

## Supplementary Information

### **Redesigning the designer drug ecstasy: non-psychoactive MDMA analogues exhibiting Burkitt's lymphoma cytotoxicity**

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## Chemistry

### General

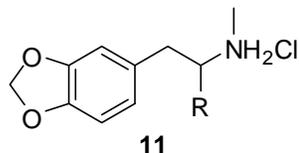
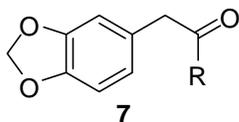
All solvents were distilled prior to use; anhydrous solvents and reagents were distilled under N<sub>2</sub>. EtOH was dried over 4A molecular sieves. THF and Et<sub>2</sub>O for organometallic reactions were distilled from sodium benzophenone ketyl. THF for reductive amination was dried over 4A sieves. Petrol denotes the hydrocarbon fraction distilling from 64–67 °C. Acid chlorides were distilled under N<sub>2</sub> prior to use. All reaction temperatures refer to bath temperatures. Organic extracts were dried over anhydrous MgSO<sub>4</sub> and then filtered. Solvents were evaporated under vacuum or under a stream of N<sub>2</sub>.

Rapid silica filtration refers to chromatography on a short column of silica (BDH, for flash chromatography, 40–63 μm) in a sintered glass funnel, in which the eluent is sucked through the column under vacuum. Analytical TLC was performed on Whatman flexible plates (250 μm layer, Al Sil G/UV254). Spots were visualised under UV light and by staining with acidified 2,6-dinitrophenylhydrazine (ketones) or ninhydrin (amines). Gas chromatography-mass spectrometry (GC-MS) was conducted on a Shimadzu GCMS QP-2010 equipped with a RESTEK RTX-5MS 30 m × 0.25 mm ID × 0.1 μm df, or a RESTEK Stabilwax 30 m × 0.23 mm ID × 0.1 μm df column, in positive ionisation mode using electron impact ionisation (EI).

Melting points were measured on a Kofler hot stage melting point apparatus and are uncorrected. Microanalyses were conducted by The Australian National University Research School of Chemistry Microanalysis Unit or by Robertson Microlit. Electrospray mass spectra were acquired from methanolic solutions on a VG Autospec or VG Micromass 7070F double focusing mass spectrometer in positive ionisation mode. Low resolution electron impact mass spectra were acquired on a Shimadzu GC-MS QP-2010 gas chromatograph-mass spectrometer in positive ionisation mode. High resolution mass spectra were acquired on a VG-Autospec mass spectrometer using fast atom bombardment (FAB) or electron impact ionisation (EI). NMR spectra were acquired on Varian Gemini 2 (300 MHz, <sup>1</sup>H; 75.5 MHz, <sup>13</sup>C), Bruker AM-300 (300 MHz, <sup>1</sup>H; 75.5 MHz, <sup>13</sup>C), Varian Inova 300 (300 MHz, <sup>1</sup>H; 75.5 MHz, <sup>13</sup>C), Varian 400 (400 MHz, <sup>1</sup>H; 100 MHz, <sup>13</sup>C), Bruker Avance 500 (500 MHz, <sup>1</sup>H; 125 MHz, <sup>13</sup>C) or Bruker AV600 (600 MHz, <sup>1</sup>H; 150.9 MHz, <sup>13</sup>C) spectrometers, as indicated. All spectra were recorded in CDCl<sub>3</sub> unless otherwise indicated. Chemical shifts are expressed in ppm, relative to CHCl<sub>3</sub> (<sup>1</sup>H, 7.26 ppm), CDCl<sub>3</sub> (<sup>13</sup>C, 77.0 ppm), CD<sub>3</sub>SOCD<sub>2</sub>H (<sup>1</sup>H, 2.50 ppm), CD<sub>3</sub>COCD<sub>2</sub>H (<sup>1</sup>H, 2.05

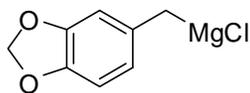
ppm) or CD<sub>3</sub>COCD<sub>3</sub> (<sup>13</sup>C, 29.8 ppm), as appropriate. Routine assignments of <sup>13</sup>C NMR spectra were made with the assistance of DEPT 135 and DEPT 90 experiments.

**Purity (>95%) of target amine hydrochlorides was established by elemental analysis:**



Compound 7	Found			Required		
	C	H	N	C	H	N
<b>j</b>	75.78	5.30	-	75.57	5.55	-
<b>m</b>	71.29	4.99	-	71.10	5.22	-
<b>p</b>	75.49	5.52	-	75.57	5.55	-
<b>t</b>	79.49	4.82	-	79.73	5.10	-
<b>Compound 11</b>						
<b>c</b>	60.55	8.00	5.17	60.58	7.82	5.43
<b>d</b>	60.83	7.23	5.37	61.05	7.09	5.48
<b>e</b>	60.72	8.04	5.24	60.58	7.82	5.43
<b>f</b>	61.64	8.11	4.98	61.87	8.16	5.15
<b>g</b>	65.74	6.04	4.73	65.86	6.22	4.80
<b>h</b>	66.69	6.67	4.37	66.77	6.59	4.58
<b>i</b>	66.49	6.44	4.40	66.77	6.59	4.58
<b>j</b>	66.49	6.48	4.33	66.77	6.59	4.58
<b>k</b>	63.66	6.10	4.34	63.45	6.26	4.35
<b>l</b>	63.68	6.10	4.38	63.45	6.26	4.35
<b>m</b>	63.59	6.04	4.13	63.45	6.26	4.35
<b>n</b>	62.26	5.31	4.53	62.04	5.53	4.52
<b>o</b>	64.78	7.91	4.72	64.53	8.12	4.70
<b>p</b>	66.96	6.60	4.58	66.77	6.59	4.58
<b>q</b>	61.68	4.92	4.03	61.80	5.76	4.00
<b>r</b>	70.22	5.92	4.03	70.27	5.90	4.10
<b>s</b>	70.41	5.77	3.90	70.27	5.90	4.10
<b>t</b>	71.53	6.21	3.66	71.83	6.03	3.81

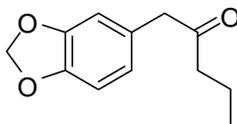
## Synthesis



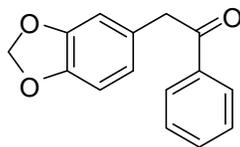
**Piperonylmagnesium chloride (6).** Magnesium turnings (20.0 g, 0.823 mol) were stirred under a stream of N<sub>2</sub> for 7 d<sup>1</sup> during which time a black powder accompanied by a magnesium mirror formed. Anhydrous Et<sub>2</sub>O (100 mL) was added and the suspension was cooled to 0 °C. A solution of piperonyl chloride<sup>2</sup> (13.753 g, 80.62 mmol) in anhydrous Et<sub>2</sub>O (200 mL) was added dropwise to the vigorously stirred suspension over 3 h. Stirring was continued and the formation of the Grignard reagent was monitored by disappearance of piperonyl chloride in the GC–MS of a hydrolysed sample (aq. NH<sub>4</sub>Cl, Et<sub>2</sub>O). After 2 h the chloride was consumed and the suspension was filtered through a glass frit via cannula. The concentration of the Grignard reagent **6** in the filtrate was determined by titration<sup>3</sup> to be 0.20 M (74%). The Grignard has a half life of 7 d when stored at –22 °C under a positive pressure of N<sub>2</sub>.

Replacing Et<sub>2</sub>O with THF gave similar yields.

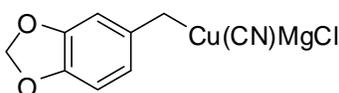
### *Addition of piperonylmagnesium chloride (6) to nitriles*



**1-(1,3-Benzodioxol-5-yl)pentan-2-one (7c) (Method A).** A 0.27 M solution of piperonylmagnesium chloride in anhydrous Et<sub>2</sub>O (9.0 mL, 2.43 mmol) was added to a stirred solution of butyronitrile (0.20 mL, 2.29 mmol) in anhydrous Et<sub>2</sub>O (10 mL). The reaction mixture was heated under reflux and monitored by GC–MS (NH<sub>4</sub>Cl, Et<sub>2</sub>O mini-workup). After 1 h the Grignard reagent had been consumed and the mixture was cooled to room temperature. Ice-water (30 mL) was added, followed by 2 M HCl (30 mL) and the flask was left to stir at room temperature overnight. The phases were separated and the aqueous phase was extracted with Et<sub>2</sub>O (3 × 30 mL). The combined organic phase was washed with saturated NaHCO<sub>3</sub> solution (30 mL), water (30 mL) and brine (30 mL), then dried and evaporated to give a colourless oil (509 mg), which was subjected to rapid silica filtration. Elution with 1:19 EtOAc/petrol gave **7c** as colourless oil (134 mg, 29%), identical with the material described below.



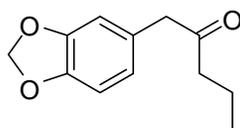
**2-(1,3-Benzodioxol-5-yl)-1-phenylethanone (7g) (Method A).** Benzonitrile (3.1 mL, 30 mmol) was added to a stirred, 0.2 M solution of piperonylmagnesium chloride in anhydrous THF (180 mL, 36 mmol) under N<sub>2</sub>. The reaction mixture was heated under reflux for 24 h, after which time TLC indicated the complete consumption of benzonitrile. The reaction was cooled to room temperature and quenched with cold 0.5 M HCl (100 mL), upon which a white precipitate immediately formed. After stirring for 20 minutes, the phases were separated and the aqueous phase was extracted with Et<sub>2</sub>O (3 × 100 mL). The extract was washed with brine (100 mL), dried and concentrated to give a brown residue (8.87 g), which was purified by flash chromatography. Elution with 1:1:18 EtOAc/toluene/petrol gave **7g** as pale yellow solid (5.76 g, 80%), identical with the material described below.



**Piperonylcuprate (8).** A 0.20 M solution of piperonylmagnesium chloride (480 mL, 96 mmol) in anhydrous Et<sub>2</sub>O was transferred via cannula into a solution of CuCN (8.68 g, 96.9 mmol) and anhydrous LiCl (8.32 g, 197 mmol) in anhydrous THF (480 mL) at -78 °C under N<sub>2</sub>, whereupon the yellow solution turned red. After stirring at -78 °C for 5 min a yellow precipitate formed, which dissolved upon warming to -45 °C. The solution of the organocuprate thus prepared was used directly in the synthesis of ketones **11b–11g**.

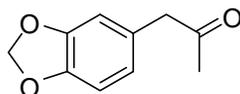
For the synthesis of ketones **11h–11t**, calculations were based on 100% conversion of piperonyl chloride into organocuprate **8**, as described above. The actual conversion is somewhat lower, thus the yields **11h–11t** below are lower estimates.

***Representative procedure for the synthesis of piperonyl ketones from 8***

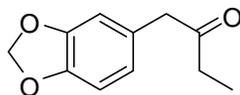


**1-(1,3-Benzodioxol-5-yl)pentan-2-one (7c).** Butyryl chloride (1.00 mL, 9.70 mmol) was added to a suspension of the bright yellow organocuprate **8** (100.0 mL, 10.0 mmol) at -78 °C. The reaction mixture was allowed to slowly warm to 0 °C over 2 h, during which time a red/brown precipitate

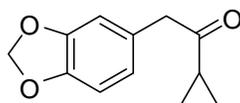
formed. The reaction mixture was poured onto ice cold 0.1 M HCl (100 mL) and the resulting white precipitate was filtered off. The phases in the filtrate were separated and the aqueous phase was extracted with Et<sub>2</sub>O (3 × 30 mL). The combined organic phase was washed with water (30 mL), brine (30 mL), dried and evaporated to give a yellow oil, which was purified by rapid silica filtration. Elution with 1:19 EtOAc/petrol gave **7c** as an off-white oil (1.692 g, 85%). R<sub>f</sub> (1:4 EtOAc/petrol): 0.4. IR (neat) cm<sup>-1</sup>: 1716 (vs, C=O). <sup>1</sup>H NMR (300 MHz): δ 6.75 (d, *J* = 7.9 Hz, 1H, H7'), 6.67 (d, *J* = 1.7 Hz, 1H, ArH4'), 6.63 (dd, *J* = 7.9; 1.7, 1H, ArH6'), 5.9 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.6 (s, 2H, H1), 2.4 (t, *J* = 7.3 Hz, 2H, H3), 1.56 (tq [apparent sextet], *J*<sub>1</sub> = *J*<sub>2</sub> = 7.4 Hz, 2H, H4), 0.86 (t, *J* = 7.4, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75.4 MHz): 208.5 (CO), 147.7 (ArO), 146.5 (ArO), 127.8 (C5'), 122.4 (C6'), 109.7 (CH), 108.3 (CH), 100.9 (CH<sub>2</sub>O<sub>2</sub>), 49.6 (C1), 43.7 (C3), 17.1 (C4), 13.6 (CH<sub>3</sub>). MS (ESI) *m/z*: 229.4 [M+Na]<sup>+</sup> (100%). This compound has been reported but not characterised.<sup>4</sup>



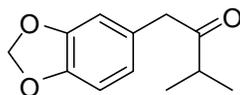
**1-(1,3-Benzodioxol-5-yl)propanone (7a)**. Following the representative procedure, the reaction of a solution of **8** (100.0 mL, 10.0 mmol) with acetyl chloride (0.70 mL, 9.8 mmol), gave **7a** as a colourless oil (1.49 g, 85%). R<sub>f</sub> (1:4 EtOAc/Petrol): 0.2. <sup>1</sup>H NMR (300 MHz): δ 6.70 (m, 3H, ArH), 5.94 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.60 (s, 2H, ArCH<sub>2</sub>), 2.14 (s, 3H, CH<sub>3</sub>). The <sup>1</sup>H and <sup>13</sup>C NMR data are identical to those reported.<sup>5</sup>



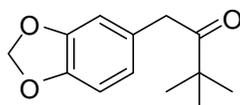
**1-(1,3-Benzodioxol-5-yl)butan-2-one (7b)**. Following the representative procedure, the reaction of a solution of **8** (100.0 mL, 10 mmol) with propionyl chloride (0.87 mL, 10.0 mmol) gave **6b** as a colourless oil (1.68 g, 87%). R<sub>f</sub> (1:4 EtOAc/Petrol): 0.4. IR (neat) cm<sup>-1</sup>: 1712 (vs, C=O). <sup>1</sup>H NMR (300 MHz): δ 6.70 (m, 3H, ArH), 5.94 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.59 (s, 2H, ArCH<sub>2</sub>), 2.47 (q, *J* = 7.3 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 1.02 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>). The <sup>1</sup>H NMR data are similar to those reported.<sup>6</sup> <sup>13</sup>C NMR (75.4 MHz): 209.1 (CO), 147.8 (ArO), 146.6 (ArO), 128.0 (C5'), 122.4 (C6'), 109.7 (CH), 108.4 (CH), 101.0 (CH<sub>2</sub>O<sub>2</sub>), 49.3 (C1), 35.0 (C3), 7.8 (CH<sub>3</sub>).



