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 subtypes. 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 antidopa-
mamine-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} antago-
nist, 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-[(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_{3} receptors
[15]. In an effort to increase such properties and gain access to new neuroleptic agents with or without re-
duced 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 bioiso-
steric 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 agonist and antagonistic activities could possibly lead to
original potent psychotropic drugs with reduced CNS side- effects.

Studies of several potent 5-HT_{3} antagonists re-
vealed 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
acetyl group or a chemical equivalent group as well as an amine residue (tertiary or quaternized).

The geometric relationships between these key pharmacophores are represented in scheme 1 [18].
The identity of this pharmacophoric model for 5-HT\textsubscript{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\textsubscript{3} antagonists. This is the case for ondansetron, granisetron and tropisetron (chart 1).

Several other studies have demonstrated that the thiazoletone ring may be regarded as a bioisosteric equivalent of the carbonyl group [19, 20]. Indeed, other 5-HT\textsubscript{3} antagonists include a thiazoletone 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\textsubscript{1A} agonistic and 5-HT\textsubscript{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). Benzothiazoline 3 was methylated on position 3 using dimethyl sulfate 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-

![Chart 1](image)

**Chart 1.**

![Chart 2](image)

**Chart 2.**

![Scheme 1](image)

**Scheme 1.**

![Scheme 2](image)

**Scheme 2.** i) 2-Propanol, K\textsubscript{2}CO\textsubscript{3}, Δ; ii) DMF, K\textsubscript{2}CO\textsubscript{3}. 
Compounds 7a–c exhibited 5-HT$_{1A}$ affinities comparable to those observed with their phenylpiperazine analogs. The 5-HT$_2$ affinities were considerably increased (100–1000-fold). The undesirable and high $\alpha_1$ 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 biososoter 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>
<thead>
<tr>
<th>Compound</th>
<th>5-HT$_{1A}$</th>
<th>5-HT$_2$</th>
<th>5-HT$_3$</th>
<th>$D_2$</th>
<th>$\alpha_1$</th>
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<tbody>
<tr>
<td>7a</td>
<td>$2 \times 10^{-8}$</td>
<td>$4 \times 10^{-6}$</td>
<td>$4 \times 10^{-7}$</td>
<td>$&gt; 10^{-4}$</td>
<td>$10^{-5}$</td>
</tr>
<tr>
<td>7b</td>
<td>$3 \times 10^{-8}$</td>
<td>$10^{-6}$</td>
<td>$4 \times 10^{-7}$</td>
<td>$&gt; 10^{-4}$</td>
<td>$10^{-5}$</td>
</tr>
<tr>
<td>7c</td>
<td>$5 \times 10^{-8}$</td>
<td>$6 \times 10^{-6}$</td>
<td>$4 \times 10^{-8}$</td>
<td>$&gt; 10^{-4}$</td>
<td>$10^{-7}$</td>
</tr>
<tr>
<td>8</td>
<td>$&gt; 10^{-4}$</td>
<td>$&lt; 10^{-6}$</td>
<td>$10^{-8}$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
</tbody>
</table>
Table II. IC₅₀ (M) of compounds of general structure A.

<table>
<thead>
<tr>
<th>Compound</th>
<th>n</th>
<th>X</th>
<th>5-HT₁₅</th>
<th>5-HT₂</th>
<th>5-HT₃</th>
<th>D₂</th>
<th>α₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>2</td>
<td>2-OC₃H₅</td>
<td>2 × 10⁻⁹</td>
<td>5 × 10⁻⁷</td>
<td>10⁻⁵</td>
<td>4 × 10⁻⁸</td>
<td>4 × 10⁻⁷</td>
</tr>
<tr>
<td>A2</td>
<td>2</td>
<td>3-CF₃</td>
<td>10⁻⁹</td>
<td>6 × 10⁻⁷</td>
<td>5 × 10⁻⁵</td>
<td>2 × 10⁻⁷</td>
<td>4 × 10⁻⁷</td>
</tr>
<tr>
<td>A3</td>
<td>4</td>
<td>2-OC₃H₅</td>
<td>8 × 10⁻¹⁰</td>
<td>10⁻⁶</td>
<td>10⁻⁵</td>
<td>10⁻⁸</td>
<td>3 × 10⁻⁸</td>
</tr>
<tr>
<td>A4</td>
<td>4</td>
<td>3-CF₃</td>
<td>2 × 10⁻⁹</td>
<td>4 × 10⁻⁷</td>
<td>10⁻⁵</td>
<td>6 × 10⁻⁸</td>
<td>5 × 10⁻⁸</td>
</tr>
</tbody>
</table>

Brücker WP 80 SY (80 MHz) apparatus, with Me₂Si as an internal standard and with CDCl₃ or DMSO-d₆ as solvent; the chemical shifts are reported in ppm in the δ scale; unless otherwise stated, coupling constants expressed in Hz are 3/2. 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
Pipperazine (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 CaCl₂, 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. ²¹H- NMR (DMSO-d₆) δ 3.00–3.50 (m, 4H), 3.60–4.00 (m, 4H), 7.00–7.20 (m, 4H), 9.60 (s, 3H).

