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Short communication

Synthesis and evaluation of new 2-piperazinylbenzothiazoles with high 5-HT_{1A} and 5-HT_3 affinities

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Summary — Original 2-piperazinylbenzothiazole derivatives were synthesized and studied as mixed ligands for serotoninergic 5-HT_{1A} and 5-HT_3 receptors. The studied compounds exhibited significant affinities for these two serotoninergic receptor subtypes. The pharmacological profile of these ligands was agonist for 5-HT_{1A} receptors and antagonist for 5-HT_3 receptor subsites. Compounds with such a pharmacological profile are of clinical relevance in the treatment of psychotropic diseases (*eg*, anxiety, depression and schizophrenia). The present paper reports the chemistry and the *in vitro* pharmacological evaluation of these ligands.

benzothiazole / benzothiazolin-2-one / serotonin / 5-HT_{1A} receptor / 5-HT_3 receptor / psychotropic disease

Introduction

The last decade has witnessed the discovery of the multiplicity of serotonin (5-HT) receptors [1–7] and several 5-HT ligands have been studied with regard to their affinity, specificity and potential therapeutic applications. It has been demonstrated that 5-HT_{1A} partial agonists, such as buspirone [8], and 5-HT_3 antagonists [9, 10], such as MDL 72222 or ICS 205-930 (chart 1), possess anxiolytic-like and antidopamine-like effects in humans. The design of MDL 72222 was based on cocaine (chart 1).

This anxiolytic activity is based on the decrease of the central serotoninergic transmission [11, 12]. 5-HT_3 receptors subtypes are involved in the manifestation of schizophrenia. Meltzer *et al* [13] have recently demonstrated that ondansetron, a potent 5-HT_3 antagonist, exhibited antidopamine-like activity without the extrapyramidal side-effects generally observed for the classical neuroleptic agents such as haloperidol (chart 1).

Our previous work has led to the design and synthesis of new 6-[*n*-(phenylpiperazin-1-yl)alkyl]-benzothiazolinones [14] (general structure **A**, chart 2) with a high but non-selective affinity for the central 5-HT_{1A} receptors. These compounds showed unusual psychotropic and analgesic properties, presumably resulting from their double interaction with the central serotoninergic 5-HT_{1A} and dopaminergic D_2 receptors [15]. In an effort to increase such properties and gain access to new neuroleptic agents with or without reduced extrapyramidal side-effects, we replaced the non-specific phenylpiperazine pharmacophore with the 2-phenylpiperazinylbenzothiazole moiety (general structure **B**, chart 2). We synthesized and tested the 4-acyl-(1-benzothiazol-2-yl)piperazine **8**. This bioisosteric replacement permitted access to chemical analogs of compounds of general structure **A**, for which it was anticipated that the 5-HT_{1A} affinity could be preserved while a considerable 5-HT_3 affinity could be introduced. The combination of these two agonistic and antagonistic activities could possibly lead to original potent psychotropic drugs with reduced CNS side- effects.

Studies of several potent 5-HT_3 antagonists revealed important information about the nature and the geometric disposition of the key-pharmacophoric elements [16, 17]. As a result of the general structure–activity relationship (SAR) observed, it was found to be necessary to introduce an aromatic moiety, a linking acyl group or a chemical equivalent group as well as an amine residue (tertiary or quarternized).

The geometric relationships between these key pharmacophores are represented in scheme 1 [18].

