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Phenylpiperazine Derivatives with Strong Affinity for $5HT_{1A}$, D_{2A} and D_3 Receptors

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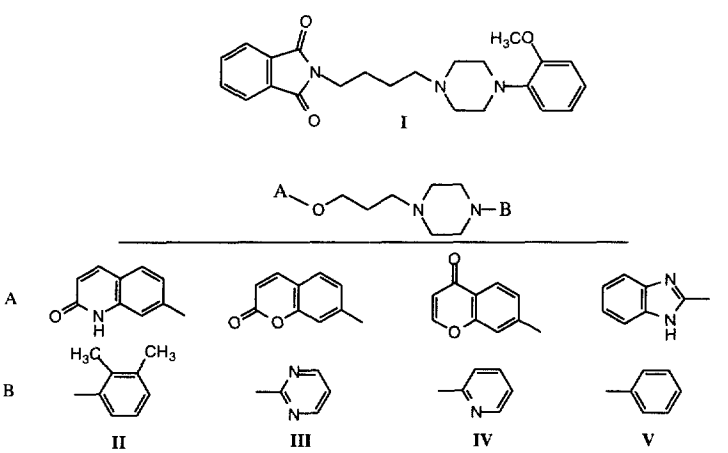
Abstract: Four 7-[3-(4-phenyl-1-piperazinyl)propoxy]coumarins were synthesized. The affinities of these compounds for DA (D_{2A}, D_3) and $5HT_{1A}$ receptors were evaluated for their ability to displace [^{3}H]-raclopride and [^{3}H]-8-OH-DPAT respectively from their specific binding sites. The affinities of the target compounds were all in the nanomolar range and followed the order $5\text{-}HT_{1A} > D_2 > D_3$.

Dopamine (DA) and serotonin (5-HT) receptors are implicated in various psychiatric and neurological disorders, including anxiety, schizophrenia and Parkinson's disease. Most "typical" antipsychotic drugs produce their pharmacological effects through blockade of postsynaptic D_2 receptors in the limbic system. However, the clinical utility of existing antipsychotics is limited by extrapyramidal side-effects due to concomitant blockade of D_2 receptors in the striatum.[1] This has spurred research aimed at characterizing presynaptic D_2 receptors (autoreceptors), the activation of which can modulate cerebral dopaminergic activity by regulating dopamine neurotransmission,[2] and the more recently identified D_3 receptors (present predominantly in the limbic system), for which many antipsychotics are also known to have strong affinity.[3] Suitably selective D_{2A} agonists[4] and D_3 receptor antagonists[5] may present fewer side-effects than typical antipsychotics.



Research hitherto has shown that the N-arylpiperazine fragment is important for CNS-activity, especially dopaminergic and serotonergic activity. Thus, compounds with a simple arylpiperazine moiety can modulate

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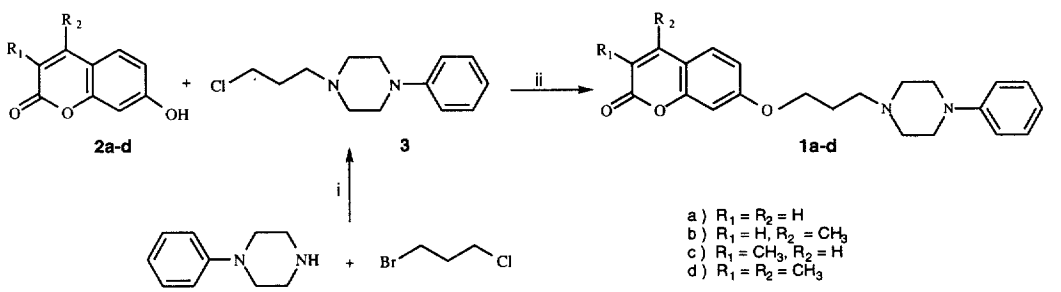
5-HT_1 receptors,[6] while slight modification of this moiety affords compounds selective for 5-HT_{1A} receptors.[7] It has also been found that linking a carbo- or heterocycle to the piperazine moiety by a lipophilic chain, as in NAN-190 (I) or the anxiolytic buspirone, can afford drugs that modulate both 5-HT_{1A} and D_2 receptors.[8] Structurally related compounds have also shown high affinity for D_{2A} autoreceptors - OPC-4392 (II)[9], PD-118717 (III),[10] PD-119819 (IV)[11] - or for D_3 receptors (compound V).[12]

In this work, our aim was to gather further data about the structural factors determining serotonergic and/or dopaminergic affinity and selectivity. To this end we prepared compounds **1a-d** (Scheme 1), which comprise a phenylpiperazine linked by a propoxy chain to a coumarin nucleus.

