

PhI(OAc)₂ iodobenzene diacetate

K₂CO₃ potassium carbonate

KOH potassium hydroxide

RT rt r.t. room temperature

Rt retention time

SOCl₂ thionyl chloride

SO₂Cl₂ sulfuryl chloride

t-BuOK potassium *tert*-butanolate

TBTU *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate

TBS tris buffered saline

THF tetrahydrofuran

TFA trifluoroacetic acid

TEAC bis(*tetra*-ethylammonium)carbonate

TLC thin layer chromatography

Tris trihydroxymethyl aminomethane

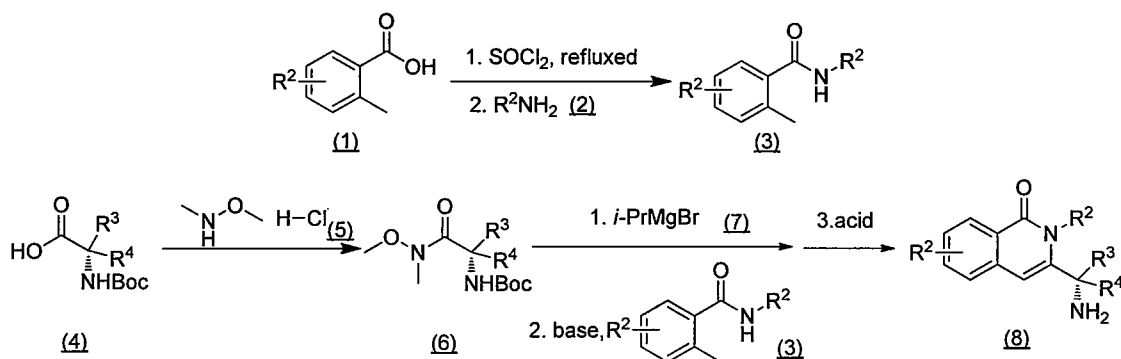
TsCl 4-toluene sulfonyl chloride

μL microliter

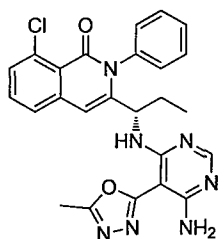
Zn zinc

[345] Representative synthetic procedures for the preparation of compounds of the disclosure are outlined below in following schemes. Unless otherwise indicated, each X, R², R³ and R⁴ carry the definitions set forth above in connection with formula (I).

Scheme 1



Example 5 (S)-3-(1-((6-amino-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)amino)propyl)-8-chloro-2-phenylisoquinolin-1(2H)-one

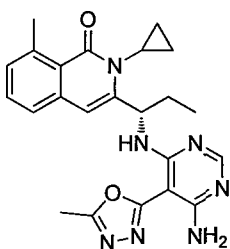


[365] To a mixture of (S)-3-(1-aminopropyl)-8-chloro-2-phenylisoquinolin-1(2H)-one (46 mg, 0.147 mmol), 6-chloro-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-amine (30 mg, 0.142 mmol) and DIPEA (55 mg, 0.42 mmol) in *n*-BuOH (1.5 mL) was heated to 125 °C for 16 hours, then cooled down to rt and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give a crude product which was further purified by preparative TLC to give the title compound as a light yellowish solid (39 mg, 56%).

MS (ESI, pos. ion) *m/z*: 488.0 [M+H]⁺; HPLC: 97%;

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.35 (s, 1H), 8.00 (s, 1H), 7.55-7.24 (m, 8H), 6.62 (s, 1H), 4.52 (m, 1H), 2.60 (s, 3H), 1.82 (m, 1H), 1.63 (m, 1H), 0.74 (m, 3H).

Example 6 (S)-3-(1-((6-amino-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)amino)propyl)-2-cyclopropyl-8-methylisoquinolin-1(2H)-one



Step 1) N-cyclopropyl-2,6-dimethylbenzamide

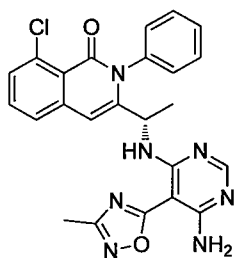
[366] To a suspension of 2,6-dimethylbenzoic acid (4.0 g, 26.64 mmol) in toluene (30 mL) was added SOCl₂ (8.0 mL, 106.54 mmol) at rt. The reaction was stirred at 90 °C overnight, then cooled down to rt, and concentrated *in vacuo*. The residue was dissolved in 30 mL of DCM, then to the solution were added NEt₃ (14.85 mL, 106.54 mmol) and cyclopropanamine (2.03 mL, 29.30 mmol) dropwise at 0 °C. The resulted solution was stirred at rt for 2 hours, and quenched with 50 mL of saturated brine. The separated organic phase was washed with 100 mL of saturated NaHCO₃ aqueous solution, and 100 mL of saturated

stirred further for 24 hours, then cooled down to rt, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 100/1) to give the title compound as a yellowish solid (46 mg, 72%).

MS (ESI, pos. ion) m/z : 452.0 $[M+H]^+$; HPLC: 96%;

^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.59-8.58 (d, $J = 5.4$ Hz, 1H), 8.11 (s, 1H), 7.38-7.34 (m, 2H), 7.22-7.21 (dd, $J = 6.6, 2.4$ Hz, 1H), 6.30 (s, 1H), 6.00-5.97 (td, $J = 7.8, 4.8$ Hz, 1H), 3.02-2.98 (m, 1H), 2.50 (s, 3H), 2.08-2.01 (m, 1H), 1.86-1.79 (m, 1H), 1.51-1.47 (m, 1H), 1.42-1.37 (m, 1H), 1.33-1.28 (m, 1H), 1.12-1.09 (t, $J = 7.8$ Hz, 3H), 0.90-0.86 (m, 1H).

Example 8 (*S*)-3-(1-((6-amino-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2*H*)-one



Step 1) 2-chloro-6-methyl-*N*-phenylbenzamide

[372] To a solution of 2-chloro-6-methylbenzoic acid (6.00 g, 35.17 mmol) in Toluene (40 mL) was added SOCl_2 (10.21 mL, 140.69 mmol) at rt. The reaction was stirred at 110 °C for 5 hours, then cooled to rt, and concentrated *in vacuo*. The residue was dissolved in DCM (50 mL), then to the solution were added NEt_3 (14.71 mL, 105.51 mmol) and then aniline (2.95 g, 31.65 mmol) at 0 °C. The resulted mixture was stirred at rt overnight, and washed with 200 mL of H_2O , 200 mL of saturated NaHCO_3 aqueous solution and 200 mL of saturated brine. The separated organic phase was concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a white solid (7.4 g, 86%).

