Eur. J. Med. Chem. 34 (1999) 69–73
© Elsevier, Paris

Laboratory note

Synthesis and pharmacological evaluation of novel 4-(4-fluorobenzoyl)piperidine derivatives as mixed 5-HT_{1A}/5-HT_{2A}/D_2 receptor ligands

Ousmane Diouf[a], Pascal Carato[a], Isabelle Lesieur[a]*,
Marie Claire Rettori[b], Daniel Henri Caignard[b]

[a]*Institut de Chimie Pharmaceutique, 3 rue du Professeur Laguesse, B.P. 83, 59006 Lille cedex, France*
[b]*ADIR, 1 rue Carle Hébert, 92415 Courbevoie cedex, France*

(Received 2 June 1997; revised 8 June 1998; accepted 25 June 1998)

Abstract – A series of novel 4-(4-fluorobenzoyl)piperidine derivatives with benzothiazolin-2-one as a pivotal template was designed, synthesised and evaluated on a battery of receptors, including serotonin 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C}, dopamine D_2 and adrenergic α_1 receptors. The 4-(4-fluorobenzoyl)piperidine moiety is known as one of the most potent pharmacophores for the 5-HT_{2A} receptor. All compounds displayed high affinities for the central 5-HT_{2A} receptors (1 to 10 nM) combined with high to moderate 5-HT_{1A} (1 to 800 nM) and D_2 (5 to 1000 nM) affinities. Such a pharmacological profile could lead to new atypical antipsychotics. © Elsevier, Paris

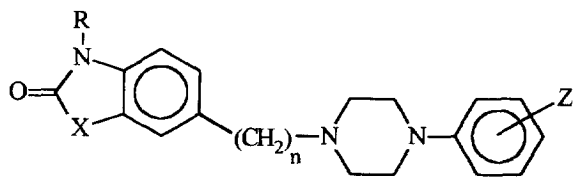
serotonin / 5-HT receptors / D_2 receptors / anxiety / antipsychotics

1. Introduction

Over the last twenty years, substantial progress has been achieved in treating anxiety and panic disorders. The serotonin (5-HT) area is of high interest in this field since serotonin and its receptor subtypes are implicated in a variety of central diseases (e.g. anxiety, depression, aberrant sexual behavior, schizophrenia) [1–5]. A growing number of various 5-HT_{1A}, 5-HT_{2A} and 5-HT_3 ligands acting at the central level are known as anxiolytic agents [6–10].

The aim of this work was to design original compounds acting simultaneously at both the central serotonin 5-HT_{1A} and 5-HT_{2A} receptor subtypes as well as at dopamine D_2 receptors. Indeed, many compounds with mixed affinities for 5-HT_{1A}, 5-HT_{2A} and D_2 receptors have been described as new anxiolytics or neuroleptics with reduced side-effects [11–13]. Previous work in the field of central serotonin receptors led us to the discovery of a series of 6-[(4-phenylpiperazin-1-yl)alkyl] benzothiazolin-2-one, benzoxazolin-2-one and, benzoxazin-3-one derivatives (*figure 1*, structure A) [14, 15] which exhibited high and selective affinities for the 5-HT_{1A} and D_2 central receptors. These compounds showed potent and selective anxiolytic and antipsychotic properties, probably as a result of their combined 5-HT_{1A} and D_2 central affinities. The lead-compound in this series was the 3-methyl-6-[2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl]benzothiazolin-2-one (*figure 1*, compound **1**) which is currently under preclinical development for its antipsychotic-like properties with a low level of extrapyramidal side-effects [15]. Pursuing our research in this area, we have designed a novel series of compounds with the same chemical templates (i.e. benzothiazolin-2-one, benzoxazolin-2-one and benzoxazin-3-one heterocycles) which could combine 5-HT_{1A}, 5-HT_{2A} and D_2 affinities leading to a potentiation of the antipsychotic properties [16–18]. We therefore decided to introduce the pharmacophoric feature of ketanserin (*figure 1*), i.e. the 2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl moiety in order to induce 5-HT_{2A} affinity. This led to compounds of general structure B [19] among which, compound **2** (*figure 1*) was selected and developed for its anxiolytic and antipanic like effects in mice and rats [20]. The affinity of compound **2** for 5-HT_{2A} receptors was similar to that observed with ketanserin. On the basis of the results

*Correspondence and reprints

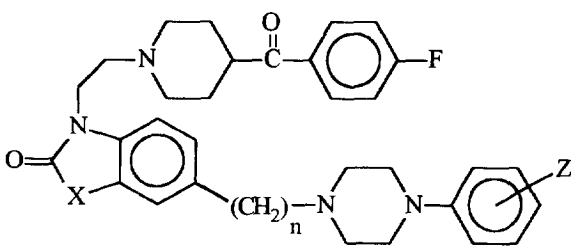


X= O, S or OCH_2; R= H or CH_3; n= 2, 3 or 4;