Chemistry

7-[3-(4-Phenyl-1-piperazinyl)propoxy]coumarins **1a-d** were prepared as shown in Scheme 1. The required 7-hydroxycoumarins **2a** and **2b** were commercial compounds, **2c** was prepared in 38% yield by Perkin reaction of 2,4-dihydroxybenzaldehyde and ethyl propionate, and **2d** was prepared in 32% yield by Pechmann reaction of resorcinol with ethyl 2-methylacetoacetate.[13] 1-(3-Chloropropyl)-4-phenylpiperazine **3** was prepared in 80% yield by alkylation of N-phenylpiperazine with 1-bromo-3-chloropropane.[5a] Coupling of 7-hydroxy coumarins **2a-d** with **3** was carried out in dry dimethylformamide, and involved *in situ* conversion of the former to the corresponding sodium salt by reaction with NaH,[14] which afforded compounds **1a-d** in 43-65% yield.[15]

Scheme 1



(i) NaOH, CH_3COCH_3, room temperature, 68 h; (ii) NaH, DMF, 100°C, 5h.

Pharmacology

Compounds **1a-d** were converted to their water-soluble hydrochloride salts for use in the assays.

5-HT_{1A} Receptor binding assays were performed as described previously[16] using tissue from rat hippocampus membranes and, as radioligand, [^{3}H]-8-OH-DPAT.

D_{2A} and D_3 Receptor binding assays were performed in mammalian cells following previously described protocols,[17] in both cases with [^{3}H]-raclopride as radioligand. D_{2A} assays used homogenated mouse fibroblast (LTK^-) cells transfected with human D_{2A} receptors, while D_3 assays used Chinese hamster ovary (CHO) cells transfected with human D_3 receptor.

Results and Discussion

From the binding data, the phenylpiperazines **1a-d** showed a mixed pharmacological profile, binding strongly to 5-HT_{1A}, D_{2A} and D_3 receptors. All the compounds had receptor binding affinities in the nanomolar range, presented as Ki values in Table 1.

Compound **1c** (K_i = 0.79 nM) showed the strongest affinity for 5-HT_{1A} receptors - stronger than both the reference compound 8-OH-DPAT[18] and NAN-190[19] (1.3 and 1.26 nM, respectively) - and also showed moderate selectivity for this receptor over the D_{2A} and D_3 subtypes (K_i = 10.8 and 18.9 nM, respectively).

The 3,4-dimethyl compound, **1d**, showed the strongest affinity for D_{2A} receptors, for which it was selective over D_3 but not 5-HT_{1A} receptors. By contrast, the affinity of the phenylpiperazines for D_3 receptors was somewhat lower than for the other receptors, compound **1c** showing the strongest binding affinity for this receptor.

These results confirm the importance of the *N*-arylpiperazine fragment in the modulation of dopaminergic and serotonergic activity. Substitution at N^4 of this fragment with a propoxycoumarin moiety afforded compounds that bind to 5-HT_{1A}, D_{2A} and D_3 receptors with affinities comparable to, or in some cases stronger than, those of the N^4-substituted-N^1-arylpiperazines I-V.

The effects of introducing methyl groups at positions 3 and/or 4 of the coumarin nucleus were as follows: the 3-methyl compound (**1c**) had six-seven times greater affinity for 5-HT_{1A} receptors, and 2 - 4 times greater affinity for D_3 receptors, than the unsubstituted, 4-methyl and 3,4-dimethyl compounds; by contrast, the 4-methyl compound (**1b**) had much lower affinity for D_3 receptors, instead presenting an interesting 5-HT_{1A}/D_{2A} mixed profile.

