

Supplementary Material (ESI) for Chemical Communications

This journal is (c) The Royal Society of Chemistry 2013

## Electronic Supplementary Information

# Synthesis of selective inhibitors of sphingosine kinase 1

Dong Jae Baek,<sup>a</sup> Neil MacRitchie,<sup>b</sup> Nigel J. Pyne,<sup>b</sup> Susan Pyne<sup>b</sup> and Robert Bittman<sup>a,\*</sup>

<sup>a</sup>*Department of Chemistry and Biochemistry, Queens College of the City University of New York, Flushing, New York 11367-1597, USA* <sup>b</sup>*Cell Biology Group, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow G4 0RE, UK*

### *Table of Contents*

<b>A. Experimental Methods</b>	S2 – S20
<b>(a) Biological methods</b>	S2 – S4
<b>(b) Synthetic procedures and compound characterization</b>	S4 – S21
<b>B. References</b>	S21

\*To whom correspondence should be addressed: Tel: +1 718-997-3279. E-mail: [robert.bittman@qc.cuny.edu](mailto:robert.bittman@qc.cuny.edu)

## **A. EXPERIMENTAL METHODS**

### **(a) Biological methods**

*Materials*--All general biochemicals and anti-actin antibody were from Sigma (Poole, UK). High glucose Dulbecco's modified Eagle's Medium (DMEM), European fetal calf serum, and penicillin-streptomycin (10000 U/mL penicillin and 10 mg/mL streptomycin) were from Invitrogen (Paisley, UK). Sphingosine was from Avanti Polar Lipids (Alabaster, AL, USA). Purified SK2 was from Enzo Life Sciences (Exeter, UK). BML-258 was from Tocris (Bristol, UK). Human pulmonary aortic smooth muscle cells, human smooth muscle cell growth medium and passaging solutions were from TCS Cellworks (Buckingham, UK). [ $\gamma$ -<sup>32</sup>P]ATP was from Perkin-Elmer (Buckingham, UK).

*Cell Culture.* Human Pulmonary Arterial Smooth Muscle Cells (PASMC) were grown in human smooth muscle cell growth medium. HEK 293 cells stably over-expressing GFP-SK1 (30-fold increase in SK1 activity *versus* vector-transfected cells)<sup>S1</sup> were cultured in DMEM supplemented with 10% European fetal calf serum, 100 U/mL penicillin, 100  $\mu$ g/mL streptomycin, 1% non-essential amino acids, and 0.8% Geneticin at 37 °C in 5% CO<sub>2</sub>.

*Preparation of Whole Cell Extracts.* PASMC cell extracts for SDS-PAGE and Western blot analysis were prepared by washing treated cells with 5 mL of PBS and then re-suspending cell pellets in whole cell lysis buffer [(137 mM NaCl, 2.7 mM KCl, 1 mM MgCl<sub>2</sub>, 1 mM CaCl<sub>2</sub>, 1% v/v NP40, 10% v/v glycerol, 20 mM Tris) (pH 8.0) containing 0.2 mM PMSF, 10  $\mu$ g/mL leupeptin, 10  $\mu$ g/mL aprotinin, 0.5 mM Na<sub>3</sub>VO<sub>4</sub>, 100  $\mu$ M NaF, and 10 mM  $\beta$ -

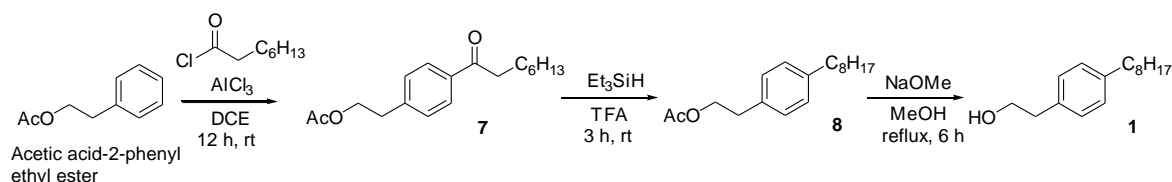
glycerophosphate]. Samples were repeatedly (x 6) passed through a 23-gauge needle using a syringe and rotated for 30 min at 4 °C to allow for efficient lysis. Cell debris was pelleted by centrifugation at 22000  $\times$  g for 10 min at 4 °C and the supernatant (whole cell extract) was collected. The protein content was measured using the Pierce BCA Assay Kit (Fisher Scientific, Loughborough, UK). For each sample, 10-20  $\mu$ g of protein, combined with Lamelli buffer [(0.5 mM Tris, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub>, 5 mM EDTA, 2% w/v SDS) (pH 6.7) containing 12.5% v/v glycerol, 0.25% w/v bromophenol blue, and 50 mM dithiothreitol], were used for SDS-PAGE and Western blotting.

*Sphingosine Kinase Activity Assays.* For SK2 activity assays, sphingosine was complexed with fatty acid free bovine serum albumin (final concentration, 0.2 mg/mL) in reaction buffer 1 containing 20 mM Tris (pH 7.4), 1 mM EDTA, 1 mM Na<sub>3</sub>VO<sub>4</sub>, 40 mM  $\beta$ -glycerophosphate, 1 mM NaF, 0.007% (v/v)  $\beta$ -mercaptoethanol, 20% (v/v) glycerol, 10  $\mu$ g/mL aprotinin, 10  $\mu$ g/mL soybean trypsin inhibitor, 1 mM PMSF, 0.5 mM 4-deoxypyridoxine, and 400 mM KCl. Inhibition of SK2 activity was determined by incubating 37 ng of purified SK2 for 30 min at 30 °C in the presence of 10  $\mu$ M sphingosine, 250  $\mu$ M of [ $\gamma$ -<sup>32</sup>P]ATP (specific activity, 4.4 $\times$ 10<sup>4</sup> cpm/nmol) in 10 mM MgCl<sub>2</sub>, and varying concentrations of the inhibitors dissolved in DMSO or control (5% v/v DMSO). For SK1 activity assays, sphingosine was solubilized in Triton X-100 (final concentration, 0.063% w/v) and combined with buffer 1 without KCl. SK1 activity was determined by incubating 30  $\mu$ g of recombinant SK1 in lysates from HEK 293 cells for 30 min at 30 °C, in the presence of 3  $\mu$ M sphingosine, 250  $\mu$ M of [ $\gamma$ -<sup>32</sup>P]ATP in 10 mM MgCl<sub>2</sub> with or without inhibitor dissolved in DMSO or control (5% v/v DMSO). SK1 and

SK2 reactions were terminated by the addition of 500  $\mu\text{L}$  of 1-butanol and were then mixed with 1 mL of 2 M KCl. The organic phase containing [ $^{32}\text{P}$ ]-S1P was extracted by washing twice with 1 mL of 2 M KCl before quantification by Cerenkov counting.

