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A NOVEL SERIES OF ARYLPIPERAZINES WITH HIGH AFFINITY AND SELECTIVITY FOR THE DOPAMINE D_3 RECEPTOR

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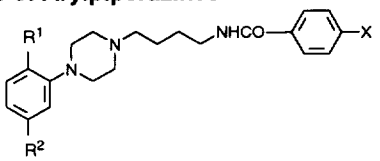
Abstract: A novel series of arylpiperazines has been synthesised which show high affinity for dopamine D_3 receptors. Several of these compounds exhibit *ca.* 100 fold selectivity for the dopamine D_3 receptor over D_1, D_2 and D_4 receptors. *In vivo* studies suggest that **4** (GR103691) may have an atypical antipsychotic profile.

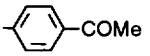
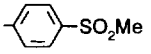
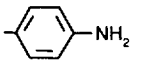
Biochemical, pharmacological and, more recently, molecular biological studies have established that there is a family of at least five dopamine receptors: D_1, D_2, D_3, D_4 and D_5.[1] Historically, the D_2 receptor has been the focus of therapeutic interest since antagonist activity at this receptor is a characteristic of most antipsychotics used in the treatment of schizophrenia.[2] However, the utility of standard antipsychotics is limited by extrapyramidal side-effects and by tardive dyskinesias, which are attributed to blockade of D_2 receptors in the striatal region of the brain.[3] The recent cloning of the D_3 receptor and the high affinity it shows for many antipsychotics has sparked much interest in this novel receptor subtype, particularly as *in situ* hybridization studies indicate its selective localisation in limbic areas of the brain.[4] This raises the intriguing possibility that a selective antagonist for the D_3 receptor might provide an effective antipsychotic free from extrapyramidal side-effects.[5] The crucial objective for medicinal chemists is to design a compound with sufficient selectivity over the D_2 receptor to allow the above hypothesis to be tested. We now report on a series of novel arylpiperazines which exhibit *ca.* 100 fold selectivity for the D_3 over the D_2 receptor.

As part of a programme to identify selective D_3 receptor antagonists we evaluated a series of aryl piperazines from our database that had previously been shown to possess D_2 affinity. One of these compounds **2** had high affinity for the D_3 receptor and, strikingly, displayed ca. 100 fold selectivity over the D_2 receptor (Table 1). Furthermore, it showed 100 fold selectivity over D_4 receptors (pKi = 7.3, CHO cells transfected with human D_4 receptor) and 1000 fold selectivity over D_1 receptors. This is in marked contrast with typical antipsychotics, such as haloperidol, which show little D_3/D_2 receptor selectivity (Table 1).[6] However, given the propensity for the arylpiperazines to

display affinity for several classes of seven transmembrane receptor, it was perhaps not surprising that **2** also showed appreciable affinity for 5-HT_{1A} and α_1 receptors.

Table I Receptor affinities of Arylpiperazines



Compd	R^1	R^2	X	Receptor Affinity (pKi)[a]				
				D_3[b]	D_2[c]	D_1[d]	5-HT_{1A}[e]	α_1[f]
1	H	H	Br	8.2	6.4	NT	6.9	NT
2	MeO	H	Br	9.3	7.4	6.3	7.9	7.9
3	MeO	MeO	Br	8.5	7.0	NT	6.6	7.5
4	MeO	H		9.5	7.4	6.4	8.5	7.9
5	MeO	H		9.5	7.6	6.8	7.7	7.9
6	MeO	H		9.7	7.7	7.0	7.9	8.0
	Haloperidol			8.1	9.0			

[a] Figures quoted are the mean of two independent determinations, each within 0.2 log units of the mean. [b] Binding affinity, Chinese hamster ovary cells transfected with human D_3 receptor using [^{3}H]-spiperone. [c] Binding affinity, mouse Ltk$^-$ cells transfected with human D_2 receptor (short form) using [^{3}H]-spiperone. [d] Binding affinity, [^{3}H]-Sch 23390 was used to label D_1 sites in rat striatal tissue. [e] Binding affinity, [^{3}H]-8-OH-DPAT was used to label 5-HT_{1A} sites in rat hippocampus. [f] Binding affinity, [^{3}H]-prazosin was used to label α_1 sites in rat heart.

