Supporting Information

Discovery of a Novel Class of Potent Human Deoxyuridine Triphosphatase Inhibitors Remarkably Enhancing the Antitumor Activity of Thymidylate Synthase Inhibitors

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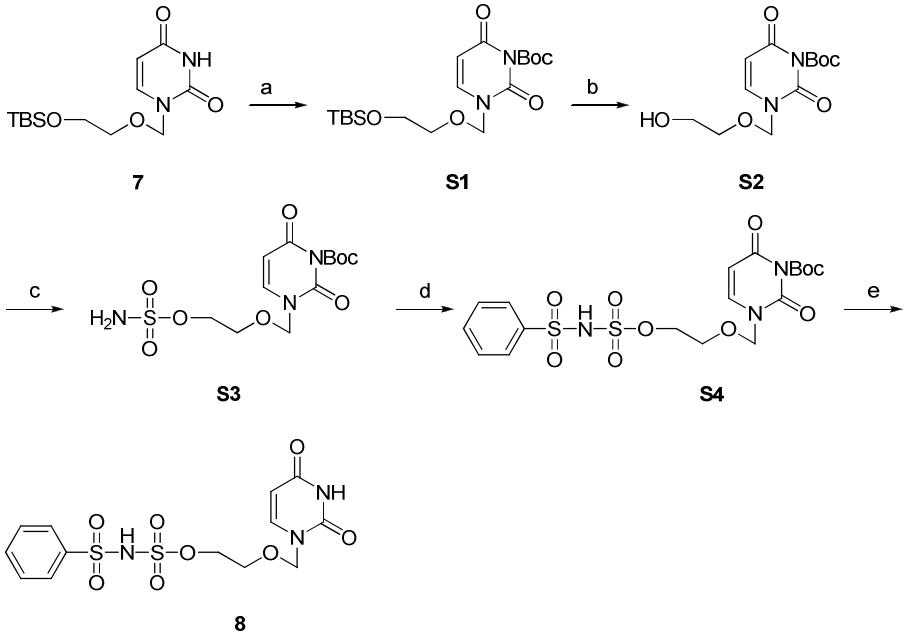
Synthesis of compounds 8, S7, S17, S18R, S18S, 27, 28, 29R, 29S, and 29R/S

Compound **8** was synthesized using a five-step sequence starting from compound **7**[2] as shown in Scheme S1. Briefly, *N*-Boc protection of **7** afforded **S1** and subsequent treatment with tetrabutylammonium fluoride (TBAF) afforded **S2**. The hydroxyl group of **S2** was treated with sulfamoyl chloride to afford **S3**. Sulfonylation of **S3** afforded **S4**, and subsequent removal of the Boc group by trifluoroacetic acid resulted in producing compound **8**.

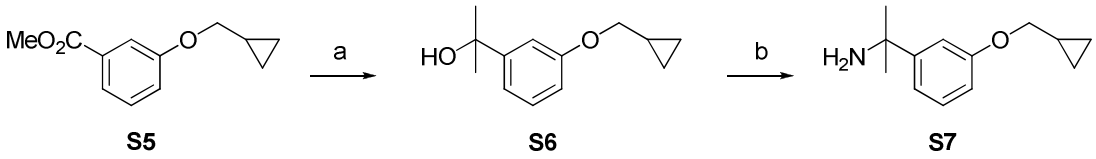
Scheme S1.[a]



[a]Reagents and conditions: (a) $(Boc)_2O$, DMAP, pyridine, room temp., 12 h; (b) 1.0 M TBAF in THF, THF, room temp.,1 h; (c) sulfamoyl chloride, Et_3N, DMF, room temp., 2.5 h; (d) benzenesulfonyl chloride, Et_3N, MeCN, room temp., 12 h; (e) trifluoroacetic acid, room temp., 1 h.

Compounds **S7** was synthesized as shown in Scheme S2. Grignard reaction of ester group of commercially available **S5**, and the subsequent conversion of the tertiary alcohol group to amino group gave amine **S7**.

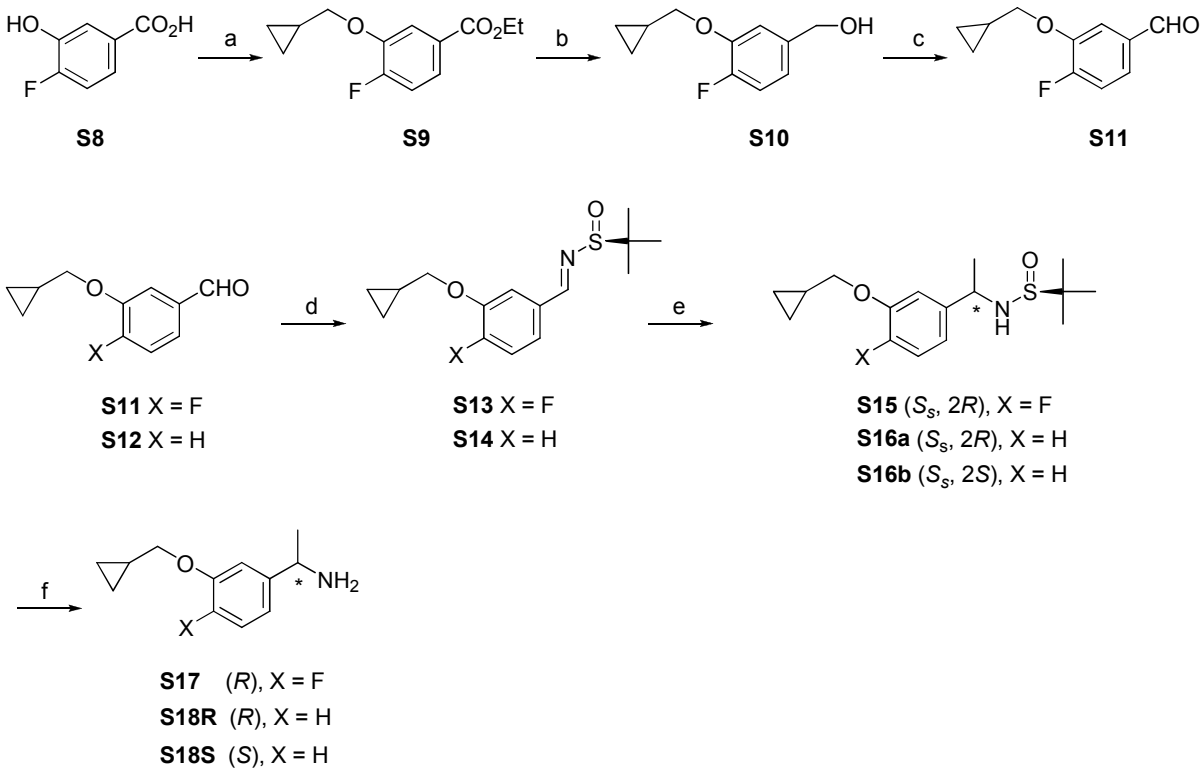
Scheme S2.[a]



[a]Reagents and conditions:(a) 3.0 M MeMgBr in Et_2O, THF, 0°C to room temp., 4 h; (b) (1) NaN_3, trifluoroacetic acid, $CHCl_3$, 0°C to room temp., 1 h; (2) 2.4 M $LiAlH_4$ in THF, THF, room temp., 12 h.

