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A NOVEL SERIES OF 2-AMINOTETRALINS WITH HIGH AFFINITY AND SELECTIVITY FOR THE DOPAMINE D_3 RECEPTOR

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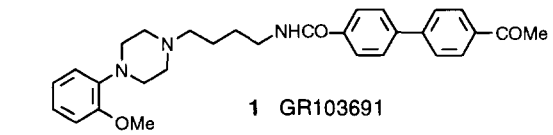
Abstract: A novel series of N-[4-(4-Phenylbenzoylamino)butyl]-1,2,3,4-tetrahydro-2-naphthylamines with high affinity and selectivity for the dopamine D_3 receptor has been prepared. The 5-cyclopropylmethyloxy **3j**, methanesulfonyloxy **3k** and trifluoromethanesulfonyloxy **3l** derivatives represent some of the highest affinity (pKi's 8.6-8.9) and most selective (200-320-fold) dopamine D_3 receptor antagonists reported to date.

Recent advances in the molecular biology of dopamine receptors have resulted in their classification into $D_{1\text{-}5}$ subtypes.[1-3] In particular, the D_2-like receptors, D_2, D_3, and D_4, have received much attention since existing drugs for the treatment of schizophrenia are believed to exert at least some of their antipsychotic effects through blockade of these receptors.[4] It has been proposed that the extra-pyramidal side-effects associated with currently available drugs result from blockade of dopamine D_2 receptors and that selective dopamine D_3 receptor antagonists would offer the potential for antipsychotic therapy free of such side-effects.[2]

Recently, a series of arylpiperazines, exemplified by **1**, was described with high affinity (pKi 9.5) for the dopamine D_3 receptor.[5] Although **1** was reported to be ca. 100-fold selective over the D_2 receptor (pKi 7.4), it was only 10-fold selective over the 5-HT_{1A} receptor (pKi 8.5). We reasoned that **1** could be formally derived from a 5-HT_{1A} agonist, 2-methoxyphenylpiperazine, and that addition of the 4-(4-phenylbenzoylamino)butyl side-chain was responsible for the high D_3 affinity of **1** and its presumed antagonist profile at the dopamine D_3 receptor. It was therefore proposed that by replacing one of the N-propyl groups of the known D_3 selective agonist 5-OH-DPAT **2**[6,7] with the 4-(4-phenylbenzoylamino)butyl side-chain, a novel series of selective dopamine D_3 antagonists **3** would be obtained. This *Letter* reports some of our initial findings regarding the D_3 affinity and selectivity of **3** and describes the functional influence of the substituents R^1 and R^2 (see Table 1).



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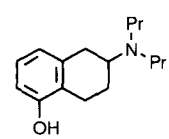
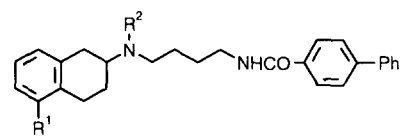


2 5-OH-DPAT



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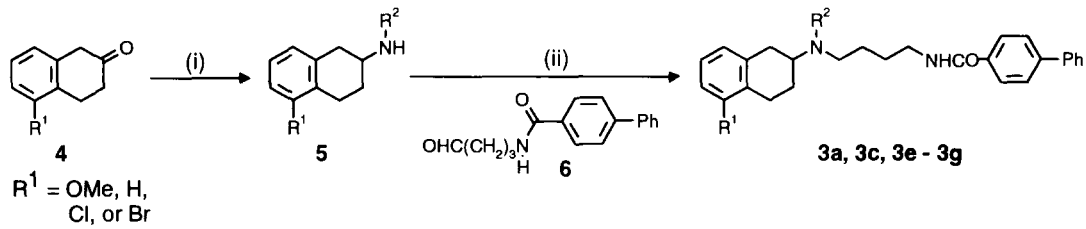
Novel compounds **3a** - **3l** (Table 1) were prepared directly from known 2-tetralones **4**, as shown in Scheme 1, or *via* subsequent modification of the 5-substituent. Reductive amination of **4** with either methylamine or *n*-propylamine in the presence of $NaBH(OAc)_3$ gave secondary amines **5** in high yield. A second reductive amination, this time using aldehyde **6**, gave final compounds **3a**, **3c**, **3e** - **3g**. O-Demethylation of **3a** and **3c** with BBr_3 in CH_2Cl_2 gave the 5-OH compounds **3b** and **3d**, respectively. Palladium-mediated cyanide displacement of the bromine in **3g** using $Zn(CN)_2$ and $Pd(PPh_3)_4$ in DMF gave nitrile **3h**, and subsequent hydrolysis using alkaline H_2O_2 gave primary amide **3i**. Alkylation of 5-OH derivative **3d** with cyclopropylmethyl bromide in DMF, using K_2CO_3 as base, gave **3j** and reaction of **3d** with methanesulfonyl chloride or trifluoromethanesulfonic anhydride gave **3k** and **3l**, respectively. All compounds were then purified by chromatography and isolated as their hydrochloride salts.

