Synthesis and Pharmacological Evaluation of 4-Phenoxy-1,2,3,4-Tetrahydroisoquinolines and 4,5,6,6a-Tetrahydrochromeno [2,3,4-de]isoquinolines

G. Giorgioni[a,*], S. Ruggieri[a], F. Claudi[a], A. Di Stefano[b], E. Ljung[c] and T. Carlsson[c]

[a]*Dipartimento di Scienze Chimiche, Università di Camerino, via S. Agostino 1, 62032, Camerino, Italy;* [b]*Dipartimento di Scienze del Farmaco, Università "G. D'Annunzio", Via dei Vestini 31, 66100 Chieti, Italy;* [c]*Neurosearch Sweden AB, Biothech Center, Arvid Wallgrens Backe 20. SE-41346 Gothenburg, Sweden*

Abstract: The novel 4-phenoxy-1,2,3,4-tetrahydroisoquinolines **6a-c** and their rigid congeners 4,5,6,6a-tetrahydrochromeno[2,3,4-de]isoquinolines **7a**,**b** were synthesized in order to obtain dopamine D_2-like receptor ligands. The new compounds were evaluated for their *in vitro* binding affinities, *in vivo* behavioral activities on rats, and for their effects on rat brain neurochemistry. Compounds **6b** (toward both D_2 and D_3 dopamine receptors) and **7a**,**b** (toward D_3 only dopamine receptors) showed the most significant affinities. However none of the new compounds was able to stimulate behavioral activity in non pre-treated rats, nor to influence brain neurochemistry.

Key Words: Dopamine receptors, D2-like, structure activity relationships, tetrahydroisoquinoline.

INTRODUCTION

Schizophrenia is a severe central nervous system (CNS) pathology that affects approximately 1% of the world population. It was first described more than one century ago, but several pathophysiological details are still unclear, although many discoveries have been made since that time. The symptoms of schizophrenia, which can be classified as positive or negative, are associated with an increased dopaminergic transmission in the mesolimbic pathway and hypodopaminergic activity in the frontal cortex, respectively. Some neurochemical explanations have been proposed to rationalize an antipsychotic therapy, but the dopamine hypothesis, which emerged forty years ago, still remains one of the main possibilities even though alone it does not fully explain such a complex illness [1].

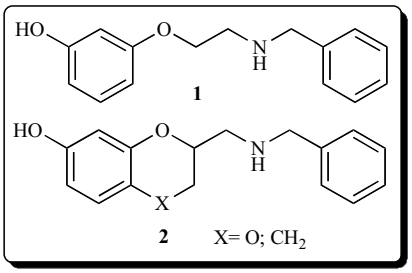
Since the discovery of chlorpromazine, the antipsychotic drugs have been the treatment of choice for schizophrenia [2]. Their usefulness for controlling the positive symptoms appears to be ascribable to their high affinity and antagonist activity at D_2 receptors. However, they have limited efficacy against the negative symptoms and are responsible for severe side effects mainly associated with the dopamine receptor antagonistic activity [3].

A newer approach seems to be represented by the use of dopamine D_2-like receptor partial agonists, namely drugs which have affinity and limited intrinsic activity at the receptor [4, 5]. Drugs endowed with such a mechanism of action act as antagonists where the dopamine activity is oversized, as well as agonists where it is reduced. In this manner, the negative side effects associated with dopaminergic antagonists treatment can be avoided [6].

*Address correspondence to this author at the Dipartimento di Scienze Chimiche, Università di Camerino, *via* S. Agostino 1, 62032, Camerino, Italy; E-mail: gianfabio.giorgioni@unicam.it

Most dopamine D_2-like agonist structures bear the pharmacophoric framework 2-(3-hydroxyphenyl)ethylamine or its bioisosters [7]. However, molecules showing dopaminergic D_2 partial agonist activity and lacking such a structural requirement have been reported as well.

Structure-activity relationship studies on several phenolic and non-phenolic structures based on the template structure N-benzyl-2-(3-hydroxyphenoxy)ethylamine **1** [8b], and its bioisosters have been described [8a-h]. These studies reported that conformational restrictions owing to benzodioxane and benzodihydropyran rings **2** beneficially affect D_2-like receptor affinity [8c]. However, conformational restriction of compound **1** obtained by locking its ethanolamine chain has not yet been investigated.



The 1,2,3,4-tetrahydroisoquinoline skeleton has been often used in the past, either alone (i. e. **3** [9]) or as a part of condensed ring systems (i. e. **4** [10]), to limit the conformational freedom of the flexible ethylamine chain. For this reason, a series of tetrahydroisoquinoline-based derivatives **6a-c** framing in a partially rigid conformation the N-benzyl-2-phenoxyethylamine moiety was chosen.

The N-benzyl-2-(3-hydroxyphenoxy)ethylamine **1** locked in a rigid conformation can be easily recognized in the skeleton of compound **5**, which has recently been reported to behave as a dopamine D_1-like receptor full agonist [11]. Com-

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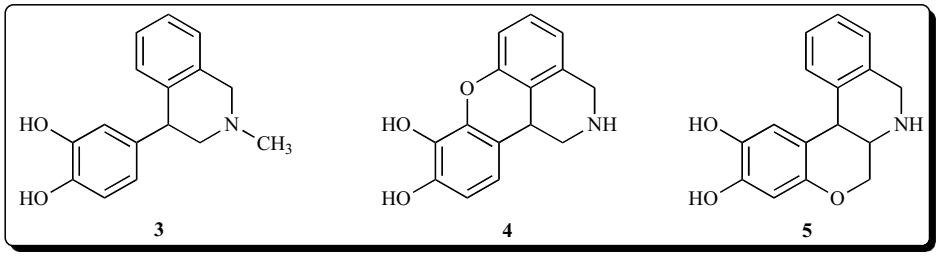


pound **5** shows good affinity toward both cloned human D_1 (K_i=98 nM) and D_5 (Ki=7 nM) receptors, moreover it also interestingly binds dopamine D_3 (K_i=390 nM) and D_4 (K_i=90 nM) receptor subtypes. The β-phenyl-dopamine moiety, previously reported as responsible for D_1-like full agonist activity [12, 13], is incorporated in the structure of compound **5**. However, the N-benzyl-2-(3-hydroxyphenoxy)ethylamine moiety **1** is embedded as well in the structure of **5**, and might play a role in conferring the D_2-like affinity to the molecule.

On the basis of these considerations, the fully rigid molecules **7a**,**b** were designed. It can be observed that **7a**,**b** are devoid of the β-phenyldopamine moiety, but maintain the structure **1** constrained in two different conformations.

Moreover, compounds **7a**,**b**, share an isomeric ring system with dinoxyline **4**, which is endowed with high affinity toward both D_1-like ($K_{0.5}$=8.3 nM) and D_2-like receptor ($K_{0.5}$=6.2 nM) [10].