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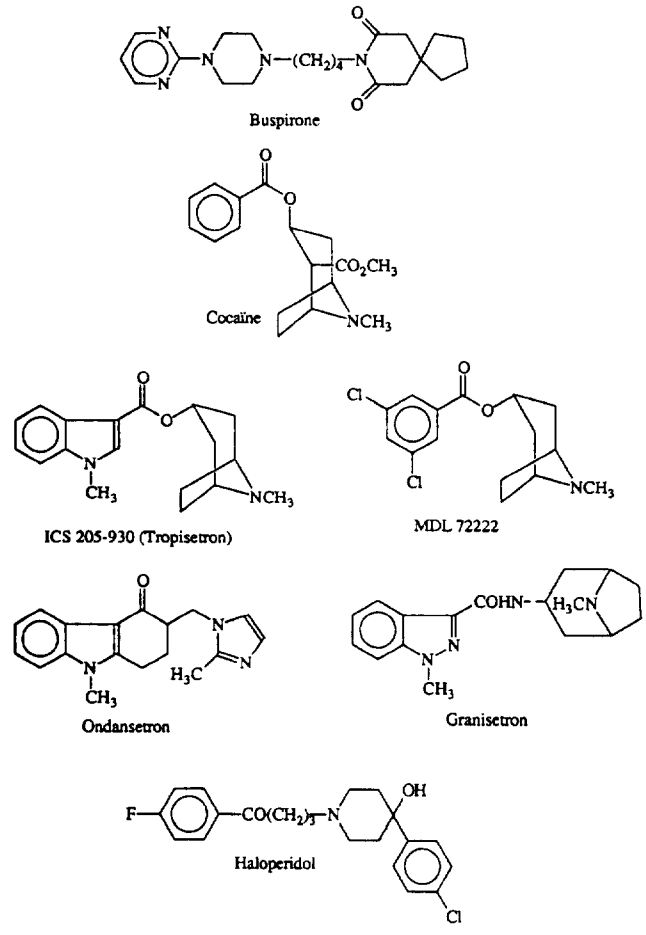


Chart 1.

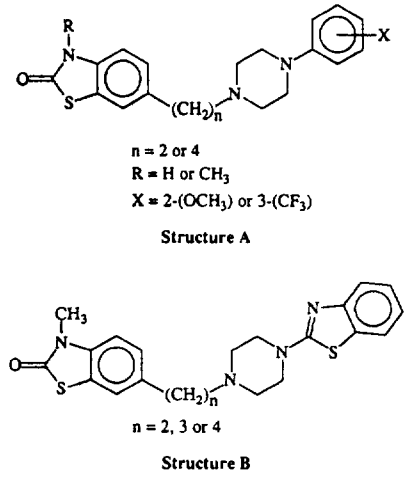


Chart 2.

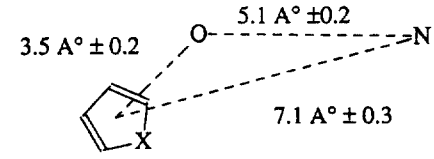
The identity of this pharmacophoric model for 5-HT_3 antagonists may help us design more potent and selective ligands. The necessary elements we describe here are present in the structure of several 5-HT_3 antagonists. This is the case for ondansetron, granisetron and tropisetron (chart 1).

Several other studies have demonstrated that the thiazole ring may be regarded as a bioisosteric equivalent of the carbonyl group [19, 20]. Indeed, other 5-HT_3 antagonists include a thiazole ring between the aromatic and basic moiety. The validity of this bioisosteric principle was recently illustrated by the synthesis and pharmacological evaluation of new 2-piperazinylbenzothiazole and 2-piperazinylbenzoxazole derivatives [21].

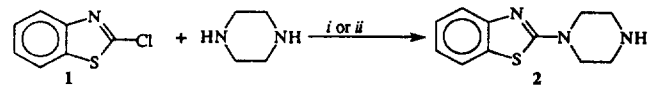
This paper reports the synthesis and binding-assay results of original 2-phenylpiperazinylbenzothiazole derivatives endowed with 5-HT_{1A} agonistic and 5-HT_3 antagonistic properties.

