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Novel 2,3,4,5-Tetrahydro-1*H*-3-benzazepines with High Affinity and Selectivity for the Dopamine D_3 Receptor

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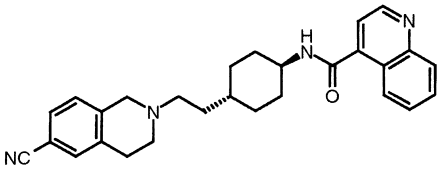
Abstract—Starting from the dopamine D_3 receptor antagonist SB-277011 **1**, a series of 2,3,4,5-tetrahydro-1*H*-3-benzazepines has been identified with high affinity for the dopamine D_3 receptor and selectivity over the D_2 receptor. The 3-acetamido-2-fluorocinnamide derivative **20** gave high D_3 receptor affinity (pK_i 8.4) with 130-fold selectivity over the D_2 receptor.

Dopaminergic neurotransmission is mediated by five receptor subtypes (D_1–D_5) which can be grouped into two receptor families. D_1-like receptors include the D_1 and D_5 subtypes, whereas D_2-like receptors include the D_2, D_3 and D_4 subtypes. Clinically effective antipsychotic agents share the property of dopamine D_2 and D_3 receptor antagonism. At the doses used in the clinic these drugs occupy D_3 as well as D_2 receptors and their antipsychotic effects could therefore be mediated via D_2 and/or D_3 receptors. Blockade of dopamine D_2 receptors in the striatum leads to serious extrapyramidal side-effects, which result in poor patient compliance and consequently poor control of the disease. However, dopamine D_3 receptors are preferentially located in limbic brain regions, such as the nucleus accumbens, where dopamine receptor blockade has been associated with antipsychotic activity. A selective dopamine D_3 receptor antagonist therefore offers the potential for an effective antipsychotic therapy, free of the serious side-effects of currently available drugs.[1–4] The presence of the dopamine D_3 receptor in projection regions of the mesocorticolimbic system also suggests a potential therapeutic role in reinforcement processes and drug abuse.[5] Recently, we described the novel tetrahydroisoquinoline SB-277011 **1**, a selective dopamine D_3 receptor antagonist with high oral bioavailability and CNS penetration in the rat.[6] As part of the investigation of structure–activity relationships around SB-277011, it was important to investigate whether modification of the tetrahydroisoquinoline ring would lead to retention of dopamine D_3 receptor affinity and selectivity.



SB-277011 **1**

Inspection of molecular models suggested that a 7-substituted 2,3,4,5-tetrahydro-1*H*-3-benzazepine would give a good overlap with the 6-substituted tetrahydroisoquinoline moiety of **1** (Fig. 1). However, the modelling also indicated the different spatial requirements of the benzazepine ring which might adversely affect D_3 affinity. This rationale led to the preparation of the 7-cyanotetrahydrobenzazepines **7**–**20** as shown in Scheme 1.

The known 7-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine **2**[7] was converted to the corresponding 7-cyano derivative **4** in five steps, the key stage involving a palladium catalysed cyanide displacement of the Boc-protected trifluoromethylsulfonate **3**. Reductive alkylation of **4** with aldehyde **5**[6] in the presence of $NaBH(OAc)_3$ introduced the cyclohexylethyl linker, and subsequent treatment with trifluoroacetic acid gave the primary amine **6**. Coupling of **6** to the appropriate acid in the

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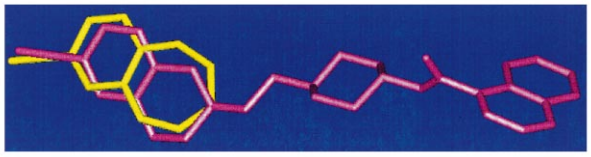


Figure 1. Overlap of a 7-cyano-2,3,4,5-tetrahydro-1*H*-benzazepine (yellow) with SB-277011 (magenta).

presence of EDC and HOBT in dichloromethane gave final compounds **7**–**20**, which were purified by chromatography and isolated as their hydrochloride salts.

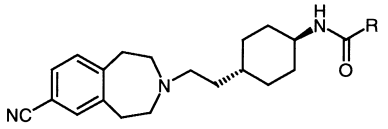
The effect of variation of the aryl carboxamide moiety on dopamine D_3 receptor affinity and selectivity over the dopamine D_2 receptor was investigated[8] (Tables 1 and 2), with the additional objectives of minimising the potential for cytochrome P450 interactions and optimising the pharmacokinetic profile.

