Supporting Information.

Sodium Late Current Blockers in Ischemia-Reperfusion: is the Bullet Magic?

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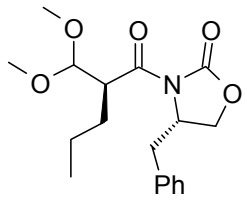
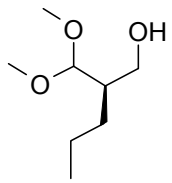
(*4S*)-3-([(*2S*)-1-Oxo-2-(dimethoxymethyl)-pentyl)]-4-(phenylmethyl)-2-oxazolidinone (4).



A solution of (S)-4-benzyl-3-pentanoyl-oxazolin-2-one **3** (2.02 g, 7.73 mmol) in dry dichloromethane (25 mL) was cooled to 0 °C and treated dropwise with $TiCl_4$ (0.85 mL, 7.73 mmol) then diisopropylethylamine (1.35 mL, 7.73 mmol). After 1 h at 0, °C trimethylorthoformate (1.01 mL, 9.27 mmol) was added dropwise and the mixture stirred for 1 h then quenched by addition of a saturated aqueous solution of ammonium chloride (25 mL). The reaction mixture was decanted and the aqueous extracted with dichloromethane. The combined organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, dichloromethane/cyclohexane/ethylacetate, 90:8:2) afforded 2.40 g (93%) of **4**. ^{1}H NMR (DMSO-d_6) . ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 1.30 (m, 2H), 1.60 (m, 1H), 1.75 (m, 1H), 2.73 (dd, J = 2.8, 13.2 Hz, 1H), 3.27 (dd, J = 9.6, 13.2 Hz, 1H), 3.37 (s, 6H), 4.15 (m, 2H), 4.52 (m, 1H), 4.62 (d, J = 8 Hz, 1H), 4.72 (m, 1H), 7.20-7.35 (m, 5H); $[\alpha]_D^{25}$ +97° (*c* 0.21, CH_3OH).

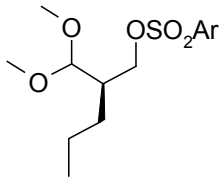
(*2R*)-(Dimethoxymethyl)-pentan-1-ol.



A solution of **4** (2.37 g, 7.06 mmol) in diethylether (60 mL) and water (0.14 mL, 0.7 mmol) was cooled to 0 °C and treated dropwise with a solution of lithium borohydride (2M) in THF (3.9 mL, 7.77 mmol). The reaction mixture was stirred for 2 h at room temperature then aqueous sodium hydroxide

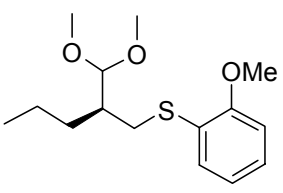
1N (30 mL) was added and the mixture stirred until the two layers became clear. The mixture was decanted, the organic layer washed with water, brine and dried over sodium sulfate, filtered then concentrated under reduced pressure. Purification by flash column chromatography (silica gel, cyclohexane/ethylacetate, 40:60) afforded 0.52 g (45%) of the compound of the title. ^{1}H NMR (DMSO-d_6) ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 6.8 Hz, 3H), 1.23-1.41 (m, 4H), 1.85 (s, 1H), 2.82 (s, 1H), 3.37 (s, 3H), 3.44 (s, 3H), 3.55-3.68 (m, 2H), 4.29 (d, J = 6 Hz, 1H).

1-(4-Methylbenzenesulfonate)-2-(*R*)-(dimethoxymethyl)-pentan-1-ol (5).



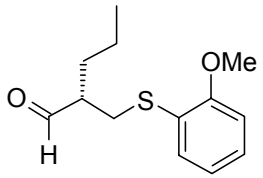
To a solution of (*2R*)-(Dimethoxymethyl)-pentan-1-ol (0.52 g, 3.21 mmol) and dimethylaminopyridine (0.04 g, 0.32 mmol) in dichloromethane (10 mL) was added p-toluenesulfonylchloride (0.62 g, 3.22 mmol) by portions. The reaction mixture was cooled to 0 °C then pyridine (0.42 mL, 5.16 mmol) was added dropwise. After standing over night at 0 °C, the reaction mixture was washed with a 10% aqueous citric acid solution then with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica gel, dichloromethane/cyclohexane, 75:25) afforded 0.39 g (39%) of **5**. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.2 Hz, 3H), 1.2-1.47 (m, 4H), 1.88 (m, 1H), 2.45 (s, 3H), 3.29 (s, 3H), 3.30 (s, 3H), 4.05 (dd, J = 1.2, 4.8 Hz, 2H), 4.22 (d, J = 6 Hz, 1H), 7.35 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H).