Z= H, 2-OCH_3, 3-CF_3, 2-F or 4-F

Structure A

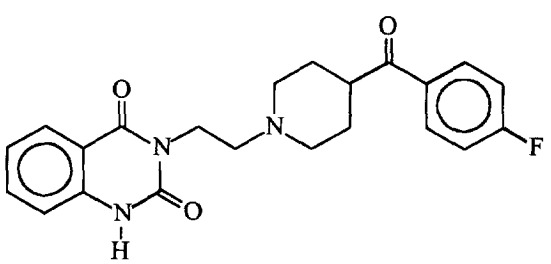
1: X= S, R= CH_3, n= 2 and Z= 2-OCH_3



X= O, S or OCH_2; n= 2, 3 or 4; Z= 2-OCH_3, 3-CF_3

Structure B

2: X= S, n= 4 and Z= 2-OCH_3



Ketanserin

Figure 1.

obtained with compounds **1** and **2**, we have initiated a third series of compounds specifically using the benzothiazolin-2-one heterocycle as a pivotal template. We have studied the influence of the position of the N-[4-(4-fluorobenzoyl)piperidin-1-yl]alkyl moiety on this heterocycle (position 3 or 6) and the length of the side-chain linking the 4-(4-fluorobenzoyl)piperidine pharmacophore to the benzothiazolin-2-one template (compounds **5–6**, *figure 2*; compounds **10–12**, *figure 3*). The role of a methoxy group at position 5 of the benzothiazolin-2-one ring (compound **6**, *figure 2*), and the relative positions of the arylpiperazinyl and 4-(4-fluorobenzoyl)piperidinyl moieties in compound **2** were also investigated (compound **13**, *figure 4*). This paper reports the synthesis and the in vitro pharmacological results obtained within this third series.

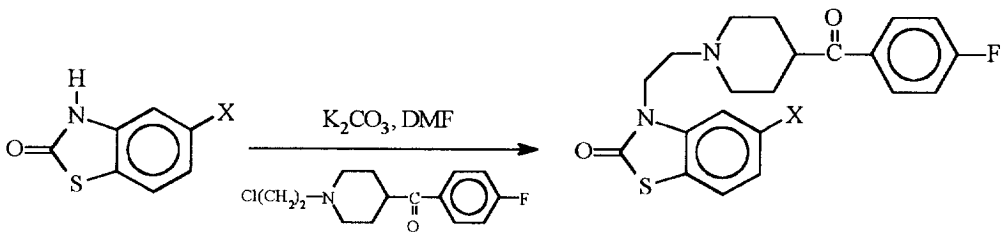
2. Chemistry

The 3-[2-(4-(4-fluorobenzoyl)piperidin-1-yl)ethyl] derivatives **5** and **6** were synthesised respectively from benzothiazolin-2-one (**3**) or 5-methoxy benzothiazolin-2-one (**4**) by action of 1-chloro-2-[4-(4-fluorobenzoyl) piperidin-1-yl]ethane in the presence of potassium carbonate in boiling DMF *(figure 2)*. Compounds **10–12** were obtained from derivatives **7–9** by the action of 4-(4-fluorobenzoyl)piperidine in refluxed acetone in the presence of triethylamine *(figure 3)*. Full details concerning the preparation of compounds **7–9** were described by Diouf et al. [21, 22]. Compound **13** was prepared from **10** using the same procedure as that of **5** and **6** *(figure 4)*.

3. Results and discussion

Binding affinities for 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, D_2 and α_1 receptors were determined for compounds **5**, **6**, **10–13** as reported in *table I*. Values concerning compounds **1**, **2** and ketanserin are also reported as references.

Compounds **5** and **6** bearing a 4-(4-fluorobenzoyl) piperidine moiety at position 3 of the benzothiazolin-2-one heterocycle display very high affinity for the 5-HT_{2A} receptor. Compound **5** in particular exhibits high 5-HT_{2A} selectivity since it displays very high 5-HT_{2A} affinity (in the nanomolar range) and no or very low affinity for the other receptors. Introduction of a methoxy group at position 5 of the heterocycle (**6**) strongly modifies this selectivity, conserving 5-HT_{2A} and increasing 5-HT_{2C} and more particularly D_2 (5-fold) and α_1 (20-fold) affinities. It also appears that the position of the 4-(4-fluorobenzoyl)piperidine pharmacophore on the heterocycle plays a key role. Compounds **10–13** bearing this side chain at position 6 display higher 5-HT_{1A}, D_2 and α_1 affinities than **5**. Moreover, for these compounds, the nature of the nitrogen substituent is of prime interest: the lack of substituent (compound **10**) leads to the highest



