Supporting Information

Discovery of 3,5-diamino-1,2,4-triazole-ureas as Potent Anaplastic Lymphoma Kinase (ALK) Inhibitors

Xianming Deng,[1,5] Jinhua Wang,[1,5] Jianming Zhang,[1,5] Taebo Sim,[1] Nam Doo Kim,[2] Takaaki Sasaki,[3] William Luther II,[4] Rani E. George,[4] Pasi A. Jänne,[3] and Nathanael S. Gray[1,*]

1. Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School and Department of Cancer Biology, Dana-Farber Cancer Institute, 250 Longwood Ave, SGM 628, Boston, MA 02115, USA. 2. Department of Biotechnology, Yonsei University, 262 Soengsanno, Seodaemun-gu, Seoul, 120-749, KOREA 3. Department of Medical Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA. 4. Department of Pediatric Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA.

5. These authors contributed equally.

** To whom correspondence should be addressed. N.S.G.: phone, 1-617-582-8590; fax, 1-617-582-8615; E-mail, Nathanael_Gray@dfci.harvard.edu .*

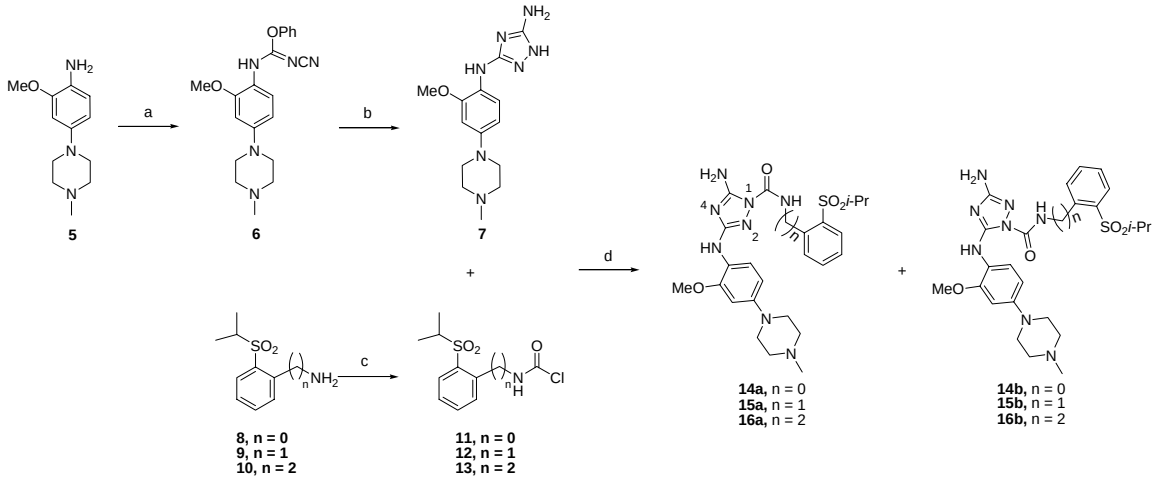
Contents

1. General chemistry.

Unless otherwise noted, reagents and solvents were obtained from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded on 600 MHz (Varian AS600), and chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS). Coupling constants (*J*) are reported in Hz. Spin multiplicities are described as s (singlet), brs (broad singlet), t (triplet), q (quartet), and m (multiplet). Mass spectra were obtained on a Waters Micromass ZQ instrument. Preparative HPLC was performed on a Waters Symmetry C18 column (19 x 50 mm, 5 μM) using a gradient of 5-95% acetonitrile in water containing 0.05% trifluoacetic acid (TFA) over 8 min (10 min run time) at a flow rate of 30 mL/min. Purities of assayed compounds were in all cases greater than 95%, as determined by reverse-phase HPLC analysis.

2. Synthetic procedure of 14-16[1].

Scheme 1. Synthesis of compounds **14-16**[a]



[a] Reagents and conditions: (a) diphenyl cyanocarbonimidate, THF, reflux; (b) hydrazine, THF, 0 °C to 75 °C; (c) triphosgene, dioxane, microwave, 150 °C, 20 min; (d) pyridine/DMF, r.t.

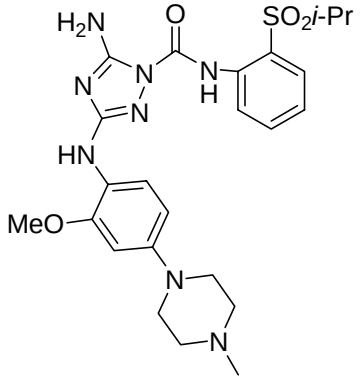
[1] Lin, R.; Connolly, P. J.; Huang, S.; Wetter, S. K.; Lu, Y.; Murray, W. V.; Emanuel, S. L.; Gruninger, R. H.; Fuentes-Pesquera, A. R.; Rugg, C. A.; Middleton, S. A.; Jolliffe, L. K. 1-Acyl-1H-[1,2,4]triazole-3,5-diamine analogues as novel and potent anticancer cyclin-dependent kinase inhibitors: synthesis and evaluation of biological activities. *J. Med. Chem.* **2005,** *48*, 4208-11.

To a stirred mixture of 2-methoxy-4-(4-methylpiperazin-1-yl)benzenamine (3.32 g, 15 mmol) in THF (24 mL) was added diphenyl cyanocarbonimidate (3.90 g, 16.5 mmol) at room temperature. The reaction mixture was then stirred at 75 ^{o}C overnight. After the reaction was complete as monitored by LC-MS, the resulting mixture was diluted with THF (15 mL) and cooled to 0 ^{o}C. To this mixture was added a solution of hydrazine (0.39 mL, 37.5 mmol) in THF (10 mL) and the resultant reaction mixture was stirred at 75 ^{o}C till the reaction went to completion (about 4 hours, monitored by LC-MS). The reaction mixture was concentrated and treated with acetone. Precipitation occurred after sonication.. Filtration gave the crude title product **7** (1.68 g), which can be used for next step without further purification. Filtrate was concentrated and purified by silica-gel column chromatography with 3.5 N NH_3 in methanol and dichloromethane (1/15, v/v) to give another portion of product **7**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.08 (br, 1H), 7.84 (d, J = 9.0 Hz, 1H), 6.60 (br, 1H), 6.57 (d, J = 2.4 Hz, 1H), 6.39 (dd, J = 9.0, 2.4 Hz, 1H), 5.80 (br, 2H), 3.81 (s, 3H), 2.98 – 3.08 (m, 4H), 2.41 – 2.43 (m, 4H), 2.19 (s, 3H). MS (ESI) *m/z* 304 $(M+H)^{+}$.

A mixture of compound **8** (0.5 mmol) and triphosgene (148.4 mg, 0.5 mmol) in 1,4-dioxane (1.0 mL) was subjected to microwave at 150 ˚C for 20 minutes. Then the reaction mixture was diluted with dichloromethane, washed with water and brine, then dried over anhydrous sodium sulfate. After concentration, the crude product **11** was used in next step without further purification.

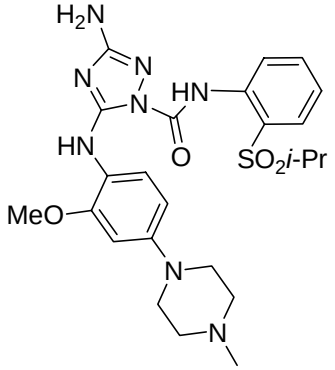
To a stirred solution of compound **7** (50 mg, 0.165 mmol) and pyridine (0.5 mL) in DMF (1.0 mL) was added **11** (0.33 mmol, dissolved in 1.0 mL DMF) at room temperature. The reaction mixture was stirred at room temperature overnight. After the reaction was complete as monitored by LC-MS, the solution was concentrated and the resulting residue was purified by reverse-phase prep-HPLC using water (0.05% TFA) /acetonitrile (0.05% TFA) gradient to afford compound **14** as TFA salt.
Compounds **15** and **16** were prepared by the synthetic procedure of **14**.

5-amino-N-(2-(isopropylsulfonyl)phenyl)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carboxamide (14a)



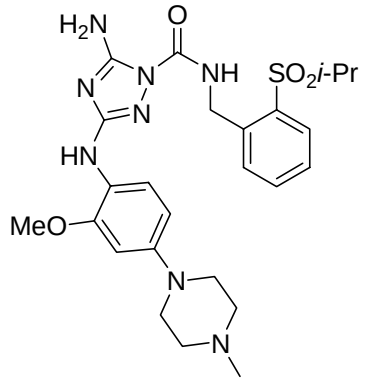
^{1}H NMR (600 MHz, CD_3OD) δ 8.61 (d, *J* = 8.4 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 7.93 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.75 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 6.62 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.92 (s, 3H), 3.43 (m, 1H), 3.16 (m, 4H), 2.64 (m, 4H), 2.35 (s, 3H), 1.29 (d, *J* = 6.6 Hz, 6H). MS (ESI) *m/z* 529 $(M+H)^+$.

