Supporting Information

Structure-Based Discovery of Potent inhibitors of Axl: Design, Synthesis, and Biological Evaluation

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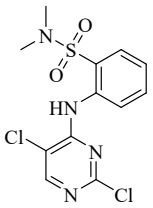
General experimental section

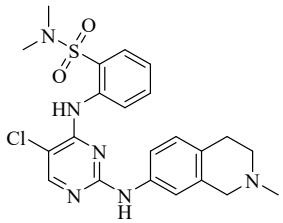
Chemistry

Unless otherwise noted, all starting materials, reagents, and solvents were commercially available and used without further purification. The intermediates and end-products were purified by flash column chromatography with silica gel 60 (200-300 Mesh). Chemical reactions were monitored by thin-layer chromatography (TLC) or liquid chromatography (LC)/mass spectrometry (MS). LC/MS was performed on an Agilent HPLC1260-MS6120 system (column: Agilent-SB-C18, 2.5 mm × 30 mm, 3.5 μm). ^{1}H NMR spectra data were obtained using $CDCl_3$, CD_3OD or DMSO-d_6 as solvent on a Bruker Avance III, 400 M or 600 M frequencies spectrometers. The coupling constant *J* is given in Hz. NMR data are reported as follow: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants and integration. The purity of all the final compounds was confirmed to be >95% as determined by HPLC on an Agilent infinity 1260 HPLC system (column: Zorbax Eclipse Plus column, C18, 4.6 mm × 150 mm, 3.5 μm; detector: diode array detector). High-resolution ESI-MS was performed on an Agilent G6500 series Q-TOF spectrometer.

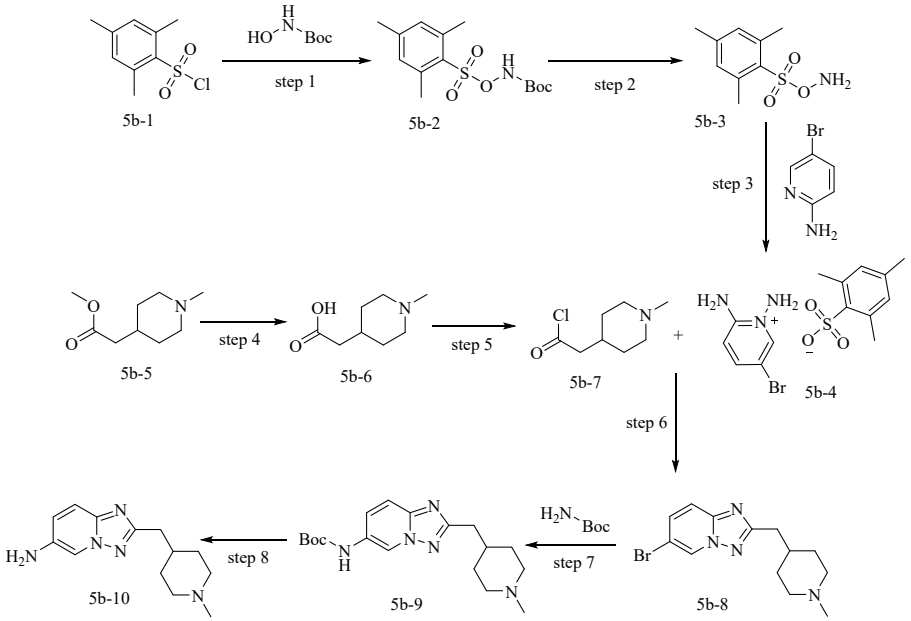
Experimental details and characterization for our compounds



2-((2,5-dichloropyrimidin-4-yl)amino)-*N,N*-dimethylbenzenesulfonamide (**4**): Commercially available 2-amino-*N,N*-dimethylbenzenesulfonamide (1.0 g，4.9 mmol) was added to a round flask and dissolved in DMF (20.0 mL). NaH (60% dispersion in mineral oil, 0.4 g, 9.8 mmol) was added to the solution at 0^{o}C. After stirring for 30 min, 2,4,5-trichloropyrimidine (1.4 g, 7.6 mmol) was added in the mixture. Another after stirring for overnight, Saturated NH_4Cl aqueous solution (20 mL) and water (80 mL) was added. Filtration and purification by flash chromatography with petroleum ether/EtOAc = 5/1 as eluent gave compound 4 (0.4 g, 1.9 mmol, 39%). ^{1}H NMR (400 MHz, CDCl3): δ 9.88 (s, 1 H), 8.62 (d, 1 H, J = 8.4 Hz), 8.30 (s, 1 H), 7.89 (dd, 1 H, J = 1.2, 8.0 Hz), 7.72-7.68 (m, 1 H), 7.33-7.29 (m, 1 H), 2.76 (s, 6 H). MS (ESI): 347.1 $[M+H]^+$.



2-((5-chloro-2-((2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)amino)pyrimidin-4-yl)amino)-*N,N*-dimethylbenzenesulfonamide (**5a**): 2-methyl-3,4-dihydro-*1H*-isoquinolin-7-amine (100.0 mg, 0.6 mmol), intermediate 4 (210.0 mg, 0.6 mmol), $Pd_2(dba)_3$ (56.0 mg, 0.06 mmol), t-butyl-Xphos (53.0 mg, 0.12 mmol), tBuONa (118.0 mg, 1.2 mmol) and tBuOH (6 mL) were added to a round flask. After degassing and refilling with N_2, the mixture was refluxed 16 h. The mixture was cooled down and concentrated *in vacuo*. The residue was purified by flash column chromatography (dichloromethane/1.2M ammonia in methanol = 500 / 1) to give a yellow solid (149.0 mg, 0.3 mmol, 52.1%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.42 (s, 1H), 9.25 (s, 1H), 8.51 (d, 1H, J = 6.8 Hz), 8.27 (s, 1 H), 7.83 (d, 1 H, J = 7.2 Hz), 7.70 (t, 1 H, J = 7.6 Hz), 7.38 (t, 1 H, J = 7.2 Hz), 7.32 (s, 1 H), 7.29 (s, 1 H), 6.97 (d, 1 H, J = 8.0 Hz), 3.33 (s, 2 H), 2.74 (t, 2 H, J = 5.2 Hz), 2.64 (s, 6 H), 2.57 (t, 2 H, J = 5.6 Hz), 2.33 (s, 3 H). MS (ESI): 473.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{22}H_{26}ClN_6O_2S^+$, 473.1418; found, 473.1416. Purity: 95.99%.



Preparation of intermediate 5b-10

tert-butyl ((mesitylsulfonyl)oxy)carbamate (**5b-2, step 1**): Triethylamine (3.8 mL, 27.0 mmol) was added to a solution of 2,4,6-trimethylbenzene-1-sulfonyl chloride (5.0 g, 22.4 mmol) tert-butyl hydroxy carbamate (3.04 g, 22.4 mmol) and EtOAc (110.0 mL). The mixture was cooled to -10^{o}C and stirred for 2 h. The organic phase was washed with water (20 mL) and brine (20 mL) without further purification.

O-(mesitylsulfonyl)hydroxylamine (**5b-3, step 2**): The organic phase of step1 was cooled to 0^{o}C. Concentrated sulfuric acid (5.5 mL, 98 mmol) was added to the mixture and stirred for 16 h. The saturated aqueous Na_2CO_3 (60 mL) was added slowly. After neutralization to pH=8 with Na_2CO_3 (6.0 g), the mixture was filtered and separated. The organic phase was washed with water (20 mL), brine (20 mL) respectively and was not further purified.

1,2-diamino-5-bromopyridin-1-ium combined with 2,4,6-trimethylbenzenesulfonate (**5b-4, step 3**): The organic phase of step2 was cooled to 5^{o}C. 5-bromopyridin-2-amine (2.0 g, 11.2 mmol) was added to the mixture and stirred for 2 h. The mixture was then filtered to give a white solid 5b-4 (3.27 g, 8.4 mmol, 75.1% for total 3 steps).

2-(1-methylpiperidin-4-yl)acetic acid (**5b-6, step 4**): To a mixture of methyl 2-(1-methylpiperidin-4-yl)acetate (2.0 g, 11.4 mmol) and CH_3OH (30 mL) was added the LiOH (15 mL, 2 mol/L, 30.0 mmol) aqueous solution. After stirring for 5 h, the mixture was acidified to pH=2 with HCl (10 mL, 20 mmol, 2 mol/L). Then the mixture was concentrated *in vacuo* to give a yellow oil. The oil was diluted in CH_3OH (100 mL) and dichloromethane (50 mL). Then Na_2SO4 solid was added in the solution. The mixture was filtered and concentrated to give a new yellow oil 5b-6 (1.3 g, 6.2 mmol, 100%).

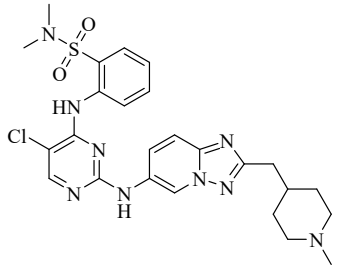
2-(1-methylpiperidin-4-yl)acetyl chloride (**5b-7, step 5**): Methyl 2-(1-methylpiperidin-4-yl)acetate (3.6 g, 18.6 mmol) was dissolved in dichloromethane (60 mL). DMF (30 mg, 0.42 mmol) and oxalyl chloride (3.0 mL, 36.0 mmol) were added to the solution successively. The mixture was stirred at room temperature for 2 h, and then concentrated to give a yellow oil 5b-7 (3.9 g, 18.4 mmol, 98.9%) without further purification.

6-bromo-2-((1-methylpiperidin-4-yl)methyl)-[1,2,4]triazolo[1,5-a]pyridine (**5b-8, step 6**): 5b-7 (3.9 g, 18.4 mmol) and 5b-4 (1.73 g, 4.46 mmol) were diluted in pyridine (9 mL) at a round flask. After stirring and refluxing for 10 h, the mixture was concentrated. The residue was diluted in dichloromethane (100 mL), then basified with saturated aqueous $NaHCO_3$. The aqueous phase was separated and extracted with dichloromethane (100 mL). Subsequently, the organic phases were combined and washed with brine (10 mL), then concentrated *in vacuo* to give a yellow solid. The residue was purified by flash column chromatography with dichloromethane /1.2M ammonia in methanol = 50/1 as eluent to give compound 5b-8 (870.0 mg, 2.8 mmol, 63.0%). MS (ESI): 309.4 $[M+H]^+$.

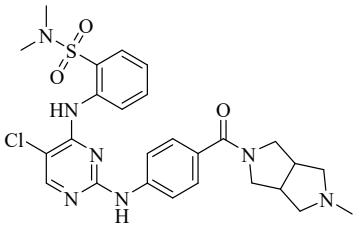
tert-butyl (2-((1-methylpiperidin-4-yl)methyl)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)carbamate (**5b-9, step 7**): To a mixture of 5b-8 (870.0 mg, 2.8 mmol) and tert-butyl carbamate (0.5 g, 4 mmol) in tBuOH (18 mL) were added Cs2CO3 (1.9 g, 5.7 mmol), XantPhos (0.33 g, 0.56 mmol) and Pd2(dba)3 (0.26 g, 0.28 mmol). After degassing and

refilling with N_2, the mixture was refluxed 16 h. The mixture was cooled down and concentrated in vacuo. The residue was purified by flash column chromatography (dichloromethane/1.2M ammonia in methanol = 100 / 1) to give a yellow oil 5b-9 (820.0 mg, 2.36 mmol, 82.0%). MS (ESI): 346.3 $[M+H]^+$.

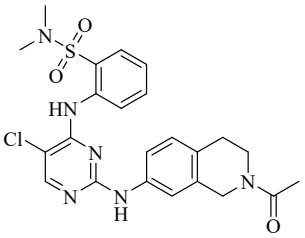
2-((1-methylpiperidin-4-yl)methyl)-[1,2,4]triazolo[1,5-a]pyridin-6-amine (**5b-10, step 8**): To a mixture of 5b-9 (800.0 mg, 2.3 mmol) and CH_3OH (30 mL) was added concentrated hydrochloric acid (3 mL). After stirring for 2 h at 50°C, the mixture was cooled and concentrated. The residue was diluted in dichloromethane (100 mL) and basified with saturated aqueous Na_2CO_3. The aqueous phase was separated and extracted with dichloromethane (100 mL). Subsequently, the organic phases were combined and washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a yellow solid. The residue was purified by flash column chromatography with eluent (dichloromethane/1.2M ammonia in methanol = 50/1) to give compound 5b-10 (280.0 mg, 1.1 mmol, 49.0%). MS (ESI): 246.1 $[M+H]^+$.



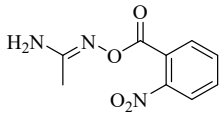
2-((5-chloro-2-((2-((1-methylpiperidin-4-yl)methyl)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)pyrimidin-4-yl)amino)-*N,N*-dimethylbenzenesulfonamide (**5b**): To a mixture of 5b-10 (140.0 mg, 0.55 mmol) and compound 4 (260.0 mg, 0.75 mmol) in tBuOH (8 mL) were added Pd2(dba)3 (46 mg, 0.05 mmol), Xantphos (58 mg, 0.1 mmol) and tBuONa (0.2 g, 2 mmol). After degassing and refilling with N_2, the mixture was refluxed 16 h. The mixture was cooled down and concentrated *in vacuo*. The residue was purified by flash column chromatography (dichloromethane/1.2M ammonia in methanol = 100/1) to give a yellow solid (50.0 mg, 0.09 mmol, 18.1%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.80 (s, 1H), 9.35 (s, 1 H), 9.30 (s, 1 H), 8.53 (s, 1H), 8.38 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.79- 7.62 (m, 3H), 7.39 (t, J = 7.6 Hz, 1H), 2.88 (d, J = 10.9 Hz, 2H), 2.72 (d, J = 6.9 Hz, 2H), 2.66 (s, 6H), 2.27 (s, 3H), 2.20-2.01 (m, 2H), 1.83 (s, 1H), 1.71 (d, J = 12.8 Hz, 2H), 1.45-1.27 (m, 2H). MS (ESI): 556.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{25}H_{31}ClN_9O_2S^+$, 556.1932; found, 556.2021. Purity: 96.71%.



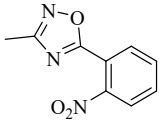
2-((5-chloro-2-((4-(5-methyloctahydropyrrolo[3,4-c]pyrrole-2-carbonyl)phenyl)amino)-pyrimidin-4-yl)amino)--*N,N*-dimethylbenzenesulfonamide (**5c**): To a mixture of (4-aminophenyl)-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)methan one (100 mg, 0.41 mmol) and compound 4 (142.0 mg, 0.4 mmol) in tBuOH (6 mL) were added Pd2(dba)3 (38.0 mg, 0.04 mmol), t-butyl XPhos (36.0 mg, 0.08 mmol) and tBuONa (80.0 mg, 0.82 mmol). After degassing and refilling with N2, the mixture was refluxed 24 h. The mixture was cooled down and concentrated in vacuo. The residue was purified by flash column chromatography (dichloromethane/1.2M ammonia in methanol = 100/1) to give a yellow solid 5d (167.0 mg, 0.4 mmol, 73.7%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.76 (s, 1 H), 9.32 (s, 1 H), 8.53 (d, J = 8.0 Hz, 1 H), 8.33 (s, 1 H), 7.84 (dd, J = 7.9, 1.1 Hz, 1 H), 7.77 (t, J = 7.8 Hz, 1 H), 7.67 (d, J = 8.5 Hz, 2 H), 7.41 (d, J = 7.4 Hz, 1 H), 7.37 (d, J = 8.6 Hz, 2 H), 3.71 (s, 2 H), 3.28 (s, 2 H), 2.77 (d, J = 2.0 Hz, 2 H), 2.65 (s, 5 H), 2.40 (m, 4 H), 2.22 (s, 3 H). MS (ESI): 556.3 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{26}H_{31}ClN_7O_3S^+$, 556.1819; found, 556.1888. Purity: 96.55%.



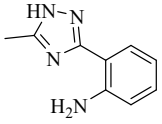
2-((5-chloro-2-((2-acetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)amino)pyrimidin-4-yl)amino)-*N,N*-dimethylbenzenesulfonamide (**5d**):To a suspension of 1-(7-amino-3,4-dihydro-1H-isoquinolin-2-yl)ethanone (90.2 mg, 0.47 mmol) and intermediate 4 (165.2 mg, 0.47 mmol) in 1-butanol (1 mL) was added cat. HCl (10.0 uL). The reaction mixture was stirred at 130 °C for 3 h in microwave conditions. After concentration, the residue was purified by flash column chromatography with eluent (MeOH/DCM = 1/30) to give the title compound 5e as a white solid (45.6 mg, 0.09 mmol, 19.2%).^{1}H NMR (400 MHz, DMSO-d6) δ 9.52 (d, J = 14.9 Hz, 1H), 9.25 (d, J = 7.6 Hz, 1H), 8.49 (dd, J = 10.5, 6.5 Hz, 1H), 8.29 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 7.9 Hz, 1H), 7.49 (d, J = 15.1 Hz, 1H), 7.39 (dd, J = 13.5, 6.7 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 4.45 (d, J = 4.4 Hz, 2H), 3.63 (t, J = 5.9 Hz, 2H), 2.79 (t, J = 5.6 Hz, 1H), 2.68 (d, J = 6.0 Hz, 1H), 2.64 (s, 6H), 2.07 (d, J = 4.2 Hz, 3H). MS (ESI): 501.1 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{23}H_{25}ClN_6O_3S^+$, 501.1397; found, 501.1490. Purity: 97.01%.



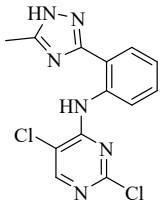
(*E*)-*N'*-((2-nitrobenzoyl)oxy)acetimidamide (**7**): To a solution of 2-nitrobenzoic acid (1.0 g, 4.38 mmol) in THF (15 mL) were added DMF (189.4 mg) and $SOCl_2$ (4.62 g, 38.8 mmol), stirred at 60°C for 3 h. The mixture was cooled down to the rt. and concentrated in *vacuo* to afford a yellow solid. *N*-Hydroxyacetamidine (2.2 g, 30 mmol) and triethylamine (4.5 g, 44 mmol) was diluted in dichloromethane (30 mL). Then the mixture was slowly added into a solution of the above-mentioned yellow solid in dichloromethane (10 mL) at -5°C, and stirred for overnight. TLC show no starting material. The residue was concentrated in *vacuo* and purified by a flash column chromatography with eluent (petroleum ether/Ethyl acetate =1/0-1/1) to give the title compound as a yellow solid (6.5 g, 29 mmol, 97% Yield). ^{1}H NMR (400 MHz, DMSO) δ 8.08 (dd, J = 7.9, 1.0 Hz, 1H), 7.91 (dd, J = 7.5, 1.4 Hz, 1H), 7.84 (td, J = 7.5, 1.3 Hz, 1H), 7.79 (td, J = 7.7, 1.6 Hz, 1H), 6.47 (s, 2H), 1.76 (s, 3H). MS (ESI): 224.0 $[M+H]^+$.



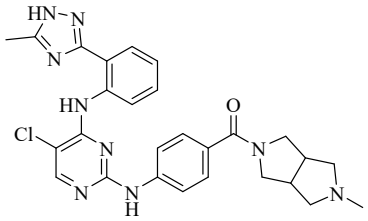
3-methyl-5-(2-nitrophenyl)-1,2,4-oxadiazole (**8**): A mixture of 7 (1.0 g, 4.7 mmol), K_2CO_3 (320.0 mg, 2.3 mmol), 1,4-dioxane (10.0 mL) was stirred at 105°C for overnight. TLC show no starting material, and hence the solvent was removed in *vacuo* and purified by a flash column chromatography with eluent (ethyl acetate) to give the title compound as a yellow solid (0.8 g, 4 mmol, 80% Yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-7.97 (m, 1H), 7.93 (dt, J = 5.5, 3.0 Hz, 1H), 7.81-7.73 (m, 2H), 2.50 (s, 3H). MS (ESI): 206.1 $[M+H]^+$.



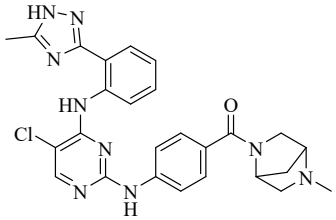
2-(5-methyl-1*H*-1,2,4-triazol-3-yl)aniline (**9**): To a solution of 8 (0.7 g, 3.0 mmol), active carbon (100.0 mg) and $FeCl_3$ (60.0 mg, 370.0 umol) in ethanol (15.0 mL, 258.0 mmol) was added hydrazine hydrate (800.0 mg, 20.0 mmol). The mixture was cooled to rt. and stirred for 5.5 h at 85°C. TLC show no starting material, the solvent was removed in *vacuo* and purified by a flash column chromatography with eluent (petroleum ether/Ethyl acetate =1/1) to give the title compound as a yellow solid (380.0 mg, 2.17 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.6 Hz, 1H), 7.23-7.17 (m, 1H), 6.77 (t, J = 8.2 Hz, 2H), 2.53 (s, 3H). MS (ESI): 175.2 $[M+H]^+$.



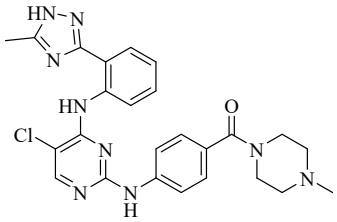
2,5-dichloro-*N*-(2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)pyrimidin-4-amine (**10**): *N,N*-diisopropylethylamine (2.0 mL, 12.0 mmol) was added into a solution of 9 (1.7 g, 9.8 mmol) and 2,4,5-trichloropyrimidine (1.8 g, 9.8 mmol) in isopropyl alcohol (60.0 mL). The mixture was stirred at 85°C for 6 h. TLC show no starting material. After filtration, the residue was washed by isopropyl alcohol (20 mL) thrice. The combined organic layer was concentrated to give a yellow solid (1.4 g, 4.4 mmol, 45%). MS (ESI): 321.2 $[M+H]^+$.



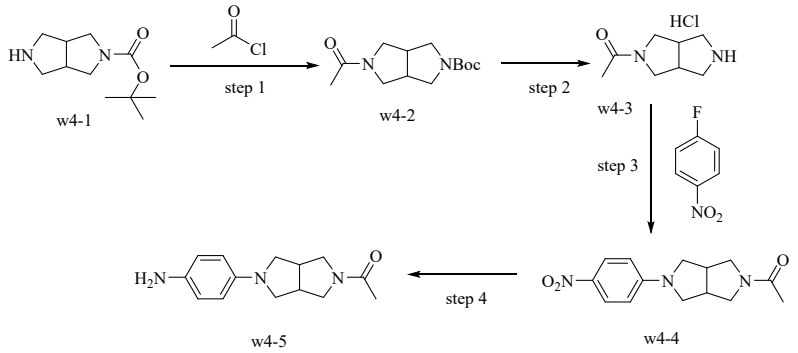
(4-((5-chloro-4-((2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (**w1**): To a solution of 10 (131.0 mg, 0.41 mmol) in 2-methylpropan-2-ol (6.0 mL) was added (4-aminophenyl)(5-methylhexahydrop yrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (100.0 mg, 0.41 mmol), $Pd_2(dba)_3$ (38.0 mg, 41.0 umol), t-butyl XPhos (36.0 mg, 82.0 umol) and tBuONa (80.0 mg, 0.82 mmol). The reaction was degassed with N_2. After refluxed for overnight, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/1.2M ammonia in methanol = 100/1) to give the title compound as yellow solid (28 mg, 53.3 umol, 13.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 14.16 (bs, 1H), 11.70 (s, 1H), 9.71 (s, 1H), 8.84-8.83 (d, J = 7.9 Hz, 1H), 8.28 (s, 1H), 8.14-8.12 (d, J = 7.5 Hz, 1H), 7.77-7.75 (d, J = 8.3 Hz, 2H), 7.44-7.42 (m, 3H), 7.22-7.18 (t, J = 7.4 Hz, 1H), 3.72 (m, 2H), 3.51 (m, 2H), 2.84 (s, 2H), 2.65 (m, 2H), 2.50 (m, 2H), 2.47 (s, 3H), 2.34 (s, 3H). MS (ESI): 530.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{27}H_{29}ClN_9O^+$, 530.2105; found, 530.2111. Purity: 98.59%.



(4-((5-chloro-4-((2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)(5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)methanone (**w2**): To a solution of 10 (139.0 mg, 0.43 mmol) in 2-methylpropan-2-ol (6.0 mL) was added (4-aminophenyl)-(5-methyl-2,5-di azabicyclo[2.2.1]heptan-2-yl)methanone (100.0 mg, 0.43 mmol), $Pd_2(dba)_3$ (40.0 mg, 43.0 umol), t-butyl XPhos (38.0 mg, 87.0 umol) and tBuONa (85.0 mg, 0.87 mmol). The reaction was degassed with N_2. After being refluxed for overnight, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/methanol = 50/1) to give the title compound as yellow solid (150.0 mg, 288.1 umol, 67%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 14.39 (bs, 1H), 11.73 (s, 1H), 9.77 (s, 1H), 8.85-8.84 (d, J = 8.2 Hz, 1H), 8.28 (s, 1H), 8.15-8.13 (d, J = 7.8 Hz, 1H), 7.80-7.78 (d, J = 6.5 Hz, 2H), 7.52-7.50 (d, J = 6.9 Hz, 1H), 7.44-7.40 (m, 2H), 7.22-7.18 (t, J = 7.5 Hz, 1H), 3.63-3.50 (m, 4H), 3.50 (s, 3H), 2.90 (s, 2H), 2.51 (s, 3H), 2.47 (s, 3H), 1.86 (m, 1H), 1.72 (m, 1H). MS (ESI): 516.5 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{26}H_{27}ClN_9O^+$, 516.1949; found, 516.1945. Purity: 96.39%.



(4-((5-chloro-4-((2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)(4-methylpiperazin-1-yl)methanone (**w3**): To a solution of 10 (139 mg, 0.43 mmol) in isopropyl alcohol (4.0 mL) was added (4-aminophenyl)-(4-methylpiperazin-1-yl)methanone (100.0 mg, 0.43 mmol), HCl/dioxane (4.0 mol/L, 0.1 mL, 0.4 mmol). After being stirred at 130°C in microwave reactor for 4 h, the reaction mixture was diluted with methanol (10.0 mL) and neutralized with saturated aqueous solution of $NaHCO_3$ (6.0 mL). The crude was collected through filtration. The crude was purified by a silica gel column chromatography with eluent (dichloromethane/1.2M ammonia in methanol = 200/1) to give the title compound as yellow solid (51.0 mg, 98.9 umol, 23.0 %).^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.15 (s, 1H), 9.69 (s, 1H), 8.84-8.82 (d, J = 8.3 Hz, 1H), 8.27 (s, 1H), 8.14-8.12 (d, J = 8.0 Hz, 1H), 7.79-7.77 (d, J = 8.4 Hz, 2H), 7.40-7.32 (m, 3H), 7.19-7.15 (t, J = 7.6 Hz, 1H), 3.50 (m, 4H), 2.43 (s, 3H), 2.33 (s, 4H), 2.21 (s, 3H). MS (ESI): 504.3 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{25}H_{27}ClN_9O^+$, 504.1949; found, 504.2020. Purity: 98.34%.



Preparation of intermediate w4-5

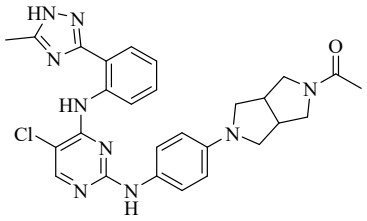
tert-butyl 5-acetylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**w4-2, step 1**): To a mixture of commercially agent w4-1 (2.0 g, 9.2 mmol) and triethylamine (2.7 mL, 19 mmol) in CH_2Cl_2 (45.0 mL) was added acetyl chloride (0.8 mL, 10.0 mmol) slowly. After being stirred at rt overnight, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/methanol = 100/1) to give the title compound as yellow oil (2.15 g, 8.46 mmol, 92 %). MS (ESI): 199.1 $[M+H-56]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72-3.68 (m, 2H), 3.61 (m, 2H), 3.44-3.41 (m, 1H), 3.36-3.30 (m, 2H), 3.22-3.20 (m, 1H), 2.98-2.93 (m, 1H), 2.87 (m, 1H), 2.06 (s, 3H), 1.47 (s, 9H).

1-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethanone hydrochloride (**w4-3**, step 2): A suspension of w4-2 (10.5 g, 41.3 mmol) in HCl/dioxane (4 mol/L, 80.0 mL) was stirred at rt for overnight. The reaction mixture was concentrated in vacuo and without further purification (7.88 g, 41.3 mmol, 100 %). MS (ESI): 155.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.64-3.60 (m, 1H), 3.51-3.43 (m, 2H), 3.36-3.32 (m, 3H), 3.07-3.03 (m, 2H), 2.98-2.92 (m, 2H), 1.93 (s, 3H).

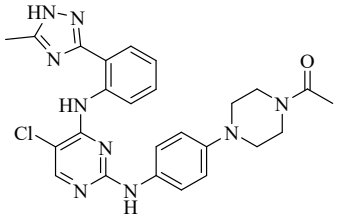
1-(5-(4-nitrophenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethanone (**w4-4, step 3**): To a suspension of w4-3 (3.0 g, 15.7 mmol) in DMSO (20.0 mL) was added 1-fluoro-4-nitro-benzene (2.0 mL, 18.7 mmol) and potassium carbonate (5.5 g, 39.3 mmol). After being stirred at 90 °C for 7 h, The reaction mixture was cooled to room temperature and diluted with H_2O (100.0 mL). After being stirred at rt for another 0.5 h, the title solid was collected through filtration (4.33 g, 15.7 mmol, 100 %). MS (ESI): 276.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.14 (d, J = 9.3 Hz, 2H), 6.51-6.49 (d, J = 9.3 Hz, 2H), 3.86-3.79 (m, 2H), 3.75-3.70 (m, 2H), 3.56-3.52 (m, 1H), 3.45-3.32 (m, 3H), 3.25-3.17 (m, 1H), 3.16-3.08 (m, 1H), 2.09 (s, 3H).

1-(5-(4-aminophenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethanone (**w4-5, step 4**): To a solution of w4-4 (6.25 g, 22.7 mmol) in EtOH (80 mL)/H_2O (16.0 mL) was added NH_4Cl (8.54 g, 159.0 mmol) and powdered Fe (5.2 g, 90.7

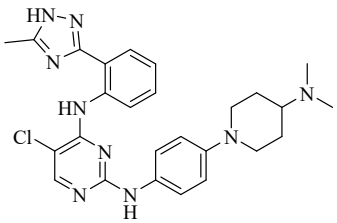
mmol). After being stirred at reflux for 7h, the reaction mixture was quenched with the aqueous solution of Na_2CO_3 (2.5 N, 16.0 mL). The reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/methanol = 100/1) to give the title compound as yellow solid (3.1 g, 12.7 mmol, 56.0 %). MS (ESI): 246.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-*d6*) δ 6.51-6.49 (d, J = 7.4 Hz, 2H), 6.38-6.36 (d, J = 7.4 Hz, 2H), 4.32 (s, 2H), 3.74-3.69 (m, 1H), 3.59-3.54 (m, 1H), 3.33-3.21 (m, 5H), 3.06-3.00 (m, 2H), 2.95-2.89 (m, 1H), 1.93 (s, 3H).



1-(5-(4-((5-chloro-4-((2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)am ino)phenyl) hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethan-1-one (**w4**): To a solution of 10 (131.0 mg, 0.41 mmol) in dioxane (6.0 mL) was added 1-(5-(4-aminophenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethanone (100.0 mg, 0.41 mmol), $Pd_2(dba)_3$ (38.0 mg, 0.041 mmol), *t*-butyl XPhos (36.0 mg, 0.082 mmol) and tBuONa (80.0 mg, 0.82 mmol). The reaction was degassed with nitrogen. After being stirred at reflux for 8h, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/methanol = 200/1) to give the title compound w4 as yellow solid (70.0 mg, 0.13 mmol, 32.0 %).^1H NMR (400 MHz, DMSO-*d6*) δ δ 14.09 (s, 1H), 11.58 (s, 1H), 9.09 (s, 1H), 8.89 (s, 1H), 8.14 - 8.09 (m, 2H), 7.43 - 7.41 (d, J = 8.5 Hz, 2H), 7.36 - 7.32 (m, 1H), 7.16 - 7.12 (m, 1H), 6.55 - 6.52 (d, J = 8.8 Hz, 2H), 3.77 - 3.72 (m, 1H), 3.62 - 3.57 (m, 1H), 3.46 - 3.42 (m, 3H), 3.31 - 3.25 (m, 1H), 3.19 - 3.12 (m, 2H), 3.09 - 3.05 (m, 1H), 3.02 - 2.97 (m, 1H), 2.47 (s, 3H), 1.95 (s, 3H). MS (ESI): 530.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{27}H_{29}ClN_9O^+$, 530.2105; found, 530.2131. Purity: 95.00%.

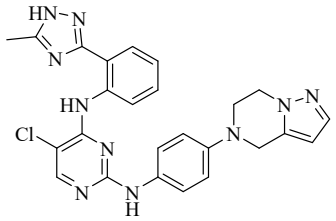


1-(4-(4-((5-chloro-4-((2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethan-1-one (**w5**): To a solution of 10 (139.0 mg, 0.43 mmol) in propan-2-ol (4.0 mL) was added 1-[4-(4-aminophenyl)piperazin-1-yl]ethanone (100.0 mg, 0.43 mmol), HCl/dioxane (4 M, 0.1 mL, 0.4 mmol). After being stirred at 130°C in microwave for 4 h, the reaction mixture was diluted with MeOH (8.0 mL) and neutralized with saturated aq. $NaHCO_3$ (6.0 mL). The mixture was concentrated in *vacuo*. And the residue was purified by a silica gel column chromatography with eluent (dichloromethane/1.2M ammonia in methanol = 200/1) to give the title compound w5 as yellow solid (17.0 mg, 34.4 umol, 8.0%).^1H NMR (400 MHz, DMSO-*d6*) δ 14.13 (s, 1H), 11.65 (s, 1H), 9.25 (s, 1H), 8.88 (s, 1H), 8.18 (s, 1H), 8.12 (s, 1H), 7.53 - 7.51 (d, J = 7.0 Hz, 2H), 7.39 (m, 1H), 7.17 (m, 1H), 6.94 - 6.92 (d, J = 7.1 Hz, 2H), 3.59 (s, 4H), 3.10 (s, 2H), 3.03 (s, 2H), 2.47 (s, 3H), 2.05 (s, 3H). MS (ESI): 504.1 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{25}H_{27}ClN_9O^+$, 504.1949; found, 504.2003. Purity: 96.70%.

