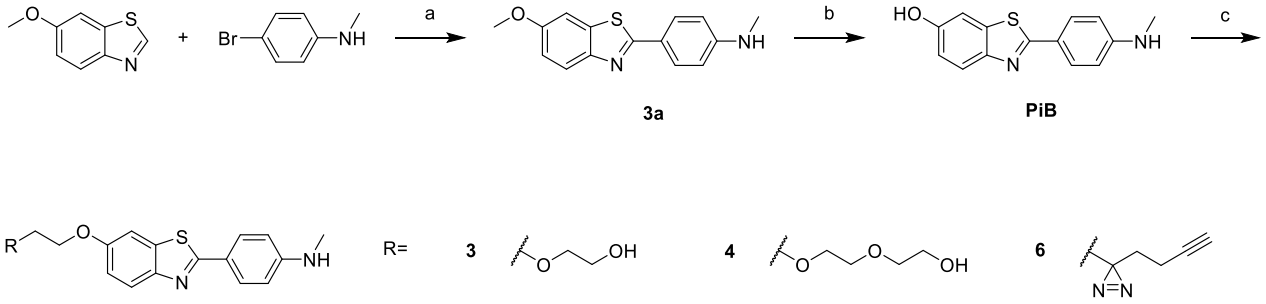
General chemical experimental information

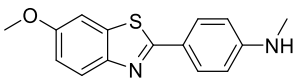
Unless otherwise noted, reagents and solvents were obtained from commercial suppliers. Reactions were run in round bottom flasks or glass vials and stirred with Teflon-coated magnetic stir bars. Reactions were monitored by thin layer chromatography or LC-MS (Agilent 6120). Acquity H-Class LC-MS with QDa mass spectrometer using water + 0.05% formic acid and acetonitrile + 0.05% formic acid. Preparative HPLC was performed on a Waters Sunfire C18 column (19 × 100 mm, 5μm) at a flow rate of 15 mL/min. All final compounds were >95% pure by LC-MS analysis. 1H NMR spectra were recorded at ambient temperature on Bruker DMX 400 (400 MHz for 1H NMR) instruments in the specified deuterated solvents.

Scheme 1. Synthesis of compounds PiB and 3, 4, 6



Reagent condition: a) $Pd(AcO)_2$, $P(^tBu)_3$, CuI, Cs_2CO_3, DMF, 150°C, N_2, 4 h; b) BBr_3, DCM, -78°C to room temperature (R.T.), N_2, 3 h; c) Cs_2CO_3, DMF, room temperature (R.T.), 1 h.

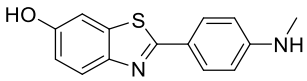
4-(6-methoxybenzo[*d*]thiazol-2-yl)-*N*-methylaniline (3a)



A solution of 6-methoxybenzo[*d*]thiazole (3.5 g, 21.2 mmol), 4-bromo-*N*-methylaniline (4.73 g, 25.5 mmol) and Cs_2CO_3 (7.6 g, 23.3 mmol) in anhydrous DMF (250 mL) was degassed with N_2 for 15 min. To this solution were sequentially added $Pd(AcO)_2$ (240 mg, 1.05 mmol), $P(^tBu)_3$ (430 mg, 2.12 mmol) and CuI (800 mg, 4.25 mmol) under N_2 atmosphere. The reaction mixture was stirred at 150°C for 4 h. After cooling to room temperature, it was diluted by water (200 mL) and extracted with EA (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Then the crude product was purified by flash column chromatography on silica gel using a gradient eluent (PE/EA = 100:0 to 70:30). Compound **3a** was obtained by vacuum drying as

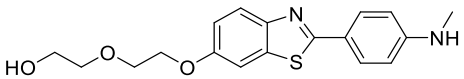
yellow solid (720 mg, 2.67 mmol) with a yield of 25.2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 – 7.70 (m, 3H), 7.61 (d, J = 1.9 Hz, 1H), 7.05 (dd, J = 8.9, 2.3 Hz, 1H), 6.64 (d, J = 8.6 Hz, 2H), 6.39 (d, J = 3.9 Hz, 1H), 3.83 (s, 3H), 2.75 (d, J = 3.5 Hz, 3H). MS-ESI: m/z calculated for $C_{15}H_{14}N_2OS$, Exact Mass: 270.08, found 271.1 $[M + H]^+$.

2-(4-(methylamino)phenyl)benzo[*d*]thiazol-6-ol (PiB)



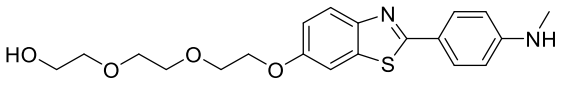
A solution of compound **3a** (720 mg, 2.67 mmol) in anhydrous DCM (10 mL) was treated with BBr_3 (9.6 mL, 1 M in DCM) at -78℃ under N_2 atmosphere. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by careful addition to ice-water (20 mL), followed by extraction with DCM (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using a gradient eluent (DCM/EA =100:0 to 10:90). **PiB** was obtained by vacuum drying as yellow solid (503 mg, 1.96 mmol) with a yield of 73.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 2.2 Hz, 1H), 6.90 (dd, J = 8.7, 2.4 Hz, 1H), 6.63 (d, J = 8.7 Hz, 2H), 2.75 (s, 3H). MS-ESI: m/z calculated for $C_{14}H_{12}N_2OS$, Exact Mass: 256.07, found 257.1 $[M + H]^+$.

