Eur J Med Chem (1993) 28, 251–257

Short communication

Syntheses of oxygen bridged, rigid catecholamine analogues. Effects on adrenergic and dopaminergic systems

A Kouvarakis[1], K Thermos[2], JP Hieble[3], HE Katerinopoulos[1]*

[1]*Department of Chemistry, School of Sciences, University of Crete, Iraklion, 71110 Crete;*
[2]*Laboratory of Pharmacology, School of Medicine, University of Crete, Iraklion, 71110 Crete, Greece;*
[3]*Department of Pharmacology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA 19406, USA*

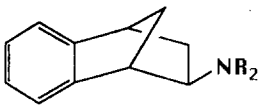
(Received 20 January 1992; accepted 19 October 1992)

Summary — A series of 2-amino-1,2,3,4-tetrahydro-1,4-epoxynaphthalenes were synthesized and tested for affinity for dopaminergic and α-adrenergic receptor subtypes *via* radioligand binding assays. The unsubstituted analogue **2a** showed weak affinity for both D_1 and α_2-adrenoceptors. This compound exhibited subtype selectivity in both dopaminergic and α adrenergic systems. Analogue **5** showed affinity only for the D_1-receptor. Most other analogues showed no affinity for either receptor at concentrations up to 10 μM. Functional studies showed compound **2a** to be an α-adrenoceptor antagonist, and confirmed its α_2-adrenoceptor selectivity predicted by the radioligand binding assay.

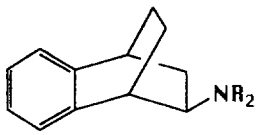
2-amino-1,2,3,4-tetrahydro-1,4-epoxynaphthalenes / α-adrenoceptors / dopamine receptors

Introduction

In recent years numerous studies to determine the structural characteristics of the catecholamine receptor sites have been reported in the literature. A number of these studies involved the synthesis of a series of 2-benzonorbornylamine **1a** and 2-aminobenzobicyclo [2.2.2] octane-type **1b** analogues. In these structures the catecholamine moiety is incorporated in the molecules in a strictly defined conformation. Upon testing for dopaminergic [1–4] and/or adrenergic [5–8] agonist action they exhibited either very low or no activity.

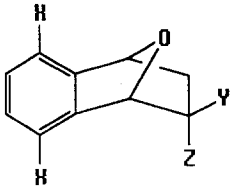


1 a

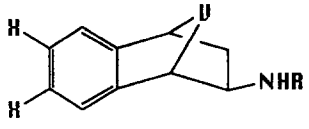


1 b

Schuster *et al* [1] have suggested that the introduction of a hydrophilic group (such as oxygen or nitrogen) replacing the lipophilic carbon bridge in these systems could increase the activity of the compounds due to favorable interactions with the receptor site. Such series of compounds, namely the 2-amino-1,4-epoxy-tetrahydronaphthalene analogues **2a–b** and **3a–b** were synthesized later by Smith *et al* [8], and evaluated for their adrenergic activity. Among the tested compounds only the *exo* analogues were active at the α_1- and α_2-receptors, although less potent than the respective known agonists methoxamine and guanabenz.



2a: X=H, Y=NH_2, Z=H
3a: X=H, Y=H, Z=NH_2
2b: X=OMe, Y=NH_2, Z=H
3b: X=OMe, Y=H, Z=NH_2



4: X=H, R=Pr, V=O
5: X=OMe, R=H, V=O
6: X=OBn, R=H, V=O
7: X=OTBDMS, R=H, V=O
8: X=OH, R=H, V=O
18: X=H, R=H, V=CH_2
19: X=H, R=Pr, V=CH_2
20: X=OMe, R=H, V=CH_2

*Correspondence and reprints

This reduction in potency was attributed to the steric bulk of the oxygen bridge preventing interaction of the drug with the receptor or preventing a conformational change in the ligand necessary for physiological activity. The inability of the oxygen to bind with the receptor site was also considered as a factor contributing to the reduction of activity. In this paper we describe the synthesis of a series of 6,7-substituted analogues of 2-amino-1,2,3,4-tetrahydro-1,4-epoxynaphthalenes and their pharmacological evaluation as D_1/D_2-dopaminergic and α_1/α_2-adrenergic ligands.