Thus, in the present study, the synthesis of compounds with general formula **6** and **7** as partially and fully rigid derivatives respectively of the template structure N-benzyl-2-(3-hydroxyphenoxy)ethylamine is described.

Since several compounds bearing small-size N-alkyl residues are reported [14] to show D_2-like receptors affinity, in the first resort, secondary amines were not considered in the investigation. The preliminary biological and pharmacological evaluations of compounds **6a-c** and **7a**,**b** are also described.

CHEMISTRY

The synthesis of the target compounds with the general formula **6** was carried out as reported in Scheme (**1**). Starting with the Mitsunobu [15] reaction between the 2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol **8** [16], and the proper phenol **9a-f** [17], the corresponding 4-aryloxy-1,2,3,4-tetrahydroisoquinolines **10a-f** were obtained.

Unfortunately the O-demethylation step of methoxy derivatives **10a** and **10b** by acidic hydrolysis was unsuccessful. Thus, to overcome the problem, the synthesis of compounds **10e** and **10f** was performed. In fact, O-benzoyl phenols were able to release the proper free phenols **6a** and **6b** under basic condition in non aqueous media.

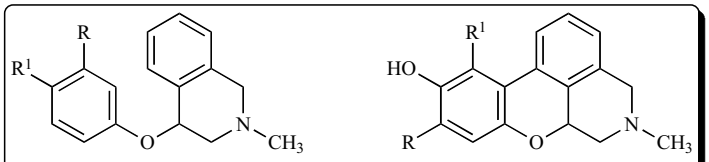
The classical acidic cleavage of the methylendioxy group of **10d** by BBr_3 to give the proper catechol **6c** failed as well. On the contrary, it was readily obtained under basic conditions [18].

The synthetic approach to prepare compound **7a**,**b**, reported in Scheme (**3**), needed the 5-bromo-2-methyl-2,3-dihydroisoquinolin-4(1H)-one **14** as key intermediate, which was synthesized following the route reported in Scheme (**2**).

Thus, methyl 2-bromo-6-methylbenzoate **11** was treated with N-bromosuccinimide (NBS) and dibenzoylperoxide (DBP) to obtain the bromide **12** [19], which gave the amine **13** by reaction with sarcosine ethyl ester in acetone. Adding ethanol to a boiling solution of **13** in toluene in presence of sodium the 5-bromo-2-methyl-2,3-dihydroisoquinolin-4(1H)-one **14** was obtained.

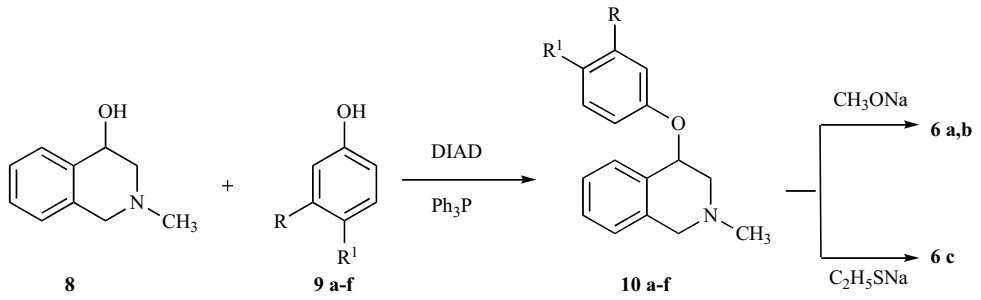
The arylbromide **14** was reacted with the proper aryl boronic acid **15 a**,**b** [20] under classical Suzuki cross-coupling reaction conditions to give the compounds **16a**,**b.** Treatment with sodium borohydride gave the alcohols **17a**,**b**, which readily underwent the intramolecular Mitsunobu reaction to give compounds **18a-b**. Acidic hydrolysis of the latter compounds gave the expected target molecules **7a**,**b**.

In a first approach to the synthesis of **7a**, a methylenedioxy group was chosen for the catechol protection. Following the same chemical pathway as that reported in Scheme (**3**), the reactions proceeded smoothly until the synthesis of **18c**. Unfortunately, the protection cleavage step failed with the attempted traditional methods [21].



6	R	R^1
a	H	OH
b	OH	H
c	OH	OH

7	R	R^1
a	H	OH
b	OH	H

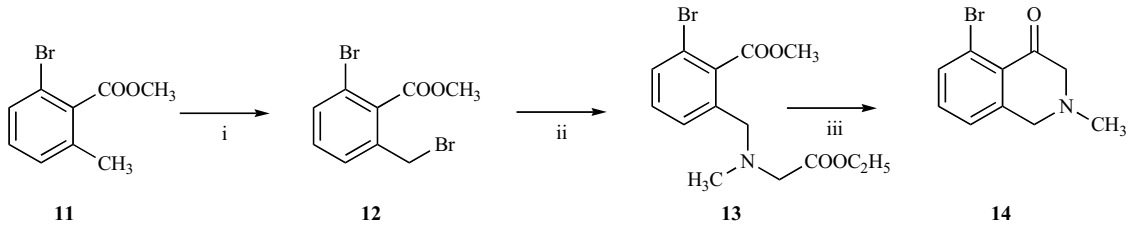


9-10	R	R^1
a	H	OMe
b	OMe	H
c	OMe	OMe
d	-OCH_2O-	
e	H	OCOPh
f	OCOPh	H

6	R	R^1
a	H	OH
b	OH	H
c	OH	OH

Scheme 1.

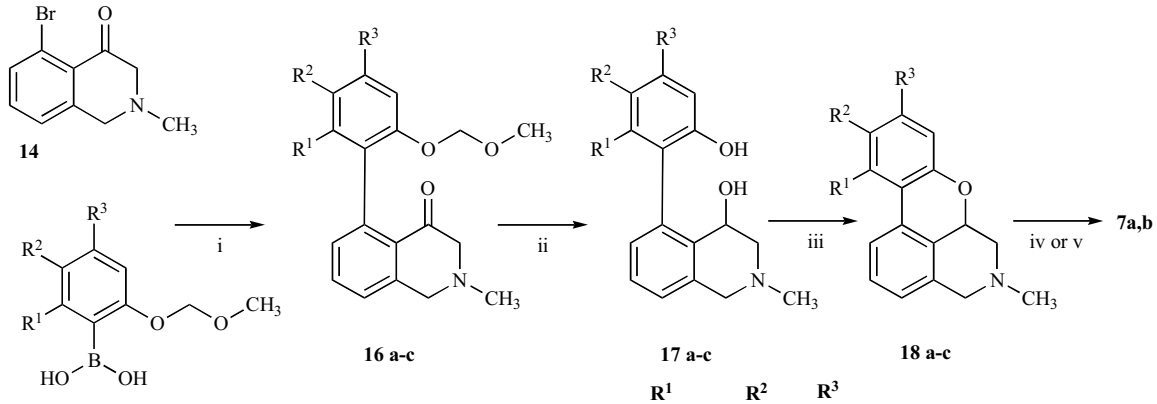
The use of pyridinium chloride at high temperature for several hours was reported to be effective both for the O-demethylation of protected catechols [22] and for the cleavage of methylenedioxy protecting group [23]. We ran such a reaction unsuccessfully on **18c**. Only very low yields of **7a** were isolated when a homogeneous solvent free mixture of **18c** and pyridinium chloride was reacted for just 10 min under 250-W microwave irradiation.



