

## Supplementary materials

### 1. Chemistry

#### General procedure for reductive amination.

Phenylbutanals **2** (1 mmol) together with benzylamine or propylamine (1 or 5 mmol) were dissolved in anhydrous methylene chloride (3.5 mL) and sodium triacetoxyborohydride was added (1.4 or 5 mmol). The reaction mixture was stirred at room temperature for 1.5-16 h under nitrogen. Next, a saturated solution of NaHCO<sub>3</sub> was added (2–3 mL) and the reaction mixture was extracted with EtOAc (3 × 1.5 mL), dried over anhydrous MgSO<sub>4</sub> and filtered. The organic layer was concentrated under reduced pressure. All compounds were purified by silica gel column chromatography (Hexane–EtOAc–Et<sub>3</sub>N).

**4-(3-Hydroxy-2,4,6-trimethylphenyl)butanal (2a)**. Colorless oil (80%), *R*<sub>f</sub> = 0.51 (Hexane–EtOAc, 70 : 30). IR  $\nu_{\max}/\text{cm}^{-1}$  (liquid film) 3474, 3007, 2949, 2882, 1716, 1480, 1456, 1410, 1386, 1246, 1212, 1094, 1012, 869. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  9.81 (t, 1H, *J* = 1.0, CHO), 6.80 (s, 1H, Ar-H-5), 4.71 (s, 1H, OH), 2.64 (t, 2H, *J* = 5.4 Hz, H-4), 2.54 (dt, 2H, *J* = 4.7, 1.0 Hz, H-2), 2.24 (s, 3H, CH<sub>3</sub>-6), 2.23 (s, 3H, CH<sub>3</sub>-2), 2.21 (s, 3H, CH<sub>3</sub>-4), 1.79 (q, 2H, *J* = 4.8 Hz, H-3). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  202.4 (CHO), 150.4 (ArC-3), 137.0 (ArC-1), 129.8 (ArC-5), 127.5 (ArC-6), 121.8 (ArC-2), 120.4 (ArC-4), 43.8 (C-2), 29.2 (C-4), 21.9 (C-3), 19.3 (CH<sub>3</sub>-6), 15.7 (CH<sub>3</sub>-4), 11.8 (CH<sub>3</sub>-2). ESI-HRMS Calcd for [M + H]<sup>+</sup> C<sub>13</sub>H<sub>19</sub>O<sub>2</sub> 207.1380; found 207.1377.

**3,3'-(4,4'-(Benzylazanediyl)bis(butane-4,1-diyl))bis(2,4,6-trimethylphenol) (3a)**. Pale yellow oil (56%), *R*<sub>f</sub> = 0.37 (Hexane–EtOAc, 70 : 30). IR  $\nu_{\max}/\text{cm}^{-1}$  (liquid film) 3581, 3441, 2941, 2856, 1581, 1479, 1454, 1377, 1304, 1205, 1121, 1088, 1026, 866, 744, 698, 621. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.33 (dd, 2H, *J* = 2.1, 0.6 Hz, ArH-3', ArH-5'), 7.30 (s, 1H, ArH-4'), 7.28 (d, 2H, *J* = 0.8 Hz, ArH-2', ArH-6'), 6.76 (s, 2H, ArH-5), 3.81 (br s, 2H, OH), 3.56 (s, 2H, NCH<sub>2</sub>-Ar), 2.53 (t, 4H, *J* = 5.4 Hz, H-4), 2.45 (t, 4H, *J* = 7.3 Hz, H-1), 2.18 (s, 12H, CH<sub>3</sub>-2, CH<sub>3</sub>-6), 2.15 (s, 6H, CH<sub>3</sub>-4), 1.58 (q, 4H, *J* = 7.3 Hz, H-3), 1.42 (m, 4H, H-2). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  150.2 (C-OH), 140.3 (ArC-1'), 138.3 (ArC-3), 129.6 (ArC-5), 128.8 (ArC-2', ArC-6'), 128.1 (ArC-3', ArC-5'), 127.6 (ArC-4'), 126.7 (ArC-4), 121.5 (ArC-2), 119.8 (ArC-6), 58.7 (N-CH<sub>2</sub>-Ar), 53.9 (C-4 butane), 30.1 (C-1 butane), 27.7 (C-3 butane), 27.4 (C-2 butane), 19.3 (CH<sub>3</sub>-4), 15.7 (CH<sub>3</sub>-6), 11.7 (CH<sub>3</sub>-2). ESI-HRMS: calcd for [M + H]<sup>+</sup> C<sub>33</sub>H<sub>46</sub>NO<sub>2</sub> 488.3529; found 488.3516.

