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Remote functionalization of SCH 39166: Discovery of potent and selective benzazepine dopamine D_1 receptor antagonists

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ABSTRACT

A series of novel benzazepine derived dopamine D_1 antagonists have been discovered. These compounds are highly potent at D_1 and showed excellent selectivity over D_2 and D_4 receptors. SAR studies revealed that a variety of functional groups are tolerated on the D-ring of known tetracyclic benzazepine analog **2**, SCH 39166, leading to compounds with nanomolar potency at D_1 and good selectivity over D_2-like receptors.

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Dopamine (DA) receptors are a class of G protein-coupled receptors that are prominent in the vertebrate central nervous system. There are five subtypes of dopaminergic receptors have been reported (D_1–D_5). These belong to two main subgroups, D_1-like and D_2-like. The D_1 like subgroup includes the D_1 and D_5 receptors, while the D_2-like subgroup includes the D_2–D_4 receptor subtypes.[1a,1b] It has been well documented that dopamine D_1 antagonism affects the dopamine reward system in the brain, eliminating or reducing the dopamine mediated food-craving component of eating.[2] Thus an antagonist of dopamine D_1 receptor might be useful for the treatment of obesity and related disorders.

The discovery of SCH 23390 (**1**), a selective dopamine D_1 antagonist, spurred a great amount of effort in the dopamine receptor research.[3] This compound is often used as a standard in dopamine assay throughout pharmaceutical industry as well as in academic laboratories. Later, a conformationally restricted analog, SCH 39166 (**2**) was discovered.[4] Several D_1 antagonists have thus been discovered such as **1a–e** as shown in Figure 1.[5–8] Compound **2** also known as ecopipam, is a selective dopamine D_1/D_5 receptor antagonist that was in phase III clinical trials for treatment of obesity.[9,10] The clinical results of ecopipam on obese humans revealed a significant dose dependent loss of body weight for patients on a low calorie diet and drug therapy versus those on diet alone. Ecopipam is better absorbed in humans than in animals, which initially presented a challenge in generating high exposure multiples for safety evaluation. A third generation compound would preferably not have this liability. Introduction of catechol isosteres on the A-ring of SCH 39166 was previously reported by our group as one way to improve PK in the series.[11] This present contribution describes the remote functionalization of D-ring of SCH 39166 and further SAR development.

A large quantity of optically pure SCH 39166 (**2**) was available in house and served as a convenient starting material for our SAR studies.[12] It had been reported that electrophilic reactions occur at the alpha position of phenol in the A-ring.[11] This undesired reactivity was circumvented by deactivating the A-ring by the protection of phenolic group with a 4-nitrobenzoyl group. At first, we decided to study bromination by use of various electrophilic brominating agents. Conditions such as Br_2/HCO_2H, NBS, Br_2/HOAc, $Hg(OAc)_2$/TFA/Br_2 or $Hg(OCOCF_3)_2$/TFA/Br_2 afforded either no product or a complicated mixture of products. After much experimentation, we have found that bromination of **3** on solid surface (neutral alumina)[13] gave mono-brominated products in about 50% isolated yields (**4**:**5** = 1:2, and traces of 3-bromo derivative) after deprotection of the phenolic group as described in Scheme 1.[14] The structure of the bromination products were assigned based on the proton NOE data. Initial analysis of the binding properties of **4** and **5** in the dopamine D_1 assay[20] suggested that compound **5** was more active (3–4-fold) than compound **4.** Thus we decided to focus on the SAR development at position 4 of the D-ring of SCH 39166 (see Scheme 1 for numbering). Other electrophilic substitution reactions such as nitration, chlorosulfonylation,

