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Design and discovery of 1,3-benzodiazepines as novel dopamine antagonists

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ABSTRACT

A series of novel 1,3-benzodiazapine based D1 antagonists was designed according to the understanding of pharmacophore models derived from SCH 23390 (**1b**), a potent and selective D1 antagonist. The new design features an achiral cyclic-amidine that maintains desired basicity. Solid phase synthesis was developed for SAR development of the novel dopamine antagonists.

The neurotransmitter dopamine plays important roles in neuronal functions involving reward processes, approach behavior, economic decision making, adaptive behavior, motion and cognition.[1] Dopamine receptors fall into two subclasses, with D1 and D5 receptors sharing homology and coupling to Gs, and D2, D3, and D4 receptors coupling to Gi. Selective D1 receptor antagonists have been studied as potential therapeutics for Parkinson's disease, psychotic behavior, substance abuse and obesity[2] in animal models and in human clinical trials.[3]

A representative benzazepine class of D1 antagonists **1a** and **1b** (SCH 23390)[4] are conformationally constrained catecholamine analogs. According to a D1 receptor mapping study,[5] a phenol OH group, an H-bond donor with a well-defined directionality,[6] and a basic nitrogen placed 7 Å apart are the key features of the pharmacophore represented by **1b**. The N3-methyl group is not required for D1 binding affinity.[7] The 'accessory phenyl' group at the C5 position is preferred to be somewhat coplanar with the phenol ring and can be replaced with a large range of other hydrophobic groups (Fig. 1).

In an effort to identify novel D1 antagonists, we decided to examine the 1,3-benzodiazepine core structure **1** as a potential replacement for the benzazepine ring in **1a** and **1b**. *N*-aryl amidine and N-guanidine model systems have pK_a values around 8–9 and 10–11, respectively (Fig. 2),[8] within a range matching the basicity of the *tert*-azepine nitrogen center in **1a** and **1b**.[9]

The geometry of the 1,3-benzodiazepine (**1**) is close to **1b** as demonstrated by superimposing the MMFF94 minimized conformations of the two core structures (Fig. 3).[10] Despite the fact that

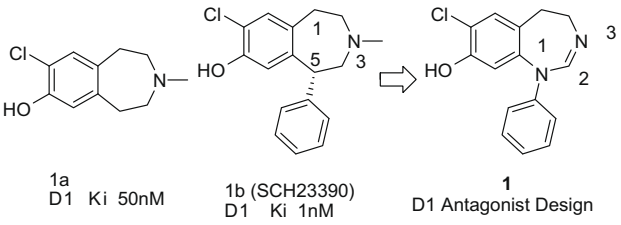

Figure 1. Novel D1 antagonist design based on **1b** (SCH 23390).

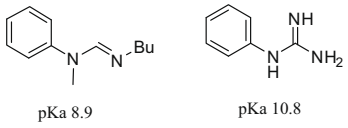

Figure 2. pK_a values of *N*-phenyl amidine and *N*-phenylguanidines.

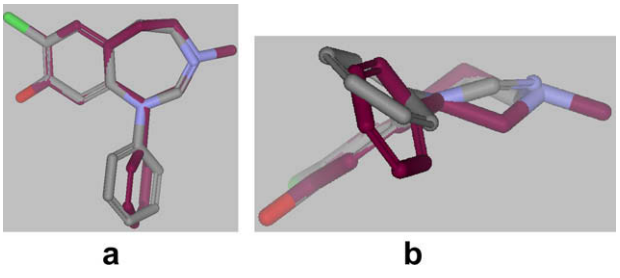

Figure 3. The top (a) and side (b) views of superimposition of minimized conformation of **1b** (purple) and **1** (grey) with hydrogens removed for clarity. Cl—green, O—orange, N—blue.

