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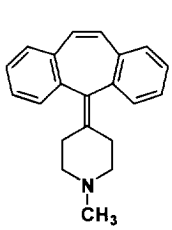
4-(3-FURYL)-2-(4-METHYLPIPERAZINO)PYRIMIDINES: POTENT 5-HT_{2A} RECEPTOR ANTAGONISTS[+]

Maria J. Mokrosz[1*], Beata Duszyńska[1], Aleksandra Kłodzińska[2], Anna Dereń-Wesołek[2], Ewa Chojnacka-Wójcik[2], Timothy C. Baranowski[3], Ibrahim M. Abdou[3], Naomi P. Redmore[3], and Lucjan Strekowski[3]

[1]*Department of Medicinal Chemistry,* [2]*Department of New Drug Research, Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, 31-343 Kraków, Poland;* [3]*Department of Chemistry, Georgia State University, Atlanta, GA 30303, USA*

Abstract: The title pyrimidines **7-12** are potent 5-HT_{2A} receptor ligands with fairly strong behavioral antagonistic activity. A comparison of the structural and binding properties within the entire group of these and other pyrimidines demonstrates two different modes of the bioactive complex formation.

Since antagonists at the 5-HT_{2A} receptor sites have recently become of therapeutic interest[1], intense studies are underway to understand the three-dimensional structure of the receptor-ligand complexes and to develop a topographic model of the 5-HT_{2A} receptors. It was Glennon who on the basis of the structure of (+) LSD proposed for the first time a comprehensive model of the 5-HT_{2A} sites, albeit without differentiating between agonists and antagonists[2]. Höltje and Jendretzki[3] suggested a general model of the 5-HT_{2A} receptors that summarized their previous studies on selective antagonists[4] and agonists.[5] Andersen[6] created a three-point topographic model for 5-HT_{2A} antagonists on the basis of a conformational analysis of indane and indole derivatives along with cyproheptadine (**1**) and ritanserin (**2**). A closely related model for the 5-HT_{2A} receptor antagonists was developed independently by Mokrosz[7-9] for heteroaryl-substituted 2-(4-methylpiperazino)-pyrimidines exemplified by compound **3**. In his model the three distances between the terminal nitrogen atom of the piperazine and the centers of the two aromatic substituents at the pyrimidine (d_1, d_2 and d_3 as shown for **3**) define the molecular topography of the 5-HT_{2A} receptor antagonists.



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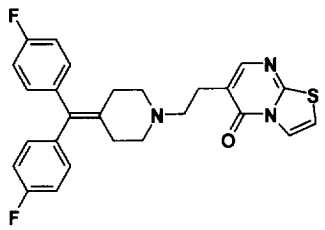

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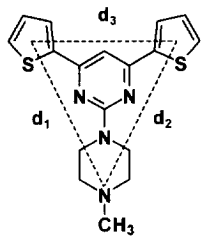

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[+] Dedicated to the memory of Professor Jerzy L. Mokrosz, Institute of Pharmacology, Polish Academy of Sciences

* E-mail: mokroszm@rabbit.if-pan.krakow.pl Fax: (4812) 37-45-00

Pyrimidines substituted with a 3-furyl group have not been investigated in detail, although a high 5-HT_{2A} receptor affinity of a derivative **7** (Table 1) has been noted. All pyrimidines studied previously, including selected compounds **3-7**, are 5-HT_{2A} receptor antagonists.[7,8] The high activity of compound **7** prompted us to synthesize a series of 2-(4-methylpiperazino)pyrimidines **8-12** (Table 1), all containing at least one 3-furyl substituent, and to evaluate these compounds as 5-HT_{2A} receptor ligands.

Materials and methods

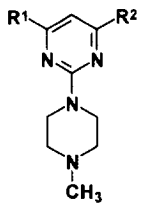
Chemistry. Compounds **8-12** were synthesized by using a general methodology[7-11].

