

Short communication

## $\beta$ -Alkoxy-substituted phenethylamines: a family of compounds potentially active at the dopamine and $\alpha$ -adrenergic receptors

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**Summary** — A series of  $\beta$ -alkoxy-substituted phenethylamines were synthesized and tested for their affinity at the D<sub>1</sub> and D<sub>2</sub> dopaminergic receptors and the  $\alpha_1$  and  $\alpha_2$  adrenoceptors. None of the tested compounds exhibited D<sub>2</sub> receptor affinity. Among the non-hydroxylated compounds that were resolved to their antipodes, the (–)-enantiomers generally showed a moderate but distinct activity at the  $\alpha_2$  receptor. Ring hydroxylation appears to be a necessary requirement for D<sub>1</sub> activity. These results are discussed in terms of the structural elements of the tested drugs as compared to those of known active compounds.

$\beta$ -substituted phenethylamine /  $\alpha$ -adrenoceptor/ dopamine receptor

### Introduction

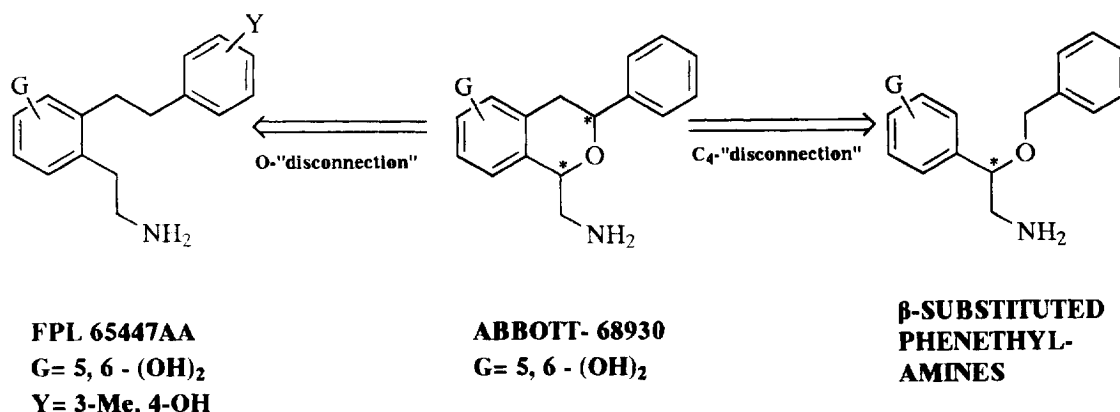
Dopamine (DA, **1**) receptors have been divided into two major subtypes, D<sub>1</sub> and D<sub>2</sub>, based on their adenylate cyclase-related activity [1]. Recent publications on the cloning of DA receptors [2–8] suggest that a greater number of subtypes exists, including D<sub>3</sub> [6], D<sub>4</sub> [7] and D<sub>5</sub> [8].

Dopaminergic system dysfunction in the central nervous system (CNS) has been related to neurological disorders such as schizophrenia and Parkinson's disease. It is therefore of great importance to develop subtype-selective dopaminergic drugs in order to avoid side effects on treatment of patients, resulting from uncontrolled interactions with more than one DA receptor subtype. Although the phenolic moieties and the side chain nitrogen atom have been characterized as necessary for the drug–receptor interaction, there are a number of functional groups which, when introduced in the molecules, can alter the potency and/or selectivity of DA analogues. Structure–activity relationship (SAR) studies have been extensively reviewed in the past [9–13].

Kebabian and coworkers reported a number of isochroman-type dopamine analogs with very high selectivity towards the D<sub>1</sub> receptor [14–16]. These 1-amino-methyl, 3-aryl or alkyl substituted compounds exhibit great enantioselectivity; the [1*R*,3*S*] enantiomers are always the active ones. Although these analogs are

semi-rigid, the combination of the position of the aromatic hydroxyls and the steric characteristics of the molecules fulfill the structural requirements for such a high D<sub>1</sub>/D<sub>2</sub> selectivity. The above authors proposed the existence of an auxiliary binding region in the D<sub>1</sub> receptor hosting the C-3 aryl or cyclohexyl substituents.

In this report we describe the synthesis and the pharmacological profile of a number of  $\beta$ -substituted phenethylamines. These structures could be considered as deriving from the 'disconnection' of the C-4 methylene of the isochroman moiety (fig 1). Such an operation yields molecules that could provide us with substantial information on the mode of interaction of substituted phenethylamines with the D<sub>1</sub> receptor: chirality on the C-3 is abolished and therefore it rests only upon the stereochemistry of the C-1 allowing for a direct evaluation on the effect of this chiral center on the compounds' selectivity. Moreover, the conformational restrictions imposed by the isochroman ring have been canceled. The selection of this type of disconnection is not without precedent; Smith *et al* [17] reported *in vivo* studies on FPL 65447AA, a structure basically resulting from the 'disconnection' of the isochroman oxygen. Although the compound is not chiral, it functions as a selective agonist at the peripheral DA<sub>1</sub> receptors, as indicated by its ability to increase the blood flow to the kidney and gut in dogs. Ring-methoxy-substituted or unsubstituted compounds