11 **12** **13** **14**

i) NBS, DBP, CCl_4; ii) sarcosine ethyl ester, K_2CO_3, Acetone; iii) a) Na, EtOH, Toluene; b) 6N HCl.

Scheme 2.



	R^1	R^2	R^3
a	OMe	OMe	H
b	H	OMe	OMe
c	-OCH_2O-		H

i) $Pd(PPh_3)_4$, 2M Na_2CO_3, toluene, reflux; ii) a: $NaBH_4$, b: MeOH/HCl; iii) PPh_3, DIAD, THF; iv) 48% HBr, CH_3COOH (from 18a-b); v) Pyridine.HCl MW 250-W (from 18c).

Scheme 3.

Table 1. K_i Values Reported in Micromolar Concentration

Cmpd	D_1	D_2	D_3	D_4	D_5
6a	N.A.	N.A.	N.A.	N.A.	N.A.
6b	N.A.	3.9320	2.0990	N.A.	N.A.
6c	N.A.	N.A.	N.A.	N.A.	N.A.
7a	N.A.	N.A.	1.7360	N.A.	N.A.
7b	N.A.	N.A.	0.8498	N.A.	N.A.
1	6.7470	0.4062	0.0115	0.0918	9.6700

N.A.= Inhibition lower than 50% at 10^{-4} M was considered not active.

PHARMACOLOGY

Competitive binding of compounds **6a-c** and **7a**,**b** at cloned D_1-D_5 dopamine receptors was evaluated by the NIMH supported Psychoactive Drug Screening Program[1].

The effects on the behavioral activity of the novel synthesized compounds **6b** and **7a**,**b** were tested *in vivo* on rats by s. c. administration of 3.7, 11, 33 and 100 μmol/kg doses. Dopamine receptor agonists with high intrinsic activity in this assay normally increase the locomotor activity while those with low intrinsic activity show a dose-related decrease in such activity. The effects on rat brain neurochemistry were also evaluated. In this assay, testing dopamine receptor agonists with high intrinsic activity a dose related decrease in DOPAC (3,4-dihydroxyphenylacetic acid) and HVA (homovanillic acid) in three brain regions (limbic, striatum and cortex) is expected.

RESULTS AND DISCUSSION

The receptor binding affinities of the new compounds and **1** are reported in Table (**1**). An analysis of data shows that in the tetrahydroisoquinoline series only compound **6b** displays micromolar affinity for D_2 and D_3 receptor subtypes.

Compounds **7a**,**b**, belonging to the tetrahydrochromenoisoquinoline series, selectively bind dopamine D_3 receptor subtype with affinity values comparable to that of **6b**. However, both the partial and fully rigid constraint of **1** reduce or annul, respectively, its conformational freedom into non-effective conformations though the D_2-like receptor family preferential binding, especially toward the D_3 receptor subtype, is maintained.

Mewshaw *et al*. reported that the constraint of the N-benzyl moiety of the general structure **2** into the rigid tetrahydroisoquinoline structure positively affected D_2 and, mainly, D_3 receptor affinity although decreased their intrinsic activity [8c]. In our case, the conformational stiffening, due to the tetrahydroisoquinoline skeleton, involving the ethylene chain between the oxygen and the nitrogen atoms, negatively affects the binding of the ligands to DA receptors. However, such a structural modification generated a stereogenic center and, in the future, the optical resolution of the racemate might be developed to investigate whether the enantiomers show higher affinity values and are able to discriminate better among DA receptor subtypes.

The behavioural activity after s.c. administration of compounds **6b** (Fig. **1**) and **7a**,**b** (Fig. **2**) in the dose range 3.7-100 μmol/Kg was evaluated *in vivo* on rats. The improvement of the locomotor activity induced by DA full agonists, nor the dose-related decrease of locomotor activity induced by DA partial agonists was observed. In fact, only no statistical significant changes in the behavioural activity were recorded compared to the control group.

The effects of compounds **6b** (Fig. **3**) and **7a**,**b** (Fig. **4**) were also evaluated on brain neurochemistry. No statistical significant changes in DOPAC and HVA levels in all three investigated brain regions were observed after s.c. administration of the tested compounds compared to the control group, whereas a dose-related decrease of their level is expected for DA agonists.

Such *in vivo* results suggest that the compounds **6b** and **7a**,**b** do not have sufficient intrinsic activity to be able to stimulate DA receptors.

In conclusion, we have here described the synthesis of new tetrahydroisoquinolines and tetrahydrochromeno[2,3,4-de]isoquinolines embedding partially or totally frozen conformations, respectively, of the template structure N-benzyl-2-(3-hydroxyphenoxy)ethylamine **1**.

The lack of other assumable template structure led us to suppose that the backbone **1** is responsible for the detected DA receptor affinity, confirming that it proves to be a suitable scaffold for the design of dopamine D_2-like ligands. However, the conformational restrictions, in particular that of the oxyethylamine chain, introduced in the new synthesized compounds seem to be detrimental for a high affinity binding to the DA receptors, but might help in developing new DA D_3 receptor ligands.

EXPERIMENTAL SECTION

Chemistry. General Procedures

Melting points were measured on a Büchi 510 apparatus and are uncorrected. Microanalyses were performed on a

[1] K_i determinations were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program (NIMH PDSP). The NIMH PDSP is Directed by Bryan L. Roth MD, PhD at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscol at NIMH, Bethesda MD, USA. Contract # NO1MH32004. Please refer to the web site (http://pdsp.med.unc.edu) and click on binding assays for details about the assays.

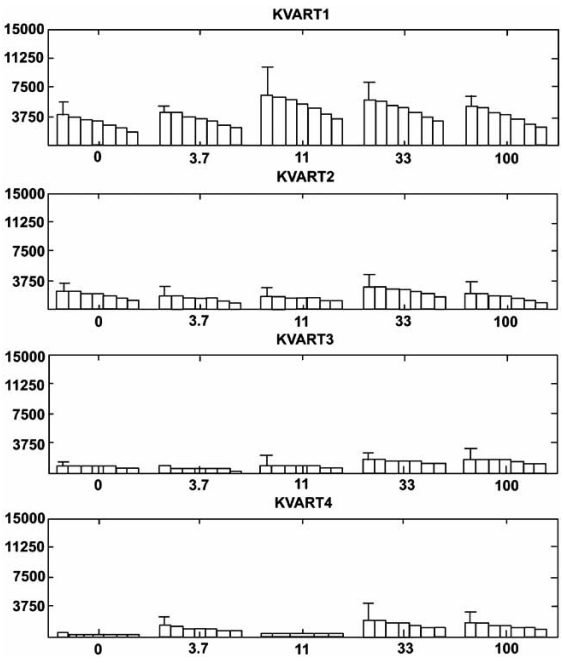


Fig. (1). Behavioural activity of compound **6b**: Dose range 3.7-100 μmol/kg. Dose 0 is the control group.