Pharmacology. The affinity of **8-12** for 5-HT_{2A} receptors of the rat brain cortex and for 5-HT_{1A} receptors of the rat brain hippocampus was assessed on the basis of their ability to displace [^{3}H]-ketanserin and [^{3}H]-8-OH-DPAT, respectively, according to the published procedures.[12] To determine the 5-HT_{2A} antagonistic effects of the compounds, their ability to inhibit the (±)-1-(4-iodo-2,5-dimethoxyphenyl)-2-propanamine (DOI)-induced head twitch in mice (each group consisted of six animals)[13] and discriminative stimulus properties of (±)DOI in rats was employed. Discrimination training (Coulbourn Instruments Model E 10-10) was based upon a procedure used by Schechter.[14] The rats were trained to press either of the two levers for reinforcements (sweet milk) on a gradually increasing (1-10) fixed ration (FR) schedule. Thereafter, the animals were trained to discriminate between (±)DOI (0.35 mg/kg, ip) and saline. The tested compounds were administered ip 60 min. before the tests.

Results and Discussion

As can be seen from Table 1, all 4-(3-furyl)pyrimidines **7-12** bind strongly to 5-HT_{2A} receptor sites and are weak 5-HT_{1A} receptor ligands. There is an astonishing difference between the SAR analysis results of 5-HT_{2A} ligands **3-6** without a 3-furyl group and the 5-HT_{2A} ligands **7-12** containing the 3-furyl substituent. Of the former series, only a di(2-thienyl)pyrimidine **3** is highly active, and all remaining monoarylpyrimidines **4-6** show weak affinity for 5-HT_{2A} receptors.

Table 1. Structure and binding data of compounds **3-12**.[a]

Structure	No	R^1	R^2	K_i ± SEM [nM]	
				5-HT_{2A}	5-HT_{1A}
	**3**[b]	2-thienyl	2-thienyl	8 ± 1	972 ± 135
	4[b]	2-thienyl	H	208 ± 16	484 ± 4
	5[b]	2-furyl	H	745 ± 5	810 ± 18
	6[b]	phenyl	H	2095 ± 28	613 ± 35
	7[b]	3-furyl	2-furyl	13 ± 1	415 ± 8
	8	3-furyl	3-furyl	8 ± 0.1	621 ± 9
	9	3-furyl	2-thienyl	10 ± 2	2239 ± 210
	10	3-furyl	phenyl	9 ± 2	1339 ± 233
3 - 12	**11**	3-furyl	H	10 ± 1	700 ± 18
	12	3-furyl	methyl	50 ± 2	265 ± 34

[a] The K_i value for binding of **1** at the 5-HT_{2A} receptor sites is 5 ± 0.2 nM. [b] Data taken from ref. 8

By contrast, the (3-furyl)pyrimidines **7-12**, regardless of a substituent at position 6 of the pyrimidine, show strong affinity toward this receptor site. This unusual result is well documented by the 70-fold greater biological activity of the 3-furyl derivative **11** in comparison to that of its 2-furyl isomer **5**. The 5-HT_{2A} receptor affinities for thienyl derivatives **3** and **4** are strikingly different, and the affinities are essentially identical for their corresponding 3-furyl analogs **8** and **11**. *In vivo* activity of **7-11** was referenced to cyproheptadine **1**, a well known 5-HT_{2A} receptor antagonist. The results (Table 2) indicate that compounds **7-11** inhibit the (±)DOI-induced head twitches in mice in a dose dependent manner. They also block discriminative stimulus properties of (±)DOI in rats (Table 3). These results demonstrate clearly the 5-HT_{2A} receptor antagonistic activity of 3-furyl derivatives **7-11**.