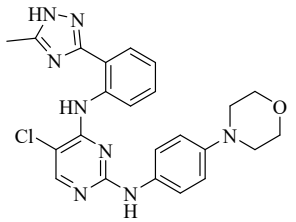


5-chloro-N^2-(4-(4-(dimethylamino)piperidin-1-yl)phenyl)-N^4-(2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)pyrimidine-2,4-diamine (**w6**): To a solution of 10 (287.0 mg, 0.89 mmol) in propan-2-ol (4.0 mL) was added 1-(4-aminophenyl)-

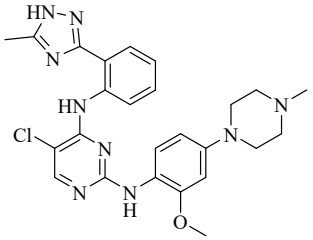
N,N-dimethyl-piperidin-4-amine (100.0 mg, 0.45 mmol), HCl/dioxane (4.0 mol/L, 0.2 mL, 0.8 mmol). After being stirred at 130°C in microwave reactor for 4 h, the reaction mixture was diluted with methanol (10.0 mL) and neutralized with saturated aqueous solution of $NaHCO_3$ (6.0 mL). The crude was collected through filtration. The crude was purified by a silica gel column chromatography with eluent (dichloromethane/1.2M ammonia in methanol = 100/1) to give the title compound as yellow solid (20.0 mg, 40.5 umol, 9.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 14.09 (s, 1H), 11.70 (s, 1H), 9.20 (s, 1H), 8.89-8.87 (m, 1H), 8.17 (s, 1H), 8.12-8.10 (d, J = 7.1 Hz, 1H), 7.48-7.46 (d, J = 8.7 Hz, 2H), 7.38-7.35 (t, J = 7.4 Hz, 1H), 7.17-7.14 (t, J = 7.6 Hz, 1H), 6.91-6.89 (d, J = 8.9 Hz, 2H), 3.65-3.62 (d, J = 12.1 Hz, 2H), 3.43-3.40 (m, 1H), 2.64-2.59 (t, J = 11.3 Hz, 3H), 2.47 (s, 3H), 2.20 (s, 6H), 1.85-1.83 (d, J = 10.9 Hz, 2H), 1.54-1.45 (m, 2H). MS (ESI): 504.1 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{26}H_{31}ClN_9^+$, 504.2313; found, 504.2375. Purity: 97.96%.



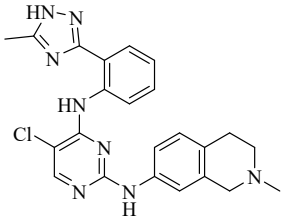
5-chloro-*N*^{2}-(4-(6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)-*N*^{4}-(2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)pyrimidine-2,4-diamine (**w7**): To a solution of 10 (150.0 mg, 0.47 mmol) in 2-methyl propan-2-ol (6.0 mL) was added 4-(6,7-dihydropyrazolo[1,5-a]pyrazin- 5(4H)-yl)aniline (100.0 mg, 0.47 mmol), $Pd_2(dba)_3$ (44.0 mg, 0.047 mmol), t-butyl XPhos (41.0 mg, 0.094 mmol) and sodium tBuONa (92.0 mg, 0.94 mmol). The reaction was degassed with nitrogen. After being stirred at reflux overnight, the reaction mixture was concentrated in vacuo. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/methanol = 100/1) to give the title compound w7 as yellow solid (101.0 mg, 0.2 mmol, 43.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 14.09 (s, 1H), 11.59 (s, 1H), 9.26 (s, 1H), 8.85 - 8.84 (d, J = 7.1 Hz, 1H), 8.19 (s, 1H), 8.15 - 8.13 (d, J = 7.4 Hz, 1H), 7.55 - 7.53 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 1.2 Hz, 1H), 7.36 - 7.32 (t, J = 7.4 Hz, 1H), 7.17 - 7.13 (t, J = 7.6 Hz, 1H), 7.05 - 7.03 (d, J = 8.9 Hz, 2H), 6.15 (s, 1H), 4.42 (s, 2H), 4.20 - 4.17 (t, J = 5.4 Hz, 2H), 3.74 - 3.72 (t, J = 5.4 Hz, 2H), 2.49 (s, 3H). MS (ESI): 499.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{25}H_{24}ClN_{10}^+$, 499.1796; found, 499.1798. Purity: 98.50%.



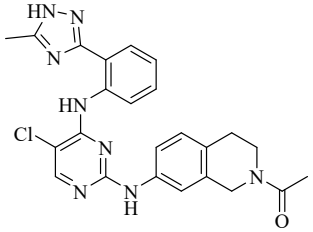
5-chloro-*N*^{4}-(2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-*N*^{2}-(4-morpholinophenyl)pyrimidine-2,4-diamine (**w8**): A solution of 10 (250.0 mg, 0.78 mmol), 4-morpholinoaniline (155.0 mg, 0.87 mmol) in 1-Butanol (10.0 mL) was added HCl/H_2O (32.0 mg, 6.0 mol/L, 0.16 mmol). And the mixture was stirred at 150°C in microwave reactor for 4 h. TLC show a little starting material, the solvent was removed in *vacuo* and purified by a flash column chromatography with eluent (dichloromethane/ammonia in methanol =100/1-10/1) to give a yellow solid (30.4 mg, 64.5 umol, 8.3%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.85 (s, 1H), 9.53 (d, J = 0.6 Hz, 1H), 8.81 (s, 2 H), 8.22 (s, 1 H), 8.11 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1 H), 7.19 (t, J = 7.4 Hz, 1 H), 7.08-6.97 (m, 2 H), 3.87-3.69 (m, 4 H), 3.14 (s, 4H), 2.47 (s, 3 H). MS (ESI): 463.1 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{23}H_{24}ClN_8O^+$, 463.1683; found, 463.1770. Purity: 98.29%.



5-chloro-N^2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-N^4-(2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)pyrimidine-2,4-diamine (**w9**): To a solution of 10 (138.0 mg, 0.43 mmol) in propan-2-ol (1.0 mL) was added 2-methoxy-4-(4-methylpiperazin-1-yl)aniline (50.0 mg, 0.22 mmol) and HCl/dioxane (4 mol/L, 0.1 mL, 0.4 mmol). After being stirred at 120 °C in microwave reactor for 2 h, the reaction mixture was diluted with methanol (10.0 mL) and neutralized with saturated aqueous $NaHCO_3$ (6.0 mL). The crude was collected through filtration. The crude was purified by a silica gel column chromatography with eluent (dichloromethane/1.2M ammonia in methanol = 100/1) to give the title compound as yellow solid (10 mg, 38.7 umol, 9.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 14.12 (s, 1H), 11.66 (s, 1H), 8.70 (s, 1H), 8.16 (s, 1H), 8.11 (s, 1H), 8.08-8.06 (d, J = 6.9 Hz, 1H), 7.42-7.40 (d, J = 8.5 Hz, 1H), 7.24-7.20 (m, 1H), 7.12-7.08 (t, J = 7.6 Hz, 1H), 6.66 (d, J = 1.6 Hz, 1H), 6.52-6.49 (dd, J = 8.8, 2.0 Hz, 1H), 3.77 (s, 3H), 3.17 (s, 4H), 2.51 (m, 4H), 2.46 (s, 3H), 2.25 (s, 3H). MS (ESI): 506.3 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{25}H_{29}ClN_9O^+$, 506.2105; found, 506.2169. Purity: 95.33%.

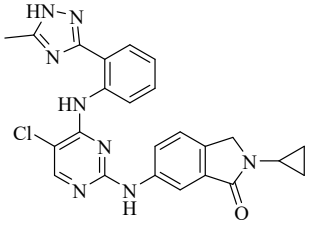


5-chloro-N^2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N^4-(2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)pyrimidine-2,4-diamine (**w10**): To a solution of 10 (190.0 mg, 0.6 mmol) in 2-methylpropan-2-ol (6.0 mL) was added 2-methyl-3,4-dihydro-1H-isoquinolin-7- amine (100.0 mg, 0.6 mmol), $Pd_2(dba)_3$ (56.0 mg, 0.06 mmol), t-butyl XPhos (53.0 mg, 0.12 mmol) and sodium 2-methylpropan-2-olate (118.0 mg, 1.2 mmol). The reaction was degassed with N_2. After being refluxed for overnight, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/1.2M ammonia in methanol = 200/1) to give the title compound as yellow solid (106.0 mg, 0.23 mmol, 39.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 14.14 (s, 1H), 11.67 (s, 1H), 9.36 (s, 1H), 8.83 (s, 1H), 8.22 (s, 1H), 8.13-8.12 (d, J = 7.6 Hz, 1H), 7.39-7.37 (m, 3H), 7.19-7.17 (t, J = 7.5 Hz, 1H), 7.02-7.01 (d, J = 8.1 Hz, 1H), 3.42 (s, 2H), 2.78-2.76 (t, J = 5.7 Hz, 2H), 2.60-2.58 (t, J = 5.8 Hz, 2H), 2.47 (s, 3H), 2.34 (s, 3H). MS (ESI): 447.3 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{23}H_{24}ClN_8^+$, 447.1734; found, 447.1759. Purity: 95.91%.

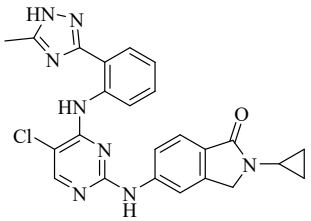


1-(7-((5-chloro-4-((2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one (**w11**): To a suspension of 1-(7-amino-3,4-dihydro-1H-isoquinolin-2-yl)ethanone (260.2 mg, 1.37 mmol) and 10 (440.1 mg, 1.37 mmol) in tBuOH (15.0 mL) were added tBuONa (0.1292 g, 1.304 mmol)，XPhos (129.1 mg, 0.26 mmol), $Pd_2(dba)_3$ (124.5 mg, 0.13 mmol). The reaction mixture was refluxed for 24 h and concentrated in *vacuo*. The residue was purified by a flash column chromatography with eluent (dichloromethane/ammonia in methanol = 35/1) to give the title compound as a beige solid (384.1 mg, 1.1 mmol, 82.5%). ^{1}H NMR (400 MHz, DMSO-d6) δ

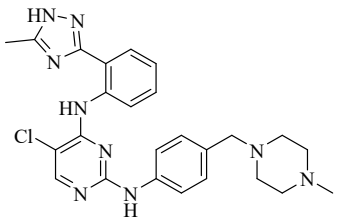
δ 14.09 (s, 1H), 11.59 (d, J = 8.0 Hz, 1H), 9.45 (d, J = 12.5 Hz, 1H), 8.79 (t, J = 8.1 Hz, 1H), 8.24 (s, 1H), 8.16 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 16.8 Hz, 1H), 7.42 (dd, J = 14.2, 6.5 Hz, 2H), 7.09 (d, J = 8.3 Hz, 1H), 4.55 (d, J = 7.2 Hz, 2H), 3.66 (t, J = 5.8 Hz, 2H), 2.82 (t, J = 5.6 Hz, 1H), 2.71 (t, J = 5.5 Hz, 1H), 2.49 (s, 3H), 2.09 (d, J = 3.7 Hz, 3H). MS (ESI): 475.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{24}H_{24}ClN_8O^+$, 475.1683; found, 475.3069. Purity: 96.07%.



6-((5-chloro-4-((2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)-2-cyclopropylisoindolin-1-one (**w12**): To a solution of 10 (95.2 mg, 0.27 mmol), 6-amino-2-cyclopropyl-isoindolin-1-one (50.8 mg, 0.27 mmol) in tBuOH (5.0 mL) was added $Pd_2(dba)_3$ (28.1 mg, 0.03 mmol), Xphos (20.0 mg, 0.04 mmol), tBuONa (52.6 mg, 0.53 mmol). The mixture was protected with N^2 and stirred at 90°C for 24 h. TLC show a little starting material, the solvent was removed in *vacuo* and purified by a flash column chromatography with eluent (dichloromethane/ methanol = 20/1) to give a yellow solid w12 (10.6 mg, 0.02 mmol, 8.3%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.78 (s, 1H), 9.67 (s, 1H), 8.91 (d, J = 8.3 Hz, 1H), 8.30 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.18 (t, J = 7.3 Hz, 2H), 4.34 (s, 2H), 2.48 (s, 3H), 2.05-1.94 (m, 2H), 0.88-0.85 (m, 2H), 0.81-0.77 (m, 2H).MS (ESI): 473.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{24}H_{22}ClN_8O^+$, 473.1527; found, 473.1617. Purity: 98.39%.

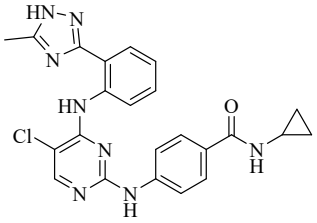


5-((5-chloro-4-((2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)-2-cyclopropylisoindolin-1-one (**w13**): To a solution of 10 (307.0 mg, 0.96 mmol) in 2-methylpropan-2-ol (6.0 mL) was added 5-amino-2-cyclopropylisoindolin-1-one (90.0 mg, 0.48 mmol), $Pd_2(dba)_3$ (48.0 mg, 0.096 mmol), XPhos (48.0 mg, 0.096 mmol) and tBuONa (94 mg, 0.96 mmol). The reaction was degassed with nitrogen. After being stirred at reflux for overnight, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/1.2M ammonia in methanol = 100/1) to give the title compound w13 as yellow solid (10.0 mg, 0.02 mmol, 4.0 %). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.62 (s, 1H), 9.81 (s, 1H), 8.76-8.74 (d, J = 8.2 Hz, 1H), 8.28 (s, 1H), 8.12-8.10 (d, J = 7.3 Hz, 1H), 7.99 (s, 1H), 7.69-7.66 (d, J = 8.4 Hz, 1H), 7.55-7.53 (d, J = 8.3 Hz, 1H), 7.48-7.44 (t, J = 7.7 Hz, 1H), 7.24-7.21 (t, J = 7.5 Hz, 1H), 4.32 (s, 2H), 2.92-2.86 (m, 1H), 2.46 (s, 3H), 0.81-0.78 (m, 4H). MS (ESI): 473.1 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{24}H_{22}ClN_8O^+$, 473.1527; found, 473.1569. Purity: 95.30%.

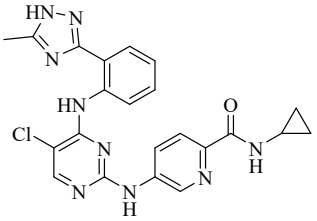


5-chloro-N^4-(2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-N^2-(4-((4-methylpiperazin-1-yl)methyl)phenyl)pyrimidine-2,4-diamine (**w14**): To a solution of 10 (1.0 g, 3.1 mmol), 4-((4-methylpiperazin-1-yl)methyl)aniline (770.0 mg, 3.8 mmol) in tBuOH (10.0 mL) was added $Pd_2(dba)_3$ (300.0 mg, 0.3 mmol), Xphos (300.0 mg, 0.6 mmol), tBuONa (0.5 g, 5.0 mmol). The mixture was protected with N_2 and stirred at 90°C for overnight. TLC show a little starting material,

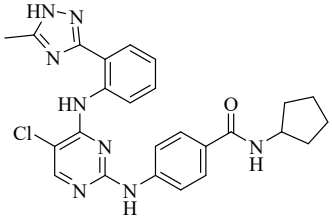
the solvent was removed in *vacuo* and purified by a flash column chromatography with eluent (ethyl acetate/methanol=50/1) to give a yellow solid (38.4 mg, 76.8 umol, 2.5%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.70 (s, 1H), 9.64 (s, 1H), 8.83 (d, J = 7.5 Hz, 1H), 8.27 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.51-7.15 (m, 5H), 3.98 (s, 2H), 3.28-3.09 (m, 4H), 2.80 (s, 3H), 2.50-2.43 (m, 7H). MS (ESI): 490.4 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{25}H_{29}ClN_9^+$, 490.2156; found, 490.2233. Purity: 97.19%.



4-((5-chloro-4-((2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)-*N*-cyclopropylbenzamide (**w15**): To a solution of 10 (182.0 mg, 0.57 mmol) in 2-methylpropan-2-ol (6.0 mL) was added 4-amino-*N*-cyclopropylbenzamide (100.0 mg, 0.57 mmol), $Pd_2(dba)_3$ (53.0 mg, 57.0 umol), t-butyl XPhos (50.0 mg, 0.11 mmol) and tBuONa (111.1 mg, 1.1 mmol). The reaction was degassed with N_2. After being refluxed for overnight, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/1.2M ammonia in methanol = 500/1) to give the title compound as yellow solid (101.0 mg, 0.22 mmol, 39.0%). ^{1}H NMR (400 MHz, DMSO) δ 14.11 (s, 1H), 11.66 (s, 1H), 9.74 (s, 1H), 8.85-8.84 (d, J = 6.6 Hz, 1H), 8.30 (s, 1H), 8.27-8.26 (d, J = 3.8 Hz, 1H), 8.16 (s, 1H), 7.79-7.74 (m, 3H), 7.48-7.44 (t, J = 7.6 Hz, 1H), 7.24-7.20(t, J = 7.3 Hz, 1H), 2.86-2.80 (m, 1H), 2.48 (s, 3H), 0.72-0.67 (m, 2H), 0.59-0.55 (m, 2H). MS (ESI): 461.3 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{23}H_{22}ClN_8O^+$, 461.1527; found, 461.1597. Purity: 96.91%.

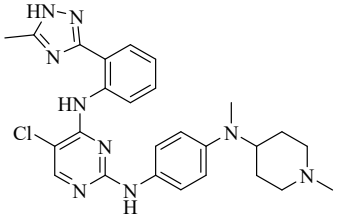


5-((5-chloro-4-((2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)-*N*-cyclopropylpicolinamide (**w16**): To a solution of 10 (181.0 mg, 0.56 mmol) in 2-methylpropan-2-ol (6.0 mL) was added 5-amino-*N*-cyclopropylpicolinamide (100.0 mg, 0.56 mmol), $Pd_2(dba)_3$ (53.0 mg, 57.0 umol), t-butyl XPhos (49.0 mg, 0.11 mmol) and tBuONa (111.0 mg, 1.1 mmol). The reaction was degassed with N_2. After being refluxed for overnight, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/1.2M ammonia in methanol = 200/1) to give the title compound as yellow solid (68.0 mg, 33.6 umol, 6.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 14.11 (s, 1H), 11.71 (s, 1H), 9.98 (s, 1H), 8.82 (d, J = 2.1 Hz, 2H), 8.53-8.52 (d, J = 4.8 Hz, 1H), 8.44-8.42 (dd, J = 8.5, 1.9 Hz, 1H), 8.34 (s, 1H), 8.18-8.16 (d, J = 7.4 Hz, 1H), 7.95-7.92 (d, J = 8.6 Hz, 1H), 7.48-7.44 (t, J = 8.0 Hz, 1H), 7.23-7.20 (t, J = 7.4 Hz, 1H), 2.92 -2.86 (m, 1H), 2.50 (m, 3H), 0.70-0.66 (m, 4H). MS (ESI): 462.1 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{22}H_{21}ClN_9O^+$, 462.1479; found, 462.1574. Purity: 96.59%.

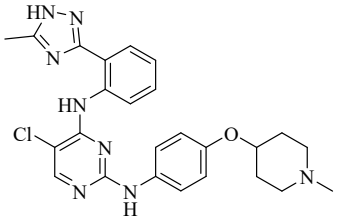


4-((5-chloro-4-((2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)-*N*-cyclopentylbenzamide (**w17**): To a solution of 10 (1.81 g, 5.64 mmol), 4-amino-*N*-cyclopentyl-benzamide (1.15 g, 5.63 mmol) in tBuOH (50.0 mL) was added $Pd_2(dba)_3$ (266.0 mg, 0.28 mmol), Xantphos (168.0 mg, 0.28 mmol), K_2CO_3 (1.2 g, 8.7 mmol).

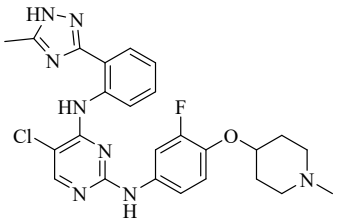
The mixture was protected with N_2 and stirred at 95°C for 24 h. The solvent was removed in *vacuo* and purified by a flash column chromatography with eluent (dichloromethane/methanol = 20/1) to give a yellow solid (632.0 mg, 1.22 mmol, 21.7%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.73 (s, 1H), 9.74 (s, 1H), 8.85 (d, J = 8.2 Hz, 1H), 8.30 (s, 1H), 8.13 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 7.2 Hz, 1H), 7.84-7.72 (m, 4H), 7.46 (t, J = 7.8 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 4.22 (dd, J = 14.1, 7.1 Hz, 1H), 2.47 (s, 3H), 1.87 (dd, J = 12.9, 7.4 Hz, 2H), 1.76-1.63 (m, 2H), 1.60-1.46 (m, 4H). MS (ESI): 489.1 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{26}H_{26}ClN_8O^+$, 489.1840; found, 489.1846. Purity: 98.47%.



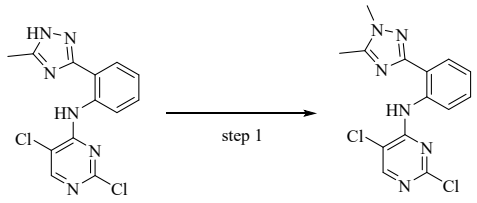
5-chloro-*N*^{2}-(4-(methyl(1-methylpiperidin-4-yl)amino)phenyl)-*N*^{4}-(2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)pyrimidine-2,4-diamine (**w18**): To a solution of 10 (220.1 mg, 0.68 mmol) in propan-2-ol (4.0 mL) was added *N*^{1}-methyl-*N*^{1}-(1-methylpiperidin-4-yl)benzene-1,4-diamine (150.0 mg, 0.68 mmol), HCl/dioxane (4.0 mol/L, 0.2 mL, 0.8 mmol). After being stirred at 130 °C in microwave reactor for 4 h, the reaction mixture was diluted with methanol (8.0 mL) and neutralized with saturated aqueous solution of $NaHCO_3$ (4.0 mL). The crude was collected through filtration. The crude was purified by a silica gel column chromatography with eluent (dichloromethane/1.2M ammonia in methanol = 200/1) to give the title compound as yellow solid (61.1 mg, 0.12 mmol, 18.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 14.12 (s, 1H), 11.66 (s, 1H), 9.11 (s, 1H), 8.89 (s, 1H), 8.15 (s, 1H), 8.11-8.09 (d, J = 7.6 Hz, 1H), 7.43-7.40 (d, J = 8.6 Hz, 2H), 7.34-7.31 (t, J = 7.7 Hz, 1H), 7.16-7.12 (t, J = 7.5 Hz, 1H), 6.80-6.78 (d, J = 9.0 Hz, 2H), 3.54-3.48 (m, 1H), 2.87-2.85 (d, J = 10.4 Hz, 2H), 2.70 (s, 3H), 2.47 (s, 3H), 2.20 (s, 3H), 2.06-2.00 (t, J = 11.4 Hz, 2H), 1.74-1.67 (m, 2H), 1.60 -1.57 (m, 2H). MS (ESI): 504.6 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{26}H_{31}ClN_9^+$, 504.2313; found, 504.2395. Purity: 95.14%.



5-chloro-*N*^{4}-(2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-*N*^{2}-(4-((1-methylpiperidin-4-yl)oxy)phenyl)pyrimidine-2,4-diamine (**w19**): To a solution of 10 (1.48 g, 4.6 mmol) in 2-methylpropan-2-ol (25.0 mL) was added 4-[(1-methyl-4-piperidyl)oxy]aniline (1.0 g, 4.6 mmol), $Pd_2(dba)_3$ (429.1 mg, 0.46 mmol), t-butyl XPhos (403.0 mg, 0.92 mmol) and tBuONa (903.2 mg, 9.2 mmol). The reaction was degassed with N_2. After refluxed for overnight, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/1.2M ammonia in imethanol = 500/1) to give the title compound as yellow solid (1.02 g, 2.08 mmol, 45.2%). ^{1}H NMR (400 MHz, DMSO-*d6*) 14.13 (s, 1H), 11.67 (s, 1H), 9.28 (s, 1H), 8.86-8.84 (d, J = 5.7 Hz, 1H), 8.19 (s, 1H), 8.12- 8.10 (d, J = 7.4 Hz, 1H), 7.54-7.52 (d, J = 8.8 Hz, 2H), 7.39-7.35 (t, J = 7.7 Hz, 1H), 7.18- 7.14 (t, J = 7.3 Hz, 1H), 6.91-6.89 (d, J = 8.9 Hz, 2H), 4.33-4.26 (m, 1H), 2.64-2.61 (m, 2H), 2.47 (s, 3H), 2.19 (s, 3H), 2.15 (m, 2H), 1.94-1.91 (m, 2H), 1.67-1.59 (m, 2H). MS (ESI): 491.1 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{25}H_{28}ClN_8O^+$, 491.1996; found, 491.2062. Purity: 99.15%.



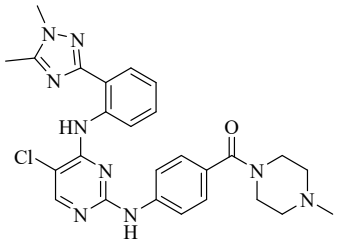
5-chloro-N^2-(3-fluoro-4-((1-methylpiperidin-4-yl)oxy)phenyl)--N^4-(2-(5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)pyrimidine-2,4-diamine (**w20**): The aqueous solution of HCl (0.05 mL, 6.0 mol/L, 0.3 mmol) was added into a solution of 10 (100.0 mg, 0.31 mmol) and 3-fluoro-4-[(1-methyl-4-piperidyl)oxy]-aniline(62.0 mg, 0.28 mmol) that dissoleved in 1-Butanol (4.0 mL). The mixture was stirred for 6 h in microwave at 130°C. The solvent was removed in *vacuo* and purified by a flash column chromatography with eluent (dichloromethane/ methanol = 10/1) to give the title compound as a pink solid(146.0 mg, 0.26 mmol, 83.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.47 (s, 1H), 11.44(s, 1 H), 8.58 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 7.5 Hz, 1 H), 7.93 (s, 1 H), 7.74 (s, 1 H), 7.54 (dd, J = 13.6, 2.0 Hz, 1 H), 7.23 (d, J = 7.7 Hz, 1 H), 6.99 (t, J = 7.5 Hz, 2 H), 6.79 (t, J = 9.0 Hz, 1 H), 4.07 (s, 1 H), 2.63 (m, 2 H), 2.38 (s, 3 H), 2.19(s, 5 H), 1.93-1.85 (m, 2 H), 1.74 (m, 2 H). ^{19}F NMR ($CDCl_3$) δ 130.82; MS (ESI): 509.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{25}H_{27}ClFN_8O^+$, 509.1902; found, 502.1988. Purity: 96.25%.



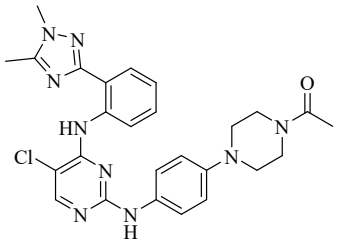
10 m1-1

Preparation of intermediate m1-1

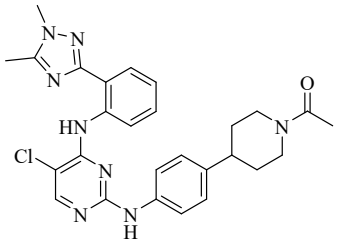
2,5-dichloro-*N*-(2-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)phenyl)pyrimidin-4-amine (**m1-1**): To a suspension of 10 (2.0 g, 6.2 mmol) in THF (30 mL) was added potassium tert-butoxide (1.14 g, 10.0 mmol) and the mixture was stirred at rt for 0.5 h. To the reaction mixture was added iodomethane (0.7 mL, 10.0 mmol). After being stirred at rt for 4h, the reaction mixture was concentrated in vacuo. The residue was purified by a silica gel column chromatography with eluent (petroleum ether/ethyl acetate = 3/1) to give the title compound as yellow solid (1.14 g, 3.4 mmol, 55.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.83 (s, 1H), 8.80-8.78 (d, J = 8.5 Hz, 1H), 8.22-8.20 (m, 2H), 7.50-7.46 (t, J = 7.9 Hz, 1H), 7.22-7.19 (t, J = 7.6 Hz, 1H), 3.92 (s, 3H), 2.55 (s, 3H). MS (ESI): 355.2 $[M+H]^+$.



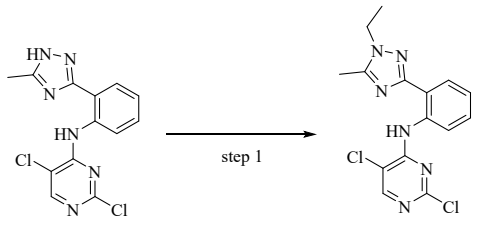
(4-((5-chloro-4-((2-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)(4-methylpiperazin-1-yl)methanone (**m1**): To a solution of m1-1 (145.0 mg, 0.43 mmol) in 2-methylpropan-2-ol (6.0 mL) was added (4-aminophenyl)-(4-methylpipera zin-1-yl)methanone (100.0 mg, 0.43 mmol), $Pd_2(dba)_3$ (40.0 mg, 0.043 mmol), *t*-butyl XPhos (38.0 mg, 0.087 mmol) and tBuONa (85.0 mg, 0.87 mmol). The reaction was degassed with nitrogen. After being stirred at reflux overnight, the reaction mixture was concentrated in *vacuo.* The residue was purified by a silica gel column chromatography with eluent (dichloromethane/methanol = 100/1) to give the title compound as yellow solid (118.0 mg, 0.23 mmol, 53.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.48 (s, 1H), 9.70 (s, 1H), 8.83-8.81 (d, J = 8.3 Hz, 1H), 8.28 (s, 1H), 8.13-8.11 (m, 1H), 7.77-7.75 (d, J = 8.5 Hz, 2H), 7.44-7.40 (t, J = 7.8 Hz, 1H), 7.34-7.32 (d, J = 8.5 Hz, 2H), 7.21-7.17 (t, J = 7.5 Hz, 1H), 3.89 (s, 3H), 3.51-3.48 (m, 4H), 2.51 (s, 3H), 2.32 (m, 4H), 2.20 (s, 3H). MS (ESI): 518.5 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{26}H_{29}ClN_9O^+$, 518.2105; found, 518.2139. Purity: 99.20%.



1-(4-(4-((5-chloro-4-((2-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethan-1-one (**m2**): To a solution of m1-1 (145.1 mg, 0.43 mmol) in dioxane (6 mL) was added 1-(4-(4-aminophenyl)piperazin-1-yl)ethanone (100.0 mg, 0.43 mmol), $Pd_2(dba)_3$ (40 mg, 0.043 mmol), t-butyl XPhos (38.0 mg, 0.087 mmol) and tBuONa (85.0 mg, 0.87 mmol). The reaction was degassed with nitrogen. After being stirred at reflux overnight, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/methanol = 100/1) to give the title compound as yellow solid (66.0 mg, 124.7 umol, 29.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.43 (s, 1H), 9.24 (s, 1H), 8.87 - 8.85 (d, J = 5.9 Hz, 1H), 8.18 (s, 1H), 8.11-8.09 (d, J = 7.8 Hz, 1H), 7.52-7.50 (d, J = 8.5 Hz, 2H), 7.39-7.35 (t, J = 7.7 Hz, 1H), 7.17-7.13 (t, J = 7.3 Hz, 1H), 6.94-6.92 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.60-3.59 (m, 4H), 3.10 (m, 2H), 3.04-3.02 (m, 2H), 2.51 (s, 3H), 2.05 (s, 3H). MS (ESI): 518.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{26}H_{29}ClN_9O^+$, 518.2105; found, 518.2127. Purity: 95.60%.



1-(4-(4-((5-chloro-4-((2-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperidin-1-yl)ethan-1-one (**m3**): To a solution of m1-1 (132.0 mg, 0.39 mmol) in dioxane (6.0 mL) was added 1-[4-(4-aminophenyl)-1-piperidyl]ethanone (86.1 mg, 0.39 mmol), $Pd_2(dba)_3$ (37.0 mg, 0.04 mmol), t-butyl XPhos (35.2 mg, 0.08 mmol) and tBuONa (77.0 mg, 0.79 mmol). The reaction was degassed with nitrogen. After being stirred at reflux overnight, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/methanol = 200/1) to give the title compound as yellow solid (8.1 mg, 16.0 umol, 4.1%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.46 (s, 1H), 9.41 (s, 1H), 8.87-8.85 (d, J = 8.4 Hz, 1H), 8.23 (s, 1H), 8.12-8.10 (d, J = 7.8 Hz, 1H), 7.61-7.58 (d, J = 8.4 Hz, 2H), 7.41-7.37 (t, J = 7.4 Hz, 1H), 7.19-7.16 (t, J = 6.6 Hz, 3H), 4.55-4.52 (d, J = 12.4 Hz, 1H), 3.94-3.89 (m, 1H), 3.89 (s, 3H), 3.16-3.09 (m, 1H), 2.76-2.68 (m, 1H), 2.62-2.51 (m, 1H), 2.51 (s, 3H), 2.04 (s, 3H), 1.82-1.75 (m, 2H), 1.63-1.56 (m, 1H), 1.48-1.41 (m, 1H). MS (ESI): 517.3 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{27}H_{30}ClN_8O^+$, 517.2153; found, 517.2151. Purity: 98.0%.

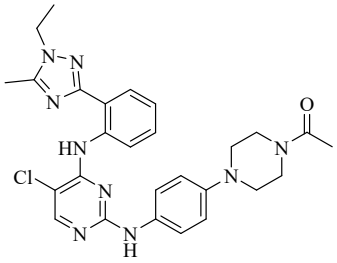


10 m4-1

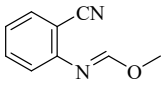
Preparation of intermediate m4-1

2,5-dichloro-*N*-(2-(1-ethyl-5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)pyrimidin-4-amine (**m4-1**): To a suspension of 10 (2.02 g, 6.2 mmol) in THF (30 mL) was added potassium tert-butoxide (1.14 g, 10.0 mmol) and the mixture was stirred at rt for 0.5 h. To the reaction mixture was added iodoethane (0.8 mL, 10.0 mmol). After being stirred at rt for 3 h, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (petroleum ether/ethyl acetate = 3/1) to give the title compound as yellow solid (1.73 g, 4.96 mmol, 80.0%). ^{1}H

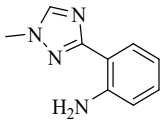
NMR (400 MHz, $CDCl_3$) δ 11.83 (s, 1H), 8.79-8.77 (d, J = 8.4 Hz, 1H), 8.24-8.23 (dd, J = 7.9, 1.2 Hz, 1H), 8.22 (s, 1H), 7.49-7.46 (m, 1H), 7.22-7.19 (t, J = 7.5 Hz, 1H), 4.22-4.20 (q, J = 7.3 Hz, 2H), 2.56 (s, 3H), 1.55-1.53 (t, J = 7.3 Hz, 3H). MS (ESI): 349.1 $[M+H]^+$.



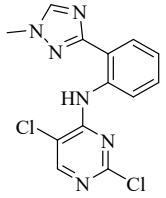
1-(4-(4-((5-chloro-4-((2-(1-ethyl-5-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)-
-piperazin-1-yl)ethan-1-one (**m4**): To a solution of m4-1 (234 mg, 0.67 mmol) in dioxane (8.0 mL) was added 1-[4-(4-aminophenyl)piperazin-1-yl]ethanone (150.1 mg, 0.67 mmol), $Pd_2(dba)_3$ (63.1 mg, 0.068 mmol), *t*-butyl XPhos (59.0 mg, 0.14 mmol) and tBuONa (131.5 mg, 1.32 mmol). The reaction was degassed with nitrogen. After being stirred at reflux overnight, the reaction mixture was concentrated in *vacuo*. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/methanol = 200/1) to give the title compound as yellow solid (103.1 mg, 0.19 mmol, 28.9 %). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.38 (s, 1H), 9.25 (s, 1H), 8.86-8.84 (d, J = 7.5 Hz, 1H), 8.19 (s, 1H), 8.14-8.12 (d, J = 7.8 Hz, 1H), 7.53-7.50 (d, J = 8.8 Hz, 2H), 7.39-7.36 (t, J = 7.6 Hz, 1H), 7.17-7.13 (t, J = 7.7 Hz, 1H), 6.94-6.92 (d, J = 8.9 Hz, 2H), 4.26-4.21 (dd, J = 14.4, 7.2 Hz, 2H), 3.60-3.59 (m, 4H), 3.11-3.08 (m, 2H), 3.04-3.02 (m, 2H), 2.53 (s, 3H), 2.05 (s, 3H), 1.42 (t, J = 7.4 Hz, 3H). MS (ESI): 532.3 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{27}H_{31}ClN_9O^+$, 532.2262; found, 532.2274. Purity: 97.5%.



methyl (*E*)-*N*-(2-cyanophenyl)formimidate (**13**): A mixture of 12 (199.3 mg, 1.69 mmol) and CF_3COOH (10.0 μL) in trimethoxymethane (5.0 mL) was stirred at 100°C for 1.5 h. The mixture was concentrated in *vacuo*. The residue was purified by a flash column chromatography with eluent (petroleum ether /Ethyl acetate =20:1) to give the title compound as an oil (143.2 mg, 0.89 mmol, 53.00%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.68-7.58 (m, 1H), 7.57-7.48 (m, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 3.99 (s, 3H). MS (ESI): 161.15 $[M+H]^+$.