MS (ESI, pos. ion) m/z : 246.0 $[M+H]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.63-7.61 (d, $J = 8.0$ Hz, 2H), 7.45 (br. s, 1H), 7.39-7.35 (t, $J = 8.0$ Hz, 2H), 7.25-7.13 (m, 4H), 2.42 (s, 3H).

Step 2) (*S*)-3-(1-aminoethyl)-8-chloro-2-phenylisoquinolin-1(2*H*)-one

[373] To a solution of 2-chloro-6-methyl-*N*-phenylbenzamide (2.00 g, 8.14 mmol) in THF (15 mL) was added *n*-BuLi (8.14 mL, 20.35 mmol) dropwise over 30 minutes at -30 °C

under N₂ atmosphere, and then the resulted dark yellowish solution was stirred at this temperature for 30 minutes, and used for the next step.

To a solution of (*S*)-*tert*-butyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (2.84 g, 12.21 mmol) in THF (20 mL) was added *i*-PrMgCl (2 M, 6.72 mL, 13.43 mmol) dropwise over 30 minutes at -30 °C under N₂ atmosphere. The reaction was stirred at -30 °C for another 30 minutes, and added to the above system dropwise at -30 °C. The resulted solution was stirred at -15 °C for 3 hours, quenched with 40 mL of H₂O, and added 100 mL of EtOAc and 100 mL of saturated NH₄Cl aqueous solution. The aqueous solution was extracted with EtOAc (100 mL x 2). The combined organic phases were washed with 100 mL of saturated NH₄Cl aq and 100 mL of saturated brine, concentrated *in vacuo* to give yellowish oil which was used for next step without for further purification.

To the solution of the above yellowish oil in 15 mL of MeOH was added 15 mL of concentrate HCl at rt. The resulted solution was stirred at 95 °C for 14 hours, cooled to rt, concentrated *in vacuo* to remove the organic solvent. The residue was extracted with PE/EtOAc (50 mL/25 mL). The aqueous layer was basified with NaHCO₃ powder to pH = 8.5, and then extracted with DCM (100 mL x 3). The combined organic phases were washed with 100 mL of saturated brine, concentrated *in vacuo*, and the residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 10/1) to give the title compound as a yellowish solid (2.0 g, 78.6%).

MS (ESI, pos. ion) *m/z*: 299.0 [M+H]⁺;

¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.54-7.41 (m, 6H), 7.27-7.26 (m, 2H), 6.71 (s, 1H), 3.72-3.69 (q, *J* = 6.6 Hz, 1H), 1.25-1.24 (d, *J* = 6.6 Hz, 3H).

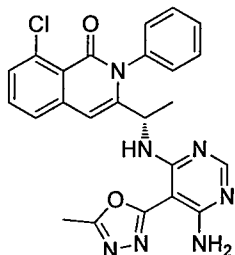
Step 3) (*S*)-3-(1-((6-amino-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2*H*)-one

[374] A mixture of (*S*)-3-(1-aminoethyl)-8-chloro-2-phenylisoquinolin-1(2*H*)-one (42 mg, 0.13 mmol), 6-chloro-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-amine (25 mg, 0.12 mmol) and DIPEA (46 mg, 0.35 mmol) in *n*-BuOH (1 mL) was heated to 125 °C for 7 hours, cooled down to rt, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as an off-white solid (17 mg, 30%).

MS (ESI, pos. ion) *m/z*: 474.0 [M+H]⁺; HPLC: 98%;

^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.29-8.28 (d, $J = 5.4$ Hz, 1H), 8.03 (s, 1H), 7.54-7.43 (m, 6H), 7.38-7.36 (dd, $J = 7.2$, 1.2 Hz, 1H), 7.34-7.33 (d, $J = 7.2$ Hz, 1H), 6.53 (s, 1H), 5.00-4.98 (m, 1H), 2.50 (s, 3H), 1.47 (d, $J = 6.8$ Hz, 3H).

Example 9 (*S*)-3-(1-((6-amino-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2*H*)-one

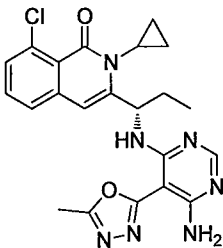


[375] To a suspension of (*S*)-3-(1-aminoethyl)-8-chloro-2-phenylisoquinolin-1(2*H*)-one (50 mg, 0.16 mmol) and 6-chloro-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-amine (45 mg, 0.21 mmol) in *n*-BuOH (5 mL) was added DIPEA (45 mg, 0.35 mmol). The resulted mixture was heated at reflux for 16 hours, and monitored by TLC (PE/EtOAc, v/v, 1/2). Then the mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a white solid (65 mg, 86%).

MS (ESI, pos, ion): 474.1 $[\text{M}+\text{H}]^+$; HPLC: 99.3%;

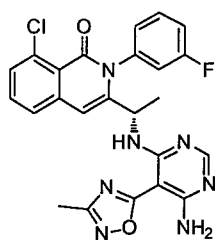
^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.88 (d, $J = 6.6$ Hz, 1H), 8.02 (s, 1H), 7.60–7.11 (m, 7H), 6.56 (s, 1H), 6.45 (s, 2H), 5.03 (dd, $J = 13.4$, 6.7 Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 1H), 2.69 (s, 3H), 1.49 (d, $J = 6.8$ Hz, 3H).

Example 10 (*S*)-3-(1-((6-amino-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)amino)propyl)-8-chloro-2-cyclopropylisoquinolin-1(2*H*)-one



[376] To a suspension of (*S*)-3-(1-aminopropyl)-8-chloro-2-cyclopropylisoquinolin-1(2*H*)-one (80 mg, 0.29 mmol) and 6-chloro-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-amine (60 mg, 0.28 mmol) in *n*-BuOH (5 mL) was added DIPEA (90 mg, 0.58 mmol). The resulted mixture was heated at reflux for 24 hours, and the reaction was monitored by TLC

Example 23 (S)-3-(1-((6-amino-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)ethyl)-8-chloro-2-(3-fluorophenyl)isoquinolin-1(2H)-one



Step 1) 2-chloro-N-(3-fluorophenyl)-6-methylbenzamide

[399] To a suspension of 2-chloro-6-methylbenzoic acid (2.0 g, 11.72 mmol) in toluene (20 mL) was added SOCl₂ (3.4 mL, 46.90 mmol) at rt. The reaction was heated to reflux and stirred further for 6 hours, then cooled to rt, and concentrated *in vacuo*. The residue was dissolved in DCM (20 mL), then to the resulted solution were added triethylamine (3.4 mL, 24.66 mmol) and 3-fluoroaniline (1.3 g, 11.74 mmol) dropwise at 0 °C. The mixture was stirred at rt overnight, then washed with saturated NaHCO₃ aqueous solution (25 mL) and brine (20 mL). The separated organic phase was dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 10/1) to give the title compound as a pink solid (2.55 g, 82.3%).

