A Selective Matrix Metalloprotease 12 Inhibitor for Potential Treatment of Chronic Obstructive Pulmonary Disease (COPD): Discovery of (S)-2-(8-(methoxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid (MMP408)

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I. Supporting Info: Biological Assays

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a. Determination of IC_{50} against human MMP-12

The assays for human MMP-12 and MMP-13 activity were performed by incubating 20 μM of the fluorogenic peptide substrate MCA-Pro-Leu-Gly-Leu-Dpa(DNP)-Ala-Arg (Anaspec, San Jose, CA) with 0.5 nM recombinant human MMP-12 or MMP-13 catalytic domain along with various concentrations of compound in 50 mM HEPES, pH 7.5, 100 mM NaCl, 5 mM $CaCl_2$, 0.005 % Brij-35 and 10% DMSO. The rate of increase in fluorescent signal was measured on a Safire plate reader (Tecan, Männedorf, Switzerland) exciting at a wavelength of 325 nm and measuring at an emission wavelength of 395 nm. The enzymes were expressed in *E. coli*, refolded from insoluble inclusion bodies, and purified.

b. Determination of IC_{50} against mouse MMP-12

The assay to measure potency in mouse MMP-12 catalytic domain was identical in format to the assay used for the human MMP enzymes with the exception that 3 nM mouse MMP-12 was required to obtain similar catalytic rates. Cleavage of 20 μM of the MCA-Pro-Leu-Gly-Leu-Dpa (DNP)-Ala-Arg peptide was measured over time, monitoring λ_{ex}: 325 nm and λ_{em}: 395 (Tecan Safire 2, Tecan, Männedorf, Switzerland).

c. Evaluation of MMP-12 inhibitors in human rhMMP-12 induced mouse lung inflammation model

8-10 week old C57Bl/6 female mice were used for these studies (Taconic, Germantown, NY). Animals were allowed to acclimate at least one week prior to study initiation. Animals were housed at Wyeth 200 CambridgePark Drive Cambridge, MA 02140 with 5-6 animals per cage. Standard mouse chow and water were offered *ad libitum*.

rhMMP-12 was diluted to a concentration of 730 μg/mL using enzyme vehicle and kept on ice at all times. Animals were anesthetized with isoflurane (Baxter Healthcare, Deerfield, IL) until they exhibited shallow breathing. An intranasal (IN) dose of 50 μL [36.5 μg] rhMMP-12 was administered to each mouse and animals were allowed to recover from anesthesia in their cages while placed on a heating pad to help

maintain normal body temperature during recovery. IN MMP-12 was administered daily for three consecutive days. Compounds were administered by oral gavage (0.2 mL/mouse) at either [30, 10, 5 mg/Kg]. Compounds were made up daily and put into solution using compound vehicle, 2% Tween 80 and 0.5% methylcellulose. On day one, a single pre-dose was given 18 hours prior to the first dose of rhMMP-12. On days two to four, compound was administered two hours prior to and four hours following rhMMP-12 administration.

Bronchoalveolar Lavage (BAL)

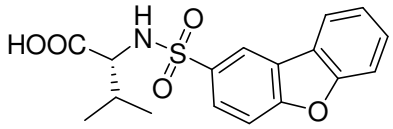
Animals were sacrificed on Day 5 by CO_2 asphyxiation. The trachea was exposed by blunt dissection, a small hole was made in the trachea and a 23 G stub adapter (BD, Franklin Park, NJ) was inserted into the trachea and tied off using 4-0 silk suture (Henry Schein, Melville, NY). Using a 1cc syringe, three consecutive 0.7 mL aliquots of room temperature phosphate buffered saline without calcium or magnesium (PBS CMF) was used to lavage the lung. Aliquots were pooled and stored on ice. BAL was centrifuged at 1500 rpm for 5 minutes to pellet the BAL cells. The supernatant was removed and the pellet was reconstituted in 300 μL of PBS. Cell counts were performed on a Cell-Dyn 3700 (Abbott, Abbott Park, IL) and differential cell counts were determined using a method previously described[1]. This method employs depolarized light scatter using a Becton Dickinson FACSVantage SE Cell Sorter (BD, San Jose, CA).

II. Supporting Info: Chemistry

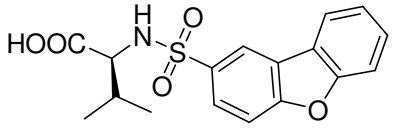
All reagents and solvents were of commercial quality and used without further purification. Column chromatography was performed using Merck silica gel 60 (230-400 mesh). Proton nuclear magnetic spectroscopy ^{1}H NMR spectra (400 MHz) were obtained on a Bruker 400 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as internal standard. Conventional abbreviations used for signal shape are: s. singlet; d. doublet (apparent); t. triplet (apparent); m. multiplet; br. broad. Low-resolution mass spectra (MS) were obtained using a Micromass Platform Electrospray

Ionization Quadrapole mass spectrometer. High resolution exact mass measurements (HRMS) were performed on a Bruker ApexIII 7T FT/ICR/MS. All intermediates were characterized by ^{1}H NMR. All new final SAR compounds were determined to be consistent with proposed structure by ^{1}H NMR, MS, HRMS and were greater than 95% pure in two solvent systems (HPLC Method 1: H_2O-CH_3CN and HPLC Method 2: H_2O-MeOH) as determined using an Agilent 1100 HPLC instrument on a C18 column.

The following two compounds **2a** and **2b** were prepared from the known 2-dibenzofuransulfonic acid[1] following the general procedures described for the preparation of compound **9**.

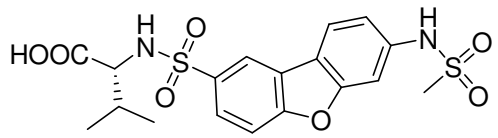


(R)-2-(dibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoic acid (2a). ^{1}H NMR (400 MHz, MeOD) δ ppm 0.91 (d, *J*=6.82 Hz, 3 H), 0.97 (d, *J*=6.82 Hz, 3 H), 1.93 - 2.15 (m, 1 H), 3.74 (d, *J*=5.56 Hz, 1 H), 7.34 - 7.44 (m, 1 H), 7.48 - 7.56 (m, 1 H), 7.57-7.65 (m, 1 H), 7.68 (d, *J*=8.59 Hz, 1 H), 7.98 (dd, *J*=8.59, 2.02 Hz, 1 H), 8.06 (d, *J*=7.83 Hz, 1 H), 8.53 (d, *J*=2.02 Hz, 1 H); HRMS: calcd for $[C_{17}H_{17}NO_5S+H]^+$, 348.09002; found (ESI-FTMS, $[M+H]^+$), 348.09067.



(S)-2-(dibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoic acid (2b). ^{1}H NMR (400 MHz, MeOD) δ ppm 0.76 (d, *J*=6.82 Hz, 3 H), 0.81 (d, *J*=6.82 Hz, 3 H), 1.76 - 1.98 (m, 1 H), 3.58 (d, *J*=5.56 Hz, 1 H), 7.22 - 7.32 (m, 1 H), 7.36 - 7.43 (m, 1 H), 7.45 - 7.51 (m, 1 H), 7.52 - 7.58 (m, 1 H), 7.83 (dd, *J*=8.59, 2.02 Hz, 1 H), 7.95 (d, *J*=7.83 Hz, 1 H), 8.40 (d, *J*=2.02 Hz, 1 H); HRMS: calcd for $[C_{17}H_{17}NO_5S+H]^+$, 348.09002; found (ESI-FTMS, $[M+H]^+$), 348.09085.

[1] Keumi *et al. J. Org. Chem.*,**1991**, 56: 4671-4677.

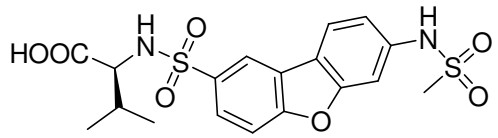


(R)-3-methyl-2-(7-(methylsulfonamido)dibenzo[b,d]furan-2-sulfonamido)butanoic acid (3a).

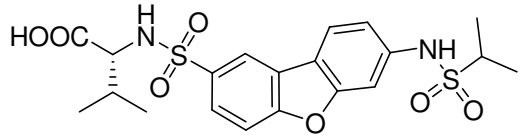
(R)-3-methyl-2-(7-(methylsulfonamido)dibenzo[b,d]furan-2-sulfonamido)butanoic acid tert-butyl ester: The intermediate (R)-tert-butyl 2-(7-aminodibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate (0.36 mmol) and DMAP (53 mg, 0.43 mmol) were mixed with 2 mL of CH_2Cl_2, followed by addition of methylsulfonyl chloride (0.40 mmol). The mixture was stirred at room temperature for two hours and purified with a silica gel column chromatography to provide the methylsulfonamide t-butyl ester as a white solid in 90% yield.

(R)-3-methyl-2-(7-(methylsulfonamido)dibenzo[b,d]furan-2-sulfonamido)butanoic acid:

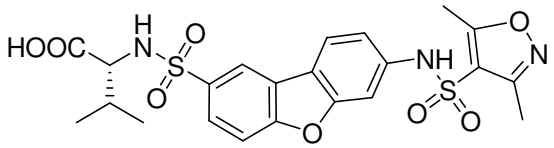
The above sulfonamide *t*-butyl ester was dissolved in 4 mL of TFA/CH_2Cl_2 (1:1). The solution was stirred at room temperature for 4 hours. The solvents were removed under reduced pressure and the residue was triturated in CH_3CN/H_2O followed by a freeze-dry process. The title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (d, *J*=6.82 Hz, 3 H), 0.83 (d, *J*=6.82 Hz, 3 H), 1.83 - 2.02 (m, 1 H), 3.09 (s, 3 H), 3.59 (dd, *J*=9.47, 5.94 Hz, 1 H), 7.29 (dd, *J*=8.46, 1.89 Hz, 1 H), 7.57 (d, *J*=1.52 Hz, 1 H), 7.80 - 7.93 (m, 2 H), 8.05 (d, *J*=9.60 Hz, 1 H), 8.24 (d, *J*=8.34 Hz, 1 H), 8.52 (d, *J*=2.02 Hz, 1 H), 10.18 (s, 1 H), 12.50 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 17.8, 19.0, 30.4, 61.3, 102.3, 112.0, 115.8, 118.5, 119.9, 122.2, 122.5, 123.6, 125.7, 136.4, 139.2, 156.9, 157.2, 172.1. HRMS: calcd for $2[C_{18}H_{20}N_2O_7S_2+H]^+$ 881.14966; found (ESI-FTMS, $[2M+H]^+$) 881.1488.