### (b) Synthetic procedures and compound characterization

*General methods.* All chemicals were reagent grade and used as purchased. Reactions were monitored by thin-layer chromatography using silica gel 60 F<sub>254</sub> aluminum-backed plates. Flash column chromatography was performed on silica gel grade 60 (230–400 mesh).  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance I spectrometer, and chemical shifts are reported in  $\delta$  units relative to deuterated solvents, which served as internal references, at 400 and 100 MHz, respectively. The purity of the products was >95% based on proton NMR spectra. High-resolution mass spectra were recorded on an Agilent Technologies G6520A Q-TOF mass spectrometer using electrospray ionization.



**Scheme S1** Synthesis of compound 1.

#### 4-Octanoylphenethyl acetate (7)<sup>S2</sup>

To a suspension of  $\text{AlCl}_3$  (1.2 g, 9.1 mmol) in 1,2-dichloroethane (25 mL) was added dropwise caprylyl chloride (1.03 mL, 6.1 mmol). After the reaction mixture had stirred at rt for 1 h, a solution of phenethyl acetate (1.0 g, 6.1 mmol) in 1,2-dichloroethane (DCE, 5

mL) was added. The mixture was stirred for 12 h at rt, poured into 1 N NaOH, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes/EtOAc (8:1), gave **7** (1.06 g, 60%) as a yellow waxy solid;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.9$  Hz, 3H), 1.24–1.37 (m, 8H), 1.59–1.67 (m, 2H), 2.04 (s, 3H), 2.94 (td,  $J = 7.4, 2.4$  Hz, 2H), 3.00 (t,  $J = 6.9$  Hz, 2H), 4.27–4.32 (m, 2H), 7.30 (d,  $J = 8.2$  Hz, 2H), 7.91 (d,  $J = 8.3$  Hz, 2H).

#### **4-Octylphenethyl acetate (**8**)<sup>S3</sup>**

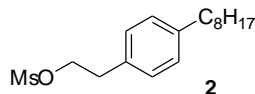
To a solution of **7** (1.0 g, 3.4 mmol) in trifluoroacetic acid (10 mL) was added triethylsilane (1.1 mL, 6.9 mmol). The reaction mixture was stirred at rt for 3 h, concentrated, and diluted with EtOAc. The solution was washed with 1 N NaOH and brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes/EtOAc (15:1), gave **8** (780 mg, 82%) as a yellow liquid;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.8$  Hz, 3H), 1.22–1.31 (m, 10H), 1.58–1.60 (m, 2H), 2.04 (s, 3H), 2.57 (td,  $J = 7.6, 1.5$  Hz, 2H), 2.88–2.93 (m, 2H), 4.24–4.29 (m, 2H), 7.11 (s, 4H).

#### **4-Octylphenethyl alcohol (**1**)<sup>S2</sup>**

To a solution of **8** (500 mg, 1.81 mmol) in MeOH (10 mL) was added sodium methoxide (195 mg, 3.61 mmol). The mixture was heated at reflux for 6 h, evaporated, and partitioned between EtOAc and water. The organic layer was separated and washed with brine. The solution was dried over  $\text{Na}_2\text{SO}_4$  and evaporated to provide **1** (390 mg, 92%) as a yellow oil;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.8$  Hz, 3H), 1.22–1.30 (m, 10H), 1.55–1.63 (m,

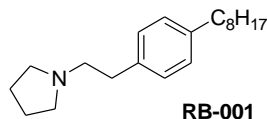
2H), 2.57 (t,  $J = 7.8$  Hz, 2H), 2.83 (t,  $J = 6.6$  Hz, 2H), 3.84 (t,  $J = 6.6$  Hz, 2H), 7.11 (s, 4H).

#### 4-Octylphenethyl methanesulfonate (**2**) (Scheme 1)



To a solution of **1**<sup>S2</sup> (200 mg, 0.853 mmol) and triethylamine (1.19 mL, 8.53 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) at 0 °C was added methanesulfonyl chloride (0.33 mL, 4.27 mmol). After being stirred at rt for 5 h, the reaction mixture was evaporated, diluted with water, and the product was extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Purification by silica gel chromatography, eluting with hexanes/EtOAc (5:1), gave 253 mg (95%) of **2** as a yellow liquid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.87 (t,  $J = 6.9$  Hz, 3H), 1.26–1.30 (m, 10H), 1.58 (m, 2H), 2.57 (t,  $J = 7.7$  Hz, 2H), 2.83 (s, 3H), 3.02 (t,  $J = 7.0$  Hz, 2H), 4.40 (t,  $J = 7.0$  Hz, 2H), 7.14 (s, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.1, 22.7, 29.3 (2C), 29.5, 31.6, 31.9, 35.3, 35.6, 37.3, 70.6, 128.8, 128.9, 133.4, 141.9; ESI-HRMS (M+Na)<sup>+</sup>  $m/z$  calcd for C<sub>17</sub>H<sub>28</sub>NaO<sub>3</sub>S 335.1657, found 335.1655.