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 10.79 (s, 1H), 7.69 (dt, *J* = 11.6, 2.2 Hz, 1H), 7.44 (ddd, *J* = 7.5, 4.5, 2.9 Hz, 1H), 7.41-7.35 (m, 3H), 7.34-7.28 (m, 1H), 7.00-6.93 (m, 1H), 2.32 (s, 3H).

Step 2) (S)-3-(1-aminoethyl)-8-chloro-2-(3-fluorophenyl)isoquinolin-1(2H)-one

[400] To a solution of 2-chloro-N-(3-fluorophenyl)-6-methylbenzamide (2.5 g, 9.48 mmol) in THF (30 mL) was added 2.4 M *n*-BuLi in hexanes (9.88 mL, 23.70 mmol) dropwise at -30 °C under N₂ atmosphere. The resulted dark orange mixture was stirred at this temperature for 30 minutes. To a solution of (*S*)-*tert*-butyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (3.3 g, 14.22 mmol) in THF (30 mL) was added 2 M *i*-PrMgCl in THF (7.11 mL, 14.22 mmol) dropwise at -30 °C under N₂ atmosphere. The resulted mixture was stirred at -30 °C for another 30 minutes. This solution was added to above reaction mixture dropwise at -30 °C. The resulted mixture was warmed to -15 °C and stirred further for 4 hours, then quenched with H₂O (20 mL). The mixture was acidified to pH=1-2 with conc. HCl at 0 °C and concentrated *in vacuo*. The residue was dissolved in MeOH (50 mL) and then was added conc. HCl aqueous solution (30 mL). The resulted mixture was stirred at reflux for 1.5 hours, then cooled to rt and concentrated *in vacuo*. The residue was diluted with H₂O (40

mL), then the mixture was neutralized to pH=7-8 with solid Na₂CO₃ and extracted with EtOAc (100 mL x 2). The combined organic phase was washed with brine (100 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 100/1) to give the title compound as an orange-yellow solid (2.5 g, yield 64.2%).

MS (ESI, pos. ion) m/z: 317.2 [M+H]⁺.

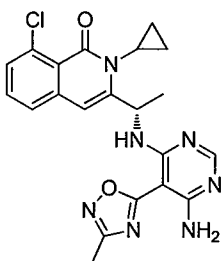
Step 3) (S)-3-(1-((6-amino-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)ethyl)-8-chloro-2-(3-fluorophenyl)isoquinolin-1(2H)-one

[401] To a suspension of 6-chloro-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-amine (50 mg, 0.236 mmol) and (S)-3-(1-aminoethyl)-8-chloro-2-(3-fluorophenyl)isoquinolin-1(2H)-one (85 mg, 0.268 mmol) was added DIPEA (61 mg, 0.473 mmol). The reaction mixture was heated to reflux and stirred further for 4 hours. The reaction was monitored by TLC (PE/EtOAc, v/v, 1/3). The reaction mixture was cooled down to rt and concentrated *in vacuo*. The residue was diluted with DCM (20 mL), and the resulted mixture was washed with water (15 mL) and brine (10 mL). The separated organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by a preparative TLC (PE/EtOAc (v/v) = 1/3) to give the title compound as a pale yellow solid (51 mg, yield 43.9%).

MS (ESI, pos, ion): 492.2 [M+H]⁺; HPLC: 96.9%;

¹H NMR (600 MHz, CDCl₃) δ(ppm): 8.30 (d, *J* = 5.6 Hz, 1H), 8.06 (d, *J* = 11.9 Hz, 1H), 7.57-7.44 (m, 3H), 7.45-7.35 (m, 2H), 7.33-7.29 (m, 1H), 7.28-7.25 (m, 1H), 7.19-7.08 (m, 2H), 6.55 (s, 1H), 5.07-4.91 (m, 1H), 2.51 (d, *J* = 1.5 Hz, 3H), 1.49 (dd, *J* = 6.7, 5.4 Hz, 3H).

Example 24 (S)-3-(1-((6-amino-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)ethyl)-8-chloro-2-cyclopropylisoquinolin-1(2H)-one



Step 1) 4,6-dichloropyrimidine-5-carbonyl chloride

[402] To a solution of 4,6-dichloropyrimidin-5-carbaldehyde (10 g, 56.50 mmol) in carbon tetrachloride (100 mL) were added sulfuryl chloride (11.44 g, 84.75 mmol) and 2,2-

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.81 (br. s, 1H), 8.43 (s, 1H), 6.16 (br. s, 1H), 2.54 (s, 3H), 1.63 (s, 1H).

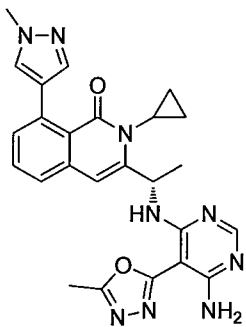
Step 8) (S)-3-(1-((6-amino-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)ethyl)-8-chloro-2-cyclopropylisoquinolin-1(2H)-one

[409] A mixture of (S)-3-(1-aminoethyl)-8-chloro-2-cyclopropylisoquinolin-1(2H)-one (30 mg, 0.114 mmol), 6-chloro-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-amine (24 mg, 0.114 mmol) and DIPEA (29 mg, 0.228 mmol) in *n*-BuOH (1 mL) was heated to 125 °C and stirred further for 4 hours, then cooled to rt, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 100/1) to give the title compound as an off-white solid (24 mg, 48%).

MS (ESI, Pos. ion) *m/z*: 438.0 [M+H]⁺; HPLC: 99%;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.45 (s, 1H), 8.12 (s, 1H), 7.38 (m, 3H), 6.40 (s, 1H), 6.08 (m, 1H), 3.00 (m, 1H), 2.49 (s, 3H), 1.64-1.63 (d, *J* = 4.0 Hz, 3H), 1.39 (m, 2H), 1.31 (m, 1H), 0.88 (m, 1H).