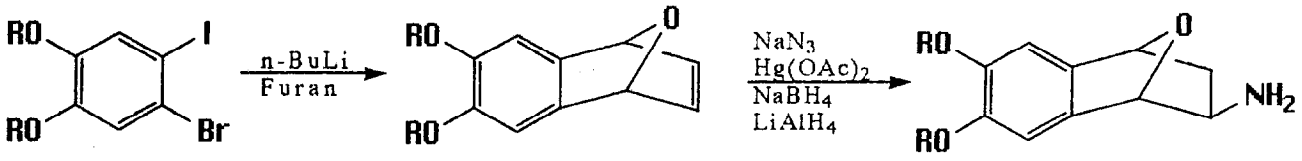
Chemistry

The *exo* 2-*N*-*n*-propylamino-1,4-epoxy-1,2,3,4-tetrahydronaphthalene **4** was derived from **2a**. This compound was synthesised by the method followed by Smith *et al* [8] with minor modifications. The key step for the synthesis of the dimethoxy analogue **5** (scheme 1) was the Diels–Alder reaction of the benzyne (generated from the reaction of 4-bromo-5-iodoveratrole **9** with *n*-BuLi) with furan in THF according to Harisson *et al* [9]. Treatment of **10** with mercuric azide and $NaBH_4$, and subsequent reduction of the resulting azide with $LiAlH_4$ furnished the desired *exo*-amine **5**. The dibenzyloxy congener was prepared by benzylation of catechol ($C_6H_5CH_2Cl$, NaH, DMF); and treatment of the diether with iodine–silver trifluoroacetate furnished the iodinated compound [10], which was brominated in DMF using catalytic amounts of iron to yield **11**. Diels–Alder reaction of the corresponding benzyne with furan and subsequent amination gave **6**. The synthesis of the dihydroxy analogue **8** involved the protection of catechol as bis-*t*-butyldimethylsilyl ether **13** (scheme 2), iodination with iodine–silver trifluoroacetate, and subsequent bromination of **14** using bromine–thallic acetate, the only bromination system that gave a satisfactory yield of **15**. Subsequent Diels–Alder reaction of **15** with *n*-BuLi and furan in ether gave **16** which was treated with mercuric azide and $NaBH_4$ to give **17**. Azide **17** was reduced with $LiAlH_4$ to give amine **7** in 15% overall yield from catechol. Catechol deprotection under mild conditions (KF, 18-C-6, DMF, RT, 48 h), furnished the final product **8**.

Pharmacology

The pharmacological behavior of compounds **2a**, **4–8**, (±) 2-amino-6,7-dihydroxytetralin (ADTN), and R–(–) apomorphine (R–(–)–APO) at the D_2-receptor, was examined by studying the ability of these agents to inhibit specific binding of [^{3}H]-spiroperidol (0.50 nM) to rat striatal membranes. Specific binding was defined as the total [^{3}H]-spiroperidol bound minus the binding remaining in the presence of 1 μM (+)-butaclamol. Binding at the D_1-receptor was examined by studying the ability of these agents to inhibit specific binding of [^{3}H]-SCH-23390 (0.30 nM) to rat striatal membranes. Specific binding was defined as the total [^{3}H]-SCH-23390 bound minus the binding remaining in the presence of either 1 μM piflutixol or 100 nm SCH-23390. Binding studies were performed as described earlier [3, 11]. The drug concentrations ranged from 0.001–100 μM. The same compounds were tested for their ability to label specific α_1- and α_2-adrenergic receptor sites. Labeling of the α_1-receptors was performed in cortical membranes using the radioligand [^{3}H]-prazosin (0.2 nM). Phentolamine (2 μM) or prazosin (100 nM) was used to define specific binding [12]. Labeling of the α_2-adrenergic receptors was performed in cortical membranes [13] using the radioligand [^{3}H]-rauwolscine (1 nM). Yohimbine (1 μM) was used to define specific binding.

Functional assays were also performed to determine putative agonist or antagonist activity of compound **2a**. Isolated superfused guinea-pig atrium and dog saphenous vein preparations were used to assess α_2-pre- and post-junctional activity, while rabbit aorta preparations were used to assess α_1-activity [14].

