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Short Communication

Synthesis of *N*-(4-aryl-1-piperazinylbutyl)-substituted 7,8-benzo-1,3-diazaspiro[4,5]decane-2,4-dione derivatives with potential anxiolytic activity

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Abstract

Continuing our studies connected with the design of new anxiolytics we have now synthesized a series of new compounds, derivatives of 7,8-benzo-1,3-diazaspiro[4,5]decane-2,4-dione bearing a 4-aryl-1-piperazinylbutyl group attached to the imide nitrogen. One single compound was submitted to the 5-HT_{1A} receptor binding assay and found to display the expected — though rather weak — receptorial affinity.

Keywords: 7,8-Benzo-1,3-diazaspiro[4,5]decane-2,4-dione derivatives; Anxiolytics

1. Introduction

In the early eighties a new generation of anxiolytics was introduced for therapeutic use. The first of the anxiolytics of generation II was buspirone — an arylpiperazine derivative — which possesses a high affinity to both 5-HT_{1A} and D_2 receptors. Functionally buspirone is a partial antagonist of 5-HT_{1A} receptors.

During the last few years it has been reported that many selective ligands of serotonin 5-HT_{1A} receptors, structural buspirone analogs, display an anxiolytic activity (gepirone, ipsapirone, tandospirone, lesopitrone and others). The pharmacological profile of these drugs differs considerably from that of buspirone, but they are all selective partial antagonists of serotonine 5-HT_{1A} receptors and display a strong anxiolytic activity.

In our previous reports the synthesis of some *N*-(4-aryl-1-piperazinylbutyl)-substituted cyclic imides, structural analogs of buspirone, was described. Some of these compounds displayed an expected affinity to 5-HT_{1A} receptors and anxiolytic activity in behavioral tests [1a,1b,2a,2b,3a,3b].

We have now designed a new series of compounds, *N*-(4-aryl-1-piperazinylbutyl) derivatives of 7,8-benzo-1,3-diazaspiro[4,5]decan-2,4-dione, with the characteristic of partial antagonists of 5-HT_{1A} receptors.

2. Chemistry

The initial compound for all syntheses was 7,8-benzo-1,3-diazaspiro-[4,5]decan-2,4-dione (**1**).

Compound **1** was condensed with 1-bromo-4-chlorobutane in the presence of catalytic quantities of KI, yielding 3-(4-chlorobutyl)-7,8-benzo-1,3-diazaspiro[4,5]decan-2,4-dione (**2**). The obtained 3-(4-chlorobutyl) derivative **2** was condensed with appropriate 4-arylpiperazines in acetonitrile in the presence of anhydrous K_2CO_3, yielding compounds **3–8** (Scheme 1). The above described method of preparation of N-substituted derivatives of cyclic imides [4a,4b,5a,5b] was much more effective than condensation with 1,4-dibromobutane and then with appropriate 4-arylpiperazine [6]. According to this second method imide **1** was heated with a large excess of 1,4-dibromobutane in acetone yielding 3-(4-bromobutyl)-7,8-benzo-1,3-diazaspiro[4,5]decan-2,4-dione (**9**) which was condensed with the appropriate 4-arylpiperazine to give the expected compound **3**, but in a low yield.

