Pergamon

*Bioorganic & Medicinal Chemistry Letters*, Vol. 7, No. 15, pp. 1995-1998, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)00350-8

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

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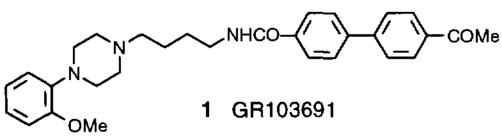
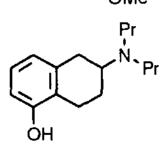
**Abstract**: A novel series of N-[4-(4-Phenylbenzoylamino)butyl]-1,2,3,4-tetrahydro-2-naphthylamines with high affinity and selectivity for the dopamine $D_3$ receptor has been prepared. The 5-cyclopropylmethyloxy **3j**, methanesulfonyloxy **3k** and trifluoromethanesulfonyloxy **3l** derivatives represent 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 $D_{1-5}$ 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]

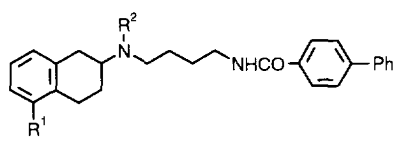
Recently, a series of arylpiperazines, exemplified by **1**, was described with high affinity (pKi 9.5) for the dopamine $D_3$ receptor.[5] Although **1** was reported to be ca. 100-fold selective over the $D_2$ receptor (pKi 7.4), it was only 10-fold selective over the 5-$HT_{1A}$ receptor (pKi 8.5). 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).




**1** GR103691




**2** 5-OH-DPAT




**3**

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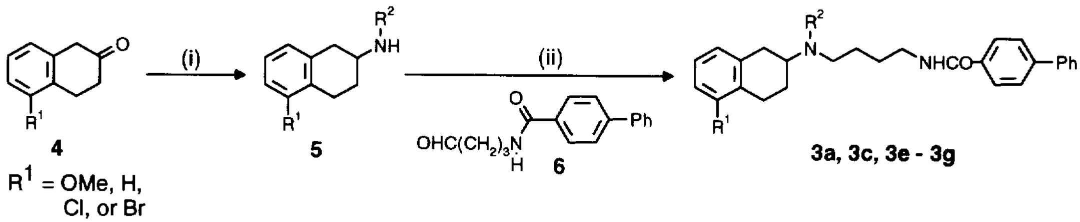
Novel compounds **3a** - **3l** (Table 1) were prepared directly from known 2-tetralones **4**, as shown in Scheme 1, or *via* subsequent modification of the 5-substituent. Reductive amination of **4** with either methylamine or *n*-propylamine in the presence of $NaBH(OAc)_3$ gave secondary amines **5** 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.**

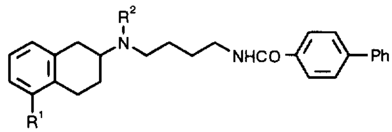



**Reagents:** (i) $R^2NH_2$, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (ii) $NaBH(OAc)_3$, $ClCH_2CH_2Cl$.

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** | $OCH_2c\text{-}C_3H_5$ | 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.

**References and Notes**

1. Grandy, D. K.; Marchionni, M. A.; Makam, H.; Stofko, R. E.; Alfano, M.; Frothingham, L.; Fischer, J. B.; Burke-Howie, K. J.; Bunzow, J. R.; Server, A. C.; Civelli, O. *Proc. Nat. Acad. Sci.* **1989**, *86*, 9762-9766.
2. Sokoloff, P.; Giros, B.; Martres, M-P.; Bouthenet, M-L.; Schwartz, J-C. *Nature.* **1990**, *347*, 146-151.
3. Van Tol, H. H. M.; Bunzow, J. R.; Guan, H-C.; Sunahara, R. K.; Seeman, P.; Niznik, H. B.; Civelli, O. *Nature.* **1991**, *350*, 610-614.
4. Seeman, P. *Synapse.* **1987**, *1*, 133-152.
5. Murray, P.J.; Harrison, L.E.; Johnson, M.R.; Robertson, G.M.; Scopes, D.I.C.; Bull, D.R.; Graham, E.A.; Hayes, A.g.; Kilpatrick, G.J.; Den Dass, I.; Large, C.; Sheehan, M.J.; Stubbs, C.M.; Turpin, M.P. *BioMed. Chem. Letts.* **1995**, *5*, 219-222.
6. Malmberg, A.; Nordvall, G.; Johansson, A.M.; Mohell, N. and Hacksell, U. *Mol. Pharmacol.* **1994**, *46*, 299-312.
7. For a recent report on the affinity for dopamine receptor subtypes of some simple alkyl and arylalkyl derivatives see van Vliet, L.A; Tepper, P.G.; Dijkstra, D.; Damsma, G.; Wikstrom, H.; Pugsley, T.A.; Akunne, H.C.; Heffner, T.G.; Glase, S.A.; Wise, L.A. *J. Med. Chem.* **1996**, *39*, 4233-4237.
8. Sokoloff, P.; Andrieux, M.; Besancon, R.; Pilon, C.; Martres, M-P.; Giros, B. and Schwartz, J-C. *Eur. J. Pharmacol. - Mol. Pharmacol. Section.* **1992**, *225*, 331-337.
9. For details of the microphysiometer method see Boyfield, I.; Brown, T.H.; Coldwell, M.C.; Cooper, D.G.; Hadley, M.S.; Hagan, J.J.; Healy, M.A.; Johns, A.J.; King, R.J.; Middlemiss, D.N.; Nash, D.J.; Riley, G.J.; Scott, E.E.; Smith, S.A. and Stemp, G. *J. Med. Chem.* **1996**, *39*, 1946-1948.
10. Hacksell, U.; Svensson, U.; Nilsson, J.L.G.; Hjorth, S.; Carlsson, A.; Wikstrom, H.; Lindberg, P. and Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469-1475.
11. $^1H$ NMR spectra were recorded at 250 MHz in $d_6$-DMSO as solvent. Compound **3f**, mpt 103-105 $^oC$; $^1H$: $\delta$ 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 $^oC$; $^1H$: $\delta$ 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).

(*Received in Belgium* 7 *April* 1997; *accepted* 27 *June* 1997)