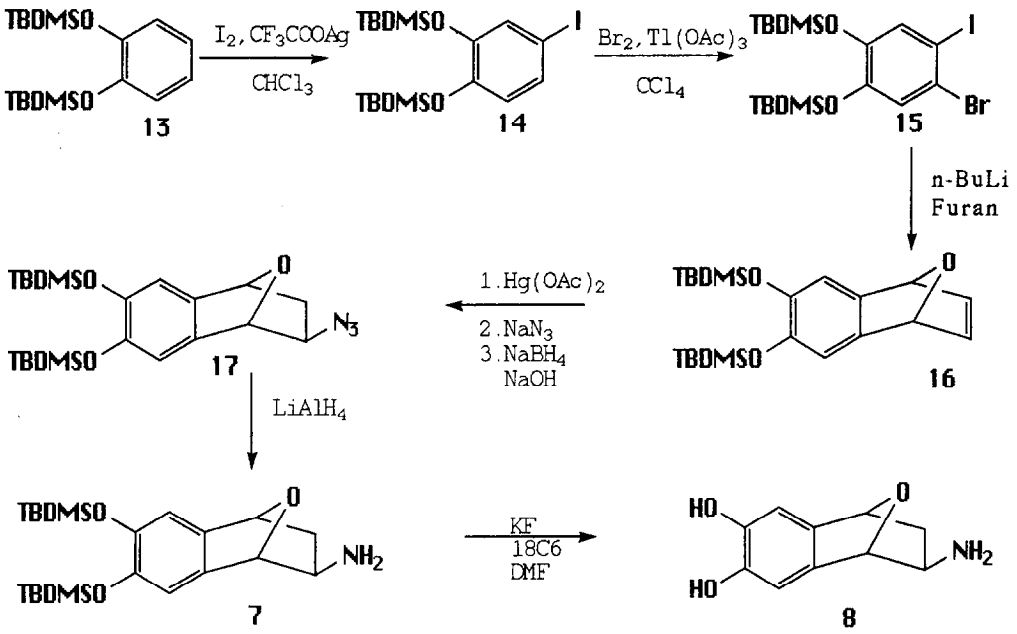


9, R= Me-
11, R=$PhCH_2$-

10, R= Me-
12, R= $PhCH_2$-

5, R=Me-
6, R=$PhCH_2$-

Scheme 1. Synthesis of dopamine analogues **5** and **6**.



Scheme 2. Synthesis of dopamine analogues **7** and **8**.

Results

Radioligand binding studies indicated that none of the compounds at concentrations up to 10 μM could displace the specific binding of [^{3}H]-spiroperidol to rat striatal membranes (table I). In contrast, compounds **2a** and **5** showed weak but measurable affinity against [^{3}H]-SCH-23390 binding to the D_1-sites in this tissue, with IC_{50} values of 5.6 and 6.0 μM, respectively. In the α-adrenergic binding assay, only compounds **2a** and **4** showed measurable affinity. Compound **2a** had a 10-fold higher affinity (IC_{50} = 0.875 μM) for α_2-adrenoceptor ([^{3}H]-rauwolscine) *vs* α_1-adrenoceptor (IC_{50} = 9 μM; [^{3}H]-prazosin) sites. In contrast, its *N-n*-propyl analogue (compound **4**) did not differentiate between the α-adrenoceptor subtypes.

Compound **2a** was tested in functional *in vitro* models for efficacy, affinity and selectivity for the α-adrenoceptor subtypes. No agonist activity at either pre- or post-junctional α_2-adrenoceptors was observed at concentrations up to 30 and 300 μM respectively, using the superfused guinea-pig atrium as a model for the prejunctional α_2-adrenoceptor, and the ring segment of canine saphenous vein to assess activity at the post-junctional α_2-adrenoceptor. However, the α_2-adrenoceptor affinity predicted for this compound by the radioligand binding assay was confirmed, since competitive blockade of the response to B-HT 920 was observed in both models. Receptor dissociation

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

Drug	*IC_{50} (μM)*	
	[^{3}H]-Spiroperidol	*[^{3}H]-SCHE-23390*
2a	NA[b]	5.6 ± 0.5
4	NA	NA
5	NA	6.0 ± 1.0
6	NA	NA
7	NA	NA
8	NA	NA
18	NA	NA
19	NA	NA
20	NA	NA
(±)-ADTN	0.70 ± 0.02	–
(–)-APO	0.22 ± 0.05	0.43 ± 0.05

[a]Values represent mean ± SD. Experiments were performed 3 times in duplicate. [b]Not active up to a concentration of 10 μM.

constants (K_B) were calculated to be 2.6 μM in the atrium (fig 1) and 12.2 μM in the saphenous vein (fig 2).

In the ring segment of the rabbit aorta, an α_1-adrenoceptor model, a slight vasoconstrictor effect (< 10% of norepinephrine maximum) was produced by compound **2a** at a concentration of 100 μM. However, this concentration did not shift the norepinephrine concentration–response curve (fig 3), suggesting that the compound has no functional affinity for the α_1-adrenoceptors.

Discussion

Although firm conclusions cannot be drawn from these SAR data we can at least indicate that the selective activity of **2a** and **5** at the D_1-receptor unveils a new element of this receptor topology. The inactivity of the corresponding carbon bridged compounds [1–4] at the D_2-receptor was attributed to an unfavorable steric interaction of the bridge with an 'obstacle' at the receptor site. It is tempting to propose that at the D_1-receptor such an obstacle does not exist, or in contrast to the D_2, is of hydrophilic nature and interacts favorably with the oxygen bridge. To further evaluate the validity of this hypothesis the carbon bridged analogues of **2a**, **4** and **5**, namely *exo* 2-aminobenzonorbornene **18**, *exo* 2-*N*-*n*-propylaminobenzonorbornene **19** and *exo* 2-amino-6,7-dimethoxybenzonorbornene **20** were tested for D_1 and D_2 activity. The complete lack of activity of the above compounds indicates that the region of the D_1-receptor interacting with the bridge element is more likely of hydrophilic than of lipophilic nature. *N*-*n*-Propyl substitution in **4** diminished activity; **6** and **7** were also totally inactive as expected, given the bulk of the protective groups. The total inactivity of the dihydroxy analogue **8** was surprising. However,