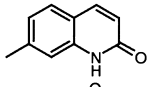
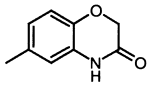
The 4-quinolinylcarboxamide **7** gave reduced dopamine D_3 receptor affinity (pK_i 7.6) compared to SB-277011 (Table 1). The 1-naphthylcarboxamide **8** had a similar profile, but the 5-quinolinyl derivative **9** was 100-fold selective for D_3 over the D_2 receptor. A 2-indolylcarboxamide moiety had previously been shown to give high dopamine D_3 affinity in the tetrahydroisoquinoline series,[6] so the corresponding benzazepine **10** was prepared. Although **10** maintained D_3 affinity, selectivity over D_2 was only 20-fold. In contrast, the 2-naphthyl derivative **11** had >100-fold selectivity. Isosteric replacement of the 2-naphthyl moiety was investigated in order to reduce lipophilicity and improve aqueous solubility. The 7-carbostyryl isostere **12** encouragingly had D_3 affinity equivalent to that of **1**, with 50-fold selectivity over D_2. Benzoxazinone **13** (D_3 pK_i 8.2) achieved the target of $\geq$100-fold selectivity over D_2, but systemic exposure of **13** following oral administration to rats was significantly lower than that of SB-277011.[6,10]

It had previously been observed in the 6-cyanotetrahydroisoquinoline series that a 4-fluorocinnamide moiety gave higher dopamine D_3 receptor affinity than the 4-quinolinylcarboxamide group.[6,11] A corresponding increase was seen with the 4-fluorocinnamide in the benzazepine series **14** (Table 2), with an encouraging 75-fold selectivity over D_2.

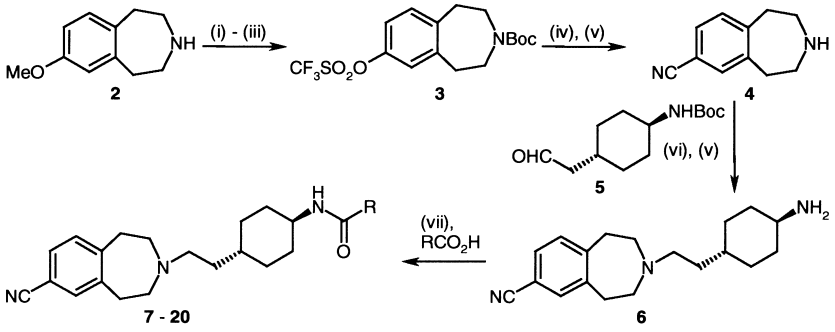
The 3- and 2-fluoro analogues, **15** and **16** respectively, had a similar profile to that of **14** but the 3-methoxy analogue **17** had significantly higher D_3 affinity (pK_i 8.5) and 180-fold selectivity over D_2. Unfortunately **17** gave no exposure following oral administration in the rat, presumably due to metabolic instability of the 3-methoxyphenyl moiety either by *O*-demethylation or hydroxylation of the activated phenyl ring. The 3-acetyl cinnamide **18** also gave high D_3 affinity, but significantly reduced selectivity over the D_2 receptor. However, the 3-acetamidocinnamide **19** retained D_3 affinity and had 130-fold selectivity over D_2. Following oral administration to rats, the systemic exposure of **19** was significantly lower than that of SB-277011. In an attempt to increase metabolic stability, a deactivating fluoro substituent was introduced. The resulting disubstituted cinnamide **20** had similar D_3 affinity and selectivity over D_2 compared with **19**, and most encouragingly, **20**

Table 1. Affinities (pK_i) of aryl carboxamide derivatives at dopamine D_3 and D_2 receptors



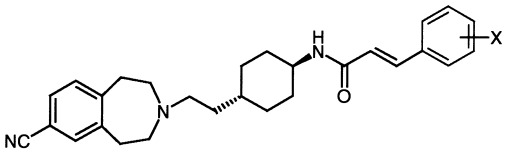
Compound[a]	R	D_3[b]	D_2[b]
SB-277011 (**1**)	—	8.0	6.0
7	4-Quinolinyl	7.6	5.9
8	1-Naphthyl	7.7	5.9
9	5-Quinolinyl	7.9	5.7
10	2-Indolyl	7.8	6.5
11	2-Naphthyl	7.7	5.5
12		8.0	6.3
13		8.2	6.1

[a]All new compounds gave satisfactory analytical and/or mass spectral data.[9]
[b]All values represent the mean of at least three experiments, each within 0.3 of the mean.



Scheme 1. Reagents: (i) 48% aq HBr, reflux, 3 h, 99%; (ii) $(Boc)_2O$, NEt_3, aq THF, 20 °C, 18 h, 93%; (iii) $(CF_3SO_2)_2O$, NEt_3, CH_2Cl_2, −20 °C, 18 h, 92%; (iv) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 100 °C, 4 h, 97%; (v) CF_3CO_2H, CH_2Cl_2, 20 °C, 4 h, 100%; (vi) $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, 0 °C, 18 h, 80%; (vii) EDC, HOBT, CH_2Cl_2, 20 °C, 18 h, 60–85%.

Table 2. Affinities (pK_i) of cinnamide derivatives at dopamine D_3 and D_2 receptors



Compound[a]	X	D_3[b]	D_2[b]
14	4-F	8.2	6.4
15	3-F	8.2	6.4
16	2-F	8.0	6.2
17	3-OMe	8.5	6.2
18	3-COMe	8.4	6.7
19	3-NHCOMe	8.5	6.3
20	2-F, 3-NHCOMe	8.4	6.3

[a,b]See footnotes to Table 1.

showed equivalent systemic exposure to SB-277011 following oral administration in the rat.