2-(2-((2-(4-(methylamino)phenyl)benzo[*d*]thiazol-6-yl)oxy)ethoxy)ethan-1-ol (3)



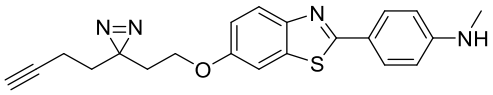
A solution of 2-(2-hydroxyethoxy)ethyl 4-methylbenzenesulfonate (94 mg, 0.36 mmol) and **PiB** (31 mg, 0.12 mmol) in anhydrous DMF (1 mL) was added Cs_2CO_3 (59 mg, 0.18 mmol). The reaction mixture was stirred at room temperature for 1 h, then diluted with a H_2O/DMSO mixture and purified by high-performance liquid chromatography using a gradient eluent (H_2O/MeCN = 90:10 to 20:80). Compound **3** was obtained by lyophilization as yellow solid (12.1 mg, 0.035 mmol) with a yield of 30.1%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 8.9 Hz, 1H), 7.76 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 2.3 Hz, 1H), 7.06 (dd, J = 8.9, 2.5 Hz, 1H), 6.64 (d, J = 8.7 Hz, 2H), 4.22 – 4.14 (m, 2H), 3.80 – 3.76 (m, 2H), 3.54 – 3.50 (m, 4H), 2.75 (s, 3H). MS-ESI: m/z calculated for $C_{18}H_{20}N_2O_3S$, Exact Mass: 344.12, found 345.0 $[M + H]^+$.

2-(2-(2-((2-(4-(methylamino)phenyl)benzo[*d*]thiazol-6-yl)oxy)ethoxy)ethoxy)ethan-1-ol (4)



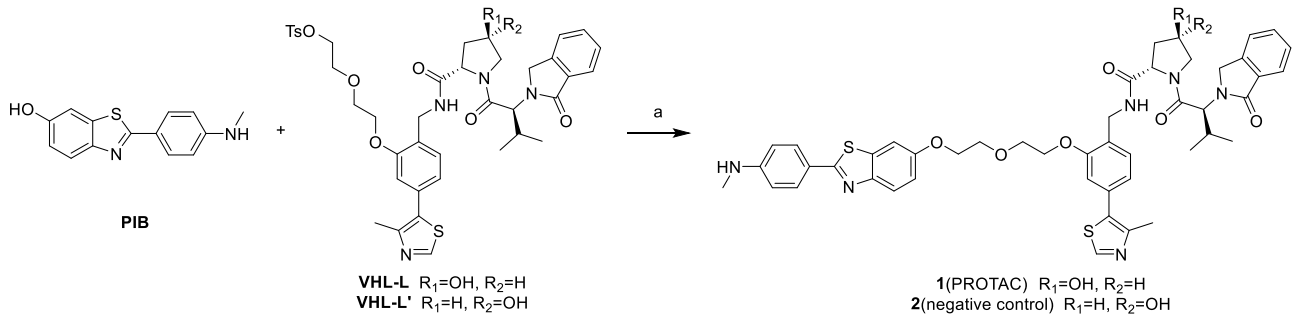
A solution of 2-(2-(2-hydroxyethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (14 mg, 0.05 mmol) and **PiB** (10 mg, 0.04 mmol) in anhydrous DMF (1 mL) was added Cs_2CO_3 (20 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 1 h, then diluted with a H_2O/DMSO mixture and purified by high-performance liquid chromatography using a gradient eluent (H_2O/MeCN = 90:10 to 20:80). Compound **4** was obtained by lyophilization as yellow solid (4.1 mg, 0.011 mmol) with a yield of 26.5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.6 Hz, 3H), 7.34 (d, *J* = 2.2 Hz, 1H), 7.08 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.65 (d, *J* = 8.7 Hz, 2H), 4.25 – 4.18 (m, 2H), 3.93 – 3.87 (m, 2H), 3.78 – 3.70 (m, 6H), 3.64 – 3.61 (m, 2H), 2.91 (s, 3H). MS-ESI: m/z calculated for $C_{20}H_{24}N_2O_4S$, Exact Mass: 388.15, found 389.1 $[M + H]^+$.

4-(6-(2-(3-(but-3-yn-1-yl)-3*H*-diazirin-3-yl)ethoxy)benzo[*d*]thiazol-2-yl)-*N*-methylaniline (6)



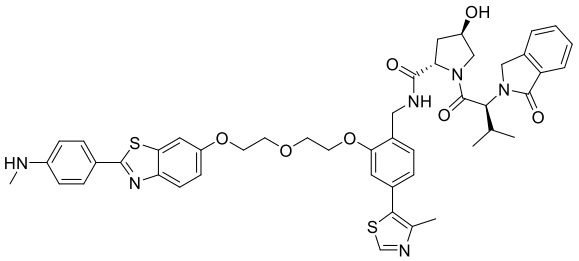
A solution of **PiB** (20 mg, 0.08 mmol) and 2-(3-(but-3-yn-1-yl)-3*H*-diazirin-3-yl) ethyl 4-methylbenzenesulfonate (27 mg, 0.09 mmol) in anhydrous DMF (1 mL) was added Cs_2CO_3 (52 mg, 0.16 mmol). The reaction mixture was stirred at 50℃ for 12 h, then diluted with a H_2O/DMSO mixture and purified by high-performance liquid chromatography using a gradient eluent (H_2O/MeCN = 80:20 to 20:80). Compound **6** was obtained by lyophilization as yellow solid (13.1 mg, 0.035 mmol) with a yield of 44.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (s, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 2.3 Hz, 1H), 7.05 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 2H), 3.90 (t, *J* = 6.1 Hz, 2H), 2.84 (t, *J* = 2.6 Hz, 1H), 2.50 (s, 3H), 2.06 (td, *J* = 7.3, 2.5 Hz, 2H), 1.92 (t, *J* = 6.0 Hz, 2H), 1.68 (t, *J* = 7.4 Hz, 2H). MS-ESI: m/z calculated for $C_{21}H_{20}N_4OS$, Exact Mass: 376.14, found 377.1 $[M + H]^+$.