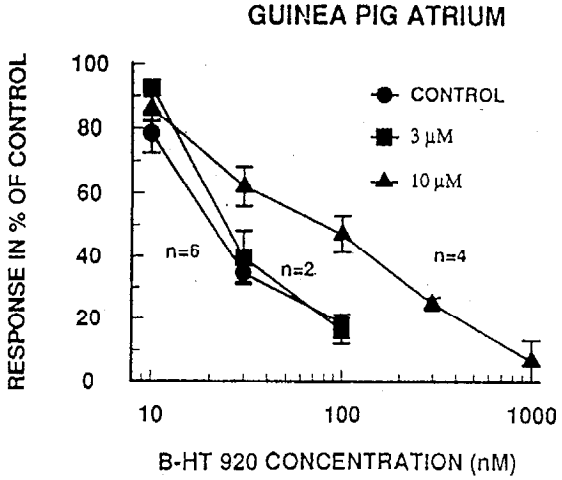


Fig. 1. Blockade of the response to B-HT 920 by compound **2a** in the guinea-pig atrium. The *n* values on the graphs refer to the number of tissue segments examined. Each tissue was obtained from a separate animal. Each point represents the mean experimental value ± SEM (± SD for n = 2). The receptor dissociation constant (K_B) was calculated to be 2.6 μM.

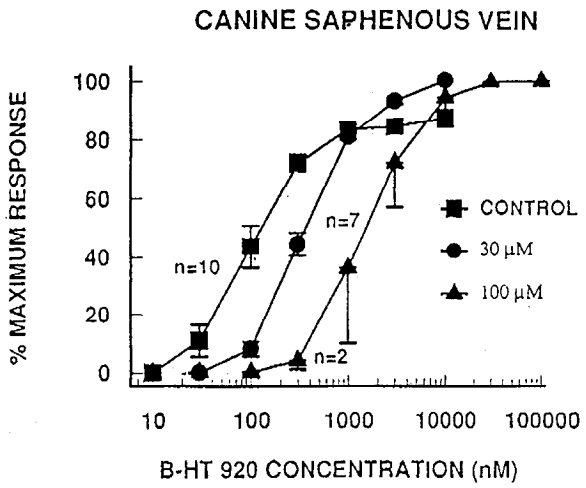


Fig 2. Blockade of the response to B-HT 920 by compound **2a** in the canine saphenous vein. Multiple tissue segments were obtained from each dog, but the compound was tested in tissues from 3 different dogs. Each point represents the mean experimental value ± SEM (± SD for n = 2). The receptor dissociation constant (K_B) was calculated to be 12.2 μM.

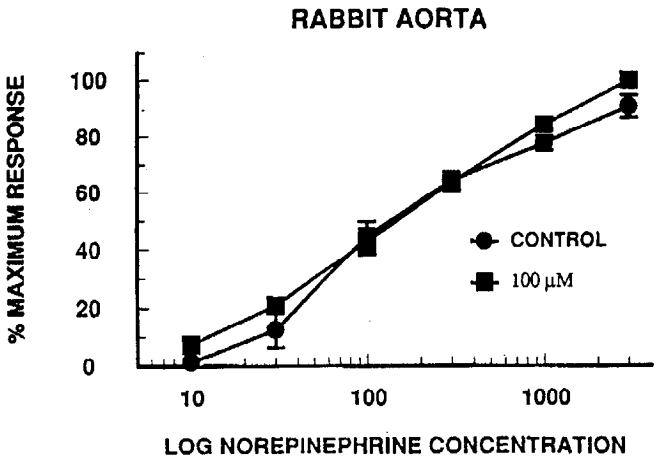


Fig 3. Blockade of norepinephrine-induced contraction in ring segments of the rabbit aorta by compound **2a**. Compound **1a** at the high concentration of 100 μM had no effect on norepinephrine response.

Table II. Inhibition of [^{3}H]-prazosin and [^{3}H]-rauwolscine binding to rat cortical membranes.

	IC_{50} (μM)	
Drug	*[^{3}H]-Prazosin*	*[^{3}H]-Rauwolscine*
2a	9	0.875
4	4	6.900
5	> 10	> 10
6	> 10	> 10
8	> 10	> 10
18	> 10	0.060
19	4	0.255
20	> 10	> 10
Noradrenaline	1.5[a]	0.750[b]

Values from [a][12]; [b][13].

substitution of the aromatic ring with strong electron donors is known to increase the instability of these systems [15]. Monitoring the stability of **8** under assay conditions showed a rapid decomposition of the ligand as indicated by a sharp decrease in its absorbance spectrum at its λ_{max} = 275 nm in contrast to the reported tolerance of its carbon analogue [1].

