Eur J Med Chem (1995) 30, 949–954

Short communication

β-Alkoxy-substituted phenethylamines: a family of compounds potentially active at the dopamine and α-adrenergic receptors

HE Katerinopoulos[1], N Tagmatarchis[1], G Zaponakis[1], N Kefalakis[1], K Kordatos[1], M Spyrakis[1], K Thermos[2]

[1]*Division of Organic Chemistry, Department of Chemistry, University of Crete,*
[2]*Laboratory of Pharmacology, School of Medicine, University of Crete, Iràklion, 71409, Crete, Greece*

(Received 14 May 1995; accepted 20 July 1995)

Summary — A series of β-alkoxy-substituted phenethylamines were synthesized and tested for their affinity at the D_1 and D_2 dopaminergic receptors and the α_1 and α_2 adrenoceptors. None of the tested compounds exhibited D_2 receptor affinity. Among the non-hydroxylated compounds that were resolved to their antipodes, the (−)-enantiomers generally showed a moderate but distinct activity at the α_2 receptor. Ring hydroxylation appears to be a necessary requirement for D_1 activity. These results are discussed in terms of the structural elements of the tested drugs as compared to those of known active compounds.

β-substituted phenethylamine / α-adrenoceptor/ dopamine receptor

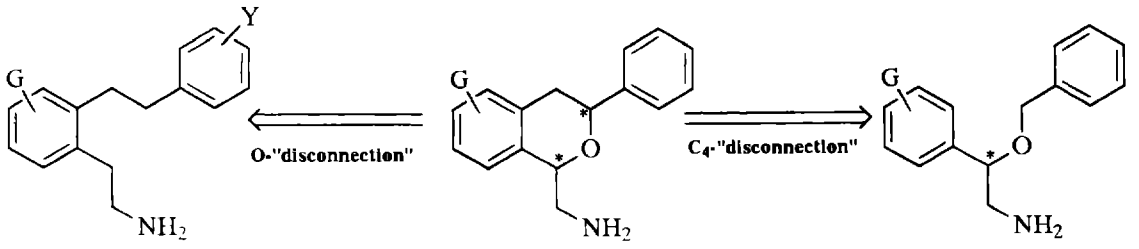
Introduction

Dopamine (DA, **1**) receptors have been divided into two major subtypes, D_1 and D_2, 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_3 [6], D_4 [7] and D_5 [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_1 receptor [14–16]. These 1-aminomethyl, 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_1/D_2 selectivity. The above authors proposed the existence of an auxiliary binding region in the D_1 receptor hosting the C-3 aryl or cyclohexyl substituents.

In this report we describe the synthesis and the pharmacological profile of a number of β-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_1 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_1 receptors, as indicated by its ability to increase the blood flow to the kidney and gut in dogs. Ring-methoxy-substituted or unsubstituted compounds



FPL 65447AA
G= 5, 6 - $(OH)_2$
Y= 3-Me, 4-OH

ABBOTT- 68930
G= 5, 6 - $(OH)_2$

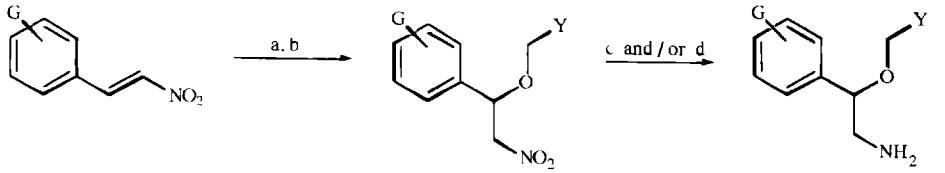
β-SUBSTITUTED PHENETHYL-AMINES

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_1 activity has been detected in non-catecholic phenethylamine analogs [18]. Pharmacological profile studies also included α_1 and α_2 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% paladium on activated carbon, a very smooth, high-yield reaction. However, the synthesis of



2	G = H	Y = Ph	**3**
4	G = H	Y = H	**5**
6	G = H	Y = Me	**7**
8	G = H	Y = Et	**9**
10	G = 3, 4-$(MeO)_2$	Y = Ph	**11**
12	G = 2-MeO	Y = Ph	**13**
14	G = H	Y = C_6H_{11}	**15**
16	G = 3, 4-$(BnO)_2$	Y = Ph	**17**
18	G = 3, 4-$(BnO)_2$	Y= C_6H_{11}	**19**
	G = 3, 4-$(OH)_2$	Y = Ph	**20**
	G = 3, 4-$(OH)_2$	Y= C_6H_{11}	**21**

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_2ONa/ YCH_2OH. b: AcOH. c: 10%Pd/C/H_2. d: PtO_2/H_2.