Chiral amine **S17** was synthesized from the aldehyde **S11** as shown in Scheme S3. **S11** was prepared from 4-fluoro-3-hydroxybenzoic acid **S8** *via* the following sequence; esterification of carboxylic acid, alkylation of phenol moiety, reduction of ester group, and oxidation of hydroxyl group. Treatment of the aldehyde **S11** with (*S*)-2-methyl-2-propanesulfineamide afforded sulfinylimine **S13**. After applying diastereoselective Grignard reaction of **S13**, the obtained **S15** was treated with acidic condition to give chiral amine **S17**. Chiral amines **S18R** and **S18S** were also obtained by the similar procedure starting from commercially available **S12** as shown in Scheme S3.

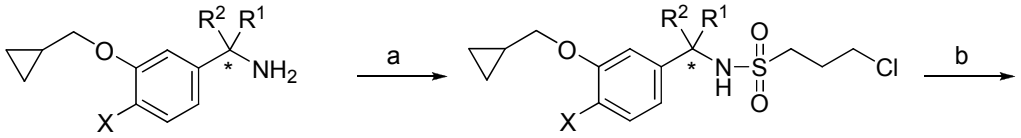
Scheme S3.[a]



[a]Reagents and conditions: (a) (1) H_2SO_4, EtOH, 100℃, 4 h; (2) (bromomethyl)cyclopropane, K_2CO_3, DMF, 90℃, 6 h; (b) 2.0 M $LiBH_4$ in THF, THF, 75℃, 16 h; (c) 2,2,6,6-tetramethylpiperidine 1-oxyl, [bis(acetoxy)iodo]benzene, CH_2Cl_2, room temp., 2 h; (d) (*S*)-(-)-2-methyl-2-propanesulfinamide, Ti(O-*i*Pr)$_4$, toluene, 90℃, 12 h; (e) 3.0 M MeMgBr in Et_2O, THF, 0℃ to room temp., 12 h; (f) 4N HCl/dioxane, MeOH, room temp., 0.5 h.

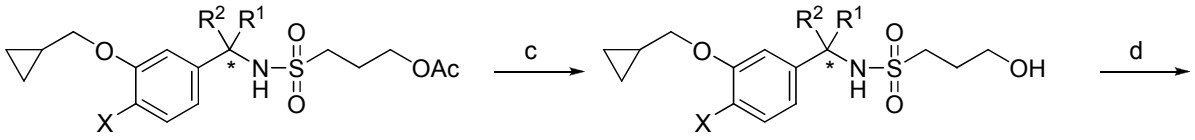
Synthesis of compound **27** was performed as shown in Scheme S4. Commercially available 3-chloropropanesulfonyl chloride was treated with amine **S7** to afford **S19**. Acetoxylation followed by acid hydrolysis afforded **S25**, which were treated with MOMCl to afford **27**. Compounds **28**, **29R**, **29S**, and **29R/S** were similarly synthesized from **S17**, **S18R**, **S18S**, and commercially available **S18R/S** as shown in Scheme S4.

Scheme S4.[a]



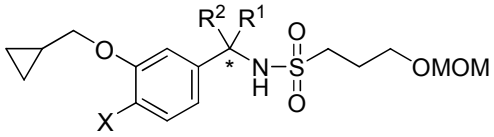
S7 R^1, R^2 = Me, X = H
S17 (*R*), R^1= H, R^2 = Me, X = F
S18R (*R*), R^1= H, R^2 = Me, X = H
S18S (*S*), R^1= Me, R^2 = H, X = H
S18R/S (*rac*), R^1 = H, R^2 = Me, X = H

S19 R^1, R^2 = Me, X = H
S20 (*R*), R^1= H, R^2 = Me, X = F
S21R (*R*) R^1= H, R^2 = Me, X = H
S21S (*S*), R^1= Me, R^2 = H, X = H
S21R/S (*rac*), R^1 = H, R^2 = Me, X = H



S22 R^1, R^2 = Me, X = H
S23 (*R*), R^1= H, R^2 = Me, X = F
S24R (*R*), R^1= H, R^2 = Me, X = H
S24S (*S*), R^1= Me, R^2 = H, X = H
S24R/S (*rac*), R^1 = H, R^2 = Me, X = H

S25 R^1, R^2 = Me, X = H
S26 (*R*), R^1= H, R^2 = Me, X = F
S27R (*R*), R^1= H, R^2 = Me, X = H
S27S (*S*), R^1= Me R^2 = H, X = H
S27R/S (*rac*), R^1 = H, R^2 = Me, X = H



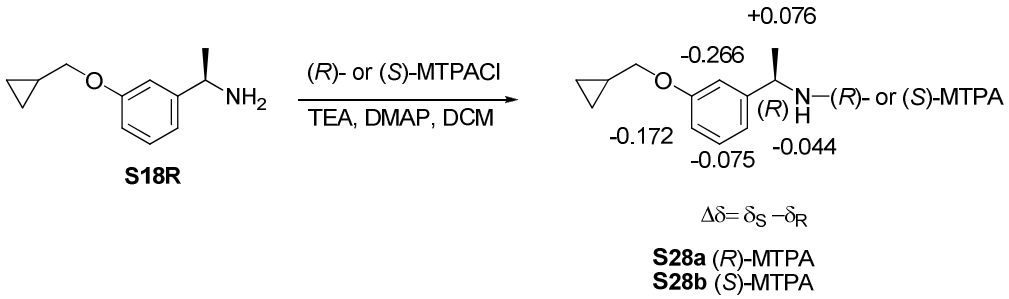
27 R^1, R^2 = Me, X = H
28 (*R*), R^1= H, R^2 = Me, X = F
29R (*R*), R^1= H, R^2 = Me, X = H
29S (*S*), R^1= Me, R^2 = H, X = H
29R/S (*rac*), R^1 = H, R^2 = Me, X = H

[a]Reagents and conditions: (a) 3-chloropropanesulfonyl chloride, Et_3N, CH_2Cl_2, room temp., 4 h; (b) AcONa, NaI, DMF, 90 °C, 6 h; (c) HCl in MeOH, reflux, 1 h; (d) MOMCl, *N*,*N*-diisopropylethylamine, CH_2Cl_2, room temp., 2 h.

Determination of the configuration of S18R

(*R*)-MTPA amide **S28a** and (*S*)-MTPA amide **S28b** were prepared as shown in Scheme S5. From their Δδ value, configuration of **S18R** was determined as *R*.

Scheme S5.