Example 25 (S)-3-(1-((6-amino-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)amino)ethyl)-2-cyclopropyl-8-(1-methyl-1*H*-pyrazol-4-yl)isoquinolin-1(2H)-one

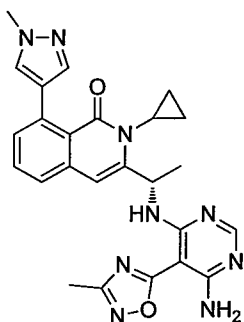


[410] To a solution of (S)-3-(1-((6-amino-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)amino)ethyl)-8-chloro-2-cyclopropylisoquinolin-1(2H)-one (51 mg, 0.1165 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (48 mg, 0.230 mmol) in DMAC/H₂O (0.6 mL/0.3 mL) were added Pd(dppf)Cl₂·CH₂Cl₂ (22 mg, 0.0264 mmol) and Na₂CO₃ (38 mg, 0.3585 mmol) at rt. The reaction was degassed with N₂ three times and heated at 120 °C for 100 minutes. The black solution was cooled to rt, then EtOAc (60 mL) was added. The separated organic layer was washed with H₂O (20 mL x 2), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a yellow solid (29.6 mg, 52.6%).

MS (ESI, pos. ion) m/z : 483.9 $[M+H]^+$;

^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.44 (d, $J = 7.0$ Hz, 1H), 8.06 (s, 1H), 7.81 (s, 1H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.51 (s, 1H), 7.42 (d, $J = 7.8$ Hz, 1H), 7.26 (d, $J = 7.4$ Hz, 1H), 7.26 (br s, 2H), 6.55 (s, 1H), 6.06-5.98 (m, 1H), 3.90 (s, 3H), 3.02-2.95 (m, 1H), 2.64 (s, 3H), 2.07-1.99 (m, 1H), 1.64 (d, $J = 6.7$ Hz, 3H), 1.38 (d, $J = 9.4$ Hz, 1H), 1.24-1.17 (m, 2H), 0.91-0.87 (m, 1H), 0.84-0.80 (m, 1H).

Example 26 (S)-3-(1-((6-amino-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)ethyl)-2-cyclopropyl-8-(1-methyl-1H-pyrazol-4-yl)isoquinolin-1(2H)-one



Step 1) (S)-tert-butyl (1-(8-chloro-2-cyclopropyl-1-oxo-1,2-dihydroisoquinolin-3-yl)ethyl)carbamate

[411] To a solution of (S)-3-(1-aminoethyl)-8-chloro-2-cyclopropylisoquinolin-1(2H)-one (1.00 g, 3.81 mmol) and sodium carbonate (806.7 mg, 50.29 mmol) in THF (6 mL) and water (6 mL) was added di-*tert*-butyl dicarbonate (1.1 mL) dropwise at rt, the reaction was stirred at rt for 2.5 hours, then diluted with H_2O (20 mL) and EtOAc (25 mL). The separated organic phase was washed with HCl aqueous solution (1M, 12 mL), and saturated brine (25 mL), dried over anhydrous Na_2SO_4 , and concentrated *in vacuo* to give the crude product as yellowish solid (1.69 g) which was used for the next step without further purification.

MS (ESI, pos. ion) m/z : 362.9 $[M+H]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.40-7.39 (d, $J = 4.4$ Hz, 2H), 7.30-7.29 (m, 1H), 6.41 (s, 1H), 5.55-5.51 (m, 1H), 4.88-4.87 (d, $J = 6.0$ Hz, 1H), 2.96-2.91 (m, 1H), 1.48-1.47 (d, $J = 7.2$ Hz, 3H), 1.45 (s, 9H), 1.37-1.30 (m, 2H), 1.10 (m, 1H), 0.87-0.81 (m, 1H).

Step 2) (S)-tert-butyl (1-(2-cyclopropyl-8-(1-methyl-1H-pyrazol-4-yl)-1-oxo-1,2-dihydroisoquinolin-3-yl)ethyl)carbamate

[412] A mixture of (*S*)-*tert*-butyl(1-(8-chloro-2-cyclopropyl-1-oxo-1,2-dihydroisoquinolin-3-yl)ethyl)carbamate (1.69 g, 4.66 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (1.46 g, 7.02 mmol) and sodium carbonate (990 mg, 9.34 mmol) in water (7 mL) and *N,N*-dimethylacetamide (7 mL) was heated to 120 °C and stirred further for 3.5 hours, then cooled to rt, and diluted with H₂O (60 mL) and EtOAc (60 mL). The separated organic phase was washed with H₂O (60 mL), and saturated brine (60 mL), and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 1/6) to give the title compound as a yellowish solid (1.4 g, 90.3% for two steps).

MS (ESI, pos. ion) *m/z*: 408.9 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.60 (s, 1H), 7.57 (s, 1H), 7.51-7.47 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.34-7.32 (d, *J* = 7.6 Hz, 1H), 7.28-7.26 (d, *J* = 8.0 Hz, 1H), 6.44 (s, 1H), 5.54-5.51 (m, 1H), 4.79-4.77 (d, *J* = 6.4 Hz, 1H), 3.96 (s, 3H), 2.91-2.85 (m, 1H), 1.48-1.46 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 9H), 1.28-1.25 (m, 2H), 1.04 (m, 1H), 0.78-0.73 (m, 1H).

Step 3) (*S*)-3-(1-aminoethyl)-2-cyclopropyl-8-(1-methyl-1*H*-pyrazol-4-yl) isoquinolin-1(2*H*)-one

[413] To a solution of (*S*)-*tert*-butyl (1-(2-cyclopropyl-8-(1-methyl-1*H*-pyrazol-4-yl)-1-oxo-1,2-dihydroisoquinolin-3-yl)ethyl)carbamate (1.40 g, 3.43 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in EtOAc (3 M, 20 mL), the mixture was stirred at rt for 2 days, then concentrated *in vacuo*. The residue was dissolved in H₂O (30 mL), and the resulted mixture was extracted with EtOAc (20 mL x 2). The aqueous layer was basified to pH = 8.5 with NaHCO₃ powder, and extracted with DCM (30 mL x 2). The combined organic phases was washed with saturated brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to give the title compound as a white solid (800 mg, 75.7%).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.61 (s, 1H), 7.58 (s, 1H), 7.52-7.48 (d, *J* = 7.6, 7.6 Hz, 1H), 7.37-7.35 (d, *J* = 8.0 Hz, 1H), 7.27-7.26 (m, 1H), 6.60 (s, 1H), 4.79 (q, *J* = 6.4 Hz, 1H), 3.96 (s, 3H), 2.93-2.88 (m, 1H), 1.46-1.44 (d, *J* = 6.5 Hz, 3H), 1.30-1.22 (m, 2H), 0.80-0.77 (m, 2H).