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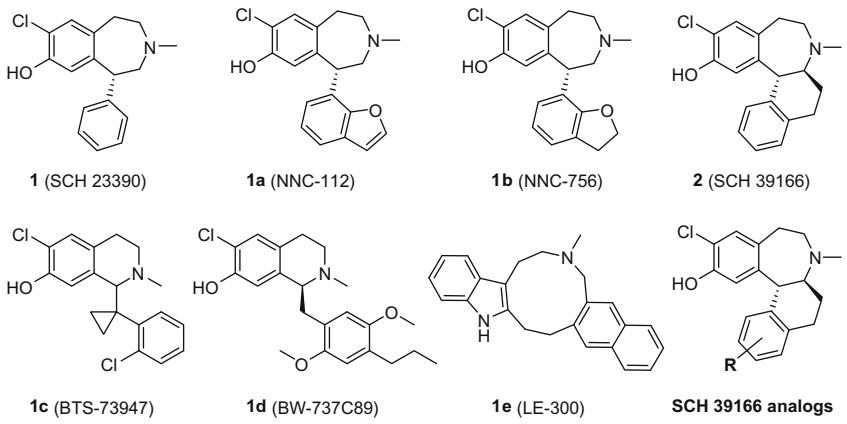
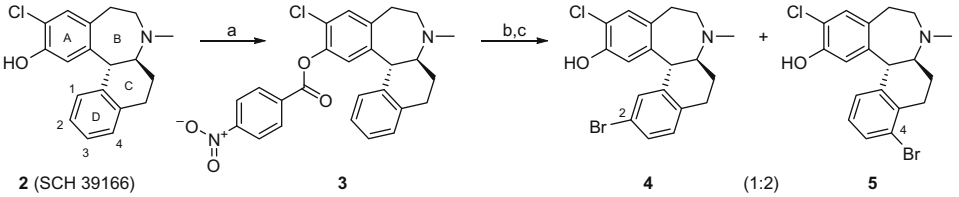
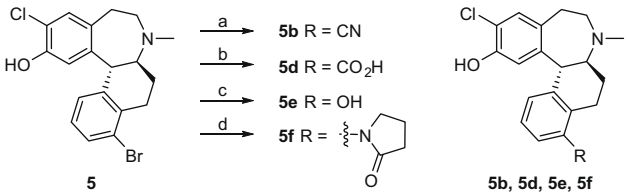


Figure 1. Representative D_1 antagonists (**1**, **2**, **1a**–**e**).



Scheme 1. Reagents and conditions: (a) 4-Nitrobenzoyl chloride, TEA, CH_2Cl_2, rt, 98%; (b) Br_2/Al_2O_3, rt, 72%; (c) KOH, THF–H_2O, rt, 51%.

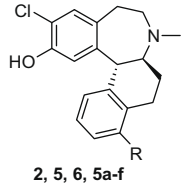


Scheme 2. Reagents and conditions: (a) $Zn(CN)_2$, $Pd_2(dba)_3$, DPPF, DMF·H_2O, 88%; (b) NaH, THF then *n*-BuLi, THF, −78 °C, then diethyl carbonate, THF, −78 °C, 88%, then LiOH, THF–H_2O, 70 °C, 76%; (c) NaOH, $CuSO_4$, H_2O, 135 °C, 41%; (d) pyrrolidinone, Cu powder, K_2CO_3, DMF, 150 °C, 25%.

and formylation were carried out and those results are reported in the following Letter by L. Qiang et al. To that end, compound **5** was converted to **5b**–**f** by protocols described in the literature (Scheme 2).[15–18] The phenolic group of the 4-Br-derivative **5** was protected with a TBS group followed by lithiation and DMF addition to provide aldehyde **6** that was condensed with various O-substituted hydroxyl amines to give oxime analogs **7a**–**d**. The intermediate **5** was also used for the standard Suzuki coupling reactions as described in Scheme 3.[19]

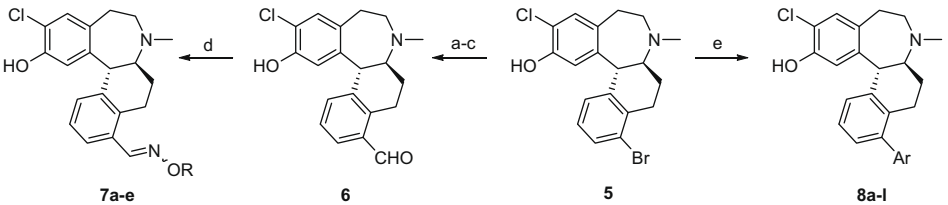
The benzazepine derivatives **5–8** were tested for their binding to dopamine receptors.[20] The 4-bromo derivative **5** was active at D_1 (K_i = 3 nM) and D_5 (K_i = 7.5 nM) and relatively inactive at D_2

Table 1
Dopamine binding properties for compounds **2**, **5**, **6**, **5a**–**f**