**3,3'-(4,4'-(Benzylazanediyl)bis(butane-4,1-diyl))bis(4-allyl-2,6-dimethylphenol) (3b)**. Pale yellow oil (53%), *R*<sub>f</sub> = 0.43 (Hexane–EtOAc, 70 : 30). IR  $\nu_{\max}/\text{cm}^{-1}$  (liquid film) 3562, 3418, 3076, 2926, 2856, 1635, 1580, 1479, 1454, 1377, 1306, 1207, 1121, 1092, 995, 910, 743, 700. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.30 (dd, 2H, *J* = 1.6, 0.6 Hz, ArH-3', ArH-5'), 7.24 (s, 1H, ArH-4'), 7.10 (d, 2H, *J* = 0.6 Hz, ArH-2', ArH-6'), 6.75 (s, 2H, ArH-5), 5.91 (m, 2H, -CH<sub>2</sub>CH=CH<sub>2</sub>), 4.99 (dd, 2H, *J* = 10.0, 1.8 Hz, -CH<sub>2</sub>CH=CH<sub>2</sub>), 4.96 (dd, 2H, *J* = 16.9, 1.8 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 3.30 (br s, 2H, OH), 3.56 (s, 2H, -NCH<sub>2</sub>-Ar), 3.27 (dd, 4H, *J* = 6.3, 1.4 Hz, -CH<sub>2</sub>CH=CH<sub>2</sub>), 2.53 (t, 4H, *J* = 8.2 Hz, H-4), 2.45 (t, 4H, *J* = 7.0 Hz, H-1), 2.19 (s, 6H, CH<sub>3</sub>-6), 2.16 (s, 6H, CH<sub>3</sub>-2), 1.57 (t, 4H, *J* = 8.1 Hz, H-3), 1.43 (m, 4H, *J* = 3.4 Hz, H-2). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  150.6 (C-OH), 139.9 (ArC-3), 138.3 (CH<sub>2</sub>CH=CH<sub>2</sub>), 138.2 (ArC-1'), 129.4 (ArC-4), 129.2 (ArC-5), 128.8 (ArC-2'), 128.7 (ArC-6'), 128.1 (ArC-3'), 128.0 (ArC-5'), 126.7 (ArC-4'), 121.7 (ArC-2), 120.2 (ArC-6), 115.2 (-CH<sub>2</sub>CH=CH<sub>2</sub>), 58.7 (R<sub>2</sub>N-CH<sub>2</sub>-Ar), 53.8 (C-4 butane), 37.2 (CH<sub>2</sub>CH=CH<sub>2</sub>), 29.5 (C-1 butane), 28.1 (C-3 butane), 27.6 (C-2 butane), 15.8 (CH<sub>3</sub>-6), 11.8 (CH<sub>3</sub>-2). ESI-HRMS: calcd for [M + H]<sup>+</sup> C<sub>37</sub>H<sub>50</sub>NO<sub>2</sub> 540.3842; found 540.3863.

