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4-BROMO-1-METHOXY-N-[2-(4-ARYL-1-PIPERAZINYL)ETHYL]-2-NAPHTHALENECARBOXAMIDES: SELECTIVE DOPAMINE D3 RECEPTOR PARTIAL AGONISTS

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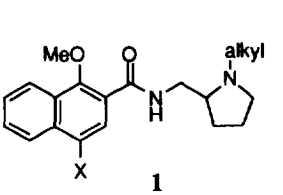
Abstract: A series of 4-bromo-1-methoxy-N-[2-(4-aryl-1-piperazinyl)ethyl]-2-naphthalenecarboxamide dopamine (DA) D3 receptor agonists has been identified. These compounds were found to be selective for DA D3 over D2 receptors and were shown to be partial to full agonists as measured by stimulation of mitogenesis in D3-transfected CHO p-5 cells.

Introduction

Most marketed antipsychotics exert their effects through antagonist activity at the dopamine (DA) D2 receptors. High levels of D2 receptor expression in the striatal as well as limbic regions of the brain may be responsible for adverse motor effects such as extrapyramidal syndrome (EPS) and tardive dyskinesia that are attributed to DA blockade. The recently cloned DA D3 receptor was found to have a much more restricted distribution with expression predominantly localized to the limbic region which is responsible for cognitive and emotional functions. Atypical antipsychotics (i. e. drugs which are known to cause fewer neurological side effects) have high affinity for the DA D3 as well as the DA D2 receptor.[1] This led to the hypothesis that a selective DA D3 antagonist may provide a novel antipsychotic agent with little or no EPS side effects.

Initial studies by Sokoloff et al.[2] indicated that methoxy naphthalene amides with a general structure **1** are DA D3 selective antagonists. We were interested in expanding the scope of this work by synthesizing and testing the aryl piperazine analogs **2**.



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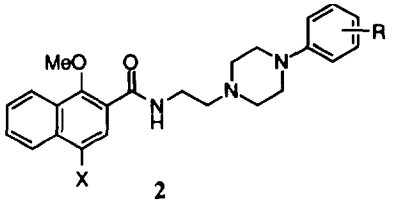
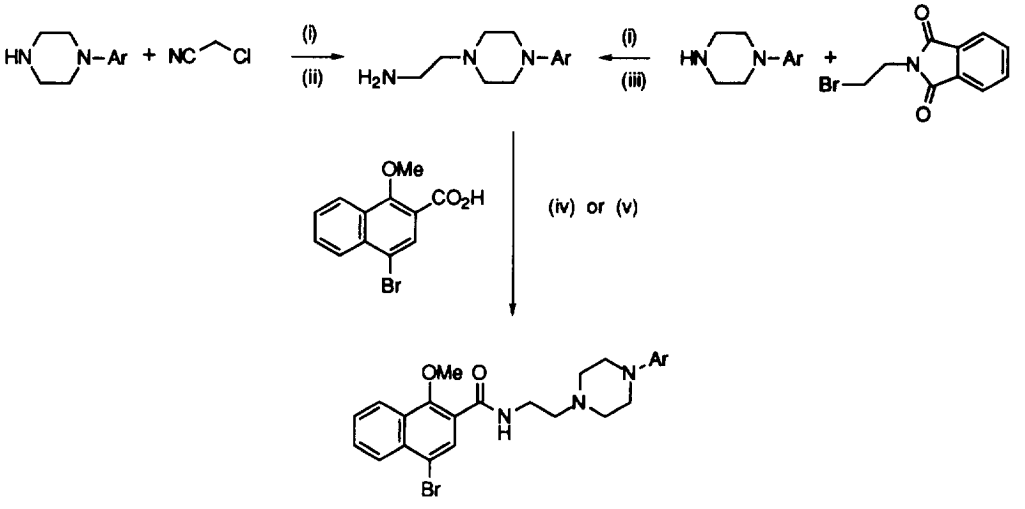


2

Chemistry

The compounds found in Tables 1 - 3 were synthesized as shown in Scheme 1.[3] The aminoethyl piperazine was prepared by reaction of an arylpiperazine with chloroacetonitrile followed by reduction with lithium aluminum hydride or aluminum hydride. In cases where the substituents on the aryl piperazine were sensitive to hydride reduction, the aryl piperazine was reacted with N-(2-bromoethyl)phthalimide followed by deprotection of the amine with hydrazine. The amide couplings of the known naphthoic acid[2] with aminoethyl piperazines were carried out under standard conditions.

Scheme 1

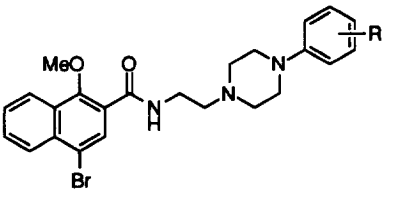


(i) K_2CO_3, CH_3CN or DMF, 80 °C, 18 h; (ii) $LiAlH_4$, THF or AlH_3, THF, Et_2O, 0 °C, 4 h; (iii) H_2NNH_2, EtOH, 25 °C, 5 h; (iv) iBuOCOCl, Et_3N, CH_2Cl_2 or THF, 0 °C, 15 h; (v) carbonyldiimidazole, CH_2Cl_2, 25 °C, 15 h.

