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New Arylpiperazine Derivatives with High Affinity for α_{1A}, D_2 and 5-HT_{2A} Receptors

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Abstract—A series of novel long-chain arylpiperazines bearing a coumarin fragment was synthesized and the compounds were evaluated for their affinity at α_1, D_2 and 5-HT_{2A} receptors. Most of the new compounds showed high affinity for the three types of receptors α_{1A}, D_2 and 5-HT_{2A} which depends, fundamentally, on the substitution of the N^4 of the piperazine ring. From the series emerged compound **6**, which had an haloperidol-like profile at D_2 and $5HT_{2A}$ receptors (pK_i values of 7.93 and 6.76 respectively). The higher α_{1A} receptor affinity (pA_2 = 9.07) of this compound could contribute to a more atypical antipsychotic profile than the haloperidol.

Introduction

It is well known that serotoninergic and dopaminergic neurotransmission modulates the activity of the CNS[1] and its deregulation is associated with the onset of schizophrenia. Moreover, other neurotransmission/neuromodulation systems, such as one of the most frequently mentioned, the adrenergic system, could be involved in this illness.

Different classical groups of drugs (phenothiazines, butyrophenones, etc.) have been used in the treatment of schizophrenia. In spite of their obvious structural differences, they all share the ability to block D_2 dopaminergic receptors and their effectiveness in the treatment of positive symptoms[2] of schizophrenia (*nonresistant schizophrenia*). Furthermore, the preferential and potent block of D_2 receptors is responsible for the induction of Parkinson-like and endocrinological adverse effects. Haloperidol is the prototype of this group of drugs, which are referred to jointly as 'typical or classical antipsychotic drugs'.

The adverse effects presented by typical antipsychotic drugs, along with their ineffectiveness in the treatment of negative symptoms[2] of schizophrenia (*resistant schizophrenia*) have led, through the years, to the arduous search for new structures (dibenzodiazepines, benzamides, etc.) that would serve as base for new molecules that not only would be effective for both types of schizophrenia but also that would not induce the adverse effects mentioned. Clozapine is the prototype of this group of drugs called 'atypical or new antipsychotic drugs'.

The vast structural differences among the various groups of drugs are accompanied by differences in the pharmacological binding profile of these to different types and subtypes of receptors, currently being accepted not only the importance of blocking dopaminergic receptors but also blocking serotoninergic[3–5] and possibly adrenergic receptors. So, blocking of the central α_{1A} adrenergic receptors has been considered a possible factor that could contribute to the atypical antipsychotic profile of clozapine.[6]

Of the numerous structures that have been synthesized in this field, the arylpiperazine fragment constitutes one of the most versatile templates for obtaining new molecules that show affinity for dopaminergic and serotoninergic receptors[3,7–15] as well as for binding to other

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receptors coupled to G protein, such as the α_{1A} adrenergic receptors.[16–19]

In previous work,[14] we prepared phenylpiperazines linked by a lipophilic propoxy chain to a coumarin nucleus, which have shown high affinity for both dopaminergic and serotoninergic receptors. On the basis of the above-reported considerations, and with the aim to gather structural factors determining the serotonergic, dopaminergic and alfa-adrenergic affinity, in the present work we describe the synthesis and pharmacological study of a series of new analogues (**4–11**) in which we mainly study the influence of the modifications in the N^4-aryl group as well as in the 4-position of the coumarin moiety, on the α_{1A}, D_2 and 5-HT_{2A} receptors using haloperidol as reference compound.

Chemistry

The 7-[3-(4-aryl-1-piperazinyl)propoxy]coumarins **4–11** were prepared as outlined in Scheme 1. The N^1-chloropropyl-N^4-arylpiperazines **3** were prepared according to the method reported previously[14] by reaction of the 1-bromo-3-chloropropane with the required arylpiperazine in acetone using NaOH as base.

The sodium salt of the 4-substituted-7-hydroxycoumarins **1** and **2** generated in situ with NaH, were then alkylated by addition of the corresponding piperazine **3** and NaI in DMF, affording the final compounds in 65–90% yield.[20] Compounds were converted to their water-soluble hydrochloride salts for use in the assays.

