Supporting Information.

Discovery of Potent, Selective, and Orally Active Carboxylic Acid Based Inhibitors of Matrix Metalloproteinase-13

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Contents

Preparation of Sulfonyl Chlorides.

5-(4'-*N*,*N*-Dimethylaminophenyl)-thiophene-2-sulfonyl chloride (8). Suzuki Coupling Method A. To a mixture of thiophene-2-boronic acid (54.44 g, 425 mmol), 4-bromo-*N*,*N*-dimethylaniline (42.5 g, 212 mmol), and Na_2CO_3 (224.3 g, 2120 mmol) in anhydrous EtOH (850 mL) was added $PdCl_2$(dppf) (1.22 g, 1.05 mmol). The mixture was heated to 55 ºC overnight, cooled to room temperature and filtered through Hyflo to remove the sodium carbonate. The solvent was removed *in vacuo* and CH_2Cl_2 (500 mL) was added to the residue. This solution was adsorbed on silica gel (100 g), reconcentrated, and eluted through a column of silica gel (600 g) using hexanes/EtOAc (4:1). The solvent was removed *in vacuo* to provide a yellow solid which was triturated with ice-cold hexanes to provide 2-(4'-*N*,*N*-dimethylaminophenyl)-thiophene as a yellow solid.

The above thiophene was converted to the sulfonyl chloride by **Chlorosulfonylation Method A** as follows. 2-(4'-*N*,*N*-Dimethylaminophenyl)-thiophene (10.15 g, 50 mmol) of was added slowly to neat chlorosulfonic acid (58.1 g, 500 mmol) cooled to 0 °C in an ice bath. The reaction mixture was stirred at 0 °C for 5 minutes after which the bath was removed and the mixture stirred for an additional 20 minutes before it was poured over ice (500 g). Ice water (200 mL) was used to effect quantitative transfer from the reaction vessel. The pH of the mixture was adjusted to 7-8 by portionwise addition of solid $NaHCO_3$. The yellow-orange precipitate was collected by vacuum filtration, washed with H_2O and air dried to provide the title compound (13.14 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.04 (s, 6 H), 6.72 (d, *J*=9.0 Hz, 2 H), 7.14 (d, *J*=4.1 Hz, 1 H), 7.51 (d, *J*=9.0 Hz, 2 H), 7.78 (d, *J*=4.1 Hz, 1 H).

5-(4'-Piperidin-1-ylphenyl)-thiophene-2-sulfonyl chloride (18a). Suzuki Coupling Method B. Thiophene-2-boronic acid (1.17 g, 9.16 mmol), 1-(4-bromophenyl)-piperidine (2.00 g, 8.33 mmol), $Pd_2(dba)_3$ (0.076 g, 0.08 mmol), (*t*-Bu)$_3$P (0.042 g, 0.21 mmol) were stirred at room temperature under N_2 in THF (20 mL). After 18 h, the reaction was filtered through silica gel using fresh EtOAc as a wash. The combined filtrates were concentrated *in vacuo*. The residue was triturated with hexanes and the resultant solid isolated by filtration to afford the coupled biaryl product. A second portion of 1-(4-thiophen-2-yl-phenyl)-piperidine **17a** was isolated from the filtrate by removal of the volatiles under reduced pressure, followed by purification of the residue by flash chromatography (5% EtOAc/hexanes).

The 1-(4-thiophen-2-yl-phenyl)-piperidine **17a** prepared above was chlorosulfonylated with $ClSO_3H$ according to the Chlorosulfonylation Method A outlined in the preparation of **8** to yield the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.58 - 1.79 (m, 6 H), 3.21 - 3.36 (m, 4 H), 6.92 (d, *J*=8.8 Hz, 2 H), 7.15 (d, *J*=4.1 Hz, 1 H), 7.49 (d, *J*=8.8 Hz, 2 H), 7.78 (d, *J*=4.1 Hz, 1 H).

5-Phenyl-thiophene-2-sulfonyl chloride (18b). 2-Phenylthiophene **17b** was prepared from phenylboronic acid and 2-bromothiophene by Suzuki Coupling Method A.

2-Phenylthiophene was converted to the sulfonyl chloride by **Chlorosulfonylation Method B** as follows. To a solution of 2-phenylthiophene (3.45 g, 21.5 mmol) in THF (200 mL) cooled to -78 °C was added *n*-BuLi (14.8 mL of a 1.6 M solution in hexanes, 23.7 mmol). After 1 h, SO_2 (g) was introduced the into the reaction vessel

atmosphere. The cold bath was removed and the reaction was stirred for 1 h. Hexanes were added and the lithium salt (4.32 g, 87%) was isolated by filtration.