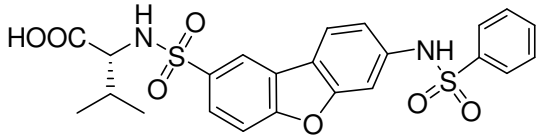
(S)-3-methyl-2-(7-(methylsulfonamido)dibenzo[b,d]furan-2-sulfonamido)butanoic acid (3b). Following the procedures described for the preparation of compound **3a** using the corresponding aniline analog derived from L-valine, **3b** was prepared as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (d, *J*=6.82 Hz, 3 H), 0.83 (d, *J*=6.82 Hz, 3 H), 1.84 - 2.03 (m, 1 H), 3.10 (s, 3 H), 3.59 (dd, *J*=9.47, 5.94 Hz, 1 H), 7.29 (dd, *J*=8.46, 1.89 Hz, 1 H), 7.58 (d, *J*=1.77 Hz, 1 H), 7.79 - 7.92 (m, 2 H), 8.08 (d, *J*=9.35 Hz, 1 H), 8.24 (d, *J*=8.34 Hz, 1 H), 8.52 (d, *J*=1.26 Hz, 1 H), 10.20 (s, 1 H), 12.52 (s, 1 H). MS (ES$^-$) 439.1.



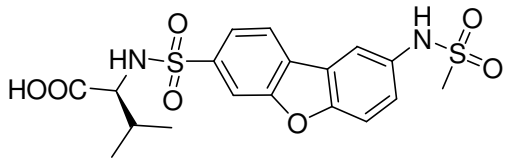
(R)-3-methyl-2-(7-(isopropylsulfonamido)dibenzo[b,d]furan-2-sulfonamido) butanoic acid (4). Following the procedures described for the preparation of compound **3a** using isopropyl sulfonyl chloride for the N-derivatization, compound **4** was prepared as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.91 (d, *J*=6.82 Hz, 3 H), 0.97 (d, *J*=6.82 Hz, 3 H), 1.36 (d, *J*=6.82 Hz, 6 H), 1.96 - 2.12 (m, 1 H), 3.32 - 3.39 (m, 1 H), 3.73 (d, *J*=5.56 Hz, 1 H), 7.28 (dd, *J*=8.34, 1.77 Hz, 1 H), 7.59 (d, *J*=2.02 Hz, 1 H), 7.67 (d, *J*=8.84 Hz, 1 H), 7.94 (dd, *J*=8.84, 2.02 Hz, 1 H), 8.00 (d, *J*=8.59 Hz, 1 H), 8.47 (d, *J*=2.02 Hz, 1 H). MS (ES$^-$) 467.1; HRMS: calcd for $[C_{20}H_{24}N_2O_7S_2+H]^+$, 469.10977; found (ESI-FTMS, $[M+H]^+$), 469.1108.



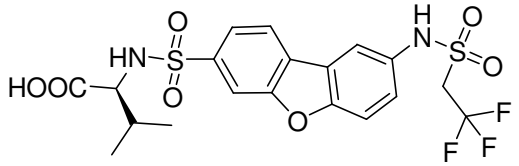
(R)-2-(7-(3,5-dimethylisoxazole-4-sulfonamido)dibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoic acid (5). Following the procedures described for the preparation of compound **3a** and using using 3,5-dimethylisoxazol-4-yl sulfonyl chloride for the N-derivatization, compound **5** was prepared as a white solid from (R)-*tert*-butyl 2-(7-aminodibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.91 (d, *J*=6.82 Hz, 3 H), 0.97 (d, *J*=6.82 Hz, 3 H), 1.97 - 2.08 (m, 1 H), 2.28 (s, 3 H), 2.50 (s, 3 H), 3.72 (d, *J*=5.81 Hz, 1 H), 7.17 (dd, *J*=8.34, 2.02 Hz, 1 H), 7.46 (d, *J*=1.77 Hz, 1 H), 7.67 (d, *J*=8.84 Hz, 1 H), 7.96 (dd, *J*=8.84, 2.02 Hz, 1 H), 8.00 (d, *J*=8.34 Hz, 1 H), 8.48 (d, *J*=2.02 Hz, 1 H). MS (ES$^-$) 520.1; HRMS: calcd for $[C_{22}H_{23}N_3O_8S_2+H]^+$, 522.09993; found (ESI-FTMS, $[M+H]^+$), 522.1015.



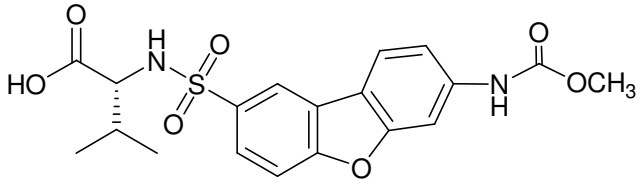
(R)-3-methyl-2-(7-(phenylsulfonamido)dibenzo[b,d]furan-2-sulfonamido)butanoic acid (6). Following the procedures described for the preparation of compound **3a** and using phenyl sulfonyl chloride for the N-derivatization, compound **6** was prepared as a white solid from (R)-tert-butyl 2-(7-aminodibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.90 (d, *J*=6.82 Hz, 3 H), 0.96 (d, *J*=6.82 Hz, 3 H), 1.95 - 2.08 (m, 1 H), 3.71 (d, *J*=5.56 Hz, 1 H), 7.12 (dd, *J*=8.46, 1.89 Hz, 1 H), 7.41 - 7.51 (m, 3 H), 7.51 - 7.59 (m, 1 H), 7.63 (d, *J*=8.84 Hz, 1 H), 7.78 - 7.85 (m, 2 H), 7.88 (d, *J*=8.34 Hz, 1 H), 7.92 (dd, *J*=8.72, 1.89 Hz, 1 H), 8.42 (d, *J*=2.02 Hz, 1 H). MS (ES$^-$) 501.1; HRMS: calcd for $[C_{23}H_{22}N_2O_7S_2+H]^+$, 503.09412; found (ESI-FTMS, $[M+H]^+$), 503.0954.



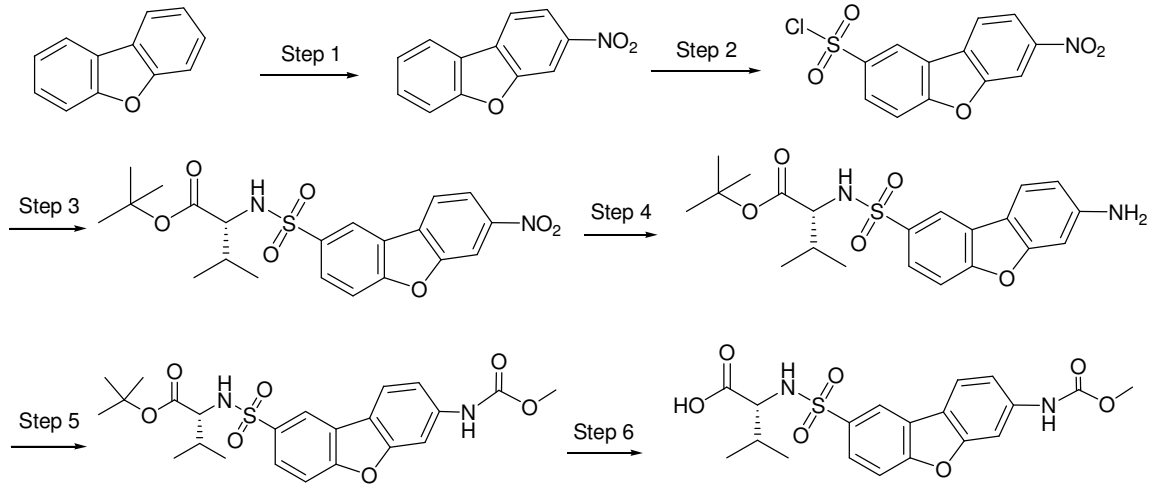
(S)-3-methyl-2-(8-(methylsulfonamido)dibenzo[b,d]furan-3-sulfonamido)butanoic acid (7). Following the procedures described for the preparation of compound **17** and using methyl sulfonyl chloride for the N-derivatization, compound **7** was prepared from (S)-*tert*-butyl 2-(8-aminodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (d, *J*=6.82 Hz, 3 H), 0.83 (d, *J*=6.82 Hz, 3 H), 1.85 - 2.02 (m, 1 H), 3.02 (s, 3 H), 3.59 (dd, *J*=9.35, 6.06 Hz, 1 H), 7.45 (dd, *J*=8.84, 2.27 Hz, 1 H), 7.75 - 7.84 (m, 2 H), 8.05 (d, *J*=1.52 Hz, 2 H), 8.18 (d, *J*=9.09 Hz, 1 H), 8.34 (d, *J*=8.08 Hz, 1 H), 9.84 (s, 1 H), 12.52 (s, 1 H). MS (ES$^-$) 439.1.



(S)-3-methyl-2-(8-(2,2,2-trifluoroethylsulfonamido)dibenzo[b,d]furan-3-sulfonamido)butanoic acid (8). Following the procedures described for the preparation of compound **17** and using 2,2,2-rifluoroethyl sulfonyl chloride for the N-derivatization, compound **8** was prepared from (S)-*tert*-butyl 2-(8-aminodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.81 (d, *J*=6.82 Hz, 3 H), 0.87 (d, *J*=6.82 Hz, 3 H), 1.87 - 2.03 (m, 1 H), 3.63 (d, *J*=5.81 Hz, 1 H), 4.06 (q, *J*=9.35 Hz, 2 H), 7.39 (dd, *J*=8.84, 2.27 Hz, 1 H), 7.58 (d, *J*=8.84 Hz, 1 H), 7.78 (dd, *J*=8.08, 1.52 Hz, 1 H), 7.95 (d, *J*=2.27 Hz, 1 H), 7.99 (d, *J*=1.52 Hz, 1 H), 8.08 (d, *J*=8.34 Hz, 1 H). MS (ES$^-$) 507.1. Anal. ($C_{24}H_{21}FN_2O_7S$) C, H, N.



(R)-2-(7-methoxycarbonylamino-dibenzofuran-2-sulfonylamino)-3-methyl-butyric acid (9). The title compound **9** was prepared following the scheme and synthetic procedures described below.



Step 1: 3-nitrodibenzo[b,d]furan. The following procedures are similar to those described in Keumi *et al*. (1991), *J. Org. Chem.*, 56: 4671-4677. Dibenzofuran (50 g) was mixed with 400 mL of trifluoroacetic acid (TFA). The resulting suspension was cooled in an ethanol ice bath and 11.7 mL of fuming nitric acid (HNO_3, >90%) was added dropwise over 10 minutes. The reaction mixture was allowed to warm to room temperature and stirred for two hours followed by filtration. The solid from the filtration was triturated with methanol (MeOH) and dried under reduced pressure to provide 45 g of 3-nitrodibenzo[b,d]furan in 70% yield.