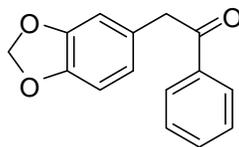
**2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethanone (7d).** Following the representative procedure, the reaction of a solution of **8** (100.0 mL, 10 mmol) with cyclopropanecarbonyl chloride (0.91 mL, 10.0 mmol) gave **7d** as a yellow oil (1.33 g, 65%).  $R_f$  (1:4 EtOAc/Petrol): 0.25. IR (neat)  $\text{cm}^{-1}$ : 3009 (m, cyclopropane C–H), 1693 (vs, C=O).  $^1\text{H}$  NMR (300 MHz):  $\delta$  6.77 (d,  $J = 7.9$  Hz, 1H, ArH7'), 6.68 (m, 2H, H4'/H6'), 5.94 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.73 (s, 2H, H2), 1.96 (m, 1H, cyclopropyl  $\alpha$ H), 1.03 (m, 2H, cyclopropyl) 0.82 (m, 2H, cyclopropyl).  $^{13}\text{C}$  NMR (75.4 MHz): 208.5 (CO), 147.8 (ArO), 146.5 (ArO), 127.9 (C5'), 122.5 (C6'), 109.8 (ArH), 108.4 (ArH), 101.0 (CH<sub>2</sub>O<sub>2</sub>), 50.2 (C2), 19.9 (cyclopropyl CH), 11.4 (cyclopropyl CH<sub>2</sub>). MS (ESI)  $m/z$ : 227 [M+Na]<sup>+</sup>, (100%).



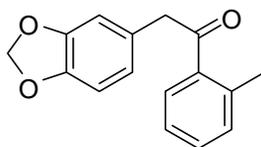
**1-(1,3-Benzodioxol-5-yl)-3-methylbutan-2-one (7e).** Following the representative procedure, the reaction of a solution of **8** (100.0 mL, 10 mmol) with isobutyryl chloride (1.0 mL, 9.6 mmol), gave **7e** as a pale yellow oil (1.65 g, 84%).  $R_f$  (1:4 EtOAc/Petrol): 0.4. IR (neat)  $\text{cm}^{-1}$ : 1712 (vs, C=O).  $^1\text{H}$  NMR (300 MHz):  $\delta$  6.76 (d,  $J = 7.9$  Hz, 1H, H7'), 6.68 (d,  $J = 1.6$  Hz, 1H, H4'), 6.63 (dd,  $J = 7.9, 1.7$ , 1H, H6'), 5.94 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.65 (s, 2H, H1), 2.72 (sept,  $J = 6.9$ , 1H, H3), 1.09 (d,  $J = 6.7$ , 6H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (75.4 MHz):  $\delta$  212.1 (CO), 147.7 (ArO), 146.5 (ArO), 127.9 (C5'), 122.5 (C6'), 109.8 (ArH), 108.3 (ArH), 100.9 (CH<sub>2</sub>O<sub>2</sub>), 47.1 (C1), 39.9 (C3), 18.3 (CH<sub>3</sub>). MS (ESI)  $m/z$ : 229 [M+Na]<sup>+</sup> (100%).



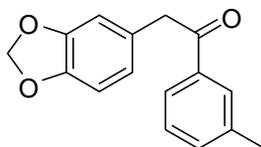
**1-(1,3-Benzodioxol-5-yl)-3,3-dimethylbutan-2-one (7f).** Following the representative procedure, the reaction of a solution of **8** (100.0 mL, 10 mmol) with pivaloyl chloride (1.20 mL, 9.74 mmol), gave **7f** as an amorphous white solid (1.37 g, 64%), mp 37–38°C.  $R_f$  (1:4 EtOAc/Petrol): 0.45. IR (neat)  $\text{cm}^{-1}$ : 1709 (vs, C=O).  $^1\text{H}$  NMR (300 MHz):  $\delta$  6.75 (d,  $J = 7.9$  Hz, 1H, ArH7'), 6.68 (d,  $J = 1.7$  Hz, 1H, ArH4'), 6.60 (dd,  $J = 7.9; 1.7$ , 1H, ArH6'), 5.93 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.70 (s, 2H, C1), 1.19 (s, 9H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (75.4 MHz): 213.0 (CO), 147.6 (ArO), 146.3 (ArO), 128.5 (C5'), 122.5 (C6'), 110.0 (CH), 108.1 (CH), 100.9 (CH<sub>2</sub>O<sub>2</sub>), 44.6 (C3), 42.8 (C1), 26.4 (CH<sub>3</sub>). MS (ESI)  $m/z$ : 243 [M+Na]<sup>+</sup> (100%).



**2-(1,3-benzodioxol-5-yl)-1-phenylethanone (7g).** Following the representative procedure, the reaction of a solution of **8** (100.0 mL, 10 mmol) with benzoyl chloride (0.37 mL, 3.2 mmol), gave **7g** as a pale yellow solid (760 mg, 98%).  $R_f$  (1:4 EtOAc/Petrol): 0.4.  $^1\text{H NMR}$  (300 MHz):  $\delta$  8.01 (m, 2H, ArH), 7.51 (m, 3H, ArH), 6.74 (m, 3H, ArH), 5.91 (s, 2H,  $\text{CH}_2\text{O}_2$ ), 4.20 (s, 2H, H<sub>2</sub>). The  $^1\text{H NMR}$  data are similar to those reported at 200 MHz.<sup>7</sup>  $^{13}\text{C NMR}$  (75.4 MHz): 197.6 (CO), 147.7 (ArO), 146.3 (ArO), 136.6 (C1'), 133.1 (ArH), 128.6 (ArH), 128.5 (ArH), 127.9 (ArH), 122.5 (C6'), 110.0 (ArH), 108.3 (ArH), 100.9 ( $\text{CH}_2\text{O}_2$ ), 45.0 (C2).

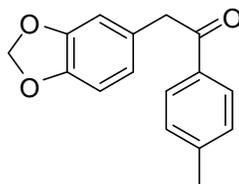


**2-(1,3-Benzodioxol-5-yl)-1-(2-methylphenyl)ethanone (7h).** Following the representative procedure, the reaction of a solution of **8** (max. 0.128 M, 39 mL, 5.0 mmol) with *o*-toluoyl chloride (767 mg, 4.96 mmol) dissolved in anhydrous THF (2 mL), gave **7h** as a pale yellow oil (724 mg, 57% based on piperonyl chloride).  $R_f$  (1:9 EtOAc/Petrol): 0.34. IR (neat)  $\text{cm}^{-1}$ : 1738 (vs, C=O).  $^1\text{H NMR}$  (600 MHz):  $\delta$  7.69 (d,  $J = 7.7$  Hz, 1H, ArH), 7.36 (ddd [apparent dt],  $J = 7.5, 7.5, 1.1$  Hz, 1H, ArH), 7.28–7.22 (m, 2H, 2 $\times$ ArH), 6.75 (d,  $J = 7.9$  Hz, 1H, H7'), 6.72 (d,  $J = 1.6$  Hz, 1H, H4'), 6.67 (dd,  $J = 7.9, 1.5$  Hz, 1H, H6'), 5.93 (s, 2H,  $\text{CH}_2\text{O}_2$ ), 4.12 (s, 2H, H<sub>2</sub>), 2.45 (s, 3H, CH<sub>3</sub>).  $^{13}\text{C NMR}$  (150 MHz):  $\delta$  201.5 (C=O), 147.8 (ArO), 146.5 (ArO), 138.5 (Ar), 137.5 (Ar), 132.0 (ArH), 131.3 (ArH), 128.5 (ArH), 128.0 (Ar), 125.6 (ArH), 122.6 (C6'), 109.9 and 108.4 (C4' and C7'), 101.0 ( $\text{CH}_2\text{O}_2$ ), 48.0 (C2), 21.3 (CH<sub>3</sub>). MS (EI)  $m/z$  (%): 254 [ $\text{M}]^{++}$ (14), 135 [ $\text{M} - \text{COC}_6\text{H}_4\text{Me}]^+$ (13), 119 [ $\text{M} - \text{CH}_2\text{C}_6\text{H}_3\text{OCH}_2\text{O}]^+$ (100). HRMS (EI): calcd for  $\text{C}_{16}\text{H}_{14}\text{O}_3$ , 254.0943; found 254.0947.

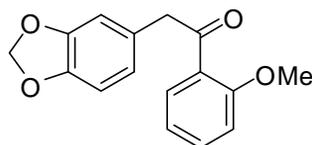


**2-(1,3-Benzodioxol-5-yl)-1-(3-methylphenyl)ethanone (7i).** Following the representative procedure, the reaction of a solution of **8** (max. 0.128 M, 39 mL, 5.0 mmol) with *m*-toluoyl chloride (778 mg, 5.03 mmol) dissolved in anhydrous THF (2 mL), gave **7i** as a white solid (1.12 g, 88%), mp 50.5–51.5 °C.

$R_f$  (1:9 EtOAc/Petrol): 0.29. IR (neat)  $\text{cm}^{-1}$ : 1709 (vs, C=O).  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.82–7.77 (m, 2H, 2 $\times$ ArH), 7.39–7.32 (m, 2H, 2 $\times$ ArH), 6.78–6.75 (m, 2H, H4' + H7'), 6.73–6.68 (m, 1H, H6'), 5.93 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.18 (s, 2H, H1), 2.41 (s, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (125 MHz):  $\delta$  197.8 (C=O), 147.8 (ArO), 146.5 (ArO), 138.4 (Ar), 136.5 (Ar), 133.9 (ArH), 129.0 (ArH), 128.5 (ArH), 128.1 (Ar), 125.8 (ArH), 122.5 (C6'), 109.9 and 108.4 (C4' and C7'), 100.9 (CH<sub>2</sub>O<sub>2</sub>), 45.0 (C2), 21.3 (CH<sub>3</sub>). MS (EI)  $m/z$  (%): 254 [M]<sup>+</sup> (24), 135 [M – COC<sub>6</sub>H<sub>4</sub>Me]<sup>+</sup> (19), 119 [M – CH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>OCH<sub>2</sub>O]<sup>+</sup> (100). HRMS (EI) calcd for C<sub>16</sub>H<sub>14</sub>O<sub>3</sub> 254.0943; found, 254.0943.

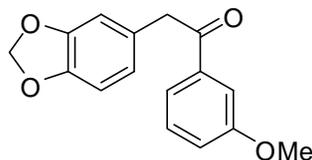


**2-(1,3-Benzodioxol-5-yl)-1-(4-methylphenyl)ethanone (7j).** Following the representative procedure, the reaction of a solution of **8** prepared (max. 0.128 M, 39 mL, 5.0 mmol) with *p*-toluoyl chloride (778 mg, 5.03 mmol) dissolved in anhydrous THF (2 mL), gave **7j** as a white solid (858 mg, 67%). A sample crystallised from hexanes as white plates, mp 83–84 °C.  $R_f$  (1:4 EtOAc/Petrol): 0.35. IR (neat)  $\text{cm}^{-1}$ : 1683 (vs, C=O).  $^1\text{H}$  NMR (400 MHz): 7.92–7.88 (AA' part of AA'BB', 2H, H2'' and H6''), 7.27–7.23 (BB' part of AA'BB', 2H, H3'' and H5''), 6.82–6.80 (m, 2H, H4' and H7'), 6.72–6.68 (m, 1H, H6'), 5.92 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.16 (s, 2H, H2), 2.35 (s, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  197.3 (C=O), 147.8 (ArO), 146.5 (ArO), 144.0 (Ar), 134.0 (Ar), 129.3 (2 $\times$ ArH), 128.7 (2 $\times$ ArH), 128.3 (C5'), 122.5 (C6'), 109.9 and 108.4 (C4' and C7'), 101.0 (CH<sub>2</sub>O<sub>2</sub>), 45.0 (C2), 21.6 (CH<sub>3</sub>). MS (EI)  $m/z$  (%): 254 [M]<sup>+</sup> (20), 135 [M – COC<sub>6</sub>H<sub>4</sub>Me]<sup>+</sup> (12), 119 [M – CH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>OCH<sub>2</sub>O]<sup>+</sup> (100). HRMS (EI) calcd for C<sub>16</sub>H<sub>14</sub>O<sub>3</sub> 254.0943; found, 254.0948. Anal. (C<sub>16</sub>H<sub>14</sub>O<sub>3</sub>) C, H. This compound has been reported but not characterised.<sup>8</sup>

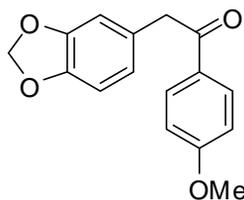


**2-(1,3-Benzodioxol-5-yl)-1-(2-methoxyphenyl)ethanone (7k).** Following the representative procedure, the reaction of a solution of **8** (max. 0.21 M, 18 mL, 3.7 mmol) with *o*-anisoyl chloride (0.67 mL, 4.5 mmol), gave **7k** as a pale yellow oil (0.58 g, 58%). IR (neat)  $\text{cm}^{-1}$ : 1683 (vs, C=O).  $^1\text{H}$  NMR (500 MHz):  $\delta$  7.68–7.63 (m, 1H, H6''), 7.50–7.41 (m, 1H, H4''), 7.03–6.94 (m, 2H, H3'', H5''), 6.75 (d,  $J$  = 8.1 Hz, 1H, H7'), 6.69–6.64 (m, 2H, H4', H6'), 5.92 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.21 (s, 2H, H2), 3.93

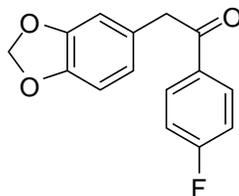
(s, 3H, OCH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz): δ 200.3 (CO), 158.3 (C2''), 147.4 (ArO), 146.3 (ArO), 133.5 (ArH), 130.7 (ArH), 128.8 (C1''), 122.7 (ArH), 120.7 (ArH), 117.8 (C5'), 111.5 (ArH), 110.2 (ArH), 108.2 (ArH), 100.8 (CH<sub>2</sub>O<sub>2</sub>), 55.5 (OCH<sub>3</sub>), 49.7 (C2). MS (EI) *m/z* (%): 270 [M]<sup>++</sup> (9), 149 [M – C<sub>6</sub>H<sub>3</sub>OCH<sub>2</sub>O]<sup>+</sup> (9), 135 [M – COC<sub>6</sub>C<sub>4</sub>OMe]<sup>+</sup> (100). HRMS (EI) calcd for C<sub>16</sub>H<sub>14</sub>O<sub>4</sub> 270.0892; found, 270.0896.



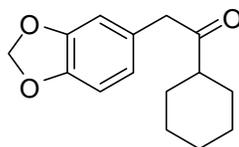
**2-(1,3-Benzodioxol-5-yl)-1-(3-methoxyphenyl)ethanone (7l).** Following the representative procedure, the reaction of a solution of **8** (max. 0.21 M, 15 mL, 3.1 mmol) with *m*-anisoyl chloride (0.64 mL, 4.5 mmol), gave **7l** as a pale yellow oil (0.57 g, 68%). IR (neat) cm<sup>-1</sup>: 1682 (vs, C=O). <sup>1</sup>H NMR (200 MHz): δ 7.62–7.57 (m, 1H, H6''), 7.53–7.50 (m, 1H, H2''), 7.37 (t, *J* = 7.8 Hz, 1H, H5''), 7.14–7.07 (m, 1H, H4''), 6.79–6.75 (m, 1H, H7', H4'), 6.71–6.68 (m, 1H, H6'), 5.94 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.18 (s, 2H, H2), 3.85 (s, 3H, OCH<sub>3</sub>). The <sup>1</sup>H NMR data are similar to those reported at 60 MHz.<sup>9</sup> MS (EI) *m/z* (%): 270 [M]<sup>++</sup> (17), 135 [M – COC<sub>6</sub>C<sub>4</sub>OMe]<sup>+</sup> (100), 107 [M – COCH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>OCH<sub>2</sub>O]<sup>+</sup> (18). HRMS (EI) calcd for C<sub>16</sub>H<sub>14</sub>O<sub>4</sub> 270.0892; found, 270.0889.



