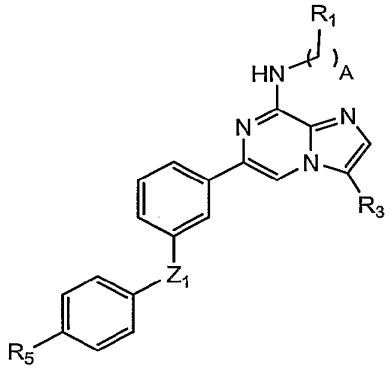
Each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl.

[0094] R_A is 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

The R_3 Variable

[0095] R_3 is hydrogen or methyl in certain compounds of the invention and pharmaceutically acceptable forms described herein.

[0096] Additional embodiments of the invention pertain to compounds of Formula 6



Formula 6.

and the pharmaceutically acceptable forms thereof.

Within Formula 6

Z_1, R_3 and A variables carry any of the definitions set forth herein for these variables.

R_1 is phenyl or heteroaryl, each of which is optionally substituted with one of

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl$(SO_2)R_{10}$, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

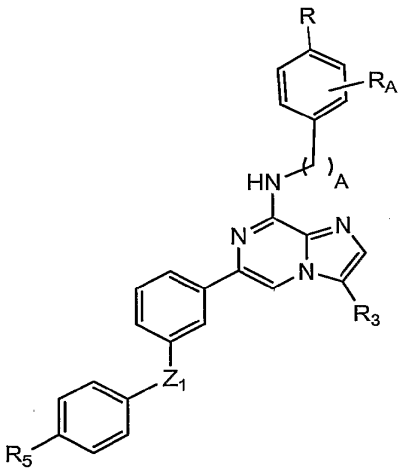
(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl.

Each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl.

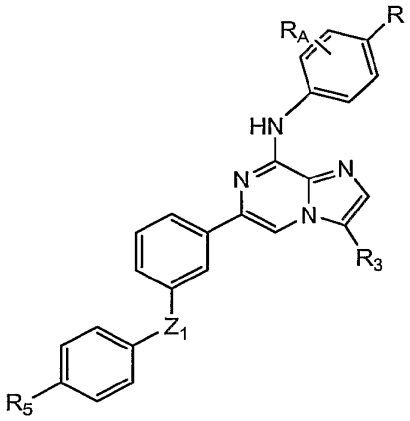
And, R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

R_5 is isopropyl or t-butyl.

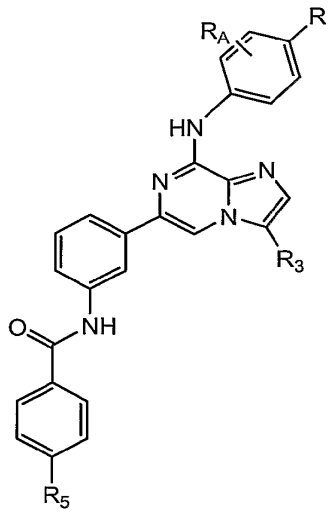
Other embodiments pertain to compounds and forms thereof of Formula 7 to Formula 9



Formula 7



Formula 8



Formula 9

Within Formula 7 to Formula 9:

R is

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl.

Each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl.

R_A is 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-

C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

R_5 is isopropyl or t-butyl.

A, Z_1, and R_3 may carry any of the definitions set forth above for these variables. It certain embodiments it is preferred that R_3 is hydrogen or methyl.

PHARMACEUTICAL PREPARATIONS

[0097] Compounds, salts, and any other pharmaceutically acceptable forms of the invention can be administered as the neat chemical, but are preferably administered as a pharmaceutical composition or formulation. Accordingly, the invention provides pharmaceutical formulations comprising a compound or pharmaceutically acceptable form of Formula I-a, together with one or more pharmaceutically acceptable carriers, excipients, adjuvants, diluents, or other ingredients.

[0098] Pharmaceutical carriers must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal being treated. The carrier can be inert or it can possess pharmaceutical benefits. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound.

[0100] Exemplary pharmaceutically acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; synthetic oils; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, and corn oil; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; phosphate buffer solutions; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

[0101] Optional active agents may be included in a pharmaceutical composition, which do not substantially interfere with the activity of the compound of the present invention.

[0102] Effective concentrations of one or more of the compounds of the invention including pharmaceutically acceptable salts, esters or other derivatives thereof are mixed with a suitable pharmaceutical carrier, excipients, adjuvant, or vehicle. In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts of the compounds or prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

[0103] Upon mixing or addition of the compound(s) of the invention, the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the chosen carrier or vehicle. The effective concentration sufficient for ameliorating the symptoms of the disease treated and may be empirically determined.

[0104] Compounds of provided herein may be administered orally, topically, parenterally, intravenously, by intramuscular injection, by inhalation or spray, sublingually, transdermally, via buccal administration, rectally, as an ophthalmic solution, or by other means, in dosage unit formulations.

[0105] Dosage formulations suitable for oral use, include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents, such as sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide pharmaceutically elegant and palatable preparations. Oral formulations contain between 0.1 and 99% of a compound of the invention and usually at least about 5% (weight %) of a compound of the present invention. Some embodiments contain from about 25% to about 50% or from 5% to 75 % of a compound of invention.

[0106] Orally administered compositions also include liquid solutions, emulsions, suspensions, powders, granules, elixirs, tinctures, syrups, and the like. The pharmaceutically

acceptable carriers suitable for preparation of such compositions are well known in the art. Oral formulations may contain preservatives, flavoring agents, sweetening agents, such as sucrose or saccharin, taste-masking agents, and coloring agents.

[0107] Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent.

Orally Administered Liquids formulations

[0108] Compounds of the invention can be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, for example. Moreover, formulations containing these compounds can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can contain conventional additives, such as suspending agents (e.g., sorbitol syrup, methyl cellulose, glucose/sugar, syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminum stearate gel, and hydrogenated edible fats), emulsifying agents (e.g., lecithin, sorbitan monsoleate, or acacia), non-aqueous vehicles, which can include edible oils (e.g., almond oil, fractionated coconut oil, silyl esters, propylene glycol and ethyl alcohol), and preservatives (e.g., methyl or propyl p-hydroxybenzoate and sorbic acid).

Suspensions

[0109] For a suspension, typical suspending agents include methylcellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate.

[0110] Aqueous suspensions contain the active material(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents; may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of

ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol substitute, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan substitute. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n- propyl p-hydroxybenzoate.

[0111] Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example peanut oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Emulsions

[0112] Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or peanut oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate.

Dispersible powders

[0113] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

Tablets and Capsules

[0114] Tablets typically comprise conventional pharmaceutically compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc.

Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules (including time release and sustained release formulations) typically comprise one or more solid diluents disclosed above. The selection of carrier components often depends on secondary considerations like taste, cost, and shelf stability.

[0115] Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methylcellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

[0116] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Injectable and Parenteral formulations

[0117] Pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables.

[0118] Compounds of the invention may be administered parenterally in a sterile medium. Parenteral administration includes subcutaneous injections, intravenous,

intramuscular, intrathecal injection or infusion techniques. The compound or compounds of the invention, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle. In many compositions for parenteral administration the carrier comprises at least about 90% by weight of the total composition. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil.

Suppositories

[0119] Compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Topical formulations

[0120] Compounds of the invention may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye. Topical compositions of the present invention may be in any form including, for example, solutions, creams, ointments, gels, lotions, milks, cleansers, moisturizers, sprays, skin patches, and the like.

[0121] Such solutions may be formulated as 0.01% -10% isotonic solutions, pH about 5-7, with appropriate salts. Compounds of the invention may also be formulated for transdermal administration as a transdermal patch.

[0122] Topical compositions containing the active compound can be admixed with a variety of carrier materials well known in the art, such as, for example, water, alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like.

[0123] Other materials suitable for use in topical carriers include, for example, emollients, solvents, humectants, thickeners and powders. Examples of each of these types of materials, which can be used singly or as mixtures of one or more materials, are as follows:

[0124] Emollients, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, iso-propyl isostearate, stearic acid, iso-butyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, iso-propyl myristate, iso-propyl palmitate, iso-propyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, and myristyl myristate; propellants, such as propane, butane, iso-butane, dimethyl ether, carbon dioxide, and nitrous oxide; solvents, such as ethyl alcohol, methylene chloride, iso-propanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran; humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, and gelatin; and powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, and ethylene glycol monostearate.

[0125] Compounds of the invention may also be topically administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Other formulations

[0126] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol, and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl methylcellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[0127] Compositions for inhalation typically can be provided in the form of a solution, suspension or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant (e.g., dichlorodifluoromethane or trichlorofluoromethane).

Additional components

[0128] The compositions of the present invention may also optionally comprise an activity enhancer. The activity enhancer can be chosen from a wide variety of molecules that function in different ways to enhance therapeutic effects of compounds of the invention. Particular classes of activity enhancers include skin penetration enhancers and absorption enhancers.

[0129] Pharmaceutical compositions of the invention may also contain additional active agents can be chosen from a wide variety of molecules, which can function in different ways to enhance the therapeutic effects of a compound of the invention. These optional other active agents, when present, are typically employed in the compositions of the invention at a level ranging from about 0.01% to about 15%. Some embodiments contain from about 0.1% to about 10% by weight of the composition. Other embodiments contain from about 0.5% to about 5% by weight of the composition.

Packaged Formulations

[0130] The invention includes packaged pharmaceutical formulations. Such packaged formulations include a pharmaceutical composition containing one or more compounds, salts, or other pharmaceutically acceptable forms thereof, of the invention in a container and instructions for using the composition to treat a mammal (typically a human patient). Preferably the instructions are for using the pharmaceutical composition to treat a patient suffering from a disease responsive to inhibition of Btk activity and/ or inhibition of B-cell proliferation. The invention includes providing prescribing information; for example, to a patient or health care provider, or as a label in a packaged pharmaceutical formulation. Prescribing information may include for example efficacy, dosage and administration, contraindication and adverse reaction information pertaining to the pharmaceutical formulation.

[0131] In all of the foregoing the compounds of the invention can be administered alone, as mixtures, or in combination with other active agents.

METHODS OF TREATMENT

[0132] Imidazo[1,2-a]pyrazines active as kinase inhibitors, in particular Btk inhibitors are described herein. These inhibitors are useful for treating diseases responsive to kinase inhibition, including diseases responsive to Btk inhibition and/ or inhibition of B-cell proliferation, in mammals. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of Formula I-a with Btk results in the inhibition of Btk activity and thus in the pharmaceutical utility of these compounds. Other kinases that may be affected in addition to Btk include, but are not limited to, other tyrosine kinases and serine/threonine kinases.

[0133] Accordingly, the invention includes a method of treating a mammal, preferably a human, having a disease responsive to inhibition of Btk activity, comprising administrating to the mammal having such a disease, an effective amount of a compound of Formula I-a.

[0134] To the extent that Btk is implicated in any of the following, alleviation of the disease, disease symptoms, preventative, and prophylactic treatment is within the scope of this invention. In addition, as noted above, the compounds of Formula I-a may also inhibit other kinases, such that alleviation of disease, disease symptoms, preventative, and prophylactic treatment of conditions associated with these kinases is also within the scope of this invention.

[0135] Methods of treatment also include inhibiting Btk activity and/ or inhibiting B-cell proliferation, by inhibiting ATP binding or hydrolysis by Btk or by some other mechanism, *in vivo*, in a patient suffering from a disease responsive to inhibition of Btk activity, by administering an effective concentration of a compound of Formula I-a to inhibit Btk activity *in vitro*. An effective concentration may be ascertained experimentally, for example by assaying blood concentration of the compound, or theoretically, by calculating bioavailability.

Diseases responsive to kinase inhibition

[0136] Certain compounds described herein are useful for treating a patient suffering from a disease responsive to kinase inhibition.

[0137] Protein kinases, the largest family of human enzymes, are now considered to be the largest druggable target class. Encompassing well over 500 proteins (2% of the human

genome), kinases play critical roles in signaling pathways controlling fundamental cellular processes such as proliferation, differentiation, and death (apoptosis). Abnormal kinase activity has been implicated in a wide range of diseases, including multiple cancers, autoimmune and/or inflammatory diseases, and acute inflammatory reactions. The multifaceted role of kinases in key cell signaling pathways provides a significant opportunity to identify novel drugs targeting kinases and signaling pathways.

Diseases responsive to Btk inhibition

[0138] The invention includes a method of treating a patient having cancer, an autoimmune and/or inflammatory disease, or an acute inflammatory reaction, by administering an effective amount of a compound of Formula I-a.

[0139] In a preferred embodiment, the condition responsive to inhibition of Btk activity and/ or B-cell proliferation is cancer, an autoimmune and/or inflammatory disease, or an acute inflammatory reaction.

[0140] Preferably, the conditions, diseases that can be affected using compounds and compositions according to the invention include, but are not limited to:

autoimmune and/or inflammatory diseases, including but not limited to psoriasis, allergy, Crohn's disease, irritable bowel syndrome, Sjogren's disease, tissue graft rejection, and hyperacute rejection of transplanted organs, asthma, systemic lupus erythematosus (and associated glomerulonephritis), dermatomyositis, multiple sclerosis, scleroderma , vasculitis (ANCA-associated and other vasculitides), autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), atherosclerosis, rheumatoid arthritis, chronic Idiopathic thrombocytopenic purpura (ITP), Addison's disease, Parkinson's disease, Alzheimer's disease, diabetes, septic shock, myasthenia gravis, and the like,

acute inflammatory reactions, including but not limited to skin sunburn, inflammatory pelvic disease, inflammatory bowel disease, urethritis, uvitis, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, and cholocystitis, and

cancer, including but not limited to, B-cell lymphoma, lymphoma (including Hodgkin's and non-Hodgkins lymphoma), hairy cell leukemia, multiple myeloma, chronic and acute myelogenous leukemia, and chronic and acute lymphocytic leukemia.

[0141] Btk is a known inhibitor of apoptosis in lymphoma B-cells. Defective apoptosis contributes to the pathogenesis and drug resistance of human leukemias and lymphomas. Thus, a method of promoting or inducing apoptosis in cells expressing Btk comprising contacting the cell with an agent that inhibits Btk activity is also provided herein.

Combination Therapy

[0142] The invention provides methods of treatment in which a compound of the invention is the only active agent given to a patient and also includes methods of treatment in which a compound of Formula I-a is given to a patient in combination with one or more additional active agent. Thus in one embodiment the invention provides a method of treating cancer, an autoimmune and/or inflammatory disease, or an acute inflammatory reaction, which comprises administering to a mammal in need thereof an effective amount of a compound of Formula I-a together with a second active agent, which is useful for treating an cancer, an autoimmune and/or inflammatory disease, or an acute inflammatory reaction. For example the second agent may be an anti-inflammatory agent. Treatment with the second active agent may be prior to, concomitant with, or following treatment with a compound of Formula I-a. In certain embodiments a compound of Formula I-a is combined with another active agent in a single dosage form. Suitable antitumor therapeutics that may be used in combination with a compound of Formula I-a include, but are not limited to chemotherapeutic agents, for example mitomycin C, carboplatin, taxol, cisplatin, paclitaxel, etoposide, doxorubicin, or a combination comprising at least one of the foregoing chemotherapeutic agents. Radiotherapeutic antitumor agents may also be used, alone or in combination with chemotherapeutic agents.

[0143] Btk inhibitors are useful as chemosensitizing agents, and, thus, are useful in combination with other chemotherapeutic drugs, in particular, drugs that induce apoptosis.

[0144] A method for increasing sensitivity of cancer cells to chemotherapy, comprising administering to a patient undergoing chemotherapy a chemotherapeutic agent together with a Btk inhibitor in an amount sufficient to increase the sensitivity of cancer cells to the chemotherapeutic agent is also provided herein.

[0145] Examples of other chemotherapeutic drugs that can be used in combination with Btk inhibitors include topoisomerase I inhibitors (camptothesin or topotecan), topoisomerase II inhibitors (e.g. daunomycin and etoposide), alkylating agents (e.g.

cyclophosphamide, melphalan and BCNU), tubulin directed agents (e.g. taxol and vinblastine), and biological agents (e.g. antibodies such as anti CD20 antibody, IDEC 8, immunotoxins, and cytokines).

[0146] Included herein are methods of treatment in which a compound of Formula I-a in administered in combination with an anti-inflammatory agent. Anti-inflammatory agents include but are not limited to NSAIDs, non-specific and COX- 2 specific cyclooxgenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor receptor (TNF) receptors antagonists, immunosuppressants and methotrexate.

[0147] Examples of NSAIDs include, but are not limited to ibuprofen, flurbiprofen, naproxen and naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine. Examples of NSAIDs also include COX-2 specific inhibitors (i.e., a compound that inhibits COX-2 with an IC_{50} that is at least 50-fold lower than the IC_{50} for COX-1) such as celecoxib, valdecoxib, lumiracoxib, etoricoxib and/or rofecoxib.

[0148] In a further embodiment, the anti-inflammatory agent is a salicylate. Salicylates include by are not limited to acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium salicylates.

[0149] The anti-inflammatory agent may also be a corticosteroid. For example, the corticosteroid may be cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, and prednisone.

[0150] In additional embodiments the anti-inflammatory agent is therapeutic agent is a gold compound such as gold sodium thiomalate or auranofin.

[0151] The invention also includes embodiments in which the anti-inflammatory agent is a metabolic inhibitor such as a dihydrofolate reductase inhibitor, such as methotrexate or a dihydroorotate dehydrogenase inhibitor, such as leflunomide.

[0152] Other embodiments of the invention pertain to combinations in which at least one anti-inflammatory compound is an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab), a TNF antagonist, such as entanercept, or infliximab, which is an anti-TNF alpha monoclonal antibody.

[0153] Still other embodiments of the invention pertain to combinations in which at least one active agent is an immunosuppressant compound such as methotrexate, leflunomide, cyclosporine, tacrolimus, azathioprine, or mycophenolate mofetil.

Dosage Levels

[0154] Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above- indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

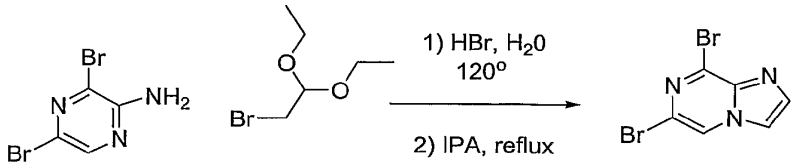
[0155] Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most autoimmune and/or inflammatory, a dosage regimen of 4 times daily or less is preferred and a dosage regimen of 1 or 2 times daily is particularly preferred.

[0156] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the patient undergoing therapy.

EXAMPLES

EXAMPLE 1. EXEMPLARY SYNTHESIS OF CERTAIN IMIDAZO[1,2-A]PYRAZIN-8-YLAMINES

Step 1. 6,8-dibromoimidazo[1,2-a]pyrazine (3)

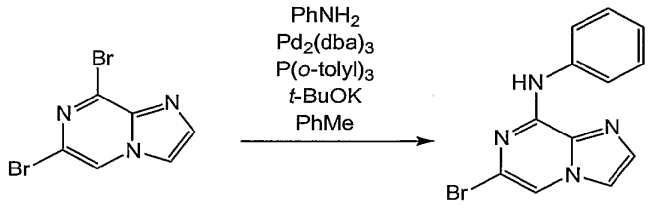


(1) (2) (3)

[0157] A mixture of bromoacetaldehyde diethyl acetal (51 grams (g)), 48% hydrobromic acid (HBr) (11 milliliters (mL)), and water (11 mL) is heated at 120 °C for 1

hour (hr). The solution is cooled, poured into a mixture of sodium bicarbonate ($NaHCO_3$) (60 g) and isopropyl alcohol (IPA) (200 mL), and stirred for 0.5 hr. The mixture is filtered, and the filtrate is treated with 3,5-dibromo-2-aminopyrazine (**1**) (33 g) and heated under reflux for 16 hr. The suspension is cooled in ice, treated with 48% HBr (3 mL) and diethyl ether (60 mL) and filtered to afford (**3**) as the hydrobromide salt.

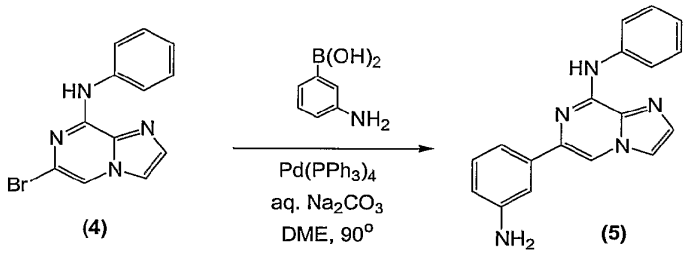
Step 2. (6-Bromo-imidazo[1,2-a]pyrazin-8-yl)-phenyl-amine (4)



(3) (4)

[0158] Tri-*o*-tolylphosphine (1.1 g) is added to a suspension of tris(dibenzylideneacetone)dipalladium (1.65 g) in degassed toluene (50 mL) and the mixture is stirred at room temperature for 15 minutes (min). 6,8-Dibromo-imidazo[1,2-a]pyrazine (5.0 g) is then added and the mixture is stirred at room temperature for 15 minutes more. Aniline (1.52 g) is added followed by potassium *t*-butoxide (2.84 g) and the mixture is stirred at room temperature for 72 hr. Water (150 mL) is added and the mixture is extracted with ethyl acetate (3 x 150 mL), the extracts are washed with water (1 x 100 mL) and brine (1 x 100 mL), dried over $MgSO_4$, and evaporated *in vacuo* to afford a gum. Trituration with diethyl ether affords (6-bromo-imidazo[1,2-a]pyrazin-8-yl)-phenyl-amine (**4**) as a brown solid.

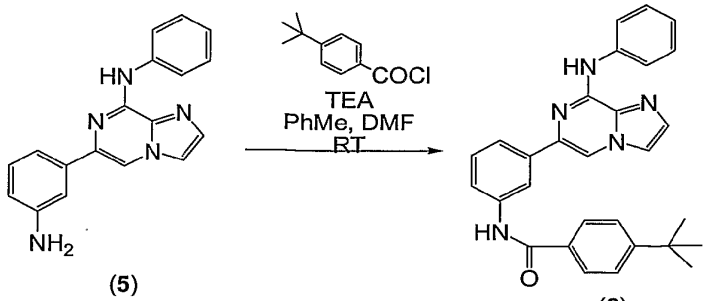
Step 3. [6-(3-Amino-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-phenyl-amine (5)



(4) (5)

[0159] A mixture of (6-bromo-imidazo[1,2-a]pyrazin-8-yl)-phenyl-amine (**4**) (1.9 g), 3-aminophenylboronic acid hemisulfate (1.35 g), tetrakis(triphenylphosphine) palladium (380 mg), 1M aqueous sodium carbonate (20 mL), and 1,2-dimethoxyethane (40 mL) is heated at 90° for 16 hr. The mixture is cooled to room temperature, treated with water (50 mL) and extracted with ethyl acetate (3 x 80 mL). The extracts are washed with water (1 x 50 mL) and brine (1 x 50 mL), dried over $MgSO_4$, and evaporated *in vacuo* to afford a gum which is purified by flash chromatography over silica gel, eluting with ethyl acetate, to afford [6-(3-amino-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-phenyl-amine (**5**) as a light brown solid.

Step 4. 4-tert-Butyl-N-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide (6)

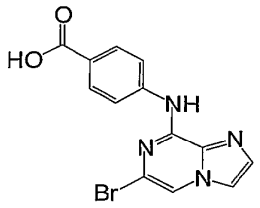


(5) (6)

[0160] A solution of [6-(3-amino-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-phenyl-amine **(5)** (50 mg), 4-*tert*-butyl-benzoyl chloride (0.83 mL of a 0.2M solution in toluene), and triethylamine (0.034 mL) in toluene (1 mL) and N,N,-dimethylformamide (1 mL) is stirred at room temperature for 16 hr. The mixture is purified by preparative thin layer chromatography over silica gel, eluting with diethyl ether/dichloromethane (1:1) to afford 4-*tert*-butyl-N-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide **(6)** as a cream foam.

EXAMPLE 2. SYNTHESIS OF *N*-(4-*TERT*-BUTYL-PHENYL)-3-{8-[4-(MORPHOLIN-4-CARBONYL)-PHENYLAMINO]-IMIDAZO[1,2-*A*]PYRAZIN-6-YL}-BENZAMIDE

Step. 1. 4-(6-Bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid (7)

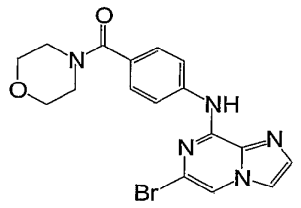


(7)

[0161] A mixture of 4-(6-Bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester (30 mmol), 1N aqueous sodium hydroxide (50 mL), and ethanol (80 mL) is heated at reflux for 1.5hr. The mixture is cooled and the ethanol removed *in vacuo*. The residue is diluted with 1N sodium hydroxide (30 mL) and washed with ethyl acetate (2 x 100 mL). The

aqueous layer is brought to pH 6 with 3N HCl, and the mixture filtered to give 4-(6-Bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid (**7**) as a light orange solid.

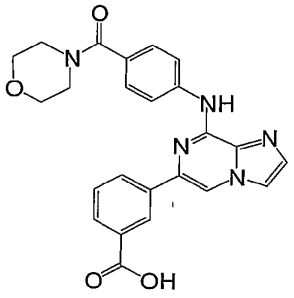
*Step 2. [4-(6-Bromo-imidazo[1,2-a]pyrazin-8-ylamino)-phenyl]-morpholin-4-yl-methanone (**8**)*



(**8**)

[0162] A mixture of 4-(6-Bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid (**7**) (0.16 mmol), benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (0.16 mmol), and N'N-diisopropylethylamine (0.48 mmol) is stirred at room temperature for 20 min. under N_2. Morpholine (0.48 mmol) is added and the mixture is stirred at room temperature for 16 hr. Water (10 mL) is added and the mixture extracted with ethyl acetate (2 x 70 mL). The extracts are subsequently washed with water (2 x 30 mL) and brine (1 x 30 mL), dried over sodium sulfate, and concentrated *in vacuo*. The residue is triturated with diethyl ether to give [4-(6-Bromo-imidazo[1,2-a]pyrazin-8-ylamino)-phenyl]-morpholin-4-yl-methanone (**8**) as a cream solid.

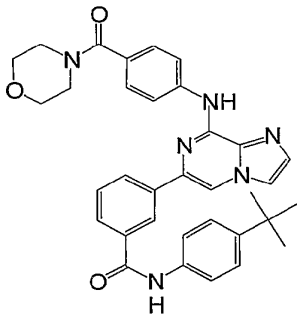
*Step 3. 3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-benzoic acid (**9**)*



(**9**)

[0163] The bromide (**8**) (2.46 mmol) is dissolved in 10 mL DME (ethylene glycol, dimethyl ether) in a sealable pressure vessel and N_2 is bubbled through for 10 min. Tetrakis(triphenylphosphine)palladium (0.24 mmol) is added and N_2 is bubbled through the reaction for another 10 minutes. 3-Carboxyphenyl boronic acid (3.1 mmol) and 1N Na_2CO_3 solution (10 mL) are then added, the vessel sealed, and the reaction heated to 95° C for 16 hrs. with vigorous stirring. After cooling to room temperature, the reaction is acidified to pH 3 with 1N HCl and extracted with ethyl acetate (3 x 25 mL). The pooled ethyl acetate layers are washed with brine, dried over sodium sulfate, and the solvent removed in vacuo. The resulting solid is then dissolved in a minimal volume of CH_2Cl_2 and precipitated out as a whitish-tan solid by slow addition of ethyl acetate (5 mL) followed by hexanes (30 mL) to yield 3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-benzoic acid (**9**).

*Step 4. N-(4-tert-Butyl-phenyl)-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-benzamide (**10**)*



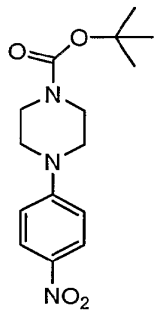
(10)

[0164] A mixture of 3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-benzoic acid (**9**) (0.23 mmol), benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate reagent (0.23 mmol) and N,N'-diisopropylethylamine (0.77 mmol) is stirred under N_2 for 15 min. in 1 mL DMF. 4-*tert*-Butyl-phenylamine (0.37 mmol) is added and the reaction stirred at rt for 8 hrs. The reaction is partitioned between ethyl acetate (15 mL) and water (15 mL) and the ethyl acetate layer washed with water (2 x 15 mL) and brine (1 x 15 mL). The organic layer is dried over sodium sulfate and the solvent removed in vacuo. The resulting crude oil is dissolved in 1 ml CH_2Cl_2 and clean yellow solid is precipitated by slow addition of diethyl ether, yielding the final product, (**10**) N-(4-*tert*-

Butyl-phenyl)-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-benzamide.

EXAMPLE 3. SYNTHESIS OF N-(3-{8-[4-(4-ACETYL-PIPERAZIN-1-YL)-PHENYLAMINO]-IMIDAZO[1,2-A]PYRAZIN-6-YL}-PHENYL)-4-*TERT*-BUTYL-BENZAMIDE

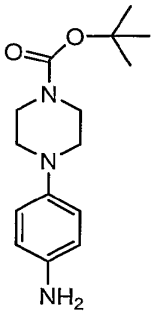
Step 1. 4-(4-Nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester



(11)

[0165] A mixture of 1-fluoro-4-nitrobenzene (20.4 mmol), piperazine-1-carboxylic acid *tert*-butyl ester (20.4 mmol), potassium carbonate (40.8 mmol), and N'N-dimethylformamide (80 mL) is heated at 60 °C for 3 hrs. The mixture is cooled to room temperature, treated with water (100 mL), extracted with ethyl acetate (3 x 80 mL). The extracts are washed with water (3 x 60 mL) and brine (1 x 75 ml), dried over magnesium sulfate, and concentrated *in vacuo* to give 4-(4-nitro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (**11**) as a yellow solid.

Step 2. 4-(4-Amino-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

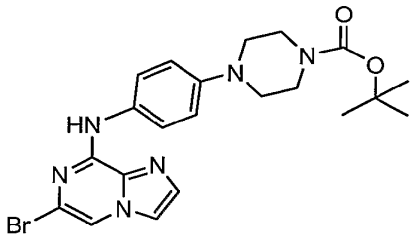


(12)

[0166] A mixture of 4-(4-nitro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (**11**) (18.9 mmol), 10% palladium–on-carbon (600mg), ethanol (100 mL), and ethyl acetate (100 mL) is hydrogenated at room temperature and 40 psi for 2 hrs. The mixture is filtered

through celite, washing with ethyl acetate (2 x 100 mL), and concentrated *in vacuo* to give 4-(4-amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (**12**) as a brown oil.

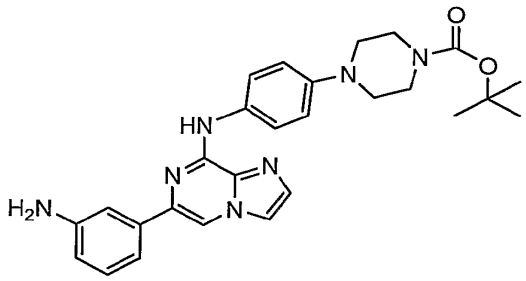
Step 3. 4-[4-(6-Bromo-imidazo[1,2-a]pyrazin-8-ylamino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester



(**13**)

[0167] A mixture of 6,8-dibromoimidazo[1,2-a]pyrazine (12.5 mmol), 4-(4-amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (**12**) (13.1 mmol), potassium carbonate (25 mmol), acetonitrile (50 mL)and N,N-dimethylacetamide (20 mL) is heated at 65 °C for 16 hrs. The mixture is cooled to room temperature, treated water (100 mL), and extracted with ethyl acetate (3 x 80 mL). The extracts are washed with water (3 x 60 mL) and brine (1 x 60 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The residue is chromatographed over silica gel, eluting with ethyl acetate, to give 4-[4-(6-bromo-imidazo[1,2-a]pyrazin-8-ylamino)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (**13**) as a light brown foam.

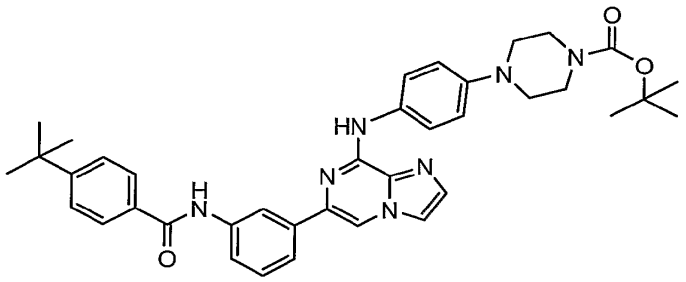
Step 4. 4-{4-[6-(3-Amino-phenyl)-imidazo[1,2-a]pyrazin-8-ylamino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester (14)



(**14**)

[0168] A mixture of 4-(6-bromoimidazo[1,2-a]pyrazin-8-ylamino)benzoic acid ethyl ester (**13**) (4.33 mmol), 3-aminophenylboronic acid hemisulfate (5.63 mmol), tetrakis(triphenylphosphine)palladium (0.2 mmol), 1N aqueous sodium carbonate solution (13 mL), and dimethoxyethane (70 mL) is heated at 95 °C for 2 days. The mixture is allowed to cool, treated with water (100 mL), and extracted with ethyl acetate (3 x 80 mL). The extracts are washed with water (2 x 75 mL) and brine (1 x 75 mL), dried over magnesium sulfate, and evaporated *in vacuo*. The residue is chromatographed over silica gel, eluting with ethyl acetate, to give 4-{4-[6-(3-amino-phenyl)-imidazo[1,2-a]pyrazin-8-ylamino]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester (**14**) as a cream solid.

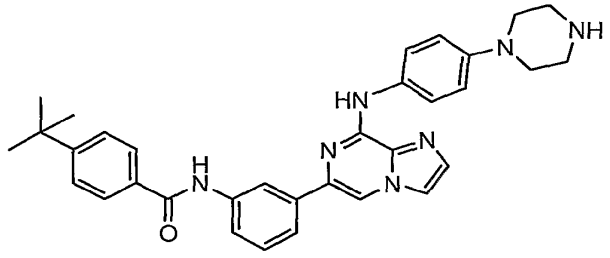
Step 5. 4-(4-{6-[3-(4-tert-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (15)



(**15**)

[0169] An ice-cold solution of 4-{4-[6-(3-Amino-phenyl)-imidazo[1,2-a]pyrazin-8-ylamino]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester (**14**) (2.35 mmol), triethylamine (3.53 mmol), and tetrahydrofuran (20 mL) is treated dropwise with a solution of 4-t-butylbenzoyl chloride (2.35 mmol) in tetrahydrofuran (10 mL). The mixture is stirred at room temperature for 1hr. Water (50 mL) is added and the mixture extracted with ethyl acetate (3 x 70 mL). The extracts are washed with water (2 x 50 mL) and brine (1 x 50 mL), dried over magnesium sulfate, and evaporated *in vacuo*. The residue is triturated with diethyl ether to give 4-(4-{6-[3-(4-*tert*-butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (**15**) as a cream solid.

