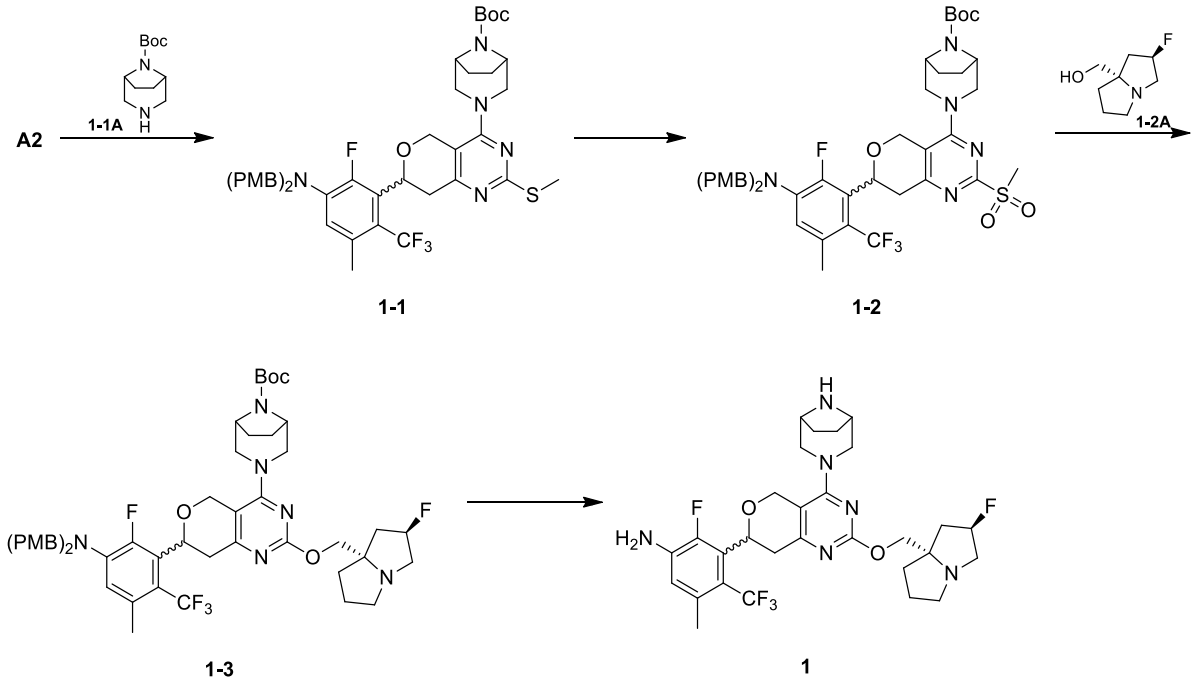
5.08 (d, *J*=9.6,1 H), 4.92 (d, *J*=15.6,1 H), 4.67 (d, *J*=15.6,1 H), 4.24 (q, *J*=10,4 H), 3.719 (s, 6 H) 3.42 - 3.59 (m, 1 H), 2.87 - 3.04 (m, 1 H), 2.47 (s, 3 H), 2.19 - 2.35 (m, 3 H).

Example 1



[00232] Step 1: Preparation of intermediate 1-1

[00233] Compound **A2** (80 mg, 105.02 μmol) and compound **1-1A** (26.75 mg, 126.03 μmol) were dissolved in N,N-dimethylformamide (2 mL), and diisopropylethylamine (40.72 mg, 315.07 μmol, 54.88 μL) was added. The reaction solution was heated to 100 °C and stirred for another 1 hour. The mixture was cooled down. The organic solvent was removed under reduced pressure. The resulting crude product was purified by preparative thin layer chromatography (developer: petroleum ether:ethyl acetate = 2:1) to give compound **1-1**. MS m/z =824.3 $[M+H]^+$.

[00234] Step 2: Preparation of intermediate 1-2

[00235] Compound **1-1** (70 mg, 84.96 μmol) was dissolved in dichloromethane (2 mL), and m-chloroperoxybenzoic acid (34.50 mg, 169.92 μmol, 85% content) was added. The reaction solution was stirred at 20 °C for another 3 hours. The organic solvent was removed under reduced pressure, and the resulting crude product was purified by preparative thin layer chromatography (developer: dichloromethane: methanol = 10:1) to give compound **1-2**. MS m/z =856.2 $[M+H]^+$.