3-amino-N-(2-(isopropylsulfonyl)phenyl)-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carboxamide (14b)



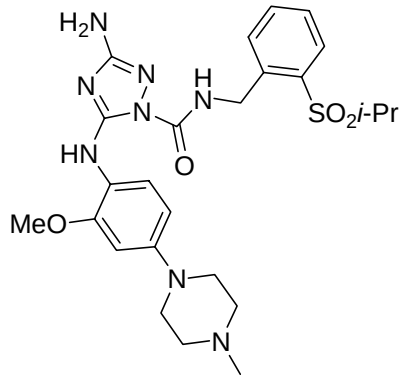
^{1}H NMR (600 MHz, DMSO-d_6) δ 10.75 (s, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.80 (t, *J* = 7.8 Hz, 1H), 7.38 – 7.41 (m, 3H), 7.25 (s, 1H), 6.63 (s, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.53 (m, 1H), 3.04 (m, 4H), 2.44 (m, 4H), 2.20 (s, 3H), 1.19 (d, *J* = 6.0 Hz, 6H). MS (ESI) *m/z* 529 $(M+H)^+$.

5-amino-N-(2-(isopropylsulfonyl)benzyl)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carboxamide (15a)



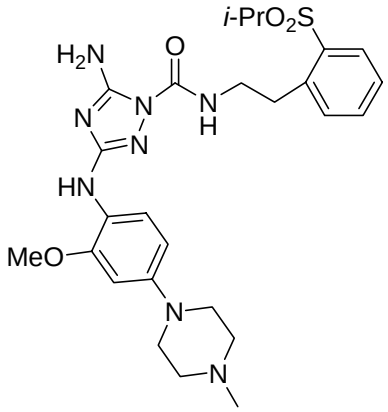
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.34 (t, J = 6.0 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.73 (dd, J = 7.8, 7.2 Hz, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.21 (br, 2H), 7.19 (s, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.45 (dd, J = 9.0, 2.4 Hz, 1H), 4.77 (d, J = 6.0 Hz, 2H), 3.84 (s, 3H), 3.77 (m, 2H), 3.63 (m, 1H), 3.52 (m, 2H), 3.15 (m, 2H), 2.91 (m, 2H), 2.85 (s, 3H), 1.20 (d, J = 6.6 Hz, 6H). MS (ESI) *m/z* 543 $(M+H)^+$.

3-amino-N-(2-(isopropylsulfonyl)benzyl)-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carboxamide (15b)



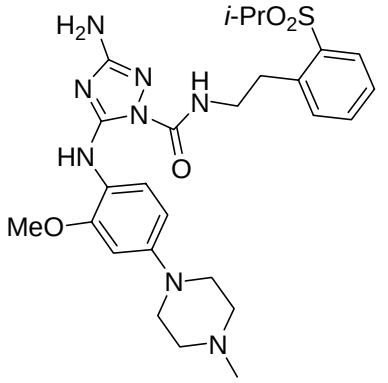
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.21 (t, J = 6.0 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.87 (dd, J = 7.8, 1.2 Hz, 1H), 7.73 (ddd, J = 7.8, 7.2, 1.2 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.54 (dd, J = 9.0, 2.4 Hz, 1H), 5.82 (br, 2H), 4.75 (d, J = 6.0 Hz, 2H), 3.84 (s, 3H), 3.79 (d, J = 12.6 Hz, 2H), 3.64 (m, 1H), 3.51 (d, J = 12.0 Hz, 2H), 3.14 (m, 2H), 2.90 (m, 2H), 2.85 (s, 3H), 1.21 (d, J = 6.6 Hz, 6H). MS (ESI) *m/z* 543 $(M+H)^+$.

5-amino-N-(2-(isopropylsulfonyl)phenethyl)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carboxamide (16a)



^{1}H NMR (600 MHz, DMSO-d_6) δ 7.99 (d, J = 9.0 Hz, 1H), 7.84 – 7.87 (m, 2H), 7.68 (ddd, J = 7.8, 7.2, 1.2 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.49 (dd, J = 7.8, 7.2 Hz, 1H), 7.16 (br, 2H), 7.09 (s, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 9.0, 2.4 Hz, 1H), 3.83 (s, 3H), 3.72 (d, J = 13.2 Hz, 2H), 3.48 – 3.53 (m, 5H), 3.26 (t, J = 7.2 Hz, 2H), 3.15 (m, 2H), 2.88 (m, 2H), 2.86 (s, 3H), 1.13 (d, J = 6.6 Hz, 6H). MS (ESI) *m/z* 557 $(M+H)^+$.

3-amino-N-(2-(isopropylsulfonyl)phenethyl)-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carboxamide (16b)

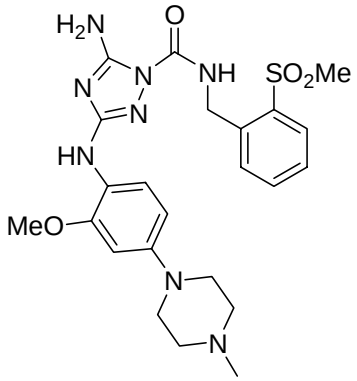


^{1}H NMR (600 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.85 – 7.87 (m, 2H), 7.67 (dt, J = 7.8, 1.2 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.54 (dd, J = 9.0, 2.4 Hz, 1H), 3.87 (s, 3H), 3.79 (d, J = 13.2 Hz, 2H), 3.55 (m, 1H), 3.48 – 3.52 (m, 4H), 3.24 (t, J = 7.2 Hz, 2H), 3.15 (m, 2H), 2.91 (m, 2H), 2.86 (s, 3H), 1.15 (d, J = 6.6 Hz, 6H). MS (ESI) *m/z* 557 $(M+H)^+$.

3. Spectral data of 17-29.

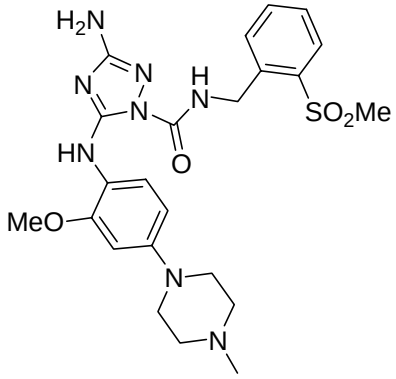
Compounds **17-29** were synthesized follow the similar procedure of synthesis of **14-16**.

N-(2-(methylsulfonyl)benzyl)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-5-amino-1H-1,2,4-triazole-1-carboxamide (17a)



^{1}H NMR (600 MHz, DMSO-d_6) δ 8.36 (t, J = 6.0 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.21 (br, 2H), 7.16 (s, 1H), 6.66 (d, J = 2.4 Hz, 1H), 6.45 (dd, J = 8.4, 1.8 Hz, 1H), 4.80 (d, J = 6.0 Hz, 2H), 3.83 (s, 3H), 3.34 (s, 3H), 3.15 (s, 3H), 3.08 (m, 2H), 2.67 (m, 2H). MS (ESI) *m/z* 515 $(M+H)^+$.

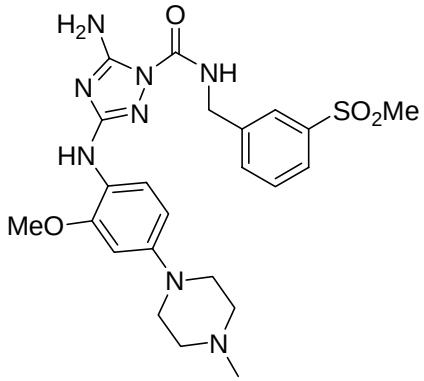
N-(2-(methylsulfonyl)benzyl)-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-3-amino-1H-1,2,4-triazole-1-carboxamide (17b)



^{1}H NMR (600 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.22 (t, J = 6.0 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.54 (dd, J = 9.0, 1.6 Hz, 1H), 5.82 (br, 2H),

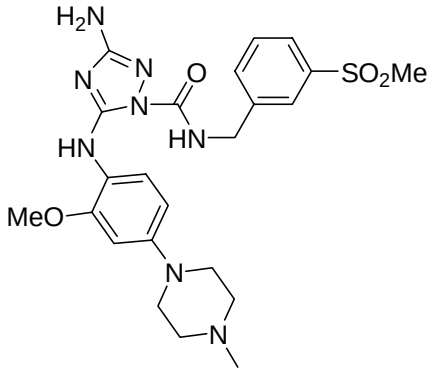
4.79 (d, *J* = 6.0 Hz, 2H), 3.84 (s, 3H), 3.34 (s, 3H), 3.20 (m, 2H), 3.15 (s, 3H), 2.79 (m, 2H). MS (ESI) *m/z* 515 $(M+H)^+$.