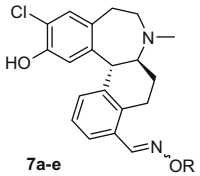
Compd	R	K_i[a] (nM)			
		D_1	D_5	D_2	D_4
2	–H	1.2	2.0	980	5520
5	–Br	3	7.5	1693	10,000
6	–CHO	2.6	3.3	1371	5972
5a[b]	$-CH_2OH$	2	7.4	1647	6281
5b	–CN	2.8	89	1328	10,000
5c[c]	$-CO_2Me$	2.3	3.7	923	4830
5d	$-CO_2H$	38	na	420	na
5e	–OH	0.6	1.4	440	3987
5f	Pyrrolidine-2-one	3.1	26.9	1370	10,000

na = not available.
[a] The standard error was 10%, and variability was less than twofold from assay to assay.
[b] Compound **5a** was obtained by the reduction of **6** using sodium borohydride.
[c] Compound **5c** was obtained by lithiation followed by dimethyl carbonate addition.



Scheme 3. Reagents and conditions: (a) TBSCl, TEA, CH_2Cl_2, rt; (b) *n*-BuLi, THF, −78 °C, DMF; (c) TBAF, THF, rt, 50% for three steps; (d) H_2N–OR.HCl, Py, 70 °C, 60–70%; (e) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, MeOH–Tol, 90 °C, 60–80%.

Table 2
Dopamine binding properties for compounds **7a–e**



7a-e

Compd	R	K_i[a] (nM)			
		D_1	D_5	D_2	D_4
7a	H	1.6	3.3	882	4370
7b	Me	4.4	22	483	7506
7c	Et	1.8	10	217	5886
7d	Bn	0.2	2.5	69	8344
7e	Ph	1.0	2.1	124	10,000

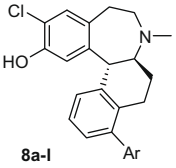
[a] The standard error was 10%, and variability was less than twofold from assay to assay.

and D_4. A wide variety of functional groups such as –CHO, $–CH_2OH$, –CN, $–CO_2Me$, –OH and pyrrolidine-2-one were well tolerated at 4-position of the D-ring as shown in Table 1 (K_i ranges from 0.6 to 3.1 nM). All these analogs showed remarkable selectivity over the D_2-like receptors. The free carboxylic acid functionality was less tolerated than the corresponding methyl ester group. Structurally similar compounds showed lower single digit nanomolar activity in a functional FLIPR assay (K_b value), confirming dopamine D_1 antagonism in this series.

The oxime analogs (**7a–e**) were also generally well tolerated in the benzazepine series as shown in Table 2. The *O*-benzyl oxime compound **7d** is the most potent in this series with a D_1 K_i of 0.2 nM, however affinity at the D_2 receptor was notably higher.

Highly potent dopamine D_1 antagonists were obtained by the introduction of an aromatic group at the 4-position of the D-ring of **2**. Almost every aromatic group was well tolerated as shown in Table 3. Simple phenyl substitution afforded subnanomolar compound **8a** (D_1 K_i = 0.2 nM). Similar results were obtained by introducing various substitutions (electron withdrawing or donating) on the pendant phenyl ring (**8b–i**). Heterocyclic rings at position 4 such as, 2-thienyl (D_1 K_i = 0.9 nM), pyridinyl (D_1 K_i = 0.3 nM), and indolyl (D_1 K_i = 0.6 nM) were also potent D_1 compounds (**8j–l**). It was observed that the introduction of some functional groups at the *para* position of pendant phenyl ring resulted in significant D_2 activity (compounds **8h** and **8l**).

Table 3
Dopamine binding properties for compounds **8a–l**



8a-l

Compd	Ar	K_i[a] (nM)			
		D_1	D_5	D_2	D_4
8a	Ph	0.2	na	79	na
8b	3-F–Ph	0.4	na	223	na
8c	3-CN–Ph	0.6	3.4	584	10,000
8d	$3\text{-}NO_2$–Ph	0.6	4.7	618	10,000
8e	$3\text{-}OCF_3$–Ph	2.3	na	1612	na
8f	3,5-di-F–Ph	0.9	na	312	na
8g	4-OMe–Ph	0.7	6.2	550	10,000
8h	$4\text{-}NMe_2$–Ph	0.7	na	12	na
8i	$4\text{-}CH_2OH$–Ph	0.7	na	89	na
8j	2-Thienyl	0.9	1.9	93	10,000
8k	4-Pyridinyl	0.3	10.5	756	5060
8l	1*H*-Indol-5-yl	0.6	na	51	na

na = not available.
[a] The standard error was 10%, and variability was less than twofold from assay to assay.