Pharmacology

Antagonism of noradrenaline at α_{1A}-adrenergic receptors was assayed using denuded thoracic aorta from male (250–350 g) Sprague–Dawley rats.[21,22] The dissociation constant of the antagonist-receptor complex, K_B (expressed as pA_2), was calculated from the equation:

$$([A^*]/[A]) - 1 = [B]/K_B$$

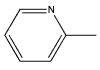
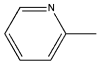
where $[A^*]/[A]$ is the ratio of concentrations of agonist giving an equal response (50% of the maximal effect) in the presence and in the absence of a given concentration of the antagonist, B.[23]

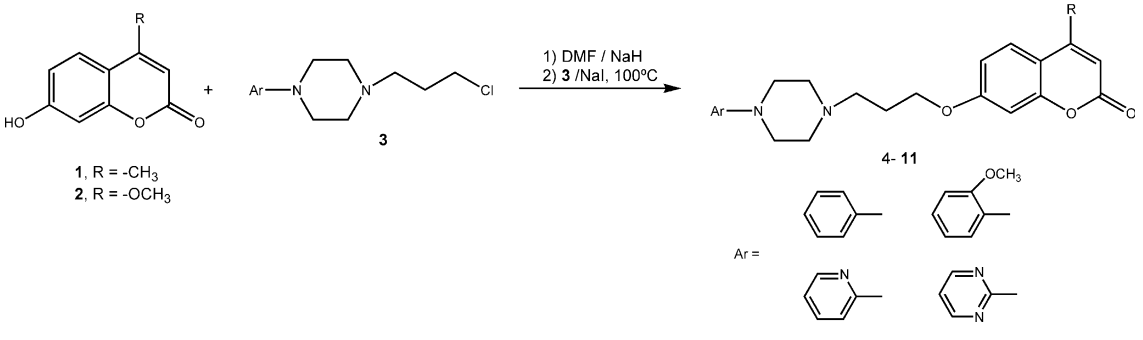
Receptor binding assays, at 5-HT_{2A} and D_2 receptors, were performed as described previously[24,25] using tissue from rat frontal cortex or striatum, and as radioligands, [^{3}H]ketanserin or [^{3}H]spiperone, respectively.

Results and Discussion

In general, in the new arylpiperazines studied, the order of affinity, for the three types of receptors assayed, was $\alpha_{1A} > D_2 > 5\text{-}HT_{2A}$, except when the aryl group at the N^4-piperazine is a pyridine (**8** and **9**), the affinity for α_{1A} receptors of these being slightly lower than that obtained for D_2 receptors. In all cases the affinity for D_2 and 5-HT_{2A} receptors was lower than that of haloperidol (Table 1).

Table 1. Receptor binding affinity for compounds **4–11**

Compd	Ar	R	α_{1A} (pA_2)	5-HT_{2A} (pK_i)	D_2 (pK_i)
4[14]		CH^3	7.93±0.07	6.03±0.05	7.34±0.04
5		OCH_3	6.45±0.10	5.71±0.16	6.25±0.07
6		CH_3	9.07±0.10	6.76±0.03	7.93±0.07
7		OCH_3	8.10±0.18	5.51±0.10	7.75±0.09
8		CH_3	6.58±0.08	5.97±0.04	7.09±0.08
9		OCH_3	6.72±0.08	6.27±0.03	6.89±0.10
10		CH_3	7.37±0.12	5.63±0.13	6.49±0.07
11		OCH_3	7.35±0.09	6.86±0.11	7.32±0.08
Haloperidol			7.76±0.03	7.28±0.13	8.53±0.12



Scheme 1.

Individually, the new compound **6** presents the highest affinity for α_{1A} and D_2 receptors, having a pA_2 of 9.07 and a pK_i of 7.93, and the second highest in affinity for 5-HT_{2A} receptors (pK_i = 6.76). Structurally, it possesses a methyl group in position 4 of coumarin and an *o*-methoxyphenyl ring at the piperazine. The substitution of the 4-methyl group of coumarin by a 4-methoxyl (**7**) produced a decrease in the affinity for the three receptors, this being more pronounced for 5-HT_{2A} receptors, although both molecules exhibited greater affinity for the α_{1A} receptors than haloperidol (7.76).

The suppression of the *o*-methoxy group from the phenyl piperazine (**4** and **5**) again gave rise to a reduction in the affinity for the three receptors that, as observed in compounds **6** and **7**, was much lower if the 4-methyl of the coumarin moiety (**4**) was substituted by a 4-methoxyl group (**5**).

The substitution of the N^4-phenyl by a pyrimidine or pyridine group (compounds **8**–**11**) produces a decrease in the affinity for α_{1A} and D_2 receptors. Moreover, unlike what occurred with the previous compounds (**4**–**7**), the presence of a methoxyl group at position 4 of coumarin nucleus did not diminish the affinity for the receptors studied, in fact in some cases a small increase or no change was observed.

The results suggest that the affinity for the three types of receptors studied depends on the substitution on the piperazine N^4(*o*-methoxyphenyl > phenyl > pyrimidine > pyridine) and to a lesser extent on the substituent at position 4 of coumarin nucleus, especially for 5-HT_{2A} receptors.