To a slurry of the above lithium salt (0.46 g, 2.0 mmol) in hexanes at 0 °C under N_2, was added sulfuryl chloride (0.16 mL, 2.0 mmol). After 20 min, the reaction was filtered through $MgSO_4$ and Celite®. The filter cake was washed with hexanes and the combined filtrates were concentrated under reduced pressure to a solid (0.42 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.31 (d, *J*=4.1 Hz, 1 H), 7.43 - 7.52 (m, 3 H), 7.60 - 7.67 (m, 2 H), 7.84 (d, *J*=4.1 Hz, 1 H).

5-(3'-Ethoxyphenyl)-thiophene-2-sulfonyl chloride (18c). Suzuki Coupling Method C. 5-Bromothiophene-2-sulfonic acid (5.00 g, 20.0 mmol), 3-ethoxyphenyl boronic acid (3.36 g, 20.0 mmol), K_2CO_3 (5.6 g, 40.0 mmol), and $PdCl_2$(dppf) (0.73 g, 1.0 mmol) were dissolved in DME (50 mL) and water (50 mL) and heated to 80 ºC. After 3 h, the reaction was cooled and diluted with Et_2O (200 mL) and water (100 mL). A solid precipitated when the mixture was adjusted to pH 6 with 3 M HCl.. Sodium chloride (30 g) was added and the mixture was stirred overnight. The off-white precipitate was collected by filtration, washed with ether/acetone (1:1, 3 x 100 mL) and air dried to constant weight (4.2 g). To a slurry of the sulfonic acid (4.1 g, 14.4 mmol) in THF (100 mL) was added dropwise neat oxalyl chloride (5.2 mL, 60.0 mmol), followed by DMF (4.6 mL). After 18 h, the reaction was concentrated under reduced pressure. The residue was partitioned between EtOAc and water. The separated organic phase was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography to afford the title sulfonyl chloride (3.4 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.45 (t, *J*=6.8 Hz, 3 H) 4.09 (q, *J*=6.8 Hz, 2 H) 6.97 (dd, *J*=8.3, 2.6 Hz, 1 H) 7.19 (d, *J*=7.5 Hz, 1 H) 7.13 (d, *J*=2.3 Hz, 1 H) 7.26 - 7.39 (m, 2 H) 7.83 (d, *J*=3.8 Hz, 1 H).

5-(3',4'-Dimethoxyphenyl)-thiophene-2-sulfonyl chloride (18d). 2-Bromothiophene and 3,4-dimethoxyphenyl boronic acid were coupled by Suzuki Coupling Method C to afford 2-(3',4'-dimethoxyphenyl)-thiophene **17d**. The 2-(3',4'-dimethoxyphenyl)-thiophene was converted to the sulfinic acid lithium salt by lithiation and trapping with SO_2, as in Chlorosulfonylation Method B: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.76 (s, 3 H), 3.82 (s, 3 H), 6.88 (d, *J*=3.77 Hz, 1 H), 6.96 (d, *J*=8.29 Hz, 1 H) 7.08 - 7.16 (m, 1 H) 7.09 (d, *J*=1.51 Hz, 1 H) 7.21 (d, *J*=3.39 Hz, 1 H).

To a suspension of the sulfinic acid salt (132 mg, 0.46 mmol) in CH_2Cl_2 (10 mL) at 0 ºC, was added NCS (62 mg, 0.46 mmol). After warming to room temperature for 15 min, the reaction was filtered through Celite®. The filtrate was concentrated to dryness to afford the title sulfonyl chloride.

5-Pyridin-4-yl-thiophene-2-sulfonyl chloride (18e). Thiophene-2-boronic acid and 4-bromopyridine were coupled by analogy to Suzuki Coupling Method A. Treatment of the biaryl **17e** with $ClSO_3H$ according to Chlorosulfonylation Method A afforded the title sulfonyl chloride: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.32 (d, *J*=3.9 Hz, 1 H), 8.05 (d, *J*=3.9 Hz, 1 H), 8.28 (d, *J*=6.8 Hz, 2 H), 8.83 (d, *J*=6.8 Hz, 2 H).