5-amino-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-(3-(methylsulfonyl)benzyl)-1H-1,2,4-triazole-1-carboxamide (18a)



^{1}H NMR (600 MHz, DMSO-d_6) δ 8.48 (t, *J* = 6.0 Hz, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.89 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.22 (br, 2H), 7.13 (s, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.46 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.49 (d, *J* = 6.0 Hz, 2H), 3.83 (s, 3H), 3.71 (d, *J* = 12.6 Hz, 2H), 3.50 (d, *J* = 11.4 Hz, 2H), 3.19 (s, 3H), 3.15 (m, 2H), 2.88 (m, 2H), 2.84 (s, 3H). MS (ESI) *m/z* 515 $(M+H)^+$.

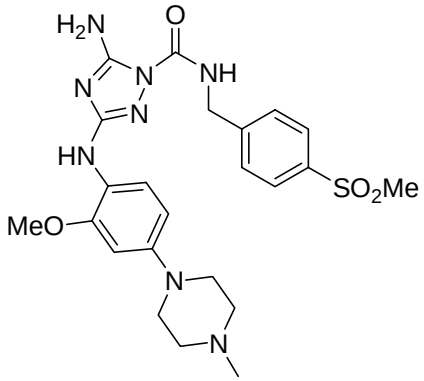
3-amino-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-(3-(methylsulfonyl)benzyl)-1H-1,2,4-triazole-1-carboxamide (18b)



^{1}H NMR (600 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.47 (t, *J* = 6.0 Hz, 1H), 8.15 (d, *J* = 9.0 Hz, 1H), 7.88 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 6.71 (s, 1H), 6.54 (d, *J* = 9.0 Hz, 1H), 5.76 (br, 2H), 4.48 (d, *J* = 6.0 Hz, 2H),

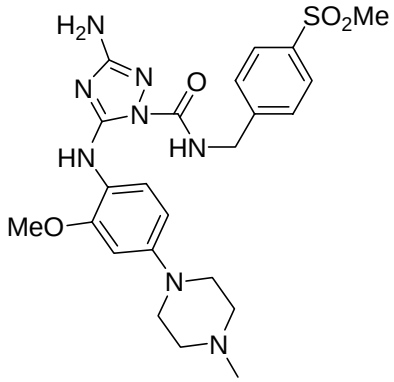
3.84 (s, 3H), 3.79 (d, *J* = 12.6 Hz, 2H), 3.49 (m, 2H), 3.19 (s, 3H), 3.15 (m, 2H), 2.90 (m, 2H), 2.85 (s, 3H). MS (ESI) *m/z* 515 $(M+H)^+$.

5-amino-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-(4-(methylsulfonyl)benzyl)-1H-1,2,4-triazole-1-carboxamide (19a)



^{1}H NMR (600 MHz, DMSO-d_6) δ 8.48 (t, *J* = 6.0 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.21 (br, 2H), 7.13 (s, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.46 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.50 (d, *J* = 6.0 Hz, 2H), 3.83 (s, 3H), 3.72 (d, *J* = 11.4 Hz, 2H), 3.63 (m, 2H), 3.17 (s, 3H), 3.14 (m, 2H), 2.88 (m, 2H), 2.85 (s, 3H). MS (ESI) *m/z* 515 $(M+H)^+$.

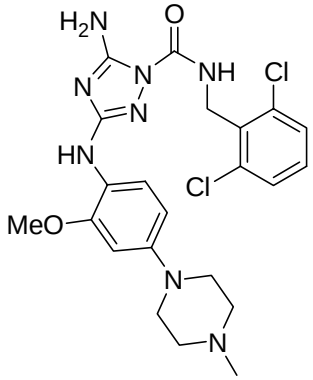
3-amino-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-(4-(methylsulfonyl)benzyl)-1H-1,2,4-triazole-1-carboxamide (19b)



^{1}H NMR (600 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.46 (t, *J* = 6.0 Hz, 1H), 8.16 (d, *J* = 9.0 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 2H), 6.71 (d, *J* = 2.4 Hz, 1H), 6.54 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.76 (br, 2H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.84 (s, 3H), 3.78 (d, *J* =

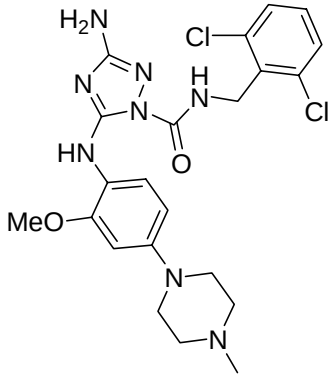
11.4 Hz, 2H), 3.50 (d, *J* = 10.8 Hz, 2H), 3.17 (s, 3H), 3.2 – 3.3 (m, 2H), 2.90 (m, 2H), 2.85 (s, 3H). MS (ESI) *m/z* 515 $(M+H)^+$.

5-amino-N-(2,6-dichlorobenzyl)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carboxamide (20a)



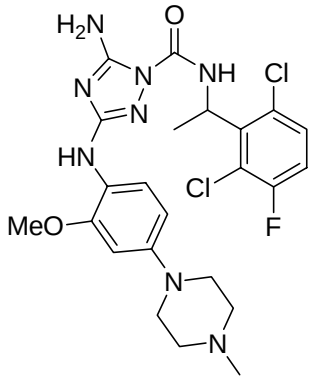
^{1}H NMR (600 MHz, DMSO-d_6) δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.80 (t, *J* = 6.0 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.24 (s, 2H), 7.18 (s, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.47 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.71 (d, *J* = 6.0 Hz, 2H), 3.81 (s, 3H), 3.74 (m, 2H), 3.50 (m, 2H), 3.15 (m, 2H), 2.87 (m, 2H), 2.85 (s, 3H). MS (ESI) *m/z* 505 $(M+H)^+$.

3-amino-N-(2,6-dichlorobenzyl)-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carboxamide (20b)



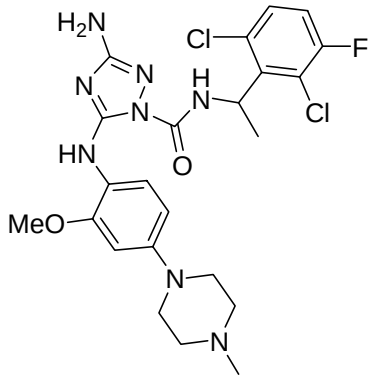
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.70 (s, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 7.58 (t, *J* = 6.0 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.37 (t, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.54 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.69 (d, *J* = 6.0 Hz, 2H), 3.87 (s, 3H), 3.79 (m, 2H), 3.50 (m, 2H), 3.15 (m, 2H), 2.91 (m, 2H), 2.85 (s, 3H). MS (ESI) *m/z* 505 $(M+H)^+$.

5-amino-N-(1-(2,6-dichloro-3-fluorophenyl)ethyl)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carboxamide (21a)



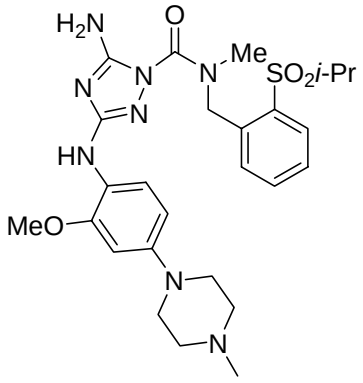
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.77 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.54 (t, J = 4.8 Hz, 1H), 7.43 (m, 1H), 7.21 (s, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.53 (m, 1H), 5.73 (m, 1H), 3.83 (s, 3H), 3.76 (m, 2H), 3.51 (m, 2H), 3.15 (m, 2H), 2.89 (m, 2H), 2.86 (s, 3H), 1.61 (d, J = 7.2 Hz, 3H). MS (ESI) *m/z* 537 $(M+H)^+$.

3-amino-N-(1-(2,6-dichloro-3-fluorophenyl)ethyl)-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carboxamide (21b)



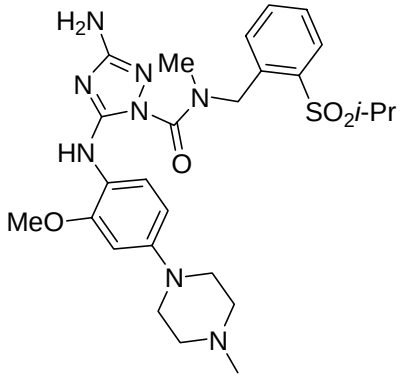
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.72 (s, 1H), 9.50 (s, 1H), 8.10 (d, J = 9.0 Hz, 1H), 7.55 (dd, J = 9.0, 5.4 Hz, 1H), 7.44 (m, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.53 (dd, J = 9.0, 2.4 Hz, 1H), 5.70 (m, 1H), 3.84 (s, 3H), 3.79 (m, 2H), 3.50 (m, 2H), 3.14 (m, 2H), 2.90 (m, 2H), 2.85 (s, 3H), 1.58 (d, J = 7.2 Hz, 3H). MS (ESI) *m/z* 537 $(M+H)^+$.