Experimental Procedure

***tert*-Butyl 3-((2-(*tert*-butyldimethylsilyloxy)ethoxy)methyl)-2,6-dioxo-2,3-dihydropyrimidine-1(6*H*)-carboxylate (S1).** To a stirred solution of 1-((2-(*tert*-butyldimethylsilyloxy)ethoxy)methyl)pyrimidine-2,4(1*H*,3*H*)-dione **7** (3.82 g, 12.7 mmol) in pyridine (60 mL) was added $(Boc)_2O$ (7.20 g, 33.0 mmol), *N*, *N*-dimethyl-4-aminopyridine (150 mg, 1.23 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 12 h. After addition of MeOH, the resulting mixture was concentrated under reduced pressure. The mixture was poured into sat. aq. $NaHCO_3$ solution, and extracted with CH_2Cl_2 two times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ($CHCl_3$/MeOH = 19/1) to afford the title compound (2.84 g, 7.09 mmol, 56%) as a colorless oil. ^{1}H NMR (270MHz, $CDCl_3$) δ 0.07 (6H, s), 0.89 (9H, s), 1.61 (9H, s), 3.65–3.68 (2H, m), 3.75–3.78 (2H, m), 5.20 (2H, s), 5.77 (1H, d, J = 8.1 Hz), 7.32 (1H, d, J = 8.1 Hz). HRMS (FAB) calcd for $C_{18}H_{32}N_2NaO_6Si$ $[M+Na]^+$ 423.1927, found 423.1925.

***tert*-Butyl 3-((2-hydroxyethoxy)methyl)-2,6-dioxo-2,3-dihydropyrimidine-1(6*H*)-carboxylate (S2).** To a stirred solution of **S1** (2.84 g, 7.09 mmol) in THF (40 mL) was added TBAF in THF (1.0 M, 10 mL, 10 mmol) at room temperature. After being stirred at room temperature for 1 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ($CHCl_3$/MeOH = 93/7) to afford the title compound (1.62 g, 5.66 mmol, 80%) as a colorless oil. ^{1}H NMR (270MHz, $CDCl_3$) δ 1.61 (9H, s), 3.70–3.77 (4H, m), 5.21 (2H, s), 5.79 (1H, d, J = 8.1 Hz), 7.31 (1H, d, J = 8.1 Hz). HRMS (FAB) calcd for $C_{12}H_{19}N_2O_6$ $[M+H]^+$ 287.1243, found 287.1230.

***tert*-Butyl 2,6-dioxo-3-((2-(sulfamoyloxy)ethoxy)methyl)-2,3-dihydropyrimidine-1(6*H*)-carboxylate (S3).** To a stirred solution of **S2** (2.40 g, 8.38 mmol) in DMF (35 mL) was added Et_3N (4.67 mL, 33.5 mmol), sulfamoyl chloride (1.94 g, 16.8 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 2.5 h. After addition of MeOH, the mixture was poured into H_2O, and extracted with EtOAc five times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with (EtOAc/MeOH = 9/1) to afford the title compound (1.90 g, 5.20 mmol, 62%) as a colorless oil. ^{1}H NMR (270MHz, $CDCl_3$) δ 1.61 (9H, s), 3.92–3.96 (2H, m), 4.30–4.33 (2H, m), 5.14 (2H, brs), 5.21 (2H, s), 5.83 (1H, d, J = 8.1 Hz), 7.31 (1H, d, J = 8.1 Hz). HRMS (FAB) calcd for $C_{12}H_{18}N_3O_8S$ $[M-H]^-$ 364.0815, found 364.0837.

***tert*-Butyl 2,6-dioxo-3-((2-(*N*-(phenylsulfonyl)sulfamoyloxy)ethoxy)methyl)-2,3-dihydropyrimidine-1(6*H*)-carboxylate (S4).** To a stirred solution of **S3** (99.1 mg, 0.27 mmol) in MeCN (1.5 mL) was added Et_3N (95 μL, 0.68 mmol), benzenesulfonyl chloride (53 μL, 0.42 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with (EtOAc/MeOH = 49/1) to afford the title compound (101 mg, 0.20 mmol, 74%) as a colorless gum. ^{1}H NMR (270MHz, $CDCl_3$) δ 1.56 (9H, s), 3.24–3.32 (2H, m), 3.73–3.80 (2H, m), 4.97 (2H, s), 5.66 (1H, d, J = 8.1 Hz), 7.29–7.35 (3H, m), 7.40–7.43 (1H, m), 7.85–7.89 (2H, m). HRMS (TOF) calcd for $C_{18}H_{23}N_3NaO_{10}S_2$ $[M+Na]^+$ 528.0723, found 528.0736.

2-((2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methoxy)ethyl phenylsulfonylsulfamate (8). A solution of **S4** (232 mg, 0.46 mmol) in trifluoroacetic acid (2.0 mL) was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with (EtOAc/MeOH = 4/1) to afford the title compound (165 mg, 0.41 mmol, 89%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69–3.71 (2H, m), 4.08–4.11 (2H, m), 5.16 (2H, s), 5.68 (1H, d, J = 7.8 Hz), 7.45–7.48 (3H, m), 7.65 (1H, d, J = 7.8 Hz), 7.88–7.91 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.5, 69.2, 78.4, 103.1, 127.9 , 129.4, 132.5, 145.3, 146.4, 152.9, 166.5. HRMS (TOF) calcd for $C_{13}H_{16}N_3O_8S_2$ $[M+H]^+$ 406.0379, found 406.0371. HPLC purity: Method A = 98.6%, t_R = 4.45 min.

2-(3-(Cyclopropylmethoxy)phenyl)propan-2-ol (S6). To a stirred solution of methyl 3-(cyclopropylmethoxy)benzoate **S5** (20.5 g, 99.4 mmol) in THF (100 mL) was added methylmagnesium bromide (1.0 M, 225 mL, 225 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 4 h. The mixture was poured into a mixture of ice and sat. aq. NH_4Cl, and extracted with EtOAc two times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with (hexane/EtOAc = 13/7) to afford the title compound (19.4 g, 94.0 mmol, 95%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.32–0.38 (2H, m), 0.61–0.68 (2H, m), 1.23–1.32 (1H, m), 1.57 (6H, s), 3.82 (2H, d, J = 6.8 Hz), 6.78 (1H, dd, J = 8.1, 2.4 Hz), 7.06–7.09 (2H, m), 7.24–7.28 (1H, m). HRMS (FAB) calcd for $C_{13}H_{18}NaO_2$ $[M+Na]^+$ 229.1204, found 229.1204.