(*2S*)-3-[(2-Methoxyphenyl)thio]-2-propyl-propanal, dimethylacetal.



To a suspension of sodium hydride (60% dispersion in oil, 0.057 g, 1.42 mmol) in dry *N,N*-dimethylformamide (5 mL), maintained at 0 °C, was added dropwise at a solution of 2-methoxybenzene thiol in *N,N*-dimethylformamide (5 mL). The reaction mixture was stirred at room temperature for 1 h then a solution of compound **5** (0.375 g, 1.18 mmol) in *N,N*-dimethylformamide (5 mL) was added dropwise. The reaction mixture was stirred for 2 h then the solvent evaporated under reduced pressure and the residue taken up in dichloromethane, washed with water, brine, dried over magnesium sulfate, filtered then concentrated under reduced pressure. Purification by flash column chromatography (silica gel, dichloromethane/cyclohexane, 60:40) afforded 0.29 g (86%) of the compound of the title. ^{1}H NMR (DMSO-d_6) ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 3H), 1.25-1.6 (m, 4H), 1.94 (m, 1H), 2.89 (dd, *J* = 12.4, 6.4 Hz, 1H), 3.06 (dd, *J* = 12.8, 5.6 Hz, 1H), 3.35 (s, 3H), 3.37 (s, 3H), 3.89 (s, 3H), 4.37 (d, *J* = 5.2 Hz, 1H), 6.84 (d, *J* = 8.1, 1H), 6.92 (m, *J* = 7.6, 0.9 Hz, 1H), 7.16 (m, *J* = 81.4 Hz, 1H), 7.31 (dd, *J* = 7.6, 1.4 Hz, 1H).

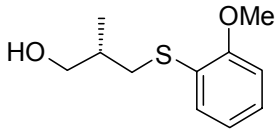
(*2S*)-3-[(2-Methoxyphenyl)thio]-2-propyl-propanal (6a3).



To a solution of (*2S*)-3-(2-methoxyphenyl)thio]-2-propyl-propanal dimethylacetal (0.28 g, 9.84 mmol) in 3% water/acetone (6 mL) was added p-toluenesulfonic acid monohydrate (0.066 g, 3.44 mmol. The mixture was heated at 50 °C for 45 min then cooled to room temperature, poured into a saturated aqueous sodium hydrogen carbonate solution and extracted with diethyl ether. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (silica gel, dichloromethane/cyclohexane, 60:40) afforded 0.23 g (98%) of **6a3**. ^{1}H NMR (DMSO-d_6) ^{1}H NMR (DMSO-d_6) δ 0.84 (t, *J* = 7.2 Hz, 3H), 1.23-1.30 (m, 2H), 1.40-1.55 (m, 1H), 1.60-1.67 (m, 1H), 3.05

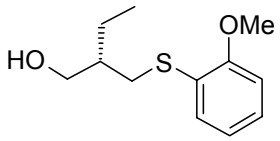
(dd, *J* = 18.4, 5.2 Hz, 1H), 3.17 (dd, *J* = 13.2, 8.0 Hz, 1H), 3.80 (s, 3H), 6.92-6.99 (m, 2H), 7.18-7.27 (m, 2H), 9.56 (d, *J* = 2.2 Hz, 1H).

(*2S*)-3-[(2-Methoxyphenyl)thio]-2-methyl-propan-1-ol (9a1).