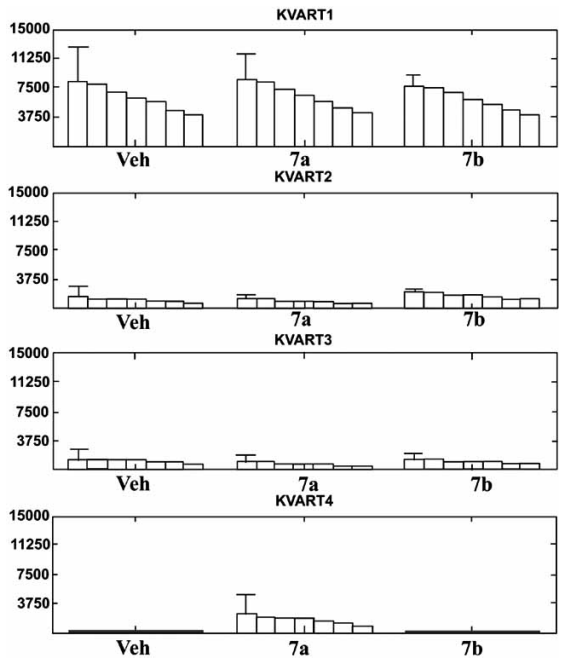


Fig. (2). Behavioural activity of compounds **7a**,**b** at 33 μmol/Kg. Veh: vehicle.

The first box (KVART 1) is the first 15 minutes after administration (s.c.), the second box (KVART 2) is the time 15-30 minutes after administration and so on. Each bar is different frequencies used in the sampling of data.

1106 Carlo Erba CHN Analyzer. Analyses were within ± 0.4% of the calculated values. HPLC analysis and mass spectra were recorded on a HPLC-DAD-RID-MS (ion trap) 1100 – LC MSD trap sl Agilent Technologies.

^{1}H-NMR spectra were recorded on a Varian VXR 200-MHz spectrometer. Chemical shift values are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (Me_4Si). The identity of all new compounds was confirmed both by elemental analyses and NMR data. MS analysis was performed only to confirm the identity of the final products. TLC was performed with Merck 60 F_{254} precoated silica on glass. Solutions were routinely dried over anhydrous sodium sulfate prior to evaporation. Chromatographic purification was performed by Merck-60 70-230 mesh ASTM silica gel columns with the reported solvent.

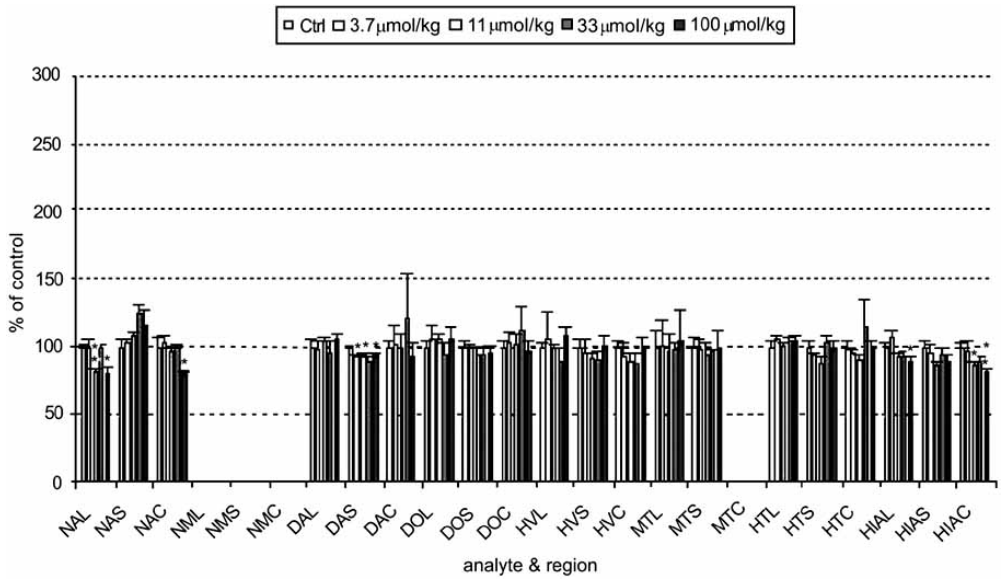


Fig. (3). Effects of compound **6b** on brain neurochemistry in rat. Dose range 3.7-100 μmol/kg.
(L=limbic region, S=striatum and C=cortex; NA=noradrenaline, DA=dopamine, DO=DOPAC, HV=HVA, HT=serotonin, HI=5-hydroxyindoleacetic acid).

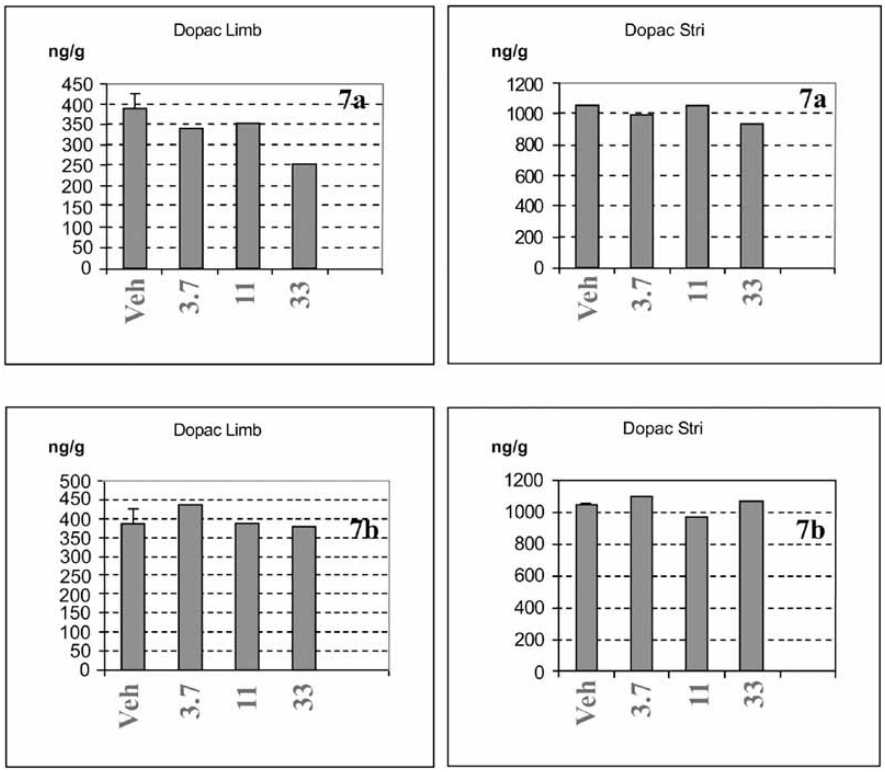


Fig. (4). Effects of compounds **7a**,**b** on DOPAC levels in limbic and striatum. Dose range 3.7-33 μmol/kg.