2-(3-(Cyclopropylmethoxy)phenyl)propan-2-amine (S7). To a stirred solution of **S6** (3.75 g, 18.2 mmol) in $CHCl_3$ (30 mL) was added NaN_3 (3.55 g, 54.6 mmol) and trifluoroacetic acid (6.74 mL 91.0 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The mixture was pored into H_2O, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with (hexane/EtOAc = 9/1) to afford the crude azide. To a stirrred solution of $LiAlH_4$ (2.0 M in THF, 20 mL, 40.0 mmol) was added dropwise a solution of the crude azide (3.18 g, 13. 7 mmol) in THF (20 mL) at 0 °C. The resulting mixture was stirred at room temperature for 12 h and then quenched by the addition of H_2O. The precipitate was removed by filtration and washed with THF/MeOH (1/1). The combined filtrate was separated and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the title compound (1.56 g, 7.60 mmol, 42% from **S6**) as a colorless oil. ^{1}H NMR (270 MHz, DMSO-d_6) δ 0.31–0.37 (2H, m), 0.57–0.62 (2H, m), 1.21–1.32 (1H, m), 1.36 (6H, s), 1.86 (2H, brs), 3.82 (2H, d, J = 7.0 Hz), 6.73 (1H, dd, J = 8.1, 2.4 Hz), 7.05–7.10 (2H, m), 7.16–7.22 (1H, m). HRMS (FAB) calcd for $C_{13}H_{20}NO$ $[M+H]^+$ 206.1545, found 206.1540.

Ethyl 3-(cyclopropylmethoxy)-4-fluorobenzoate (S9). To a stirred solution of 4-fluoro-3-hydroxybenzoic acid **S8** (12.0 g, 76.9 mmol) in EtOH (175 mL) was added conc. H_2SO_4 (4.1 mL, 76.9 mmol) at room temperature, and the mixture was heated to reflux at 100 °C for 4 h. After cooled to room temperature, the mixture was concentrated under reduced pressure. H_2O and Na_2CO_3 were added to this residue, and the aqueous layer was extracted with EtOAc two times. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was co-evaporated with toluene two times, and then dissolved in DMF (80 mL). To the mixture was added (bromomethyl)cyclopropane (8.58 mL, 88.5 mmol) and K_2CO_3 (21.3 g, 154 mmol) at room temperature, and the resulting mixture was stirred at 90 °C for 6 h. After cooled to room temperature, the mixture was poured into H_2O and extracted with toluene two times. The organic layer was washed with 1N NaOH, brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the title compound (18.2 g, 76.4 mmol, 99%) as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.35–0.41 (2H, m), 0.61–0.70 (2H, m), 1.24–1.36 (4H, m), 3.93 (2H, d, J = 6.8 Hz), 4.37 (2H, q, J = 7.0 Hz), 7.07–7.14 (1H, m), 7.60–7.65 (2H, m). HRMS (FAB) calcd for $C_{13}H_{16}FO_3$ $[M+H]^+$ 239.1083, found 239.1084.

(3-(Cyclopropylmethoxy)-4-fluorophenyl)methanol (S10). To a stirred solution of **S9** (18.2 g, 76.4 mmol) in THF (100 ml) was added $LiBH_4$ in THF (2.0 M, 100 mL, 200 mmol) was added dropwise at room temperature, and the resulting mixture was heated to reflux at 75 °C for 16 h. After cooled to 0 °C, H_2O was then added dropwise to the mixture at the same temperature. The aqueous

layer was extracted with EtOAc two times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the title compound (14.7 g, 74.9 mmol, 98%) as a white solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.33–0.39 (2H, m), 0.61–0.69 (2H, m), 1.22-1.31 (1H, m), 3.88 (2H, d, J = 6.8 Hz), 4.63 (2H, s), 6.83–6.88 (1H, m), 6.97–7.08 (2H, m). HRMS (EI) calcd for $C_{11}H_{13}FO_2$ [M] 196.09, found 196.0894.

3-(Cyclopropylmethoxy)-4-fluorobenzaldehyde (S11). To a stirred solution of **S10** (14.7 g, 74.9 mmol) in CH_2Cl_2 (100 mL) was added [bis(acetoxy)iodo]benzene (26.5 g, 82.3 mmol) and 2,2,6,6-tetramethylpiperidine 1-oxyl (1.72 g, 11.0 mmol) at room temperature, and the resulting mixture was stirred at the same temperature for 2 h. To the mixture was added sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$, and the aqueous layer was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with (hexane/EtOAc = 3/2) to afford the title compound (9.10 g, 46.9 mmol, 63 %) as a light orange solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.35–0.39 (2H, m), 0.62–0.67 (2H, m), 1.22–1.32 (1H, m), 3.95 (2H, d, J = 7.1 Hz), 7.20–7.27 (1H, m), 7.41–7.51 (2H, m), 9.90 (1H, s). HRMS (EI) calcd for $C_{11}H_{11}FO_2$ [M] 194.0743, found 194.0771.

(*S*,*E*)-*N*-(3-(Cyclopropylmethoxy)-4-fluorobenzylidene)-2-methylpropane-2-sulfinamide (S13). S13 was prepared from **S11** (6.60 g, 34.0 mmol) as described for the preparation of **S14**. A colorless oil (9.67 g, 32.5 mmol, 96%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.38–0.41 (2H, m), 0.64–0.70 (2H, m), 1.26 (9H, s), 1.27–1.33 (1H, m), 3.94 (2H, d, J = 6.8 Hz), 7.13–7.18 (1H, m), 7.34–7.38 (1H, m), 7.46–7.49 (1H, m), 8.49 (1H, s). HRMS (FAB) calcd for $C_{15}H_{21}FNO_2S$ $[M+H]^+$ 298.1277, found 298.1289.

(*S*,*E*)-*N*-(3-(Cyclopropylmethoxy)benzylidene)-2-methylpropane-2-sulfinamide (S14). To a stirred solution of 3-(cyclopropylmethoxy)benzaldehyde **S12** (21.5 g, 122 mmol) in toluene (150 mL) was added (*S*)-(-)-2-methyl-2-propanesulfinamide (15.8 g, 129 mmol), tetraisopropyl orthotitanate (51.0 mL, 172 mmol) at room temperature. The resulting mixture was stirred at 90 °C for 12 h. After cooled to room temperature, the reaction mixture was quenched by the addition of sat. aq. $NaHCO_3$. The precipitate was removed by filtration through a pad of Celite and washed with EtOAc. The combined filtrate was separated and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the title compound (34.1 g, 122 mmol, quant.) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.35–0.40 (2H, m), 0.65–0.71 (2H, m), 1.26–1.33 (10H, m), 3.86 (2H, dd, J = 7.0 Hz), 7.04–7.09 (1H, m), 7.34–7.40 (3H, m), 8.54 (1H, s). HRMS (FAB) calcd for $C_{15}H_{22}NO_2S$ $[M+H]^+$ 280.1371, found 280.1376.

(*S*)-*N*-((*R*)-1-(3-(Cyclopropylmethoxy)-4-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (S15). S15 was prepared from **S13** (1.45 g, 4.89 mmol) as described for the preparation of **S16a**. A white solid (1.04 g, 3.32 mmol, 68%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.32–0.38 (2H, m), 0.61–0.66 (2H, m), 1.20 (9H, s), 1.22–1.32 (1H, m), 1.50 (3H, d, J = 6.8 Hz), 3.28 (1H, brs), 3.86 (2H, d, J = 6.8 Hz), 4.49–4.53 (1H, m), 6.82–6.88 (1H, m), 6.91–6.99 (1H, m), 7.02–7.06 (1H, m). HRMS (FAB) calcd for $C_{16}H_{25}FNO_2S$ $[M+H]^+$ 314.1590, found 314.1615.

