Supporting Information

Design, Synthesis, and Evaluation of Highly Potent FAK-Targeting PROTACs

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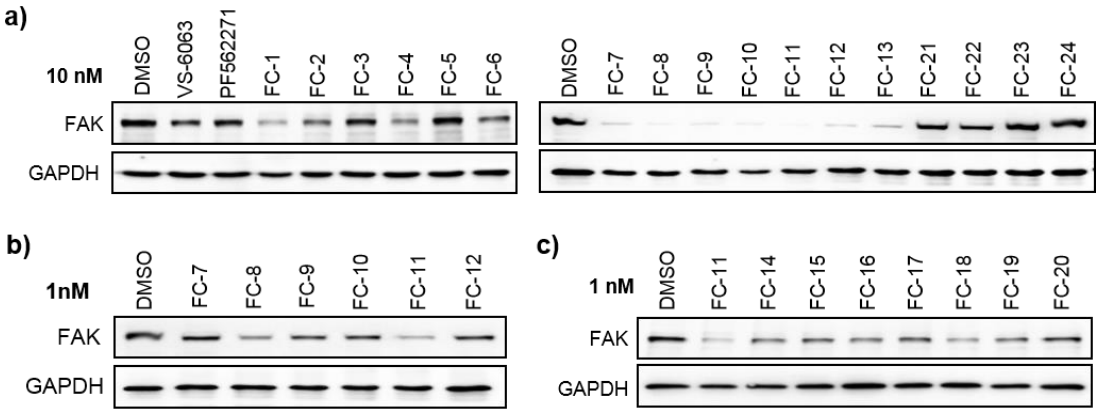


Figure S1. Screening of FAK-PROTACs. a) FAK degradation effect of FC-1 to FC-13 and the negative control of FC-21 to FC-24 in PA1 cells at 10 nM for 8 h. **b/c)** FAK degradation activity of FC-7 ~ FC-12 and FC-14~ FC-20 in PA1 cells at 1 nM for 8 h.

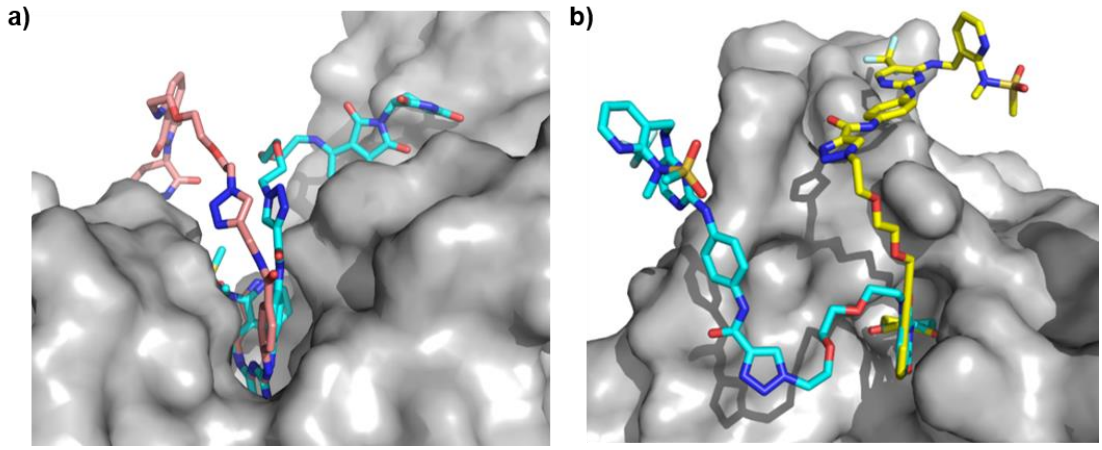


Figure S2. The model of FAK-PROTACs with FAK protein and Cereblon protein. a) Binding of FC-11 (cyans), FC-5 (lightpink) with FAK protein; **b)** Binding of FC-11 (cyans), FC-17 (yellow) with cereblon protein.

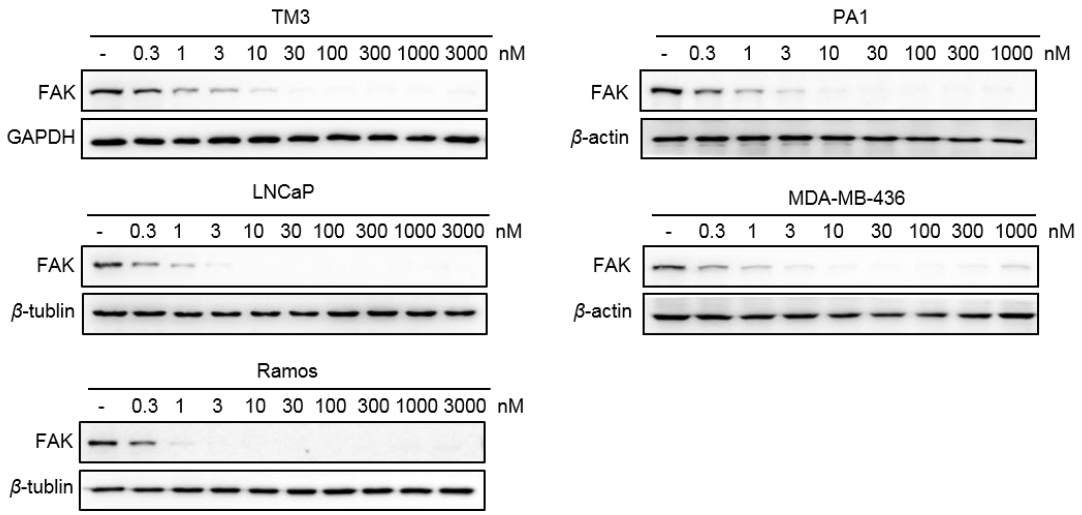


Figure S3. Representative FAK degradation at the indicated dose of FC-11 in different cell lines for 8 h incubation.

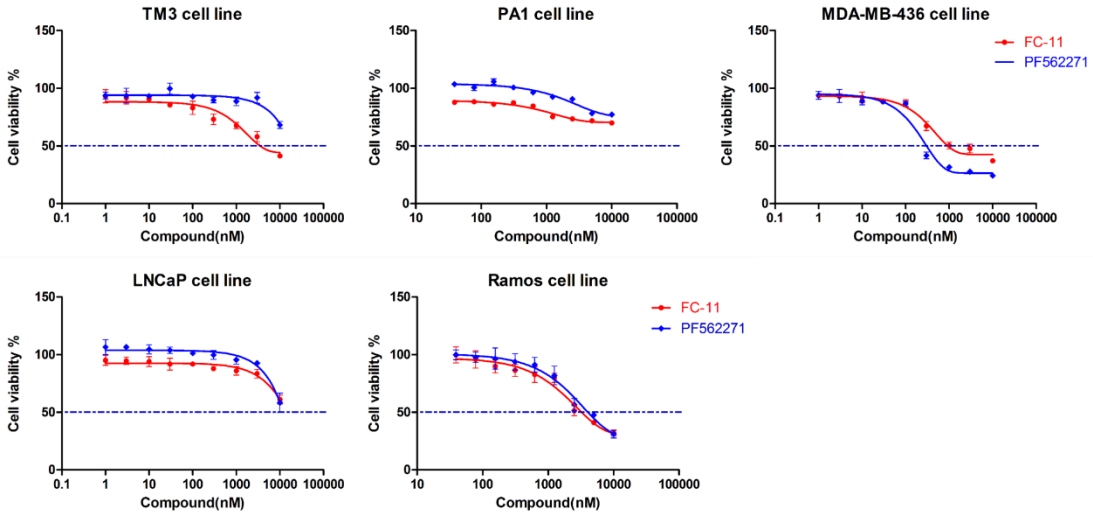


Figure S4. Cell proliferation activities on the tested cell lines. Dose dependent proliferation of the tested cells by FC-11 and PF562271 treatment after 72 h with MTS assay (n = 3).

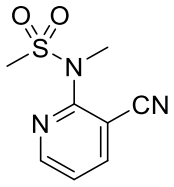
Cell culture. PA1 (CRL-1572), MDA-MB-436 (HTB-130), Ramos (CRL-1596), LNCaP (CRL-1740) and TM3 (CRL-1714) were derived from ATCC (Manassas, VA, USA). MDA-MB-436 was maintained in Dulbecco's Modified Eagle's medium (DMEM, Gibco) supplemented with 10% fetal bovine serum (FBS, Gibco). PA1 was cultured in McCoy's 5A (Gibco) supplemented with 10% heat-inactivated FBS. Ramos and LNCaP were cultured in RPMI 1640 (Gibco) with 10% FBS. TM3 was cultured in DMEM/Ham's F12 1:1 (Gibco) with 2.5% FBS and 5% horse serum (Gibco). All cell lines were tested for mycoplasma free with Mycoplasma Detection Kit-Quick Test (B39032, Biotool.com) and used between passage number 5-9 from thawing. Cells were cultured in a humidified incubator with 5% CO_2 at 37 ºC.

Antibodies. Antibodies used in this study are: FAK (#3285) was obtained from Cell Signaling Technology (MA, USA), pFAK Antibody (2D11, sc-81493) was purchased from Santa Cruz Biotechnology (CA, USA), GAPDH (ab8226, 1:10000 for Western Blotting) was purchased from Abcam (Cambridge, MA, USA). *β*-tubulin (KM9003) and *β*-actin (KM9001T) were purchased from Sungene.

Chemical materials. All commercial materials (Selleck, Alfa Aesar, Aladdin, J&K Chemical LTD, Energy Chemical) were used without further purification. All solvents were analytical grade. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE Ⅲ 400 MHz spectrometer in CD_3OD, $CDCl_3$, DMSO-d_6 using solvent peak as a standard. All ^{13}C NMR spectra were recorded with complete proton decoupling. Low-resolution mass spectral analyses were performed with an Agilent 6340 or Waters AQUITY UPLCTM/MS. All reactions were carried out in sealed tube with Teflon cap. Analytical TLC was performed on Yantai Chemical Industry Research Institute silica gel 60 F254 plates and flash column chromatography was performed on Qingdao Haiyang Chemical Co. Ltd silica gel 60 (200-300 mesh). The rotavapor was BUCHI's Rotavapor R-3.

