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High Potent and Selective Arylpiperazine Derivatives as Ligands for the 5-HT_{1A} Receptor

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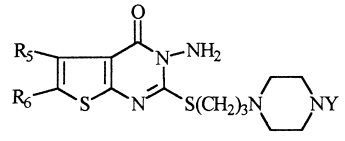
Abstract—This paper reports the synthesis and affinities on the 5-HT_{1A} versus the α_1A receptors of new arylpiperazinylalkyl-thiothienopyrimidine and thiadiazole derivatives **16**–**24**. Arylpiperazines **16**–**23** show affinities values in the nanomolar range for the 5-HT_{1A} receptor. The compound **16** is highly potent (K_i 0.26 nM, selectivity 28), the derivatives **20** and **21** are less potent, but highly selective (K_i 9.40 and 5.06 nM, selectivity 207 and 73, respectively).

Introduction

Serotonin modulates the activity of central nervous system and peripheral tissues; so far it acts on 14 receptor subtypes and plays a role in a wide range of physiological and pathophysiological processes. The interest toward the 5-HT_{1A} serotonin receptor subtype is due to its involvement in psychiatric disorders such as anxiety and depression.

For many years we have been synthesizing and studying derivatives containing the arylpiperazinylalkyl-thiothienopyrimidine system A, as ligands for the 5-HT_{1A} serotonin receptor, obtaining high potent and selective compounds.[1–3]

A



The structure–affinity relationships study has allowed to establish optimal structural features of our compounds in the ligand-receptor binding site interaction. The fundamental elements are the pharmacophoric arylpiperazinylalkyl moiety, the amino group in the N3 position of the pyrimidine nucleus and the properly substituted thienopyrimidine system.[2,3]

The aim of this study[4] is to develop ligands with higher affinity for the 5-HT_{1A} receptor than for the α_1-adrenoreceptor, which show some common features in their binding sites and to have further structure–affinity relationships.

The new compounds **16** and **17** have a three methylene chain and a hydrogen and a propyl group in position 5 and 6 of the thiophene ring and the orthomethoxyphenyl moiety on the N4 piperazine ring.

Derivatives **18**–**21** have two hydrogen or a hydrogen and an ethyl group on the thiophene ring and the orthonitro or the 2-pyrimidinyl moiety on the N4 piperazine ring.

Compound **22**, with the amino group in the position 4 of the pyrimidine nucleus was also prepared to have additional information on the important role played by the N3 amino group.[2,3]

A simplified structure containing the 1,3,4-thiadiazole ring properly substituted (**23** and **24**) was also synthesized, since 1,2,4-triazole derivatives were found as high potent and selective ligands for the 5-HT_{1A} receptor.[5]

Chemistry

Compounds **16**–**24** were prepared according to Scheme 1. The monopotassium salts of the 2-thioxothieno[2,3-*d*]pyrimidines **9**–**12**,[2,3,6] of 4-amino-5,6-dimethyl-thieno-[2,3-*d*]pyrimidine-2(1*H*)-thione **13** and of 2-(2-ethoxy-

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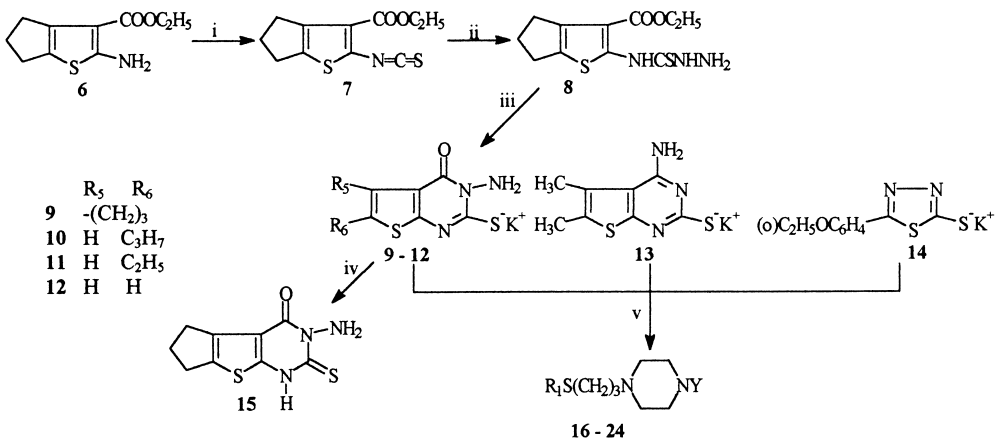