5-amino-N-(2-(isopropylsulfonyl)benzyl)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-methyl-1H-1,2,4-triazole-1-carboxamide (22a)



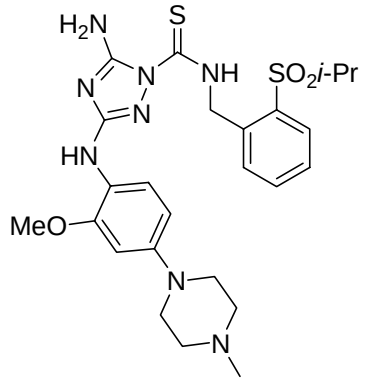
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.80 (t, J = 7.8 Hz, 1H), 7.61 – 7.65 (m, 2H), 7.30 (br, 2H), 7.13 (br, 1H), 6.59 (s, 1H), 5.25 (br, 2H), 3.77 (s, 3H), 3.61 (br, 2H), 3.50 (d, J = 12.0 Hz, 2H), 3.36 (m, 1H), 3.13 (s, 3H), 2.95 – 3.05 (m, 2H), 2.80 – 2.87 (m, 5H), 1.04 (br, 6H). MS (ESI) *m/z* 557 $(M+H)^+$.

3-amino-N-(2-(isopropylsulfonyl)benzyl)-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-methyl-1H-1,2,4-triazole-1-carboxamide (22b)



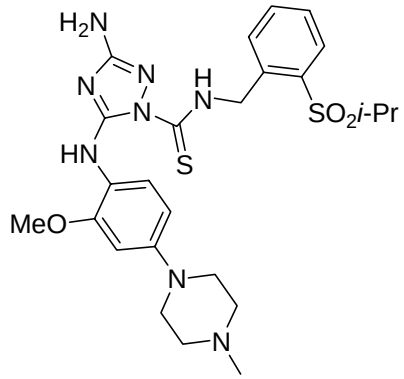
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.14 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.54 (dd, J = 9.0, 2.4 Hz, 1H), 3.85 (s, 3H), 3.79 (m, 2H), 3.50 – 3.52 (m, 4H), 3.13 – 3.15 (m, 3H), 2.91 (m, 2H), 2.85 (s, 3H), 1.18 (d, J = 6.6 Hz, 6H). MS (ESI) *m/z* 557 $(M+H)^+$.

5-amino-N-(2-(isopropylsulfonyl)benzyl)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carbothioamide (23a)



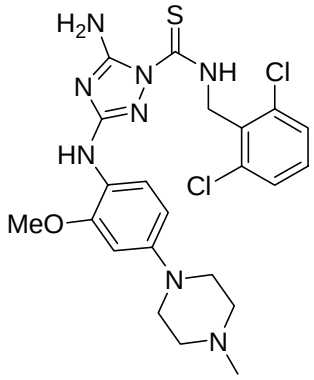
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.92 (t, J = 6.6 Hz, 1H), 8.31 (s, 2H), 8.00 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.72 (dd, J = 7.8, 7.2 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.43 (s, 1H), 6.69 (s, 1H), 6.47 (d, J = 9.0 Hz, 1H), 5.15 (d, J = 6.6 Hz, 2H), 3.84 (s, 3H), 3.74 (m, 2H), 3.66 (m, 1H), 3.51 (m, 2H), 3.15 (m, 2H), 2.92 (m, 2H), 2.85 (s, 3H), 1.23 (d, J = 6.6 Hz, 6H). MS (ESI) *m/z* 559 $(M+H)^+$.

3-amino-N-(2-(isopropylsulfonyl)benzyl)-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carbothioamide (23b)



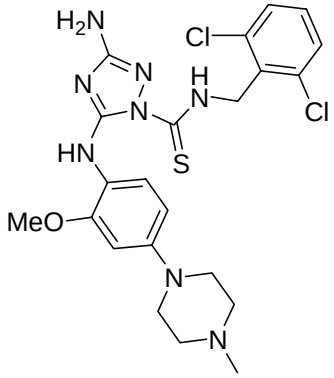
^{1}H NMR (600 MHz, DMSO-d_6) δ 11.53 (s, 1H), 9.81 (t, J = 6.0 Hz, 1H), 8.21 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.71 (dd, J = 7.8, 7.2 Hz, 1H), 7.57 (t, J = 7.2 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.57 (dd, J = 9.0, 2.4 Hz, 1H), 6.10 (s, 2H), 5.12 (d, J = 6.0 Hz, 2H), 3.85 (s, 3H), 3.68 (m, 2H), 3.65 (m, 1H), 3.53 (m, 2H), 3.16 (m, 2H), 2.92 (m, 2H), 2.85 (s, 3H), 1.22 (d, J = 6.6 Hz, 6H). MS (ESI) *m/z* 559 $(M+H)^+$.

5-amino-N-(2,6-dichlorobenzyl)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carbothioamide (24a)



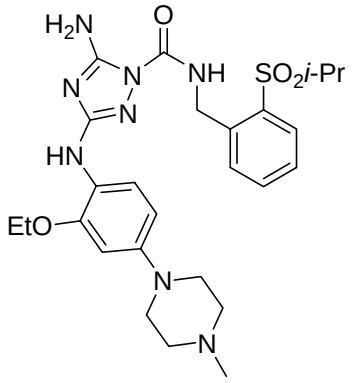
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.30 (t, J = 5.4 Hz, 1H), 8.32 (s, 2H), 7.76 (d, J = 9.0 Hz, 1H), 7.49 – 7.54 (m, 3H), 7.41 (t, J = 7.8 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 6.45 (dd, J = 9.0, 3.0 Hz, 1H), 5.02 (d, J = 5.4 Hz, 2H), 3.85 (s, 3H), 3.75 (m, 2H), 3.50 (m, 2H), 3.15 (m, 2H), 2.90 (m, 2H), 2.85 (s, 3H). MS (ESI) *m/z* 521 $(M+H)^+$.

3-amino-N-(2,6-dichlorobenzyl)-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carbothioamide (24b)



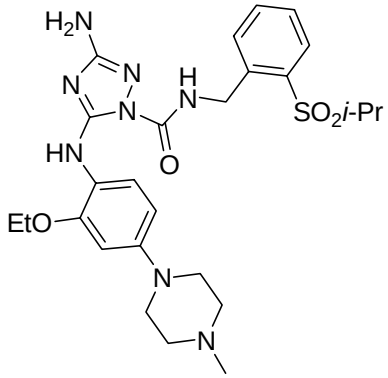
^{1}H NMR (600 MHz, DMSO-d_6) δ 11.50 (s, 1H), 9.01 (t, J = 5.4 Hz, 1H), 8.18 (d, J = 9.0 Hz, 1H), 7.51 – 7.53 (m, 2H), 7.41 (t, J = 7.8 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.56 (dd, J = 9.0, 2.4 Hz, 1H), 6.11 (s, 2H), 4.96 (d, J = 5.4 Hz, 2H), 3.88 (s, 3H), 3.80 – 3.87 (m, 2H), 3.48 - 3.54 (m, 2H), 3.11 – 3.19 (m, 2H), 2.88 – 2.94 (m, 2H), 2.85 (s, 3H). MS (ESI) *m/z* 521 $(M+H)^+$.

5-amino-3-(2-ethoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-(2-(isopropylsulfonyl)benzyl)-1H-1,2,4-triazole-1-carboxamide (25a)



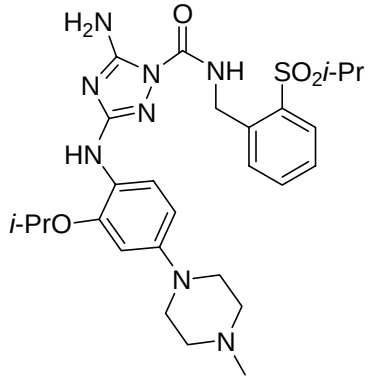
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.34 (t, J = 6.0 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.74 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.20 (br, 2H), 7.09 (s, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.45 (dd, J = 8.4, 2.4 Hz, 1H), 4.77 (d, J = 6.0 Hz, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.71 (d, J = 12.6 Hz, 2H), 3.61 (m, 1H), 3.49 (d, J = 12.0 Hz, 2H), 3.15 (m, 2H), 2.88 (m, 2H), 2.84 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.19 (d, J = 6.6 Hz, 6H). MS (ESI) *m/z* 543 $(M+H)^+$.MS (ESI) *m/z* 557 $(M+H)^+$.