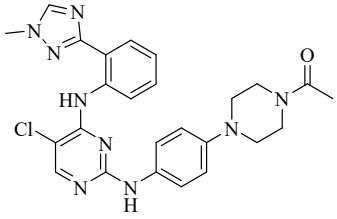


2-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline (**14-m5**): A mixture of methylhydrazine (4.65 g, 40.4 mmol) and 13 (4.3 g, 26.8 mmol) in DCM (30.0 mL) was stirred at rt for 12 h. The mixture was concentrated in *vacuo*. The residue was purified by a flash column chromatography with eluent (petroleum ether/Ethyl acetate = 20/1) to give the title compound as a white solid (670.2 mg, 3.85 mmol, 14.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-7.95 (m, 2H), 7.19 (t, J = 7.5 Hz, 1H), 6.87-6.68 (m, 2H), 5.57 (s, 2H), 3.99 (s, 3H). MS (ESI): 175.2 $[M+H]^+$.

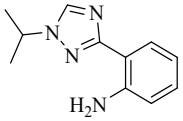


2,5-dichloro-*N*-(2-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)pyrimidin-4-amine (**24-m5**): To a suspension of 14-m5 (670.1 mg, 3.85 mmol) in DMF (25.0 mL) was added NaH (314.2 mg, 7.86 mmol, 60 mass%). The was gradully added 2,4,5-trichloropyrimidine (1.12 g, 6.13 mmol) at 0°C, and the reaction mixture was stirred at rt. for 12 h and then quenched with water. The aqueous phase was extracted with ethyl acetate. The organic layers were concentrated

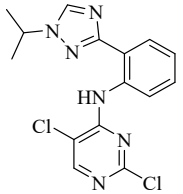
in *vacuo*. the residue was purified by a flash column chromatography with eluent (petroleum ether/ethyl acetate = 3/1) to give the title compound as a yellow solid (223.5 mg, 0.7 mmol, 18.09%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (s, 1H), 8.79 (d, J = 8.5 Hz, 1H), 8.31-8.24 (m, 1H), 8.23 (s, 1H), 8.16 (s, 1H), 7.50 (t, J = 7.3 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 4.02 (d, J = 21.1 Hz, 3H). MS (ESI): 321.1 $[M+H]^+$.



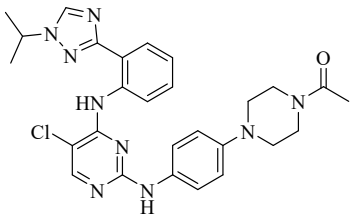
1-(4-(4-((5-chloro-4-((2-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethan-1-one (**m5**): The aqueous solution of HCl (0.01 mL, 6 mol/L, 0.06 mmol) was added in a solution of 24-m5 (400 mg, 1.245 mmol), 1-[4-(4-aminophenyl)piperazin-1-yl]-ethanone (275 mg, 1.2541 mmol) in nBuOH (6.0 mL). The mixture microwave for 6 h at 120°C. The solvent was removed in *vacuo* and purified by a flash column chromatography with eluent (dichloromethane/methanol = 100/1-10/1) to give a yellow solid m5 (326.1 mg, 0.64 mmol, 51.4%). ^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.22 (s, 1H), 9.25 (s, 1H), 8.86 (s, 1H), 8.72 (s, 1H), 8.19 (s, 1H), 8.16 (dd, J = 7.8, 1.5 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.40 (t, J = 7.4 Hz, 1H), 7.20-7.16 (m, 1H), 6.93 (d, J = 9.0 Hz, 2H), 3.99 (s, 3H), 3.59 (dd, J = 10.1, 8.2 Hz, 4H), 3.12-3.08 (m, 2H), 3.05-3.01 (m, 2H), 2.05 (s, 3H). MS (ESI): 504.1$[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{25}H_{27}ClN_9O^+$, 504.1949; found, 504.2028. Purity: 98.92%.



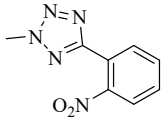
2-(1-isopropyl-1*H*-1,2,4-triazol-3-yl)aniline (**14-m6**): To a solution of 13 (3.0 g, 18.7 mmol) in MeCN (50.0 mL) was added *iso*-propylhydrazine hydrochloride (2.07 g, 18.7 mmol) and solid $NaHCO_3$ (1.57 g, 18.7 mmol). The reaction mixture was stirred at rt for overnight. The reaction mixture was quenched with water (101.0 ml) and extracted with ethyl acetate (200 mL*3), the combined organic layer was washed with brine (100.0 mL*2), dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and purified by a silica gel column chromatography (petroleum ether/ethyl acetate = 3/1) to give the title compound as a yellow liquid (0.46 g, 2.24 mmol, 12.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.60 (s, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.59 (t, J = 7.4 Hz, 1H), 6.38 (s, 2H), 4.65-4.55 (m, 1H), 1.50 (d, J = 6.6 Hz, 6H). MS (ESI): 203.2 $[M+H]^+$.



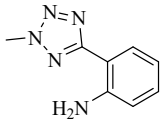
2,5-dichloro-*N*-(2-(1-isopropyl-1*H*-1,2,4-triazol-3-yl)phenyl)pyrimidin-4-amine (**24-m6**): To a solution of 14-m6 (0.4 g, 1.98 mmol) in i-PrOH (30.0 ml) were added 2,4,5-trichloropyrimidine (0.54 g, 2.96 mmol) and DIPEA (0.51 g, 3.96 mmol), the reaction mixture was refluxed for overnight. The reaction mixture was filtered and collected the filter cake to give the title compound as a white solid (0.58 g, 1.66 mmol, 84.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.56 (s, 1H), 8.81 (s, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.49 (s, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 4.72-4.62 (m, 1H), 1.52 (d, J = 6.7 Hz, 6H). MS (ESI): 349.2 $[M+H]^+$.



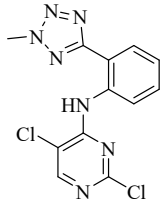
1-(4-(4-((5-chloro-4-((2-(1-isopropyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethan-1-one (**m6**): To a solution of 24-m6 (0.25 g, 0.72 mmol) in nBuOH (8 ml) were added 1-(4-(4-aminophenyl)piperazin-1-yl)ethanone (0.16 g, 0.72 mmol) and conc.HCl (0.02 g, 0.14 mmol). The reaction mixture was stirred at 140°C for 4 h under microwave irradiation. The reaction mixture was concentrated *in vacuo* and purified by a silica gel column chromatography with eluent (dichloromethane/methanol = 30/1) to give the title compound as a pink solid (0.2 g, 0.38 mmol, 53.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.09 (s, 1H), 9.27 (s, 1H), 8.80 (s, 2H), 8.20 (q, *J* = 1.9 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.21-7.17 (m, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 4.83 -4.71 (m, 1H), 3.59 (dd, *J* = 10.5, 7.4 Hz, 4H), 3.11-3.08 (m, 2H), 3.05-3.01 (m, 2H), 2.05 (s, 3H), 1.55 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-*d*6) δ (ppm) 168.77, 160.44, 158.47, 155.82, 155.26, 146.79, 143.21, 137.29, 133.20, 129.77, 128.42, 123.03, 122.01, 121.71, 118.82, 116.91, 52.47, 50.09, 49.69, 46.07, 41.25, 22.57, 21.66. MS (ESI): 532.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{27}H_{31}ClN_9O^+$, 532.2340; found, 532.2327. Purity: 99.3%.



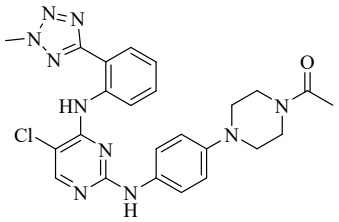
2-methyl-5-(2-nitrophenyl)-2*H*-tetrazole (**16**): To a suspension of 15 (750.2 mg, 3.93 mmol) in DMF (15 mL) was added NaH (178.3 mg, 6.69 mmol). Then gradually added iodomethane (0.3 mL) at 0°C, and the reaction mixture was stirred at rt for 3 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layers were concentrated in *vacuo* and the residue was purified by a flash column chromatography (petroleum ether/ethyl acetate = 10/1) to give the title compound as a white solid (540.0 mg, 2.63 mmol, 67.06%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (dd, J = 7.7, 1.4 Hz, 1H), 7.89 (dd, J = 8.1, 1.2 Hz, 1H), 7.73 (td, J = 7.6, 1.3 Hz, 1H), 7.66 (td, J = 7.8, 1.4 Hz, 1H), 4.44 (s, 3H).



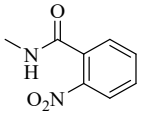
2-(2-methyl-2*H*-tetrazol-5-yl)aniline (**17**): A mixture of 16 (540.0 mg, 2.63 mmol) and Pd/C (764.2 mg, 10 mass%) in ethanol (20.0 mL) was stirred under H_2 atmosphere for 12 h at rt. Then the mixture was concentrated in *vacuo*. The residue was purified by a flash column chromatography with eluent (petroleum ether/ethyl acetate = 10/1) to give the title compound as a yellow solid (386.3 mg, 2.2 mmol, 83.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 7.9 Hz, 1H), 7.25 (d, J = 7.9 Hz, 1H), 6.83 (t, J = 8.5 Hz, 2H), 5.45 (s, 2H), 4.43 (s, 3H) (s, 3H). MS (ESI): 176.2 $[M+H]^+$



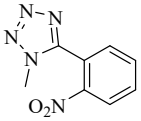
2,5-dichloro-*N*-(2-(2-methyl-2*H*-tetrazol-5-yl)phenyl)pyrimidin-4-amine (**24-m7**): To a suspension of 17 (546.5 mg, 3.12 mmol) in DMF (15.0 mL) was added NaH (153.2 mg, 3.83 mmol). Then gradually added 2,4,5-trichloropyrimidine (925.6 mg, 5.05 mmol) at 0°C, and the reaction mixture was stirred at rt for 7 h. Then the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layers were concentrated in *vacuo* and the residue was purified by a flash column chromatography with eluent (petroleum ether/ethyl acetate = 10/1) to give the title compound as a white solid (250.3 mg, 0.78 mmol, 24.9 %). 1H NMR (400 MHz, $CDCl_3$) δ 10.46 (d, J = 11.4 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.73 (d, J = 12.4 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1H), 7.28 (s, 1H), 7.23-7.17 (m, 1H), 4.48 (s, 3H). MS (ESI): 322.1 $[M+H]^+$.



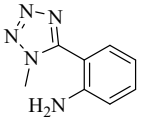
1-(4-(4-((5-chloro-4-((2-(2-methyl-2*H*-tetrazol-5-yl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethan-1-one (**m7**): To a suspension of 24-m7 (110.2 mg, 0.34 mmol), 1-[4-(4-aminophenyl)piperazin-1-yl]ethanone (75.3 mg, 0.34 mmol) in 1-Butanol (1.5 mL) were added cat. HCl (10 uL). The reaction mixture was stirred at 140 °C for 3 h under microwave conditions. The residue was purified by a flash column chromatography with eluent (dichloromethane/methanol = 30/1) to give the title compound as a yellow solid (86.5 mg, 0.17 mmol, 50.1 %). ^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.20 (s, 1H), 9.28 (s, 1H), 8.74 (s, 1H), 8.22 (s, 1H), 8.17 (d, J = 7.7 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.49 (d, J = 8.2 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 4.49 (s, 3H), 3.59 (d, J = 3.0 Hz, 5H), 3.13-3.07 (m, 2H), 3.06-3.00 (m, 2H), 2.05 (s, 3H). MS (ESI): 505.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{24}H_{26}ClN_{10}O^+$, 505.1901; found, 505.1970. Purity: 97.65%.



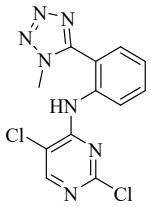
N-methyl-2-nitrobenzamide (**21**): A mixture of 2-nitrobenzoic acid (20.1 g, 120.4 mmol) and thionyl chloride (50 mL) was stirred at 80 °C for 5 h. The mixture was concentrated in *vacuo* and afforded a yellow oil (22.2 g, 119.7 mmol). To a mixture of above yellow oil of MeCN (150.0 mL) were added methanamine hydrochloride (16.32 g, 241.7 mmol) and Na_2CO_3 (20.15 mg, 240 mmol). The mixture was stirred at 80°C for 4 h, cooled down and concentrated in *vacuo*. The residue was purified by a flash column chromatography with eluent (dichloromethane) to give the title compound as a white solid (14.6 mg, 81.6 mmol, 67.8 %) without further purification. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.59 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 7.5 Hz, 1H), 7.69 (dd, J = 11.2, 4.4 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 2.76 (d, J = 4.6 Hz, 3H).



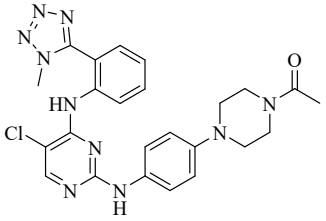
1-methyl-5-(2-nitrophenyl)-1*H*-tetrazole (**22**): To a suspension of 21 (13.62 g, 75.6 mmol) in MeCN (150.0 mL) was added NaN_3 (5.13 g, 78.1 mmol). The trifluoromethanesulfonic anhydride (20.0 mL, 116.5 mmol) was gradually added at 0°C, and the reaction mixture was stirred at 0°C for 7 h. The mixture was concentrated in *vacuo* and the residue was purified by a flash column chromatography with eluent (ethyl acetate) to give the title compound as a yellow solid (10.1 g, 49.3 mmol, 65.2 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49-8.30 (m, 1H), 8.03-7.78 (m, 2H), 7.71-7.52 (m, 1H), 3.95 (s, 3H).



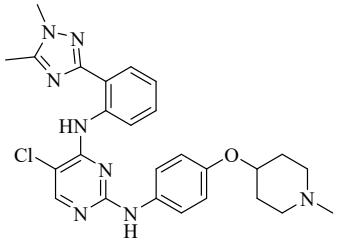
2-(1-methyl-1*H*-tetrazol-5-yl)aniline (**23**): A mixture of 22 (10.1 g, 49.3 mmol) and Pd/C (12.25 g, 10 mass%) in ethanol (10 mL) was stirred under H_2 atmosphere for 12 h at 95°C, cooled down to rt and concentrated in *vacuo*. The residue was purified by a flash column chromatography with eluent (petroleum ether/ethyl acetate = 20/1) to give the title compound as a yellow solid (4.3 g, 24.6 mmol, 49.9 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 1H), 6.83 (dd, J = 15.3, 7.7 Hz, 2H), 5.04 (s, 2H), 4.15 (s, 3H). MS (ESI): 176.1 $[M+H]^+$.



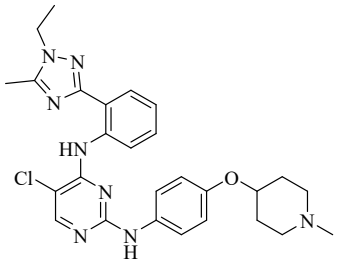
2,5-dichloro-*N*-(2-(1-methyl-1H-tetrazol-5-yl)phenyl)pyrimidin-4-amine (**24-m8**): To a suspension of 23 (4.32 g, 24.7 mmol) in DMF (30.0 mL) was added NaH (1.12 g, 42.0 mmol). The was gradually added 2,4,5-trichloropyrimidine (5.56 g, 30.3 mmol) at 0°C, and the reaction mixture was stirred at 0°C for 7 h and then quenched with water and extracted with ethyl acetate. The organic layer was concentrated in *vacuo* and the residue was purified by a flash column chromatography with eluent (dichloromethane/petroleum ether =1/3) to give the title compound as a yellow solid (3.42 g, 10.6 mmol, 43.0 %).^{1}H NMR (600 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.51 (d, J = 8.4 Hz, 1H), 8.20 (s, 1H), 8.00 (s, 1H), 7.69-7.61 (m, 1H), 7.52 (dd, J = 7.8, 1.3 Hz, 1H), 7.41-7.31 (m, 1H), 4.23 (s, 3H). MS (ESI): 322.0 $[M+H]^+$.



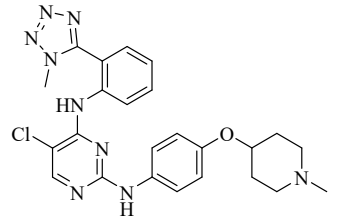
1-(4-(4-((5-chloro-4-((2-(1-methyl-1*H*-tetrazol-5-yl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethan-1-one (**m8**): To a suspension of 24-m8 (150.3 mg, 0.47 mmol) and 1-[4-(4-aminophenyl)piperazin-1-yl]ethanone (102.3 mg, 0.47 mmol) in 1-Butanol (1.5 mL) were added HCl (10 uL). The reaction mixture was stirred at 140°C for 3 h under microwave conditions. The residue was purified by a flash column chromatography with eluent (dichloromethane/methanol = 30/1) to give the title compound as a yellow solid (98.5 mg, 0.2 mmol, 41.8 %). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.28 (s, 1H), 9.07 (s, 1H), 8.26-7.91 (m, 2H), 7.83-7.62 (m, 2H), 7.57-7.29 (m, 3H), 6.81 (d, J = 7.8 Hz, 2H), 4.03 (s, 3H), 3.57 (s, 4H), 3.01 (d, J = 24.4 Hz, 4H), 2.04 (s, 3H). MS (ESI): 505.3 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{24}H_{26}ClN_{10}O^+$, 505.1901; found, 505.1897. Purity: 98.55%.



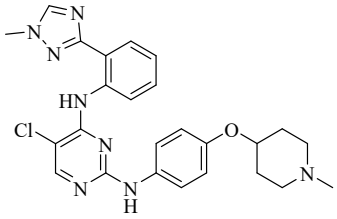
5-chloro-N^4-(2-(1,5-dimethyl-1H-1,2,4-triazol-3-yl)phenyl)-N^2-(4-((1-methylpiperidin-4-yl)oxy)phenyl)pyrimidine-2,4-diamine (**m9**): To a solution of m1-1 (154.0 mg, 0.46 mmol) in 2-methylpropan-2-ol (6.0 mL) was added 4-[(1-methyl-4-piperidyl)oxy]aniline (100.0 mg, 0.46 mmol), $Pd_2(dba)_3$ (43.0 mg, 0.046 mmol), t-butyl XPhos (40.0 mg, 0.09 mmol) and tBuONa (90.2 mg, 0.92 mmol). The reaction was degassed with nitrogen. After being stirred at reflux overnight, the reaction mixture was concentrated in vacuo. The residue was purified by a silica gel column chromatography with eluent (dichloromethane/methanol = 100/1) to give the title compound as yellow solid (95.1 mg, 0.19 mmol, 41.1 %) ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.44 (s, 1H), 9.31 (s, 1H), 8.85-8.83 (d, J = 6.6 Hz, 1H), 8.19 (s, 1H), 8.11-8.09 (d, J = 7.8 Hz, 1H), 7.56-7.54 (d, J = 8.7 Hz, 2H), 7.38-7.34 (t, J = 7.8 Hz, 1H), 7.17-7.13 (t, J = 7.5 Hz, 1H), 6.95-6.93 (d, J = 8.8 Hz, 2H), 4.45 (s, 1H), 3.88 (s, 3H), 2.97 (m, 2H), 2.70 (s, 2H), 2.51 (s, 3H), 2.48 (s, 3H), 2.07-2.03 (m, 2H), 1.82-1.80 (m, 2H). MS (ESI): 505.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{26}H_{30}ClN_8O^+$, 505.2153; found, 505.2254. Purity: 95.61%.



5-chloro-N^4-(2-(1-ethyl-5-methyl-1H-1,2,4-triazol-3-yl)phenyl)-N^2-(4-((1-methylpiperidin-4-l)oxy)phenyl)pyrimidine-2,4-diamine (**m10**): To a solution of m4-1 (241.1 mg, 0.69 mmol) in 2-methylpropan-2-ol (8.0 mL) was added 4-[(1-methyl-4-piperidyl)oxy]aniline (150.2 mg, 0.7 mmol), $Pd_2(dba)_3$ (64.0 mg, 0.069 mmol), *t*-butyl XPhos (61.0 mg, 0.14 mmol) and sodium 2-methylpropan-2-olate (135.5 mg, 1.4 mmol). The reaction was degassed with nitrogen. After being stirred at reflux overnight, the reaction mixture was concentrated in vacuo. The residue was purified by a silica gel column chromatography (dichloromethane/methanol = 50/1) to give the title compound as yellow solid (85.2 mg, 166.3 umol, 24.1 %) ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.38 (s, 1H), 9.28 (s, 1H), 8.83-8.82 (d, J = 7.0 Hz, 1H), 8.20 (s, 1H), 8.14-8.12 (dd, J = 7.8, 1.1 Hz, 1H), 7.54-7.52 (d, J = 8.8 Hz, 2H), 7.38-7.34 (t, J = 7.7 Hz, 1H), 7.17- 7.14 (t, J = 7.5 Hz, 1H), 6.92-6.90 (d, J = 8.9 Hz, 2H), 4.37-4.31 (m, 1H), 4.26-4.21 (q, J = 7.2 Hz, 2H), 2.76-2.73 (m, 2H), 2.53 (s, 3H), 2.37-2.331 (m, 2H), 2.29 (s, 3H), 1.98-1.94 (m, 2H), 1.72-1.65 (m, 2H), 1.44-1.40 (t, J = 7.2 Hz, 3H). MS (ESI): 519.3 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{27}H_{32}ClN_8O^+$, 519.2309; found, 519.2403. Purity: 97.5%.

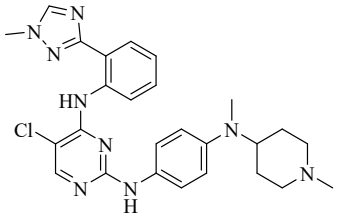


5-chloro-N^4-(2-(1-methyl-1H-tetrazol-5-yl)phenyl)-N^2-(4-((1-methylpiperidin-4-yl)oxy)phenyl)pyrimidine-2,4-diamine (**m11**): To a suspension of 24-m8 (177.2 mg, 0.55 mmol) and 4-[(1-methyl-4-piperidyl)oxy]aniline (113.8 mg, 0.55 mmol) in 1-Butanol (1.5 mL) were added cat. HCl (10 uL). The reaction mixture was stirred at 140°C for 4 h under microwave conditions. The residue was purified by a flash column chromatography with eluent (dichloromethane/methanol = 30/1) to give the title compound as a yellow solid (91.6 mg, 185.4 umol, 33.7 %). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.28 (s, 1H), 9.15 (s, 1H), 8.07 (d, J = 6.5 Hz, 2H), 7.76 (d, J = 7.5 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.55-7.30 (m, 3H), 6.83 (d, J = 8.8 Hz, 2H), 4.47 (s, 1H), 4.03 (s, 3H), 3.10 (s, 2H), 2.92 (s, 2H), 2.60 (s, 3H), 2.08 (d, J = 4.1 Hz, 2H), 1.89 (d, J = 13.8 Hz, 2H). MS (ESI): 492.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{24}H_{26}ClN_9O^+$, 492.1914; found, 492.2024. Purity: 95.22%.

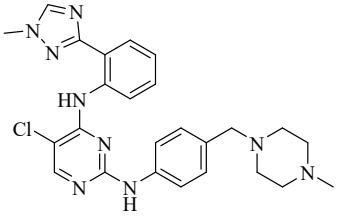


5-chloro-N^4-(2-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)-N^2-(4-((1-methylpiperidin-4-yl)oxy)phenyl)pyrimidine-2,4-diamine (**m12**): To a suspension of 24-m5 (100.1 mg, 0.31 mmol) and 4-[(1-methyl-4-piperidyl)oxy]aniline (63.8 mg, 0.31 mmol) in 1-Butanol (4.0 mL) was added cat. HCl (50 uL). The reaction mixture was stirred at 120°C for 6 h under microwave conditions. The residue was purified by a flash column chromatography with eluent (dichloromethane/methanol = 100/1-10/1) to give the title compound as a yellow solid (85.0 mg, 0.17 mmol, 54.6 %). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.22 (s, 1H), 9.33 (s, 1H), 8.83 (d, J = 8.1 Hz, 1H), 8.73 (s, 1H), 8.20 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 4.63-4.41 (m, 1H), 3.99 (s, 3H), 3.21-3.12 (m, 2H), 3.07-2.90 (m, 2H), 2.65 (s, 3H), 2.18-2.05 (m, 2H), 1.97-1.83 (m,

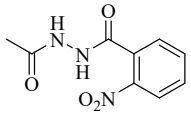
2H). MS (ESI): 491.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{25}H_{28}ClN_8O^+$, 491.1996; found, 492.2077. Purity: 98.12%.



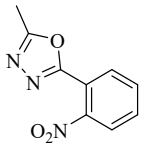
5-chloro-*N*^{2}-(4-(methyl(1-methylpiperidin-4-yl)amino)phenyl)-*N*^{4}-(2-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)pyrimidine-2,4-diamine (**m13**): To a suspension of 24-m5 (250.2 mg, 0.78 mmol) and *N*^{1}-methyl-*N*^{1}-(1-methylpiperidin-4-yl)benzene-1,4-diamine (170.2 mg, 0.78 mmol) in 1-Butanol (8.0 mL) was added cat. HCl (20 uL). The reaction mixture was stirred at 140°C for 4 h under microwave conditions. The residue was purified by a flash column chromatography with eluent (dichloromethane/methanol = 25/1) to give the title compound as a yellow solid (80.2 mg, 0.16 mmol, 20.4 %). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.23 (s, 1H), 9.17 (s, 1H), 8.89 (s, 1H), 8.73 (s, 1H), 8.16 (d, *J* = 10.0 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 4.00 (s, 3H), 3.79 (d, *J* = 11.0 Hz, 1H), 2.93 (s, 2H), 2.70 (s, 3H), 2.63 (s, 3H), 2.03 (dd, *J* = 22.7, 11.0 Hz, 2H), 1.75 (d, *J* = 12.8 Hz, 2H), 1.23 (s, 2H). MS (ESI): 504.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{26}H_{31}ClN_9^+$, 504.2391; found, 504.2406. Purity: 97.3%.



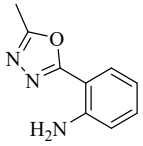
5-chloro-*N*^{4}-(2-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-*N*^{2}-(4-((4-methylpiperazin-1-yl)methyl)phenyl)pyrimidine-2,4-diamine (**m14**): To a suspension of 24-m5 (321.4 mg, 1.0 mmol) and 4-((4-methylpiperazin-1-yl)methyl)aniline (204.8 mg, 1.0 mmol) in tBuOH (15.0 mL) were added tBuONa (151.2 mg, 1.5 mmol), $Pd_2(dba)_3$ (94.6 mg, 0.100 mmol), t-butyl Xphos (87.6 mg, 0.2 mmol). The reaction mixture was refluxed for 24 h. After concentration in *vacuo*, the residue was purified by a flash column chromatography with eluent (dichloromethane /methanol = 50/1) to give the title compound as a yellow solid (135.6 mg, 0.28 mmol, 28.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.24 (s, 1H), 9.49 (s, 1H), 8.84 (d, J = 8.5 Hz, 1H), 8.75 (s, 1H), 8.24 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.40 (t, J = 7.8 Hz, 1H), 7.20 (t, J = 7.7 Hz, 3H), 4.00 (s, 3H), 3.45 (s, 2H), 3.31-3.18 (m, 4H), 2.38 (ddd, J = 18.9, 14.2, 8.3 Hz, 4H), 2.29 (s, 3H). MS (ESI): 490.3 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{25}H_{29}ClN_9^+$, 490.2156; found, 490.2238. Purity: 97.83%.



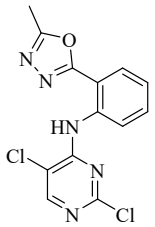
N′-acetyl-2-nitrobenzohydrazide (**18**): To a solution of 2-nitrobenzoic acid (5.0 g, 30.0 mmol) in THF (30.0 mL) were added DMF (0.25 mL) and $SOCl_2$ (5.7 g, 48.0 mmol), followed stirred at 60°C for 3 h. The mixture was cooled down to the rt. and concentrated in vacuo to afford a yellow solid. Acehydrazide (4.0 g, 54.0 mmol) and triethylamine (6.5 mL, 47.0 mmol) were diluted in dichloromethane (30 mL) to afford a yellow solution. The above-mentioned solid was dissolved in dichloromethane (20.0 mL) at 0°C and slowly added to the solution. The mixture was stirred for overnight. Filtration and drying gave the desired yellow solid (4.13 g, 16.3 mmol, 54.4%) without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 2H), 8.07 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 3.8 Hz, 2H), 7.62 (dt, J = 12.5, 4.2 Hz, 1H), 2.08 (s, 3H). MS (ESI): 222.1 $[M-H]^+$.



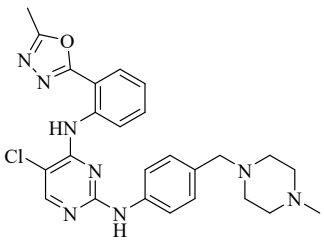
2-methyl-5-(2-nitrophenyl)-1,3,4-oxadiazole (**19**): To a solution of 18 (0.5 g, 2.24 mmol) in toluene (5.0 mL) was added $POCl_3$ (0.25 mL, 2.7 mmol), followed warmed to 90°C and stirred for 24 h. The mixture was cooled and concentrated to remove the toluene. The mixture was basified with saturated aqueous Na_2CO_3 (10.0 mL), and then extracted with dichloromethane (30.0 mL). The organic phase was washed with water (10.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford a yellow solid. The residue was purified by flash column chromatography with eluent (petroleum ether/Ethyl acetate = 1/1) to give compound (450.0 mg, 2.2 mmol, 98%).^{1}H NMR (400 MHz, CDCl3) δ 8.03 (dd, J = 7.8, 1.4 Hz, 1H), 7.97 (dd, J = 7.5, 1.6 Hz, 1H), 7.82-7.69 (m, 2H), 2.61 (s, 3H).



2-(5-methyl-1,3,4-oxadiazol-2-yl)aniline (**20**): To a solution of 19 (450.0 mg, 2.2 mmol) in ethanol (15.0 mL) was added hydrazine hydrate (0.5 g, 10.0 mmol), $FeCl_3$ (60 mg, 0.37 mmol), and active carbon (100.0 mg), followed warmed to 80°C and stirred for 5.5 h. The mixture was cooled to rt. and stirred for another 8 h. After filtration, the residue was washed twice with ethanol (10 mL) and methanol (10 mL), respectively. The filtrate was concentrated to give a yellow solid. The residue was purified by flash silica gel column chromatography with eluent (petroleum ether/ethyl acetate = 1/1-0/1) to give compound (400.0 mg, 2.28 mmol, 99.8%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.8, 1.4 Hz, 1H), 7.97 (dd, J = 7.5, 1.6 Hz, 1H), 7.82-7.69 (m, 2H), 2.61 (s, 3H). MS (ESI): 176.2 $[M+H]^+$.

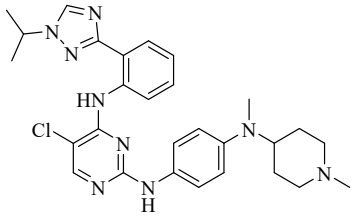


2,5-dichloro-*N*-(2-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)pyrimidin-4-amine (**24-m15**): To a mixture of 20 (400.0 mg, 2.28 mmol) and 2,4,5-trichloropyrimidine (1.0 g, 5.45 mmol) in tBuOH (8 mL) were added $Pd_2(dba)_3$ (300.0 mg, 0.3 mmol), XPhos (300.0 mg, 0.6 mmol) and tBuONa (400.0 mg, 4.0 mmol). After degassing and refilling with N_2, the mixture was refluxed for 24 h. The mixture was cooled down and concentrated in *vacuo*. The residue was purified by flash column chromatography with eluent (petroleum ether/ethyl acetate = 1:5-1:1) to give a yellow solid 10a (90.0 mg, 0.28 mmol, 10.0%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.53 (d, J = 7.5 Hz, 2H), 7.98 (dd, J = 7.9, 1.2 Hz, 1H), 7.70 (t, J = 7.9 Hz, 1H), 7.39 (t, J = 7.3 Hz, 1H), 2.61 (s, 3H). MS (ESI): 322.2 $[M+H]^+$.



5-chloro-N^4-(2-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)-N^2-(4-((4-methylpiperazin-1-yl)methyl)phenyl)pyrimidine-2,4-diamine (**m15**): To a mixture of 24-m15 (80.0 mg, 0.25 mmol) and 4-[(4-methylpiperazin-1-yl)methyl]aniline (80.0 mg, 0.39 mmol) in tBuOH (4.0 mL) were added $Pd_2(dba)_3$ (26.1 mg, 0.03 mmol), XPhos (25.6 mg, 0.05 mmol) and tBuONa (37.5 mg, 0.38 mmol). After degassing and refilling with N_2, the mixture was refluxed for overnight. The mixture was cooled down and concentrated in *vacuo*. The residue was purified by flash column chromatography with

eluent (ethyl acetate/methanol = 50/1) to give a white solid 11b (7.9 mg, 15.0 umol, 6.1%). ^{1}H NMR (400 MHz, CDCl3) δ 10.92 (s, 1H), 8.90 (d, J = 8.5 Hz, 1H), 8.18 (s, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.58-7.49 (m, 3H), 7.31 (s, 1H), 7.21 (dd, J = 16.3, 8.6 Hz, 3H), 3.62 (s, 2H), 2.86-2.77 (m, 4H), 2.68 (s, 3H), 2.60 (s, 3H), 2.41-2.32 (m, 2H), 2.29-2.19 (m, 2H), 2.11-1.99 (m, 4H). MS (ESI): 491.3 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{25}H_{28}ClN_8O^+$, 491.1960; found, 491.1966. Purity: 95.01%.