Scheme 2. Synthesis of compounds 1 and 2



Reagent condition: a) Cs_2CO_3, DMSO, 70℃, overnight.

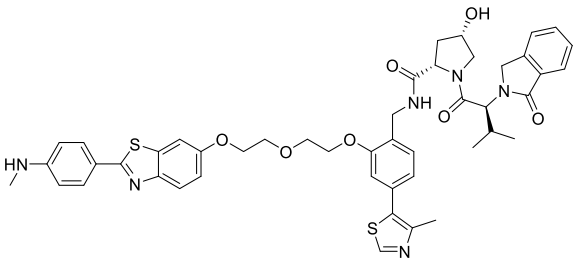
(*2S*,*4R*)-4-hydroxy-1-((*S*)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)-*N*-(2-(2-(2-((2-(4-(methylamino)phenyl)benzo[*d*]thiazol-6-yl)oxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (1)



A solution of **PiB** (13 mg, 0.05 mmol) and VHL-L (40 mg, 0.05 mmol) in anhydrous DMSO (1 mL) was added Cs_2CO_3 (32.5 mg, 0.10 mmol). The reaction mixture was stirred at 70℃ overnight, then diluted with a H_2O/DMSO mixture and purified by high-performance liquid chromatography using a gradient eluent (H_2O/MeCN = 80:20 to 20:80). Compound **1** was obtained by lyophilization as yellow solid (11.2 mg, 0.013 mmol) with a yield of 25.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.32 (d, *J* = 5.7 Hz, 1H), 7.70 (dd, *J* = 8.5, 5.8 Hz, 3H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 2.6 Hz, 3H), 7.47 – 7.40 (m, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.03 – 6.97 (m, 2H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.57 (d, *J* = 8.6 Hz, 2H), 4.64 (d, *J* = 10.8 Hz, 1H), 4.51 – 4.45 (m, 1H), 4.41 (s, 1H), 4.38 – 4.34 (m, 1H), 4.34 – 4.28 (m, 1H), 4.30 – 4.20 (m, 3H), 4.19 – 4.12 (m, 4H), 3.85 – 3.80 (m, 4H), 3.72 – 3.70 (m, 1H), 3.63 – 3.62 (m, 1H), 2.68 (s, 3H), 2.40 (s, 3H), 2.29 – 2.22 (m, 1H), 2.02 – 1.95 (m, 1H), 1.90 – 1.80 (m, 1H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.66 (d, *J* = 6.5 Hz, 3H). MS-ESI: m/z calculated for $C_{47}H_{50}N_6O_7S_2$, Exact Mass: 874.32, found 875.1 $[M + H]^+$.

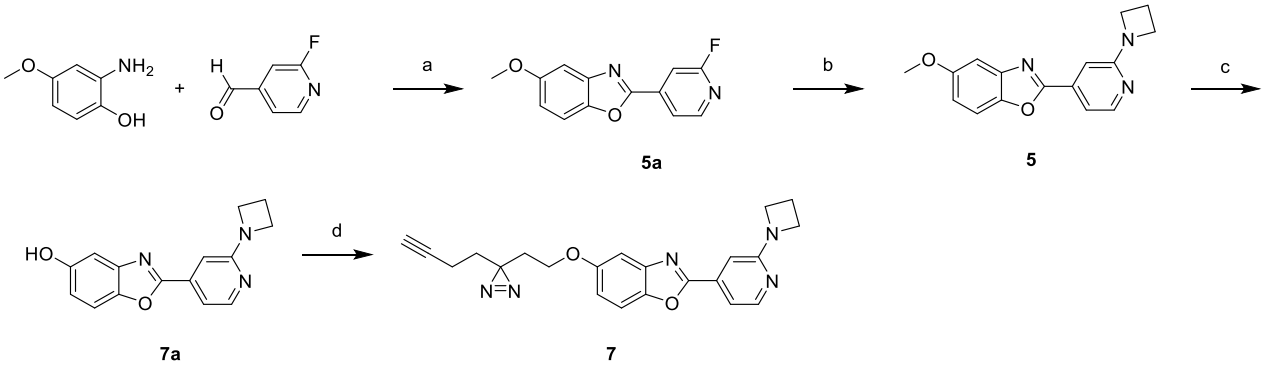
(*2S*,*4S*)-4-hydroxy-1-((*S*)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)-*N*-(2-(2-(2-((2-(4-(methylamino)phenyl)benzo[*d*]thiazol-6-yl)oxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-

yl)benzyl)pyrrolidine-2-carboxamide (2)