Methyl 2-bromo-6-{[(2-ethoxy-2-oxoethyl)(methyl)amino] methyl}benzoate (13)

A mixture of methyl 2-bromo-6-(bromomethyl)benzoate **12** (1.8 g, 5.84 mmol), sarcosine ethylester hydrochloride (0.988 g, 6.43 mmol) and anhydrous potassium carbonate in acetone (100 ml) was stirred at room temperature overnight. After filtration, acetone was removed under reduced pressure. The residue was dissolved in diethyl ether and the solution was extracted twice with 2N solution of HCl. The acidic solution was basified with anhydrous potassium carbonate and extracted with ether (3x25 ml). The separated organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was removed in vacuum to give the crude product, which was used without further purification. Yield (crude) 45 %. ^{1}H-NMR ($CDCl_3$) δ: 7.46-7.43 (m, 1H, ArH); 7.28-7.13 (m, 1H, ArH); 4.16-4.09 (m, 2H, OCH_2C); 3.87 (s, 3H, OCH_3); 3.74 (s, 2H, CH_2); 3.22 (s, 2H, CH_2); 2.31 (s, 3H, NCH_3); 1.25-1.21 (t, J=7.09 Hz, 3H, $OCCH_3$).

5-Bromo-2-methyl-2,3-dihydroisoquinolin-4(1H)-one hydrochloride (14)

Sodium (0.1 g) was carefully added portionwise to a solution of methyl 2-bromo-6-{[(2-ethoxy-2-oxoethyl)(methyl) amino]methyl}benzoate **13** (0.86 g, 2.5 mmol) in dry toluene (20 ml). The mixture was warmed to 60°C, under nitrogen atmosphere. Dry ethanol was added to start the reaction (1 ml) and the mixture was refluxed for 4 hours. After cooling to the room temperature water was added to quench the reaction. The aqueous solution was separated and extracted several times with ethyl acetate. The collected organic solutions were extracted with 6N HCl solution. The acidic solution was refluxed under stirring for 18 hours. The hot brownish mixture was evaporated under reduced pressure to give the product as a solid that was recrystallized from boiling ethanol. Yield 37%; m.p. 233-236°C. ^{1}H-NMR (DMSO-d_6) δ: 12.41 (bs, 1H, N^+H); 7.85-7.53 (m, 3H, ArH); 4.71 (s, 2H, NCH_2CO); 4.25 (s, 2H, $ArCH_2N$); 2.94 (s, 3H, NCH_3).

General Procedure for Preparation of Compounds 10 a-f

Diisopropyldiazodicarboxylate (DIAD; 1.1 mmol) was slowly added at room temperature by a syringe pump to a solution of triphenylphosphine (1.1 mmol), 2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol **8** (1 mmol), phenol **9a-f** (1.2 mmol) in freshly distilled dry THF (2.5 ml). The mixture was stirred at room temperature overnight then evaporated to dryness. The residue was triturated with diethyl ether and the suspension filtered. The clear solution was evaporated and the oily residue purified by column chromatography (AcOEt – hexane 50%). The collected pure fractions were evaporated and the residue dissolved in a 3M HCl solution in dry methanol. The solution was stirred for 10 min and then the solvent was removed under reduced pressure. The solid residue was recrystallized from ethanol-diethyl ether.

4-(4-Methoxyphenoxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (10a)

Yield 32%. M.p. 183-185°C. ^{1}H-NMR (DMSO-d_6) δ 10.40-10.20 (bs, 1H, NH^+); 7.42-7.33 (m, 4H, ArH); 7.14-7.10 (m, 2H, ArH); 6.96-6.91 (m, 2H, ArH); 5.61 (bs, 1H, ArCHO); 4.48-4.40 (m, 2H, $ArCH_2N$); 3.85-3.60 (m, 5H, CCH_2N-OCH_3); 2.98 (s, 3H, NCH_3).

4-(3-Methoxyphenoxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (10b)

Yield 31%. M.p. 140-143°C. ^{1}H-NMR (DMSO-d_6) δ: 10.26 (bs, 1H, NH^+); 7.54-7.24 (m, 5H, ArH); 6.79-6.63 (m, 3H, ArH); 5.81 (bs, 1H, ArCHO); 4.52-4.40 (m, 2H, $ArCH_2N$); 3.85-3.60 (m, 5H, CCH_2N-OCH_3); 2.97 (s, 3H, NCH_3).

4-(3,4-Dimethoxyphenoxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (10c)

Yield 16 %. M.p. 198-201°C. ^{1}H-NMR (DMSO-d_6) δ: 10.34 (bs, 1H, NH^+); 7.43-7.30 (m, 4H, ArH); 6.97-6.68 (m, 3H, ArH); 5.66 (bs, 1H, ArCHO); 4.60-4.36 (m, 2H, $ArCH_2N$); 3.82-3.62 (m, 8H, $2OCH_3$-CCH_2N); 2.97 (s, 3H, NCH_3).

4-(1,3-Benzodioxol-5-yloxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (10d)

Yield 33%. M.p. 161-163°C. ^{1}H-NMR (DMSO-d_6) δ: 10.49 (bs, 1H, N^+H); 7.46-7.30 (m, 4H, ArH); 6.91-6.87 (m, 2H, ArH); 6.63-6.60 (m, 1H, ArH); 6.00 (s, 2H, OCH_2O); 5.62 (bs, 1H, ArCHO); 4.60-4.30 (m, 2H, $ArCH_2N$); 3.88-3.57 (m, 2H, CCH_2N); 2.96 (s, 3H, NCH_3).

4-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-4-yloxy)phenyl benzoate (10e)

Yield 12 %. R_f= 0.15 (ethylacetate-hexane 50:50). ^{1}H-NMR ($CDCl_3$) δ: 8.25 (m, 2H, ArH); 7.67-7.44 (m, 4H, ArH); 7.28-7.06 (m, 7H, ArH); 5.45 (t, 1H, ArCHO); 3.77 (d, J=16 Hz, 1H, ArCHN); 3.56 (d, J=16 Hz, 1H, ArCHN); 3.05-2.85 (m, 2H, CCH_2N); 2.51(s, 3H, NCH_3).