5-chloro-*N*^{4}-(2-(1-isopropyl-1H-1,2,4-triazol-3-yl)phenyl)-*N*^{2}-(4-(methyl(1-methylpiperidin-4-yl)amino)phenyl)pyrimidine-2,4-diamine (**m16**): To a solution of 24-m6 (0.25 g, 0.72 mmol) in n-BuOH (8.0 ml) were added *N*^{1}-methyl-*N*^{1}-(1-methyl-4-piperidyl)benzene-1,4-diamine (0.16 g, 0.72 mmol) and conc.HCl (0.02 g, 0.14 mmol). The reaction mixture was stirred at 140°C for 4 h under microwave conditions. The reaction mixture was concentrated in *vacuo* and purified by a silica gel column chromatography with eluent (dichloromethane/methanol = 20/1) to give the title compound as a pink solid (110.3 mg, 0.2 mmol, 28.9%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.10 (s, 1H), 9.17 (s, 1H), 8.81 (s, 2H), 8.19 (d, *J* = 10.6 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 4.73 – 4.62 (m, 1H), 3.77 (s, 1H), 2.81 (d, *J* = 22.1 Hz, 2H), 2.70 (s, 3H), 2.59 (s, 3H), 1.99 (dd, *J* = 22.8, 11.1 Hz, 2H), 1.73 (d, *J* = 12.7 Hz, 2H), 1.54 (d, *J* = 6.6 Hz, 6H), 1.22 (s, 2H). ^{13}C NMR (151 MHz, DMSO-*d6*): δ (ppm) 160.46, 158.71, 155.80, 155.27, 145.94, 143.20, 137.39, 131.22, 129.68, 128.40, 122.86, 122.45, 121.92, 118.74, 115.17, 104.50, 54.61, 53.95, 52.46, 32.42, 26.59, 22.56. MS (ESI): 532.2 $[M+H]^+$. HRMS: $[M+H]^+$ calcd for $C_{28}H_{35}ClN_9^+$, 532.2704; found, 532.2717. Purity: 96.8%.

Biology

Axl (h)

Axl (h) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 250 µM KKSRGDYMTMQIG, 10 mM Magnesium acetate and [γ-^{33}P]-ATP (specific activity and concentration as required). The reaction is initiated by the addition of the Mg/ATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of phosphoric acid to a concentration of 0.5%. 10 µL of the reaction is then spotted onto a P30 filtermat and washed four times for 4 minutes in 0.425% phosphoric acid and once in methanol prior to drying and scintillation counting.

Aurora-B (h)

Aurora-B (h) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 30 µM AKRRRLSSLRA, 10 mM Magnesium acetate and [γ-33P]-ATP (specific activity and concentration as required). The reaction is initiated by the addition of the Mg/ATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of phosphoric acid to a concentration of 0.5%. 10 µL of the reaction is then spotted onto a P30 filtermat and washed four times for 4 minutes in 0.425% phosphoric acid and once in methanol prior to drying and scintillation counting.

JAK2 (h)

JAK2 (h) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 100 µM KTFCGTPEYLAPEVRREPRILSEEEQEMFRDFDYIADWC, 10 mM Magnesium acetate and [γ-33P]-ATP (specificactivity and concentration as required). The reaction is initiated by the addition of the Mg/ATP mix. After incubation for40 minutes at room temperature, the reaction is stopped by the addition of phosphoric acid to a concentration of 0.5%.10 µL of the reaction is then spotted onto a P30 filtermat and washed four times for 4 minutes in 0.425% phosphoricacid and once in methanol prior to drying and scintillation counting.

ALK (h)

ALK (h) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 250 μM KKKSPGEYVNIEFG, 10 mM Magnesiumacetate and [γ-33P]-ATP (specific activity and concentration as required). The reaction is initiated by the addition of theMg/ATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of phosphoricacid to a concentration of 0.5%. 10 μL of the reaction is then spotted onto a P30 filtermat and washed four times for 4minutes in 0.425% phosphoric acid and once in methanol prior to drying and scintillation counting.

IGF-1R (h)

IGF-1R (h) is incubated with 50 mM Tris pH 7.5, 0.1 mM EGTA, 0.1 mM Na3VO4, 0.1% β-mercaptoethanol, 250 μMKKKSPGEYVNIEFG, 10 mM MnCl2, 10 mM Magnesium acetate and [γ-33P]-ATP (specific activity and concentration asrequired). The reaction is initiated by the addition of the Mg/ATP mix. After incubation for 40 minutes at roomtemperature, the reaction is stopped by the addition of phosphoric acid to a concentration of 0.5%. 10 μL of thereaction is then spotted onto a P30 filtermat and washed four times for 4 minutes in 0.425% phosphoric acid and oncein methanol prior to drying and scintillation counting.

Kinase selectivity assay

Table S1 Percentages of enzymatic inhibitions exerted by the representative compound m16 over a panel of 75 kinases.

Kinase	Inhibition (%)	Kinase	Inhibition (%)	Kinase	Inhibition (%)
Abl	80±4	Fes	34±2	Ros	16±1
ACTR2	-5±9	Fgr	60±0	TTK	44±1
ALK	49±5	FGFR4	16±2	Txk	73±1
AMPKα1	-2±2	Flt3	94±1	TYK2	15±8
ASK1	-1±1	Fyn	58±8	ULK1	21±4
Aurora A	99±0	GCK	12±1	ZAK	-7±0
Axl	98±1	Haspin	2±4	ErbB2	17±3
BTK	29±2	Hck	50±3	ErbB4	0±5
B-Raf	24±2	HIPK1	-2±1	MST1	0±2
CaMKIβ	1±5	HPK1	50±4	PDGFRβ	36±1
Cdc7/cyclinB1	5±3	IGF-1R	55±3	ZAP-70	-21±5
CDK1/cyclinB	-4±4	IKKα	31±7	ATM	-3±2
CDK2/cyclinE	8±3	JAK1	19±3	DNA-PK	-11±4
CDK4/cyclinD3	-5±1	KDR	88±2	PI3K(p110α/p85α)	0±0
CDK7/cyclinH/MAT1	-15±3	LKB1	4±0	PI3K(p110δ/p85α)	6±1
CHK1	14±0	LTK	10±2	Tec	1±5
CHK2	16±1	MAPK1	15±4	SGK	14±3
CK1δ	-13±1	MEK1	11±3	PRK1	42±6
CK2	-19±2	Mer	101±0	EphA2	47±1
CLIK1	-2±3	Met	88±2	EphA4	-11±1
c-Kit	27±1	mTOR	-2±1	EphA7	6±5
DAPK1	1±8	PDGFRα	32±3	EphB1	49±2
DMPK	6±3	PDK1	5±3	EphB2	-9±7
EGFR	3±4	PTK5	32±5	EphB3	-7±0
FAK	60±3	Ret	88±0	EphB4	31±5

[a]All the inhibition (%) values were calculated by subtracting activity (%) from 100 and presented as the mean ±SD.

Cell Proliferation Assay

Table S2 The details of cell line proliferation inhibitory assay.

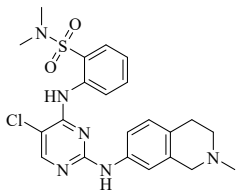
Cell lines	cell	**m16**[a]		staurosporine[a]	
	number/well	CC50 (uM)	Max inhibition%	CC50 (uM)	Max inhibition%
143B	3000	1.34	64	0.01	97
HT29	3000	0.50	89	0.01	96
MV411	8000	0.07	99	0.0001	102
MSTO-211H	3000	0.45	80	0.03	90

namalwa	10000	0.49	72	0.05	97
PC-3	3000	5.59	62	0.16	73
SW620	3000	0.35	89	0.01	91
T24	3000	0.93	73	0.00	97
Hel92.1-7	8000	0.46	77	0.01	91
Raji	8000	4.56	61	N/A	34
RS4;11	8000	0.14	92	0.004	94
SU-DHL-4	8000	0.04	92	0.001	93
SUN16	8000	0.15	94	0.02	90
calu-3	10000	0.11	73	0.37	63
K562	10000	N/A	53	0.17	88
KU812	10000	0.23	81	0.04	88
SNU-5	10000	0.36	66	0.01	94
MDA-MB-231	3000	N/A	50	0.001	93
CAL27	3000	0.11	83	0.04	98
Hep 3B 2.1-7	3000	0.08	94	0.03	93
KYSE510	3000	0.12	96	0.07	99
OVCAR-3	3000	0.22	77	0.01	81
T.Tn	3000	0.12	87	0.01	99
ASPC-1	5000	0.75	82	0.04	95
BXPC-3	3000	0.38	74	0.002	99
MGC803	3000	0.10	76	0.01	96
NCI-H2052	3000	1.18	69	0.02	90
EVSA-T	6000	1.15	83	0.07	80
Fadu	3000	0.08	76	0.02	100
Hela	2000	0.20	98	0.01	101
Panc-1	8000	N/A	52	0.12	78
U87	3000	3.01	79	0.56	80
A375	8000	23.90	53	0.12	81
HCC827	3000	2.05	91	0.01	88
NCI-H226	3000	1.24	69	0.06	98
A549	3000	0.29	85	0.02	96
hepg2	6000	0.35	63	0.04	88
MCF-7	3000	5.19	58	0.05	87
molm-13	8000	0.21	87	<0.001	84
NCI-H1954	3000	1.21	91	0.004	86
Caki-1	3000	0.49	72	<0.001	95
Colo205	6000	0.35	89	0.001	95

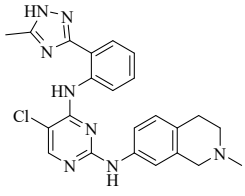
[a]The start concentration of compound **m16** and control was 10 uM, 1 uM, respectively.

Microsomal stability of compound 5a and w10

Table S3. Liver microsomal stability of two compounds, **5a**, **w10**.



5a



w10

Cpd.	Human		Rat	
	$T_{1/2}$ min	Clint mL/min/kg	$T_{1/2}$ min	Clint mL/min/kg
5a	2.4	CL_{hep} = 720.4 $CL_{in\ vivo}$ = 20.1	2.4	CL_{hep} = 1041.0 $CL_{in\ vivo}$ = 52.4
w10	31.6	CL_{hep} = 55.1 $CL_{in\ vivo}$ = 15.0	6.1	CL_{hep} = 404.6 $CL_{in\ vivo}$ = 48.6

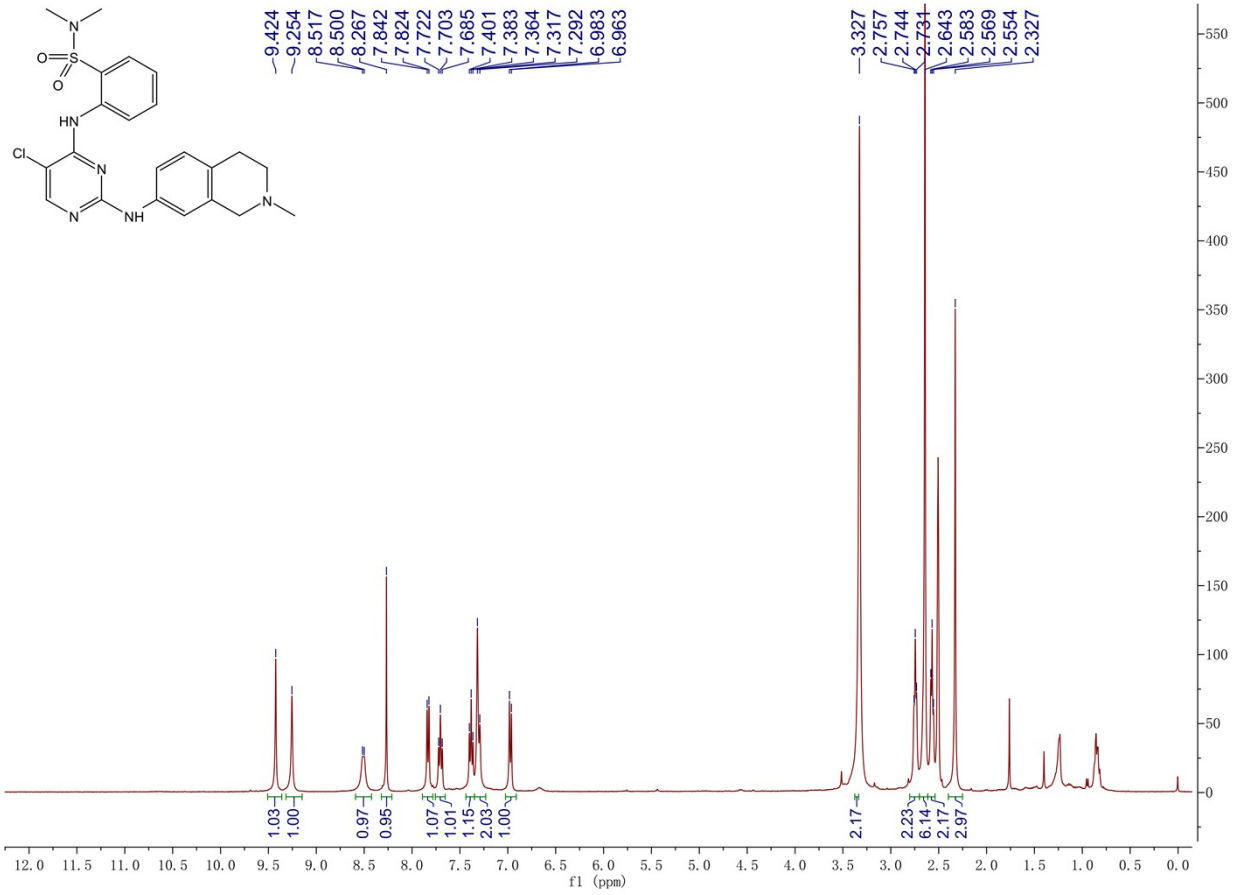
ND. = no data.

Pharmacokinetic parameters obtained in rats.

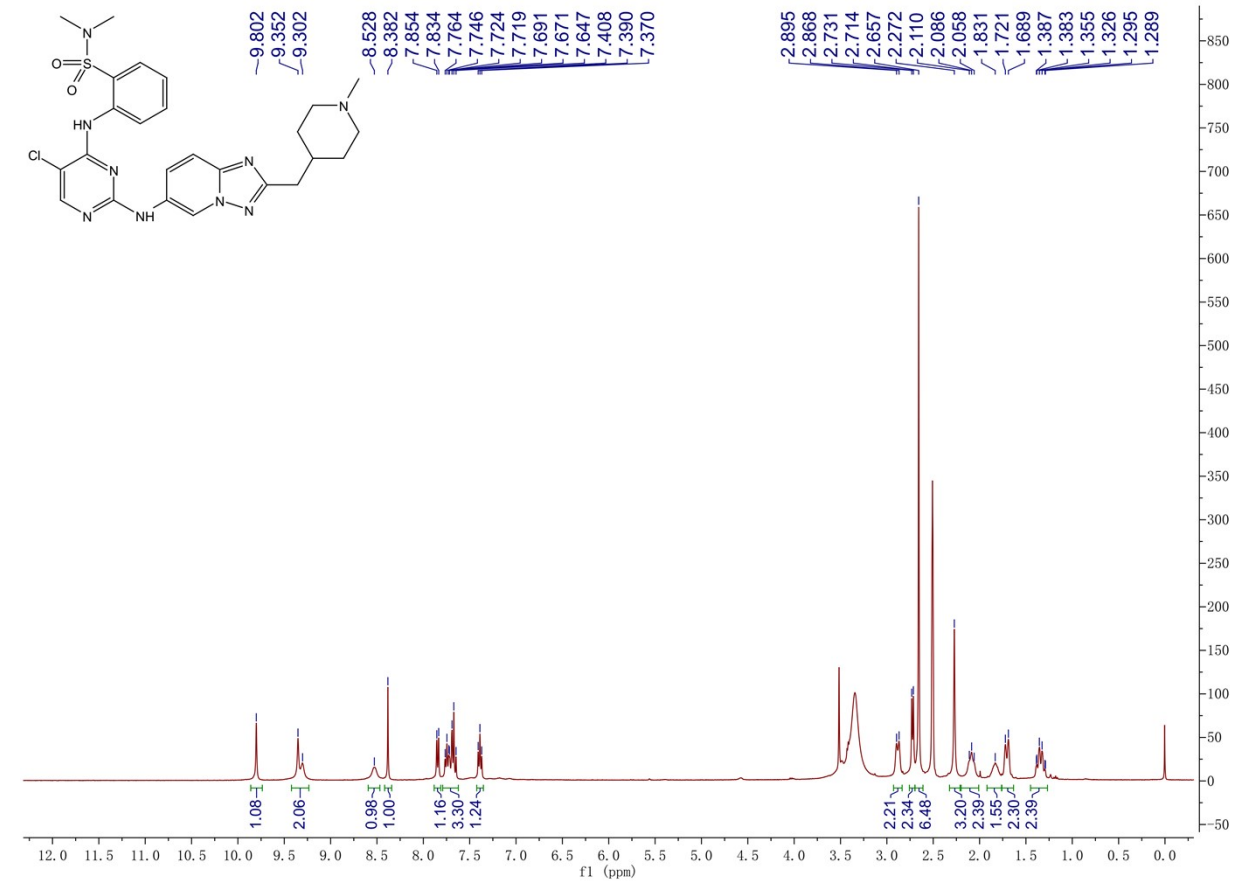
Table S4. Pharmacokinetic Data of compound **m12** and **m13** in Rats

Parameter	m12		m13	
	PO 5 mg/kg	IV 1 mg/kg	PO 5 mg/kg	IV 1 mg/kg
AUC_{last} (ng.h/mL)	239	259	221	145
C_{max} (ng/mL)	44.2	81.3	40.9	45.7
CL (mL/h/kg)	NA	2.82	NA	2.20
$T_{1/2}$ (h)	15.4	3.85	16.1	3.95
F %	18.3		30.4	

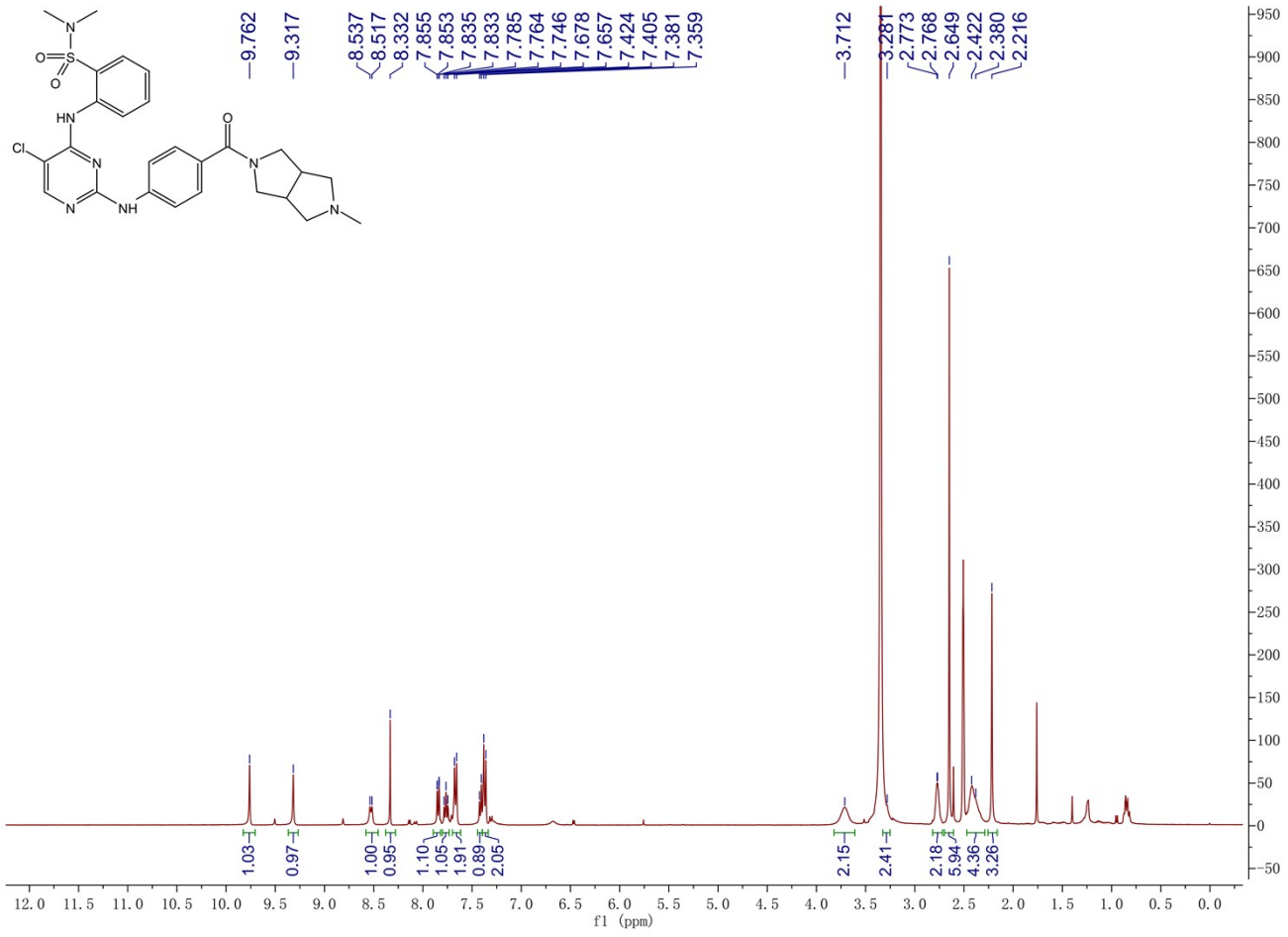
[1]H NMR spectrums of compound 5a.



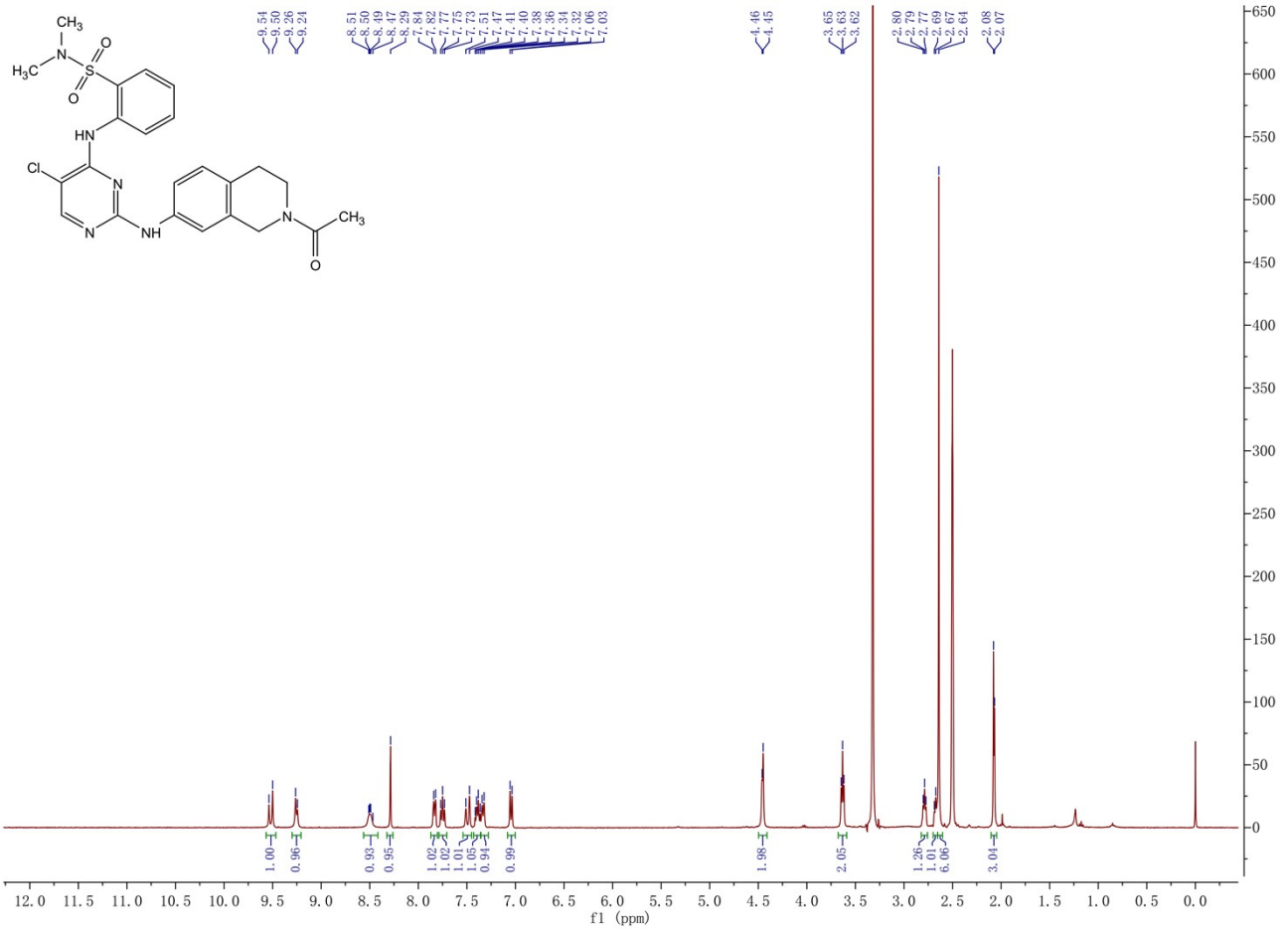
[1]H NMR spectrums of compound 5b.



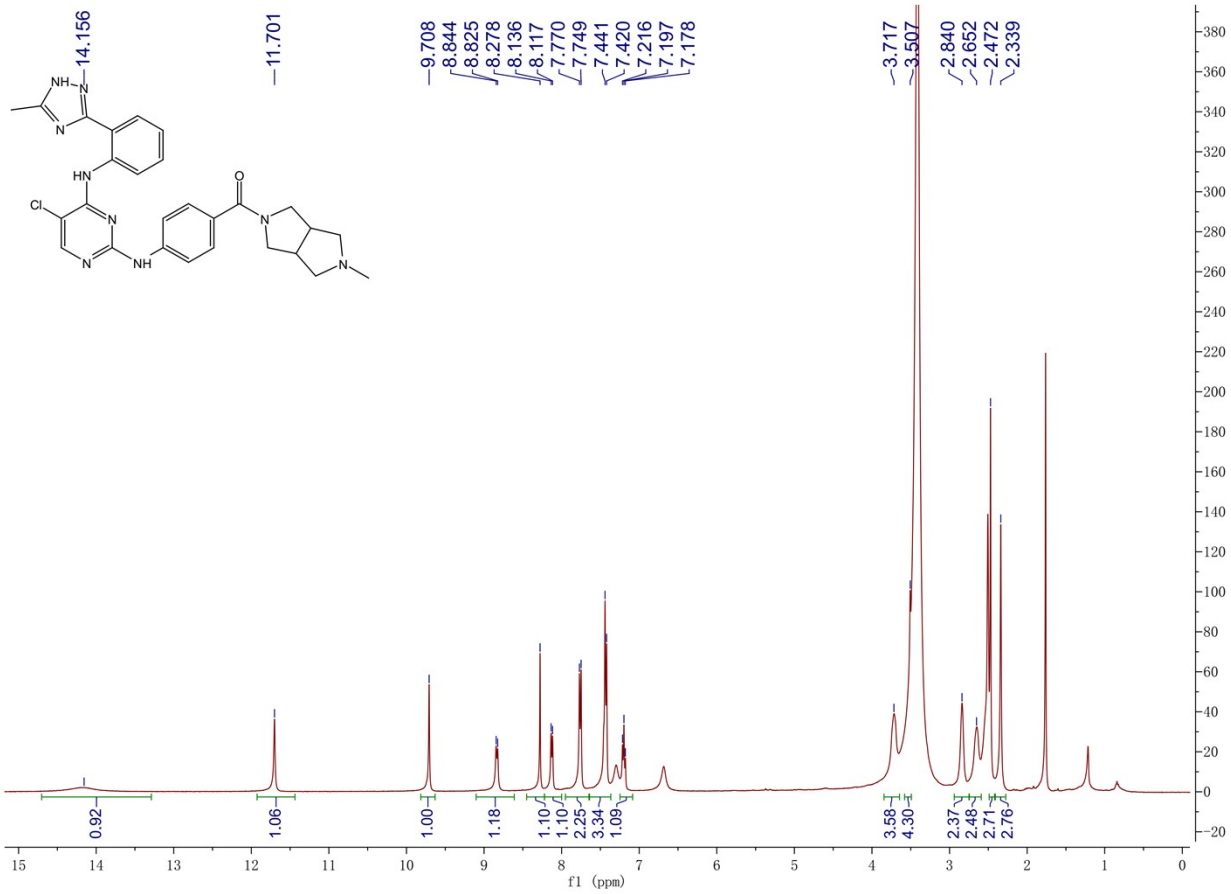
[1]H NMR spectrums of compound 5c.



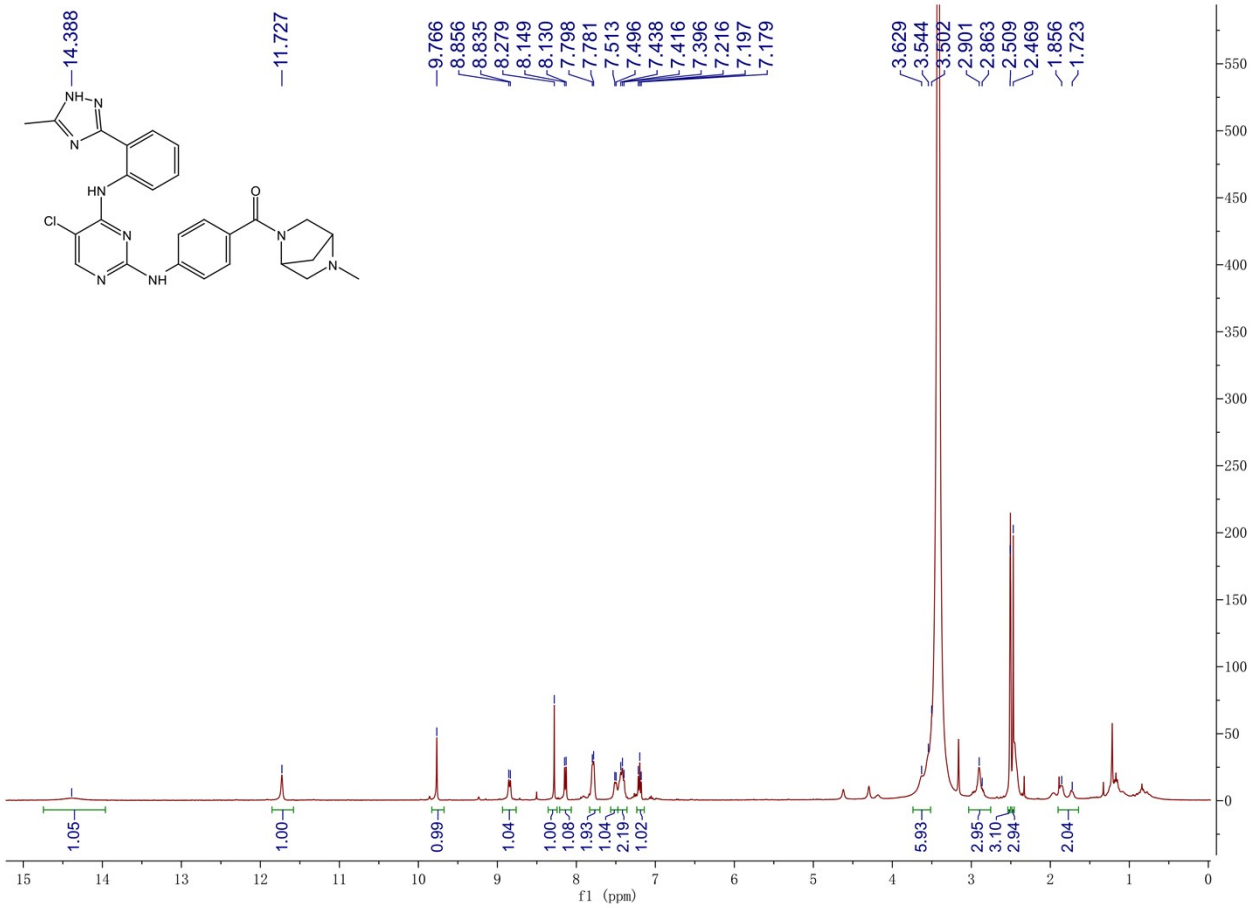
[1]H NMR spectrums of compound 5d.



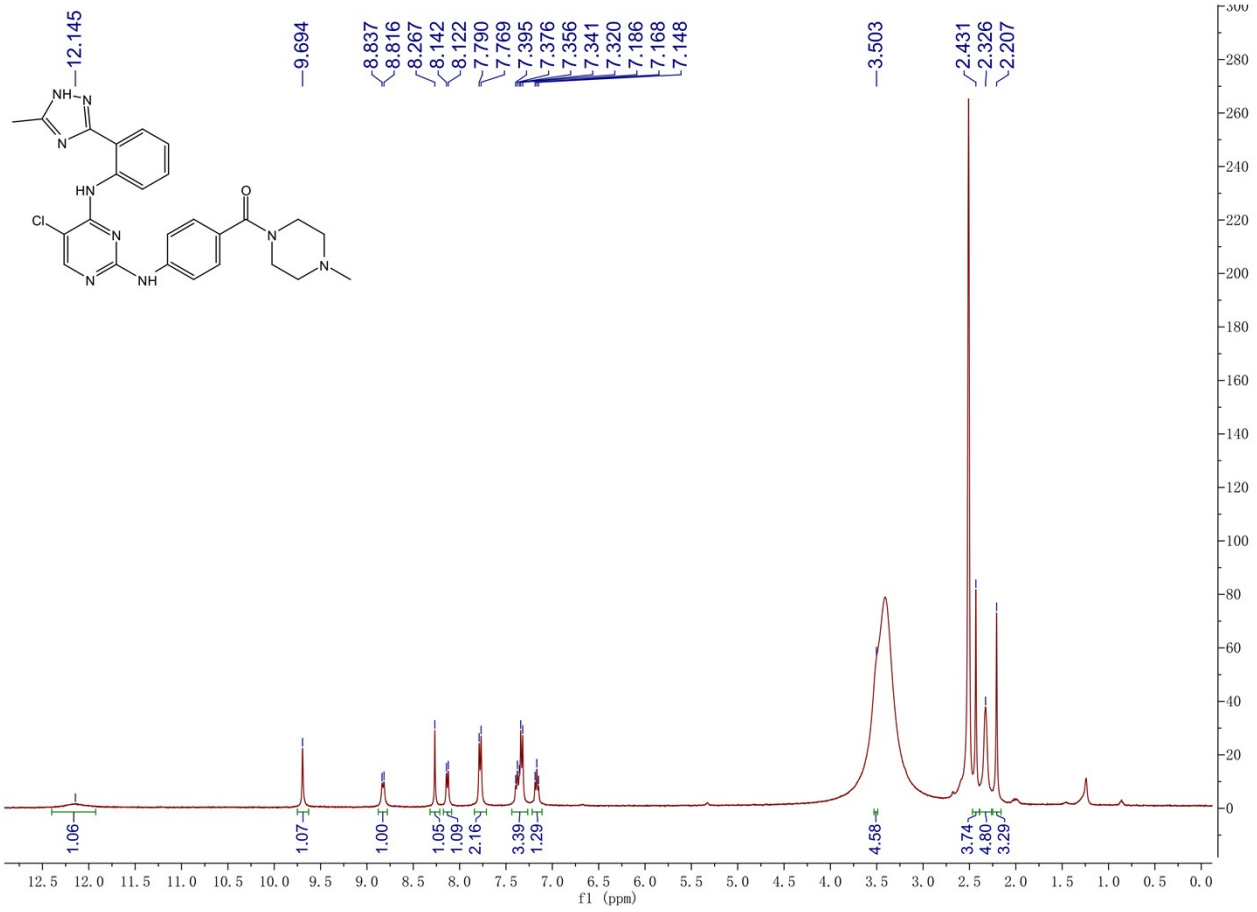
^{1}H NMR spectrums of compound w1.



