# Design and Synthesis of 2-Naphthoate Esters as Selective Dopamine $D_4$ Antagonists

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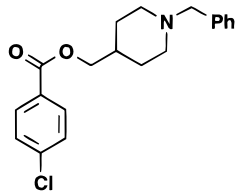
Existing drugs for the treatment of schizophrenia have poor side-effect profiles, in particular causing major movement disorders known as extrapyramidal side effects (EPS).[1] Schizophrenia has been associated with up-regulation of the dopaminergic system, and existing drugs are believed to exert their antipsychotic effects *via* blockade of $D_2$-like receptors.[2] Recent advances in the molecular biology of dopamine receptors have allowed these $D_2$-like receptors to be classified as $D_2$, $D_3$, and $D_4$.[3−5] On the basis of studies of receptor distribution, it has been proposed that the EPS caused by existing drugs are due to the blockade of $D_2$ receptors in the striatum. Studies based on the distribution of mRNA suggest that $D_4$ receptors are preferentially located in cortical and other areas of the brain associated with antipsychotic activity and have low density in the striatum.[5,6] A selective $D_4$ antagonist thus has the potential to be an effective antipsychotic agent lacking the EPS of current therapy.

Two further pieces of evidence have also driven the search for selective $D_4$ antagonists. The atypical antipsychotic agent clozapine has been shown to be approximately 10-fold selective[5] for $D_4$ over $D_2$ receptors. Clozapine has higher efficacy than other antipsychotic agents and low propensity to cause EPS, and it has therefore been proposed that the $D_4$ selectivity of clozapine may contribute to its highly beneficial profile. In addition, it has been reported that $D_4$ receptor levels are elevated in schizophrenia,[7,8] although the evidence for this has been questioned.[9]

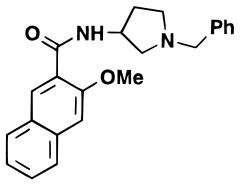
There is therefore a clear need for a selective $D_4$ antagonist to explore the potential of such a compound in the treatment of schizophrenia. The only compound reported to date with high selectivity is NGD 94-1, but no structure has been revealed.[10] This Communication describes the discovery of the first compound with >1000-fold selectivity for the $D_4$ over the $D_2$ receptor.

Compounds were screened on human cloned $D_4$ and $D_2$ (long) receptors[11] using [$^3$H]nemonapride and [$^{125}$I]-iodosulpride, respectively, as the radioligands, and results are reported as p$K_i$ values.[12] From a program of rapid parallel synthesis based on known dopaminergic structural motifs, the ester **1** and naphthamide **2** emerged as leads with p$K_i$ values of 7.6 and 8.4 at $D_4$ receptors and selectivities of 80 and 10, respectively, against $D_2$ receptors.

On the basis of these leads, a series of 3-methoxy-2-naphthyl derivatives was prepared. Esters **3** and **4** and amide **5** were obtained from 3-methoxynaphthalene-2-carboxylic acid **11** *via* conversion to the acid chloride