[00236] Step 3: Preparation of intermediate 1-3

[00313] Compound **9-8** (750 mg, 1.24 mmol) and 2-methylthiourea (701.63 mg, 3.73 mmol) were added to ethanol (10 mL) under nitrogen, and sodium carbonate (263.39 mg, 2.49 mmol) was added. The reaction solution was heated to 60 °C and stirred for another 15 hours. The organic solvent was removed under reduced pressure. Water (10 mL) was added to the residue. The mixture was adjusted to a pH of 5-6 with 2M aqueous hydrochloric acid solution, and extracted with ethyl acetate (30 mL*3). The combined organic phase was washed with saturated brine (10 mL). The organic solvent was removed under reduced pressure to give crude compound **9-9**, which was directly used in the next step without further purification. MS m/z: 666.4 $[M+Na]^+$.

[00314] Step 5: Preparation of intermediate 9-10

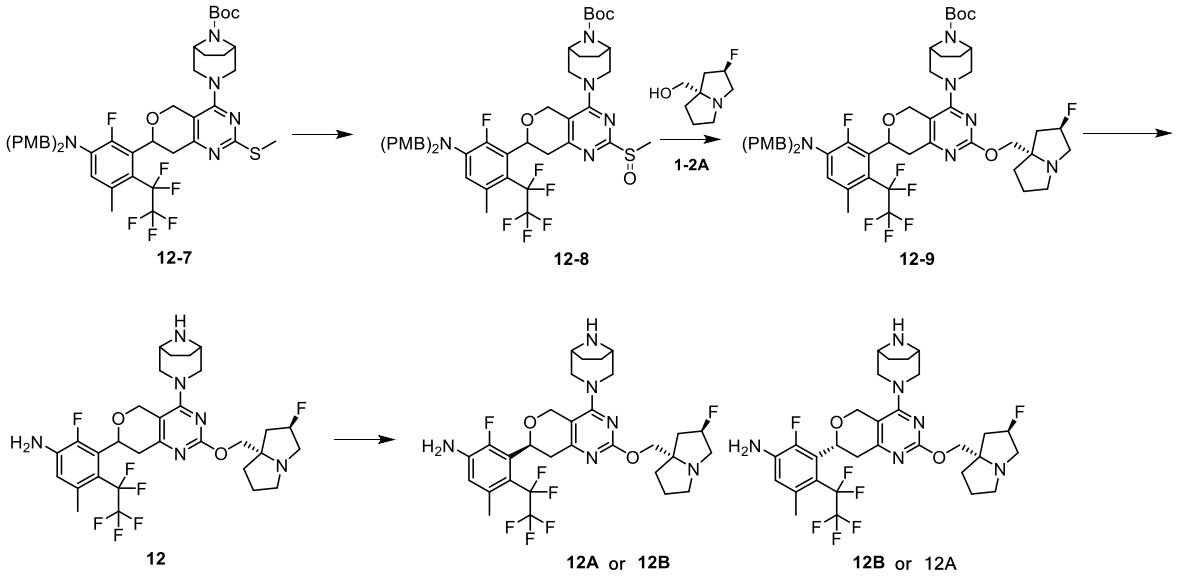
[00315] Compound **9-9** (855 mg, 1.33 mmol) was dissolved in N,N-dimethylformamide (10 mL) at 20 °C, and N,N-diisopropylethylamine (515.68 mg, 3.99 mmol, 694.99 μL) and N-phenylbis(trifluoromethanesulfonimide) (570.17 mg, 1.60 mmol) were added. The reaction solution was stirred at this temperature for another 3 hours. The reaction solution was diluted with ethyl acetate (50 mL). The mixture was washed with water (15 mL *4), dried over anhydrous sodium sulfate, and filtered. The organic solvent was removed under reduced pressure. The resulting crude product was purified by silica gel column chromatography (eluent: ethyl acetate/petroleum ether=0~15%) to give compound **9-10**. MS m/z: 776.1 $[M+H]^+$.

[00316] Step 6: Preparation of intermediate 9-11

[00317] Compound **9-10** (240 mg, 309.38 μmol) and compound **1-1A** (78.81 mg, 371.25 μmol) were dissolved in N,N-dimethylformamide (2 mL), and diisopropylethylamine (119.95 mg, 928.13 μmol, 161.66 μL) was added. The reaction solution was heated to 100 °C and stirred for another 1 hour. The mixture was cooled down. The organic solvent was removed under reduced pressure. The resulting crude product was purified by silica gel column chromatography (eluent: ethyl acetate/petroleum ether=0~45%) to give compound **9-11**. MS m/z: 838.5 $[M+H]^+$.