The epoxynaphthalene system appears to also be compatible with affinity for adrenergic receptors. It has been proposed [16] that in conformationally defined systems, rigidity may compensate for the lack of the β-hydroxyl by fixing the side chain in a conformation similar to that assumed by the β-hydroxyphenethylamines upon binding to the receptor. The radioligand binding studies show both the oxygen **2a** and carbon bridged **18** compounds to have selective affinity for α_2 *versus* α_1-adrenoceptors. This suggests, as proposed by Smith *et al* [8], that the α_2-adrenoceptor may more easily accomodate the additional structural elements of the bridged aminotetraline analogues. Interestingly, *n*-propyl substitution of the nitrogen atom reduces the α-adrenoceptor subtype selectivity of both compound **2a** and **18**, by reducing the affinity for the α_2-adrenoceptor and also increasing the α_1-adrenoceptor affinity.

The results from the *in vitro* functional assays are in agreement with the binding data, since **2a** acts as a weak antagonist of the action of B-HT 920 at both pre- and post-junctional α_2-adrenoceptors, but does not influence the α_1-adrenoceptor-mediated action of norepinephrine. The slight vasocontrictor action of compound **2a** in the rabbit aorta cannot be due to activation of the α_1-adrenoceptor, since if it were indeed a partial agonist at this receptor, receptor theory would require blockade of the response to norepinephrine. In conclusion, the oxygen bridge-induced rigidity of this ring system, although reducing absolute potency, increases its selectivity for both D_1-receptors and α_2-adrenoceptors.

Experimental protocols

Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. IR spectra were taken on a Perkin–Elmer Model 735 spectrophotometer. NMR spectra were taken on a Varian FT-80A, 80 MHz spectrometer; proton chemical shifts are reported in ppm relative to tetramethylsilane. The NMR spectra of the final amines were recorded on the free bases. Mass spectra were taken on a DuPont 21-492 double focussing mass spectrometer. Elemental analysis were taken by the analytical laboratory of the Chemistry Department of University of Salonica, Greece and are within 0.4% of the theoretical values of the indicated elements unless otherwise stated. All tested compounds, except **8** which was used as the free base, were in the form of oxalate salts, recrystallized from ethanol–water.

exo-2-Amino-1,4-epoxy-1,2,3,4-tetrahydronaphthalene ***2a***
Compound **2a** was synthesized in 33% yield as described by Smith [8] and isolated as the oxalate salt in analytically pure form. Spectral data and mp of the product were identical to those in the literature.

exo-2-N-n-Propylamino-1,4-epoxy-1,2,3,4-tetrahydronaphthalene ***4***
A mixture of **2a** (1.08 g, 6.71 mmol), *n*-propyl iodide (1.26 g, 7.38 mmol), Na_2HPO_4 (4.76 g, 33.54 mmol), and 50 ml acetonitrile were stirred at room temperature for 17 h. The solvent was removed *in vacuo*, the residue added to 50 ml CH_2Cl_2, the precipitate formed filtered, and the filtrate washed with water and brine. Removal of solvent furnished the crude product which was purified by flash chromatography (silica, 2% MeOH/CH_2Cl_2) to give 290 mg of product and 170 mg of unreacted amine (84% conversion, 27% yield). The product was isolated as its oxalate salt, mp: 210–213°C. IR ν (cm^{-1}) 3367, 1068, ^{1}H-NMR (acetone-d_6), δ: 7.12 (s, 4H), 5.26 (d, J = 4 Hz, 1H), 5.14 (s, 1H), 2.8–2.5 (m, 4H), 1.75–1.30 (m, 4H), 0.85 (t, J = 0.4 Hz, 3H). MS *m/z* 203 (M^+). Anal calcd for ($C_{13}H_{17}NO{\cdot}0.5C_2H_2O_4{\cdot}0.5\ H_2O$); C: 65.35, H: 7.44, N: 5.44. Found: C: 65.24, H: 7.08, N: 5.52.

exo-2-Amino-1,4-epoxy-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene ***5***
This compound was prepared (following the same method as in **2a**) from **10** to yield the amine (40%), a thick liquid [17], which was isolated as the oxalate salt, mp: 226–227°C. IR 3225, 3200, 1600, 1260, 1100 cm^{-1}; NMR ($CDCl_3$), δ: 7.13 (s, 1H), 7.08 (s, 1H), 5.27 (d, J = 5 Hz, 1H), 4.83 (s, 1H), 3.83 (s, 6H), 2.13–1.10 (m, 5H); MS *m/e* 221 (M^+). Anal calcd for ($C_{12}H_{15}NO_3{\cdot}C_2H_2O_4$); C: 60.21, H: 6.13, N: 5.02. Found: C: 60.01, H: 5.81, N: 5.26.