**2,4,6-Trimethyl-3-(4-propylaminobutyl)-phenol (3c)**. Pale yellow oil (54%). IR  $\nu_{\max}/\text{cm}^{-1}$  (liquid film) 3560, 3415, 3074, 2926, 2853, 1637, 1580, 1477, 1450, 1375, 1300, 1205, 1120, 1090, 995, 908, 740, 698. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.77 (s, 2H, ArH-5), 3.31 (br s, 2H, OH), 2.65 (t, 4H, *J* = 7.4 Hz, H-4), 2.59 (t, 2H, *J* = 7.5 Hz, NCH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 2.46 (t, 4H, *J* = 7.1 Hz, H-1), 2.21 (s, 6H, CH<sub>3</sub>-6), 2.20 (s, 6H, CH<sub>3</sub>-2), 2.19 (s, 6H, CH<sub>3</sub>-4), 1.61 (t, 4H, *J* = 7.6 Hz, H-3), 1.50 (m, 2H, *J* = 7.4 Hz, NCH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 1.44 (m, 4H, H-2), 0.92 (t, 3H, *J* = 7.4 Hz, NCH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  150.3 (ArOH), 137.9 (ArC-3), 129.8 (ArC-5), 128.9 (ArC-4), 128.2 (ArC-2), 124.8 (ArC-6), 57.7 (NCH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 53.9 (C-4 butane), 29.3 (C-1 butane), 27.9 (C-3 butane), 27.3 (C-2 butane), 23.3 (NCH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 18.9 (CH<sub>3</sub>-4), 15.5 (CH<sub>3</sub>-6), 11.8 (NCH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 11.3 (CH<sub>3</sub>-2). ESI-HRMS: calcd for [M + H]<sup>+</sup> C<sub>29</sub>H<sub>46</sub>NO<sub>2</sub> 440.3450; found 440.3452.

**3-Phenylpropanal (4)**.<sup>27</sup> Obtained from primary alcohol by oxidation procedure: Pyridinium chlorochromate, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 2 h. Pale yellow oil (85%). *R*<sub>f</sub> = 0.67 (Hexane–EtOAc, 80 : 20). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  9.83 (td, 1H, *J* = 0.6 Hz, CHO), 7.31 (tt, 2H, *J* = 7.1, 0.6 Hz, ArH-2, ArH-6), 7.22 (td, 3H, *J* = 6.5, 1.3 Hz, ArH-3, ArH-4, ArH-5), 2.97 (t, 2H, *J* = 7.4 Hz, H-3), 2.79 (tq, 2H, *J* = 7.1, 0.6 Hz, H-2).

**2,4,6-Trimethyl-3-(4-propylaminobutyl)-phenol (5a).** Pale yellow oil (36%),  $R_f = 0.37$  (Hexane–EtOAc, 70:30). IR  $\nu_{\max}/\text{cm}^{-1}$  (liquid film) 3285, 2933, 2874, 2732, 1676, 1578, 1477, 1379, 1222, 1092, 1026, 1013, 917, 865, 752.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  6.77 (s, 1H, ArH-5), 4.60 (br s, 1H, NH), 3.31 (s, 1H, OH), 2.65 (t, 2H,  $J = 7.4$  Hz, H-4), 2.59 (t, 2H,  $J = 7.5$  Hz,  $\text{NCH}_2\text{-CH}_2\text{-CH}_3$ ), 2.42 (t, 2H,  $J = 7.5$  Hz, H-1), 2.21 (s, 3H,  $\text{CH}_3$ -6), 2.20 (s, 3H,  $\text{CH}_3$ -2), 2.19 (s, 3H,  $\text{CH}_3$ -4), 1.61 (q, 2H,  $J = 7.6$  Hz, H-3), 1.50 (m, 2H,  $J = 7.4$  Hz,  $\text{NCH}_2\text{-CH}_2\text{-CH}_3$ ), 1.44 (m, 2H, H-2), 0.92 (t, 3H,  $J = 7.4$  Hz,  $\text{NCH}_2\text{-CH}_2\text{-CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  150.6 (C-OH), 138.0 (ArC-3), 129.6 (ArC-5), 127.4 (ArC-6), 122.1 (ArC-4), 120.5 (ArC-2), 51.9 ( $\text{NCH}_2\text{-CH}_2\text{-CH}_3$ ), 49.8 (C-4 butane), 30.4 (C-3 butane), 29.9 (C-1 butane), 27.4 (C-2 butane), 23.1 ( $\text{NCH}_2\text{-CH}_2\text{-CH}_3$ ), 15.9 ( $\text{CH}_3$ -4), 20.0 ( $\text{CH}_3$ -6), 11.9 ( $\text{CH}_3$ -2), 11.8 ( $\text{NCH}_2\text{-CH}_2\text{-CH}_3$ ). ESI-HRMS: calcd for  $[\text{M} + \text{H}]^+$   $\text{C}_{16}\text{H}_{28}\text{NO}$  250.2171; found 250.2160.