3: X= H

4: X= OCH_3

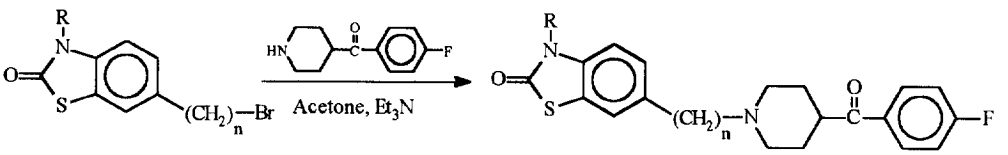
5: X= H

6: X=OCH_3

Figure 2.

5-HT_{2A} and 5-HT_{2C} affinities. Moreover, **10** exhibits better 5-HT_{2A}/5-HT_{2C} selectivity ratio than ketanserin, the 5-HT_{2A} ligand of reference, and can serve therefore as a precious pharmacological tool. The length of the link between the aromatic ring of the benzothiazolin-2-one template and the nitrogen atom of the 4-(4-fluoro-benzoyl)piperidine moiety has a negligible influence, only the 5-HT_{1A} affinity being 5-fold better with two methylene units (**11**).

Comparison of **5** with **2** shows that deletion of the arylpiperazinobutyl side chain from position 6 strongly increases the 5-HT_{2A} selectivity, lowering the 5-HT_{1A}, D_2 and α_1 affinities. According to these results, it clearly appears that the arylpiperazinobutyl moiety is an essential



7: R= H, n= 2

8: R= CH_3, n= 2

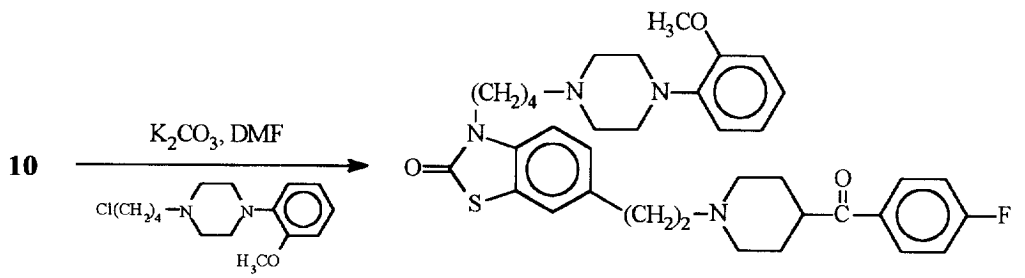
9: R= CH_3, n=4

10: R= H, n= 2

11: R= CH_3, n= 2

12: R= CH_3, n=4

Figure 3.



13

Figure 4.

Table I. K_i values (nM) of compounds **5**, **6**, **10–13**.

Compounds	Receptors				
	5-HT_{1A} [a]	5-HT_{2A} [b]	5-HT_{2C} [c]	D_2 [d]	α_1 [e]
Ketanserin	–	35	50	–	–
1	2	500	4000	40	10
2	7	2	200	8	> 100
5	300	2	100	1000	1000
6	800	3	50	200	60
10	100	1	10	30	–
11	20	10	200	30	0.7
12	100	10	300	30	0.7
13	1	4	100	5	–

Tissue preparations and radioligands used for affinity determinations; [a] rat hippocampus and [^{3}H]-8-OH-DPAT; [b] rat cortex and [^{3}H] Ketanserin; [c] rat choroïd plexus and [^{3}H]-*N*-methylmesulergine; [d] rat striatum and [^{3}H]-YM 09151.2; [e] rat cortex and [^{3}H] Prazosin.

feature for the binding to these receptors, but as previously mentioned for compounds **10–12**, the position of the substituent on the heterocycle has to be taken into account. Compound **13** and its positional isomer **2** have a similar profile and their affinity values are in the same range.

In conclusion, compounds **5** and **13** are the most interesting, **5** being the best for 5-HT_{2A} selectivity and **13** possessing the best 5-HT_{1A}, 5-HT_{2A} and D_2 affinities which could lead to a profile of an atypical antipsychotic drug. Compound **13** is currently undergoing clinical trials.