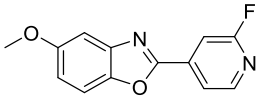
Compound **2** was obtained by the procedure of compound **1** as yellow solid (8.6 mg, 0.010 mmol) with a yield of 19.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.42 (s, 1H), 7.77 (dd, J = 7.1, 4.9 Hz, 3H), 7.71 (d, J = 7.6 Hz, 1H), 7.61 (s, 3H), 7.53 – 7.47 (m, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.10 – 7.03 (m, 2H), 7.01 (d, J = 7.7 Hz, 1H), 6.64 (d, J = 7.4 Hz, 2H), 4.75 – 4.72 (m, 1H), 4.57 – 4.55 (m, 1H), 4.46 – 4.44 (m, 1H), 4.42 – 4.40 (m, 1H), 4.39 – 4.38 (m, 1H), 4.35 – 4.31 (m, 3H), 4.24 – 4.20 (m, 4H), 3.98 – 3.94 (m, 1H), 3.92 – 3.87 (m, 4H), 3.58 – 3.52 (m, 1H), 2.75 (s, 3H), 2.47 (d, J = 1.3 Hz, 3H), 2.36 – 2.29 (m, 2H), 1.82 – 1.71 (m, 1H), 0.96 (d, J = 5.9 Hz, 3H), 0.75 (d, J = 5.9 Hz, 3H). MS-ESI: m/z calculated for $C_{47}H_{50}N_6O_7S_2$, Exact Mass: 874.32, found 875.1 $[M + H]^+$.

Scheme 3. Synthesis of compounds 5 and 7



Reagent condition: a) TEA, DDQ, MeOH, DCM, room temperature (R.T.), 1 h; b) EtOH, 80°C, 12 h; c) BBr_3, DCM, -78°C to room temperature (R.T.), N_2, 3 h; d) Cs_2CO_3, MeCN, 50°C, 12 h.

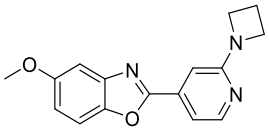
2-(2-fluoropyridin-4-yl)-5-methoxybenzo[*d*]oxazole (5a)



A solution of 2-amino-4-methoxyphenol (175 mg, 1.00 mmol) and 2-fluoroisonicotinaldehyde (250 mg, 2.00 mmol) in anhydrous MeOH (5 mL) was added TEA (0.31 mL, 2.4 mmol). After stirring for 30 min at room temperature, a solution of DDQ (227 mg, 1.00 mmol) in DCM (5 mL) was added

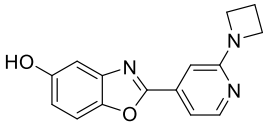
dropwise over 5 min. The resulting mixture was stirred at room temperature for an additional 30 min until completion. Then it was diluted by water (20 mL) and extracted with EA (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Then the crude product was purified by flash column chromatography on silica gel using a gradient eluent (PE/EA = 100:0 to 40:60). Compound **5a** was obtained by vacuum drying as pink solid (157 mg, 0.643 mmol) with a yield of 64.3%. MS-ESI: m/z calculated for $C_{13}H_9FN_2O_2$, Exact Mass: 244.06, found 245.1 $[M + H]^+$.

2-(2-(azetidin-1-yl)pyridin-4-yl)-5-methoxybenzo[*d*]oxazole (5)



A solution of compound **5a** (122 mg, 0.50 mmol) and azetidine (57 mg, 1.00 mmol) in anhydrous EtOH (5 mL) was stirred at 80℃ for 12 h. After cooling to room temperature, the reaction mixture was diluted by water (20 mL) and extracted with EA (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Then the crude product was purified by flash column chromatography on silica gel using a gradient eluent (PE/EA = 100:0 to 70:30). Compound **5** was obtained by vacuum drying as yellow solid (125 mg, 0.444 mmol) with a yield of 88.9%. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.22 (d, *J* = 5.8 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.42 (d, *J* = 2.6 Hz, 1H), 7.33 (d, *J* = 5.7 Hz, 1H), 7.17 – 7.07 (m, 2H), 4.17 (t, *J* = 7.5 Hz, 4H), 3.84 (s, 3H), 2.46 – 2.36 (m, 2H). MS-ESI: m/z calculated for $C_{16}H_{15}N_3O_2$, Exact Mass: 281.12, found 282.0 $[M + H]^+$.

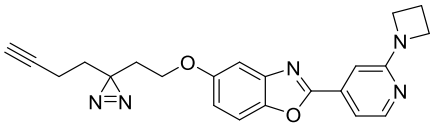
2-(2-(azetidin-1-yl)pyridin-4-yl)benzo[*d*]oxazol-5-ol (7a)



A solution of compound **5** (84 mg, 0.300 mmol) in anhydrous DCM (5 mL) was added BBr_3 (0.6 mL, 1 M in DCM) at -78℃ under N_2 atmosphere. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 3 h, The reaction was quenched by careful addition to ice-water (20 mL), followed by extraction with DCM (3 × 15 mL). The combined organic layers were

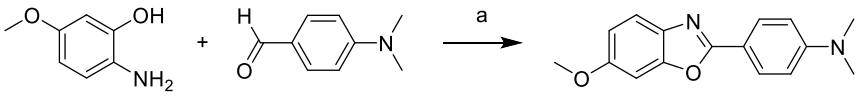
dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using a gradient eluent (DCM/EA =100:0 to 10:90). Compound **7a** was obtained by vacuum drying as a yellow solid (53 mg, 0.199 mmol) with a yield of 66.2%. MS-ESI: m/z calculated for $C_{15}H_{13}N_3O_2$, Exact Mass: 267.10, found 268.1 $[M + H]^+$.