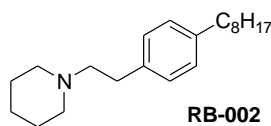
#### 1-(4-Octylphenethyl)pyrrolidine (RB-001)



To a solution of **2** (15 mg, 0.040 mmol) in 3 mL of acetonitrile was added pyrrolidine (80 μL, 0.90 mmol). The reaction mixture was stirred at 50 °C for 24 h and concentrated. Purification by silica gel chromatography, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (5:1), gave 11 mg (80%) of **RB-001** as a slightly yellow waxy solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.88 (t,  $J$

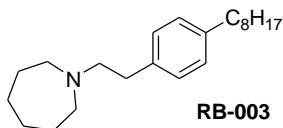
= 6.8 Hz, 3H), 1.20–1.29 (m, 10H), 1.56–1.60 (m, 2H), 2.03–2.06 (m, 4H), 2.13–2.19 (m, 2H), 2.56 (t,  $J = 7.8$  Hz, 2H), 3.03–3.10 (m, 6H), 7.10–7.15 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.7, 23.4, 29.3, 29.5, 31.0, 31.5, 31.9, 32.7, 35.6, 53.4, 53.9, 57.4, 128.5, 128.8, 134.3, 141.7; ESI-HRMS ( $\text{M}+\text{H}$ ) $^+$   $m/z$  calcd for  $\text{C}_{20}\text{H}_{34}\text{N}$  288.2691, found 288.2689.

### 1-(4-Octylphenethyl)piperidine (RB-002)



To a solution of **2** (100 mg, 0.32 mmol) in 5 mL of acetonitrile was added 4-hydroxypiperidine (162 mg, 1.60 mmol). The reaction mixture was stirred at 50 °C for 12 h and concentrated. Purification by silica gel chromatography, eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (5:1), gave 87 mg (86%) of **RB-002** as a colorless oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87 (t,  $J = 6.8$  Hz, 3H), 1.23–1.29 (m, 10H), 1.54–1.60 (m, 4H), 1.77–1.80 (m, 4H), 2.56 (t,  $J = 7.8$  Hz, 2H), 2.71–2.78 (m, 6H), 2.91–2.95 (m, 2H), 7.09–7.14 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.7, 23.6, 25.8, 29.3, 29.4, 29.5, 31.6, 31.9, 35.6, 54.1, 60.5, 128.6, 128.7, 136.1, 141.0; ESI-HRMS ( $\text{M}+\text{H}$ ) $^+$   $m/z$  calcd for  $\text{C}_{21}\text{H}_{36}\text{N}$  302.2847, found 302.2842.

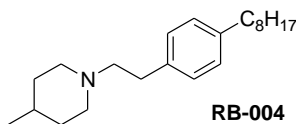
### 1-(4-Octylphenethyl)azepane (RB-003)



The azepane derivative **RB-003** was prepared from **2** according to a coupling procedure similar to that described for compound **RB-001**, using hexamethyleneimine. Yield = 76%;

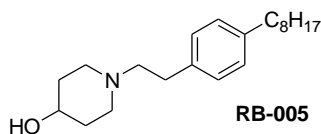
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.8$  Hz, 3H), 1.22–1.32 (m, 10H), 1.54–1.61 (m, 2H), 1.69–1.84 (m, 4H), 1.92–2.13 (m, 4H), 2.56 (t,  $J = 7.7$  Hz, 2H), 3.14–3.24 (m, 6H), 7.11–7.15 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.7, 23.5, 26.9, 29.3, 29.4, 29.5, 30.3, 31.5, 31.9, 35.5, 54.5, 58.8, 128.6, 129.0, 133.3, 142.1; ESI-HRMS ( $\text{M}+\text{H}$ ) $^+$   $m/z$  calcd for  $\text{C}_{22}\text{H}_{38}\text{N}$  316.3004, found 316.3002.

#### 4-Methyl-1-(4-octylphenethyl)piperidine (RB-004)



Compound **RB-004** was prepared from **2** according to a coupling procedure similar to that described for compound **RB-001**, using 4-methylpiperidine. Yield = 73%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87 (t,  $J = 6.8$  Hz, 3H), 0.99 (d,  $J = 6.2$  Hz, 3H), 1.25–1.32 (m, 10H), 1.52–1.66 (m, 5H), 1.74–1.77 (m, 2H), 2.31–2.36 (m, 2H), 2.56 (t,  $J = 7.8$  Hz, 2H), 2.81–2.85 (m, 2H), 2.98–3.02 (m, 2H), 3.25–3.28 (m, 2H), 7.11 (dd,  $J = 8.2, 10.6$  Hz, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 19.8, 21.3, 22.7, 25.5, 29.3, 29.4, 29.5, 31.5, 32.5, 35.6, 53.4, 128.6, 128.7, 132.7, 141.3; ESI-HRMS ( $\text{M}+\text{H}$ ) $^+$   $m/z$  calcd for  $\text{C}_{22}\text{H}_{38}\text{N}$  316.3004, found 316.3003.

#### 1-(4-Octylphenethyl)piperidin-4-ol (RB-005)

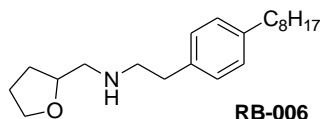


To a solution of **2** (30 mg, 0.096 mmol) in 5 mL of acetonitrile was added 4-



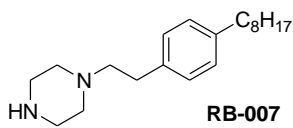
hydroxypiperidine (49 mg, 0.48 mmol). The reaction mixture was stirred at 50 °C for 12 h and concentrated. Purification by silica gel chromatography, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (5:1), gave 27 mg (90%) of **RB-005** as a colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.22–1.30 (m, 10H), 1.55–1.68 (m, 6H), 1.94–1.97 (m, 2H), 2.24 (t, *J* = 9.1 Hz, 2H), 2.54–2.61 (m, 4H), 2.76–2.80 (m, 2H), 2.84–2.89 (m, 2H), 3.71–3.75 (m, 1H), 7.08–7.12 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.1, 22.7, 29.3, 29.4, 29.5, 31.6, 31.9, 33.4, 34.4, 35.6, 51.0, 60.6, 128.4, 128.6, 137.4, 140.7; ESI-HRMS (M+H)<sup>+</sup> *m/z* calcd for C<sub>21</sub>H<sub>36</sub>NO 318.2797, found 318.2793.