5-(6'-Methoxypyridin-3-yl)-thiophene-2-sulfonyl chloride (18f). Thiophene-2-boronic acid and 5-bromo-2-methoxypyridine were coupled by analogy to Suzuki Coupling Method A. Treatment of the biaryl **17f** with $ClSO_3H$ according to Chlorosulfonylation Method A afforded the title sulfonyl chloride: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.01 (s, 3 H) 6.85 (d, *J*=8.7 Hz, 1 H) 7.24 (d, *J*=4.1 Hz, 1 H) 7.80 (dd, *J*=8.7, 2.64 Hz, 1 H) 7.85 (d, *J*=4.1 Hz, 1 H) 8.48 (d, *J*=2.3 Hz, 1 H).

5-(4'-Methoxyphenyl)-thiophene-2-sulfonyl chloride (18g). By the procedures outlined in the preparation of **18c**, bromothiophene-2-sulfonic acid and 4-methoxyphenyl boronic acid were converted to the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.87 (s, 3 H) 6.97 (d, *J*=8.9 Hz, 2 H) 7.20 (d, *J*=4.1 Hz, 1 H) 7.55 (d, *J*=8.9 Hz, 2 H) 7.82 (d, *J*=4.1 Hz, 1 H).

5-(4'-Trifluoromethoxyphenyl)-thiophene-2-sulfonyl chloride (18h). Thiophene-2-boronic acid and 5-bromo-2-trifluoromethoxybenzene were coupled by analogy to Suzuki Coupling Method A. Using Chlorosulfonylation Method B above, **t**he resulting 2-(4'-trifluoromethoxyphenyl)-thiophene **17h** was converted to the title sulfonyl chloride: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.28 - 7.41 (m, 3 H) 7.66 (d, *J*=9.04 Hz, 2 H) 7.86 (d, *J*=4.14 Hz, 1 H).

5-(4'-Methylphenyl)-thiophene-2-sulfonyl chloride (18i). 4-Methylphenylboronic acid and 2-bromo-thiophene were treated according to Suzuki Coupling Method C to yield 2-p-tolyl-thiophene. The solid was converted to 5-(4'-methylphenyl)-thiophene-2-sulfonyl chloride as described for **18d** above. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.41 (s, 3 H) 7.24 -7.28 (m, 3 H) 7.53 (d, *J*=8.29 Hz, 2 H) 7.83 (d, *J*=4.14 Hz, 1 H).

5-(4'-Trifluoromethylphenyl)-thiophene-2-sulfonyl chloride (18j). 4-Trifluoromethylphenylboronic acid and 2-bromo-thiophene were treated according to Suzuki Coupling Method C to yield 2-(4-trifluoromethyl-phenyl)-thiophene. The solid was converted to 5-(4'-trifluoromethylphenyl)-thiophene-2-sulfonyl chloride as described for **18d** above. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.14 (d, *J*=3.77 Hz, 1 H) 7.47 (d, *J*=3.77 Hz, 1 H) 7.75 (d, *J*= 8.7 Hz, 2 H) 7.86 (d, *J*= 7.9 Hz 2 H).

5-(4'-*n*-Propoxyphenyl)-thiophene-2-sulfonyl chloride (18k). Thiophene-2-boronic acid (55.5 g, 434 mmol), 4-bromophenol (25.0 g, 144 mmol), $PdCl_2$(dppf) (10.24 g, 14 mmol), and Na_2CO_3 (152.6 g, 1440 mmol)

in EtOH (500 mL) were heated to 60 ºC for 16 h in a flame-dried round bottom flask under nitrogen fitted with a mechanical stirrer and a reflux condenser. After cooling, the reaction was filtered through Celite®. The filter cake was washed with fresh EtOH. The combined EtOH filtrates were concentrated under reduced pressure. The residue was dissolved in hexanes and filtered through a plug of silica to afford 2-(4'-hydroxyphenyl)-thiophene **17k** as a solid (16.1 g, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.85 (s, 1 H) 6.81 - 6.88 (m, 2 H) 7.04 (dd, *J*=4.90, 3.77 Hz, 1 H) 7.16 - 7.23 (m, 2 H) 7.41 - 7.54 (m, 2 H).

2-(4'-Propoxyphenyl)-thiophene was prepared using a Mitsunobu reaction. To a solution of 2-(4'-hydroxyphenyl)thiophene (8.0 g, 45.4 mmol) and triphenylphosphine (13.69 g, 52.2 mmol) in THF (55 mL) were added propyl alcohol (3.28 g, 54.5 mmol) and diethyl azodicarboxylate (9.09 g, 52.2 mmol), respectively. The reaction was stirred for 18 h. The solution was concentrated and the residue treated with hexane, resulting in the formation of a precipitate. The hexane was decanted and the solids were washed further with hexane. The combined hexane washings were filtered through a plug of silica and concentrated to give a 2-(4'-propoxyphenyl)-thiophene.