3-amino-5-(2-ethoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-(2-(isopropylsulfonyl)benzyl)-1H-1,2,4-triazole-1-carboxamide (25b)



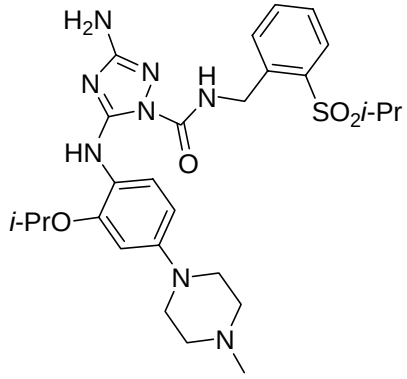
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.82 (s, 1H), 8.26 (t, J = 6.6 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.54 (dd, J = 9.0, 2.4 Hz, 1H), 5.80 (br, 2H), 4.73 (d, J = 6.6 Hz, 2H), 4.08 (q, J = 7.2 Hz, 2H), 3.75 (d, J = 12.6 Hz, 2H), 3.63 (m, 1H), 3.50 (m, 2H), 3.13 (m, 2H), 2.88 (m, 2H), 2.85 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.20 (d, J = 7.2 Hz, 6H). MS (ESI) *m/z* 557 $(M+H)^+$.

5-amino-3-(2-isopropoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-(2-(isopropylsulfonyl)benzyl)-1H-1,2,4-triazole-1-carboxamide (26a)



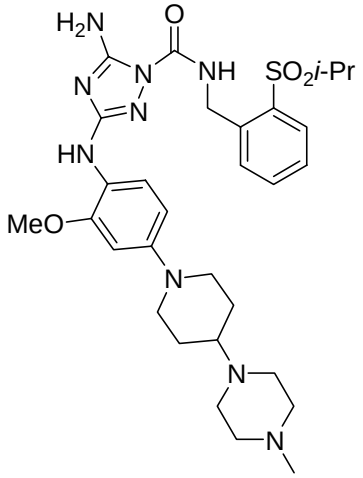
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.35 (t, J = 6.0 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.74 (t, J = 7.2 Hz, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.55 (dd, J = 7.8, 7.2 Hz, 1H), 7.21 (br, 2H), 7.02 (s, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.46 (dd, J = 8.4, 2.4 Hz, 1H), 4.77 (d, J = 6.0 Hz, 2H), 4.68 (m, 1H), 3.70 (d, J = 12.6 Hz, 2H), 3.62 (m, 1H), 3.49 (d, J = 13.2 Hz, 2H), 3.15 (m, 2H), 2.87 (m, 2H), 2.84 (s, 3H), 1.28 (d, J = 7.2 Hz, 6H), 1.17 (d, J = 6.6 Hz, 6H). MS (ESI) *m/z* 571 $(M+H)^+$.

3-amino-5-(2-isopropoxy-4-(4-methylpiperazin-1-yl)phenylamino)-N-(2-(isopropylsulfonyl)benzyl)-1H-1,2,4-triazole-1-carboxamide (26b)



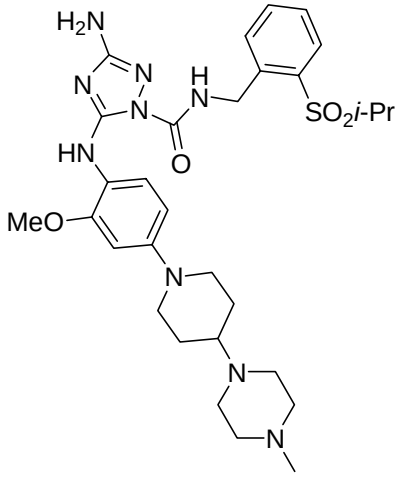
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.84 (s, 1H), 8.27 (t, J = 6.0 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 7.80 (d, J = 7.2 Hz, 1H), 7.72 (dd, J = 7.8, 7.2 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.55 (dd, J = 7.8, 7.2 Hz, 1H), 6.75 (s, 1H), 6.55 (d, J = 9.0 Hz, 1H), 5.81 (br, 2H), 4.73 (d, J = 6.0 Hz, 2H), 4.64 (m, 1H), 3.75 (d, J = 13.2 Hz, 2H), 3.62 – 3.66 (m, 3H), 3.13 (m, 2H), 2.88 (m, 2H), 2.85 (s, 3H), 1.24 (d, J = 6.0 Hz, 6H), 1.16 (d, J = 6.6 Hz, 6H). MS (ESI) *m/z* 571 $(M+H)^+$.

5-amino-N-(2-(isopropylsulfonyl)benzyl)-3-(2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carboxamide (27a)



^{1}H NMR (600 MHz, DMSO-d_6) δ 8.36 (t, J = 6.0 Hz, 1H), 8.03 (d, J = 9.6 Hz, 1H), 7.86 (dd, J = 7.8, 1.2 Hz, 1H), 7.72 (dt, J = 7.8, 1.2 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.28 (s, 1H), 7.23 (s, 2H), 6.72 (s, 1H), 6.57 (m, 1H), 4.78 (d, J = 6.0 Hz, 2H), 3.83 (s, 3H), 3.5 – 3.8 (m, 5H), 2.9 – 3.1 (m, 8H), 2.76 (s, 3H), 2.70 (m, 1H), 2.00 (m, 2H), 1.65 (m, 2H), 1.21 (d, J = 6.6 Hz, 6H). MS (ESI) *m/z* 626 $(M+H)^+$.

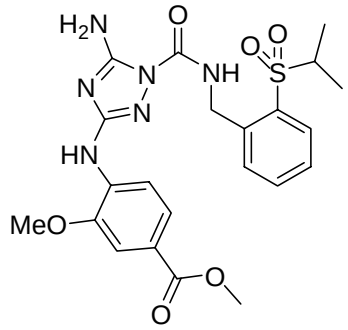
3-amino-N-(2-(isopropylsulfonyl)benzyl)-5-(2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenylamino)-1H-1,2,4-triazole-1-carboxamide (27b)



^{1}H NMR (600 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.21 (t, J = 6.6 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.86 (dd, J = 7.8, 1.2 Hz, 1H), 7.73 (dt, J = 7.8, 1.2 Hz, 1H), 7.59 (d, J = 7.8 Hz,

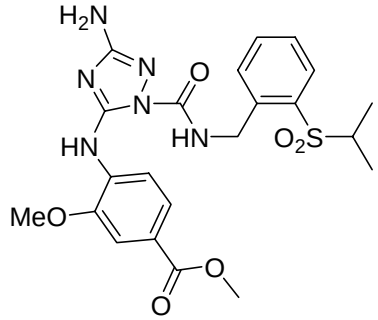
1H), 7.57 (t, *J* = 7.8 Hz, 1H), 6.77 (s, 1H), 6.62 (m, 1H), 4.75 (d, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 3.76 (d, *J* = 11.4 Hz, 2H), 3.64 (m, 1H), 3.55 (m, 2H), 2.89 – 3.20 (m, 8H), 2.81 (s, 3H), 2.78 (m, 1H), 2.05 (m, 2H), 1.57 (m, 2H), 1.22 (d, *J* = 6.6 Hz, 6H). MS (ESI) *m/z* 626 $(M+H)^+$.

Methyl 4-(5-amino-1-(2-(isopropylsulfonyl)benzylcarbamoyl)-1H-1,2,4-triazol-3-ylamino)-3-methoxybenzoate (28a)



^{1}H NMR (600 MHz, DMSO-d_6) δ 8.53 (t, *J* = 6.0 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 7.86 – 7.88 (m, 2H), 7.74 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 1.8 Hz, 1H), 7.32 (m, 2H), 4.80 (d, *J* = 6.0 Hz, 2H), 3.91 (s, 3H), 3.80 (s, 3H), 3.62 (m, 1H), 1.20 (d, *J* = 6.6 Hz, 6H). MS (ESI) *m/z* 503 $(M+H)^+$.

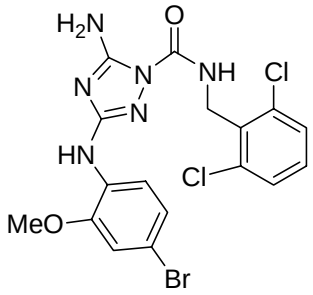
Methyl 4-(5-amino-2-(2-(isopropylsulfonyl)benzylcarbamoyl)-2H-1,2,4-triazol-3-ylamino)-3-methoxybenzoate (28b)



^{1}H NMR (600 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.36 (t, *J* = 6.0 Hz, 1H), 7.86 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.73 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.60 – 7.63 (m, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 1.8 Hz, 1H), 5.96 (s, 2H), 4.76 (d, *J* = 6.0 Hz,

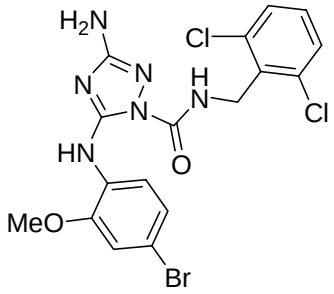
2H), 3.91 (s, 3H), 3.82 (s, 3H), 3.65 (m, 1H), 1.21 (d, *J* = 6.0 Hz, 6H). MS (ESI) *m/z* 503 $(M+H)^+$.