#### 2-(4-Octylphenyl)-*N*-((tetrahydrofuran-2-yl)methyl)ethanamine (**RB-006**)



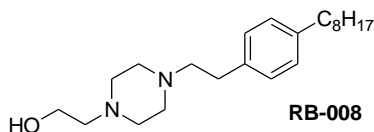
The secondary amine derivative **RB-006** was prepared from **2** according to a coupling procedure similar to that described for compound **RB-001**, using tetrahydrofurfurylamine. Yield = 87%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.89 (t, *J* = 6.7 Hz, 3H), 1.26–1.39 (m, 10H), 1.49–1.60 (m, 4H), 1.84–1.91 (m, 2H), 2.56 (t, *J* = 7.7 Hz, 2H), 2.68–2.78 (m, 2H), 2.81–2.90 (m, 2H), 2.94–2.97 (m, 2H), 3.73 (dd, *J* = 7.0, 14.0 Hz, 1H), 3.83 (dd, *J* = 7.0, 14.4 Hz, 1H), 4.02–4.06 (m, 1H), 7.11 (dd, *J* = 8.3, 10.7 Hz, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.1, 22.7, 25.7, 29.3, 29.4, 29.5, 29.7, 31.6, 31.9, 35.4, 35.6, 51.3, 53.9, 128.5, 128.6, 136.6, 140.9; ESI-HRMS (M+H)<sup>+</sup> *m/z* calcd for C<sub>21</sub>H<sub>36</sub>NO 318.2797, found 318.2795.

#### 1-(4-Octylphenethyl)piperazine (**RB-007**)



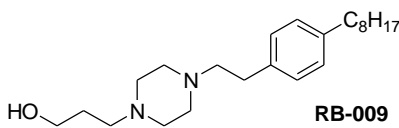
Compound **RB-007** was prepared from **2** according to a coupling procedure similar to that described for compound **RB-001**, using piperazine. Yield = 72%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87 (t,  $J = 6.8$  Hz, 3H), 1.23–1.32 (m, 10H), 1.55–1.60 (m, 2H), 2.49–2.64 (m, 8H), 2.75–2.79 (m, 2H), 3.01 (t,  $J = 4.6$  Hz, 4H), 7.07–7.12 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.7, 29.3, 29.4, 29.5, 31.6, 31.9, 32.9, 35.6, 45.2, 53.1, 60.9, 128.4, 128.5, 137.1, 140.8; ESI-HRMS ( $\text{M}+\text{H}$ ) $^+$   $m/z$  calcd for  $\text{C}_{20}\text{H}_{35}\text{N}_2$  303.2800, found 303.2797.

#### 2-(4-(4-Octylphenethyl)piperazin-1-yl)ethanol (**RB-008**)



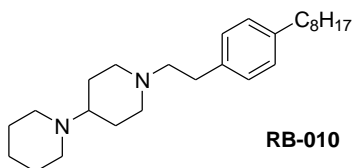
Compound **RB-008** was prepared from **2** according to a coupling procedure similar to that described for compound **RB-001**, using 1-(2-hydroxyethyl)piperazine. Yield = 63%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87 (t,  $J = 6.9$  Hz, 3H), 1.26–1.30 (m, 10H), 1.55–1.62 (m, 2H), 2.49–2.62 (m, 14H), 2.76–2.80 (m, 2H), 3.63 (t,  $J = 5.4$  Hz, 2H), 7.08–7.13 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.7, 29.3, 29.4, 29.5, 31.6, 31.9, 33.2, 35.6, 52.8, 53.2, 57.7, 59.2, 60.6, 128.5, 128.6, 137.2, 140.8; ESI-HRMS ( $\text{M}+\text{H}$ ) $^+$   $m/z$  calcd for  $\text{C}_{22}\text{H}_{39}\text{N}_2\text{O}$  347.3062, found 347.3061.

#### 3-(4-(4-Octylphenethyl)piperazin-1-yl)propan-1-ol (**RB-009**)



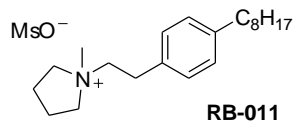
Compound **RB-009** was prepared from **2** according to a coupling procedure similar to that described for compound **RB-001**, using 1-(3-hydroxypropyl)piperazine. Yield = 75%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (t,  $J = 6.8$  Hz, 3H), 1.25–1.32 (m, 10H), 1.54–1.62 (m, 2H), 1.75 (q,  $J = 5.5$  Hz, 2H), 2.56 (t,  $J = 7.8$  Hz, 4H), 2.59–2.64 (m, 4H), 2.69 (t,  $J = 5.7$  Hz, 4H), 2.75–2.79 (m, 4H), 3.81 (t,  $J = 5.2$  Hz, 2H), 7.09 (s, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.7, 26.9, 29.3, 29.4, 29.5, 29.7, 31.6, 31.9, 33.0, 35.6, 52.8, 53.1, 58.6, 60.3, 128.4, 128.5, 137.0, 140.8; ESI-HRMS ( $\text{M}+\text{H}$ ) $^+$   $m/z$  calcd for  $\text{C}_{23}\text{H}_{41}\text{N}_2\text{O}$  361.3219, found 361.3217.

#### 1'-(4-Octylphenethyl)-1,4'-bipiperidine (RB-010)



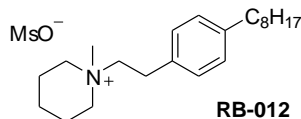
Compound **RB-010** was prepared from **2** according to a coupling procedure similar to that described for compound **RB-001**, using 1,4'-bipiperidine. Yield = 70%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87 (t,  $J = 6.8$  Hz, 3H), 1.26–1.29 (m, 10H), 1.42–1.45 (m, 2H), 1.54–1.70 (m, 8H), 1.81 (d,  $J = 12.3$  Hz, 2H), 1.99 (dt,  $J = 11.7, 1.6$  Hz, 2H), 2.30–2.36 (m, 1H), 2.53–2.58 (m, 8H), 2.74–2.79 (m, 2H), 3.07 (d,  $J = 11.6$  Hz, 2H), 7.07–7.12 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.7, 24.8, 26.3, 27.6, 29.3, 29.4, 29.5, 31.6, 31.9, 33.5, 35.6, 50.1, 53.6, 60.8, 62.9, 128.4, 128.6, 137.5, 140.6; ESI-HRMS ( $\text{M}+\text{H}$ ) $^+$   $m/z$  calcd for  $\text{C}_{26}\text{H}_{45}\text{N}_2$  385.3582, found 385.3577.