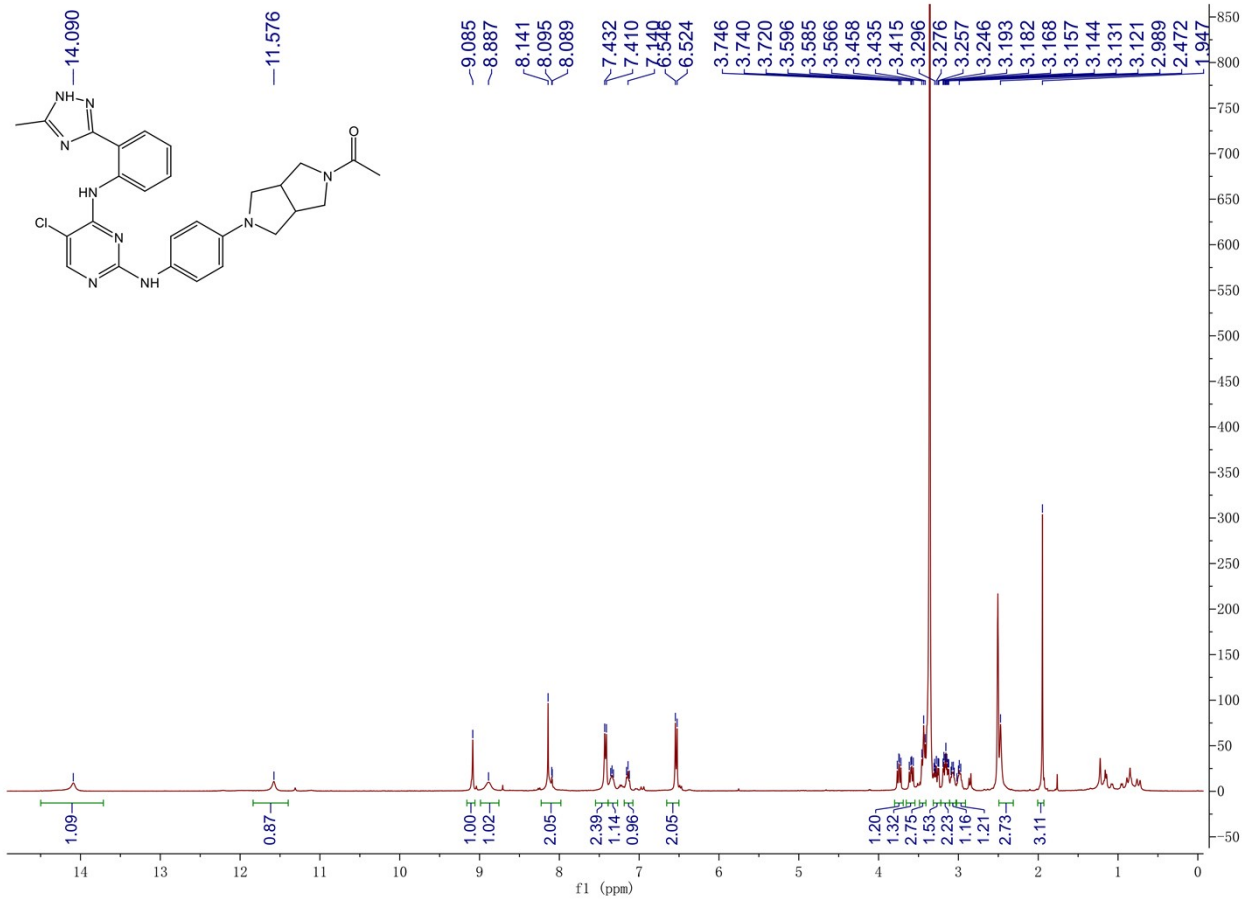
[1]H NMR spectrums of compound w2.



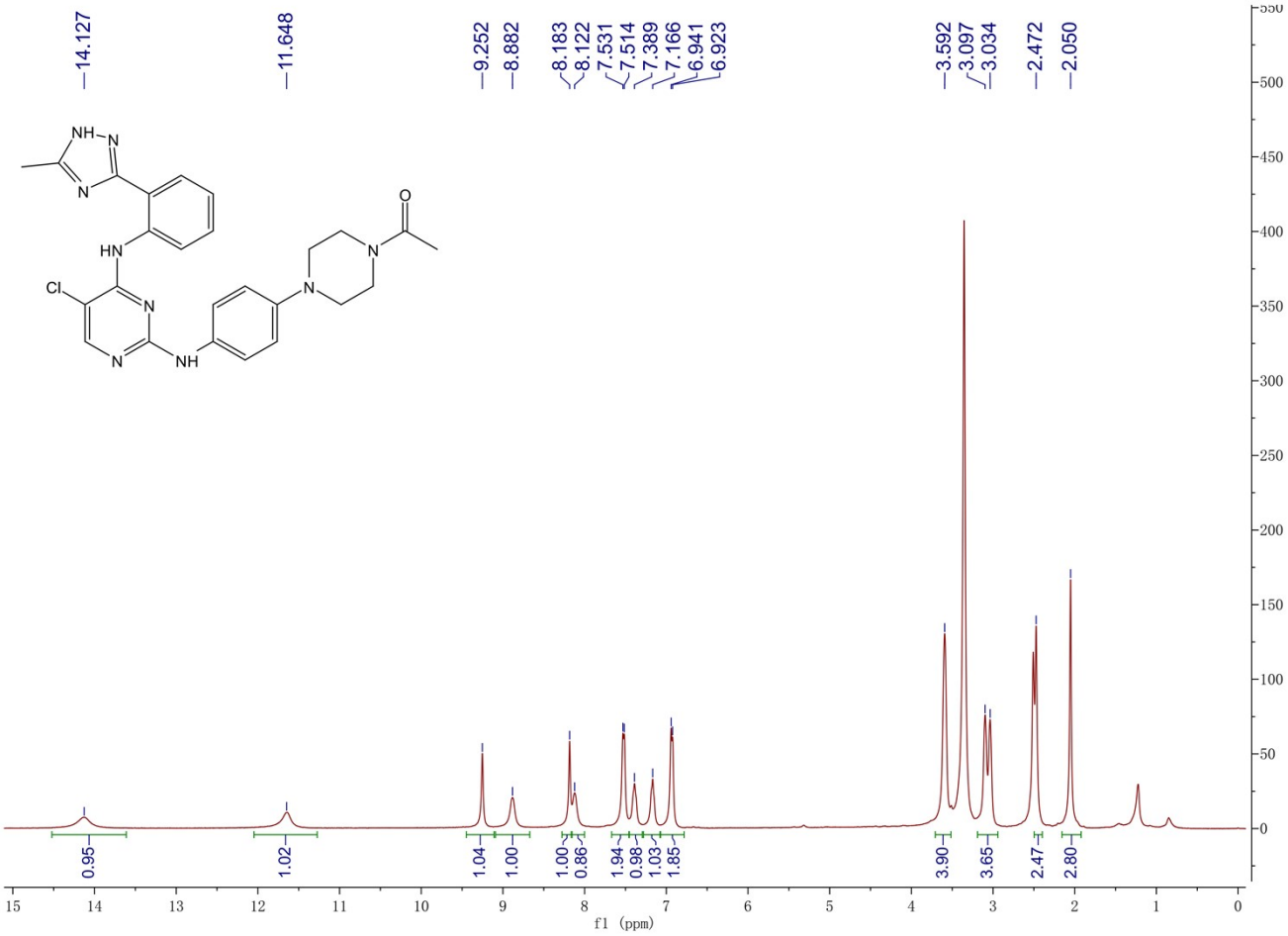
[1]H NMR spectrums of compound w3.



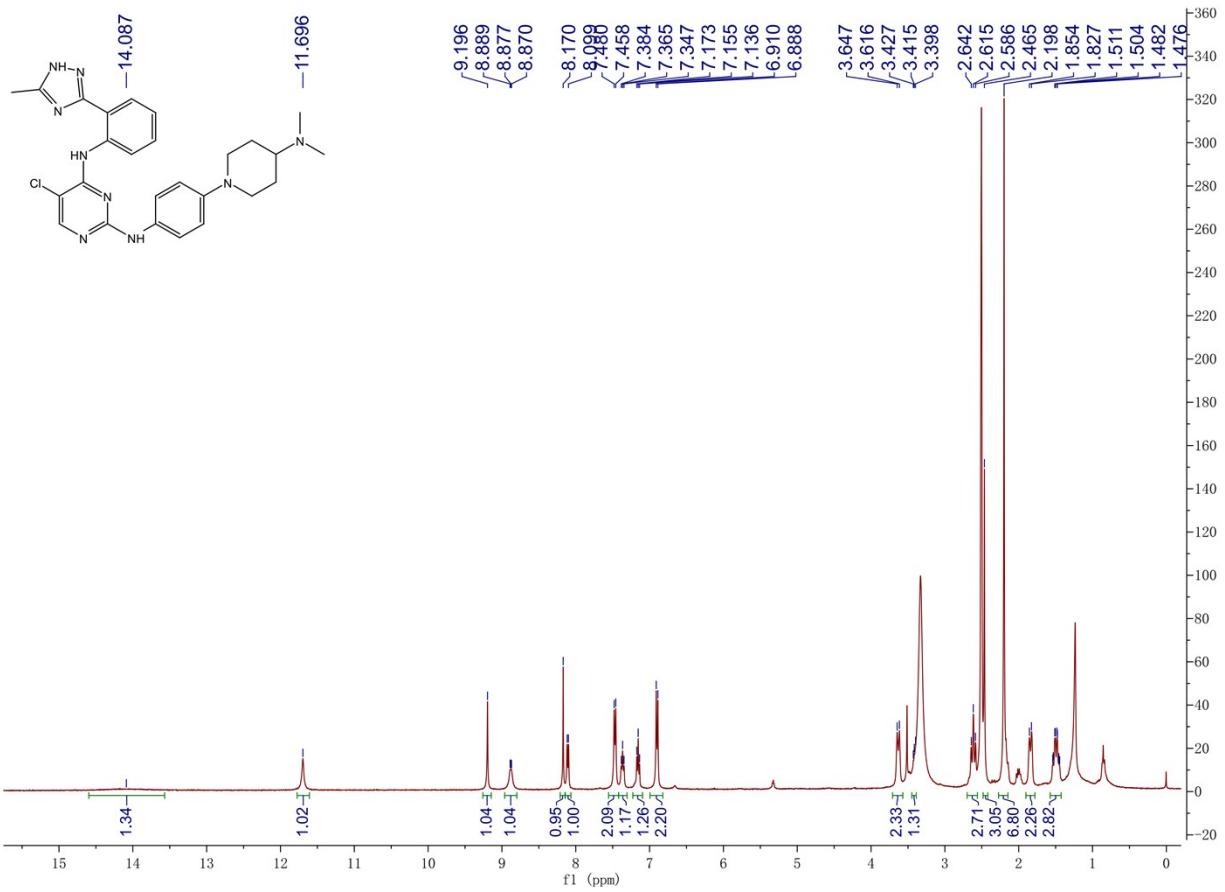
[1]H NMR spectrums of compound w4.



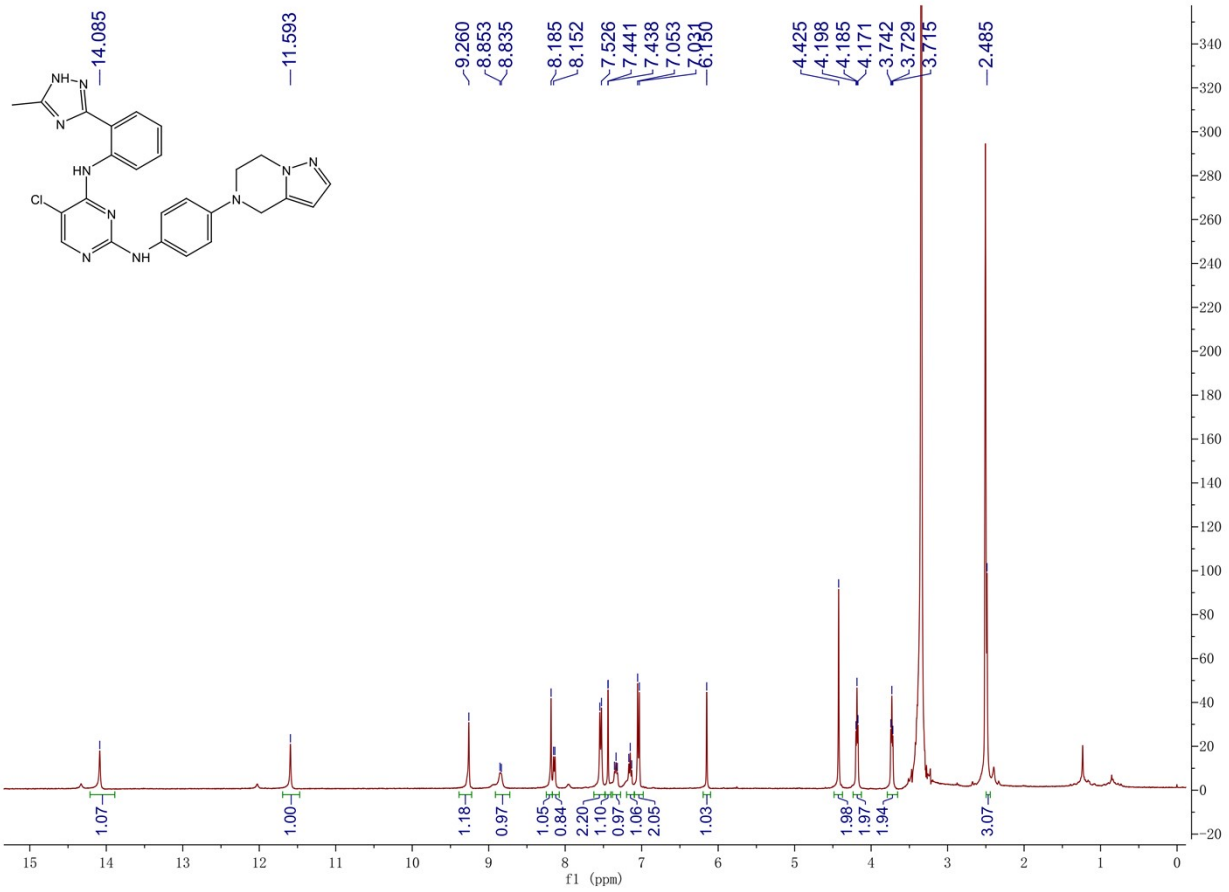
[1]H NMR spectrums of compound w5.



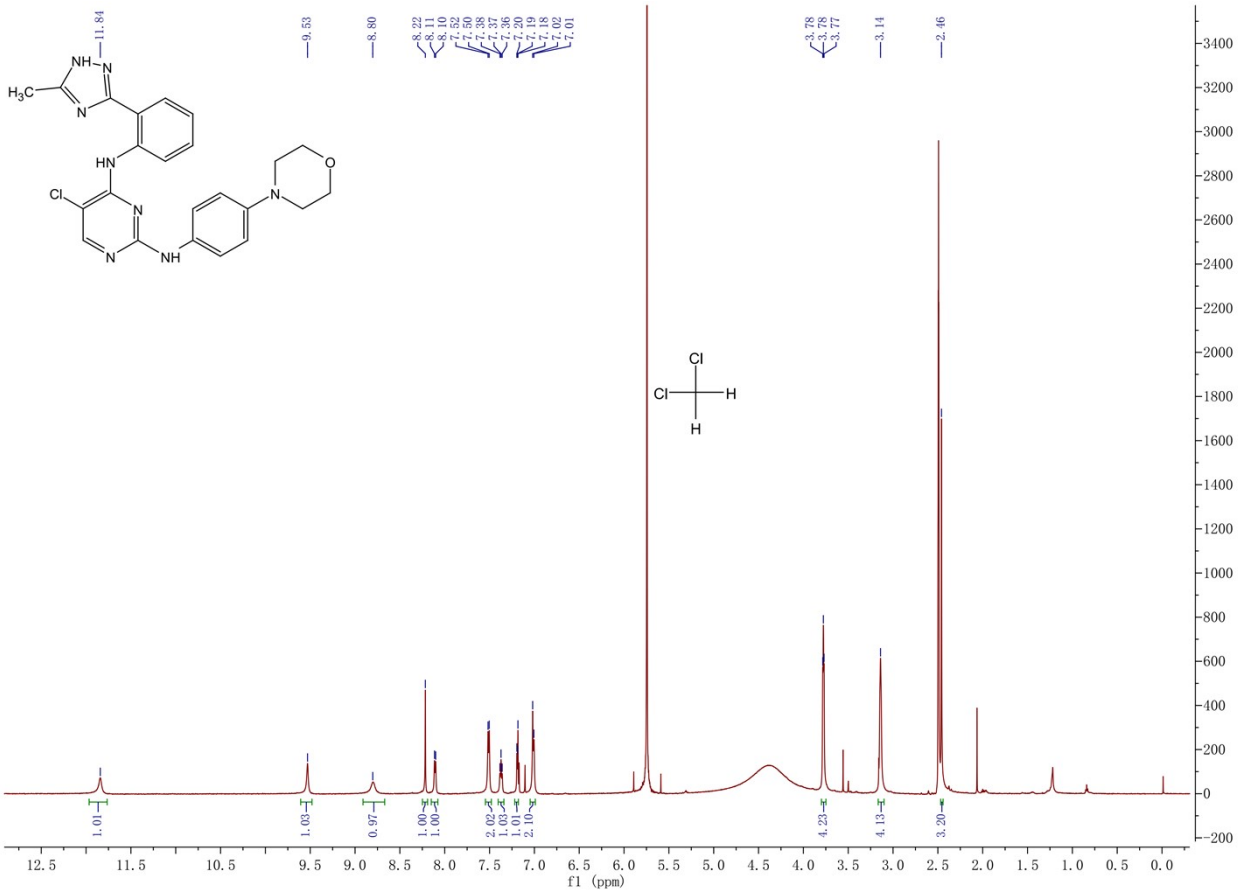
[1]H NMR spectrums of compound w6.



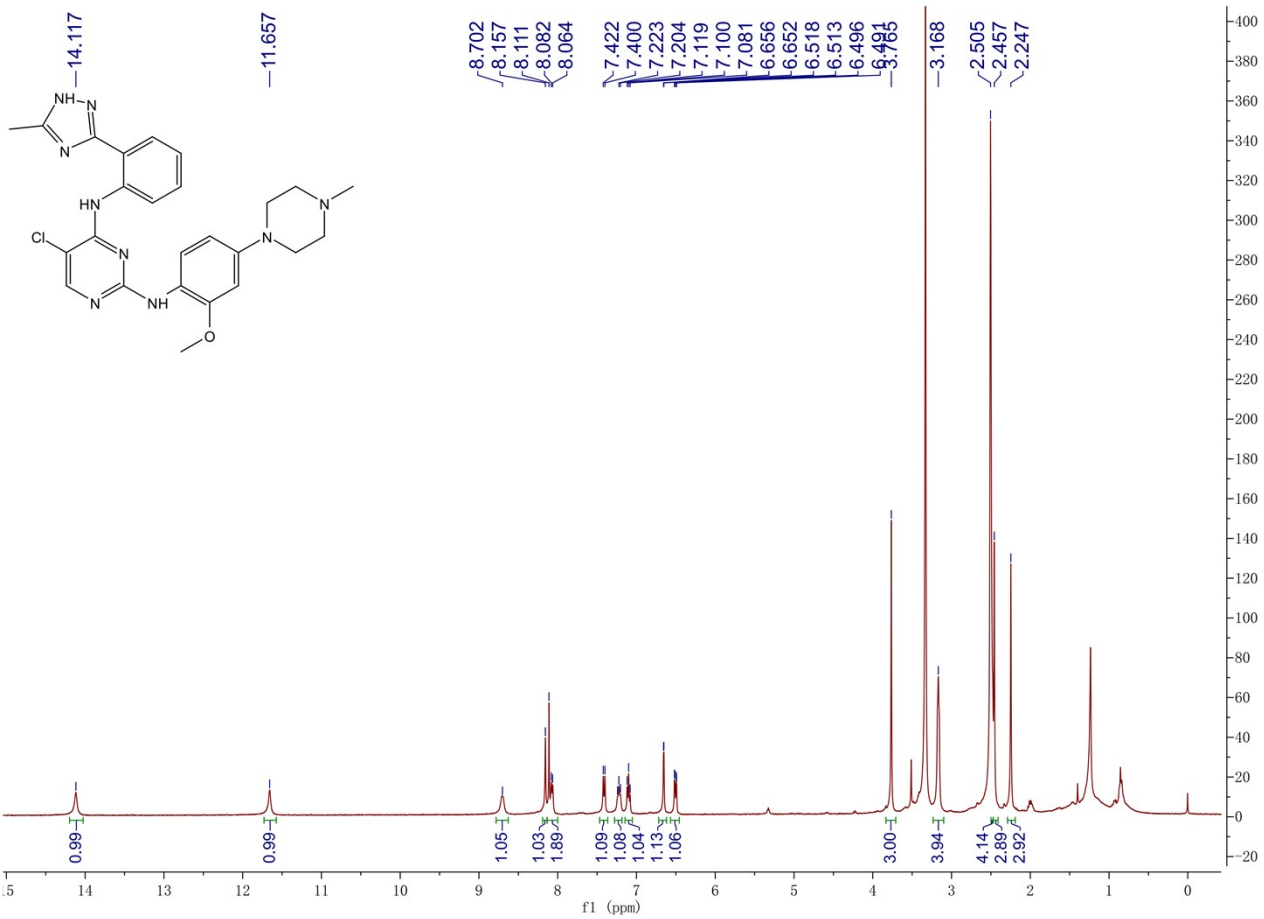
[1]H NMR spectrums of compound w7.



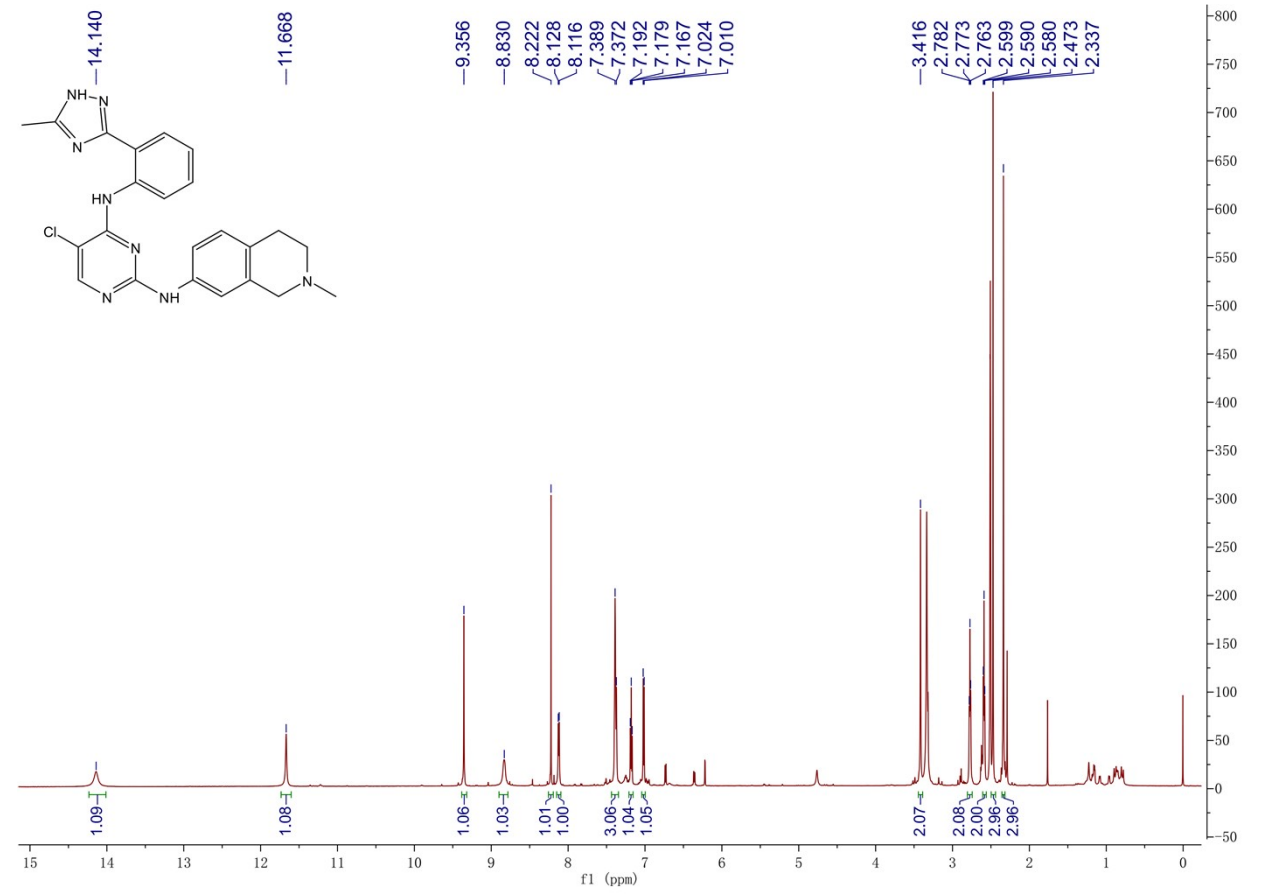
[1]H NMR spectrums of compound w8.



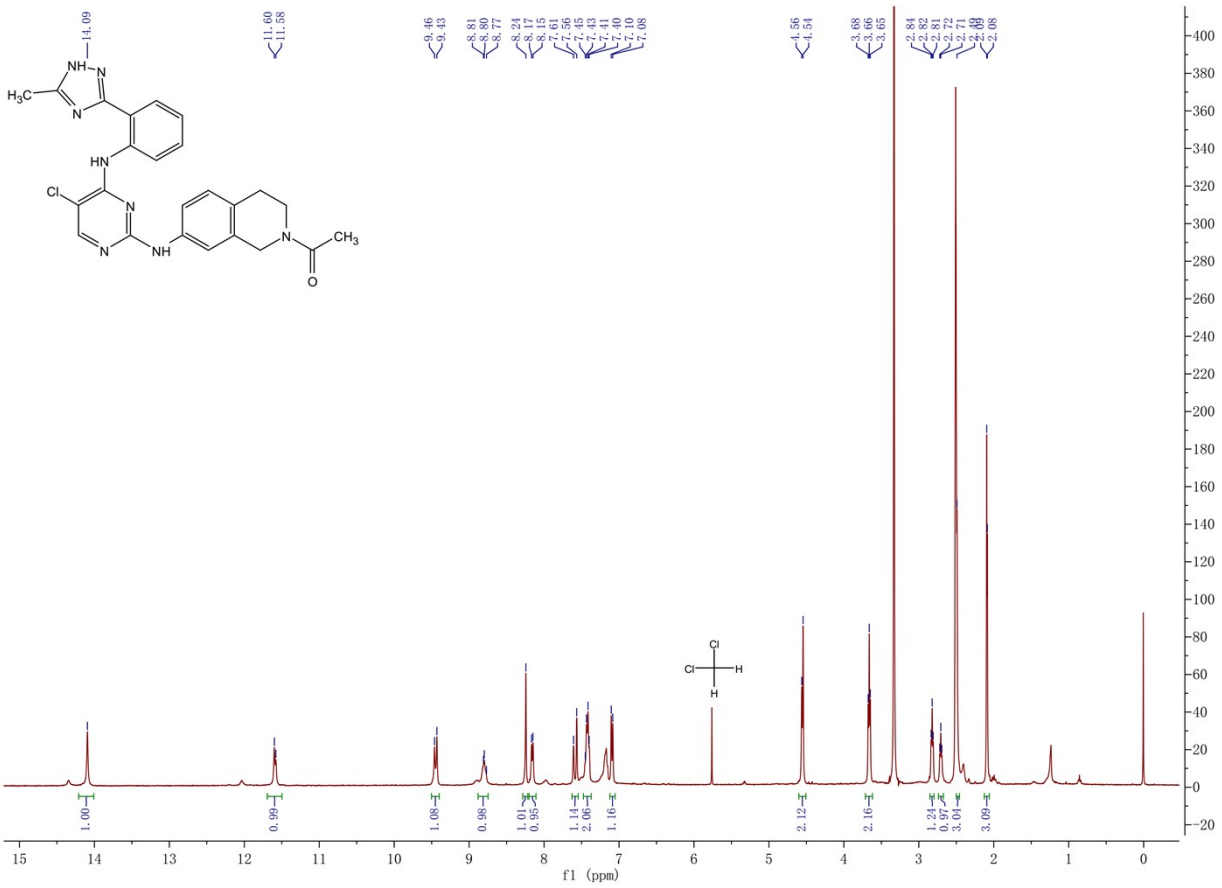
[1]H NMR spectrums of compound w9.



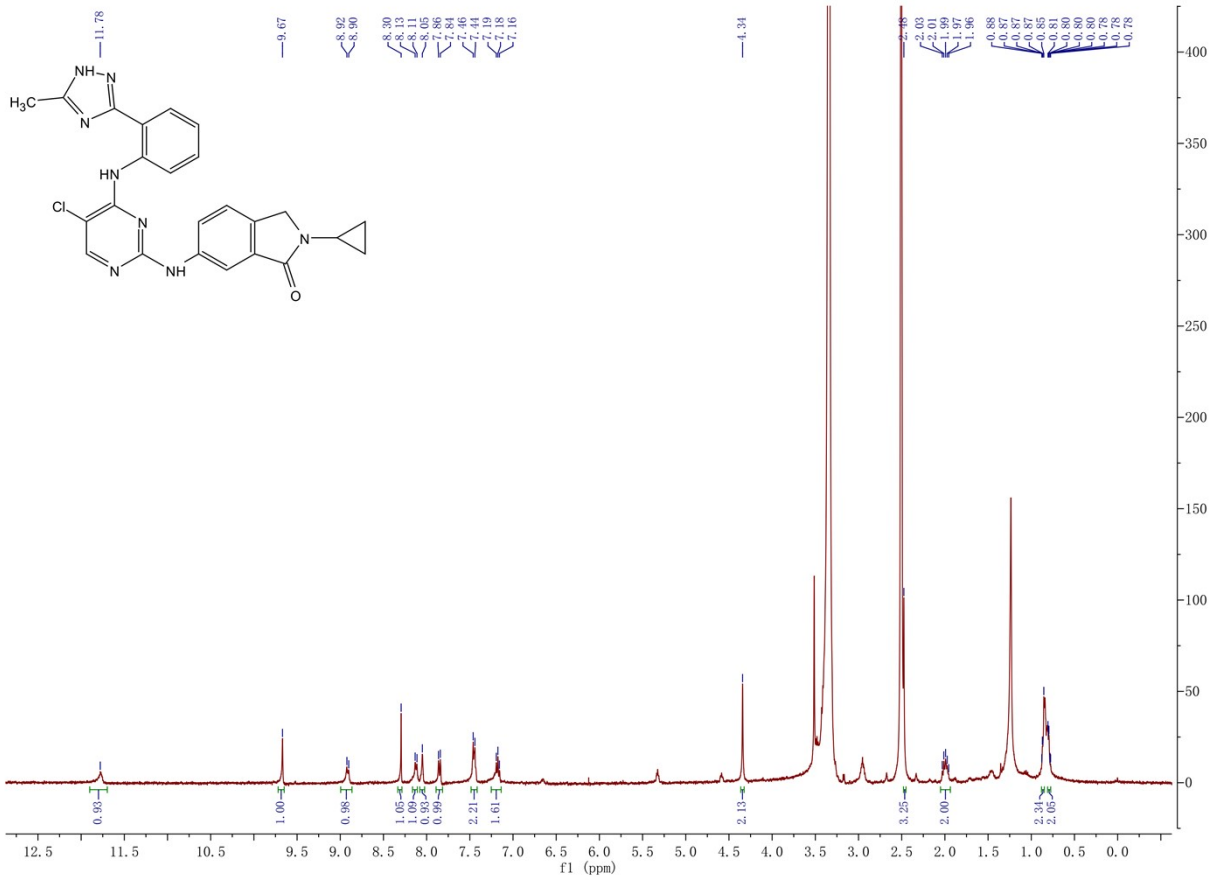
[1]H NMR spectrums of compound w10.



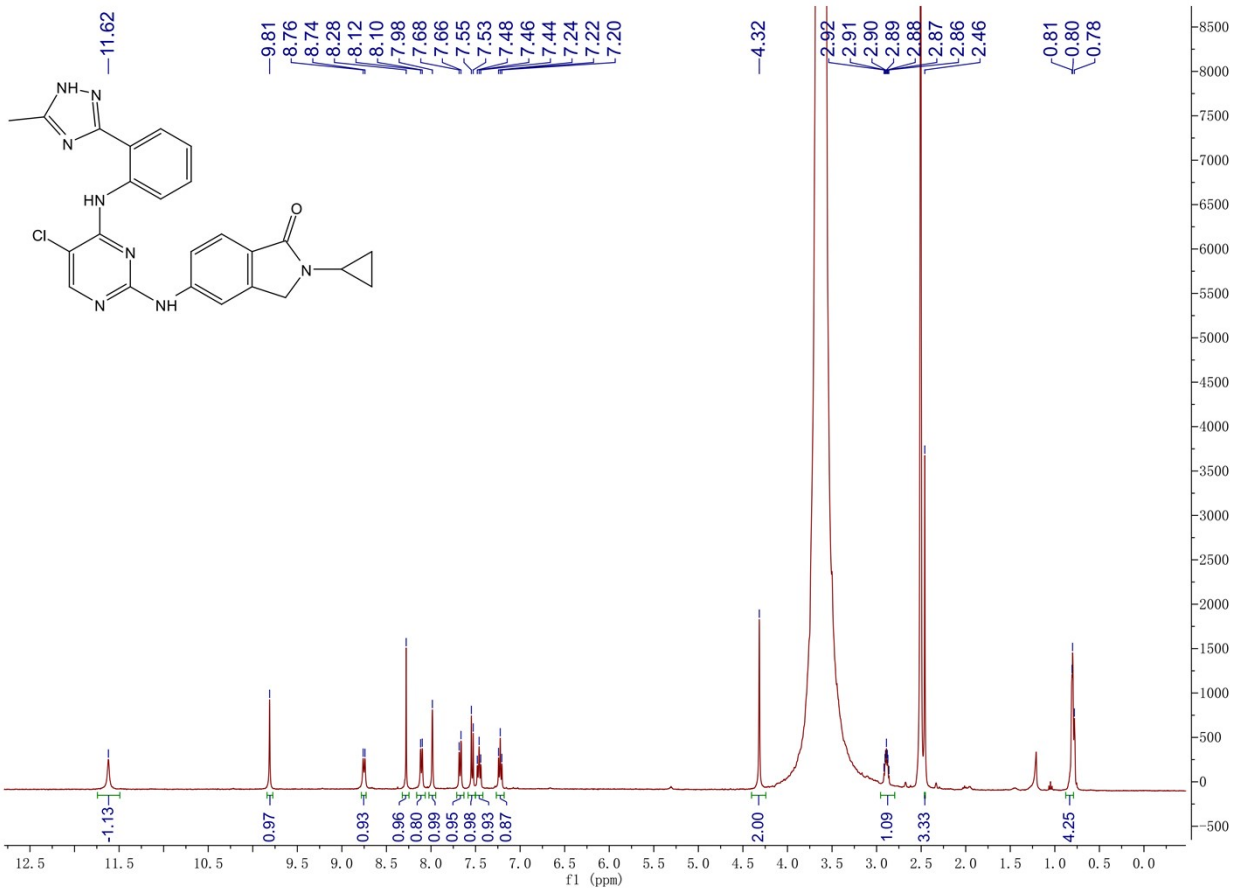
[1]H NMR spectrums of compound w11.