3-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-4-yloxy)phenyl benzoate (10f)

Yield 28 %; R_f= 0.12 (ethyl acetate-hexane 50:50). ^{1}H-NMR ($CDCl_3$) δ: 8.29-8.16 (m, 2H, ArH); 7.66-7.21 (m, 7H, ArH); 7.18-7.06 (m, 1H, ArH); 7.04-6.84 (m, 3H, ArH); 5.47 (t, 1H, ArCHO); 3.96-3.48 (m, 2H, $ArCH_2N$); 3.04-2.85 (m, 2H, CCH_2N); 2.50 (s, 3H, NCH_3).

General Procedure for Preparation of Compounds 6a-b

Compound **10e** or **10f** (0.11 g, 0.31 mmol) was added to a solution of sodium (1.00 g) in dry methanol (25 ml). The mixture was stirred 4 hours at room temperature. The solvent was removed under reduced pressure and water (30 ml) was carefully added to the residue. The obtained solution was washed with diethyl ether, made acidic with 6N HCl solution and washed again with diethyl ether. The mixture was carefully basified adding anhydrous sodium bicarbonate then extracted with dichloromethane. The separated organic phase was dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate to give a white solid.

Data for 4-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yloxy)phenol (6a)

Yield 89%. M.p.=177°C; ^{1}H-NMR ($CDCl_3$) δ: 7.52-7.32 (m, 1H, ArH); 7.32-7.12 (m, 2H, ArH); 7.17-6.82 (m, 3H, ArH); 6.77-6.60 (m, 2H, ArH); 5.25 (t, 1H, ArCHO); 3.70 (d, J=15 Hz, 1H, ArCHN); 3.53 (d, J=15 Hz, 1H ArCHN); 2.96-2.87 (m, 2H, CCH_2N); 2.45 (s, 3H, NCH_3). ESIMS: m/z (MH^+) 256.

6a *Hydrochloride*: The product was dissolved in 3M HCl methanolic solution and stirred 15 minutes at room temperature. The solvent was evaporated under vacuum and the solid residue recrystallized from ethanol. M.p.=230-231°C. Anal. ($C_{16}H_{17}NO_2$.HCl) C, H, N. ESIMS: m/z (MH^+) 256.

Data for 3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yloxy) phenol (6b)

Yield 90%. M.p. 184-186°C. ^{1}H-NMR ($CDCl_3$) δ: 7.43-7.39 (m, 1H, ArH); 7.31-7.14 (m, 4H, ArH); 6.72-6.46 (m, 3H, ArH); 5.44 (t, 1H, ArCHO); 3.79-3.52 (m, 2H, $ArCH_2N$); 2.94-2.86 (m, 2H, CCH_2N); 2.50 (s, 3H, NCH_3).

6b *Hydrochloride*: The product was dissolved in 3M HCl methanolic solution and stirred 15 minutes at room temperature. The solvent was evaporated under vacuum and the solid residue recrystallized from ethanol. M.p.=245-246°C. Anal. ($C_{16}H_{17}NO_2$.HCl.H_2O) C, H, N. ESIMS: m/z (MH^+) 256.

4-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-4-yloxy)benzene-1,2-diol hydrochloride (6c)

Sodium ethanethiolate (1.26 g, 15 mmol) was added to solution of 4-(1,3-benzodioxol-5-yloxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.21 g; 0.74 mmol) in anhydrous DMF (10 ml) under nitrogen athmosphere. The flask was fitted with a condenser and the mixture reacted 10 hours at 80° C. The solvent was removed under vacuum, the residue dissolved in 2N NaOH, and the solution washed with dichloromethane. The basic solution was made acidic by 2N HCl and washed with dichloromethane. The acidic solution was made basic adding anhydrous $NaHCO_3$ and extracted with dichloromethane. The organic solution was dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The crude residue was dissolved in 3M HCl methanolic solution and stirred 15 minutes at room temperature. The solvent was evaporated under vacuum and the solid residue obtained was recrystallized from ethanol-ethyl acetate. Yield 40%. M.p.=195-196° C. ^{1}H-NMR (DMSO-d_6) δ: 7.38-7.24 (m, 4H, ArH); 6.70 (d, J = 7.5, 1H, ArH); 6.59 (s, 1H, ArH); 6.46 (d, J = 7.5, 1H, ArH); 5.72-5.31 (m, 1H, ArCHO); 4.60-4.20 (m, 2H, $ArCH_2N$); 3.90-3.49 (m, 2H, CCH_2N); 2.94 (s, 3H, NCH_3). Anal. ($C_{16}H_{17}NO_3$.HCl.1/2H_2O) C, H, N. ESIMS: m/z (MH^+) 272.

2,3-Dimethoxy-6-(methoxymethoxy)phenylboronic acid (15a)

A solution of 1,2-dimethoxy-4-methoxymethoxybenzene (4.00 g, 20.18 mmol) in freshly distilled THF (60 ml) was added to a 1.6 M solution of n-butyllithium in hexane (25.22 ml, 40.36 mmol) cooled to -30°C and under nitrogen atmosphere. The mixture was stirred at the same temperature for 1 hour. Trimethyl borate (4.58 ml, 40.36 mmol) was added dropwise and the mixture left to warm to the room temperature overnight. The reaction was cooled on ice bath and a 5% solution of HCl was carefully added up to pH 6.5. The whole mixture was extracted with dichloromethane, the organic fraction washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was used without further purification. Yield (crude) 87%. ^{1}H-NMR (DMSO-d_6) δ: 7.42 (bs, 2H, $B(OH)_2$); 6.98-

6.89 (m, 2H, ArH); 5.23 (s, 2H, OCH_2O); 3.92 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 3.48 (s, 3H, OCH_3).

4,5-Dimethoxy-2-(methoxymethoxy)phenylboronic acid (15b)

A 2.5 M solution of n-butyllithium in hexane (1.58 ml, 3.96 mmol) was added dropwise to a cooled (-78° C) solution of 1-bromo-4,5-dimethoxy-2-(methoxymethoxy)benzene [24] (1.00 g, 3.6 mmol) in freshly distilled THF (10 ml) under nitrogen atmosphere. The mixture was stirred at the same temperature for 30 minutes then treated with trimethyl borate (1.22 ml, 10.8 mmol) and allowed to warm to the room temperature overnight. The reaction was cooled on ice bath and a 5% solution of HCl was carefully added up to pH 6.5. The whole mixture was extracted with dichloromethane, the organic fraction washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was triturated in hexane, filtered and recrystallized from hexane. Yield (crude) 69%. M.p.= 99-101° C. ^{1}H-NMR (DMSO-d_6) δ: 7.59 (bs, 2H, $B(OH)_2$); 7.13 (s, 1H, ArH); 6.74 (s, 1H, ArH); 5.23 (s, 2H, OCH_2O); 3.76 (s, 3H, OCH_3); 3.69 (s, 3H, OCH_3); 3.38 (s, 3H, OCH_3).