### 1-Methyl-1-(4-octylphenethyl)pyrrolidinium methanesulfonate (RB-011)



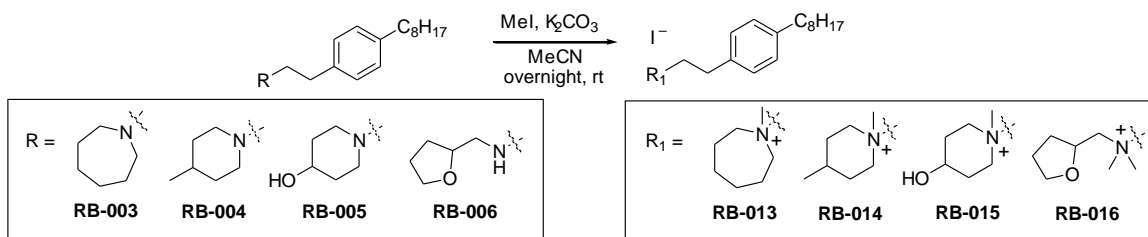
To a solution of **2** (10 mg, 0.032 mmol) in 3 mL of acetonitrile was added 1-methylpyrrolidine (34.1  $\mu$ L, 0.32 mmol). The reaction mixture was stirred at 50  $^{\circ}$ C for 12 h and concentrated. The residue was washed with hexane to give 12 mg (92%) of **RB-011** as a yellow liquid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.8$  Hz, 3H), 1.26–1.30 (m, 10H), 1.54–1.58 (m, 2H), 2.22 (m, 4H), 2.55 (t,  $J = 7.8$  Hz, 2H), 2.75 (s, 3H), 3.01 (t,  $J = 8.2$  Hz, 2H), 3.25 (s, 3H), 3.70–3.77 (m, 6H), 7.13 (d,  $J = 8.0$  Hz, 2H), 7.22 (d,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 21.5, 22.7, 29.3 (2C), 29.5, 30.1, 31.5, 31.9, 35.5, 48.2, 64.4, 64.6, 128.9, 129.1, 132.2, 142.3; ESI-HRMS ( $\text{M}$ ) $^+$   $m/z$  calcd for  $\text{C}_{21}\text{H}_{37}\text{N}^+$  303.2926, found 303.2875.

### 1-Methyl-1-(4-octylphenethyl)piperidinium methanesulfonate (RB-012)



To a solution of **2** (10 mg, 0.032 mmol) in 3 mL of acetonitrile was added 1-methylpiperidine (38.9  $\mu$ L, 0.32 mmol). The reaction mixture was stirred at 50  $^{\circ}$ C for 12 h and concentrated. The residue was washed with hexane to give 12 mg (90%) of **RB-012** as a yellow liquid;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.8$  Hz, 3H), 1.26–1.29 (m, 10H), 1.57 (t,  $J = 7.3$  Hz, 2H), 1.72–1.88 (m, 6H), 2.55 (t,  $J = 7.7$  Hz, 2H), 2.75 (s, 3H), 3.00–

3.05 (m, 2H), 3.30 (s, 3H), 3.52–3.56 (m, 2H), 3.64–3.70 (m, 4H), 7.15 (d,  $J = 8.0$  Hz, 2H), 7.12 (d,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 20.2, 20.7, 22.7, 28.2, 29.3 (2C), 29.5, 31.5, 31.9, 35.5, 39.7, 48.5, 61.0, 128.9, 129.1, 132.1, 142.3; ESI-HRMS ( $\text{M}$ )<sup>+</sup>  $m/z$  calcd for  $\text{C}_{22}\text{H}_{39}\text{N}^+$  317.3082, found 317.3032.



**Scheme S2** Synthesis of compounds **RB-013–016**.

### 1-Methyl-1-(4-octylphenethyl)azepanium iodide (**RB-013**)

To a solution of **RB-003** (10 mg, 0.032 mmol) in MeCN (3 mL) was added  $\text{K}_2\text{CO}_3$  (22 mg, 0.16 mmol) at rt. After the suspension was stirred for 10 min, MeI (10  $\mu\text{L}$ , 0.16 mmol) was added. The reaction mixture was stirred overnight at rt. The reaction mixture was diluted with water, and the product was extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was washed with hexane to give 12 mg (84%) of **RB-013** as a colorless oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.8$  Hz, 3H), 1.24–1.32 (m, 10H), 1.54–1.57 (m, 2H), 1.72–1.77 (m, 4H), 1.91–1.96 (m, 4H), 2.54 (t,  $J = 7.7$  Hz, 2H), 3.11–3.15 (m, 2H), 3.42 (s, 3H), 3.71–3.73 (m, 4H), 3.77–3.81 (m, 2H), 7.12 (d,  $J = 8.0$  Hz, 2H), 7.30 (d,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 22.1, 22.7, 27.3, 29.0, 29.3, 29.5, 29.7, 31.5, 31.9, 35.6, 51.5, 65.1, 65.6, 129.1, 129.2, 131.9, 142.3; ESI-HRMS

(M<sup>+</sup>) *m/z* calcd for C<sub>23</sub>H<sub>40</sub>N<sup>+</sup> 330.3161, found 331.3153.

#### **1,4-Dimethyl-1-(4-octylphenethyl)piperidinium iodide (RB-014)**

Compound **RB-014** was prepared from **RB-004** according to a coupling procedure similar to that described for compound **RB-013**. Yield = 90%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 1.22–1.35 (m, 10H), 1.51–1.64 (m, 5H), 1.80–1.84 (m, 2H), 2.53 (t, *J* = 7.8 Hz, 2H), 3.08–3.12 (m, 2H), 3.26 (s, 3H), 3.60–3.82 (m, 4H), 4.04–4.10 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.2, 20.9, 22.7, 28.1, 29.3, 29.4, 29.7, 31.5, 31.9, 35.6, 44.9, 61.0, 67.9, 129.1, 129.4, 131.4, 142.2; ESI-HRMS (M<sup>+</sup>) *m/z* calcd for C<sub>23</sub>H<sub>40</sub>N<sup>+</sup> 330.3161, found 330.3156.