[00318] Step 7: Preparation of intermediate 9-12

[00319] Compound **9-11** (260 mg, 310.28 μmol) was dissolved in dichloromethane (2 mL) at 20 °C, and m-chloroperoxybenzoic acid (125.98 mg, 620.55 μmol, 85% content) was added. The reaction solution was stirred at this temperature for another 15 hours. The organic solvent



[00352] Step 1: Preparation of intermediate 12-1

[00353] To a 100 milliliters of stuffy jar were added the raw material **A1-4** (5 g, 10.59 mmol) and copper powder (3.36 g, 52.93 mmol) under nitrogen, and then DMSO (40 mL) and pentafluoroiodoethane (5.21 g, 21.17 mmol) were added. After sealing, the mixture was heated to 120 °C and stirred for 12 hours. To the reaction solution were added 50 milliliters of saturated brine and 200 milliliters of methyl tert-butyl ether. The mixture was stirred for 10 minutes, and filtered. The mixture was left to stand and the layers were separated to remove the aqueous phase. The organic phase was concentrated under reduced pressure. The residue is purified by chromatography purification system (eluent: 5 % ethyl acetate/petroleum ether) to give compound **12-1**. MS m/z =512.1[M+H]$^+$.

[00354] Step 2: Preparation of intermediate 12-2

[00355] Sodium hydride (1.56 g, 39.10 mmol, 60% content) was added to tetrahydrofuran (50 mL) at 0 °C (in an ice-water bath) under nitrogen. After the mixture was stirred for 15 minutes, ethyl acetoacetate (4.54 g, 39.10 mmol) was added dropwise. After the mixture was stirred for another 15 minutes, n-butyl lithium (2.5 M, 15.64 mL) was added dropwise. The mixture was stirred for 30 minutes, and a solution of the raw material **12-1** (4 g, 7.82 mmol) in tetrahydrofuran (10 mL) was added dropwise. The obtained mixture was naturally warmed to room temperature and stirred at 25 °C for 1 hour. The reaction was quenched by slowly adding 50 milliliters of saturated aqueous ammonium chloride solution to the reaction solution. To the mixture was added 100 milliliters of methyl tert-butyl ether and the mixture was stirred for 5

cancer GP2D cell was established. 0.2 mL (2×10^6) of GP2D cells (Matrigel was added, and volume ratio was 1:1) were inoculated subcutaneously on the right back of each mouse. When the average tumor volume reached 149 mm^3, the administration was started by group, with 6 mice in each group. On the day of the assay, the animals were administered the corresponding drugs according to the corresponding groups. The first group G1 was set as a negative control group, which was given 5%DMSO+95%(10%HP-β-CD) alone by gavage administration. The second group G2 to the fourth group G4 were given compound **1** hydrochloride, and the dosage and protocol of administration were shown in Table 13.

[00739] Table 13 Pharmacodynamic study of the assay compound on transplanted tumor of human diffuse large B lymphoma TMD8 in mouse

Group	Number of animals	Assay compound	Dosage (mg/kg)	Administration concentration (mg/mL)	Administration volume (mL/kg)	Route and frequency of administration
G1	6	Negative control	(N/A)	(N/A)	(N/A)	PO,BID*20
G2	6	Compound **1** hydrochloride	3	0.3	10	PO,BID*20
G3	6	Compound **1** hydrochloride	10	1	10	PO,BID*20
G4	6	Compound **1** hydrochloride	30	3.0	10	PO,BID*20

[00740] Note: PO means oral administration, QD means once daily, BID means twice daily.

[00741] During the assay, the body weight of animals and the tumor size were measured twice a week. Meanwhile clinical symptoms of animals were observed and recorded every day. Each administration was referenced to the most recent body weight of animals.

[00742] The length (a) and width (b) of a tumor were measured with a digital vernier caliper. The calculation formula of tumor volume (Tumor volume, TV) was: $TV=a\times b^2/2$.

[00743] Assay results:

[00744] Compound **1** hydrochloride has a significant inhibitory effect on the xenograft tumor of human colon cancer GP2D in mouse. After 20 days of administration, the tumor volume inhibition rate TGI (%) of the second group G2 (3 mg/kg, PO, BID) was 19.4% on the 20th day; the tumor volume inhibition rates TGI (%) of the third group G3 (10 mg/kg, PO, BID) and the fourth group G4 (30 mg/kg, PO, BID) were 53.9% and 83.7% on the 20th day, respectively; the detailed results are shown in Table 14.

[00745] Table 14 Effects of the assay compound on animal tumor size in xenograft tumor