Scheme 1. Reagents and conditions: (i) $CSCl_2$, $CHCl_3/H_2O$, $NaHCO_3$, room temperature; (ii) $N_2H_4H_2O$, $CHCl_3$, room temperature; (iii) KOH, EtOH, reflux; (iv) HCl, H_2O, room temperature; (v) 1-(3-chloropropyl)-4-(2-methoxyphenyl, 2-nitrophenyl or 2-pyrimidinyl)piperazine, EtOH, reflux.

phenyl)-5-thioxo[1,3,4]thiadiazole **14**, reacted at reflux in ethanol with the appropriate chloroalkylpiperazines to give the arylpiperazinylalkylthio derivatives **16–24**. The monopotassium salts **13** and **14** were obtained by heating the corresponding thioxo derivatives[7,8] in an ethanolic potassium hydroxide solution. The monopotassium salt **9** was obtained from the isothiocyanate **7** and hydrazine monohydrate in chloroform at room temperature, with subsequent heating of derivative **8** in an ethanolic potassium hydroxide solution. The isothiocyanate **7** was obtained by reaction of the amino ester **6**[9] with thiophosgene in a solution of chloroform/water. Acidification of an aqueous solution of potassium salt **9** gave the thioxo compound **15**. Compounds **7–9** and **15–24** were obtained under the same experimental condition adopted for analogue derivatives.[2,3] The proposed structures of compounds **8**, **15–24** were confirmed by elemental analyses, IR and ^{1}H NMR spectra.[10]

Pharmacology

5-HT_{1A} and α_1A receptors binding assays were performed on compounds **16–24** as previously described[2] using, respectively: tissues from rat hippocampus membranes and [^{3}H]-8-OH-DPAT as radioligand, and tissues from rat cortex membranes and [^{3}H]-prazosin as radioligand.

As a comparison, previously published K_i values of compounds **1–5**, were included.[2,3]

Results and Discussion

From the binding data reported in Table 1 as K_i values, the arylpiperazines **16–23** show affinity in the nanomolar range and selectivity for the 5-HT_{1A} versus the α_1A receptor.

The 5,6-dihydro-3-amino-2[3-[4-(2-methoxyphenyl)-1-piperazinyl]propy]thio]-3*H*,7*H*-cyclopenta-[4,5]thieno[2,3-*d*] pyrimidin-4-one **16** shows a very strong affinity (K_i 0.26 nM); this affinity is stronger than the reference compounds serotonin,[3] 8-OH-DPAT[11] and NAN-190[11] (K_i 1.47, 1.3 and 1.26 nM, respectively), and similar to our reference compounds **1** and **2** (K_i 0.16 and 0.19 nM).[2,3] It also shows a good selectivity (selectivity 28).

The presence of the propyl group in the position 6 of the thiophene ring (**17**) decreases the affinity and selectivity for the 5-HT_{1A} receptor (K_i 1.40 nM, selectivity 14). This result confirms that bulk substituents on this position decrease affinity for the 5-HT_{1A} receptor ($CH_3 \sim C_2H_5 > C_3H_7 > C_6H_5$).[2,3]

The substitution of the orthomethoxy group in compound **2** with the orthonitro (**18**) decreases the affinity for the 5-HT_{1A} and α_1A receptors and also the selectivity (5-HT_{1A} K_i 9.69 nM, α_1A K_i 194.8 nM, selectivity 20).