Conclusions

Using the dopamine D_3 receptor antagonist SB-277011 as a starting point, and from examination of molecular models, a series of 2,3,4,5-tetrahydro-1*H*-3-benzazepines has been identified with high affinity for the dopamine D_3 receptor and selectivity over the D_2 receptor. Where comparisons are available, the benzazepines have slightly lower dopamine D_3 receptor affinity than the corresponding tetrahydroisoquinolines,[6] although selectivity over the D_2 receptor is similar. From the series of benzazepines described above, the 3-acetamido-2-fluorocinnamide derivative **20** has been identified having 100-fold selectivity over the D_2 receptor. Subsequent evaluation showed that **20** was >100-fold selective over a range of other receptors with a clean P450 profile, had equivalent systemic exposure to SB-277011 in the rat, and was CNS penetrant,[10] with a brain:blood ratio of 0.4:1. Compound **20** therefore represents a structurally distinct tool compound for the continued investigation of the role of dopamine D_3 receptors in the CNS.

References and Notes

1. Sokoloff, P.; Giros, B.; Martres, M.-P.; Bouthenet, M.-L.; Schwartz, J.-C. *Nature* **1990**, *347*, 146.
2. Schwartz, J.-C.; Levesque, D.; Martres, M.-P.; Sokoloff, P. *Clin. Neuropharmacol.* **1993**, *16*, 295.
3. Shafer, R. A.; Levant, B. *Psychopharmacology* **1998**, *135*, 1.
4. Joyce, J. N.; Meador-Woodruff, J. H. *Neuropsychopharmacology* **1997**, *16*, 375.
5. Pilla, M.; Perachon, S.; Sautel, F.; Garrido, F.; Mann, A.; Wermuth, C. G.; Schwartz, J.-C.; Everitt, B. J.; Sokoloff, P. *Nature* **1999**, *400*, 371.
6. Stemp, G.; Ashmeade, T.; Branch, C. L.; Hadley, M. S.; Hunter, A. J.; Johnson, C. N.; Nash, D. J.; Thewlis, K. M.; Vong, A. K. K.; Austin, N. E.; Jeffrey, P.; Avenell, K. Y.; Boyfield, I.; Hagan, J. J.; Middlemiss, D. N.; Reavill, C.; Riley, G. J.; Routledge, C.; Wood, M. *J. Med. Chem.* **2000**, *43*, 1878.
7. Kanao, M.; Hashizume, T.; Ichikawa, Y.; Irie, K.; Satoh, Y.; Isoda, S. *Chem. Pharm. Bull.* **1982**, *30*, 180.
8. Compounds were evaluated in binding assays using displacement of ^{125}I-iodosulpride from human D_3 and D_2 receptors, expressed in CHO cells.
9. ^{1}H NMR spectra were recorded at 250 MHz in $CDCl_3$ as solvent. Compound **20**, mp 274.5–275.5 °C dec. (HCl salt); mass spectrum (API^+): Found 503 (MH^+). $C_{30}H_{35}FN_4O_2$ requires 502. ^{1}H (free base) δ: 1.04–1.20 (m, 5H), 1.40–1.50 (m, 2H), 1.70–1.82 (m, 2H), 2.00–2.10 (m, 2H), 2.24 (s, 3H), 2.40–2.52 (m, 2H), 2.60–2.70 (m, 4H), 2.90–3.00 (m, 4H), 3.80–3.90 (m, 1H), 5.45 (d, J = 5 Hz, 1H), 6.42 (d, J = 10 Hz, 1H), 7.08–7.25 (m, 3H), 7.30–7.45 (m, 3H), 7.71 (d, J = 10 Hz, 1H), 8.30 (m, 1H).
10. Systemic exposure following oral administration and CNS penetration at steady-state were investigated in the rat. For determination of systemic exposure, compounds were suspended in 1% (w/v) methylcellulose aq at a concentration of 1.5 mg free base/mL and administered at a target dose of 3 mg free base/kg. Blood samples were removed at 0.5, 1, 2, 3, 4, 6 and 10 h post-dose and analysed by LC/MS/MS. For CNS penetration studies, compounds were dissolved in 2% (v/v) DMSO in 5% (w/v) dextrose aq and administered at a constant infusion rate over 12 h at a target dose rate of 0.3 mg free base/kg/h. Blood samples were removed during the latter part of the infusion to confirm steady-state blood concentrations. Blood and brain samples were analysed by LC/MS/MS.
11. Austin, N. E.; Avenell, K. Y.; Boyfield, I.; Branch, C. L.; Coldwell, M. C.; Hadley, M. S.; Jeffrey, P.; Johns, A.; Johnson, C. N.; Nash, D. J.; Riley, G. J.; Smith, S. A.; Stacey, R. C.; Stemp, G.; Thewlis, K. M.; Vong, A. K. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 179.