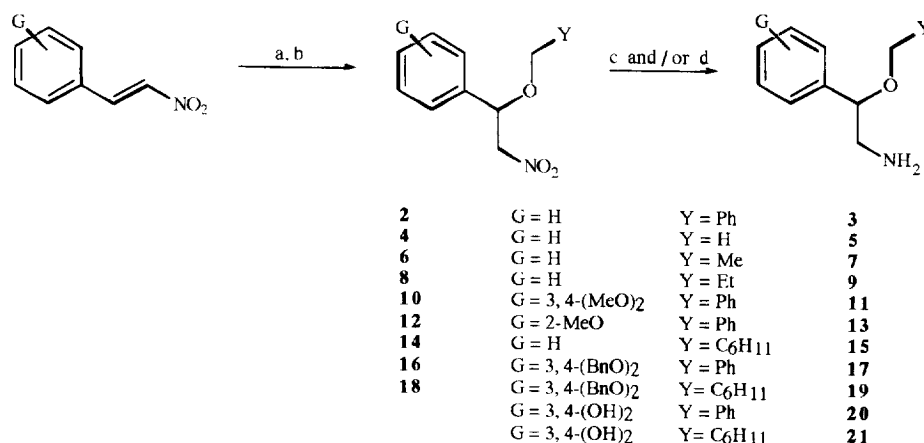
**Fig 1.** Disconnections of ring elements of the isochroman group leading to acyclic phenethylamine analogs.

were selected for this study, given that a weak but distinct D<sub>1</sub> activity has been detected in non-catecholic phenethylamine analogs [18]. Pharmacological profile studies also included α<sub>1</sub> and α<sub>2</sub> receptor binding since ring alkoxy-substituted phenethylamines were reported to function as enantioselective centrally acting hypotensive agents [19].

## Chemistry

β-Substituted phenethylamines were prepared *via* a modification of a method described by Howe *et al* [19]. Reaction of commercially available nitrostyrenes

with an alcoholic solution of sodium alkoxides (1 equiv), yielded β-substituted phenylnitroethanes, which were reduced to the desired amines with platinum oxide or, in the case of benzyloxy substituent, with platinum on activated carbon (fig 2). The latter catalyst was selected on the basis of its ability to selectively reduce nitro groups without causing hydrogenolysis of benzyl ethers. Resolution of enantiomers was achieved by recrystallization of the salts of racemic amines with (+)- or (−)-tartaric acid. The dihydroxy, cyclohexylmethyl analog **21** was prepared by hydrogenolysis of the bis-benzyloxy-protected precursor **19** using 5% palladium on activated carbon, a very smooth, high-yield reaction. However, the synthesis of



**Fig 2.** Synthesis of β-substituted phenethylamines from the corresponding nitrostyrenes. Starting materials were either commercially available or prepared *via* reaction of the corresponding benzaldehydes with nitromethane. a: Y-CH<sub>2</sub>ONa/YCH<sub>2</sub>OH. b: AcOH. c: 10% Pd/C/H<sub>2</sub>. d: PtO<sub>2</sub>/H<sub>2</sub>.

the benzyloxy-substituted compound **20** was cumbersome. Attempts to remove the methyl protective groups of **11** by treatment of the compound with either 48% HBr or BBr<sub>3</sub> yielded tarry materials. A total synthesis using *t*-butyldimethylsilyl ethers to protect the catechol moiety failed at the final deprotection step under a host of conditions mentioned in the literature; the description of this approach is beyond the purpose of this publication. Hydrogenolysis of the bis-benzyl analog **17** was also problematic since the compound itself is a substituted dibenzyl ether, which can be cleaved under these conditions. A number of experiments yielded either partially deprotected material or the totally debenzylated compound, *ie* noradrenaline. Finally, under careful monitoring and using 5% Pd/C (Fluka) as catalyst, a 0.08 M solution of **17** in ethanol was hydrogenated for 2.5 h to yield 95% of pure material. Attempts to resolve the bis-benzyloxy precursors **17** and **19** to their enantiomers were totally fruitless, regardless of chiral reagents and reaction conditions used. HPLC experiments using various chiral columns (see *Experimental protocols*) also failed to give a satisfactory separation of the enantiomeric pairs.

