Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 21, pp. 2541-2546, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00446-7

DISCOVERY OF SELECTIVE DOPAMINE D3 LIGANDS: I. DIMERIC 2-[4-(3-AMINOPROPOXY)PHENYL]BENZIMIDAZOLE ANTAGONISTS

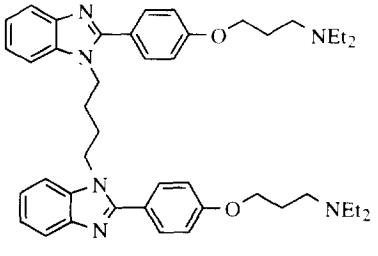
Jon Wright*, Dennis Downing, Thomas Heffner, Thomas Pugsley, Robert MacKenzie and Lawrence Wise

Departments of Chemistry and Therapeutics, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105

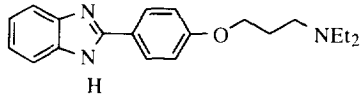
Abstract: A novel series of dimeric 2-[4-(3-aminopropoxy)phenyl]benzimidazole dopamine (DA) D3 receptor antagonists has been discovered. Most of the dimeric structure is needed for DA binding activity; however, a second basic nitrogen atom is not required. A representative compound had no effects on DA synthesis in rat brain but inhibited spontaneous locomotor activity in mice and stimulated locomotor activity in habituated rats.

It has been proposed that some of the symptoms of schizophrenia arise from dopamine (DA) neuronal hyperactivity.[1] DA antagonists (e.g., haloperidol) are effective in the treatment of schizophrenia possibly due to modulation of DA neuronal activity in limbic brain areas. However, their use is often accompanied by neurological side effects such as tardive dyskinesia and extrapyramidal syndromes.[2] These side effects may result from concurrent attenuation of DA neuronal activity in the striatum.

Both the efficacy and neurological side effects of DA antagonists have been correlated with their affinity for DA D2 receptors which are widespread in limbic and striatal regions of the brain. These receptors have now been shown to include D2, D3 and D4 subtypes. It has been speculated that DA antagonists may have some of their antipsychotic effects via blockade of DA D3 receptors,[3] which are expressed at higher levels in limbic than striatal brain structures.[4] A selective DA D3 antagonist might have an atypical profile (i.e., antipsychotic activity, but with reduced neurological side effects). Our goal was to discover novel, selective D3 antagonists and examine their effects on DA neuronal activity and in rodent behavioral tests.



1

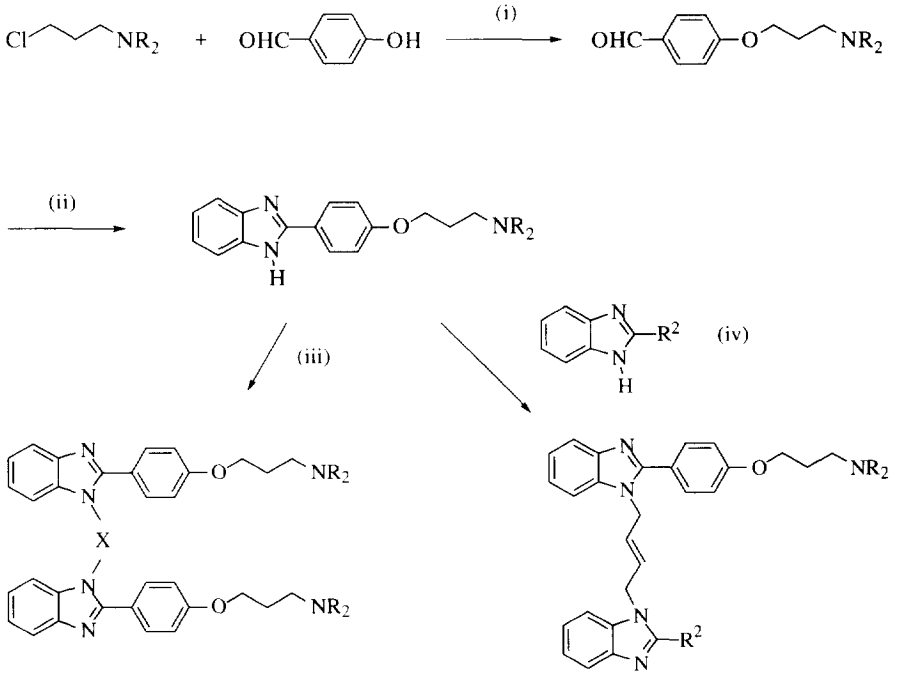


2

High volume screening of our chemical library for compounds with selective DA D3 binding activity revealed that **1** bound strongly to DA D3 receptors (K_i = 28 nM) but had weak affinity for DA D2 receptors (K_i = 1495 nM).[5] The related monomeric compound **2** possessed no significant affinity for DA receptors, suggesting that the dimeric structure is important for binding activity.