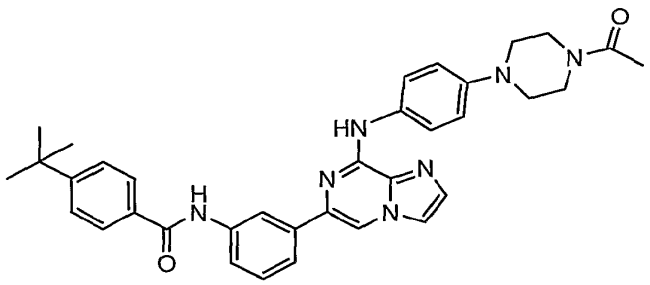
Step 6. 4-tert-Butyl-N-{3-[8-(4-piperazin-1-yl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide (16)



(16)

[0170] A mixture of 4-(4-{6-[3-(4-*tert*-butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (**15**) (2.0 mmol), 1M HCl in diethyl ether (20 mL), and dioxane (60 mL) is stirred at room temperature for 16 hr. Water (100 mL) is added and the pH brought to 11 with 1N NaOH. The mixture is extracted with ethyl acetate (3 x 80 mL), the extracts washed with water (2 x 70 mL) and brine (1 x 70 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The residue is slurried with diethyl ether and filtered to give 4-*tert*-butyl-N-{3-[8-(4-piperazin-1-yl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide (**16**) as a cream solid.

Step 7. N-(3-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-tert-butyl-benzamide (17)



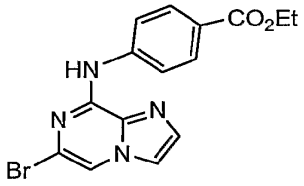
(17)

[0171] A mixture of 4-*tert*-butyl-N-{3-[8-(4-piperazin-1-yl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide (**16**) (0.55 mmol), triethylamine (1.1 mmol), acetic anhydride (0.60 mmol), and dichloromethane (10 mL) is stirred at room temperature for 1hr. Water (30 mL) is added, the mixture extracted with dichloromethane (2

x 50 mL), the extracts washed with water (2 x 30 mL) and brine (1 x 30 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The residue is triturated with diethyl ether and ethyl acetate to give N-(3-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-*tert*-butyl-benzamide (**17**) as a cream solid.

EXAMPLE 4. SYNTHESIS OF 4-*TERT*-BUTYL-N-(3-{8-[4-(MORPHOLINE-4-CARBONYL)-PHENYLAMINO]-IMIDAZO[1,2-A]PYRAZIN-6-YL}-PHENYL)-BENZAMIDE

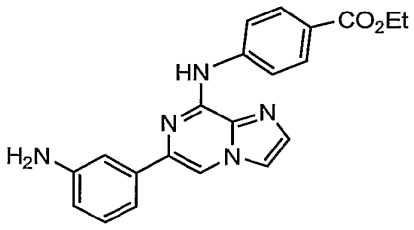
Step 1. 4-(6-Bromo-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester (18)



(**18**)

[0172] A mixture of 6,8-dibromoimidazo[1,2-a]pyrazine (0.18mol), 4-aminobenzoic acid ethyl ester (2) (0.18mol), and N,N-dimethylacetamide (30 mL) is heated at 160 °C for 30 min. The mixture is cooled to room temperature, treated with ethyl acetate (150 mL), stirred, and filtered to afford an orange/brown solid. This solid is slurried with ethyl acetate and saturated sodium bicarbonate solution to give 4-(6-bromoimidazo[1,2-a]pyrazin-8-ylamino)benzoic acid ethyl ester (**18**) freebase.

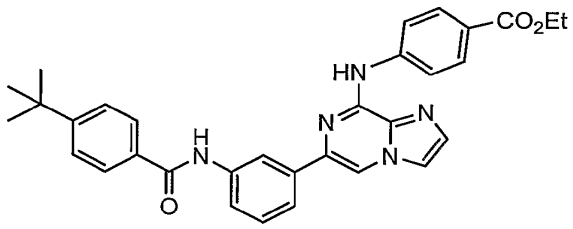
Step 2. 4-[6-(3-Amino-phenyl)-imidazo[1,2-a]pyrazin-8-ylamino]-benzoic acid ethyl ester (19)



(**19**)

[0173] A mixture of 4-(6-bromoimidazo[1,2-a]pyrazin-8-ylamino)benzoic acid ethyl ester (**18**) (55.3 mmol), 3-aminophenylboronic acid hemisulfate (72 mmol), tetrakis(triphenylphosphine)palladium (2.8 mmol), 1N aqueous sodium carbonate solution (166 mmol), and dimethoxyethane (200 mL) is heated at reflux for 4 days. The mixture is allowed to cool, treated with water (200 mL), and extracted with ethyl acetate (4 x 100 mL). The extracts are washed with water (2 x 150 mL) and brine (1 x 100 mL), dried over magnesium sulfate, and evaporated *in vacuo*. The residue is triturated with dichloromethane and diethyl ether to give 4-[6-(3-aminophenyl)imidazo[1,2-a]pyrazin-8-ylamino]benzoic acid ethyl ester (**19**) as a yellow solid .

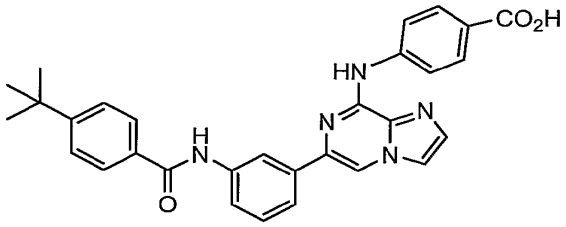
*Step 3. 4-{6-[3-(4-tert-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester (**20**)*



(**20**)

[0174] An ice-cold solution of 4-[6-(3-aminophenyl)imidazo[1,2-a]pyrazin-8-ylamino]benzoic acid ethyl ester (**19**) (44.2 mmol), triethylamine (66.4 mmol), and tetrahydrofuran (140 mL) is treated dropwise with a solution of 4-t-butylbenzoyl chloride (44.2 mmol) in tetrahydrofuran (60 mL) and the mixture is stirred at room temperature for 1hr. Water (100 mL) is added and the mixture extracted with ethyl acetate (3 x 100 mL), the extracts are washed with water (2 x 100 mL) and brine (1 x 100 mL), dried over magnesium sulfate and evaporated *in vacuo*. The residue is triturated with dichloromethane to give 4-{6-[3-(4-*tert*-butyl-benzoylamino)phenyl]imidazo[1,2-a]pyrazin-8-ylamino}benzoic acid ethyl ester (**20**) as a pale orange solid.

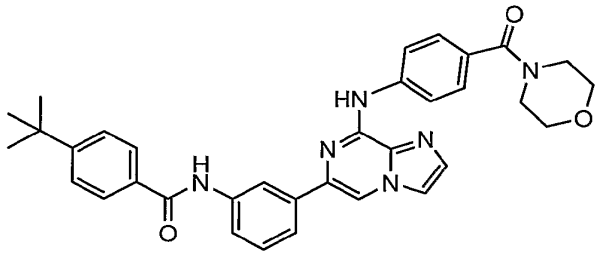
*Step 4. 4-{6-[3-(4-tert-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid (**21**)*



(21)

[0175] A mixture of 4-{6-[3-(4-*tert*-butyl-benzoylamino)phenyl]imidazo[1,2-a]pyrazin-8-ylamino}benzoic acid ethyl ester (**20**) (30 mmol), 1N aqueous sodium hydroxide (50 mL), and ethanol (80 mL) is heated at reflux for 1.5 hrs. The mixture is cooled and the ethanol removed *in vacuo*. The residue is diluted with 1N sodium hydroxide (30 mL) and washed with ethyl acetate (2 x 100 mL). The aqueous layer is brought to pH 6 with 3 N HCl, and the mixture is filtered to give 4-{6-[3-(4-*tert*-butyl-benzoylamino)phenyl]imidazo[1,2-a]pyrazin-8-ylamino}benzoic acid (**21**) as a cream solid.

Step 5. 4-tert-Butyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide (22)



(22)

[0176] A mixture of 4-{6-[3-(4-*tert*-butyl-benzoylamino)phenyl]imidazo[1,2-a]pyrazin-8-ylamino}benzoic acid (**21**) (0.16 mmol), benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (0.16 mmol), and N'N-diisopropylethylamine (0.48 mmol) is stirred at room temperature for 20 min. Morpholine (0.48 mmol) is added and the mixture is stirred at room temperature or 16 hrs. Water (10 mL) is added and the mixture extracted with ethyl acetate (2 x 70 mL), the extracts are washed with water (2 x 30 mL) and brine (1 x 30 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The residue is triturated with diethyl ether to give 4-*tert*-B\butyl-N-

(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]imidazo[1,2-a]pyrazin-6-yl}-phenyl)benzamide (**22**) as a cream solid.

EXAMPLE 5. ADDITIONAL IMIDAZO[1,2-A]PYRAZIN-8-YLAMINES

[0177] The following compounds are synthesized via the procedure set forth in Examples 1 to 4. In some instances changes in starting materials and reaction conditions that will be readily apparent to those skilled in the art of organic synthesis may be required.

[0178] LC-MS data reported in this example is obtained as follows:

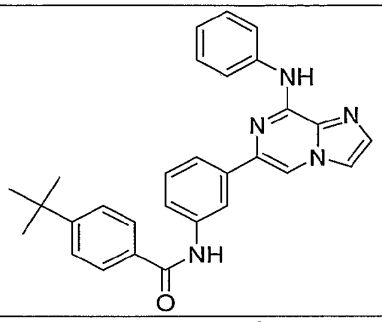
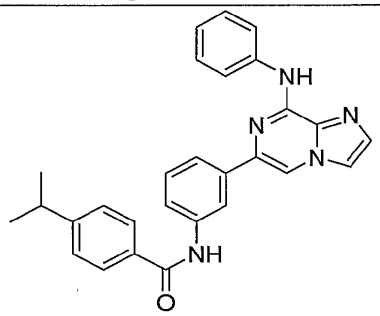
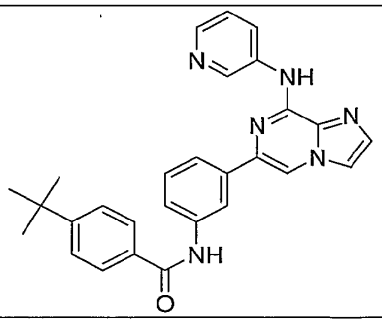
[0179] LC conditions: RP-HPLC is performed on an AGILENT 1100 Binary HPLC system. The column is a Restek Ultra IBD 5 μm 1.0 x 30 mm (Cat. #: 9175331). The Mobile Phase contains component A, 0.2% Formic Acid/Water), and component B, Acetonitrile. The following Gradient is used:

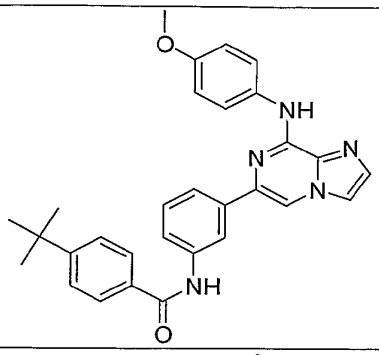
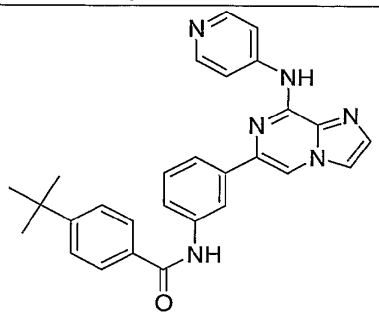
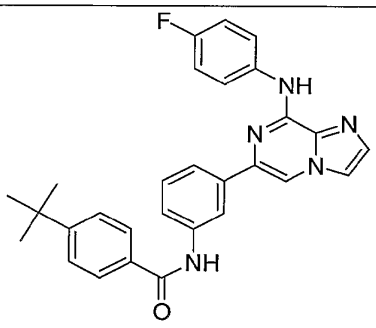
Time (min.)	% B	Flow Rate (µl/min)
0	10	500
1.8	60	500
2.0	95	500
2.2	95	500
2.4	10	500

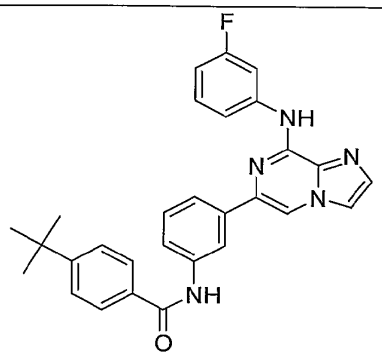
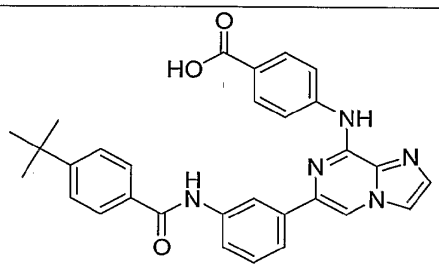
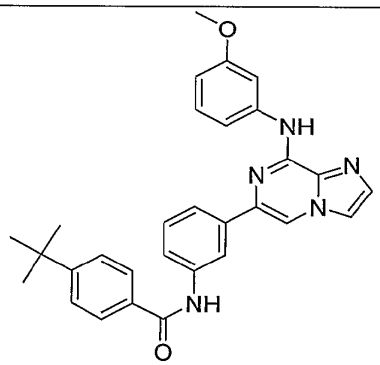
[0180] MS conditions: Electrospray MS is performed on a MICROMASS LCT equipped with a LockSpray source for accurate mass measurements. Spectra are acquired in positive ion mode from 100-1000 Da at an acquisition rate of 1 spectrum/0.9s with a 0.1s interscan delay. The instrument is tuned for a resolution of 5000 (FWHM). Every 5th scan is taken from the reference position of the Lockspray source. Leucine enkephalin (556.2771 $[M+H]^+$) is used as the reference, or lock mass.

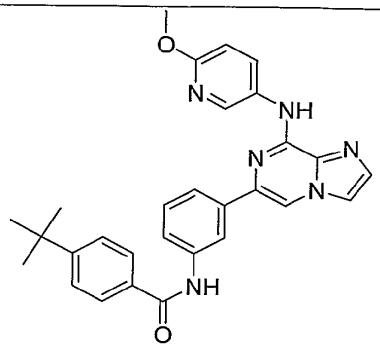
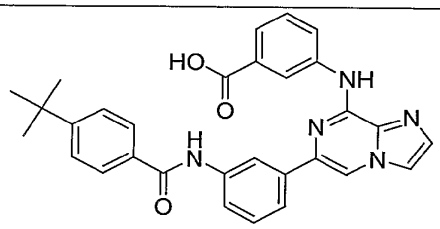
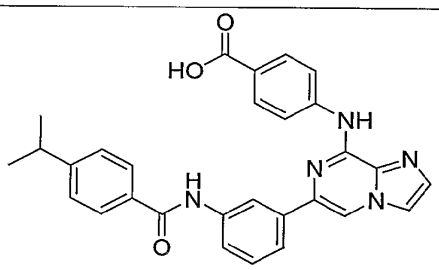
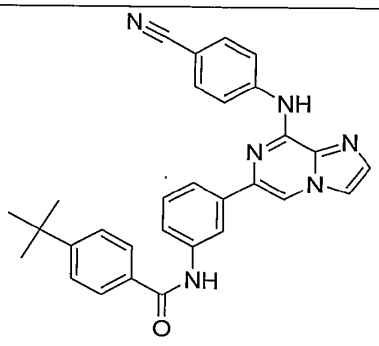
[0181]

TABLE I

Cmp. #	Structure	Name and Molecular Formula	MW	MS m/z (M^+ 1)
23		4-*tert*-Butyl-N-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide MF=$C_{29}H_{27}N_5O$	461.22	462.21
24		4-Isopropyl-N-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide MF=$C_{28}H_{25}N_5O$	447.21	448.21
25		4-*tert*-Butyl-N-{3-[8-(pyridin-3-ylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide MF=$C_{28}H_{26}N_6O$	462.21	463.07

Cmp. #	Structure	Name and Molecular Formula	MW	MS m/z (M^+1)
26		4-*tert*-Butyl-N-{3-[8-(4-methoxy-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide $MF=C_{30}H_{29}N_5O_2$	491.23	492.10
27		4-*tert*-Butyl-N-{3-[8-(pyridin-4-ylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide $MF=C_{28}H_{26}N_6O$	462.22	463.19
28		4-*tert*-Butyl-N-{3-[8-(4-fluoro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide $MF=C_{29}H_{26}FN_5O$	479.21	480.10

Cmp. #	Structure	Name and Molecular Formula	MW	MS m/z (M^+ 1)
29		4-*tert*-Butyl-N-{3-[8-(3-fluoro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide $MF=C_{29}H_{26}FN_5O$	479.21	480.10
30		4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid $MF=C_{30}H_{27}N_5O_3$	505.21	506.08
31		4-*tert*-Butyl-N-{3-[8-(3-methoxy-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide $MF=C_{30}H_{29}N_5O_2$	491.23	492.08

Cmp. #	Structure	Name and Molecular Formula	MW	MS m/z (M^+1)
32		4-*tert*-Butyl-N-{3-[8-(6-methoxy-pyridin-3-ylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide $MF=C_{29}H_{28}N_6O_2$	492.22	493.08
33		3-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid $MF=C_{30}H_{27}N_5O_3$	505.21	506.25
34		4-{6-[3-(4-Isopropyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid $MF=C_{29}H_{25}N_5O_3$	491.19	492.19
35		4-*tert*-Butyl-N-{3-[8-(4-cyano-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide $MF=C_{30}H_{26}N_6O$	486.22	487.28

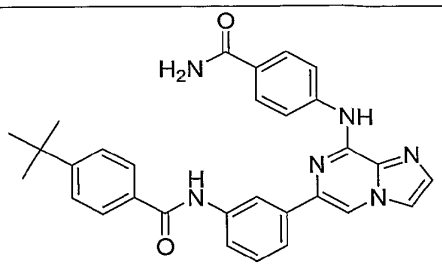
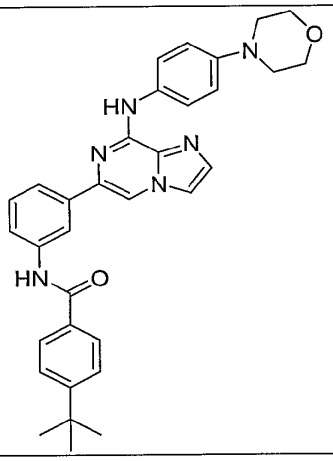
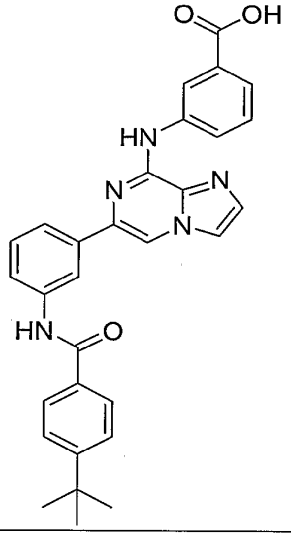
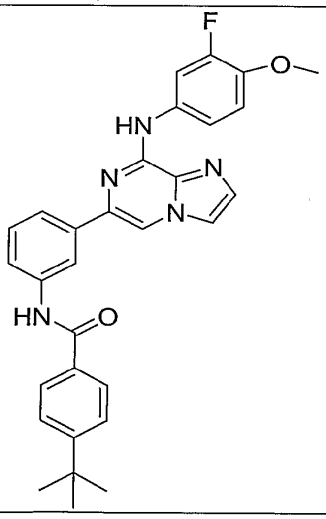
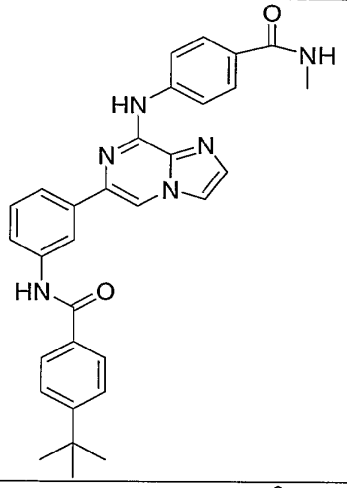
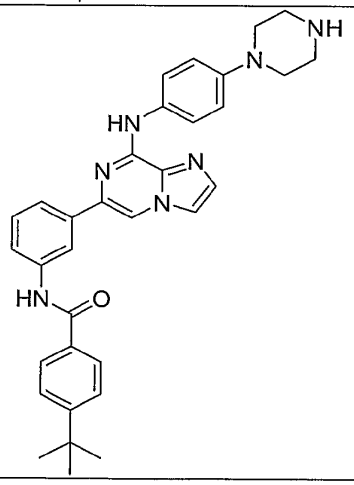
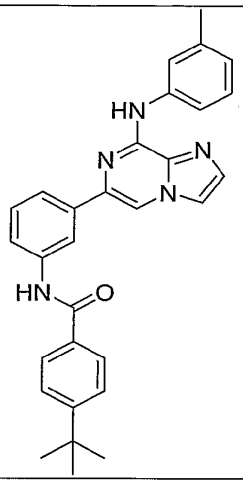
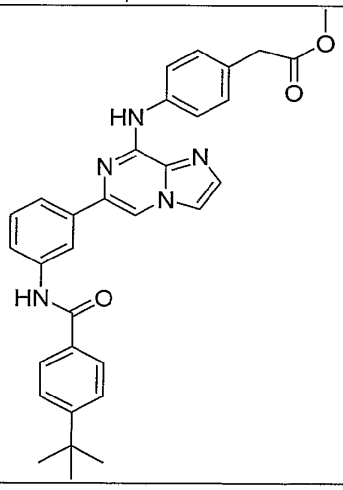
Cmp. #	Structure	Name and Molecular Formula	MW	MS m/z (M^+ 1)
36		4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzamide MF=$C_{30}H_{28}N_6O_2$	504.22	505.21

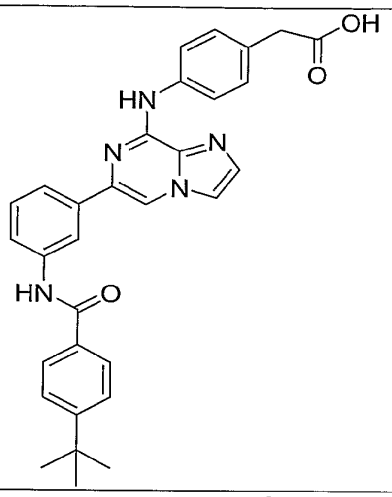
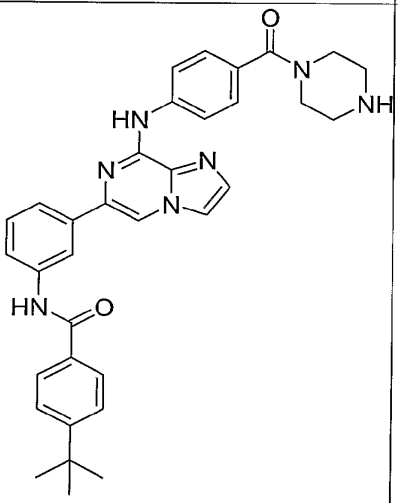
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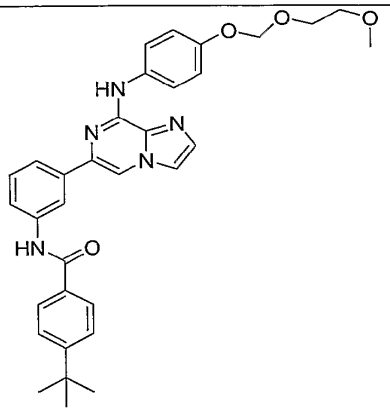
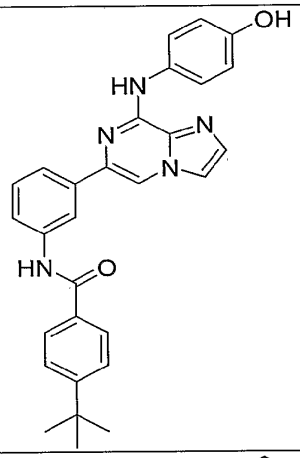
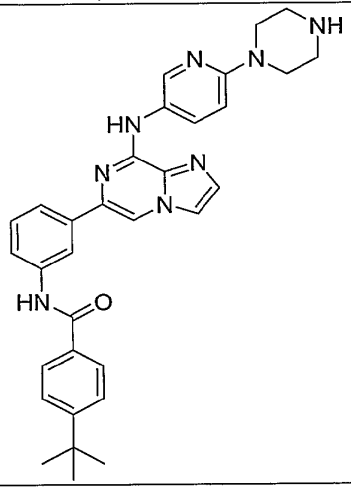
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^+ 1)
37		4-*tert*-Butyl-N-{3-[8-(4-morpholin-4-yl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C33H34N6O2	546.27	547.11

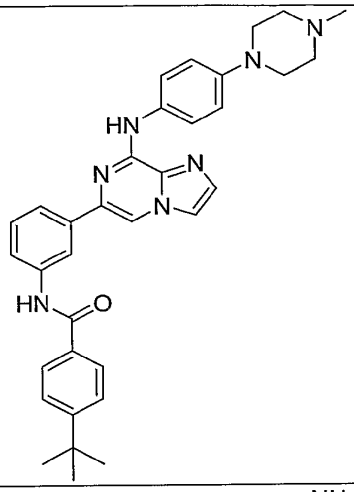
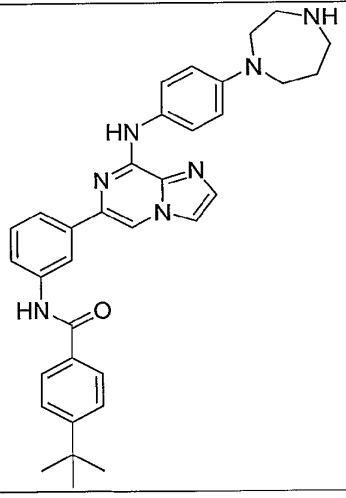
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
38		3-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid C30H27N5O3	505.21	506.25
39		4-*tert*-Butyl-N-{3-[8-(3-fluoro-4-methoxy-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C30H28FN5O2	509.22	510.26

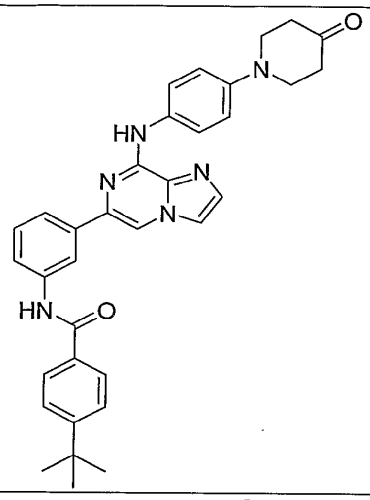
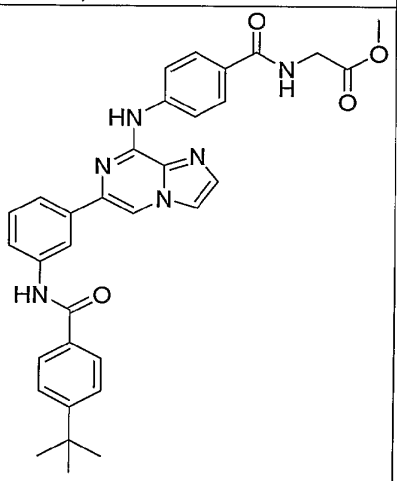
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
40		4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic N-Methyl amide C31H30N6O2	518.24	519.21
41		4-*tert*-Butyl-N-{3-[8-(4-piperazin-1-yl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C33H35N7O	545.29	546.19

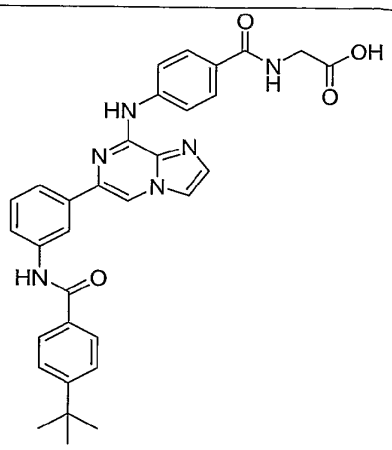
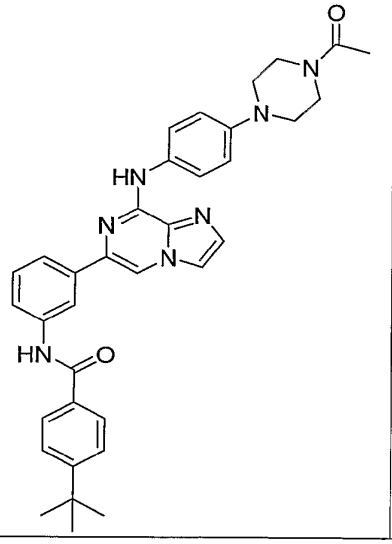
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
42		4-*tert*-Butyl-N-[3-(8-m-tolylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide C30H29N5O	475.23	476.22
43		(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-acetic acid methyl ester C32H31N5O3	533.24	534.22

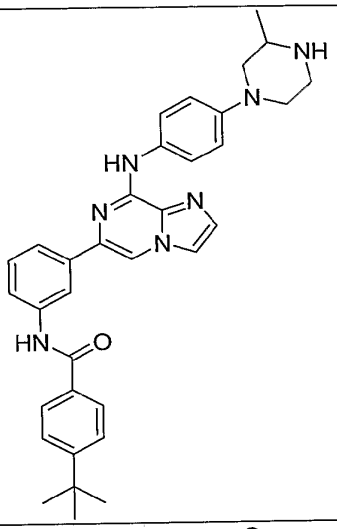
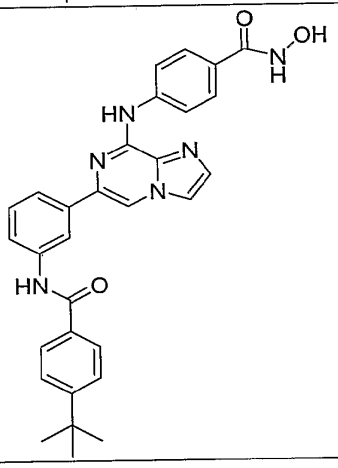
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
44		(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-acetic acid C31H29N5O3	519.22	520.22
45		4-*tert*-Butyl-N-(3-{8-[4-(piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C34H35N7O2	573.28	574.85

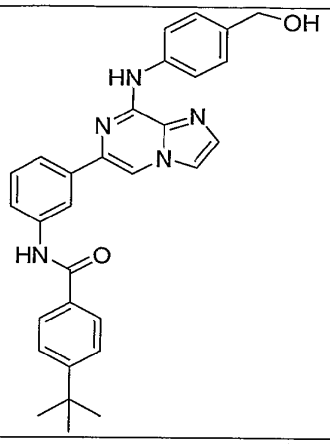
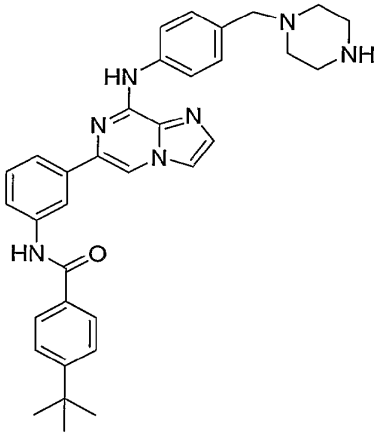
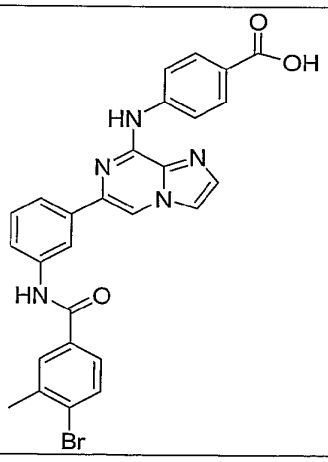
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
46		4-*tert*-Butyl-N-(3-{8-[4-(2-methoxy-ethoxymethoxy)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C33H35N5O4	565.26	566.25
47		4-*tert*-Butyl-N-{3-[8-(4-hydroxy-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C29H27N5O2	477.22	478.22
48		4-*tert*-Butyl-N-{3-[8-(6-piperazin-1-yl-pyridin-3-ylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C32H34N8O	546.28	547.24

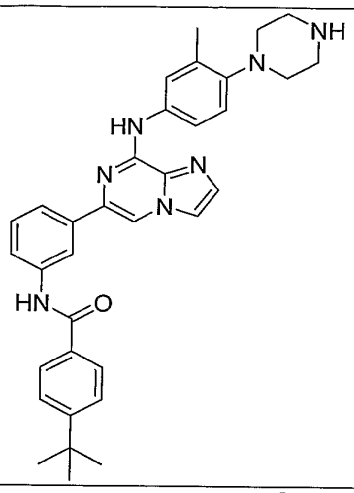
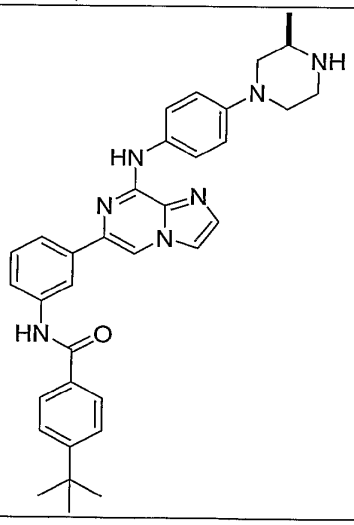
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
49		4-*tert*-Butyl-N-(3-{8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C34H37N7O	559.31	560.26
50		4-*tert*-Butyl-N-{3-[8-(4-[1,4]diazepan-1-yl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C34H37N7O	559.31	561.17

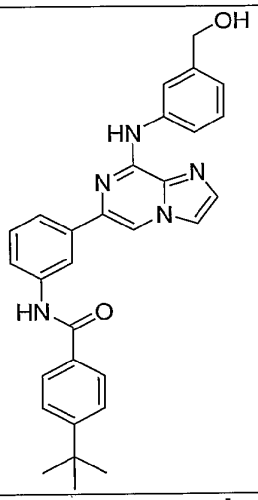
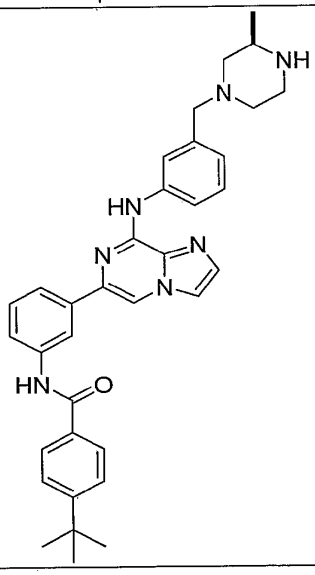
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
51		4-*tert*-Butyl-N-(3-{8-[4-(4-oxo-piperidin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C34H34N6O2	558.27	559.22
52		(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoylamino)-acetic acid methyl ester C33H32N6O4	576.24	577.29

