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DISCOVERY OF SELECTIVE DOPAMINE D4 RECEPTOR ANTAGONISTS: 1-ARYLOXY-3-(4-ARYLOXYPIPERIDINYL)-2-PROPANOLS

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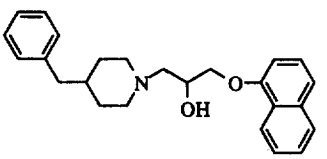
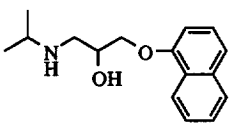
Abstract: High volume screening identified 3-(4-benzylpiperidinyl)-1-naphthoxy-2-propanol as a selective dopamine D4 receptor ligand. A systematic structure–activity study revealed that the benzyl group could be replaced with phenoxy and the naphthalene with phenyl to improve potency almost tenfold. The (*R*) enantiomer of this compound had a D4 affinity of 2 nM and was over 100-fold weaker at dopamine D2 and D3 receptors.

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 that are widely distributed in limbic and striatal regions of the brain. DA D2 receptors have now been shown to include D2, D3, and D4 receptor subtypes. The antipsychotic agent clozapine has an 'atypical' profile (i.e., effective against the symptoms of schizophrenia with reduced neurological side effects) that may stem from a modest selectivity for blockade of DA D4 receptors versus D2 receptors.[3] In addition, D4 receptors are expressed at higher levels in cortical and limbic compared to striatal brain structures.[4] Hence selective D4 antagonists may have potential as atypical antipsychotic agents. Our goal was to discover novel, selective D4 antagonists.



1

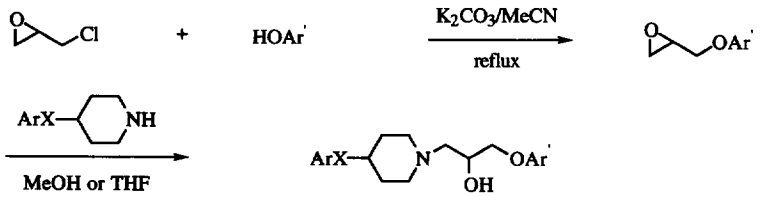


2

High volume screening of our chemical library for compounds with selective DA D4 binding activity revealed that **1** bound strongly to DA D4 receptors (K_i = 26 nM) but had weak affinity for DA D2 receptors (K_i = 1438 nM) and DA D3 receptors (K_i = 608 nM).[5] Part of the structure of **1** overlays that of propranolol (**2**), a potent β-adrenergic receptor antagonist. However, compound **1** has weak affinity for adrenergic β-1 and β-2 receptors (K_i values 3706 and 1042 nM, respectively).

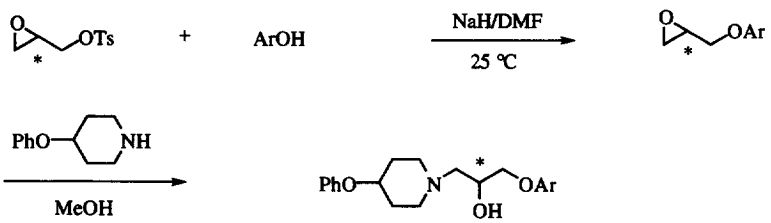
We prepared analogues of **1** to optimize potency and selectivity for DA D4 receptors. The general synthesis of racemic compounds is shown in Scheme 1.[6]

Scheme 1



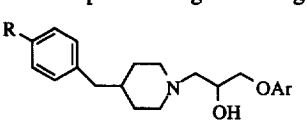
We synthesised both enantiomers of **16** using the route shown in Scheme 2. It was important to use the conditions described; competitive attack at the epoxide with subsequent elimination lowered the optical purity of the product otherwise. Indeed, if chiral epichlorohydrin is used instead of glycidyl tosylate, attack at the epoxide predominates and the opposite enantiomer is the major product. The optical purity of the final products is easily assayed by normal-phase chiral HPLC on a Daicel AD column.[7]

Scheme 2



To initiate our SAR study, we examined the effect of replacing the naphthyl group of **1** with phenyl. This change was well tolerated (compound **3**, Table 1). However, only chloro was tolerated in the 4 position of the phenyl; nitro or methoxy groups reduced affinity for D4 receptors (compounds **4–6**). Substitution on the left-hand phenyl ring was poorly tolerated. Compounds **7–10** all had lower affinity for D4 receptors compared to parent **1**. It appeared that simple aromatic substitution on the phenyl group or replacement of the naphthyl group of **1** would not lead to significantly more potent analogues.