Table 4
PK profiles of selected compounds[a]

Compd	Rat PK (10 mg/kg po) $AUC_{0-6\ h}$ (h μg/mL)	C_{max} (ng/mL)	T_{max} (h)
2	156	72	0.5
8g	76	18	2
8j	353	90	2
8k	75	43	0.5

[a] Data are from pooled samples from two mice in cassette-accelerated rapid rat protocol as described in Ref. 21.

Having achieved the required dopamine D_1 potency, several compounds were selected for pharmacokinetic investigations in rat. The PK profiles are shown in Table 4.[21] The historic compound, SCH 39166 showed a reasonable pharmacokinetic profile, however introduction of 2-thienyl group at position 4 in the D-ring of **2** considerably increased the AUC and C_{max} (**8j**). On the other hand, 4-methoxy phenyl or 4-pyridinyl substitution (compounds **8g** and **8k)** did not improve the pharmacokinetic profile.

In summary we have achieved a large number of extremely potent dopamine D_1 antagonists based on the SCH 39166 scaffold. A highly substitutable sweet spot was discovered for optimizing overall compound properties. Compound **8j** showed a modestly improved pharmacokinetic profile. Further efforts in this series were discontinued as results from long term clinical trials of ecopipam revealed untoward mechanism-based side effects.[10b]

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14. *A typical experimental method is given below:* Compound **3** (5 g, 10.8 mmol) was mixed with 10 g of neutral alumina (chromatography grade, 50–200 micron). In a separate bottle, bromine (17.27 g, 10 equiv) was mixed with 10 g of alumina. The above mixtures were shaken together for 30 minutes and charged onto a small silica gel column. The excess bromine was eluted with hexane followed by dichloromethane. The column was eluted with 5% methanol/dichloromethane to get the bromination products (4.2 g). This was redissolved in 50 mL of THF–H_2O (9:1) and treated with 15 mL 1 N KOH. The mixture was stirred for 4 h, then neutralized with acetic acid. The contents were poured into a satd $NaHCO_3$/dichloromethane mixture and extracted with dichloromethane. The solvent was removed in vacuo and the products were isolated by silica gel chromatography eluting with 50% acetone/hexane. The products were further purified by repeated crystallization from ethanol. This purification method gave 1.2 g of compound **5** and 0.5 g of compound **4**: ES-MS: calcd for $C_{19}H_{20}BrClNO^+$ = 392.04, 394.04; found = 394.1 $(M+1)^+$.
15. Compound **5b** was prepared according to the following reference Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, 8193.

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18. Compound **5f** was prepared according to the following reference Aebischer, E.; Bacher, E.; Demnitz, F. W. J.; Keller, T. H.; Kurzmeyer, M.; Ortiz, M. L.; Pombo-Villar, E.; Weber, H.-P. *Heterocycles* **1998**, *48*, 2225.
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20. Ltk- cells stably expressing D_1 and D_2 receptors at a density of 4–7 pmol/mg protein were lysed in hypotonic buffer and centrifuged at 48,000*g*. Membrane pellets were frozen and stored at −80 °C for use in binding assays. Receptor affinities were determined by equilibrium binding experiments in which bound and free radioligand were separated by rapid filtration, and bound counts were quantified by liquid scintillation counting. For D_1 binding, the radioligand was [^{3}H] SCH 23390 (0.3 nM), and nonspecific binding was defined by addition of 10 μM unlabeled SCH 23390. For D_2 binding, the radioligand was [^{3}H] methylspiperone (0.5 nM) and nonspecific binding was defined using 10 μM (−)-sulpride. Competition binding data was analyzed using Graphpad Prism, in which curves fit a one-site competition model with a Hill Slope equal to or approximately 1. Mean K_i values from four separate determinations are reported. The SEM was below 15% in each case.
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