Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 3097–3099

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Evaluation of 5-HT_{2A} and 5-HT_{2C} Receptor Binding Affinities of Novel Pyrimidine Derivatives

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Received 13 June 2002; accepted 31 July 2002

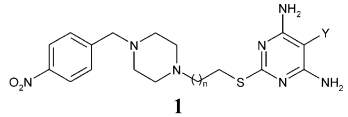
Abstract—In an effort to find potential anxiolytic and/or antipsychotic agents with selective 5-HT_{2C} affinity a series of new pyrimidine derivatives was prepared and the binding affinities for 5-HT_{2A} and 5-HT_{2C} receptors were determined.

Serotonin (5-hydroxytriptamin, 5-HT) is an important neurotransmitter in the central nervous system.[1] The ongoing study of 5-HT receptors has resulted in the identification of seven classes (5-HT_1–5-HT_7) and several subclasses of the 5-HT receptors.[2] 5-HT_2 serotonin receptors have significant clinical interest because of their potential involvement in cardiovascular function and certain mental disorders. The 5-HT_2 family of receptors is subdivided into three subtypes: 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. Due to the high degree of sequence homology of the 5-HT_2 receptor subtypes, numerous substrates (methysergide, metergolin, mianserin, ritanserin) display similar affinities to these receptors.[3,4] A lot of efforts have been made to synthesize compounds displaying outstanding selectivity for one of the 5-HT_2 receptor subtypes over the others. Ketanserin, risperidone and MDL 100907 exhibit selectivity for the 5-HT_{2A} site.[4,5] The structure of the selective compounds in regard to the 5-HT_{2C}/5-HT_{2B}[6] and 5-HT_{2C}[7] receptors are also given in the literature. Here we describe the discovery of a series of new 2,4-diaminopyrimidine compounds exhibiting affinities for the 5-HT_{2A} and 5-HT_{2C} receptors too. Some of the compounds are selective regarding the 5-HT_{2A} or 5-HT_{2C} receptors, respectively.

In binding assays, compound **1a** was found to bind both to 5-HT_{2C} and 5-HT_{2A} receptors. Compound **1a** contains a 4,6-diamino-2-thiopyrimidine moiety coupled with a *N*-benzylpiperazine unit by ethylene spacer. Binding data shown in Table 1 indicate that neither a longer spacer (**1b**) nor the introduction of a large lipophilic group into the 5-position of the pyrimidine ring (**1c**) increased 5-HT_{2C} and 5-HT_{2A} receptor affinity. However, 5-benzylpyrimidine derivative **1d** displayed substantially higher affinity than compound **1a**.

Upon this hit a variety of new, structurally related 2-(piperazinylethylthio)pyrimidines (**4**–**17**) was synthesized

Table 1. 5-HT_{2A} and 5-HT_{2C} binding measurements for compounds **1**



1

Compd	Y	*n*	Inhibition of receptor binding (%) (mol/L)	
			5-HT_{2A}	5-HT_{2C}
1a	H	1	89 (10^{-5})	77 (10^{-5})
1b	H	2	54 (10^{-5})	21 (10^{-5})
1c		1	10 (10^{-5})	32 (10^{-5})
1d		1	99 (10^{-6})	67 (10^{-6})

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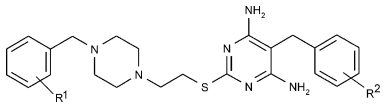
PII: S0960-894X(02)00660-1

Table 2. Receptor affinities for compounds **4**–**17** (effect of R^1, R^2 substituents on affinity and selectivity over 5-HT_{2A})