2-(2-(azetidin-1-yl)pyridin-4-yl)-5-(2-(3-(but-3-yn-1-yl)-*3H*-diazirin-3-yl)ethoxy)benzo[*d*]oxazole (7)



A solution of 2-(3-(but-3-yn-1-yl)-*3H*-diazirin-3-yl)ethyl 4-methylbenzenesulfonate (14 mg, 0.045 mmol) and compound **7a** in anhydrous MeCN (1 mL) was added Cs_2CO_3 (29 mg, 0.090 mmol). The reaction mixture was stirred at 50℃ for 12 h, then diluted with a H_2O/DMSO mixture and purified by high-performance liquid chromatography using a gradient eluent (H_2O/MeCN = 90:10 to 25:75). Compound **7** was obtained by lyophilization as white solid (3.0 mg, 0.008 mmol) with a yield of 17.2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, J = 2.1 Hz, 1H), 8.17 (dd, J = 8.7, 1.9 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 7.27 (d, J = 2.1 Hz, 1H), 6.94 (dd, J = 8.7, 2.3 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 4.11 (t, J = 7.4 Hz, 4H), 3.89 (t, J = 6.0 Hz, 2H), 2.85 (t, J = 2.4 Hz, 1H), 2.42 – 2.36 (m, 2H), 2.06 (td, J = 7.3, 2.3 Hz, 2H), 1.91 (t, J = 5.9 Hz, 2H), 1.69 (t, J = 7.4 Hz, 2H). MS-ESI: m/z calculated for $C_{22}H_{21}N_5O_2$, Exact Mass: 387.17, found 388.2 $[M + H]^+$.

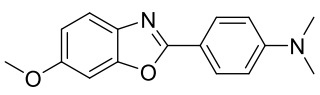
Scheme 4. Synthesis of compounds HQY1027



HQY1027

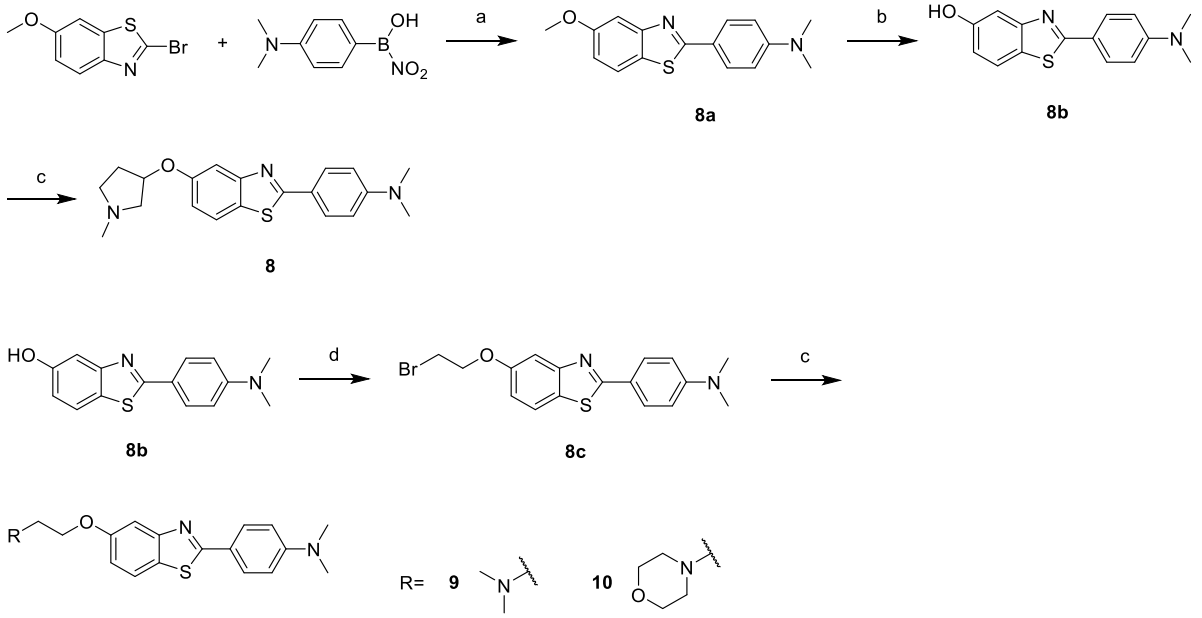
Reagent condition: a) TEA, DDQ, MeOH, DCM, room temperature (R.T.), 1 h.

4-(6-methoxybenzo[*d*]oxazol-2-yl)-*N*-methylaniline (HQY1027)



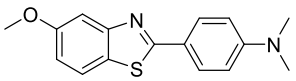
A solution of 4-dimethylaminobenzaldehyde (298 mg, 2.00 mmol) and 2-amino-5-methoxyphenol (175 mg, 1.00 mmol) in anhydrous MeOH (5 mL) were added TEA (0.31 mL, 2.4 mmol). After stirring for 30 min at room temperature, a solution of DDQ (227 mg, 1.00 mmol) in DCM (5 mL) was added dropwise over 5 min. The resulting mixture was stirred at room temperature for an additional 30 min until completion. Then it was diluted by water (20 mL) and extracted with EA (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Then the residue was purified by C18 flash column chromatography using a gradient eluent (H_2O/MeCN = 100:0 to 20:80, H_2O contains 0.05% HCl). **HQY1027** was obtained by lyophilization as yellow solid (166 mg, 0.617 mmol) with a yield of 61.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.6 Hz, 1H), 7.34 (s, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 3.03 (s, 6H). MS-ESI: m/z calculated for $C_{16}H_{16}N_2O_2$, Exact Mass: 268.12, found 269.1 $[M + H]^+$.