To a solution of sodium hydroxide (2.2 g, 55 mmol) in water (60 mL) was added to 2-methoxybenzenethiol (5.6 g, 40 mmol). The reaction mixture was heated at 90 °C then (S)-3-bromo-2-methyl-propanol **7** (6.8 g, 44 mmol) was added and heating was continued for 2 h. The reaction mixture was cooled to room temperature then poured into water and the mixture extracted with dichloromethane. The combined organic layer was washed with brine, dried over sodium sulfate, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica gel, dichloromethane) afforded 7.9 g (93%) of **9a1**. ^{1}H NMR ^{1}H NMR ($CDCl_3$) δ 1.05 (d, *J* = 7.2 Hz, 3H), 1.85 (t, *J* = 5.6 Hz, 1H), 1.90-2.01 (m, 1H), 2.81 (dd, *J* = 12.4, 6.8 Hz, 1H), 3 (dd, *J* = 12.8, 6.8 Hz, 1H), 3.60 (m, 2H), 3.89 (s, 3H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.92 (t, *J* = 7.5Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.30 (dd, *J* = 7.6, 1.0 Hz, 1H); $[\alpha]_D^{25}$ +24.3° (*c* 0.21, CH_3OH).

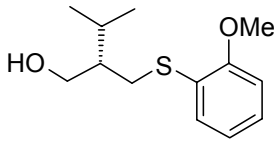
(*2S*)-3[-(2-Methoxyphenyl)thio]-2-ethyl-propan-1-ol (9a2).



A solution of 2-methoxybenzenethiol (0.47 mL, 3.83 mmol) in dry *N*,*N*-dimethylformamide (5 mL) was added dropwise to a suspension of sodium hydride (60% dispersion in oil, 0.184 g, 4.6 mmol) in *N*,*N*-dimethylformamide (10 mL) maintained at 0 °C. The reaction mixture was stirred for 1 h at room temperature then treated with a solution of toluene-4-sulfonic acid (S)-2-hydroxymethyl-butyl ester **8a2** (0.99 g, 3.83 mmol) in *N*,*N*-dimethylformamide (5 mL). The reaction mixture was stirred for 2 h then

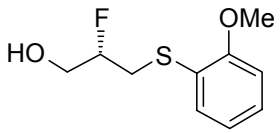
the solvent evaporated off under reduced pressure. The residue was taken up in dichloromethane and washed with water, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, dichloromethane/methanol, 98:2) afforded 0.89 g (99%) of **9a2**. ^{1}H NMR ($CDCl_3$) ^{1}H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.49 (m, 2H), 1.74 (m, 1H), 1.80 (m, 1H), 2.97 (m, 2H), 3.68 (m, 1H), 3.76 (m, 1H), 3.90 (s, 3H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.93 (m, *J* = 7.5, 0.8 Hz, 1H), 7.19 (m, *J* = 7.8, 1.4 Hz, 1H), 7.32 (dd, *J* = 7.7, 1.4 Hz, 1H).

(*2S*)-3-[(2-Methoxyphenyl)thio]-2-*i*propyl-propan-1-ol (9a4).



The compound of the title was obtained as described for **9a2**, starting from 2-methoxybenzenethiol (0.25 mL, 2.09 mmol) and toluene-4-sulfonic acid (S)-2-hydroxymethyl-3-methyl-butyl ester **8a4** (0.57 g, 2.09 mmol). Purification by flash column chromatography (silica gel, cyclohexane/ethylacetate, 70:30) afforded 1.03 g (53%) of **9a4**. ^{1}H NMR (DMSO-d_6) ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 6.5 Hz, 6H), 1.62-1.69 (m, 1H), 1.77 (m, 1H), 2.69 (t, *J* = 5.2 Hz, 1H), 3.58-3.78 (m, 4H), 4.52 (m, 2H), 7.26-7.37 (m, 5H); $[\alpha]_D^{25}$ +14.8° (*c* 0.39, $CDCl_3$).

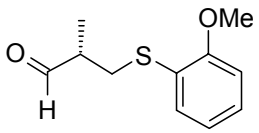
(*2S*)-3-[(2-Methoxyphenyl)thio]-2-fluoro-propan-1-ol (9a5).