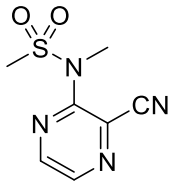
Synthesis and spectroscopic characterization of compounds

General procedure A: click reaction route to triazole core. To a stirred solution of the corresponding alkyne (1 eq) and the corresponding azide (1 eq) in *t*-BuOH were added $CuSO_4$ (0.5 eq), sodium ascorbate (3 eq) and water (10% to *t*-BuOH). The mixture was stirred at 70 ºC under argon for 8 h. Then the mixture was dissolved in EA and washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (DCM:MeOH = 40:1), yielding the corresponding triazole (I.Y. = 40% - 80%).



(1) *N*-(3-cyanopyridin-2-yl)-*N*-methylmethanesulfonamide.

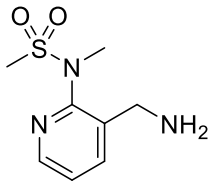
To the *N*-methylmethanesulfonamide (1.0 eq, 1.09 g) in DMF was added *t*-BuOK (1.0 eq, 1.12g). The mixture was stirred for 20 min and 2-fluoronicotinonitrile (10 mmol, 1.12 g) was added. The resulting mixture was reflux for 2 h. The reaction was cooled and poured into water, extracted with DCM, washed with brine, dried, filtered, and the solvent was evaporated. The resulting residue was purified by flash chromatography on silica gel (PE:EA = 5:1), yielding 1.18 g compound **1** (I.Y. = 56%). ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 8.65 (dd, *J* = 1.88 Hz, *J* = 4.88 Hz, 1H), 8.06 (dd, *J* = 1.88 Hz, *J* = 7.76 Hz, 1H) , 7.41 (dd, *J* = 4.88 Hz, *J* = 7.76 Hz, 1H), 3.38 (s, 3H), 3.18 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$, ppm): 156.06, 152.17 ,142.74, 122.77, 115.33, 109.50, 37.90, 37.35. LC-MS: calculated for $C_8H_{10}N_3O_2S$ $[M+H]^+$: 212.04, found 212.30.



(2) N-(3-cyanopyrazin-2-yl)-N-methylmethanesulfonamide.

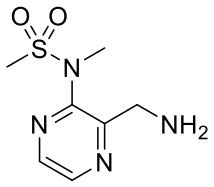
A solution of chloropyrazine-2-carbonitrile (10 mmol, 1.4 g) in acetonitrile at 25 ℃ was treated sequentially with Cs_2CO_3 (1.4 eq, 4.6 g) and N-methylmethanesulfonamide (1.2 eq, 1.32 g). The mixture was then heated to 80 ºC.

After about 20 h the mixture was cooled to 25 ºC and filtered. The solids were washed with EA 3 times, and the combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. The resultant residue was purified by column chromatography (PE:EA = 4:1) to provide 840 mg compound **2** (I.Y. = 40%). ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 8.64(d, *J* = 2.24 Hz, 1H), 8.62(d, *J* = 2.28 Hz, 1H) , 3.41(s, 3H), 3.22(s, 3H).



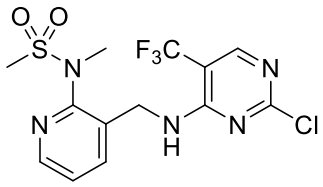
(3) *N*-(3-(aminomethyl)pyridin-2-yl)-N-methylmethanesulfonamide.

10% Pd/C (240 mg, 20% by weight) was added to a solution of compound **1** (5.59 mmol, 1.18 g) in EtOH/DMF under argon. The solution was purged and refilled with hydrogen 3 times. The solution was stirred at room temperature for 16 h. After filtration, the solvent was evaporated to give the crude residue. The resulting residue was purified by flash chromatography on silica gel (DCM:MeOH = 30:1), yielding 700 mg *N*-(3-(aminomethyl)pyridin-2-yl)-*N*-methylmethanesulfonamide (I.Y. = 60%). ^{1}H-NMR(400MHz, DMSO-*d*$_6$, ppm): 8.40(dd, *J* = 1.68 Hz, *J* = 4.64 Hz, 1H), 8.06(dd, *J* = 1.40 Hz, *J* = 7.64 Hz, 1H) , 7.45(dd, *J* = 4.72 Hz, *J* = 7.68 Hz, 1H), 3.85(s, 2H), 3.13(s, 3H), 3.12(s, 3H), 2.89(s, 2H). ^{13}C-NMR(100MHz, DMSO-*d*$_6$, ppm): 152.24, 146.88, 138.16, 124.03, 54.90, 40.67, 37.31, 36.06. LC-MS: calculated for $C_8H_{14}N_3O_2S$ $[M+H]^+$: 216.07, found 216.38.



(4) N-(3-(aminomethyl)pyrazin-2-yl)-N-methylmethanesulfonamide.

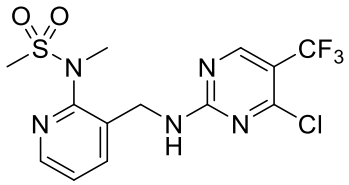
Synthetic method in accordance with the route of compound **3**. ^{1}H-NMR(400MHz, DMSO-*d*$_6$, ppm): 8.67(d, *J* = 2.40 Hz, 1H), 8.51(d, *J* = 2.32 Hz, 1H), 3.96(s, 2H), 3.19(s, 3H), 3.14(s, 3H), 1.87(s, 2H). LC-MS: calculated for $C_7H_{13}N_4O_2S$ $[M+H]^+$: 217.07, found 217.14.



(5)

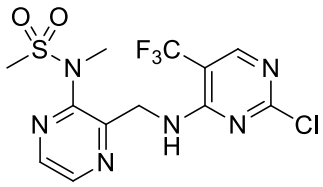
***N*-(3-(((2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)amino)methyl)pyridin-2-yl)-N-methylmethanesulfonamide**.

To a solution of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (1 eq, 81 mg) in methanol were added TEA (1 eq, 52 μL) and compound **3** (0.37 mmol, 80 mg) at 0 ºC. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was then concentrated and re-dissolved in EA. The solution was washed with $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (PE:EA = 7:1), yielding 66 mg compound **5** (I.Y. = 45%). ^{1}H-NMR(400MHz, DMSO-d_6, ppm): 8.54(t, J = 5.60 Hz, 1H), 8.45(m, 2H) , 7.76(dd, J = 1.48 Hz, J = 7.72 Hz, 1H), 7.44(dd, J = 4.68 Hz, J = 7.72 Hz, 1H), 4.73(d, J = 5.36 Hz, 2H), 3.26(s, 3H), 3.11(s, 3H). ^{13}C-NMR(100MHz, DMSO-d_6, ppm): 162.58, 158.36, 155.74, 155.69, 152.30, 147.69, 137.24, 133.33, 124.80, 124.15, 122.10, 105.53, 105.21, 104.88, 37.09, 35.77. LC-MS: calculated for $C_{13}H_{14}ClF_3N_5O_2S$ $[M+H]^+$: 396.04, found 396.41.



(6)

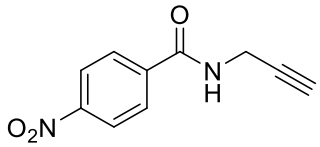
N-(3-(((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)methyl)pyridin-2-yl)-N-methylmethanesulfonamide.



(7)

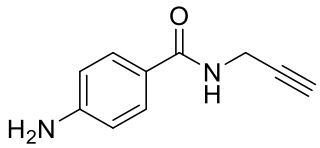
N-(3-(((2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)amino)methyl)pyrazin-2-yl)-N-methylmethanesulfonamide.

Synthetic method in accordance with the route of compound **5**. ^{1}H-NMR(400MHz, DMSO-d_6, ppm): 8.63(d, J = 2.44 Hz, 1H), 8.54(d, J = 2.36 Hz, 1H) , 8.43(s, 1H), 8.41(t, J = 5.36 Hz, 1H), 4.85(d, J = 5.44 Hz, 2H), 3.31(s, 3H), 3.14(s, 3H). ^{13}C-NMR(100MHz, DMSO-d_6, ppm): 162.45, 158.40, 155.71, 155.65, 152.18, 148.84, 143.78, 142.20, 124.87, 105.39, 105.05, 55.22, 41.96, 36.77, 35.97. LC-MS: calculated for $C_{12}H_{13}ClF_3N_6O_2S$ $[M+H]^+$: 397.04, found 397.08.



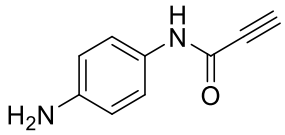
(8) 4-nitro-N-(prop-2-yn-1-yl)benzamide.

To a solution of 4-nitrobenzoic acid (5 mmol, 836 mg) in $SOCl_2$, the reaction was refluxed 2 h, and then the mixture was concentrated, got crude 4-nitrobenzoyl chloride. A mixture of 4-nitrobenzoyl chloride, prop-2-yn-1-amine (1.5 eq, 480μL) and potassium carbonate (3 eq, 2.1g) in THF was stirred under argon at room temperature for 18 h. The solvent was removed in vacua and the residue was partitioned between DCM and water. The aqueous phase was extracted with further DCM and the combined organic phase were dried (Na_2SO_4). The solvent was removed in vacua to furnish the desired compound. Yielding 950 mg compound **8** (I.Y. = 93%). ^{1}H-NMR(400MHz, DMSO-d_6, ppm): 9.29(t, J = 8.64 Hz, 1H), 8.33(d, J = 8.80 Hz, 2H), 8.09(d, J = 8.80 Hz, 2H), 4.10(dd, J = 2.44 Hz, J = 5.44 Hz, 2H), 3.17(t, J = 2.40 Hz, 1H). ^{13}C-NMR(100MHz, DMSO-d_6, ppm): 164.35, 149.15, 139.37, 128.81, 123.59, 80.79, 73.23, 28.74.