5-amino-3-(4-bromo-2-methoxyphenylamino)-N-(2,6-dichlorobenzyl)-1H-1,2,4-triazole-1-carboxamide (29a)



^{1}H NMR (600 MHz, DMSO-d_6) δ 8.03 (d, *J* = 9.0 Hz, 1H), 7.93 (t, *J* = 6.0 Hz, 1H), 7.47 – 7.49 (m, 3H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.28 (s, 2H), 7.11 (d, *J* = 2.4 Hz, 1H), 7.02 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.71 (d, *J* = 6.0 Hz, 2H), 3.84 (s, 3H). MS (ESI) *m/z* 485 $(M+H)^+$.

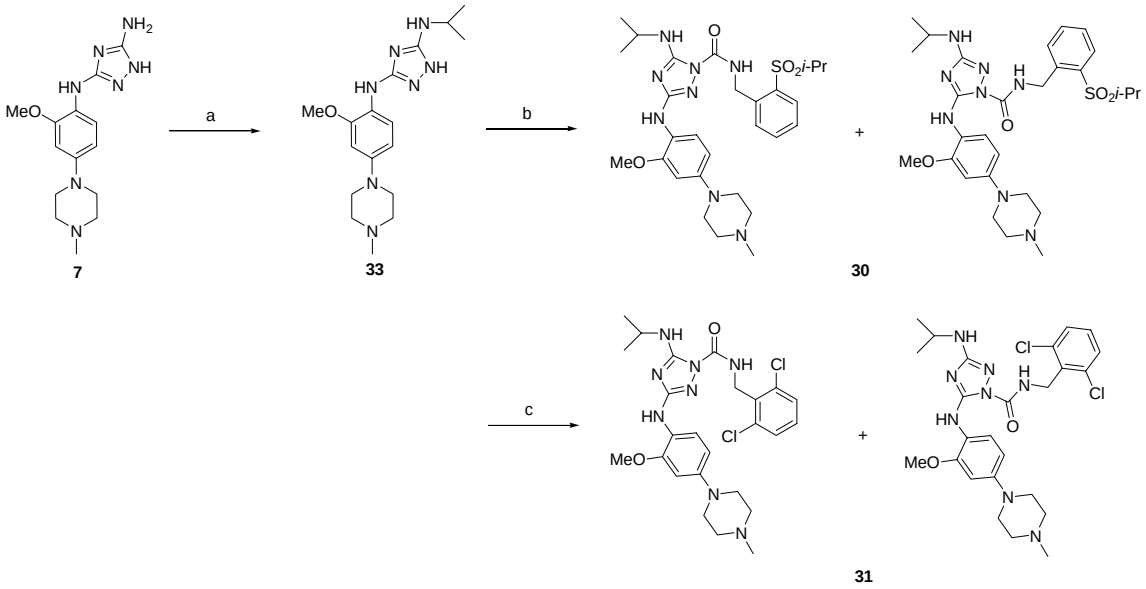
3-amino-5-(4-bromo-2-methoxyphenylamino)-N-(2,6-dichlorobenzyl)-1H-1,2,4-triazole-1-carboxamide (29b)



^{1}H NMR (600 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.26 (d, *J* = 9.0 Hz, 1H), 7.69 (t, *J* = 6.0 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.15 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.87 (s, 2H), 4.70 (d, *J* = 6.0 Hz, 2H), 3.91 (s, 3H). MS (ESI) *m/z* 485 $(M+H)^+$.

4. Synthetic procedure of 30 and 31.

Scheme 2. Synthesis of compounds **30** and **31**[a]



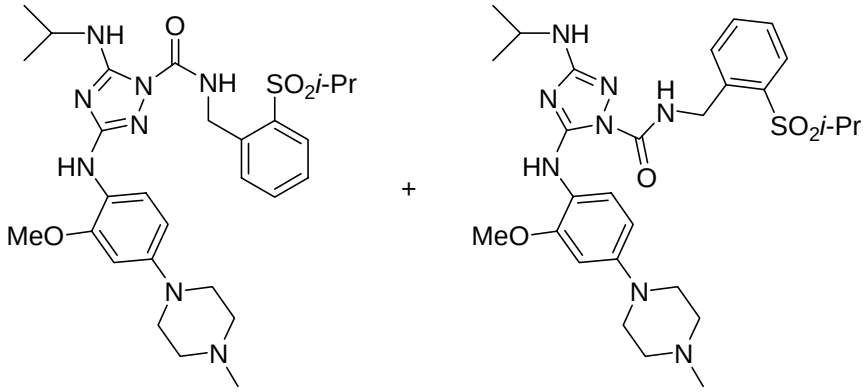
[a] Reagents and conditions: (a) acetone, $NaBH(OAc)_3$, AcOH/DMF; (b) 2-(isopropyl sulfonyl)benzylcarbamic chloride, pyridine, DMF, r.t.; (c) 2,6-dichlorobenzylcarbamic chloride, pyridine, DMF, r.t.

To a stirred mixture of compound **7** (30.3 mg, 0.1 mmol) and acetone (7.34 μL, 0.1 mmol) in AcOH/DMF (0.03 mL/1.5 mL) was added $NaBH(OAc)_3$ (63.6 mg, 0.3 mmol in one portion at 0 ^{o}C. Then the reaction mixture was gradually warmed up to room temperature and stirred for two days.

After the reaction was complete as monitored by LC-MS, the resulting mixture was diluted with ethyl acetate, cooled to 0 ^{o}C, and neutralized by addition of 10% NaOH solution. Then the mixture was further diluted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, filtered through a pad of celite and concentrated under reduced pressure. The resulting residue was purified by reverse-phase prep-HPLC to afford compound **33**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.11 (br, 1H), 7.85 (d, J = 9.0 Hz, 1H), 6.58 (m, 2H), 6.40 (dd, J = 9.0, 2.4 Hz, 1H), 6.20 (br, 1H), 3.82 (s, 3H), 3.56 (m, 1H), 3.02 (m, 4H), 2.44 (m, 4H), 2.20 (s, 3H), 1.10 (d, J = 6.6 Hz, 6H). MS (ESI) *m/z* 346 $(M+H)^{+}$.

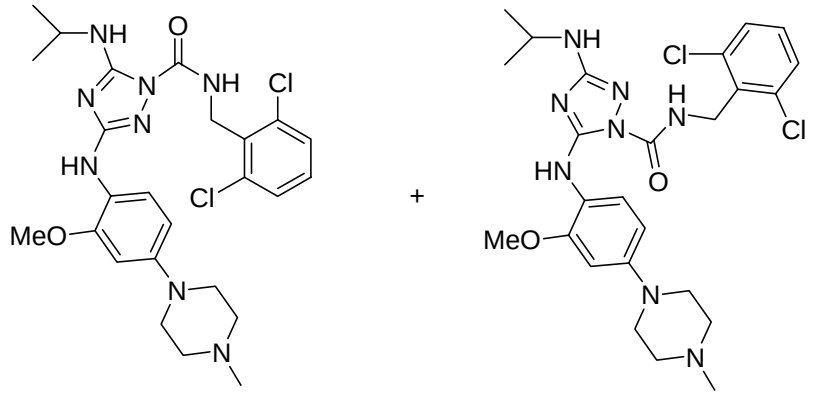
Compounds **30** and **31** were synthesized with similar procedures to those of compounds **14-16**.

Mixture of 5-(isopropylamino)-*N*-(2-(isopropylsulfonyl)benzyl)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1*H*-1,2,4-triazole-1-carboxamide and 3-(isopropylamino)-*N*-(2-(isopropylsulfonyl)benzyl)-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1*H*-1,2,4-triazole-1-carboxamide (30)



^{1}H NMR (600 MHz, DMSO-d_6) (mixture of isomers) δ 9.70 (s, 0.89H), 8.30 (t, J = 6.6 Hz, 0.11H), 8.19 (t, J = 6.6 Hz, 0.89H), 8.01 (d, J = 9.0 Hz, 0.89H), 7.94 (d, J = 8.4 Hz, 0.11H), 7.86 (d, J = 7.2 Hz, 1H), 7.73 (dd, J = 8.4, 7.2 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.56 (dd, J = 8.4, 7.2 Hz, 1H), 7.21 (s, 0.11H), 7.03 (d, J = 8.4 Hz, 0.11H), 6.62 (d, J = 2.4 Hz, 0.89H), 6.61 (d, J = 2.4 Hz, 0.11H), 6.46 (dd, J = 9.0, 2.4 Hz, 0.89H), 6.40 (dd, J = 8.4, 2.4 Hz, 0.11H), 6.29 (d, J = 8.4 Hz, 0.89H), 4.76 (d, J = 6.6 Hz, 2H), 3.82 (s, 0.33H), 3.81 (s, 2.67H), 3.64 – 3.69 (m, 2H), 3.08 (m, 4H), 2.43 (m, 4H), 2.21 (s, 3H), 1.20 (d, J = 7.2 Hz, 6H). MS (ESI) *m/z* 585 $(M+H)^+$.