Following precedent,[1] a solution of 2-(4'-propoxyphenyl)-thiophene (4.89 g, 23.9 mmol) in THF (120 mL) at 0 ºC was added *t*-BuLi (21.2 mL of a 1.7 M solution in pentane). After 15 min at 0 ºC, SO_2(g) was introduced. After 15 min, NCS (3.51 g, 26.3 mmol) was added. The reaction was warmed to room temperature over 1 h. The reaction was partitioned between EtOAc and a saturated aqueous solution of NaCl. The separated organic phase was dried (Na_2SO_4), concentrated, and purified by flash chromatography (5 to 10% EtOAc/hexanes) to afford the title sulfonyl chloride: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 (t, *J*=7.54 Hz, 3 H) 1.75 - 1.92 (m, 2 H) 3.95 (t, *J*=6.40 Hz, 2 H) 6.96 (d, *J*=9.04 Hz, 2 H) 7.20 (d, *J*=4.14 Hz, 1 H) 7.56 (d, *J*=8.67 Hz, 2 H) 7.81 (d, *J*=4.14 Hz, 1 H).

5-(4'-Ethoxyphenyl)-thiophene-2-sulfonyl chloride (18l). 2-(4'-Ethoxyphenyl)-thiophene was prepared from 2-(4'-hydroxyphenyl)-thiophene **17k** and ethanol by Mitsunobu reaction as described for **18k** above. The resulting 2-(4'-ethoxyphenyl)-thiophene was converted to 5-(4'-isopropoxyphenyl)-thiophene-2-sulfonyl chloride as described for **18i** above: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.45 (t, *J*=6.97 Hz, 3 H) 4.09 (q, *J*=7.16 Hz, 2 H) 6.96 (d, *J*=9.04 Hz, 2 H) 7.20 (d, *J*=4.14 Hz, 1 H) 7.56 (d, *J*=8.67 Hz, 2 H) 7.81 (d, *J*=4.14 Hz, 1 H).

5-(4'-*iso*-Propoxyphenyl)-thiophene-2-sulfonyl chloride (18m). 2-(4'-Isopropoxyphenyl)-thiophene was prepared from 2-(4'-hydroxyphenyl)-thiophene **17k** and isopropanol by Mitsunobu reaction as described for **18k** above. The resulting 2-(4'-iso-propoxyphenyl)-thiophene was converted to 5-(4'-isopropoxyphenyl)-thiophene-2-sulfonyl chloride as described for **18k** above: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.36 (d, *J*=6.03 Hz, 6 H) 4.62 (t, *J*=6.03 Hz, 1 H) 6.94 (d, *J*=9.04 Hz, 2 H) 7.19 (d, *J*=4.14 Hz, 1 H) 7.55 (d, *J*=8.67 Hz, 2 H) 7.81 (d, *J*=4.14 Hz, 1 H).

5-(4'-Methoxyethoxyphenyl)-thiophene-2-sulfonyl chloride (18n). 2-(4'-Methoxyethoxyphenyl)-thiophene was prepared from 2-(4'-hydroxyphenyl)-thiophene **17i** and methoxyethanol by Mitsunobu reaction as described for **18k** above. The resulting 2-(4'-methoxyethoxyphenyl)-thiophene was converted to 5-(4'-methoxyethoxyphenyl)-thiophene-2-sulfonyl chloride as described for **18k** above: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.45 (s, 3 H) 3.73 - 3.82 (m, 2 H) 4.13 - 4.21 (m, 2 H) 7.00 (d, *J*=8.67 Hz, 2 H) 7.18 (d, *J*=4.14 Hz, 1 H) 7.55 (d, *J*=8.67 Hz, 2 H).

4'-Dimethylaminobiphenyl-4-sulfonyl chloride (19a). Phenylboronic acid and (4-bromophenyl)dimethylamine were treated according to Suzuki Coupling Method C to yield biphenyl-4-yl-diethyl-amine. The solid biphenyl-4-yl-dimethylamine (1.8 g, 8 mmol) was added to chlorosulfonic acid (3 ml) at -5 ^{o}C and stirred for 30 minutes. The mixture was slowly and carefully added to ice (exotherm), the mixture extracted with diethyl ether and the combined organic layers dried over $MgSO_4$, filtered and concentrated to give the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.04 (s, 6 H) 6.81 (d, *J*=8.7 Hz, 2 H) 7.56 (d, *J*=9.0, 2 H) 7.75 (d, *J*=8.7 Hz, 2 H) 8.02 (d, *J*=8.3 Hz, 2 H).

