Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 883–886

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

cis- and *trans*-*N*-Benzyl-octahydrobenzo[*g*]quinolines. Adrenergic and Dopaminergic Activity Studies

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Received 31 October 2000; revised 5 January 2001; accepted 31 January 2001

Abstract—In vitro assays on a series of *cis*- and *trans*-octahydrobenzo[*g*]quinolines indicated an unusual trend of affinities at the dopaminergic receptors and α adrenoceptors. The *trans N*-benzyl analogues exhibited affinity at the α_2 as well as the D1-like receptors whereas their *N*-unsubstituted congeners showed a distinct preference for the α_2 adrenoceptor. Enhanced activity for the α_2 receptors was also exhibited by the *cis N*-benzylated isomers. These observations are interpreted by theoretical calculations.

Introduction

We have recently reported the synthesis of a series of octahydrobenzo[*g*]quinolines along with the preparation of their -[*f*] isomers.[1] The synthetic methodology—aiming at the preparation of α adrenergic and dopaminergic drugs—involved the reaction of 3-(2′-(methoxycarbonyl)-ethyl)-2-tetralones with benzylamine, followed by $LiAlH_4$ reduction of the intermediate enamide and subsequent $NaBH_4$ reduction of the enamine double bond (Scheme 1). This process, although furnishing the *trans* analogues **1a**–**b** as the predominant products, allows for the isolation of small amounts of the minor *cis* isomers. Initial SAR studies on octahydrobenzo[*g*]quinolines focused on the *trans* compounds, expected by literature precedents to be the active isomers.[2] However, preliminary evaluation of the pharmacological profile of **1a** indicated that some activity also rests on the *cis* isomer. Prompted to evaluate the pattern of activity of the *cis* congeners we isolated **1b** and tested it for α_1, α_2, D1, and D2 receptor affinity.

Results and Discussion

Binding assay results are presented in Tables 1 and 2.

Comparison of activities of the *trans* secondary amines **2a** and **2b** with their *N*-benzylated *cis* and *trans* congeners reveals an unusual trend of activities. As reported previously, *trans* **2a** exhibits affinity only for the α_2 receptor ($IC_{50} = 130$ nM).[1] Its *N*-benzylated derivative, *trans* **1a** binds weakly to the D1 receptor ($IC_{50} = 1.2$ μM), shows moderate affinity for the α_1 and strong affinity for the α_2 adrenoceptor as indicated by the respective IC_{50} values of 218 and 5.9 nM. The *cis* **1a** isomer has a pharmacological profile similar to that of *trans* **2a**: it is dopaminergically inactive and shows (moderate) affinity for the α_2 receptor with an $IC_{50} = 214$ nM.

The 7-methoxy-substituted analogues exhibit the same trend of affinities. The secondary amine *trans* **2b** binds only at the α_2 adrenoceptor ($IC_{50} = 67.5$ nM), whereas introduction of the *N*-benzyl moiety in *trans* **1b** expands the affinity of the drug to the D1, α_1, and α_2 receptors with a distinct preference to the latter ($IC_{50} = 6.0$ nM). The *cis N*-benzyl isomer (*cis* **1b**) is dopaminergically inactive and exhibits 18 times higher affinity ($IC_{50} = 38$ nM) for the α_2, than that for the α_1 receptor ($IC_{50} = 667$ nM).