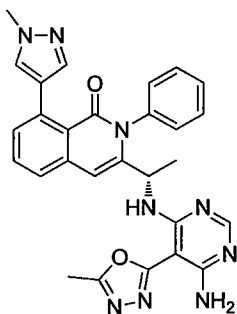
Step 4) (*S*)-3-(1-((6-amino-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)ethyl)-2-cyclopropyl-8-(1-methyl-1*H*-pyrazol-4-yl)isoquinolin-1(2*H*)-one

[414] To a solution of (*S*)-3-(1-aminoethyl)-2-cyclopropyl-8-(1-methyl-1*H*-pyrazol-4-yl) isoquinolin-1(2*H*)-one (40 mg, 0.1297 mmol) in butan-1-ol (0.5 mL) and *N*-ethyl-*N*-isopropyl-propan-2-amine (0.1 mL) was added 6-chloro-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-amine (30 mg, 0.14 mmol) at rt. The reaction was heated to 100 °C and stirred further for 4 hours, then cooled to rt. Water (30mL) was added to the reaction, and the resulted mixture was extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 30/1) to give the title compound as a yellow solid (46.6 mg, 74%).

MS (ESI, pos. ion) *m/z*: 483.8 [M+H]⁺;

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.45 (d, *J* = 6.8 Hz, 1H), 8.13 (s, 1H), 7.61 (s, 1H), 7.58 (s, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.30 (s, 1H), 6.43 (s, 1H), 6.19-6.09 (m, 1H), 3.96 (s, 3H), 3.01-2.90 (m, 1H), 2.49 (s, 3H), 1.65 (d, *J* = 6.8 Hz, 3H), 1.36-1.30 (m, 2H), 0.89-0.81 (m, 2H).

Example 27 (*S*)-3-(1-((6-amino-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)amino)ethyl)-8-(1-methyl-1*H*-pyrazol-4-yl)-2-phenylisoquinolin-1(2*H*)-one

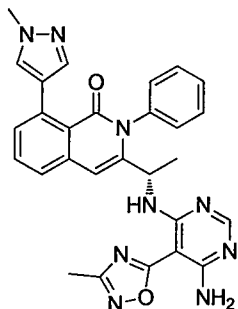


[415] To a solution of (*S*)-3-(1-((6-amino-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2*H*)-one (144 mg, 0.30 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (124 mg, 0.60 mmol) in *N,N*-dimethylacetamide (3 mL) and water (1 mL) was added sodium carbonate (102 mg, 0.96235 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (47 mg, 0.0564 mmol) at rt. The reaction was degassed with N₂ for three times, then heated to 120 °C and stirred further for 3 hours. H₂O (30 mL) was added to the mixture, and the aqueous layer was extracted with DCM (20mL x 3). The combined organic layers was dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 30/1) to give the title compound as a yellow solid (28 mg, 18%).

MS (ESI, pos. ion) m/z : 520.3 $[M+H]^+$;

^1H NMR (600 MHz, CDCl_3) δ (ppm): 8.60 (d, $J = 7.0$ Hz, 1H), 8.00 (s, 1H), 7.59 (s, 1H), 7.57 (s, 1H), 7.54 (t, $J = 7.7$ Hz, 1H), 7.50-7.46 (m, 1H), 7.44-7.41 (m, 1H), 7.40-7.37 (m, 2H), 7.31-7.28 (m, 2H), 6.58 (s, 1H), 4.99-4.95 (m, 1H), 3.86 (s, 3H), 2.68 (s, 3H), 1.46 (d, $J = 6.8$ Hz, 3H).

Example 28 (S)-3-(1-((6-amino-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)ethyl)-8-(1-methyl-1H-pyrazol-4-yl)-2-phenylisoquinolin-1(2H)-one



Step 1) (S)-tert-butyl (1-(8-chloro-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl) carbamate

[416] To a solution of (S)-3-(1-aminoethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one (201 mg, 0.6727 mmol) in DCM (8 mL) was added *N,N*-diethylethanamine (0.28 mL, 2.0 mmol) and di-*tert*-butyl dicarbonate (0.23 mL, 1.0 mmol) at rt. The reaction was stirred at rt for 3.5 hours, then H_2O (20 mL) was added, and the aqueous layer was extracted with DCM (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give the title compound as a white solid (262 mg, 98%).

MS (ESI, pos. ion) m/z : 399.9 $[M+H]^+$;

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.56-7.39 (m, 6H), 7.31-7.26 (m, 2H), 6.54 (s, 1H), 4.67 (brs, 1H), 4.38 (br s, 1H), 1.40 (s, 9H), 1.24 (d, $J = 6.8$ Hz, 3H).

Step 2) (S)-tert-butyl (1-(8-(1-methyl-1H-pyrazol-4-yl)-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl)carbamate

[417] To a solution of (S)-tert-butyl (1-(8-chloro-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl)carbamate (270 mg, 0.6769 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (283 mg, 1.360 mmol) in *N,N*-dimethylacetamide (4 mL) and water (2 mL) was added sodium carbonate (210 mg, 1.98 mmol) and $\text{Pd(dppf)Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (95 mg, 0.114 mmol, 98.0 mass%) at rt. The reaction was

degassed with N₂ for three times, then heated to 120 °C and stirred further for 2 hours. H₂O (30 mL) was added to the mixture, and the aqueous layer was extracted with DCM (20 mL x 3). The combined organic layers were dried with anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 30/1) to give the title compound as a yellow solid (285 mg, 95%).

MS (ESI, pos. ion) *m/z*: 445.9 [M+H]⁺.

Step 3) (S)-3-(1-aminoethyl)-8-(1-methyl-1*H*-pyrazol-4-yl)-2-phenylisoquinolin-1(2*H*)-one

[418] To a mixture of (*S*)-*tert*-butyl 1-(8-(1-methyl-1*H*-pyrazol-4-yl)-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethylcarbamate (280 mg, 0.63 mmol) in DCM (1 mL) was added a solution of HCl in EtOAc (3M, 3 mL) at rt. The reaction was stirred at rt for 3 hours, then saturated NaHCO₃ (20 mL) aqueous solution was added to the mixture, and the aqueous layer was extracted with EtOAc (20 mL x 7). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give the title compound as a yellow solid (96mg, 44.3%).

MS (ESI, pos. ion) *m/z*: 345.0 [M+H]⁺;

¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.61-7.56 (m, 3H), 7.55-7.41 (m, 5H), 7.32 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.25-7.23 (m, 1H), 6.73 (s, 1H), 3.87 (s, 3H), 3.66 (q, *J* = 6.5 Hz, 1H), 1.27 (d, *J* = 6.5 Hz, 3H).