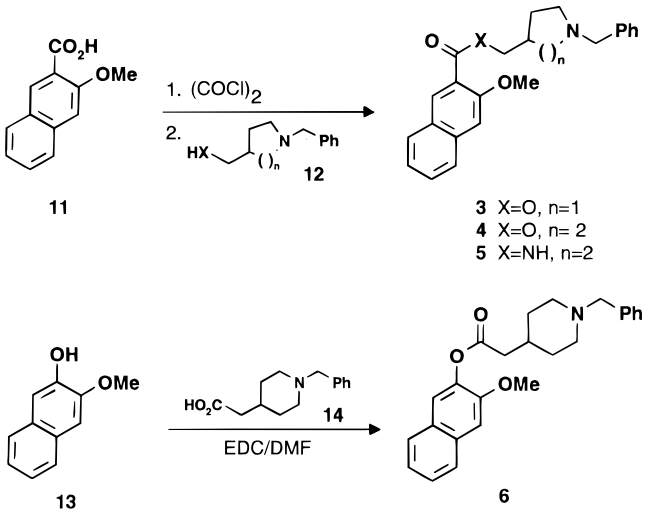

**1** pKi's: $D_4$ 7.6, $D_2$ 5.7




**2** pKi's: $D_4$ 8.4, $D_2$ 7.4

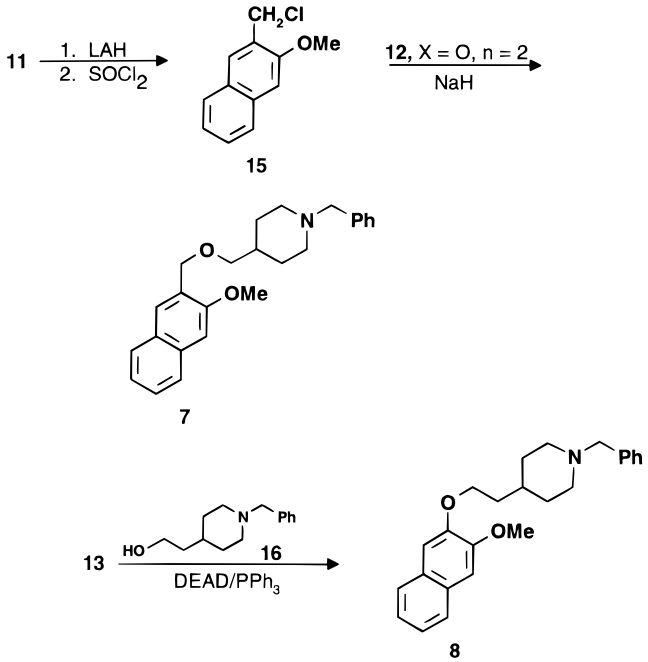
followed by reaction with the appropriate alcohol or amine **12** (Scheme 1). Ester **6** was obtained from

**Scheme 1**




3-methoxy-2-naphthol **13** by coupling with acid **14**. Reduction of **11** with LAH followed by treatment with $SOCl_2$ gave chloride **15** which reacted with the anion derived from alcohol **12** (X = O, $n$ = 2) to give ether **7** (Scheme 2). Coupling of **13** with alcohol **16** under

**Scheme 2**




Mitsunobu conditions gave **8**. Conversion of **11** to the Weinreb amide followed by reaction with MeLi gave **17**, which was condensed with pyridine-4-carboxaldehyde.

S0022-2623(96)00017-9 CCC: $12.00 

**Scheme 3**

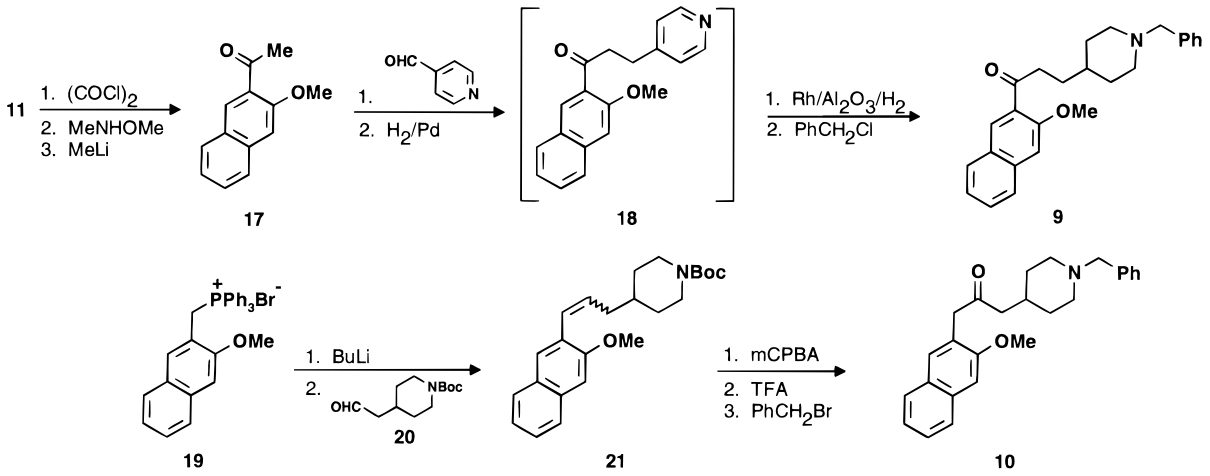
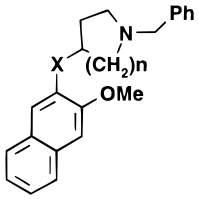
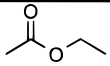
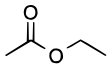
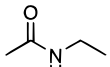
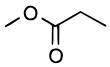
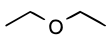
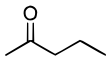
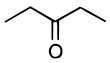