## Pharmacology

The pharmacological behavior of the synthesized compounds at the dopaminergic system was examined by studying the ability of these agents to inhibit specific binding of [<sup>3</sup>H]spiroperidol (0.50 nM) and [<sup>3</sup>H]SCH-23390 (0.30 nM) to D<sub>2</sub> and D<sub>1</sub> dopamine receptors, respectively, in rat striatal membranes. The binding studies were performed as described previously [20, 21]. The concentrations of the compounds tested ranged from 0.001 to 10 μM. The same compounds were tested for their ability to label specific α<sub>1</sub> and α<sub>2</sub> adrenergic receptor sites in rat cortical membranes. [<sup>3</sup>H]Prazosin (0.2 nM) and [<sup>3</sup>H]rauwolscine (1.0 nM) were used to label α<sub>1</sub> and α<sub>2</sub> adrenergic receptors, respectively, as described previously [18, 22, 23].

## Results and discussion

As the data in table I indicate, none of the non-hydroxylated compounds was active at either dopaminergic receptor. However, a weak but distinct affinity to the α<sub>2</sub> adrenoceptor was shown by (–)-**3**, (–)-**5** and

**Table I.** Inhibition of [<sup>3</sup>H]spiroperidol, [<sup>3</sup>H]SCH-23390, [<sup>3</sup>H]prazosin and [<sup>3</sup>H]rauwolscine binding to rat striatal membranes and rat cortical membranes<sup>a</sup>.

Drug	IC <sub>50</sub> (μM)			
	[ <sup>3</sup> H]Spiroperidol	[ <sup>3</sup> H]SCH-23390	[ <sup>3</sup> H]Prazosin	[ <sup>3</sup> H]Rauwolscine
(±)- <b>3</b>	NA <sup>b</sup>	NA	NA	NA
(+)- <b>3</b>	NA	NA	NA	NA
(–)- <b>3</b>	NA	NA	NA	7.0
(±)- <b>5</b>	NA	NA	NA	NA
(+)- <b>5</b>	NA	NA	NA	NA
(–)- <b>5</b>	NA	NA	NA	2.0
(±)- <b>7</b>	NA	NA	NA	NA
(±)- <b>9</b>	NA	NA	NA	NA
(±)- <b>11</b>	NA	NA	NA	NA
(+)- <b>11</b>	NA	NA	NA	NA
(–)- <b>11</b>	NA	NA	NA	NA
(±)- <b>13</b>	NA	NA	1.2	NA
(±)- <b>15</b>	NA	NA	NA	NA
(+)- <b>15</b>	NA	NA	NA	NA
(–)- <b>15</b>	NA	NA	NA	6.0
(±)- <b>17</b>	NA	NA	NA	NA
(±)- <b>19</b>	NA	NA	NA	NA
(±)- <b>20</b>	NA	2.0	NA	6.1
(±)- <b>21</b>	NA	1.4	NA	5.5
Noradrenaline	–	–	1.5 <sup>b</sup>	0.750 <sup>c</sup>
(±)-ADTN	0.70 ± 0.02	–	–	–
(–)-APO	0.22 ± 0.05	0.43 ± 0.05	–	–

<sup>a</sup>Experiments were performed 3 times in duplicate. Values from <sup>b</sup>reference 12, <sup>c</sup>reference 13. NA: not active up to a concentration of 10 μM.

(-)-**15** with respective  $IC_{50}$  values of 7.0, 2.0, and 6.0  $\mu$ M as compared with a 0.75  $\mu$ M value for norepinephrine. Compound **13**, the *ortho*-substituted analog, exhibited an affinity ( $IC_{50}$  = 1.2  $\mu$ M) at the  $\alpha_1$  adrenoceptor which is comparable to that of norepinephrine ( $IC_{50}$  = 1.5  $\mu$ M). Hydroxylation of the aromatic ring at positions analogous to those of ABOTT-68930 and FPL 65447AA, resulted in  $D_1$ -active compounds such as **20** and **21**, which maintain their  $\alpha_2$  activity.

Although these results are not conclusive, at this stage of the project it could be suggested that the presence of the catechol hydroxyls is necessary for efficient binding at the DA receptors sites. On the other hand, such a restriction is not present at the  $\alpha_2$  site, which, however, should maintain some degree of enantioselectivity at the side chain binding region. Ring substitution by bulky groups (such as benzyloxy) deprives the molecules of activity at either type of receptor. The presence of the *meta*- and *para*-methoxy groups abolishes  $\alpha_2$  activity whereas the *ortho*-methoxy is tolerated only by the  $\alpha_1$  binding site.

Analog **20** and **21** exhibited affinity to the  $D_1$  receptor ( $IC_{50}$  = 2.0 and 1.4  $\mu$ M, respectively) weaker to that of (-)-apomorphine ( $IC_{50}$  = 0.22  $\mu$ M). When the racemates of Abbott-68930 and its cyclohexyl methylene congener [15] were tested in binding studies to rat caudate preparations, they were found to be two orders of magnitude more potent than the known  $D_1$  agonist SKF38393 ( $EC_{50}$  = 2.1, 3.1 and 386 nM, respectively). These data are at least suggestive that the conformational restrictions imposed by the isochroman ring of the Abbott compounds is a decisive factor for the activity of these analogs. Unfortunately no conclusions can be drawn about the enantioselectivity at the  $D_1$  receptor due to the lack of availability of enantiomers of the hydroxylated compounds (see *Chemistry*). Asymmetric synthesis of these congeners and determination of the absolute configuration of the active drugs by X-ray crystallographic studies would enable us to evaluate the importance of the stereochemistry at the C-1 carbon. These investigations are currently underway in our laboratory.