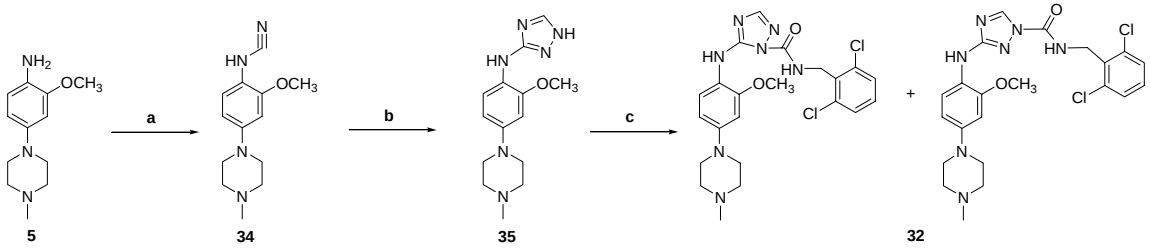
Mixture of *N*-(2,6-dichlorobenzyl)-5-(isopropylamino)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1*H*-1,2,4-triazole-1-carboxamide and *N*-(2,6-dichlorobenzyl)-3-(isopropylamino)-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1*H*-1,2,4-triazole-1-carboxamide (31)



^{1}H NMR (600 MHz, DMSO-d_6) (mixture of isomers) δ 9.74 (s, 0.64H), 8.14 (d, J = 9.0 Hz, 0.64H), 7.89 (d, J = 9.0 Hz, 0.36H), 7.82 (t, J = 6.0 Hz, 0.36H), 7.65 (t, J = 6.0 Hz, 0.64H), 7.50 (d, J = 8.4 Hz, 1.28H), 7.48 (d, J = 8.4 Hz, 0.72H), 7.38 (t, J = 8.4 Hz, 0.64H), 7.36 (t, J = 8.4 Hz, 0.36H), 7.28 (s, 0.36H), 6.73 (d, J = 2.4 Hz, 0.64H), 6.66 (d, J = 2.4 Hz, 0.36H), 6.54 (dd, J = 9.0, 2.4 Hz, 0.64H), 6.47 (dd, J = 9.0, 2.4 Hz, 0.36H), 4.71 (d, J = 6.0 Hz, 2H), 3.88 (s, 1.92H), 3.8 – 3.9 (m, 1H), 3.82 (s, 1.08H), 3.7 – 3.8 (m, 2H), 3.65 (m, 1H), 3.51 (m, 2H), 3.13 (m, 2H), 2.91 (m, 2H), 2.86 (s, 3H), 1.20 (d, J = 6.0 Hz, 2.16H), 1.10 (d, J = 6.0 Hz, 3.84H). MS (ESI) *m/z* 547 $(M+H)^+$.

5. Synthetic procedure of 32.

Scheme 3. Synthesis of compound **32**[a]



[a] Reagents and conditions: (a) BrCN, Et_2O/THF; (b) NH_2-NH_2, HCHO, MeOH/H_2O; (c) 2,6-dichlorobenzylcarbamic chloride, pyridine, DMF, r.t.

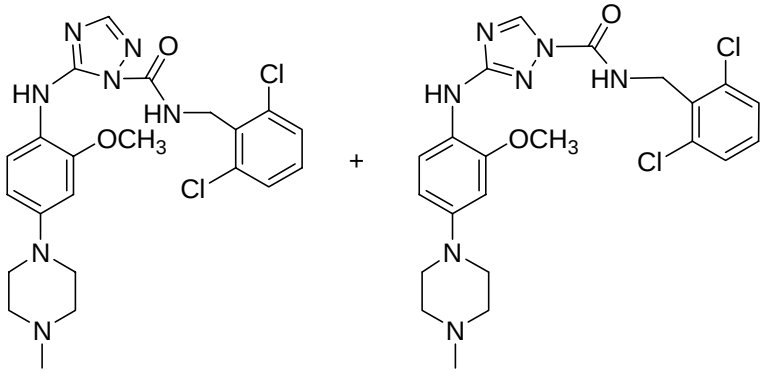
To a stirred solution of cyanogen bromide (254 mg, 2.4 mmol) in Et_2O/THF (8 mL/8 mL) was added a solution of compound **5** (884 mg, 4 mmol) in Et_2O/THF (4 mL/4 mL) at 0 ^oC. Then the reaction was gradually warmed up to room temperature and stirred for three days. After the reaction was complete as monitored by LC-MS, the reaction mixture was

filtered. Filtrate was concentrated and purified by silica-gel column chromatography with 3.5 N NH_3 in methanol and dichloromethane (1/10, v/v) to give compound **34** (110 mg, 11%).

To a stirred solution of **34** (42 mg, 0.17 mmol) in methanol/water (1.7 mL/0.34 mL) were added hydrazine (5.3 μL, 0.17 mmol) and 36% formaldehyde (15 μL, 0.17 mmol) at room temperature. Then the reaction was stirred at 50 ^oC till the reaction went to completion (about 5 hours, monitored by LC-MS). The reaction mixture was concentrated and purified by silica-gel column chromatography with 3.5 N NH_3 in methanol and dichloromethane (1/30, v/v) to give compound **35** (31 mg, 63%).

Compound **32** was synthesized with similar procedures to those of compounds **14-16**.

Mixture of *N*-(2,6-dichlorobenzyl)-5-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1*H*-1,2,4-triazole-1-carboxamide and *N*-(2,6-dichlorobenzyl)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-1*H*-1,2,4-triazole-1-carboxamide (32)



^1H NMR (600 MHz, DMSO-d_6) (mixture of isomers) δ 9.70 (s, 0.83H), 8.82 (s, 0.17H), 8.63 (t, J = 5.4 Hz, 0.83H), 8.41 (t, J = 5.4 Hz, 0.17H), 8.11 (d, J = 8.4 Hz, 0.83H), 7.83 (d, J = 8.4 Hz, 0.17H), 7.79 (s, 0.83H), 7.60 (s, 0.17H), 7.44 – 7.47 (m, 2H), 7.35 – 7.38 (m, 1H), 6.67 (d, J = 2.4 Hz, 0.83H), 6.60 (d, J = 2.4 Hz, 0.17H), 6.50 (dd, J = 8.4, 2.4 Hz, 0.83H), 6.42 (dd, J = 8.4, 2.4 Hz, 0.17H), 4.72 – 4.74 (m, 2H), 3.87 (s, 2.49H), 3.80 (s, 0.51H), 3.08 (m, 3.32H), 3.05 (m, 0.68H), 2.43 (m, 4H), 2.20 (m, 3H). MS (ESI) *m/z* 490 $(M+H)^+$.

6. Procedures for cellular assay.

Oncogenic ALK transformed Ba/F3 cell lines with expression of NPM-ALK or TEL-ALK kinase fusion protein were generated by retroviral transduction of cells with pMSCV IRES puro/Luc vector.[2] EML4-ALK transformed Ba/F3 cells was generated as previous described. All cell lines were cultured with 5% CO_2 at 37 °C in RPMI 1640 (Invitrogen) with 10% fetal bovine serum (FBS) and supplemented with 1% L-glutamine. Parental Ba/F3 cells were similarly cultured with 10% WEHI-conditioned medium as a source of IL-3. 48 hours cell proliferation studies were obtained using the CellTiter-Glo assay (for Ba/F3, Tel-ALK or NPM Ba/F3 cells Promega, Madison, WI) or MTS assay (EML4-ALK) as previous described.[3,4] IC50 values were generated by using XLFit software.