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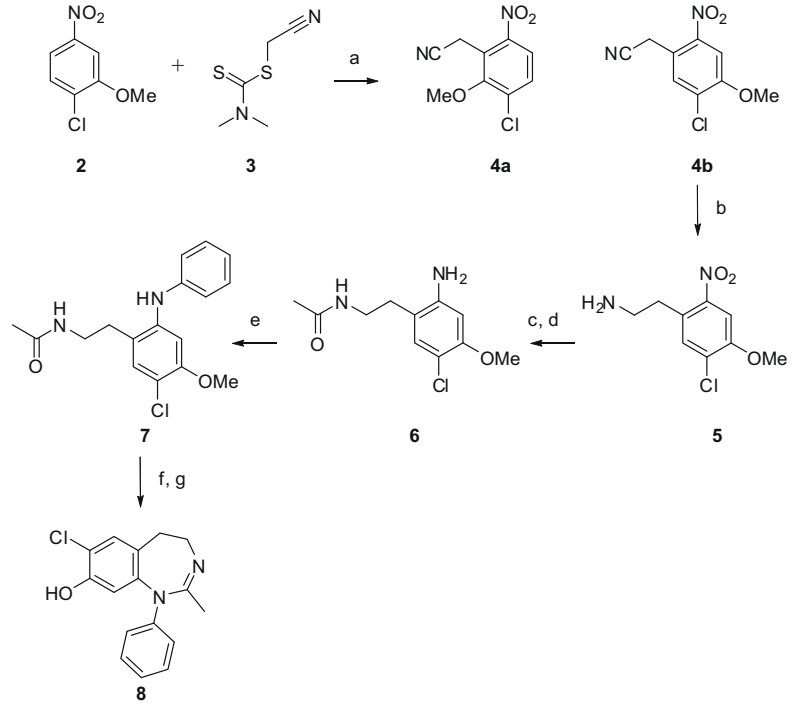
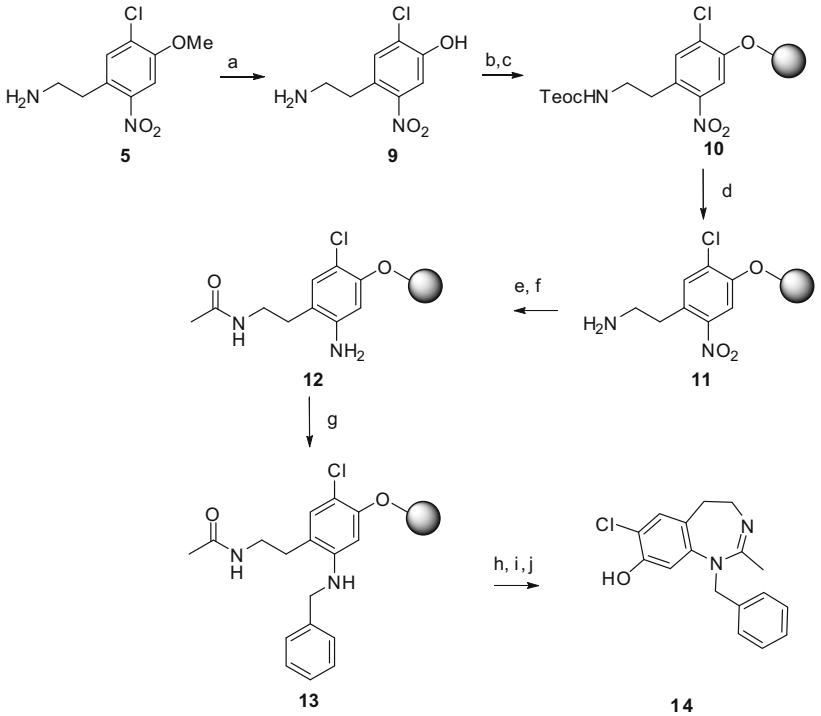
the C5 sp^3 center with the attached phenyl group in **1b** is replaced with a sp^2 nitrogen (N1) in **1**, both scaffolds can place the substituents in approximately the same region based on the minimized conformations. The new achiral scaffold offers ease of synthesis and an attractive way to explore SAR at the C2 and N1 positions. In addition, absence of the metabolically labile N3-methyl group in the new core may address this major metabolic pathway observed in SCH23390 and improve bioavailability.[11]

The preparation of a prototype 1,3-benzodiazepine **8** was accomplished using the synthetic route shown in Scheme 1.

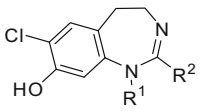


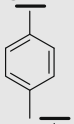
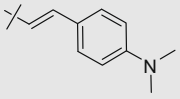
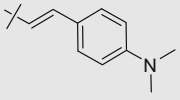
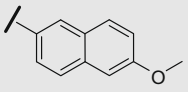
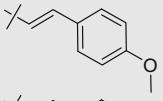
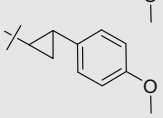
Scheme 1. Reagents and conditions: (a) DMSO/NaOH 60% yield, **4a**/**4b** ratio 1:2; (b) BH_3/THF; (c) acetic anhydride/TEA/DCM; (d) $SnCl_2{\cdot}2H_2O$; (e) $PhB(OH)_2/Cu(OAc)_2$/TEA/4 Å MS; (f) $POCl_3$; (g) BBr.