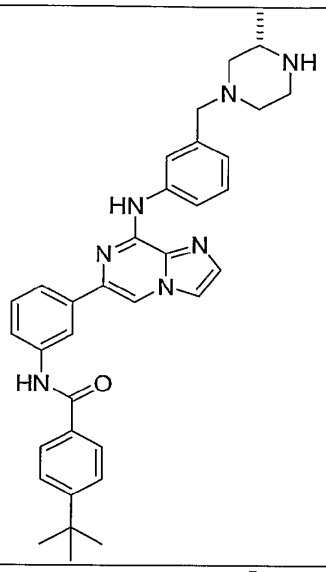
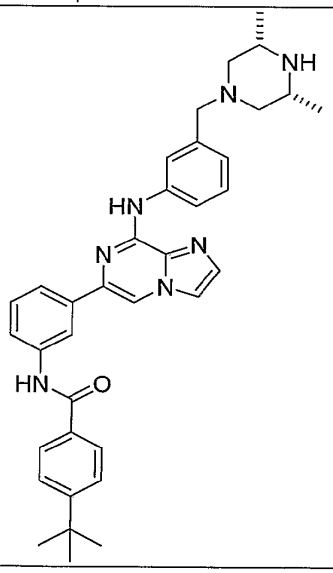
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
53		(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoylamino)-acetic acid C32H30N6O4	562.23	563.26
54		N-(3-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-*tert*-butyl-benzamide C35H37N7O2	587.3	588.31

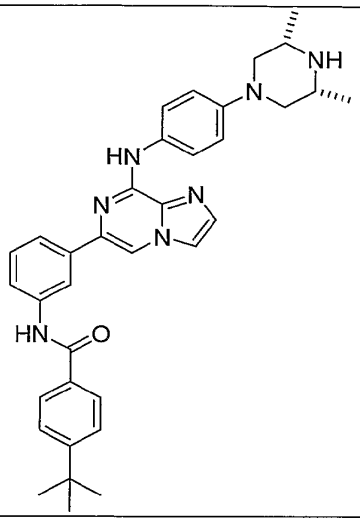
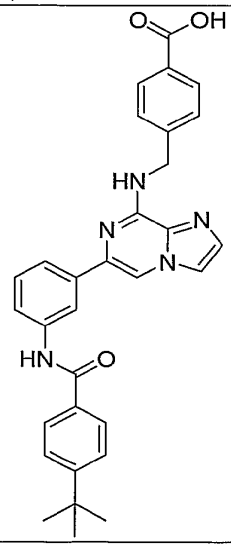
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
55		4-*tert*-Butyl-N-(3-{8-[4-(3-methyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C34H37N7O	559.31	560.35
56		4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic hydroxyl amide C30H28N6O3	520.22	521.26

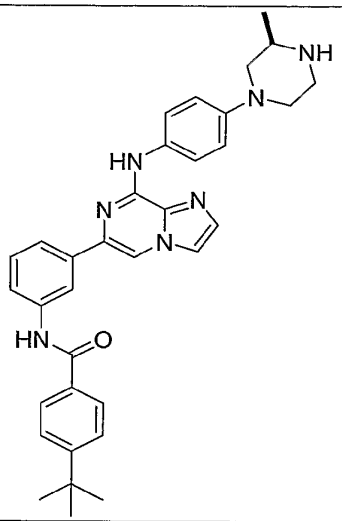
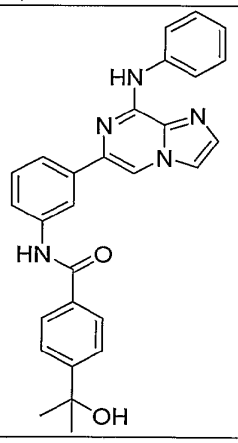
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
57		4-*tert*-Butyl-N-{3-[8-(4-hydroxymethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C30H29N5O2	491.23	492.28
58		4-*tert*-Butyl-N-{3-[8-(4-piperazin-1-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C34H37N7O	559.31	560.37
59		4-{6-[3-(4-Bromo-3-methyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid C27H20BrN5O3	541.07	542.14

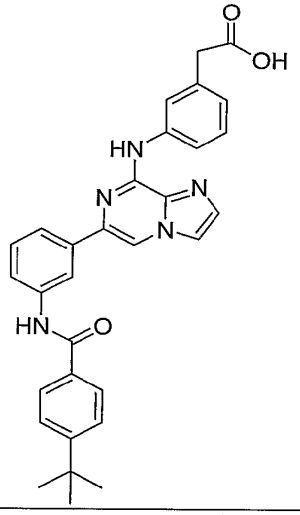
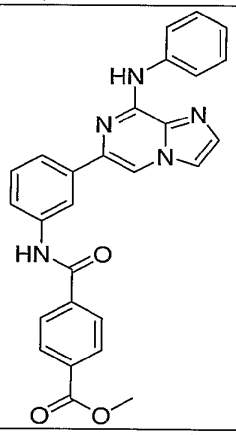
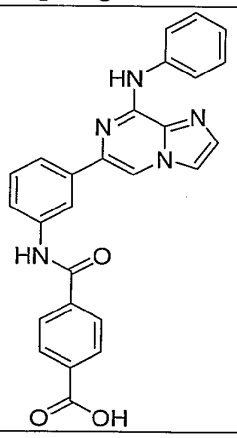
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
60		4-*tert*-Butyl-N-{3-[8-(3-methyl-4-piperazin-1-yl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C34H37N7O	559.31	560.35
61		4-*tert*-Butyl-N-(3-{8-[4-(3-methyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C34H37N7O	559.31	560.26

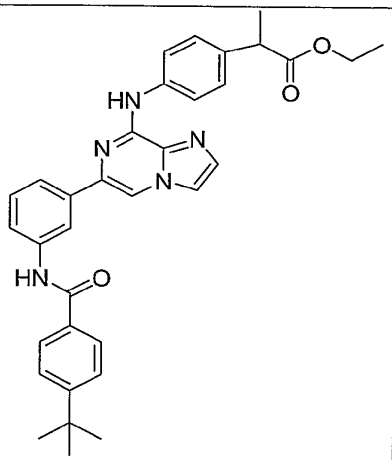
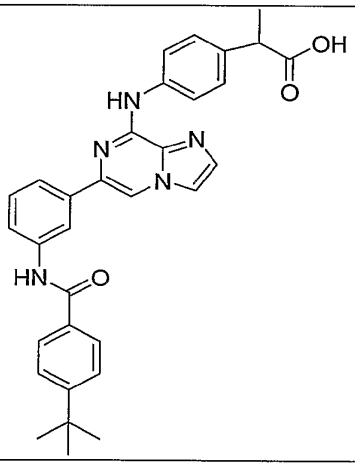
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
62		4-*tert*-Butyl-N-{3-[8-(3-hydroxymethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C30H29N5O2	491.23	492.28
63		4-*tert*-Butyl-N-(3-{8-[3-(3-methyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C35H39N7O	573.32	574.4

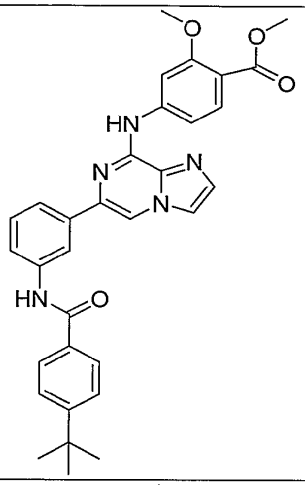
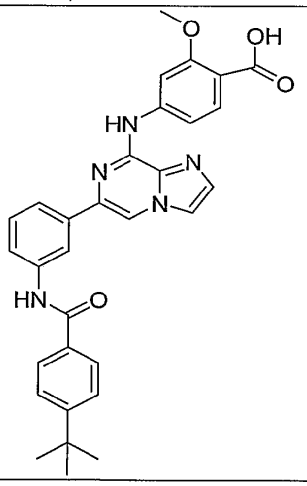
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64		4-*tert*-Butyl-N-(3-{8-[3-(3-methyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C35H39N7O	573.32	574.35
65		4-*tert*-Butyl-N-(3-{8-[3-(3,5-dimethyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin -6-yl}-phenyl)-benzamide C36H41N7O	587.33	588.39

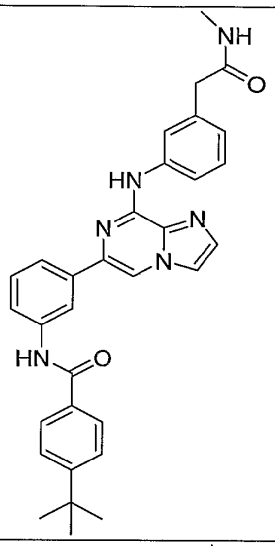
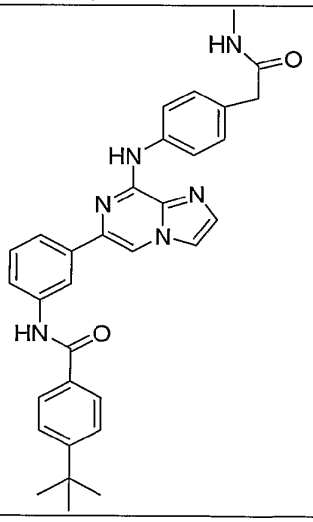
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
66		4-*tert*-Butyl-N-(3-{8-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl} -phenyl)-benzamide C35H39N7O	573.32	574.42
67		4-({6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-methyl)-benzoic acid C31H29N5O3	519.22	520.4

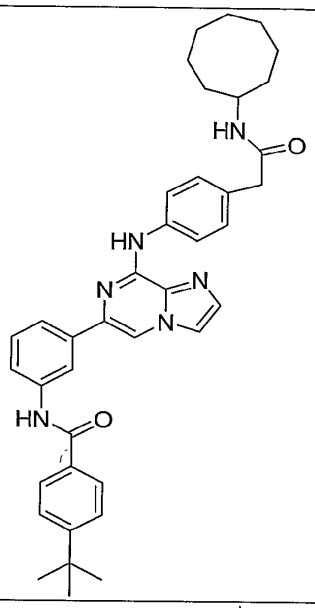
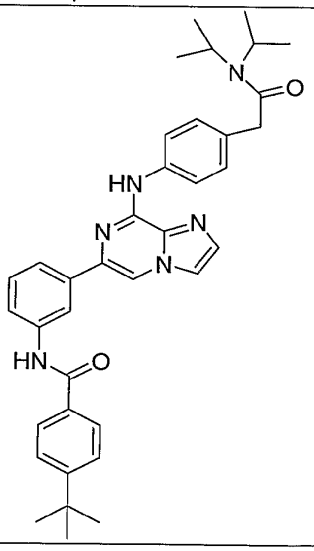
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
68		4-*tert*-Butyl-N-(3-{8-[4-(3-methyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C34H37N7O	559.3	560.47
69		4-(1-Hydroxy-1-methyl-ethyl)-N-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide C28H25N5O2	463.2	464.36

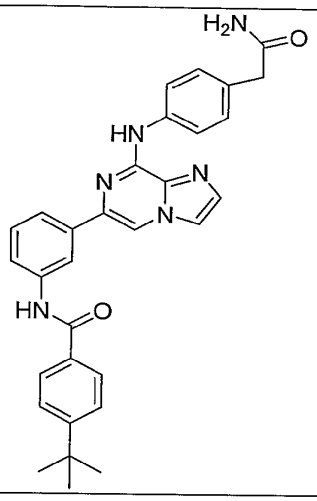
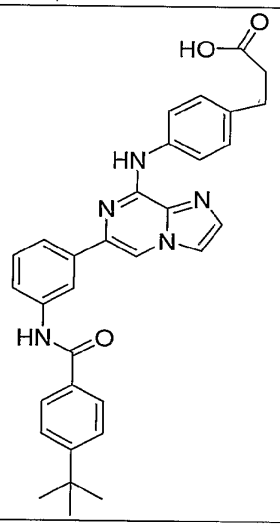
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
70		(3-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-acetic acid C31H29N5O3	519.22	520.4
71		N-[3-(8-Phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-terephthalamic acid methyl ester C27H21N5O3	463.16	464.32
72		N-[3-(8-Phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-terephthalamic acid C26H19N5O3	449.14	450.36

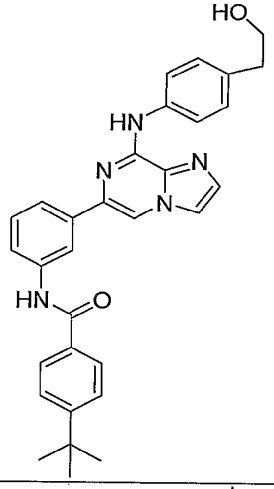
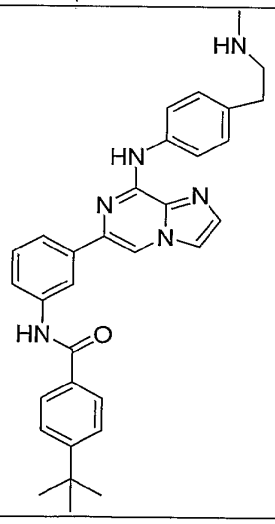
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
73		2-(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-propionic acid ethyl ester C34H35N5O3	561.27	562.45
74		2-(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-propionic acid C32H31N5O3	533.24	534.43

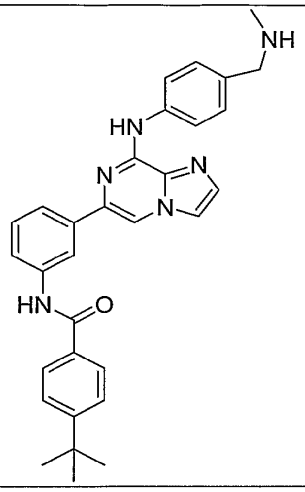
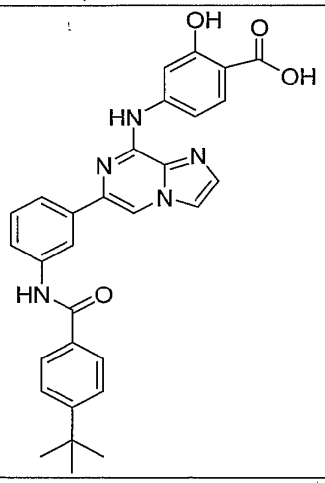
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
75		4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-2-methoxy-benzoic acid methyl ester C32H31N5O4	549.23	550.42
76		4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-2-methoxy-benzoic acid C31H29N5O4	535.22	536.42

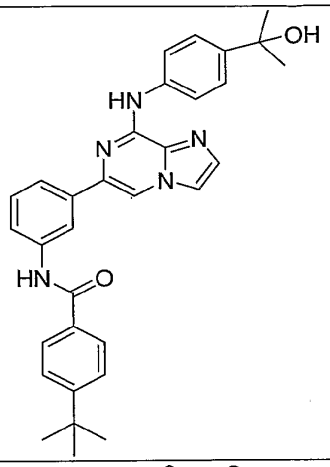
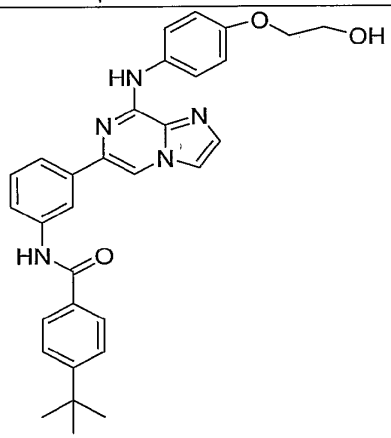
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
77		4-*tert*-Butyl-N-{3-[8-(3-methylcarbamoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl} -benzamide C32H32N6O2	532.26	533.4
78		4-*tert*-Butyl-N-{3-[8-(4-methylcarbamoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl} -benzamide C32H32N6O2	532.25	533.41

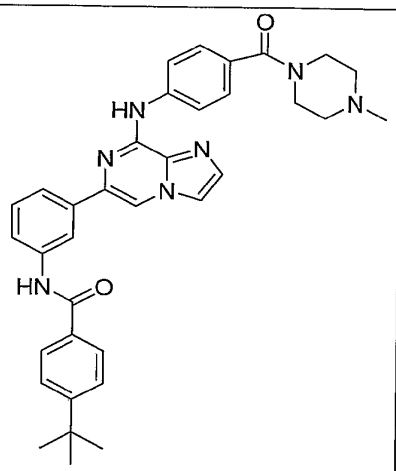
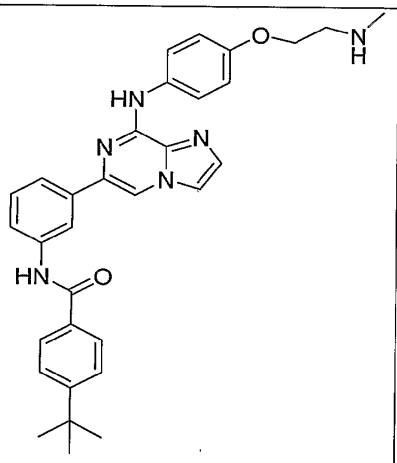
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
79		4-*tert*-Butyl-N-{3-[8-(4-cyclooctylcarbamoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C39H44N6O2	628.35	629.51
80		4-*tert*-Butyl-N-[3-(8-{4-[(diisopropylcarbamoyl)-methyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide C37H42N6O2	602.34	603.49

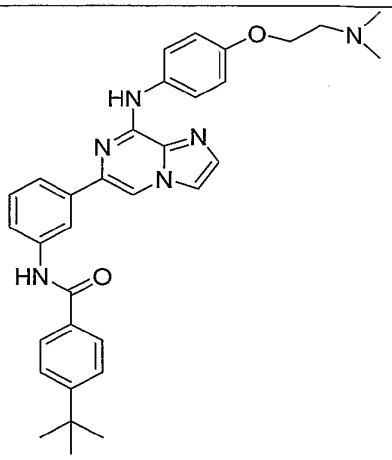
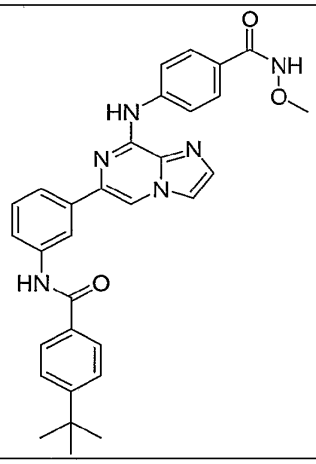
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
81		4-*tert*-Butyl-N-{3-[8-(4-carbamoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C31H30N6O2	518.24	519.48
82		3-(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-propionic acid C32H31N5O3	533.24	534.22

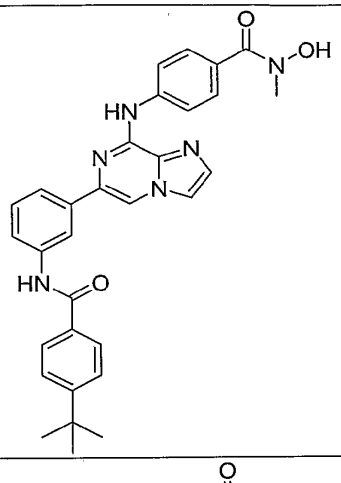
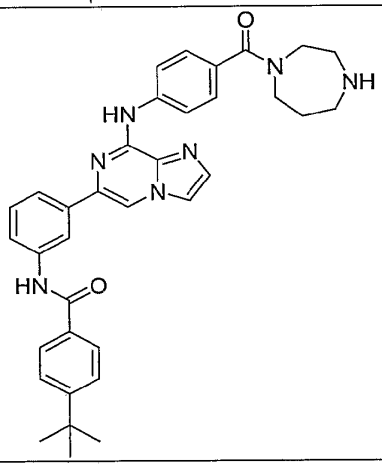
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
83		4-*tert*-Butyl-N-(3-{8-[4-(2-hydroxy-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C31H31N5O2	505.25	506.4
84		4-*tert*-Butyl-N-(3-{8-[4-(2-methylamino-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C32H34N6O	518.3	519.45

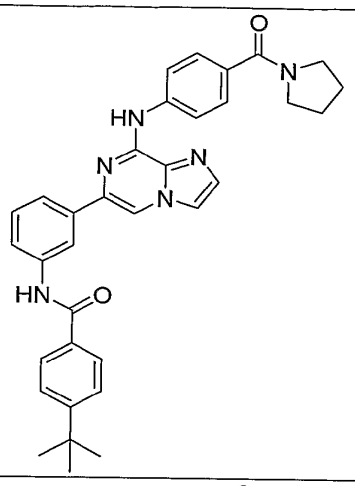
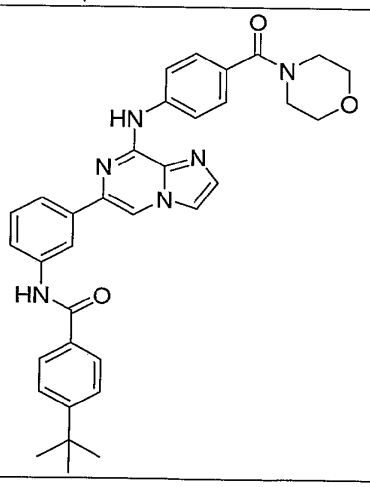
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
85		4-*tert*-Butyl-N-{3-[8-(4-methylaminomethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C31H32N6O	504.26	505.43
86		4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-2-hydroxy-benzoic acid C30H27N5O4	521.2	522.31

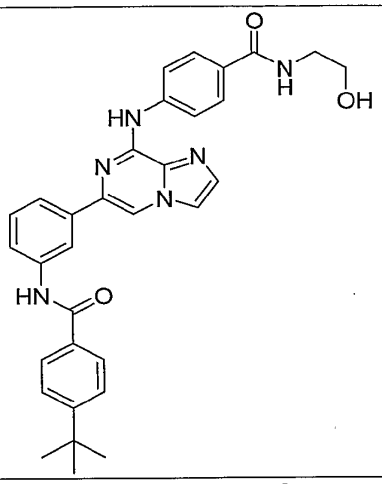
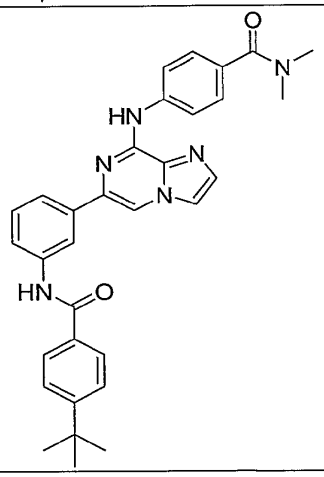
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
87		4-*tert*-Butyl-N-(3-{8-[4-(1-hydroxy-1-methyl-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C32H33N5O2	519.26	520.27
88		4-*tert*-Butyl-N-(3-{8-[4-(2-hydroxy-ethoxy)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C31H31N5O3	521.24	522.25

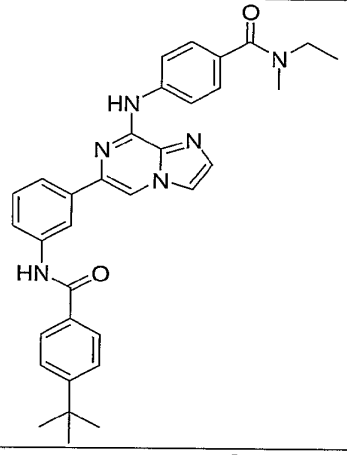
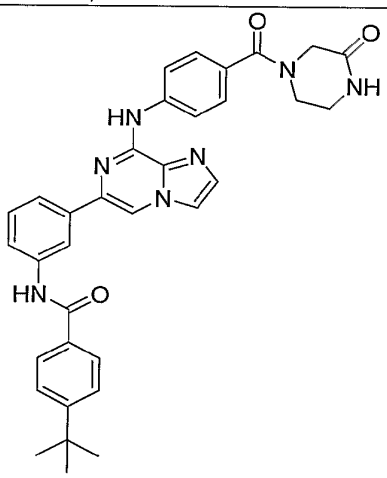
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
89		4-*tert*-Butyl-N-(3-{8-[4-(4-methyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C35H37N7O2	587.3	588.28
90		4-*tert*-Butyl-N-(3-{8-[4-(2-methylamino-ethoxy)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C32H34N6O2	534.27	535.27

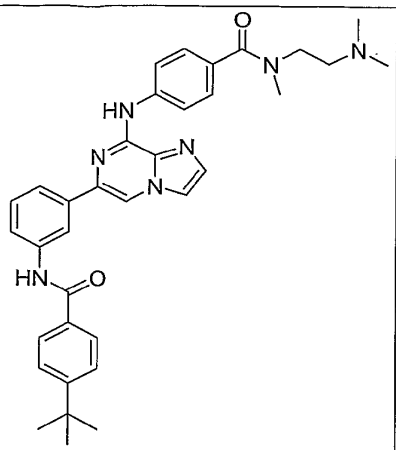
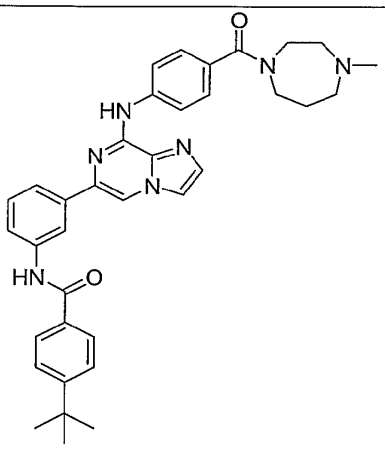
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
91		4-*tert*-Butyl-N-(3-{8-[4-(2-dimethylamino-ethoxy)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C33H36N6O2	548.28	549.28
92		4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic methoxy amide C31H30N6O3	534.23	535.25

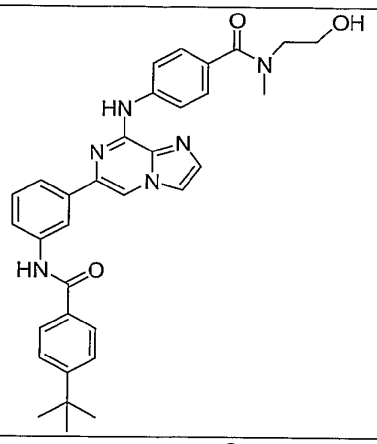
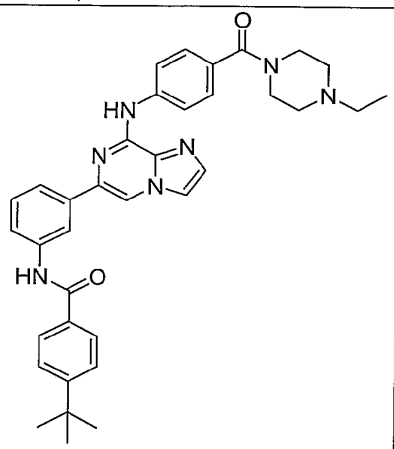
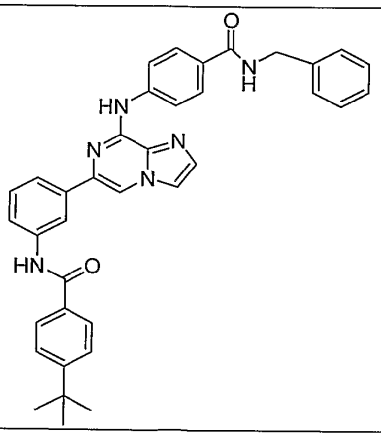
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
93		4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic hyrdoxyl methyl amide C31H30N6O3	534.23	535.25
94		4-*tert*-Butyl-N-(3-{8-[4-([1,4]diazepane-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C35H37N7O2	587.3	588.27

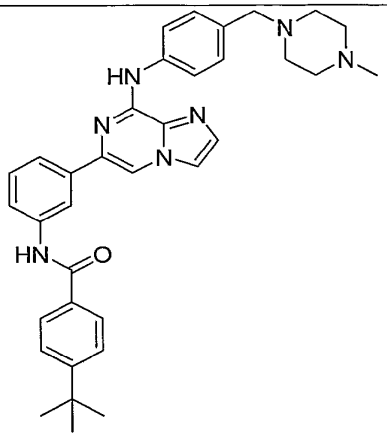
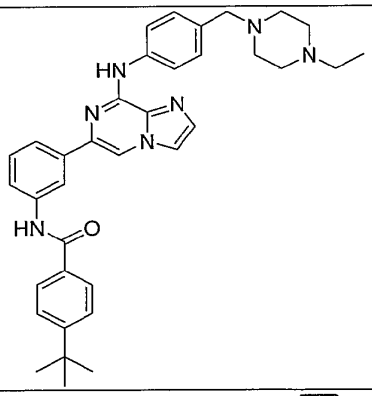
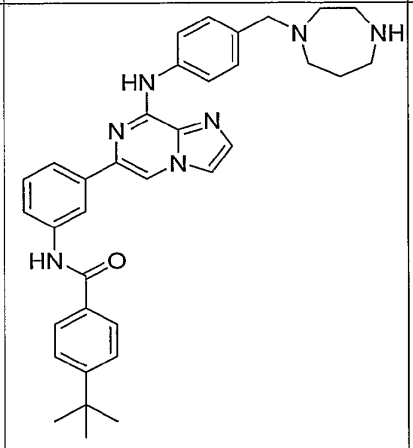
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
95		4-*tert*-Butyl-N-(3-{8-[4-(pyrrolidine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C34H34N6O2	558.27	559.25
96		4-*tert*-Butyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C34H34N6O3	574.26	575.24

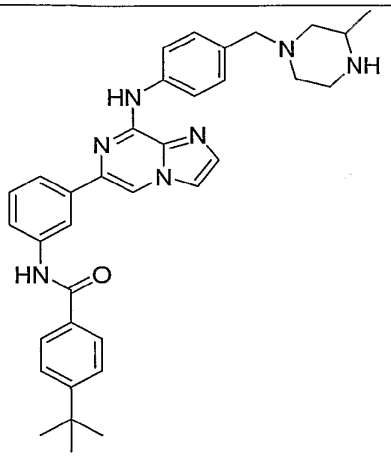
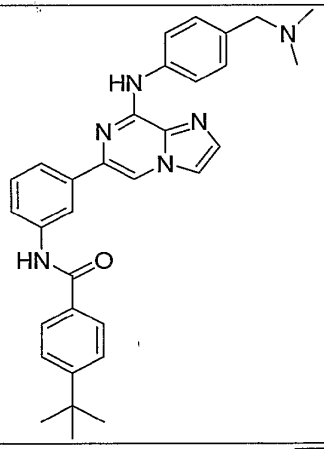
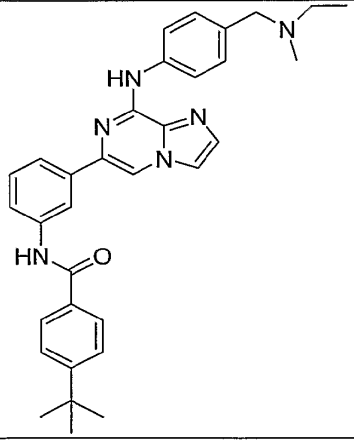
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
97		4-*tert*-Butyl-N-(3-{8-[4-(ethoxyamine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C33H34N6O3	548.25	549.22
98		4-*tert*-Butyl-N-(3-{8-[4-(dimethylamine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C32H32N6O2	532.25	533.22

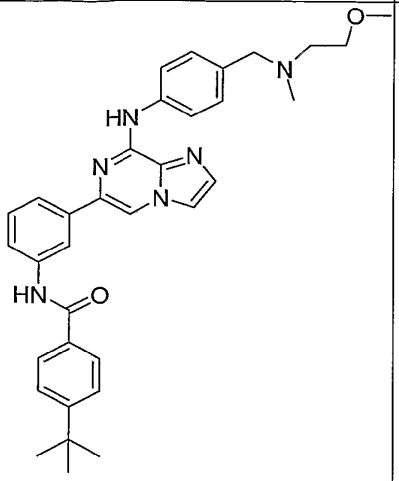
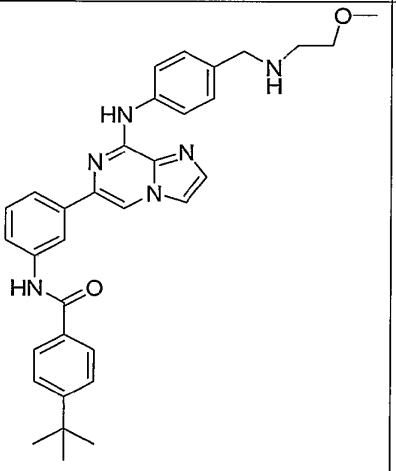
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99		4-*tert*-Butyl-N-(3-{8-[4-(methylethylamine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C33H34N6O2	546.27	547.24
100		4-*tert*-Butyl-N-(3-{8-[4-(3-oxo-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C34H33N7O3	587.26	588.28

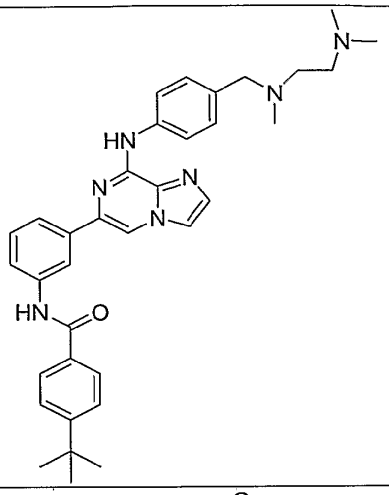
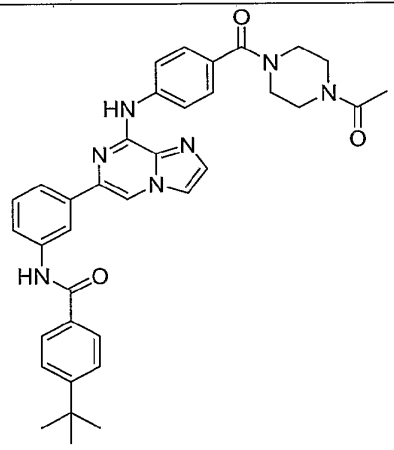
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
101		4-*tert*-Butyl-N-(3-{8-[N,N,N'-Trimethyl-ethane-1,2-diamine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C35H39N7O2	589.31	590.35
102		4-*tert*-Butyl-N-(3-{8-[4-(4-methyl-[1,4]diazepane-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C36H39N7O2	601.31	602.32

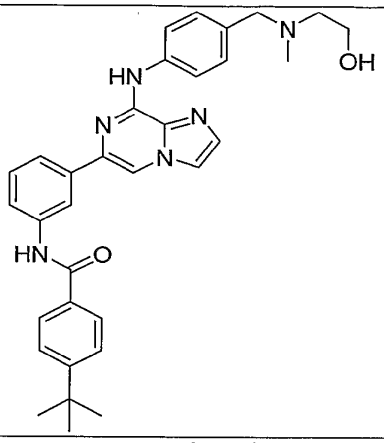
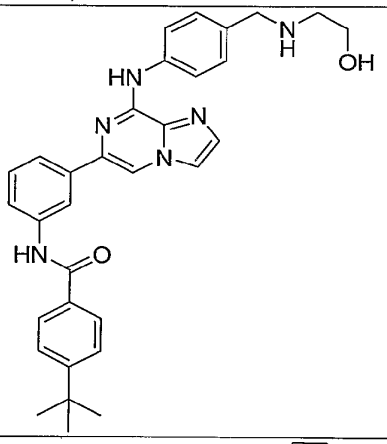
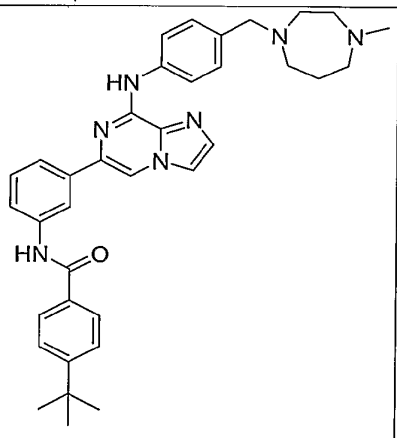
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
103		4-*tert*-Butyl-N-(3-{8-[4-(N-methyl ethoxyamine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C33H34N6O3	562.26	563.29
104		4-*tert*-Butyl-N-(3-{8-[4-(4-ethyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C36H39N7O2	601.31	602.38
105		4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic benzyl amide C37H34N6O2	595.26	596.32