Step 2: 7-nitrodibenzo[b,d]furan-2-sulfonyl chloride. To a round-bottom flask containing 3-nitrodibenzo[b,d]furan (21.4 g, 100 mmol) in 200 mL of chloroform ($CHCl_3$) was slowly added chlorosulfonic acid (15.2 g, 130 mmol) at 0 °C. The resulting suspension

was allowed to warm to room temperature and stirred for 4 hours. After being cooled to 0^{o}C, the reaction mixture was filtered and 24.1 g of 7-nitrodibenzo [b,d]furan-2-sulfonic acid was collected from the filtrate as a white solid in 81% yield. 7-nitrodibenzo[b,d]furan-2-sulfonic acid (2.93 g, 10 mmol) obtained from Step 2 was mixed with 15 mL of thionyl chloride ($SOCl_2$) followed by slow addition of a few drops of dimethylformamide (DMF). The mixture was stirred at 80 °C for 24 hours. The reaction mixture was filtered and excess $SOCl_2$ in the filtrate was removed under reduced pressure. The crude product from the filtrate was isolated as a solid and triturated with ice water to provide 2.78 g of 7-nitrodibenzo[b,d]furan-2-sulfonyl chloride as an off-white solid in 89% yield.

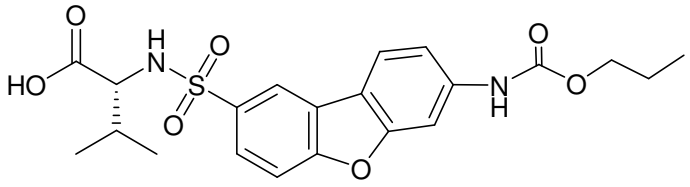
Step 3: (R)-tert-butyl 3-methyl-2-(7-nitrodibenzo[b,d]furan-2-sulfonamido)butanoate. 7-Nitrodibenzo[b,d]furan-2-sulfonyl chloride (570 mg, 1.83 mmol) from Step 3 and (R)-*tert*-butyl 2-amino-3-methylbutanoate hydrochloride (422 mg, 2.0 mmol) were mixed with 5 mL of dichloromethane (CH_2Cl_2) followed by slow addition of N,N-diisopropylethylamine (520 mg, 4 mmol) at 0 °C. The resulting mixture was stirred for 4 hours and allowed to warm to room temperature. The reaction mixture was purified by column chromatography to provide the (R)-valine sulfonamide as a white solid in 88% yield.

Step 4: (R)-tert-butyl 2-(7-aminodibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate. The nitro sulfonamide obtained in Step 4 (480 mg) was mixed with 20 mL of MeOH and 100 mg of palladium on carbon (Pd/C) (10%). The reaction was carried out in a Parr shaker at room temperature under hydrogen (50 psi) overnight. The reaction mixture was filtered through Celite® and concentrated to provide (R)-tert-butyl 2-(7-aminodibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate (430 mg) as an off-white solid in quantitative yield.

Step 5: (R)-tert-butyl 2-(7-methoxycarbonylamino-dibenzofuran-2-sulfonylamino)-3-methyl-butyric acid. The aryl amine (0.25 mmol) from Step 5 and dimethylaminopyridine (DMAP, 37 mg, 0.3 mmol) were dissolved in 2 mL of CH_2Cl_2, followed by the addition of methyl chloroformate (0.28 mmol). The mixture was stirred at room temperature

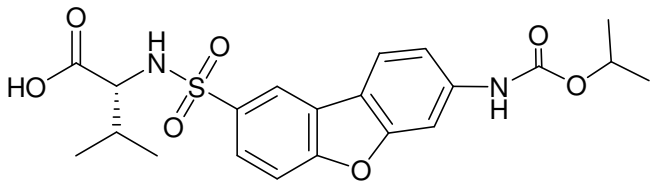
overnight and purified by silica gel column chromatography to provide (R)-tert-butyl 2-(7-methoxycarbonylamino-dibenzofuran-2-sulfonylamino)-3-methyl-butyric acid as a white solid in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86 (d, *J*=6.82 Hz, 3 H), 1.02 (d, *J*=6.82 Hz, 3 H), 1.05 - 1.14 (m, 9 H), 1.98 - 2.14 (m, 1 H), 3.71 (dd, *J*=9.85, 4.55 Hz, 1 H), 3.84 (s, 3 H), 5.22 (d, *J*=9.85 Hz, 1 H), 6.95 (s, 1 H), 7.19 (dd, *J*=8.34, 2.02 Hz, 1 H), 7.60 (d, *J*=8.08 Hz, 1 H), 7.84 (d, *J*=8.84 Hz, 1 H), 7.89 (dd, *J*=8.59, 2.02 Hz, 1 H), 7.91 - 7.98 (m, 1 H), 8.37 (d, *J*=1.52 Hz, 1 H).

Step 6: (R)-2-(7-methoxycarbonylamino-dibenzofuran-2-sulfonylamino)-3-methyl-butyric acid (**9**). The sulfonamide t-butyl ester (0.2 mmol) from Step 6 was dissolved in 2 mL of TFA/CH_2Cl_2 (1:1), and the solution was stirred at room temperature for 3 hours. The solvents were removed under reduced pressure and the residue was triturated in acetonitrile/water followed by a freeze-dry process. (S)-2-(7-methoxycarbonylamino-dibenzofuran-2-sulfonylamino)-3-methyl-butyric acid was obtained as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.91 (d, *J*=6.82 Hz, 3 H), 0.96 (d, *J*=6.82 Hz, 3 H), 1.93 - 2.14 (m, 1 H), 3.71 (d, *J*=5.56 Hz, 1 H), 3.78 (s, 3 H), 7.34 (dd, *J*=8.46, 1.89 Hz, 1 H), 7.66 (d, *J*=9.35 Hz, 1 H), 7.92 (dd, *J*=8.59, 2.02 Hz, 1 H), 7.94 - 8.04 (m, 2 H), 8.45 (d, *J*=1.26 Hz, 1 H), 9.62 (s, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 17.7, 18.9, 30.3, 51.8, 61.2, 100.6, 111.7, 114.5, 117.0, 119.5, 121.8, 123.8, 125.2, 136.1, 140.0, 153.9, 156.9, 157.0, 172.0. HRMS: calcd for $[C_{19}H_{20}N_2O_7S\text{-}H]^-$ 419.09185; found (ESI-FTMS, $[M\text{-}H]^-$) 419.0916.

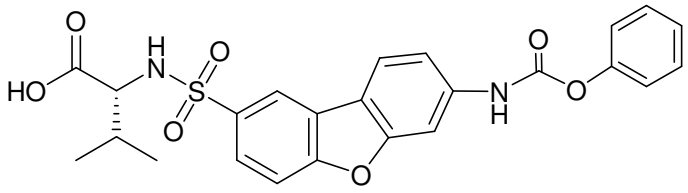


(R)-3-methyl-2-(7-(propoxycarbonylamino)dibenzo [b,d]furan-2-sulfonamido) butanoic acid (10). Following procedures for the preparation of **9** and using propyl chloroformate for the N-derivatization step, compound **10** was prepared as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.91 (d, *J*=6.82 Hz, 3 H), 0.96 (d, *J*=6.82 Hz, 3 H),

1.02 (t, *J*=7.45 Hz, 3 H), 1.67 - 1.81 (m, 2 H), 1.95 - 2.10 (m, 1 H), 3.71 (d, *J*=5.56 Hz, 1 H), 4.14 (t, *J*=6.57 Hz, 2 H), 7.35 (dd, *J*=8.46, 1.89 Hz, 1 H), 7.66 (d, *J*=8.59 Hz, 1 H), 7.91 (dd, *J*=8.72, 1.89 Hz, 1 H), 7.93 - 8.04 (m, 2 H), 8.44 (d, *J*=2.02 Hz, 1 H); HRMS: calcd for $[C_{21}H_{24}N_2O_7S\text{-}H]^-$ 448.1304; found (ESI-FTMS, $[M\text{-}H]^-$) 448.1313.

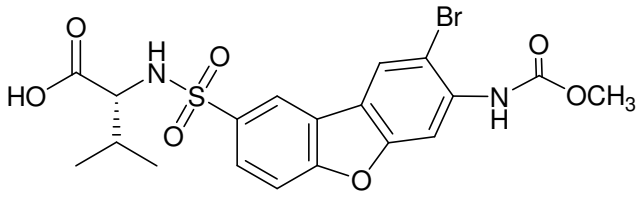


(R)-2-(7-(isopropoxycarbonylamino)dibenzo [b,d]furan-2-sulfonamido)-3-methylbutanoic acid (11). Following procedures for the preparation of **9** and using isopropyl chloroformate for the N-derivatization step, compound **11** was prepared as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.90 (d, *J*=6.82 Hz, 3 H), 0.96 (d, *J*=6.82 Hz, 3 H), 1.33 (d, *J*=6.06 Hz, 6 H), 1.94 - 2.12 (m, 1 H), 3.71 (d, *J*=5.56 Hz, 1 H), 4.93 - 5.06 (m, 1 H), 7.34 (dd, *J*=8.34, 1.77 Hz, 1 H), 7.66 (d, *J*=8.84 Hz, 1 H), 7.91 (dd, *J*=8.72, 1.89 Hz, 1 H), 7.94 - 8.01 (m, 2 H), 8.44 (d, *J*=1.26 Hz, 1 H); HRMS: calcd for $[C_{21}H_{24}N_2O_7S\text{-}H]^-$ 447.1226; found (ESI-FTMS, $[M\text{-}H]^-$) 447.1216.