We prepared analogues of **1** to optimize potency and selectivity for DA D3 receptors. The general syntheses of these compounds are shown in Scheme 1.[6] The butane-linked analogue **1** was most conveniently prepared via catalytic hydrogenation of butene **3** (5% palladium on carbon/methanol). Unsymmetrical dimers were made using a 50:50 mixture of each benzimidazole [step (iv)] and separating the two symmetrical products from the desired unsymmetrical product by chromatography.[7]

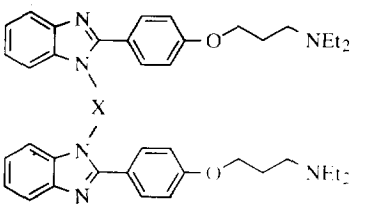
Scheme 1

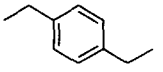


(i) NaH, DMF, 60 °C, 12 h; (ii) 1,2-Diaminobenzene, $NaHSO_3$, MeOH, reflux, 4 h; (iii) NaH, DMF; 0.5 eq Br-X-Br; (iv) 1 eq of each monomer, 2.2 eq NaH, DMF; 1 eq *trans*-1,4-dichloro-2-butene.

To initiate our SAR study, we examined alternative links between the two benzimidazoles (Table 1). Replacing the 1,4-butyl link of **1** with *trans*-2-butene (compound **3**) results in comparable DA D3 receptor affinity. The requirement for this increase in rigidity was specific; the *cis*-2-butene **4** and the dibenzyl **5** analogues had lower affinity. Increasing the length of the link was also detrimental (compound **6**).

Table 1: DA receptor binding for analogues of **1**

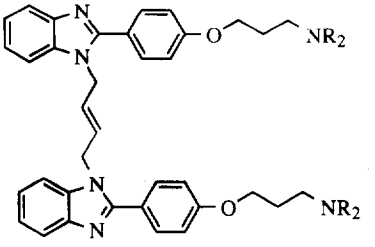


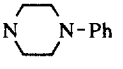
Compound	X	D3 Binding K_i nM	D2 Binding K_i nM
1	-$(CH_2)_4$-	28	1495
3	1,4-*trans*-2-butenyl	35	2345
4	1,4-*cis*-2-butenyl	87	1518
5		184	3438
6	-$(CH_2)_6$-	131	1750

In Table 2 the SAR of the amino groups is evaluated. DA D3 binding affinity increases with moderate increases in the size of the di-N-alkyl substituent. The binding affinities of the di-N-propyl and di-N-butyl analogues are similar, suggesting that this effect is maximized with the di-N-propyl analogue **8**. The piperidine and pyrrolidine analogues **10** and **11** were also very potent at DA D3 receptors. However, the pyrrolidine analogue **11** was less interesting as its selectivity was compromised. The morpholine analogue **12** had surprisingly low affinity for DA receptors, considering that the piperidine **10** had good affinity. It may be that the electronegative morpholine oxygen atom would be forced into the proximity of an electronegative region in the receptor. The 4-phenylpiperazine analogue **13** also had weak binding affinity. This could be due to the same effect or steric crowding.

Compounds **14** and **15** (Table 3) confirm that most of the second unit of the dimer is important for DA receptor binding. However, a second basic nitrogen does not appear to be necessary as compounds **16**-**18** all have strong affinity for DA D3 receptors. The high DA D3 binding affinity of the unsymmetrical dimer **18** compared to the symmetrical phenyl piperazine dimer **13** (Table 2) is further evidence that the two ends of the molecule can exist in different environments in the receptor.

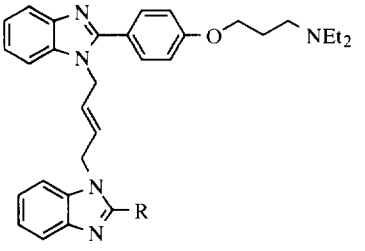
Table 2: DA receptor binding for amino analogues of **1**

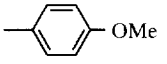
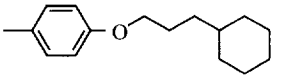
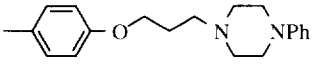


Compound	NR_2	D3 Binding K_i nM	D2 Binding K_i nM
7	NMe_2	144	4985
8	NPr_2	5	343
9	NBu_2	8	472
10		10	517
11		9	56
12		>2040	>3333
13		275	3945