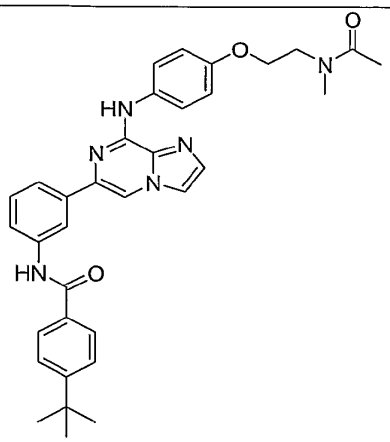
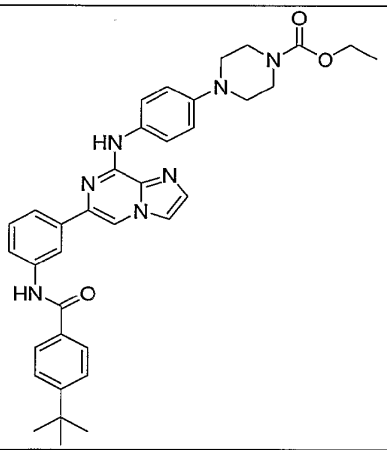
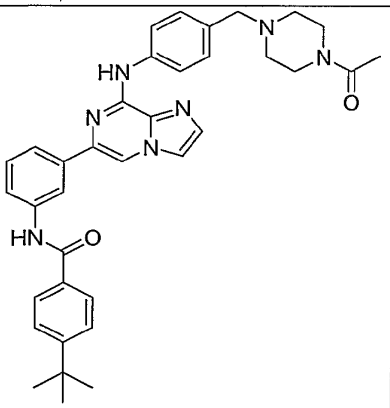
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
106		4-*tert*-Butyl-N-(3-{8-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C35H39N7O	573.32	574.39
107		4-*tert*-Butyl-N-(3-{8-[4-(4-ethyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C36H41N7O	587.33	588.42
108		4-*tert*-Butyl-N-{3-[8-(4-[1,4]diazepan-1-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C35H39N7O	573.32	574.39

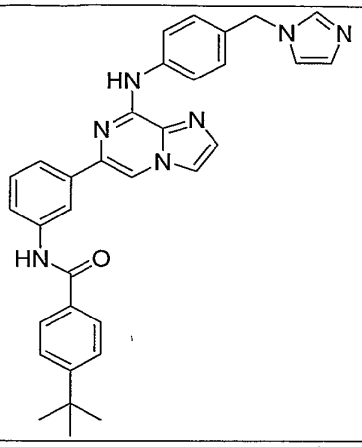
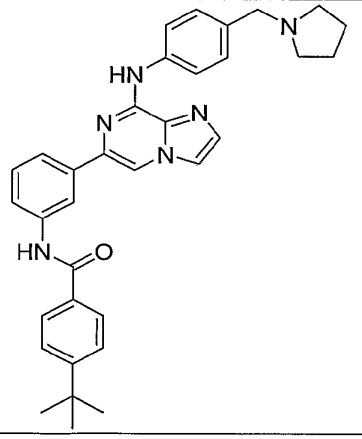
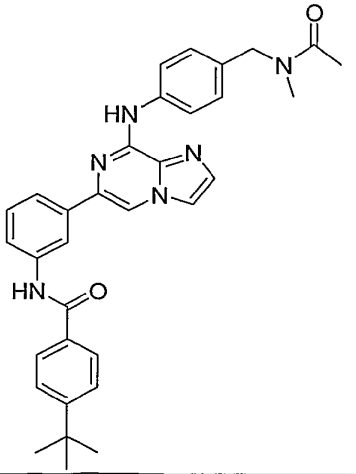
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
109		4-*tert*-Butyl-N-(3-{8-[4-(3-methyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C35H39N7O	573.32	574.38
110		4-*tert*-Butyl-N-{3-[8-(4-dimethylaminomethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C32H34N6O	518.27	519.33
111		4-*tert*-Butyl-N-[3-(8-{4-[(ethyl-methyl-amino)-methyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide C33H36N6O	532.29	533.33

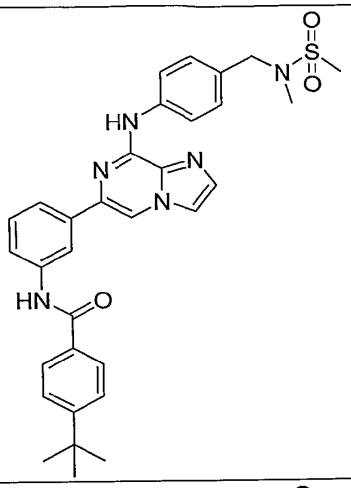
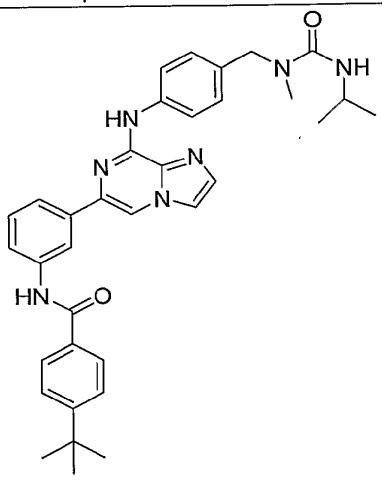
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
112		4-*tert*-Butyl-N-{3-[8-(4-{[(2-methoxy-ethyl)-methyl-amino]-methyl}-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C34H38N6O2	562.31	563.33
113		4-*tert*-Butyl-N-[3-(8-{4-[(2-methoxy-ethylamino)-methyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide C33H36N6O2	548.28	549.32

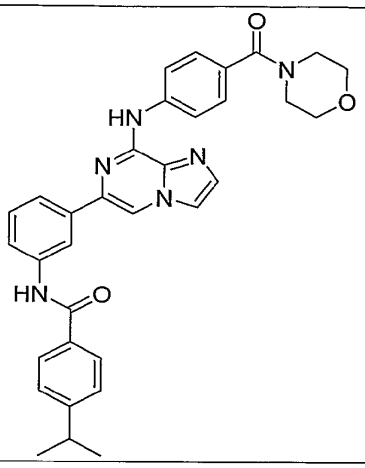
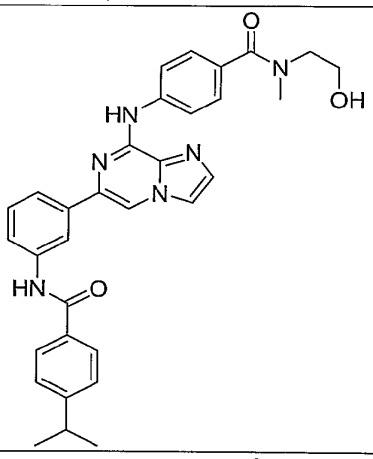
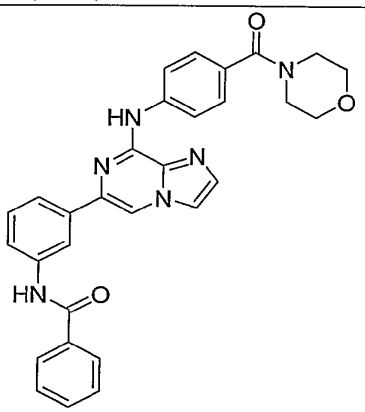
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
114		4-*tert*-Butyl-N-{3-[8-(4-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C35H41N7O	575.33	576.39
115		N-(3-{8-[4-(4-Acetyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-*tert*-butyl-benzamide C36H37N7O3	615.29	616.31

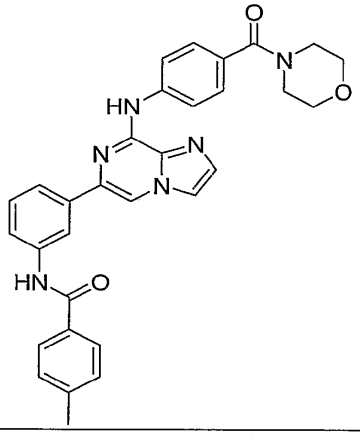
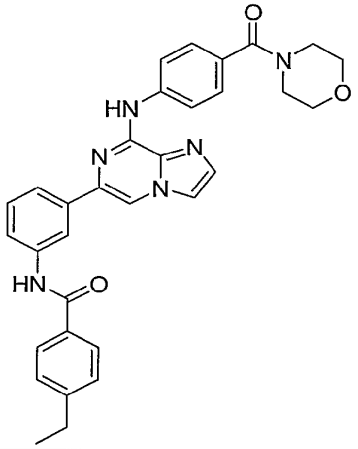
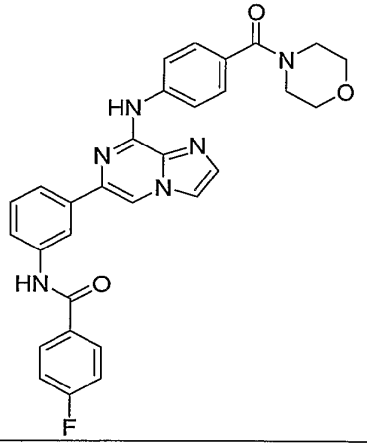
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
116		4-*tert*-Butyl-N-{3-[8-(4-{[(2-hydroxy-ethyl)-methyl-amino]-methyl}-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C33H36N6O2	548.28	549.32
117		4-*tert*-Butyl-N-[3-(8-{4-[(2-hydroxy-ethylamino)-methyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide C32H34N6O2	534.27	535.32
118		4-*tert*-Butyl-N-(3-{8-[4-(4-methyl-[1,4]diazepan-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C36H41N7O	587.33	588.37

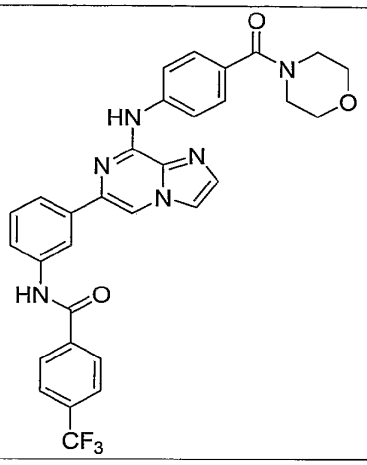
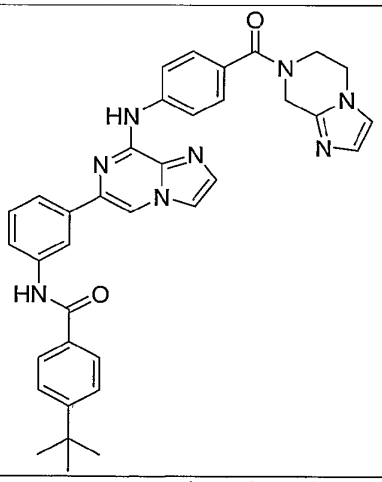
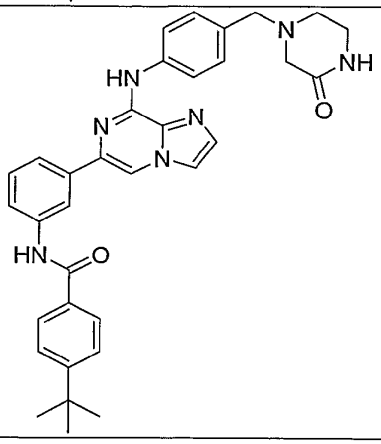
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
119		N-[3-(8-{4-[2-(Acetyl-methyl-amino)-ethoxy]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-4-*tert*-butyl-benzamide C34H36N6O3	576.28	577.32
120		4-(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-piperazine-1-carboxylic acid ethyl ester C36H39N7O3	617.31	618.31
121		N-(3-{8-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-*tert*-butyl-benzamide C36H39N7O2	601.31	602.26

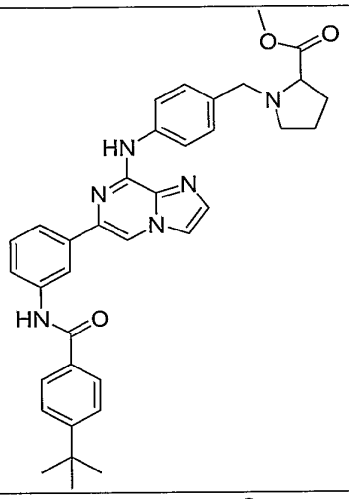
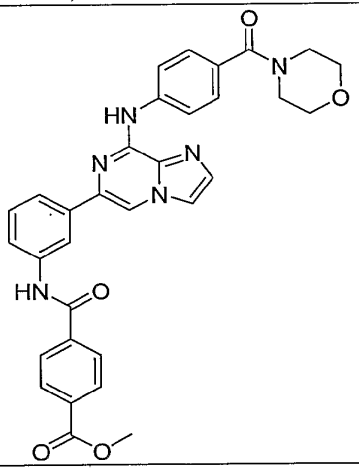
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
122		4-*tert*-Butyl-N-{3-[8-(4-imidazol-1-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C33H31N7O	541.25	542.27
123		4-*tert*-Butyl-N-{3-[8-(4-pyrrolidin-1-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl} -benzamide C34H36N6O	544.29	545.3
124		N-[3-(8-{4-[(Acetyl-methyl-amino)-methyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-4-*tert*-butyl-benzamide C33H34N6O2	546.27	547.33

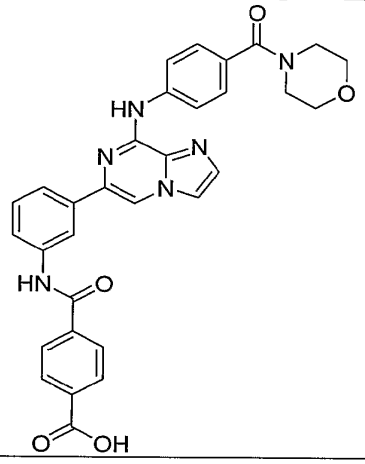
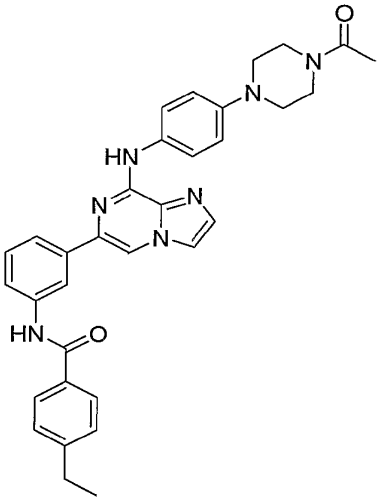
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
125		4-*tert*-Butyl-N-[3-(8-{4-[(methanesulfonyl-methyl-amino)-methyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide C32H34N6O3S	582.24	583.27
126		4-*tert*-Butyl-N-(3-{8-[4-(3-isopropyl-1-methyl-ureidomethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C35H39N7O2	589.31	590.35

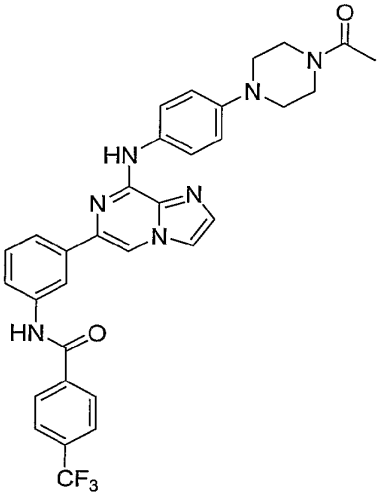
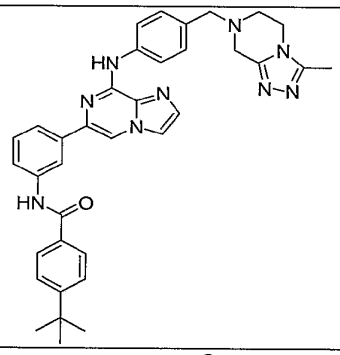
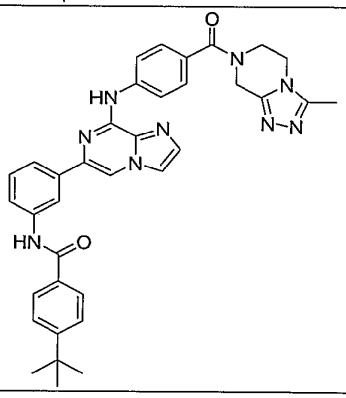
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
127		4-Isopropyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C33H32N6O3	560.25	561.28
128		N-{3-[8-(4-{[(2-Hydroxy-ethyl)-methyl-amino]-carbonyl}-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-4-isopropyl-benzamide C32H32N6O3	548.25	549.25
129		N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C30H26N6O3	518.2	519.22

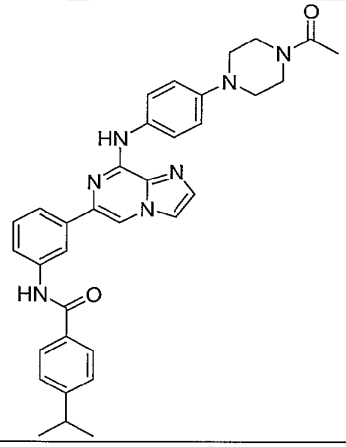
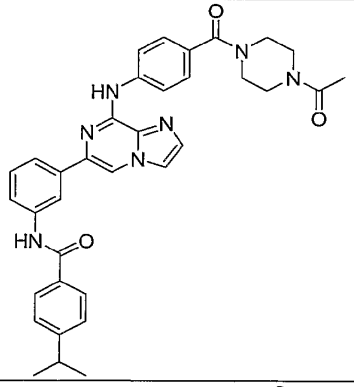
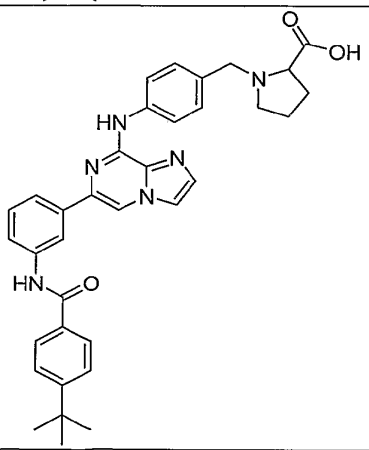
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
130		4-Methyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C31H28N6O3	532.22	533.17
131		4-Ethyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C32H30N6O3	546.23	547.17
132		4-Fluoro-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C30H25FN6O3	536.19	537.21

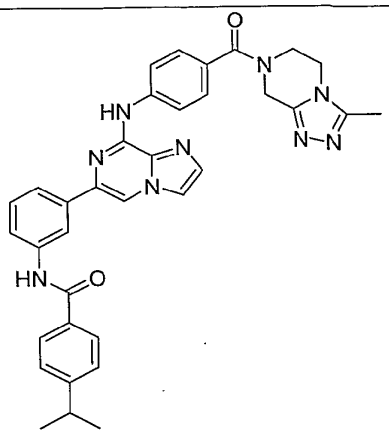
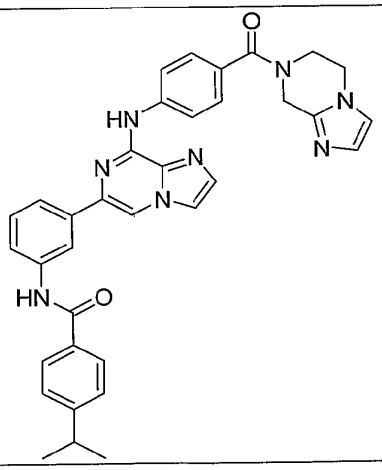
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
133		N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-trifluoromethyl-benzamide C31H25F3N6O3	586.19	587.2
134		4-*tert*-Butyl-N-(3-{8-[4-(5,6-dihydro-8H-imidazo[1,2-a]pyrazine-7-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C36H34N8O2	610.28	611.21
135		4-*tert*-Butyl-N-(3-{8-[4-(3-oxo-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C34H35N7O2	573.28	574.18

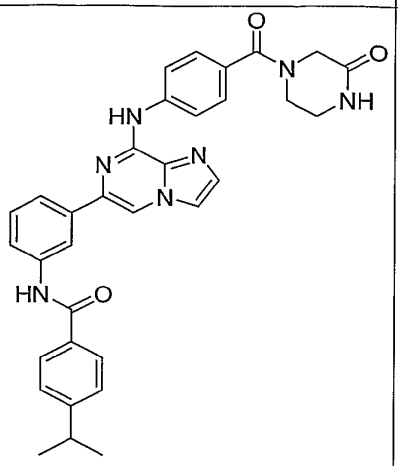
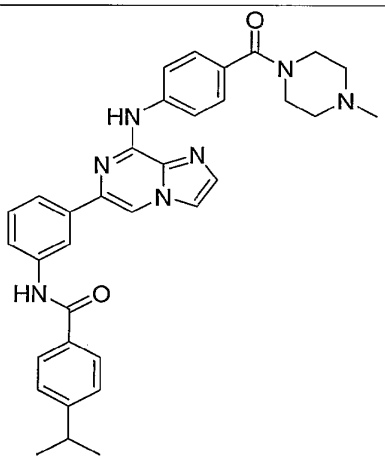
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
136		1-(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzyl)-pyrrolidine-2-carboxylic acid methyl ester C36H38N6O3	602.3	603.39
137		N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-terephthalamic acid methyl ester C32H28N6O5	576.21	577.36

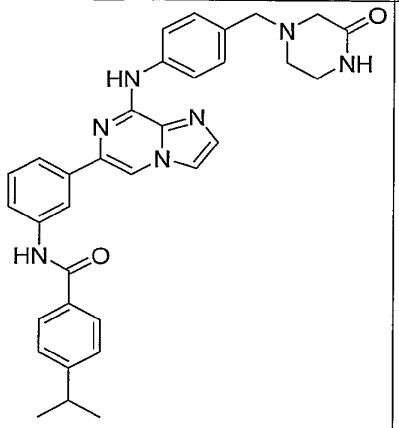
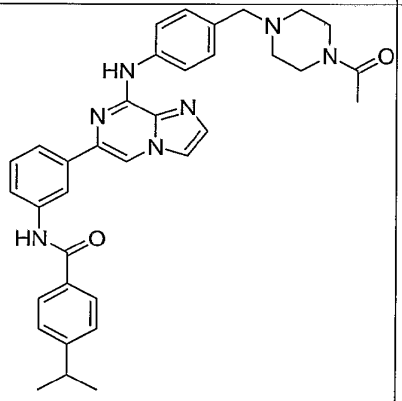
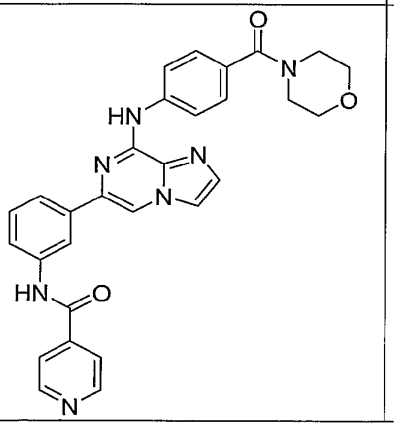
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
138		N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-terephthalamic acid C31H26N6O5	562.19	563.33
139		N-(3-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-ethyl-benzamide C33H33N7O2	559.26	560.25

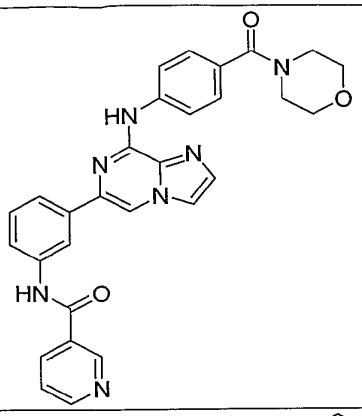
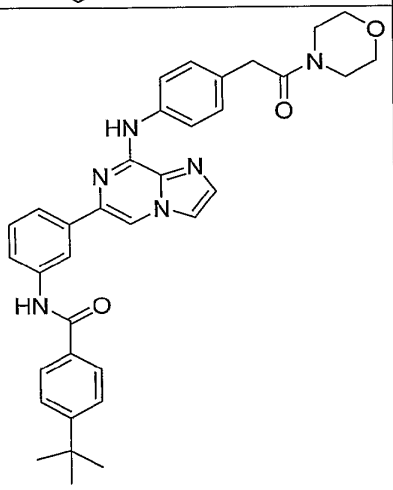
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
140		N-(3-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-trifluoromethyl-benzamide C32H28F3N7O2	599.22	600.22
141		4-*tert*-Butyl-N-(3-{8-[4-(3-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C36H37N9O	611.31	612.41
142		4-*tert*-Butyl-N-(3-{8-[4-(3-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C36H35N9O2	625.29	626.4

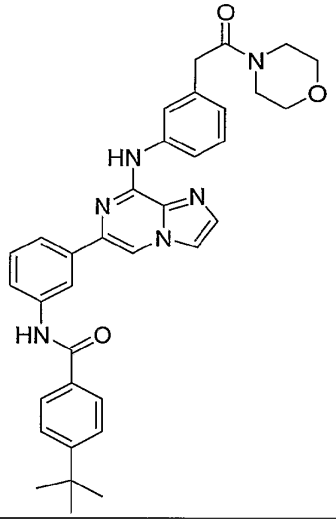
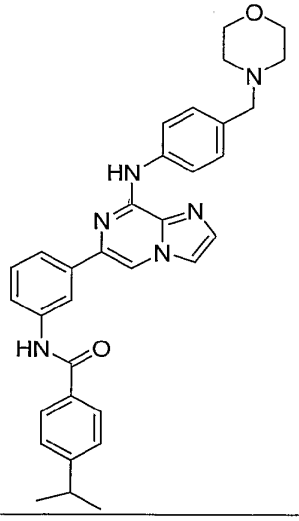
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
143		N-(3-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-isopropyl-benzamide C34H35N7O2	573.28	574.38
144		N-(3-{8-[4-(4-Acetyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-isopropyl-benzamide C35H35N7O3	601.28	602.27
145		1-(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzyl)-pyrrolidine-2-carboxylic acid C35H36N6O3	588.28	589.25

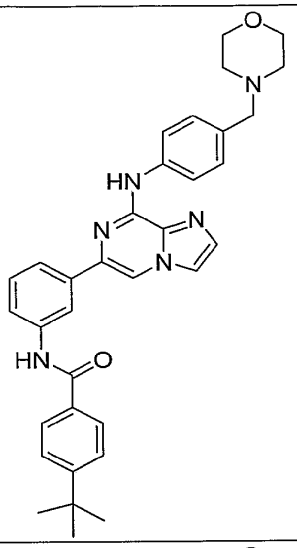
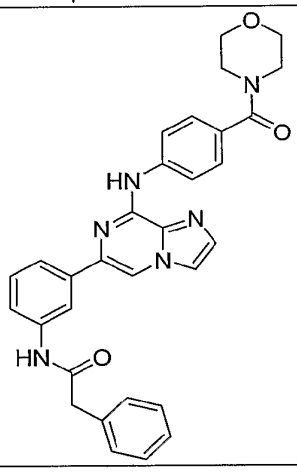
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
146		4-Isopropyl-N-(3-{8-[4-(3-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C35H33N9O2	611.27	612.26
147		N-(3-{8-[4-(5,6-Dihydro-8H-imidazo[1,2-a]pyrazine-7-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-isopropyl-benzamide C35H32N8O2	596.26	597.26

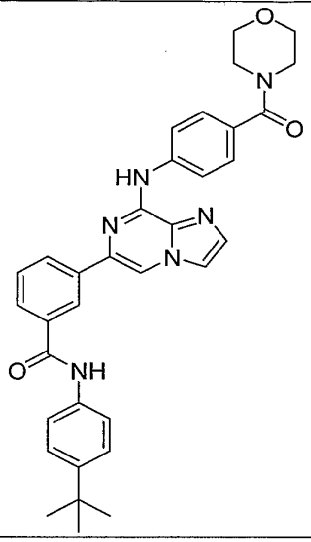
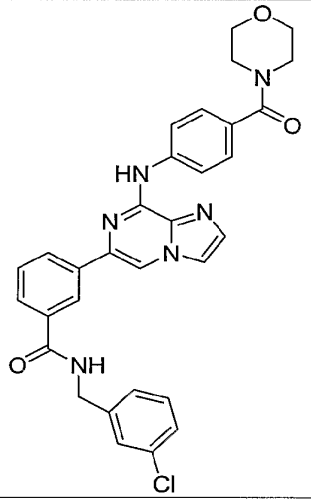
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
148		4-Isopropyl-N-(3-{8-[4-(3-oxo-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C33H31N7O3	573.24	574.27
149		4-Isopropyl-N-(3-{8-[4-(4-methyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C34H35N7O2	573.28	574.29

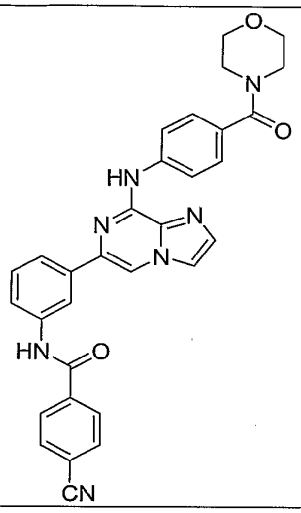
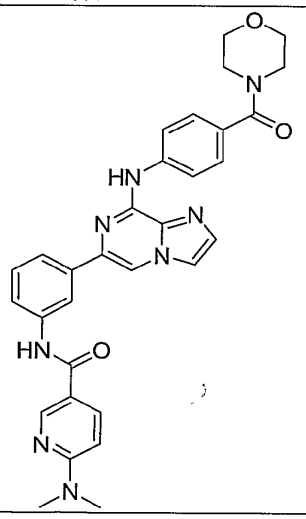
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
150		4-Isopropyl-N-(3-{8-[4-(3-oxo-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C33H33N7O2	559.26	560.29
151		N-(3-{8-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-isopropyl-benzamide C35H37N7O2	587.3	588.31
152		N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-isonicotinamide C29H25N7O3	519.2	520.2

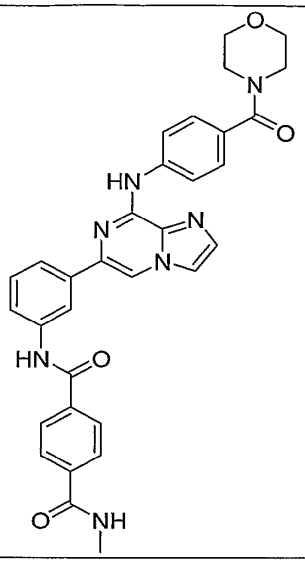
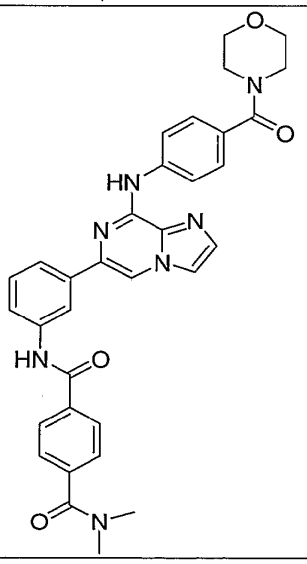
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
153		N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide C29H25N7O3	519.2	520.19
154		4-*tert*-Butyl-N-(3-{8-[4-(2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C35H36N6O3	588.28	589.28

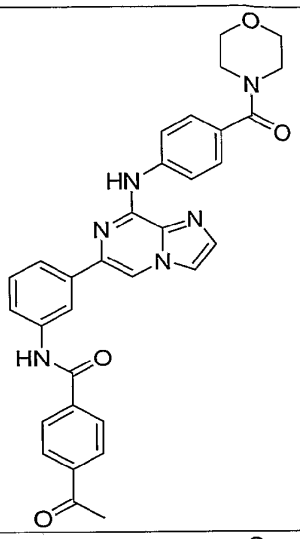
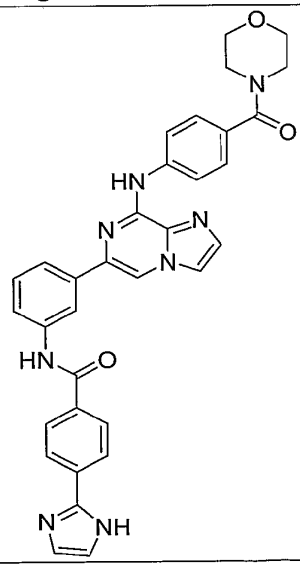
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
155		4-*tert*-Butyl-N-(3-{8-[3-(2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C35H36N6O3	588.28	589.29
156		4-Isopropyl-N-{3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C33H34N6O2	546.27	547.28

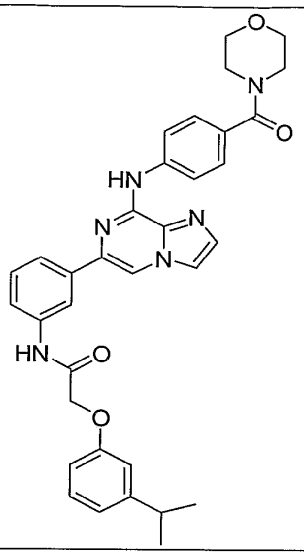
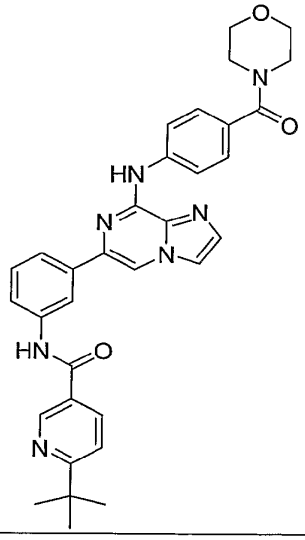
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
157		4-*tert*-Butyl-N-{3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide C34H36N6O2	560.28	561.43
158		N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-2-phenyl-acetamide C31H28N6O3	532.22	533.21

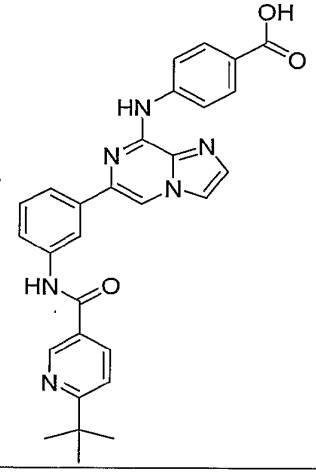
Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
159		N-(4-*tert*-Butyl-phenyl)-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-benzamide C34H34N6O3	574.27	575.23
160		N-(3-Chloro-benzyl)-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-benzamide C31H27ClN6O3	566.18	567.17

Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
161		4-Cyano-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C31H25N7O3	543.2	544.32
162		6-Dimethylamino-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide C31H30N8O3	562.24	563.26

Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
163		N-Methyl-N'-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-terephthalamide C32H29N7O4	575.22	576.25
164		N,N-Dimethyl-N'-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-terephthalamide C33H31N7O4	589.24	590.26

Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
165		4-Acetyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C32H28N6O4	560.21	561.25
166		4-(1H-Imidazol-2-yl)-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide C33H28N8O3	584.22	585.31

Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
167		2-(3-Isopropyl-phenoxy)-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-acetamide C34H34N6O4	590.26	591.32
168		6-*tert*-Butyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide C33H33N7O3	575.26	576.24

Cmp. #	STRUCTURE	NAME	MW	MS m/z (M^{+1})
169		4-(6-{3-[(6-*tert*-Butyl-pyridine-3-carbonyl)-amino]-phenyl}-imidazo[1,2a] pyrazin-8-ylamino)-benzoic acid C29H26N6O3	506.2	507.21

[0181] The compounds disclosed in synthetic Examples 1 to 5 were tested in the Btk biochemical assay described in Example 6 and found to exhibit an IC_{50} value less than or equal to 1 micromolar certain of these compounds were found to exhibit an IC_{50} value less than or equal to 100 nM, and certain of these compounds exhibited an IC_{50} value less than or equal to 10 nM. Some of the compounds disclosed in synthetic Examples 1 to 5 were tested in the B-cell proliferation assay of Example 8 and determined to exhibit an IC_{50} value less than or equal to 10 micromolar, certain of these compounds exhibited an IC_{50} value less than or equal to 1 micromolar, and certain of these compounds exhibited an IC_{50} value less than or equal to 500 nM in this assay. Certain of these compounds do not inhibit T-cell proliferation and have IC_{50} values greater than or equal to 5 micromolar when assayed under conditions described in Example 9. The compounds assayed in the Example 8 and Example 9 exhibited IC_{50} values for inhibition of T-cell proliferation that were at least 3-fold, and in some instances 5-fold, or even 10-fold greater than the IC_{50} values of these compounds for inhibition of B-cell proliferation.