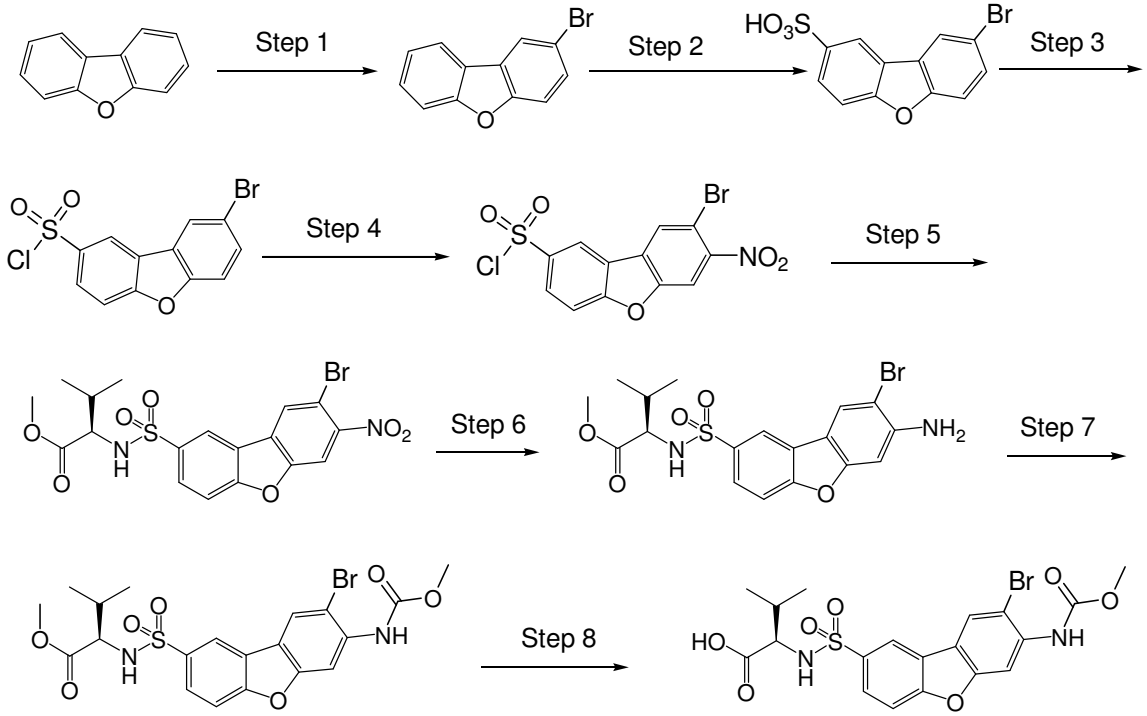


(R)-3-methyl-2-(7-(phenoxycarbonylamino)dibenzo[b,d]furan-2-sulfonamido) butanoic acid (12). Following procedures for the preparation of **9** and using phenyl chloroformate for the N-derivatization step, compound **12** was prepared as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.91 (d, *J*=6.82 Hz, 3 H), 0.97 (d, *J*=6.82 Hz, 3 H), 1.95 - 2.11 (m, 1 H), 3.72 (d, *J*=5.81 Hz, 1 H), 7.17 - 7.30 (m, 3 H), 7.38 - 7.48 (m, 3 H), 7.68 (d, *J*=8.84 Hz, 1 H), 7.93 (dd, *J*=8.72, 1.89 Hz, 1 H), 7.99 - 8.08 (m, 2 H), 8.48 (d,

J=2.02 Hz, 1 H); HRMS: calcd for $[C_{24}H_{22}N_2O_7S\text{-}H]^-$ 481.1069; found (ESI-FTMS, $[M\text{-}H]^-$) 481.1153.



(R)-2-(8-bromo-7-(methoxycarbonylamino)dibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoic acid (13a). The title compound **13a** was prepared following the scheme and procedures described below.



Step 1: 2-Bromodibenzo[b,d]furan. A round-bottomed flask was charged with dibenzofuran (15 g, 89 mmol) and acetic acid (90 mL), and then bromine (6.1 mL) was added slowly via addition funnel. The mixture was heated at 55 ^oC overnight, and then was cooled to 0 ^oC. The resulting precipitate was filtered and dried to give 2-

bromodibenzo[b,d]furan (11.3 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.33 - 7.38 (m, 1 H) 7.42 - 7.59 (m, 4 H) 7.88 - 7.92 (m, 1 H) 8.07 (d, *J*=2.02 Hz, 1 H).

Step 2: 8-Bromodibenzo[b,d]furan-2-sulfonic acid. A round-bottomed flask was charged with 2-bromodibenzo[b,d]furan (6 g, 24 mmol) and dichloromethane (100 mL), and then chlorosulfonic acid (2.0 mL, 1.2 equiv.) was slowly added to the suspension. The mixture was stirred at rt for 4h and the precipitate was collected through filtration to give 8-bromodibenzo[b,d]furan-2-sulfonic acid (5.0 g, 63%). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.73 - 7.79 (m, 1 H) 7.82 - 7.89 (m, 2 H) 8.24 (d, *J*=8.59 Hz, 1 H) 8.45 - 8.50 (m, 1 H) 8.71 (s, 1 H). MS (ESI-LCMS) *m/z* 325.4.

Step 3: 8-Bromodibenzo[b,d]furan-2-sulfonyl chloride. 8-Bromodibenzo[b,d]furan-2-sulfonic acid (5.0 g, 15 mmol) was treated with thionyl chloride (70 mL) and DMF (2 drops), and the mixture was stirred at 80 ^{o}C overnight. The solvent was removed under reduced pressure, and the solid was collected via filtration and washed with ice water to give 8-bromodibenzo[b,d]furan-2-sulfonyl chloride (4.23 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.52 - 7.56 (m, 1 H), 7.69 (dd, *J*=8.59, 2.02 Hz, 1 H), 7.69 (m, 1 H), 7.77 (d, *J*=8.59 Hz, 1 H), 8.15 - 8.24 (m, 2 H), 8.63 (dd, *J*=2.27, 0.51 Hz, 1 H).

Step 4: 8-Bromo-7-nitrodibenzo[b,d]furan-2-sulfonyl chloride. A solution of 8-bromodibenzo[b,d]furan-2-sulfonyl chloride (1.0 g, 2.9 mmol) in TFA (25 mL) was treated with fuming nitric acid (0.36 mL) and stirred at ambient temperature overnight. The resulting precipitate was collected via filtration to give 8-bromo-7-nitrodibenzo[b,d]furan-2-sulfonyl chloride (1.00 g, 89%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.86 - 7.91 (m, 1 H), 8.19 (s, 1 H), 8.31 (dd, *J*=8.84, 2.27 Hz, 1 H), 8.43 (s, 1 H), 8.73 (dd, *J*=2.02, 0.51 Hz, 1 H).

Step 5: 2-(8-Bromo-7-nitrodibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate. 8-Bromo-7-nitrodibenzo[b,d]furan-2-sulfonyl chloride (1.00 g, 2.58 mmol) was dissolved in dichloromethane (10 mL), and then was treated with D-valine methyl ester hydrochloride (1.1 equiv.) and Hunig's base (2.5 equiv.). The reaction mixture was stirred at ambient temperature overnight. After addition of water (20 mL), the product was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were

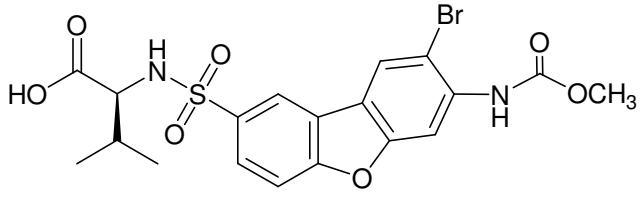
washed with saturated ammonium chloride (aq.) (2 x 10 mL), brine (2 x 10 mL), and dried over sodium sulfate. Concentration under reduced pressure afforded (R)-methyl 2-(8-bromo-7-nitrodibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate (1.19 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92 (d, *J*=6.82 Hz, 3 H), 1.04 (d, *J*=6.82 Hz, 3 H), 2.10 - 2.20 (m, 1 H), 3.48 (s, 3 H), 3.92 - 3.97 (m, 1 H), 5.64 (d, *J*=10.36 Hz, 1 H), 7.75 (dd, *J*=8.84, 0.51 Hz, 1 H), 8.01 - 8.08 (m, 2 H), 8.12 (s, 1 H), 8.60 (dd, *J*=2.02, 0.51 Hz, 1 H). MS (ESI-LCMS) *m/z* 483.3. HRMS: calcd for $[C_{18}H_{17}BrN_2O_7S+H]^+$, 485.00126; found (ESI-FTMS, $[M+H]^+$), 485.00175.

Step 6: (R)-methyl 2-(8-bromo-7-aminodibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate. A solution of (R)-methyl 2-(8-bromo-7-nitrodibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate (1.0 g, 2.1 mmol) in ethyl acetate (8 mL) was treated with tin (II) chloride (2.32 g, 10 equiv.) and the mixture was stirred at 50 ^{o}C overnight. After addition of water (20 mL), the product was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed brine (2 x 10 mL), and dried over sodium sulfate. Concentration under reduced pressure afforded (R)-methyl 2-(8-bromo-7-aminodibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate (0.828 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90 (d, *J*=6.82 Hz, 3 H), 0.98 (d, *J*=6.82 Hz, 3 H), 2.01 - 2.09 (m, 3 H), 3.81 - 3.86 (m, 1 H), 4.45 (s, 2 H), 5.25 - 5.31 (m, 1 H), 6.92 (s, 1 H), 7.53 (dd, *J*=8.59, 0.51 Hz, 1 H), 7.80 (dd, *J*=8.59, 2.02 Hz, 1 H), 7.92 (s, 1 H), 8.27 (d, *J*=2.02 Hz, 1 H), MS (LC-ESIMS) *m/z* 455.2; HRMS: calcd for $[C_{18}H_{19}BrN_2O_5S+H]^+$, 455.02708; found (ESI-FTMS, $[M+H]^+$), 455.0266.

Step 7: (R)-methyl 2-(8-bromo-7-(methoxycarbonylamino)dibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate. A solution of (R)-methyl 2-(8-bromo-7-aminodibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate (50 mg) in dichloromethane (2 mL) was treated with methyl chloroformate (1.1 equiv.) and Hunig's base (2.5 equiv.), and the reaction mixture was stirred at ambient temperature for 2 h. After addition of water (5 mL), the product was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated ammonium chloride (aq.) (2 x 5 mL), brine (2 x 5 mL), and dried over sodium sulfate. (R)-methyl 2-(8-bromo-7-(methoxycarbonylamino)dibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate was

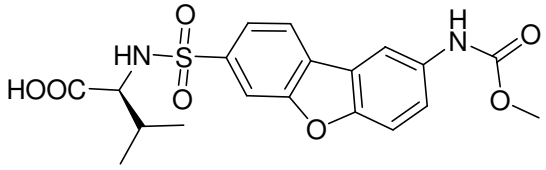
obtained by removal of solvent (45 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.88 - 0.96 (m, 3 H), 0.98 - 1.07 (m, 3 H), 2.06 - 2.19 (m, 1 H), 3.46 (s, 3 H), 3.87 (s, 3 H), 3.89 - 3.98 (m, 1 H), 7.35 - 7.44 (m, 1 H), 7.57 - 7.65 (m, 1 H), 7.75 - 7.98 (m, 2 H), 8.34 - 8.50 (m, 2 H); MS (LCMS-ESI) *m/z* 513.1; MS (LCMS-ESI) *m/z* 511.5; HRMS: calcd for $[C_{20}H_{21}BrN_2O_7S+H]^+$, 513.03256; found (ESI-FTMS, $[M+H]^+$), 513.03257.

