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Short communication

7-3-Chlorophenypiperazinylalkyl derivatives of 8-alkoxy-purine-2, 6-dione as a serotonin receptor ligands with potential antidepressant activity

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ABSTRACT

Background: The previous study showed that arylpiperazine can condition affinity to α-adrenoceptors, 5-HT_{1A}/5-HT_{2A} receptors and compounds with arylpiperazine had antidepressant-like effect. The aim of this study was to determine the antidepressant-like activity of new arylpiperazines containing novel 8-alkoxy-purine-2,6-dione fragments.
Methods: New 3-chloroarylpiperazinylalkyl analogs of 8-alkoxy-purine-2,6-dione and their purine-2,6,8-trione analogs (**2**–**5**) were tested for their α_1, α_2, 5-HT_{1A},5-HT_{2A}, and 5-HT_7 receptor affinities in radioreceptor binding study. Moreover, in search for potential antidepressant properties of these compounds, the forced swim test in mice was conducted.
Results: Compounds **2** and **3** were potent 5-HT_{1A} receptor ligands with K_i within the range on 12–15 nM. All investigated compounds were found to be highly active 5-HT_{2A} receptor (K_i 15–28 nM) and α_1 adrenoceptor (K_i 21–89 nM) ligands. In the forced swim test all the compounds showed a significantly activity in spite of their reducing ability of locomotor activity. The most potent effect was produced by compound **4** and **5**, which reduced the immobility time in this test in all used doses.
Conclusion: In our study the most potent antidepressant-like activity was produced by compounds **4** and **5**, which are selective for the 5-HT_{2A} and α_1 receptors.

Introduction

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has implicated in many functions and disorders of central nervous system (CNS). 5-HT interacts with seven distinct families of the receptors located pre- and/or postsynaptically and the role of different receptor subtypes in the pathophysiology of mood disorders is the matter of dispute [1–3]. The role of 5-HT_{1A} and 5-HT_{2A} receptors is well established and some of its ligands have been used in treatment of depression, anxiety and schizophrenia [4–7]. Recently it was suggested that administration of antidepressant drugs according to a profile consistent with the activity of the 5-HT_7 receptors (fluoxetine, amitriptyline) induces the immediate early gene Fos in the CNS, which is indicative of neuronal activation. Upon chronic exposure that effect was diminished and was correlated with down regulation of 5-HT_7 receptors [8]. Thus, antidepressant treatment may modulate and dysrhythmic circadian function in depression, in which 5-HT_7 receptors might be one of the key factors. Moreover such antipsychotics as risperidone and clozapine show a high affinity for 5-HT_7 receptors and features of antagonists had led to an assumption that these receptors may be important for unique actions of certain antipsychotic drugs [9,10].

From chemical point of view one of the most explored class of 5-HT receptor ligands are 1-arylpiperazines [11,12]. The structural modifications of this pharmacophore led to 4-substituted derivatives with flexible aliphatic chain of different length, called long chain arylpiperazines (LCAPs). Many original papers and reviews were showed that structural modification within LCAPs at the terminal part (amide or imide moiety) or substituent at phenyl

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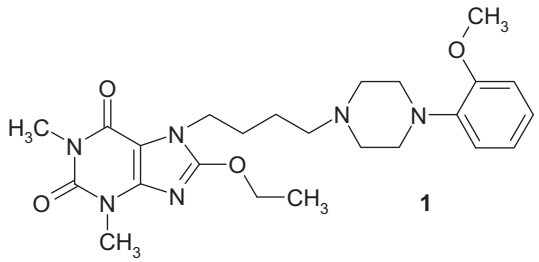
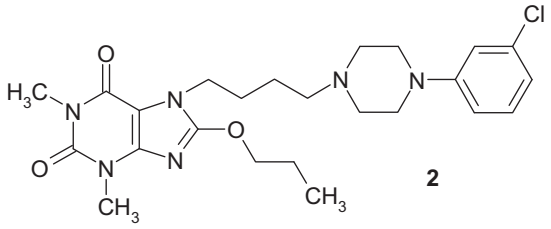


1

5-HT$_{1A}$ K_i = 11 nM
5-HT$_{2A}$ K_i = 253 nM
5-HT$_7$ K_i = 54 nM
pre and postsynaptic agonist 5-HT$_{1A}$ receptors
anxiolytic, antidepressant agent



2

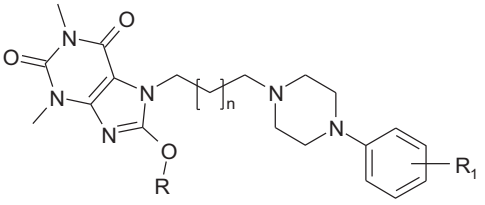
5-HT$_{1A}$ K_i = 15 nM
5-HT$_{2A}$ K_i = 28 nM
5-HT$_7$ K_i = 125 nM
partial postsynaptic 5-HT$_{1A}$ agonist

Fig. 1. Chemical structure of compounds **1** and **2**.

ring, led to ligands with good selectivity and activity for selected 5-HT receptors [13].