EXAMPLE 6. BIOCHEMICAL BTK ASSAY

[0182] A generalized procedure for one standard biochemical Btk Kinase Assay used to test compounds disclosed in this application is as follows.

[0183] A master mix minus Btk enzyme is prepared containing 1X Cell Signaling kinase buffer (25 mM Tris-HCl, pH 7.5, 5 mM β-glycerophosphate, 2 mM dithiothreitol, 0.1 mM Na_3VO_4, 10 mM $MgCl_2$), 0.5 μM Promega PTK Biotinylated peptide substrate 2, and 0.01% BSA. A master mix plus Btk enzyme is prepared containing 1X Cell Signaling kinase buffer, 0.5 μM PTK Biotinylated peptide substrate 2, 0.01% BSA, and 100 ng/well (0.06 mU/well) Btk enzyme. Btk enzyme is prepared as follows: full length human wildtype Btk (accession number NM-000061) with a C-terminal V5 and 6x His tag was subcloned into pFastBac vector for making baculovirus carrying this epitope-tagged Btk. Generation of baculovirus was done based on Invitrogen's instructions detailed in its published protocol "Bac-toBac Baculovirus Expression Systems" (Cat. Nos. 10359-016 and 10608-016). Passage 3 virus was used to infect Sf9 cells to overexpress the recombinant Btk protein. The Btk protein was then purified to homogeneity using Ni-NTA column. The purity of the final

protein preparation was greater than 95% based on the sensitive Sypro-Ruby staining. A solution of 200 μM ATP is prepared in water and adjusted to pH7.4 with 1N NaOH. A quantity of 1.25 μL of compounds in 5%DMSO is transferred to a 96-well ½ area Costar polystyrene plate . Compounds are tested singly and with an 11-point dose-responsive curve (starting concentration is 10 μM; 1:2 dilution). A quantity of 18.75 μL of master mix minus enzyme (as a negative control) and master mix plus enzyme is transferred to appropriate wells in 96-well ½ area costar polystyrene plate. 5 μL of 200 μM ATP is added to that mixture in the 96-well ½ area Costar polystyrene plate for final ATP concentration of 40 μM. The reaction is allowed to incubate for 1 hour at room temperature. The reaction is stopped with Perkin Elmer 1X detection buffer containing 30 mM EDTA, 20 nM SA-APC, and 1 nM PT66 Ab. The plate is read using time-resolved fluorescence with a Perkin Elmer Envision using excitation filter 330 nm, emission filter 665 nm, and 2nd emission filter 615 nm. IC_{50} values are subsequently calculated.

EXAMPLE 7. RAMOS CELL BTK ASSAY

[0184] Another generalized procedure for a standard cellular Btk Kinase Assay used to test compounds disclosed in this application is as follows.

[0185] Ramos cells are incubated at a density of $0.5x10^7$ cells/ml in the presence of test compound for 1 hr at 37 °C. Cells are then stimulated by incubating with 10 μg/ml anti-human IgM $F(ab)_2$ for 5 minutes at 37 °C. Cells are pelleted, lysed, and a protein assay is performed on the cleared lysate. Equal protein amounts of each sample are subject to SDS-PAGE and western blotting with either anti-phosphoBtk(Tyr223) antibody (Cell Signaling Technology #3531) to assess Btk autophosphorylation or an anti-Btk antibody (BD Transduction Labs #611116) to control for total amounts of Btk in each lysate.

EXAMPLE 8. B-CELL PROLIFERATION ASSAY

[0186] B-cells are purified from spleens of 8-16 week old Balb/c mice using a B-cell isolation kit (Miltenyi Biotech, Cat # 130-090-862). Testing compounds are diluted in 0.25% DMSO and incubated with 2.5×10^5 purified mouse splenic B-cells for 30 min prior to addition of 10μg/ml of an anti-mouse IgM antibody (Southern Biotechnology Associates Cat # 1022-01) in a final volume of 100 μl. Following 24 hr incubation, 1 μCi ^{3}H-thymidine is

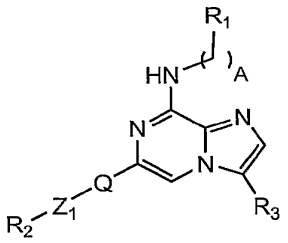
added and plates are incubated an additional 36 hr prior to harvest using the manufacturer's protocol for SPA[^{3}H] thymidine uptake assay system (Amersham Biosciences # RPNQ 0130). SPA-bead based fluorescence is counted in a microbeta counter (Wallace Triplex 1450, Perkin Elmer).

EXAMPLE 9. T CELL PROLIFERATION ASSAY

[0187] T cells are purified from spleens of 8-16 week old Balb/c mice using a Pan T cell isolation kit (Miltenyi Biotech, Cat # 130-090-861). Testing compounds are diluted in 0.25% DMSO and incubated with 2.5 x 10^5 purified mouse splenic T cells in a final volume of 100 μl in flat clear bottom plates precoated for 90 min at 37°C with 10 μg/ml each of anti-CD3 (BD # 553057) and anti-CD28 (BD # 553294) antibodies. Following 24 hr incubation, 1 μCi ^{3}H-thymidine is added and plates incubated an additional 36 hr prior to harvest using the manufacturer's protocol for SPA[^{3}H] thymidine uptake assay system (Amersham Biosciences # RPNQ 0130). SPA-bead based fluorescence was counted in a microbeta counter (Wallace Triplex 1450, Perkin Elmer).

What is claimed is:

1. A compound of Formula 1



(Formula 1)

or a pharmaceutically acceptable form thereof, wherein

A is 0 or 1;

R_1 is phenyl or heteroaryl, each of which is substituted with one of

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl$(SO_2)R_{10}$, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl,

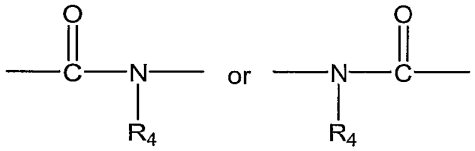
each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl;

R_2 is C_1-C_7 alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, (heterocycloalkyl) C_0-C_2alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, or

R_2 is (phenyl)C_0-C_2alkyl, (phenoxy)C_0-C_2alkyl, or (heteroaryl)C_0-C_2alkyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, -SO_2NH_2, oxo, -COOH, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_2-C_6alkanoyl, C_1-C_6hydroxyalkyl, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6alkyl, mono- and di- C_1-C_6alkylamino, mono- and di-C_1-C_6alkylcarboxamide, C_1-C_6alkoxycarbonyl, phenyl, heteroaryl, and –(C=O)R_{13} wherein R_{13} is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, C_1-C_3haloalkyl, heterocycloalkyl, phenyl, or heteroaryl;

Z_1 is



wherein

R_4 is hydrogen, or

R_4 is C_1-C_6alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each of which is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6 alkyl, mono- and di-C_1-C_6 alkylamino, and -C(O)R_{14} wherein R_{14} is C_1-C_6 alkyl, C_1-C_3haloalkyl, or phenyl;

Q is phenyl or pyridyl; and

R_3 is hydrogen, halogen, or C_1-C_7 alkyl, or

R_3 is heterocycloalkyl, C_3-C_7cycloalkyl, or heteroaryl, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, -SO_2NH_2, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3halooalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6-alkoxy)C_1-C_6 alkoxy, mono- and di-C_1-C_6alkylamino, aminoC_1-C_6 alkyl, and -C(O)R_{14}.

2. A compound or form thereof of Claim 1 wherein A is 0.

3. A compound or form thereof of Claim 1 wherein A is 1.

4. A compound or form thereof of any one of Claims 1 to 3 wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$, where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl,

each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

5. A compound or form thereof of Claim 4, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

6. A compound or form thereof of Claim 5, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

7. A compound or form thereof of Claim 6, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

8. A compound or form thereof of Claim 4 wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

each of which (ii) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

9. A compound or form thereof of Claim 8 wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, or (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

10. A compound or form thereof of Claim 9 wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, or (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

11. A compound or form thereof of Claim 4 wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, [1,4]diazepanyl, phenyl, imidazolyl, or 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazine, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

12. A compound or form thereof of Claim 11, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, [1,4]diazepanyl, phenyl, imidazolyl, or 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazine, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

13. A compound or form thereof of Claim 4, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of (iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl$(SO_2)R_{10}$, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_7cycloalkyl, or heterocycloalkyl,

each of which (iii) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

14. A compound or form thereof of Claim 13 wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of -C_1-C_4alkyl(C=O)OR_{10}, -C_0-C_4alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_4alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_4alkylNR_{10}(C=O)R_{11}, -C_0-C_4alkyl$(SO_2)R_{10}$, or -C_0-C_4alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, or [1,4]diazepanyl, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

15. A compound or form thereof of Claim 4 wherein

R_1 is phenyl or pyridyl,

each of which is substituted with one of (iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl, each of which (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

16. A compound or form thereof of Claim 15, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

–L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, [1,4]diazepanyl, phenyl, imidazolyl, or 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazine, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

17. A compound or form thereof of Claim 16, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

–L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, [1,4]diazepanyl, phenyl, imidazolyl, or 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazine, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

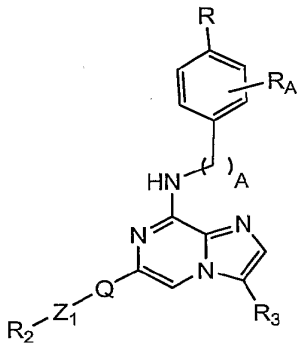
18. A compound or form thereof of Claim 17, wherein

L is phenyl or pyridyl, each of which is substituted with one of

–CH_2-, -(C=O)-, or -(CH_2)(C=O)-, and G is pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, or [1,4]diazepanyl, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, -COOH, -$CONH_2$, C_1-C_2alkyl, C_1-C_2alkoxy, C_2-C_2alkanoyl, C_1-C_2alkoxycarbonyl, mono- and di-C_1-C_2alkylamino, and mono- and di-C_1-C_2alkylcarboxamide, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

19. A compound or form thereof of Claim 4, having a structure of Formula 2



Formula 2

wherein R is

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

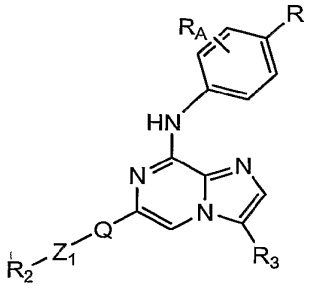
(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl,

each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_A is 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

20. A compound or form thereof of Claim 19 having a structure of Formula 3



Formula 3.

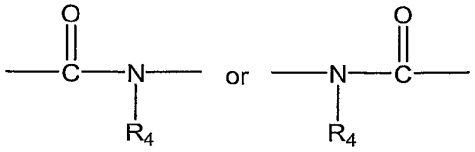
21. A compound or form thereof of any one of Claims 1 to 20, wherein

R_2 is (phenyl)C_0-C_2alkyl, (phenoxy)C_0-C_2alkyl, or (pyridyl)C_0-C_2alkyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, -SO_2NH_2, oxo, -COOH, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_2-C_6alkanoyl, C_1-C_6hydroxyalkyl, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6alkyl, mono- and di-C_1-C_6 alkylamino, mono- and di-C_1-C_6alkylcarboxamide, C_1-C_6alkoxycarbonyl, phenyl, heteroaryl, and –(C=O)R_{13} wherein R_{13} is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, C_1-C_3haloalkyl, heterocycloalkyl, phenyl, or heteroaryl.

22. A compound or form thereof of Claim 21, wherein

R_2 is (phenyl)C_0-C_2alkyl, (phenoxy)C_0-C_2alkyl, or (pyridyl)C_0-C_2alkyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, cyano, amino, halogen, -SO_2NH_2, oxo, -COOH, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_4alkanoyl, C_1-C_4hydroxyalkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, mono- and di-C_1-C_6alkylamino, mono- and di-C_1-C_6alkylcarboxamide, C_1-C_4alkoxycarbonyl, phenyl, and imidazolyl.

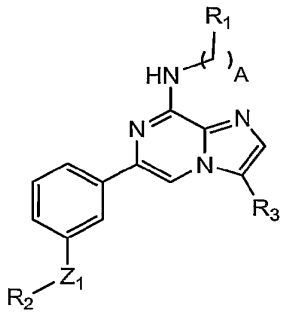
23. A compound or form thereof of any one of Claim 1 to 22 wherein Z_1 is



and R_4 is hydrogen, C_1-C_6alkyl, or C_3-C_7cycloalkyl.

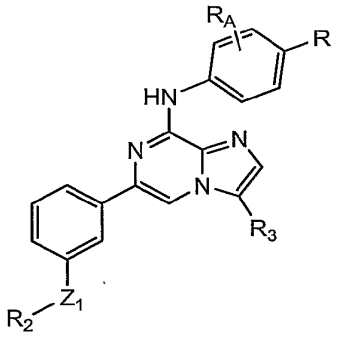
24. A compound or form thereof of Claim 23, wherein R_4 is hydrogen or methyl.

25. A compound or form thereof of Claim 4, having a structure of Formula 4



Formula 4.

26. A compound or form thereof of Claim 25, having a structure of Formula 5



Formula 5

wherein R is

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

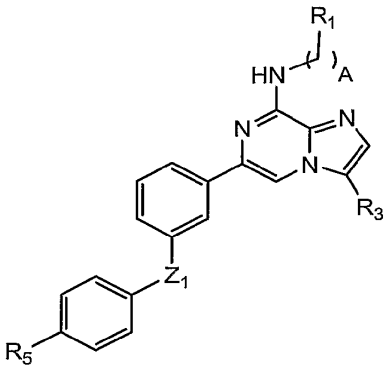
(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl,

each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl; and

R_A is 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

27. A compound or form thereof of any one of Claims 1 to 26, wherein R_3 is hydrogen or methyl.

28. A compound having a structure of Formula 6



Formula 6

or a pharmaceutically acceptable form thereof, wherein

A is 0 or 1;

R_1 is phenyl or heteroaryl, each of which is optionally substituted with one of

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl,

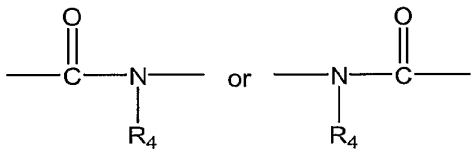
each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, $-SO_2NH_2$, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl;

R_3 is hydrogen, halogen, or C_1-C_7 alkyl, or

R_3 is heterocycloalkyl, C_3-C_7cycloalkyl, or heteroaryl, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, $-SO_2NH_2$, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3halooalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6-alkoxy)C_1-C_6 alkoxy, mono- and di-C_1-C_6alkylamino, aminoC_1-C_6 alkyl, and $-C(O)R_{14}$;

Z_1 is



wherein

R_4 is hydrogen, or

R_4 is C_1-C_6alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each of which is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6 alkyl, mono- and di-C_1-C_6 alkylamino, and $-C(O)R_{14}$ wherein R_{14} is C_1-C_6 alkyl, C_1-C_3haloalkyl, or phenyl; and

R_5 is isopropyl or t-butyl.

29. A compound or form thereof of Claim 28 wherein A is 0.

30. A compound or form thereof of Claim 28 wherein A is 1.

31. A compound or form thereof of any one of Claims 28 to 30 wherein

R_1 is phenyl or pyridyl, each of which is optionally substituted with one of

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl, or

(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl,

each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

32. A compound or form thereof of Claim 31, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

33. A compound or form thereof of Claim 32, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

34. A compound or form thereof of Claim 33, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH, and R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

35. A compound or form thereof of Claim 31 wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of (ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl, and

each of which (ii) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

36. A compound or form thereof of Claim 35 wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

37. A compound or form thereof of Claim 36 wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

38. A compound or form thereof of Claim 31 wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, [1,4]diazepanyl, phenyl, imidazolyl, or 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazine each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

39. A compound or form thereof of Claim 38, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, [1,4]diazepanyl, phenyl, imidazolyl, or 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazine, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

40. A compound or form thereof of Claim 31, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of (iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl$(SO_2)R_{10}$, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_7cycloalkyl, or heterocycloalkyl,

each of which (iii) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

41. A compound or form thereof of Claim 40 wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

-C_1-C_4alkyl(C=O)OR_{10}, -C_0-C_4alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_4alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_4alkylNR_{10}(C=O)R_{11}, -C_0-C_4alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, or[1,4]diazepanyl, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide; and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

42. A compound or form thereof of Claim 31 wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of (iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl,

each of which (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

43. A compound or form thereof of Claim 42, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

–L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, [1,4]diazepanyl, phenyl, imidazolyl, or 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazine, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide, and

R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

44. A compound or form thereof of Claim 43, wherein

R_1 is phenyl or pyridyl, each of which is substituted with one of

–L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, [1,4]diazepanyl, phenyl, imidazolyl, or 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-a]pyrazine, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, and mono- and di-C_1-C_4alkylcarboxamide, and

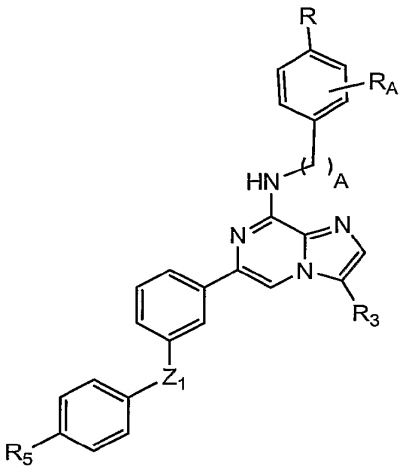
R_1 is substituted with from 0 to 3 substituents independently chosen from hydroxy, cyano, halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

45. A compound or form thereof of Claim 44, wherein

L is phenyl or pyridyl, each of which is substituted with one of

–CH_2-, -(C=O)-, or -(CH_2)(C=O)-, and G is pyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, or [1,4]diazepanyl, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, -COOH, -$CONH_2$, C_1-C_2alkyl, C_1-C_2alkoxy, C_2-C_2alkanoyl, C_1-C_2alkoxycarbonyl, mono- and di-C_1-C_2alkylamino, and mono- and di-C_1-C_2alkylcarboxamide.

46. A compound or form thereof of Claim 31, having a structure of Formula 7



Formula 7

wherein R is

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl,

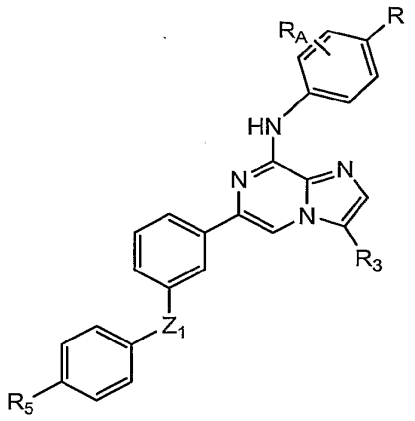
(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl,

each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_A is 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-

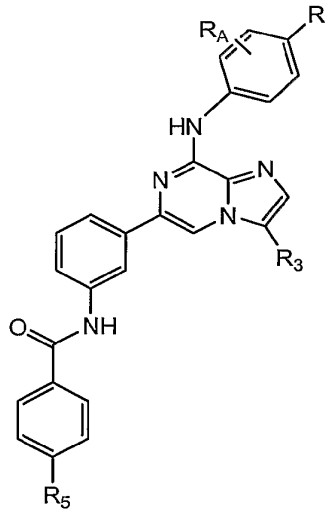
C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl.

47. A compound or form thereof of Claim 46, having a structure of Formula 8



Formula 8.

48. A compound or form thereof of Claim 47, having a structure of Formula 9



Formula 9.

49. A compound or form thereof of any one of Claims 29 to 48, wherein R_3 is hydrogen or methyl.

50. A compound or form thereof of any one of Claims 1 to 49, wherein the compound exhibits an IC_{50} of 1 micromolar or less in an in vitro biochemical assay of Btk activity.

51. A compound or form thereof according of any one of Claims 1 to 49, wherein the compound exhibits an IC_{50} of 100 nanomolar or less in an in vitro biochemical assay of Btk activity.

52. A compound or form thereof of any one of Claims 1 to 49, wherein the compound exhibits an IC_{50} of 10 nanomolar or less in an in vitro biochemical assay of Btk activity.

53. A compound or form thereof of any one of Claims 1 to 52 wherein the compound exhibits a IC_{50} of 10 micromolar or less in an assay for inhibition of B-cell proliferation.

54. `A compound or form thereof of any one of Claims 1 to 52 wherein the compound exhibits a IC_{50} of 1 micromolar or less in an assay for inhibition of B-cell proliferation.

55. `A compound or form thereof of any one of Claims 1 to 52 wherein the compound exhibits a IC_{50} of 500 nanomolar or less in an assay for inhibition of B-cell proliferation.

56. A compound or form thereof of any one of Claims 1 to 55, wherein the compound exhibits an IC_{50} value in an assay for inhibition of T-cell proliferation that is at least 3-fold greater than an IC_{50} value the compound exhibits in an assay for inhibition of B-cell proliferation.

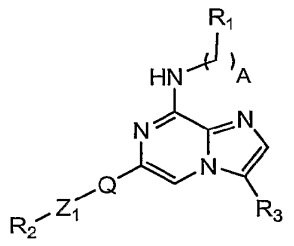
57. A compound or form thereof of any one of Claims 1 to 55, wherein the compound exhibits an IC_{50} value in an assay for inhibition of T-cell proliferation that is at least 5-fold greater than an IC_{50} value the compound exhibits in an assay for inhibition of B-cell proliferation.

58. A compound or form thereof of any one of Claims 1 to 55, wherein the compound exhibits an IC_{50} value in an assay for inhibition of T-cell proliferation that is at least 10-fold greater than an IC_{50} value the compound exhibits in an assay for inhibition of B-cell proliferation.

59. A pharmaceutical composition, comprising a compound or form thereof of any one of Claims 1 to 58, together with at least one pharmaceutically acceptable carrier or excipient.

60. A pharmaceutical composition of Claim 59, wherein the composition is formulated as an injectable fluid, an aerosol, a cream, a gel, a tablet, a pill, a capsule, a syrup, ophthalmic solution, or a transdermal patch.

61. A packaged pharmaceutical composition, comprising
a pharmaceutical composition in a container; and instructions for using the composition to treat a patient suffering from an disease responsive to Btk inhibition, wherein the pharmaceutical composition comprises
(a) at least one pharmaceutically acceptable carrier or excipient and
(b) a compound of Formula I-a



Formula I-a

or a pharmaceutically acceptable form thereof, wherein
A is 0 or 1;
R_1 is phenyl or heteroaryl, each of which is optionally substituted with one of
(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,
(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,
(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl,
(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl,
each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-

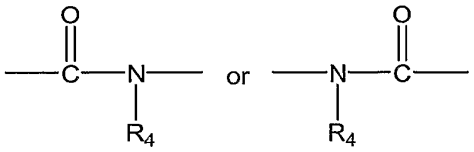
C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, $-SO_2NH_2$, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl;

R_2 is C_1-C_7 alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, (heterocycloalkyl)C_0-C_2alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, or

R_2 is (phenyl)C_0-C_2alkyl, (phenoxy)C_0-C_2alkyl, or (heteroaryl)C_0-C_2alkyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, $-SO_2NH_2$, oxo, -COOH, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_2-C_6alkanoyl, C_1-C_6hydroxyalkyl, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6alkyl, mono- and di- C_1-C_6alkylamino, mono- and di-C_1-C_6alkylcarboxamide, C_1-C_6alkoxycarbonyl, phenyl, and heteroaryl, and $-(C=O)R_{13}$ wherein R_{13} is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, C_1-C_3haloalkyl, heterocycloalkyl, phenyl, or heteroaryl;

Z_1 is



wherein

R_4 is hydrogen, or

R_4 is C_1-C_6alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each of which is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6 alkyl, mono- and di-C_1-C_6 alkylamino, and $-C(O)R_{14}$ wherein R_{14} is C_1-C_6 alkyl, C_1-C_3haloalkyl, or phenyl;

Q is phenyl or pyridyl; and

R_3 is hydrogen, halogen, or C_1-C_7 alkyl, or

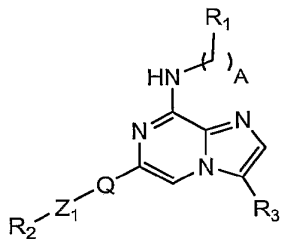
R_3 is heterocycloalkyl, C_3-C_7cycloalkyl, or heteroaryl, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, $-SO_2NH_2$, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3halooalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6-alkoxy)C_1-C_6 alkoxy, mono- and di-C_1-C_6alkylamino, aminoC_1-C_6 alkyl, and $-C(O)R_{14}$.

62. A packaged pharmaceutical composition, comprising a pharmaceutical composition of Claim 59 in a container; and instructions for using the composition to treat a patient suffering from an disease responsive to Btk inhibition

63. The packaged pharmaceutical composition of Claim 61 or Claim 62 wherein the disease responsive to Btk inhibition is cancer.

64. The packaged pharmaceutical composition of Claim 61 or Claim 62wherein the disease responsive to Btk inhibition is an autoimmune disease, an inflammatory disease, or an acute inflammatory reaction.

65. A method for treating a patient having a disease responsive to inhibition of Btk activity, comprising administering to the patient an effective amount of a compound, or form thereof, of Formula I-a



Formula I-a

or a pharmaceutically acceptable form thereof, wherein

A is 0 or 1;

R_1 is phenyl or heteroaryl, each of which is optionally substituted with one of

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl,

(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl,

each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

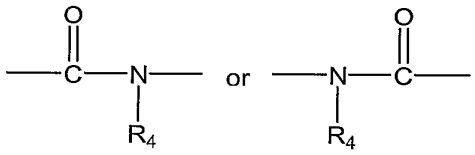
R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-

C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl;

R_2 is C_1-C_7 alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, (heterocycloalkyl)C_0-C_2alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, or

R_2 is (phenyl)C_0-C_2alkyl, (phenoxy)C_0-C_2alkyl, or (heteroaryl)C_0-C_2alkyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, -SO_2NH_2, oxo, -COOH, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_2-C_6alkanoyl, C_1-C_6hydroxyalkyl, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6alkyl, mono- and di- C_1-C_6alkylamino, mono- and di-C_1-C_6alkylcarboxamide, C_1-C_6alkoxycarbonyl, phenyl, and heteroaryl, and –(C=O)R_{13} wherein R_{13} is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, C_1-C_3haloalkyl, heterocycloalkyl, phenyl, or heteroaryl;

Z_1 is



wherein

R_4 is hydrogen, or

R_4 is C_1-C_6alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each of which is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6 alkyl, mono- and di-C_1-C_6 alkylamino, and -C(O)R_{14} wherein R_{14} is C_1-C_6 alkyl, C_1-C_3haloalkyl, or phenyl;

Q is phenyl or pyridyl; and

R_3 is hydrogen, halogen, or C_1-C_7 alkyl, or

R_3 is heterocycloalkyl, C_3-C_7cycloalkyl, or heteroaryl, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, -SO_2NH_2, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-

C_3halooalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6-alkoxy)C_1-C_6 alkoxy, mono- and di-C_1-C_6alkylamino, aminoC_1-C_6 alkyl, and -C(O)R_{14}.

66. A method for treating a patient having a disease responsive to inhibition of Btk activity, comprising administering an effective amount of a compound or form thereof of any one of Claim 1 to Claim 58 to the patient.

67. The method of Claim 65 or Claim 66 wherein the patient is a human.

68. The method of Claim 65 or Claim 66 wherein the patient is a cat or dog.

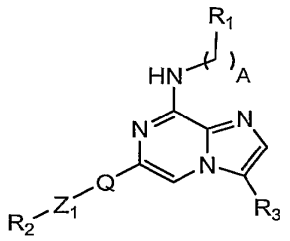
69. The method of Claim 65 or Claim 66 wherein the disease responsive to Btk inhibition is cancer.

70. The method of Claim 65 or Claim 66, wherein the disease responsive to Btk inhibition is an autoimmune disease, an inflammatory disease, or an acute inflammatory reaction.

71. The method of Claim 65 or Claim 66 wherein the compound or form is administered orally.

72. The method of Claim 65 or Claim 66 wherein the compound or form is administered intravenously, by intramuscularly, or parenterally.

73. A method for increasing sensitivity of cancer cells to chemotherapy, comprising administering to a patient undergoing chemotherapy with a chemotherapeutic agent an amount of a compound of Formula I-a, or a pharmaceutically acceptable form thereof, sufficient to increase the sensitivity of cancer cells to the chemotherapeutic agent, wherein Formula I-a is



Formula I-a

in which

A is 0 or 1;

R_1 is phenyl or heteroaryl, each of which is optionally substituted with one of

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl,

(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl,

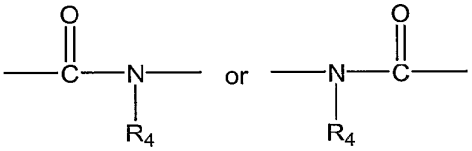
each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, $-SO_2NH_2$, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl;

R_2 is C_1-C_7 alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, (heterocycloalkyl)C_0-C_2alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, or

R_2 is (phenyl)C_0-C_2alkyl, (phenoxy)C_0-C_2alkyl, or (heteroaryl)C_0-C_2alkyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, $-SO_2NH_2$, oxo, -COOH, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_2-C_6alkanoyl, C_1-C_6hydroxyalkyl, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6alkyl, mono- and di- C_1-C_6alkylamino, mono- and di-C_1-C_6alkylcarboxamide, C_1-C_6alkoxycarbonyl, phenyl, and heteroaryl, and $-(C{=}O)R_{13}$ wherein R_{13} is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, C_1-C_3haloalkyl, heterocycloalkyl, phenyl, or heteroaryl;

Z_1 is



wherein

R_4 is hydrogen, or

R_4 is C_1-C_6alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each of which is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6 alkyl, mono- and di-C_1-C_6 alkylamino, and $-C(O)R_{14}$ wherein R_{14} is C_1-C_6 alkyl, C_1-C_3haloalkyl, or phenyl;

Q is phenyl or pyridyl; and

R_3 is hydrogen, halogen, or C_1-C_7 alkyl, or

R_3 is heterocycloalkyl, C_3-C_7cycloalkyl, or heteroaryl, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen,

$-SO_2NH_2$, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3halooalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6-alkoxy)C_1-C_6 alkoxy, mono- and di-C_1-C_6alkylamino, aminoC_1-C_6 alkyl, and $-C(O)R_{14}$.

74. A method of reducing medication error and enhancing therapeutic compliance of a patient being treated for a disease responsive to Btk inhibition, the method comprising providing a packaged pharmaceutical preparation of Claim 61 or Claim 62 wherein the instructions additionally include contraindication and adverse reaction information pertaining to the packaged pharmaceutical composition.

75. A method for increasing sensitivity of cancer cells to chemotherapy, comprising administering to a patient undergoing chemotherapy with a chemotherapeutic agent an amount of a compound of any one of Claims 1 to 58, or a pharmaceutically acceptable form thereof, sufficient to increase the sensitivity of cancer cells to the chemotherapeutic agent.

76. A method for inhibiting ATP hydrolysis, the method comprising contacting cells expressing Btk with a compound or form thereof of any one of Claims 1 to 58 in an amount sufficient to detectably decrease the level of ATP hydrolysis *in vitro*.

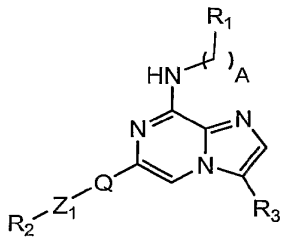
77. The method of Claim 76 wherein the cells are present in a mammal.

78. The method of Claim 77 wherein the mammal is a human.

79. The method of Claim 77 wherein the mammal is a cat or dog.

80. A method for determining the presence of Btk in a sample, comprising contacting the sample with a compound or form thereof of any one of Claims 1 to 58 under conditions that permit detection of Btk activity, detecting a level of Btk activity in the sample, and therefrom determining the presence or absence of Btk in the sample.

81. The use of a compound of Formula I-a, or a pharmaceutically acceptable form thereof, for the manufacture of a medicament for the treatment of a disease responsive to Btk inhibition, wherein Formula I-a is



Formula I-a

in which

A is 0 or 1;

R_1 is phenyl or heteroaryl, each of which is optionally substituted with one of

(i) oxo, -CHO, –COOH, -$CONH_2$, or –CONHOH,

(ii) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6hydroxyalkyl, C_1-C_6hydroxyalkoxy, (mono- or di-C_1-C_6alkylamino)C_1-C_6alkoxy, (C_1-C_6alkoxy)(C_1-C_6alkylamino)C_0-C_6alkyl, (C_1-C_6alkoxy)(C_1-C_6alkoxy)C_1-C_6alkoxy, heterocycloalkyl, aryl, or heteroaryl,

(iii) -C_1-C_6alkyl(C=O)OR_{10}, -C_0-C_6alkyl(C=O)$NR_{10}R_{11}$, -C_1-C_6alkyl$NR_{10}(SO_2)R_{11}$, -C_0-C_6alkylNR_{10}(C=O)R_{11}, -C_0-C_6alkyl(SO_2)R_{10}, or -C_0-C_6alkylNR_{10}(C=O)$NR_{11}R_{12}$ where R_{10}, R_{11}, and R_{12} are independently hydrogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, or heterocycloalkyl,

(iv) –L-G, where L is C_1-C_2alkyl, C_0-C_2alkoxy, -(C=O)-, or -(C_1-C_2alkyl)(C=O)-, and G is heterocycloalkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl,

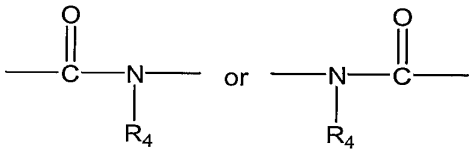
each of which (ii), (iii), and (iv) is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, amino, oxo, -COOH, -$CONH_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylthio, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_4alkoxycarbonyl, mono- and di-C_1-C_4alkylamino, mono- and di-C_1-C_4alkylcarboxamide, and phenyl, and

R_1 is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, -SO_2NH_2, halogen, C_1-C_6 alkyl, C_2-C_6alkanoyl, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_6 alkylthio, C_3-C_7cycloalkyl, (C_1-C_6 alkoxy)C_0-C_6alkyl, (mono- and di-C_1-C_6 alkylamino)C_0-C_6 alkyl, and C_1-C_6alkoxycarbonyl;

R_2 is C_1-C_7 alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, (heterocycloalkyl)C_0-C_2alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, or

R_2 is (phenyl)C_0-C_2alkyl, (phenoxy)C_0-C_2alkyl, or (heteroaryl)C_0-C_2alkyl, each of which is substituted with 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, -SO_2NH_2, oxo, -COOH, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_2-C_6alkanoyl, C_1-C_6hydroxyalkyl, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6alkyl, mono- and di- C_1-C_6alkylamino, mono- and di-C_1-C_6alkylcarboxamide, C_1-C_6alkoxycarbonyl, phenyl, and heteroaryl, and –(C=O)R_{13} wherein R_{13} is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, C_1-C_3haloalkyl, heterocycloalkyl, phenyl, or heteroaryl;

Z_1 is



wherein

R_4 is hydrogen, or

R_4 is C_1-C_6alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl, each of which is substituted with 0 or 1 or more substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, aminoC_1-C_6 alkyl, mono- and di-C_1-C_6 alkylamino, and -C(O)R_{14} wherein R_{14} is C_1-C_6 alkyl, C_1-C_3haloalkyl, or phenyl;

Q is phenyl or pyridyl; and

R_3 is hydrogen, halogen, or C_1-C_7 alkyl, or

R_3 is heterocycloalkyl, C_3-C_7cycloalkyl, or heteroaryl, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halogen, -SO_2NH_2, oxo, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkoxy, C_1-C_3halooalkyl, C_1-C_3haloalkoxy, C_1-C_6 alkylthio, (C_1-C_6-alkoxy)C_1-C_6 alkoxy, mono- and di-C_1-C_6alkylamino, aminoC_1-C_6 alkyl, and -C(O)R_{14}.