(*S*)-*N*-((*R*)-1-(3-(Cyclopropylmethoxy)phenyl)ethyl)-2-methylpropane-2-sulfinamide (S16a) and (*S*)-*N*-((*S*)-1-(3-(Cyclopropylmethoxy)phenyl)ethyl)-2-methylpropane-2-sulfinamide (S16b). To a stirred solution of **S14** (7.50 g, 26.8 mmol) in THF (18 mL) was added dropwise methylmagnesium bromide in Et_2O (3.0M, 17.9 mL, 53. 7 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 12 h, and then sat. aq. NH_4Cl was added. The resulting mixttire was partitioned between EtOAc and H_2O, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with (hexane/EtOAc = 1/1) to afford **S16a** (4.78 g, 16.2 mmol, 60%) and **S16b** (1.02 g, 3.45 mmol, 13%) as a yellow oil.

S16a: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.33–0.36 (2H, m), 0.62–0.66 (2H, m), 1.22 (9H, s), 1.23–1.31 (1H , m), 1.53 (3H, d, J = 6.8 Hz), 3.27 (1H, brs), 3.79 (2H, d, J = 6.8 Hz), 4.50–4.57 (1H, m), 6.79–6.83 (1H, m), 6.88–6.92 (2H, m), 7.21–7.26 (1H, m). HRMS (FAB) calcd for $C_{16}H_{26}NO_2S$ $[M+H]^+$ 296.1684, found 296.1690.

S16b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.33–0.36 (2H, m), 0.62–0.67 (2H, m), 1.23 (9H, s), 1.23–1.31 (1H , m), 1.51 (3H, d, J = 7.2 Hz), 3.40 (1H, brs), 3.80 (2H, d, J = 6.8 Hz), 4.49–4.52 (1H, m),

6.80–6.83 (1H, m), 6.90–6.93 (2H, m), 7.22–7.26 (1H, m). HRMS (TOF) calcd for $C_{16}H_{26}NO_2S$ $[M+H]^+$ 296.1684 found 296.1676.

(*R*)-1-(3-(Cyclopropylmethoxy)-4-fluorophenyl)ethanamine hydrochloride (S17). S17 was prepared from **S15** (1.04 g, 3.32 mmol) as described for the preparation of **S18R**. A pale yellow solid (815 mg, 3.32 mmol, quant.). ^{1}H NMR (270 MHz, DMSO-d_6) δ 0.31–0.37 (2H, m), 0.57–0.65 (2H, m), 1.24–1.32 (1H, m), 1.50 (3H, d, J = 6.8 Hz), 3.93 (2H, d, J = 7.3 Hz), 4.33–4.37 (1H, m), 7.02–7.07 (1H, m),7.21–7.29 (1H, m), 7.43 (1H, dd, J = 8.4, 1.9 Hz), 8.51 (3H, brs). HRMS (FAB) calcd for $C_{12}H_{17}FNO$ $[M+H]^+$ 210.1294, found 210.1293.

(*R*)-1-(3-(Cyclopropylmethoxy)phenyl)ethanamine hydrochloride (S18R). To a solution of **S16a** (4.70 g, 15.9 mmol) in MeOH (20 mL) was added HCl in dioxane (4 M, 9.40 mL, 37.6 mmol) at room temperature, and the resulting mixture was stirred at same temperature for 0.5 h. The mixture was concentrated under reduced pressure. The residue was co-evaporated with toluene tree times to give the title compound (3.60 g, 15.8 mmol, 99%) as a white solid. ^{1}H NMR (270 MHz, DMSO-d_6) δ 0.30–0.35 (2H, m), 0.55–0.62 (2H, m), 1.21–1.27 (1H, m), 1.50 (3H, d, J = 6.8 Hz), 3.84 (2H, d, J = 7.0 Hz), 4.33 (1H, q, J = 6.8 Hz), 6.86–6.94 (1H, m), 7.04 (1H, d, J = 7.6 Hz), 7.13 (1H, s), 7.31 (1H, t, J = 8.1 Hz), 8.49 (3H, brs). HRMS (FAB) calcd for $C_{12}H_{18}NO$ $[M+H]^+$ 192.1388, found 192.1383.

(*S*)-1-(3-(Cyclopropylmethoxy)phenyl)ethanamine hydrochloride (S18S). S18S was prepared from **S16b** (1.02 g, 3.45 mmol) as described for the preparation of **S18R**. A white solid (786 mg, 3.40 mmol, quant.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.30–0.34 (2H, m), 0.56–0.60 (2H, m), 1.21–1.27 (1H, m), 1.49 (3H, d, J = 7.1 Hz), 3.83 (2H, d, J = 7.1 Hz), 4.31–4.38 (1H, m), 6.90–6.93 (1H, m), 7.03 (1H, d, J = 7.8 Hz), 7.11 (1H, s), 7.31 (1H, t, J = 7.8 Hz), 8.42 (3H, brs). HRMS (TOF) calcd for $C_{12}H_{18}NO$ $[M+H]^+$ 192.1388, found 192.1382.

3-Chloro-*N*-(2-(3-(cyclopropylmethoxy)phenyl)propan-2-yl)propane-1-sulfonamide (S19). To a stirred solution of **S7** (1.54 g, 7.50 mmol) in CH_2Cl_2 (7.5 mL) was added Et_3N (1.36 mL, 9.76 mmol) and 3-chloropropanesulfonyl chloride (1.10 mL, 9.05 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 4 h. The mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with 1N HCl, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with (hexane/EtOAc = 3/2) to afford the title compound (2.41 g, 6.98 mmol, 93%) as an orange oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.32–0.38 (2H, m), 0.62–0.68 (2H, m), 1.22–1.31 (1H, m), 1.75 (6H, s), 2.14–2.24 (2H, m), 2.88 (2H, t, J = 7.6 Hz), 3.57 (2H, t, J = 6.3 Hz), 3.81 (2H, d, J = 6.8 Hz), 4.52 (1H, brs), 6.80–6.83 (1H, m), 7.06–7.13 (2H, m), 7.26–7.32 (1H, m). HRMS (FAB) calcd for $C_{16}H_{24}ClNNaO_3S$ $[M+Na]^+$ 368.1063, found 368.1053.

(*R*)-3-Chloro-*N*-(1-(3-(cyclopropylmethoxy)-4-fluorophenyl)ethyl)propane-1-sulfonamide (S20). S20 was prepared from **S17** (815 mg, 3.32 mmol) as described for the preparation of **S19**. A yellow oil (976 mg, 2.79 mmol, 84%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.34–0.40 (2H, m), 0.63–0.70 (2H, m), 1.22–1.31 (1H, m), 1.53 (3H, d, J = 6.2 Hz), 2.08–2.19 (2H, m), 2.83–2.92 (2H, m), 3.54 (2H, t, J = 6.2 Hz), 3.89 (2H, d, J = 7.3 Hz), 4.43 (1H, brs), 4.56–4.64 (1H, m), 6.87–6.93 (2H, m), 7.03–7.10 (1H, m). HRMS (FAB) calcd for $C_{15}H_{20}ClFNO_3S$ $[M-H]^-$ 348.0836, found 348.0857.