The compound of the title was obtained as described for **9a2** starting from 2-methoxybenzenethiol (1.72 g, 12.3 mmol) and toluene-4-sulfonic acid (S)-2-fluoro-3-methoxymethoxypropyl ester (3.59 g, 12.3 mmol). Purification by flash column chromatography (silica gel, dichloromethane) afforded 0.77 g (83%) of **9a5**. ^{1}H NMR (CDCl3) δ 1.87 (t, *J* = 6.4 Hz, 1H), 3.08-3.25 (m, 2H), 3.75-3.9 (m, 2H), 3.90

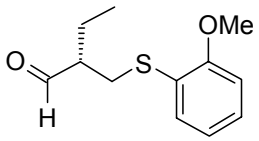
(s, 3H), 4.65 (m, J_{HF} = 48 Hz, 1H), 6.87-6.95 (m, 2H), 7.24-7.27 (m, 1H), 7.37-7.39 (m, 1H); $[\alpha]_D^{25}$ +2.4° (*c* 0.33, CH_3OH).

(*2S*)-3-[(2-Methoxyphenyl)thio]-2-methyl-propanal (6a1).



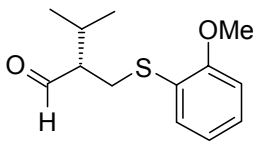
Dimethylsulfoxide (8.5 mL, 119.8 mmol) was added dropwise to a solution of oxalylchloride (5.2 mL, 59.6 mmol) in dichloromethane (50 mL) maintained at –78 °C. After 15 min, a solution of **9a1** (12.7 g, 60 mmol) in dichloromethane (100 mL) was added and the mixture stirred at -78 °C for 3 h then treated with neat triethylamine (slow addition, 16.8 mL, 119.8 mmol). The reaction mixture was stirred for 15 min at -78 °C then warmed to -20 °C and stirring continued for 45 min. The product of the title was not isolated but engaged in the reductive amination step.

(*2S*)-3-[(2-Methoxyphenyl)thio]-2-ethyl-propanal (6a2).



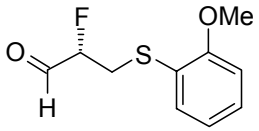
Compound **6a2** (0.84 g, 3.71 mmol) was obtained from intermediate **9a2** as described for compound **6a1**.

(*2S*)-3-[(2-Methoxyphenyl)thio]-2-*i*propyl-propanal (6a4).



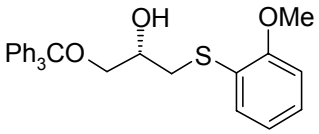
Compound **6a4** (0.43 g, 1.79 mmol) was obtained from intermediate **9a4** as described for compound **6a1**.

(*2S*)-3-(2-Methoxyphenyl)thio]-2-fluoro-propanal (6a5).



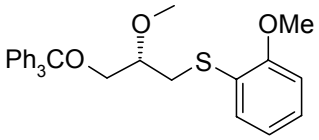
Compound **6a5** (1.38 g, 6.38 mmol) was obtained from intermediate **9a5** as described for compound **6a1**.

(*2S*)-1-(Triphenylmethylether)-3-(2-methoxyphenyl)thio-1,2-propanediol (11).



Chlorotriphenylmethane (27.5 g, 98.6 mmol) was added by portions to a solution of (S)-3-(2-methoxyphenyl)thio-propane-1,2-diol (19.3 g, 90 mmol) and pyridine (11 mL, 136 mmol) in acetonitrile (150 mL). The mixture was stirred at room temperature for 5 h then the solvent removed under reduced pressure. Residual pyridine was eliminated by evaporation with toluene then the residue taken up in dichloromethane and washed with water and brine. The combined organic layer was dried over sodium sulfate, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica gel, dichloromethane/cyclohexane, 70:30) afforded 34.8 g (85%) of **11**. ^{1}H NMR ($CDCl_3$) δ 2.80 (d, 1H), 2.93 (dd, 1H), 3.14 (dd, 1H), 3.23 (d, 2H), 3.77 (m, 1H), 3.87 (s, 3H), 6.88 (m, 2H), 7.25 (m, 10H), 7.34 (dd, 1H), 7.41 (d, 6H); $[\alpha]_D^{25}$ –7.1° (*c* 0.22, CH_3OH).