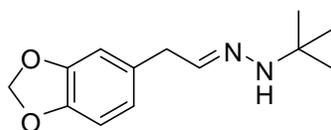
**2-(1,3-Benzodioxol-5-yl)-1-(4-methoxyphenyl)ethanone (7m).** Following the representative procedure, the reaction of a solution of **8** (max. 0.128 M, 39 mL, 5.0 mmol) with *p*-anisoyl chloride (778 mg, 5.03 mmol) dissolved in anhydrous THF (2 mL), gave **7m** as a yellow solid (620 mg, 49%). A sample crystallised from methanol as yellow plates, mp 100–100.5 °C. R<sub>f</sub> (1:9 EtOAc/Petrol): 0.18. IR (neat) cm<sup>-1</sup>: 1682 (vs, C=O). <sup>1</sup>H NMR (600 MHz): 8.00–7.96 (AA' part of AA'BB', 2H, H2'' and H6''), 6.94–6.90 (BB' part of AA'BB', 2H, H3'' and H5''), 6.75 (d, *J* = 7.5 Hz, 1H, H7') 6.75 (d, *J* = 1.6 Hz, 1H, H4'), 6.70 (dd, *J* = 7.9, 1.6 Hz, 1H, H6'), 5.91 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.13 (s, 2H, H2), 3.85 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz): δ 196.2 (C=O), 163.5 (C4''), 147.8 (ArO), 146.4 (ArO), 130.8 (2×ArH), 129.5 (Ar), 128.5 (Ar), 122.4 (C6'), 113.7 (2×ArH), 109.9 and 108.3 (C4' and C7'), 100.9 (CH<sub>2</sub>O<sub>2</sub>), 55.4 (CH<sub>3</sub>), 44.8 (C2). MS (EI) *m/z* (%): 270 [M]<sup>++</sup> (9), 135 [M – COC<sub>6</sub>C<sub>4</sub>OMe]<sup>+</sup> (100), 107 [M – COCH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>OCH<sub>2</sub>O]<sup>+</sup> (10). HRMS (EI) calcd for C<sub>16</sub>H<sub>14</sub>O<sub>4</sub> 270.0892; found, 270.0892.



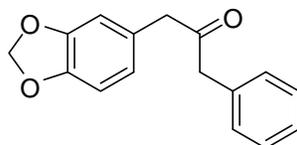
**2-(1,3-benzodioxol-5-yl)-1-(4-fluorophenyl)ethanone (7n).** Following the representative procedure, the reaction of a solution of **8** (max. 0.21 M, 18 mL, 3.7 mmol) with 4-fluorobenzoyl chloride (0.72 g, 4.5 mmol), gave **7n** as a pale yellow oil (0.68 g, 71%). IR (neat)  $\text{cm}^{-1}$ : 1685 (vs, C=O).  $^1\text{H}$  NMR (500 MHz):  $\delta$  8.04–8.00 (m, 2H, H2", H6"), 7.14–7.10 (m, 2H, H3", H5"), 6.76 (d,  $J = 8.0$  Hz, 1H, H7'), 6.74–6.73 (m, 1H, H4'), 6.71–6.68 (m, 1H, H6'), 5.93 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.16 (s, 2H, H2).  $^{13}\text{C}$  NMR (125 MHz):  $\delta$  196.0 (C1), 165.9 (d,  $J = 255.1$  Hz, C4"), 147.9 (ArO), 146.6 (ArO), 132.9 (d,  $J = 3.1$  Hz, C1"), 131.2 (d,  $J = 9.4$  Hz, C2", C6"), 127.8 (C5'), 122.5 (C6'), 115.7 (d,  $J = 21.9$  Hz, C3", C5"), 109.8 (ArH), 108.5 (ArH), 101.0 (CH<sub>2</sub>O<sub>2</sub>), 45.1 (C2). MS (EI)  $m/z$  (%): 258 [ $\text{M}]^{++}$  (33), 149 (78), 135 [ $\text{M} - \text{COC}_6\text{C}_4\text{F}$ ]<sup>+</sup> (74), 123 [ $\text{M} - \text{COCH}_2\text{C}_6\text{H}_3\text{OCH}_2\text{O}$ ]<sup>+</sup> (100), 121 [ $\text{M} - \text{CH}_2\text{COC}_6\text{C}_4\text{F}$ ]<sup>+</sup> (14), 95 [ $\text{M} - \text{COCH}_2\text{C}_6\text{H}_3\text{OCH}_2\text{O}$ ]<sup>+</sup> (34). HRMS (EI) calcd for C<sub>15</sub>H<sub>11</sub>FO<sub>3</sub> 258.0692; found, 258.0693.



**2-(1,3-benzodioxol-5-yl)-1-cyclohexylethanone (7o).** Following the representative procedure, the reaction of a solution of **8** prepared from piperonyl chloride (max. 0.21 M, 20 mL, 4.1 mmol) with cyclohexanecarbonyl chloride (0.60 mL, 4.5 mmol), gave **7o** as a pale yellow oil (0.65 g, 64%). IR (neat)  $\text{cm}^{-1}$ : 1706 (vs, C=O).  $^1\text{H}$  NMR (500 MHz):  $\delta$  6.75 (d,  $J = 7.9$  Hz, 1H, H7'), 6.68–6.66 (m, 1H, H4'), 6.64–6.61 (m, 1H, H6'), 5.94 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.63 (s, 2H, H2), 2.47–2.42 (m, 1H, H1"), 1.85–1.74 (m, 1H, CH<sub>2</sub>), 1.69–1.62 (m, 1H, CH<sub>2</sub>), 1.40–1.31 (m, 1H, CH<sub>2</sub>), 1.30–1.13 (m, 1H, CH<sub>2</sub>).  $^{13}\text{C}$  NMR (125 MHz):  $\delta$  211.3 (C1), 147.8 (ArO), 146.5 (ArO), 128.0 (C5'), 122.5 (C6'), 110.8 (ArH), 108.3 (ArH), 100.9 (CH<sub>2</sub>O<sub>2</sub>), 50.0 (C1"), 47.4 (C2), 28.5 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 25.6 (CH<sub>2</sub>). MS (EI)  $m/z$  (%): 246 [ $\text{M}]^{++}$  (53), 135 [ $\text{M} - \text{COC}_6\text{H}_{10}$ ]<sup>+</sup> (100), 111 [ $\text{M} - \text{CH}_2\text{C}_6\text{H}_3\text{OCH}_2\text{O}$ ]<sup>+</sup> (37). HRMS (EI) calcd for C<sub>15</sub>H<sub>18</sub>O<sub>3</sub> 246.1256; found, 246.1251.

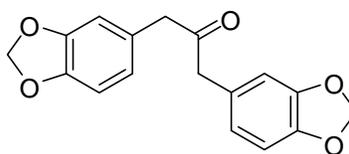


**1-(2-(1,3-benzodioxol-5-yl)ethylidene)-2-*t*-butylhydrazine (9).** Sodium hydroxide (1.44 g, 36.0 mmol) was added portionwise to a stirred solution of 2-*t*-butylhydrazine hydrochloride (4.48 g, 35.9 mmol) in water (14 mL), cooled in an ice-water bath. Acetic acid (0.36 mL, 6.3 mmol) was added dropwise, followed by homopiperonal<sup>10</sup> (5.89 g, 35.9 mmol), and the resulting mixture was purged with Ar and stirred at room temperature with the exclusion of light for 2 h. The reaction mixture was extracted with Et<sub>2</sub>O (3 × 50 mL). The extract was washed with water (50 mL) and brine (50 mL), dried and evaporated to give **9** as a yellow oil (6.72 g, 96%), comprising a 7:3 mixture of *E/Z* isomers (denoted A and B), which was used without purification. <sup>1</sup>H NMR (500 MHz): 7.01 (t, *J* = 5.7 Hz, 0.7H, H1'<sub>A</sub>), 6.76 (d, *J* = 7.9 Hz, 0.3H, H7''<sub>B</sub>), 6.74 (d, *J* = 7.9 Hz, 0.7H, H7''<sub>A</sub>), 6.71–6.69 (m, 1H, H4''<sub>A+B</sub>), 6.68–6.64 (m, 1H, H6''<sub>A+B</sub>), 6.63 (t, *J* = 4.9 Hz, 0.3H, H1'<sub>B</sub>), 5.94 (s, 0.6H, CH<sub>2</sub>O<sub>2B</sub>), 5.92 (s, 1.4H, CH<sub>2</sub>O<sub>2A</sub>), 3.43 (d, *J* = 5.7 Hz, 0.7H, H2'<sub>A</sub>), 3.33 (d, *J* = 4.9 Hz, 0.3H, H2'<sub>B</sub>), 1.191 (s, 2.7H, CCH<sub>3B</sub>), 1.187 (s, 6.3H, CCH<sub>3A</sub>). <sup>13</sup>C NMR (125 MHz): 148.0 (ArO<sub>B</sub>), 147.7 (ArO<sub>A</sub>), 146.3 (ArO<sub>B</sub>), 146.1 (ArO<sub>A</sub>), 140.5 (C1'<sub>A</sub>), 139.6 (C1'<sub>B</sub>), 131.8 (C5''<sub>A</sub>), 130.8 (C5''<sub>B</sub>), 121.6 (C6''<sub>A</sub>), 121.5 (C6''<sub>B</sub>), 109.3 and 108.3 (C4''<sub>A</sub> and C7''<sub>A</sub>), 109.0 and 108.4 (C4''<sub>B</sub> and C7''<sub>B</sub>), 101.0 (CH<sub>2</sub>O<sub>2B</sub>), 100.8 (CH<sub>2</sub>O<sub>2A</sub>), 53.4 (CCH<sub>3B</sub>), 53.3 (CCH<sub>3A</sub>), 38.6 (C2'<sub>A</sub>), 32.8 (C2'<sub>B</sub>), 28.5 (CCH<sub>3B</sub>), 28.4 (CCH<sub>3A</sub>). HRMS (EI): calcd for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>, 234.1368; found 234.1371.

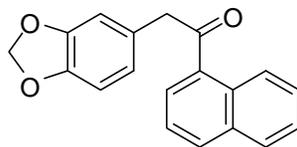


**1-(1,3-benzodioxol-5-yl)-3-phenylpropan-2-one (7p).** A 1.57 M solution of BuLi in hexanes (3.95 mL, 6.20 mmol) was added to a stirred solution of **9** (1.38 g, 5.91 mmol) in anhydrous THF (20 mL) at –78 °C under Ar. After stirring with the exclusion of light for 30 min, benzyl bromide (772 μL, 6.50 mmol) was added and the resulting mixture was allowed to warm to room temperature over 4 h. A saturated aqueous solution of NH<sub>4</sub>Cl (20 mL) was added, followed by extraction with Et<sub>2</sub>O (3 × 10 mL). The extract was washed with water (2 × 10 mL) and brine (10 mL), dried and evaporated to give the crude diazene intermediate as a yellow oil. This was dissolved in cold 1:1 TFA/H<sub>2</sub>O (2 mL) and stirred at room temperature with the exclusion of light for 3 h. The reaction mixture was diluted with water (50 mL) and extracted with Et<sub>2</sub>O (3 × 25 mL). The extract was washed with portions of 5 M NaOH (5 mL until basic), water (2 × 25 mL) and brine (25 mL), dried and evaporated to give a dark oil, which was adsorbed onto Celite and subjected to flash column chromatography. Elution with 1:49–1:19 EtOAc/hexanes gave **7p** as a pale yellow oil which solidified upon standing (452 mg, 36%), mp 56–58 °C. [lit.<sup>11</sup> 91–92 °C]. R<sub>f</sub> (1:4 EtOAc/petrol): 0.50. IR (neat) cm<sup>-1</sup>: 1717 (C=O). <sup>1</sup>H NMR (500

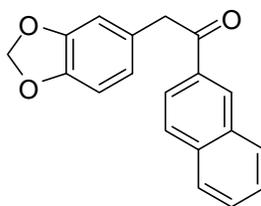
MHz): 7.35–7.30 (m, 2H, H3" and H5"), 7.29–7.24 (m, 1H, H4"), 7.18–7.14 (m, 2H, H2" and H5"), 6.75 (d,  $J = 8.0$  Hz, 1H, H7'), 6.62 (d,  $J = 2.0$  Hz, 1H, H4'), 6.59 (dd,  $J = 7.8, 1.8$  Hz, 1H, H6'), 5.94 (s, 2H, OCH<sub>2</sub>O), 3.72 (s, 2H, H3), 3.62 (s, 2H, H1). <sup>13</sup>C NMR (125 MHz): 205.8 (C=O), 147.9 (ArO), 146.7 (ArO), 134.0, 129.5 (ArH), 128.7 (ArH), 127.5 (Ar), 127.1 (ArH), 122.6 (C6'), 109.8, 108.4, 101.0 (OCH<sub>2</sub>O), 49.0 (CH<sub>2</sub>), 48.6 (CH<sub>2</sub>). MS (EI)  $m/z$ : 255 (40%), 254 (100%), 135 (86%). HRMS (EI) calcd for C<sub>16</sub>H<sub>14</sub>O<sub>3</sub> 254.0943; found, 254.0955 Anal. (C<sub>16</sub>H<sub>14</sub>O<sub>3</sub>) C, H. These data differ significantly from those reported for "benzyl piperonyl ketone".<sup>12</sup> Indeed it appears as though the reference<sup>12</sup> actually describes the synthesis of phenyl piperonyl ketone, and the compound has been misnamed and this error has been propagated in Chemical Abstracts.



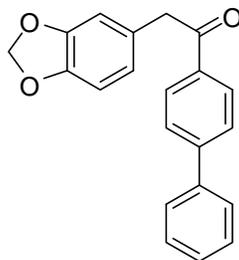
**1,3-bis(1,3-benzodioxol-5-yl)propan-2-one (dipiperonyl ketone) (7q).** A solution of homopiperonylic acid **10** (1.80 g, 10.0 mmol) in anhydrous DCM (30 mL) was added to a stirred solution of DMAP (0.34 g, 2.78 mmol) and DCC (2.07 g, 10.0 mmol) in anhydrous DCM (20 mL) under N<sub>2</sub>. The resulting orange solution was stirred for 24 h during which time a colourless precipitate formed. The suspension was filtered through a short column of Celite and washed through with DCM. The filtrate was concentrated under vacuum to yield an amorphous orange solid which was subjected to flash chromatography. Elution with 1:10:89 toluene/EtOAc/petrol gave a yellow solid which crystallised from ethanol to afford **7q** as off-white needles (0.75 g, 50 %), mp 85–86 °C [lit.<sup>13</sup> 79 °C].  $R_f$  (1:4 EtOAc/petrol): 0.30. IR (neat) cm<sup>-1</sup>: 1716 (C=O). <sup>1</sup>H NMR (500 MHz): 6.76 (d,  $J = 7.9$  Hz, 2H, H7', H7"), 6.63 (d,  $J = 1.8$  Hz, 2H, H4', H4"), 6.60 (dd,  $J = 7.9, 1.8$  Hz, 2H, H6, H6"), 5.95 (s, 4H, H2', H2"), 3.62 (s, 4H, H1, H3). The <sup>1</sup>H NMR data are similar to those reported.<sup>13</sup> <sup>13</sup>C NMR (125 MHz):  $\delta$  205.9 (C=O), 147.9 (ArO), 146.7 (ArO), 127.5 (C5', C5"), 122.6 (ArH), 109.8 (ArH), 108.4 (ArH), 101.0 (C2', C2"), 48.5 (C1, C3).