Scheme 1.



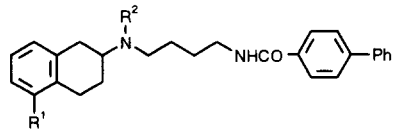
Reagents: (i) R^2NH_2, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (ii) $NaBH(OAc)_3$, $ClCH_2CH_2Cl$.

Compounds **3a** - **3l** were evaluated using displacement of ^{125}I-iodosulpride from human D_3 and D_2 receptors, expressed in CHO cells, and results are shown in Table 1. The dopamine D_3 receptor has been shown to be weakly coupled to adenylate cyclase in CHO cells.[8] Functional activity of the compounds was therefore determined *in vitro* using microphysiometry.[9]

Encouragingly, the initial compounds prepared in the N-methyl series, **3a** and **3b**, demonstrated that D_3 selective ligands could be obtained using the approach outlined above. Although 5-OMe **3a** displayed only modest D_3 affinity (pKi 7.9) and selectivity (25-fold), in the functional assay this compound was found to be an antagonist at the dopamine D_3 receptor. However, 5-OH **3b** which had increased D_3 affinity (pKi 8.6) and selectivity (50-fold) compared to **3a** was shown to be an agonist. This change in functional response may reflect different binding modes of **3a** and **3b** at the D_3 receptor, with the 5-OH group of **3b** activating the receptor *via* H-bond donation to a serine residue on trans-membrane helix 5.[6] The presence of a well-defined N-propyl pocket in dopamine receptors has been known for some time.[6,10] The N-propyl analogues **3c** and **3d** were therefore prepared. These compounds displayed a marked increase in both D_3 affinity and selectivity, with both compounds being over 100-fold selective. The 5-OH compound **3d**, like the N-methyl analogue **3b**, was an agonist. However, in marked contrast to the 5-OMe, N-Me analogue **3a**, the corresponding N-propyl analogue **3c** was also shown to be an agonist. This suggests that the N-propyl group of **3c** constrains the 5-OMe group to occupy a similar region of the receptor to that of the 5-OH group of **3d**. The 5-OMe group of **3c** then acts as an H-bond acceptor with one of the serine residues on helix 5, leading to receptor activation. In order to test this hypothesis, the unsubstituted tetralin **3e**, which would not be able to activate the D_3 receptor *via* H-bonding,

was prepared. It was most encouraging to find that not only did **3e** retain high D_3 affinity (pKi 8.8) and selectivity (200-fold), but in the functional assay this compound was shown to be an antagonist.

Table 1. Affinities of 2-Aminotetralin Derivatives at Dopamine D_3 and D_2 Receptors



Compound[a]	R^1	R^2	D_3[b]	D_2[b]	Selectivity	D_3 Function[c]
3a	OMe	Me	7.9	6.5	25	Antagonist
3b	OH	Me	8.6	6.9	50	Agonist
3c	OMe	Pr	9.1	6.9	160	Agonist
3d	OH	Pr	9.7	7.6	125	Agonist
3e	H	Pr	8.8	6.5	200	Antagonist
3f	Cl	Pr	8.8	6.4	250	Antagonist
3g	Br	Pr	8.9	6.6	200	Antagonist
3h	CN	Pr	9.3	7.0	200	Agonist
3i	$CONH_2$	Pr	8.4	6.2	160	Agonist
3j	OCH_2c-C_3H_5	Pr	8.6	6.1	320	Antagonist
3k	OSO_2Me	Pr	8.9	6.6	200	Antagonist
3l	OSO_2CF_3	Pr	8.8	6.4	250	Antagonist