#### **4-Hydroxy-1-methyl-1-(4-octylphenethyl)piperidinium iodide (RB-015)**

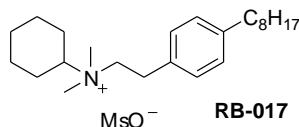
Compound **RB-015** was prepared from **RB-005** according to a coupling procedure similar to that described for compound **RB-013**. Yield = 84%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.87 (t, *J* = 6.7 Hz, 3H), 1.25–1.28 (m, 10H), 1.50–1.57 (m, 2H), 2.02–2.11 (m, 3H), 2.23–2.28 (m, 2H), 2.51 (t, *J* = 6.9 Hz, 2H), 3.04–3.11 (m, 2H), 3.37 (d, *J* = 9.2 Hz, 3H), 3.62–3.76 (m, 6H), 4.18–4.24 (m, 1H), 7.13 (dd, *J* = 2.1, 7.2 Hz, 2H), 7.29 (dd, *J* = 2.2, 6.5 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.1, 22.7, 27.8, 28.2, 28.4, 28.7, 29.3, 29.4, 29.5, 31.6, 31.9, 35.6, 57.6, 58.4, 129.1, 129.2, 131.9, 142.3; ESI-HRMS (M<sup>+</sup>) *m/z* calcd for C<sub>22</sub>H<sub>38</sub>NO<sup>+</sup> 332.2953, found 332.2946.

#### ***N,N*-Dimethyl-2-(4-octylphenyl)-*N*-((tetrahydrofuran-2-yl)methyl)ethanaminium**

### iodide (RB-016)

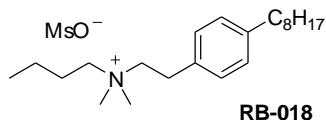
Compound **RB-016** was prepared from **RB-006** according to a coupling procedure similar to that described for compound **RB-013**. Yield = 88%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87 (t,  $J = 6.7$  Hz, 3H), 1.26–1.29 (m, 10H), 1.55–1.67 (m, 6H), 1.89–1.99 (m, 2H), 2.25–2.54 (m, 2H), 2.56 (t,  $J = 7.7$  Hz, 2H), 3.03–3.13 (m, 2H), 3.47 (s, 3H), 3.48 (s, 3H), 3.81–3.88 (m, 1H), 3.93–3.99 (m, 1H), 4.34–4.39 (m, 1H), 7.13 (d,  $J = 8.0$  Hz, 2H), 7.22 (d,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.7, 24.9, 29.2, 29.3, 29.5, 30.4, 31.5, 31.9, 35.6, 52.4, 60.2, 69.3, 72.9, 129.0, 129.2, 131.6, 142.4; ESI-HRMS ( $\text{M}^+$ )  $m/z$  calcd for  $\text{C}_{23}\text{H}_{40}\text{NO}^+$  346.3110, found 346.3102.

### *N,N*-Dimethyl-*N*-(4-octylphenethyl)cyclohexanaminium iodide (RB-017)



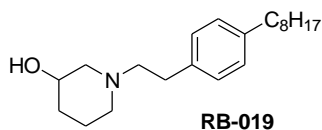
Compound **RB-017** was prepared from **2** according to a coupling procedure similar to that described for compound **RB-011**, using *N,N*-dimethylcyclohexylamine. Yield = 76%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.7$  Hz, 3H), 1.26–1.29 (m, 10H), 1.35–1.45 (m, 5H), 1.51–1.58 (m, 2H), 1.96 (d,  $J = 12.1$  Hz, 2H), 2.20 (d,  $J = 11.6$  Hz, 2H), 7.55 (t,  $J = 7.7$  Hz, 2H), 2.73 (s, 3H), 3.04–3.08 (m, 2H), 3.25 (s, 6H), 3.48 (m, 1H), 3.58–3.62 (m, 2H), 7.12 (d,  $J = 7.9$ , 2H), 7.22 (d,  $J = 7.9$ , 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.7, 24.7, 24.8, 24.9, 25.3, 26.2, 26.6, 28.6, 29.3, 29.5, 31.5, 31.9, 35.3, 39.7, 48.5, 63.1, 72.2, 128.9, 129.1, 132.4, 142.2; ESI-HRMS ( $\text{M}^+$ )  $m/z$  calcd for  $\text{C}_{24}\text{H}_{42}\text{N}^+$  344.3317, found 344.3313.

### ***N,N*-Dimethyl-*N*-(4-octylphenethyl)butan-1-aminium iodide (RB-018)**



Compound **RB-018** was prepared from **2** according to a coupling procedure similar to that described for compound **RB-011**, using *N*-*n*-butyldimethylamine. Yield = 65%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.88 (t, *J* = 6.7 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H), 1.21–1.29 (m, 10H), 1.27–1.40 (m, 2H), 1.54–1.58 (m, 2H), 1.59–1.68 (m, 2H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.72 (s, 3H), 3.01–3.05 (m, 2H), 3.30 (m, 3H), 3.45–3.49 (m, 2H), 3.58–3.62 (m, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.1, 19.6, 22.6, 24.6, 28.8, 29.2, 29.3, 29.4, 31.5, 31.9, 35.5, 39.7, 51.0, 63.7, 64.2, 128.9, 129.1, 132.2, 142.2; ESI-HRMS (M<sup>+</sup>) *m/z* calcd for C<sub>22</sub>H<sub>40</sub>N<sup>+</sup> 318.3161, found 318.3156.