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_3 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 [^{3}H]spiroperidol (0.50 nM) and [^{3}H]SCH-23390 (0.30 nM) to D_2 and D_1 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_1 and α_2 adrenergic receptor sites in rat cortical membranes. [^{3}H]Prazosin (0.2 nM) and [^{3}H]rauwolscine (1.0 nM) were used to label α_1 and α_2 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_2 adrenoceptor was shown by (–)-**3**, (–)-**5** and

Table I. Inhibition of [^{3}H]spiroperidol, [^{3}H]SCHE-23390, [^{3}H]prazosin and [^{3}H]rauwolscine binding to rat striatal membranes and rat cortical membranes[a].

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

[a]Experiments were performed 3 times in duplicate. Values from [b]reference 12, [c]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 μM as compared with a 0.75 μM value for norepinephrine. Compound **13**, the *ortho*-substituted analog, exhibited an affinity (IC_{50} = 1.2 μM) at the α_1 adrenoceptor which is comparable to that of norepinephrine (IC_{50} = 1.5 μM). 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 α_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 α_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 α_2 activity whereas the *ortho*-methoxy is tolerated only by the α_1 binding site.

Analogs **20** and **21** exhibited affinity to the D_1 receptor (IC_{50} = 2.0 and 1.4 μM, respectively) weaker to that of (–)-apomorphine (IC_{50} = 0.22 μM). 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 ±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 benzoxide 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 benzoxide 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 = 10 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-Methoxy nitrostyrene (1.5 g, 8.4 mmol) reacted with sodium benzoxide 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, $CDCl_3$), 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 ν (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 benzoxide as described above to give 2.2 g (68%) of the product as a thick yellow liquid. NMR (80 MHz, $CDCl_3$), 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 ν (cm^{-1}) 3033, 2927, 1555, 1381, 1268, 1137, 1023, 735, 697. MS (*m/z*) 469 (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, $CDCl_3$); 7.80–7.35 (m, 10H), 7.10–6.95 (m, 31), 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 ν (cm^{-1}) 3032, 2925, 2852, 1557, 1450, 1380, 1261, 1162, 1026, 735, 697. MS (*m/z*) 475 (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 PtO_2 (or 10 Pt/C), 0.2 equiv and the system was hydrogenated at 1 atm 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 Na_2SO_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, $CDCl_3$), 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 (M^+). Anal $C_{15}H_{17}NO{\cdot}0.5C_4H_6O_6{\cdot}H_2O$ (C, H, N).

2-Methoxy-2-phenylethylamine ***5*** Compound **4** (0.7 g, 3.8 mmol) was reduced over PtO_2 as described above to yield 240 mg (42%) of **5**. NMR (250 MHz, $CDCl_3$), 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 (M^+). Anal $C_9H_{13}NO{\cdot}C_4H_6O_6{\cdot}0.5H_2O$ (C, H, N).

2-Ethoxy-2-phenylethylamine ***7***. Compound **6** (110 mg, 0.6 mmol) was reduced over PtO_2 to yield 30 mg (30.5%) of **7** MS (*m/z*) 165 (M^+). Oxalate salt mp 176.5°C. NMR of oxalate salt (80 MHz, D_2O), 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 PtO_2 to yield 100 mg (23.3%) of **9**. NMR (80 MHz, $CDCl_3$), 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 D_2O), 0.85 (t, J = 6 Hz, 3H). MS (*m/z*) 179 (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, C_6D_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 $(M\text{-}CH_2{=}NH_2)^+$. Anal $C_{17}H_{21}NO_3{\cdot}C_4H_6O_6$ C) (calc 57.66, found 58.12), 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, C_6D_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 $(M\text{-}CH_2{=}NH_2)^+$. Tartrate salt mp 155°C. Anal $C_{16}H_{19}NO_2{\cdot}C_4H_6O_6$ (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, $CDCl_3$), 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 ν (cm^{-1}) 3371, 3032, 2922, 2852, 1452, 1263, 736, 797. MS (*m/z*) 203 $(M\text{-}CH_2NH_2)^+$. Anal $C_{19}H_{29}NO{\cdot}C_4H_6O_6{\cdot}H_2O$ (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, $CDCl_3$), 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 D_2O). IR ν (cm^{-1}) 3372, 3031, 2926, 1263, 1179, 1134, 1074, 1026, 737, 697. MS (*m/z*) 439 (M^+). Anal $C_{33}H_{35}NO_9{\cdot}C_4H_6O_6{\cdot}0.5H_2O$ (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, $CDCl_3$), 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 (M^+). IR ν (cm^{-1}) 3371, 3032, 2922, 2852, 1452, 1263, 1179, 1134, 1026, 736, 697. Anal $C_{33}H_{41}NO_9{\cdot}C_4H_6O_6$ (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, CD_3OD), 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 $(M\text{-}CH_2{=}NH_2^+)$. Anal $C_{15}H_{17}NO_3{\cdot}1.5H_2O$ (C (calc 62.92, found 63.37) H, N).