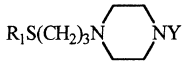
The substitution with the orthonitrophenyl moiety (**19**) versus the corresponding orthomethoxyphenyl derivative **3** (5-HT_{1A} K_i 0.65 nM, α_1A K_i 2.48 nM, selectivity 3.8)[2] leads to a decrease of affinity on both receptors; such a decrease is more evident on the α_1A receptor (5-HT_{1A} K_i 3 nM and α_1A K_i 39.87 nM, selectivity 13). Therefore, the presence of orthonitrophenyl moiety increases selectivity in **4** and **19** but not in **18**.

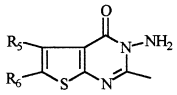
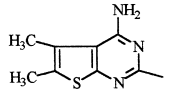
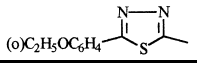
Compounds **20** and **21**, which have the 2-pyrimidinyl moiety instead of the orthomethoxyphenyl on the N4 piperazine ring, show a similar affinity among them (5-HT_{1A} K_i 9.40 and 5.06 nM) and are highly selective (selectivity 207 and 73).

Compound **20** is at present the most selective of the arylpiperazinylalkylthiothieno-pyrimidinones prepared by us,[2,3] and one of the most selective for the 5-HT_{1A} versus the α_1A receptor among the known arylpiperazines.

The behavior of derivatives **5**, **20** and **21** (K_i 3.72, 9.40 and 5.06 nM, selectivity 117, 207 and 73, respectively), showing a good affinity and a noteworthy increase in selectivity, confirms the important role played by the 2-pyrimidinyl moiety,[2,3] which negatively affects the α_1A receptor binding site interaction.

Table 1. Receptor binding affinities K_i±sd (nM) of compounds **1–5**, **16–24** on 5-HT_{1A} and α_1A receptors



Comp.	R_1	R_5	R_6	Y	5-HT_{1A}	α_1A	Selectivity
1[a]		CH_3	CH_3	$C_6H_4OCH_3$(o)	0.16±0.01	6.26±0.85	39
2[a]		H	C_2H_5	$C_6H_4OCH_3$(o)	0.19±0.05	21.96±6.16	115
3[a]		H	H	$C_6H_4OCH_3$(o)	0.65±0.02	2.48±0.42	3.8
4[a]		CH_3	CH_3	$C_6H_4NO_2$(o)	1.46±0.2	123±13	53
5[a]		CH_3	CH_3	2-pyrimidinyl	3.72±0.27	434±83	117
16		-$(CH_2)_3$—		$C_6H_4OCH_3$(o)	0.26±0.02	7.39±1.1	28
17		H	C_3H_7	$C_6H_4OCH_3$(o)	1.40±0.03	19.65±3.3	14
18		H	C_2H_5	$C_6H_4NO_2$(o)	9.69±0.9	194.8±21.5	20
19		H	H	$C_6H_4NO_2$(o)	3.0±0.5	39.87±7	13
20		H	C_2H_5	2-pyrimidinyl	9.40±1.6	1946±514	207
21		H	H	2-pyrimidinyl	5.06±0.20	366.31±53.3	73
22				$C_6H_4OCH_3$(o)	2.45±0.3	10.8±2	4.4
23				$C_6H_4OCH_3$(o)	6.84±0.5	31.50±5.2	4.6
24				$C_6H_4NO_2$(o)	135±13	437±39	3

[a]Previously published data,[2,3] reported here for comparison.

The result of compound **22**, which has a good affinity for both receptors (5-HT_{1A} K_i 2.45 and α_1A K_i 10.8 nM, selectivity 4.4), confirms the fundamental role of the N3 amino group of compounds **1**, **16** and **17** (K_i 0.16, 0.26 and 1.40 nM, selectivity 39, 28 and 14, respectively). Its presence in this position strongly increases affinity for the 5-HT_{1A} receptor and selectivity, too.