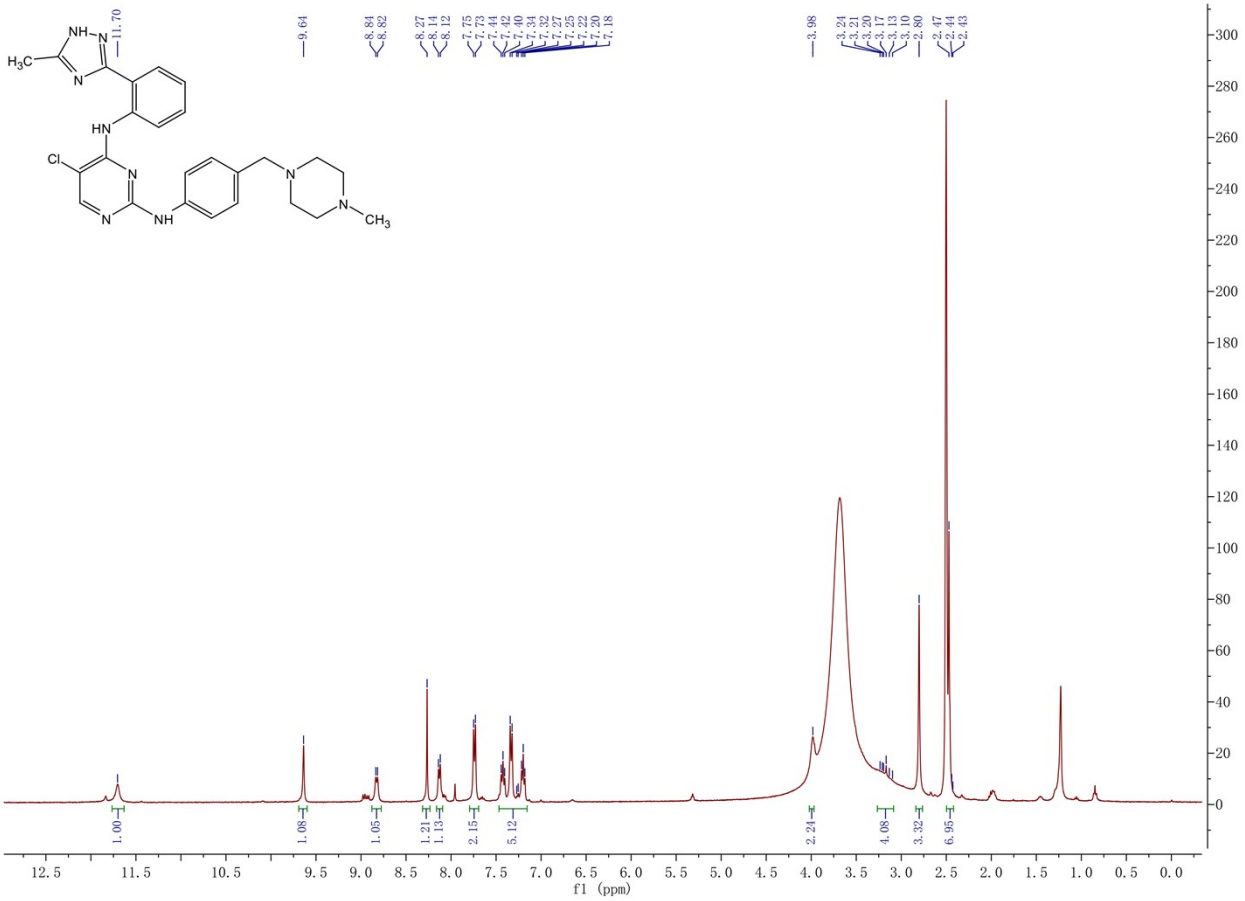
[1]H NMR spectrums of compound w12.



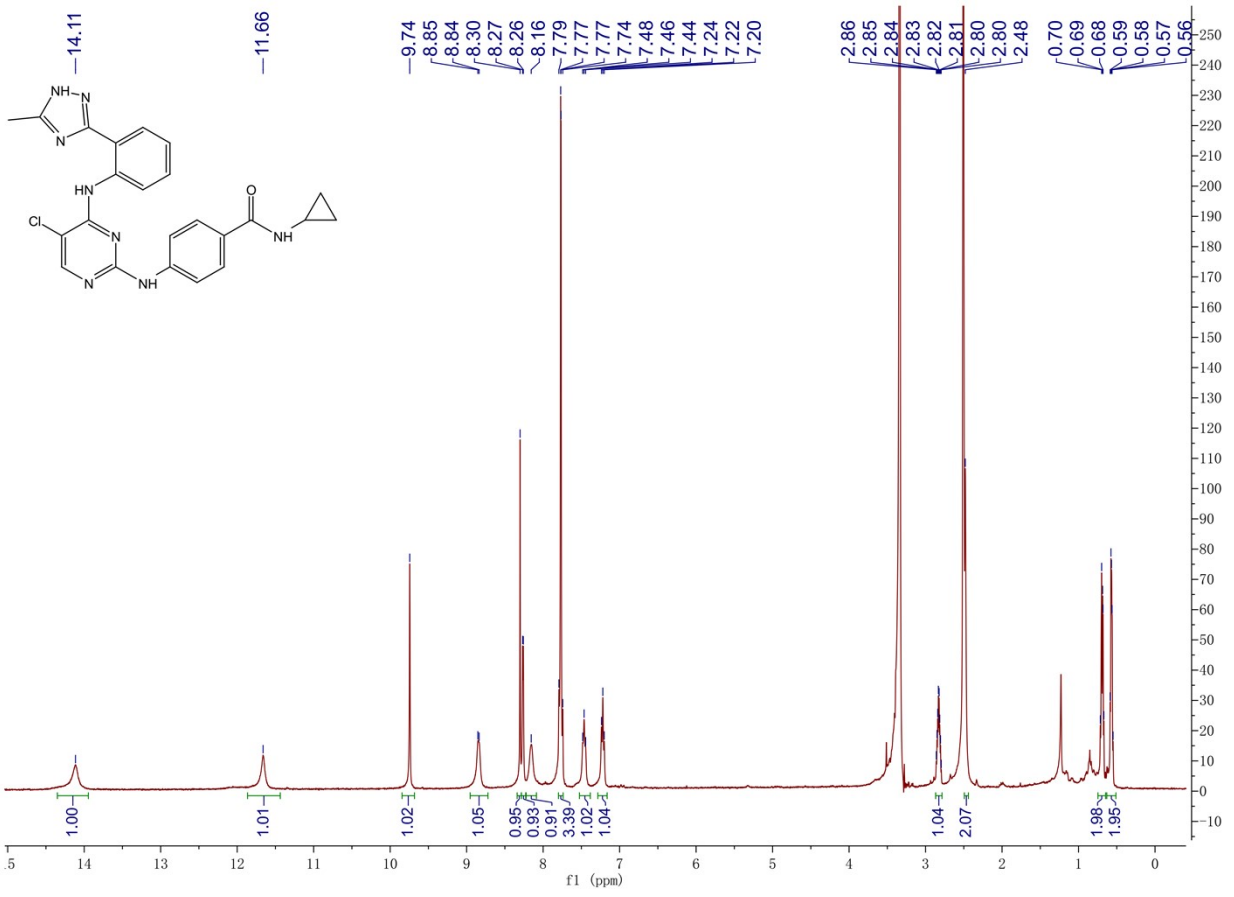
[1]H NMR spectrums of compound w13.



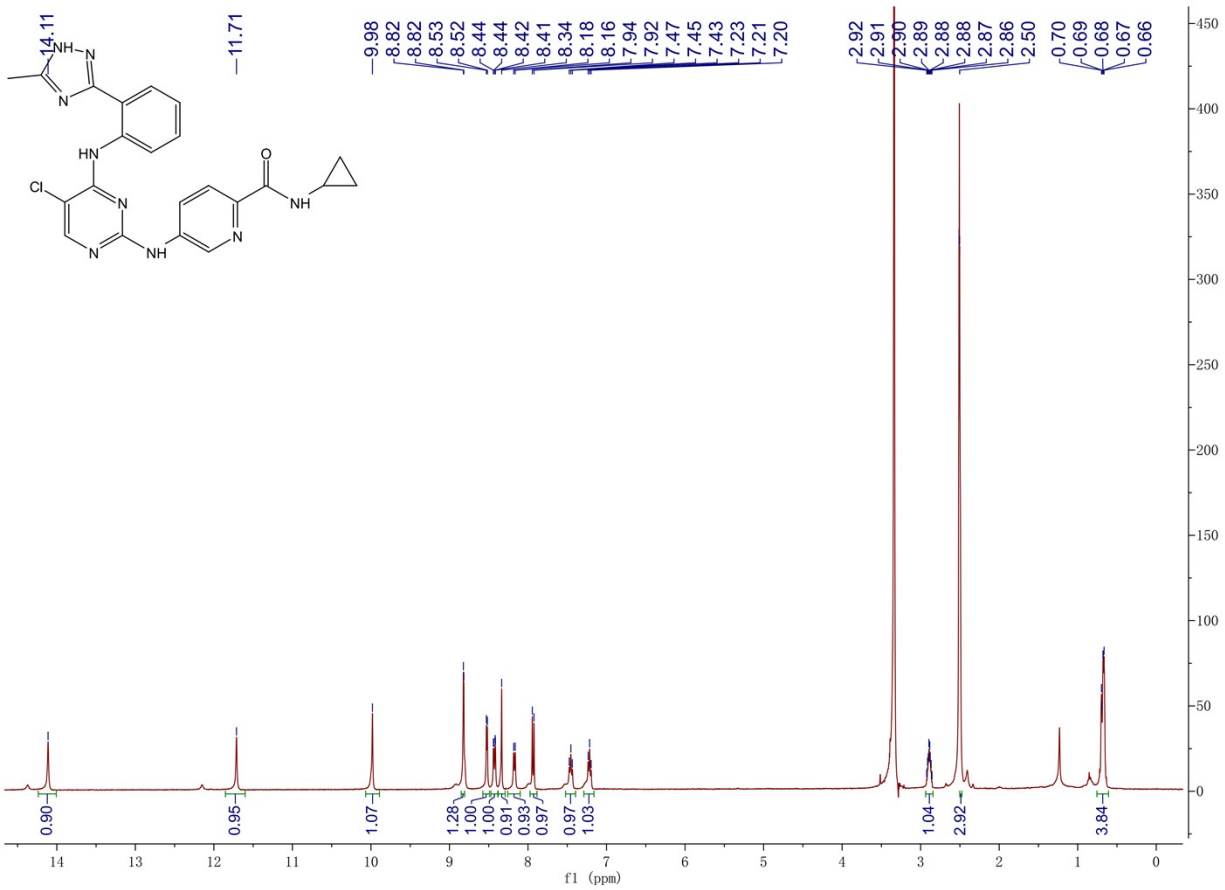
[1]H NMR spectrums of compound w14.



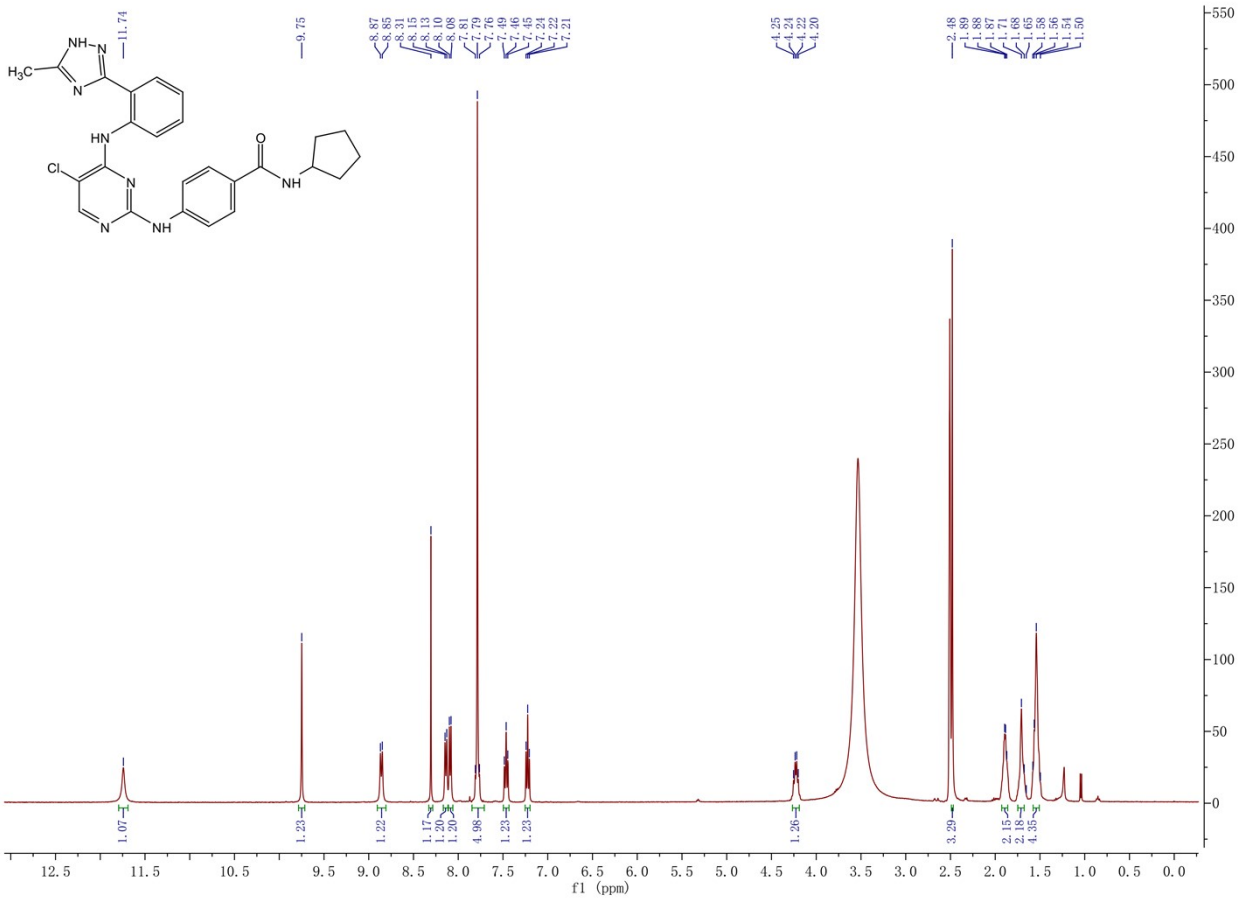
^{1}H NMR spectrums of compound w15.



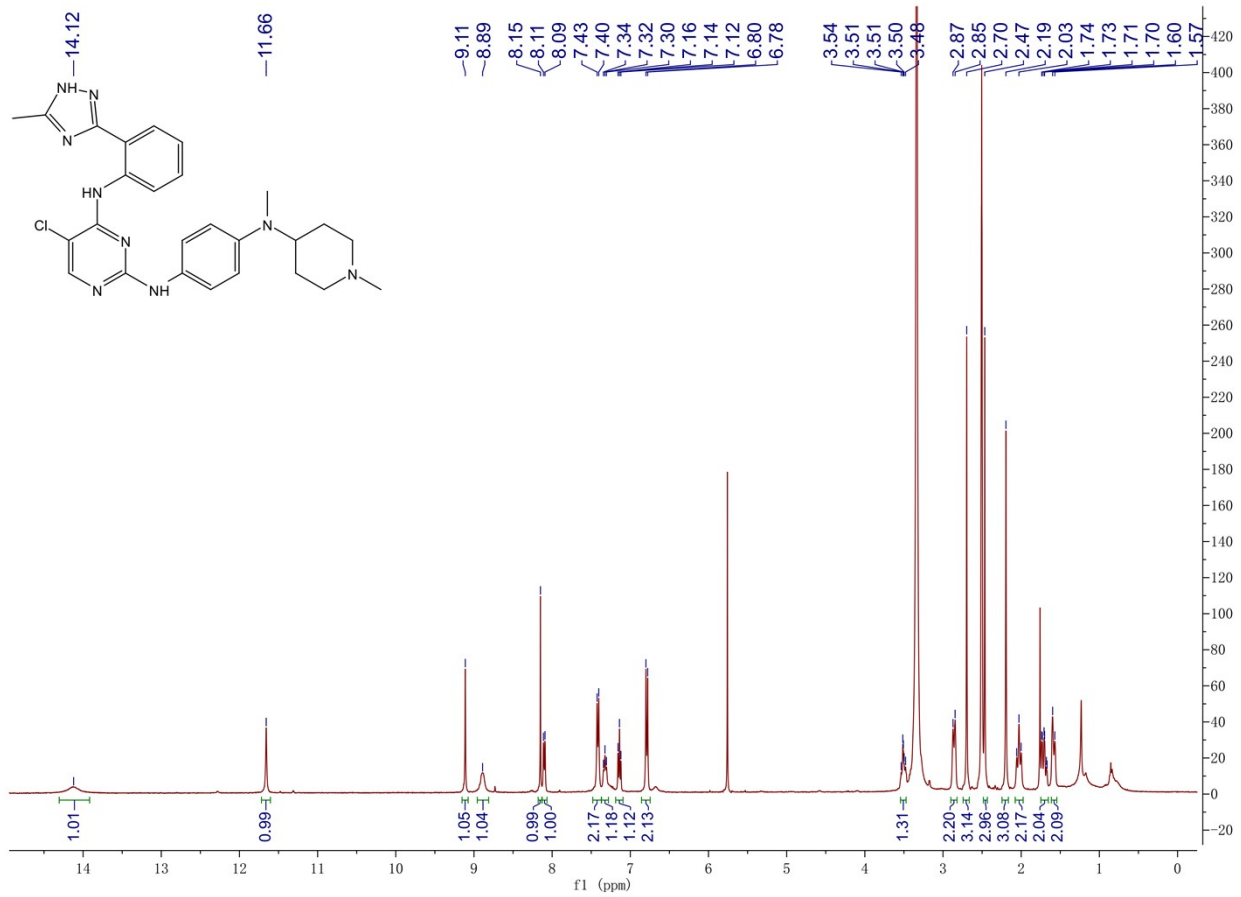
[1]H NMR spectrums of compound w16.



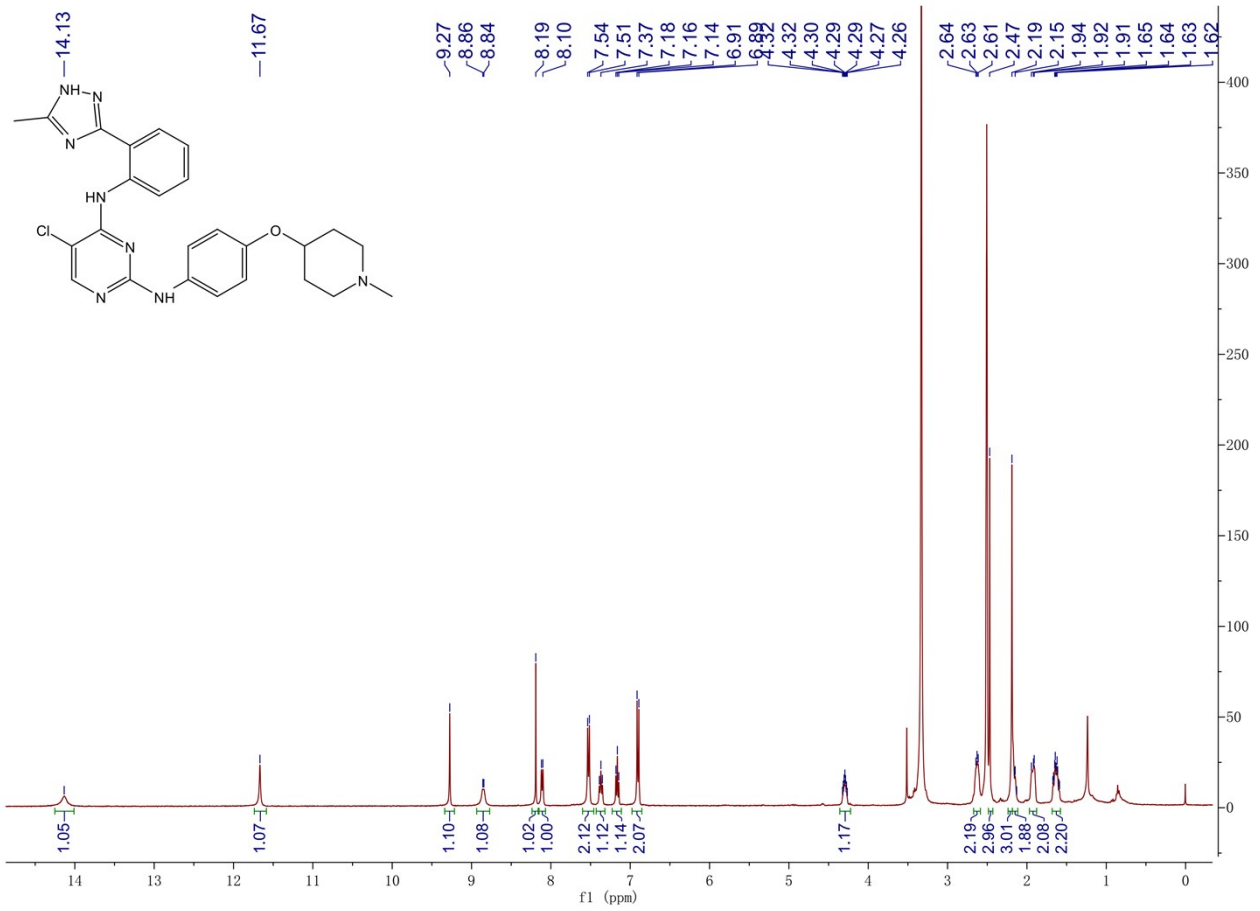
[1]H NMR spectrums of compound w17.



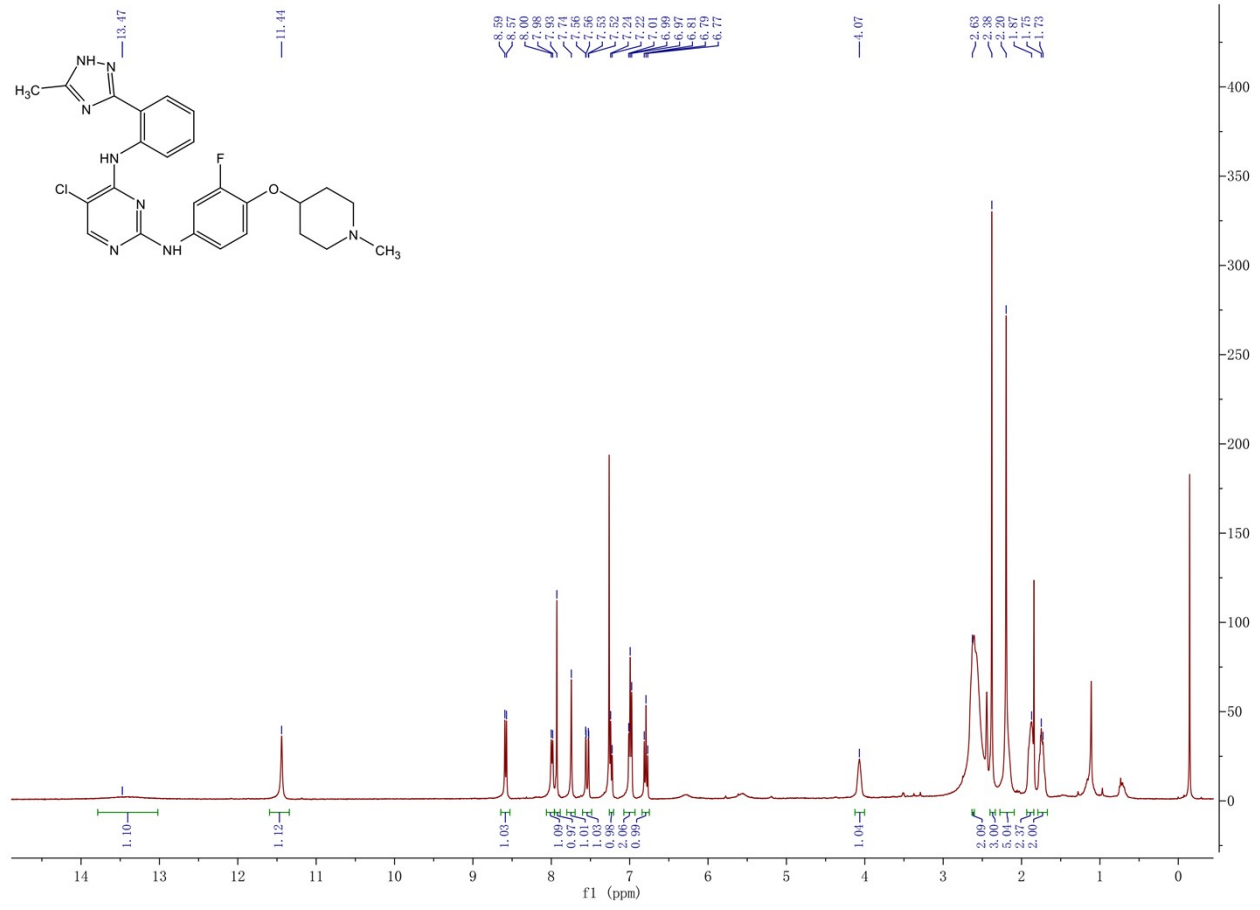
[1]H NMR spectrums of compound w18.



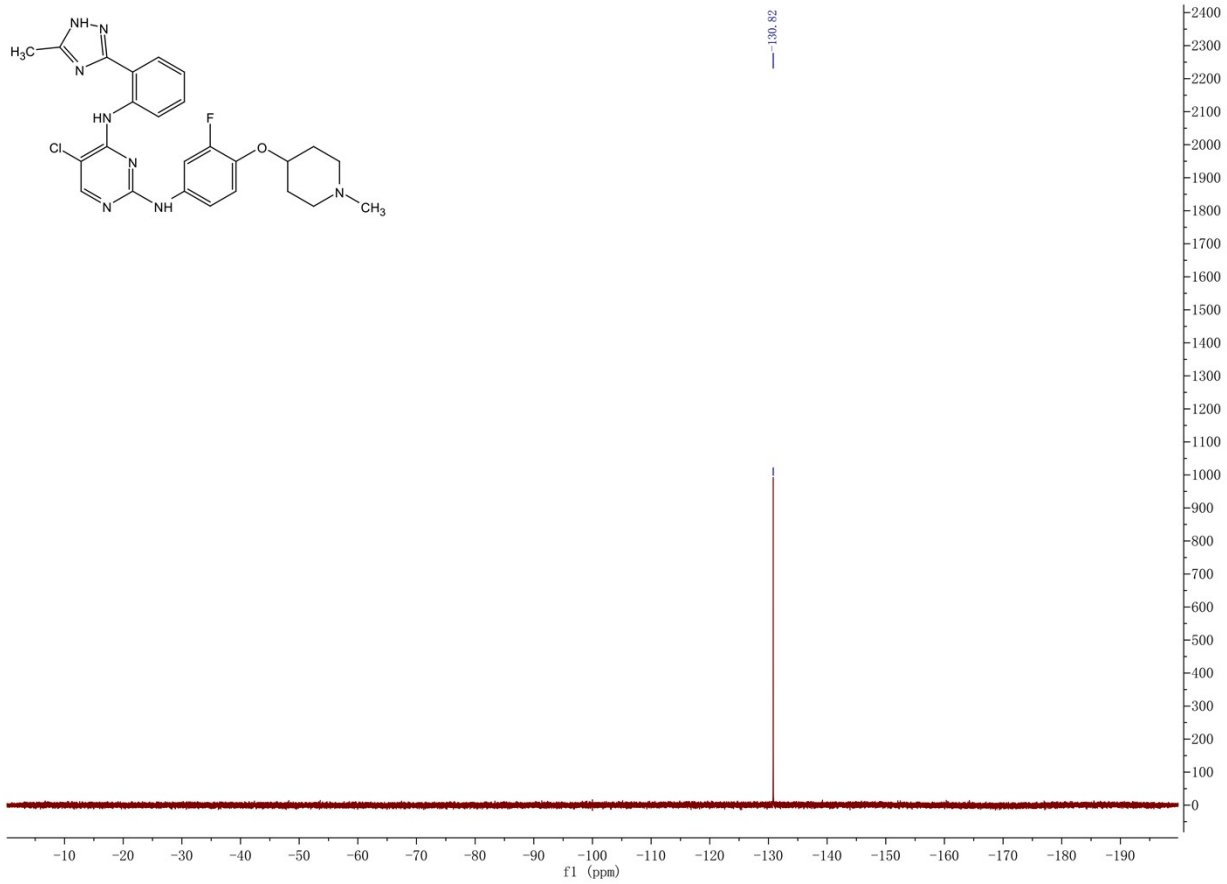
[1]H NMR spectrums of compound w19.



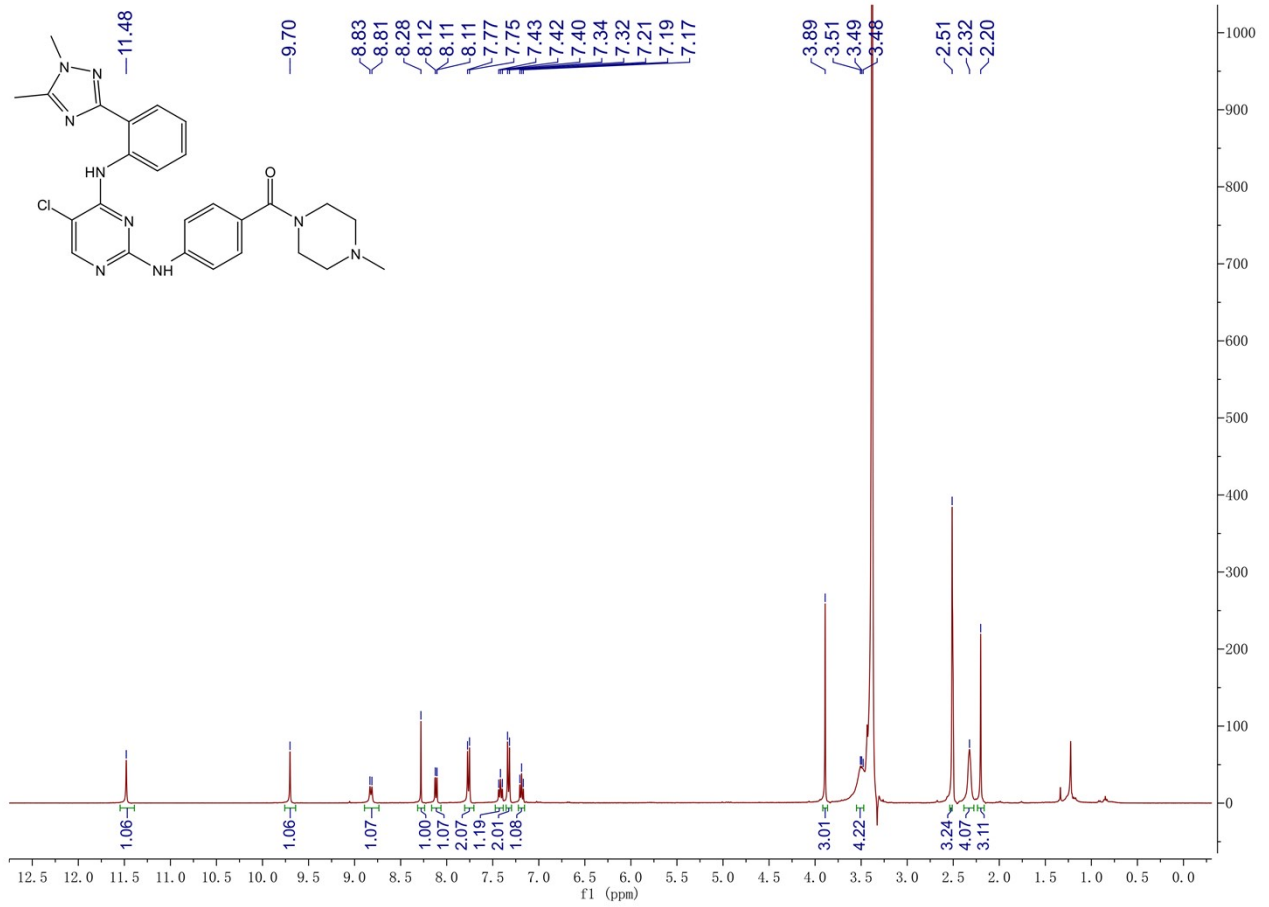
[1]H NMR spectrums of compound w20.



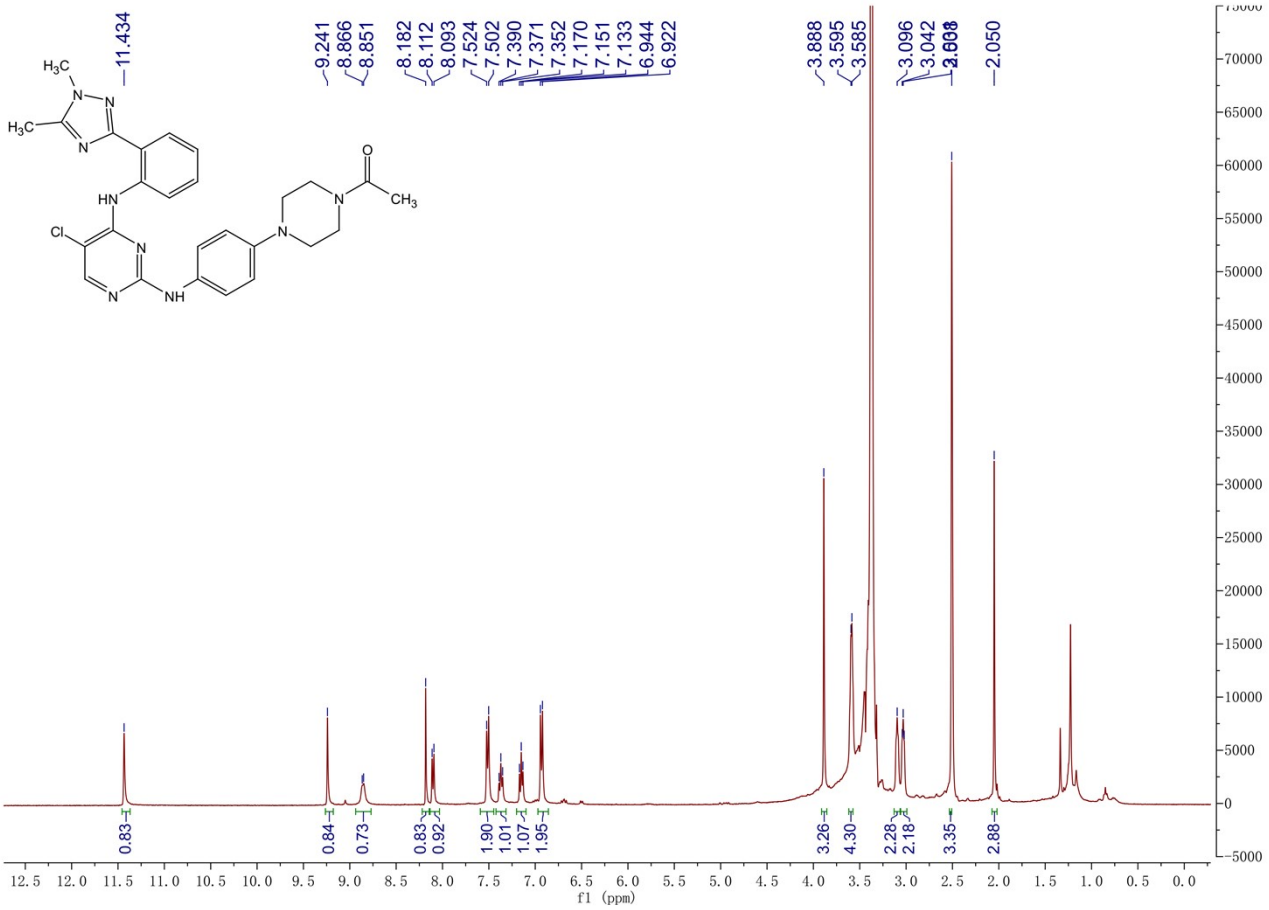
^{19}F NMR spectrums of compound w20.



