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1-(2-METHOXYPHENYL)-4-ALKYLPIPERAZINES: EFFECT OF THE N-4 SUBSTITUENT ON THE AFFINITY AND SELECTIVITY FOR DOPAMINE D_4 RECEPTOR

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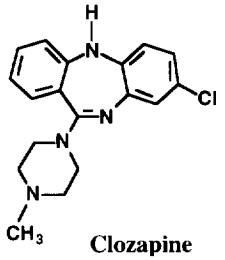
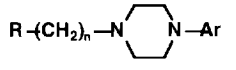
Abstract: Binding data on dopaminergic D_2 and D_4 and adrenergic α_1 receptors of nine 1-(2-methoxyphenyl)piperazine derivatives are reported. The benzamide derivative **11** and ketone **12** displayed the highest affinity for human cloned D_4 receptor (K_i= 1.3 nM and 1.7 nM, respectively). The former showed to be also selective versus D_2 and α_1 receptors. © 1997 Elsevier Science Ltd.

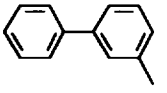
Introduction. The discovery of D_3 and D_4 receptors, classified as D_2-like receptors,[1,2] has stimulated the research to obtain new antipsychotic agents with lower extrapyramidal symptoms (EPS) than those of the current therapy. D_3 and D_4 receptors are particularly concentrated in mesolimbic and mesolimbocortical areas of the CNS, respectively,[3,4] regions which are implicated in schizophrenia.[5] Conversely, D_2 receptors, which are the target of current antipsychotics, are concentrated in the nigrostriatal region and their blokade causes EPS effects.[4] Further interest in D_4 receptors as an alternative target for antipsychotic therapy, derives from the discovery of clozapine, an atypical antipsychotic agent with a low incidence of EPS due to its relatively preferential blokade of D_4 over D_2 receptors (approximately 10-fold selectivity).[2] Furthermore, there are reports that the level of the D_4 receptor was 6-fold elevated in schizophrenic brain tissue.[5] Therefore, a selective D_4 receptor antagonist could be used as novel EPS-free antipsychotic agent. Several structures have been recently found to be active on D_4 receptors in different laboratories;[6] among these we noted some 1-arylpiperazine derivatives having general formula **1**, and in particular the D_4 most active compounds were 1-(2-methoxyphenyl)piperazine **1a,b** (K_i= 8.0 nM and 1.3 nM, respectively).[7,8] Unfortunately, both compounds showed high affinity towards D_2 receptors too.

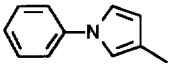


Clozapine



1

1a: R=  n= 1 **Ar= 2-MeO-Ph**

1b: R=  n= 1 **Ar= 2-MeO-Ph**

At the same time, in our laboratory, several 1-(2-methoxyphenyl)-4-alkylpiperazines[9-12] were synthesized for SAR studies on 5-HT_{1A} receptors, in our effort to find compounds with a potential antipsychotic activity derived from a dual 5-HT_{1A}/D_2 receptors affinity. We thought to reinvestigate some of these compounds and other related derivatives in order to know whether the dopaminergic component, previously found by binding assays on striatum rat tissue, was a D_4 type. In this paper, starting from the general structure **1**, we changed the

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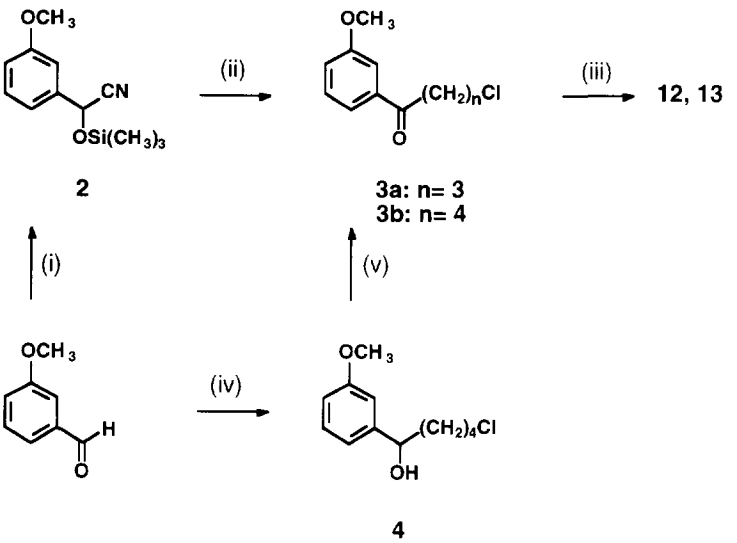
nature of R to obtain compounds **5-13** and evaluated their affinity on human D_4, D_2 (rat brain striatum), and α_1 receptors.