Chemistry

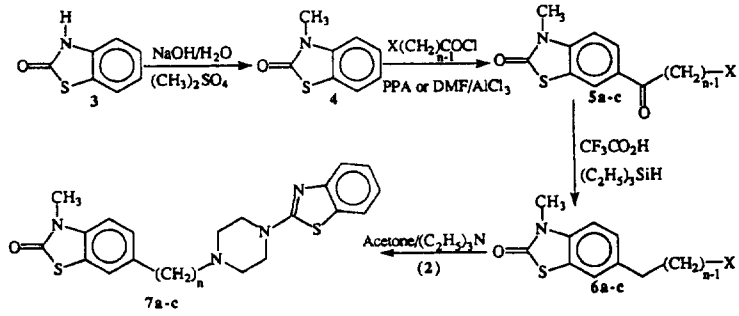
The 1-(benzothiazol-2-yl)piperazine **2** was previously synthesized by Herrin *et al* [22], using 2-propanol as a solvent in the presence of potassium carbonate, 2-chlorobenzothiazole and piperazine. This procedure yielded 75% of the desired product. In this work, we used dimethylformamide as a solvent and the same reagents, and obtained 90% yield of pure **2** (scheme 2). The 3-methyl-6-(*n*-halogenoalkyl)benzothiazolinones **6a–c** were obtained as follows (scheme 3). Benzothiazolinone **3** was methylated on position 3 using dimethylsulfate and sodium hydroxide in aqueous medium. The 3-methylbenzothiazolinone was then acylated by a Friedel–Crafts reaction. The carbonyl group of compounds **5a–c** was reduced by the triethylsilane/trifluoroacetic acid reagent for the reduc-



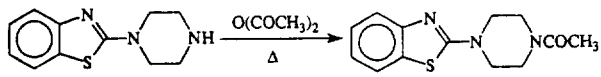
Scheme 1.



Scheme 2. i) 2-Propanol, K_2CO_3, Δ; ii) DMF, K_2CO_3.



Scheme 3.



Scheme 4.

tion of aromatic ketones [23]. The final step was performed by condensing **2** and **6** in anhydrous acetone in the presence of triethylamine.

Compound **8** was obtained by refluxing acetic anhydride in the presence of the 1-(benzothiazol-2-yl)piperazine. This process yielded 88% of the pure desired product (scheme 4).

Pharmacological results and discussion

IC_{50}s (M) for 5-HT_{1A}, 5-HT_{1C}, 5-HT_2, D_2 and α_1 receptors were determined for compounds of general structure **B**. These parameters are reported in the table I.

The binding-assay data obtained with the 1-(benzothiazol-2-yl)-4-acetylpiperazine **8** reveal high and selective affinity for the 5-HT_3 receptors. These results confirm the validity of our design. Indeed, compounds with two, three or four methylene groups in the connecting chain between the arylpiperazine and benzothiazolinone moieties (**7a–c**) were studied and show a rather similar binding profile. This indicates that the length of the connecting chain does not affect the overall affinity profile, but the best affinities at 5-HT_{1A} and 5-HT_3 receptors were found with a 4-methylene connecting chain. This result can be expected when considering the SAR of buspirone analogs where a 4-methylene connecting chain is also found [24]. For the purpose of comparison, the results obtained with several compounds of general structure **A** are reported in table II.

Compounds **7a–c** exhibited 5-HT_{1A} affinities comparable to those observed with their phenylpiperazine analogs. The 5-HT_3 affinities were considerably increased (100–1000-fold). The undesirable and high α_1 affinity exhibited by compounds of general structure **A** was strongly decreased. The D_2 affinity of these ligands was also diminished.

The nature of the 5-HT_3 pharmacophore is now well established (see *Introduction*). Our intention was to associate a high 5-HT_3 affinity with the high affinity of compounds **A** at 5-HT_{1A} receptors. In this respect, replacement of the carbonyl moiety typical of 5-HT_3 agonists by its thiazol bioisoster indeed led to the desired profile. Owing to their dual affinity at 5-HT_{1A} and 5-HT_3 receptors (which are implicated in mental disorders), these ligands could possibly find application as neuroleptics with reinforced action.