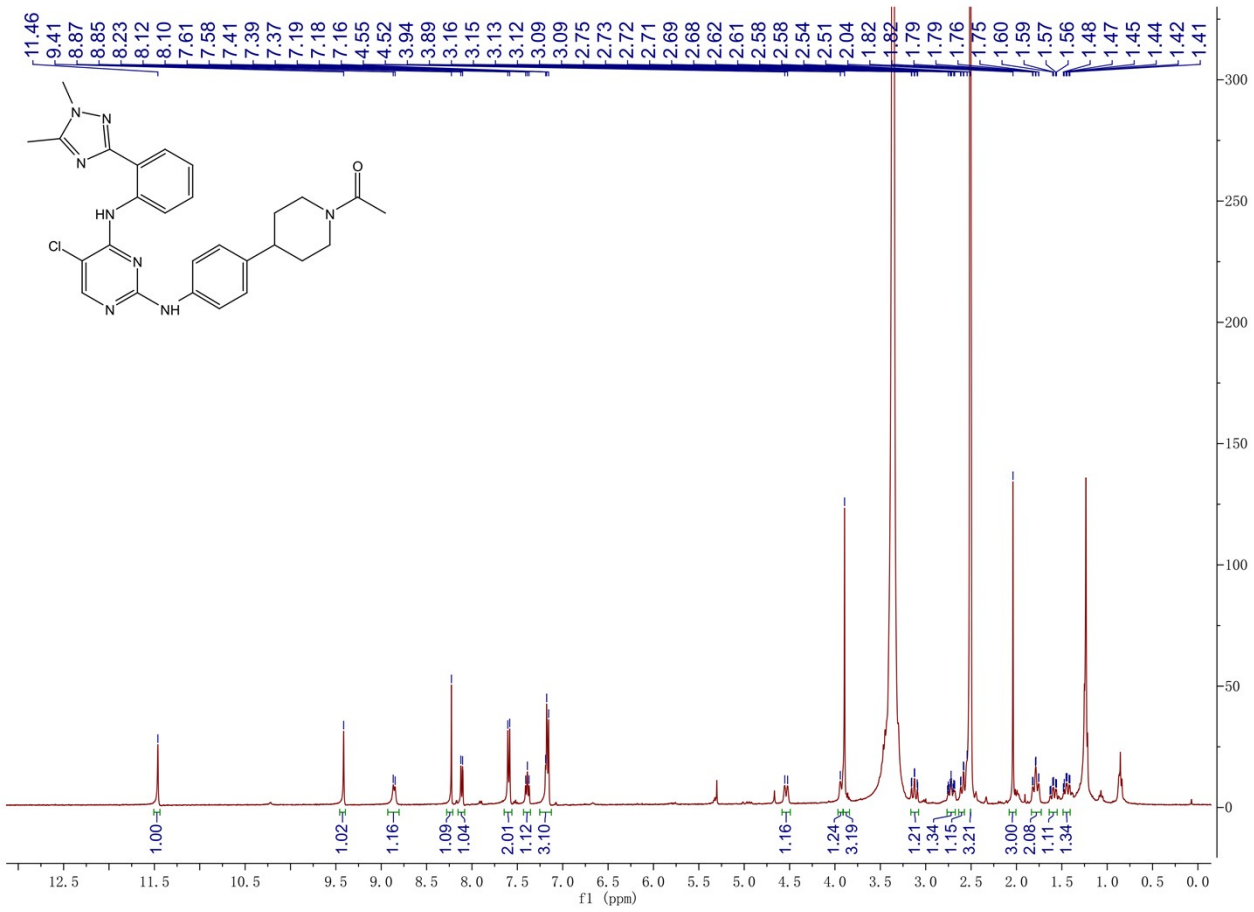
^{1}H NMR spectrums of compound m1.



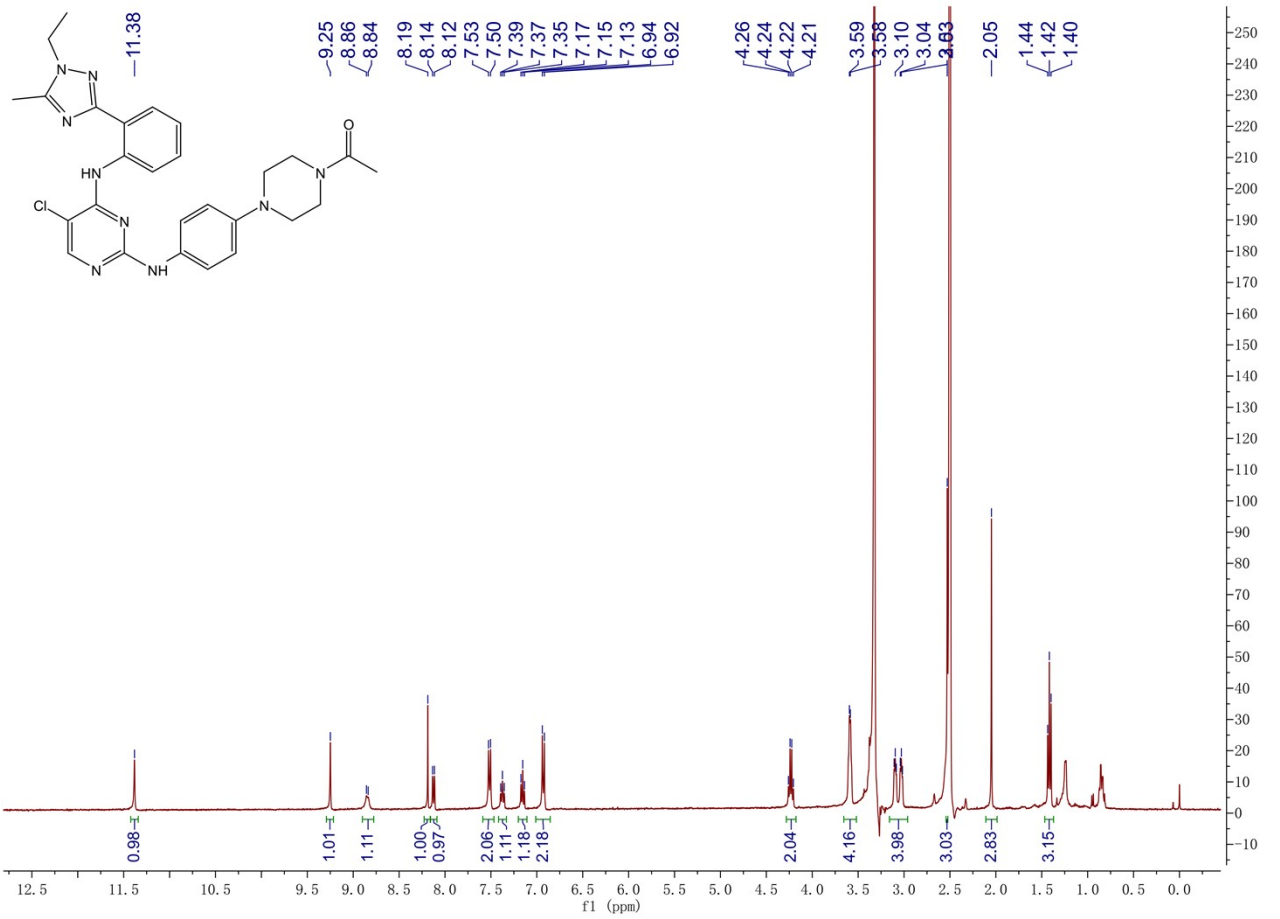
[1]H NMR spectrums of compound m2.



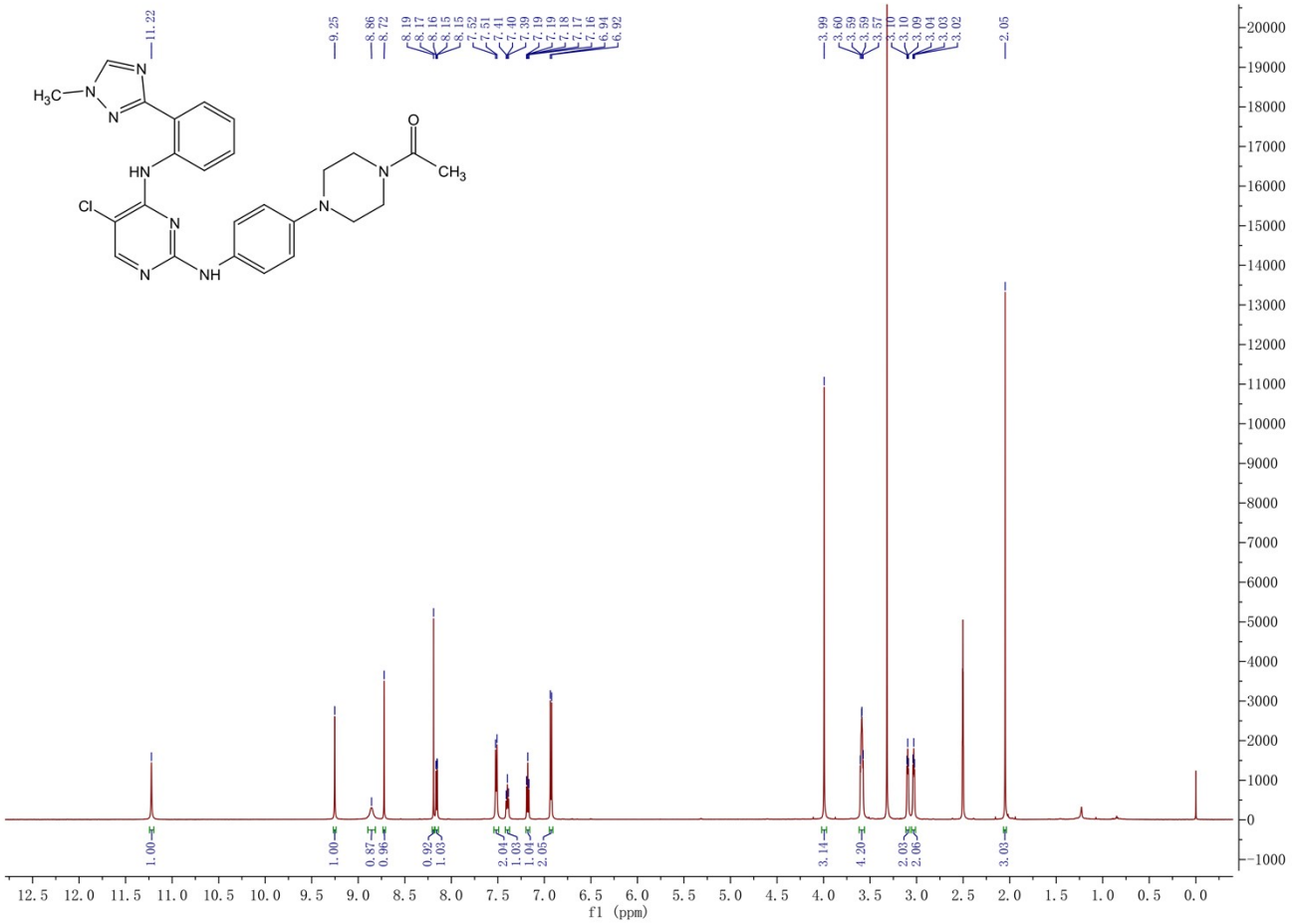
[1]H NMR spectrums of compound m3.



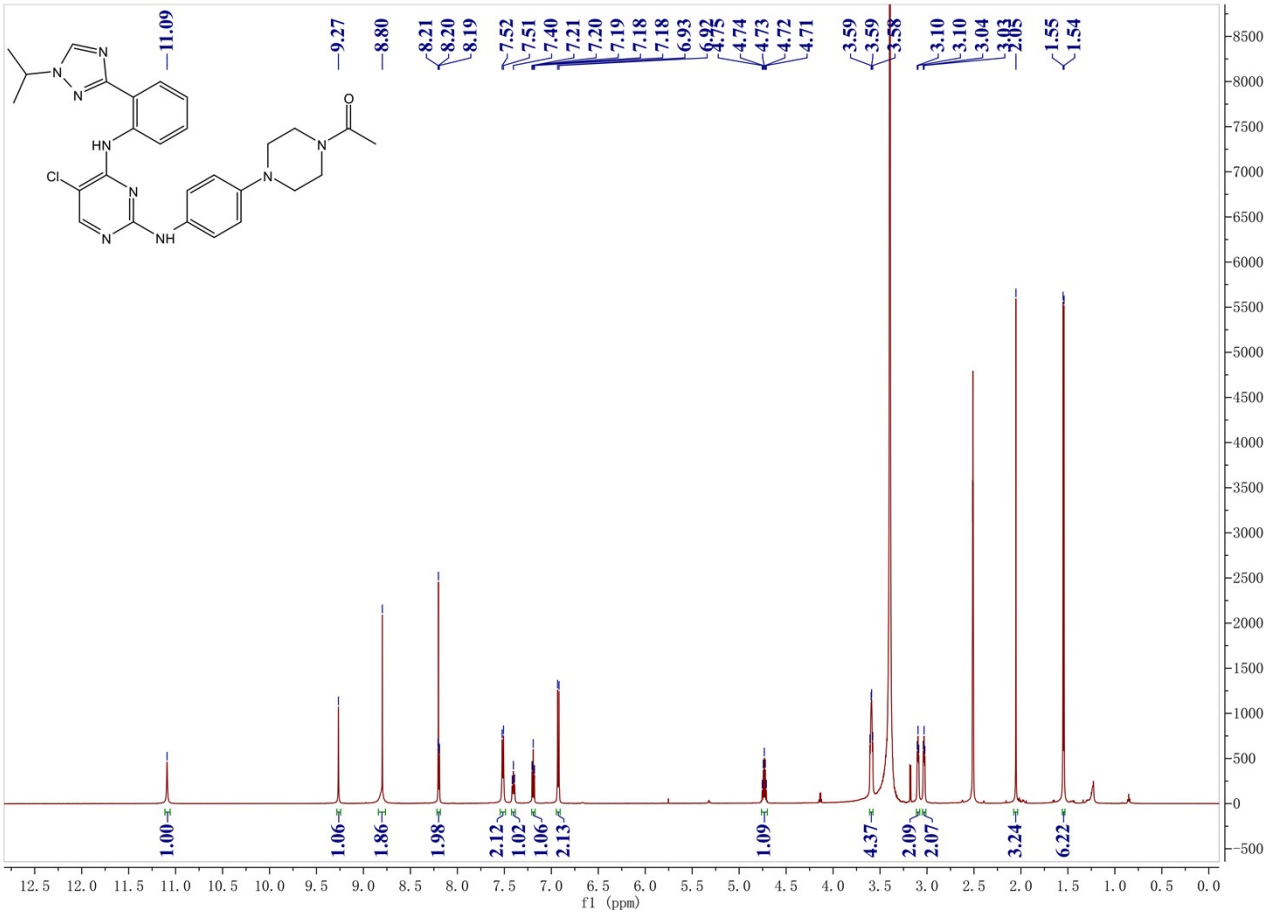
[1]H NMR spectrums of compound m4.



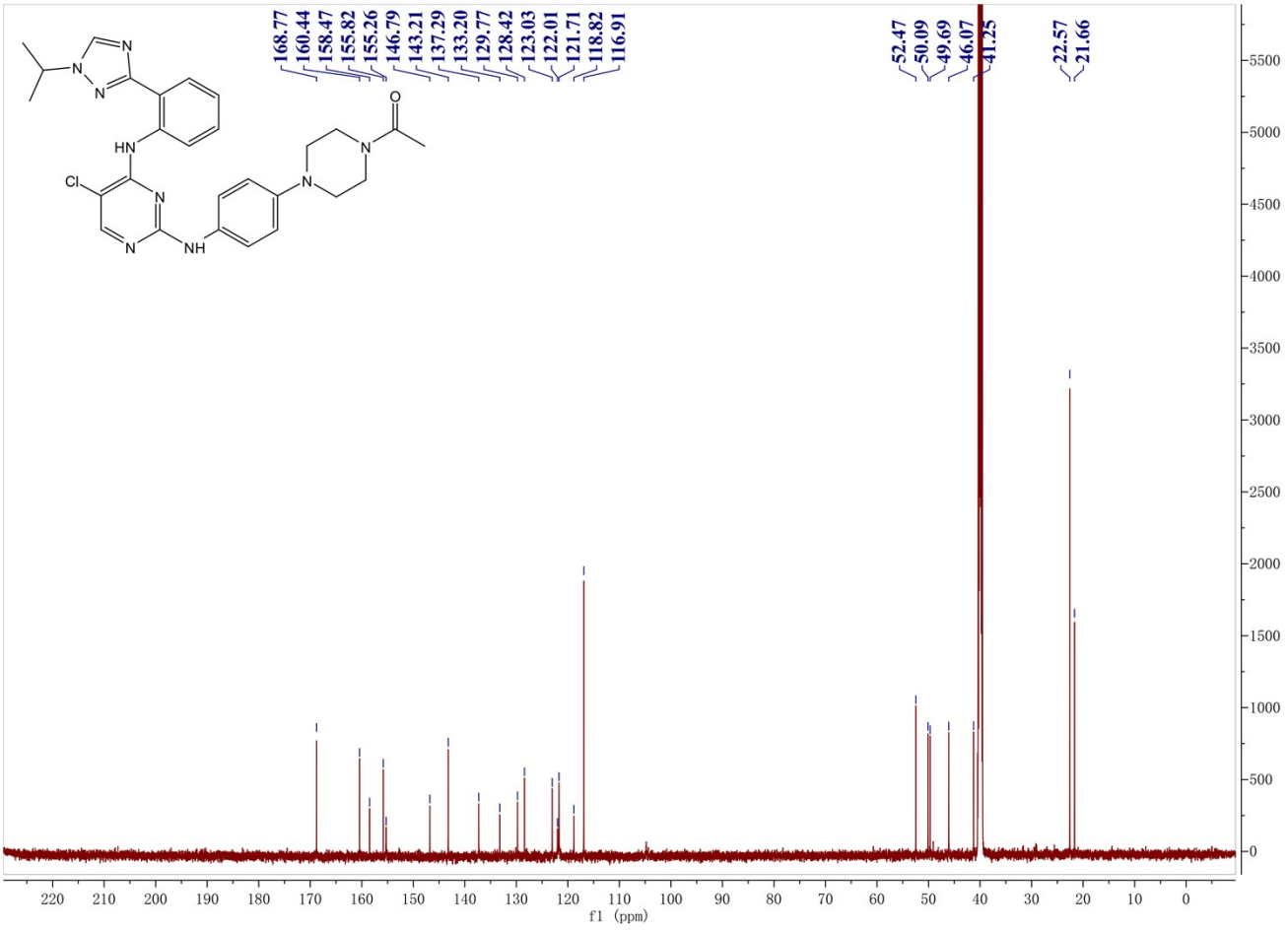
^{1}H NMR spectrums of compound m5.



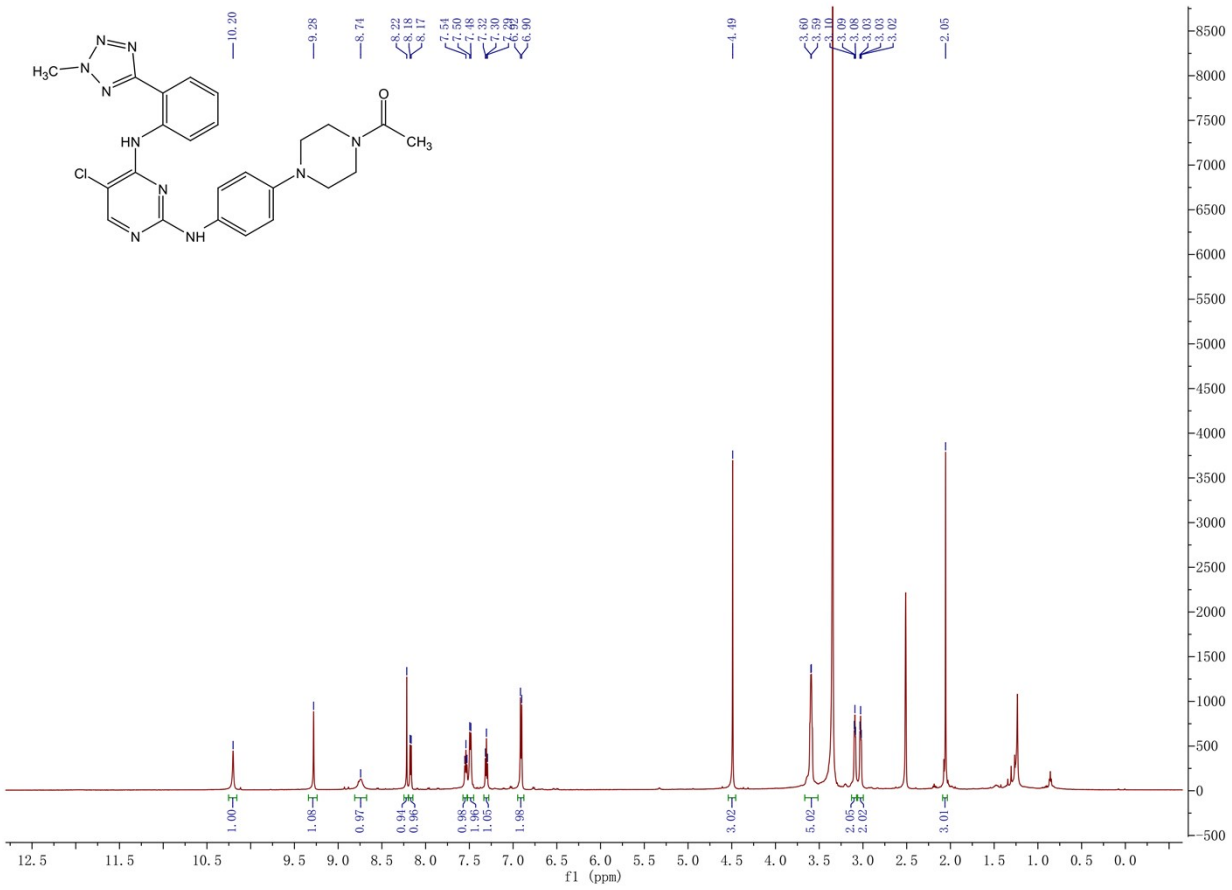
[1]H NMR spectrums of compound m6.



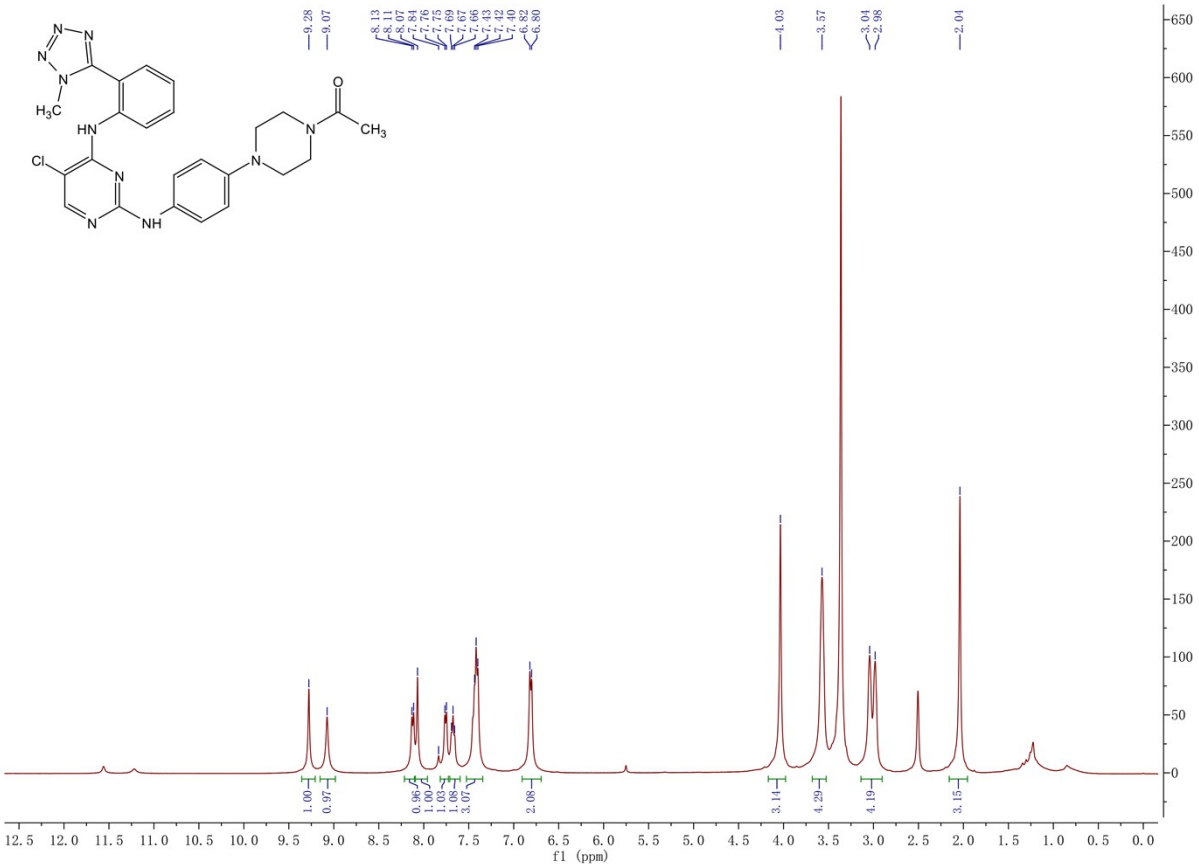
[13]C NMR spectrums of compound m6.



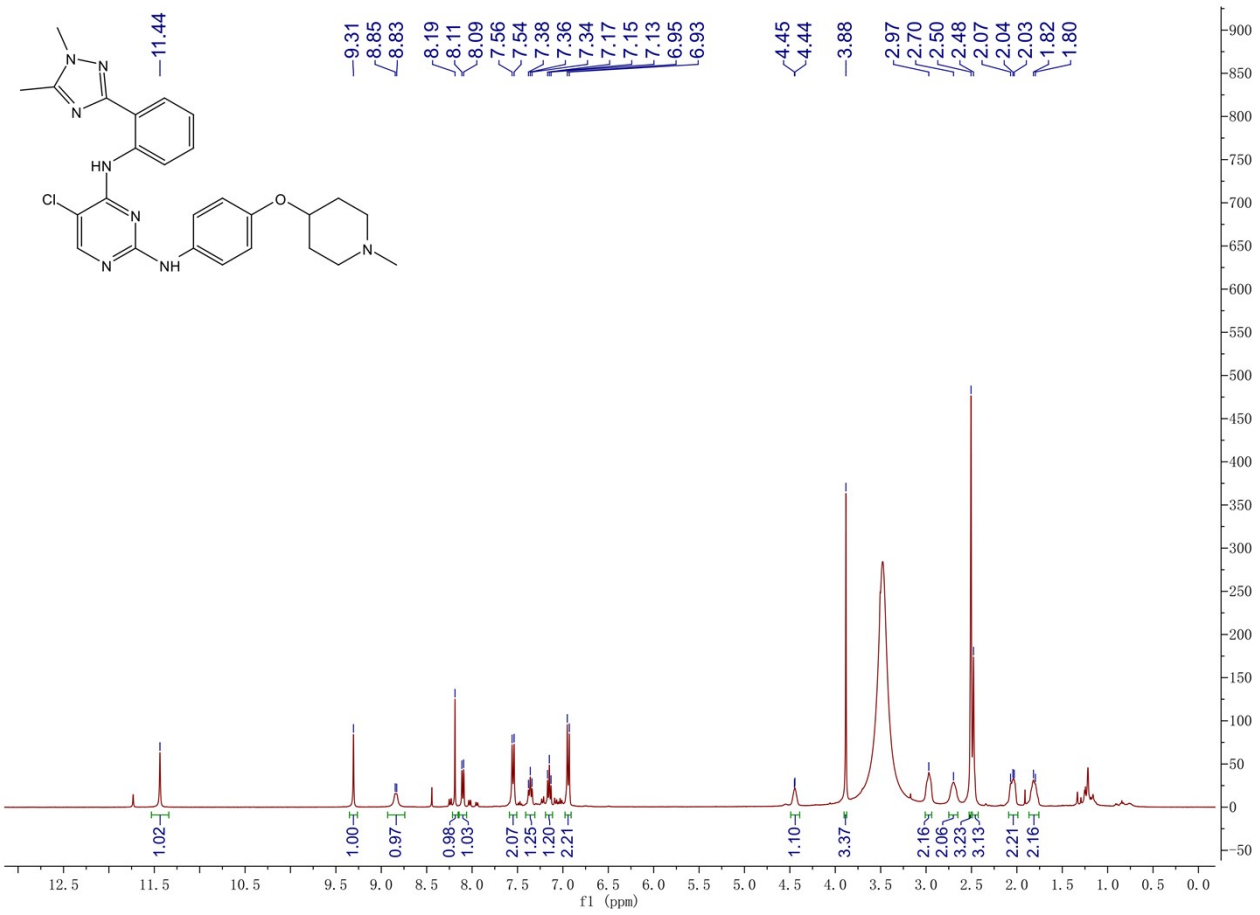
^{1}H NMR spectrums of compound m7.



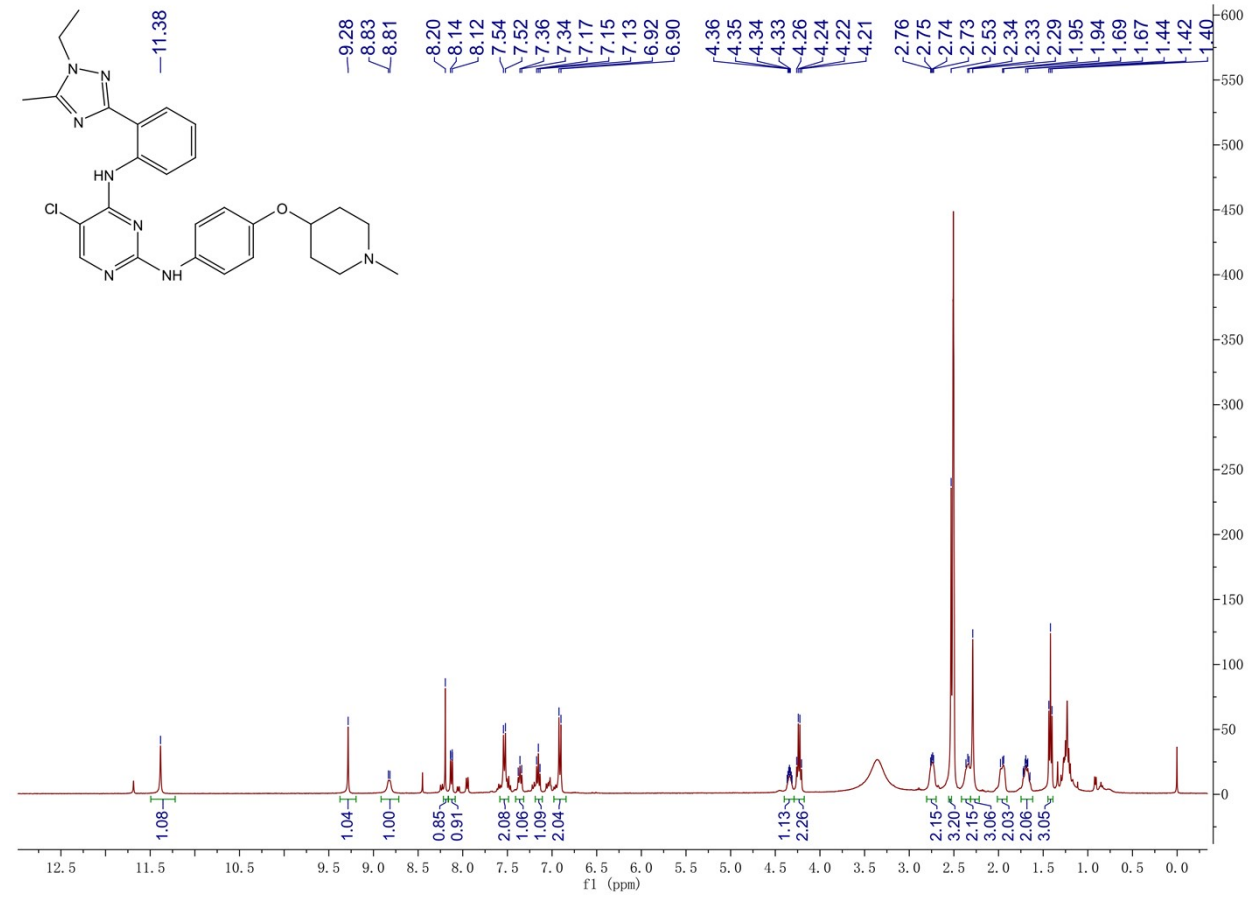
^{1}H NMR spectrums of compound m8.



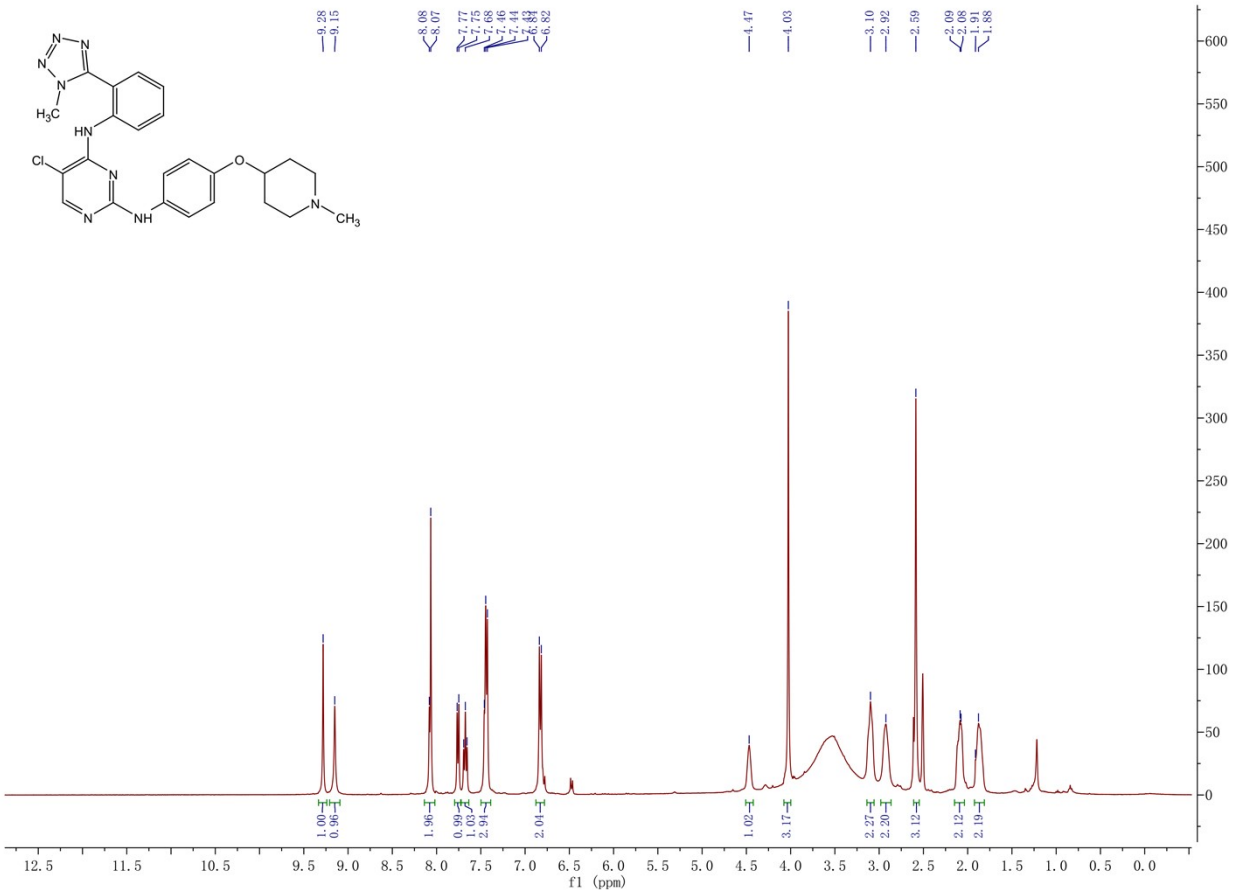
^{1}H NMR spectrums of compound m9.