**Table 1.** Dopamine Receptor Affinity of 3-Methoxy-2-naphthyl Esters, Amides, Ethers, and Ketones



| compd[a] | X | n | mp °C | $D_4$[d] | $D_2$[d] | Selectivity[e] |
|---|---|---|---|---|---|---|
| **3** |  | 1 | 115-118[c] | 7.7 | 5.0 | 500 |
| **4** |  | 2 | 182-183[c] | 8.3 | 5.5 | 630 |
| **5** |  | 2 | 128-130[c] | 7.7 | 6.9 | 6 |
| **6** |  | 2 | 100-102[b] | 8.2 | 5.1 | 1260 |
| **7** |  | 2 | 122-125[c] | 7.5 | 6.0 | 30 |
| **8** |  | 2 | 111-112[b] | 7.6 | 5.8 | 60 |
| **9** |  | 2 | 206-208[c] | 7.5 | 6.4 | 12 |
| **10** |  | 2 | 99-102[b] | 6.7 | 5.9 | 6 |

[a] All new compounds received satisfactory analytical and/or spectroscopic data (see Supporting Information for full details of their preparation. [b] Free base. [c] HCl salt. [d] p$K_i$ values represent the means of at least two determinations. For compounds **4** and **6** values are the means of four determinations. [e] Selectivity for $D_4$ compared to $D_2$.

Subsequent reductions and benzylation gave ketone **9** (Scheme 3). Alkene **21** was prepared as a mixture of isomers from reaction of phosphonium salt **19** and aldehyde **20**. Oxidation of **21** to the epoxide with mCPBA, followed by rearrangement, deprotection, and benzylation, gave ketone **10**.

The affinities of compounds **3**−**10** for $D_4$ and $D_2$ receptors are shown in Table 1.

The pyrrolidinyl naphthoate **3** gave an encouraging improvement in selectivity compared to ester **1**. Expansion of the pyrrolidine ring to piperidine **4** further improved $D_4$ affinity and maintained the high selectivity of **3**. However, replacement of the ester moiety by related functionalities both reduced $D_4$ affinity and increased $D_2$ affinity, resulting in marked reductions in selectivity. Only by reversal of the ester linkage of **4** to give **6** was high $D_4$ affinity and selectivity maintained. The affinity order at $D_4$ receptors was esters **4**, **6** > amide **5**, ethers **7**, **8**, ketone **9** > ketone **10**, whereas at $D_2$ receptors the affinity order was amide **5** > ketone **9** > ethers **7**, **8**, ketone **10** > esters **4**, **6**. It is interesting to note that only the esters **4** and **6**, which possess two electronegative areas capable of accepting hydrogen bonds, show both high $D_4$ affinity and selectivity. The almost complete loss of selectivity with amide **5**, despite the retention of relatively high $D_4$ affinity, is remarkable and may be due to the formation of an intramolecular hydrogen bond between the amide NH and 3-methoxyl group, which has been shown to be a key feature in benzamide dopamine antagonists.[13]

In conclusion, naphthoate esters with high $D_4$ affinity and selectivity have been described. To our knowledge compound **6** is the first compound to be reported in the literature with >1000-fold selectivity over its affinity

for the $D_2$ receptor.[14] Functional studies *in vitro* have shown that **4** and **6** are antagonists at the $D_4$ receptor.[15] These compounds therefore represent tools for the *in vitro* determination of the distribution and function of dopamine $D_4$ receptors in the brain.

**Acknowledgment.** We thank Christopher Harmer and Jason Martin for their enthusiastic technical assistance.

**Supporting Information Available:** Experimental details for the preparation of relevant compounds (4 pages). Ordering information is given on any current masthead page.