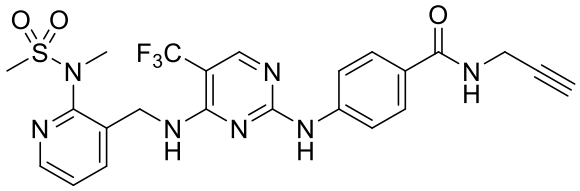
(9) 4-amino-N-(prop-2-yn-1-yl)benzamide.

To s suspension of compound **8** (4.65 mmol, 950mg) in a mixture of ethanol and water (4:1) was added iron powder (10 eq, 2.61 g) and NH_4Cl (2.5 eq, 630 mg). The mixture was refluxed for 2 h, cooled and filtered through celite. The filtrate was diluted with water and extracted with DCM 3 times. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (DCM:MeOH = 40:1), yielding 630 mg compound **9** (I.Y. = 77%). ^{1}H-NMR(400MHz, DMSO-*d*$_6$, ppm): 8.42(t, *J* = 5.68 Hz, 1H), 7.58(d, *J* = 8.60 Hz, 2H), 6.54(d, *J* = 8.64 Hz, 2H), 5.64(s, 2H), 3.99(dd, *J* = 2.48 Hz, *J* = 5.60 Hz, 2H), 3.06(t, *J* = 2.44 Hz, 1H). ^{13}C-NMR(100MHz, DMSO-*d*$_6$, ppm): 165.91, 151.82, 128.83, 120.46, 112.54, 81.97, 72.37, 28.21. LC-MS: calculated for $C_{10}H_{11}N_2O$ $[M+H]^+$: 175.08, found 175.24.



(10) ***N*****-(4-aminophenyl)propiolamide**.

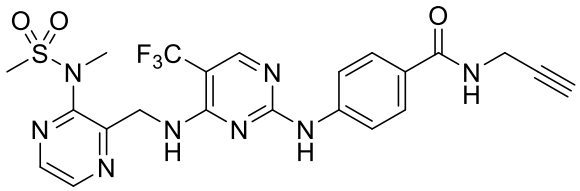
To a solution of benzene-1,4-diamine (1.5 eq, 1.62g) and propiolic acid (10 mmol, 620 μL) in DEE/DMF were added DMAP (0.01 eq, 12.2 mg) and DCC (1.0 eq, 2.06 g) in $CHCl_3$ at 0 ºC. The reaction was allowed to warm to room temperature and stirred 1 h. The reaction was then cooled to 0 ºC, filtered, re-dissolved in EA. The solution was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (DCM:MeOH = 30:1), yielding 600 mg compound **10** (I.Y. = 38%). ^{1}H-NMR(400MHz, DMSO-*d*$_6$, ppm): 10.35(s, 1H), 7.24(d, *J* = 8.60 Hz, 2H), 6.50(d, *J* = 8.64 Hz, 2H), 4.97 (s, 2H), 4.25(s, 1H). LC-MS: calculated for $C_9H_9N_2O$ $[M+H]^+$: 161.06, found 161.28.



(11)

4-((4-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoro methyl)pyrimidin-2-yl)amino)-N-(prop-2-yn-1-yl)benzamide.

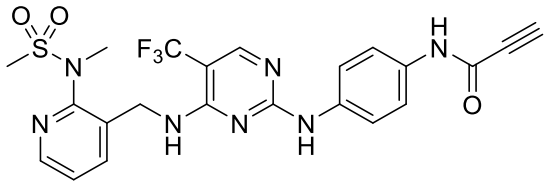
A mixture of compound **5** (0.063 mmol, 25 mg), compound **9** (1.0 eq, 11 mg) and AcOH (5 drops) in *t*-amyl alcohol were refluxed 4 h. After cooling, the reaction mixture was extracted with DCM 3 times. The combined organic phases were washed twice with in each water, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (PE:EA = 1:1), yielding 20 mg compound **11** (I.Y. = 60%). ^{1}H-NMR(400MHz, DMSO-d_6, ppm): 9.82(s, 1H), 8.69(t, J = 5.44 Hz, 1H), 8.45(dd, J = 1.56 Hz, J = 4.64 Hz, 1H), 8.31(s, 1H), 7.69-7.55(m, 6H), 7.53(dd, J = 4.72 Hz, J = 7.72 Hz, 1H), 4.85(d, J = 5.56 Hz, 2H), 4.02(dd, J = 2.32 Hz, J = 5.40 Hz, 2H), 3.16 (m, 6H), 3.09(t, J = 2.40 Hz, 1H). LC-MS: calculated for $C_{23}H_{23}F_3N_7O_3S$ $[M+H]^+$: 534.15, found 534.55.



(12)

4-((4-(((3-(N-methylmethylsulfonamido)pyrazin-2-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-N-(prop-2-yn-1-yl)benzamide.

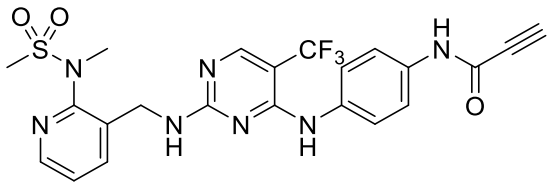
Synthetic method in accordance with the route of compound **11**. ^{1}H-NMR(400MHz, DMSO-d_6, ppm): 9.86(s, 1H), 8.70(m, 2H), 8.58(d, J = 2.40 Hz, 1H), 8.31(s, 1H), 7.70(d, J = 8.84 Hz, 2H), 7.65(d, J = 5.56 Hz, 2H), 7.42(t, J = 4.96 Hz, 1H), 5.01(d, J = 5.00 Hz, 2H), 4.03(dd, J = 2.40 Hz, J = 5.44 Hz, 2H), 3.23 (s, 3H), 3.19(s, 3H), 3.09(t, J = 2.44 Hz, 1H). LC-MS: calculated for $C_{22}H_{22}F_3N_8O_3S$ $[M+H]^+$: 535.14, found 535.31.



(13)

***N*-(4-((4-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)propiolamide**.

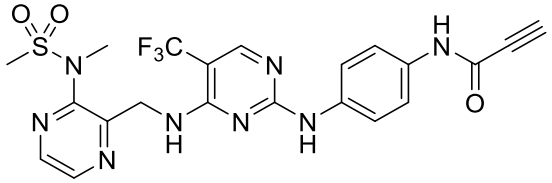
Synthetic method in accordance with the route of compound **11**. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 8.41(d, *J* = 3.44 Hz, 1H), 8.12(s, 2H), 7.98(d, *J* = 14.80 Hz, 1H), 7.75(d, *J* = 7.40 Hz, 1H), 7.49-7.42(m, 4H), 7.27-7.23(m, 1H), 6.13(s, 1H), 4.93(d, *J* = 4.80 Hz, 2H), 3.27 (s, 3H), 3.07(s, 3H), 2.92(s, 1H). LC-MS: calculated for $C_{22}H_{21}F_3N_7O_3S$ $[M+H]^+$: 520.13, found 520.59.



(14)

N-(4-((2-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)propiolamide.

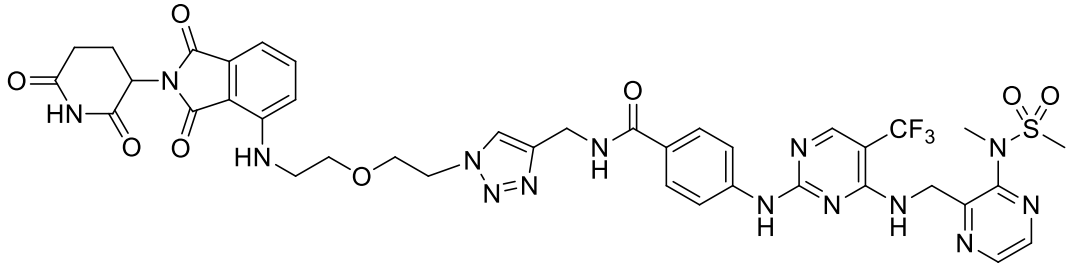
Synthetic method in accordance with the route of compound **11**. LC-MS: calculated for $C_{22}H_{21}F_3N_7O_3S$ $[M+H]^+$: 520.13, found 520.68.



(15)

N-(4-((4-(((3-(N-methylmethylsulfonamido)pyrazin-2-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)propiolamide.

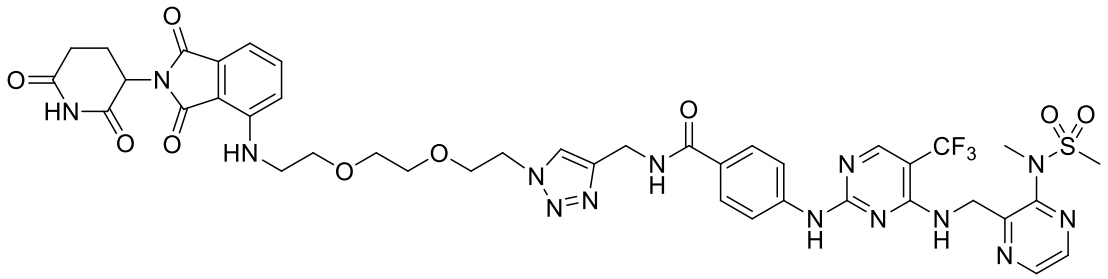
Synthetic method in accordance with the route of compound **11**. ^{1}H-NMR(400MHz, DMSO-d_6, ppm): 10.70(s, 1H), 9.57(s, 1H), 8.66(d, *J* = 2.44 Hz, 1H), 8.55(d, *J* = 2.04 Hz, 1H), 8.23(s, 1H), 7.41(m, 5H), 4.97(d, *J* = 4.84 Hz, 2H), 4.34(s, 1H), 3.20(s, 3H), 3.18(s, 3H). LC-MS: calculated for $C_{21}H_{20}F_3N_8O_3S$ $[M+H]^+$: 521.13, found 521.63.



16 (FC-1)

N-((1-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-4-((4-(((3-(N-methylmethylsulfonamido)pyrazin-2-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzamide.