Scheme 5. Synthesis of compounds 8 – 10



Reagent condition: a) $Pd(dppf)_2Cl_2$, K_2CO_3, Dioxane. H_2O, 80℃, N_2, 4 h; b) BBr_3, DCM, -78℃ to 35℃, N_2, 3 h; c) K_2CO_3, MeCN, 70℃, 12 h; d) K_2CO_3, MeCN, 70℃, 12 h.

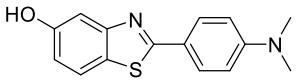
4-(6-methoxybenzo[*d*]thiazol-2-yl)-*N*,*N*-dimethylaniline (8a)



8a

A mixture of 2-bromo-6-methoxybenzo[*d*]thiazole (242 mg, 1 mmol), (4-(dimethylamino)phenyl) boronic acid (165 mg, 1 mmol) and K_2CO_3 (207 mg, 1.5 mmol) was dissolved in dioxane (5 mL) and water (1 mL) in a pressure-resistant vessel. After the addition of $Pd(dppf)_2Cl_2$ (36.5 mg, 0.05 mmol), the reaction mixture was stirred at 80°C under a nitrogen atmosphere for 4 h. Then it was diluted by water (20 mL) and extracted with EA (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient eluent (PE/EA = 100:0 to 70:30) to afford **8a** (72 mg, 0.2667 mmol) as a yellow solid in 26.7% yield. MS-ESI: m/z calculated for $C_{16}H_{16}N_2OS$, Exact Mass: 284.10, found 285.1 $[M + H]^+$.

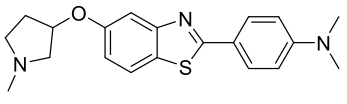
2-(4-(dimethylamino)phenyl)benzo[*d*]thiazol-5-ol (8b)



8b

To a solution of **8a** (137 mg, 0.482 mmol) in DCM (5 mL) was added dropwise a solution of boron tribromide in DCM (1 M, 964 μL) under a nitrogen atmosphere at -78°C. Then the reaction mixture was warmed to 35°C and stirred for 3 h. Upon completion, the reaction was quenched with 20 mL ice water and extracted with DCM (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient eluent (DCM/MeOH = 100:0 to 80:20) to afford **8b** (112 mg, 0.415 mmol) as a yellow solid in 86.1% yield. MS-ESI: m/z calculated for $C_{15}H_{14}N_2OS$, Exact Mass: 270.08, found 271.1 $[M + H]^+$.

***N*,*N*-dimethyl-4-(5-((1-methylpyrrolidin-3-yl)oxy)benzo[*d*]thiazol-2-yl)aniline (8)**

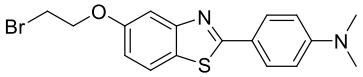


8

To a solution of **8b** (5.4 mg, 0.02 mmol) and 3-bromo-1-methylpyrrolidine (16.3 mg, 0.10 mmol) were

dissolved in MeCN (1 mL), then K_2CO_3 (5.5 mg, 0.04 mmol) was added, and the reaction mixture was stirred at 70℃ for 12 h. Upon completion, the mixture was filtered and purified by C18 flash column chromatography using a gradient eluent (H_2O/MeCN = 100:0 to 35:65, H_2O contains 0.05% TFA). **8** was obtained by lyophilization as yellow solid (3.1 mg, 0.009 mmol) with a yield of 43.9%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.84 (d, J = 8.1 Hz, 2H), 7.69 (s, 1H), 7.09 (d, J = 7.9 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 5.27 – 5.16 (m, 1H), 3.02 (s, 6H), 2.98 – 2.94 (m, 1H), 2.92 – 2.85 (m, 2H), 2.70 – 2.59 (m, 1H), 2.51 (s, 3H), 2.39 – 2.27 (m, 1H), 2.20 – 2.05 (m, 1H). MS-ESI: m/z calculated for $C_{20}H_{23}N_3OS$, Exact Mass: 353.16, found 354.1 $[M + H]^+$.

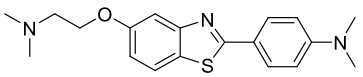
4-(5-(2-bromoethoxy)benzo[*d*]thiazol-2-yl)-*N*,*N*-dimethylaniline (8c)



8c

To a solution of **8b** (27 mg, 0.1 mmol) and 1,2-dibromoethane (31 mg, 0.12 mmol) were dissolved in MeCN (1 mL), then Cs_2CO_3 (65 mg, 0.2 mmol) was added, and the reaction mixture was stirred at 70℃ for 12 h. Then it was diluted by water (20 mL) and extracted with EA (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient eluent (DCM/EA = 100:0 to 0:100) to afford **8c** (32 mg, 0.0851 mmol) as a gray solid in 85.1% yield. MS-ESI: m/z calculated for $C_{17}H_{17}BrN_2OS$, Exact Mass: 376.02, found 377.1 $[M + H]^+$.