82. . The use of a compound any one of Claims 1 to 58, or a pharmaceutically acceptable form thereof, for the manufacture of a medicament for the treatment of a disease responsive to Btk inhibition,

83. The use of Claim 81 or Claim 82, wherein the disease is cancer.

84. The use of Claim 81 or Claim 82, wherein the disease is an autoimmune disease, an inflammatory disease, or an acute inflammatory reaction.

85. A method for inhibiting B-cell proliferation comprising contacting cells expressing Btk with a compound or form thereof, of any one of Claim 1 to 58, in an amount sufficient to detectably decrease Btk activity *in vitro*.

86. A compound or pharmaceutically acceptable form thereof wherein the compound is

4-*tert*-Butyl-N-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

4-Isopropyl-N-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

4-*tert*-Butyl-N-{3-[8-(pyridin-3-ylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-methoxy-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-{3-[8-(pyridin-4-ylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-fluoro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-{3-[8-(3-fluoro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-*tert*-Butyl-N-{3-[8-(3-methoxy-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-{3-[8-(6-methoxy-pyridin-3-ylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

3-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-{6-[3-(4-Isopropyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-*tert*-Butyl-N-{3-[8-(4-cyano-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-morpholin-4-yl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

3-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-*tert*-Butyl-N-{3-[8-(3-fluoro-4-methoxy-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic N-Methyl amide;

4-*tert*-Butyl-N-{3-[8-(4-piperazin-1-yl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-[3-(8-m-tolylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-acetic acid methyl ester;

(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-acetic acid;

4-*tert*-Butyl-N-(3-{8-[4-(piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(2-methoxy-ethoxymethoxy)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-hydroxy-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-{3-[8-(6-piperazin-1-yl-pyridin-3-ylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-[1,4]diazepan-1-yl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(4-oxo-piperidin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoylamino)-acetic acid methyl ester;

(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoylamino)-acetic acid;

N-(3-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-*tert*-butyl-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(3-methyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic hydroxyl amide;

4-*tert*-Butyl-N-{3-[8-(4-hydroxymethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-piperazin-1-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-{6-[3-(4-Bromo-3-methyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-*tert*-Butyl-N-{3-[8-(3-methyl-4-piperazin-1-yl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(3-methyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-{3-[8-(3-hydroxymethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-(3-{8-[3-(3-methyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[3-(3-methyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[3-(3,5-dimethyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-({6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-methyl)-benzoic acid;

4-*tert*-Butyl-N-(3-{8-[4-(3-methyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-(1-Hydroxy-1-methyl-ethyl)-N-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

(3-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-acetic acid;

N-[3-(8-Phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-terephthalamic acid methyl ester;

N-[3-(8-Phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-terephthalamic acid;

2-(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-propionic acid ethyl ester;

2-(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-propionic acid;

4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-2-methoxy-benzoic acid methyl ester;

4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-2-methoxy-benzoic acid;

4-*tert*-Butyl-N-{3-[8-(3-methylcarbamoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-methylcarbamoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-cyclooctylcarbamoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-[3-(8-{4-[(diisopropylcarbamoyl)-methyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-carbamoylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

3-(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-propionic acid;

4-*tert*-Butyl-N-(3-{8-[4-(2-hydroxy-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(2-methylamino-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-methylaminomethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-2-hydroxy-benzoic acid;

4-*tert*-Butyl-N-(3-{8-[4-(1-hydroxy-1-methyl-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(2-hydroxy-ethoxy)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(4-methyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(2-methylamino-ethoxy)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(2-dimethylamino-ethoxy)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic methoxy amide;

4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic hyrdoxyl methyl amide;

4-*tert*-Butyl-N-(3-{8-[4-([1,4]diazepane-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(pyrrolidine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(ethoxyamine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(dimethylamine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(methylethylamine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(3-oxo-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[N,N,N'-Trimethyl-ethane-1,2-diamine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(4-methyl-[1,4]diazepane-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(N-methyl ethoxyamine-4-carbonyl)-phenylamino]-imidazo[1,2-

a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(4-ethyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic benzyl amide;

4-*tert*-Butyl-N-(3-{8-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(4-ethyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-[1,4]diazepan-1-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(3-methyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-dimethylaminomethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-[3-(8-{4-[(ethyl-methyl-amino)-methyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-{[(2-methoxy-ethyl)-methyl-amino]-methyl}-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-[3-(8-{4-[(2-methoxy-ethylamino)-methyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

N-(3-{8-[4-(4-Acetyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-*tert*-butyl-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-{[(2-hydroxy-ethyl)-methyl-amino]-methyl}-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-[3-(8-{4-[(2-hydroxy-ethylamino)-methyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(4-methyl-[1,4]diazepan-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

N-[3-(8-{4-[2-(Acetyl-methyl-amino)-ethoxy]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-4-*tert*-butyl-benzamide;

4-(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-phenyl)-piperazine-1-carboxylic acid ethyl ester;

N-(3-{8-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-*tert*-butyl-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-imidazol-1-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-pyrrolidin-1-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

N-[3-(8-{4-[(Acetyl-methyl-amino)-methyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-4-*tert*-butyl-benzamide;

4-*tert*-Butyl-N-[3-(8-{4-[(methanesulfonyl-methyl-amino)-methyl]-phenylamino}-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(3-isopropyl-1-methyl-ureidomethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-Isopropyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

N-{3-[8-(4-{[(2-Hydroxy-ethyl)-methyl-amino]-carbonyl}-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-4-isopropyl-benzamide;

N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-Methyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-Ethyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-Fluoro-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-trifluoromethyl-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(5,6-dihydro-8H-imidazo[1,2-a]pyrazine-7-carbonyl)-phenylamino]-

imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(3-oxo-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

1-(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzyl)-pyrrolidine-2-carboxylic acid methyl ester;

N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-terephthalamic acid methyl ester;

N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-terephthalamic acid;

N-(3-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-ethyl-benzamide;

N-(3-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-trifluoromethyl-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(3-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[4-(3-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

N-(3-{8-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-isopropyl-benzamide;

N-(3-{8-[4-(4-Acetyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-isopropyl-benzamide;

1-(4-{6-[3-(4-*tert*-Butyl-benzoylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzyl)-pyrrolidine-2-carboxylic acid;

4-Isopropyl-N-(3-{8-[4-(3-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

N-(3-{8-[4-(5,6-Dihydro-8H-imidazo[1,2-a]pyrazine-7-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-isopropyl-benzamide;

4-Isopropyl-N-(3-{8-[4-(3-oxo-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-Isopropyl-N-(3-{8-[4-(4-methyl-piperazine-1-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-Isopropyl-N-(3-{8-[4-(3-oxo-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

N-(3-{8-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-4-isopropyl-benzamide;

N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-isonicotinamide;

N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide;

4-*tert*-Butyl-N-(3-{8-[4-(2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-*tert*-Butyl-N-(3-{8-[3-(2-morpholin-4-yl-2-oxo-ethyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

4-Isopropyl-N-{3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

4-*tert*-Butyl-N-{3-[8-(4-morpholin-4-ylmethyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

N-(3-{8-[4-(Morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-2-phenyl-acetamide;

N-(4-*tert*-Butyl-phenyl)-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-benzamide;

N-(3-Chloro-benzyl)-3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-benzamide;

4-Cyano-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

6-Dimethylamino-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide;

N-Methyl-N'-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-terephthalamide;

N,N-Dimethyl-N'-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-terephthalamide;

4-Acetyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-

phenyl)-benzamide;

4-(1H-Imidazol-2-yl)-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-benzamide;

2-(3-Isopropyl-phenoxy)-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-acetamide;

6-*tert*-Butyl-N-(3-{8-[4-(morpholine-4-carbonyl)-phenylamino]-imidazo[1,2-a]pyrazin-6-yl}-phenyl)-nicotinamide; or

4-(6-{3-[(6-*tert*-Butyl-pyridine-3-carbonyl)-amino]-phenyl}-imidazo[1,2a] pyrazin-8-ylamino)-benzoic acid.

INTERNATIONAL SEARCH REPORT

Inter | Application No
PCT/US2004/018227

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/519 A61P37/02

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/060492 A (CYTOPIA PTY LTD ; BURNS CHRISTOPHER JOHN (AU); WILKS ANDREW FREDERICK) 8 August 2002 (2002-08-08) page 52; example 3 pages 3-5,18 page 58; example 70	1-27, 50-79, 81-85
A	WO 02/076985 A (BONDINELL WILLIAM E ; LAGO MARIA AMPARO (US); SMITHKLINE BEECHAM CORP) 3 October 2002 (2002-10-03) page 1; claim 1	1-86
P,X	WO 03/089434 A (CELLULAR GENOMICS INC) 30 October 2003 (2003-10-30) figure 2; example 8 page 28; example bb	1-86

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 2004	30/12/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Grassi, D

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Intern[illegible] Application No
PCT/US2004/018227

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/022562 A (CELLULAR GENOMICS INC) 18 March 2004 (2004-03-18) claims 1,67,68	1-86

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

›rmation on patent family members

Intern Application No
PCT/US2004/018227

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02060492 A	08-08-2002	WO 02060492 A1	08-08-2002
		CA 2436487 A1	08-08-2002
		EP 1363702 A1	26-11-2003
		JP 2004528295 T	16-09-2004
		US 2004102455 A1	27-05-2004
WO 02076985 A	03-10-2002	WO 02076985 A1	03-10-2002
WO 03089434 A	30-10-2003	WO 03089434 A2	30-10-2003
		US 2003212073 A1	13-11-2003
WO 2004022562 A	18-03-2004	WO 2004022562 A1	18-03-2004
		US 2004067951 A1	08-04-2004

Form PCT/ISA/210 (patent family annex) (January 2004)

Electronic Patent Application Fee Transmittal

Application Number:	15019543
Filing Date:	09-Feb-2016
Title of Invention:	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS
First Named Inventor/Applicant Name:	Tjeerd A. Barf
Filer:	Andrea Reister/Jenn Augsburger
Attorney Docket Number:	015332.1182-US02

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
CORRECTION OF INVENTORSHIP ON MERITS	1819	1	600	600
		Total in USD ($)		**920**

Electronic Acknowledgement Receipt	
EFS ID:	28881434
Application Number:	15019543
International Application Number:	
Confirmation Number:	1984
Title of Invention:	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS
First Named Inventor/Applicant Name:	Tjeerd A. Barf
Customer Number:	26853
Filer:	Andrea Reister/Jenn Augsburger
Filer Authorized By:	Andrea Reister
Attorney Docket Number:	015332.1182-US02
Receipt Date:	10-APR-2017
Filing Date:	09-FEB-2016
Time Stamp:	15:51:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$920
RAM confirmation Number	041117INTEFSW00002547500740
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		15019543-RespOA-CorrInv-IDS.pdf	11734164 d33730e502d4ee063df823c7056bb805d042d60a	yes	31

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal Letter	1	2
Amendment/Req. Reconsideration-After Non-Final Reject	3	4
Specification	5	5
Claims	6	8
Applicant Arguments/Remarks Made in an Amendment	9	10
Request under Rule 48 correcting inventorship	11	12
Application Data Sheet	13	17
Oath or Declaration filed	18	25
Transmittal Letter	26	30
Information Disclosure Statement (IDS) Form (SB08)	31	31

Warnings:

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing

Information:

2	Foreign Reference	WO0017203A1.pdf	12258539 ca2696debf919226c09cfcc0951641ed66ff13bd	no	304

Warnings:

Information:

3	Foreign Reference	WO2005014599A1.pdf	6425981 14e32a38a2a07f268f55f07d15a2bf12240a313e	no	181
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	34143 a86109c234212ceed8fca12a63fb6919f2d06ffe	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	30452827		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

Docket No.: 015332.1182-US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Tjeerd A. Barf et al.

Application No.: 15/019,543 Confirmation No.: 1984

Filed: February 9, 2016 Art Unit: 1626

For: 4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

Examiner: Golam M. Shameem

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed are the following items for filing in connection with the above-referenced Patent Application:

1. Amendment in Response to Non-Final Office Action Under 37 C.F.R. § 1.111;
2. Request to Correct Inventorship Under 37 C.F.R. § 1.48;
3. Corrected Application Data Sheet;
4. Eight (8) executed Declarations For Utility or Design Application using an Application Data Sheet; and
5. Information Disclosure Statement with Form SB08 and two (2) foreign patent documents.

DC: 6393665-1

Please charge our Deposit Account No. 50-0740 in the amount of $920 in payment of the following fees: processing fee ($140); fee for correction of inventorship after first action ($600); and information disclosure statement fee ($180). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or that should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-0740, under Docket No. 015332.1182-US02.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 50-0740.

Dated: April 10, 2017

Respectfully submitted,

By _____

Einar Stole
Registration No.: 47,272
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Attorneys for Applicant

Document code: WFEE

United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/019,543	02/09/2016	Tjeerd A. Barf	015332.1182-US02	1984

26853 7590 01/10/2017

COVINGTON & BURLING, LLP
Attn: Patent Docketing
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956

EXAMINER	
SHAMEEM, GOLAM M	

ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
01/10/2017	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 15/019,543	Applicant(s) BARF ET AL.	
	Examiner GOLAM M M SHAMEEM	Art Unit 1626	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/30/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-18* is/are pending in the application.

5a) Of the above claim(s) *12-18* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-11* is/are rejected.

8)☒ Claim(s) *4* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☒ All b)☐ Some** c)☐ None of the:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Priority

This application is a DIV of 14/233,418 01/17/2014, is acknowledged.

Status of Claims

Claims 1-18 are currently pending in the application.

Receipt is acknowledged of amendment / response filed on November 30, 2016 and that has been entered.

Claims 12-18 are withdrawn from further consideration pursuant to 37 C.F.R. 1.142 (b) as being drawn to a non-elected subject matter.

Information Disclosure Statement

Receipt is acknowledged of Information Disclosure Statement (IDS), filed on 02/09/2016, which has been entered in the file.

Response to Election/Restriction

In response to the restriction requirement Applicants have elected Group I, which includes claims 1-11 drawn to a method of treating a Bruton's Tyrosine Kinase (Btk) mediated disorder in a subject comprising administering a therapeutically effective amount of a compound of Formula (I), is acknowledged.

Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a). Therefore, the requirement for restriction is still deemed proper and made it final.

Applicants preserve their right to file a divisional on the non-elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The expressions "treating a Bruton's Tyrosine Kinase (Btk) mediated disorder" (claim 1, line 1, page 98, and all other occurrences, if any) which broaden the enabling disclosure because it is unclear what **kind** of disease or "disorder" the applicant is intending to encompass with this broad expressions and/or how the disease or "disorder" is treated and therefore, the specification fails to provide sufficient support to treat any diseases or disorders, such as, rheumatoid arthritis, osteoarthritis, diabetes, Crohn's disease, multiple sclerosis, hepatitis etc. mediated by Bruton's Tyrosine Kinase (Btk) receptor. The type or mode of action and functionality of treatable diseases are not defined in the claims or anywhere in the specification so as to ascertain the metes and bounds of the claimed subject matter.

The recitations "treating a Bruton's Tyrosine Kinase (Btk) mediated disorder" which are not described in such a way as to satisfy the statutory requirements within the purview of 35 U.S.C. § 112 first paragraph because the specification does not provide essential description to carry out the invention and thus lacks enablement as well. As stated in the MPEP 2164.01 (a), there are many factors [1) The nature of the invention, 2) The state of the prior art, 3) The level of ordinary skill in the art, 4) The level of predictability in the art, 5) The amount of direction and guidance provided by the inventor, 6) The existence of working examples, 7) The breadth of the claims, and 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure (*In re Wands, 8 USPQ 2d 1400, 1404 (CAFC, 1988)*] to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." Therefore, it is not likely that a **single** compound would be predicted to be able to prevent, delay or treat the progression of any diseases or disorders associated with Bruton's Tyrosine Kinase (Btk) mediated receptor as claimed in the instant application. Based on the unpredictable nature of the invention and state of the prior art and the extreme breadth of the claims, one skilled in the art could not perform the claimed methods of use without undue experimentation, see *In re Armbruster 185 USPQ 152 CCPA 1975.* Thus, the specification fails to provide sufficient support of the broad use of the method claims 1-11 and to treat all kinds of diverse diseases or disorders associated with Bruton's Tyrosine Kinase (Btk) mediated receptor activity. Therefore, it is suggested to amend the claims within the context and scope of the claims [such as, **limiting specific diseases** and incorporating them in to claim 1, e.g., A method of treating a Bruton's Tyrosine Kinase (Btk) mediated disorder wherein the disorder is selected

from group consisting of--- (diseases recited on claims 2-5, that actually contemplated in the specification and that have **enough support**)] in order to overcome the rejection.

Objections

Claim 4 (numbered twice) is objected to because of numbering error. Correction is requested.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Golam Shameem, Ph.D. whose telephone number is (571) 272-0706. The examiner can normally be reached on Monday-Thursday from 7:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane, can be reached at (571) 272-0699. The Unofficial fax phone number for this Group is (703) 308-7922. The Official fax phone number for this Group is (571) 273-8300. When filing a FAX in Technology Center 1600, please indicate in the Header (upper right) "Official" for papers that are to be entered into the file, and "Unofficial" for draft documents and other communications with the PTO that are not for entry into the file of the application. This will expedite processing of your papers.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [joseph.mckane@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees will not communicate with applicant via Internet e-mail where sensitive data will be exchanged or where there exists a possibility that sensitive data could be identified unless there is of record an express waiver of the confidentiality

requirements under 35 U.S.C. 122 by the applicant. See the Interim Internet Usage Policy published by the Patent and Trademark Office Official Gazette on February 25, 1997 at 1195 OG 89.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR only. For more information about the pair system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (571) 272-1600.

/Golam M. M. Shameem/

Primary Examiner
Art Unit 1626
Technology Center 1600

Notice of References Cited	Application/Control No. 15/019,543	Applicant(s)/Patent Under Reexamination BARF ET AL.	
	Examiner GOLAM M M SHAMEEM	Art Unit 1626	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-9,290,504 B2	03-2016	Barf; Tjeerd A.	C07D487/04	1/1
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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BIB DATA SHEET

CONFIRMATION NO. 1984

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
15/019,543	02/09/2016	544	1626	015332.1182-US02

APPLICANTS

Merck Sharp & Dohme B.V., Haarlem, NETHERLANDS;

INVENTORS

Tjeerd A. Barf, Ravenstein, NETHERLANDS;
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Jan-Gerard Sterrenburg, Renkum, NETHERLANDS;
Jacobus C. H. M. Wijkmans, Oss, NETHERLANDS;

**** CONTINUING DATA ***************************

This application is a DIV of 14/233,418 01/17/2014 PAT 9290504
which is a 371 of PCT/EP2012/063552 07/11/2012
which claims benefit of 61/509,397 07/19/2011

**** FOREIGN APPLICATIONS ***************************

EUROPEAN PATENT OFFICE (EPO) 11174578.2 07/19/2011

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

02/24/2016

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /GOLAM M SHAMEEM/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NETHERLANDS	0	19	2

ADDRESS

COVINGTON & BURLING, LLP
Attn: Patent Docketing
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956
UNITED STATES

TITLE

4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

FILING FEE RECEIVED		
1740	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue)

BIB (Rev. 05/07).

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	6163	A61K31/4985.CPC.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/05/06 15:57
L2	89307	C07D487/04.CPC.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/05/06 15:57
L3	1359	1 AND 2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/05/06 15:57
L4	1359	3 AND ((A61K31/4985 OR A61K31/5377 OR C07D487/04).CPC.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/05/06 15:58
L5	1120	4 AND (BTK OR INHIBITORS OR THERAPHY OR PHARMACEUTICAL OR TREATMENT OR METHOD)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/05/06 16:00
L6	1059	4 AND (BTK OR INHIBITORS OR THERAPHY OR PHARMACEUTICAL OR TREATMENT)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/05/06 16:00
L7	991	4 AND (BTK OR INHIBITORS OR THERAPHY OR PHARMACEUTICAL)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/05/06 16:00
L8	664	4 AND (BTK OR INHIBITORS OR THERAPHY)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/05/06 16:00
L9	664	4 AND (BTK OR INHIBITORS)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/05/06 16:00
L10	114	4 AND (BTK)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2015/05/06 16:01

5/6/2015 4:01:27 PM

SANDOZ INC. IPR2023-00478 Ex. 1023, p. 573 of 891

14233418.trn05/06/2015

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NEWS	19	JUL 24	Batch search results for DGENE, USGENE and PCTGEN now available for 30 days
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NEWS	23	OCT 23	CPC Thesaurus based on official CPC Scheme

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14233418.trn05/06/2015

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 NEWS 24  DEC 22  2015 MeSH Thesaurus Installed in MEDLINE with a Special
                  Message for Customers Doing Pharmacovigilance Research
 NEWS 25  DEC 24  CAS Expands Coverage of Reactions from Dissertations in
                  CASREACT
 NEWS 26  DEC 24  Additional Experimental Spectra Now Available in CAS REGISTRY
                  in STN
 NEWS 27  JAN 8   Latest Version of Emtree Introduces 937 New Terms
 NEWS 28  JAN 9   Derwent World Patents Index: Latest Manual Code Revision
                  Goes Live
 NEWS 29  JAN 26  Revision of DWPI Fragmentation Codes for 2015
 NEWS 30  JAN 26  Annual MEDLINE Reload on STN Features Enhanced Clinical Trial
                  Information and the 2015 MeSH Thesaurus
 NEWS 31  MAR 23  Enhanced Coverage of Latin America (AR, MX) in Derwent World
                  Patent Index
 NEWS 32  APR 15  USPATFULL/USPAT2 Now Include Corporate Patent Applicant
                  Information

 NEWS EXPRESS 27 MAY 2014 CURRENT WINDOWS VERSION IS V8.5.2.1,
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=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files.  For example, the EXPAND
command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.25       0.25

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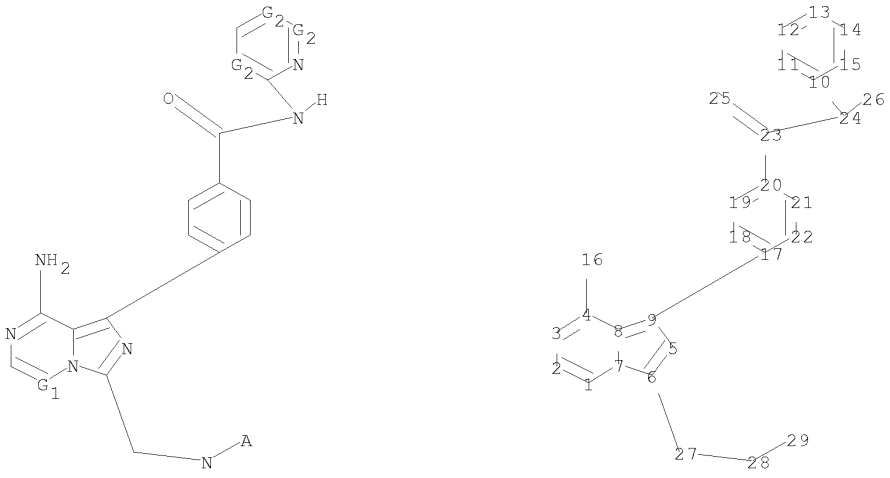
TSCA INFORMATION NOW CURRENT THROUGH JANUARY 9, 2015

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Uploading C:\Users\gshameem\Documents\14233418.str



chain nodes :
16 23 24 25 26 27 28 29
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 17 18 19 20 21 22
chain bonds :
4-16 6-27 9-17 10-24 20-23 23-24 23-25 24-26 27-28 28-29
ring bonds :
1-2 1-7 2-3 3-4 4-8 5-6 5-9 6-7 7-8 8-9 10-11 10-15 11-12 12-13 13-14
 14-15 17-18 17-22 18-19 19-20 20-21 21-22
exact/norm bonds :

14233418.trn05/06/2015

1-2 1-7 2-3 3-4 4-8 4-16 5-6 5-9 6-7 6-27 7-8 8-9 9-17 10-11 10-15
10-24 11-12 12-13 13-14 14-15 20-23 23-24 23-25 24-26 27-28 28-29
normalized bonds :
17-18 17-22 18-19 19-20 20-21 21-22
isolated ring systems :
containing 1 : 10 : 17 :

G1:C,N,CH

G2:C,O,S,N,CH

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:CLASS 17:Atom 18:Atom 19:Atom
20:Atom 21:Atom 22:Atom 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS
28:CLASS 29:CLASS

L1   STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1   STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using the Structure Drawing program.

=> s l1
SAMPLE SEARCH INITIATED 10:52:57 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -   58 TO ITERATE

100.0% PROCESSED   58 ITERATIONS   2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
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PROJECTED ITERATIONS: 704 TO   1616
PROJECTED ANSWERS: 2 TO   124

L2   2 SEA SSS SAM L1

=> s l1 sss full
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FULL SCREEN SEARCH COMPLETED -   1074 TO ITERATE

100.0% PROCESSED   1074 ITERATIONS   13 ANSWERS
SEARCH TIME: 00.00.01

L3   13 SEA SSS FUL L1

=> FIL HCAPLUS
COST IN U.S. DOLLARS   SINCE FILE   TOTAL

11:08<gshameem>Page 4

	ENTRY	SESSION
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FILE LAST UPDATED: 5 May 2015 (20150505/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Apr 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Sep 2014

HCAplus includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2015.

HCAplus now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

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L4           1 L3

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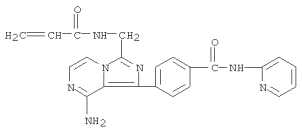
L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2013:129551 HCAPLUS
DOCUMENT NUMBER: 158:243948
TITLE: Preparation of imidazopyrazinylbenzamide derivatives and analogs for use as Btk inhibitors
INVENTOR(S): Barf, Tjeerd A.; Jans, Christiaan Gerardus Johannes Maria; De Man, Adrianus Petrus Antonius; Oubrie, Arthur A.; Raaijmakers, Hans C. A.; Rewinkel, Johannes
Bernardus Maria; Sterrenburg, Jan-Gerard; Wijkmans, Jacobus C. H. M.
PATENT ASSIGNEE(S): MSD Oss B.V., Neth.
SOURCE: PCT Int. Appl., 114pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013010868	A1	20130124	WO 2012-EP63552	20120711
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
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EP 2734522	A1	20140528	EP 2012-733505	20120711
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JP 2014520870	T	20140825	JP 2014-520606	20120711
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IN 2014CN00408	A	20150403	IN 2014-CN408	20140117
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PRIORITY APPLN. INFO.:			EP 2011-174578 A	20110719
			US 2011-61509397 P	20110719
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L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:243948; MARPAT 158:243948
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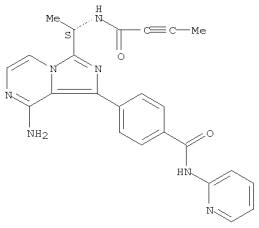
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AB Title compds. I [A = CH or N; D = N or CR7; E = N or CR8; each L independently = N or CR9; X = CH, N, O, or S; Y = CR6, N, O, or S; Z = bond, CH, or N; R1 = (un)substituted C(O)alkyl, S(O)alkyl, alkyl, etc.; R2 and R3 independently = H, alkyl, or cycloalkyl; R4, R6, and R8 independently = H or alkyl; R5 = H, halo, CN, (un)substituted alkyl, etc.; or R5 and R6 together may form an (un)substituted cycloalkenyl or heterocycloalkenyl; R7 and R9 independently = H, halo, or alkoxy; or R7 and R8 together with the C atom to which they are attached form an aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as brutons tyrosine kinase (Btk) inhibitors. Thus, e.g., II was prepared by a multistep procedure (preparation given). I were evaluated in Btk enzyme activity assays, e.g., II demonstrated an EC50 value of <10 nM.
IT 1420477-83-3P 1420477-84-4P 1420477-93-5P
1420478-02-9P 1420478-23-4P 1420478-29-0P
1420478-30-3P 1420478-49-4P 1420478-54-1P
1420478-59-6P 1420478-66-5P 1420478-67-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of imidazopyrazinylbenzamide derivs. and analogs for use as Btk inhibitors)
RN 1420477-83-3 HCAPLUS
CN Benzamide, 4-[8-amino-3-[[(1-oxo-2-propen-1-yl)amino]methyl]imidazo[1,5-a]pyrazin-1-yl]-N-2-pyridinyl- (CA INDEX NAME)



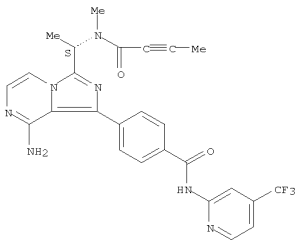
L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
RN 1420477-84-4 HCAPLUS
CN Benzamide, 4-[8-amino-3-[(1S)-1-[(1-oxo-2-butyn-1-yl)amino]ethyl]imidazo[1,5-a]pyrazin-1-yl]-N-2-pyridinyl- (CA INDEX NAME)

Absolute stereochemistry.



RN 1420477-93-5 HCAPLUS
CN Benzamide, 4-[8-amino-3-[(1S)-1-[methyl(1-oxo-2-butyn-1-yl)amino]ethyl]imidazo[1,5-a]pyrazin-1-yl]-N-[4-(trifluoromethyl)-2-pyridinyl]- (CA INDEX NAME)

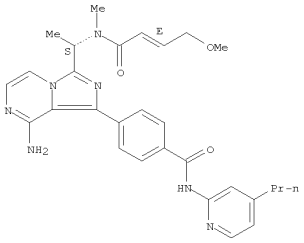
Absolute stereochemistry.



RN 1420478-02-9 HCAPLUS
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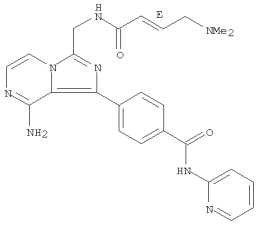
L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
(CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



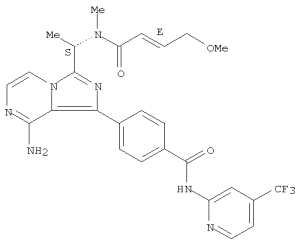
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Double bond geometry as shown.



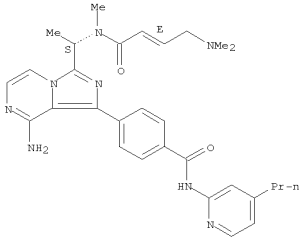
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L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
Absolute stereochemistry.
Double bond geometry as shown.



RN 1420478-30-3 HCAPLUS
CN Benzamide, 4-[8-amino-3-[(1S)-1-[[(2E)-4-(dimethylamino)-1-oxo-2-buten-1-yl]methylamino]ethyl]imidazo[1,5-a]pyrazin-1-yl]-N-(4-propyl-2-pyridinyl)- (CA INDEX NAME)

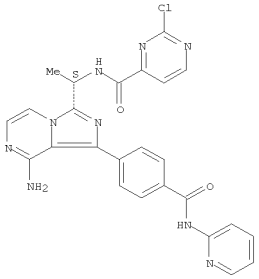
Absolute stereochemistry.
Double bond geometry as shown.



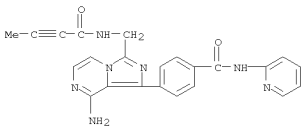
L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)

pyridinylamino)carbonyl]phenyl]imidazo[1,5-a]pyrazin-3-yl]ethyl]-2-chloro- (CA INDEX NAME)

Absolute stereochemistry.



RN 1420478-66-5 HCAPLUS
CN Benzamide, 4-[8-amino-3-[[(1-oxo-2-butyn-1-yl)amino]methyl]imidazo[1,5-a]pyrazin-1-yl]-N-2-pyridinyl- (CA INDEX NAME)

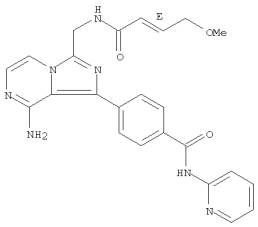


RN 1420478-67-6 HCAPLUS
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Absolute stereochemistry.

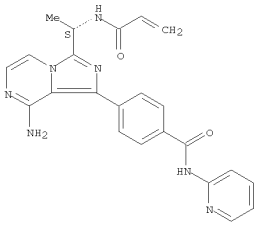
L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
RN 1420478-49-4 HCAPLUS
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Double bond geometry as shown.



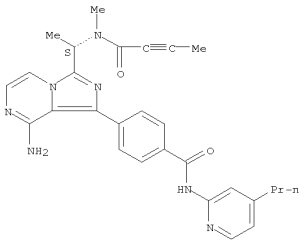
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Absolute stereochemistry.



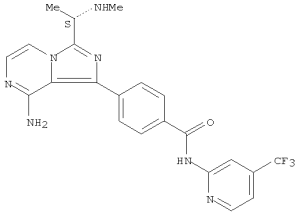
RN 1420478-59-6 HCAPLUS
CN 4-Pyrimidinecarboxamide, N-[(1S)-1-[8-amino-1-[4-[(2-

L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)



IT 1420479-17-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of imidazopyrazinylbenzamide derivs. and analogs for use as Btk inhibitors)
RN 1420479-17-9 HCAPLUS
CN Benzamide, 4-[8-amino-3-[(1S)-1-(methylamino)ethyl]imidazo[1,5-a]pyrazin-1-yl]-N-[4-(trifluoromethyl)-2-pyridinyl]- (CA INDEX NAME)

Absolute stereochemistry.