For several years we have been interested in developing agents in class of LCAPs with terminal part based on theophylline (1,3-dimethyl-3,7-dihydropurine-2,6-dione) moiety, which were mainly evaluated toward 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors and examined in functional *in vivo* models of anxiety and depression [11,14,15]. Compilation of our previous work showed that structural modifications consisted in shifting the arylpiperazinylalkyl substituent from the 8- to the 7-position of 1,3-dimethyl-3,7-dihydropurine-2,6-dione and introducing simultaneously an alkoxy moiety to the 8-position led to compounds with the highest receptor affinity for 5-HT$_{1A}$, 5-HT$_{2A}$ and 5-HT$_7$ receptors. The selected compounds **1** and **2** tested pharmacologically showed features of a potential agonist of pre- and post-synaptic 5-HT$_{1A}$ receptors (**1**) or partial agonist of postsynaptic sites (**2**) (Fig. 1) [16]. Finally, the most interesting compound **1** (7-[4-(4-phenylpiperazin-1-yl)-butyl]-8-ethoxy-1,3-dimethyl-3,7-dihydropurine-2,6-dione) evaluated in preclinical animal models of anxiety and depression showed potential anxiolytic and antidepressant activities [16].

Table 1
Structure and binding affinity data for serotonin 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_7$ and adrenergic α_1 and α_2 receptors of the investigated compounds.



Compound	R	N	R_1	K_i (nM) ± SEM				
				5-HT$_{1A}$	5-HT$_{2A}$	5-HT$_7$	α_1	α_2
1	C_2H_5	2	o-OCH_3	11 ± 1[a]	253 ± 14[a]	54 ± 2[a]	NT	NT
2	C_3H_7	2	m-Cl	15 ± 1[a]	28 ± 2[a]	125 ± 9[a]	89	132
3	C_2H_5	2	m-Cl	12 ± 2	15 ± 1	51 ± 4	21	60
4	C_2H_5	1	m-Cl	190 ± 28	23 ± 2	130 ± 10	51	90
5	C_3H_7	1	m-Cl	288 ± 18	25 ± 2	267 ± 21	52	200
	Mianserin[b]			97	121	NT	67	126

NT – not tested.
[a] Data taken from Ref. [16].
[b] Data taken from Ref. [27].

In this paper we continuing our research with 7-{4-[4-(3-chlorophenyl)-piperazin-1-yl]} analogs of active compound **1** (Fig. 1) [16]. The selected 7-{4-[4-(3-chlorophenyl)-piperazin-1-yl]-alkyl}-8-alkoxy-1,3-dimethyl-3,7-dihydropurine-2,6-diones (**2**–**5**) (Table 1): the potent: 5-HT$_{2A}$ ligands (**4** and **5**), 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_7$ ligands (**3**) and 5-HT$_{1A}$, and 5-HT$_{2A}$ (**2**) ligands were pharmacologically evaluated in the forced swim test, a preclinical test for detection of antidepressant activity. Moreover, the effect on the spontaneous locomotor activity of mice of **2**–**5** was also tested. Taking into account that some antidepressant agents, *e.g.* imipramine, mianserine, used as a references drugs or structurally similar to evaluated compounds **2**–**5**, antidepressants as trazodone, etoperidone or nefazodone acting on adrenergic system, additionally α_1 and α_2 adrenoreceptor affinities of these compounds were determined.

Materials and methods

Chemistry

The structures of the investigated compounds **2**–**5** are presented in Table 1. Compounds **2**–**5** were synthesized by nucleophylic substitution of previously obtained 7-chloroalkyl-8-alkoxy-1,3-dimethyl-3,7-dihydropurine-2,6-diones with the appropriate phenylpiperazines in the presence of K_2CO_3. The synthesis and physicochemical data of compounds **2**–**5** are described elsewhere [16]. The investigated compounds were pharmacologically tested as hydrochloride salts.

Materials

[^{3}H]Clonidine (Amersham, Germany), [^{3}H]prazosin (Amersham, Germany), [^{3}H]-8-OH-DPAT, [^{3}H]-ketanserin, imipramine (Imipraminum hydrochloricum, Polpharma, Poland), mianserine (Organon, Netherlands) were used.

Animals

The experiments were carried out on male Albino-Swiss mice (body weight 18–26 g). Animals were housed in constant temperature facilities exposed to 12:12 h light-dark cycle and maintained on a standard pellet diet and tap water given *ad libitum*. The control and experimental groups consisted of six to eight animals each. All the procedures were approved by the Local Ethics Committee of the Jagiellonian University in Kraków (29/2007).