[a] All new compounds gave satisfactory analytical and/or mass spectral data.[11] [b] Affinities are pKi values. All values represent the mean of at least 2 experiments, each within 0.2 of the mean. [c] Microphysiometer.[9]

Introduction of halogens at the 5-position, **3f** and **3g**, maintained the high D_3 affinity and selectivity observed with **3e**. These compounds were also antagonists. Replacement of halogen by groups with the ability to H-bond, such as CN or $CONH_2$, gave compounds **3h** and **3i** respectively, with high D_3 affinities and selectivities. However, as expected from the discussion above, these compounds were found to be agonists. Increasing the size of the substituent from methoxy to cyclopropylmethoxy **3j** was also tolerated, but in contrast to **3c** this compound was an antagonist. Presumably, in this case, the more bulky cyclopropylmethyl group either hinders H-bond formation between the oxygen and the serine residues present at helix 5 of the receptor, or forces the molecule to adopt an alternative binding conformation, therefore preventing any subsequent receptor conformational change which could result in an agonist response. In agreement with this observation with **3j**, the methanesulfonyloxy **3k** and trifluoromethanesulfonyloxy **3l** derivatives were also shown to be antagonists with high D_3 affinities and selectivities.

In conclusion, the replacement of one of the N-propyl groups of 5-OH-DPAT **2** with a 4-(4-phenylbenzoylamino)butyl side-chain, together with modifications to the 5-OH substituent, has resulted in a series of agonists and antagonists with high affinity and selectivity for the dopamine D_3 receptor. The 5-OH **3d**,

5-CN **3h** and 5-$CONH_2$ **3i** derivatives were found to be agonists, whereas the unsubstituted tetralin **3e** and the 5-OCH_2c-C_3H_5 **3j**, 5-OSO_2Me **3k** and 5-OSO_2CF_3 **3l** derivatives represent some of the highest affinity and most selective dopamine D_3 receptor antagonists reported to date. Although agonists, such as **3b**, displayed high selectivity (ca. 250-fold) over the $5HT_{1A}$ receptor, it was disappointing to find that antagonists, such as **3a**, **3j** and **3l**, were only modestly selective (20 - 40-fold) over this receptor. Nevertheless, these compounds provide useful tools for further characterising both the mechanisms of dopamine D_3 receptor activation and the role of this receptor in the central nervous system.

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11. ^1H NMR spectra were recorded at 250 MHz in d_6-DMSO as solvent. Compound **3f**, mpt 103-105 °C; ^1H: δ 0.93 (t, 3H), 1.64 (m, 2H), 1.78 (m, 5H), 2.36 (m, 1H), 2.74 (m, 1H), 2.90-3.40 (m, 9H), 3.67 (m, 1H), 7.13 (d, J = 9 Hz, 1H), 7.19 (t, J = 9 Hz, 1H), 7.29 (d, J = 9 Hz, 1H), 7.41 (m, 1H), 7.50 (t, J =9 Hz, 2H), 7.73 (m, 4H), 7.96 (m, 2H), 8.63 (br m, 1H), 10.11 (br s, 1H). Compound **3j**, mpt 101-103 °C; ^1H: δ 0.30 (m, 2H), 0.54 (m, 2H), 0.93 (t, 3H), 1.20 (m, 1H), 1.63 (m, 2H), 1.76 (m, 3H), 2.29 (m, 1H), 2.45-2.62 (m, 2H), 2.93-3.45 (m, 10H), 3.63 (m, 1H), 3.81 (d, 2H), 6.70 (d, J = 9 Hz, 1H), 6.75 (d, J = 9 Hz, 1H), 7.09 (t, J = 9 Hz, 1H), 7.41 (m, 1H), 7.50 (t, J = 9 Hz, 2H), 7.74 (m, 4H), 7.94 (d, J = 9 Hz, 2H), 8.59 (m, 1H), 9.48 (br s, 1H).

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