Chemistry. The procedure for the synthesis of the tetralin derivatives **5-9** has been already reported.[10,11] The benzamide **11** was prepared by condensing 4-(2-aminoethyl)-1-(2-methoxyphenyl)piperazine with 3-methoxybenzoic acid under the same conditions used for the synthesis of the analog **10**.[13] The synthetic pathway followed to obtain ketones **12** and **13** is depicted in Scheme 1. 3-Methoxybenzaldehyde was reacted with trimethylsilyl cyanide to give the trimethylsilyl cyanohydrin derivative **2**. The latter was transformed into its anion with lithium diisopropylamide (LDA) and then was alkylated with 1-bromo-3-chloropropane.[14] The protected cyanohydrin so obtained, gave ketone **3a** by subsequent treatment with dilute hydrochloric acid. The same method was not useful to prepare the chloro-derivative **3b** because of the very poor yield encountered. Thus, 3-methoxybenzaldehyde was reacted with (4-chloro-*n*-butyl)magnesium bromide to give the expected alcohol **4**. Oxidation of the latter with Jones' reagent gave the ketone **3b**. The final compounds **12** and **13** were prepared by reaction of 1-(2-methoxyphenyl)piperazine with chloroketones **3a,b**, respectively.

Scheme 1

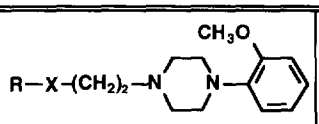
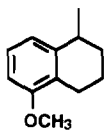
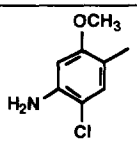
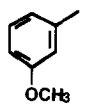


(i) $(CH_3)_3SiCN$, ZnI_2, $CHCl_3$, r.t. overnight, 95%;(ii) a) LDA, THF, -78 °C b) $Br(CH_2)_3Cl$ c) HCl 2N, r.t., overnight; 21 %; (iii) 1-(2-methoxyphenyl)piperazine, CH_3CN, reflux, 18 h, 61%; (iv) $MgBr(CH_2)_4Cl$, THF, reflux, 3h, 64%; (v) Jones' reagent, r.t., 6h, 90%.

Results and Discussion. The D_4 receptor binding affinities of the compounds studied showed K_i values between 67 and 1.3 nM, (Table 1) independently from the nature and length of the intermediate chain between the terminal tetralin group, **5-9**, or the aryl group, **10-13**, and the 1-(2-methoxyphenyl)piperazine moiety. Only compounds **11** and **12** showed very high D_4 receptor affinity (K_i = 1.3 and 1.7 nM, respectively). Benzamide **11** displayed also high selectivity vs D_2 and α_1 receptors (108 and 138 as K_i ratio, respectively). Further

studies are in progress on 1-arylpiperazine derivatives in order to find structural requirements for D_4 receptor affinity and selectivity versus D_2 and α_1 receptors.

Table 1. Binding Affinities.[15]

			K_i (nM)[a]			selectivity (K_i ratio)	
compd	**R**	**X**	**D_4**[16]	**D_2**[17]	**α_1**[18]	**D_2/D_4**	**D_4/α_1**
5		-CH_2-	37	7.0[b]	1.0[b]	0.2	0.03
6		-$(CH_2)_2$-	43	5.0[b]	65[b]	0.1	2
7		-CONH-	22	150[c]	142[c]	7	6
8		-$CONHCH_2$-	49	40[c]	70[c]	0.8	1
9		-NHCO-	67	253[c]	125[c]	4	2
10		-CONH-	19	32[d]	8.0	2	0.3
11		-CONH-	1.3	141	180	108	138
12		-$COCH_2$-	1.7	3.0	19	2	11
13		-$CO(CH_2)_2$-	43	56	41	1	1
haloperidol			3.6	1.7		0.5	
clozapine			13	117		9	

[a] Data represent the average of three assays (each sample in triplicate). S.E.M. for all reported data was <10%. [b] See ref. 10. [c] See ref. 11. [d] See ref. 13.

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16) Binding of [^{3}H]YM-09151-2 for D_4 dopamine receptor subtype $D_{4.2}$ human cloned produced in Sf9 cells baculovirus expression (DuPont NEN) was performed (see Boyfield, I.; Brown, T. H.; Coldwell, M. C.; Cooper, D. G.; Hadley, M. S.; Hagan, J. J.; Healy, M. A.; Jones, A.; King, R. J.; Middlemiss, D. N.; Nash, D. J. Riley, G. J.; Scott, E. E.; Smith, S. A.; Stemp, G. *J. Med. Chem.* **1996**, *39*, 1946-1948) using 0.06 nM of [^{3}H]YM-09151-2 (K_d= 0.06 nM), 500 µL of diluted membranes $D_{4.2}$ dopamine receptor human cloned in buffer at pH 7.4 (50 mM Tris·HCl, 5 mM $MgCl_2$, 5 mM EDTA, 5 mM KCl, 1.5 mM $CaCl_2$) and 100 µL of various concentration of drugs in 1 mL of total volume. The tubes were incubated at 25 °C for 60 minutes and filtered over Whatman GF/C presoaked in P.E.I. 0.3%, then washed two times with 1 mL of ice cold buffer (50 mM Tris·HCl, pH 7.4). Nonspecific binding was determinated in presence of haloperidol 1 µM. Clozapine was used as reference compound.
17) Binding of [^{3}H]spiperone for D_2 dopamine receptor was performed (see Briley, H.; Langer, S. Z. *Eur. J. Pharmacol.* **1978**, *50*, 283-284) using 0.3 nM of [^{3}H]spiperone (K_d= 0.2 nM), 450 µL of diluted rat striatum membranes, 300 mL of various concentration of drugs in 3 mL of total volume. Nonspecific binding was determinated in the presence of haloperidol 1 µM.
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