2-Cyclohexylmethyloxy-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_3OD), 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-$CH_2NH_2^+$). Anal $C_{15}H_{23}NO_3 \cdot 0.5H_2O$ (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_2SO_4, 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: [α] = −61.2 (c = 1, EtOH) and [α] = +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: [α] = +46 (c = 1, EtOH) and [α] = −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 [α] = −72.0 (c = 1, EtOH) and [α] = +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: [α] = −41.4 (c = 1, EtOH) and [α] = +41.2 (c = 0.5, EtOH).

Pharmacology Dopamine and α-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 [^{3}H]spiroperidol, [^{3}H]SCH-23390, [^{3}H]-prazosin and [^{3}H]rauwolscine binding assays were performed as described in Kouvarakis *et al* [18]. Specific binding was defined in the presence of (+)butaclamol (1 μM) and piflutixol (1 μM) for the D_2 and D_1 receptors, respectively, and prazosin (1 nM) and yohimbine (1 μM) for the α_1 and α_2 receptors, respectively.

Acknowledgments

We would like to express our gratitude to the Laboratory of Organic Chemistry of the University of Salonika for the elemental analyses, the Institute of Physical Chemistry of the National Centre for Scientific Research 'Democritos' for the high resolution NMR spectra, and M Papadokostaki and M Traka for their excellent technical assistance. The contribution of S DiDomenico Jr at the Abbott Laboratories, IL, USA is gratefully acknowledged. This work was partly supported by grants from the Special Committee for Research, University of Crete, the Greek Ministry of Industry and Research (91ED881), and the Ministry of Health (KESY #223).

References

1 Kebabian JW, Calne DB (1979) *Nature (Lond)* 277, 93–96
2 Dearry A, Gingrich JA, Falardau P, Fremeau RT Jr, Bates MD, Caron MG (1990) *Nature (Lond)* 347, 72–76
3 Zhou QY, Grandy DK, Thambi L *et al* (1990) *Nature (Lond)* 347, 76–80
4 Sunahara RK, Niznic HB, Weiner DM *et al* (1990) *Nature (Lond)* 347, 80–83
5 Bunzow JR, Van Tol HM, Grandy DK *et al* (1988) *Nature (Lond)* 336, 783–787
6 Sokoloff P, Giros B, Martres MP, Bouthenet ML, Schwartz JC (1990) *Nature (Lond)* 347, 146–151
7 Van Tol HM, Bunzow JR, Guan HC *et al* (1991) *Nature (Lond)* 350, 610–619
8 Sunahara RK, Guan HC, O'Dowd BF *et al* (1991) *Nature (Lond)* 350, 614–619
9 Seeman P (1980) *Pharmacol Rev* 32, 229–313
10 Kaiser C, Jain T (1985) *Med Res Rev* 5, 145
11 Seeman P, Watanabe M, Grigoriades D *et al* (1985) *Mol Pharmacol* 28, 391–399
12 Katerinopoulos HE, Schuster DI (1986) *Drugs Future* 12, 223–253
13 Cannon JG (1983) *Ann Rev Pharmacol Toxicol* 23, 103–130
14 DeNinno MP, Schoenleber R, Asin KE, MacKenzie R, Kebabian JW (1990) *J Med Chem* 33, 2950–2952
15 DeNinno MP, Schoenleber R, Perner RJ *et al* (1991) *J Med Chem* 34, 2561–2569
16 Michaelides MR, Schoenleber R, Thomas S *et al* (1991) *J Med Chem* 34, 2946–2953
17 Smith GW, Christie MI, Ince F *et al* (1992) 4th International Conference in Peripheral Dopamine, Oporto, Portugal
18 Kouvarakis A, Thermos K, Hieble JP, Katerinopoulos HE (1993) *Eur J Med Chem* 28, 251–257
19 Howe R, Young EHP, Ainley AD (1969) *J Med Chem* 12, 998–1001
20 Katerinopoulos HK, Thermos K, Vassilatis D, Schuster DI (1988) *Eur J Med Chem* 23, 391–396
21 Billard W, Ruperto V, Crosby G, Iorio LC, Barnett A (1984) *Life Sci* 35, 1885–1893
22 Bylund DB (1987) *In The Alpha-1 Adrenergic Receptors* (Ruffolo R Jr, ed), Humana Press, Clifton, NJ, USA, 19–96
23 U'Prichard DC (1984) *Ann NY Acad Sc* 430, 55–75