**3-(4-Benzylaminobutyl)-2,4,6-trimethylphenol (5b).** Colourless oil (63%),  $R_f = 0.43$  (Hexane–EtOAc, 70 : 30). IR  $\nu_{\max}/\text{cm}^{-1}$  (liquid film) 3276, 2930, 2872, 2728, 1670, 1573, 1470, 1370, 1202, 1091, 1026, 920, 867, 750.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.30 (m, 2H, ArH-3, ArH-5'), 7.24 (s, 1H, ArH-4'), 7.01 (m, 2H, ArH-2', ArH-6'), 6.75 (s, 1H, ArH-5), 4.87(m, 3H, NH,  $\text{CH}_2\text{-Ar}$ ), 3.78 (br s, 1H, OH), 2.86 (t, 2H,  $J = 7.4$  Hz, H-4), 2.55 (t, 2H,  $J = 7.5$  Hz, H-1), 2.22 (s, 3H,  $\text{CH}_3$ -6), 2.20 (s, 3H,  $\text{CH}_3$ -2), 2.18 (s, 3H,  $\text{CH}_3$ -4), 1.62 (q, 2H,  $J = 7.6$  Hz, H-3), 1.44 (m, 2H, H-2).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  150.4 (C-OH), 139.1 (ArC-1'), 137.8 (ArC-3), 129.6 (ArC-5), 128.8 (ArC-2', ArC-6'), 128.3 (ArC-3', ArC-5'), 128.1 (ArC-4'), 127.9 (ArC-6), 121.7 (ArC-4), 120.1 (C-2), 52.4 ( $\text{NCH}_2\text{Ar}$ ), 49.6 (C-4 butane), 30.1 (C-3 butane), 29.3 (C-1 butane), 27.0 (C-2 butane), 19.0 ( $\text{CH}_3$ -6), 15.6 ( $\text{CH}_3$ -4), 11.8 ( $\text{CH}_3$ -2). ESI-HRMS: calcd for  $[\text{M} + \text{H}]^+$   $\text{C}_{20}\text{H}_{28}\text{NO}$  298.2093; found 298.2096.