Results and Discussion

Table 1 summarizes the effects of various phenylpiperazine substituents on human DA receptor binding versus the antagonist ligand [^{3}H]spiperone.[4] In general, ortho substitution on the aryl piperazine gave compounds with higher affinity and selectivity for DA D3 receptors over D2 receptors. In every case the DA D3 affinity for para substituted analogs was weaker than the ortho and meta analogs. An increase in the alkyl chain length of compound **3** from ethyl to propyl and butyl led to a moderate decrease in D3 receptor affinity and selectivity (propyl: D3 = 55 nM, D2 = 311 nM and butyl: D3 = 88 nM, D2 = 735 nM).

Table 1: Effects of phenyl piperazine substitution on DA receptor binding

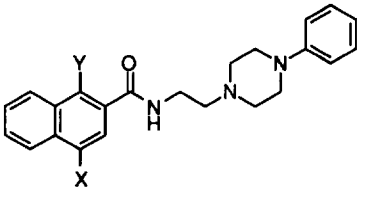


Compound	R	hD3 binding[a] (K_i nM)	hD2 binding[a] (K_i nM)
3	H	24	1892
4	2-Me	66	484
5	3-Me	339	1207
6	4-Me	260	996
7	2,3-diMe	50	1173
8	2-Cl	39	517
9	3-Cl	40	703
10	4-Cl	132	35% @ 10μM
11	2,3-diCl	8	35% @ 10μM
12	2-OMe	76	303
13	3-OMe	652	1288
14	4-OMe	731	5692
15	2-NO_2	24	151
16	3-NO_2	652	1288
17	4-NO_2	731	5692

[a][^{3}H]spiperone in rat striatum; K_i values were obtained from 4 - 6 concentrations, run in triplicate, by a non-linear regression analysis.

Changes in naphthalene substitution were poorly tolerated (Table 2). As in the case of previously studied benzamide compounds,[5] the adjacent methoxy group appears to be important because hydrogen bonding with the amide hydrogen locks the structure into a rigid conformation. Halogen substitution para to the methoxy group also seems to be required. Unlike the pyrrolidine analog where X = CN (**1**),[6] the corresponding phenyl piperazine analog with cyano substitution on the naphthalene ring **19** has significantly weaker D3 binding affinity.

Table 2: Effects of naphthalene substitution on DA receptor binding



Compound	Y	X	hD3 binding[a] (K_i nM)	hD2 binding[a] (K_i nM)
1	OMe	Br	24	1892
18	OMe	Cl	55	2529
19	OMe	CN	131	71
20	OMe	H	270	7000
21	OEt	Br	267	>10μM
22	OH	Br	>10μM	>10 μM
23	H	Br	>10 μM	>10μM

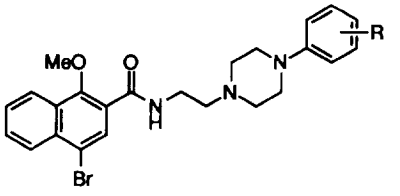
[a]See footnote for Table 1.

To determine the level of agonist activity, the effect on mitogenesis in D3-transfected CHO p-5 cells[4,7] was measured for a number of compounds (Table 3). Considering that compounds of the original pyrrolidine series were shown to be antagonists,[1,6] we were surprised to find that most of the compounds in the phenyl piperazine series caused a stimulation of mitogenesis at levels indicative of partial to full agonist activity. The maximal effects produced ranged from 17% to 100% of that of the full DA agonist quinpirole (100%, EC_{50} = 1.3 nM).

Because of their D3 affinity and selectivity, compounds **3** and **11** were evaluated in vivo. When administered at 10 mg/kg ip to rats, neither compound showed any significant effect on DA synthesis in either the limbic or striatal areas of the brain.[9] Reversal of the γ-butyrolactone-induced DA synthesis in these two regions was also measured. Compound **3** again showed no significant effect, while compound **11** showed a modest decrease of 45% in the limbic region, suggestive of a partial DA D2/D3 agonist effect.[10] Interestingly, these compounds also had moderate affinity for the DA D4 receptor (34 nM and 65 nM, respectively). Both compounds inhibited exploratory locomotor activity in rats with an ED_{50} value of 20 mg/kg after ip administration.[11]

In summary, replacement of the pyrrolidine in the originally described 2-methoxynaphthamide series with arylpiperazine has resulted in a class of compounds that have one to two orders of magnitude lower affinity, but are more selective, for the DA D3 receptor with respect to the D2 receptor. These compounds are also significantly different in that they are partial to full agonists.

Table 3: Stimulation of mitogenesis in D3-transfected CHO p-5 cells. Percent maximal effect compared to that of the full DA agonist quinpirole.



Compound	R	hD3 binding[a] (K_i nM)	DA D3 receptor mitogenesis[b]	
			% maximal effect[c]	EC_{50}[d] (nM)
3	H	24	55	68
4	2 Me	66	17	>1000
7	2,3 diMe	50	31	68
8	2 Cl	39	57	83
9	3 Cl	40	83	28
11	2,3 diCl	8	100	13

[a]See footnote for Table 1. [b]measurement of [^{3}H]thymidine incorporation in CHO p-5 cells expressing human D3 receptors. [c]Percent maximal effect compared to that of the full DA agonist quinpirole (100%).[8] [d]EC_{50} values were obtained from 10 concentrations, n = 4.

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3. All new compounds had satisfactory ^{1}H NMR, IR, MS and microanalysis.
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8. This number represents the intrinsic activity of the compound. It is the maximal thymidine uptake of a test compound relative to the maximal thymidine uptake achieved by the full agonist quinpirole.
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 in reference 4.
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