4-(5-(2-(dimethylamino)ethoxy)benzo[*d*]thiazol-2-yl)-*N*,*N*-dimethylaniline (9)

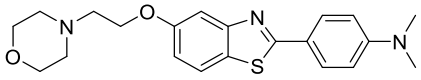


9

To a solution of **8c** (5.4 mg, 0.02 mmol) and dimethylamine (1.3 mg, 0.03 mmol) were dissolved in MeCN (1 mL), then K_2CO_3 (5.5 mg, 0.04 mmol) was added, and the reaction mixture was stirred at 70℃ for 12 h. Upon completion, the mixture was filtered and purified by C18 flash column chromatography using a gradient eluent (H_2O/MeCN = 100:0 to 35:65, H_2O contains 0.05% TFA). **9** was obtained by lyophilization as yellow solid (2.0 mg, 0.006 mmol) with a yield of 29.3%. ^{1}H NMR

(400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.72 (s, 1H), 7.14 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 4.44 – 4.33 (m, 2H), 3.59 – 3.55 (m, 2H), 3.02 (s, 6H), 2.89 (s, 6H). MS-ESI: m/z calculated for $C_{19}H_{23}N_3OS$, Exact Mass: 341.16, found 342.1 $[M + H]^+$.

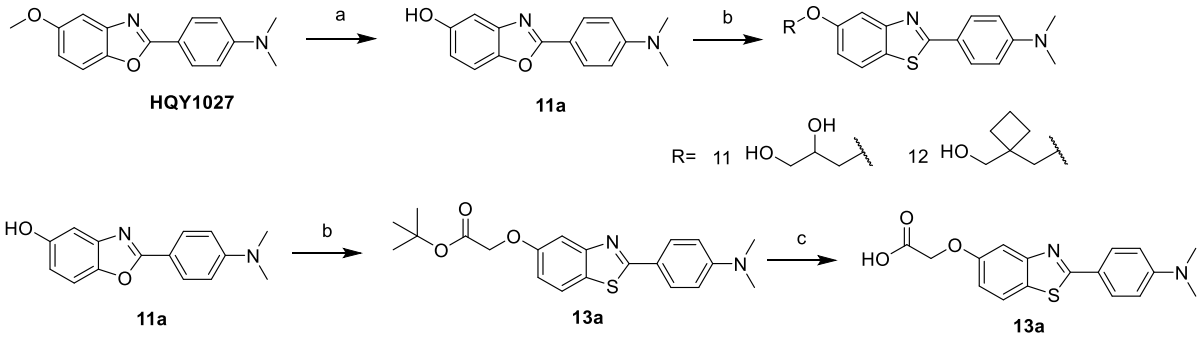
***N*,*N*-dimethyl-4-(5-(2-morpholinoethoxy)benzo[*d*]thiazol-2-yl)aniline (10)**



10

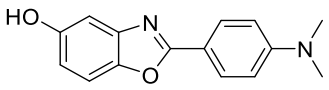
To a solution of **8c** (5.4 mg, 0.02 mmol) and morpholine (2.6 mg, 0.03 mmol) were dissolved in MeCN (1 mL), then K_2CO_3 (5.5 mg, 0.04 mmol) was added, and the reaction mixture was stirred at 70℃ for 12 h. Upon completion, the mixture was filtered and purified by C18 flash column chromatography using a gradient eluent (H_2O/MeCN = 100:0 to 35:65, H_2O contains 0.05% TFA). **10** was obtained by lyophilization as yellow solid (2.5 mg, 0.007 mmol) with a yield of 32.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.84 (d, *J* = 9.3 Hz, 2H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.15 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 2H), 4.46 – 4.41 (m, 2H), 4.03 – 3.98 (m, 2H), 3.75 – 3.62 (m, 4H), 3.59 – 3.50 (m, 2H), 3.28 – 3.18 (m, 2H), 3.02 (s, 6H). MS-ESI: m/z calculated for $C_{21}H_{25}N_3O_2S$, Exact Mass: 383.17, found 384.1 $[M + H]^+$.

Scheme 6. Synthesis of compounds 11 – 13



Reagent condition: a) BBr_3, DCM, -78℃ to 35℃, N_2, 3 h; b) Cs_2CO_3, MeCN, 70℃, 12 h; c) TFA, DCM, room temperature (R.T.), 3 h.

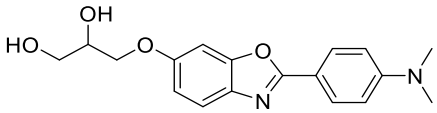
2-(4-(dimethylamino)phenyl)benzo[*d*]oxazol-6-ol (11a)



11a

To a solution of **HQY1027** (67 mg, 0.25 mmol) in DCM (5 mL) was added dropwise a solution of boron tribromide in DCM (1 M, 500 μL) under a nitrogen atmosphere at -78℃. Then the reaction mixture was warmed to 35°C and stirred for 3 h. Upon completion, the reaction was quenched with 20 mL ice water and extracted with DCM (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient eluent (DCM/MeOH = 100:0 to 80:20) to afford compound **11a** (55 mg, 0.217 mmol) as a yellow solid in 86.6% yield. MS-ESI: m/z calculated for $C_{15}H_{14}N_2O_2$, Exact Mass: 254.11, found 255.1 $[M + H]^+$.