1,2-Bisbenzyloxy-4-bromo-5-iodobenzene ***11***
To a solution of 1,2-bisbenzyloxy-4-iodobenzene [10] (2.41 g, 5.79 mmol) in 30 ml DMF was added traces of Fe powder and then a solution of bromine (0.84 ml, 8.7 mmol) in 5 ml 1,2-dichloroethane was added dropwise under vigorous stirring. The mixture was further stirred for 1.5 h, then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, water and brine, the organic layer dried over $MgSO_4$, the solvents removed *in vacuo*, and the crude product recrystallized from ethyl acetate to yield 2.8 g (98%) white crystals, mp: 134–137°C. IR ν (cm^{-1}) 1575, 1190, 750, 700; ^{1}H-NMR (DMSO-d_6), 7.3 (br, s, 10H), 7.2 (s, 1H), 7.1 (s, 1H), 5.05 (br, s, 4H); MS *m/z* 494, 496 (M^+, M = 2^+).

6,7-Bisbenzyloxy-1,4-epoxy-1,4-dihydronaphthalene ***12***
To a solution of **11** (980 mg, 1.97 mmol) in 25 ml THF was added 25 ml furan and the solution was cooled to –78°C. A 1.6-M solution of *n*-BuLi in hexanes (1.02 ml, 2.0 mmol), was added dropwise and the system was stirred at –78°C for 1 h. The solution was then poured onto 45 g dry ice, diluted with ether, and washed with water and brine. Flash chromatography (silica, 15% ether/toluene) furnished 0.41 g (59%) of the product, mp: 98–100°C. IR ν (cm^{-1}) 1600, 1050, 730, 690; ^{1}H-NMR ($CDCl_3$) δ: 7.25 (br, s, 10H), 6.9 (s, 4H), 5.55 (s, 2H), 5.03 (s, 4H); MS *m/z* 356 (M^+).

exo 2-Amino-6,7-bisbenzyloxy-1,4-epoxy-1,2,3,4-tetrahydronaphthalene ***6***
Compound **6** was prepared in 45% yield from **11** by the method followed for **2a**. The liquid product was precipitated from ether as the oxalate salt, mp: 192–195°C. IR ν (cm^{-1}) 3350, 3270, 1325, 1060, 725, 690; ^{1}NMR ($CDCl_3$) δ: 7.3 (br, s, 10H), 6.83 (s, 1H), 6.77 (s, 1H), 5.20 (d, J = 4 Hz, 1H), 5.03 (s, 4H), 4.76 (s, 1H), 3.30–2.70 (m, 1H), 2.10–1.00 (m, 4H); MS *m/z* 373 (M^+). Anal calcd for ($C_{24}H_{23}NO_3 \cdot C_2H_2O_4 \cdot 0.5\ H_2O$); C: 66.09, H: 5.55, N: 2.96. Found: C: 66.2, H: 5.7, N: 3.28.

1,2-Bis(t-butyldimethylsilyloxy)-4-iodobenzene ***14***
Silver trifluoroacetate (7.52 g, 34.05 mmol), was added to a solution of 1,2-bis(*t*-butyldimethylsilyloxy)benzene (11.51 g, 34.05 mmol), in 20 ml of dry $CHCl_3$. To this mixture was added dropwise and under vigorous stirring, a solution of iodine (8.65 g, 34.05 mmol), in 20 ml dry $CHCl_3$. The solution turned red and TLC (silica, hexane) indicated presence of the product R_f = 0.4. The solution was washed with 30 ml 5% $Na_2S_2O_5$ solution, 3 x 50 ml H_2O, and 3 x 50 ml brine. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. Flash chromatography (silica, hexane) of the crude material gave 15.62 g (99%) of a thick liquid. IR ν (cm^{-1}) 2920, 1340, 920, 690; ^{1}H-NMR ($CDCl_3$) δ: 7.10 (d, J = 0.5 Hz, 1H), 7.00 (d, J = 8 Hz, 1H), 6.45 (dd, J = 8 and 0.5 Hz, 1H), 0.96 (s, 18H), 0.18 (s, 12H).

1,2-Bis(t-butyldimethylsilyloxy)-4-bromo-5-iodobenzene ***15***
In a 500-ml round-bottomed flask was placed a solution of **14** (7.19 g, 15.4 mmol) in 20 ml dry CCl_4 and thallic acetate [18, 19] (19.0 g, 46.4 mmol). To this suspension was added dropwise a solution of bromine (2.64 g, 15.4 mmol), in 10 ml dry CCl_4. After the addition was completed the system was washed with 5% $NaHSO_3$ solution, saturated $NaHCO_3$ solution, H_2O and brine, the organic layer was dried over $MgSO_4$ and the solvent was removed to give 5.1 g (61%) of a clear liquid. IR ν (cm^{-1}) 1490, 1266, 840. ^{1}H-NMR ($CDCl_3$) δ: 7.00 (s, 2H), 5.55 (s, 2H), 0.96 (s, 18H), 0.18 (s, 12H).