Step 4) (S)-3-(1-((6-amino-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)ethyl)-8-(1-methyl-1*H*-pyrazol-4-yl)-2-phenylisoquinolin-1(2*H*)-one

[419] To a solution of (*S*)-3-(1-aminoethyl)-8-(1-methyl-1*H*-pyrazol-4-yl)-2-phenylisoquinolin-1(2*H*)-one (95 mg, 0.276 mmol) in *N*-ethyl-*N*-isopropyl-propan-2-amine (0.2 mL) and butan-1-ol (1.5 mL) was added 6-chloro-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-amine (85 mg, 0.402 mmol) at rt. The mixture was heated to 100 °C and stirred further for 1 hours, then H₂O (30 mL) was added to the mixture, and the aqueous layer was extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 30/1) to give the title compound as a white solid (112 mg, 78%).

MS (ESI, pos. ion) *m/z*: 520.8 [M+H]⁺;

6.0, 8.0 and 24 h time points and centrifuged at 3,000 or 4000 rpm for 2 to 10 min. The plasma solutions are collected, stored at -20 °C or -70 °C until analyzed by LC/MS/MS as described above.

Table 3 Pharmacokinetic profiles in Rats

Example #	iv dosing					F (%)
	dose (mg/kg)	T _{1/2} (h)	AUC _{last} (ng.h/mL)	Cl/F (L/h/kg)	V _{ss} (L/kg)	
Ex. 1	1	0.63	178	5.58	3.99	46.34
Ex. 2	1	1.16	215	4.74	4.42	46.57
Ex. 3	1	0.74	131	7.68	4.96	12.71
Ex. 4	1	0.98	498	2.00	2.40	78.78
Ex. 5	1	0.53	320	3.13	1.87	106.3
Ex. 6	1	0.86	266	3.74	4.08	48.66
Ex. 7	1	2.30	307	3.26	7.96	42.95
Ex. 8	1	0.92	291	3.47	1.94	93.06
Ex. 9	1	1.38	964	1.04	1.04	66.87
Ex. 10	1	1.44	333	3.00	5.35	81.33
Ex. 12	1	0.70	555	1.80	1.42	32.09
Ex. 13	1	1.66	465	2.17	4.42	67.9
Ex. 15	1	0.86	758	1.36	0.92	48.92
Ex. 16	1	0.61	186	5.36	2.94	11.44
Ex. 18	1	0.775	323	3.10	1.66	38.15
Ex. 20	1	0.81	341	2.92	2.65	64.61
Ex. 22	1	1.32	167	5.99	6.07	16.23
Ex. 24	1	0.75	139	7.20	5.46	12.28

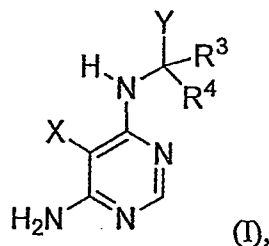
Table 4 Pharmacokinetic profiles in Dogs and Monkeys

Example #	Species	iv dosing					F (%)
		dose (mg/kg)	T _{1/2} (h)	AUC _{last} (ng.h/mL)	Cl/F (L/h/kg)	V _{ss} (L/kg)	
Ex. 8	Dog	1	1.70	1350	0.73	1.43	52.85
	Monkey	1	0.65	711	1.46	1.20	13.1
Ex. 9	Dog	1	1.25	695	1.42	2.04	72.99
	Monkey	1	1.23	1120	0.89	1.17	179.7

Example C: Kinase Activity Assay

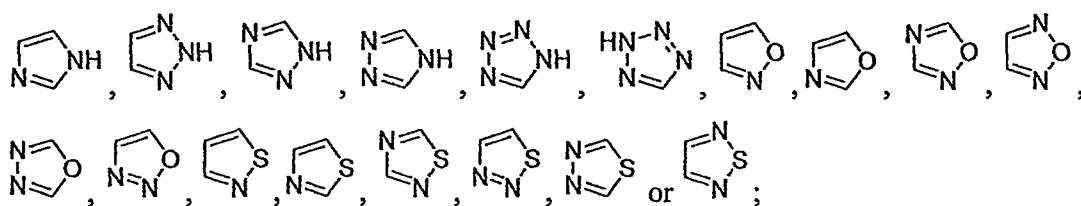
The claims defining the invention are as follows:

1. A compound having Formula (I):



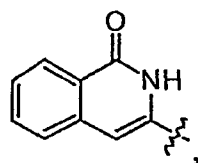
or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a pharmaceutically acceptable salt or a prodrug thereof, wherein:

X is a monovalent heteroaryl group derived from one of the following structures:



and wherein X is optionally substituted by 1, 2 or 3 R^1 groups;

Y is



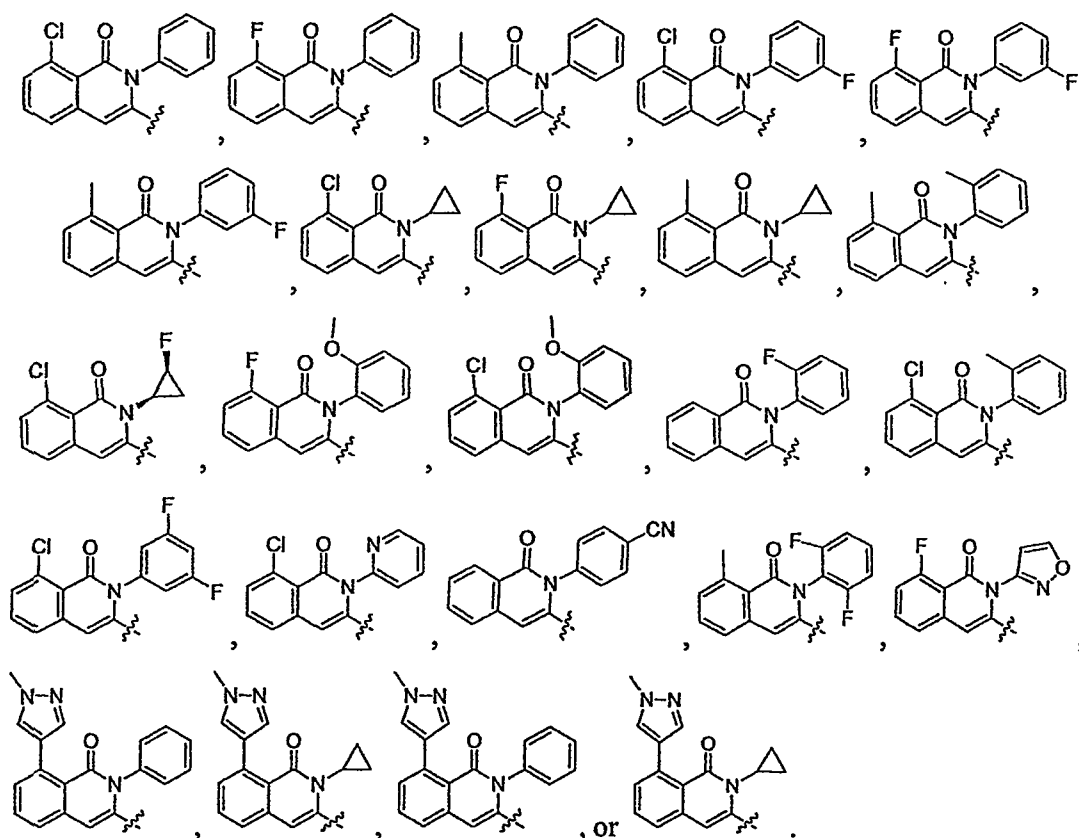
wherein Y is optionally substituted by 1 or 2 R^2 groups;