Compound **10** was chosen for further evaluation. It exhibited effects consistent with DA D3 receptor antagonist activity in vitro; it did not cause DA agonist-like stimulation of mitogenesis in D3-transfected CHO p-5 cells and it antagonized the stimulation of mitogenesis produced by the DA agonist quinpirole (IC_{50} 19 nM).[8] This potency correlates well with the DA D3 receptor binding reported above (10 nM). Unlike non-selective DA antagonists, when administered ip in rats, compound **10** caused only weak, insignificant effects on DA synthesis in mesolimbic and striatal areas of the brain.[9] Compound **10** inhibited exploratory locomotor activity in mice[10] after ip administration (ED_{50} 7.1 mg/kg), but had no effect in the same test after oral administration in rats up to 30mg/kg. However, it caused a dose-dependent increase in locomotor activity in rats (3-30 mg/kg sc) showing low basal activity after a period of habituation to the test chambers. This profile has been seen with other D3 antagonist compounds.[11]

Table 3: DA receptor binding for unsymmetrical analogues of **1**



Compound	R	D3 Binding K_i nM	D2 Binding K_i nM
14	methyl	1201	>3333
15	phenyl	133	6530
16		26	1414
17		39	1027
18		19	803

In conclusion, we have discovered a novel series of selective dopamine D3 antagonists. While many of these compounds have a dimeric structure, symmetry does not seem to be necessary for good affinity for DA D3 receptors. Indeed, the second basic nitrogen atom may be removed with negligible effect. However, in the NEt_2 series, most of the second half is needed for activity. These compounds appear to have no effect on DA synthesis in rat brain but have some effects in locomotor tests in rodents. The utility of these compounds for the treatment of schizophrenia remains to be demonstrated. In any case, these compounds should be useful in the quest to understand the role of DA D3 receptors.

References and Notes

1. Meltzer, H. Y.; Stahl, S. M. *Schizophr. Bull.* **1976**, *2*, 19.
2. Baldessarini, R. J.; Tarsy, D. *Annu. Rev. Neurosci.* **1980**, *3*, 23.
3. Schwartz, J.-C.; Sokoloff, P.; Giros, B.; Martres, M. P.; Bouthenet, M. L. in *Novel Antipsychotic Drugs*;

Meltzer, H. Y., Ed.; Raven: New York, 1992; pp 135-144.

4. Sokoloff, P.; Giros, B.; Martres, M. P.; Andrieux, M.; Besancon, R.; Pilon, C.; Bouthenet, M. L.; Souil, E.; Schwartz, J. C. *Arzneim.-Forsch./Drug Res.* **1992**, *42*, 224.

5. Binding assays were carried out in triplicate at cloned human D2L and D3 receptors transfected into CHO- K1 cells versus [^{3}H]spiperone as previously described: Wright, J. L.; Caprathe, B. W.; Downing, D. M.; Glase, S. A.; Heffner, T. G.; Jaen, J. C.; Johnson, S. J.; Kesten, S. R.; MacKenzie, R. G.; Meltzer, L. T.; Pugsley, T. A.; Smith, S. J.; Wise, L. D.; Wustrow, D. J. *J. Med. Chem.* **1994**, *37*, 3523.

6. All new compounds had satisfactory ^{1}H NMR, IR, MS and microanalysis.

7. For unsymmetrical products **14** - **17**, 2-methyl and 2-phenylbenzimidazole are commercially available; the synthesis of 2-(4-methoxyphenyl)benzimidazole has been reported: Perry, R. J.; Wilson, B. D. *J. Org. Chem.* **1993**, *58*, 7016; 2[4-(3-cyclohexylpropoxy)phenyl]benzimidazole was synthesised by reaction of 4-hydroxybenzaldehyde, sodium salt, with 3-cyclohexylpropyl bromide followed by the conditions outlined in step (ii) of Scheme 1.

8. (a) Lajiness, M. E.; Chio, C. L.; Huff, R. M. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 1573. (b) Chio, C. L.; Lajiness, M. E.; Huff, R. M. *Mol. Pharm.* **1994**, *45*, 51.

9. DOPA accumulation in rat brain after administration of compounds was used as a measure of effects on DA synthesis. This test was carried out according to methods described previously: Walters, J. R.; Roth, R. H. *Biochem. Pharmacol.* **1976**, *25*, 649.

10. Effects on locomotor activity in rodents were determined according to methods described previously: (a) Strömbom, U. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1976**, *292*, 167. (b) Martin, G. E.; Bendesky, R. J. *J. Pharmacol. Exp. Ther.* **1984**, *229*, 706. (c) Svensson, L.; Ahlenius, S. *Eur. J. Pharmacol.* **1983**, *88*, 393.

11. Svensson, K.; Johansson, A. M.; Magnusson, T.; Carlsson, A. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1986**, *334*, 234.

(*Received in USA* 27 *August* 1995; *accepted* 26 *September* 1995)