(*R*)-3-Chloro-*N*-(1-(3-(Cyclopropylmethoxy)phenyl)ethyl)propane-1-sulfonamide (S21R). S21R was prepared from **S18R** (3.68 g, 16.2 mmol) as described for the preparation of **S19**. A yellow oil (4.74 g, 14.3 mmol, 88%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.34–0.38 (2H, m), 0.62–0.68 (2H, m), 1.24–1.31 (1H, m), 1.54 (3H, d, J = 6.8 Hz), 2.08–2.17 (2H, m), 2.79–2.93 (2H, m), 3.48–3,52 (2H, m), 3.81 (2H, d, J = 7.0 Hz), 4.44 (1H, brs), 4.58–4.62 (1H, m), 6.82–6.91 (3H, m), 7.26–7.30 (1H, m). HRMS (FAB) calcd for $C_{15}H_{22}ClNNaO_3S$ $[M+Na]^+$ 354.0907, found 354.0917.

(*S*)-3-Chloro-*N*-(1-(3-(cyclopropylmethoxy)phenyl)ethyl)propane-1-sulfonamide (S21S). S21S was prepared from **S18S** (786 mg, 3.40 mmol) as described for the preparation of **S19**. A yellow oil (1.10 g, 3.31 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34–0.38 (2H, m), 0.64–0.67 (2H, m), 1.24–1.31 (1H, m), 1.54 (3H, d, J = 6.8 Hz), 2.06–2.19 (2H, m), 2.76–2.83 (1H, m), 2.89–2.96 (1H, m), 3.48–3,52 (2H, m), 3.80 (2H, d, J = 7.1 Hz), 4.48 (1H, brs), 4.57–4.64 (1H, m), 6.82–6.91 (3H, m), 7.26–7.30 (1H, m). HRMS (TOF) calcd for $C_{15}H_{26}ClN_2O_3S$ $[M+NH_4]^+$ 349.1353, found 349.1358.

3-Chloro-*N*-(1-(3-(cyclopropylmethoxy)phenyl)ethyl)propane-1-sulfonamide (S21R/S). **S21R/S** was prepared from 1-(3-(cyclopropylmethoxy)phenyl)ethanamine **S18R/S** (564 mg, 2.95 mmol) as described for the preparation of **S19**. A light brown oil (630 mg, 1.90 mmol, 64%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.34–0.39 (2H, m), 0.62–0.68 (2H, m), 1.21–1.31 (1H, m), 1.54 (3H, d, J = 6.8 Hz), 2.08–2.17 (2H, m), 2.75–2.81 (1H, m), 2.87–2.95 (1H, m), 3.47–3.52 (2H, m), 3.81 (2H, d, J = 7.0 Hz), 4.54–4.63 (2H, m), 6.81–6.92 (3H, m), 7.24–7.30 (1H, m). HRMS (FAB) calcd for $C_{15}H_{21}ClNO_3S$ $[M-H]^-$ 330.093, found 330.0920.

3-(*N*-(2-(3-(Cyclopropylmethoxy)phenyl)propan-2-yl)sulfamoyl)propyl acetate (S22). To a stirred solution of **S19** (2.41 g, 6.97 mmol) in DMF (8.0 mL) was added AcONa (1.90 g, 23.2 mmol), and NaI (2.40 g, 16.0 mmol) at room temperature, the resulting mixture was stirred at 90 °C for 6 h. After cooled to room temperature, the mixture was poured into H_2O, and extracted with EtOAc two times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with (hexane/EtOAc = 1/1) to afford the title compound (1.73 g, 4.68 mmol, 67%) as a brown oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.33–0.37 (2H, m), 0.62–0.68 (2H, m), 1.22–1.30 (1H, m), 1.75 (6H, s), 1.97–2.08 (5H, m), 2.73–2.79 (2H, m), 3.80–3.82 (2H,m), 4.04–4.08 (2H, m), 4.56 (1H, brs), 6.79–6.83 (1H, m), 7.03–7.09 (2H, m), 7.23–7.29 (1H, m). HRMS (FAB) calcd for $C_{18}H_{26}NO_5S$ $[M-H]^-$ 368.1532, found 368.1543.

(*R*)-3-(*N*-(1-(3-(Cyclopropylmethoxy)-4-fluorophenyl)ethyl)sulfamoyl)propyl acetate (S23). **S23** was prepared from **S20** (976 mg, 2.79 mmol) as described for the preparation of **S22**. A yellow oil (673 mg, 1.80 mmol, 65%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.34–0.38 (2H, m), 0.62–0.68 (2H, m), 1.24–1.31 (1H, m), 1.52 (3H, d, J = 6.8 Hz), 1.95–2.04 (5H, m), 2.68–2.86 (2H, m), 3.89 (2H, d, J = 7.0 Hz), 4.01–4.07 (2H, m), 4.40 (1H, brs), 4.57–4.62 (1H, m), 6.84–6.91 (2H, m), 7.03–7.10 (1H, m). HRMS (FAB) calcd for $C_{17}H_{23}FNO_5S$ $[M-H]^-$ 372.1281, found 372.1263.

(*R*)-3-(*N*-(1-(3-(Cyclopropylmethoxy)phenyl)ethyl)sulfamoyl)propyl acetate (S24R). S24R was prepared from **S21R** (537 mg, 1.62 mmol) as described for the preparation of **S22**. A dark orange oil (370 mg, 1.04 mmol, 64%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.32–0.39 (2H, m), 0.62–0.69 (2H, m), 1.22–1.29 (1H, m), 1.53 (3H, d, J = 6.8 Hz), 1.90–2.05 (5H, m), 2.63–2.87 (2H, m), 3.80 (2H, d, J = 6.8 Hz), 3.96–4.02 (2H, m), 4.55–4.62 (2H, m), 6.81–6.97 (3H, m), 7.24–7.30 (1H, m). HRMS (FAB) calcd for $C_{17}H_{24}NO_5S[M-H]^-$ 354.1375, found 354.1409.

(*S*)-3-(*N*-(1-(3-(Cyclopropylmethoxy)phenyl)ethyl)sulfamoyl)propyl acetate (S24S). S24S was prepared from **S21S** (1.10 g, 3.31 mmol) as described for the preparation of **S22**. A light yellow oil (870 mg, 2.45 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34–0.38 (2H, m), 0.64–0.68 (2H, m), 1.24–1.28 (1H, m), 1.54 (3H, d, J = 6.8 Hz), 1.90–2.04 (5H, m), 2.65–2.72 (1H, m), 2.80–2.87 (1H, m), 3.80 (2H, d, J = 6.6 Hz), 3.94–4.04 (2H, m), 4.50 (1H, brs), 4.57–4.63 (1H, m), 6.81–6.91 (3H, m), 7.25–7.30 (1H, m). HRMS (TOF) calcd for $C_{17}H_{29}N_2O_5S$ $[M+NH_4]^+$ 373.1797, found 373.1794.