The 1,3,4-thiadiazole orthomethoxyphenylpiperazine derivative **23** shows good affinity, but little selectivity (5-HT_{1A} K_i 6.84 nM, selectivity 4.6); the orthonitrophenylpiperazine derivative **24** has much less affinity for the 5-HT_{1A} and α_1A receptors and poor selectivity (5-HT_{1A} K_i 135 nM, selectivity 3). The binding data of this ring system, once again show the importance of the orthomethoxy group on the phenylpiperazine moiety for serotonergic activity.[2,3]

In conclusion, the behavior of these compounds confirms the importance of the non-pharmacophoric portion which, together with piperazine substituents, can modify the affinity and selectivity for the 5-HT_{1A} receptor.[2,3]

References and Notes

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10. Physical and chemical properties of compounds **8**, **15–24**:
8: ethanol/dioxane (43%); mp 188–189 °C (dec). IR (KBr) 3280 and 3150 (NH), 1675 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.29 (t, $J=7$ Hz, 3H, CH_2CH_3), 2.28 (m, 2H, $CH_2CH_2CH_2$), 2.80 (m, 4H, $CH_2CH_2CH_2$), 4.25 (q, $J=7$ Hz, 2H,CH_2CH_3). Anal. ($C_{11}H_{15}N_3O_2S_2$) C, H, N, S.

15: ethanol/dioxane (25%); mp >265 °C (dec). IR (KBr) 3310 and 3125 (NH), 1685 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.37 (m, 2H, $CH_2CH_2CH_2$), 2.83 (t, $J=6.8$ Hz, 4H, $CH_2CH_2CH_2$), 4.95 (s, 2H, NH_2), 13.91 (br s, 1H, NH). Anal. ($C_9H_9N_3OS_2$) C, H, N, S.

16: ethanol (20%); mp 138–140 °C; IR (KBr) 3320 and 3270 (NH), 1670 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.88 (m, 2H, $CH_2CH_2CH_2$), 2.45 (m, 8H, CH_2N, piperazine H, $CH_2CH_2CH_2$), 2.90 (t, $J=7$ Hz, 4H, $2CH_2$), 2.98 (m, 4H, piperazine H), 3.05 (t, $J=7.6$ Hz, 2H, SCH_2), 3.77 (s, 3H, OCH_3), 5.72 (s, 2H, NH_2), 6.89–6.92 (m, 4H, ArH). Anal. ($C_{23}H_{29}N_5O_2S_2$) C, H, N, S.

17: ethanol (30%); mp 102–104 °C; IR (KBr) 3335 and 3275 (NH), 1680 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.93 (t, $J=7$ Hz, 3H, $CH_2CH_2CH_3$), 1.64 (m, 2H, $CH_2CH_2CH_3$), 1.85 (m, 2H, $CH_2CH_2CH_2$), 2.45 (m, 6H, CH_2N and piperazine H), 2.78 (t, $J=7.4$ Hz, 2H, $CH_2CH_2CH_3$), 2.98 (m, 4H, piperazine H), 3.05 (t, $J=7.2$ Hz, 2H, SCH_2), 3.77 (s, 3H, OCH_3), 5.74 (s, 2H, NH_2), 6.87–6.93 (m, 4H, ArH), 7.04 (s, 1H, thiophene H). Anal. ($C_{23}H_{31}N_5O_2S_2$) C, H, N, S.

18: purified by column chromatography (ethyl acetate) (40%); R_f: 0.39; mp 70-71 °C; IR (KBr) 3315 and 3200 (NH), 1680 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.25 (t, $J=7.4$ Hz, 3H, CH_2CH_3), 1.83 (m, 2H, $CH_2CH_2CH_2$), 2.45 (m, 6H, CH_2N and piperazine H), 2.81 (q, $J=7.4$ Hz, 3H, CH_2CH_3), 3.03 (m, 6H, SCH_2 and piperazine H), 5.73 (s, 2H, NH_2), 7.03–7.80 (m, 5H, ArH and thiophene H). Anal. ($C_{21}H_{26}N_6O_3S_2$) C, H, N, S.