**2-(1,3-benzodioxol-5-yl)-1-(1-naphthyl)ethanone (7r).** Following the representative procedure, the reaction of a solution of **8** (max. 0.2 M, 25 mL, 5 mmol) with 1-naphthoyl chloride (1.14 g, 5.98 mmol) gave a brown residue, which was subjected to flash chromatography. Elution with 1:24 EtOAc/petrol gave **7r** as a yellow oil (0.928 g, 63%).  $R_f$  (1:9 EtOAc/petrol): 0.20. IR (KBr disc)  $\text{cm}^{-1}$ : 1680 (vs, C=O).  $^1\text{H}$  NMR (300 MHz):  $\delta$  8.61-8.54 (m, 1H, H2"), 7.80-7.84 (m, 3H, ArH), 7.60-7.46 (m, 3H, ArH), 6.82-6.74 (m, 3H, H4', H6', H7'), 5.92 (s, 2H, H2'), 4.28 (s, 2H, H2).  $^{13}\text{C}$  NMR (75.5 MHz):  $\delta$  201.6 (C=O), 147.8, 146.6, 135.4, 133.9, 132.8, 130.4, 128.4, 128.02, 127.96, 127.8, 126.5, 125.8, 124.3, 122.6 (Ar), 109.9, 108.4 (ArO), 101.0 (OCH<sub>2</sub>O), 48.5 (C2). MS (EI)  $m/z$ : 290 [ $\text{M}]^{++}$  (23%), 156 (15%), 155 (100%). HRMS (EI)  $m/z$ : calcd for C<sub>19</sub>H<sub>14</sub>O<sub>3</sub> 290.0943; found, 290.0938.

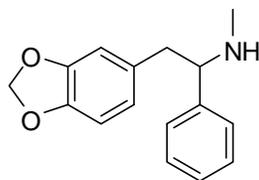


**2-(1,3-benzodioxol-5-yl)-1-(2-naphthyl)ethanone (7s).** Following the representative procedure, the reaction of a solution of **8** (max. 0.2 M, 25 mL, 5 mmol) with 2-naphthoyl chloride (1.14 g, 5.98 mmol), gave a brown residue, which was subjected to flash chromatography. Elution with 1:3 toluene/petrol gave **7s** as an amorphous, pale yellow solid (1.085 g, 75%), mp 84–85 °C, which crystallised from methanol as colourless crystals.  $R_f$  (1:9 EtOAc/petrol): 0.21. IR (KBr disc)  $\text{cm}^{-1}$ : 1682 (vs, C=O).  $^1\text{H}$  NMR (300 MHz):  $\delta$  8.54 (sl br s, 1H, H1"), 8.06 (dd,  $J = 8.6$  Hz,  $J = 1.7$  Hz, 1H, ArH), 7.96 (sl br d,  $J = 7.7$  Hz, 1H, Ar), 7.90–7.85 (m, 2H, ArH), 7.64–7.53 (m, 2H, ArH), 6.82–6.73 (m, 3H, ArH), 5.91 (s, 2H, H2'), 4.32 (s, 2H, H2).  $^{13}\text{C}$  NMR (75.5 MHz):  $\delta$  197.5 (C=O), 147.7, 146.4, 135.4, 133.7, 132.3, 130.2, 129.5, 128.43, 128.38, 128.1, 127.6, 126.7, 124.1, 122.5 (Ar), 109.8, 108.3 (ArO), 100.9 (OCH<sub>2</sub>O), 45.0 (C2). MS (EI)  $m/z$ : 290 [ $\text{M}]^{++}$  (20%), 155 (100%), 127 (45%). HRMS (EI)  $m/z$ : calcd for C<sub>19</sub>H<sub>14</sub>O<sub>3</sub> 290.0943; found, 290.0942.



**2-(1,3-benzodioxol-5-yl)-1-(biphenyl-4-yl)ethanone (7t).** Following the representative procedure, the reaction of a solution of **8** (max. 0.2 M, 25 mL, 5 mmol) with 4-biphenylcarbonyl chloride (1.302 g, 6.009 mmol) gave a brown residue, which was subjected to flash chromatography. Elution with 1:30 EtOAc/petrol gave **7t** as an amorphous pale yellow solid (1.113 g, 71%), which crystallised from methanol as an off-white powder, mp 130–131 °C.  $R_f$  (1:9 EtOAc/petrol): 0.12. IR (KBr disc)  $\text{cm}^{-1}$ : 1672 (vs, CO).  $^1\text{H}$  NMR (300 MHz,  $d_6$ -acetone):  $\delta$  8.19–8.11 (m, 2H, H2"/ H6"), 7.85–7.76 (m, 2H, Ar), 7.75–7.68 (m, 2H, Ar), 7.54–7.39 (m, 3H, Ar), 6.87–6.84 (m, 1H, Ar), 6.83–6.77 (m, 2H, Ar), 5.96 (s, 2H, H2'), 4.32 (s, 2H, H2).  $^{13}\text{C}$  NMR (75.5 MHz,  $d_6$ -acetone):  $\delta$  197.5 (CO), 148.6, 147.3, 146.2, 140.5, 136.4 (Ar), 130.0, 129.9, 129.8, 129.1, 128.0, 127.9, 123.5 (ArH), 110.8, 108.9 (ArO), 101.9 (OCH<sub>2</sub>O), 45.4 (C2). MS (EI)  $m/z$ : 316 [M]<sup>+</sup> (16%), 181 (100%), 153 (18%), 152 (23%). HRMS (EI)  $m/z$ : calcd for C<sub>21</sub>H<sub>16</sub>O<sub>3</sub> 316.1099; found, 316.1101. Anal. (C<sub>21</sub>H<sub>16</sub>O<sub>3</sub>) C, H.

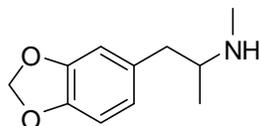
### **Representative procedure for reductive aminations**



**2-(1,3-benzodioxol-5-yl)-N-methyl-1-phenylethanamine (11g).** Glacial acetic acid (0.97 mL, 17 mmol) was added dropwise to a stirred mixture of (**7g**) (398 mg, 1.66 mmol), 33% ethanolic methylamine (2.06 mL, 16.6 mmol) and powdered 3A molecular sieves (0.45 g) in dry THF (2 mL) at 0 °C under a positive pressure of N<sub>2</sub>. After 10 min, NaCNBH<sub>3</sub> (104 mg, 1.66 mmol) was added and the reaction mixture was stirred at 50 °C for 24 h. On cooling the reaction mixture was quenched with 1 M HCl [**CAUTION, HCN**], vacuum filtered through a pad of Celite and washed through with H<sub>2</sub>O, MeOH and Et<sub>2</sub>O. The filtrate was basified with 1 M NaOH (50 mL) then extracted with Et<sub>2</sub>O (2 × 40 mL). The extract was washed with water (3 × 40 mL) and brine (40 mL), dried and evaporated to afford a viscous yellow/brown oil, which was purified by rapid silica filtration. Elution with 4:19:1

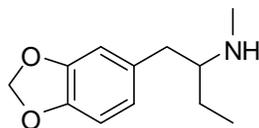
EtOAc/petrol/AcOH followed by 4:19:1 EtOAc/petrol/ $\text{NEt}_3$  afforded **11g** as a colourless, viscous oil (339 mg, 80%).  $R_f$  (1:1:99  $\text{NEt}_3/\text{MeOH}/\text{DCM}$ ): 0.25. IR (neat)  $\text{cm}^{-1}$ : 3337 (w, NH).  $^1\text{H}$  NMR (300 MHz):  $\delta$  7.30 (m, 5H, ArH), 6.70 (d,  $J = 7.8$  Hz, 1H, H7'), 6.63 (d,  $J = 1.6$  Hz, 1H, H4'), 6.58 (dd,  $J = 7.9$  Hz; 1.6 Hz, 1H, H6'), 5.92 (s, 2H,  $\text{CH}_2\text{O}_2$ ), 3.68 (ABX, 1H, H1), 2.86 (ABX, 2H, H2a/b), 2.22 (s, 3H,  $\text{NCH}_3$ ).  $^{13}\text{C}$  NMR (75.5 MHz): 147.6 (ArO), 146.1 (ArO), 142.6 (ArC), 132.3 (ArC), 128.4 (ArH), 127.4 (ArH), 127.3 (ArH), 122.3 (ArH), 109.5 (ArH), 108.1 (ArH), 100.8 ( $\text{CH}_2\text{O}_2$ ), 66.9 (C1), 44.5 (C2), 34.4 ( $\text{NCH}_3$ ). MS (ESI)  $m/z$ : 256 ( $[\text{M}+\text{H}]^+$ , 100%).

The amine **11g** was dissolved in methanolic HCl and the solvent was evaporated under a stream of  $\text{N}_2$ . The residue crystallised from *i*-PrOH, giving 2-(1,3-benzodioxol-5-yl)-*N*-methyl-1-phenylethanaminium chloride as white needles, mp 210–212 °C.  $^1\text{H}$  NMR (300 MHz):  $\delta$  10.36 (br s, 1H, NH), 10.03 (br s, 1H, NH), 7.32–7.46 (m, 5H, ArH), 6.56 (d,  $J = 7.7$  Hz, 1H, H7'), 6.40 (m, 2H, H4'/H6'), 5.84 (s, 2H,  $\text{CH}_2\text{O}_2$ ), 4.08 (m, 1H, H1), 3.77 (dd,  $J = 13.0, 3.9$  Hz, 1H, H2a), 3.32 (dd,  $J = 13.0, 11.1$  Hz, 1H, H2b), 2.49 (dd [apparent t],  $J = 5.3$  Hz, 3H,  $\text{NCH}_3$ ). Anal. ( $\text{C}_{16}\text{H}_{18}\text{ClNO}_2$ ) C, H, N.



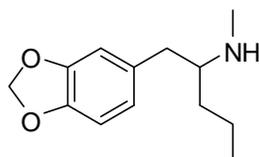
**1-(1,3-benzodioxol-5-yl)-*N*-methylpropan-2-amine (MDMA) (1).** Following the representative procedure, the reductive amination of **7a** (0.89 g 5.0 mmol) afforded **1** as a colourless oil (0.87 g, 90%).  $^1\text{H}$  NMR (600 MHz):  $\delta$  6.74 (d,  $J = 7.9$  Hz, 1H, H7'), 6.68 (d,  $J = 1.7$  Hz, 1H, H4'), 6.63 (dd,  $J = 7.9, 1.7$  Hz, 1H, H6'), 5.93 (s, 2H,  $\text{CH}_2\text{O}_2$ ), 2.76–2.68 (m, 1H, H2), 2.61 (dd,  $J = 13.5, 7.2$  Hz, 1H, H1a or b), 2.54 (dd,  $J = 13.5, 6.2$  Hz, 1H, H1a or b), 2.39 (s, 3H,  $\text{NCH}_3$ ), 1.52 (br s, 1H, NH), 1.04 (d,  $J = 6.2$  Hz, 3H,  $\text{CH}_3$ ). The  $^1\text{H}$  NMR data are consistent with those reported at 300 MHz.<sup>14</sup>

The hydrochloride, 1-(1,3-benzodioxol-5-yl)-*N*-methylpropan-2-aminium chloride, crystallised from isopropanol as colourless cubes, mp 152–153 °C [lit.<sup>15</sup> mp 152–153 °C].  $^1\text{H}$  NMR (600 MHz):  $\delta$  9.62 (br s, 2H,  $\text{NH}_2$ ), 6.74 (d,  $J = 7.9$  Hz, 1H, H7'), 6.70 (d,  $J = 1.7$  Hz, 1H, H4'), 6.67 (dd,  $J = 7.9, 1.7$  Hz, 1H, H6'), 5.93 (AB, 2H,  $\text{CH}_2\text{O}_2$ ), 3.37 (dd,  $J = 13.2, 4.1$  Hz, 1H, H1a or b), 3.30–3.23 (m, 1H, H2), 2.76 (dd,  $J = 13.2, 10.5$  Hz, 1H, H1a or b), 2.69 (s, 3H,  $\text{NCH}_3$ ), 1.34 (d,  $J = 6.5$  Hz, 3H,  $\text{CH}_3$ ). The data are slightly different from those reported at 300 MHz.<sup>6</sup>



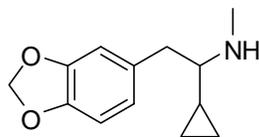
**1-(1,3-benzodioxol-5-yl)-N-methylbutan-2-amine (MBDB) (11b).** Following the representative procedure, the reductive amination of **7b** (330 mg 1.72 mmol) afforded **11b** as a colourless, viscous oil (308 mg, 87%).  $R_f$  (1:1:99  $\text{NEt}_3/\text{MeOH}/\text{DCM}$ ): 0.15. IR (neat)  $\text{cm}^{-1}$ : 3337 (w, NH).  $^1\text{H}$  NMR (300 MHz):  $\delta$  6.72 (d,  $J = 7.9$  Hz, 1H, H7'), 6.68 (d,  $J = 1.6$  Hz, 1H, H4'), 6.62 (dd,  $J = 7.8, 1.7$ , 1H, H6'), 5.91 (s, 2H,  $\text{CH}_2\text{O}_2$ ), 2.68–2.50 (m, 3H, H2 + H1a/b), 2.36 (s, 3H,  $\text{NCH}_3$ ), 1.59 (br s, 1H, NH), 1.43 (m, 2H, H3a/b), 0.92 (apparent t,  $J = 7.4$  Hz, 3H, H4).  $^{13}\text{C}$  NMR (75.4 MHz): 147.6 (ArO), 145.8 (ArO), 133.3 (C5'), 122.1 (C6'), 109.4 (ArH), 108.1 (ArH), 100.7 ( $\text{CH}_2\text{O}_2$ ), 62.2 (C2), 39.4 (C1), 33.7 ( $\text{NCH}_3$ ), 25.4 (C3), 9.8 (C4). MS (ESI)  $m/z$ : 208 ( $[\text{M}+\text{H}]^+$  (100%).

The hydrochloride, 1-(1,3-benzodioxol-5-yl)-N-methylbutan-2-aminium chloride, crystallised from *i*-PrOH as white needles, mp 152–155 °C (lit.<sup>6</sup> 156 °C).  $^1\text{H}$  NMR (300 MHz):  $\delta$  9.60 (br s, 1H, NH), 9.43 (br s, 1H, NH), 6.74 (m, 3H, ArH), 5.94 (s, 2H,  $\text{CH}_2\text{O}_2$ ), 3.21 (m, 2H, H1a + H2), 2.87 (dd,  $J = 12.9, 8.5$  Hz, 1H, H1b), 2.64 (br s, 3H,  $\text{NCH}_3$ ), 1.77 (br s, 3H,  $\text{CH}_2\text{CH}_3$ ), 1.08 (apparent t,  $J = 7.4$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ). The  $^1\text{H}$  NMR data are significantly different to those reported.<sup>6</sup>



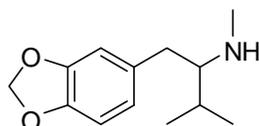
**1-(1,3-benzodioxol-5-yl)-N-methylpentan-2-amine (11c).** Following the representative procedure, the reductive amination of **7c** (390 mg 1.89 mmol) afforded **11c** as a colourless, viscous oil (292 mg, 70%).  $R_f$  (1:1:99  $\text{NEt}_3/\text{MeOH}/\text{DCM}$ ): 0.15. IR (neat)  $\text{cm}^{-1}$ : 3329 (w, NH).  $^1\text{H}$  NMR (300 MHz):  $\delta$  6.74 (d,  $J = 7.8$  Hz, 1H, H7'), 6.68 (d,  $J = 1.6$  Hz, 1H, H4'), 6.63 (dd,  $J = 7.8, 1.7$  Hz, 1H, H6'), 5.93 (s, 2H,  $\text{CH}_2\text{O}_2$ ), 2.68–2.50 (m, 3H, H1a/b + H2), 2.37 (s, 3H,  $\text{NCH}_3$ ), 1.55 (br s, 1H, NH), 1.40–1.32 (m, 4H,  $\text{CH}_2\text{CH}_2$ ), 0.91 (apparent t,  $J = 7$  Hz, 3H, H5).  $^{13}\text{C}$  NMR (75.4 MHz): 147.6 (ArO), 145.8 (ArO), 133.3 (C5'), 122.1 (C6'), 109.4 (ArH), 108.1 (ArH), 100.8 ( $\text{CH}_2\text{O}_2$ ), 60.7 (C2), 39.9 (C1), 35.4 (C3), 33.7 ( $\text{NCH}_3$ ), 18.9 (C4), 14.3 (C5). MS (ESI)  $m/z$ : 222 ( $[\text{M}+\text{H}]^+$ , 100%).