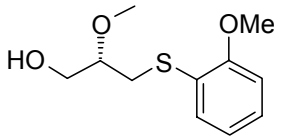
(*2S*)-1-(Triphenylmethylether)-2-methoxy-3-(2-methoxyphenyl)thio-propan-1-ol (12a1).



Compound **11** (34 g, 74 mmol) in tetrahydrofurane (50 mL) was added dropwise to a suspension of sodium hydride (60% dispersion in oil, 3.5 g, 87.5 mmol) in tetrahydrofurane (30 mL). The mixture was stirred at room temperature for 3.5 h then treated with methyliodide (5.1 mL, 82 mmol) and stirring continued for 2.5 h. The solvent was evaporated off and the residue taken up in dichloromethane then

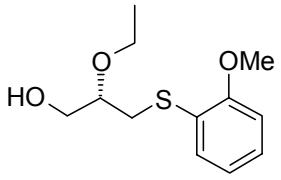
washed with water and brine. The combined organic layer was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The compound **12a1** (35.8 g) was not purified but used as such in the next step.

(*2S*)-2-Methoxy-3-(2-methoxyphenyl)thio-propan-1-ol (9a7).



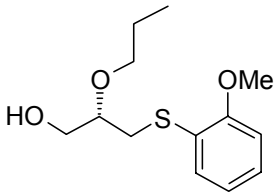
Compound **12a1** (35.8 g) was treated with an ethanolic (2.5N) solution of hydrogen chloride (150 mL). The reaction mixture was stirred at room temperature for 4 h then the solid formed filtered off and the organic layer was concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, dichloromethane/ethylacetate, 90:10) to afford 13.4 g (80%) of **9a7**. ^{1}H NMR ($CDCl_3$) δ 1.99 (t, 1H), 2.97 (dd, 1H), 3.15 (dd, 1H), 3.42 (s, 3H), 3.44 (m, 1H), 3.65 (m, 1H), 3.83 (m, 1H), 3.90 (s, 3H), 6.87 (d, 1H), 6.93 (t, 1H) 7.23 (m, 1H), 7.35 (dd, 1H); $[\alpha]_D^{25}$ –15.5° (*c* 0.07, CH_3OH).

(*2S*)-2-Ethoxy-3-(2-methoxyphenyl)thio-propan-1-ol (9a8).



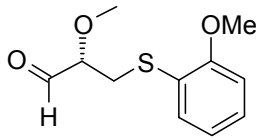
Compound **9a8** (0.24 g, 75%) was obtained from intermediate **12a2** (0.64 g, 1.32 mmol) then purification by flash column chromatography (silica gel, dichloromethane). ^{1}H NMR ($CDCl_3$) δ 1.19 (t, *J* = 6.8 Hz, 3H), 2.03 (t, *J* = 6 Hz, 1H), 2.97 (dd, *J* = 13.2, 7.2 Hz, 1H), 3.13 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.50-3.55 (m, 2H), 3.62-3.68 (m, 2H), 3.79 (m, 1H), 3.89 (s, 3H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 7.21 (m, *J* = 8.1, 1.3 Hz, 1H), 7.34 (dd, J = 7.5, 1.0 Hz).

(*2S*)-2-Propyloxy-3-(2-methoxyphenyl)thio-propan-1-ol (9a9).



Compound **9a9** (0.29 g, 74%) was obtained from intermediate **12a3** (0.77 g, 1.54 mmol) then purification by flash column chromatography (silica gel, dichloromethane/ethylacetate, 98:2). ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.6 Hz, 3H), 1.53-1.62 (m, 2H), 2.02 (t, *J* = 6.4 Hz, 1H), 2.96 (dd, *J* = 13.2, 7.6 Hz, 1H), 3.14 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.39-3.42 (m, 1H), 3.51-3.56 (m, 2H), 3.61-3.67 (m, 1H), 3.78-3.82 (m, 1H), 3.90 (s, 3H), 6.86 (dd, *J* = 8.1, 0.7 Hz, 1H), 6.92 (m, *J* = 7.5, 0.9 Hz, 1H), 7.21 (m, *J* = 8.1, 1.5 Hz, 1H), 7.34 (dd, *J* = 7.5, 1.5 Hz, 1H).

(*2S*)-3-(2-Methoxyphenyl)thio]-2-methoxyl-propanal (6a7).