each R^1 and R^2 is independently H, F, Cl, CN, $-C(=O)OR^a$, OR^a , $-(C_1-C_4)alkylene-OR^a$, $(C_1-C_6)alkyl$, $(C_3-C_8)cycloalkyl$, $-(C_1-C_4)alkylene-(C_3-C_8)cycloalkyl$, $(C_6-C_{10})aryl$, $-(C_1-C_4)alkylene-(C_6-C_{10})aryl$, 5-10 membered heteroaryl or $-(C_1-C_4)alkylene-(5-10 \text{ membered heteroaryl})$, wherein each of the $(C_1-C_6)alkyl$, $(C_3-C_8)cycloalkyl$, $-(C_1-C_4)alkylene-(C_3-C_8)cycloalkyl$, $(C_6-C_{10})aryl$, $-(C_1-C_4)alkylene-(C_6-C_{10})aryl$, 5-10 membered heteroaryl and $-(C_1-C_4)alkylene-(5-10 \text{ membered heteroaryl})$ is optionally substituted with 1, 2, 3 or 4 substituents independently selected from F, Cl, CN, OR^a , NR^aR^b , $(C_1-C_3)alkyl$, $-(C_1-C_4)alkylene-OR^a$ and $-(C_1-C_4)alkylene-NR^aR^b$;

each of R^3 and R^4 is independently H or (C_1-C_3) alkyl, wherein each of the (C_1-C_3) alkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from F, Cl, Br, CN, OR^a , NR^aR^b , (C_1-C_6) alkyl, $-(C_1-C_4)$ alkylene- OR^a and $-(C_1-C_4)$ alkylene- NR^aR^b ; and

each R^a , R^b and R^c is independently H or (C_1-C_6) alkyl, wherein the (C_1-C_6) alkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from F, CN, N_3 , OH, NH_2 , (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_1-C_4) alkoxy and (C_1-C_4) alkylamino.

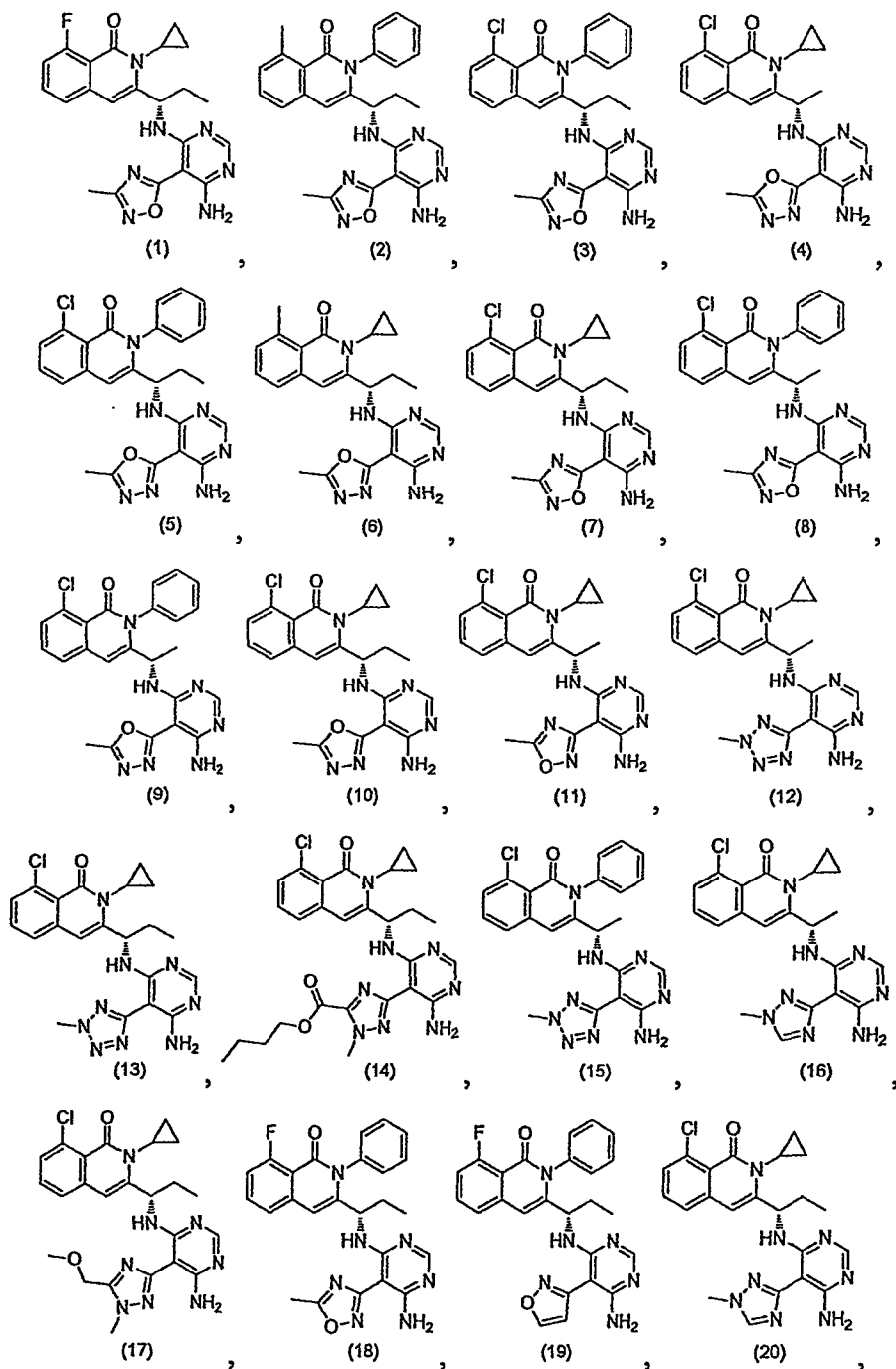
2. The compound according to claim 1, wherein Y is