**4-Allyl-3-(4-benzylaminobutyl)-2,6-dimethylphenol (5c).** Pale yellow oil (76%),  $R_f = 0.45$  (Hexane–EtOAc, 70 : 30). IR  $\nu_{\max}/\text{cm}^{-1}$  (liquid film) 3265, 3060, 2930, 2870, 1676, 1575, 1479, 1452, 1370, 1300, 1212, 1092, 915, 740, 698.  $^1\text{H}$  NMR( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.31 (s, 2H, ArH-2', ArH-6'), 7.27 (m, 2H, ArH-3', ArH-5'), 6.99 (m, 1H, ArH-4'), 6.75 (s, 1H, ArH-5), 5.92 (m, 1H,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.98 (dd, 1H,  $J = 10.1, 1.8$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.93 (dd, 2H,  $J = 16.9, 1.8$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 3.56 (s, 2H,  $\text{NCH}_2\text{Ar}$ ), 3.27 (dd, 2H,  $J = 6.3, 1.4$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 2.52 (t, 2H,  $J = 7.5$  Hz, H-4), 2.43 (t, 2H,  $J = 7.5$  Hz, H-1), 2.20 (s, 3H,  $\text{CH}_3$ -6), 2.16 (s, 3H,  $\text{CH}_3$ -2), 1.67 (q, 2H,  $J = 7.6$  Hz, H-3), 1.57 (m, 2H,  $J = 7.4$  Hz, H-2).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  150.5 (ArOH), 138.2 (ArC-3), 138.4 (C-1), 129.5 (ArC-4), 128.2 (ArC-5), 121.8 (ArC-2), 120.2 (ArC-6), 129.3 (ArC-3', ArC-5'), 128.8 (ArC-2', ArC-6'), 128.2 (ArC-4'), 115.2 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 53.8 ( $\text{NCH}_2\text{Ar}$ ), 53.6 (C-4 butane), 37.4 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 29.7 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 29.6 (C-1 butane), 28.5 (C-3 butane), 27.6 (C-2 butane), 15.8 ( $\text{CH}_3$ -6), 11.8 ( $\text{CH}_3$ -2). ESI-HRMS: calcd for  $[\text{M} + \text{H}]^+$   $\text{C}_{22}\text{H}_{30}\text{NO}$  324.2249; found 324.2246.

**(3-Phenylpropyl)propylamine (6).** Oil (81%),  $R_f = 0.94$  (Hexane–EtOAc– $\text{NH}_3$ , 15 : 85 : 5). IR  $\nu_{\max}/\text{cm}^{-1}$  (liquid film) 3306, 3062, 3026, 2956, 2931, 2873, 2810, 1943, 1870, 1802, 1674, 1603, 1496, 1454, 1378, 1271, 1128, 1079, 1031, 908, 803, 746, 699.  $^1\text{H}$  NMR( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.28 (td, 4H,  $J = 7.5, 1.4$  Hz, ArH-2, ArH-6), 7.19 (d, 6H,  $J = 7.2$  Hz, ArH-3, ArH-4, ArH-5), 5.29 (s, 1H, NH), 2.66 (t, 2H,  $J = 7.2$  Hz,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ), 2.64 (t, 2H,  $J = 7.3$  Hz, H-1), 2.56 (t, 2H,  $J = 7.4$  Hz, H-3), 1.83 (q, 2H,  $J = 7.7$  Hz, H-2), 1.49 (sextet, 2H,  $J = 7.4$  Hz,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ), 0.91 (t, 3H,  $J = 7.3$  Hz,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  142.2 (ArC-1), 128.4 (ArC-3, ArC-5), 128.3 (ArC-2, ArC-6), 125.7 (ArC-4), 51.9 ( $\text{NCH}_2\text{CH}_2\text{CH}_3$ ), 49.6 (C-1), 33.7 (C-3), 31.8 (C-2), 23.3 ( $\text{NCH}_2\text{CH}_2\text{CH}_3$ ), 11.8 (C-3  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ). ESI-HRMS: calcd for  $[\text{M} + \text{H}]^+$   $\text{C}_{12}\text{H}_{20}\text{N}$  178.1596; found 178.1603.