## Experimental protocols

### Chemistry

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 1760X FTIR spectrometer. NMR spectra were taken on a Varian FT-80A, 80 MHz and a AC 250 Bruker FT-NMR spectrometer; proton chemical shifts are reported in ppm relative to tetramethylsilane. Mass spectra were taken on a Hewlett Packard Model 5890 gas chromatograph coupled with a Hewlett Packard 5971A mass selective detector. HPLC chiral separation attempts for compounds **17** and **19** were performed

at the Abbott laboratories, IL, USA, using a Rainin Dynamax instrument, Chiracel OD and Chiracel AD chiral columns and eluent conditions varying from 95:5 to 98:2 hexane/*i*-propyl alcohol. Elemental analysis were taken by the Analytical Laboratory of the Chemistry Department of University of Salonika, Greece, and are within  $\pm 0.4\%$  of the theoretical values of the indicated elements unless otherwise stated.

### General method of preparation of 1-aryl-2-nitroethyl alkyl benzyl ethers

A 1.5 M solution of sodium alkoxide in the corresponding alcohol was added at room temperature to a 2 M solution of an equivalent amount of the substituted nitrostyrene in dry ether. The system was stirred briefly and an excess of acetic acid was added. The mixture was poured into cold water, the product was extracted with ether, the organic layer was washed with water and saturated NaCl solution, dried over  $Na_2SO_4$  and the solvent was removed to give the product which was further purified by flash chromatography using ether/petroleum as eluent.

*1-Phenyl-2-nitroethyl benzyl ether 2.* Nitrostyrene (4.47 g, 30 mmol) reacted with sodium benzoate as described above to give 2.35 g (30%) of product. NMR (250 MHz,  $CDCl_3$ ), 7.46–7.2 (m, 10H), 5.15 (dd,  $J$  = 3.4 and 10.0 Hz, 1H), 4.68 (dd,  $J$  = 10.0 and 12.3 Hz, 1H), 4.51 (d,  $J$  = 11.5 Hz, 1H), 4.38 (dd,  $J$  = 3.4 and 12.3 Hz, 1H), 4.33 (d,  $J$  = 11.5 Hz, 1H). MS ( $m/z$ ) 257 ( $M^+$ ).

*1-Phenyl-2-nitroethyl methyl ether 4.* Nitrostyrene (3.86 g, 26 mmol) was treated with sodium methoxide according to the above-described method to yield 2.80 g of product (60%). NMR (250 MHz,  $CDCl_3$ ), 7.43–7.01 (m, 5H), 5.04 (dd,  $J$  = 3.3 and 10.0 Hz, 1H), 4.62 (dd,  $J$  = 10.0 and 16.0 Hz, 1H), 4.33 (dd,  $J$  = 3.3 and 16.0 Hz, 1H), 3.28 (s, 3H). MS ( $m/z$ ) 181 ( $M^+$ ).

*1-Phenyl-2-nitroethyl ethyl ether 6.* Nitrostyrene (1.5 g, 10 mmol) was treated with sodium ethoxide as described above to yield 0.12 g (6%) of the product. NMR (80 MHz,  $CDCl_3$ ), 7.35 (br, s, 5H), 5.05 (dd,  $J$  = 4.0 and 8.0 Hz, 1H), 4.65 (d,  $J$  = 4 Hz, 1H), 4.60 (d,  $J$  = 8.0 Hz, 1H), 3.35 (q,  $J$  = 6 Hz, 2H), 1.10 (t,  $J$  = 6 Hz, 3H). IR ( $cm^{-1}$ ) 1564, 1390, 1113, 722. MS ( $m/z$ ) 195 ( $M^+$ ).

*1-Phenyl-2-nitroethyl propyl ether 8.* Nitrostyrene (1.5 g, 10 mmol) was treated with sodium propoxide to yield 500 mg (24%) of the product. NMR (80 MHz,  $CDCl_3$ ), 7.25 (br, s, 5H), 4.95 (dd,  $J$  = 8 and 12 Hz, 1H), 4.55 (d,  $J$  = 8 Hz, 1H), 4.5 (d,  $J$  = 12 Hz, 1H), 3.15 (t,  $J$  = 6 Hz, 2H), 1.45 (m, 2H), 1.45 (t,  $J$  = 6 Hz, 3H). MS ( $m/z$ ) 209 ( $M^+$ ).