4'-Methylbiphenyl-4-sulfonyl chloride (19b). 4-Methylphenylboronic acid and 4-bromophenylsulfonic acid were treated as in example **19d** to afford the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.43 (s, 3 H) 7.31 (d, *J*=7.9 Hz, 2 H) 7.53 (d, *J*=7.9 Hz, 2 H) 7.76 - 7.82 (m, 2 H) 8.06 - 8.10 (m, 2 H).

4'-Fluorobiphenyl-4-sulfonyl chloride (19c). Phenylboronic acid and 1-bromo-4-fluorobenzene were treated according to Suzuki Coupling Method C. The product was additionally purified by flash chromatography (silica, EtOAc/Hexanes, 1/20) to afford the title sulfonyl chloride: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.20 (t, *J*=8.7 Hz, 2 H) 7.60 (dd, *J*=8.9, 5.1 Hz, 2 H) 7.77 (d, *J*=8.7 Hz, 2 H) 8.10 (d, *J*=8.3 Hz, 2 H).

4'-Methoxybiphenyl-4-sulfonyl chloride (19d). A solution of 4-methoxyphenylboronic acid (7.6 g, 50 mmol), 4-bromophenylsulfonic acid (11.85 g, 50 mmol), potassium carbonate (13.8 g, 100 mmol) and $PdCl_2$(dppf) (3.66 g, 5 mmol) in 300 mL of a 1:1 mixture of dimethoxyethane and H_2O was heated to 80 °C for 3.5 h under an atmosphere of nitrogen. The reaction mixture was cooled to room temperature and added to a

mixture of H_2O (1300 mL) and diethyl ether (500 mL). The insoluble precipitate was isolated by filtration. This solid material was then slurried with acetone and filtered to yield a gray solid which was washed with diethyl ether and dried *in vacuo* to give 4-(4'-methoxylphenyl)phenylsulfonic acid.

Oxalyl chloride (18.2 mL, 208 mmol) was added dropwise over 20 minutes to a suspension of 11 g (41.6 mmol) 4-(4'-methoxyphenyl)phenylsulfonic acid in THF (1000 mL). The mixture was stirred for a further 15 minutes then cooled to 0 °C before 16.1 mL (208 mmol) of DMF was added dropwise. The mixture was stirred at room temperature for 18 h. The reaction was then cooled to 0 °C and 4M HCl was carefully added until no more exothermic reaction was observed. Brine and diethyl ether were added and the layers separated. The organic layer was extracted with brine and the combined aqueous layers were extracted with EtOAc. The combined organic layers were then dried over $MgSO_4$ and filtered. The solution was partially purified by filtration through a very short pad of silica. The solvent was removed *in vacuo* and the residue triturated with hexane:diethyl ether, 1:1 to give a solid which was isolated by filtration and recrystallized from diethyl ether to give the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.88 (s, 3 H) 6.97 - 7.06 (m, 2 H) 7.55 - 7.61 (m, 2 H) 7.76 (d, *J*=8.7 Hz, 2 H) 8.06 (d, *J*=8.7 Hz, 2 H).

4'-Ethoxybiphenyl-4-sulfonyl chloride (19e). 4-Ethoxyphenylboronic acid and 4-bromophenylsulfonic acid were converted to the title compound by analogy to **20d** above: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.44 (q, *J*=7.3 Hz, 3 H) 4.10 (q, *J*=7.2 Hz, 2 H) 7.01 (d, *J*=8.7 Hz, 2 H) 7.48 - 7.62 (m, 2 H) 7.76 (d, *J*=8.7 Hz, 2 H) 8.06 (d, *J*=8.7 Hz, 2 H).

5-(4-Trifluoromethylphenyl)-furan-2-sulfonyl chloride (21a). To a solution of 2-(tributylstannyl)furan (6.3 g, 20.0 mmol) and 4-bromobenzytrifluoride (2.95 mL, 21.0 mmol) in toluene (100 mL) under nitrogen was added $(Ph_3P)_4Pd$ (50 mg, 0.04 mmol). The reaction was heated at reflux for 1 h before an additional portion of $(Ph_3P)_4Pd$ (50 mg, 0.04 mmol) was added. After 4 h, the cooled reaction was filtered through Celite® and silica gel. The filter cake was washed with toluene. The combined filtrates were concentrated *in vacuo*. The residue was purified by flash chromatography (5% EtOAc/hexanes) to afford a yellow oil. The oil crystallized from Et_2O/hexane to afford 2-(4'-trifluoromethylphenyl)-furan (3.28 g, 77%).