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REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS

L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

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FULL ESTIMATED COST | 20.61 | 252.27

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DICTIONARY FILE UPDATES: 5 MAY 2015 HIGHEST RN 1698944-98-7

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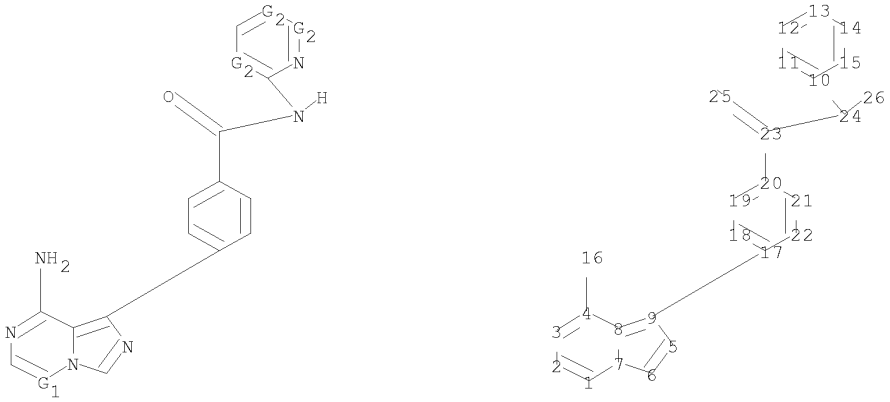
TSCA INFORMATION NOW CURRENT THROUGH JANUARY 9, 2015

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chain nodes :
16 23 24 25 26
ring nodes :

```
1  2  3  4  5  6  7  8  9  10  11  12  13  14  15  17  18  19  20  21  22
chain bonds :
4-16  9-17  10-24  20-23  23-24  23-25  24-26
ring bonds :
1-2  1-7  2-3  3-4  4-8  5-6  5-9  6-7  7-8  8-9  10-11  10-15  11-12  12-13  13-14
 14-15  17-18  17-22  18-19  19-20  20-21  21-22
exact/norm bonds :
1-2  1-7  2-3  3-4  4-8  4-16  5-6  5-9  6-7  7-8  8-9  9-17  10-11  10-15  10-24
11-12  12-13  13-14  14-15  20-23  23-24  23-25  24-26
normalized bonds :
17-18  17-22  18-19  19-20  20-21  21-22
isolated ring systems :
containing 1 : 10 : 17 :


G1:C,N,CH

G2:C,O,S,N,CH

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:Atom  12:Atom  13:Atom  14:Atom  15:Atom  16:CLASS  17:Atom  18:Atom  19:Atom
20:Atom  21:Atom  22:Atom  23:CLASS  24:CLASS  25:CLASS  26:CLASS



L5      STRUCTURE UPLOADED

=> d l5
L5 HAS NO ANSWERS
L5              STR

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

Structure attributes must be viewed using the Structure Drawing program.


=> s l5
SAMPLE SEARCH INITIATED 10:55:48 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -       63 TO ITERATE

100.0% PROCESSED       63 ITERATIONS                              50 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          784 TO     1736
PROJECTED ANSWERS:             671 TO     1569

L6           50 SEA SSS SAM L5

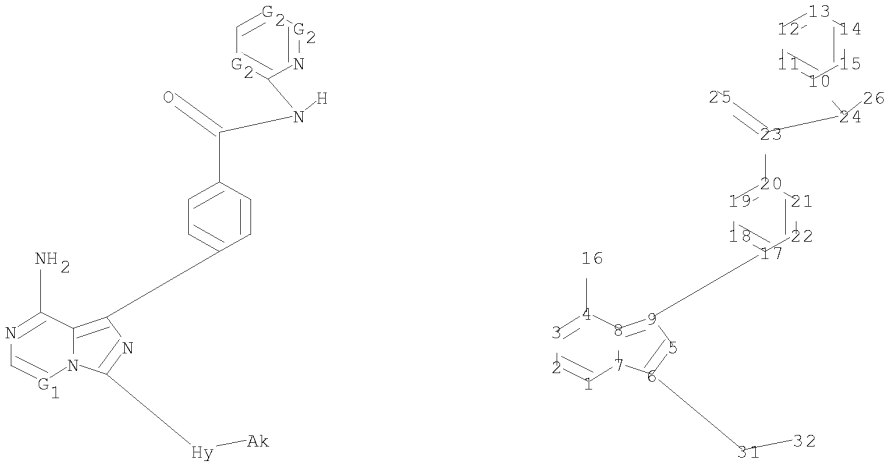
=> s l5 sss full
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FULL SEARCH INITIATED 10:55:54 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 1143 TO ITERATE

100.0% PROCESSED 1143 ITERATIONS 1034 ANSWERS
SEARCH TIME: 00.00.01

L7 1034 SEA SSS FUL L5

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chain nodes :
16 23 24 25 26 31 32
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 17 18 19 20 21 22
chain bonds :
4-16 6-31 9-17 10-24 20-23 23-24 23-25 24-26 31-32
ring bonds :
1-2 1-7 2-3 3-4 4-8 5-6 5-9 6-7 7-8 8-9 10-11 10-15 11-12 12-13 13-14
14-15 17-18 17-22 18-19 19-20 20-21 21-22
exact/norm bonds :
1-2 1-7 2-3 3-4 4-8 4-16 5-6 5-9 6-7 6-31 7-8 8-9 9-17 10-11 10-15
10-24 11-12 12-13 13-14 14-15 20-23 23-24 23-25 24-26 31-32
normalized bonds :
17-18 17-22 18-19 19-20 20-21 21-22
isolated ring systems :
containing 1 : 10 : 17 :

G1:C,N,CH

G2:C,O,S,N,CH

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:CLASS 17:Atom 18:Atom 19:Atom
20:Atom 21:Atom 22:Atom 23:CLASS 24:CLASS 25:CLASS 26:CLASS 31:CLASS
32:CLASS

```
L8      STRUCTURE UPLOADED

=> d l8
L8 HAS NO ANSWERS
L8              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using the Structure Drawing program.


=> s l8
SAMPLE SEARCH INITIATED 10:58:15 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -       63 TO ITERATE

100.0% PROCESSED       63 ITERATIONS                            46 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          784 TO     1736
PROJECTED ANSWERS:             514 TO     1326

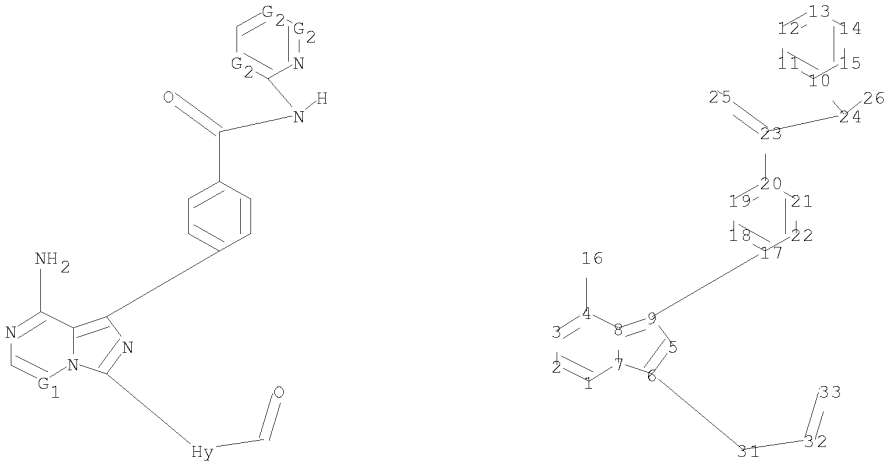
L9           46 SEA SSS SAM L8

=> s l8 sss full
FULL SEARCH INITIATED 10:58:30 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     1143 TO ITERATE

100.0% PROCESSED     1143 ITERATIONS                          749 ANSWERS
SEARCH TIME: 00.00.01

L10         749 SEA SSS FUL L8

=>
Uploading C:\Users\gshameem\Documents\14233418c.str
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chain nodes :
16 23 24 25 26 31 32 33
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 17 18 19 20 21 22
chain bonds :
4-16 6-31 9-17 10-24 20-23 23-24 23-25 24-26 31-32 32-33
ring bonds :
1-2 1-7 2-3 3-4 4-8 5-6 5-9 6-7 7-8 8-9 10-11 10-15 11-12 12-13 13-14
14-15 17-18 17-22 18-19 19-20 20-21 21-22
exact/norm bonds :
1-2 1-7 2-3 3-4 4-8 4-16 5-6 5-9 6-7 6-31 7-8 8-9 9-17 10-11 10-15
10-24 11-12 12-13 13-14 14-15 20-23 23-24 23-25 24-26 31-32 32-33
normalized bonds :
17-18 17-22 18-19 19-20 20-21 21-22
isolated ring systems :
containing 1 : 10 : 17 :

G1:C,N,CH

G2:C,O,S,N,CH

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:CLASS 17:Atom 18:Atom 19:Atom
20:Atom 21:Atom 22:Atom 23:CLASS 24:CLASS 25:CLASS 26:CLASS 31:CLASS
32:CLASS 33:CLASS