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20. Compound **5**: Yield 65%; mp 139–141 °C. ^{1}H NMR ($CDCl_3$), δ: 7.67 (d, 1H, H-5, J = 8.75 Hz), 7.26 (m, 2H, *m*-), 6.85 (m, 5H, *o*-, *p*-, H-6, H-8), 5.55 (s, 1H, H-3), 4.09 (t, 2H, CH_2O, J = 6.25 Hz), 3.95 (s, 3H, OCH_3), 3.20 (m, 4H, $N^4(CH_2)_2$), 2.59 (m, 6H, $(CH_2)_2N^1CH_2$), 2.04 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$), δ: 167.23, 163.80, 163.07, 155.50, 151.70, 129.49, 124.42, 120.08, 116.44, 112.86, 109.22, 101.47, 87.98, 67.18, 56.60, 55.32, 53.70, 49.55, 26.93. FAB-MS: m/z = 395 (M^+1, 100%). Anal. calcd for $C_{23}H_{26}N_2O_4$ (394.47): C 70.03, H 6.64, N 7.10. Found: C 70.15, H 6.59, N 7.24.
Compound **6**: Yield 68%; mp 133–134 °C. ^{1}H NMR ($CDCl_3$), δ: 7.48 (d, 1H, H-5, J = 8.70 Hz), 6.95 (m, 4H, Ph), 6.86 (dd, 1H, H-6, J = 8.80, 2.60 Hz), 6.82 (d, 1H, H-8, J = 2.60 Hz), 6.11 (s, 1H, H-3), 4.10 (t, 2H, CH_2O, J = 6.30 Hz), 3.86 (s, 3H, OCH_3), 3.10 (m, 4H, $N^4(CH_2)_2$), 2.69 (m, 4H, $(CH_2)_2N^1$), 2.60 (m, 2H, N^1CH_2), 2.38 (s, 3H, CH_3), 2.04 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$), δ: 162.53, 161.69, 155.70, 152.91, 152.69, 141.74, 125.87, 123.30, 121.40, 118.62, 113.90, 113.02, 112.28, 111.63, 101.87, 67.29, 55.76, 55.40, 53.91, 51.06, 26.94, 19.04. FAB-MS: m/z = 409 (M^+1, 100%). Anal. calcd for $C_{24}H_{28}N_2O_4$ (408.49): C 70.57, H 6.91, N 6.86. Found: C 70.26, H 7.07, N 6.80.
Compound **7**: Yield 70%; mp 125–128 °C. ^{1}H NMR ($CDCl_3$), δ: 7.68 (d, 1H, H-5, J = 8.70 Hz), 6.95 (m, 4H, Ph), 6.83 (dd, 1H, H-6, J = 8.70, 2.30 Hz), 6.79 (d, 1H, H-8, J = 2.30 Hz), 5.54 (s, 1H, H-3), 4.10 (t, 2H, CH_2O, J = 6.30 Hz), 3.95 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.10 (m, 4H, $N^4(CH_2)_2$), 2.67 (m, 4H, $(CH_2)_2N^1$), 2.58 (t, 2H, N^1CH_2), 2.07–1.98 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$), δ: 167.24, 163.80, 163.10, 155.50, 152.69, 141.74, 124.39, 123.29, 121.40, 118.61, 112.90, 111.63, 109.18, 101.46,

87.95, 67.27, 56.59, 55.74, 55.40, 53.91, 51.06, 26.93. FAB-MS: $m/z = 425$ (M^{+1}, 100%). Anal. calcd for $C_{24}H_{28}N_2O_5$ (424.49): C 67.91, H 6.65, N 6.60. Found: C 67.84, H 6.73, N 6.66.

Compound **8**: Yield 70%; mp 110–113 °C. ^{1}H NMR ($CDCl_3$), δ: 8.17 (m, 1H, H-6 pyr, $J = 4.98$, 1.96, 0.74 Hz), 7.48 (m, 1H, H-4 pyr, $J = 8.68$, 6.97, 1.96 Hz), 7.45 (d, 1H, H-5, $J = 8.74$ Hz), 6.85 (dd, 1H, H-6, $J = 8.74$, 2.42 Hz), 6.80 (d, 1H, H-8, $J = 2.42$ Hz), 6.62 (m, 2H, H-3 and H-5 pyr), 6.11 (s, 1H, H-3), 4.10 (t, 2H, CH_2O, $J = 6.28$ Hz), 3.56 (m, 4H, $N^4(CH_2)_2$), 2.58 (m, 6H, $(CH_2)_2N^1CH_2$), 2.37 (s, 3H, CH_3), 2.05 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$), δ: 162.47, 161.69, 159.88, 155.68, 152.94, 148.33, 137.87, 125.90, 113.94, 113.75, 112.96, 112.30, 107.50, 101.88, 67.13, 55.37, 53.46, 45.56, 26.83, 19.04. EI–MS: $m/z = 379$ (M^+, 12%), 107 (100%). Anal. calcd for $C_{22}H_{25}N_3O_3$ (379.46): C 69.64, H 6.64, N 11.07). Found: C 69.38, H 6.85, N 11.12.