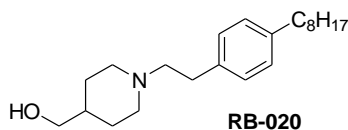
### **1-(4-Octylphenethyl)piperidin-3-ol (RB-019)**



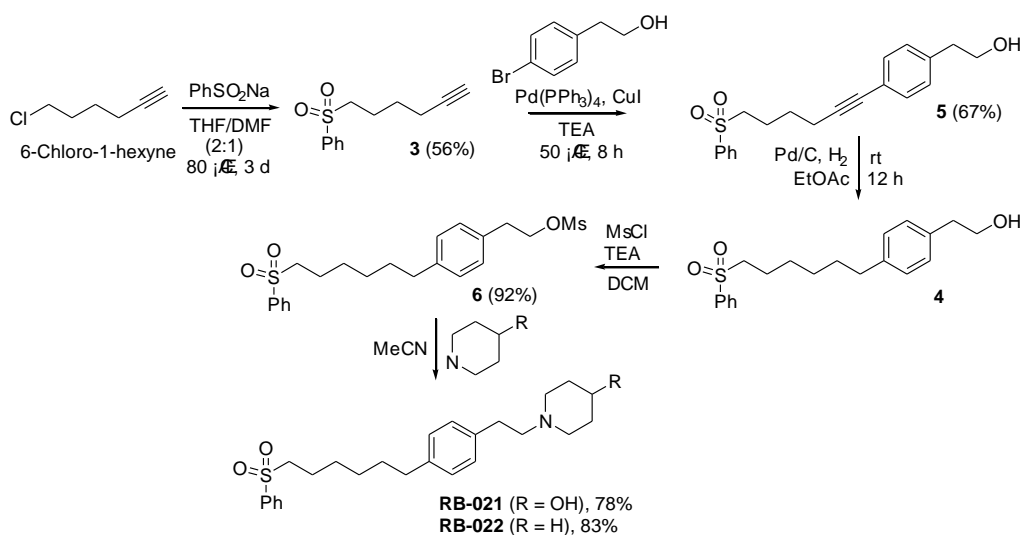
Compound **RB-019** was prepared from **2** according to a coupling procedure similar to that described for compound **RB-005**, using 3-hydroxypiperidine. Yield = 82%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.20–1.30 (m, 10H), 1.57–1.60 (m, 5H), 1.86–1.89 (m, 1H), 2.39–2.43 (m, 1H), 2.54–2.67 (m, 7H), 2.78–2.81 (m, 2H), 7.10 (s, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.1, 21.4, 22.7, 29.3, 29.4, 29.5, 31.6, 31.9, 32.7, 35.6, 53.6, 60.1, 60.3, 66.0, 128.5, 128.6, 136.9, 140.8; ESI-HRMS (M+H)<sup>+</sup> *m/z* calcd for C<sub>21</sub>H<sub>36</sub>NO 318.2797, found 318.2792.



**(1-(4-Octylphenethyl)piperidin-4-yl)methanol (RB-020)**



Compound **RB-020** was prepared from **2** according to a coupling procedure similar to that described for compound **RB-005**, using 4-piperidine methanol. Yield = 87%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.8$  Hz, 3H), 1.21–1.32 (m, 10H), 1.54–1.61 (m, 2H), 1.69–1.75 (m, 3H), 1.89–1.92 (m, 2H), 2.39–2.48 (m, 2H), 2.56 (t,  $J = 7.8$  Hz, 2H), 2.88–2.92 (m, 2H), 3.01–3.05 (m, 2H), 3.36 (d,  $J = 11.0$  Hz, 2H), 3.56 (d,  $J = 5.4$  Hz, 2H), 7.10–7.14 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.7, 27.0, 29.3, 29.4, 29.5, 31.3, 31.5, 31.9, 35.6, 37.4, 53.1, 59.7, 66.7, 128.6, 128.8, 135.0, 141.5; ESI-HRMS ( $\text{M}+\text{H}$ ) $^+$   $m/z$  calcd for  $\text{C}_{22}\text{H}_{38}\text{NO}$  332.2953, found 332.2948.



**Scheme S3** Synthesis of **RB-021** and **RB-022**.

### **(Hex-5-ynylsulfonyl)benzene (3)**

To a solution of 6-chloro-1-hexyne (100 mg, 0.86 mmol) in 12 mL of THF/DMF (2:1) was added benzenesulfinic acid sodium salt (422 mg, 2.6 mmol) in a sealed tube. The reaction mixture was stirred at 80 °C for 3 d. The reaction mixture was then diluted with water, and the product was extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Purification by silica gel chromatography, elution with hexane/EtOAc (3:1), afforded 17 mg (56%) of **3** as a colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.61 (quin, *J* = 7.3 Hz, 2H), 1.81–1.89 (m, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 2.19 (dt, *J* = 6.9, 2.6 Hz, 2H), 3.11–3.15 (m, 2H), 7.56–7.60 (m, 2H), 7.65–7.69 (m, 1H), 7.90–7.92 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 17.9, 21.8, 26.8, 55.6, 69.3, 83.0, 128.0, 129.3, 133.7, 139.0, 128.0, 129.3, 133.7, 139.0; ESI-HRMS (M+Na)<sup>+</sup> *m/z* calcd for C<sub>12</sub>H<sub>14</sub>NaO<sub>2</sub>S 245.0612, found 245.0612.

### **2-(4-(6-(Phenylsulfonyl)hex-1-ynyl)phenyl)ethanol (5)**

To a deaerated solution of 2-(4-bromophenyl)ethanol (100 mg, 0.50 mmol), bis(triphenylphosphine)palladium dichloride (29 mg, 0.025 mmol), and copper(I) iodide (4.8 mg, 0.025 mmol) in anhydrous triethylamine (10 mL) was added alkyne **3** (221 mg, 0.99 mmol) at rt. The reaction mixture was heated at 50 °C for 8 h. After saturated aqueous ammonium chloride solution was added, the mixture was extracted with EtOAc. The combined solution was washed with water, brine, and dried. Flash column chromatography with hexanes/EtOAc (1:2) as the eluent gave **5** (114 mg, 67%) as a yellow oil; <sup>1</sup>H NMR

(400 MHz, CDCl<sub>3</sub>)  $\delta$  1.63 (br s, 1H), 1.68 (quin,  $J = 7.3$  Hz, 2H), 1.87–1.95 (m, 2H), 2.41 (t,  $J = 6.9$  Hz, 2H), 2.85 (t,  $J = 6.6$  Hz, 2H), 3.14–3.18 (m, 2H), 3.84 (dd,  $J = 6.1, 10.9$  Hz, 2H), 7.14 (d,  $J = 8.2$  Hz, 2H), 7.26 (d,  $J = 8.1$  Hz, 2H), 7.53–7.57 (m, 2H), 7.63–7.67 (m, 1H), 7.91–7.93 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.0, 22.0, 27.1, 39.0, 55.9, 63.5, 81.4, 88.4, 121.7, 128.1, 129.0, 129.3, 131.7, 133.8, 138.4, 139.1; ESI-HRMS (M+Na)<sup>+</sup>  $m/z$  calcd for C<sub>20</sub>H<sub>22</sub>NaO<sub>3</sub>S 365.1187, found 365.1183.