## References

(1) Marder, S. R.; Wirshing, W. C.; Van Putten, T. Drug Treatment of Schizophrenia. *Schizophr. Res.* **1991**, *4*, 81−90.
(2) Seeman, P. Dopamine Receptors and the Dopamine Hypothesis of Schizophrenia. *Synapse* **1987**, *1*, 133−152.
(3) 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. Cloning of the cDNA and Gene for a Human $D_2$ Dopamine Receptor. *Proc. Nat. Acad. Sci. U.S.A.* **1989**, *86*, 9762−9766.
(4) Sokoloff, P.; Giros, B.; Martres, M.-P.; Bouthenet, M.-L.; Schwartz, J.-C. Molecular Cloning and Characterisation of a Novel Dopamine Receptor $D_3$ as a Target for Neuroleptics. *Nature* 1990, *347*, 146−151.
(5) Van Tol, H. H. M.; Bunzow, J. R.; Guan, H.-C.; Sunahara, R. K.; Seeman, P.; Niznik, H. B.; Civelli, O. Cloning of the Gene for a Human Dopamine $D_4$ Receptor with high affinity for the Antipsychotic Clozapine. *Nature* **1991**, *350*, 610−614.
(6) Matsumoto, M.; Hidaka, K.; Tada, S.; Tasaki, Y.; Yamaguchi, T. Full Length cDNA Cloning and Distribution of Human Dopamine $D_4$ Receptor. *Mol. Brain Res.* **1995**, *29*, 157−62.
(7) Seeman, P.; Guan, H.-C.; Van Tol, H. H. M. Dopamine $D_4$ Receptors Elevated in Schizophrenia. *Nature* **1993**, *365*, 441−445.
(8) Murray, A. M.; Hyde T. M.; Knable, M. B. Distribution of Putative $D_4$ Dopamine Receptors in Postmortem Striatum from Patients with Schizophrenia. *J. Neurosci.* **1995**, *15*, 2186−2191.
(9) Reynolds, G. P.; Mason, S. L. Are Striatal Dopamine $D_4$ Receptors Increased in Schizophrenia? *J. Neurochem.* **1994**, *63*, 1576−1577.
(10) Tallman, J. F. NGD 94-1: Preclinical Profile of a Specific Dopamine-4 ($D_4$) Receptor Antagonist. American College of Neuropsychopharmacology 33rd Annual Meeting, San Juan, Puerto Rico, December 12−16, 1994.
(11) Human cloned dopamine $D_{4.4}$ receptors were expressed in HEK 293 cells; see: McHale, M.; Coldwell, M. C.; Herrity, N.; Boyfield, I.; Winn, F. M.; Ball, S.; Cook, T.; Robinson, J. H.; Gloger, I.S. Expression and Functional Characterisation of a Synthetic Version of the Human $D_4$ Dopamine Receptor in a Stable Human Cell Line. *FEBS Lett.* **1994**, *345*, 147−150. Human cloned dopamine $D_2$ (long) receptors expressed in CHO cells were obtained from the Garvan Institute (Melbourne).
(12) Binding experiments were carried out as follows. The test compounds (10 concentrations, 0.01 nM to 0.01 mM) were incubated with the $D_2$ (CHO) and $D_{4.4}$ (HEK293) receptor homogenates at 37 °C for 40 min together with 0.1 nM [$^{125}$I] iodosulpride (2000 Ci/mmol; Amersham, U.K.) (for $D_2$) and 0.8 nM [$^3$H]YM-09151 (86 Ci/mmol, NEN Research Products, U.K.) (for $D_4$). The buffer contained 50 mM Tris (pH 7.4 at 37 °C), 120 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, and 0.1% (w/v) bovine serum albumin, and the total volume was 0.5 mL. Nonspecific was defined with 0.1 mM YM-09151. Following incubation, samples were filtered using a Canberra Packard Filtermate and washed four times with ice-cold 50 mM Tris (pH 7.4 at 37 °C). The radioactivity on the filters was measured using a Canberra Packard Topcount. Competition curves were analysed using INFLEXION (Bowen, W. P.; Jerman, J. C. Inflexion: Automated analysis of radio-ligand binding data with Microsoft Excel. *Br J. Pharmacol.* **1994**, *113*, 440P).
(13) Högberg, T. Novel Substituted Salicylamides and Benzamides as Selective $D_2$-receptor Antagonists. *Drugs Future* **1991**, *16*, 333−357.
(14) The binding profile of compound **6** has been determined against the following human cloned receptors; $pK_i$ values are in parentheses: $D_3$ (5.2); $5HT_{1a}$ (5.7); $5HT_{2a}$ (6.6); $5HT_{2c}$ (6.6).
(15) Functional studies using cloned $D_2$ (long) and $D_{4.4}$ receptors were carried out *in vitro* using a Cytosensor Microphysiometer (Molecular Devices). Cells were seeded into 12 mm Transwell inserts at 300 000 cells/cup in culture medium containing foetal calf serum (FCS). The cells were incubated for 6 h at 37 °C in 5% $CO_2$, before changing to medium without FCS. After a further 16−18 h, cups were loaded into the sensor chambers of the microphysiometer and the chambers perfused with running medium (bicarbonate-free Dulbecco's modified Eagles medium containing 2 mM glutamine and 44 mM NaCl). For agonist experiments, cells were exposed to increasing concentrations of agonist at half-hour intervals. For antagonist experiments, cells were exposed five times (at half-hour intervals) to a single concentration of quinpirole (30 nM) before addition of the first antagonist concentration. After a 30 min interval, cells were again stimulated with quinpirole (in the continued presence of the antagonist), before the second (higher) antagonist concentration was applied. In all, responses in the presence of five increasing concentrations of antagonist were determined. Peak acidification rate to each agonist concentration was determined and concentration−response curves fitted using RoboFit (Tilford N. S.; Bowen, W. P.; Baxter, G. S. RoboFit: A Versatile Macro-Driven Template for Curve Fitting, Analysis and Presentation in Microsoft Excel. *Br. J. Pharmacol.* **1995**, *115*, 160P).

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