Experimental protocols

Compounds **1–8** were characterized by elemental analysis, IR, and ^{1}H-NMR spectra. IR spectra were recorded on a Perkin-Elmer 297 spectrometer, using KBr discs; wave numbers are expressed in cm^{-1}. The ^{1}H-NMR spectra were obtained on a

Table I. IC_{50} (M) of compounds of general structure **B**.

Compound	*n*	*Receptor*				
		5-HT$_{1A}$	*5-HT$_2$*	*5-HT$_3$*	*D$_2$*	*a$_1$*
7a	2	6×10^{-8}	4×10^{-6}	4×10^{-7}	$> 10^{-4}$	10^{-5}
7b	3	2×10^{-8}	10^{-6}	4×10^{-7}	$> 10^{-4}$	10^{-5}
7c	4	5×10^{-8}	6×10^{-6}	4×10^{-8}	$> 10^{-4}$	10^{-7}
8	–	$> 10^{-4}$	$< 10^{-6}$	10^{-8}	–	–

Table II. IC_{50} (M) of compounds of general structure **A**.

Compound	*n*	*X*	*Receptor*				
			5-HT$_{1A}$	*5-HT$_2$*	*5-HT$_3$*	*D$_2$*	*α_1*
A1	2	2-OCH_3	2×10^{-9}	5×10^{-7}	10^{-5}	4×10^{-8}	4×10^{-7}
A2	2	3-CF_3	10^{-9}	6×10^{-7}	5×10^{-5}	2×10^{-7}	4×10^{-7}
A3	4	2-OCH_3	8×10^{-10}	10^{-6}	10^{-5}	10^{-8}	3×10^{-8}
A4	4	3-CF_3	2×10^{-9}	4×10^{-7}	10^{-5}	6×10^{-8}	5×10^{-8}

Brücker WP 80 SY (80 MHz) apparatus, with Me_4Si as an internal standard and with $CDCl_3$ or DMSO-d_6 as solvent; the chemical shifts are reported in ppm in the δ scale; unless otherwise stated, coupling constants expressed in Hz are ^3J. Melting points were determined using a Büchi SMP-20 apparatus, and are uncorrected. Elemental analyses were determined by the CNRS Center d'analyse in Vernaison (France). Elementary analysis were within ± 0.4% of the theoretical values.

1-(Benzothiazol-2-yl)piperazine hydrochloride **2**
Piperazine (2.15 g, 0.025 mol) was dissolved in anhydrous dimethylformamide (50 ml). Under stirring, 2-chlorobenzothiazole (1.7 g, 0.010 mol) was added in one portion and the mixture was heated under reflux for 1.5 h. The precipitate formed was removed by filtration. Cold water (50 ml) was added to the filtrate, which was made acidic with concentrated HCl and extracted with chloroform. The aqueous solution was made basic with aqueous NaOH solution and the desired product was extracted with chloroform. The organic layer was dried over $CaCl_2$, evaporated *in vacuo* and the resulting oil was treated with an ethanolic HCl solution to give the corresponding hydrochloride. This was filtered, dried and recrystallized from absolute ethanol (6.20 g, 86%). Mp > 260°C. **2** ^{1}H-NMR (DMSO-d_6) δ 3.00–3.50 (m, 4H), 3.60–4.00 (m, 4H), 7.00–8.20 (m, 4H), 9.60 (s, 3H).

3-Methylbenzothiazolin-2-one **4**
Benzothiazolinone (151.10 g, 1 mol) was dissolved in a 1 N aqueous solution of sodium hydroxide (1 l). This solution was stirred at room temperature and dimethylsulfate (95 ml, 1 mol) was added dropwise. After 2 h, the resulting solid was filtered, washed with water and recrystallized from *n*-propanol (145.40 g, 88%). Mp 72–74°C. **4** ^{1}H-NMR (DMSO-d_6) δ 3.50 (s, 3H), 7.00–7.50 (m, 4H).