7. Crystal structures of 29a and 29b.

A crystal mounted on a diffractometer was collected data at 90 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer ($Mo_{K\alpha}$ radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.3° scans in ω at 28° in 2θ. Data integration up to 0.72 Å resolution was carried out using SAINT V7.23A (Bruker diffractometer, 2005) with reflection spot size optimisation. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2005). The structure was solved by the direct methods procedure and refined by least-squares methods again F^2 using SHELXS-97 and SHELXL-97 (Sheldrick, 2000). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. The Ortep plots produced

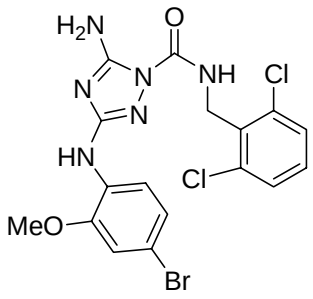
[2] Galkin, A. V.; Melnick, J. S.; Kim, S.; Hood, T. L.; Li, N.; Li, L.; Xia, G.; Steensma, R.; Chopiuk, G.; Jiang, J.; Wan, Y.; Ding, P.; Liu, Y.; Sun, F.; Schultz, P. G.; Gray, N. S.; Warmuth, M. Identification of NVP-TAE684, a potent, selective, and efficacious inhibitor of NPM-ALK. *Proc. Natl. Acad. Sci. U. S. A.* **2007,** *104*, 270-5.

[3] Adrian, F. J.; Ding, Q.; Sim, T.; Velentza, A.; Sloan, C.; Liu, Y.; Zhang, G.; Hur, W.; Ding, S.; Manley, P.; Mestan, J.; Fabbro, D.; Gray, N. S. Allosteric inhibitors of Bcr-abl-dependent cell proliferation. *Nat. Chem. Biol.* **2006**, *2*, 95-102.

[4] Sasaki, T.; Okuda, K.; Zheng, W.; Butrynski, J.; Capelletti, M.; Wang, L.; Gray, N. S.; Wilner, K.; Christensen, J. G.; Demetri, G.; Shapiro, G. I.; Rodig, S. J.; Eck, M. J.; Jänne, P. A. The Neuroblastoma-Associated F1174L ALK Mutation Causes Resistance to an ALK Kinase Inhibitor in ALK-Translocated Cancers. *Cancer Res.* **2010**, *70*, 10038-10043.

with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0 (Accelrys, 2007).

Figure S1. Crystal structures of 29a.



29a

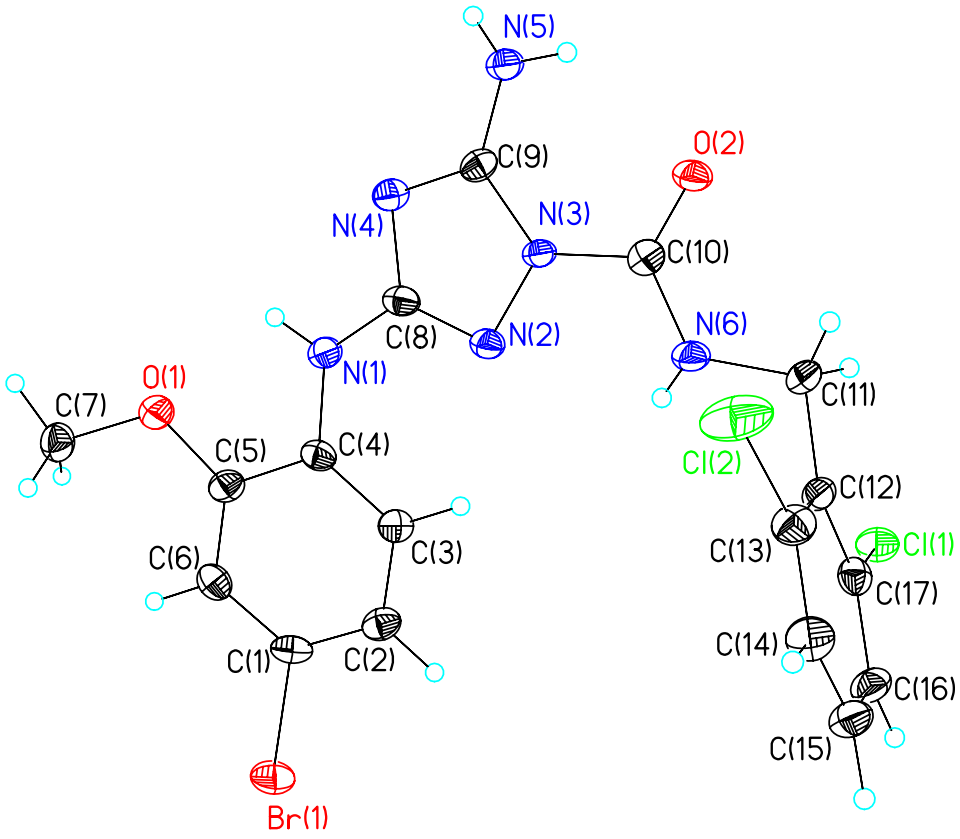
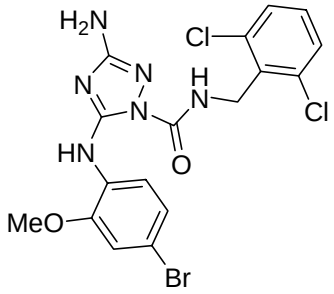
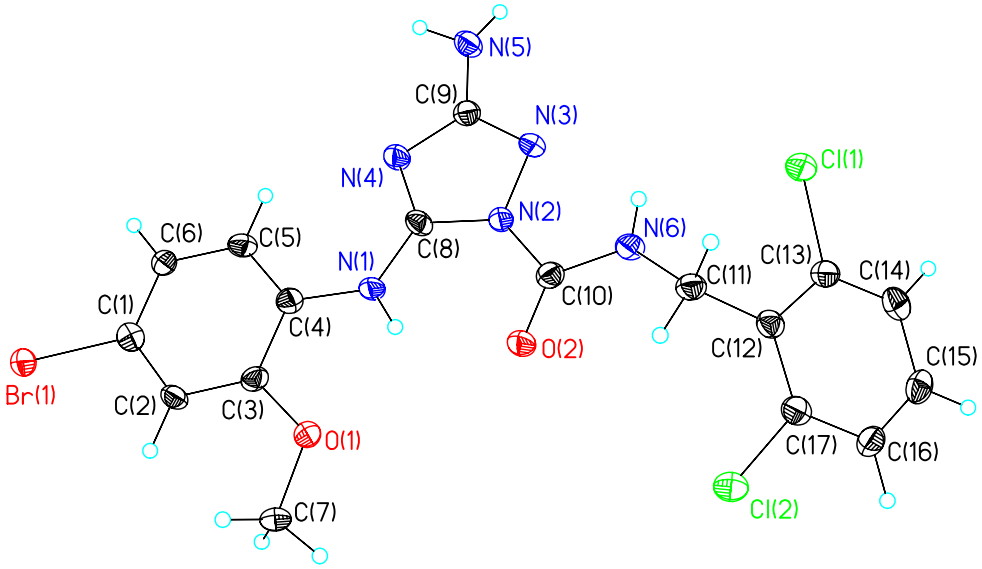


Figure S2. Crystal structures of 29b.



29b



8. Molecular Docking Study

To better understand the structure feature effect, we performed a molecular modeling study using Glide[5] based upon the recently reported co-crystal structure of ALK with **1** (PDB code: 2XB7).[6] This study suggests that both compounds **15a** and **15b** bind to the ALK hinge segment using a tridentate hydrogen-bonding interaction which is similar to the hinge interaction of **1** with ALK (Please see supplementary Figure S3.). The primary amino group (5-NH_2) is predicted to make a hydrogen-bond with the backbone oxygen of Glu1197 while the N^4 and 3-NH group of the triazole ring form hydrogen-bonds with the backbone nitrogen and oxygen of Met1199, respectively. As shown in Figure S3A, the overall conformations of **1** and **15a** are overlapped well, and the sulfonyl oxygens of **15a** are positioned within hydrogen-bonding distance (2.63 Å) with Lys1150. Compound **15b** is predicted to possess similar hinge interaction as compound **1** (Figure S3B), but the repulsive steric interactions from the 2-methoxy group and isopropylsulfonyl group may predispose the compound to a conformation less favorable for binding to ALK.

[5] Glide, version 3.5. http://www.schrodinger.com.

[6] Bossi, R. T.; Saccardo, M. B.; Ardini, E.; Menichincheri, M.; Rusconi, L.; Magnaghi, P.; Orsini, P.; Avanzi, N.; Borgia, A. L.; Nesi, M.; Bandiera, T.; Fogliatto, G.; Bertrand, J. A. Crystal structures of anaplastic lymphoma kinase in complex with ATP competitive inhibitors. *Biochemistry* **2010**, *49*, 6813-25.

Figure S3. Molecular docking study of **15a** and **15b** with ALK-KD structure (PDB entry 2XB7). (A) Binding conformation of **1** (green) and **15a** (yellow) in the ATP binding site of ALK. Hydrogen bonds to the hinge region are indicated by dashed lines. (B) Binding conformation of **1** (green) and **15b** (purple) in the ATP binding site of ALK.