This reversal of activity of *cis* and *trans* octahydrobenzo[*g*]quinolines calls for an interpretation that should be based on the topology of each receptor and the structural requirements that each analogue may fulfill for an efficient 'docking' in the receptor sites. Differences in the pharmacological profile of the *trans* **2a**–**b** and *trans* **1a**–**b** congeners may be attributed to the presence of the *N*-benzyl moiety: the secondary amines are

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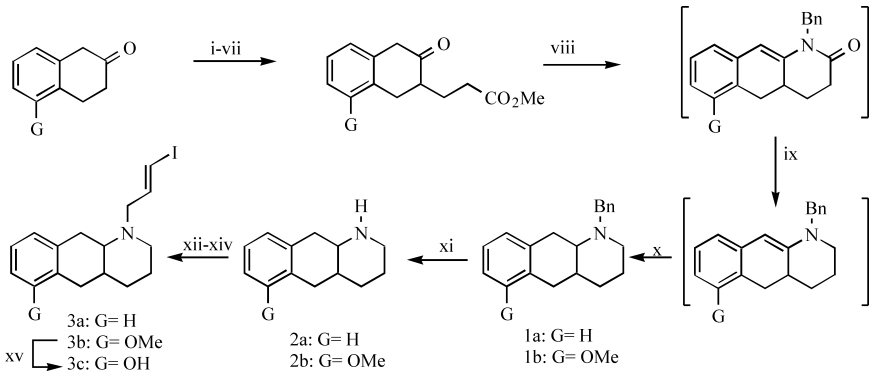
0960-894X/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0960-894X(01)00076-2



Scheme 1. Reagents and conditions: (i) $(CH_3O)_2CO$, CH_3ONa, reflux; (ii) LDA (2 equiv.), allyl bromide, −78 °C; (iii) LiCl, DMSO, H_2O, reflux; (iv) $HOCH_2CH_2OH$, *p*-TsOH, reflux; (v) disiamyl borane, H_2O_2, NaOH, 0 °C; (vi) Jones reagent, 0 °C; (vii) CH_3OH, H_2SO_4 (conc.), rt; (viii) $BnNH_2$, AcOH, reflux; (ix) $LiAlH_4$, rt; (x) $NaBH_4$, rt; (xi) H_2, 10%Pd/C, EtOH, rt; (xii) allylbromide; (xiii) Bu_3SnH, AIBN; $PhCH_3$, reflux; (xiv) I_2; (xv) HBr 48%, reflux.

binding only at the α_2 receptor while *N*-benzylation results in efficient interaction of *trans* **1a–b** with the D1 and α_1 receptors and a 10-fold increase in their α_2 affinity. Similar differences in the profile of the *trans* **1a–b** and *cis* **1a–b** isomers may be due to conformational changes resulting from the *trans* and *cis* fusion of the B and C rings in each system. The *cis* **1a–b** isomers are dopaminergically inactive and exhibit a distinct preference to the α_2 adrenoceptor.

To further elucidate the structural aspects which this pattern of activities is based on, we performed ab initio calculations to study the orientation of the functional groups of the energy-minimized conformers. Results are depicted in Figures 1 and 2.

With the aromatic moieties of *cis* and *trans* **1b** superimposed, rings B and C of t*rans* **1b** are extended at the same plane of the aromatic ring in contrast to the *cis* **1b** isomer where the *cis* fusion of the B and C rings 'locks' the system in a conformation significantly deviating from the desired antiperiplanar conformation of the phenethylamine moiety,[2] thus diminishing dopaminergic activity (Fig. 1). This pattern of activity may also reveal differences in 'receptor tolerance'. It has long been proposed that the presence of 'lipophilic pockets' is a crucial factor for the binding of drugs to dopamine receptors. These lipophilic cavities may effectively fit nitrogen substituents such as small aliphatic chains with an optimum interaction with the propyl moiety, (a fact known as the '*N*-propyl phenomenon')[2,3] although tolerance to *N*-substituents as large as iodopropenyl has been reported in the literature.[1,4] Although the above results are not decisive, it is tempting to propose that these 'lipophilic pockets' have different orientation in each receptor. D2 receptors appear intolerant to the structural systems assayed in this study. As mentioned before, only the presence of additional receptor binding moieties, such as the 6-hydroxyl group in compound **3c**, allows for an efficient 'docking' into the receptor cavity, still resulting in moderate D2-activity.[1] The D1 receptor appears tolerant to conformations with only minor deviations of coplanarity of the B and C rings (compounds *trans* **1a–b**), yet the presence of the benzyl group appears crucial for the drug's affinity.