3-Methyl-6-(bromoacetyl)benzothiazolin-2-one **5a**
Aluminium chloride (210 g, 1.60 mol) and 3-methylbenzothiazolinone (33 g, 0.20 mol) in anhydrous dimethylformamide (43 ml) were heated at 70°C under stirring. Bromoacetyl chloride (19.8 ml, 0.24 mol) was added dropwise and the reaction was then continued for 1 h. After cooling, the mixture was poured onto ice and the resulting precipitate was filtered, washed with water, dried and recrystallized from 95% ethanol (37.80 g, 66%). Mp 164–165°C. **5a** ^{1}H-NMR (DMSO-d_6) δ 3.46 (s, 3H), 4.95 (s, 2H), 7.44 (d, J = 8.7 Hz, 1H), 8.07 (dd, J_1 = 8.7 Hz, J_2 = 1.7 Hz, 1H), 8.37 (d, J = 1.7 Hz, 1H). Anal $C_{10}H_8BrNO_2S$ (C, H, N).

3-Methyl-6-(3-chloropropionyl)benzothiazolin-2-one **5b**
Compound **5b** was prepared by treatment of 3-methylbenzothiazolinone (33 g, 0.20 mol) with 3-chloropropionyl chloride (22.9 ml, 0.24 mol) in the presence of aluminium chloride (210 g, 1.60 mol) in dimethylformamide (43 ml) as described for compound **5a** (30.60 g, 60%). Mp 174–177°C. **5b** ^{1}H-NMR (DMSO-d_6) δ 3.48 (m, 2H), 3.51 (s, 3H), 3.90 (m, 2H), 7.17 (d, J = 8.4 Hz, 1H), 8.00 (dd, J_1 = 8.4 Hz, J_2 = 1.4 Hz, 1H), 8.10 (d, J = 1.4 Hz, 1H). Anal $C_{11}H_{10}ClNO_2S$ (C, H, N).

3-Methyl-6-(4-bromobutyryl)benzothiazolin-2-one **5c**
3-Methylbenzothiazolinone (16.52 g, 0.1 mol) and polyphosphoric acid (200 g) were heated at 60°C and to the stirred mixture was added dropwise 4-chlorobutyryl chloride (14.1 ml, 0.125 mol). The mixture was heated at 120°C for 3 h and, after cooling, was poured onto ice. The solid precipitate corresponding to the 3-methyl-6-(4-hydroxybutyryl)benzothiazolinone was filtered, washed with water, dried and recrystallized from toluene. The resulting pure product was redissolved in anhydrous acetone (100 ml). HBr was bubbled into the solution and the mixture was stirred at room temperature for 1 h. The solvent was evaporated *in vacuo* and the residue was recrystallized from 95% alcohol (19.60 g, 62%). Mp 96–97°C. **5c** ^{1}H-NMR (DMSO-d_6) δ 2.29 (m, 2H), 3.18 (t, J = 5.82 Hz, 2H), 3.53 (m, 5H), 7.11 (d, J = 8.9 Hz, 1H), 8.00 (m, 2H). Anal $C_{12}H_{12}BrNO_2S$ (C, H, N).

General procedure for 3-methyl-6-(n-halogenoalkyl)benzothiazolin-2-one derivatives **6a–c**
Compound **5a–c** (0.1 mol) was dissolved in trifluoroacetic acid (70 ml). The solution was stirred at room temperature and triethylsilane (39.90 ml, 0.25 mol) was added dropwise. After 20 h, the mixture was poured onto ice. The resulting precipitate was filtered, washed with water, dried and recrystallized from cyclohexane yielding compounds **6a–c** (80–86%).

6a n = 2, X = Br. Mp 97–98°C. ^{1}H-NMR ($CDCl_3$) δ 3.20 (t, J = 5.51 Hz, 2H), 3.40 (s, 3H), 3.50–3.80 (m, 2H), 6.70–7.30 (m, 3H). Anal $C_{10}H_{10}BrNOS$ (C, H, N).