The hydrochloride, 1-(1,3-benzodioxol-5-yl)-N-methylpentan-2-aminium chloride, crystallised from *i*-PrOH as white needles, mp 154–158°C.  $^1\text{H}$  NMR (300 MHz):  $\delta$  9.56 (br s, 1H, NH), 9.47 (br s, 1H, NH), 6.74 (m, 3H, ArH), 5.95 (s, 2H,  $\text{CH}_2\text{O}_2$ ), 3.30–3.15 (m, 2H, H1a + H2), 2.86 (m, 1H, H1b), 2.63 (apparent t,  $J = 5.5$  Hz, 3H,  $\text{NCH}_3$ ), 1.74–1.36 (m, 4H,  $\text{CH}_2\text{CH}_2$ ), 0.90 (apparent t,  $J = 7.2$  Hz, 3H, H5). Anal. ( $\text{C}_{13}\text{H}_{20}\text{ClNO}_2$ ) C, H, N.



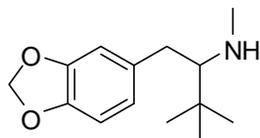
**2-(1,3-benzodioxol-5-yl)-1-cyclopropyl-N-methylethanamine (11d).** Following the representative procedure, the reductive amination of **7d** (420 mg 2.20 mmol) afforded **11e** as a colourless, viscous oil (314 mg, 70%).  $R_f$  (1:1:99  $\text{NEt}_3/\text{MeOH}/\text{DCM}$ ): 0.2. IR (neat)  $\text{cm}^{-1}$ : 3344 (w, NH).  $^1\text{H}$  NMR (300 MHz):  $\delta$  6.73 (d,  $J = 7.8$  Hz, 1H, ArH7'), 6.67 (d,  $J = 1.6$  Hz, 1H, ArH4'), 6.65 (dd,  $J = 7.9, 1.6$  Hz, 1H, ArH6'), 5.92 (s, 2H,  $\text{CH}_2\text{O}_2$ ), 2.83 (dd,  $J = 13.6, 4.8$  Hz, 1H, H2a), 2.66 (dd,  $J = 13.6, 7.9$  Hz, 1H, H2b), 2.44 (s, 3H,  $\text{NCH}_3$ ), 1.77 (ddd [apparent dt],  $J = 8.3, 8.3, 4.9$  Hz, 1H, H1), 1.37 (br s, 1H, NH), 0.72-52 (m, 2H), 0.42 (m, 1H), 0.26 (apparent sextet, 1H), -0.01 (apparent sextet, 1H).  $^{13}\text{C}$  NMR (75.4 MHz):  $\delta$  147.5 (ArO), 145.9 (ArO), 133.1 ( $\text{C}5'$ ), 122.2 ( $\text{C}6'$ ), 109.6 (ArH), 108.1 (ArH), 100.8 ( $\text{CH}_2\text{O}_2$ ), 66.6 (C2), 41.4 (C1), 34.6 ( $\text{NCH}_3$ ), 15.5 (CH), 5.1 ( $\text{CH}_2$ ), 1.64 ( $\text{CH}_2$ ). MS (ESI)  $m/z$ : 220 ( $[\text{M}+\text{H}]^+$ , 100%)

The hydrochloride, 2-(1,3-benzodioxol-5-yl)-1-cyclopropyl-N-methylethanaminium chloride, crystallised from *i*-PrOH/ $\text{Et}_2\text{O}$  as white needles, mp 156–158°C.  $^1\text{H}$  NMR (300 MHz):  $\delta$  9.62 (br s, 2H,  $\text{NH}_2$ ), 6.75 (m, 3H, ArH), 5.93 (s, 2H,  $\text{CH}_2\text{O}_2$ ), 3.37 (dd,  $J = 13.5$  Hz; 4.5 Hz, 1H, H2a), 3.05 (dd,  $J = 13.5$  Hz; 9.5 Hz, 1H, H2b), 2.76 (dd [apparent t],  $J = 5.6$  Hz, 3H,  $\text{NCH}_3$ ), 2.44 (m, 1H, H1), 1.06 (m, 1H), 0.69 (m, 1H), 0.49 (m, 2H), -0.16 (m, 1H). Anal. ( $\text{C}_{13}\text{H}_{18}\text{ClNO}_2$ ) C, H, N.



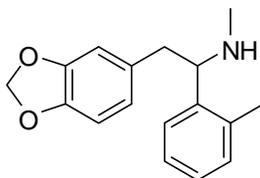
**1-(1,3-benzodioxol-5-yl)-N,3-dimethylbutan-2-amine (11e).** Following the representative procedure, the reductive amination of **7e** (578 mg 2.80 mmol) afforded **11e** as a colourless, viscous oil (522 mg, 84%).  $R_f$  (1:1:99  $\text{NEt}_3/\text{MeOH}/\text{DCM}$ ): 0.15. IR  $\text{cm}^{-1}$ : 3344 (w, NH).  $^1\text{H}$  NMR (300 MHz):  $\delta$  6.73 (d,  $J = 7.8$  Hz, 1H, H7'), 6.69 (d,  $J = 1.6$  Hz, 1H, H4'), 6.64 (dd,  $J = 7.8, 1.6$  Hz, 1H, H6'), 5.92 (s, 2H,  $\text{CH}_2\text{O}_2$ ), 2.68-2.58 (m, 1H, H2), 2.48-2.39 (m, 2H, H1a/b), 2.32 (s, 3H,  $\text{NCH}_3$ ), 1.87 (dq [apparent dsept],  $J = 6.9, 6.9, 3.2$  Hz, 1H, H3) 1.37 (br s, 1H, NH), 0.95 (d,  $J = 6.9$  Hz, 3H,  $\text{CHCH}_3$ ), 0.91 (d,  $J = 6.8$  Hz, 3H,  $\text{CHCH}_3$ ).  $^{13}\text{C}$  NMR (75.4 MHz):  $\delta$  147.6 (ArO), 145.8 (ArO), 134.0 ( $\text{C}5'$ ), 122.0 ( $\text{C}6'$ ), 109.3 (ArH), 108.1 (ArH), 100.8 ( $\text{CH}_2\text{O}_2$ ), 66.7 (C2), 36.0 (C1), 34.8 (C3), 33.7 ( $\text{NCH}_3$ ), 18.4 ( $\text{CH}_3$ ), 17.6 ( $\text{CH}_3$ ). MS (ESI)  $m/z$ : 222 ( $[\text{M}+\text{H}]^+$ , 100%)

The hydrochloride, 1-(1,3-benzodioxol-5-yl)-*N*,3-dimethylbutan-2-aminium chloride, crystallised from *i*-PrOH as white needles, mp 210–212 °C. <sup>1</sup>H NMR (300 MHz): δ 9.52 (br s, 1H, NH), 9.12 (br s, 1H, NH), 6.82 (dd, *J* = 7.9, 1.6 Hz, 1H, ArH6'), 6.76 (d, *J* = 7.9 Hz, 1H, ArH7'), 6.76 (d, *J* = 1.6 Hz, 1H, ArH4'), 5.95 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.01 (m, 3H, H1a/b + H2), 2.53 (dd [apparent t], *J* = 5.5, 5.5 Hz, 3H, NCH<sub>3</sub>), 2.28 (dq [apparent dsept], *J* = 7.0, 7.0, 2.6 Hz 1H, H3), 1.20 (d, *J* = 7.0 Hz, 3H, CHCH<sub>3</sub>), 1.11 (d, *J* = 6.9 Hz, 3H, CHCH<sub>3</sub>). Anal. (C<sub>13</sub>H<sub>20</sub>ClNO<sub>2</sub>) C, H, N.



**1-(1,3-benzodioxol-5-yl)-*N*,3,3-trimethylbutan-2-amine (11f).** Following the representative procedure, the reductive amination of **7f** (395 mg 1.79 mmol) afforded **11f** as a colourless, viscous oil (290 mg, 69%). *R<sub>f</sub>* (1:1:99 NEt<sub>3</sub>/MeOH/DCM): 0.2. IR cm<sup>-1</sup> (neat): 3360 (w, NH). <sup>1</sup>H NMR (500 MHz): δ 6.74 (d, *J* = 1.7 Hz, 1H, H4'), 6.73 (d, *J* = 7.7 Hz, 1H, H7'), 6.67 (dd, *J* = 7.7, 1.7 Hz, 1H, H6'), 5.93 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 2.89 (dd, *J* = 12.9, 2.1 Hz, 1H, H1a), 2.22 (dd, *J* = 12.9, 9.9 Hz, 1H, H1b), 2.18 (dd, *J* = 9.9, 2.1 Hz, 1H, H2), 2.17 (s, 3H, NHCH<sub>3</sub>), 1.12 (br, s, 1H, NH), 0.95 (s, 9H, *t*-Bu). <sup>13</sup>C NMR (125 MHz): 147.5 (ArO), 145.7 (ArO), 135.1 (C5'), 121.9 (C6'), 109.3 (ArH), 108.1 (ArH), 100.8 (CH<sub>2</sub>O<sub>2</sub>), 71.7 (C2), 38.5 (NCH<sub>3</sub>), 37.6 (C1), 35.6 (C3), 27.0 (*t*-Bu). MS (ESI) *m/z*: 236 ([M+H]<sup>+</sup>, 100%)

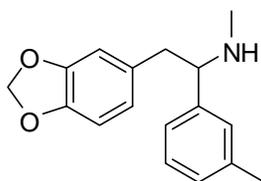
The hydrochloride, 1-(1,3-benzodioxol-5-yl)-*N*,3,3-trimethylbutan-2-aminium chloride, crystallised from *i*-PrOH as white needles, mp 224–226°C. <sup>1</sup>H NMR (500 MHz): δ 9.63 (br s, 1H, NH), 8.50 (br s, 1H, NH), 7.00 (d, *J* = 8.1 Hz, 1H, H6'), 6.86 (br s, 1H, 4'), 6.78 (d, *J* = 7.9 Hz, 1H, H7'), 5.98 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.19 (dd, *J* = 15.2 Hz; 9.0 Hz 1H, H1a), 3.05 (br d, *J* = 13.9 Hz, 1H, H1b), 2.78 (m, 1H, H2), 2.43 (dd (apparent t), *J* = 4.9 Hz, 4.9 Hz, 3H, NCH<sub>3</sub>), 1.23 [s, 9H, (CH<sub>3</sub>)<sub>3</sub>]. Anal. (C<sub>14</sub>H<sub>22</sub>ClNO<sub>2</sub>) C, H, N.



**2-(1,3-Benzodioxol-5-yl)-*N*-methyl-1-(2-methylphenyl)ethanamine (11h).** Following the representative procedure, the reductive amination of **7h** (298 mg 1.17 mmol) afforded **11h** as a colourless, viscous oil (241 mg, 76%). *R<sub>f</sub>* (1:5:44 NEt<sub>3</sub>/EtOAc/Petrol): 0.26. IR (neat) cm<sup>-1</sup>. 3337 (w,

NH).  $^1\text{H}$  NMR (300 MHz):  $\delta$  7.49 (d,  $J = 7.5$  Hz, 1H, ArH), 7.29–7.22 (m, 1H, ArH), 7.19–7.10 (m, 2H, 2 $\times$ ArH), 6.73 (d,  $J = 7.8$  Hz, 1H, H7'), 6.65 (d,  $J = 1.5$  Hz, 1H, H4'), 6.61 (dd,  $J = 7.8, 1.6$  Hz, 1H, H6'), 5.92 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.00 (dd,  $J = 8.4, 5.2$  Hz, 1H, H1), 2.84 (dd,  $J = 13.6, 5.2$  Hz, 1H, H2a), 2.72 (dd,  $J = 13.6, 8.4$  Hz, 1H, H2b), 2.30 (s, 3H, CH<sub>3</sub>), 2.22 (s, 3H, CH<sub>3</sub>), 1.63 (br s, 1H, NH).  $^{13}\text{C}$  NMR (75 MHz):  $\delta$  147.5 (ArO), 146.0 (ArO), 141.1 (Ar), 135.7 (Ar), 132.7 (Ar), 130.2 (ArH), 126.4 (ArH), 126.2 (ArH), 125.7 (ArH), 122.1 (H6'), 109.3 and 108.1 (H4' and H7'), 100.7 (CH<sub>2</sub>O<sub>2</sub>), 61.8 (H1), 43.8 (H2), 34.5 (NCH<sub>3</sub>), 19.3 (ArCH<sub>3</sub>). MS (EI)  $m/z$  (%): 135 [M – CH(NHMe)C<sub>6</sub>H<sub>4</sub>Me]<sup>+</sup> (13), 134 [M – CH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>OCH<sub>2</sub>O]<sup>+</sup> (100).

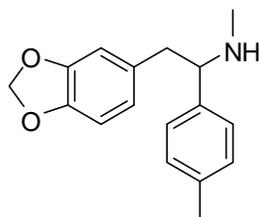
The hydrochloride, 2-(1,3-benzodioxol-5-yl)-1-(2-methylphenyl)-*N*-methylethanaminium chloride, crystallised from *i*-PrOH as white needles, mp 197–198 °C.  $^1\text{H}$  NMR (300 MHz, d<sub>6</sub>-DMSO):  $\delta$  9.27 (br s, 2H, NH), 7.73–7.67 (m [apparent d], 1H, ArH), 7.37–7.29 (m [apparent t], 1H, ArH), 7.27–7.20 (m [apparent t], 1H, ArH), 7.14–7.09 (m [apparent d], 1H, ArH), 6.73 (d,  $J = 7.9$  Hz, 1H, H7'), 6.57 (d,  $J = 1.5$  Hz, 1H, H4'), 6.45 (dd,  $J = 7.9, 1.6$  Hz, 1H, H6'), 5.93 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.60–4.52 (m [apparent dd], 1H, H1), 3.43–3.37 (br m, 1H, H2a), 3.02–2.92 (m [apparent dd], 1H, H2b), 2.43 (s, 3H, NCH<sub>3</sub>). Anal. (C<sub>17</sub>H<sub>20</sub>ClNO<sub>2</sub>) C, H, N.



**2-(1,3-benzodioxol-5-yl)-*N*-methyl-1-(3-methylphenyl)ethanamine (11i).** Following the representative procedure, the reductive amination of **7i** (285 mg 1.12 mmol) afforded **11i** as a colourless, viscous oil (250 mg, 83%).  $R_f$  (1:10:89 NEt<sub>3</sub>/EtOAc/Petrol): 0.14. IR (neat) cm<sup>-1</sup>: 3336 (w, NH).  $^1\text{H}$  NMR (500 MHz):  $\delta$  7.27–7.19 (dd [apparent t],  $J_1 = J_2 = 7.5$  Hz, 1H, ArH), 7.15–7.12 (m, 1H, ArH), 7.11–7.05 (m, 2H, 2 $\times$ ArH), 6.72 (d,  $J = 7.9$  Hz, 1H, H7'), 6.66 (d,  $J = 1.7$  Hz, 1H, H4'), 6.61 (dd,  $J = 7.9, 1.7$  Hz, 1H, H6'), 5.94–5.93 (m, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.62 (dd,  $J = 8.8, 5.2$  Hz, 1H, H1), 2.86 (dd,  $J = 13.7, 5.2$  Hz, 1H, H2a), 2.78 (dd,  $J = 13.7, 8.8$  Hz, 1H, H2b), 2.36 (s, 3H, NCH<sub>3</sub>), 2.21 (s, 3H, ArCH<sub>3</sub>), 1.59 (br s, 1H, NH).  $^{13}\text{C}$  NMR (125 MHz):  $\delta$  147.6 (ArO), 146.1 (ArO), 143.3 (Ar), 137.9 (Ar), 132.7 (Ar), 128.2 (ArH), 127.9 (ArH), 127.8 (ArH), 124.4 (ArH), 122.2 (C6'), 109.4 and 108.1 (C4' and C7'), 100.8 (CH<sub>2</sub>O<sub>2</sub>), 66.9 (C1), 44.8 (C2), 34.7 (NCH<sub>3</sub>), 21.4 (ArCH<sub>3</sub>). MS (EI)  $m/z$  (%): 135 (15), 134 (100).

