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# DISCOVERY OF SELECTIVE DOPAMINE D3 LIGANDS: II. 2-[4-[3-(4-ARYL-1-PIPERAZINYL)PROPOXY]PHENYL]BENZIMIDAZOLE PARTIAL AGONISTS

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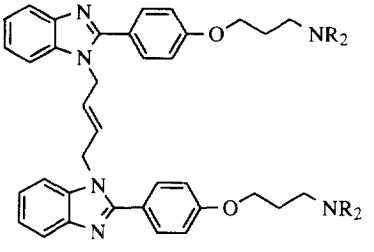
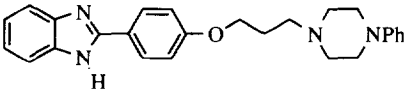
**Abstract:** A novel series of 2-[4-[3-(4-aryl-1-piperazinyl)propoxy]phenyl]benzimidazole dopamine D3 receptor agonists has been discovered. The aryl group was crucial for activity and Topliss analysis confirmed that phenyl was optimal for DA D3 receptor binding and selectivity. The phenyl analogue **3** was a partial agonist in a second messenger assay. It increased DA synthesis in rat brain and inhibited exploratory locomotor activity in rodents.

In part I of this series,[1] we discussed the potential role dopamine (DA) D3 receptors may play in the antipsychotic activity of traditional DA antagonists. It has been suggested that a selective DA D3 antagonist might display antipsychotic activity without neurological side effects.[2] We introduced a novel series of dimeric 2-[4-(3-aminopropoxy)phenyl]benzimidazoles that showed remarkable binding selectivity for DA D3 receptors. A representative compound **1** displayed DA D3 antagonist properties, but unlike traditional non-selective DA antagonists, it did not affect DA synthesis in rat brain. Compound **1** did inhibit spontaneous locomotor activity in mice and stimulated locomotor activity in habituated rats, a profile previously seen with DA D3 antagonists.[3]



**1** $NR_2$ =

**2** $NR_2$ =

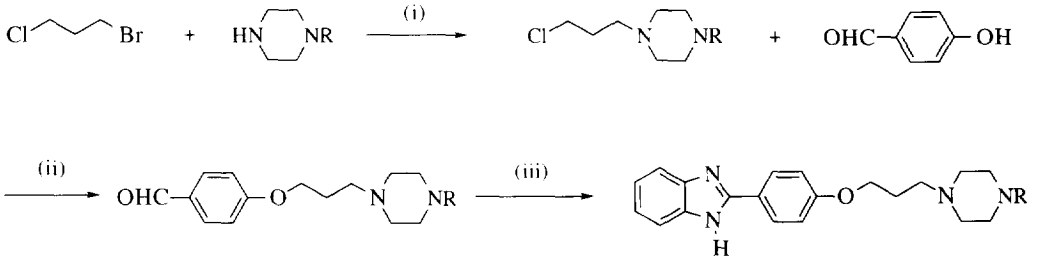


**3**

During our SAR studies of the dimeric 2-[4-(3-aminopropoxy)phenyl]benzimidazoles, we discovered that the phenylpiperazine dimer **2** showed no significant binding to DA receptors. However, the synthetic precursor to **2**, monomer **3**, had high affinity for DA D3 receptors ($K_i$ = 1.5 nM) with much weaker affinity for D2 receptors ($K_i$ = 406 nM).[4] We prepared arylpiperazine analogues of **3** in order to explore the potency and selectivity of this novel lead for DA D3 receptors.

The synthesis of **3** and analogues is shown in Scheme 1.[5] Step (i) could be performed with 2 equivalents of the piperazine[6] instead of using triethylamine to neutralize the HBr formed. However, the piperazines were often in short supply and the use of triethylamine allowed all of the piperazine to be converted to product.

**Scheme 1**

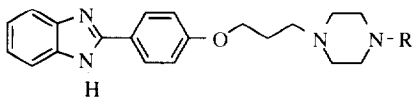



(i) $Et_3N$, $CH_2Cl_2$, reflux, 2 h; (ii) NaH, DMF, 60 °C, 12 h; (iii) 1,2-Diaminobenzene, $NaHSO_3$, MeOH, reflux, 4 h