This pharmacological profile could be related to the activity of dihydrexidine[5,6] (Chart 1), a full efficacy D1 agonist structurally similar to our systems: superimposition of the aromatic rings in *trans* **1a** and dihydrexidine indicates a similar orientation of the aromatic ring D in dihydrexidine and the *N*-benzyl substituent in *trans* **1a** (Fig. 2). It is worth noticing here that the D1 binding compounds have also the highest affinity for the α_2 receptor, an affinity profile we observed in previous studies.[1,7]

Table 1. Inhibition of [^{3}H]-spiroperidol and [^{3}H]-SCH-23390 binding to rat striatal membranes[a]

Drug	IC_{50} (μM)	
	[^{3}H]-Spiroperidol	[^{3}H]-SCH-23390
trans **2a**	NA[b]	NA
trans-**1a**	NA	1.20±0.70
cis-**1a**	NA	NA
trans **2b**	NA	NA
trans-**1b**	NA	0.45±0.21
cis-**1b**	NA	NA
(±) ADTN[c]	0.70±0.02	—
(−) APO[d]	0.22±0.05	0.43±0.05

[a]Experiments were performed 2–4 times in duplicate.
[b]Not active up to a concentration of 5 μM.
[c]5,6-Dihydroxy-2-aminotetralin.
[d]Apomorphine.

Table 2. Inhibition of [^{3}H]-prazosin and [^{3}H]-rauwolscine binding to rat cortical membranes[a]

Drug	IC_{50} (nM)	
	[^{3}H]-Prazosin	[^{3}H]-Rauwolscine
trans **2a**	NA[b]	130±61
trans-**1a**	218±110	5.9±1.9
cis-**1a**	739±260	214±109
trans **2b**	2.200±700	67.5±3.5
trans-**1b**	588±115	6.0±1.8
cis-**1b**	667±177	38±24
Noradrenaline	1500[c]	750[c]

[a]Experiments were performed 2–4 times in duplicate.
[b]Not active up to a concentration of 5 μM.
[c]Values from ref 18.

The dependence of the receptor binding properties of octahydrobenzoquinolines on the *cis*/*trans* fusion of their ring system has been considered before. According to a D2 receptor model described by Teeter et al.[8] the *cis* and *trans* *N*-phenethyl analogues of octahydrobenzo-[*f*]quinolines must adopt different orientations relative to the receptor's transmembrane helices in order to efficiently bind onto the D2 site. These tricyclic octahydrobenzoquinoline systems are considered 'good measuring sticks' for the evaluation of an 'ancillary pocket' fitting the nitrogen substituent. The α_2 affinity observed in both *cis* and *trans* systems is in agreement with earlier observations on benzo[*f*]quinoline SAR studies, leading to the suggestion that 'the spatial orientation of the terminal nitrogen relative to the benzene ring is not as crucial for the α_2 adrenoceptor activity' as it is for the dopaminergic system in study.[9]

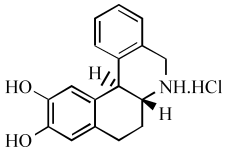


Chart 1. Dihydrexidine.

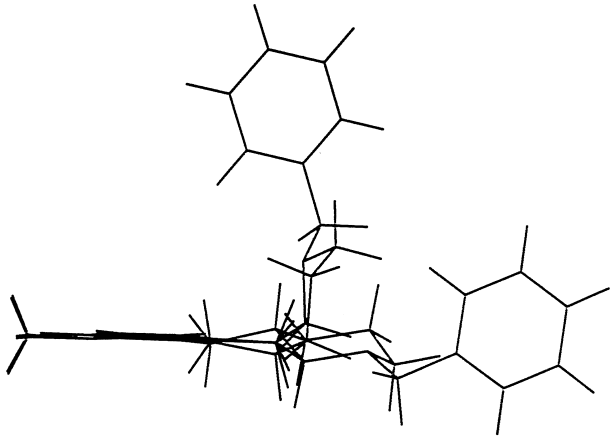


Figure 1. With the aromatic rings of *cis*- and *trans*-**1b** superimposed, the *trans* compound extends to an antiperiplanar conformation of the phenethylamine moiety, whereas the *cis* congener adopts an angular geometry. The distance between the nitrogen atoms in the two isomers is 2.636 Å.