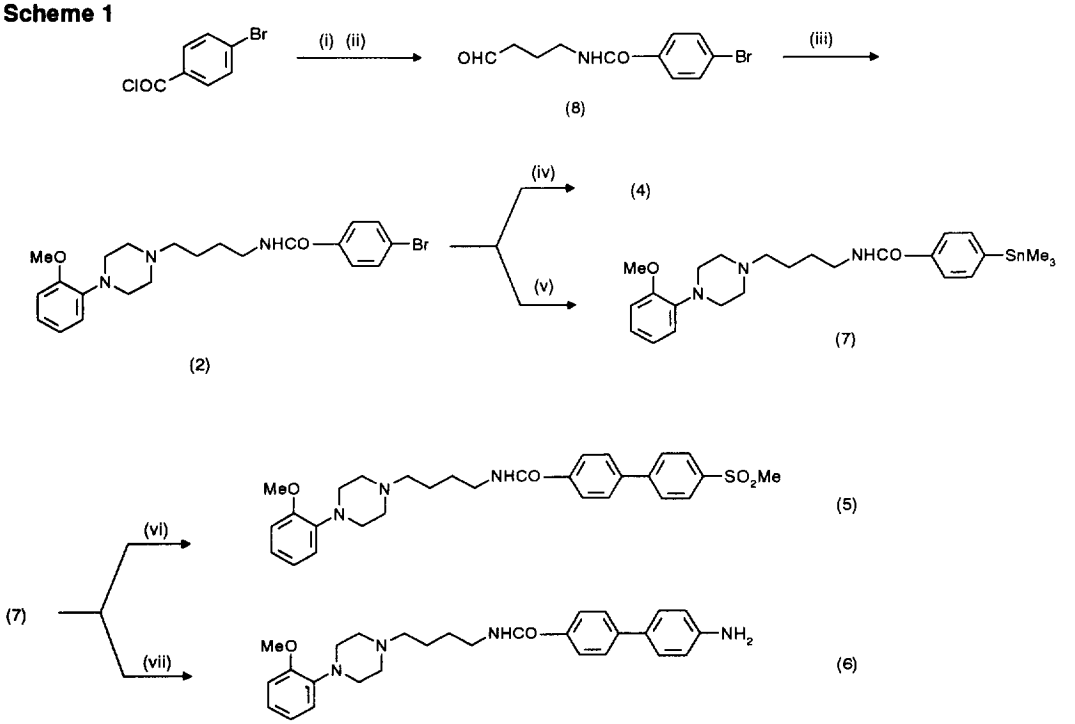
We therefore elected to modify lead structure **2** with a view to maximizing selectivity for the D_3 receptor. Removal of the 2-methoxy substituent from **2** gave a compound **1** which displayed a general lowering of affinity across all the receptors evaluated, although the level of D_3/D_2 receptor selectivity was maintained. In contrast, introduction of a 5-methoxy group **3** lowered D_3 affinity and resulted in a less selective compound. Decreasing the length of the tetramethylene linker to 3 and 2 methylenes markedly reduced D_3 receptor affinity (pKi <6.5) whereas increasing to 5 methylenes gave a compound with a D_3 pKi = 7.9. Expanding the benzamide grouping by incorporating substituted 1,1'-biaryls also modulated affinities at the various receptors, although the changes were modest. The 4'-acetyl derivative **4** (GR103691) showed the best selectivity over dopamine receptors (D_4 pKi = 7.2) and also good selectivity over the following receptors: 5-HT_3 (pKi <5), 5-HT_2 (pK_B <5), α_1 (pK_B = 7.8), α_2 (pK_B = 6.8). Its selectivity over 5-HT_{1A} receptors was reduced by 5 fold. However, the 4'-methylsulphone and the 4'-amino derivatives, **5** and **6** respectively, displayed the best activity/selectivity profiles overall.

We have evaluated GR103691 in the VTA/SNr (ventral tegmental area/substantia nigra zona reticulata) muscimol-induced locomotor activity (LMA) model[7] in the rat to assess its selectivity for the mesolimbic over nigrostriatal dopamine systems in the brain. In this model low doses of the

atypical antipsychotic clozapine can attenuate the stimulant effects of a VTA infusion of muscimol (ED_{50}=0.002mg/kg.,sc) whereas 500 fold higher doses are required to reduce SNr mediated LMA. Haloperidol does not discriminate between LMA evoked by a muscimol infusion into either the VTA or the SNr (ED_{50}=0.05mg/kg.,s.c.). Interestingly, GR103691 displayed an atypical profile: it blocked VTA muscimol-induced LMA (ED_{50}=0.3mg/kg.,sc) but had no effect on SNr mediated LMA (ED_{50} >10mg/kg.,sc). It remains to be determined whether this profile is a result of the high affinity and selectivity of this compound for the D_3 receptor.