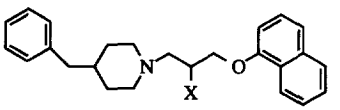
Table 1: DA receptor binding for analogues of **1**



Compound	R	Ar	D4 Binding K_i (nM)
1	H	1-naphthyl	26
3	H	Ph	34
4	H	4-ClPh	18
5	H	4-NO_2Ph	59
6	H	4-MeOPh	123
7	Cl	1-naphthyl	45
8	F	1-naphthyl	32
9	MeO	1-naphthyl	74
10	Me	1-naphthyl	52

In Table 2 the role of the hydroxyl group on DA D4 receptor affinity is examined. Removal of the hydroxy (compound **11**) or replacement with methyl (compound **12**) gave analogues with weaker affinity, suggesting some binding role for the hydroxy group. The methoxy analogue **13** was also slightly weaker, although the approximately twofold difference does not suggest that the hydroxy group has a strong hydrogen-donating role.

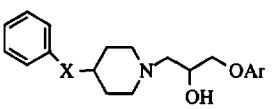
Table 2: DA receptor binding for hydroxy analogues of **1**



Compound	X	D4 Binding K_i (nM)
1	OH	26
11	H	50
12	Me	72
13	OMe	45

The compounds in Table 3 describe replacement of the benzyl group of **1**. While there might be a small improvement by replacing the benzyl group with phenoxy, the improvement is enhanced when the 1-naphthyl group is simultaneously replaced by phenyl (compound **16**). This appears to be a cooperative effect; neither change alone gave a significant increase in binding affinity (compounds **15** and **3**, Table 1).

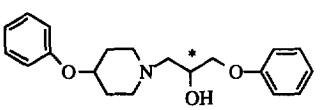
Table 3: DA receptor binding for benzyl analogues of **1**



Compound	X	Ar	D4 Binding K_i (nM)	D2 Binding K_i (nM)
1	CH_2	1-naphthyl	26	1438
14	S	1-naphthyl	32	-
15	O	1-naphthyl	18	2336
16	O	Ph	3.6	911

Compound **16** is significantly more potent than our mass screen lead **1** and contains a chiral center. The DA binding of the enantiomers of **16** is shown in Table 4. The *R*-enantiomer, compound **17**, is more potent at DA receptors than the *S*-enantiomer, compound **18**. Compound **17** was the most potent analogue discovered during this SAR study and has 100-fold higher affinity for D4 receptors as compared to D2 or D3 receptors.

Table 4: DA receptor binding for **16** and enantiomers



Compound	*	D4 Binding K_i (nM)	D2 Binding K_i (nM)	D3 Binding K_i (nM)
16	R/S	3.6	911	537
17	R	2.0	244	220
18	S	11.6	709	457

Compound **17** is a potent, selective D4 ligand and was subjected to further testing. Like many compounds in this series, it exhibited effects consistent with DA D4 receptor antagonist activity in vitro; it did not cause DA agonist-like stimulation of mitogenesis in D4-transfected CHO p-5 cells and it antagonized the stimulation of mitogenesis produced by the DA agonist quinpirole (IC_{50} 9.5 nM).[8,9] Unlike nonselective DA antagonists, when administered at 10 mg/kg ip in rats, compound **17** did not affect DA synthesis in hippocampal or striatal areas of the brain.[9]

In conclusion, we have discovered a novel series of potent, selective dopamine D4 antagonists. At present, we do not have evidence that these compounds have potential as antipsychotic agents in humans. In any case, these compounds should be useful in the quest to understand the role of DA D4 receptors.

References and Notes

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6. All new compounds had satisfactory ^{1}H NMR, IR, MS and microanalysis.
7. Chiral HPLC analyses were performed on a 4.6 × 250 mm Daicel Chiralpak AD column eluting with 20% isopropanol/hexane (both containing 0.1% diethylamine) at 1.0 mL/min. Typical retention times were 8.7 min for **17** and 11.3 min for **18**.
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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: Pugsley, T. A.; Davis, M. D.; Akunne, H. C.; MacKenzie, R. G.; Shih, Y. H.; Damsma, G.; Wikstrom, H.; Whetzel, S. Z.; Georgic, L. M.; Cooke, L. W.; DeMattos, S. B.; Corbin, A. E.; Glase, S. A.; Wise, L. D.; Dijkstra, D.; Heffner, T. G. *J. Pharm. Exp. Ther.* **1995**, *275(3)*, 1355.

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