L11 STRUCTURE UPLOADED

```
=> d l11
L11 HAS NO ANSWERS
L11             STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using the Structure Drawing program.


=> s l11
SAMPLE SEARCH INITIATED 10:59:58 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -       63 TO ITERATE

100.0% PROCESSED       63 ITERATIONS                              38 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:           784 TO     1736
PROJECTED ANSWERS:              391 TO     1129

L12          38 SEA SSS SAM L11

=> s l11 sss full
FULL SEARCH INITIATED 11:00:06 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     1143 TO ITERATE

100.0% PROCESSED     1143 ITERATIONS                            608 ANSWERS
SEARCH TIME: 00.00.01

L13         608 SEA SSS FUL L11

=> FIL HCAPLUS
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     697.03     949.30

FILE 'HCAPLUS' ENTERED AT 11:00:13 ON 06 MAY 2015
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FILE COVERS 1907 - 6 May 2015 VOL 162 ISS 20
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FILE LAST UPDATED: 5 May 2015 (20150505/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Apr 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Sep 2014

HCAplus includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2015.

HCAplus now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d his

     (FILE 'HOME' ENTERED AT 10:52:02 ON 06 MAY 2015)

     FILE 'REGISTRY' ENTERED AT 10:52:21 ON 06 MAY 2015
L1             STRUCTURE UPLOADED
L2               2 S L1
L3              13 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 10:53:11 ON 06 MAY 2015
L4               1 S L3

     FILE 'REGISTRY' ENTERED AT 10:55:26 ON 06 MAY 2015
L5             STRUCTURE UPLOADED
L6              50 S L5
L7            1034 S L5 SSS FULL
L8             STRUCTURE UPLOADED
L9              46 S L8
L10            749 S L8 SSS FULL
L11            STRUCTURE UPLOADED
L12             38 S L11
L13            608 S L11 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 11:00:13 ON 06 MAY 2015

=> s l7
L14             6 L7

=> s l10
L15             6 L10

=> s l13
L16             4 L13

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      35176506 PY<=2011
L17             0 L14 AND PY<=2011
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14233418.trn05/06/2015

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=> s l15 and py<=2011
      35176506 PY<=2011
L18           0 L15 AND PY<=2011

=> s l16 and py<=2011
      35176506 PY<=2011
L19           0 L16 AND PY<=2011

=> d l14 ibib abs total
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L14 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2014:1236257 HCAPLUS
DOCUMENT NUMBER: 161:275941
TITLE: Pyrazolopyrimidines and imidazolopyrazine as Btk inhibitors and their preparation
INVENTOR(S): Wu, Hao; Kim, Ronald M.; Liu, Jian; Liu, Shilan; Yang,
Chundao; Zheng, Shuling
PATENT ASSIGNEE(S): Merck Sharp & Dohme Corp., USA
SOURCE: PCT Int. Appl., 110pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014116504	A1	20140731	WO 2014-US11950	20140117
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
WO 2014113942	A1	20140731	WO 2013-CN70898	20130123
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				

PRIORITY APPLN. INFO.: WO 2013-CN70898 A 20130123

OTHER SOURCE(S): MARPAT 161:275941
GI

L14 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention provides compds. of formula I and II as Bruton's Tyrosine Kinase (Btk) inhibitor and pharmaceutically acceptable salts, and pharmaceutical comps. comprising these compds. and to their use in therapy. Compds. of formula I and II wherein R5 is H, CN, (un)substituted C1-4 alkyl and (un)substituted C1-5 alkoxy; M is triazolopiperidinyl, tetrahydroindazolyl, and triazolopyrazinyl; and pharmaceutically acceptable salts thereof, are claimed. Example compound III was prepared by cross-coupling reaction of 4-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)-1-methyl-4,5,6,7-tetrahydro-1H-indazol-4-ol with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide. The invention compds. were evaluated for their Btk inhibitory activity. From the assay, it was determined that compound III exhibited IC50 value of 7.2 nM.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2014:1232980 HCAPLUS
DOCUMENT NUMBER: 161:275940
TITLE: Pyrazolopyrimidines and imidazolopyrazine as Btk inhibitors and their preparation
INVENTOR(S): Wu, Hao; Kim, Ronald M.; Liu, Jian; Liu, Shilan; Yang,
Chundao; Zheng, Shuling
PATENT ASSIGNEE(S): Merck Sharp & Dohme Corp., USA
SOURCE: PCT Int. Appl., 113pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014113942	A1	20140731	WO 2013-CN70898	20130123
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
WO 2014116504	A1	20140731	WO 2014-US11950	20140117
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				

PRIORITY APPLN. INFO.: WO 2013-CN70898 A 20130123

OTHER SOURCE(S): CASREACT 161:275940; MARPAT 161:275940
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention provides compds. of formula I and II as Bruton's Tyrosine Kinase (Btk) inhibitor and pharmaceutically acceptable salts, and

L14 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
pharmaceutical comps. comprising these compds. and to their use in therapy. Compds. of formula I and II wherein R5 is H, CN, (un)substituted C1-4 alkyl and (un)substituted C1-5 alkoxy; M is triazolopiperidinyl, tetrahydroindazolyl, and triazolopyrazinyl; and pharmaceutically acceptable salts thereof, are claimed. Example compd. III was prepd. by cross-coupling reaction of 4-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)-1-methyl-4,5,6,7-tetrahydro-1H-indazol-4-ol with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide. The invention compds. were evaluated for their Btk inhibitory activity. From the assay, it was detd. that compd. III exhibited IC50 value of 7.2 nM.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2014:1203970 HCAPLUS
DOCUMENT NUMBER: 161:275936
TITLE: Preparation of bicyclic heterocycles as Btk inhibitors for therapy
INVENTOR(S): Kim, Ronald M.; Liu, Jian; Gao, Xiaolei; Boga, Sobhana
Babu; Guiadeen, Deodialsingh; Kozlowski, Joseph A.; Yu, Wensheng; Anand, Rajan; Yu, Younong; Selyutin, Oleg B.; Gao, Ying-Duo; Wu, Hao; Liu, Shilan; Yang, Chundao; Wang, Hongjian
PATENT ASSIGNEE(S): Wuxi Apptec (Shanghai) Co., Ltd., Peop. Rep. China; Merck Sharp & Dohme Corp.
SOURCE: U.S. Pat. Appl. Publ., 217pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140206681	A1	20140724	US 2014-14160587	20140122
WO 2014113932	A1	20140731	WO 2013-CN70876	20130123
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
WO 2014114185	A1	20140731	WO 2014-CN82	20140122
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
PRIORITY APPLN. INFO.:			WO 2013-CN70876	A 20130123

L14 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
CN 2014-10010914 A 20140109

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 161:275936
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides Bruton's Tyrosine Kinase (Btk) inhibitor compds. according to Formula I (wherein in bicyclic ring E-G, A1-A4 are independently (un)substituted C or N, with at least 1 being N; R5 is H, halo, aryl, etc.; R12 is H, C1-3 alkyl, etc.; R13 is H and C1-4 alkoxy; in aromatic ring K, B1-B4 are N or (un)substituted CH; in heteroarom. ring L, W is CH, N or S, X is (un)substituted CH, N, O or S, Y is (un)substituted CH, (un)substituted NH, O or S, and Z is (un)substituted CH, N or a bond; Q is C(O), (un)substituted CH2, etc.; T is (un)substituted CH2, O, (un)substituted NH, or a bond; U is (un)substituted CH2, O, or (un)substituted NH; V is (un)substituted CH2, O, or a bond; Rc is H, halo, C1-6 alkyl, etc.) or a pharmaceutically acceptable salt thereof or to pharmaceutical compns. comprising these compds. and to their use in therapy. In particular, the present invention relates to the use of I as Btk inhibitors in the treatment of Btk mediated disorders. Synthetic procedures for preparing I are exemplified. Example compound II was prepared from intermediate III by cyclization using carbonyldiimidazole and deprotection. Example compds. of the invention were tested as BTK enzymic inhibitors using a LANCE TR-FRET assay. In this assay II had an IC50 value of 5.5 nM.

L14 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2013:129551 HCAPLUS
DOCUMENT NUMBER: 158:243948
TITLE: Preparation of imidazopyrazinylbenzamide derivatives and analogs for use as Btk inhibitors
INVENTOR(S): Barf, Tjeerd A.; Jans, Christiaan Gerardus Johannes Maria; De Man, Adrianus Petrus Antonius; Oubrie, Arthur A.; Raaijmakers, Hans C. A.; Rewinkel, Johannes
Bernardus Maria; Sterrenburg, Jan-Gerard; Wijkmans, Jacobus C. H. M.
PATENT ASSIGNEE(S): MSD Oss B.V., Neth.
SOURCE: PCT Int. Appl., 114pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013010868	A1	20130124	WO 2012-EP63552	20120711
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2841886	A1	20130124	CA 2012-2841886	20120711
AU 2012285987	A1	20140206	AU 2012-285987	20120711
KR 2014036324	A	20140325	KR 2014-7003955	20120711
IL 230511	A	20140331	IL 2012-230511	20120711
EP 2734522	A1	20140528	EP 2012-733505	20120711
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
CN 103889987	A	20140625	CN 2012-80045383	20120711
JP 2014520870	T	20140825	JP 2014-520606	20120711
MX 2014000746	A	20140507	MX 2014-746	20140117
US 20140155385	A1	20140605	US 2014-14233418	20140117
IN 2014CN00408	A	20150403	IN 2014-CN408	20140117
CR 20140030	A	20140603	CR 2014-30	20140120
PRIORITY APPLN. INFO.:			EP 2011-174578	A 20110719
			US 2011-61509397	P 20110719
			WO 2012-EP63552	W 20120711

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:243948; MARPAT 158:243948
GI

L14 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

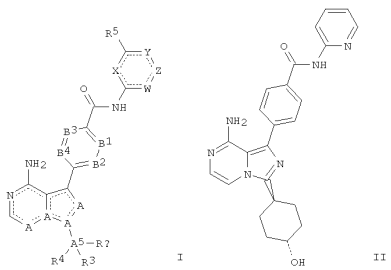
AB Title compds. I [A = CH or N; D = N or CR7; E = N or CR8; each L independently = N or CR9; X = CH, N, O, or S; Y = CR6, N, O, or S; Z = bond, CH, or N; R1 = (un)substituted C(O)alkyl, S(O)alkyl, alkyl, etc.; R2 and R3 independently = H, alkyl, or cycloalkyl; R4, R6, and R8 independently = H or alkyl; R5 = H, halo, CN, (un)substituted alkyl, etc.; or R5 and R6 together may form an (un)substituted cycloalkenyl or heterocycloalkenyl; R7 and R9 independently = H, halo, or alkoxy; or R7 and R8 together with the C atom to which they are attached form an aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as brutons tyrosine kinase (Btk) inhibitors. Thus, e.g., II was prepared by a multistep procedure (preparation given). I were evaluated in Btk enzyme activity assays, e.g., II demonstrated an EC50 value of <10 nM.
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2013:125799 HCAPLUS
DOCUMENT NUMBER: 158:216028
TITLE: Bicyclic heterocycles as BTK inhibitors and their preparation
INVENTOR(S): De Man, Adrianus P. A.; Sterrenburg, Jan-Gerard; Raaijmakers, Hans C. A.; Kaptein, Allard; Oubrie, Arthur; Rewinkel, Johannes B. M.; Jans, Christiaan G. J. M.; Wijkmans, Jacobus C. H. M.; Barf, Tjeerd A.; Cooper, Alan B.; Kim, Ronald M.; Boga, Sobhana Babu; Zhu, Hugh Y.; Gao, Xiaolei; Yao, Xin; Anand, Rajan; Wu, Hao; Liu, Shilan; Yang, Chundao; Alhassan, Abdul-Basit; Wang, James; Yu, Younong; Liu, Jian; Vaccaro, Henry M.
PATENT ASSIGNEE(S): Merck Sharp & Dohme Corp., USA; MSD Oss B.V.
SOURCE: PCT Int. Appl., 476pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013010380	A1	20130124	WO 2012-CN971	20120719
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
EP 2548877	A1	20130123	EP 2011-174570	20110719
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
CA 2841899	A1	20130124	CA 2012-2841899	20120719
AU 2012286426	A1	20140130	AU 2012-286426	20120719
EP 2734529	A1	20140528	EP 2012-814549	20120719
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR				
KR 2014068020	A	20140605	KR 2014-7003924	20120719
CN 103917545	A	20140709	CN 2012-80045511	20120719
JP 2014520866	T	20140825	JP 2014-520495	20120719
IN 2014CN00339	A	20141212	IN 2014-CN339	20140115
MX 2014000747	A	20141015	MX 2014-747	20140117
US 20140221333	A1	20140807	US 2014-14233478	20140404

L14 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
PRIORITY APPLN. INFO.: EP 2011-174570 A 20110719
US 2011-61509446 P 20110719
WO 2012-CN971 W 20120719

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:216028; MARPAT 158:216028
GI



AB Provided are 6-5 membered fused pyridine ring compds. of formula I or pharmaceutically acceptable salts thereof, pharmaceutical compns. comprising these compds. and their use in therapy. In particular, provided is the use of 6-5 membered fused pyridine ring compds. in the treatment of Bruton's Tyrosine Kinase (BTK) mediated disorders. Compds. of formula I wherein dashed bonds are single and double bonds forming an aromatic ring system; each A is independently C, CH, CR11 and N, forming a bicyclic ring system containing at least one nitrogen per ring; A5 is C and N; B1 is N and CR7; B2 is N and CR8; B3 is N and CR9; B4 is N and CR10; W is CH and N; X is CH, N, O, S and a bond; Y is CR6, N, O and S; Z is CH, N and a bond; Rx is H, C1-6 alkyl, C1-5 heteroalkyl, etc.; R3 H, C1-3 alkyl and C3-7 cycloalkyl; R4 is H, OH, C1-3 alkyl and C1-3 alkoxy; A5R3R4Rx may be taken together to form azabicycloheptyl; R3R4 may be taken together to form C3-6 cycloalkyl; R5 is H, halo, CN, C1-4 alkyl, etc.; R6 is H, halo, C1-3 alkyl, CN, etc.; R5R6 may be taken together to form (un)substituted C3-7 cycloalkenyl and C2-6 heterocycloalkenyl; R7, R8, R9 and R10 are independently H, halo, OH, CF3, etc.; R7R8 may be taken together to form

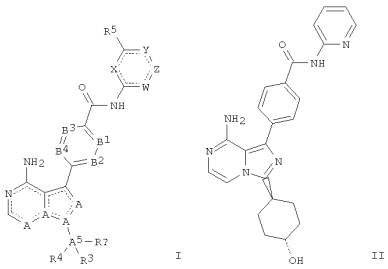
L14 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
C6-10 aryl and C1-9 heterocycyl; R11 is D, H, halo, TMS, CN, etc.; pharmaceutically acceptable salts thereof, are claimed. Example compd. II was prepd. by cross-coupling reaction of trans-4-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)cyclohexyl acetate with 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid followed by hydrolysis. All the invention compds. were evaluated for their BTK inhibitory activity. From the assay, it was detd. that compd. II exhibited an EC50 value in the range of ≥ 10 nM to < 100 nM.
OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2013:125798 HCAPLUS
DOCUMENT NUMBER: 158:216027
TITLE: Bicyclic heterocycles as BTK inhibitors and their preparation
INVENTOR(S): De Man, Adrianus Petrus Antonius; Sterrenburg, Jan-Gerard; Raaijmakers, Hans C. A.; Kaptein, Allard; Oubrie, Arthur A.; Rewinkel, Johannes Bernardus Maria; Jans, Christiaan Gerardus Johannes Maria; Wijkmans, Jacobus C. H. M.; Barf, Tjeerd A.; Gao, Xiaolei; Boga, Sobhana Babu; Yao, Xin; Zhu, Hugh Y.; Cooper, Allen B.; Kim, Ronald M.
PATENT ASSIGNEE(S): MSD Oss B.V., Neth.
SOURCE: Eur. Pat. Appl., 175pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 2548877	A1	20130123	EP 2011-174570	20110719
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CA 2841899	A1	20130124	CA 2012-2841899	20120719
WO 2013010380	A1	20130124	WO 2012-CN971	20120719
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
AU 2012286426	A1	20140130	AU 2012-286426	20120719
EP 2734529	A1	20140528	EP 2012-814549	20120719
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR				
KR 2014068020	A	20140605	KR 2014-7003924	20120719
CN 103917545	A	20140709	CN 2012-80045511	20120719
JP 2014520866	T	20140825	JP 2014-520495	20120719
MX 2014000747	A	20141015	MX 2014-747	20140117
US 20140221333	A1	20140807	US 2014-14233478	20140404

PRIORITY APPLN. INFO.: EP 2011-174570 A 20110719
US 2011-61509446 P 20110719
WO 2012-CN971 W 20120719

L14 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
GI



I

II

AB Provided are 6-5 membered fused pyridine ring compds. of formula I or pharmaceutically acceptable salts thereof, pharmaceutical compns. comprising these compds. and their use in therapy. In particular, provided is the use of 6-5 membered fused pyridine ring compds. in the treatment of Bruton's Tyrosine Kinase (BTK) mediated disorders. Compds. of formula I wherein dashed bonds are single and double bonds forming an aromatic ring system; each A is independently C, CH, CR11 and N, forming a bicyclic ring system containing at least one nitrogen per ring; A5 is C and N; B1 is N and CR7; B2 is N and CR8; B3 is N and CR9; B4 is N and CR10; W is CH and N; X is CH, N, O, S and a bond; Y is CR6, N, O and S; Z is CH, N and a bond; Rx is H, C1-6 alkyl, C1-5 heteroalkyl, etc.; R3 H, C1-3 alkyl and C3-7 cycloalkyl; R4 is H, OH, C1-3 alkyl and C1-3 alkoxy; A5R3R4Rx may be taken together to form azabicycloheptyl; R3R4 may be taken together to form C3-6 cycloalkyl; R5 is H, halo, CN, C1-4 alkyl, etc.; R6 is H, halo, C1-3 alkyl, CN, etc.; R5R6 may be taken together to form (un)substituted C3-7 cycloalkenyl and C2-6 heterocycloalkenyl; R7, R8, R9 and R10 are independently H, halo, OH, CF3, etc.; R7R8 may be taken together to form C6-10 aryl and C1-9 heterocyclyl; R11 is D, H, halo, TMS, CN, etc.; pharmaceutically acceptable salts thereof, are claimed. Example compound II was prepared by cross-coupling reaction of trans-4-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)cyclohexyl acetate with

L14 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid followed by hydrolysis. All the invention compds. were evaluated for their BTK inhibitory activity. From the assay, it was detd. that compd. II exhibited an EC50 value in the range of ≥ 10 nM to < 100 nM.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
(1 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

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11:08<gshameem>Page 21

L15 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2014:1236257 HCAPLUS
DOCUMENT NUMBER: 161:275941
TITLE: Pyrazolopyrimidines and imidazolopyrazine as Btk inhibitors and their preparation
INVENTOR(S): Wu, Hao; Kim, Ronald M.; Liu, Jian; Liu, Shilan; Yang,
Chundao; Zheng, Shuling
PATENT ASSIGNEE(S): Merck Sharp & Dohme Corp., USA
SOURCE: PCT Int. Appl., 110pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014116504	A1	20140731	WO 2014-US11950	20140117
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
WO 2014113942	A1	20140731	WO 2013-CN70898	20130123
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				

PRIORITY APPLN. INFO.: WO 2013-CN70898 A 20130123

OTHER SOURCE(S): MARPAT 161:275941
GI

L15 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention provides compds. of formula I and II as Bruton's Tyrosine Kinase (Btk) inhibitor and pharmaceutically acceptable salts, and pharmaceutical comps. comprising these compds. and to their use in therapy. Compds. of formula I and II wherein R5 is H, CN, (un)substituted C1-4 alkyl and (un)substituted C1-5 alkoxy; M is triazolopiperidinyl, tetrahydroindazolyl, and triazolopyrazinyl; and pharmaceutically acceptable salts thereof, are claimed. Example compound III was prepared by cross-coupling reaction of 4-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)-1-methyl-4,5,6,7-tetrahydro-1H-indazol-4-ol with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide. The invention compds. were evaluated for their Btk inhibitory activity. From the assay, it was determined that compound III exhibited IC50 value of 7.2 nM.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2014:1232980 HCAPLUS
DOCUMENT NUMBER: 161:275940
TITLE: Pyrazolopyrimidines and imidazolopyrazine as Btk inhibitors and their preparation
INVENTOR(S): Wu, Hao; Kim, Ronald M.; Liu, Jian; Liu, Shilan; Yang,
Chundao; Zheng, Shuling
PATENT ASSIGNEE(S): Merck Sharp & Dohme Corp., USA
SOURCE: PCT Int. Appl., 113pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014113942	A1	20140731	WO 2013-CN70898	20130123
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
WO 2014116504	A1	20140731	WO 2014-US11950	20140117
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				

PRIORITY APPLN. INFO.: WO 2013-CN70898 A 20130123

OTHER SOURCE(S): CASREACT 161:275940; MARPAT 161:275940
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention provides compds. of formula I and II as Bruton's Tyrosine Kinase (Btk) inhibitor and pharmaceutically acceptable salts, and pharmaceutical comps. comprising these compds. and to their use in therapy. Compds. of formula I and II wherein R5 is H, CN, (un)substituted C1-4 alkyl and (un)substituted C1-5 alkoxy; M is triazolopiperidinyl, tetrahydroindazolyl, and triazolopyrazinyl; and pharmaceutically acceptable salts thereof, are claimed. Example compd. III was prepd. by cross-coupling reaction of 4-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)-1-methyl-4,5,6,7-tetrahydro-1H-indazol-4-ol with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide. The invention compds. were evaluated for their Btk inhibitory activity. From the assay, it was detd. that compd. III exhibited IC50 value of 7.2 nM.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2014:1203970 HCAPLUS
DOCUMENT NUMBER: 161:275936
TITLE: Preparation of bicyclic heterocycles as Btk inhibitors
for therapy
INVENTOR(S): Kim, Ronald M.; Liu, Jian; Gao, Xiaolei; Boga, Sobhana
Babu; Guiadeen, Deodialsingh; Kozlowski, Joseph A.; Yu, Wensheng; Anand, Rajan; Yu, Younong; Selyutin, Oleg B.; Gao, Ying-Duo; Wu, Hao; Liu, Shilan; Yang, Chundao; Wang, Hongjian
PATENT ASSIGNEE(S): Wuxi Apptec (Shanghai) Co., Ltd., Peop. Rep. China; Merck Sharp & Dohme Corp.
SOURCE: U.S. Pat. Appl. Publ., 217pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140206681	A1	20140724	US 2014-14160587	20140122
WO 2014113932	A1	20140731	WO 2013-CN70876	20130123
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
WO 2014114185	A1	20140731	WO 2014-CN82	20140122
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
PRIORITY APPLN. INFO.:			WO 2013-CN70876	A 20130123

L15 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
CN 2014-10010914 A 20140109

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 161:275936
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides Bruton's Tyrosine Kinase (Btk) inhibitor compds. according to Formula I (wherein in bicyclic ring E-G, A1-A4 are independently (un)substituted C or N, with at least 1 being N; R5 is H, halo, aryl, etc.; R12 is H, C1-3 alkyl, etc.; R13 is H and C1-4 alkoxy; in aromatic ring K, B1-B4 are N or (un)substituted CH; in heteroarom. ring L, W is CH, N or S, X is (un)substituted CH, N, O or S, Y is (un)substituted CH, (un)substituted NH, O or S, and Z is (un)substituted CH, N or a bond; Q is C(O), (un)substituted CH2, etc.; T is (un)substituted CH2, O, (un)substituted NH, or a bond; U is (un)substituted CH2, O, or (un)substituted NH; V is (un)substituted CH2, O, or a bond; Rc is H, halo, C1-6 alkyl, etc.) or a pharmaceutically acceptable salt thereof or to pharmaceutical compns. comprising these compds. and to their use in therapy. In particular, the present invention relates to the use of I as Btk inhibitors in the treatment of Btk mediated disorders. Synthetic procedures for preparing I are exemplified. Example compound II was prepared from intermediate III by cyclization using carbonyldiimidazole and deprotection. Example compds. of the invention were tested as BTK enzymic inhibitors using a LANCE TR-FRET assay. In this assay II had an IC50 value of 5.5 nM.

L15 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2013:129551 HCAPLUS
DOCUMENT NUMBER: 158:243948
TITLE: Preparation of imidazopyrazinylbenzamide derivatives and analogs for use as Btk inhibitors
INVENTOR(S): Barf, Tjeerd A.; Jans, Christiaan Gerardus Johannes Maria; De Man, Adrianus Petrus Antonius; Oubrie, Arthur A.; Raaijmakers, Hans C. A.; Rewinkel, Johannes Bernardus Maria; Sterrenburg, Jan-Gerard; Wijkmans, Jacobus C. H. M.
PATENT ASSIGNEE(S): MSD Oss B.V., Neth.
SOURCE: PCT Int. Appl., 114pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013010868	A1	20130124	WO 2012-EP63552	20120711
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2841886	A1	20130124	CA 2012-2841886	20120711
AU 2012285987	A1	20140206	AU 2012-285987	20120711
KR 2014036324	A	20140325	KR 2014-7003955	20120711
IL 230511	A	20140331	IL 2012-230511	20120711
EP 2734522	A1	20140528	EP 2012-733505	20120711
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
CN 103889987	A	20140625	CN 2012-80045383	20120711
JP 2014520870	T	20140825	JP 2014-520606	20120711
MX 2014000746	A	20140507	MX 2014-746	20140117
US 20140155385	A1	20140605	US 2014-14233418	20140117
IN 2014CN00408	A	20150403	IN 2014-CN408	20140117
CR 20140030	A	20140603	CR 2014-30	20140120
PRIORITY APPLN. INFO.:			EP 2011-174578	A 20110719
			US 2011-61509397	P 20110719
			WO 2012-EP63552	W 20120711

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:243948; MARPAT 158:243948
GI

L15 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

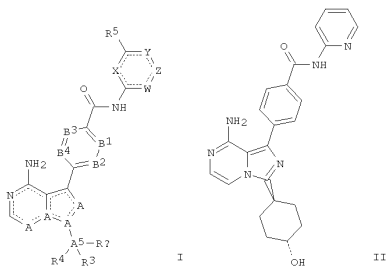
AB Title compds. I [A = CH or N; D = N or CR7; E = N or CR8; each L independently = N or CR9; X = CH, N, O, or S; Y = CR6, N, O, or S; Z = bond, CH, or N; R1 = (un)substituted C(O)alkyl, S(O)alkyl, alkyl, etc.; R2 and R3 independently = H, alkyl, or cycloalkyl; R4, R6, and R8 independently = H or alkyl; R5 = H, halo, CN, (un)substituted alkyl, etc.; or R5 and R6 together may form an (un)substituted cycloalkenyl or heterocycloalkenyl; R7 and R9 independently = H, halo, or alkoxy; or R7 and R8 together with the C atom to which they are attached form an aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as brutons tyrosine kinase (Btk) inhibitors. Thus, e.g., II was prepared by a multistep procedure (preparation given). I were evaluated in Btk enzyme activity assays, e.g., II demonstrated an EC50 value of <10 nM.
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2013:125799 HCAPLUS
DOCUMENT NUMBER: 158:216028
TITLE: Bicyclic heterocycles as BTK inhibitors and their preparation
INVENTOR(S): De Man, Adrianus P. A.; Sterrenburg, Jan-Gerard; Raaijmakers, Hans C. A.; Kaptein, Allard; Oubrie, Arthur; Rewinkel, Johannes B. M.; Jans, Christiaan G. J. M.; Wijkmans, Jacobus C. H. M.; Barf, Tjeerd A.; Cooper, Alan B.; Kim, Ronald M.; Boga, Sobhana Babu; Zhu, Hugh Y.; Gao, Xiaolei; Yao, Xin; Anand, Rajan; Wu, Hao; Liu, Shilan; Yang, Chundao; Alhassan, Abdul-Basit; Wang, James; Yu, Younong; Liu, Jian; Vaccaro, Henry M.
PATENT ASSIGNEE(S): Merck Sharp & Dohme Corp., USA; MSD Oss B.V.
SOURCE: PCT Int. Appl., 476pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013010380	A1	20130124	WO 2012-CN971	20120719
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
EP 2548877	A1	20130123	EP 2011-174570	20110719
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CA 2841899	A1	20130124	CA 2012-2841899	20120719
AU 2012286426	A1	20140130	AU 2012-286426	20120719
EP 2734529	A1	20140528	EP 2012-814549	20120719
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR				
KR 2014068020	A	20140605	KR 2014-7003924	20120719
CN 103917545	A	20140709	CN 2012-80045511	20120719
JP 2014520866	T	20140825	JP 2014-520495	20120719
IN 2014CN00339	A	20141212	IN 2014-CN339	20140115
MX 2014000747	A	20141015	MX 2014-747	20140117
US 20140221333	A1	20140807	US 2014-14233478	20140404

L15 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
PRIORITY APPLN. INFO.: EP 2011-174570 A 20110719
US 2011-61509446 P 20110719
WO 2012-CN971 W 20120719

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:216028; MARPAT 158:216028
GI



AB Provided are 6-5 membered fused pyridine ring compds. of formula I or pharmaceutically acceptable salts thereof, pharmaceutical compns. comprising these compds. and their use in therapy. In particular, provided is the use of 6-5 membered fused pyridine ring compds. in the treatment of Bruton's Tyrosine Kinase (BTK) mediated disorders. Compds. of formula I wherein dashed bonds are single and double bonds forming an aromatic ring system; each A is independently C, CH, CR11 and N, forming a bicyclic ring system containing at least one nitrogen per ring; A5 is C and N; B1 is N and CR7; B2 is N and CR8; B3 is N and CR9; B4 is N and CR10; W is CH and N; X is CH, N, O, S and a bond; Y is CR6, N, O and S; Z is CH, N and a bond; Rx is H, C1-6 alkyl, C1-5 heteroalkyl, etc.; R3 H, C1-3 alkyl and C3-7 cycloalkyl; R4 is H, OH, C1-3 alkyl and C1-3 alkoxy; A5R3R4Rx may be taken together to form azabicycloheptyl; R3R4 may be taken together to form C3-6 cycloalkyl; R5 is H, halo, CN, C1-4 alkyl, etc.; R6 is H, halo, C1-3 alkyl, CN, etc.; R5R6 may be taken together to form (un)substituted C3-7 cycloalkenyl and C2-6 heterocycloalkenyl; R7, R8, R9 and R10 are independently H, halo, OH, CF3, etc.; R7R8 may be taken together to form

L15 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
C6-10 aryl and C1-9 heterocycyl; R11 is D, H, halo, TMS, CN, etc.; pharmaceutically acceptable salts thereof, are claimed. Example compd. II was prepd. by cross-coupling reaction of trans-4-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)cyclohexyl acetate with 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid followed by hydrolysis. All the invention compds. were evaluated for their BTK inhibitory activity. From the assay, it was detd. that compd. II exhibited an EC50 value in the range of ≥ 10 nM to < 100 nM.
OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

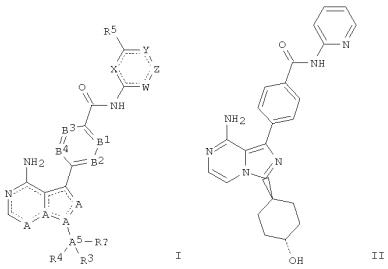
L15 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2013:125798 HCAPLUS
DOCUMENT NUMBER: 158:216027
TITLE: Bicyclic heterocycles as BTK inhibitors and their preparation
INVENTOR(S): De Man, Adrianus Petrus Antonius; Sterrenburg, Jan-Gerard; Raaijmakers, Hans C. A.; Kaptein, Allard; Oubrie, Arthur A.; Rewinkel, Johannes Bernardus Maria; Jans, Christiaan Gerardus Johannes Maria; Wijkmans, Jacobus C. H. M.; Barf, Tjeerd A.; Gao, Xiaolei; Boga, Sobhana Babu; Yao, Xin; Zhu, Hugh Y.; Cooper, Allen B.; Kim, Ronald M.
PATENT ASSIGNEE(S): MSD Oss B.V., Neth.
SOURCE: Eur. Pat. Appl., 175pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 2548877	A1	20130123	EP 2011-174570	20110719
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WO 2013010380	A1	20130124	WO 2012-CN971	20120719
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
AU 2012286426	A1	20140130	AU 2012-286426	20120719
EP 2734529	A1	20140528	EP 2012-814549	20120719
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KR 2014068020	A	20140605	KR 2014-7003924	20120719
CN 103917545	A	20140709	CN 2012-80045511	20120719
JP 2014520866	T	20140825	JP 2014-520495	20120719
MX 2014000747	A	20141015	MX 2014-747	20140117
US 20140221333	A1	20140807	US 2014-14233478	20140404

PRIORITY APPLN. INFO.: EP 2011-174570 A 20110719
US 2011-61509446 P 20110719
WO 2012-CN971 W 20120719

SANDOZ INC. IPR2023-00478 Ex. 1023, p. 597 of 891

L15 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
GI



I

II

AB Provided are 6-5 membered fused pyridine ring compds. of formula I or pharmaceutically acceptable salts thereof, pharmaceutical compns. comprising these compds. and their use in therapy. In particular, provided is the use of 6-5 membered fused pyridine ring compds. in the treatment of Bruton's Tyrosine Kinase (BTK) mediated disorders. Compds. of formula I wherein dashed bonds are single and double bonds forming an aromatic ring system; each A is independently C, CH, CR11 and N, forming a bicyclic ring system containing at least one nitrogen per ring; A5 is C and N; B1 is N and CR7; B2 is N and CR8; B3 is N and CR9; B4 is N and CR10; W is CH and N; X is CH, N, O, S and a bond; Y is CR6, N, O and S; Z is CH, N and a bond; Rx is H, C1-6 alkyl, C1-5 heteroalkyl, etc.; R3 H, C1-3 alkyl and C3-7 cycloalkyl; R4 is H, OH, C1-3 alkyl and C1-3 alkoxy; A5R3R4Rx may be taken together to form azabicycloheptyl; R3R4 may be taken together to form C3-6 cycloalkyl; R5 is H, halo, CN, C1-4 alkyl, etc.; R6 is H, halo, C1-3 alkyl, CN, etc.; R5R6 may be taken together to form (un)substituted C3-7 cycloalkenyl and C2-6 heterocycloalkenyl; R7, R8, R9 and R10 are independently H, halo, OH, CF3, etc.; R7R8 may be taken together to form C6-10 aryl and C1-9 heterocyclyl; R11 is D, H, halo, TMS, CN, etc.; pharmaceutically acceptable salts thereof, are claimed. Example compound II was prepared by cross-coupling reaction of trans-4-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)cyclohexyl acetate with

L15 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid followed by hydrolysis. All the invention compds. were evaluated for their BTK inhibitory activity. From the assay, it was detd. that compd. II exhibited an EC50 value in the range of ≥ 10 nM to < 100 nM.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

14233418.trn05/06/2015

=> d l16 ibib abs total

11:08<gshameem>Page 26

L16 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2014:1203970 HCAPLUS
DOCUMENT NUMBER: 161:275936
TITLE: Preparation of bicyclic heterocycles as Btk inhibitors
for therapy
INVENTOR(S): Kim, Ronald M.; Liu, Jian; Gao, Xiaolei; Boga, Sobhana
Babu; Guiadeen, Deodialsingh; Kozlowski, Joseph A.; Yu, Wensheng; Anand, Rajan; Yu, Younong; Selyutin, Oleg B.; Gao, Ying-Duo; Wu, Hao; Liu, Shilan; Yang, Chundao; Wang, Hongjian
PATENT ASSIGNEE(S): Wuxi Apptec (Shanghai) Co., Ltd., Peop. Rep. China; Merck Sharp & Dohme Corp.
SOURCE: U.S. Pat. Appl. Publ., 217pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140206681	A1	20140724	US 2014-14160587	20140122
WO 2014113932	A1	20140731	WO 2013-CN70876	20130123
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
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WO 2014114185	A1	20140731	WO 2014-CN82	20140122
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RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
PRIORITY APPLN. INFO.:			WO 2013-CN70876	A 20130123

L16 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)

			CN 2014-10010914	A 20140109

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 161:275936
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides Bruton's Tyrosine Kinase (Btk) inhibitor compds. according to Formula I (wherein in bicyclic ring E-G, A1-A4 are independently (un)substituted C or N, with at least 1 being N; R5 is H, halo, aryl, etc.; R12 is H, C1-3 alkyl, etc.; R13 is H and C1-4 alkoxy; in aromatic ring K, B1-B4 are N or (un)substituted CH; in heteroarom. ring L, W is CH, N or S, X is (un)substituted CH, N, O or S, Y is (un)substituted CH, (un)substituted NH, O or S, and Z is (un)substituted CH, N or a bond; Q is C(O), (un)substituted CH2, etc.; T is (un)substituted CH2, O, (un)substituted NH, or a bond; U is (un)substituted CH2, O, or (un)substituted NH; V is (un)substituted CH2, O, or a bond; Rc is H, halo, C1-6 alkyl, etc.) or a pharmaceutically acceptable salt thereof or to pharmaceutical compns. comprising these compds. and to their use in therapy. In particular, the present invention relates to the use of I as Btk inhibitors in the treatment of Btk mediated disorders. Synthetic procedures for preparing I are exemplified. Example compound II was prepared from intermediate III by cyclization using carbonyldiimidazole and deprotection. Example compds. of the invention were tested as BTK enzymic inhibitors using a LANCE TR-FRET assay. In this assay II had an IC50 value of 5.5 nM.

L16 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2013:129551 HCAPLUS
DOCUMENT NUMBER: 158:243948
TITLE: Preparation of imidazopyrazinylbenzamide derivatives and analogs for use as Btk inhibitors
INVENTOR(S): Barf, Tjeerd A.; Jans, Christiaan Gerardus Johannes Maria; De Man, Adrianus Petrus Antonius; Oubrie, Arthur A.; Raaijmakers, Hans C. A.; Rewinkel, Johannes
Bernardus Maria; Sterrenburg, Jan-Gerard; Wijkmans, Jacobus C. H. M.
PATENT ASSIGNEE(S): MSD Oss B.V., Neth.
SOURCE: PCT Int. Appl., 114pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013010868	A1	20130124	WO 2012-EP63552	20120711
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2841886	A1	20130124	CA 2012-2841886	20120711
AU 2012285987	A1	20140206	AU 2012-285987	20120711
KR 2014036324	A	20140325	KR 2014-7003955	20120711
IL 230511	A	20140331	IL 2012-230511	20120711
EP 2734522	A1	20140528	EP 2012-733505	20120711
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
CN 103889987	A	20140625	CN 2012-80045383	20120711
JP 2014520870	T	20140825	JP 2014-520606	20120711
MX 2014000746	A	20140507	MX 2014-746	20140117
US 20140155385	A1	20140605	US 2014-14233418	20140117
IN 2014CN00408	A	20150403	IN 2014-CN408	20140117
CR 20140030	A	20140603	CR 2014-30	20140120
PRIORITY APPLN. INFO.:			EP 2011-174578	A 20110719
			US 2011-61509397	P 20110719
			WO 2012-EP63552	W 20120711

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:243948; MARPAT 158:243948
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L16 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

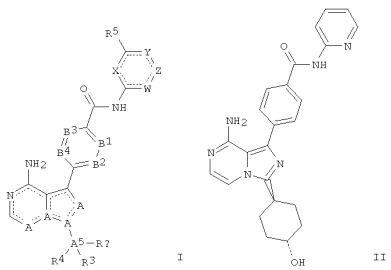
AB Title compds. I [A = CH or N; D = N or CR7; E = N or CR8; each L independently = N or CR9; X = CH, N, O, or S; Y = CR6, N, O, or S; Z = bond, CH, or N; R1 = (un)substituted C(O)alkyl, S(O)alkyl, alkyl, etc.; R2 and R3 independently = H, alkyl, or cycloalkyl; R4, R6, and R8 independently = H or alkyl; R5 = H, halo, CN, (un)substituted alkyl, etc.; or R5 and R6 together may form an (un)substituted cycloalkenyl or heterocycloalkenyl; R7 and R9 independently = H, halo, or alkoxy; or R7 and R8 together with the C atom to which they are attached form an aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as brutons tyrosine kinase (Btk) inhibitors. Thus, e.g., II was prepared by a multistep procedure (preparation given). I were evaluated in Btk enzyme activity assays, e.g., II demonstrated an EC50 value of <10 nM.
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2013:125799 HCAPLUS
DOCUMENT NUMBER: 158:216028
TITLE: Bicyclic heterocycles as BTK inhibitors and their preparation
INVENTOR(S): De Man, Adrianus P. A.; Sterrenburg, Jan-Gerard; Raaijmakers, Hans C. A.; Kaptein, Allard; Oubrie, Arthur; Rewinkel, Johannes B. M.; Jans, Christiaan G. J. M.; Wijkmans, Jacobus C. H. M.; Barf, Tjeerd A.; Cooper, Alan B.; Kim, Ronald M.; Boga, Sobhana Babu; Zhu, Hugh Y.; Gao, Xiaolei; Yao, Xin; Anand, Rajan; Wu, Hao; Liu, Shilan; Yang, Chundao; Alhassan, Abdul-Basit; Wang, James; Yu, Younong; Liu, Jian; Vaccaro, Henry M.
PATENT ASSIGNEE(S): Merck Sharp & Dohme Corp., USA; MSD Oss B.V.
SOURCE: PCT Int. Appl., 476pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013010380	A1	20130124	WO 2012-CN971	20120719
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EP 2548877	A1	20130123	EP 2011-174570	20110719
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AU 2012286426	A1	20140130	AU 2012-286426	20120719
EP 2734529	A1	20140528	EP 2012-814549	20120719
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR				
KR 2014068020	A	20140605	KR 2014-7003924	20120719
CN 103917545	A	20140709	CN 2012-80045511	20120719
JP 2014520866	T	20140825	JP 2014-520495	20120719
IN 2014CN00339	A	20141212	IN 2014-CN339	20140115
MX 2014000747	A	20141015	MX 2014-747	20140117
US 20140221333	A1	20140807	US 2014-14233478	20140404

L16 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
PRIORITY APPLN. INFO.: EP 2011-174570 A 20110719
US 2011-61509446 P 20110719
WO 2012-CN971 W 20120719

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 158:216028; MARPAT 158:216028
GI



AB Provided are 6-5 membered fused pyridine ring compds. of formula I or pharmaceutically acceptable salts thereof, pharmaceutical compns. comprising these compds. and their use in therapy. In particular, provided is the use of 6-5 membered fused pyridine ring compds. in the treatment of Bruton's Tyrosine Kinase (BTK) mediated disorders. Compds. of formula I wherein dashed bonds are single and double bonds forming an aromatic ring system; each A is independently C, CH, CR11 and N, forming a bicyclic ring system containing at least one nitrogen per ring; A5 is C and N; B1 is N and CR7; B2 is N and CR8; B3 is N and CR9; B4 is N and CR10; W is CH and N; X is CH, N, O, S and a bond; Y is CR6, N, O and S; Z is CH, N and a bond; Rx is H, C1-6 alkyl, C1-5 heteroalkyl, etc.; R3 H, C1-3 alkyl and C3-7 cycloalkyl; R4 is H, OH, C1-3 alkyl and C1-3 alkoxy; A5R3R4Rx may be taken together to form azabicycloheptyl; R3R4 may be taken together to form C3-6 cycloalkyl; R5 is H, halo, CN, C1-4 alkyl, etc.; R6 is H, halo, C1-3 alkyl, CN, etc.; R5R6 may be taken together to form (un)substituted C3-7 cycloalkenyl and C2-6 heterocycloalkenyl; R7, R8, R9 and R10 are independently H, halo, OH, CF3, etc.; R7R8 may be taken together to form

L16 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
C6-10 aryl and C1-9 heterocycyl; R11 is D, H, halo, TMS, CN, etc.; pharmaceutically acceptable salts thereof, are claimed. Example compd. II was prepd. by cross-coupling reaction of trans-4-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)cyclohexyl acetate with 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid followed by hydrolysis. All the invention compds. were evaluated for their BTK inhibitory activity. From the assay, it was detd. that compd. II exhibited an EC50 value in the range of ≥ 10 nM to < 100 nM.
OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

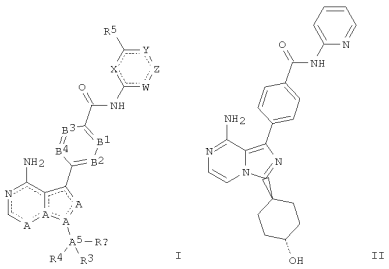
L16 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2015 ACS on STN
ACCESSION NUMBER: 2013:125798 HCAPLUS
DOCUMENT NUMBER: 158:216027
TITLE: Bicyclic heterocycles as BTK inhibitors and their preparation
INVENTOR(S): De Man, Adrianus Petrus Antonius; Sterrenburg, Jan-Gerard; Raaijmakers, Hans C. A.; Kaptein, Allard; Oubrie, Arthur A.; Rewinkel, Johannes Bernardus Maria; Jans, Christiaan Gerardus Johannes Maria; Wijkmans, Jacobus C. H. M.; Barf, Tjeerd A.; Gao, Xiaolei; Boga, Sobhana Babu; Yao, Xin; Zhu, Hugh Y.; Cooper, Allen B.; Kim, Ronald M.
PATENT ASSIGNEE(S): MSD Oss B.V., Neth.
SOURCE: Eur. Pat. Appl., 175pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 2548877	A1	20130123	EP 2011-174570	20110719
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WO 2013010380	A1	20130124	WO 2012-CN971	20120719
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AU 2012286426	A1	20140130	AU 2012-286426	20120719
EP 2734529	A1	20140528	EP 2012-814549	20120719
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KR 2014068020	A	20140605	KR 2014-7003924	20120719
CN 103917545	A	20140709	CN 2012-80045511	20120719
JP 2014520866	T	20140825	JP 2014-520495	20120719
MX 2014000747	A	20141015	MX 2014-747	20140117
US 20140221333	A1	20140807	US 2014-14233478	20140404

PRIORITY APPLN. INFO.: EP 2011-174570 A 20110719
US 2011-61509446 P 20110719
WO 2012-CN971 W 20120719

SANDOZ INC. IPR2023-00478 Ex. 1023, p. 601 of 891

L16 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
GI



I

II

AB Provided are 6-5 membered fused pyridine ring compds. of formula I or pharmaceutically acceptable salts thereof, pharmaceutical compns. comprising these compds. and their use in therapy. In particular, provided is the use of 6-5 membered fused pyridine ring compds. in the treatment of Bruton's Tyrosine Kinase (BTK) mediated disorders. Compds. of formula I wherein dashed bonds are single and double bonds forming an aromatic ring system; each A is independently C, CH, CR11 and N, forming a bicyclic ring system containing at least one nitrogen per ring; A5 is C and N; B1 is N and CR7; B2 is N and CR8; B3 is N and CR9; B4 is N and CR10; W is CH and N; X is CH, N, O, S and a bond; Y is CR6, N, O and S; Z is CH, N and a bond; Rx is H, C1-6 alkyl, C1-5 heteroalkyl, etc.; R3 H, C1-3 alkyl and C3-7 cycloalkyl; R4 is H, OH, C1-3 alkyl and C1-3 alkoxy; A5R3R4Rx may be taken together to form azabicycloheptyl; R3R4 may be taken together to form C3-6 cycloalkyl; R5 is H, halo, CN, C1-4 alkyl, etc.; R6 is H, halo, C1-3 alkyl, CN, etc.; R5R6 may be taken together to form (un)substituted C3-7 cycloalkenyl and C2-6 heterocycloalkenyl; R7, R8, R9 and R10 are independently H, halo, OH, CF3, etc.; R7R8 may be taken together to form C6-10 aryl and C1-9 heterocyclyl; R11 is D, H, halo, TMS, CN, etc.; pharmaceutically acceptable salts thereof, are claimed. Example compound II was prepared by cross-coupling reaction of trans-4-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)cyclohexyl acetate with

L16 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2015 ACS on STN (Continued)
4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid followed by hydrolysis. All the invention compds. were evaluated for their BTK inhibitory activity. From the assay, it was detd. that compd. II exhibited an EC50 value in the range of ≥ 10 nM to < 100 nM.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 8

Complete if Known	
Application Number	Divisional of 14/233,418
Filing Date	February 9, 2016
First Named Inventor	Tjeerd A. Barf
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	015332.1182-US02

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA*	US-7,825,118	11-02-2010	Honigberg et al.	
	AB*	US-7,960,396	06-14-2011	Honigberg et al.	
	AC*	US-8,377,946	02-19-2013	Chen et al.	
	AD*	US-8,658,794	02-25-2014	de Man et al.	
	AE*	US-20060084654-A1	04-20-2006	Beck et al.	
	AF*	US-20080076921-A1	03-27-2008	Honigberg et al.	
	AG*	US-20110257203-A1	10-20-2011	Honigberg et al.	
	AH*	US-20120053189-A1	03-01-2012	Loury	
	AI*	US-20120095026-A1	04-19-2012	Honigberg et al.	
	AJ*	US-20120129821-A1	05-24-2012	Honigberg et al.	
	AK*	US-20120135944-A1	05-31-2012	Honigberg et al.	
	AL*	US-20120165328-A1	06-28-2012	Honigberg et al.	
	AM*	US-20130018032-A1	01-17-2013	Chen et al.	
	AN*	US-20130079327-A1	03-28-2013	Yamamoto et al.	
	AO*	US-20140073593-A1	03-13-2014	Conklin et al.	
	AP*	US-20140206681-A1	07-24-2014	Kim et al.	
	AQ*	US-20140212425-A1	07-31-2014	Chang et al.	

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	BA**	WO-2008121742-A2	10-09-2008	Pharmacyclics, Inc		
	BB**	WO-2010126960-A1	11-04-2010	Locus Pharmaceuticals, Inc		
	BC**	WO-2011095556-A1	08-11-2011	Organon NV		
	BD**	EP-2548877-A1	01-23-2013	MSD Oss B.V.		
	BE**	WO-2001019828-A2	03-22-2001	BASF Aktiengesellschaft		
	BF**	WO-2002080926-A1	10-17-2002	Abbott GmbH & Co. KG		

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Art Unit	Not Yet Assigned
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	BG**	WO-2003065995-A2	08-14-2003	Supergen, Inc.		
	BH**	WO-2005037836-A2	04-28-2005	OSI Pharmaceuticals, Inc.		
	BI**	WO-2005097800-A1	10-20-2005	OSI Pharmaceuticals, Inc.		
	BJ**	WO-2007061737-A2	05-31-2007	OSI Pharmaceuticals, Inc.		
	BK**	WO-2007064883-A2	06-07-2007	Bayer Pharmaceuticals Corp.		
	BL**	WO-2007064993-A2	06-07-2007	OSI Pharmaceuticals, Inc.		

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Sheet 3 of 8

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First Named Inventor	Tjeerd A. Barf
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	BM**	WO-2007106503-A2	09-20-2007	OSI Pharmaceuticals, Inc.		
	BN**	WO-2009076170-A2	06-18-2009	Novartis AG		
	BO**	WO-2011119663-A1	09-29-2011	Glaxosmithkline LLC		
	BP**	WO-2011152351-A1	12-08-2011	Ono Pharmaceutical Co., Ltd.		
	BQ**	WO-2011153514-A2	12-08-2011	Pharmacyclics, Inc.		
	BR**	WO-2012158843-A2	11-22-2012	Univ. California		

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Sheet 4 of 8

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Filing Date	February 9, 2016
First Named Inventor	Tjeerd A. Barf
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	015332.1182-US02

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	BS**	WO-2013003629-A2	01-03-2013	Pharmacyclics, Inc.		
	BT**	WO-2013010380-A1	01-24-2013	Merck Sharp & Dohme Corp.		
	BU**	WO-2013010868-A1	01-24-2013	MSD Oss B.V.		
	BV**	WO-2013010869-A1	01-24-2013	MSD Oss B.V.		
	BW**	WO-2013059738-A2	04-25-2013	Pharmacyclics, Inc.		
	BX**	WO-2014143807-A2	09-18-2014	Stromatt, Scott		

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Sheet	5	of	8

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Filing Date	February 9, 2016
First Named Inventor	Tjeerd A. Barf
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	015332.1182-US02

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	BY**	WO-2014159745-A1	10-02-2014	Pharmacyclics, Inc.		
	BZ**	WO-2014168975-A1	10-16-2014	Pharmacyclics, Inc.		
	BA1**	WO-2015018522-A1	02-12-2015	Oncoethix SA		

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Art Unit	Not Yet Assigned
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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA**	Berge et al., "Pharmaceutical salts," 66(1) J. Pharm. Sci. 1-19 (1977).	
	CB**	Bingham et al., "Over one hundred solvates of sulfathiazole," Chem. Commun. 603-04 (2001).	
	CC**	Caira et al., "Preparation and Crystal Characterization of a Polymorph, a Monohydrate, and an Ethyl Acetate Solvate of the Antifungal Fluconazole," 93(3) J. Pharma. Sci. 601-11 (2004).	
	CD**	Davis et al., "Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma," 463 Nature 88-92 (2010).	
	CE**	Dhar et al., "Synthesis and SAR of p38α MAP kinase inhibitors based on heterobicyclic scaffolds," 17 Bioorg. & Med. Chem. Lett. 5019-24 (2007).	
	CF**	Gaudet et al., "A Homogeneous Fluorescence Polarization Assay Adaptable for a Range of Protein Serine/Threonine and Tyrosine Kinases," 8(2) J. Biomol. Screening 164-75 (2003).	
	CG**	Gennaro (ed.), *Remington: The Science and Practice of Pharmacy*, 20th edition (2000).	
	CH**	Gilfillan et al., "The tyrosine kinase network regulating mast cell activation," 288 Immun. Rev. 149-69 (2009).	
	CI**	Gould, "Salt selection for basic drugs," 33 Int'l J. Pharmaceutics 201-217 (1986).	
	CJ**	Greene & Wuts, *Protective Groups in Organic Synthesis*, 2d Edition (1991).	

Examiner Signature	/GOLAM M SHAMEEM/	Date Considered	12/01/2016

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	CK**	Harder et al., "Gain- and Loss-of-Function Lyn Mutant Mice Define a Critical Inhibitory Role for Lyn in the Myeloid Lineage," 15 Immunity 603-15 (2001).	
	CL**	Hartz et al., "Synthesis and Evaluation of Imidazo[1,5-α]pyrazines as Corticotropin Releasing Hormone Receptor Ligands," 12 Bioorg. & Med. Chem. Lett. 291-94 (2002).	
	CM**	Higuchi *et al.* (eds.), *Pro-drugs as Novel Delivery Systems,* 14 A.C.S. Symposium Series (1975).	
	CN**	Ji et al., "A novel, potent, and selective insulin-like growth factor-I receptor kinase inhibitor blocks insulin-like growth factor-I receptor signaling *in vitro* and inhibits insulin-like growth factor-I receptor-dependent tumor growth *in vivo*," 6(8) Mol. Cancer Ther. 2158-67 (2007).	
	CO**	King et al., "Nucleofugality effects in the pyridine promoted formation of esters from 2-substituted ethanesulfonyl chlorides," 66 Can. J. Chem. 1109-16 (1988).	
	CP**	Klinghoffer et al., "Src family kinases are required for integrin but not PDGFR signal transduction," 18(9) EMBO J. 2459-71 (1999).	
	CQ**	Lim et al., "Anti-CD20 monoclonal antibodies: historical and future perspectives," 95(1) Haematologica 135-43 (2010).	
	CR**	Lowell et al., "Deficiency of the Hck and Src Tyrosine Kinases Results in Extreme Levels of Extramedullary Hematopoiesis," 87(5) Blood 1780-92 (1996).	
	CS**	Mitchell et al., Synthesis of *C*-nucleoside isosteres of 9-(2-hydroxyethoxymethyl)guanine (acyclovir)," 21(3) J. Heterocyclic Chem. 697-99 (1984).	
	CT**	Mukaiyama et al., "Synthesis and c-Src inhibitory activity of imidazo[1,5-α]pyrazine derivatives as an agent for treatment of acute ischemic stroke," 15 Bioorg. & Med. Chem. 868-85 (2007).	

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	CU**	Mulvihill et al., "1,3-Disubstituted-imidazo[1,5-α]pyrazines as insulin-like growth-factor-I receptor (IGF-IR) inhibitors," 17 Bioorg. & Med. Chem. Lett. 1091-97 (2007).	
	CV**	Mulvihill et al., "Novel 2-phenylquinolin-7-yl-derived imidazo[1,5-α]pyrazines as potent insulin-growth factor-I receptor (IGF-IR) inhibitors," 16 Bioorg. & Med. Chem. 1359-75 (2008).	
	CW**	Odom et al., "Negative Regulation of Immunoglobulin E-dependent Allergic Responses by Lyn Kinase," 199(11) J. Exp. Med. 1491-1502 (2004).	
	CX**	Pan et al., "Discovery of Selective Irreversible Inhibitors for Bruton's Tyrosine Kinase," 2 ChemMedChem 58-61 (2007).	
	CY**	Roby et al., "Alterations in Reproductive Function in Src Tyrosine Kinase Knockout Mice," 26 Endocrine 169-76 (2005).	
	CZ**	Roche (ed.), *Bioreversible Carriers in Drug Design*, Pergamon Press (1987).	
	CA1**	Shinohara et al., "Tyrosine Kinases Btk and Tec Regulate Osteoclast Differentiation by Linking RANK and ITAM Signals," 132 Cell 794-806 (2008).	
	CB1**	van Tonder et al., "Preparation and Physicochemical Characterization of 5 Niclosamide Solvates and 1 Hemisolvate," 5(1) AAPS PharmSciTech Article 12 (2004).	

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15019543	BARF ET AL.
	Examiner	Art Unit
	GOLAM M SHAMEEM	1626

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 31/4985	12/01/16	GS
C07D 487/04	12/01/16	GS

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST, STN, INVENTOR SEARCH	12/01/16	GS

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15019543	BARF ET AL.
	Examiner	Art Unit
	GOLAM M SHAMEEM	1626

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/01/2016								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								
	11	✓								
	12	N								
	13	N								
	14	N								
	15	N								
	16	N								
	17	N								
	18	N								

Docket No.: 015332.1182-US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Tjeerd A. Barf et al.

Application No.: 15/019,543 | Confirmation No.: 1984

Filed: February 9, 2016 | Group Art Unit: 1626

For: 4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS | Examiner: Golam M. Shameem

RESPONSE TO RESTRICTION REQUIREMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

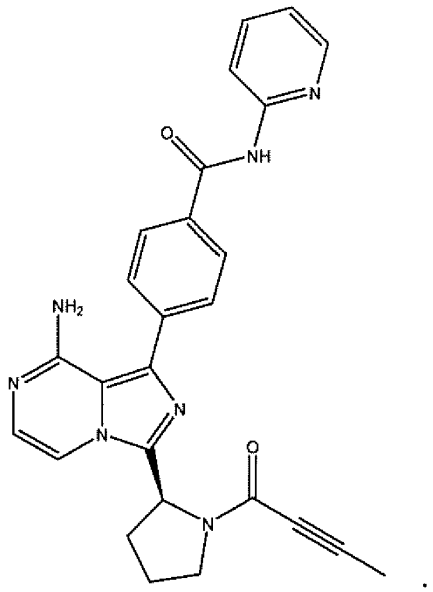
Dear Sir:

In the Office Action dated September 30, 2016 (Paper No. 20160928-2371), the Examiner set forth a restriction requirement and a further requirement for election of a single species.

In response to the **restriction requirement**, Applicant provisionally elects **Group I, claims 1-11**, drawn to a method of treating a Bruton's Tyrosine Kinase mediated disorder in a subject comprising administering a therapeutically effective amount of a compound of Formula (I). Claims 1-11 are readable on the elected invention of Group I.

In response to the **election of species requirement**, Applicant provisionally elects the following species that is found on page 36, in Example 6, of the subject application as originally filed:

(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure set forth below:



Claims 1-5 and 8 in Group I are readable on the elected species.

Favorable consideration of the application is respectfully requested.

Dated: November 30, 2016

Respectfully submitted,

By _____
Einar Stole
Registration No.: 47,272
Melody H. Wu
Registration No.: 52,376
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
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(202) 662-6000
Attorneys for Applicant

Electronic Acknowledgement Receipt	
EFS ID:	27647295
Application Number:	15019543
International Application Number:	
Confirmation Number:	1984
Title of Invention:	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS
First Named Inventor/Applicant Name:	Tjeerd A. Barf
Customer Number:	26853
Filer:	Andrea Reister/Jenn Augsburger
Filer Authorized By:	Andrea Reister
Attorney Docket Number:	015332.1182-US02
Receipt Date:	30-NOV-2016
Filing Date:	09-FEB-2016
Time Stamp:	11:41:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		15019043-RespRR.pdf	64316 2edde408d59d35ed7f78c0c2740829d5a7620301	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	2
	Response to Election / Restriction Filed	3	4
Warnings:			
Information:			
	Total Files Size (in bytes):	64316	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

Docket No.: 015332.1182-US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Tjeerd A. Barf et al.

Application No.: 15/019,543 | Confirmation No.: 1984

Filed: February 9, 2016 | Group Art Unit: 1626

For: 4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS | Examiner: Golam M. Shameem

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed is the following item for filing in connection with the above-referenced Patent Application:

1. Response to Restriction Requirement.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or that should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-0740, under Docket No. 015332.1182-US02.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor

(including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 50-0740.

Dated: November 30, 2016

Respectfully submitted,

By _____

Einar Stole
Registration No.: 47,272
Melody H. Wu
Registration No.: 52,376
COVINGTON & BURLING LLP
One CityCenter
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Washington, DC 20001-4956
(202) 662-6000
Attorneys for Applicant

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/019,543	02/09/2016	Tjeerd A. Barf	015332.1182-US02	1984

26853 7590 09/30/2016

COVINGTON & BURLING, LLP
Attn: Patent Docketing
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956

EXAMINER	
SHAMEEM, GOLAM M	

ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
09/30/2016	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 15/019,543	Applicant(s) BARF ET AL.	
	Examiner GOLAM M M SHAMEEM	Art Unit 1626	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02/09/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-18* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *1-18* are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.