Scheme 2. Reagents and conditions: (a) BBr_3; (b) TMS-ethyl *p*-nitrophenyl carbonate/K_2CO_3/THF/H_2O; (c) brominated Wang resin/$Bu_4N^+I^-$/DIEA/DMF,60 °C/6 h; (d) TBAF/THF; (e) acetic anhydride/DIEA/DCM; (f) $SnCl_2{\cdot}2H_2O$/DIEA; (g) pre-formation of imine overnight, $NaBH_4$/DCE/MeOH; (h) 50%TFA/DCM; (i) HCl salt conversion; (j) $POCl_3$/DCE, 85 °C/4.5 h, then HPLC purification.

Table 1
1,3-Benzodiazepines[a]



Compound	R^1	R^2	D1 K_i (nM)	D2/D1
8		Me	200	36
14		Me	930	3
15		Me	87	32
16		Me	181	55
17		Me	321	31
18			154	23
19			370	8
20	H		198	4
21	H		442	17
22	H		475	42
23	H		284	7
24	H		206	3
25	H		311	3
26	H		1500	1

[a] Each K_i value is an average of three determinations, and the standard errors for all K_i determinations are less than 10%.

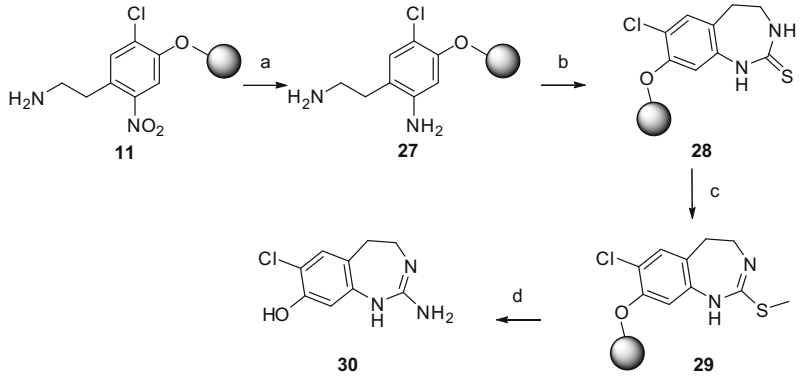
Compound **3**, which was generated with *N*,*N*-dimethyl thiocarbamate and chloroacetonitrile, reacted with commercially available *m*-MeO-*p*-Cl-nitrobenzene to produce a 1:2 mixture of **4a** and **4b** with a combined yield of 60%.[12] The nitrile **4b** was reduced using BH_3–THF to give amine **5**, which was subsequently acetylated and reduced using $SnCl_2{\cdot}2H_2O$ to give amide **6**. Aniline N-arylation chemistry using phenyl boronic acid with anhydrous $Cu(OAc)_2$ generated compound **7**.[13] Cyclization of compound **7** under reflux with $POCl_3$ generated diazepine **8** after demethylation using BBr_3 in DCM in high yield.[14]

Compound **8** binds to human D1 dopamine receptors with an affinity of 200 nM.[15] Even though its affinity is two orders of magnitude weaker than SCH 23390, diazepine **8** is still an attractive starting point for further optimization. The C2 SAR development would offer an opportunity for further improvement of binding affinity. Enhancement of the basicity of the amidine group through replacement of the N-1 phenyl with an alkyl or benzyl group may also lead to better D1 receptor binding affinity. In order to efficiently expand the SAR of this scaffold, we decided to develop a solid phase synthesis route (Scheme 2). Thus phenol **9**, obtained by demethylation of **5**, was reacted with Teoc–OSu to give corresponding Teoc carbamate, which was subsequently loaded onto the brominated Wang resin. The loading level was determined to be 0.8 mmol/g after TFA cleavage of **10** to give compound **9**. Treatment of **10** with TBAF led to the resin bound intermediate **11** which was subsequently acetylated with acetic anhydride to give **12**. Amide **12** was reduced using $SnCl_2{\cdot}2H_2O$ in the presence of DIEA to prevent premature cleavage of the intermediate from the resin. Subsequent reductive alkylation of **12** following an imine pre-formation and fast $NaBH_4$ reduction sequence led to the resin bound **13**. After TFA cleavage, **13** was cyclized with $POCl_3$ followed by HPLC purification to generate the final diazepine **14**.