Step 8: (R)-2-(8-bromo-7-(methoxycarbonylamino)dibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoic acid. A solution of (R)-methyl 2-(8-bromo-7-(methoxycarbonylamino)dibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoate (45 mg) in THF/H_2O (1:1, v/v, 2 mL) was treated with lithium hydroxide (3.0 equiv.). After stirring at ambient temperature for 16 hours, water was added, and the pH was adjusted to ~ 3 by the addition of 1 N HCl. After filtration, the crude solid was purified with HPLC to give (R)-2-(8-bromo-7-(methoxycarbonylamino)dibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoic acid (39 mg) as a white solid in 89% yield. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.13 (d, *J* = 6.82 Hz, 3 H), 1.20 (d, *J* = 6.82 Hz, 3 H), 2.25 - 2.33 (m, 1 H), 3.97 (d, *J* = 5.56 Hz, 1 H), 4.04 (s, 3 H), 7.89 (dd, *J* = 8.84, 0.51 Hz, 1 H), 8.18 (dd, *J* = 8.72, 1.89 Hz, 1 H), 8.38 (s, 1 H), 8.46 (s, 1 H), 8.69 (dd, *J* = 2.02, 0.51 Hz, 1 H); ^{13}C NMR (400 MHz, DMSO-d_6) 17.7, 19.0, 30.3, 52.1, 61.2, 112.2, 120.7, 121.3, 122.5, 125.3, 126.5, 136.1, 136.5, 154.5, 155.3, 157.5, 172.0. HRMS: calcd for $[C_{19}H_{19}BrN_2O_7S+H]^+$, 499.01691; found (ESI-FTMS, $[M+H]^+$), 499.01655. Anal. ($C_{19}H_{19}BrN_2O_7S$) C, H, N.

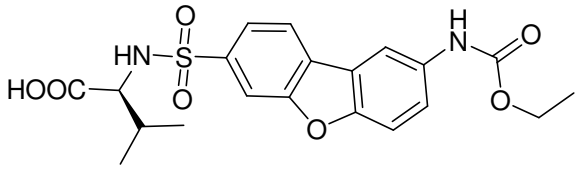


(S)-2-(8-bromo-7-(methoxycarbonylamino)dibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoic acid (13b). Following procedures described in the preparation of compound **13a** and using L-valine methyl ester hydrochloride, (S)-2-(8-bromo-7-methoxycarbonylamino)dibenzo[b,d]furan-2-sulfonamido)-3-methylbutanoic acid was

prepared as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.13 (d, *J* = 6.82 Hz, 3 H), 1.20 (d, *J* = 6.82 Hz, 3 H), 2.25 - 2.33 (m, 1 H), 3.97 (d, *J* = 5.56 Hz, 1 H), 4.04 (s, 3 H), 7.89 (dd, *J* = 8.84, 0.51 Hz, 1 H), 8.18 (dd, *J* = 8.72, 1.89 Hz, 1 H), 8.38 (s, 1 H), 8.46 (s, 1 H), 8.69 (dd, *J* = 2.02, 0.51 Hz, 1 H); ^{13}C NMR (400 MHz, DMSO-d_6) 17.7, 19.0, 30.3, 52.1, 61.2, 112.2, 120.8, 121.3, 122.5, 125.4, 126.5, 136.0, 136.5, 154.5, 155.3, 157.5, 172.0. MS (LCMS-ESI) *m/z* 499.1; HRMS: calcd for $[C_{19}H_{19}BrN_2O_7S+H]^+$, 499.01691; found (ESI-FTMS, $[M+H]^+$), 499.01737. Anal. ($C_{19}H_{19}BrN_2O_7S$) C, H, N.

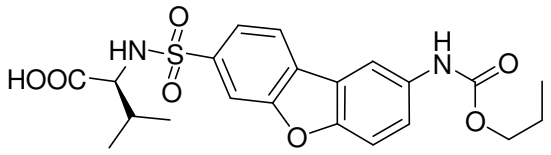


(S)-2-(8-(methoxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid (14). Following procedures for the preparation of **17** and using methyl chloroformate for the *N*-derivatization step, compound **14** was prepared as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.93 (d, *J*=6.82 Hz, 3 H), 0.99 (d, *J*=6.82 Hz, 3 H), 2.01 - 2.13 (m, 1 H), 3.75 (d, *J*=5.56 Hz, 1 H), 3.80 (s, 3 H), 7.51 - 7.62 (m, 2 H), 7.87 (dd, *J*=8.21, 1.64 Hz, 1 H), 8.07 (d, *J*=1.01 Hz, 1 H), 8.13 (d, *J*=7.58 Hz, 1 H), 8.27 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 17.6, 18.9, 30.3, 51.7, 61.3, 110.2, 110.7, 112.1, 120.6, 121.3, 121.4, 122.5, 127.0, 135.3, 140.0, 152.4, 154.2, 154.8, 172.0. MS (ES-) 419.10; HRMS: calcd for $[C_{19}H_{20}N_2O_7S+H]^+$, 421.10640; found (ESI-FTMS, $[M+H]^+$), 421.1069. Anal. ($C_{19}H_{20}N_2O_7S$) C, H, N.

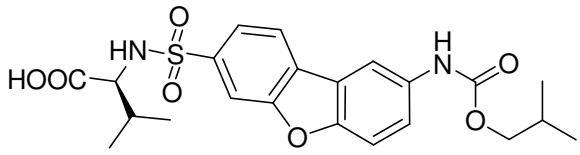


(S)-2-(8-(ethoxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid (15). Following procedures for the preparation of **17** and using ethyl chloroformate for the *N*-derivatization step, compound **15** was prepared as a white solid in 95% yield.

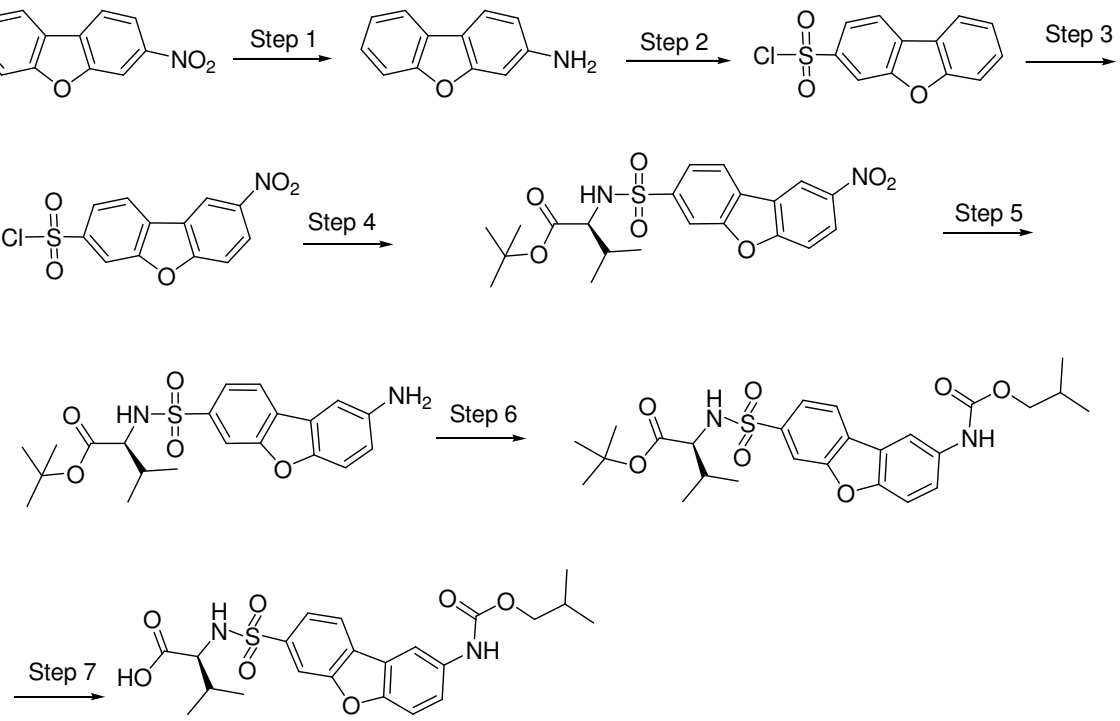
^{1}H NMR (400 MHz, MeOD) δ ppm 0.88 (d, *J*=6.82 Hz, 3 H), 0.95 (d, *J*=6.82 Hz, 3 H), 1.31 (t, *J*=7.07 Hz, 3 H), 1.93 - 2.11 (m, 1 H), 3.71 (d, *J*=5.56 Hz, 1 H), 4.20 (q, *J*=7.07 Hz, 2 H), 7.44 - 7.55 (m, 3 H), 7.81 (dd, *J*=8.34, 1.52 Hz, 1 H), 8.01 (d, *J*=1.01 Hz, 1 H), 8.06 (d, *J*=8.59 Hz, 1 H), 8.20 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 14.5, 17.7, 18.9, 30.3, 60.2, 61.3, 110.2, 110.6, 112.0, 120.5, 121.3, 122.5, 127.0, 135.4, 140.0, 152.4, 153.8, 154.8, 154.9, 172.0. HRMS: calcd for $[C_{20}H_{22}N_2O_7S+H]^+$, 435.12205; found (ESI-FTMS, $[M+H]^+$), 435.1216. Anal. ($C_{20}H_{22}N_2O_7S$) C, H, N.



(S)-3-methyl-2-(8-(propoxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido) butanoic acid (16). Following procedures for the preparation of **17** and using propyl chloroformate for the *N*-derivatization step, compound **16** was prepared as a white solid in 94% yield. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.13 (d, *J*=6.82 Hz, 3 H), 1.19 (d, *J*=6.82 Hz, 3 H), 1.25 (t, *J*=7.45 Hz, 3 H), 1.88 - 2.04 (m, 2 H), 2.18 - 2.35 (m, 1 H), 3.95 (d, *J*=5.56 Hz, 1 H), 4.36 (t, *J*=6.57 Hz, 2 H), 7.72 - 7.82 (m, 2 H), 8.06 (dd, *J*=8.08, 1.52 Hz, 1 H), 8.27 (d, *J*=1.01 Hz, 1 H), 8.33 (d, *J*=8.59 Hz, 1 H), 8.47 (s, 1 H). HRMS: calcd for $[C_{21}H_{24}N_2O_7S+H]^+$ 449.13770; found (ESI-FTMS, $[M+H]^+$) 449.1386.



(S)-2-(8-(isobutoxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid (17). The title compound **17** was prepared following the scheme and procedures described below.



Step 1: Dibenzo[b,d]furan-3-amine. 3-Nitrodibenzo[b,d]furan (See the preparation of compound **9**) (2.13 g, 10 mmol) was mixed with 20 mL of MeOH and 0.5 g of Pd/C (10%). The reaction was carried out using a Parr shaker at room temperature under hydrogen (50 psi) overnight. The reaction mixture was filtered through Celite®, and removal of MeOH under reduced pressure gave 1.80 g of dibenzo[b,d]furan-3-amine as an off-white solid in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.69 (dd, *J*=8.08, 2.02 Hz, 1 H), 6.85 (d, *J*=2.02 Hz, 1 H), 7.22 - 7.36 (m, 2 H), 7.47 (d, *J*=7.83 Hz, 1 H), 7.69 (d, *J*=8.34 Hz, 1 H), 7.75 - 7.84 (m, 1 H).