3-(*N*-(1-(3-(Cyclopropylmethoxy)phenyl)ethyl)sulfamoyl)propyl acetate (S24R/S). S24R/S was prepared from **S21R/S** (630 mg, 1.90 mmol) as described for the preparation of **S22**. A light brown oil (470 mg, 1.32 mmol, 69%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.33–0.39 (2H, m), 0.62–0.69 (2H, m), 1.24–1.30 (1H, m), 1.53 (3H, d, J = 6.8 Hz), 1.94–2.05 (5H, m), 2.68–2.72 (1H, m), 2.84–2.88 (1H, m), 3.81 (2H, d, J = 6.8 Hz), 3.95–4.01 (2H, m), 4.56–4.62 (1H, m), 4.90 (1H, brs), 6.81–6.92 (3H, m), 7.24–7.30 (1H, m). HRMS (FAB) calcd for $C_{17}H_{24}NO_5S$ $[M-H]^-$ 354.1375, found 354.1354.

***N*-(2-(3-(Cyclopropylmethoxy)phenyl)propan-2-yl)-3-hydroxypropane-1-sulfonamide (S25).** A solution of **S22** (1.73 g, 4.68 mmol) in HCl in MeOH (10 mL) was heated to reflux at 85 °C for 1 h. After cooled to rom temperature, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel eluting with (hexane/EtOAc = 3/7) to afford the title compound (691 mg, 2.11 mmol, 45%) as a light yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.33–0.37 (2H, m), 0.62–0.68 (2H, m), 1.22–1.30 (1H, m), 1.75 (6H, s), 1.94–2.03 (2H, m), 2.88 (2H, t, J = 7.3 Hz), 3.66–3.70 (2H, m), 3.81 (2H, d, J = 7.1 Hz), 4.58 (1H, brs), 6.79–6.83 (1H, m), 7.07–7.11 (2H, m), 7.25–7.31 (1H, m). HRMS (FAB) calcd for $C_{16}H_{25}NNaO_4S$ $[M+Na]^+$ 350.1402, found 350.1420.

(*R*)-N-(1-(3-(Cyclopropylmethoxy)-4-fluorophenyl)ethyl)-3-hydroxypropane-1-sulfonamide (S26). S26 was prepared from **S23** (673 mg, 1.80 mmol) as described for the preparation of **S25**. A

light yellow oil (446 mg, 1.35 mmol, 75%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.34–0.39 (2H, m), 0.62–0.69 (2H, m), 1.24–1.31 (1H, m), 1.53 (3H, d, J = 6.5 Hz), 1.90–1.96 (2H, m), 2.79–2.94 (2H, m), 3.64–3.69 (2H, m), 3.89 (2H, d, J = 7.0 Hz), 4.59–4.64 (2H, m), 6.80–7.09 (3H, m). HRMS (FAB) calcd for $C_{15}H_{21}FNO_4S$ $[M-H]^-$330.1175, found 330.1176.

(*R*)-*N*-(1-(3-(Cyclopropylmethoxy)phenyl)ethyl)-3-hydroxypropane-1-sulfonamide (S27R). **S27R** was prepared from **S24R** (370 mg, 1.04 mmol) as described for the preparation of **S25**. An orange oil (246 mg, 0.78 mmol, 75%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.32–0.38 (2H, m), 0.62–0.66 (2H, m), 1.22–1.31 (1H, m), 1.54 (3H, d, J = 6.6 Hz), 1.88–1.96 (2H, m), 2.78–2.95 (2H, m), 3.58–3.66 (2H, m), 3.81 (2H, d, J = 6.9 Hz), 4.57–4.70 (2H, m), 6.81–6.92 (3H, m), 7.24–7.30 (1H, m); HRMS (FAB) calcd for $C_{15}H_{22}NO_4S$ $[M-H]^-$ 312.1270, found 312.1272.

(*S*)-*N*-(1-(3-(Cyclopropylmethoxy)phenyl)ethyl)-3-hydroxypropane-1-sulfonamide (S27S). **S27S** was prepared from **S24S** (870 mg, 2.45 mmol) as described for the preparation of **S25**. A colorless oil (670 mg, 2.14 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34–0.38 (2H, m), 0.63–0.67 (2H, m), 1.22–1.31 (1H, m), 1.54 (3H, d, J = 6.8 Hz), 1.87–1.94 (2H, m), 2.76–2.83 (1H, m), 2.88–2.95 (1H, m), 3.59–3.67 (2H, m), 3.81 (2H, d, J = 6.6 Hz), 4.57–4.63 (1H, m), 4.64 (1H, brs), 6.81–6.84 (1H, m), 6.88–6.92 (2H, m), 7.24–7.29 (1H, m). HRMS (TOF) calcd for $C_{15}H_{24}NO_4S$ $[M+H]^+$ 314.1426, found 314.1430.

***N*-(1-(3-(Cyclopropylmethoxy)phenyl)ethyl)-3-hydroxypropane-1-sulfonamide (S27R/S).** **S27R/S** was prepared from **S24R/S** (470 mg, 1.32 mmol) as described for the preparation of **S25**. A colorless oil (242 mg, 0.77 mmol, 58%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.34–0.37 (2H, m), 0.62–0.68 (2H, m), 1.22–1.31 (1H, m), 1.54 (3H, d, J = 6.8 Hz), 1.86–1.95 (2H, m), 2.77–2.95 (2H, m), 3.58–3.64 (2H, m), 3.81 (2H, d, J = 6.8 Hz), 4.56–4.63 (1H, m), 4.80 (1H, brs), 6.81–6.84 (1H, m), 6.89–6.92 (2H, m), 7.24–7.30 (1H, m). HRMS (FAB) calcd for $C_{15}H_{22}NO_4S$ $[M-H]^-$ 312.1270, found 312.1257.

***N*-(2-(3-(Cyclopropylmethoxy)phenyl)propan-2-yl)-3-(methoxymethoxy)propane-1-sulfonamide (27).** To a stirred solution of **S25** (691 mg, 2.11 mmol) in CH_2Cl_2 (10 mL) was added *N*,*N*-diisopropylethylamine (1.20 mL, 6.89 mmol), and MOMCl (337 μL, 4.44 mmol) at room temperature, the resulting mixture was stirred at the same temperature for 2 h. The mixture was concentrated under reduced pressure, and the residue was poured into sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc and the organic layer was washed with sat. aq. NH_4Cl, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with (hexane/EtOAc = 2/3) to afford the title compound (495 mg, 1.33 mmol, 63%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.34–0.39 (2H, m), 0.62–0.69 (2H, m), 1.21–1.33 (1H, m), 1.75 (6H, s), 1.95–2.05 (2H, m), 2.83–2.90 (2H, m), 3.32 (3H, s), 3.53 (2H, t, J = 6.2 Hz), 3.81 (2H, d, J = 7.0 Hz), 4.57 (2H, s), 4.72 (1H, brs), 6.80 (1H, ddd, J = 8.1, 2.7, 1.1 Hz), 7.05–7.10 (2H, m), 7.23–7.30 (1H, m). HRMS (FAB) calcd for $C_{18}H_{28}NO_5S$ $[M-H]^-$ 370.1688, found 370.1694.