#### **2-(4-(6-(Phenylsulfonyl)hexyl)phenyl)ethanol (4)**

Compound **5** (40 mg, 0.12 mmol) was dissolved in EtOAc (5 mL), and 10% Pd/C (40 mg, 100 wt %) was added. The reaction mixture was hydrogenated at rt for 12 h. The catalyst was removed by filtration through a pad of Celite and rinsed with EtOAc. Product **4** was obtained without purification as a colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.22–1.41 (m, 4H), 1.56 (quin,  $J = 7.6$  Hz, 2H), 1.65 (br s, 1H), 1.66–1.74 (m, 2H), 2.54 (t,  $J = 7.6$  Hz, 2H), 2.83 (t,  $J = 6.6$  Hz, 2H), 3.05–3.09 (m, 2H), 3.84 (t,  $J = 6.6$  Hz, 2H), 7.08 (d,  $J = 8.0$  Hz, 2H), 7.13 (d,  $J = 8.0$  Hz, 2H), 7.55–7.59 (m, 2H), 7.64–7.68 (m, 1H), 7.89–7.91 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  22.6, 28.1, 28.6, 31.0, 35.3, 38.8, 56.2, 63.7, 128.0, 128.6, 129.0, 129.6, 133.7, 135.8, 139.1, 140.5; ESI-HRMS (M+Na)<sup>+</sup>  $m/z$  calcd for C<sub>20</sub>H<sub>26</sub>NaO<sub>3</sub>S 369.1500, found 369.1499.

#### **4-(6-(Phenylsulfonyl)hexyl)phenethyl methanesulfonate (6)**

Compound **6** was prepared from **4** according to a coupling procedure similar to that described for compound **8**. Yield = 92%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.24–1.42 (m, 4H),

1.55 (quin,  $J = 7.6$  Hz, 2H), 1.67–1.74 (m, 2H), 2.55 (t,  $J = 7.6$  Hz, 2H), 2.85 (s, 3H), 3.02 (t,  $J = 7.0$  Hz, 2H), 3.05–3.09 (m, 2H), 4.40 (t,  $J = 7.0$  Hz, 2H), 7.09 (d,  $J = 8.2$  Hz, 2H), 7.13 (d,  $J = 8.1$  Hz, 2H), 7.53–7.59 (m, 2H), 7.64–7.68 (m, 1H), 7.89–7.91 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  22.6, 28.1, 28.6, 31.0, 35.3, 37.3, 56.2, 70.5, 128.0, 129.0, 129.3, 133.6, 133.7, 139.2, 141.2; ESI-HRMS ( $\text{M}+\text{Na}$ ) $^+$   $m/z$  calcd for  $\text{C}_{21}\text{H}_{28}\text{NaO}_5\text{S}_2$  447.1276, found 447.1275.

#### **1-(4-(6-(Phenylsulfonyl)hexyl)phenethyl)piperidin-4-ol (RB-021)**

Compound **RB-021** was prepared from **6** according to a coupling procedure similar to that described for compound **RB-005**. Yield = 78%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.26–1.32 (m, 4H), 1.38 (quin,  $J = 7.4$  Hz, 2H), 1.55 (quin,  $J = 7.5$  Hz, 2H), 1.66–1.78 (m, 5H), 2.08–2.18 (m, 2H), 2.53 (t,  $J = 7.6$  Hz, 2H), 2.78–2.83 (m, 2H), 2.92–2.94 (m, 2H), 2.98–3.08 (m, 4H), 3.96–3.98 (m, 1H), 7.06 (d,  $J = 8.0$  Hz, 2H), 7.11 (d,  $J = 8.0$  Hz, 2H), 7.55–7.59 (m, 2H), 7.64–7.68 (m, 1H), 7.89–7.90 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  22.6, 28.1, 28.5, 31.0, 33.2, 34.4, 35.3, 50.4, 51.1, 56.2, 60.1, 67.7, 128.1, 128.6, 129.3, 133.7, 139.1, 140.6; ESI-HRMS ( $\text{M}+\text{H}$ ) $^+$   $m/z$  calcd for  $\text{C}_{25}\text{H}_{36}\text{NO}_3\text{S}$  430.2416, found 430.2413.

#### **1-(4-(6-(Phenylsulfonyl)hexyl)phenethyl)piperidine (RB-022)**

Compound **RB-022** was prepared from **6** according to a coupling procedure similar to that described for compound **RB-002**. Yield = 83%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.25–1.42 (m, 6H), 1.51–1.59 (m, 4H), 1.66–1.74 (m, 4H), 1.89–1.93 (m, 4H), 2.53 (t,  $J = 7.6$  Hz, 2H), 2.95–3.08 (m, 6H), 7.07 (d,  $J = 8.0$  Hz, 2H), 7.12 (d,  $J = 8.0$  Hz, 2H), 7.56–7.59 (m, 2H),

7.64–7.68 (m, 1H), 7.89–7.91 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  22.6, 23.0, 24.0, 28.2, 28.6, 29.7, 31.0, 35.3, 39.5, 53.9, 54.4, 56.3, 59.4, 128.1, 128.4, 129.3, 133.7, 193.2; ESI-HRMS (M+H) $^+$   $m/z$  calcd for  $\text{C}_{25}\text{H}_{36}\text{NO}_2\text{S}$  414.2466, found 414.2468.

## B. References

- [S1] K. G. Lim, F. Tonelli, Z. Li, X. Lu, R. Bittman, S. Pyne and N. J. Pyne, *J. Biol. Chem.* 2011, **286**, 18633.
- [S2] M. Kiuchi, K. Adachi, T. Kohara, M. Minoguchi, T. Hanano, Y. Aoki, T. Mishina, M. Arita, N. Nakao, M. Ohtsuki, Y. Hoshino, K. Teshima, K. Chiba, S. Sasaki and T. Fujita, *J. Med. Chem.* 2000, **43**, 2946.
- [S3] G. Seidel, D. Laurich and A. Fürstner, *J. Org. Chem.* 2004, **69**, 3950.