**Bis-(3-phenylpropyl)propylamine (7).** Yellow oil (60%),  $R_f = 0.84$  (Hexane–EtOAc– $\text{NH}_3$ , 15 : 85 : 5). IR  $\nu_{\max}/\text{cm}^{-1}$  (liquid film) 3085, 3062, 3026, 2954, 2863, 2800, 2740, 1942, 1870, 1802, 1737, 1603, 1496, 1454, 1378, 1298, 1272, 1158, 1078, 1030, 907, 746, 698.  $^1\text{H}$  NMR( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.27 (td, 4H,  $J = 7.5, 1.4$  Hz, ArH-2, ArH-6), 7.18 (d, 6H,  $J = 7.2$  Hz, ArH-3, ArH-4, ArH-5), 2.62 (t, 4H,  $J = 7.7$  Hz, H-1), 2.46 (t, 4H,  $J = 7.7$  Hz, H-3), 2.37 (t, 2H,  $J = 7.4$  Hz, H-1,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ), 1.75 (qt, 4H,  $J = 7.7, 1.6$  Hz, H-2), 1.43 (sext, 2H,  $J = 7.3$  Hz, H-2,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ), 0.88 (t, 3H,  $J = 7.3$  Hz, H-3,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  142.6 (ArC-1), 128.4 (ArC-3, ArC-5), 128.3 (ArC-2, ArC-6), 125.7 (ArC-4), 56.2 (C-1,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ), 53.7 (C-1), 33.7 (C-3), 28.9 (C-2), 20.3 (C-2,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ), 12.0 (C-3,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ ). ESI-HRMS: calcd for  $[\text{M} + \text{H}]^+$   $\text{C}_{21}\text{H}_{30}\text{N}$  296.2378; found 296.2380.

**Benzyl (3-phenylpropyl)amine (8).** Oil (60%),  $R_f = 0.48$  (Hexane–EtOAc– $\text{NH}_3$ , 15 : 85 : 5). IR  $\nu_{\max}/\text{cm}^{-1}$  (liquid film) 3059, 3026, 2938, 2854, 2795, 2330, 1940, 1944, 1870, 1730, 1603, 1495, 1456, 1368, 1076, 1020, 744, 690.  $^1\text{H}$  NMR( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.28 (td, 2H,  $J = 7.4, 1.5$  Hz, ArH-2, ArH-6), 7.27 (m, 5H, ArH'), 7.18 (d, 3H,  $J = 7.1$  Hz, ArH-3, ArH-4, ArH-5), 4.90 (s, 1H, NH), 2.68 (t, 2H,  $J = 7.2$  Hz, H-1), 2.63 (t, 2H,  $J = 7.3$  Hz, H-3), 3.79 ( $\text{NCH}_2\text{Ar}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  142.2 (ArC-1), 140.5 (ArC-1'), 128.4 (ArC-3, ArC-5), 128.3 (ArC-2', ArC-6'), 128.1 (ArC-2, ArC-6), 126.9 (ArC-4'), 125.8 (ArC-4), 54.1 ( $\text{NCH}_2\text{Ar}$ ), 49.0 (C-1), 33.7 (C-3), 31.8 (C-2). ESI-HRMS: calcd for  $[\text{M} + \text{H}]^+$   $\text{C}_{16}\text{H}_{20}\text{N}$  226.1596; found 226.1595.

**Benzyl-bis-(3-phenylpropyl)amine (9).** Pale yellow oil (20%),  $R_f = 0.60$  (Hexane–EtOAc, 80 : 20). IR  $\nu_{\max}/\text{cm}^{-1}$  (liquid film) 3084, 3061, 3026, 2941, 2797, 1944, 1872, 1805, 1732, 1603, 1495, 1454, 1367, 1258, 1122, 1078, 1028, 908, 800, 744, 698.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.28 (m, 4H, ArH-2, ArH-6), 7.24 (m, 2H, ArH-2', ArH-6'), 7.16 (m, 6H, ArH-3, ArH-4, ArH-5), 7.13 (m, 3H, ArH-3', ArH-4', Ar-5'), 3.59 (s, 2H,  $\text{NCH}_2\text{Ar}$ ), 2.61 (t, 4H,  $J = 5.0$  Hz, H-1), 2.50 (t, 4H,  $J = 4.9$  Hz, H-3), 1.80 (q, 4H,  $J = 5.0$  Hz, H-2).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  142.6 (ArC-1), 140.1 (ArC-1'), 128.9 (ArC-3), 128.4 (ArC-2), 128.3 (ArC-3'), 128.2 (ArC-2'), 126.7 (ArC-4'), 125.6 (ArC-4), 58.7 (ArCH<sub>2</sub>-N), 53.4 (C-1 propane), 33.7 (C-3 propane), 29.0 (C-2 propane). ESI-HRMS: calcd for  $[\text{M} + \text{H}]^+ \text{C}_{25}\text{H}_{30}\text{N}$  344.2301; found 344.2300.