4. Experimental protocols

Compounds **5**, **6**, **10–13** were characterized by elemental analysis, IR and ^{1}H-NMR spectra. The ^{1}H-NMR spectra were obtained on a Brücker WP 80SY (80 MHz) apparatus, with Me_4Si as an internal standard and with $CDCl_3$ or DMSO-d_6 as solvent. Melting points were determined using a Büchi SMP-20 apparatus, and are uncorrected. Elemental analyses were determined by the CNRS Center of Vernaison (France) and are within ±0.4% of the theoretical values.

4.1. General procedure for the preparation of the 3-[2-(4-(4-fluorobenzoyl)piperidin-1-yl)ethyl]benzothiazolin-2-one hydrochloride derivatives 5 and 6

To a stirred solution of **3** or **4** (0.01 mol) in DMF (40 mL) was added anhydrous K_2CO_3 (0.04 mol, 5.52 g) and 1-(2-chloroethyl)-4-(4-fluorobenzoyl)piperidine hydrochloride (0.012 mol, 3.67 g). The reaction mixture was stirred and heated under reflux for 24 h. After cooling, the mixture was poured into ice-water. The resulting precipitate was collected by filtration, dried and dissolved in absolute ethanol. The solution was saturated with gaseous HCl to give the corresponding hydrochloride of **5** and **6**.

5: (60% yield), m.p. > 250 °C. ^{1}H-NMR ($CDCl_3$) δ 2.10–2.30 (m, 2H), 3.00–3.40 (m, 9H), 4.30–4.60 (m, 2H), 7.00–8.20 (m, 8H), 11.20 (s, 1H). Anal. $C_{21}H_{21}FN_2O_2S$•HCl•3.5H_2O (C, H, N).

6: (65% yield), m.p. > 250 °C. ^{1}H-NMR (DMSO-d_6) δ 1.80–2.10 (m, 4H), 3.10–3.40 (m, 6H), 3.80–4.00 (m, 4H), 4.50 (m, 2H), 6.90–8.20 (m, 7H), 11.50 (s, 1H). Anal. $C_{22}H_{23}FN_2O_3S$•HCl (C, H, N).

4.2. General procedure for the preparation of the 6-[n-(4-(4-fluorobenzoyl)piperidin-1-yl)alkyl]benzothiazolin-2-one hydrochloride derivatives 10–12

Compounds **7–9** (0.010 mol) were dissolved in anhydrous acetone (70 mL). Triethylamine (0.032 mol, 4.2 mL) and 4-(4-fluorobenzoyl)piperidine hydrochloride (0.012 mol, 3.67 g) were added and the mixture was heated under reflux for 24 h. The solvent was evaporated in vacuo and the hydrochloride salts were isolated by treatment with a 2 N aqueous solution of HCl. The precipitates were filtered, dried and recrystallized from absolute ethanol yielding compounds **10–12**.

10: (65% yield), m.p. 193–195 °C. ^{1}H-NMR (DMSO-d_6) δ 2.00 (m, 4H), 3.10 (m, 4H), 3.30 (m, 2H), 3.70 (m, 3H), 7.10 (d, 1H, J_1 = 8.00 Hz), 7.20 (dd, 1H, J_1 = 8.00 Hz, J_2 = 1.40 Hz), 7.40 (m, 2H), 7.50 (d, 1H, J_2 = 1.40 Hz), 8.10 (m, 2H), 10.80 (s, 1H), 12.00 (s, 1H). Anal. $C_{21}H_{21}FN_2O_2S$•HCl•H_2O (C, H, N).

11: (67% yield), m.p. 224–226 °C. ^{1}H-NMR (DMSO-d_6) δ 1.70–2.10 (m, 6H), 3.10–3.30 (m, 8H), 3.40–3.60 (m, 2H), 7.30–7.50 (m, 4H), 7.60 (s, 1H), 8.10–8.30 (m, 2H), 10.75 (s, 1H). Anal. $C_{22}H_{23}FN_2O_2S$•HCl (C, H, N).

12: (52% yield), m.p. 188–190 °C. ^{1}H-NMR (DMSO-d_6) δ 1.10–1.40 (m, 4H), 1.60–2.00 (m, 4H), 3.20–3.70 (m, 12H), 7.30–7.60 (m, 4H), 7.80 (s, 1H), 8.10–8.30 (m, 2H), 11.00 (s, 1H). Anal. $C_{24}H_{27}FN_2O_2S$•HCl (C, H, N).