Step 2: Dibenzo[b,d]furan-3-sulfonyl chloride. A mixture of dibenzo[b,d]furan-3-amine (6 g, 32.4 mmol), glacial acetic acid (60 mL), and concentrated hydrochloric acid (60 mL) was added slowly to sodium nitrite ($NaNO_2$, 2.68 g, 38.8 mmol) in 20 mL of H_2O at -20°C to give a yellow suspension. The suspension was stirred for 30 minutes, and subsequently treated with a mixture of sulfur dioxide (30 mL) in 40 mL of 50% AcOH and dihydrate of copper (I) chloride ($CuCl_2.2H_2O$, 11.5 g, 676.2 mmol) at -23°C. The mixture was slowly warmed to room temperature and stirred for 21 hours. Once the

disappearance of the starting material was confirmed by thin layer chromatography (TLC), the reaction mixture was quenched with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate, brine, dried over sodium sulfate, and concentrated under reduced pressure to provide 4.44 g of dibenzo[b,d]furan-3-sulfonyl chloride as a white solid in 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 - 7.50 (m, 1 H), 7.58 - 7.72 (m, 2 H), 8.01 - 8.10 (m, 2 H), 8.13 - 8.20 (m, 1 H), 8.26 (d, *J*=1.77 Hz, 1 H).

Step 3: 8-Nitrodibenzo[b,d]furan-3-sulfonyl chloride. Dibenzo[b,d]furan-3-sulfonyl chloride (10.64 g, 40 mmol) was dissolved in 60 mL of CH_2Cl_2 and the resulting solution was stirred for 30 minutes at room temperature. After addition of 100 mL of TFA to the solution, nitric acid (10.6g, 168 mmol) was added dropwise. The mixture was stirred at room temperature for 6 hours and monitored by ^{1}H NMR, and the desired product precipitated out of the reaction mixture. CH_2Cl_2 was removed under reduced pressure. More TFA (60 mL) was added, and the reaction mixture was filtered. The filter cake was washed with cold water to provide 10.11 g of 8-nitrodibenzo[b,d]furan-3-sulfonyl chloride as a yellow solid in 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.82 (d, *J*=9.09 Hz, 1 H), 8.29 (d, *J*=8.34 Hz, 1 H), 8.36 (d, *J*=1.01 Hz, 1 H), 8.57 (dd, *J*=9.09, 2.27 Hz, 1 H), 9.01 (d, *J*=2.02 Hz, 1 H).

Step 4: (S)-tert-Butyl 3-methyl-2-(8-nitrodibenzo[b,d]furan-3-sulfonamido)butanoate. L-Valine *t*-butyl ester (HCl salt, 14.98 g, 71.4 mmol) and N, N-diisopropylethylamine (20 g, 24.9 mL) were mixed in CH_2Cl_2 (250 mL), and 8-nitrodibenzo[b,d]furan-3-sulfonyl chloride from Step 3 (22.26 g, 71.4 mmol) was added slowly at 0°C. The reaction was allowed to warm up to room temperature for 2 hours. Water (200 mL) was added into the reaction flask and CH_2Cl_2 was removed under reduced pressure with continuous stirring. The desired product precipitated out as a white solid in the aqueous media after complete removal of CH_2Cl_2. The suspension was filtered and the filter cake was washed with water and dried to give 30.4 g of (S)-tert-butyl 3-methyl-2-(8-nitrodibenzo[b,d]furan-3-sulfonamido)butanoate in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86 (d, *J*=6.82 Hz, 3 H), 1.02 (d, *J*=6.82 Hz, 3 H), 1.13 (s, 9 H), 2.02 - 2.15 (m, 1 H), 3.74 (dd, *J*=9.98,

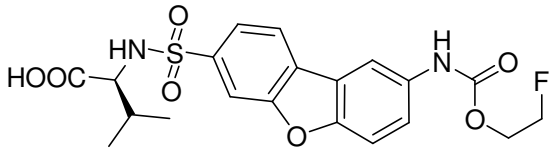
4.42 Hz, 1 H), 5.23 (d, *J*=9.85 Hz, 1 H), 7.75 (d, *J*=8.59 Hz, 1 H), 7.95 (dd, *J*=8.34, 1.52 Hz, 1 H), 8.11 - 8.18 (m, 2 H), 8.50 (dd, *J*=9.09, 2.27 Hz, 1 H), 8.94 (d, *J*=2.02 Hz, 1 H).

Step 5: (S)-tert-Butyl 2-(8-aminodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate. (S)-Tert-butyl 3-methyl-2-(8-nitrodibenzo[b,d]furan-3-sulfonamido) butanoate (6.12 g) and 0.6 g of 10% Pd/C (50% water) in MeOH (150 mL) was placed in a Parr shaker under hydrogen atmosphere (50 psi) for 6 hours. The suspension was filtered through Celite®, and concentration of the filtrate under reduced pressure afforded 5.70 g of (S)-tert-butyl 2-(8-aminodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate as a white solid in 98% yield. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 0.84 (d, *J*=6.82 Hz, 3 H), 0.98 (d, *J*=6.82 Hz, 3 H), 1.09 (s, 9 H), 1.95 - 2.13 (m, 1 H), 3.68 (dd, *J*=9.85, 4.80 Hz, 1 H), 3.85 (s, 2 H), 5.33 (m, 1 H), 6.92 (dd, *J*=8.72, 2.40 Hz, 1 H), 7.24 (d, *J*=2.27 Hz, 1 H), 7.40 (d, *J*=8.84 Hz, 1 H), 7.75 (dd, *J*=8.21, 1.64 Hz, 1 H), 7.88 - 8.02 (m, 2 H).

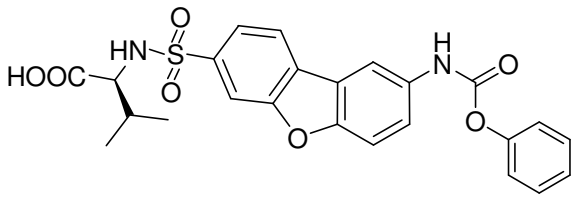
Step 6: (S)-tert-butyl 2-(8-(isobutoxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate. (S)-tert-Butyl 2-(8-aminodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate (0.5 mmol) from Step 5 and DMAP (0.6 mmol) were dissolved in 5 mL of CH_2Cl_2, followed by slow addition of isobutyl chloroformate (0.55 mmol). The mixture was stirred at room temperature overnight, then put directly on a silica gel column chromatography for purification to provide the desired carbamate (S)-tert-butyl 2-(8-(isobutoxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate as a white solid in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86 (d, *J*=6.82 Hz, 3 H), 1.01 (t, *J*=6.57 Hz, 9 H), 1.10 (s, 9 H), 1.91 - 2.14 (m, 2 H), 3.71 (dd, *J*=9.85, 4.55 Hz, 1 H), 4.01 (d, *J*=6.57 Hz, 2 H), 5.21 (d, *J*=9.85 Hz, 1 H), 6.81 (s, 1 H), 7.36 (dd, *J*=8.84, 2.27 Hz, 1 H), 7.53 (d, *J*=8.84 Hz, 1 H), 7.82 (dd, *J*=8.08, 1.52 Hz, 1 H), 8.00 (d, *J*=8.34 Hz, 1 H), 8.03 (d, *J*=1.52 Hz, 1 H), 8.24 (s, 1 H).

Step 7: (S)-2-(8-(Isobutoxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid. The carbamate t-butyl ester (0.4 mmol, Step 6) was dissolved in 4 mL of TFA/CH_2Cl_2 (1:1), and the solution was stirred at room temperature for 3 hours. The solvents were removed under reduced pressure and the residue was triturated in CH_3CN/water followed by a freeze-dry process. The desired final product, (S)-2-(8-

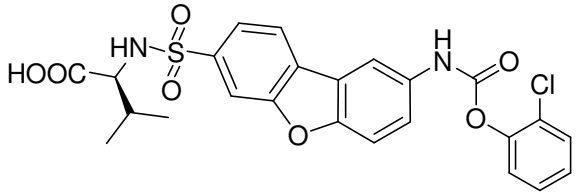
(Isobutoxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid, was obtained as a white solid in 98% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (d, *J*=6.82 Hz, 3 H), 0.83 (d, *J*=6.82 Hz, 3 H), 0.96 (d, *J*=6.57 Hz, 6 H), 1.88 - 2.01 (m, 2 H), 3.60 (dd, *J*=9.47, 5.94 Hz, 1 H), 3.92 (d, *J*=6.57 Hz, 2 H), 7.58 (dd, *J*=8.97, 2.15 Hz, 1 H), 7.72 (d, *J*=9.09 Hz, 1 H), 7.79 (dd, *J*=8.08, 1.52 Hz, 1 H), 8.03 (d, *J*=1.77 Hz, 1 H), 8.17 (d, *J*=9.35 Hz, 1 H), 8.26 (d, *J*=8.34 Hz, 1 H), 8.35 (s, 1 H), 9.85 (s, 1 H), 12.52 (s, 1 H); HRMS: calcd for $[C_{22}H_{26}N_2O_7S+H]^+$ 463.15335; found (ESI-FTMS, $[M+H]^+$) 463.1544. Anal. ($C_{22}H_{26}N_2O_7S$) C, H, N.



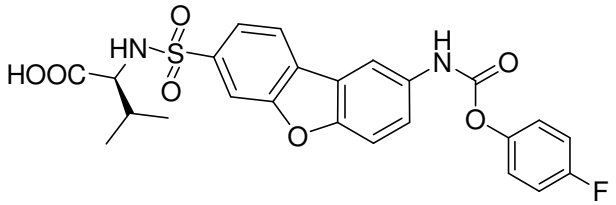
(S)-2-(8-((2-fluoroethoxy)carbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid (18). Following procedures for the preparation of **17** and using 2-fluoroethyl chloroformate for the *N*-derivatization step, compound **18** was prepared as a white solid in 100% yield. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.13 (d, *J*=6.82 Hz, 3 H), 1.19 (d, *J*=6.82 Hz, 3 H), 2.17 - 2.36 (m, 1 H), 3.95 (d, *J*=5.56 Hz, 1 H), 4.54 - 4.63 (m, 1 H), 4.63 - 4.72 (m, 1 H), 4.77 - 4.87 (m, 1 H), 4.88 - 5.00 (m, 1 H), 7.70 - 7.84 (m, 2 H), 8.07 (d, *J*=8.08 Hz, 1 H), 8.27 (s, 1 H), 8.33 (d, *J*=8.08 Hz, 1 H), 8.47 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 17.7, 18.9, 30.3, 61.3, 63.5, 63.7, 81.1, 82.8, 110.2, 110.8, 112.1, 120.6, 121.4, 122.5, 127.0, 135.1, 140.0, 152.5, 153.5, 154.8, 172.0. HRMS: calcd for $[C_{20}H_{21}FN_2O_7S+H]^+$ 453.11263; found (ESI-FTMS, $[M+H]^+$) 453.1135. Anal. ($C_{20}H_{21}FN_2O_7S$) C, H, N.