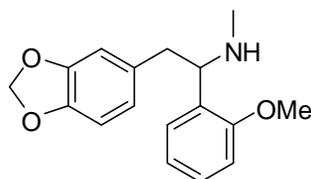
The hydrochloride, 2-(1,3-benzodioxol-5-yl)-1-(3-methylphenyl)-*N*-methylethanaminium chloride, crystallised from *i*-PrOH as colourless rods, mp 219–223 °C.  $^1\text{H}$  NMR (600 MHz):  $\delta$  10.35 (br s, 1H,

NH), 9.97 (br s, 1H, NH), 7.26–7.21 (br m, 3H, 3×ArH), 7.16–7.13 (m, 1H, ArH), 6.54 (d,  $J = 7.8$  Hz, 1H, H7'), 6.45–6.41 (m, 2H, C4' and C6'), 5.85 (m, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.07–3.98 (m, 1H, H1), 3.78–3.72 (m [apparent dd], 1H, H2a), 3.37–3.29 (m [apparent t], 1H, H2b), 2.48 (br s, 3H, NCH<sub>3</sub>), 2.34 (s, 3H, ArCH<sub>3</sub>). Anal. (C<sub>17</sub>H<sub>20</sub>ClNO<sub>2</sub>) C, H, N.



**2-(1,3-benzodioxol-5-yl)-N-methyl-1-(4-methylphenyl)ethanamine (11j).** Following the representative procedure, the reductive amination of **7j** (257 mg 1.12 mmol) afforded **11j** as a colourless, viscous oil (227 mg, 83%).  $R_f$  (1:5:44 NEt<sub>3</sub>/EtOAc/Petrol): 0.13. IR (neat) cm<sup>-1</sup>: 3336 (w, NH). <sup>1</sup>H NMR (600 MHz):  $\delta$  7.21–7.17 (AA' part of AA'BB', 2H, H2'' and H6''), 7.15–7.12 (BB' part of AA'BB', 2H, H3'' and H5''), 6.71 (d,  $J = 7.9$  Hz, 1H, H7'), 6.66 (d,  $J = 1.7$  Hz, 1H, H4'), 6.60 (dd,  $J = 7.9, 1.7$  Hz, 1H, H6'), 5.92 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.63 (dd,  $J = 8.6, 5.4$  Hz, 1H, H1), 2.85 (dd,  $J = 13.7, 5.4$  Hz, 1H, H2a), 2.78 (dd,  $J = 13.7, 8.6$  Hz, 1H, H2b), 2.34 (s, 3H, CH<sub>3</sub>), 2.21 (s, 3H, NCH<sub>3</sub>), 1.61 (br s, 1H, NH). <sup>13</sup>C NMR (150 MHz):  $\delta$  147.6 (ArO), 146.0 (ArO), 140.2 (Ar), 136.6 (Ar), 132.7 (Ar), 129.0 (C3'' and C5''), 127.2 (C2'' and C6''), 122.2 (C6'), 108.4 and 108.1 (C4' and C7'), 100.8 (CH<sub>2</sub>O<sub>2</sub>), 66.6 (C1), 44.8 (C2), 34.6 (NCH<sub>3</sub>), 21.1 (ArCH<sub>3</sub>). MS (EI)  $m/z$  (%): 205 (24), 134 (100).

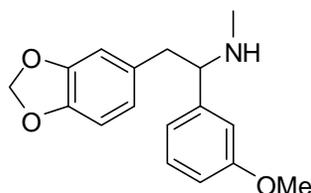
The hydrochloride, 2-(1,3-benzodioxol-5-yl)-1-(4-methylphenyl)-N-methylethanaminium chloride, crystallised from *i*-PrOH as amorphous solid, mp 220–221 °C. <sup>1</sup>H NMR (300 MHz):  $\delta$  10.33 (br s, 1H, NH), 9.97 (br s, 1H, NH), 7.34–7.28 (AA' part of AA'BB', 2H, H3'' and H5''), 7.19–7.13 (BB' part of AA'BB', 2H, H2'' and H6''), 6.57 (dd,  $J = 7.5, 0.8$  Hz, 1H, H7'), 6.45–6.38 (m, 2H, H4' and H6'), 5.85 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.09–3.97 (m [apparent t], 1H, H1), 3.74 (dd,  $J = 13.1, 4.1$  Hz, 1H, H2a), 3.31 (dd,  $J = 12.9, 11.4$  Hz, 1H, H2b), 2.47 (t,  $J = 5.4$  Hz, 3H, NCH<sub>3</sub>), 2.31 (s, 3H, ArCH<sub>3</sub>). Anal. (C<sub>17</sub>H<sub>20</sub>ClNO<sub>2</sub>) C, H, N.



**2-(1,3-benzodioxol-5-yl)-1-(2-methoxyphenyl)-N-methylethanamine (11k).** Following the representative procedure, the reductive amination of **7k** (360 mg, 1.33 mmol) afforded **11k** as a pale

yellow, viscous oil (328 mg, 86%).  $R_f$  (95:5 CHCl<sub>3</sub>/MeOH): 0.22. IR (neat) cm<sup>-1</sup>: 3347 (w, NH). <sup>1</sup>H NMR (500 MHz):  $\delta$  7.26 (dd, 1H, H6''), 7.23–7.20 (m, 1H, H4''), 6.93 (td,  $J = 7.8$  Hz; 1.5 Hz, 1H, H5''), 6.88 (dd,  $J = 7.5$  Hz; 0.7 Hz, 1H, H3''), 6.69 (d,  $J = 7.8$  Hz, 1H, H7'), 6.66 (d,  $J = 1.6$  Hz, 1H, H4'), 6.59 (dd,  $J = 8.0$  Hz; 1.6 Hz, 1H, H6'), 5.91 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.09 (ABX, 1H, H1), 3.83 (s, 3H, OCH<sub>3</sub>), 2.96 (ABX, 1H, H2a), 2.72 (ABX, 1H, H2b), 2.22 (s, 3H, NCH<sub>3</sub>), 1.67 (br s, 1H, NH). <sup>13</sup>C NMR (125 MHz):  $\delta$  157.40 (C2''), 147.45 (ArO), 145.83 (ArO), 133.48 (ArC), 130.93 (ArC), 127.67 (ArH), 127.63 (ArH), 122.19 (ArH), 120.56 (ArH), 110.46 (ArH), 109.54 (ArH), 107.97 (ArH), 100.72 (CH<sub>2</sub>O<sub>2</sub>), 60.72 (C1), 55.31 (OCH<sub>3</sub>), 42.60 (C2), 34.60 (NCH<sub>3</sub>). MS (EI)  $m/z$  (%): 205 (24), 134 (100).

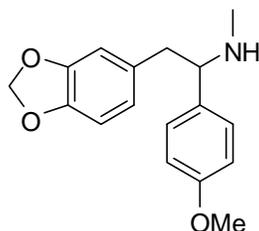
The hydrochloride, 2-(1,3-benzodioxol-5-yl)-1-(2-methoxyphenyl)-*N*-methylethanaminium chloride, crystallised from *i*-PrOH as white prisms, mp 166–167 °C. <sup>1</sup>H NMR:  $\delta$  10.50 (br s, 1H, NH<sub>2</sub>), 9.35 (br s, 1H, NH<sub>2</sub>), 7.32–7.27 (m, 1H, H4''), 7.23 (br s, 1H, H6''), 6.91 (t,  $J = 7.4$  Hz, 1H, H5''), 6.87 (d,  $J = 8.2$  Hz, 1H, H5''), 6.55 (d,  $J = 7.9$  Hz, 1H, H7'), 6.46 (d,  $J = 1.6$  Hz, 1H, H4'), 6.43 (dd,  $J = 7.9$  Hz; 1.6 Hz, 1H, H6'), 5.83 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.52–4.42 (bm, 1H, H1), 3.85 (s, 3H, OCH<sub>3</sub>), 3.70 (dd,  $J = 13.1$  Hz; 4.2 Hz, 1H, H2a), 3.35 (dd,  $J = 13.0$  Hz; 11.1 Hz, 1H, H2b), 2.50 (s, 3H, NCH<sub>3</sub>). Anal. (C<sub>17</sub>H<sub>20</sub>ClNO<sub>3</sub>) C, H, N.



**2-(1,3-benzodioxol-5-yl)-1-(3-methoxyphenyl)-*N*-methylethanamine (11I).** Following the representative procedure, the reductive amination of **7I** (400 mg, 1.48 mmol) afforded **11I** as a colourless, viscous oil (311 mg, 74%).  $R_f$  (95:5 CHCl<sub>3</sub>/MeOH): 0.27. IR (neat) cm<sup>-1</sup>: 3349 (w, NH). <sup>1</sup>H NMR (500 MHz):  $\delta$  7.25–7.22 (m, 1H, H5''), 6.89–6.86 (m, 2H, H2'', H6''), 6.81–6.78 (m, 1H, H4''), 6.71 (d,  $J = 7.8$  Hz, 1H, H7'), 6.65 (d,  $J = 1.6$  Hz, 1H, H4'), 6.60 (dd,  $J = 7.8$  Hz; 1.6 Hz, 1H, H6'), 5.92 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.81 (s, 3H, OCH<sub>3</sub>), 3.64 (ABX, 1H, H1), 2.86 (ABX, 1H, H2a), 2.77 (ABX, 1H, H2b), 2.22 (s, 3H, NCH<sub>3</sub>), 1.54 (br s, 1H, NH). <sup>13</sup>C NMR (125 MHz):  $\delta$  159.75 (C3''), 147.62 (ArO), 146.07 (ArO), 145.18 (ArC), 132.59 (ArC), 129.28 (ArH), 122.25 (ArH), 119.73 (ArH), 112.60 (ArH), 112.55 (ArH), 109.44 (ArH), 108.15 (ArH), 100.82 (CH<sub>2</sub>O<sub>2</sub>), 66.93 (C1), 55.20 (OCH<sub>3</sub>), 44.78 (C2), 34.66 (NCH<sub>3</sub>). MS (EI)  $m/z$  (%): 151 (13), 150 (100).

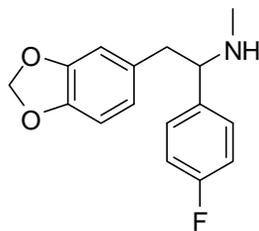
The hydrochloride, 2-(1,3-benzodioxol-5-yl)-1-(3-methoxyphenyl)-*N*-methylethanaminium chloride, crystallised from *i*-PrOH as white microcrystalline needles, mp 193–194 °C. <sup>1</sup>H NMR:  $\delta$  10.15 (br s, 2H, NH<sub>2</sub>), 7.24 (dd,  $J = 8.3$  Hz; 7.8 Hz, 1H, H4''), 7.13–7.11 (m, 1H, H2''), 6.93–6.90 (m, 1H, H6''), 6.87

(ddd,  $J = 8.3$  Hz; 2.5 Hz; 0.8 Hz, 1H, H4''), 6.58 (d,  $J = 7.9$  Hz, 1H, H7'), 6.45 (d,  $J = 1.5$  Hz, 1H, H4'), 6.43 (dd,  $J = 7.9$  Hz; 1.7 Hz, 1H, H6'), 5.85 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.04 (dd,  $J = 10.9$  Hz; 4.1 Hz, 1H, H1), 3.83 (s, 3H, OCH<sub>3</sub>), 3.74 (dd,  $J = 13.2$  Hz; 4.1 Hz, 1H, H2a), 3.33 (dd,  $J = 13.1$  Hz; 11.1 Hz, 1H, H2b), 2.50 (s, 3H, NCH<sub>3</sub>). Anal. (C<sub>17</sub>H<sub>20</sub>ClNO<sub>3</sub>) C, H, N.



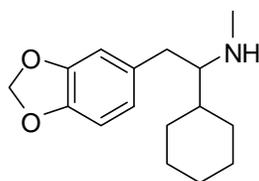
**2-(1,3-benzodioxol-5-yl)-N-methyl-1-(4-methoxyphenyl)ethanamine (11m).** Following the representative procedure, the reductive amination of **7m** (203 mg 0.75 mmol) afforded **11m** as a colourless, viscous oil (137 mg, 64%).  $R_f$  (1:40:59 NEt<sub>3</sub>/EtOAc/Petrol): 0.10. IR (neat) cm<sup>-1</sup>: 3337 (w, NH). <sup>1</sup>H NMR (500 MHz):  $\delta$  7.22–7.18 (AA' part of AA'BB', 2H, H2'' and H6''), 6.88–6.84 (BB' part of AA'BB', 2H, H3'' and H5''), 6.69 (d,  $J = 7.9$  Hz, 1H, H7'), 6.63 (d,  $J = 1.5$  Hz, 1H, H4'), 6.57 (dd,  $J = 7.9, 1.5$  Hz, 1H, H6'), 5.88 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 3.61 (dd,  $J = 8.1, 5.9$  Hz, 1H, H1), 2.82 (dd,  $J = 13.6, 5.9$  Hz, 1H, H2a), 2.78 (dd,  $J = 13.6, 8.2$  Hz, 1H, H2b), 2.20 (s, 3H, NCH<sub>3</sub>), 1.58 (br s, 1H, NH). <sup>13</sup>C NMR (125 MHz):  $\delta$  158.5 (OCH<sub>3</sub>), 147.4 and 145.8 (C3a' and C7a'), 135.2 (Ar), 132.6 (Ar), 128.1 (C2'' and C6''), 122.1 (C6'), 113.5 (C3'' and C5''), 109.3 and 107.9 (C4' and C7'), 100.6 (CH<sub>2</sub>O<sub>2</sub>), 66.1 (C1), 55.0 (OCH<sub>3</sub>), 44.7 (C2), 34.4 (NCH<sub>3</sub>). MS (EI)  $m/z$  (%): 270 (9), 136 (16), 135 (100), 107 (10).

The hydrochloride, 2-(1,3-benzodioxol-5-yl)-1-(4-methoxyphenyl)-N-methylethanaminium chloride, crystallised from *i*-PrOH as colourless rods, mp 201–202 °C. <sup>1</sup>H NMR (300 MHz):  $\delta$  10.27 (br s, 1H, NH), 9.95 (br s, 1H, NH), 7.39–7.32 (AA' part of AA'BB', 2H, H2'' and H6''), 6.92–6.84 (BB' part of AA'BB', 2H, H3'' and H5''), 6.60–6.55 (m [apparent dd], 1H, H7'), 6.44–6.38 (m, 2H, H4' and H6'), 5.85 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.08–3.96 (m [apparent t], 1H, H1), 3.78 (s, 3H, OCH<sub>3</sub>), 3.78–3.70 (br m, 1H, H2a), 3.30 (dd,  $J = 12.8, 11.5$  Hz, 1H, H2b), 2.47 (t,  $J = 5.3$  Hz, 3H, NCH<sub>3</sub>). Anal. (C<sub>17</sub>H<sub>20</sub>ClNO<sub>2</sub>) C, H, N.