*4.3. 3-[4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl]-6-[2-(4-(4-fluorobenzoyl)piperidin-1-yl)ethyl]benzothiazolin-2-one hydrochloride (**13**)*

Compound **13** was prepared by treatment of **10** (0.01 mol, 4.20 g) with 1-(2-methoxyphenyl)-4-(4-chlorobutyl)piperazine hydrochloride (0.012 mol, 3.66 g) in the presence of K_2CO_3 (0.04 mol, 5.52 g) in refluxing DMF (60 mL) as described for compounds **5** and **6**. Compound **13** was recrystallized from absolute ethanol (30% yield), m.p. > 250 °C. ^{1}H-NMR (DMSO-d_6) δ 1.75 (m, 4H), 2.00 (m, 4H), 3.05 (m, 10H), 3.30 (m, 2H), 3.50 (m, 4H), 3.70 (m, 2H), 3.80 (m, 4H), 4.00 (m, 2H), 6.95 (m, 4H), 7.35 (m, 4H), 7.60 (s, 1H), 8.10 (dd, 2H, J_1 = 8.50 Hz, J_2 = 2.80 Hz), 10.90 (s, 2H). Anal. $C_{36}H_{43}FN_4O_3S$•2HCl•H_2O (C, H, N).

References

[1] Moulignier A., Rev. Neurol. (Paris) 150 (1994) 3–15.

[2] Hoyer D., Clarke E.D., Fozard R.J., Harting R.P., Martini R.G., Mylecharane J.E., Saxena R.P., Humphrey P.A.P., Pharmacol. Rev. 46 (1994) 157–203.

[3] Iqbal N., VanPraag H.M., Eur. Neuropharmacol. 5 (1995) 11–23.

[4] Lanfumey L., Hamon M., Actual. Chim. Ther. 22 (1995) 115–126.

[5] Brier A., Schizophr. Res. 14 (1995) 187–202.

[6] Blin O., Azorin J.M., Bouhours P., J. Clin. Psychopharmacol. 16 (1996) 38S–44S.

[7] Foreman M.M., Fuller W.R., Rasmussen K., Nelson L.D., Calligaro O.D., Zhang L., Barrett J.E., Booher N.R., Paget J.C., Flaugh E.M., J. Pharmacol. Exp. Ther. 270 (1994) 1270–1281.

[8] Andrews N., Hogg S., Gonzalez E.L., File E.S., Eur. J. Pharmacol. 264 (1994) 259–264.

[9] Baldwin D., Rudge S., Psychopharmacol. 9 (1995) 41–45.

[10] Den Boer J.A., Westenberg H.G.M., De Leeuw A.S., VanVliet I.M., Int. Clin. Psychopharmacol. 9 (1995) 47–52.

[11] Meltzer H.Y., Matsubara S., Lee J.C., Psychopharmacol. Bull. 25 (3) (1989) 390–392.

[12] Janssen P.A.J., Niemegeers C.J.E., Awouters F., Schelleken K.H.L., Megen A.A.H.P., Meert T.F., Ther. 244 (1988) 685–693.

[13] Reitz A.B., Bennett D.J., Blum P.S., Codd E.E., Maryanoff C.A., Ortegon M.E., Renzi M.J., Scott M.K., Schank R.P., Vaught J.L., J. Med. Chem. 37 (1994) 1060–1062.

[14] Taverne T., Lesieur I., Depreux P., Caignard D.H., Guardiola B., Chem. Abstr. 117 (1992) 69855j; Eur. Pat. 4025465.

[15] Taverne T., Diouf O., Depreux P., Poupaert J.H., Lesieur D., Guardiola-Lemaître B., Renard P., Rettori M.C., Caignard D.H., J. Med. Chem. 41 (1998) 2010–2018.

[16] Albinsson A., Björk A., Svartengren J., Klint T., Andersson G., Eur. J. Pharmacol. 261 (1994) 285–294.

[17] Barrett J.E., Vanover K.E., Psychopharmacol. 112 (1993) 1–12.

[18] Barrett J.E., Zhang L., Drug Dev. Res. 24 (1991) 179–188.

[19] Diouf O., Depreux P., Lesieur D., Guardiola B., Caignard D.H., Adam G., Chem. Abstr. 119 (1994) 255788x; Fr. Appl. Pat. (1993) 93/2, 528; Eur. Appl. Pat. (1994) EP613898.

[20] Griebel G., Blanchard D.C., Rettori M.C., Guardiola-Lemaître B., Blanchard R.J., Pharmacol. Biochem. Behav. 54 (2) (1996) 509–516.

[21] Diouf O., Carato P., Depreux P., Bonte J.P., Caignard D.H., Guardiola-Lemaître B., Rettori M.C., Belzung C., Lesieur D., Bioorg. Med. Chem. Lett. 7 (20) (1998) 2579–2584.

[22] Diouf O., Depreux P., Lesieur D., Poupaert J.H., Caignard D.H., Eur. J. Med. Chem. 30 (1995) 715–719.