Compound **6a7** (1.2 g, 30%) was obtained from **9a7** (4 g, 17.5 mmol) as described for compound **6a1** then purification by flash column chromatography (silica gel, dichloromethane/ethylacetate, 95:5). ^{1}H NMR ($CDCl_3$) δ 3.13 (dd, 1H), 3.23 (dd, 1H), 3.47 (s, 3H), 3.70 (m, 1H), 3.90 (s, 3H), 6.88 (dd, 1H), 6.92 (td, 1H), 7.26 (td, 1H), 7.38 (dd, 1H), 9.68 (d, 1H).

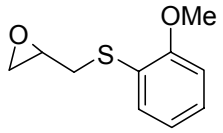
(*2S*)-3-(2-Methoxyphenyl)thio]-2-ethoxyl-propanal (6a8).

Compound **6a8** (0.22 g) was obtained from **9a8** (0.23 g, 0.95 mmol) as described for compound **6a1** but was not purified at this stage.

(*2S*)-3-(2-Methoxyphenyl)thio]-2-propyloxyl-propanal (6a9).

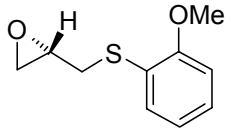
Compound **6a9** (0.29 g) was obtained from **9a9** (0.28 g, 1.11 mmol) as described for compound **6a1** but not purified at this stage.

1-(2-Methoxyphenylthio)-2,3-epoxypropane (13).



Epichlorhydrine (14 mL, 179 mmol) was slowly added to a solution of 2-methoxybenzenethiol (12.5 g, 89 mmol) in water (20 mL) and pyridine (7.2 mL, 89 mmol) at 0 °C. The reaction mixture was stirred overnight at room temperature then treated with an aqueous solution of hydrogen chloride (2N) and extracted with dichloromethane. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica gel, cyclohexane/ethylacetate, 90:10) gave **13** as a colorless oil (5.5 g, 31%). ^{1}H NMR ($CDCl_3$) δ 2.48-2.50 (m, 1H), 2.73-2.76 (m, 1H), 2.88-2.93 (m, 1H), 3.14-3.18 (m, 2H), 3.90 (s, 3H), 6.87 (d, J = 8.1 Hz, 1H), 6.92 (m, J = 7.5, 0.8 Hz, 1H), 7.25 (m, J = 8.1, 1.5 Hz, 1H), 7.40 (dd, J = 7.5, 1.5 Hz, 1H).

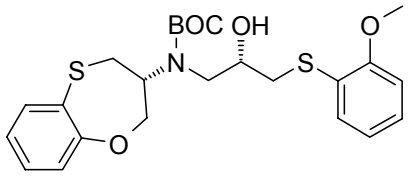
(S)-1-(2-Methoxyphenylthio)-2,3-epoxypropane (S)-13.



2-Methoxybenzenethiol (1 mL, 8.22 mmol) was added dropwise to a solution of potassium hydroxide (0.46 g, 8.22 mmol) in water (10 mL) and ethanol (10 mL). The reaction mixture was stirred for 4 h at room temperature then cooled to -10 °C and (S)-epichlorhydrine (2 mL, 24.6 mmol) was slowly added. The mixture was stirred for 1 h at -10 °C then warmed to room temperature, diluted with water and extracted with dichloromethane. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica gel, cyclohexane/diethylether, 80:20) gave (*S*)-**13** as a colorless oil (1.17 g, 73%). ^{1}H NMR (DMSO-d_6) δ 2.53-2.56 (m, 1H), 2.70-2.73 (m, 1H), 3.04-3.10 (m, 3H), 3.82 (s, 3H),

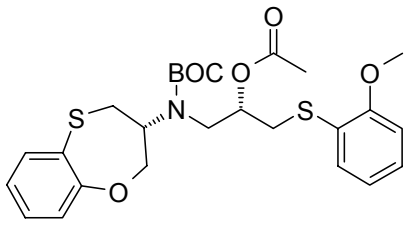
6.93 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 7.20 (t, J = 8.1 Hz, 1H), 7.34 (dd, J = 7.5, 0.6 Hz, 1H); $[\alpha]_D^{25}$ +6.7° (*c*, CH_3OH).