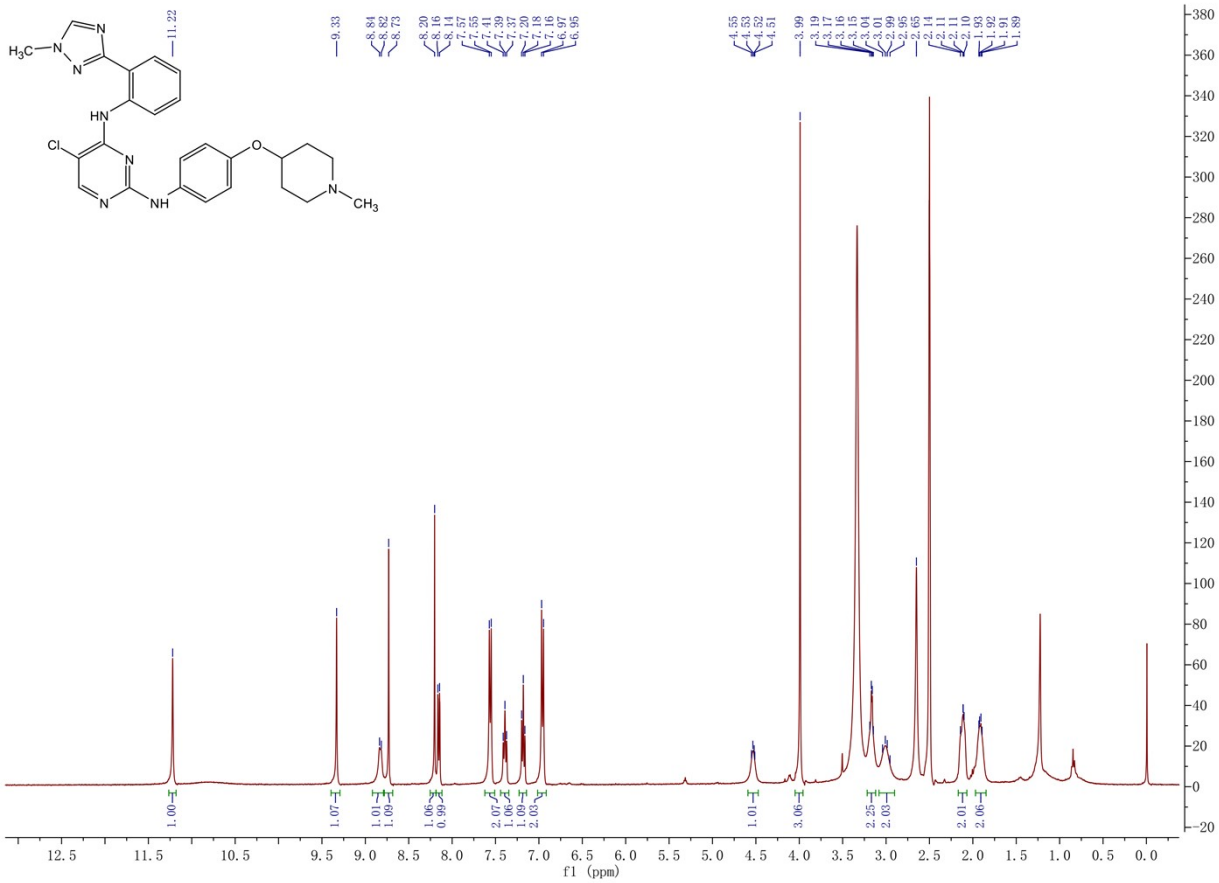
[1]H NMR spectrums of compound m10.



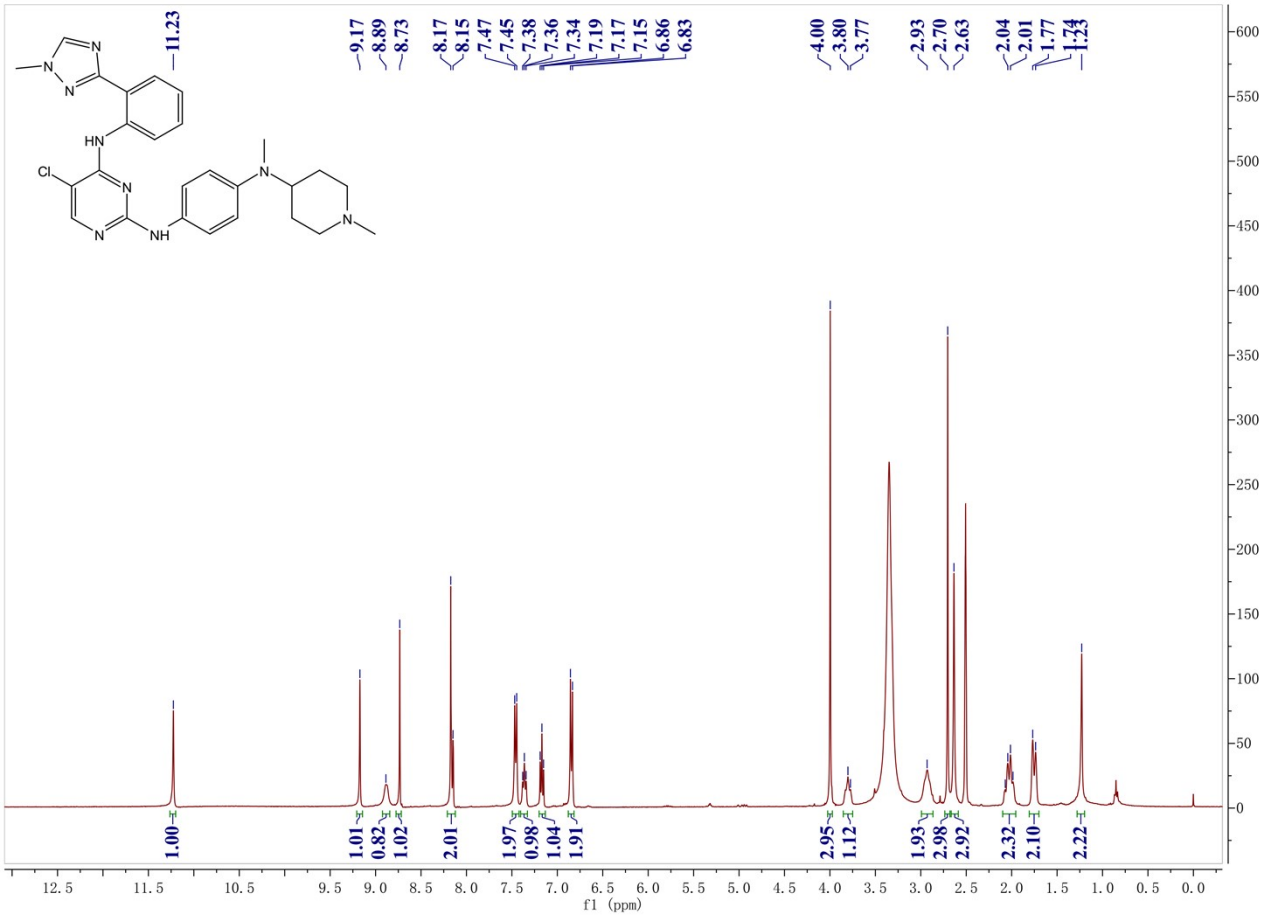
[1]H NMR spectrums of compound m11.



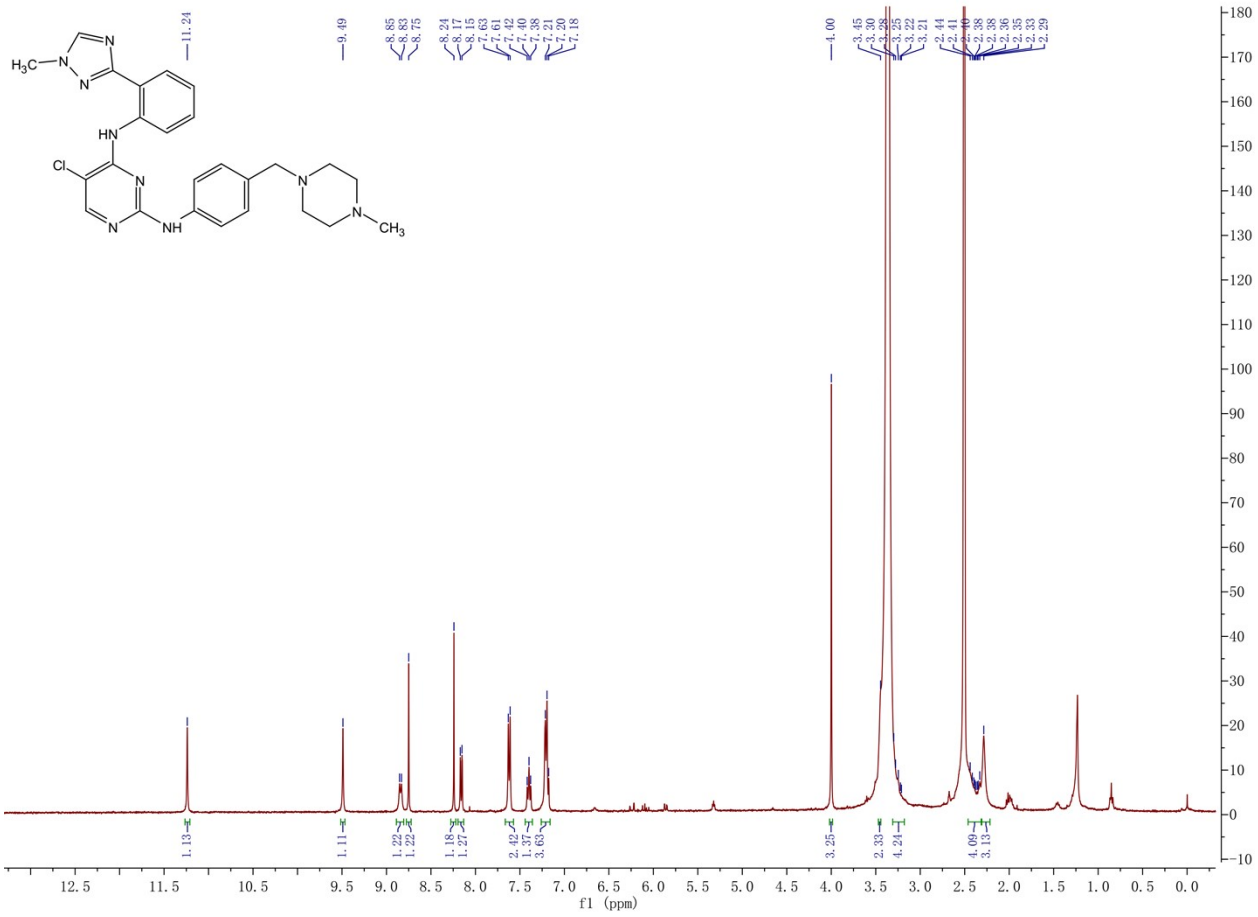
[1]H NMR spectrums of compound m12.



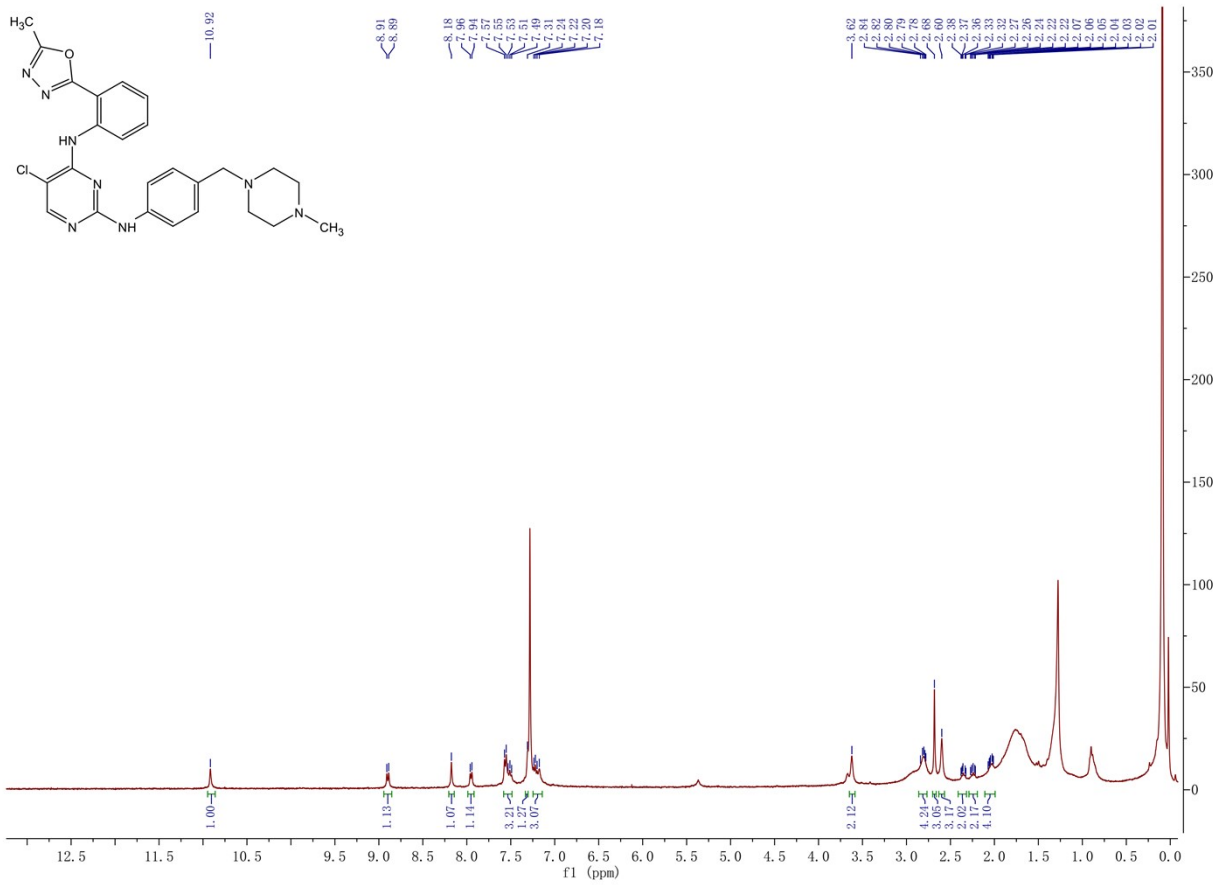
[1]H NMR spectrums of compound m13.



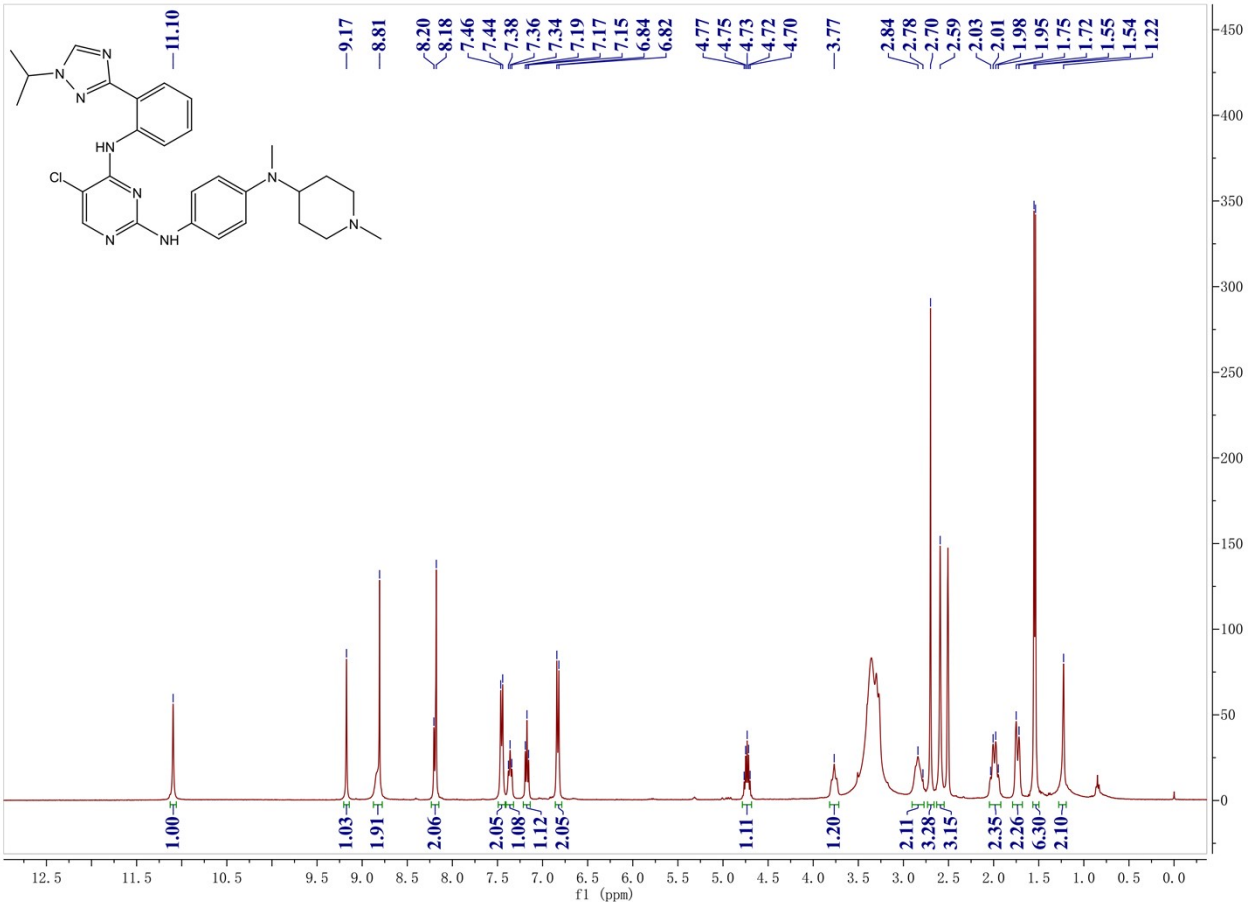
[1]H NMR spectrums of compound m14.



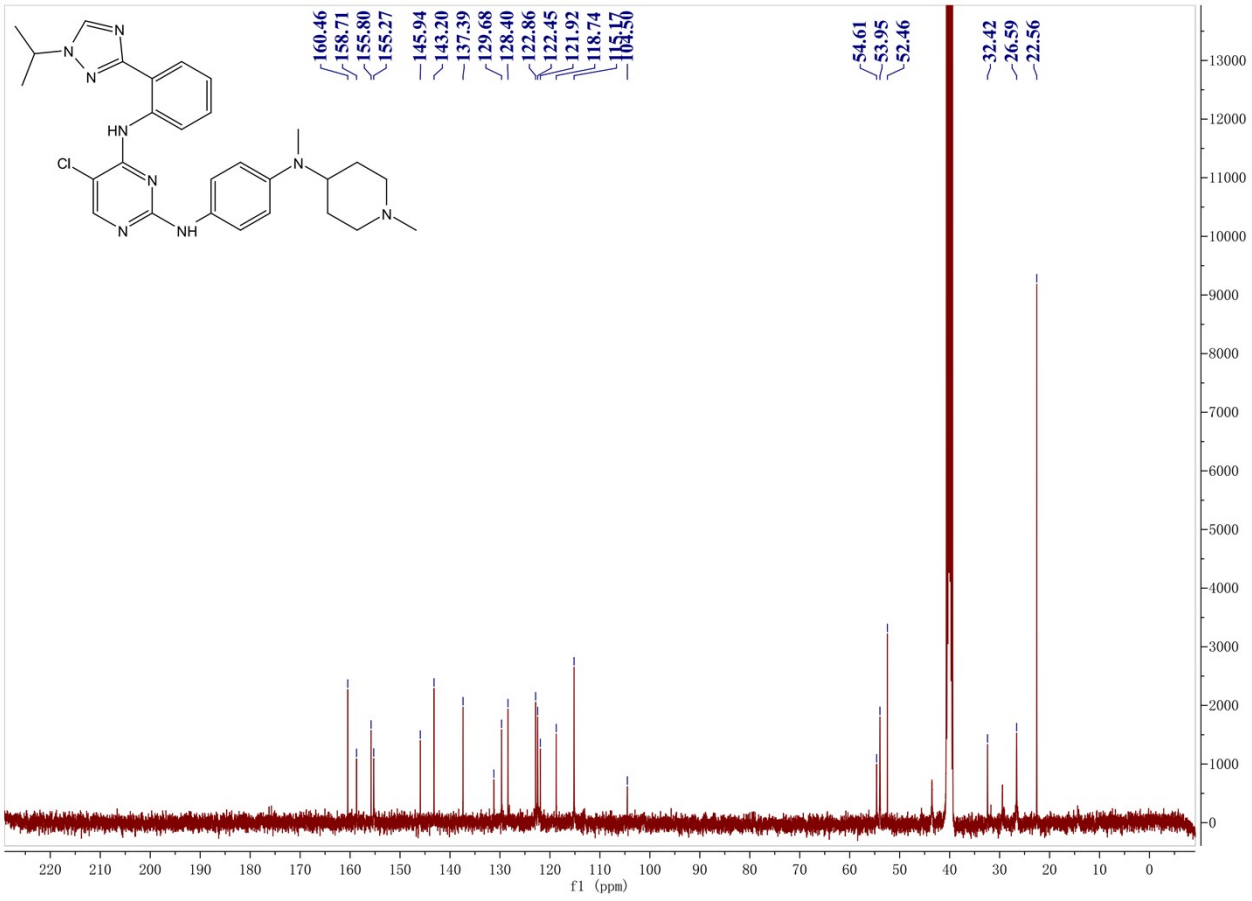
^{1}H NMR spectrums of compound m15.



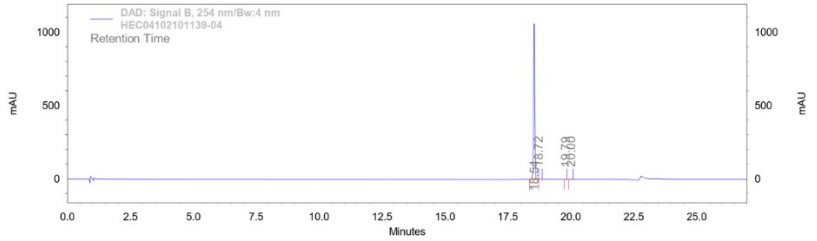
[1]H NMR spectrums of compound m16.

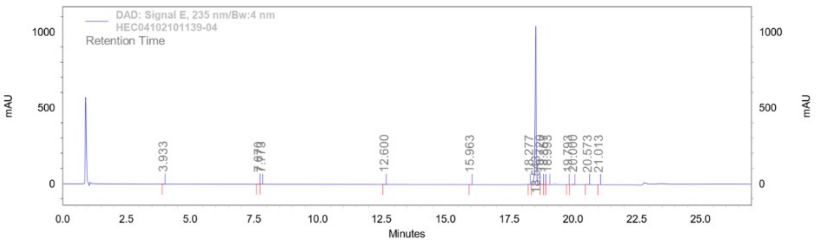


[13]C NMR spectrums of compound m16.


160.46
158.71
155.80
155.27
145.94
143.20
137.39
129.68
128.40
122.86
122.45
121.92
118.74
115.17
104.50
54.61
53.95
52.46
32.42
26.59
22.56
HN
Cl
N
NH
f1 (ppm)

HPLC purity determination of compound m6





DAD: Signal B, 254 nm/Bw:4 nm Results

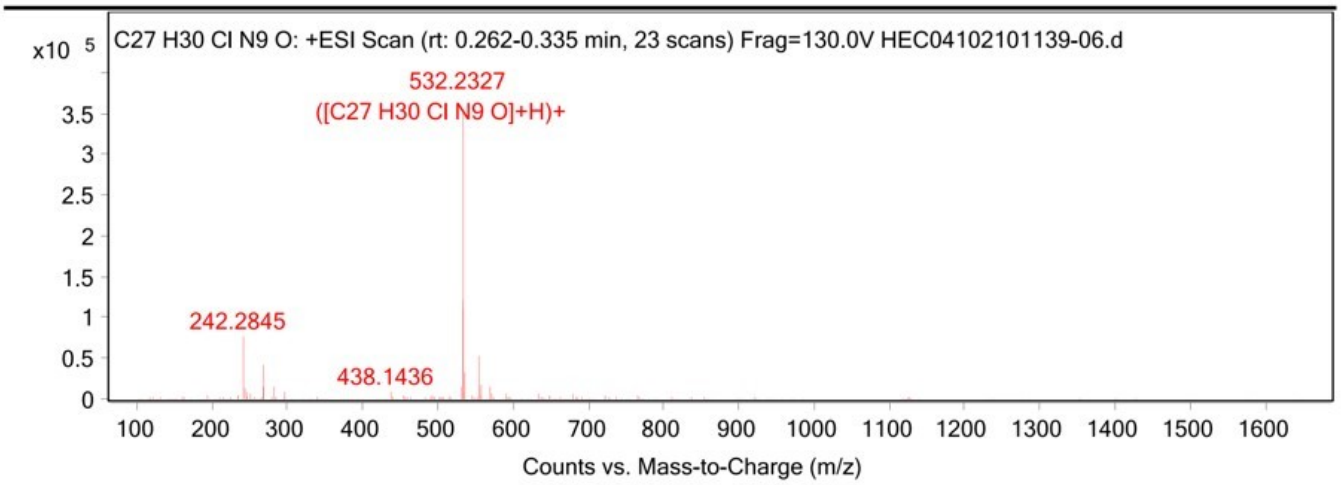
R T	Height	Area	Resolution (USP)	Asymmetry	Theoretical plates (USP)	Peak purity	Area %
18.54	2219227	7245256	0.00	0.94	779969	0.814	99.75
18.72	2020	7071	0.00	0.00	0	1.000	0.10
19.79	665	1933	0.00	1.06	989713	1.000	0.03
20.00	2709	8960	2.51	0.89	877652	1.000	0.12
Totals	2224621	7263220					100.00

DAD: Signal E, 235 nm/Bw:4 nm Results

Retention Time	Area	Peak purity	Resolution (USP)	Theoretical plates (USP)	Asymmetry	Area Percent
3.933	1156	1.000	0.00	25294	1.44	0.02
7.670	2494	1.000	31.39	48589	0.00	0.03
7.773	1579	1.000	0.81	72658	0.00	0.02
12.600	1298	1.000	42.79	209069	1.20	0.02
15.963	1000	1.000	32.56	439330	1.60	0.01
18.277	1139	1.000	27.86	1098598	1.48	0.02
18.543	7134504	0.814	3.47	780877	0.94	99.30
18.720	12045	1.000	0.00	0	0.00	0.17
18.857	3144	1.000	0.00	34936	0.00	0.04
18.993	2526	1.000	0.48	196069	0.00	0.04
19.793	1822	1.000	6.47	1092582	1.17	0.03
20.000	15933	1.000	2.54	849493	0.81	0.22
20.573	5362	1.000	5.69	513670	0.86	0.07
21.013	838	1.000	4.32	893818	1.64	0.01
Totals	7184840					100.00

Qualitative analysis of compound m6.

Qualitative Analysis Report

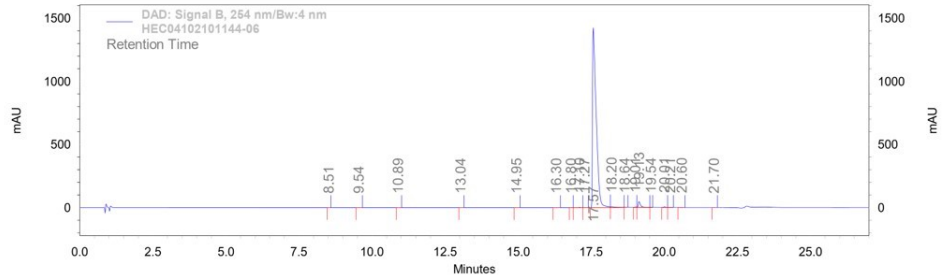


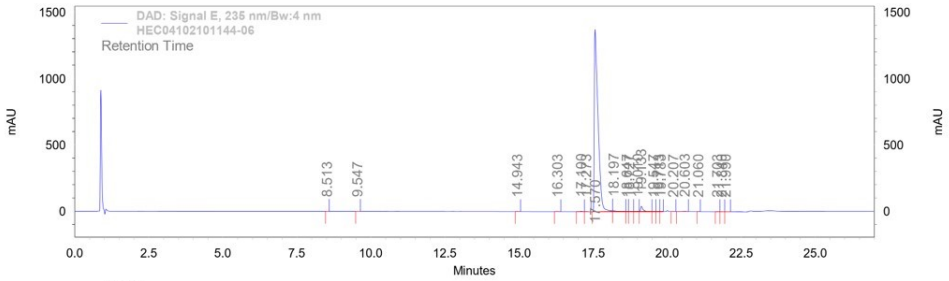
Peak List

m/z	z	Abund	Formula	Ion
242.2845	1	77283		
266.6209	2	41415.93		
267.6201	2	16091.39		
532.2327	1	353656.94	C27 H30 Cl N9 O	(M+H)+
533.2361	1	109081.36	C27 H30 Cl N9 O	(M+H)+
534.2318	1	120697.7	C27 H30 Cl N9 O	(M+H)+
535.2337	1	33519.77	C27 H30 Cl N9 O	(M+H)+
554.2154	1	51735.68		
555.218	1	16581.64		
556.2134	1	17365.6		

--- End Of Report ---

HPLC purity determination of compound m16





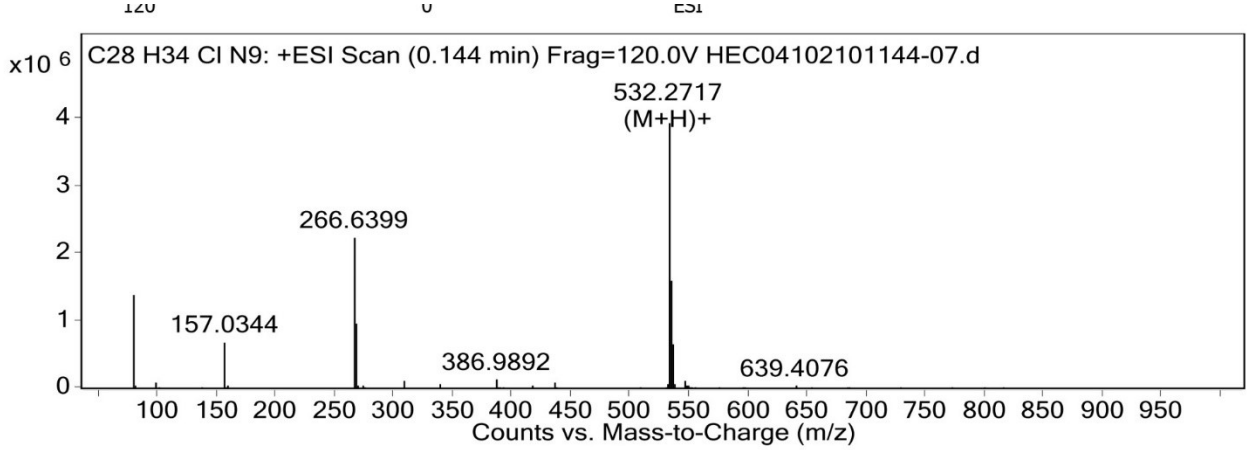
DAD: Signal B, 254 nm/Bw:4 nm Results

R T	Height	Area	Resolution (USP)	Asymmetry	Theoretical plates (USP)	Peak purity	Area %
8.51	370	1429	0.00	1.32	108605	1.000	0.01
9.54	983	5076	8.62	1.05	78221	1.000	0.02
10.89	472	2672	9.63	1.47	93354	1.000	0.01
13.04	613	3036	15.40	1.31	145625	1.000	0.01
14.95	1497	7083	14.43	1.06	217624	1.000	0.03
16.30	2261	13859	9.31	1.07	159707	1.000	0.05
16.80	373	1422	3.75	1.28	422229	1.000	0.01
17.10	4836	21532	2.79	0.96	394605	1.000	0.08
17.27	1593	6748	1.61	0.00	417250	1.000	0.03
17.57	2986800	26058872	1.69	3.02	83165	0.880	97.03
18.20	10303	134046	1.18	0.00	7757	1.000	0.50
18.64	961	4076	0.00	0.00	0	1.000	0.02
19.01	6314	20377	0.00	0.00	770107	1.000	0.08
19.13	96115	517216	1.12	2.03	332962	0.822	1.93
19.54	406	1289	3.42	0.00	575647	1.000	0.00
20.01	10296	38574	4.76	0.97	699131	1.000	0.14
20.21	1384	6853	1.80	0.00	389236	1.000	0.03
20.60	1342	7316	3.10	0.85	454890	1.000	0.03
21.70	802	3689	8.98	1.15	500667	1.000	0.01
Totals	3127721	26855165					100.00

DAD: Signal E, 235 nm/Bw:4 nm Results

Retention Time	Area	Peak purity	Resolution (USP)	Theoretical plates (USP)	Asymmetry	Area Percent
8.513	927	1.000	0.00	0	1.25	0.00
9.547	2548	1.000	0.00	102999	1.14	0.01
14.943	7039	1.000	44.94	243236	1.19	0.03
16.303	12341	1.000	9.65	164750	0.97	0.05
17.100	19410	1.000	5.92	397094	1.35	0.07
17.273	7111	1.000	1.59	394364	0.00	0.03
17.570	25148805	0.880	1.68	83294	3.02	96.83
18.197	166549	1.000	0.00	0	0.00	0.64
18.647	15914	1.000	0.00	10158	0.00	0.06
18.727	24082	1.000	0.10	8795	0.00	0.09
19.010	36094	1.000	0.62	416787	0.00	0.14
19.133	468642	0.795	0.98	324339	2.10	1.80
19.547	6908	1.000	2.01	80169	0.00	0.03
19.713	6120	1.000	0.78	263362	0.00	0.02
19.783	3090	1.000	0.46	283125	0.00	0.01
20.207	6159	1.000	3.15	453653	1.07	0.02
20.603	30977	1.000	3.48	581122	0.78	0.12
21.060	1742	1.000	4.52	807375	1.10	0.01
21.703	4534	1.000	5.66	421663	0.00	0.02
21.840	2155	1.000	1.06	491629	0.00	0.01
21.990	1497	1.000	1.03	278381	0.00	0.01
Totals	25972644					100.00

Qualitative analysis of compound m16.



Peak List

m/z	z	Abund	Formula	Ion
79.0224	1	1380035		
157.0344	1	691111.38		
266.6399	2	2241917.5		
267.1397	2	908730.44		
267.6379	2	969834.75		
268.1395	2	244864.78		
532.2717	1	3934664.75	C28 H35 Cl N9	(M+H)+
533.2736	1	1532703	C28 H35 Cl N9	(M+H)+
534.2695	1	1610509	C28 H35 Cl N9	(M+H)+
535.2705	1	650468.69		