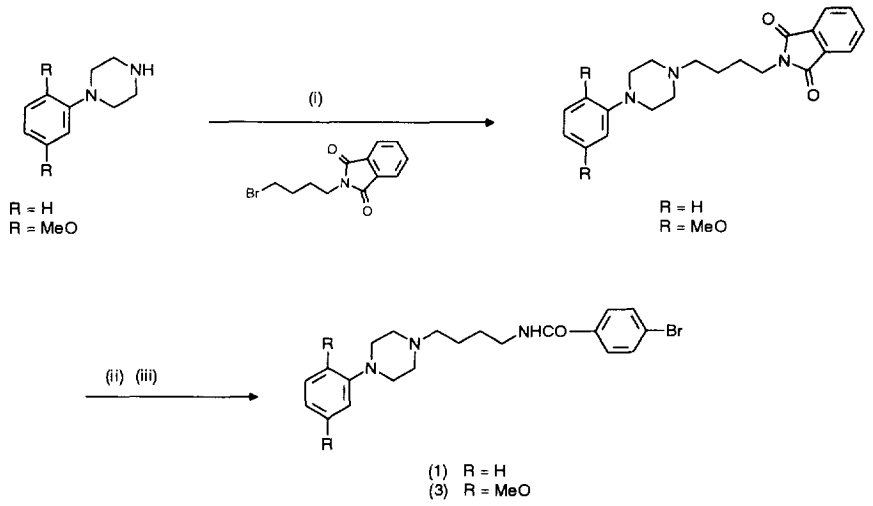
Compounds were synthesised as outlined in Schemes 1 and 2. The bromobenzamide **2**, prepared via reductive amination of 1-(2-methoxyphenyl)piperazine with the aldehyde **8**, served as a central intermediate for the synthesis of **4**-**6**. Thus, a palladium (0) catalysed boronic acid **9** coupling of **2**, followed by acid catalysed hydrolysis, provided the acetophenone **4**. Alternatively, conversion of **2** to the stannane **7** facilitated palladium-catalysed access to the sulphone **5** and the aniline **6**. Modifications to the methoxyphenylpiperazine moiety were prepared via alkylation of the appropriate arylpiperazine with N-(4-bromobutyl)phthalimide. Subsequent de-phthaloylation and benzamide formation gave **1** and **3** in high overall yield.[8]

Scheme 1



(i) $HO(CH_2)_4NH_2$, Et_3N, CH_2Cl_2; 71% (ii) $(COCl)_2$, DMSO, Et_3N; 93% (iii) 1-(2-methoxyphenyl)piperazine, $NaBH(OAc)_3$, AcOH, $ClCH_2CH_2Cl$; 63% (iv) (a) 4-$(HO)_2BC_6H_4C(OCH_2)_2Me$ (**9**), $Pd(PPh_3)_4$, Na_2CO_3, DME-H_2O; 83% (b) HCl, EtOH-H_2O; 86% (v) $(Me_3Sn)_2$, $Pd(PPh_3)_4$, xylene, Δ; 76% (vi) 4-$BrC_6H_4SO_2Me$, $Pd(PPh_3)_4$, xylene, Δ; 81% (vii) (a) 4-$BrC_6H_4NO_2$, $Pd(PPh_3)_4$, xylene, Δ; 77% (b) H_2, Pd-C, DMF; 45%

Scheme 2



(i) Xylene, K_2CO_3, Δ (R = H, 86%; R = MeO, 69%) (ii) $N_2H_4.H_2O$, EtOH, Δ (R = H, 86%; R = MeO, 96%) (iii) 4-$ClC(O)C_6H_4Br$, Et_3N, CH_2Cl_2 (R = H, 70%; R = MeO, 84%)

In summary, we have disclosed a novel series of arylpiperazines which show high affinity for the dopamine D_3 receptor. Several of these compounds, although having some affinity for 5-HT_{1A} and α_1 receptors, show up to 100 fold selectivity over D_1, D_2 and D_4 receptors and as such should be useful tools for furthering our understanding of the physiological function of dopamine D_3 receptors and their possible role in mediating psychiatric illness.

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6. Recently a series of arylpiperazines has been disclosed which have high affinity for the D_3 receptor but show no selectivity over D_2, 5-HT_{1A}, α_1 and α_2 receptors. Reitz, A.B.; Bennett, D.J.; Blum, P.S.; Codd, E.E.; Maryanoff, C.A.; Ortegon, M.E.; Renzi, M.J.; Scott, M.K.; Shank, R.P.; Vaught, J.L. *J.Med.Chem.* **1994**, *37*, 1060. In addition, certain 5-substituted 2-aminotetralins have been reported to display modest selectivity (ca. 15 fold) for the D_3 with respect to the D_2 receptor. Haadsma-Svensson, S.R.; Smith, M.W.; Lin, C-H.; Duncan, J.N.; Sonesson, C.; Wikstrom, H.; Waters, N.; Carlsson, A,; Svensson, K. *Bioorg.Med.Chem.Lett.* **1994**, *4*, 689.
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8. All new compounds exhibited satisfactory spectral and elemental analysis data.

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