6b n = 3, X = Cl. Mp 41–43°C. ^{1}H-NMR ($CDCl_3$) δ 2.10 (m, 2H), 2.80 (t, J = 7.60 Hz, 2H), 3.40 (s, 3H), 3.60 (t, J = 5.70 Hz, 2H), 7.20–7.40 (m, 3H). Anal $C_{11}H_{12}ClNOS$ (C, H, N).

6c n = 4, X = Br. Mp 64–66°C .^{1}H-NMR ($CDCl_3$) δ 1.80–2.00 (m, 4H), 2.70 (m, 2H), 3.40–3.50 (m, 5H), 7.20–7.40 (m, 3H). Anal $C_{12}H_{14}BrNOS$ (C, H, N).

General procedure for 3-methyl-6-[n-(4-benzothiazol-2-ylpiperazin-1-yl)alkyl]benzothiazolin-2-one derivatives 7a–c

Compound **6a–c** (0.1 mol) was dissolved in anhydrous acetone (70 ml). Triethylamine (0.032 mol, 4.2 ml) and **2** (0.01 mol, 2.92 g) were added and the mixture was heated to reflux for 24 h. The solvent was evaporated *in vacuo* and the hydrochloride salt was isolated by treatment with a 2 N aqueous solution of HCl. The precipitate was filtered dried and recrystallized from absolute ethanol yielding compounds **7a–c** (52–57%).

7a n = 2. Mp > 250°C. ^{1}H-NMR (DMSO-d_6) δ 3.00–3.50 (m, 15H), 7.00–7.90 (m, 7H), 12.00 (s, 2H). Anal $C_{21}H_{22}N_4OS_2$, 2HCl (C, H, N).

7b n = 3. Mp > 250°C. ^{1}H-NMR (DMSO-d_6) δ 1.80–2.20 (m, 2H), 2.70–2.90 (m, 4H) 3.20–3.60 (m, 11H), 7.20–8.00 (m, 7H), 11.80 (s, 2H). Anal $C_{22}H_{24}N_4OS_2$, 2HCl (C, H, N).

7c n = 4. Mp > 250°C. ^{1}H-NMR (DMSO-d_6) δ 1.50–2.00 (m, 4H), 2.60–3.00 (m, 4H), 3.20–3.40 (m, 11H), 7.00–8.00 (m, 7H), 11.50 (s, 2H). Anal $C_{23}H_{26}N_4OS_2$, 2HCl (C, H, N).

1-(Benzothiazol-2-yl)-4-acetylpiperazine 8

1-Benzothiazol-2-ylpiperazine **2** (0.01 mol, 2.2 g) and acetic anhydride (20 ml) were heated at reflux for 2 h. After cooling, the volume was reduced by evaporation and diethylether (20 ml) was added. The precipitate formed was filtered, dried and recrystallized from anhydrous acetone (2.30 g, 88%). mp 177–179°C. **8** ^{1}H-NMR ($CDCl_3$) δ 2.20 (s, 3H), 3.40–4.00 (m, 8H), 7.00–7.70 (m, 4H). Anal $C_{13}H_{15}N_3OS$ (C, H, N).

Affinity determinations

IC_{50}s for 5-HT_{1A}, 5-HT_{2A}, 5-HT_3, D_2 and α_1 receptors were determined for compounds of general structures **A** and **B**. 5-HT_{1A} receptor affinity was determined using hippocampus homogenate as tissue preparation and [^{3}H]-8-OH-DPAT as a radioligand. 5-HT_{2A} receptor affinity was determined using rat cortex and [^{3}H]ketanserin. 5-HT_3 receptor affinity was determined using rat ileum and [^{3}H]quipazine. D_2 receptor affinity was determined using rat striatum and tritiated YM 09151.2. The α_1 receptor affinity was determined using rat cortex and [^{3}H]prazosin.

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