*1-(3,4-Dimethoxyphenyl)-2-nitroethyl benzyl ether 10.* 3,4-Dimethoxynitrostyrene (3.77 g, 18 mmol), was treated with sodium benzoate to yield 2.72 g (48%) of product. NMR (80 MHz,  $C_6D_6$ ), 7.2 (m, 3H), 6.4, (m, 5H), 4.85 (dd,  $J$  = 4 and 10 Hz, 1H), 4.35 (d,  $J$  = 12 Hz, 1H), 4.22 (dd,  $J$  = 4 and 12 Hz, 1H), 4.05 (d,  $J$  = 12 Hz, 1H), 3.65 (dd,  $J$  = 4 and 12 Hz, 1H), 3.30 (s, 3H), 3.25 (s, 3H). MS ( $m/z$ ) 317 ( $M^+$ ).

*1-(2-Methoxyphenyl)-2-nitroethyl benzyl ether 12.* 2-Methoxynitrostyrene (1.5 g, 8.4 mmol) reacted with sodium benzoate as described above to give 1.6 g (67%) of product. NMR (80 MHz, acetone- $d_6$ ), 7.15 (m, 9H), 5.60 (dd,  $J$  = 4 and 8 Hz, 1H), 4.6 (d,  $J$  = 8 Hz, 1H), 4.57 (dd,  $J$  = 8 and 16 Hz, 1H), 4.5 (dd,  $J$  = 4 and 16 Hz, 1H), 4.3 (d,  $J$  = 8 Hz, 1H), 3.8 (s, 3H). MS ( $m/z$ ) 287 ( $M^+$ ).

**1-Phenyl-2-nitroethylmethylcyclohexyl ether 14.** Nitrostyrene (3.0 g, 20 mmol) reacted with sodium cyclohexylmethylenoxide as described above to give 3.5 g (67%) of the product as a yellow liquid. NMR (80 MHz,  $\text{CDCl}_3$ ), 7.32 (s, 5H), 4.97 (dd,  $J_1 = 4$  Hz,  $J_2 = 9$  Hz, 1H), 4.55 (dd,  $J_1 = 9$  Hz,  $J_2 = 11$  Hz, 1H), 4.25 (dd,  $J_1 = 4$  Hz,  $J_2 = 11$  Hz, 1H), 3.14 (d,  $J = 2$  Hz, 1H), 3.09 (d,  $J = 2$  Hz, 1H), 1.75–0.85 (m, 11H). IR  $\nu$  ( $\text{cm}^{-1}$ ) 3032, 2924, 2852, 1558, 1452, 1380, 1157, 763, 700.

**1-(3,4-Dibenzyloxyphenyl)-2-nitroethylbenzyl ether 16.** 3,4-Dibenzyloxy nitrostyrene (2.5 g, 6.9 mmol) reacted with sodium benzoate as described above to give 2.2 g (68%) of the product as a thick yellow liquid. NMR (80 MHz,  $\text{CDCl}_3$ ), 7.40–7.20 (m, 15H), 6.95–6.80 (m, 3H), 5.20 (s, 2H), 5.15 (s, 2H), 4.97 (dd,  $J_1 = 4$  Hz,  $J_2 = 9$  Hz, 1H), 4.57 (dd,  $J_1 = 9$  Hz,  $J_2 = 12$  Hz, 1H), 4.41 (d,  $J = 10$  Hz, 1H), 4.19 (d,  $J = 10$  Hz, 1H), 4.22 ( $J_1 = 4$  Hz,  $J_2 = 12$  Hz, 1H). IR  $\nu$  ( $\text{cm}^{-1}$ ) 3033, 2927, 1555, 1381, 1268, 1137, 1023, 735, 697. MS ( $m/z$ ) 469 ( $\text{M}^+$ ).

**1-(3,4-Dibenzyloxyphenyl)-2-nitroethylmethylcyclohexyl ether 18.** 3,4-Dibenzyloxy nitrostyrene (3.0 g, 8.3 mmol) reacted with sodium cyclohexylmethylenoxide as described above to give 3.5 g (89%) of the product as a thick yellow liquid. NMR (80 MHz,  $\text{CDCl}_3$ ), 7.80–7.35 (m, 10H), 7.10–6.95 (m, 3H), 5.20 (s, 2H), 5.15 (s, 2H), 4.97 (dd,  $J_1 = 4$  Hz,  $J_2 = 9$  Hz, 1H), 4.53 (dd,  $J_1 = 9$  Hz,  $J_2 = 11$  Hz, 1H), 4.25 (dd,  $J_1 = 4$  Hz,  $J_2 = 11$  Hz, 1H), 3.20–3.05 (m, 2H), 1.85–0.95 (m, 11H). IR  $\nu$  ( $\text{cm}^{-1}$ ) 3032, 2925, 2852, 1557, 1450, 1380, 1261, 1162, 1026, 735, 697. MS ( $m/z$ ) 475 ( $\text{M}^+$ ).