5-(Methoxymethoxy)benzo[d][1,3]dioxol-4-ylboronic acid (15c)

A solution of 5-(methoxymethoxy)-1,3-benzodioxole (2.00 g, 10.98 mmol) in freshly distilled THF (30 ml) was added to a 2.5 M solution of n-butyllithium in n-hexane (8.8 ml, 21.96 mmol) cooled at -30°C and under nitrogen atmosphere. The mixture was stirred at the same temperature for 1 hour. Trimethyl borate (2.49 ml, 21.96 mmol) was added dropwise and the mixture left to warm to the room temperature overnight. The reaction was cooled on ice bath and a 5% solution of HCl was carefully added up to pH 6.5. The whole mixture was extracted with dichloromethane, the organic fraction washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was used without further purification. A small sample was recrystallized from hexane for analytical purpose. Yield (crude) 55%. M.p.= 64-66°C. ^{1}H-NMR ($CDCl_3$) δ: 6.75 (d, J = 8.46, 1H, ArH); 6.45 (d, J = 8.46, 1H, ArH); 5.89 (s, 2H, OCH_2O); 5.05 (s, 2H, OCH_2O); 3.37 (s, 3H, OCH_3).

General Procedure for Preparation of Compounds 16a-c

A mixture of the proper boronic acid **15a-c** (1.08 mmol), ethanol (2 ml), and a 2M sodium carbonate solution was added to a solution of 5-bromo-2-methyl-2,3-dihydroisoquinolin-4(1H)-one **14** (1.81 mmol) and tetrakis palladium triphenylphosphine (0.07 mmol) in toluene (30 ml). The heterogeneous mixture was stirred overnight at the reflux temperature, under nitrogen atmosphere. After cooling, saturated solution of sodium bicarbonate was added and the two phases separated. The organic layer was washed with saturated solution of sodium bicarbonate then dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The solid residue was purified by column chromatography using ethyl acetate as eluant.

Data for 5-(2,3-dimethoxy-6-(methoxymethoxy)phenyl)-2-methyl-2,3-dihydroisoquinolin-4(1H)-one (16a)

Yield 78%. ^{1}H-NMR ($CDCl_3$) δ: 7.55-7.46 (m, 1H, ArH); 7.27-7-18 (m, 2H, ArH); 6.88-6.80 (d, 2H, ArH); 4.92-4.80 (dd, 2H, OCH_2O); 3.85 (s, 3H, OCH_3); 3.80 (s, 2H, CH_2); 3.50 (s, 3H, OCH_3); 3.27-3.18 (m, 5H, CH_2 and OCH_3); 2.42 (s, 3H, NCH_3).

Data for 5-(4,5-dimethoxy-2-(methoxymethoxy)phenyl)-2-methyl-2,3-dihydroisoquinolin-4(1H)-one (16b)

Yield 79%. ^{1}H-NMR ($CDCl_3$) δ: 7.51-7.46 (m, 1H, ArH); 7.22-7.17 (m, 2H, ArH); 6.80 (s, 1H, ArH); 6.65 (s, 1H, ArH); 4.94-4.86 (m, 2H, OCH_2O); 3.88 (s, 3H, OCH_3); 3.80-3.74 (m, 5H, CH_2 and OCH_3); 3.30-3.20 (m, 5H, CH_2 and OCH_3); 2.47 (s, 3H, NCH_3).

Data for 5-(5-(methoxymethoxy)benzo[d][1,3]dioxol-4-yl)-2-methyl-2,3-dihydroisoquinolin-4(1H)-one (16c)

Yield 98%. ^{1}H-NMR ($CDCl_3$) δ: 7.54-7.49 (m, 1H, ArH); 7.28-7.24 (m, 2H, ArH); 6.71-6.60 (m, 2H, ArH); 5.85-5.82 (dd, 2H, OCH_2O); 4.93-4.80 (m, 2H, OCH_2O); 3.78-3.76 (m, 2H, CH_2); 3.27-3.18 (m, 5H, CH_2 and OCH_3); 2.46 (s, 3H, NCH_3).

General Procedure for Preparation of Compounds 17a-c

Sodium borohydride (10 mmol) was added portionwise to a solution of the starting material (**16a-c**, 2.34 mmol) in dry methanol (25 ml). The mixture was stirred at room temperature for 2 hours then sodium borohydride (5 mmol) was added portionwise once again. The mixture was stirred at room temperature for further 2 hours. The solvent was evaporated under vacuum. The solid residue was dissolved in a 2.5 M solution of HCl in methanol (35 ml) and stirred at room temperature overnight. The solvent was removed under reduced pressure. The solid residue was dissolved in water and the acidic solution washed with ethyl acetate and made basic with anhydrous sodium carbonate. The solution was extracted with dichloromethane. The separated organic phase was washed with brine dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The solid residue was recrystallized from ethyl acetate-hexane.

Data for 5-(6-hydroxy-2,3-dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (17a)

Yield 60%. ^{1}H-NMR ($CDCl_3$) δ: 7.42-7.30 (m, 1H, ArH); 7.25-7.08 (m, 2H, ArH); 6.95-6.80 (m, 2H, ArH); 4.40-4.35 (m, 1H, OCHAr); 4.15-3.95 (m, 1H, CH_2); 3.85 (s, 3H, OCH_3); 3.55 (s, 3H, OCH_3); 3.45-3.30 (m, 1H, CH_2); 3.15-3.05 (m, 1H, CH_2); 2.52 (s, 3H, NCH_3); 2.50-2.35 (m, 1H, CH_2).

Data for 5-(2-hydroxy-4,5-dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (17b)

Yield 61%. ^{1}H-NMR ($CDCl_3$) δ: 7.31 (t, 1H, ArH); 7.12-7.06 (m, 2H, ArH); 6.67 (s, 1H, ArH); 6.54 (s, 1H, ArH); 4.51-4.45 (m, 1H, OCHAr); 4.05 (d, J=15.4, 1H, CH_2); 3.87 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 3.42 (d, J=15.4, 1H, CH_2); 3.05 (d, J=10.5, 1H, CH_2); 2.51-2.47 (m, 4H, 1H of CH_2 and NCH_3).

Data for 5-(5-hydroxybenzo[d][1,3]dioxol-4-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (17c)

Yield 57%. ^{1}H-NMR ($CDCl_3$) δ: 7.36 (t, J=7.62, 1H, ArH); 7.20 (d, J=7.62, 1H, ArH); 7.12 (d, J=7.62, 1H, ArH); 6.72 (d, J=8.42, 1H, ArH); 6.56 (d, J=8.42, 1H, ArH); 5.88-

5.81 (m, 2H, OCH_2O); 4.51-4.47 (m, 1H, OCHAr); 3.99 (d, J=15.2, 1H, CH_2); 3.40 (d, J=15.2, 1H, CH_2); 3.05 (d, J=12.8, 1H, CH_2); 2.54-2.49 (m, 4H, CH_2 and NCH_3).