The importance of the phenylpiperazine group for DA D3 binding potency was examined via preparation and testing of the analogues shown in Table 1. Replacement of phenylpiperazine with methylpiperazine (compound **4**) greatly reduces DA binding. This result clearly separates the SAR of this series from that of the previously described dimeric series. In that series, dialkylamines where the most active; phenylpiperazine was inactive. As the phenyl was important for DA D3 binding, we undertook a Topliss analysis of substituents on the phenyl ring.[7] The 4-chlorophenyl analogue **5** had weaker DA binding than the phenyl parent **3**. The Topliss analysis thus suggested the 4-methoxyphenyl analogue **6**, which also had weaker DA D3 binding but improved D2 binding. In this case the analysis proposed the 3-chlorophenyl analogue **7**. This compound also had weaker affinity for DA D3 receptors. The Topliss analysis, along with several other analogues not reported here, concluded that aromatic substitution on the phenylpiperazine group of **3** will not enhance DA D3 binding.

An unexpected result was seen with 2-substituted phenyl compounds **8**-**10**. These had high affinity for DA D3 receptors but were disappointingly non-selective due to strong binding to D2 receptors. The 2-pyridylpiperazine and 2-pyrimidylpiperazine analogues **11** and **12** were both reasonably potent at DA D3 receptors but were again less interesting due to moderate affinity for D2 receptors.

**Table 1:** DA receptor binding for **3** and analogues



| Compound | R | D3 Binding $K_i$ nM | D2 Binding $K_i$ nM |
|---|---|---|---|
| **3** | Ph | 1.5 | 406 |
| **4** | Me | 2000 | >3333 |
| **5** | 4-ClPh | 27 | 865 |
| **6** | 4-MeOPh | 130 | 293 |
| **7** | 3-ClPh | 155 | 1403 |
| **8** | 2-ClPh | 18 | 126 |
| **9** | 2-PrSPh | 1.3 | 8.0 |
| **10** | 2-MeOPh | 1.7 | 8.8 |
| **11** | 2-Pyridyl | 8 | 70 |
| **12** | 2-Pyrimidyl | 15 | 269 |

From this study, compound **3** showed optimal affinity and selectivity for DA D3 receptors and was evaluated further. In contrast to the dimeric antagonist **1** previously described, **3** caused stimulation of mitogenesis in D3-transfected CHO p-5 cells, an agonist profile.[8] The maximal effect produced by **3** was 53% of that of the full DA agonist quinpirole ($EC_{50}$ 1.3 nM). When administered at 10 mg/kg ip in rats, compound **3** stimulated DA synthesis in mesolimbic (99% increase above controls) and striatal (47% increase) areas of the brain.[9] Compound **3** inhibited exploratory locomotor activity in rodents[10] after ip administration (mice $ED_{50}$ 2.3 mg/kg, rats 7.1 mg/kg), but had no effect in the same test after oral administration (30 mg/kg) in rats.

In summary, we have discovered a novel series of selective DA D3 partial agonists. The phenylpiperazine analogue **3** was the most potent and selective. Despite significant agonist effects in an *in vitro* second messenger assay, **3** increased DA synthesis *in vivo*, a profile usually associated with DA antagonists. Compound **3** also inhibited exploratory locomotor activity in rodents. These results appear to support the suggestion that activation of DA D3 receptors in rodent brain causes an increase in DA synthesis and inhibition of locomotor activity, opposite to the effects seen when DA D2 receptors are activated.[11]

**References and Notes**

1. Wright, J.; Downing, D.; Heffner, T.; Pugsley, T.; MacKenzie, R.; Wise, L. preceding paper.

2. Schwartz, J.-C.; Sokoloff, P.; Giros, B.; Martres, M. P.; Bouthenet, M. L. *Novel Antipsychotic Drugs*; Meltzer, H. Y., Ed.; Raven: New York, 1992; pp 135-144.

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

4. 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.

5. Compounds **3-12** all had satisfactory $^1$H NMR, IR, MS and C, H & N microanalysis.

6. The aryl piperazine starting materials are all known.

7. Topliss, J. G. *J. Med. Chem.* **1972**, *15*, 1006.

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. The inhibition of DA synthesis test was carried out according to methods described previously: Walters, J. R.; Roth, R. H. *Biochem. Pharmacol.* **1976**, *25*, 649.

10. Inhibition of spontaneous locomotor activity in rodents was carried out 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*, 706-711. (c) Svensson, L.; Ahlenius, S. *Eur. J. Pharmacol.* **1983**, *88*, 393.

11. Sautel, F.; Griffon, N.; Lévesque, D.; Pilon, C.; Schwartz, J.-C.; Sokoloff, P. *Neuroreport* **1995**, *6*, 329.

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