**General method of preparation of 2-aryl-2-alkoxyethylamines**  
To a 0.1 M solution of 1-aryl-2-nitroethyl alkyl (or benzyl) ether in ethanol was added  $\text{PtO}_2$  (or 10 Pt/C), 0.2 equiv and the system was hydrogenated at 1 atm  $\text{H}_2$  for 20 h. The catalyst was removed by filtration and the solvent was removed *in vacuo*. The solid residue was redissolved in ether, and the product was extracted with 0.1 M HCl solution. The aqueous layer was washed with ether, neutralized with 1 N NaOH, and the product was extracted with ether. The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and the solvent was removed *in vacuo*. Pure amines were isolated as oxalate or tartrate salts, which were recrystallized from 95% ethanol.

**2-Benzyloxy-2-phenylethylamine 3.** Compound 2 (2.11 g, 8.2 mmol) as reduced as described above to yield 0.51 g (27%) of 3. NMR (250 MHz,  $\text{CDCl}_3$ ), 7.41–7.25 (m, 10H), 4.51 (d,  $J = 11.7$  Hz, 1H), 4.37 (dd,  $J = 4.5$  and 7.5 Hz, 1H), 4.31 (d,  $J = 11.5$  Hz, 1H), 2.95 (dd,  $J = 7.5$  and 13.5 Hz, 1H), 2.84 (dd,  $J = 4.5$  and 13.2 Hz, 1H), 2.03 (br, s, 2H). MS ( $m/z$ ) 227 ( $\text{M}^+$ ). Anal  $\text{C}_{15}\text{H}_{17}\text{NO} \cdot 0.5\text{C}_4\text{H}_6\text{O}_6 \cdot \text{H}_2\text{O}$  (C, H, N).

**2-Methoxy-2-phenylethylamine 5.** Compound 4 (0.7 g, 3.8 mmol) was reduced over  $\text{PtO}_2$  as described above to yield 240 mg (42%) of 5. NMR (250 MHz,  $\text{CDCl}_3$ ), 7.4–7.22 (m, 5H), 4.14 (dd,  $J = 4.8$  and 7.0 Hz, 1H), 3.28 (s, 3H), 3.26–2.81 (two overlapping dd, 2H), 1.86 (br, s, 2H). MS ( $m/z$ ) 151 ( $\text{M}^+$ ). Anal  $\text{C}_9\text{H}_{13}\text{NO} \cdot \text{C}_4\text{H}_6\text{O}_6 \cdot 0.5\text{H}_2\text{O}$  (C, H, N).

**2-Ethoxy-2-phenylethylamine 7.** Compound 6 (110 mg, 0.6 mmol) was reduced over  $\text{PtO}_2$  to yield 30 mg (30.5%) of 7. MS ( $m/z$ ) 165 ( $\text{M}^+$ ). Oxalate salt mp 176.5°C. NMR of oxalate salt (80 MHz,  $\text{D}_2\text{O}$ ), 7.35 (br, s, 5H), 4.15 (m, 1H), 3.4–3.0 (m, 4H), 1.15 (t,  $J = 8$  Hz, 3H).

**2-Propoxy-2-phenylethylamine 9.** Compound 8 (0.5 g, 2.4 mmol) was reduced over  $\text{PtO}_2$  to yield 100 mg (23.3%) of

9. NMR (80 MHz,  $\text{CDCl}_3$ ), 7.25 (s, 5H), 4.90 (m, 1H), 3.10 (t,  $J = 6$  Hz, 2H), 1.6 (overlapping sextet,  $J = 6$  Hz, 2H, and br, s, 2H exch in  $\text{D}_2\text{O}$ ), 0.85 (t,  $J = 6$  Hz, 3H). MS ( $m/z$ ) 179 ( $\text{M}^+$ ). GC-MS as well as NMR spectra indicated the presence of an isomeric compound ( $m/z$  179) which was separated by precipitation of 9 as an oxalate salt; mp 115°C.

**2-Benzyloxy-2-(3,4-dimethoxyphenyl)-ethylamine 11.** Compound 10 (2.72 g, 8.58 mmol) was reduced over 10% Pt on activated carbon as described above to yield 530 mg (22%) of 11. NMR (80 MHz,  $\text{C}_6\text{D}_6$ ), 7.25 (s, 5H), 6.80–6.45 (m, 3H), 4.45 (d,  $J = 11$  Hz, 1H), 4.24 (d,  $J = 11$  Hz, 1H), 4.12 (dd,  $J = 3$  and 8 Hz, 1H), 3.35 (s, 6H), 2.9 (d,  $J = 3$  Hz, 1H), 2.85 (d,  $J = 8$  Hz, 1H), 1.25 (br, s, 2H). MS ( $m/z$ ) 257 ( $\text{M}-\text{CH}_2=\text{NH}_2^+$ ). Anal  $\text{C}_{17}\text{H}_{21}\text{NO}_3 \cdot \text{C}_4\text{H}_6\text{O}_6$  (C, H, N).