3,4-Dihydro-*N*-[(*2S*)-3-[(2-methoxyphenyl)thio]-2-hydroxypropyl]-2*H*-(*3R*)-1,5-benzoxathiepin-3-*tert*-butoxycarbonylamine (14).



A solution of Boc-anhydride (3.05 g, 14 mmol) in dichloromethane (10 mL) was slowly added at -10 °C to a solution of compound **18a** (4.6 g, 12 mmol) and dimethylaminopyridine (0.15 g, 1.2 mmol) in dichloromethane (20 mL). The mixture was stirred overnight then warmed to room temperature and poured into water and extracted with dichloromethane. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica gel, dichloromethane/ethylacetate, 99:1) gave **14** as a colorless oil (4.3 g, 75%). ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.87-2.92 (m, 2H), 3.05-3.24 (m, 5H), 3.90 (s, 3H), 4.07-4.16 (m, 2H), 4.80-4.82 (m, 1H), 6.85-6.97 (m, 4H), 7.12 (t, J = 6.7 Hz, 1H), 7.21 (t, J = 8.9 Hz, 1H), 7.32 (dd, J = 7.7, 1.5 Hz, 1H), 7.44 (dd, J = 7.6, 1.5 Hz, 1H).

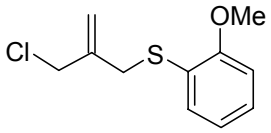
3,4-Dihydro-*N*-[(*2S*)-3-[(2-methoxyphenyl)thio]-2-methylcarbonyloxypropyl]-2*H*-(*3R*)-1,5-benzoxathiepin-3-*tert*-butoxycarbonylamine.



A solution of **14** (1.5 g, 3.1 mmol) and triethylamine (0.65 mL, 4.6 mmol) in dichloromethane (20 mL) was treated at 0°C with acetyl chloride (0.33 mL, 4.6 mmol). The reaction mixture was stirred overnight then a 10% aqueous citric acid solution was added and the product extracted with

dichoromethane. The combined organic layer was washed with water, brine, dried over magnesium sulfate, filtered and concentrated under vacuo. The compound is not purified but engaged in the next step.

2-Chloromethyl-3-(2-methoxyphenyl)thio-1-propene (15a).



Potassium carbonate (2.27 g, 16.4 mmol) was added by portions to a solution of 2-methoxybenzenethiol (2 mL, 16.4 mmol) in acetone (10 mL). The reaction mixture cooled to 0 °C and treated with a solution of 3-chloromethyl-1-propene (1.9 mL, 16.4 mmol) in acetone (10 mL). The mixture was stirred overnight at room temperature then the solid filtered off and the solvent removed under reduced pressure. The residue was taken up in dichloromethane then washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The compound was purified by flash column chromatography (silica gel, cyclohexane/diethylether, 70:30) to give **15a** as a colorless oil (2.39g, 63%); ^{1}H NMR (DMSO-d_6) δ 3.68 (s, 2H), 3.82 (s, 3H), 4.33 (s, 2H), 5.09 (s, 1H), 5.23 (s, 1H), 6.90 (m, J = 7.6, 0.9 Hz, 1H), 6.98 (d, J = 8 Hz, 1H), 7.20 (m, J = 8.0, 1.5 Hz, 1H), 7.26 (dd, J = 7.6, 1.5 Hz, 1H).

Cell culture. HEK-293 cells stably transfected with human SCN5A (hH1A) were kindly provided by Professor Abriel (University of Lausanne, CH). The HEK-293 cell line (ATCC CRL-1573) was permanently transfected with a receptor gene using a gene pulser transfection apparatus (Bio-Rad). Cells were grown under standard conditions in Falcon plates. Cells were removed with trypsin-EDTA (Invitrogen, 0.125 % trypsin) in PBS. Cell suspension was diluted in culture medium containing: DMEM (Gibco), 10% of heat-inactivated foetal calf serum (Gibco), 0.1 M; L-glutamine (Serva), 0.04 M; pyruvate (Sigma), 8.6 mmol; penicillin (Serva), 7 mmol; streptomycin (Serva) and zeocine (Invitrogen) 2 mmol. Cells were seeded in 35 mm Petri dishes at the density of 10 000 cells per dish and cultured for 2 or 3 days.