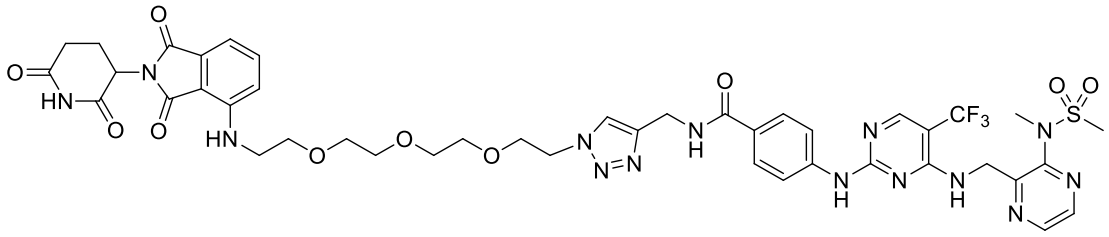
Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 10.60(s, 1H), 8.83(s, 1H), 8.58(d, *J* = 1.84 Hz, 1H), 8.43(s, 1H), 8.16(s, 1H), 7.99(s, 1H), 7.84(d, *J* = 8.32 Hz, 2H), 7.71(d, *J* = 8.36 Hz, 2H), 7.50(t, *J* = 7.72 Hz, 1H), 7.32(s, 1H), 7.10(d, *J* = 7.12 Hz, 1H), 6.86(m, 2H), 6.43(s, 1H), 5.07(m, 3H), 4.81-4.69(m, 2H), 4.56(m, 2H), 3.87(m, 2H), 3.66(t, *J* = 4.64 Hz, 2H), 3.41(m, 2H), 3.21(s, 3H), 3.09(s, 3H), 2.85(m, 3H), 2.13(m, 1H). LC-MS: calculated for $C_{39}H_{40}F_3N_{14}O_8S$ $[M+H]^+$: 921.27, found 921.79.



17 (FC-2)

N-((1-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-4-((4-(((3-(N-methylmethylsulfonamido)pyrazin-2-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzamide.

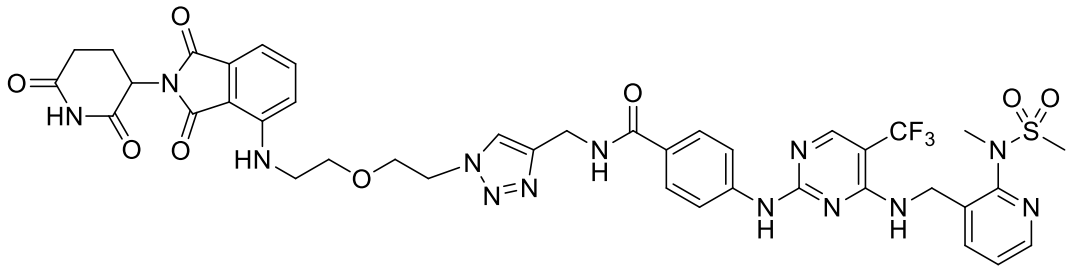
Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 10.48(s, 1H), 8.59(d, *J* = 1.88 Hz, 1H), 8.44(s, 2H), 8.22(s, 1H), 7.84(m, 2H), 7.70(d, *J* = 8.36 Hz, 2H), 7.45(t, *J* = 7.76 Hz, 1H), 7.29(s, 1H), 7.10-6.79(m, 4H), 6.34(s, 1H), 5.07(d, *J* = 3.28 Hz, 2H), 4.99(m, 1H), 4.74-4.62(m, 2H), 4.50(t, *J* = 4.64 Hz, 2H), 3.85(t, *J* = 4.72 Hz, 2H), 3.63-3.56(m, 6H), 3.38(t, *J* = 5.28 Hz, 2H), 3.23(s, 3H), 3.09(s, 3H), 2.85-2.74(m, 3H), 2.11(m, 1H). LC-MS: calculated for $C_{41}H_{44}F_3N_{14}O_9S$ $[M+H]^+$: 965.30, found 965.87.



18 (FC-3)

N-((1-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-4-((4-(((3-(N-methylmethylsulfonamido)pyrazin-2-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzamide.

Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 9.96(s, 1H), 8.91(s, 1H), 8.60(d, *J* = 2.36 Hz, 1H), 8.45(d, *J* = 2.28 Hz, 1H), 8.20(s, 1H), 7.88(d, *J* = 8.60 Hz, 2H), 7.75(d, *J* = 8.60 Hz, 2H), 7.48(t, *J* = 7.64 Hz, 1H), 7.35(s, 1H), 7.14-6.88(m, 4H), 6.44(t, *J* = 5.52 Hz, 1H), 5.10(d, *J* = 3.84 Hz, 2H), 4.96(m, 1H), 4.73(m, 2H), 4.51(t, *J* = 4.76 Hz, 2H), 3.85(t, *J* = 4.92 Hz, 2H), 3.68(t, *J* = 5.36 Hz, 2H), 3.64-3.55(m, 8H), 3.48(m, 2H), 3.23(s, 3H), 3.10(s, 3H), 2.88-2.74(m, 3H), 2.13(m, 1H). LC-MS: calculated for $C_{43}H_{48}F_3N_{14}O_{10}S$ $[M+H]^+$: 1009.33, found 1009.86.

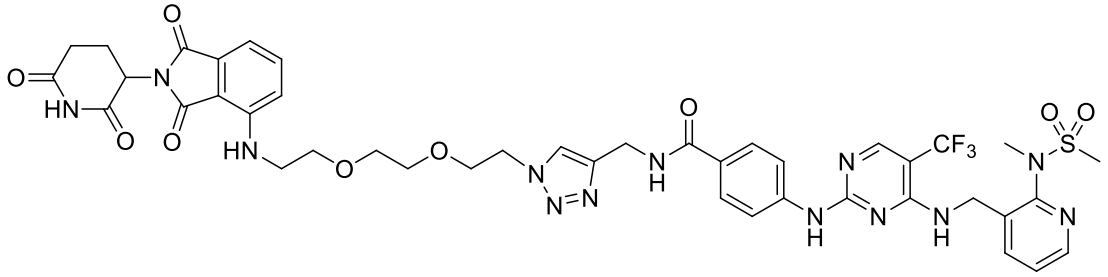


19 (FC-4)

N-((1-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-4-((4-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzamide.

Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 11.00(s, 1H), 8.43(d, *J* = 4.32 Hz, 1H), 8.29(s, 1H), 8.19(s, 1H), 7.95(s, 1H), 7.80(d, *J* = 7.60 Hz, 1H), 7.64(d, *J* = 8.40 Hz, 2H), 7.51-7.47(m, 3H), 7.26(m, 1H), 7.11(d, *J* = 7.08 Hz, 1H), 7.03(s, 1H), 6.86(d, *J* = 8.52 Hz, 1H), 6.45(t, *J* = 4.96 Hz, 1H), 6.13(s, 1H), 5.10(m, 1H), 4.95(d, *J* = 4.80 Hz, 2H), 4.81-4.51(m, 4H), 3.86(t, *J* = 4.40 Hz, 2H), 3.69(t, *J* =

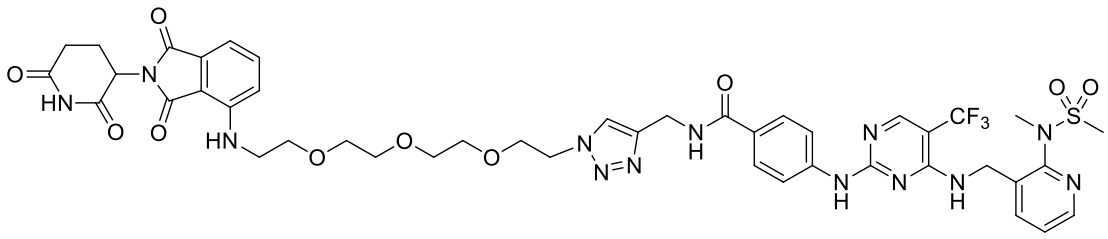
4.80 Hz, 2H), 3.43(d, *J* = 4.80 Hz, 2H), 3.26(s, 3H), 3.07(s, 3H), 2.87(m, 3H), 2.13(m, 1H). LC-MS: calculated for $C_{40}H_{41}F_3N_{13}O_8S$ $[M+H]^+$: 920.28, found 920.94.



20 (FC-5)

N-((1-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-4-((4-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzamide.

Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 10.48(s, 1H), 8.41(d, *J* = 4.16 Hz, 1H), 8.29(s, 1H), 8.21(s, 1H), 7.79-7.52(m, 6H), 7.44(t, *J* = 7.52 Hz, 1H), 7.26(m, 1H), 7.12(s, 1H), 7.05(d, *J* = 7.04 Hz, 1H), 6.84(d, *J* = 8.48 Hz, 1H), 6.38(s, 1H), 6.11(s, 1H), 4.95(m, 3H), 4.64(m, 2H), 4.49(m, 2H), 3.85(t, *J* = 4.60 Hz, 2H), 3.60(m, 6H), 3.36(t, *J* = 4.64 Hz, 2H), 3.25(s, 3H), 3.06(s, 3H), 2.84-2.73(m, 3H), 2.10(m, 1H). LC-MS: calculated for $C_{42}H_{45}F_3N_{13}O_9S$ $[M+H]^+$: 964.31, found 964.73.

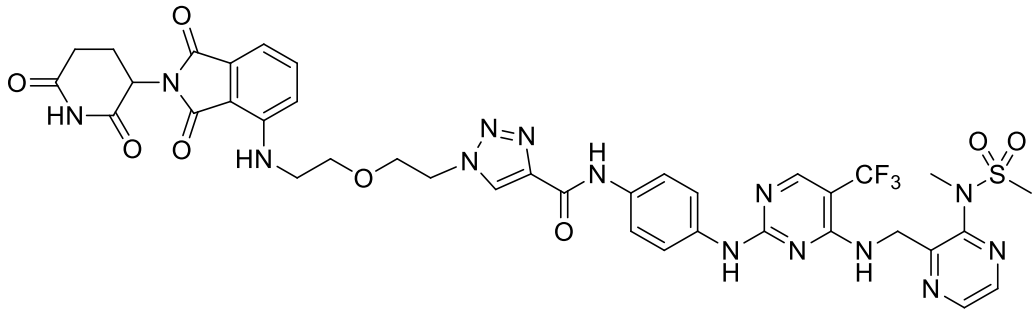


21 (FC-6)

N-((1-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)-4-((4-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)benzamide.

Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 10.65(s, 1H), 8.41(dd, *J* = 1.32 Hz, *J* = 4.60 Hz, 1H), 8.35(s, 1H), 8.21(s, 1H), 7.79-7.76(m, 2H), 7.67(d, *J* = 8.64 Hz, 2H), 7.56(d, *J* = 8.64 Hz, 2H), 7.45(t, *J* = 7.48 Hz, 1H), 7.26(m, 1H), 7.15(m,

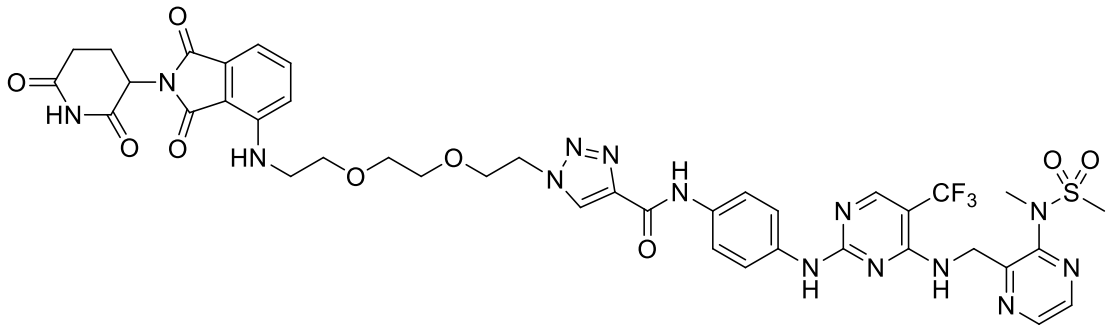
1H), 7.06(d, *J* = 7.12 Hz, 1H), 6.87(d, *J* = 8.56 Hz, 1H), 6.42(t, *J* = 5.48 Hz, 1H), 6.13(s,1H), 4.95(m, 3H), 4.66(d, *J* = 5.36 Hz, 2H), 4.48(t, *J* = 4.68 Hz, 2H), 3.83(t, *J* = 4.88 Hz, 2H), 3.65(t, *J* = 5.24 Hz, 2H), 3.57-3.53(m, 8H), 3.41(m, 2H), 3.24(s, 3H), 3.06(s, 3H), 2.94-2.72(m, 3H), 2.10(m, 1H). LC-MS: calculated for $C_{44}H_{49}F_3N_{13}O_{10}S$ $[M+H]^+$: 1008.33, found 1008.91.



22 (FC-7)

1-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)-N-(4-((4-(((3-(N-methylmethylsulfonamido)pyrazin-2-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide.

Synthesized *via* procedure A. ^{1}H-NMR(400MHz, DMSO-d_6, ppm): 11.09(s, 1H), 10.29(s, 1H), 9.57(s, 1H), 8.69(d, *J* = 2.32 Hz, 1H), 8.62(s, 1H), 8.57(d, *J* = 2.16 Hz, 1H), 8.25(s, 1H), 7.60-7.44(m, 5H), 7.37(s, 1H), 7.11(d, *J* = 8.60 Hz, 1H), 7.02(d, *J* = 7.64 Hz, 1H), 6.62(t, *J* = 5.60 Hz, 1H), 5.04(dd, *J* = 5.24 Hz, *J* = 12.48 Hz, 1H), 4.99(d, *J* = 4.88 Hz, 2H), 4.65(t, *J* = 4.64 Hz, 2H), 3.92(t, *J* = 4.60 Hz, 2H), 3.64(t, *J* = 5.32 Hz, 2H), 3.45(m, 2H), 3.23(s, 3H), 3.19(s, 3H), 2.89-2.54(m, 3H), 1.99-1.97(m, 1H). LC-MS: calculated for $C_{38}H_{38}F_3N_{14}O_8S$ $[M+H]^+$: 907.26, found 907.92.

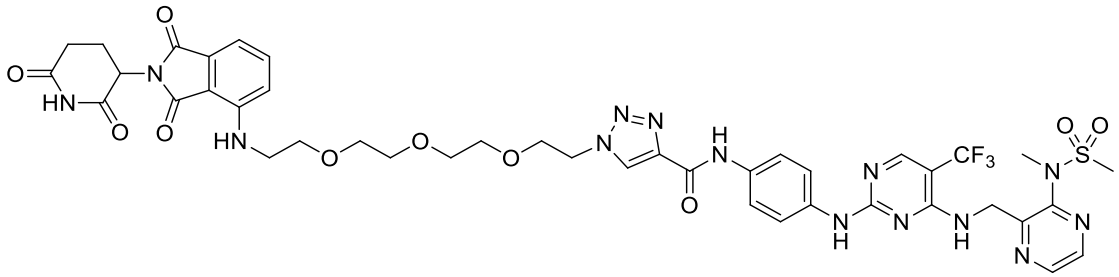


23 (FC-8)

1-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)-N-(4-((4-(((3-(N-methylmethylsulfonamido)pyrazin-2-yl)methyl)amino

)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide.

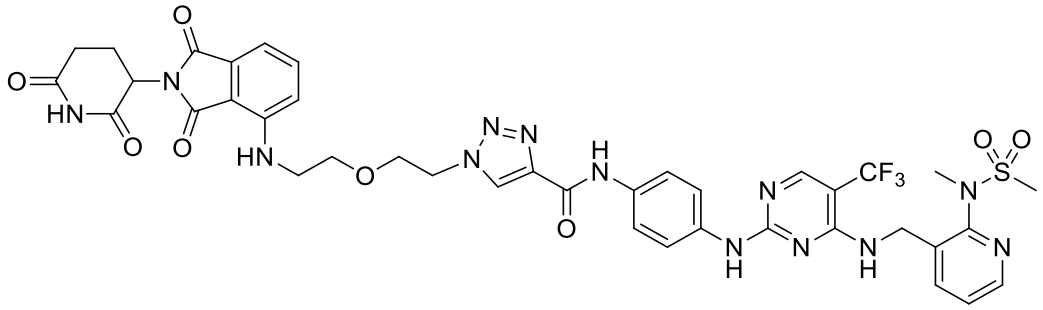
Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 9.85(s, 1H), 8.97(s, 1H), 8.58-8.43(m, 4H), 8.17(s, 1H), 7.65(m, 4H), 7.45(t, *J* = 7.64 Hz, 1H), 7.07(d, *J* = 7.00 Hz, 1H), 6.90(d, *J* = 8.52 Hz, 1H), 6.80(s, 1H), 6.51(s, 1H), 5.10-4.94(m, 3H), 4.59(m, 2H), 3.91(m, 2H), 3.70(t, *J* = 4.64 Hz, 2H), 3.64(m, 4H), 3.47(t, *J* = 4,76 Hz, 2H), 3.28(s, 3H), 3.08(s, 3H), 2.88-2.72(m, 3H), 2.12(m, 1H). LC-MS: calculated for $C_{40}H_{42}F_3N_{14}O_9S$ $[M+H]^+$: 951.29, found 951.91.



24 (FC-9)

1-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)-N-(4-((4-(((3-(N-methylmethylsulfonamido)pyrazin-2-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide.

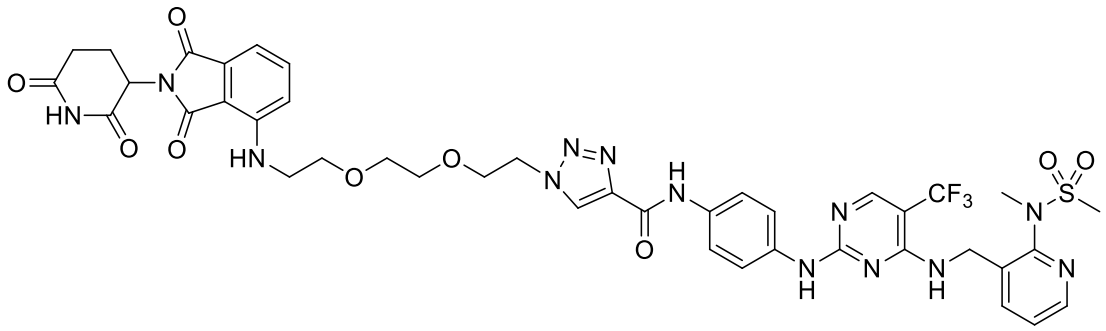
Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 9.76(s, 1H), 8.78(s, 1H), 8.58-8.43(m, 5H), 7.69(m, 4H), 7.46(s, 1H), 7.08(d, *J* = 6.20 Hz, 1H), 6.91(d, *J* = 6.84 Hz,, 2H), 6.43(s, 1H), 5.09-4.96(m, 3H), 4.60(m, 2H), 3.90(m, 2H), 3.71-3.63(m, 10H), 3.48(m, 2H), 3.29(s, 3H), 3.08(s, 3H), 2.89-2.76(m, 3H), 2.13(m, 1H). LC-MS: calculated for $C_{42}H_{46}F_3N_{14}O_{10}S$ $[M+H]^+$: 995.31, found 995.89.



25 (FC-10)

1-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)-*N*-(4-((4-(((2-(*N*-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1*H*-1,2,3-triazole-4-carboxamide.

Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 8.88(s, 1H), 8.43(dd, *J* = 1.80 Hz, *J* = 4.68 Hz, 1H), 8.27(s, 1H), 8.18(s, 1H), 7.81(d, *J* = 7.84 Hz, 1H), 7.59-7.46(m, 6H), 7.25(m, 1H), 7.09(d, *J* = 7.04 Hz, 2H), 6.86(d, *J* = 8.52 Hz, 1H), 6.46(t, *J* = 5.28 Hz, 1H), 6.04(s, 1H), 4.95-4.88(m, 3H), 4.65(q, *J* = 4.52 Hz, 2H), 3.97(t, *J* = 4.68 Hz, 2H), 3.71(t, *J* = 5.12 Hz, 2H), 3.46(q, *J* = 5.48 Hz, 2H), 3.28(s, 3H), 3.07(s, 3H), 2.76-2.60(m, 3H), 2.10-2.00(m, 1H). LC-MS: calculated for $C_{39}H_{39}F_3N_{13}O_8S$ $[M+H]^+$: 906.26, found 906.88.