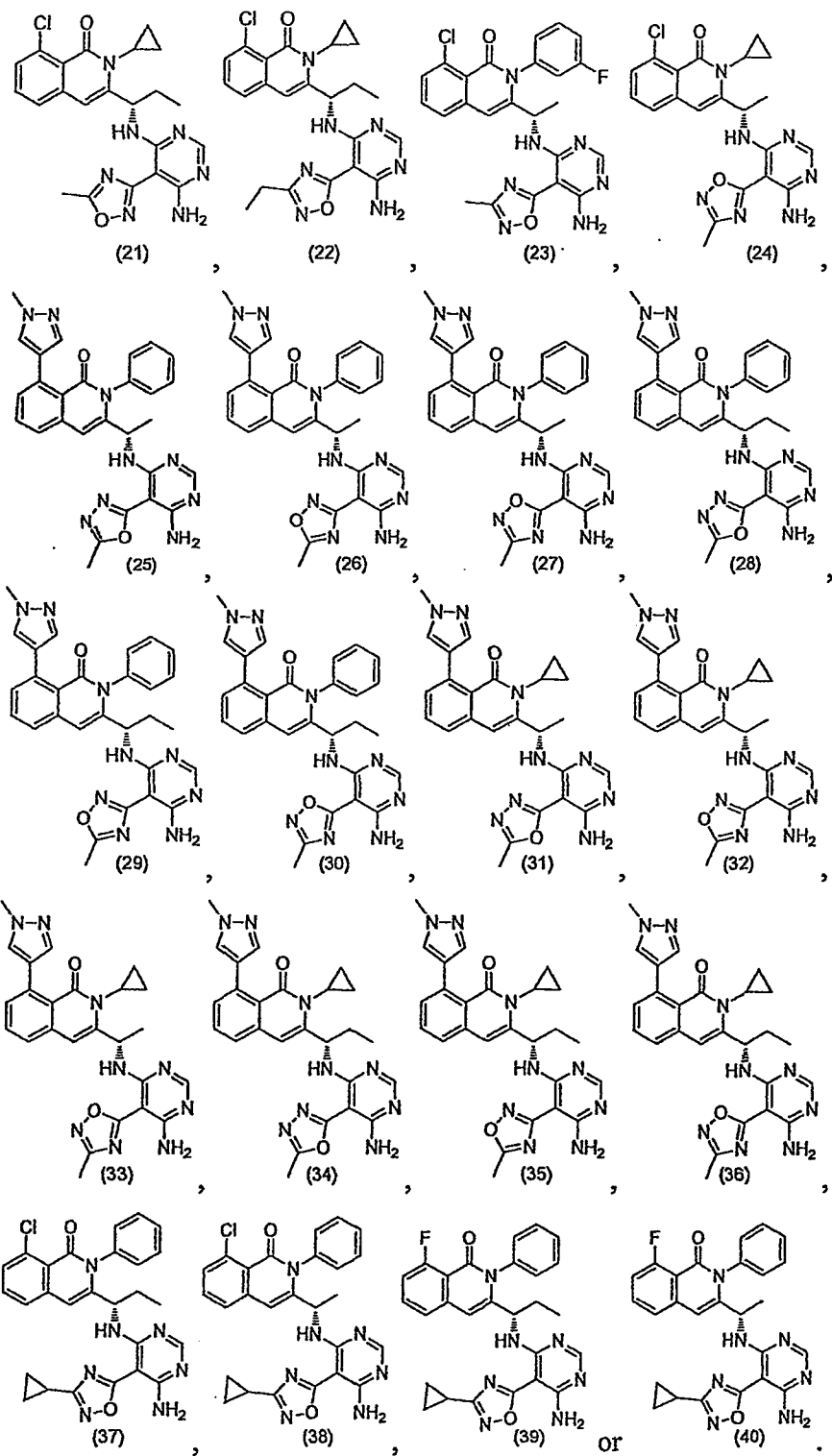


3. The compound according to claim 1, wherein each R^1 and R^2 is independently H, F, Cl, CN, $-C(=O)OR^a$, OR^a , $-(C_1-C_2)$ alkylene- OR^a , (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, $-(C_1-C_2)$ alkylene- (C_3-C_6) cycloalkyl, phenyl, $-(C_1-C_2)$ alkylene-phenyl, 5-6 membered heteroaryl or $-(C_1-C_2)$ alkylene-(5-6 membered heteroaryl), wherein each of the (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, $-(C_1-C_2)$ alkylene- (C_3-C_6) cycloalkyl, phenyl, $-(C_1-C_2)$ alkylene-phenyl, 5-6 membered heteroaryl and $-(C_1-C_2)$ alkylene-(5-6 membered

heteroaryl) is optionally substituted with 1, 2, 3 or 4 substituents independently selected from F, Cl, CN, OR^a, NR^aR^b and (C₁-C₃)alkyl.

4. The compound of claim 1 having one of the following structures:





5. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4, and one or more pharmaceutically acceptable carriers, excipients, diluents, adjuvants, vehicles or a combination thereof.

6. The pharmaceutical composition according to claim 5 further comprising one or more additional therapeutic agents.

7. Use of a compound according to any one of claims 1 to 4, or a pharmaceutical composition according to claim 5 or claim 6 in the manufacture of a medicament for the treatment of a disorder mediated by inappropriate PI3-kinase activity.

8. Use of a compound according to any one of claims 1 to 4 or a pharmaceutical composition according to claim 5 or claim 6 in the manufacture of a medicament for modulating the activity of the PI3-kinase.

9. The use of claim 8, wherein the PI3-kinase is PI3K δ .

10. The use of claim 7, wherein the disorder is a respiratory disease, a viral infection, a non-viral respiratory infection, an allergic disease, an autoimmune disease, an inflammatory disorder, a cardiovascular disease, a hematologic malignancy, a neurodegenerative disease, pancreatitis, multiorgan failure, kidney disease, platelet aggregation, cancer, sperm motility, transplantation rejection, graft rejection, lung injury, or pain.

11. The use of claim 7, wherein the disorder is asthma, chronic obstructive pulmonary disease (COPD), viral respiratory tract infections, viral exacerbation of respiratory diseases, aspergillosis, leishmaniasis, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, thrombosis, atherosclerosis, hematologic malignancy, neurodegenerative disease, pancreatitis, multiorgan failure, kidney disease, platelet aggregation, cancer, sperm motility, transplantation rejection, graft rejection, lung injury, pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trauma), trigeminal neuralgia or central pain.