To a suspension of the above furan (1.06 g, 5.00 mmol) in THF at -78 ºC was added *n*-BuLi (2.1 mL of a 2.5 M solution in hexanes). The reaction was stirred at -78 ºC for 45 min before SO_2(g) was introduced to the reaction vessel and the reaction was allowed to warm to room temperature. The reaction was diluted with hexane and filtered. The yellow solid was dried *in vacuo* to afford the sulfinic acid lithium salt: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 6.43 (d, *J*=3.39 Hz, 1 H), 7.06 (d, *J*=3.39 Hz, 1 H), 7.68 - 7.96 (m, 4 H).

To the above salt (55 mg, 0.19 mmol) in CH_2Cl_2 (10 mL) at 0 ºC was added NCS (26 mg, 0.19 mmol). The reaction was stirred 15 minutes at 0 ºC and 15 minutes at room temperature before filtering through Celite®. The filtrate was concentrated under reduced pressure to afford the title compound as a yellow syrup, which was used directly in the next transformation.

5-(3,4-Difluorophenyl)-furan-2-sulfonyl chloride (21b). Using the procedure outlined for **21a**, 2-(tributylstannyl)furan and 3,4-difluorobromobenzene were converted to 5-(3,4-difluorophenyl)-furan-2-sulfinic acid lithium salt: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 6.57 - 6.66 (m, 1 H) 6.90 - 6.98 (m, 1 H) 7.52 - 7.65 (m, 1 H) 7.67 - 7.84 (m, 2 H).

The above salt was chlorinated with NCS as in **21a** and was used directly in the next transformation.

5-(3,4-Methylenedioxyphenyl)-furan-2-sulfonyl chloride (21c). Using the procedure outlined for **21a**, 2-(tributylstannyl)furan and 3,4-methylenedioxybromobenzene were converted to 5-(3,4-methylenedioxyphenyl)-furan-2-sulfinic acid lithium salt. The salt above was chlorinated with NCS as in **21a** to afford the title sulfonyl chloride: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.03 (s, 2 H) 6.65 (d, *J*=3.8 Hz, 1 H) 6.90 (d, *J*=7.9 Hz, 1 H) 7.20 - 7.29 (m, 1 H) 7.29 - 7.44 (m, 2 H).

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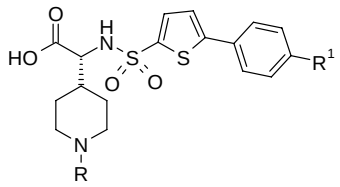
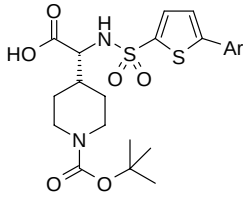
Table 2. Pairwise Changes to the BOC and *N*,*N*-Dimethylamine Moieties.



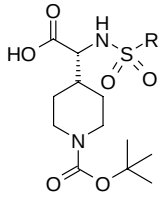
Cmpd	R	R^1	Molecular Formula	C, H, N Calculated	C, H, N Found
9	*t*-BuO_2C	Me_2N	C24H32N3O6S2. 1*K	51.32, 5.74, 7.48	50.99, 5.57, 7.31
23	H	Me_2N	C19H25N3O4S2. 2*HCl, 0.5*H2O		
22a	*t*-BuO_2C	1-piperidinyl	C27H37N3O6S2. 1*H2O	55.75, 6.76, 7.22	55.37, 6.36, 7.09

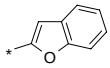
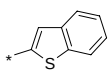
Table 3. Replacement of Dimethylaminophenyl Moiety.



Cmpd	Ar	Molecular Formula	C, H, N Calculated	C, H, N Found
22b	Ph	C22H27N2O6S2 . 1*K, 0.75*H2O	49.65, 5.4, 5.26	49.66, 5.3, 5.17
22c	3-EtOPh	C24H32N2O7S2	54.94, 6.15, 5.34	54.65, 6.04, 5.11
22d	3,4-diMeOPh	C23H30N2O7S2	54.1, 5.92, 5.49	53.76, 5.68, 5.24
22e	4-pyr	C21H27N3O6S2	52.37, 5.65, 8.73	52.19, 5.57, 8.41
22f	2-pyr	C21H27N3O6S2	50.49, 5.85, 8.41	50.84, 5.65, 8.02
22g	2-MeO-5-pyr	C22H29N3O7S2		

Table 4. Additional Aromatic Ring Replacements.