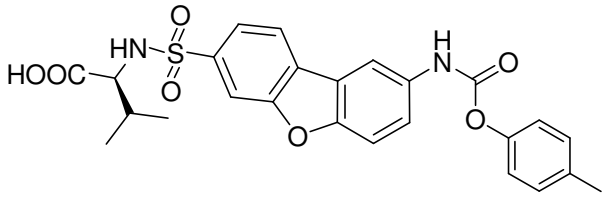
(S)-3-methyl-2-(8-(phenoxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido) butanoic acid (19). Following procedures for the preparation of **17** and using phenyl chloroformate for the *N*-derivatization step, compound **19** was prepared as a white solid in 93% yield. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.13 (d, *J*=6.82 Hz, 3 H), 1.19 (d, *J*=6.82 Hz, 3 H), 2.17 - 2.35 (m, 1 H), 3.95 (d, *J*=5.56 Hz, 1 H), 7.39 - 7.52 (m, 3 H), 7.59 - 7.70 (m, 2 H), 7.84 (d, *J*=1.26 Hz, 2 H), 8.07 (dd, *J*=8.08, 1.52 Hz, 1 H), 8.28 (d, *J*=1.52 Hz, 1 H), 8.35 (d, *J*=8.08 Hz, 1 H), 8.54 (s, 1 H), 10.23 (s, 1 H). HRMS: calcd for $[C_{24}H_{22}N_2O_7S+H]^+$ 483.12205; found (ESI-FTMS, $[M+H]^+$) 483.1229.



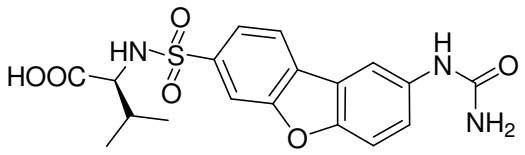
(S)-2-(8-((2-chlorophenoxy)carbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid (20). Following procedures for the preparation of **17** and using 2-chlorophenyl chloroformate for the *N*-derivatization step, compound **20** was prepared as a white solid in 96% yield. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.70 (d, *J*=6.82 Hz, 3 H), 0.76 (d, *J*=6.82 Hz, 3 H), 1.72 - 1.93 (m, 1 H), 3.51 (d, *J*=5.56 Hz, 1 H), 7.02 - 7.22 (m, 3 H), 7.31 (dd, *J*=8.08, 1.52 Hz, 1 H), 7.42 (s, 2 H), 7.64 (dd, *J*=8.21, 1.64 Hz, 1 H), 7.85 (d, *J*=1.01 Hz, 1 H), 7.92 (d, *J*=8.08 Hz, 1 H), 8.10 (s, 1 H), 10.02 (s, 1 H). HRMS: calcd for $[C_{24}H_{21}ClN_2O_7S+NH_4]^+$ 534.10963; found (ESI-FTMS, $[M+NH_4]^+$) 534.1096.



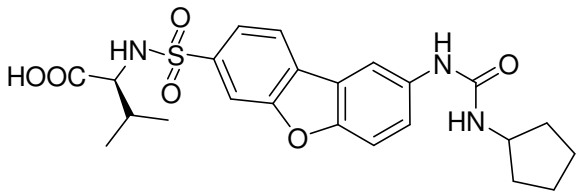
(S)-2-(8-((4-fluorophenoxy)carbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid (21). Following procedures for the preparation of **17** and using 4-fluorophenyl chloroformate for the *N*-derivatization step, compound **21** was prepared as a white solid in 90% yield. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.93 (d, *J*=6.82 Hz, 3 H), 0.99 (d, *J*=6.57 Hz, 3 H), 1.94 - 2.16 (m, 1 H), 3.75 (d, *J*=5.56 Hz, 1 H), 7.08 - 7.22 (m, 2 H), 7.21 - 7.31 (m, 2 H), 7.54 - 7.65 (m, 2 H), 7.86 (dd, *J*=8.08, 1.52 Hz, 1 H), 8.07 (d, *J*=1.52 Hz, 1 H), 8.08 - 8.17 (m, 1 H), 8.31 (s, 1 H). HRMS: calcd for $[C_{24}H_{21}FN_2O_7S+H]^+$ 501.11263; found (ESI-FTMS, $[M+H]^+$) 501.1125.



(S)-3-methyl-2-(8-(p-tolyloxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido)butanoic acid (22). Following procedures for the preparation of **17** and using 4-toluyl chloroformate for the *N*-derivatization step, compound **22** was prepared as a white solid in 99% yield. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.13 (d, *J*=6.82 Hz, 3 H), 1.19 (d, *J*=6.82 Hz, 3 H), 2.18 - 2.34 (m, 1 H), 2.58 (s, 3 H), 3.95 (d, *J*=5.56 Hz, 1 H), 7.26 - 7.35 (m, 2 H), 7.45 (d, *J*=8.34 Hz, 2 H), 7.83 (d, *J*=1.52 Hz, 2 H), 8.07 (dd, *J*=8.21, 1.64 Hz, 1 H), 8.28 (d, *J*=1.52 Hz, 1 H), 8.35 (d, *J*=8.34 Hz, 1 H), 8.53 (s, 1 H), 10.18 (s, 1 H). HRMS: calcd for $[C_{25}H_{24}N_2O_7S+H]^+$ 497.13770; found (ESI-FTMS, $[M+H]^+$) 497.1377.

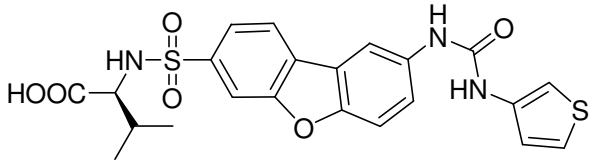


(S)-3-methyl-2-(8-ureidodibenzo[b,d]furan-3-sulfonamido)butanoic acid (23). Following general literature procedures for the preparation of **17** and using potassium cyanate[2] for the *N*-derivatization step, compound **23** was prepared as a pale yellow solid in 70% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (d, *J*=6.82 Hz, 3 H), 0.83 (d, *J*=6.82 Hz, 3 H), 1.85 - 2.02 (m, 1 H), 3.59 (dd, *J*=9.47, 5.94 Hz, 1 H), 5.91 (s, 3 H), 7.50 (dd, *J*=8.84, 2.27 Hz, 1 H), 7.65 (d, *J*=8.84 Hz, 1 H), 7.77 (dd, *J*=8.21, 1.64 Hz, 1 H), 8.00 (d, *J*=1.01 Hz, 1 H), 8.10 - 8.19 (m, 1 H), 8.26 (d, *J*=8.08 Hz, 1 H), 8.30 (d, *J*=2.02 Hz, 1 H), 8.74 (s, 1 H), 12.49 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 17.7, 18.9, 30.3, 61.2, 110.0, 110.1, 111.8, 120.2, 121.2, 121.3, 122.4, 127.2, 136.7, 139.7, 151.8, 154.7, 156.1, 171.9. HRMS: calcd for $[C_{18}H_{19}N_3O_6S+H]^+$ 406.10673; found (ESI-FTMS, $[M+H]^+$) 406.1079.

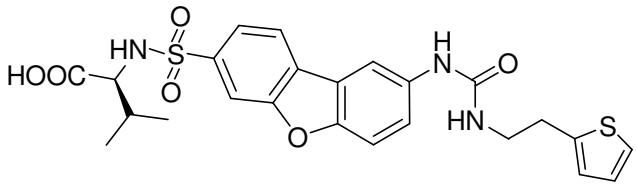


(S)-2-(8-(3-cyclopentylureido)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid (24). Following procedures for the preparation of **17** and using cyclopentyl isocynate for the *N*-derivatization step, compound **24** was prepared as a white solid in 79% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (d, *J*=6.82 Hz, 3 H), 0.83 (d, *J*=6.57 Hz, 3 H), 1.31 - 1.47 (m, 2 H), 1.49 - 1.61 (m, 2 H), 1.60 - 1.73 (m, 2 H), 1.79 - 2.03 (m, 3 H), 3.59 (dd, *J*=9.35, 6.06 Hz, 1 H), 3.87 - 4.07 (m, 1 H), 6.22 (d, *J*=7.07 Hz, 1 H), 7.47 (dd, *J*=9.09, 2.27 Hz, 1 H), 7.65 (d, *J*=8.84 Hz, 1 H), 7.77 (dd, *J*=8.21, 1.64 Hz, 1 H), 8.00 (d, *J*=1.26 Hz, 1 H), 8.15 (d, *J*=9.35 Hz, 1 H), 8.25 (d, *J*=8.34 Hz, 1 H), 8.28 (d, *J*=2.27 Hz, 1 H), 8.46 (s, 1 H), 12.53 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 17.1, 18.9, 23.1, 30.3, 32.7, 50.9, 61.2, 109.9, 110.1, 111.8, 120.0, 121.2, 121.3, 122.4, 127.2, 136.7, 139.7, 151.7, 154.7, 154.9, 171.9. HRMS: calcd for $[C_{23}H_{27}N_3O_6S+H]^+$ 474.16933; found (ESI-FTMS, $[M+H]^+$) 474.1696.

2 Harriman, G. C.; Brewer, M.; Bennett, R.; Kuhn, C.; Bazin, M.; Larosa, G.; Skerker, P.; Cochran, N.; Gallant, D.; Baxter, D.; Picarella, D.; Jaffee, B.; Luly, J. R.; Briskin, M. J. Bioorg & Med. Chem. Latt. **2008**, *18*, 2509.