**2-(1,3-benzodioxol-5-yl)-1-(4-fluorophenyl)-N-methylethanamine (11n).** Following the representative procedure, the reductive amination of **7n** (400 mg 1.55 mmol) afforded **11n** as a pale yellow, viscous oil (298 mg, 70%).  $R_f$  (95:5 CHCl<sub>3</sub>/MeOH): 0.27. IR (neat) cm<sup>-1</sup>: 3338 (w, NH). <sup>1</sup>H NMR (500 MHz):  $\delta$  7.26–7.22 (m, 2H, H3'', H5''), 7.03–6.97 (m, 2H, H2'', H6''), 6.70 (d,  $J$  = 7.8 Hz, 1H, H7'), 6.63 (d,  $J$  = 1.5 Hz, 1H, H4'), 6.55 (dd,  $J$  = 7.8 Hz; 1.5 Hz, 1H, H6'), 5.91–5.93 (m, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.68 (ABX, 1H, H1), 2.86 (ABX, 2H, H2a/b), 2.20 (s, 3H, NCH<sub>3</sub>), 1.56 (br s, 1H, NH). <sup>13</sup>C NMR (125 MHz):  $\delta$  162.90, 160.95 (ArF), 147.65 (ArO), 146.12 (ArO), 138.95 (ArC), 132.32 (ArC), 128.74 (ArH), 128.68 (ArH), 122.26 (ArH), 115.04 (ArH), 115.20 (ArH), 109.42 (ArH), 108.18 (ArH), 100.86 (CH<sub>2</sub>O<sub>2</sub>), 66.31 (C1), 44.90 (C2), 34.58 (NCH<sub>3</sub>). MS (EI)  $m/z$  (%): 139 (21), 138 (100).

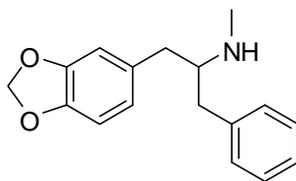
The hydrochloride, 2-(1,3-benzodioxol-5-yl)-1-(4-fluorophenyl)-N-methylethanaminium chloride, crystallised from *i*-PrOH as white needles, mp 224–225 °C. <sup>1</sup>H NMR (500 MHz):  $\delta$  10.23 (br s, 2H, NH<sub>2</sub>), 7.46–7.43 (m, 2H, H3'', H5''), 7.07–7.02 (m, 2H, H2'', H6''), 6.57 (d,  $J$  = 7.9 Hz, 1H, H7'), 6.43 (d,  $J$  = 1.6 Hz, 1H, H4'), 6.38 (dd,  $J$  = 7.9 Hz; 1.7 Hz, 1H, H6'), 5.86 (ABq,  $J$  = 1.5 Hz, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.08 (dd,  $J$  = 11.2 Hz; 4.1 Hz, 1H, H1), 3.76 (dd,  $J$  = 13.2 Hz; 4.0 Hz, 1H, H2a), 3.28 (dd,  $J$  = 13.1 Hz; 11.2 Hz, 1H, H2b), 2.49 (s, 3H, NCH<sub>3</sub>). Anal. (C<sub>16</sub>H<sub>17</sub>ClFNO<sub>2</sub>) C, H, N.



**2-(1,3-benzodioxol-5-yl)-1-cyclohexyl-N-methylethanamine (11o).** Following the representative procedure, the reductive amination of **7o** (400 mg, 1.62 mmol) afforded **11o** as a colourless, viscous oil (360 mg, 85%).  $R_f$  (95:5 CHCl<sub>3</sub>/MeOH): 0.20. IR (neat) cm<sup>-1</sup>: 3344 (w, NH). <sup>1</sup>H NMR (500 MHz):  $\delta$  6.73 (d,  $J$  = 7.8 Hz, 1H, H7'), 6.68 (d,  $J$  = 1.6 Hz, 1H, H4'), 6.62 (dd,  $J$  = 7.8 Hz; 1.6 Hz, 1H, H6'), 5.92 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 2.67 (ABX, 1H, H1), 2.43 (ABX, 2H, H2a/b), 2.31 (s, 3H, NCH<sub>3</sub>), 1.80–1.65 (m, 5H, 2 × CH<sub>2</sub>, NH), 1.50–1.45 (m, 1H, H1''), 1.28–1.14 (m, 6H, 3 × CH<sub>2</sub>). <sup>13</sup>C NMR (125 MHz):  $\delta$  147.62 (ArO), 145.74 (ArO), 134.21 (C5'), 121.98 (ArH), 109.30 (ArH), 108.12 (ArH), 100.76 (CH<sub>2</sub>O<sub>2</sub>), 66.44

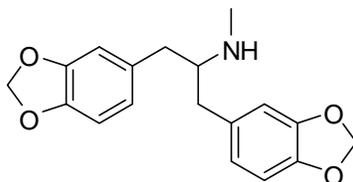
(C1), 39.64 (C1"), 36.70 (C2), 34.81 (NCH<sub>3</sub>), 29.14 (CH<sub>2</sub>), 28.60 (CH<sub>2</sub>), 26.84 (CH<sub>2</sub>), 26.77 (CH<sub>2</sub>), 26.67 (CH<sub>2</sub>). MS (EI) *m/z* (%): 178 (9), 135 (9), 126 (100), 95 (14).

The hydrochloride, 2-(1,3-benzodioxol-5-yl)-1-cyclohexyl-*N*-methylethanaminium chloride, crystallised from *i*-PrOH as white microcrystalline prisms, mp 242–243 °C (phase change >120 °C). <sup>1</sup>H NMR (500 MHz): δ 9.30 (br s, 2H, NH<sub>2</sub>), 6.80 (dd, *J* = 7.9 Hz; 1.7 Hz, 1H, H6'), 6.77–6.75 (m, 2H, H4', H7'), 5.95 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.10 (ABM, 1H, H1), 3.10–2.93 (ABM, 2H, H2a/b), 2.52 (s, 3H, NCH<sub>3</sub>), 1.92–1.77 (m, 4H), 1.70–1.64 (m, 2H), 1.55–1.44 (m, 2H), 1.34–1.14 (m, 3H). Anal. (C<sub>16</sub>H<sub>24</sub>ClNO<sub>2</sub>) C, H, N.



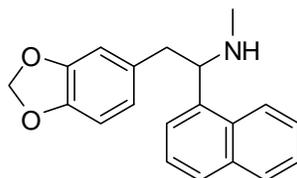
**1-(1,3-benzodioxol-5-yl)-*N*-methyl-3-phenylpropan-2-amine (11p).** Following the general procedure, the reductive amination of **7p** (0.242 g, 0.953 mmol) afforded **11p** as a pale yellow oil (0.226 g, 88%). *R<sub>f</sub>* (95:5 CHCl<sub>3</sub>/MeOH): 0.29. IR (neat) cm<sup>-1</sup>: 3337 (w, NH). <sup>1</sup>H NMR (500 MHz): δ 7.32–7.28 (m, 2H, H3", H5"), 7.25–7.17 (m, 2H, H2", H4", H6"), 6.74 (d, *J* = 7.8 Hz, 1H, H7'), 6.67 (d, *J* = 1.6 Hz, 1H, H4'), 6.63 (dd, *J* = 7.8 Hz; 1.6 Hz, 1H, H6'), 5.93 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 2.90–2.84 (m, 1H, H1), 2.73 (dd, *J* = 13.7 Hz; 7.0 Hz, 1H, CH<sub>2</sub>), 2.66 (dd, *J* = 6.3 Hz; 2.6 Hz, 1H, CH<sub>2</sub>), 2.63 (dd, *J* = 6.2 Hz; 2.7 Hz, 1H, CH<sub>2</sub>), 2.58 (dd, *J* = 13.8 Hz; 6.2 Hz, 1H, CH<sub>2</sub>), 2.40 (s, 3H, NCH<sub>3</sub>), 1.49 (br s, 1H, NH). <sup>13</sup>C NMR (125 MHz): δ 147.64 (ArO), 145.92 (ArO), 139.40 (ArC), 133.12 (ArC), 129.28 (ArH), 128.42 (ArH), 126.17 (ArH), 122.20 (ArH), 109.47 (ArH), 108.16 (ArH), 100.80 (CH<sub>2</sub>O<sub>2</sub>), 62.84 (C1), 40.12 (CH<sub>2</sub>), 39.86 (CH<sub>2</sub>), 34.15 (NCH<sub>3</sub>). MS (FAB+) *m/z*: 270 [M+H]<sup>+</sup> (100%).

The hydrochloride, 1-(1,3-benzodioxol-5-yl)-*N*-methyl-3-phenylpropan-2-aminium chloride, crystallised from *i*-PrOH as white prisms, mp 170–171 °C. <sup>1</sup>H NMR (500 MHz): δ 9.57 (br s, 2H, NH<sub>2</sub>), 7.32–7.28 (m, 2H, H3", H5"), 7.25–7.18 (m, 3H, H2", H4", H6"), 6.72 (d, *J* = 7.9 Hz, 1H, H7'), 6.69 (dd, *J* = 7.9 Hz; 1.7 Hz, 1H, H6'), 6.66 (d, *J* = 1.5 Hz, 1H, H4'), 5.92 (s, 2H, CH<sub>2</sub>O<sub>2</sub>), 3.46 (app pent, 1H, H1), 3.35 (dd, *J* = 14.2 Hz; 6.4 Hz, 1H, CH<sub>2</sub>), 3.28 (dd, *J* = 14.3 Hz; 6.5 Hz, 1H, CH<sub>2</sub>), 3.00 (dd, *J* = 14.2 Hz; 7.4 Hz, 1H, CH<sub>2</sub>), 2.92 (dd, *J* = 14.3 Hz; 7.1 Hz, 1H, CH<sub>2</sub>), 2.48 (s, 3H, NCH<sub>3</sub>). Anal. (C<sub>17</sub>H<sub>20</sub>ClNO<sub>2</sub>) C, H, N.



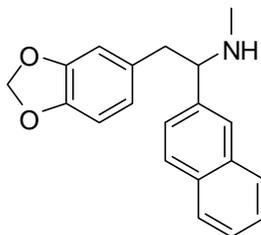
**1,3-bis(1,3-benzodioxol-5-yl)-N-methylpropan-2-amine (11q).** Following the representative procedure, the reductive amination of **7q** (0.297 g, 1.00 mmol) afforded **11q** as an amber oil (0.209 g, 67 %). IR (neat)  $\text{cm}^{-1}$ : 3335 (NH).  $^1\text{H}$  NMR (500 MHz):  $\delta$  6.74 (d,  $J = 7.9$  Hz, 2H, H7', H7''), 6.67 (d,  $J = 1.7$  Hz, 2H, H4', H4''), 6.62 (dd,  $J = 7.9, 1.7$  Hz, 2H, H6', H6''), 5.93 (s, 4H, H2', H2''), 2.79 (tt [apparent quintet],  $J = 6.2, 7.0$  Hz, 1H, H2), 2.63 (dd,  $J = 13.8, 7.0$  Hz, 2H, H1a, H3a), 2.56 (dd,  $J = 13.8, 6.2$  Hz, 2H, H1b, H3b), 2.39 (s, 3H, NCH<sub>3</sub>), 1.50 (br s, 3H, NH + H<sub>2</sub>O).  $^{13}\text{C}$  NMR (125 MHz):  $\delta$  147.7 (ArO), 145.9 (ArO), 133.1 (C5', C5''), 122.2 (ArH), 109.5 (ArH), 108.2 (ArH), 100.8 (C2', C2''), 63.0 (C2), 39.8 (C1, C3), 34.2 (NCH<sub>3</sub>). MS (EI)  $m/z$ : 313 ([M<sup>+</sup>], 0.02 %), 178 (100 %).

The hydrochloride, 1,3-bis(1,3-benzodioxol-5-yl)-N-methylpropan-2-aminium chloride, crystallised from MeOH/*i*-PrOH as colourless needles, mp 253–254 °C.  $^1\text{H}$  NMR (500 MHz,  $d_6$ -DMSO):  $\delta$  8.74 (br s, 2H, NH<sub>2</sub>), 6.84 (d,  $J = 8.0$  Hz, 2H, H7', H7''), 6.84 (d,  $J = 1.6$  Hz, 2H, H4', H4''), 6.69 (dd,  $J = 8.0, 1.6$  Hz, 2H, H6', H6''), 5.98 (dd,  $J = 1.7$  Hz, 1.0 Hz, 4H, H2', H2''), 3.64 (tt [apparent quintet],  $J = 6.6$  Hz, 1H, H2), 2.94 (dd,  $J = 14.3$  Hz; 6.2 Hz, 2H, H1a, H3a), 2.69 (dd,  $J = 14.3$  Hz; 7.3 Hz, 2H, H1b, H3b), 2.49 (s, 3H, NCH<sub>3</sub>); Anal. (C<sub>18</sub>H<sub>20</sub>ClNO<sub>4</sub>) C, H, N.



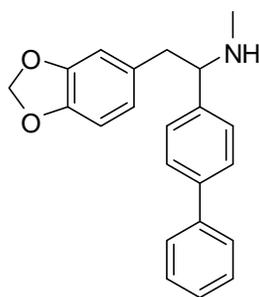
**2-(1,3-benzodioxol-5-yl)-N-methyl-1-(1-naphthyl)ethanamine (11r).** Following the representative procedure, the reductive amination of **7r** (0.290 g, 0.950 mmol) afforded **11r** as a yellow oil (0.239 g, 79%). IR (KBr disc)  $\text{cm}^{-1}$ : 3374 (NH).  $^1\text{H}$  NMR (300 MHz):  $\delta$  8.23 (br d,  $J = 8.1$  Hz, 1H, ArH), 7.93–7.85 (m, 1H, ArH), 7.79 (d,  $J = 8.2$  Hz, 1H, ArH), 7.68 (br d,  $J = 6.7$  Hz, 1H, ArH), 7.56–7.46 (m, 3H, ArH), 6.74–6.68 (m, 2H, H4'/H7'), 6.65 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H, H6'), 5.93 (AB,  $J = 1.4$  Hz, 2H, H2'), 4.68 (dd,  $J = 8.4$  Hz,  $J = 4.9$  Hz, 1H, H1), 4.23–4.08 (br s, 1H, NH), 3.15 (dd,  $J = 13.8$  Hz,  $J = 4.9$  Hz, 1H, H2a or H2b), 2.95 (dd,  $J = 13.8$  Hz,  $J = 8.5$  Hz, 1H, H2a or H2b), 2.28 (s, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (75.5 MHz):  $\delta$  147.8, 146.4 (C3a'/C7a') 137.4, 134.1, 132.3, 131.8 (Ar), 129.2, 127.8, 126.1, 125.8, 125.7, 125.5, 124.1, 122.6 122.5 (ArH), 109.6, 108.4 (C4'/C7'), 101.0 (OCH<sub>2</sub>O), 67.1 (NCH<sub>3</sub>), 44.6 (C2), 34.6 (C1). MS (ESI)  $m/z$ : 306 [M+H]<sup>+</sup> (25%).