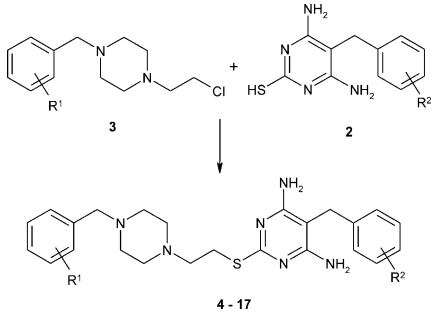


Compd	R^1	R^2	Binding affinity $K_i \pm$SEM (nM)		Selectivity 5-$HT_{2C/2A}$
			5-HT_{2A}	5-HT_{2C}	
4	4-Me	4-OMe	12.5±4.7	300.1±65.2	0.04
5	2-Me	4-OMe	11.5±0.5	16.4±2.3	0.7
6	2-Cl	4-OMe	5.7±0.1	10.4±0.4	0.6
7	2-Cl	3,4,5-OMe	4.3±0.3	18.3±0.7	0.2
8	2-Cl	H	18.3±2.6	11.9±1.7	1.5
9	2-Cl	2-Cl	11.8±0.5	8.7±2.2	1.4
10	2-Cl	2-OH	22.8±5.4	5.5±1.2	4.2
11	2-CF_3	H	61.1±5.4	21.4±4.1	2.9
12	2-CF_3	2-OMe	47.7±7.0	7.7±0.2	6.2
13	3-CF_3	2-OMe	60.4±6.2	5.5±0.7	11.0
14	3-CF_3	3-OMe	44.6±10.3	4.9±0.2	9.1
15	3-CF_3	2-OEt	69.9±7.7	9.1±0.4	7.7
16	3-CF_3	2-$OCHMe_2$	120.7±15.3	8.6±0.8	14.0
17	3-CF_3	2-OH	93.2±19.3	6.2±1.1	15.0

5-HT_{2A} and 5-HT_{2C} receptor binding affinity was measured as described by Leysen et al.[12] and Pazos et al.[13] Each compound was tested at 12 concentrations for determining K_i. These values represent mean±standard errors of a minimum of two experiments.

possessing benzyl-type substituents at the 5-position of the pyrimidine ring (Table 2). Compounds were prepared by alkylation of 2-mercaptopyrimidines **2**[10] with *N*-benzyl-*N*′-(2-chloroethyl)piperazines **3**[9] in methyl or ethyl alcohol in the presence of potassium iodide and potassium carbonate[8] (Scheme 1). All products were characterized by elemental analysis data, ^{1}H NMR and IR spectroscopy.[11]

Compound **4** showed a good affinity for 5-HT_{2A} receptors and weak binding at the 5-HT_{2C} receptors, however, methyl substituent at the 2-position of the piperazine benzyl group (**5**) led to significant increase in 5-HT_{2C} receptor affinity while 5-HT_{2A} receptor affinity was less affected by this variation. A series of (2-chlorobenzyl)pirerazine derivatives (**6**–**10**) was prepared and the substituents of the pyrimidine benzyl group were varied. Methoxy substituted derivatives **6** and **7** were slightly selective for 5-HT_{2A}, however, unsubstituted compound **8** was the first one exhibiting 5-HT_{2C} selectivity. Chloro substituent in the 2-position of the pyrimidine benzyl group (**9**) produced good affinities with modest 5-HT_{2C} selectivity. 2-Hydroxy derivative **10** was the most selective in this series. Compounds with



Scheme 1. Synthesis of 2-(piperazinylethylthio)pyrimidines (**4**–**17**).

(2-trifluoromethylbenzyl)piperazine moiety were also tested and a slightly better selectivity was found for derivative **12.** Surprisingly, structural isomer **13** gave even better selectivity which was reduced by moving the methoxy substituent into the 3-position **(14)**. Encouraged by these results a series of (3-trifluoromethylbenzyl)piperazine derivatives was synthesized with various substituents in the 2-position of the pyrimidine benzyl group. Compound **17** was the most potent in this series and has a 15-fold 5-$HT_{2C/2A}$ selectivity. This compound has been selected for further evaluation.

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11. Representative data follow for **17** 3HCl: Anal. calcd for $C_{25}H_{29}F_3N_6OS{\cdot}3HCl$: C, 47.82, H, 5.14, N, 13.38, Cl, 16.94. Found: C, 47.52, H, 5.19, N, 13.14, Cl, 16.70. ^1H NMR (400 MHz, D_2O) δ 7.90 (d, $J=7.7$ Hz, 1H), 7.78 (d, $J=7.8$ Hz, 1H), 7.72 (t, $J=7.6$ Hz, 1H), 7.24 (dt, $J=7.7$ Hz, 1.6 Hz, 1H), 7.11 (dd, $J=7.7$ Hz, 1.6 Hz, 1H), 7.00 (dd, $J=8.0$ Hz, 0.8 Hz, 1H), 6.94 (dt, $J=7.5$ Hz, 1.0 Hz, 1H), 4.75 (s, 2H), 4.50 (s, 2H), 3.73 (s, 2H), 3.59 (m, 8H), 3.54 (m, 2H). IR (KBr): 3352, 3178, 1642, 1492 cm^{-1}.
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