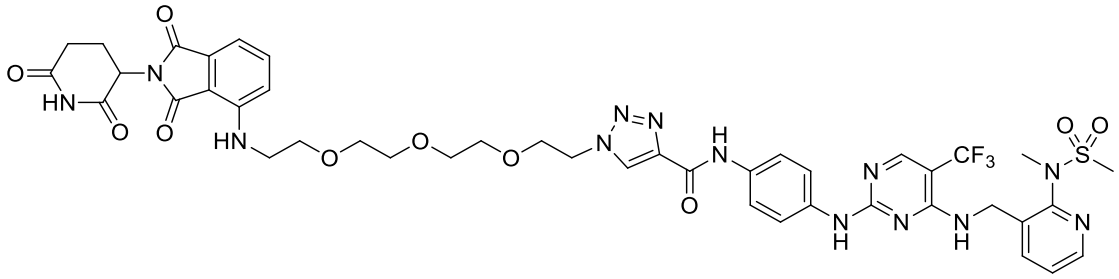


26 (FC-11)

1-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)-*N*-(4-((4-(((2-(*N*-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1*H*-1,2,3-triazole-4-carboxamide.

Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 10.05(s, 1H), 8.85(s, 1H), 8.40(d, *J* = 4.12 Hz, 2H), 8.17(s, 1H), 7.87(s, 1H), 7.79(d, *J* = 7.16 Hz, 1H), 7.52-7.41(m, 5H), 7.26-7.23(m, 1H), 7.07(d, *J* = 7.08 Hz, 1H), 6.89(d, *J* = 8.56 Hz, 1H), 6.52(t, *J* = 5.12 Hz, 1H), 6.08(s, 1H), 4.96-4.93(m, 3H), 4.60(q, *J* = 4.52 Hz, 2H), 3.92(t, *J* = 4.92 Hz, 2H), 3.72(t, *J* = 5.08 Hz, 2H), 3.64(s, 4H), 3.45(dd, *J* = 5.56 Hz, *J* = 10.48 Hz, 2H), 3.27(s, 3H), 3.06(s, 3H), 2.88-2.73(m, 3H), 2.13-2.10(m, 1H). ^{13}C-NMR(100MHz, $CDCl_3$, ppm): 172.91, 169.72, 169.45, 167.74, 160.60, 158.92, 157.85, 154.48, 152.77, 148.21, 146.73, 143.29, 139.19, 136.05, 135.51, 133.88, 132.93, 132.52, 127.18, 126.13, 124.37, 123.45, 120.73, 120.38, 116.83, 111.62,

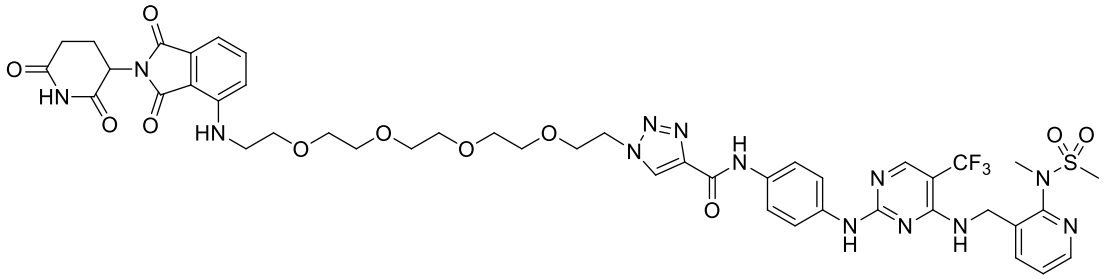
110.30, 70.59, 70.53, 69.27, 50.71, 48.95, 42.30, 40.59, 37.64, 35.51, 31.95, 31.53, 29.72, 29.39, 22.89, 22.72, 14.16. LC-MS: calculated for $C_{41}H_{43}F_3N_{13}O_9S$ $[M+H]^+$: 950.29, found 950.77.



27 (FC-12)

1-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy) ethoxy)ethoxy)ethyl)-*N*-(4-((4-(((2-(*N*-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1*H*-1,2,3-triazole-4-carboxamide.

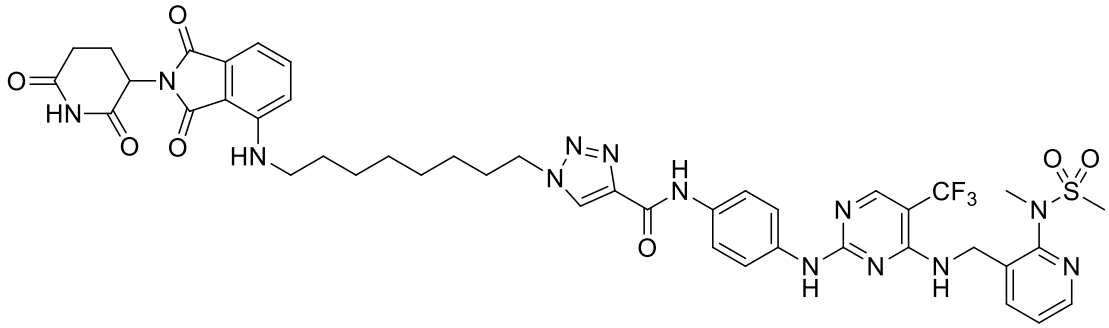
Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 10.43(s, 1H), 8.90(s, 1H), 8.41(m, 2H), 8.19(s, 2H), 7.77(d, *J* = 7.16 Hz, 1H), 7.56(d, *J* = 8.80 Hz, 2H), 7.48-7.42(m, 3H), 7.26-7.22(m, 1H), 7.08(d, *J* = 7.04 Hz, 1H), 6.90(d, *J* = 8.56 Hz, 1H), 6.43(t, *J* = 5.52 Hz, 1H), 6.10(s, 1H), 4.97-4.94(m, 3H), 4.59(t, *J* = 4.48 Hz, 2H), 3.89(t, *J* = 4.68 Hz, 2H), 3.72-3.68(m, 4H), 3.63-3.61(m, 6H), 3.47(q, *J* = 5.60 Hz, 2H), 3.27(s, 3H), 3.06(s, 3H), 2.89-2.75(m, 3H), 2.12-2.10(m, 1H). LC-MS: calculated for $C_{43}H_{47}F_3N_{13}O_{10}S$ $[M+H]^+$: 994.32, found 994.85.



28 (FC-13)

1-(14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxatetradecyl)-*N*-(4-((4-(((2-(*N*-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1*H*-1,2,3-triazole-4-carboxamide.

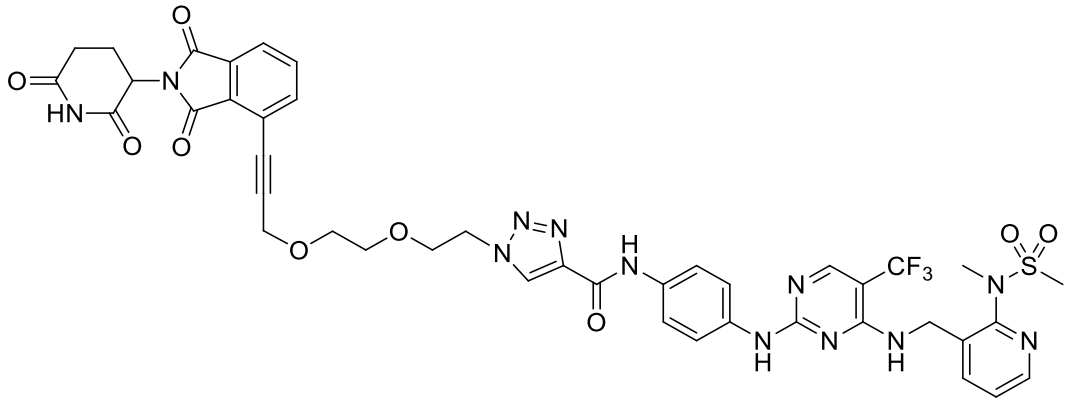
Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 10.25(s, 1H), 8.92(s, 1H), 8.40(d, *J* = 8.80 Hz, 1H), 8.35(s, 1H), 8.19(s, 1H), 8.09(s, 1H), 7.77(d, *J* = 7.74 Hz, 1H), 7.58(d, *J* = 8.72 Hz, 2H), 7.48-7.43(m, 3H), 7.26-7.22(m, 1H), 7.08(d, *J* = 7.08 Hz, 1H), 6.90(d, *J* = 8.52 Hz, 1H), 6.45(t, *J* = 5.44 Hz, 1H), 6.09(s, 1H), 4.96-4.93(m, 3H), 4.59(t, *J* = 4.56 Hz, 2H), 3.88(t, *J* = 4.72 Hz, 2H), 3.68-3.59(m, 14H), 3.44(q, *J* = 5.20 Hz, 2H), 3.27(s, 3H), 3.05(s, 3H), 2.88-2.72(m, 3H), 2.13-2.03(m, 1H). LC-MS: calculated for $C_{45}H_{51}F_3N_{13}O_{11}S$ $[M+H]^+$: 1038.34, found 1038.84.



29 (FC-14)

1-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)-N-(4-((4-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide.