(*R*)-*N*-(1-(3-(Cyclopropylmethoxy)-4-fluorophenyl)ethyl)-3-(methoxymethoxy)propane-1-sulfonamide (28). 28 was prepared from **S26** (446 mg, 1.35 mmol) as described for the preparation of **27**. A yellow oil (262 mg, 0.70 mmol, 52%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.34–0.40 (2H, m), 0.62–0.68 (2H, m), 1.24–1.31 (1H, m), 1.52 (3H, d, J = 6.8 Hz), 1.89–1.99 (2H, m), 2.73–2.94 (2H, m), 3.30 (3H, s), 3.46–3.52 (2H, m), 3.88 (2H, d, J = 6.8 Hz), 4.45 (1H, brs), 4.54–4.62 (3H, m), 6.84–6.94 (2H, m), 7.01–7.09 (1H, m). HRMS (FAB) calcd for $C_{17}H_{25}FNO_5S$ $[M-H]^-$ 374.1437, found 374.1461.

(*R*)-*N*-(1-(3-(Cyclopropylmethoxy)Phenyl)ethyl)-3-(methoxymethoxy)propane-1-sulfonamide (29R). 29R was prepared from **S27R** (246 mg, 0.78 mmol) as described for the preparation of **27**. A yellow oil (219 mg, 0.61 mmol, 79%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.34–0.38 (2H, m), 0.61–0.68 (2H, m), 1.22–1.31 (1H, m), 1.53 (3H, d, J = 6.8 Hz), 1.86–2.00 (2H, m), 2.74–2.95 (2H, m), 3.29 (3H, s), 3.42–3.48 (2H, m), 3.80 (2H, d, J = 6.8 Hz), 4.53 (2H, s), 4.55 (1H, brs), 4.56–4.62 (1H, m), 6.80–6.91 (3H, m), 7.23–7.29 (1H, m). HRMS (FAB) calcd for $C_{17}H_{26}NO_5S$ $[M-H]^-$ 356.1532, found 356.1526.

(*S*)-*N*-(1-(3-(Cyclopropylmethoxy)phenyl)ethyl)-3-(methoxymethoxy)propane-1-sulfonamide (29S). Compound **29S** was prepared from **S27S** (670 mg, 2.14 mmol) as described for the preparation of **27**. A colorless oil (534 mg, 1.49 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34–

0.37 (2H, m), 0.63–0.68 (2H, m), 1.22–1.30 (1H, m), 1.54 (3H, d, *J* = 6.8 Hz), 1.86–2.00 (2H, m), 2.74–2.81 (1H, m), 2.88–2.95 (1H, m), 3.29 (3H, s), 3.43–3.49 (2H, m), 3.80 (2H, d, *J* = 6.8 Hz), 4.53 (2H, s), 4.53 (1H, brs), 4.57–4.63 (1H, m) , 6.80–6.83 (1H, m), 6.86–6.91 (2H, m), 7.23–7.28 (1H, m). HRMS (TOF) calcd for $C_{17}H_{28}NO_5S$ $[M+H]^+$ 358.1688, found 358.1694.

***N*-(1-(3-(Cyclopropylmethoxy)phenyl)ethyl)-3-(methoxymethoxy)propane-1-sulfonamide (29R/S). 29R/S** was prepared from **S27R/S** (242 mg, 0.77 mmol) as described for the preparation of **27**. A colorless oil (112 mg, 0.31 mmol, 40%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.34–0.38 (2H, m), 0.61–0.68 (2H, m), 1.22–1.31 (1H, m), 1.53 (3H, d, *J* = 6.8 Hz), 1.86–2.00 (2H, m), 2.74–2.81 (1H, m), 2.88–2.95 (1H, m), 3.29 (3H, s), 3.42–3.48 (2H, m), 3.80 (2H, d, *J* = 7.0 Hz), 4.52 (2H, s), 4.55–4.62 (1H, m), 4.85 (1H, brs), 6.79–6.92 (3H, m), 7.23–7.28 (1H, m). HRMS (FAB) calcd for $C_{17}H_{26}NO_5S$ $[M-H]^-$ 356.1532, found 356.1537.

(*R*)-MTPA amide S28a. To a stirred solution of **S18R** (26.0 mg, 0.11 mmol) in CH_2Cl_2 (1.25 mL) was added Et_3N (40 μL, 0.29 mmol), DMAP (2.0 mg, 0.016 mmol) and (*S*)-MTPACl (34 μL, 0.18 mmol) at room temperature, and the resulting mixture was stirred at the same temperature for 16h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with (hexane/EtOAc = 1/1) to afford the title compound (40.3 mg, 0.099 mmol, 90%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.31–0.35 (2H, m), 0.56–0.61 (2H, m), 1.21–1.26 (1H, m), 1.35 (3H, d, *J* = 7.2 Hz), 3.38 (3H, s), 3.81 (2H, d, *J* = 6.8 Hz), 5.04–5.07 (1H, m), 6.80 (1H, dd, *J* = 8.4, 2.8 Hz), 6.94 (1H, d, *J* = 7.6 Hz), 6.98 (1H, s), 7.23 (1H, t, *J* = 8.0 Hz), 7.46–7.50 (3H, m), 7.52–7.57 (2H, m), 8.79 (1H, brs). HRMS (FAB) calcd for $C_{22}H_{25}F_3NO_3$ $[M+H]^+$ 408.1787, found 408.1777.

(*S*)-MTPA amide S28b. To a stirred solution of **S18R** (26.0 mg, 0.11 mmol) in CH_2Cl_2 (1.25 mL) was added Et_3N (40 μL, 0.29 mmol), DMAP (2.0 mg, 0.016 mmol) and (*R*)-MTPACl (34 μL, 0.18 mmol) at room temperature, and the resulting mixture was stirred at the same temperature for 16h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with (hexane/EtOAc = 1/1) to afford the title compound (41.3 mg, 0.10 mmol, 92%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.28–0.31 (2H, m), 0.55–0.59 (2H, m), 1.16–1.21 (1H, m), 1.43 (3H, d, *J* = 6.8 Hz), 3.53 (3H, s), 3.61–3.70 (2H, m), 5.02–5.07 (1H, m), 6.72 (1H, s), 6.76 (1H, dd, *J* = 8.4, 2,4 Hz), 6.77 (1H, d, *J* = 6.4 Hz), 7.16 (1H, t, *J* = 7.6 Hz), 7.37–7.45 (5H, m), 8.79 (1H, brs). HRMS (FAB) calcd for $C_{22}H_{25}F_3NO_3$ $[M+H]^+$ 408.1787, found 408.1777.

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