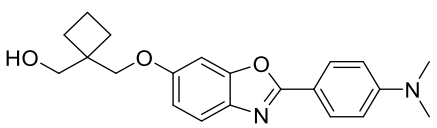
3-((2-(4-(dimethylamino)phenyl)benzo[*d*]oxazol-6-yl)oxy)propane-1,2-diol (11)



11

To a solution of **11a** (5.1 mg, 0.02 mmol) and 3-bromopropane-1,2-diol (6.1 mg, 0.04 mmol) were dissolved in MeCN (1 mL), then Cs_2CO_3 (13 mg, 0.04 mmol) was added, and the reaction mixture was stirred at 70℃ overnight. Upon completion, the mixture was filtered and purified by C18 flash column chromatography using a gradient eluent (H_2O/MeCN = 100:0 to 25:75, H_2O contains 0.05% TFA). **11** was obtained by lyophilization as yellow solid (3.3 mg, 0.007 mmol) with a yield of 32.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 8.9 Hz, 2H), 7.55 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 6.94 (dd, J = 8.6, 2.1 Hz, 1H), 6.85 (d, J = 8.9 Hz, 2H), 4.07 (dd, J = 9.8, 3.9 Hz, 1H), 3.96 – 3.92 (m, 1H), 3.61 – 3.55 (m, 1H), 3.52 – 3.46 (m, 1H), 3.83 (d, J = 5.1 Hz, 1H), 3.03 (s, 6H). MS-ESI: m/z calculated for $C_{18}H_{20}N_2O_4$, Exact Mass: 328.14, found 329.1 $[M + H]^+$.

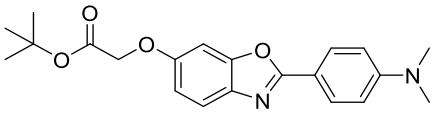
(1-(((2-(4-(dimethylamino)phenyl)benzo[*d*]oxazol-6-yl)oxy)methyl)cyclobutyl)methanol (12)



12

To a solution of **11a** (5.1 mg, 0.02 mmol) and 3-(bromomethyl)-3-oxetanemethanol (7.2 mg, 0.04 mmol) were dissolved in MeCN (1 mL), then Cs_2CO_3 (13 mg, 0.04 mmol) was added, and the reaction mixture was stirred at 70℃ overnight. Upon completion, the mixture was filtered and purified by C18 flash column chromatography using a gradient eluent (H_2O/MeCN = 100:0 to 25:75, H_2O contains 0.05% TFA). **12** was obtained by lyophilization as yellow solid (2.8 mg, 0.008 mmol) with a yield of 39.5%. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.94 (d, *J* = 8.9 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 6.97 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.85 (d, *J* = 8.9 Hz, 2H), 4.43 (q, *J* = 5.9 Hz, 4H), 4.22 (s, 2H), 3.73 (s, 2H), 3.03 (s, 6H). MS-ESI: m/z calculated for $C_{20}H_{22}N_2O_4$, Exact Mass: 354.16, found 355.1 $[M + H]^+$.

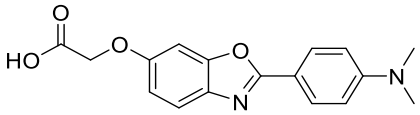
***tert*-butyl 2-((2-(4-(dimethylamino)phenyl)benzo[d]oxazol-6-yl)oxy)acetate (13a)**



13a

To a solution of **11a** (10.2 mg, 0.04 mmol) and *tert*-butyl 2-bromoacetate (11.7 mg, 0.06 mmol) were dissolved in MeCN (1 mL), then Cs_2CO_3 (19.5 mg, 0.06 mmol) was added, and the reaction mixture was stirred at 70℃ overnight. Upon completion, the mixture was filtered and purified by C18 flash column chromatography using a gradient eluent (H_2O/MeCN = 100:0 to 10:90, H_2O contains 0.05% TFA). **13a** was obtained by lyophilization as yellow solid (7.8 mg, 0.021 mmol) with a yield of 52.9%. MS-ESI: m/z calculated for $C_{21}H_{24}N_2O_4$, Exact Mass: 368.17, found 369.1 $[M + H]^+$.

2-((2-(4-(dimethylamino)phenyl)benzo[*d*]oxazol-6-yl)oxy)acetic acid (13)



13

To a solution of **13a** (7.8 mg, 0.021 mmol) were dissolved in DCM (4 mL), then TFA (1 mL) was added, and the reaction mixture was stirred at room temperature for 3 h. Upon completion, the mixture was filtered, and concentrated under reduced pressure, then purified by C18 flash column chromatography using a gradient eluent (H_2O/MeCN = 100:0 to 35:65, H_2O contains 0.05% TFA). **13** was obtained by lyophilization as yellow solid (3.4 mg, 0.011 mmol) with a yield of 51.9%. ^{1}H NMR

(400 MHz, DMSO-d_6) δ 7.94 (d, J = 7.0 Hz, 2H), 7.57 (d, J = 6.7 Hz, 1H), 7.32 (s, 1H), 6.95 (d, J = 8.7 Hz, 1H), 6.85 (d, J = 7.2 Hz, 2H), 4.76 (s, 2H), 3.03 (s, 6H). MS-ESI: m/z calculated for $C_{17}H_{16}N_2O_4$, Exact Mass: 312.11, found 313.1 $[M + H]^+$.