3-Methylbenzothiazolin-2-one 4
Benzothiazoline (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. ¹H-NMR (DMSO-d₆) δ 3.50 (s, 3H), 7.00–7.50 (m, 4H).

3-Methyl-6-(bromoacetyl)benzothiazolin-2-one 5a
Aluminum chloride (210 g, 1.60 mol) and 3-methylbenzothiazoline (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 (37.90 g, 66%). Mp 164–165°C. ¹H-NMR (DMSO-d₆) δ 3.46 (s, 3H), 4.95 (s, 2H), 7.44 (d, J = 8.7 Hz, 1H), 8.07 (dd, J₁ = 8.7 Hz, J₂ = 1.7 Hz, 1H), 8.37 (d, J = 1.7 Hz, 1H). Anal C₁₀H₁₁BrNO₂S (C, H, N).

3-Methyl-6-(3-chloropropionyl)benzothiazolin-2-one 5b
Compound 5b was prepared by treatment of 3-methylbenzothiazoline (33 g, 0.20 mol) with 3-chloropropionyl chloride (22.9 ml, 0.24 mol) in the presence of aluminum chloride (210 g, 1.60 mol) in dimethylformamide (43 ml) as described for compound 5a (30.60 g, 60%). Mp 174–177°C. ¹H-NMR (DMSO-d₆) δ 3.48 (m, 2H), 3.51 (s, 3H), 3.90 (m, 2H), 7.17 (d, J = 8.4 Hz, 1H), 8.00 (dd, J₁ = 8.4 Hz, J₂ = 1.4 Hz, 1H), 8.10 (d, J = 1.4 Hz, 1H). Anal C₁₀H₁₃ClNO₂S (C, H, N).

3-Methyl-6-(4-bromobutyl)benzothiazolin-2-one 5c
3-Methylbenzothiazoline (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-chlorobutyl 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-hydroxybutyl)benzothiazoline was washed, with water, dried and recrystallized from toluene. The resulting purity 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. ¹H-NMR (DMSO-d₆) 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 C₁₀H₁₅BrNO₂S (C, H, N).

General procedure for 3-methyl-6-(n-halogenoalkyl)benzothiazolin-2-one derivatives 6a–c
Compound 6a–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. ¹H-NMR (CDCl₃) 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 C₁₀H₁₉BrNO₂S (C, H, N).

6b n = 3, X = Cl. Mp 41–43°C. ¹H-NMR (CDCl₃) 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 C₁₁H₁₇ClNO₂S (C, H, N).

6c n = 4, X = Br. Mp 64–66°C. ¹H-NMR (CDCl₃) δ 1.80–2.00 (m, 4H), 2.70 (m, 2H), 3.40–3.50 (m, 5H), 7.20–7.40 (m, 3H). Anal C₁₂H₁₄BrNO₂S (C, H, N).
**General procedure for 3-methyl-6-n-(4-benzothiazol-2-yl)piperazin-1-yl)alkylbenzothiazolin-2-one derivatives 7a–e**

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–e (52–57%).

7a n = 2. Mp > 250°C. 1H-NMR (DMSO-d$_6$) δ 3.00–3.50 (m, 1H), 7.00–7.90 (m, 7H), 12.00 (s, 2H). Anal C$_{20}$H$_{27}$N$_2$O$_5$, 2HCl (C, H, N).

7b n = 3. Mp > 250°C. 1H-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$_{34}$N$_2$O$_5$, 2HCl (C, H, N).

7c n = 4. Mp > 250°C. 1H-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$_{38}$N$_2$O$_5$, 2HCl (C, H, N).

**1-(Benzothiazol-2-yl)-4-acetylpirperazine 8**

1-Benzothiazol-2-ylpirperazine 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 diethyl ether (20 ml) was added. The precipitate formed was filtered, dried and recrystallized from anhydrous acetone (2.30 g, 88%). mp 177–179°C. 8 1H-NMR (CDCl$_3$) δ 2.20 (s, 3H), 3.40–4.00 (m, 8H), 7.00–7.70 (m, 4H). Anal C$_{15}$H$_{19}$N$_2$O (C, H, N).

**Affinity determinations**

IC$_{50}$ for 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_{3}$, D$_2$ and 8 receptors were determined for compounds of general structures A and B. 5-HT$_{1A}$ receptor affinity was determined using hippocampal 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 8 receptor affinity was determined using rat cortex and [$^3$H]prazosin.

**References**

13. Meltzer HY (1991) 5th World Congress of Biological Psychiatry, Satellite Symposium, Florence, Italy