**2-Benzyloxy-2-(2-methoxyphenyl)ethylamine 13.** Compound 12 was reduced over 10% Pt on activated carbon to yield 0.5 g (59%) of 13. NMR (80 MHz,  $\text{C}_6\text{D}_6$ ), 7.0 (m, 9H), 4.95 (dd,  $J = 4$  and 7 Hz, 1H), 4.5 (d,  $J = 2$  Hz, 1H), 4.2 (d,  $J = 12$  Hz, 1H), 3.25 (s, 3H), 3.1 (d,  $J = 4$  Hz, 1H), 3.0 (d,  $J = 7$  Hz, 1H). MS ( $m/z$ ) 227 ( $\text{M}-\text{CH}_2=\text{NH}_2^+$ ). Tartrate salt mp 155°C. Anal  $\text{C}_{16}\text{H}_{19}\text{NO}_2 \cdot \text{C}_4\text{H}_6\text{O}_6$  (C, H, N).

**2-Cyclohexylmethyloxy-2-phenylethylamine 15.** Compound 14 (2.5 g, 95 mmol) was reduced over 10% Pt on activated carbon to yield 1.1 g (50%) of 15. NMR (80 MHz,  $\text{CDCl}_3$ ), 7.25 (s, 5H), 4.17 (t,  $J = 5$  Hz, 1H), 3.17 (d,  $J = 2$  Hz, 1H), 3.09 (d,  $J = 2$  Hz, 1H), 2.82 (d,  $J = 5$  Hz, 1H), 1.90–1.10 (m, 13H). IR  $\nu$  ( $\text{cm}^{-1}$ ) 3371, 3032, 2922, 2852, 1452, 1263, 736, 797. MS ( $m/z$ ) 203 ( $\text{M}-\text{CH}_2\text{NH}_2^+$ ). Anal  $\text{C}_{19}\text{H}_{29}\text{NO} \cdot \text{C}_4\text{H}_6\text{O}_6 \cdot \text{H}_2\text{O}$  (C, H, N).

**2-Benzyloxy-2-(3,4-dibenzyloxyphenyl)ethylamine 17.** Compound 16 (0.2 g, 0.43 mmol) was reduced over 10% Pt on activated carbon to yield 0.1 g (54%) of 17. NMR (80 MHz,  $\text{CDCl}_3$ ), 7.40–7.25 (m, 15H), 5.15 (s, 4H), 4.42 (d,  $J = 11$  Hz, 1H), 4.17 (d,  $J = 11$  Hz, 1H), 4.10 (dd,  $J_1 = 4$  Hz,  $J_2 = 2$  Hz, 1H), 2.87 (d,  $J = 4$  Hz, 1H), 2.8 (d,  $J = 2$  Hz, 1H), 1.5 (br, s, 2H, exch with  $\text{D}_2\text{O}$ ). IR  $\nu$  ( $\text{cm}^{-1}$ ) 3372, 3031, 2926, 1263, 1179, 1134, 1074, 1026, 737, 697. MS ( $m/z$ ) 439 ( $\text{M}^+$ ). Anal  $\text{C}_{33}\text{H}_{35}\text{NO}_9 \cdot \text{C}_4\text{H}_6\text{O}_6 \cdot 0.5\text{H}_2\text{O}$  (C, H, N).

**2-Cyclohexylmethyloxy-2-(3,4-dibenzyloxyphenyl)ethylamine 19.** Compound 18 (0.5 g, 1.1 mmol) was reduced over 10% Pt on activated carbon to yield 0.15 g (32%) of 19. NMR (80 MHz,  $\text{CDCl}_3$ ), 7.37–7.20 (m, 10H), 6.90–6.75 (m, 3H), 5.15 (s, 2H), 5.10 (s, 2H), 4.07 (dd,  $J = 5$  and 6 Hz, 1H), 3.07 (d,  $J = 2$  Hz, 1H), 3.00 (d,  $J = 2$  Hz, 1H), 2.85–2.70 (m, 2H), 1.70–0.90 (m, 13H). MS ( $m/z$ ) 445 ( $\text{M}^+$ ). IR  $\nu$  ( $\text{cm}^{-1}$ ) 3371, 3032, 2922, 2852, 1452, 1263, 1179, 1134, 1026, 736, 697. Anal  $\text{C}_{33}\text{H}_{41}\text{NO}_9 \cdot \text{C}_4\text{H}_6\text{O}_6$  (C, H, N).