Table 2. The inhibition effects of **1** and **7 - 11** (ID_{50}) on the (±)DOI-induced (2.5 mg/kg, ip) head twitch response in mice

No	ID_{50} (mg/kg, i.p.)[a]
1	0.4 (03 -06)
7	2.7 (1.1 -6.5)
8	2.4 (1.5 -3.8)
9	4.2 (2.8 - 6.3)
10	3.9 (2.3 - 6.6)
11	9.7 (6.3 - 15.0)

[a] ID_{50} - a dose inhibiting the effect by 50 %; confidence limits (95 %) given in parentheses.

Table 3. Results of a dose-response test and antagonism studies in rats trained to discriminate (±)DOI (0.35 mg/kg) from saline

Compound	Dose mg/kg	N[a]	%(±)DOI-appropriate responding (±) SEM)	Responses/min (±) SEM)
saline	-	7/7	4.8 ± 4.8	80.3 ± 9.9
(±)DOI	0.15	8/8	37.5 ± 18.3	81.3 ± 6.9
	0.25	9/9	63.1 ± 14.8	79.5 ± 4.9
	0.35	6/6	100.0	74.7 ± 5.7
(±)DOI[b] +				
1	1	9/9	7.1 ± 4.9	85.8 ± 4.4
7	10	8/8	4.0 ± 2.9	85.1 ± 3.7
8	5	9/9	31.1 ± 15.7	84.3 ± 4.6
	10	6/6	2.8 ± 2.8	72.5 ± 6.9
9	10	8/8	47.3 ± 16.4	60.3 ± 7.5
	15	7/7	11.2 ± 11.2	66.2 ± 6.9
10	10	7/7	7.2 ± 5.8	86.6 ± 9.8
11	20	6/6	6.6 ± 4.3	84.7 ± 8.8

[a] Number of responding animals/number of animals to receive the drug. [b] (±)DOI (0.35 mg/kg) was administered to animals pretreated with compounds **1**, **7-11**.

In an equilibrium conformation in solution of 4-arylpyrimidines the 5-membered heteroaryl group tends to be co-planar with the pyrimidine ring and the phenyl group is deviated from co-planarity by about 30°. The energy difference between two low energy conformations of heteroarylpyrimidines is about 1 kcal/mol or less, and the energy barrier for rotation around the aryl-pyrimidine bond is less than 5 kcal/mol for all systems.[7,8] It appears, thus, that the diverse affinities of molecules **3-12** toward 5-HT_{2A} receptors cannot be explained exclusively in terms of thermodynamic factors associated with conformational changes of these molecules upon formation of bioactive complexes. The crucial difference between furyl groups and remaining 2x substituents is the ability of the oxygen atom of the furan to form hydrogen bonds.[15] It can be suggested that, for stereochemical reasons, the 2-furyl group is not involved in hydrogen bond formation with the 5-HT_{2A} receptor sites, and the bioactive complex is stabilized by hydrophobic and dipole-dipole interactions. Similar mechanisms are apparently operative for a 2-thienyl group, and the hydrophobic forces alone may account for the low activity of a phenyl derivative **6**. By contrast, the 3-furyl group apparently reaches other regions of the receptor where the ligand-receptor interaction is strongly stabilized by specific hydrogen bond formation. The results presented in this paper, in particular those for the isomers **5** and **11**, clearly demonstrate that two different bioactive complexes are formed by two related sets of ligands, **3-6** and **7-12**. We are currently designing additional derivatives to address the problem of whether the interactions involve the same pocket or two different 5-HT_{2A} receptor sites.

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11 All new compounds were pure by TLC and spectroscopic (^1H and ^{13}C NMR) standards and gave satisfactory elemental analyses. **8**, mp 114-115°C; **8**•1.5HBr•0.5H_2O, mp >250°C (dec.); **9**, mp 87-88.5°C; **9**•2HCl, mp 245-247°C (dec.); **10**, mp 101-102°C; **10**•2HCl, mp 262-263°C (dec.); **11**, an oil; **11**•2HBr, mp > 200°C (dec.); **12**, an oil; **12**•2HBr, mp > 200°C (dec.).
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