Cmpd	R	Molecular Formula	C, H, N Calculated	C, H, N Found
29		C20H26N2O7S	54.78, 5.98, 6.39	54.92, 5.94, 6.29
30		C20H26N2O6S2	52.85, 5.76, 6.16	52.94, 5.68, 5.94

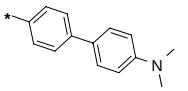
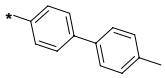
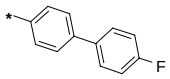
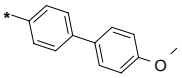
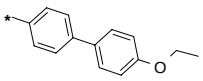
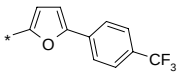
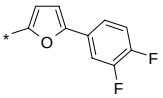
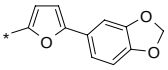
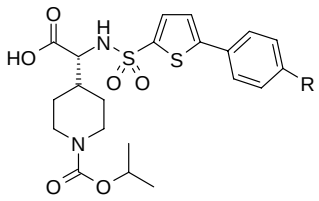
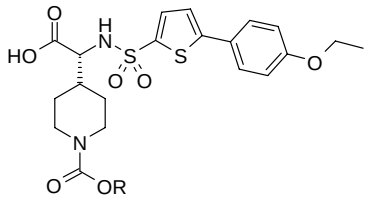
31		C26H35N3O6S, 0.5*H2O	59.3, 6.89, 7.98	59.23, 6.67. 8.23
32		C25H32N2O6S, 0.6*H2O	60.13, 6.7, 5.61	59.99, 6.46, 5.68
33		C24H29FN2O6S . 0.5*H2O	57.47, 6.03, 5.59	57.46, 5.64, 5.98
34		C25H32N2O7S	59.51, 6.39, 5.55	59.41, 6.39, 5.8
35		C26H34N2O7S	60.21, 6.61, 5.4	59.85, 6.26, 5.04
36		C23H26F3N2O7S, 1*K 2*H2O	45.54, 4.98, 4.62	45.39, 5.0, 4.4
37		C22H25F2N2O7S, 1*K, 0.75*H2O	47.86, 4.84, 5.07	47.83, 4.5, 4.88
38		C23H27N2O9S, 1*K, 0.75*H2O	49.32, 5.13, 5.0	49.3, 4.97, 4.92

Table 5. 4-Phenyl Substitutions.



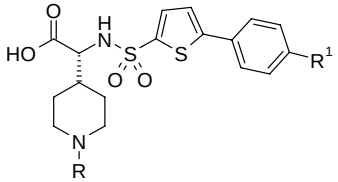
Cmpd	R	Molecular Formula	C, H, N Calculated	C, H, N Found
24a	1-piperidinyl	C26H35N3O6S2 0.5*H2O	55.89, 6.49, 7.59	55.83, 6.73, 7.37
24b	H	C21H26N2O6S2		
24c	OH	C21H26N2O7S2, 0.25*H2O		
24d	OMe	C22H28N2O7S2 0.5*H2O	52.26, 5.78, 8.54	52.24, 5.87, 8.44
24e	OCF_3	C22H25F3N2O7S2		
24f	OEt	C23H30N2O7S2	54.1, 5.92, 5.49	53.87, 5.83, 5.3
24g	O^nPr	C24H32N2O7S2	54.94, 6.15, 5.34	54.64, 5.94, 5.27
24h	O^iPr	C24H32N2O7S2, 0.3*H2O	54.38, 6.2, 5.28	54.35, 6.14, 5.08
24i	$O(CH_2)_2OMe$	C24H32N2O8S2	54.94, 6.15, 5.34	54.75, 5.85, 5.24
24j	CH_3	C22H28N2O6S2	54.98, 5.87, 5.83	54.74, 5.57, 5.59
24k	CF_3	C22H25F3N2O6S2	49.43, 4.71, 5.24	49.72, 4.76, 4.95

Table 6. SAR of Carbamate Analogs.