19: purified by column chromatography (ethyl acetate:cyclohexane, 5:5) (30%); R_f: 0.16; mp 133–135 °C; IR (KBr) 3315 and 3200 (NH), 1690 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.86 (m, 2H, $CH_2CH_2CH_2$), 2.57 (m, 6H, CH_2N and piperazine H), 3.06 (m, 6H, SCH_2 and piperazine H), 5.76 (s, 2H, NH_2), 7.08–7.81 (m, 6H, ArH and thiophene H). Anal. ($C_{19}H_{22}N_6O_3S_2$) C, H, N, S.

20: purified by column chromatography (ethyl acetate) (60%); R_f 0.23; mp 105–108 °C; IR (KBr) 3225 and 3105 (NH), 1680 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.26 (t, $J=7.6$ Hz, 3H, CH_2CH_3), 1.85 (m, 2H, $CH_2CH_2CH_2$), 2.44 (m, 6H, CH_2N and piperazine H), 2.83 (q, $J=7.6$ Hz, 2H, CH_2CH_3), 3.06 (t, $J=6.8$ Hz, 2H, SCH_2), 3.74 (m, 4H, piperazine H), 5.75 (s, 2H, NH_2), 6.62 (t, $J=4.6$ Hz, 1H, ArH), 7.05 (s, 1H, thiophene H), 8.35 (d, $J=4.6$ Hz, 2H, ArH). Anal. ($C_{19}H_{25}N_7OS_2$) C, H, N, S.

21: ethanol (25%); mp 162–164 °C; IR (KBr) 3380 and 3220 (NH), 1685 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.87 (m, 2H, $CH_2CH_2CH_2$), 2.45 (m, 6H, CH_2N and piperazine H), 3.08 (t, $J=6.8$ Hz, 2H, SCH_2), 3.76 (m, 4H, piperazine H), 5.77 (s, 2H, NH_2), 6.62 (t, $J=4.6$ Hz, 1H, ArH), 7.33 (d, $J=5.8$ Hz, 1H, thiophene H), 7.44 (d, $J=5.8$ Hz, 1H, thiophene H), 8.35 (d, $J=4.6$ Hz, 2H, ArH). Anal. ($C_{17}H_{21}N_7OS_2$) C, H, N, S.

22: ethanol (60%); mp 128–133 °C; IR (KBr) 3515, 3300 and 3135 (NH) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.83 (m, 2H, $CH_2CH_2CH_2$), 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.49 (m, 6H, CH_2N and piperazine H), 2.96 (m, 4H, piperazine H), 3.09 (t, $J=6.8$ Hz, 2H, SCH_2), 3.77 (s, 3H, OCH_3), 6.85–6.94 (m, 4H, ArH). Anal. ($C_{22}H_{29}N_5OS_2$) C, H, N, S.

23: ethanol (50%); mp 96-98 °C; ^1H NMR (DMSO-d_6) δ 1.43 (t, $J=7$ Hz, 3H, CH_2CH_3), 1.91 (m, 2H, $CH_2CH_2CH_2$), 2.45 (m, 6H, CH_2N and piperazine H), 2.90 (m, 4H, piperazine H), 3.33 (t, $J=7$ Hz, 2H, SCH_2), 3.71 (s, 3H, OCH_3), 4.24 (q, $J=7$ Hz, 3H, CH_2CH_3), 6.79–8.25 (m, 8H, ArH). Anal. ($C_{24}H_{30}N_4O_2S_2$) C, H, N, S.

24: purified by column chromatography (ethyl acetate/cyclohexane, 5:5) (50%); R_f: 0.22; mp 102–104 °C; ^1H NMR (DMSO-d_6) δ 1.47 (t, $J=7$ Hz, 3H, CH_2CH_3), 1.94 (m, 2H, $CH_2CH_2CH_2$), 2.47 (m, 6H, CH_2N and piperazine H), 2.98 (m, 4H, piperazine H), 3.37 (t, $J=7.2$ Hz, 2H, SCH_2), 4.27 (q, $J=7$ Hz, 3H, CH_2CH_3), 7.07–8.30 (m, 8H, ArH). Anal. ($C_{23}H_{27}N_5O_3S_21/2H_2O$) C, H, N, S.

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