isolation of cardiac myocytes. Male Sprague-Dawley rats (220-250g) were killed with an overdose of pentobarbital sodium (250 mg/kg ip), and the heart was rapidly excised and washed in ice-cold, oxygenated, Tyrode solution (in mmol: NaCl 120, KCl 5, $MgCl_2$ 1, HEPES 20, Na-pyruvate 4.5, glucose 20, pH 7.3) for 1 min. Hearts were then cannulated and successively perfused (37 °C) with the following oxygenated solutions: for 4 min with tyrode solution, for 6 min with a nominally calcium-free tyrode and for 15 min with the same solution complemented with 1 mg/mL collagenase (Type IA, 1 mg/mL, Sigma Chemicals, St Louis, MO, USA) and protease (type XIV, 0.3 mg/mL, Sigma Chemicals, St Louis, MO, USA). When the heart became flaccid it was then washed with a 0.05 mmol calcium-Tyrode solution for 5 min. Ventricles were then removed and cut into small pieces and kept at room temperature in KB solution (in mmol: KCl 70, K glutamate 5, KH_2PO_4 20, $MgSO_4$ 5, $CaCl_2$ 0.08, EGTA 5, creatine 5, Na_2ATP 5, taurine 20, HEPES 10, D-glucose 10, pH 7.2 with KOH).

Compd	Salt	Calculated (C,H,N)	Found
2	Bromhydrate	C, 52.63; H, 5.74; N, 3.07	C, 52.26; H, 5.66; N, 3.21
3	Maleate	C, 55.97; H, 5.51; N, 2.84	C, 55.69; H, 5.52; N, 2.79
4	Maleate	C, 55.97; H, 5.51; N, 2.84	C, 56.06; H, 5.53; N, 2.93
5	Maleate	C, 55.97; H, 5.51; N, 2.84	C, 55.99; H, 5.59; N, 2.96
6	Maleate	C, 55.97; H, 5.51; N, 2.84	C, 55.83; H, 5.40; N, 2.93
7	Maleate	C, 58.63; H, 5.95; N, 2.85	C, 58.42; H, 6.14; N, 2.82
8	Fumarate	C, 58.63; H, 5.95; N, 2.85	C, 58.48; H, 6.07; N, 2.95
9	Fumarate	C, 58.63; H, 5.95; N, 2.85	C, 58.71; H, 6.09; N, 2.96
10	Maleate	C, 57.84; H, 5.70; N, 2.93	C, 57.66; H; 5.59; N, 3.10
11	Maleate	C, 55.74; H, 5.29; N, 2.83	C, 55.85; H, 5.24; N, 2.82
12	Maleate	C, 56.79; H,5.76; N, 2.76	C, 56.42; H, 5.81; N, 2.96
13	Maleate	C, 57.56; H, 5.99; N, 2.69	C, 57.29; H, 6.01; N, 2.80
14	Maleate	C, 58.30; H, 6.21; N, 2.61	C, 58.11; H, 6.26; N, 2.65
15	Maleate.H_2O[a]	C, 55.63; H, 5.60; N, 2.63	C, 55.45; H, 5.61; N, 2.63; H_2O, 0.33
16	Maleate	C, 60.29; H, 5.23; N, 2.34	C, 62.10; H, 5.32; N, 2.52
17	Oxalate	C, 57.00; H, 5.44; N, 3.02	C, 56.82; H, 5.36; N, 3.20
18	Fumarate. H_2O[a]	C, 59.32; H, 6.18; N, 2.98	C, 59.03; H, 6.20; N, 2.97; H_2O, 0.5
19	Maleate	C, 60.09; H, 6.40; N, 2.70	C, 60.13; H, 6.29; N, 2.87
20	Maleate	C, 60.09; H, 6.40; N, 2.70	C, 60.03; H, 6.61; N, 2.83
21	Maleate	C, 60.33; H, 6.04; N, 2.71	C, 60.15; H, 6.05; N, 2.86

Elemental analyses. [a] Water percentage was determined by the Karl Fisher method with a coulometer.