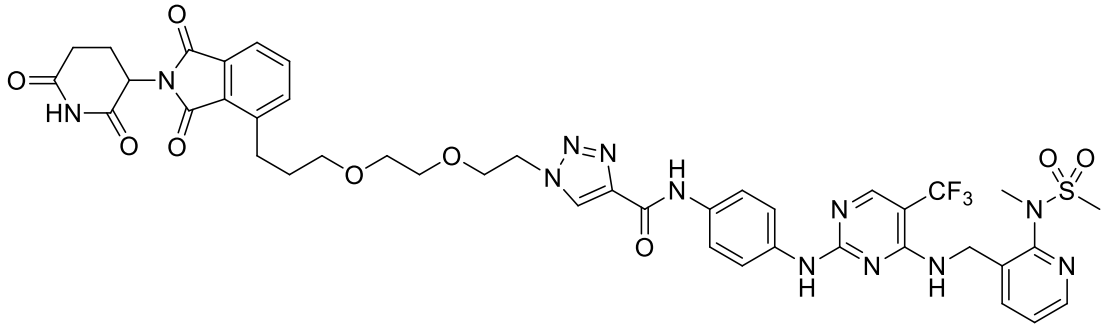
Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 10.45(s, 1H), 8.94(s, 1H), 8.39(d, *J* = 3.56 Hz, 1H), 8.18(m, 3H), 7.76(d, *J* = 7.40 Hz, 1H), 7.58(d, *J* = 8.72 Hz, 2H), 7.50-7.41(m, 3H), 7.24(dd, *J* = 4.80 Hz, *J* = 7.60 Hz, 1H), 7.06(d, *J* = 7.08 Hz, 1H), 6.86(d, *J* = 8.56 Hz, 1H), 6.22(t, *J* = 5.36 Hz, 1H), 6.12(s, 1H), 4.96-4.92(m, 3H), 4.40(t, *J* = 6.96 Hz, 2H), 3.25(s, 3H), 3.22(m, 2H), 3.05(s, 3H), 2.88-2.73(m, 3H), 2.13-2.11(m, 1H), 1.92(m, 2H), 1.64(t, *J* = 6.60 Hz, 2H), 1.32-1.22(m, 8H). LC-MS: calculated for $C_{43}H_{47}F_3N_{13}O_7S$ $[M+H]^+$: 946.34, found 946.87.



30 (FC-15)

1-(2-(2-((3-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)prop-2-yn-1-yl)oxy)ethoxy)ethyl)-*N*-(4-((4-(((2-(*N*-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1*H*-1,2,3-triazole-4-carboxamide.

Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 10.16(s, 1H), 8.88(s, 1H), 8.40(d, *J* = 3.16 Hz, 1H), 8.36(s, 1H), 8.18(s, 1H), 8.01(s, 1H), 7.79-7.63(m, 4H), 7.55(d, *J* = 8.24 Hz, 2H), 7.47(d, *J* = 8.12 Hz, 2H), 7.25-7.22(m, 1H), 6.09(s, 1H), 5.05(d, *J* = 8.12 Hz, 1H), 4.93(m, 1H), 4.60(m, 2H), 4.49(m, 2H), 3.92(m, 2H), 3.83(m, 2H), 3.70(m, 2H), 3.26(s, 3H), 3.05(s, 3H), 2.89-2.77(m, 3H), 2.13-2.05(m, 1H). LC-MS: calculated for $C_{42}H_{40}F_3N_{12}O_9S$ $[M+H]^+$: 945.26, found 945.92.

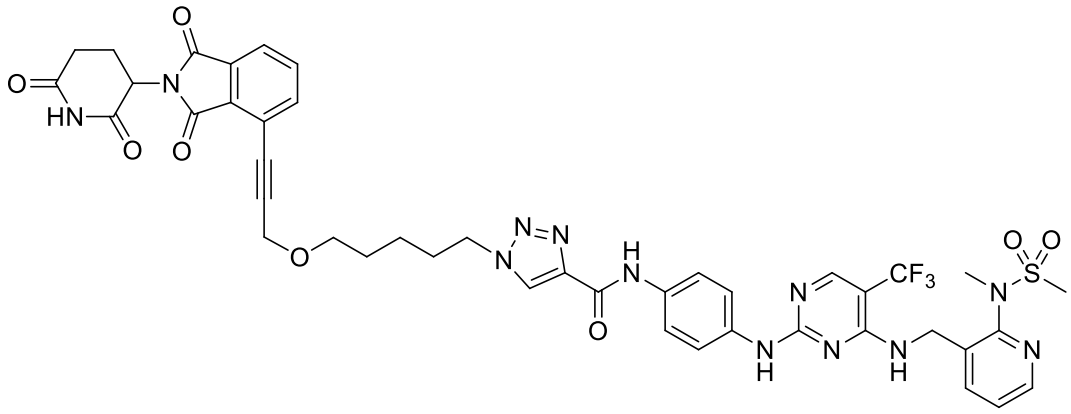


31 (FC-16)

1-(2-(2-(3-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)propoxy)ethoxy)ethyl)-*N*-(4-((4-(((2-(*N*-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1*H*-1,2,3-triazole-4-carboxamide.

Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 10.19(s, 1H), 8.91(s, 1H), 8.40(dd, *J* = 1.76 Hz, *J* = 4.68 Hz, 1H), 8.36(s, 1H), 8.19(s, 1H), 8.00(s, 1H), 7.77(dd, *J* = 1.24 Hz, *J* = 7.64 Hz, 1H), 7.67(d, *J* = 7.08 Hz, 1H), 7.59-7.51(m, 4H),

7.47(d, *J* = 8.92 Hz, 2H), 7.25(dd, *J* = 4.76 Hz, *J* = 7.68 Hz, 1H), 6.10(s, 1H), 5.01(dd, *J* = 5.28 Hz, *J* = 12.00 Hz, 1H), 4.93(d, *J* = 4.96 Hz, 2H), 4.61(t, *J* = 4.68 Hz, 2H), 3.91(t, *J* = 4.88 Hz, 2H), 3.62-3.53(m, 4H), 3.51(t, *J* = 6.20 Hz, 2H), 3.26(s, 3H), 3.14(t, *J* = 7.60 Hz, 2H), 3.05(s, 3H), 2.89-2.75(m, 3H), 2.13-2.10(m, 1H), 1.95-1.92(m, 2H). LC-MS: calculated for $C_{42}H_{44}F_3N_{12}O_9S$ $[M+H]^+$: 949.29, found 949.82.

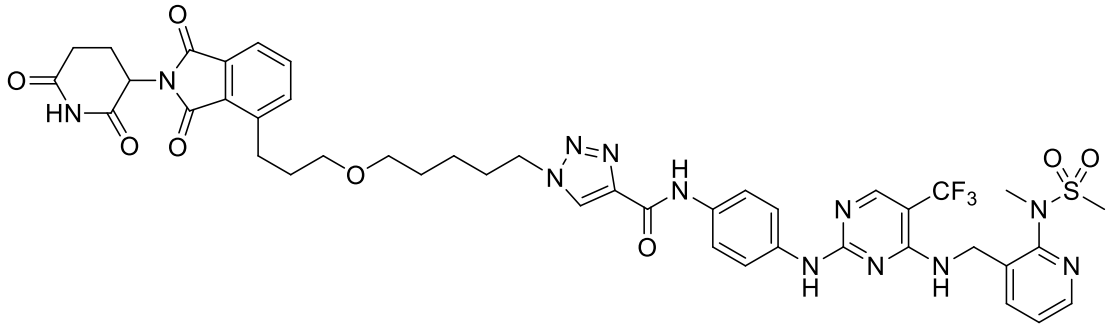


32 (FC-17)

1-(5-((3-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)prop-2-yn-1-yl)oxy) pentyl)-N-(4-((4-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5 -(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide

.

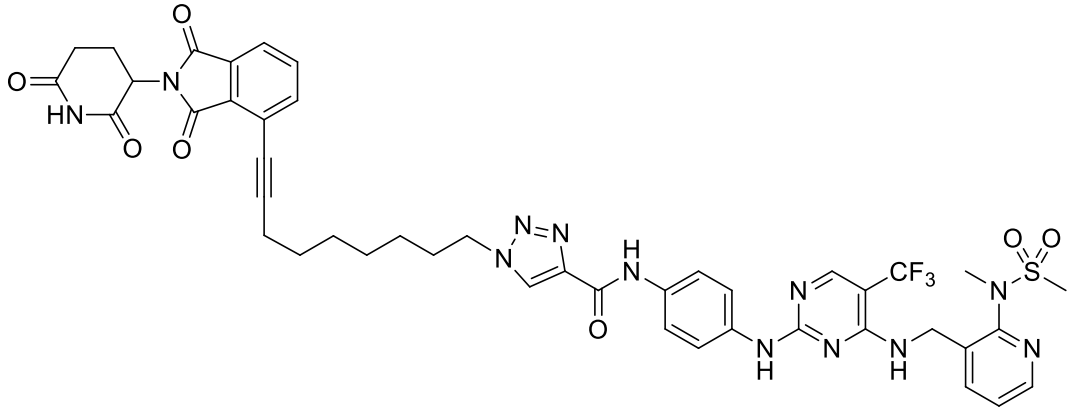
Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 10.40(s, 1H), 8.91(s, 1H), 8.41(d, *J* = 3.84 Hz, 1H), 8.15(m, 3H), 7.82-7.68(m, 4H), 7.57(d, *J* = 8.36 Hz, 2H), 7.46(d, *J* = 8.56 Hz, 2H), 7.26(m, 1H), 6.11(s, 1H), 5.11(dd, *J* = 4.88 Hz, *J* = 10.76 Hz, 1H), 4.92(s,2H), 4.43(m,3H), 3.70(t, *J* = 6.12 Hz, 2H), 3.26(s, 3H), 3.06(s, 3H), 2.92-2.81(m, 3H), 2.16(m, 1H), 2.03-1.97(m, 3H), 1.72-1.67(m, 2H), 1.50-1.45(m, 2H). LC-MS: calculated for $C_{43}H_{42}F_3N_{12}O_8S$ $[M+H]^+$: 943.28, found 943.83.



33 (FC-18)

1-(5-(3-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)propoxy)pentyl)-N-(4-((4-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide.

Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 9.31(s, 1H), 8.94(s, 1H), 8.42(dd, *J* = 1.76 Hz, *J* = 4.68 Hz, 1H), 8.30(s, 1H), 8.19(s, 1H), 8.15(s, 1H), 7.77(dd, *J* = 1.40 Hz, *J* = 7.68 Hz, 1H), 7.71(d, *J* = 6.60 Hz, 1H), 7.63-7.48(m, 6H), 7.23(m, 1H), 6.16(s, 1H), 4.99(m, 3H), 4.45(t, *J* = 7.04 Hz, 2H), 3.47(t, *J* = 6.16 Hz, 2H), 3.41(t, *J* = 6.16 Hz, 2H), 3.27(s, 3H), 3.16(t, *J* = 6.56 Hz, 2H), 3.06(s, 3H), 2.90-2.77(m, 3H), 2.36-1.57(m, 9H). LC-MS: calculated for $C_{43}H_{46}F_3N_{12}O_8S$ $[M+H]^+$: 947.32, found 947.92.

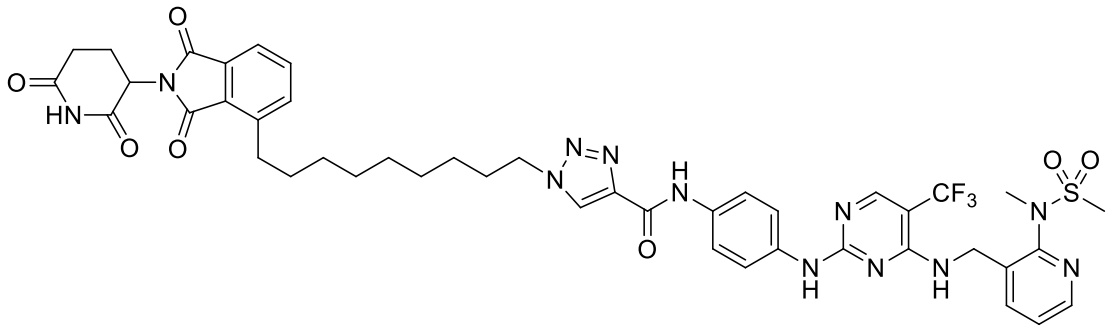


34 (FC-19)

1-(9-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)non-8-yn-1-yl)-N-(4-((4-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide.

Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 10.04(s, 1H), 8.92(s, 1H), 8.41(s, 1H), 8.15-7.26(m, 12H), 6.09(s, 1H), 5.06-4.93(m, 3H), 4.40(m,2H), 4.12(d, *J* = 6.56 Hz, 1H), 3.26(s, 3H), 3.06(s, 3H), 2.87-2.84(m, 3H), 2.51(s, 2H),

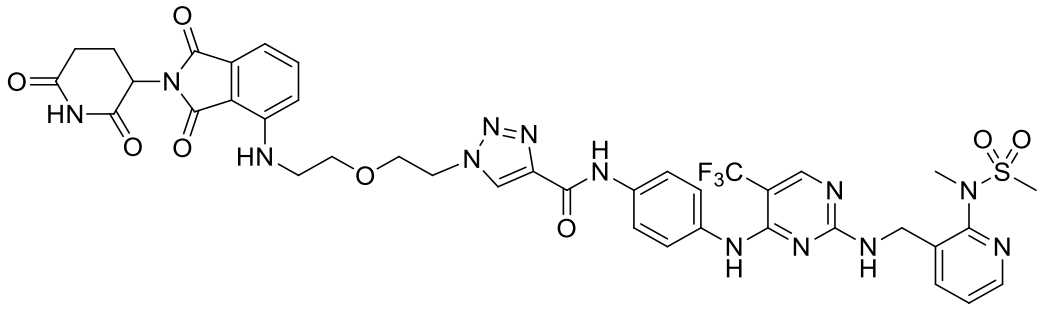
2.14-1.25(m, 10H). LC-MS: calculated for $C_{44}H_{44}F_3N_{12}O_7S$ $[M+H]^+$: 941.31, found 941.84.



35 (FC-20)

1-(9-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)nonyl)-N-(4-((4-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide.

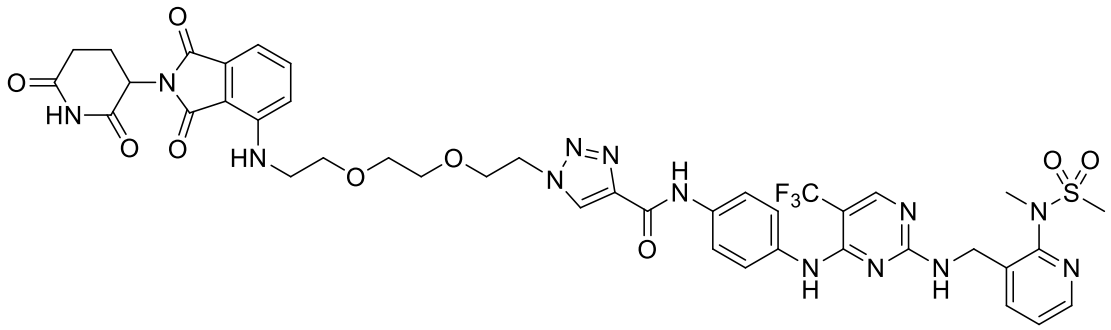
Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 9.45(s, 1H), 8.95(s, 1H), 8.42(dd, *J* = 1.76 Hz, *J* = 4.68 Hz, 1H), 8.15(m, 3H), 7.77(dd, *J* = 1.32 Hz, *J* = 7.68 Hz, 1H), 7.72(d, *J* = 7.24 Hz, 1H), 7.64(m, 3H), 7.51(m, 3H), 7.25(m, 1H), 6.15(s, 1H), 5.01(dd, *J* = 5.28 Hz, *J* = 12.20 Hz, 1H), 4.95(d, *J* = 4.60 Hz, 2H), 4.42(t, *J* = 7.08 Hz, 2H), 3.27(s, 3H), 3.07(m, 5H), 2.92-2.74(m, 3H), 2.35-1.60(m, 15H). LC-MS: calculated for $C_{44}H_{48}F_3N_{12}O_7S$ $[M+H]^+$: 945.34, found 945.92.



36 (FC-21)

1-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)-N-(4-((2-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide.

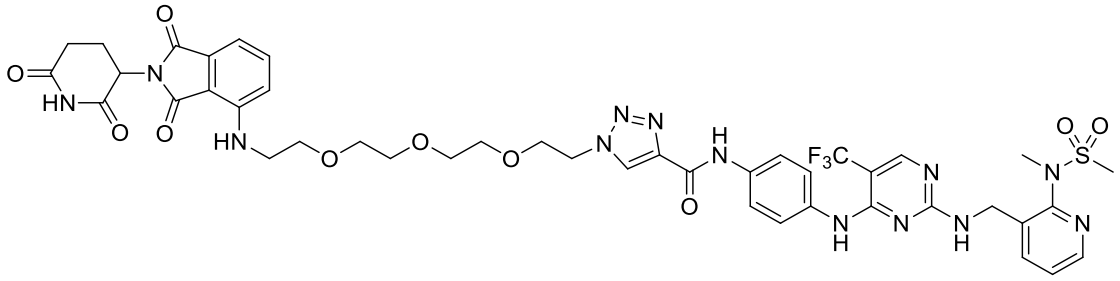
Synthesized *via* procedure A. LC-MS: calculated for $C_{39}H_{39}F_3N_{13}O_8S$ $[M+H]^+$: 906.26, found 906.97.



37 (FC-22)

1-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)-N-(4-((2-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide.

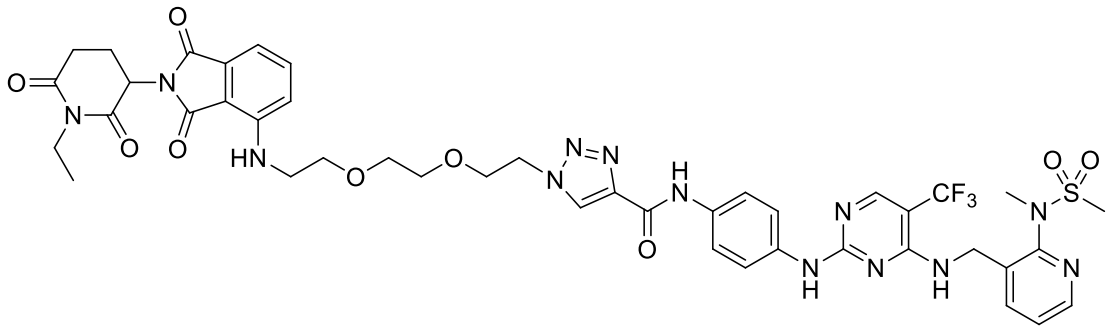
Synthesized *via* procedure A. LC-MS: calculated for $C_{41}H_{43}F_3N_{13}O_9S$ $[M+H]^+$: 950.29, found 950.96.



38 (FC-23)

1-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)-N-(4-((2-(((2-(N-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide.

Synthesized *via* procedure A. LC-MS: calculated for $C_{43}H_{47}F_3N_{13}O_{10}S$ $[M+H]^+$: 994.32, found 994.94.



39 (FC-24)

1-(2-(2-(2-((2-(1-ethyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)-*N*-(4-((4-(((2-(*N*-methylmethylsulfonamido)pyridin-3-yl)methyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-1*H*-1,2,3-triazole-4-carboxamide.

Synthesized *via* procedure A. ^{1}H-NMR(400MHz, $CDCl_3$, ppm): 8.90(s, 1H), 8.39(s, 2H), 8.17(s, 1H), 7.77(d, *J* = 6.68 Hz, 1H), 7.58-7.39(m, 6H), 7.24(m, 1H), 7.03(d, *J* = 6.60 Hz, 1H), 6.89(d, *J* = 8.20 Hz, 1H), 6.47(s, 1H), 6.07(s, 1H), 4.92(m, 3H), 4.59(s, 2H), 3.91(s, 2H), 3.81(d, *J* = 4.84 Hz, 2H), 3.70-3.64(m, 6H), 3.48(d, *J* = 3.84 Hz, 2H), 3.26(s, 3H), 3.06(s, 3H), 2.94-2.87(m, 1H), 2.78-2.72(m, 2H), 2.05-2.03(m, 1H), 1.10-1.08(m, 3H). LC-MS: calculated for $C_{43}H_{47}F_3N_{13}O_9S$ $[M+H]^+$: 978.32, found 978.89.

^{1}H-NMR spectra of FC-11