## 2. Biological studies

### Inhibition assays

#### Parasite growth inhibition assay.

*Trypanosoma cruzi* epimastigotes from the CL–Brener strain were cultured in BHT medium at 28°C. Trypanocidal activity of test compounds was measured as previously described.<sup>24</sup> Briefly, cultures ( $3\text{--}4 \times 10^6$  parasites/mL) were incubated with increasing amounts of each compound dissolved in DMSO (1% final concentration). Concentrations assayed ranged between 5 and 100  $\mu\text{g}/\text{mL}$  with benznidazole used as positive control. Parasite growth was monitored by cell counting in a Neubauer chamber. Growth inhibition percentages were calculated as the ratio between parasite growth in the presence or absence of each compound after 72 hours of culture. Percentages of parasite growth inhibition for each concentration were plotted to determine the 50% inhibitory concentration ( $\text{IC}_{50}$ ). Each experiment was conducted in triplicate and reported results correspond to the average of three independent experiments.

#### Cytotoxicity assay.

Compound cytotoxicity on HeLa cells was measured by the MTT cell proliferation assay. HeLa cells were seeded into 96-well microtiter plates at a concentration of  $4 \times 10^3$  cells/well in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 5% fetal bovine serum. After 24 hours, test compounds were added (5 and 10  $\mu\text{g}/\text{mL}$ ) and incubated at 37°C in a 5%  $\text{CO}_2$  atmosphere. 48 hours after, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrasodium bromide) was added and incubated for 1 hour. Next, the culture medium was eliminated and the insoluble reduced product (Formazan salt) was dissolved in DMSO and quantified spectrophotometrically at 540 nm. Each experiment was conducted in triplicate and reported results correspond to the average of three independent experiments.

#### Evaluation of the impact of **3a** on *Trypanosoma cruzi* oxidative state.

To evaluate the impact of **3a** on the redox state of the parasites, compound toxicity at concentrations around its  $\text{IC}_{50}$  was determined in the presence or absence of  $\text{H}_2\text{O}_2$ . Parasite growth inhibition was evaluated using **3a** (4 and 6  $\mu\text{g}/\text{mL}$ ),  $\text{H}_2\text{O}_2$  (5  $\mu\text{M}$ , 10  $\mu\text{M}$  and 20  $\mu\text{M}$ ) or a combination of both, as previously described.

#### Trypanothione reductase inhibition assays.

Inhibition assays of Trypanothione reductase activity were measured by monitoring DTNB reduction at 405 nm ( $\epsilon_{\text{TNB}} = 13.6 \text{ mM}^{-1} \cdot \text{cm}^{-1}$ ) and 30°C, in a final volume of 250  $\mu\text{L}$ , using a Multiskan Ascent one-channel vertical light path filter photometer (Thermo Electron Co.). The reaction mixture contained 100 mM TRIS-HCl pH 7.5, 2 mM EDTA, 200  $\mu\text{M}$  NADPH, 5  $\mu\text{M}$   $\text{TS}_2$ , 4 nM  $\text{TcTR}$ , 500  $\mu\text{M}$  DTNB and different concentrations of **3a** (3 to 200  $\mu\text{M}$ ). Time-dependent kinetic constants were determined using the equation described by Fairlamb *et al.*<sup>26</sup> Inhibitor stock solutions were prepared using DMSO. DMSO final concentration in the reaction mixture did not exceed 1% (v/v). Kinetic constants are the mean of at least three independent data sets, and they are reproducible within  $\pm 10\%$ .