Compound **9**: Yield 86%; mp 163–164.5 °C. ^{1}H NMR ($CDCl_3$), δ: 8.17 (m, 1H, H-6 pyr, $J = 4.74$, 1.80, 0.74 Hz), 7.66 (d, 1H, H-5, $J = 8.76$ Hz), 7.45 (m, 1H, H-4 pyr, $J = 8.85$, 6.86, 1.80 Hz), 6.81 (dd, 1H, H-6, $J = 8.76$, 2.35 Hz), 6.78 (d, 1H, H-6, $J = 2.35$ Hz), 6.62 (m, 2H, H-3 and H-5 pyr), 5.54 (s, 1H, H-3), 4.10 (t, 2H, CH_2O, $J = 6.28$ Hz), 3.95 (s, 3H, OCH_3), 3.54 (m, 4H, $N^4(CH_2)_2$), 2.56 (m, 6H, $(CH_2)_2N^1CH_2$), 2.04 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$), δ: 167.22, 163.78, 163.06, 159.93, 155.49, 148.34, 137.82, 124.41, 113.68, 112.85, 109.21, 107.44, 101.47, 87.97, 67.14, 56.59, 55.36, 53.49, 45.61, 26.90. FABMS: $m/z = 396$ (M^{+1}, 100%). Anal. calcd for $C_{22}H_{25}N_3O_4$ (395.45): C 66.82, H 6.37, N 10.63. Found: C 67.00, H 6.51, N 10.78.

Compound **10**: Yield 90%; mp 123–125 °C. ^{1}H NMR ($CDCl_3$), δ: 8.27 (d, 2H, H-4 and H-5 pyrim, $J = 4.78$ Hz), 7.46 (d, 1H, H-5, $J = 8.74$ Hz), 6.83 (dd, 1H, H-6, $J = 8.74$, 2.36 Hz), 6.78 (d, 1H, H-8, $J = 2.36$ Hz), 6.46 (t, 1H, H-5, pyrim, $J = 4.70$ Hz), 6.09 (s, 1H, H-3), 4.08 (t, 2H, CH_2O, $J = 6.26$ Hz), 3.81 (m, 4H, $N^4(CH_2)_2$), 2.53 (m, 6H, $(CH_2)_2N^1CH_2$), 2.36 (s, 3H, CH_3), 2.07 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$), δ: 162.47, 162.03, 161.68, 158.09, 155.66, 152.94, 125.90, 113.90, 112.96, 112.27, 110.24, 101.83, 67.12, 55.37, 53.54, 44.06, 26.89, 19.06. EI–MS: $m/z = 380$ (M^+, 25%), 108 (100%). Anal. calcd for $C_{21}H_{24}N_4O_3$ (380.44): C 66.30, H 6.36, N 14.73. Found: C 66.23, H 6.30, N 14.91.

Compound **11**: Yield 69%; mp 172–174 °C. ^{1}H NMR ($CDCl_3$), δ: 8.29 (d, 2H, H-4 and H-6 pyrim, $J = 4.75$ Hz), 7.67 (d, 1H, H-5, $J = 8.75$ Hz), 6.81 (dd, 1H, H-6, $J = 8.78$, 2.30 Hz), 6.78 (d, 1H, H-8, $J = 2.30$ Hz), 6.47 (t, 1H, H-5 pyrim, $J = 4.75$ Hz), 5.55 (s, 1H, H-3), 4.09 (t, 2H, CH_2O, $J = 6.25$ Hz), 3.96 (s, 3H, OCH_3), 3.82 (t, 4H, $N^4(CH_2)_2$), 2.54 (m, 6H, $(CH_2)_2N^1CH_2$), 2.04 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR ($CDCl_3$), δ: 168.10, 164.05, 163.80, 162.53, 158.1, 156.09, 124.41, 112.89, 110.25, 109.14, 101.44, 87.97, 67.12, 56.60, 55.40, 53.54, 44.06, 26.88. EIMS: $m/z = 396$ (M^+, 15%), 108 (100%). Anal. calcd for $C_{21}H_{24}N_4O_4$ (396.44): C 63.62, H 6.10, N 14.13. Found: C 63.78, H 6.07, N 7.24.

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