6,7-Bis(t-butyldimethylsilyloxy)-1,4-epoxy-1,4-dihydronaphthalene ***16***
To a solution of **15** (3.0 g, 5.5 mmol), in 25 ml dry ether were added 30 ml furan and the system was cooled to –78°C. A 1.6 M solution of *n*-butyl lithium in hexanes (3.5 ml, 5.5 mmol), was added dropwise and the system was allowed to reach room temperature overnight. The mixture was then poured over 40 g of dry ice, 20 ml of water were added, and the organic layer was separated and washed with brine, dried over $MgSO_4$ and the solvent was removed to yield the crude product which was purified by flash chromatography (silica, 5% ether/petroleum ether). The product yield was 1.73 g (77%). IR ν (cm^{-1}) 1420, 1266. ^{1}H-NMR ($CDCl_3$) δ: 6.8 (s, 2H), 6.7 (s, 2H), 0.96 (s, 18H), 0.18 (s, 12H). MS *m/z* 404 (M^+).

exo 2-Amino-6,7-Bis(t-butyldimethylsilyloxy)-1,4-epoxy-1,2,3,4-tetrahydronaphthalene 7
This compound was prepared from **16** as described by Smith [8] in 32% yield and was isolated as the oxalate salt, mp: 154–157°C (d). IR ν (cm^{-1}) 3400, 1580, 1340, 795; ^{1}H-NMR ($CDCl_3$) δ: 6.7 (s, 1H), 6.65 (s, 1H), 5.25 (d, J = 4 Hz, 1H), 4.8 (s, 1H), 2.4 (m, 2H), 1.9–1.5 (m, 3H), 0.96 (s, 18H), 0.18 (s, 12H). MS *m/z* 378 (M^+-[CH_2 = CH-NH_2]). Anal calcd for ($C_{22}H_{39}NO_3Si_2 \cdot C_2H_2O_4 \cdot 0.5\ H_2O$); C: 55.35, H: 8.13, N: 2.69. Found: C: 55.03, H: 7.8, N: 2.69.

exo 2-Amino-6,7-dihydroxy-1,4-epoxy-1,2,3,4-tetrahydronaphthalene ***8***
In a 25-ml round-bottomed flask were placed **7** (30 mg, 0.07 mmol), 2 ml dry DMF, solid KF (7.9 ml, 0.135 mmol), and a trace of 18-crown-6. The system was stirred at room temperature for 48 h. The solvent was then removed at high vacuum at room temperature and the residue treated with small amounts of water and CH_2Cl_2 to quantitatively yield the desired product. IR ν (cm^{-1}) 3367, 1068. ^{1}H-NMR (DMSO–d_6) δ: 7.75 (s, 2H), 6.75 (s, 1H), 6.65 (s, 1H), 5.07 (d, J = 4 Hz, 1H), 4.65 (s, 1H), 3.4 (m, 1H), 2.90–2.75 (m, 2H), 2.75–2.60 (m, 2H). MS *m/z* 193 (M^+), 150 (M^+-[CH_2 = CH-NH_2]). Anal calcd for $C_{10}H_{11}NO_3 \cdot H_2O$ + 3 ($KF \cdot H_2O$); C: 27.33, H: 4.58, N: 3.19. Found: C: 27.08, H: 4.58, N: 2.52. Since the elemental analysis indicated the presence of inorganic components in the product, a sample was reacted with bis(trimethylsilyl) trifluoroacetamide and a GC–MS spectrum was taken to give as the only product the bis(trimethylsilyl)-derivative of **8**.

Synthesis of carbon bridged compounds
exo 2-Aminobenzonorbornene **18** [20], *exo* 2-*N*-*n*-propylaminobenzonorbornene **19** [21] and *exo* 2-amino-6,7-dimethoxybenzonorbornene **20** [1, 2] were synthesized according to procedures in the literature and isolated in analytically pure form.

Pharmacology

Dopamine receptor binding assays: Male Sprague–Dawley rats (200–250 g) were killed by decapitation and the striata removed. Membrane preparations and the [^{3}H]-spiroperidol binding assays were performed according to Katerinopoulos and Thermos, 1989 [4].