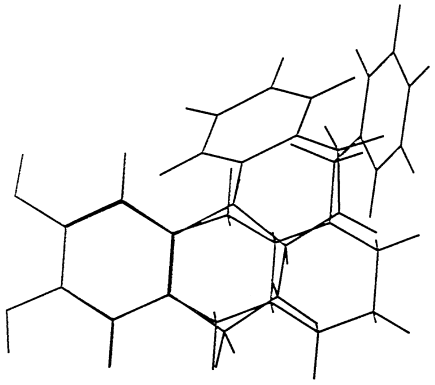


Figure 2. Superimposed structures of *trans*-**1a** and dihydrexidine. The nitrogen atoms distance is 0.5 Å. Another isoenergetic conformation of dihydrexidine brings the benzyl groups to a closer proximity; however the N–N distance increases to 2.0 Å. In either case the *N*-benzyl moieties extend towards the direction of a possible 'ancillary pocket'.

Apparently, one cannot draw any conclusions from these studies regarding the function of the drugs as agonists or antagonists. Radioligand binding assays and the affinities of drugs for a specific receptor cannot be used as an index of the drug's activity. DA-agonist activity has been reported for a number of *trans* octahydrobenzo[*g*]quinolines with at least one hydroxy or methoxy substituent at the 6-position; *N*-propyl substitution though, was consistently necessary for optimal activity.[15–17] Similarly, α_2-agonist activity was reported for 6,7-dihydroxy congeners, the *N*-propyl analogue being the one most potent. The affinity of the *trans* **1b** analogue for both D1 and α_1/α_2 receptors might be related to an agonist profile, however functional studies are essential to assess the potential of this compound.

In conclusion, the results of our study provide additional information on the dopaminergic receptor and adrenoceptor topology, contributing to the ongoing efforts for the strategic planning of drug design.

Theoretical Treatment

In order to find out the bonding properties and the orientation of the functional groups of these structures we performed ab-initio geometry optimizations. All the calculations were performed with the GAUSSIAN 94 program package.[10] The first principle treatment of the structures presented here involves Density Functional Theory (DFT) calculations with the three-parameter hybrid functional of Becke[11] using the Lee–Yang–Parr correlation functional,[12] (B3LYP). The atomic basis set that we used, LANL2DZ, developed by Hay and Wadt,[10] includes relativistic effective core potentials for heavy atoms (like iodine) and is of double zeta quality. The ab-initio treatment of such large systems is computationally expensive, but produces results free of parameters and more accurate than molecular mechanic calculations, commonly used for this type of systems.[13] The method that we use here, DFT/B3LYP, has also proved to be very accurate for small organic molecules.[14] All the geometries presented in this work are fully optimized with this method.

Pharmacology

The pharmacological behavior of the octahydrobenzo[*g*]quinoline derivatives was examined with radioligand binding assays as previously described.[18] The dopaminergic activity of these compounds was studied by examining their inhibition of the specific binding of [^{3}H]-spiroperidol and [^{3}H]-SCH23390 to D2 and D1 receptors, respectively, in rat striatal membranes. The same compounds were also tested for α_1 and α_2 adrenergic activity. [^{3}H]-prazosin and [^{3}H]-rauwolscine were used to label the α_1 and α_2 adrenergic receptors in rat cortical membranes, respectively. Compounds that

displayed inhibitory constant (IC_{50}) values of more than 5 μM were characterized as inactive.

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