Similarly, solid phase N-arylation chemistry using boronic acid and $Cu(OAc)_2$ were used to generate N1-arylbenzodiazapines.[16] The affinities for human D1 and D2 receptors were determined for a number of benzodiazepines generated in this fashion (Table 1). The highest affinity was observed with R^1 as 3-thienyl (**15**). Methyl substitutions on phenyl (**16** and **17**) had little impact on binding affinity, while replacing phenyl with benzyl (**14**) led to an approximately fourfold increase in the K_i value. Other C2-substitutions were shown to lack major impact on binding affinity. For example, replacement of C2-Me with 2-(*p*-dimethylaminophenyl)vinyl did not change the D1 affinity or D1/D2 selectivity (**8**, 200 nM vs **18**, 154 nM**).** N1-substituents are not required to maintain comparable level of D1 receptor affinity; for example, **23**. This mirrors similar findings with the benzazepine class of D1 antagonist represented by **1a**.[4a] However, the fact that diazepine **26**, having the smallest R^2 groups, showed the weakest D1 affinity indicates that either R^1 or R^2 must be a relatively large hydrophobic group (Scheme 3).

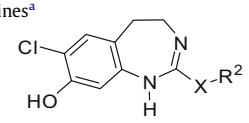
One major difference between the diazepine ring in **1** and azepine in **1b** is basicity, with the 1,3-benzodiazepines being at least an order of magnitude less basic. It was of interest to determine whether increased basicity would lead to improved D1 receptor binding affinity. One way to boost the basicity of the benzodiazepines is to replace the cyclic *N*-aryl amidine with a cyclic *N*-aryl guanidine.[8b] Synthetically, this was easily done with a slight modification of the solid phase chemistry. Therefore, resin bound compound **11** was reduced with $SnCl_2{\cdot}2H_2O$ in the presence of an excess triethylamine. Thiophosgene treatment of **27** under basic conditions led to cyclic thiourea **28,** which was further activated though treatment with MeI to give **29**. Subsequent treatment with ammonia in THF led to diazepine **30** after TFA cleavage and HPLC purification.

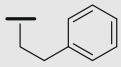
In contrast to **1a**, the un-substituted 2-amino-1,3-benzodiazepine (**30**) lacks D1 receptor affinity (Table 2). Substitution on the exocyclic amino group led to improved D1 binding affinity with the most hydrophobic group (**31**) having the lowest K_i value. This agrees with the SAR trend in the cyclic-amidine series in Table 1 (**20**–**26**). It is clear that the cyclic *N*-aryl guanidine did not improve the binding affinity compared to the cyclic *N*-aryl amidine counterpart.



Scheme 3. Reagents and conditions: (a) $SnCl_2{\cdot}2H_2O$/TEA (b) thiophosgene/TEA; (c) MeI; (d) (i) NH_3/THF/sealed tube/Heat, (ii) TFA, (iii) HPLC purification.

Table 2
SAR 2-aminobenzodiazepines[a]



Compound	X	R^2	D1 K_i (nM)	D2/D1
30	NH	H	10,200	1
31	NH		129	12
32	NH		391	12
33	NH		465	1
34	S		445	2
35	NH		575	6
36	NH	Me	783	13
37	S	Me	900	5

[a] Each K_i value is an average of three determinations, and the standard errors for all K_i determinations are less than 10%.

Another fundamental difference between the benzazepine and benzodiazepine scaffolds is the geometry of the basic nitrogen. Even though the basicity of benzodiazepines based on phenyl amidine or phenyl guanidine scaffold may approach the same range of a *tert*-amine, the amidine nitrogen (sp^2) geometry differs from that of the *tert*-amine (sp^3) in **1b** (Fig. 3). If the directionality of these interactions involving the nitrogen electron lone pair, or its protonated form, is important, the triangular coplanar geometry of the amidine would result in some intrinsic differences which will alter the binding affinities. Further investigation in this direction may offer more insight to this question and would certainly facilitate exploration of similar designs applicable to other dopamine and serotonin receptor ligands.

Acknowledgments

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14. (a) All new compounds gave satisfactory ^1H NMR and MS in accord with their assigned structure. All final targets showed LC–MS purities >95%. (b) Analytical data for **8**: LC–MS, $M^+ = 287$. ^1H NMR (CD_3OD, ppm), δ 7.58–7.63, m, 3H; 7.49–751, m, 2H; 7.27, s, 1H; 6.49, s, 1H; 3.76–3.77, m, 2H; 3.32–3.33, m, 2H; 2.20, s, 3H.
15. Ltk- cells stably expressing D_1 and D_2 receptors were processed for D1 and D2 receptor binding with [^3H] SCH 23390 as the ratio ligand. For detailed assay information, see Ref. 6.
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