Table 1. Receptor binding affinity Ki ± SEM (nM), for compounds **1a-d**

Compound	5-HT_{1A}	n	D_{2A}	n	D_3	n
1a	5.61 ± 0.07	2	16.0 ± 1.7	4	49.7 ± 14.0	3
1b	5.54 ± 0.02	2	13.7 ± 2.6	4	73.8 ± 9.9	3
1c	0.79 ± 0.08	2	10.8 ± 2.2	4	18.9 ± 6.0	2
1d	5.31 ± 0.35	2	5.92 ± 0.5	4	44.7 ± 15.0	2

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15. *7-[3-(4-phenyl-1-piperazinyl)propoxy]coumarin* (**1a**). 55% yield; mp 106-8 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (d, 1H, H-4, *J* = 9.50), 7.38 (d, 1H, H-5, *J* = 8.32), 7.27 (m, 2H, *m*-), 6.98-6.78 (m, 5H, *o*-, *p*-, H-6, H-8), 6.25 (d, 1H, H-3, *J* = 9.50), 4.13 (t, 2H, CH_2O, *J* = 6.00), 3.36 (m, 4H, $N(CH_2)_2$), 2.86 (m, 6H, $(CH_2)_2NCH_2$), 2.21 (m, 2H, $CH_2C\underline{H}_2CH_2$); IR 2814, 1726, 1609, 1495, 1228, 1045. Rf 0.33 (ethyl acetate-hexane 3:2). Anal. ($C_{22}H_{24}N_2O_3 \cdot HCl \cdot 2H_2O$) C, H, N.
4-Methyl-7-[3-(4-phenyl-1-piperazinyl)propoxy]coumarin (**1b**). 65% yield; mp 123-5 °C; ^{1}H NMR ($CDCl_3$) δ 7.49 (d, 1H, H-5, *J* = 8.70), 7.27 (m, 2H, *m*-), 6.98-6.81 (m, 5H, *o*-, *p*-, H-6, H-8), 6.14 (d, 1H, H-3, *J* = 1.15), 4.12 (t, 2H, CH_2O, *J* = 6.25), 3.25 (m, 4H, $N(CH_2)_2$), 2.67 (m, 6H, $(CH_2)_2NCH_2$), 2.40 (d, 3H, CH_3, *J* = 1.15), 2.09 (m, 2H, $CH_2C\underline{H}_2CH_2$); IR 2816, 1712, 1612, 1495, 1264, 1070. Rf 0.23 (ethyl acetate-hexane 2:1). Anal. ($C_{23}H_{26}N_2O_3 \cdot HCl \cdot 0.5H_2O$) C, H, N.
3-Methyl-7-[3-(4-phenyl-1-piperazinyl)propoxy]coumarin (**1c**). 43% yield; mp 129-31 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (d, 1H, H-4, *J* = 1.00), 7.34-7.23 (m, 3H, H-5, *m*-), 7.27 (m, 2H, *m*-), 6.98-6.81 (m, 5H, *o*-, *p*-, H-6, H-8), 4.12 (t, 2H, CH_2O, *J* = 6.00), 3.36 (m, 4H, $N(CH_2)_2$), 2.79 (m, 6H, $(CH_2)_2NCH_2$), 2.22 (m, 2H, $CH_2C\underline{H}_2CH_2$), 2.19 (d, 3H, CH_3, *J* = 1.00); IR 2819, 1708, 1621, 1500, 1261, 1070. Rf 0.17 (ethyl acetate-hexane 1:1). Anal. ($C_{23}H_{26}N_2O_3 \cdot HCl \cdot H_2O$) C, H, N.
3,4-Dimethyl-7-[3-(4-phenyl-1-piperazinyl)propoxy]coumarin (**1d**). 62% yield; mp 139-41 °C; ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 1H, H-5, *J* = 8.80), 7.28 (m, 2H, *m*-), 6.98-6.78 (m, 5H, *o*-, *p*-, H-6, H-8), 4.12 (t, 2H, CH_2O, *J* = 6.00), 3.38 (m, 4H, $N(CH_2)_2$), 2.88 (m, 6H, $(CH_2)_2NCH_2$), 2.37 (s, 3H, CH_3), 2.23 (m, 2H, $CH_2C\underline{H}_2CH_2$), 2.19 (s, 3H, CH_3); IR 2776, 1699, 1499, 1236, 1089, 1048. Rf 0.30 (ethyl acetate-hexane 1:1). Anal. ($C_{24}H_{28}N_2O_3 \cdot HCl$) C, H, N.
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