General Procedure for Preparation of Compounds 18a-c

DIAD (0.37 ml, 1.88 mmol) was added dropwise to a solution of triphenylphosphine (0.49 g, 1.88 mmol) and the proper compound **17a-c** (1.71 mmol) in dry THF (15 ml). The mixture was stirred at the room temperature overnight. The clear solution was evaporated to dryness, the residue was triturated in ether and the suspension filtered. The clear solution was washed with 2N NaOH and then extracted with 2N HCl. The acidic solution was made basic with anhydrous sodium carbonate and then extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and evaporated under vacuum. The residue was purified by silica gel filtration using ethyl acetate as eluant.

Data for 10,11-dimethoxy-5-methyl-4,5,6,6a-tetrahydrochromeno[2,3,4-*de*]isoquinoline (18a)

Yield 25%. ^{1}H-NMR ($CDCl_3$) δ: 8.26 (d, J=7.87, 1H, ArH); 7.31 (t, J=7.85, 1H, ArH); 7.01 (d, J=7.85, 1H, ArH); 6.85 (d, J=8.81, 1H, ArH); 6.76 (d, J=8.81, 1H, ArH); 5.05-4.93 (m, 1H, OCHAr); 3.95-3.83 (m, 7H, $2OCH_3$ and 1H of CH_2); 3.49-3.40 (m, 2H, CH_2); 2.63-2.55 (m, 4H, 1H of CH_2 and NCH_3).

Data for 9,10-dimethoxy-5-methyl-4,5,6,6a-tetrahydrochromeno[2,3,4-*de*]isoquinoline (18b)

Yield 63%. ^{1}H-NMR ($CDCl_3$) δ: 7.46 (d, J=7.90, 1H, ArH); 7.36 (t, J=7.85, 1H, ArH); 7.22 (s, 1H, ArH); 7.08 (d, J=7.89, 1H, ArH); 6.61 (s, 1H, ArH); 5.18-5.05 (m, 1H, OCHAr); 3.95 (s, 3H, CH_3); 3.88-3.83 (m, 4H, OCH_3 and 1H of CH_2); 3.49-3.38 (m, 2H, CH_2); 2.70-2.58 (m, 4H, 1H of CH_2 and NCH_3).

Data for 5-methyl-10,11-methylendioxy-4,5,6,6a-tetrahydrochromeno[2,3,4-*de*]isoquinoline (18c)

Yield 40%. ^{1}H-NMR ($CDCl_3$) δ: 7.82 (d, J=7.65, 1H, ArH); 7.27 (t, J=7.65, 1H, ArH); 7.24 (d, J=7.65, 1H, ArH); 6.64 (d, J=8.35, 1H, ArH); 6.45 (d, J=8.35, 1H, ArH); 6.01 (dd, J'=1.45, J"=24.50, 2H, OCH_2O); 5.06-5.01 (m, 1H, OCHAr); 3.85 (d, J=15.07, 1H, CH_2); 3.42-3.34 (m, 2H, CH_2); 2.59-2.49 (m, 4H, CH_2 and NCH_3).

5-Methyl-4,5,6,6a-tetrahydrochromeno[2,3,4-*de*]isoquinoline-10,11-diol hydrobromide (7a)

A solution of 10,11-dimethoxy-5-methyl-4,5,6,6a-tetrahydrochromeno[2,3,4-*de*]isoquinoline **18a** (0.1 g, 0.34 mmol) in 48% HBr solution (1.5 ml) and acetic acid (3.5 ml) was reacted at the reflux temperature for 8 hours. The solvent was removed under reduced pressure and the residue recrystallized from ethanol. Yield 85%. M.p. 250-251°C. ^{1}H-NMR (DMSO-d_6) δ: 10.42 (bs, 1H, NH^+); 9.44 (s, 1H, OH); 9.26 (s, 1H, OH); 8.37 (d, J=7.78, 1H, ArH); 7.47 (t, J=7.75, 1H, ArH); 7.22 (d, J=7.45, 1H, ArH); 6.75 (d, J=8.70, 1H, ArH); 6.40 (d, J=8.70, 1H, ArH); 5.07-4.97 (m, 1H, OCHAr); 4.53-4.35 (m, 2H, CH_2); 4.12-3.84 (m, 1H, CH_2); 3.63-3.55 (m, 1H, CH_2); 3.02 (s, 3H, NCH_3). Anal. ($C_{16}H_{15}NO_3$.HBr) C, H, N. ESIMS: m/z (MH^+) 270.

5-Methyl-4,5,6,6a-tetrahydrochromeno[2,3,4-de]isoquinoline-9,10-diol hydrobromide (7b)

A solution of 9,10-dimethoxy-5-methyl-4,5,6,6a-tetrahydrochromeno[2,3,4-*de*]isoquinoline **18b** (0.11 g, 0.37 mmol in 48% HBr solution (1.5 ml) and glacial acetic acid (3 ml) was refluxed for 8 hours then evaporated to dryness. The solvent was removed under reduced pressure and the residue recrystallized from ethanol. Yield: 60%. M.p. 270-271°C. ^{1}H-NMR (DMSO-d_6) δ: 10.42 (bs, 1H, NH^+); 9.38 (s, 1H, OH); 8.72 (s, 1H, OH); 7.40-7.20 (m, 2H, ArH); 7.38 (s, 1H, ArH); 7.05 (d, J=7.0, 1H, ArH); 6.40 (s, 1H, ArH); 4.49-4.85 (m, 1H, OCHAr); 3.81 (d, J=9.0, 1H, CH); 3.43-3.23 (m, 3H, 3CH); 2.33 (s, 3H, NCH_3). Anal. ($C_{16}H_{15}NO_3$.HBr) C, H, N. ESIMS: m/z (MH^+) 270.

Pharmacology. Materials

Locomotor Activity

Locomotor recordings were started after subcutaneous (s.c.) injection of test article. Locomotor activity was recorded for 60 min in a motility meter box (Digiscan activity monitor RXYZM (16) TAO, Omnitech Inc., USA.) The arena where activity is recorded measures 42x42x30 cm. A sound and light-attenuating box measuring 55x55x45 cm surrounds the arena. For these recordings, the location (centre of gravity and vertical position) of the animal was sampled at frequencies up to 25 Hz. The recordings were stored and subsequently analysed.

Neurochemistry

Animals were killed by decapitation 60 min after the injection of test compounds. Brains were dissected into striatum, cortex and limbic regions. The tissue samples were immediately frozen and stored at -80°C. The tissue was homogenized and centrifuged for analysis of eluate with respect to concentrations (ng/g tissue) of norepinephrine, dopamine, 5-hydroxytryptamine, normetanephrine, 3-methoxytyramine, 3,4-dihydroxyphenylalanine, 5-hydrocyindoleacetic acid and homovanillic acid by HPLC separations and electrochemical detection.

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