**2-Benzyloxy-2-(3,4-dihydroxyphenyl)ethylamine 20.** To a solution of 17 (0.25 g, 0.57 mmol) in 7.0 ml absolute ethanol was added 80 mg of 5% Pd on activated carbon and the system was hydrogenated at atmospheric pressure for 2.5 h. At that point, 2 ml chloroform was added to the system, the mixture was filtered and the solvents were removed *in vacuo* and the residue was recrystallized from ethanol to yield 0.14 g (95%) of product. NMR (250 MHz,  $\text{CD}_3\text{OD}$ ), 7.30 (m, 5H), 6.87 (s, 1H), 6.83 (d,  $J = 7.5$  Hz, 1H), 6.75 (d,  $J = 7.5$  Hz, 1H), 4.55 (br, d,  $J = 12$  Hz, 1H), 4.48 (d,  $J = 11$  Hz, 1H), 4.32 (d,  $J = 11$  Hz, 1H), 3.30 (dd,  $J_1 = J_2 = 12$  Hz, 1H), 3.15 (br, d,  $J = 12$  Hz, 1H). MS ( $m/z$ ) 229 ( $\text{M}-\text{CH}_2=\text{NH}_2^+$ ). Anal  $\text{C}_{15}\text{H}_{17}\text{NO}_3 \cdot 1.5\text{H}_2\text{O}$  (C, H, N).

2-Cyclohexylmethoxy-2-(3,4-dihydroxyphenyl)ethylamine **21**. To a solution of **19** (0.19 g, 0.43 mmol) in 7 ml absolute ethanol was added 45 mg of 5% Pd on activated carbon and the system was hydrogenated at atmospheric pressure for 2.5 h. At that point, 2 ml chloroform was added to the system, the mixture was filtered and the solvents were removed *in vacuo* and the residue was recrystallized from ethanol to yield 0.11 g (97%) of a green solid. NMR (250 MHz, CD<sub>3</sub>OD), 6.80 (s, 1H), 6.78 (d,  $J = 8.4$  Hz, 1H), 6.69 (d,  $J = 8.4$  Hz, 1H), 4.40 (br, d,  $J = 9.5$  Hz, 1H), 3.15 (m, 2H), 3.05 (dd,  $J_1 = J_2 = 9.5$  Hz, 1H), 3.00 (br, d,  $J = 9.5$  Hz, 1H), 1.70 (m, 4H), 1.30 (m, 5H), 0.95 (m, 2H). MS ( $m/z$ ) 235 (M-CH<sub>2</sub>NH<sub>2</sub><sup>+</sup>). Anal C<sub>15</sub>H<sub>23</sub>NO<sub>3</sub>·0.5H<sub>2</sub>O (C, H, N).

#### Resolution of enantiomers. General method

To a 1.5 M solution of the racemic amine in 80% ethanol/water, was added equimolar amount of (+)-tartaric acid. The precipitated salt was repeatedly recrystallized to a constant melting point. The crystallization solutions were combined, the solvents were removed *in vacuo* and the residue was neutralized with 0.1 N NaOH solution and extracted with ether. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, the solvent was removed *in vacuo* and the residue was treated as above with equimolar amount of (-)-tartaric acid to give the enantiomeric tartrate. Optical rotations were detected on the neutral amines which were recovered from the salts by treatment with 3 N NaOH solution.

Amine **3** was treated as above to give (-)-**3**·(+)-tartrate mp 148–149°C and (+)-**3**·(-)-tartrate mp 150–151°C. Optical rotations:  $[\alpha] = -61.2$  ( $c = 1$ , EtOH) and  $[\alpha] = +63.2$  ( $c = 1$ , EtOH).

Amine **5** was treated as above to give (+)-**5**·(+)-tartrate mp 187°C and (-)-**5**·(-)-tartrate mp 190°C. Optical rotations:  $[\alpha] = +46$  ( $c = 1$ , EtOH) and  $[\alpha] = -62$  ( $c = 0.5$ , EtOH).

Amine **11** was treated as above to give (-)-**11**·(+)-tartrate mp 146°C and (+)-**11**·(-)-tartrate mp 164–165°C. Optical rotations  $[\alpha] = -72.0$  ( $c = 1$ , EtOH) and  $[\alpha] = +80.6$  ( $c = 0.5$ , EtOH).

Amine **15** was treated as above to give (-)-**15**·(+)-tartrate mp 146°C and (+)-**15**·(-)-tartrate mp 146°C. Optical rotations:  $[\alpha] = -41.4$  ( $c = 1$ , EtOH) and  $[\alpha] = +41.2$  ( $c = 0.5$ , EtOH).

#### Pharmacology. Dopamine and $\alpha$ -adrenergic receptor binding assays

Male Sprague–Dawley rats (200–250 g) were sacrificed by decapitation and the striata and cortex removed. Membrane preparations and the [<sup>3</sup>H]spiroperidol, [<sup>3</sup>H]SCH-23390, [<sup>3</sup>H]prazosin and [<sup>3</sup>H]rauwolscine binding assays were performed as described in Kouvarakis *et al* [18]. Specific binding was defined in the presence of (+)butaclamol (1  $\mu$ M) and piflutixol (1  $\mu$ M) for the D<sub>2</sub> and D<sub>1</sub> receptors, respectively, and prazosin (1 nM) and yohimbine (1  $\mu$ M) for the  $\alpha_1$  and  $\alpha_2$  receptors, respectively.

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