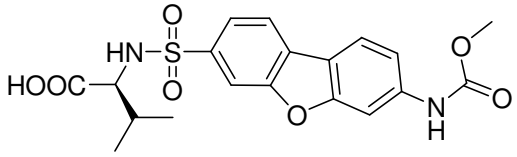


(S)-3-methyl-2-(8-(3-thiophen-3-ylureido)dibenzo[b,d]furan-3-sulfonamido)butanoic acid (25). Following procedures for the preparation of **17** and using 3-thiophen-3-yl isocynate for the *N*-derivatization step, compound **25** was prepared as a white solid in 80% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (d, *J*=6.82 Hz, 3 H), 0.84 (d, *J*=6.57 Hz, 3 H), 1.82 - 2.03 (m, 1 H), 3.60 (dd, *J*=9.35, 6.06 Hz, 1 H), 7.09 (dd, *J*=5.05, 1.26 Hz, 1 H), 7.27 - 7.36 (m, 1 H), 7.45 (dd, *J*=5.05, 3.03 Hz, 1 H), 7.56 (dd, *J*=8.84, 2.27 Hz, 1 H), 7.71 (d, *J*=8.84 Hz, 1 H), 7.79 (dd, *J*=8.21, 1.39 Hz, 1 H), 8.03 (d, *J*=1.26 Hz, 1 H), 8.16 (d, *J*=9.60 Hz, 1 H), 8.31 (d, *J*=8.08 Hz, 1 H), 8.37 (d, *J*=2.27 Hz, 1 H), 8.86 (s, 1 H), 9.04 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 17.7, 18.9, 30.3, 61.2, 105.66, 110.2, 110.9, 112.0, 120.7, 121.3, 121.4, 122.5, 124.6, 127.1, 135.9, 137.3, 139.8, 152.2, 152.5, 154.8, 172.0. HRMS: calcd for $[C_{22}H_{21}N_3O_6S_2+H]^+$ 488.09445; found (ESI-FTMS, $[M+H]^+$) 488.0948.

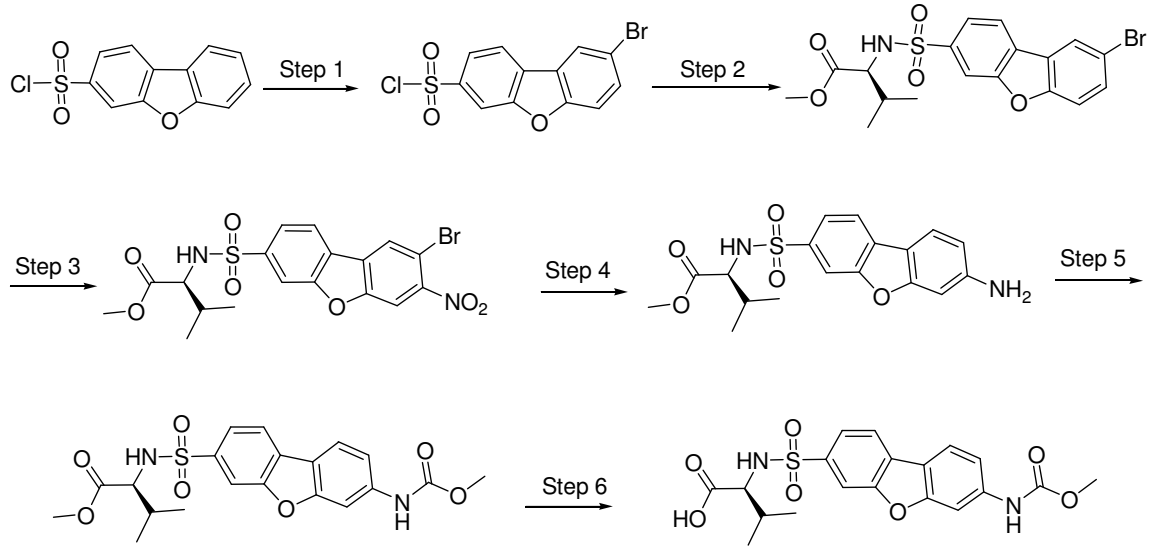


(S)-3-methyl-2-(8-(3-(2-(thiophen-2-yl)ethyl)ureido)dibenzo[b,d]furan-3-sulfonamido)butanoic acid (26) . Following procedures for the preparation of **17** and using using 2-(thiophen-2-yl)ethyl isocynate for the *N*-derivatization step, compound **26** was prepared as a white solid in 80% yield. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.12 (d, *J*=6.05 Hz, 3 H), 1.19 (d, *J*=6.06 Hz, 3 H), 2.26 (s, 2 H), 3.31 (t, *J*=6.69 Hz, 2 H), 3.72 (t, 2 H), 3.96 (s, 1 H), 7.08 - 7.22 (m, 2 H), 7.45 (dd, *J*=5.05, 1.01 Hz, 1 H), 7.64 (dd, *J*=8.84, 2.27 Hz, 1 H), 7.77 (d, *J*=8.84 Hz, 1 H), 8.07 (d, *J*=8.30 Hz, 1 H), 8.26 (s, 1 H),

8.33 (d, *J*=8.34 Hz, 1 H), 8.42 (d, *J*=2.02 Hz, 1 H). HRMS: calcd for $[C_{24}H_{25}N_3O_6S_2+H]^+$ 516.12575; found (ESI-FTMS, $[M+H]^+$) 516.1247.



(S)-2-(7-(methoxycarbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid (27). The title compound was prepared following the scheme and synthetic procedures described below.



Step 1: 8-Bromodibenzo[b,d]furan-3-sulfonyl chloride. Dibenzo[b,d]furan-3-sulfonyl chloride (5.3 g, 20 mmol) was mixed with AcOH (glacial, 120 mL) and bromine (10 mL, 10 equiv.). The mixture was stirred in a 70 ^oC oil bath for 4 hours. The excess bromine was removed by bubbling nitrogen through the reaction mixture and trapped with saturated aqueous Na_2SO_3 solution. The resulting solution was cooled down to ambient temperature and filtered, providing 5.4 g of 8-bromodibenzo[b,d]furan-3-sulfonyl chloride as a light brown solid.

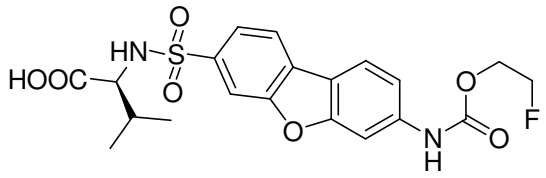
Step 2: (S)-methyl 2-(8-bromodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate. A solution of 8-bromodibenzo[b,d]furan-3-sulfonyl chloride (3.46 g, 10 mmol) and (S)-

methyl 2-amino-3-methylbutanoate hydrochloride (1.1 equiv.) in 30 mL of CH_2Cl_2 was treated with N, N-diisopropylethylamine (3.84 mL, 2.2 equiv.). The mixture was stirred at room temperature for 5 hours, then was loaded onto a silica gel column and purified by column chromatography. Following purification, 4.7 g of (S)-methyl 2-(8-bromodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate was obtained as a white solid.

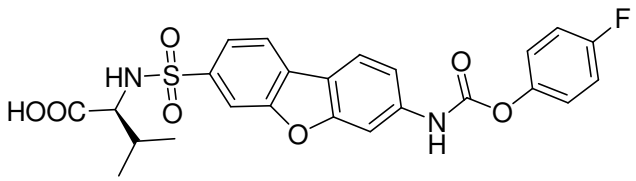
Step 3: (S)-methyl 2-(8-bromo-7-nitrodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate. A mixture of (S)-Methyl 2-(8-bromodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate (724 mg, 1.6 mmol) and HNO_3 (0.27 g, 4.2 mmol) in 15 mL of TFA and 1 mL of CH_2Cl_2 was stirred at room temperature for 5 hours. The solvent was removed under reduced pressure and the crude product was purified by column chromatography to provide 625 mg of (S)-methyl 2-(8-bromo-7-nitrodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate as a yellow solid.

Step 4: (S)-methyl 2-(7-aminodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate. (S)-Methyl 2-(8-bromo-7-nitrodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate (11.56 g, 23.8 mmol) was mixed with 200 mL of MeOH and 700 mg of Pd/C (10%), then the reaction was carried out using Parr shaker at room temperature under 50 psi H_2 overnight. The reaction mixture was filtered through Celite®, and subsequent removal of MeOH gave 8.92 g of (S)-methyl 2-(7-aminodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate as a gray solid.

Step 5 & 6: The desired carbamate was prepared by reaction of methyl chloroformate with (S)-methyl 2-(7-aminodibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoate and subsequent saponification (HOAc/HCl/Water, 60 ^{o}C) to afford compound **27** as a white solid in 92% yield. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.13 (d, *J*=6.82 Hz, 3 H), 1.19 (d, *J*=6.82 Hz, 3 H), 2.17 - 2.34 (m, 1 H), 3.94 (d, *J*=5.56 Hz, 1 H), 4.01 (s, 3 H), 7.57 (dd, *J*=8.46, 1.64 Hz, 1 H), 8.04 (dd, *J*=8.08, 1.52 Hz, 1 H), 8.14 - 8.22 (m, 2 H), 8.24 (d, *J*=1.52 Hz, 1 H), 8.28 (d, *J*=8.08 Hz, 1 H), 9.85 (s, 1 H).



(S)-2-(7-((2-fluoroethoxy)carbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid (28). Following procedures for the preparation of **27** and using 2-fluoroethyl chloroformate for the *N*-derivatization step, compound **28** was obtained as a white solid in 94% yield. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.12 (d, *J*=5.05 Hz, 3 H), 1.19 (d, *J*=5.05 Hz, 3 H), 2.25 (s, 1 H), 4.57 - 4.63 (m, 1 H), 4.64 - 4.72 (m, 1 H), 4.79 - 4.85 (m, 1 H), 4.90 - 4.98 (m, 1 H), 7.59 (m, 1 H), 8.04 (d, *J*=7.58 Hz, 1 H), 8.20 (d, *J*=8.59 Hz, 2 H), 8.24 (s, 1 H), 8.29 (d, *J*=7.83 Hz, 1 H). HRMS: calcd for $[C_{20}H_{21}FN_2O_7S+H]^+$ 453.11263; found (ESI-FTMS, $[M+H]^+$), 453.1133. Anal. ($C_{20}H_{21}FN_2O_7S$) C, H, N.



(S)-2-(7-((4-fluorophenoxy)carbonylamino)dibenzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid (29). Following procedures for the preparation of **27** and using 4-fluorophenyl chloroformate for the *N*-derivatization step, compound **29** was obtained as a white solid in 86% yield. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.12 (d, *J*=5.31 Hz, 3 H), 1.19 (d, *J*=5.56 Hz, 3 H), 2.25 (s, 1 H), 3.96 (s, 1 H), 7.32 - 7.42 (m, 2 H), 7.42 - 7.51 (m, 2 H), 7.67 (dd, *J*=8.34, 1.77 Hz, 1 H), 8.06 (d, *J*=8.08 Hz, 1 H), 8.19 - 8.29 (m, 3 H), 8.32 (d, *J*=7.83 Hz, 1 H); HRMS: calcd for $[C_{24}H_{21}FN_2O_7S+H]^+$, 501.11263; found (ESI-FTMS, $[M+H]^+$), 501.1125. Anal. ($C_{24}H_{21}FN_2O_7S$) C, H, N.