[^{3}H]-SCH-23390 binding assay

Into 13 x 100 mm glass test tubes were placed [^{3}H]-SCH-23390 (NEN; 78 Ci/mmol), test ligands (dissolved in a minimum vol of ethanol and Tris–HCl buffer (50 mM, pH 7.4) containing EDTA (disodium salt; 5 mM), ascorbic acid (1.1 mM), nialamide (10 μM) (Tean buffer) and striatal membranes (800 μl) in a total vol of 1 ml. The final concentration of [^{3}H]-SCH-23390 was 0.3 nM. The tubes were incubated at 37°C for 15 min and the binding reaction was terminated by filtration of GF/B filters, using a Millipore filtration apparatus under vacuum. Specific binding was defined as the total [^{3}H]-SCH-23390 bound minus the amount bound in the presence of piflutixol (1 μM) or SCH-23390 (100 nM).

Adrenergic receptor assays

Membranes were prepared from the cortex of brains removed from male Sprague–Dawley rats [4]. For the α_1-adrenoceptor assays [^{3}H]-prazosin (NEN; 79 Ci/mmol; 0.2 nM) was incubated in the presence of test ligands and cortical membranes in a total vol of 1.0 ml, for 60 min at 25°C. The

binding reaction was terminated by filtration over GF/B filters. Specific binding was defined in the presence of either phentolamine (2 μM) or prazosin (100 nM). For the α_2-adrenoceptor assays [^{3}H]-rauwolscine (NEN, 88 Ci/mmol; 1 nM) was incubated in the presence of test ligands and cortical membranes in a total vol of 1.0 ml, for 120 min at 4°C. Specific binding was defined in the presence of yohimbine (1 μM). Functional assays were performed using isolated tissue preparations. Isolated superfused guinea pig atrium, dog saphenous vein and rabbit aorta were used to measure pre- and postjunctional α_2- and α_1-adrenoceptor activity, according to the procedure of Hieble *et al* [14]. The Krebs solution used in the guinea pig atrium experiments contained cocaine (6 μM), whereas in the saphenous vein experiments the Krebs solution contained cocaine (6 μM) and prazosin (100 nM).

Acknowledgments

This work was supported by grants from the Greek Ministry of Health (KESY # 223) and the Special Account for Research Funds of the University of Crete. The authors also thank the Organic Chemistry Laboratory of the Chemistry Department, University of Salonica, for the elemental analyses.

References

1 Schuster DI, Katerinopoulos HE, Holden WL, Narula APS, Libes RB, Murphy RB (1982) *J Med Chem* 25, 850–854
2 Burn P, Crooks PA, Heatly F, Costal B, Naylor RJ, Noria V (1982) *J Med Chem* 25, 363–368
3 Katerinopoulos HE, Thermos K, Vassilatis DK, Schuster DI (1988) *Eur J Med Chem* 23, 391–396
4 Katerinopoulos HE, Thermos K (1989) *Eur J Med Chem* 24, 615–617
5 Burn P, Crooks PA, Waldron C, Hicks PE (1981) *J Pharm Pharmacol* 33, 83P
6 Hicks PE, Waldron C, Burn P, Crooks PA (1983) *J Pharm Pharmacol* 35, 94–99
7 DeMarinis RB, Bryan WM, Shah DH, Hieble JP, Pendleton RJ (1981) *J Med Chem* 24, 1432–1437
8 Smith ECR, Riley TN, Borne RF, Waters IW (1987) *J Med Chem* 30, 1105–1110
9 Harisson R, Heaney H, Lees P (1968) *Tetrahedron* 24, 4589–4594
10 Musso H, Pietsch H (1967) *Chem Ber* 100, 2854–2866
11 Billard W, Ruperto V, Crosby G, Iorio LC, Barnett A (1984) *Life Sci* 35, 1885
12 Bylund DB (1987) *The Alpha-1 Adrenergic Receptors* (Ruffolo R Jr, ed) Humana Press, Clifton, NJ, 19–96
13 U'Prichard DC (1984) *Ann NY Acad Sci* 430, 55
14 Hieble JP, DeMarinis RM, Fowler PJ, Matthews WD (1986) *J Pharmacol Exp Ther* 236, 90–96
15 Grunewald GL, Pleis MA, Rafferty MF (1982) *Life Sci* 31, 993–1000
16 Kobinger W, Pichler L (1982) *J Cardiovasc Pharmacol* 4 (suppl 1), 581–585
17 Katerinopoulos HE (1984) PhD thesis, Archiv NY Univ, NY
18 McKillop A, Bromley D (1969) *Tetrahedron Lett* 1623–1626
19 McKillop A, Bromley D (1972) *J Org Chem* 37, 88–92
20 Wood LE, Daniels R, Bauer L, Gearien JE (1981) *J Pharmacol Sci* 70, 199–204
21 Grunewald GL, Pleiss MA, Gatchell CL, Pazhenchevsky R, Rafferty M (1984) *Chromatography* 16, 317–331