The hydrochloride, 2-(1,3-benzodioxol-5-yl)-*N*-methyl-1-(1-naphthyl)ethanaminium chloride, crystallised from *i*-PrOH as colourless needles, mp 213.5–215 °C. <sup>1</sup>H NMR (600 MHz, d<sub>6</sub>-DMSO): δ 10.35-9.20 (br d, 2H, NH<sub>2</sub>), 8.18-8.04 (br m, 2H, ArH), 7.96-7.91 (m, 2H, ArH), 7.62 (m, 1H, ArH), 7.52-7.48 (m, 2H, ArH), 6.72 (d, *J* = 1.1 Hz, 1H, H4'), 6.60 (d, *J* = 7.9 Hz, 1H, H7'), 6.51 (br d, *J* = 7.8 Hz, 1H, H6'), 5.83 (AB, *J* = 0.9 Hz, 2H, OCH<sub>2</sub>O), 5.44 (br s, 1H, H1), 3.60 (dd, *J* = 13.5 Hz, *J* = 4.8 Hz, 1H, H2a or H2b), 3.31-3.23 (m, 1H, H2a or H2b), 2.43 (s, 3H, NCH<sub>3</sub>). Anal. (C<sub>20</sub>H<sub>20</sub>ClNO<sub>2</sub>) C, H, N.



**2-(1,3-benzodioxol-5-yl)-*N*-methyl-1-(2-naphthyl)ethanamine (11s).** Following the representative procedure, the reductive amination of **7s** (0.416 g, 1.43 mmol) afforded **11s** as an amorphous off-white solid (0.368 g, 84%). IR (KBr disc) cm<sup>-1</sup>: 3341 (NH). <sup>1</sup>H NMR (300 MHz): δ 7.86–7.78 (m, 3H, Ar), 7.74 (sl br s, 1H, H1"), 7.52–7.42 (m, 3H, Ar), 6.73–6.70 (m, 2H, H4'/ H7'), 6.62 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H, H6'), 5.93 (AB, *J* = 1.5 Hz, 2H, OCH<sub>2</sub>O), 3.87 (dd, *J* = 8.1, 5.9 Hz, 1H, H1), 2.95 (ABX, *J* = 13.7, 8.2, 5.9 Hz, 2H, H2a/H2b), 2.47–2.38 (br s, 1H, NH), 2.25 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (75.5 MHz): δ 147.8 (ArO), 146.3 (ArO) 140.4, 133.5, 133.1, 132.5 (Ar), 128.4, 127.9, 127.8, 126.5, 126.1, 125.7, 125.4, 122.5 (ArH), 109.6, 108.3 (C4'/C7'), 101.0 (CH<sub>2</sub>O<sub>2</sub>), 67.1 (C1), 44.6 (C2), 34.6 (CH<sub>3</sub>). MS (EI) *m/z*: 306 (25%), 276 (23%), 275 (100%), 145 (11%).

The hydrochloride, 2-(1,3-benzodioxol-5-yl)-*N*-methyl-1-(2-naphthyl)ethanaminium chloride, crystallised from MeOH as a colourless powder, mp 242–244°C. <sup>1</sup>H NMR (600 MHz, d<sub>6</sub>-DMSO): δ 9.68–9.16 (br s, 2H, NH<sub>2</sub>), 7.96 (d, *J* = 8.6 Hz, 1H, ArH), 7.94–7.91 (m, 2H, ArH), 7.88-7.85 (m, 1H, ArH), 7.67 (dd, *J* = 8.6 Hz, *J* = 1.7 Hz, 1H, ArH), 7.57-6.93 (m, 2H, ArH), 6.71 (d, *J* = 1.7 Hz, 1H, H4'), 6.69 (d, *J* = 7.9 Hz, 1H, H7'), 6.53 (dd, *J* = 8.0 Hz, *J* = 1.7 Hz, 1H, H6'), 5.89 (AB 1.0 Hz, 2H, CH<sub>2</sub>O<sub>2</sub>), 4.57-4.53 (m, 1H, H1), 3.46-3.44 (m, 1H, H2a or H2b), 3.20 (AB, *J* = 13.6 Hz, *J* = 10.3 Hz 1H, H2a or H2b), 2.39 (s, 3H, NCH<sub>3</sub>). Anal. (C<sub>20</sub>H<sub>20</sub>ClNO<sub>2</sub>) C, H, N.



**2-(1,3-benzodioxol-5-yl)-1-biphenyl-4-yl-N-methylethanamine (11t).** Following the representative procedure, the reductive amination of **7t** (0.427 g, 1.35 mmol) gave **11t** as a pale yellow solid (0.324 g, 73%). IR (KBr disc)  $\text{cm}^{-1}$ : 3324 (NH).  $^1\text{H}$  NMR (300 MHz):  $\delta$  7.65-7.54 (m, 4H, ArH), 7.47-7.31 (m, 5H, ArH), 6.73 (d,  $J = 7.9$  Hz, 1H, H7'), 6.68 (d,  $J = 1.3$  Hz, 1H, H4'), 6.62 (dd,  $J = 7.9$  Hz,  $J = 1.4$  Hz, 1H, H6'), 5.93 (s, 2H, OCH<sub>2</sub>O), 3.74 (dd,  $J = 7.9$  Hz,  $J = 6.0$  Hz, 1H, H1), 2.91 (ddd,  $J = 13.6$  Hz,  $J = 8.2$  Hz,  $J = 5.8$  Hz, 2H, H2a/H2b), 2.63-2.36 (br s, 1H, NH), 2.25 (s, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (75.5 MHz):  $\delta$  147.8, 146.3 (C3a'/C7a') 141.9, 141.0, 140.3, 132.5 (Ar), 128.9, 127.9, 127.3, 127.3, 127.2, 122.5 (ArH), 109.6, 108.4 (C4'/C7'), 101.0 (OCH<sub>2</sub>O), 66.7 (NCH<sub>3</sub>), 44.6 (C2), 34.6 (C1). MS (EI)  $m/z$ : 332 (39%), 302 (21%), 301 (100%), 145 (45%).

The hydrochloride, 2-(1,3-benzodioxol-5-yl)-1-biphenyl-4-yl-N-methylethanaminium chloride, crystallised from *i*-PrOH as a colourless plates, mp 218–220 °C.  $^1\text{H}$  NMR (600 MHz, *d*<sub>6</sub>-DMSO):  $\delta$  9.85-9.35 (br s, 2H, NH<sub>2</sub>), 7.72-7.67 (m, 4H, ArH), 7.59-7.55 (m, 2H, ArH), 7.47-7.44 (m, 2H, ArH), 7.39-7.35 (m, 1H, ArH), 6.75-6.72 (m, 2H, H4'/H7'), 6.55 (dd,  $J = 8.0$  Hz,  $J = 1.6$  Hz, 1H, H6'), 5.93 (AB,  $J = 1.0$  Hz, 2H, OCH<sub>2</sub>O), 4.47 (dd,  $J = 10.3$  Hz,  $J = 5.0$  Hz, 1H, 3.46 (dd,  $J = 13.5$  Hz,  $J = 4.8$  Hz, 1H, H2a or H2b), 3.13 (dd,  $J = 13.5$  Hz,  $J = 10.4$  Hz, 1H, H2a or H2b), 2.38 (s, 3H, NCH<sub>3</sub>). Anal. (C<sub>22</sub>H<sub>22</sub>ClNO<sub>2</sub>) C, H, N.

## Biological Assays

### Anti-proliferative actions against a Burkitt's lymphoma cell line

The L3055 cell line is derived from a patient with sporadic-type Epstein-Barr virus-negative Burkitt's lymphoma and is maintained in culture at "early passage" by resurrecting ampoules frozen between passage 8–15 and reculturing for no more than 75 passages in total. Such cells retain their "biopsy phenotype" including sensitivity to pro-apoptotic signals such as provided by MDMA. Cells are cultured at 37 °C in RPMI 1640 supplemented with 10% prescreened and heat-inactivated fetal calf serum, 2 mM L-glutamine and antibiotics. Cytotoxicity was measured by staining of treated cells with

propidium iodide (PI). PI is an impermeable fluorescent dye which binds to double-stranded DNA, therefore PI stains only dead, not live cells. Cells cultured for 24 h  $\pm$  compound as detailed in ref.<sup>16</sup> were collected in FACS polystyrene tubes and diluted with FACS buffer and kept on ice. PI at a final concentration of 0.85  $\mu\text{g}/\text{mL}$  or 1.15  $\mu\text{g}/\text{mL}$  was added prior to the FACS readout. For each sample 4000–10000 events were taken consistently within each experiment. Data were fitted to a four-parameter logistic equation using the iterative curve-fitting program, Kaleidagraph.

### Neuroblastoma toxicity assays

Human dopaminergic neuroblastoma SH-SY5Y cells (<sup>17</sup>ATCC) (P10 to P30) were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (6.4 g/L NaCl, 3.7 g/L NaHCO<sub>3</sub>, 400 mg/L KCl, and 584 mg/L L-glutamine) supplemented with 5% bovine calf serum in a sterile humidified chamber (37 °C, 95% CO<sub>2</sub>, 5% O<sub>2</sub>) until confluent. Cells were passed using 0.1% trypsin for 5 min, then pelleted by centrifuging at 1400 rpm. Twenty four hours following addition to 96 well plates, cells were incubated with concentration response curves (1–600  $\mu\text{M}$ ) of MDMA (**1**), **11g**, **11r** or **11s**. Media was used as vehicle for all four compounds. The redox sensitive dye Alamar Blue (0.4% of final volume) was added immediately following addition of the compounds, and cells were incubated for 24 hours. Cell viability was assessed by measuring the change in fluorescence of Alamar Blue (ex. 544nm, em. 590nm) using a FLUOstar OPTIMA.  $n = 6$ , where each  $n$  is the mean of six replicates. Data were analysed using ANOVA followed by Dunnett's multiple comparison's test.

### Prepulse Inhibition Studies

Male Wistar rats (72) were assigned to one of three groups (MDMA, PMA and **11g**) and tested with four doses (4.4, 8.8, 44 and 88  $\mu\text{mol}/\text{kg}$ ) in a randomised, Latin square within-subjects design. Testing with saline vehicle was conducted before and after testing with drugs and the results of these two test days averaged to give vehicle control values.

The PPI testing procedure has been described previously.<sup>18</sup> Briefly, animals were pretreated with the appropriate drug and placed into Med Associates (St Albans, VT) startle chambers. White noise (70 dB) background was played throughout the test session. White noise startling stimuli (40 ms duration) of 70–120 dB in 5 dB increments were presented in every possible combination randomly with 10 ms white noise prepulse stimuli (70–95 dB in 5 dB increments) which preceded the startling stimuli by 50 ms. Stimulus intensity-response magnitude curves were fitted to the data as described previously<sup>18</sup> and

prepulse inhibition calculated using  $100 * (R_{MAX \text{ pulse alone}} - R_{MAX \text{ prepulse+pulse}} / R_{MAX \text{ pulse alone}})$ , where  $R_{MAX}$  = the maximum response achievable from a subject under a given drug and prepulse condition.

## **Receptor/Transporter Binding protocol**

### ***Tissue preparation***

Female Sprague-Dawley rats (250 g) were killed by decapitation following CO<sub>2</sub> narcosis. Brains were immediately removed and placed into ice-cold Krebs' buffer (134 mM NaCl, 5 mM KCl, 1.3 mM CaCl<sub>2</sub>, 1 mM MgSO<sub>4</sub>, 25 mM NaHCO<sub>3</sub>, 1.25 mM KH<sub>2</sub>PO<sub>4</sub>, and 10 mM glucose). Various brain regions (cerebral cortex, striatum, cerebellum and remaining brain) were dissected out and placed separately into ice-cold Tris buffer (pH 7.4) prior to sonication. Brain homogenates were then centrifuged for 20 min (4 °C, 20,000 rcf), resuspended and spun again. Following centrifugation, supernatant was removed, and the pellet resuspended, vortexed and placed in a 37 °C water bath for 20 min. Following a final centrifugation step supernatant was removed and the pellet re-suspended. Protein concentration was determined by a variant of the Folin's phenol reagent method described by Lowry et al.<sup>19</sup>

### ***Homogenate binding - Radioligands and drugs***

[<sup>3</sup>H]-Ketanserin (specific activity: 67 Ci/mmol) and [<sup>3</sup>H]-GBR12935 (specific activity: 43 Ci/mmol), [<sup>3</sup>H]WAY 100635 (specific activity: 74 Ci/mmol), [<sup>3</sup>H]mesulergine (specific activity: 72 Ci/mmol), [<sup>3</sup>H]-nisoxetine (specific activity: 85 Ci/mmol), [<sup>3</sup>H]GR125743 (specific activity: 72 Ci/mmol), [<sup>3</sup>H]-citalopram (specific activity: 84 Ci/mmol, NAN-190, GR127935, spiperone, SB206553, maprotiline, paroxetine and GBR12909 are commercially available and were used as supplied.

### ***Receptor and transporter binding assays***

An initial receptor binding screen was employed in which the ability of a single 10 μM concentration of compound to displace at least 50% of specific binding was assessed. Compounds which failed to reach this threshold were not subjected to full profiling at that site. The reactions were conducted using 380 μL 96-well plates. For full dose-effect assays, concentrations of 1 mM, 300 μM, 100 μM, 30 μM, 10 μM, 1 μM, 300 nM, 100 nM, 30 nM, 10 nM, 1 nM of drug were incubated in the presence of the radioligand with and without non-specific displacer and brain homogenate. Binding conditions relating to brain region used, ligand and ion concentration as well as incubation conditions employed for each of the assays are shown below.

**Table S1. Experimental details for receptor/transporter binding studies.**

receptor / transporter	origin (concentration)	radioligand (concentration)	non-specific (concentration )	ionic conditions	incubation conditions
5HT <sub>1A</sub>	cerebral cortex (2 mg/mL)	[ <sup>3</sup> H]WAY100635 (2.0 nM)	NAN-190 (10 mM)	–	60 min, 25°C
5HT <sub>1B/D</sub>	whole brain (3 mg/mL)	[ <sup>3</sup> H]GR125743 (1 nM)	GR127935 (10 mM)	Mg <sup>2+</sup> (10 mM)	60 min, 25°C
5HT <sub>2A</sub>	cerebral cortex (2 mg/mL)	[ <sup>3</sup> H]-ketanserin (2.5 nM)	spiperone (10 mM)	–	45 min, 4°C
5HT <sub>2C</sub>	whole brain (2 mg/mL)	[ <sup>3</sup> H]mesulergine (2.5 nM)	SB206553 (10 mM)	–	60 min, 25°C
NET	cerebellum (2 mg/mL)	[ <sup>3</sup> H]nisoxetine (2.0 nM)	maprotiline (10 mM)	Na <sup>+</sup> (300 mM) K <sup>+</sup> (5 mM)	60 min, 4°C
SERT	whole brain (2 mg/mL)	[ <sup>3</sup> H]citalopram (2.5 nM)	paroxetine (10 mM)	Na <sup>+</sup> (120 mM) K <sup>+</sup> (5 mM)	60 min, 25°C
DAT	striatum (2 mg/mL)	[ <sup>3</sup> H]GBR12935 (5.6 nM)	GBR12909 (10 mM)	Na <sup>+</sup> (125 mM) K <sup>+</sup> (0 mM)	45 min, 25°C

After incubation, the membranes were rapidly washed in 50 mM Tris buffer (20 sec wash at 10 mL/sec) and filtered under vacuum through glass fibre filters using a cell harvester. For SERT and DAT assays, filters were pre-soaked in a 50 mM Tris (pH 7.4) solution containing 0.1% polyethyleneimine and with 0.1% bovine serum albumin added to the filtration buffer. Filters were then dissolved in scintillation fluid and radioactivity determined with a scintillation counter.

### **Statistical analysis**

Following removal of the outliers, values of three triplicate experiments were averaged, and expressed as a percentage of total displacement. Dose-response curves were constructed and the half maximal inhibitory concentration (IC<sub>50</sub>) determined via non-linear regression analysis (GraphPad Prism 5.02, GraphPad Software Inc, La Jolla, CA, USA). The inhibition constant ( $K_i$ ) was calculated using the Cheng-Prusoff equation.<sup>20</sup>

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