Cmpd	R	Molecular Formula	C, H, N Calculated	C, H, N Found
24l	Me	C21H26N2O7S2	52.27, 5.43, 5.81	52.09, 5.66, 5.77
24m	Et	C22H28N2O7S2 0.5*H2O	52.26, 5.78, 5.54	52.38, 5.7, 5.37
24n	^{n}Pr	C23H30N2O7S2	54.1, 5.92, 5.49	53.76, 5.68, 5.24
24o	^{n}Bu	C24H32N2O7S2	54.94, 6.15, 5.34	54.58, 6.25, 5.41
24p	^{i}Bu	C24H32N2O7S2	54.94, 6.15, 5.34	54.66, 6.19, 5.17
24q	$CHEt_2$	C25H34N2O7S2	55.74, 6.36, 5.2	55.54, 6.18, 5.26
24r	$CH_2{}^{t}$Bu	C25H34N2O7S2	55.74, 6.36, 5.2	55.35, 6.05, 5.35
24s	^{t}Bu	C24H32N2O7S2	54.94, 6.15, 5.34	54.87, 6.21, 5.32
24t	cyclopentyl	C25H32N2O7S2	55.95, 6.01, 5.22	55.88, 6.08, 4.95
24u	4-THP	C25H32N2O8S2 1*H2O	52.62, 6.01, 4.91	52.59, 5.62, 5.21

Table 7. Piperidine Substitutions.



Cmpd	R	R^1	Molecular Formula	C, H, N Calculated	C, H, N Found
25a	$CONH^{t}$Bu	OMe	C23H31N3O6S2		
25b	$CONH^{i}$Pr	OMe	C22H29N3O6S2		
25c	$CONH^{i}$Pr	OEt	C23H31N3O6S2	54.2, 6.13, 8.25	54.06, 6.1, 8.15
25d	$CONEt_2$	OMe	C23H31N3O6S2 0.75*H2O	52.81, 6.16, 8.03	52.41, 5.79, 7.78
26a	CO^{i}Pr	OMe	C22H28N2O6S2 0.5*H2O	55.03, 6.10, 5.13	54.82, 5.93, 4.91
26b	CO^{t}Bu	OEt	C24H32N2O6S2 0.5*H2O	55.69, 6.43, 5.41	55.96, 6.39, 5.3
26c	$COCH_2{}^{t}$Bu	OEt	C25H34N2O6S2	57.45, 6.56, 5.36	57.08, 6.87, 5.75
26d	COcyclohexyl	OEt	C26H34N2O6S2	58.4, 6.41, 5.24	58.02, 6.25, 5.07
26e	CO-4-THP	OEt	C25H32N2O7S2 0.5*H2O	55.03, 6.1, 5.13	54.82, 5.93, 4.91
27a	SO_2Ph-4-Me	OMe	C25H28N2O7S3		
27b	SO_2Ph	OMe	C24H26N2O7S3		
27c	SO_2Ph	OEt	C25H28N2O7S3	53.17, 5.0, 4.96	52.89, 4.98, 4.7
27d	SO_2CH_2Ph	OEt	C26H30N2O7S3	53.96, 5.22, 4.84	53.87, 4.99, 4.66
27e	$SO_2{}^{i}$Bu	OEt	C23H32N2O7S3	50.72, 5.92, 5.14	50.43, 5.77, 5.35
27f	$SO_2{}^{n}$Bu	OEt	C23H32N2O7S3 1*H2O	49.09, 6.09, 4.98	49.27, 5.99, 5.03
27g	$SO_2{}^{i}$Pr	OEt	C22H30N2O7S3	49.79, 5.7, 5.28	49.43, 5.55, 5.22
27h	$SO_2{}^{n}$Pr	OEt	C22H30N2O7S3 0.5*H2O	48.96, 5.79, 5.19	48.99, 5.79, 5.24
27i	SO_2Me	OEt	C20H26N2O7S3 0.5*H2O	46.95, 5.32, 5.48	46.69, 5.2, 5.42
28a	Bn	OEt	C26H30N2O5S2 0.5*H2O	59.63, 5.97, 5.35	59.45, 5.71, 5.31
28b	^{i}Bu	OEt	C23H32N2O5S2 0.25*H2O	56.94, 6.75, 5.77	56.94, 6.78, 5.54
28c	$CH_2{}^{t}$Bu	OEt	C24H34N2O5S2 0.25*H2O	54.48, 6.19, 5.29	54.35, 6.14, 5.08

[1] Chan, M. F.; Wu, C.; Raju, B. G.; Kogan, T.; Kois, A.; Verner, E. J.; Castillo, R. S.; Yalamorri, V.; Balaji, V. N. Thienyl-, furyl- and pyrrolyl-sulfonamides and derivatives thereof that modulate the activity of endothelin. US Patent 5,962,490, October 5, 1999.