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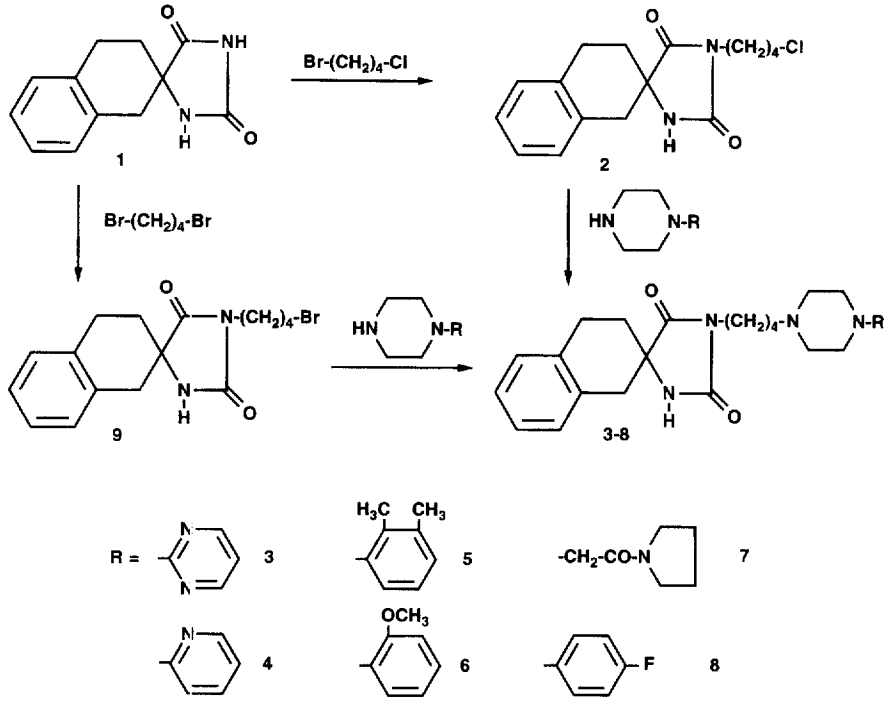

Scheme 1. Synthesis of 3-substituted derivatives of 7,8-benzo-1,3-diazaspiro[4,5]decan-2,4-dione.

The new compounds were characterized by ^{1}H NMR and IR spectra and elemental analysis. The physicochemical data of the obtained compounds are described in Table 1.

The IR spectra exhibit an NH band at 3200–3275 cm^{-1} and two CO bands respectively at 1690–1700 and 1750–1760 cm^{-1}.

The ^{1}H NMR spectra contain a characteristic resonance signal of the proton of the NH group established at 5.85–5.94 ppm. The 'smooth look' of this signal testifies of a very weak mobility of this proton. In the inflexible part of the molecule condensed with the aromatic ring, protons of CH_2 groups have a different magnetic environment. They appear in geminal couplings with easy to distinguish coupling of protons of the $C^{(6)}H_2$ group. In the 4-aryl-1-piperazinylbutyl substituent free rotation round C–C bonds appears in the average magnetic environment. The only characteristic is vicinal couplings of the CH_2–CH_2 groups, $J_{vic} = 7.5$ Hz.

Table 1
Physicochemical properties of compounds **2–9**

Compound No.	Yield (%)	Crystallization solvent	M.p. (°C)	Analyses
2	75	80% EtOH	138–139	$C_{16}H_{19}ClN_2O_2$
3	34 [a]	hexane	167–168	$C_{24}H_{30}N_6O_2$
4	40	hexane	135–136	$C_{25}H_{31}N_5O_2$
5	46	octane	156–157	$C_{28}H_{36}N_4O_2$
6	45	octane	169–170	$C_{27}H_{34}N_4O_3$
7	40	hexane	159–161	$C_{26}H_{37}N_5O_3$
8	52	octane	177–178	$C_{26}H_{31}FN_4O_2$
9	48	60% EtOH	137–139	$C_{16}H_{19}BrN_2O_2$

[a] Relative to Method I.

The first of the obtained compounds, 3-{4-[(2-pyrimidinyl)-1-piperazinyl]-butyl}-7,8-benzo-1,3-diazaspiro[4,5]-decan-2,4-dione (**3**), was transformed into the hydrochloride and in this form submitted to a primary screening test of its 5-HT$_{1A}$ receptor affinity.

3. Pharmacology: results and discussion

The biological activity of compound **3** was determined by means of receptor binding studies. Radiobinding reactions with the rats brain receptors of 5-HT$_{1A}$ subtype were performed using ligand [^{3}H] 8-hydroxy-2-(di-n-propylamino)tetraline (8-OH-DPAT). As a reference drug buspirone was used (Bristol Myers). The 5-HT$_{1A}$ receptor affinity of the tested compound was two orders of magnitude lower than that of buspirone ($K_i = 4.6 \times 10^{-5}$ M in comparison to 5.5×10^{-7} M for buspirone). Though compound **3** expressed only rather weak affinity to the 5-HT$_{1A}$ receptor, a search for anxiolytics in that chemical group would be worthwhile.

4. Experimental

4.1. Chemistry

Melting points were determined on a Kofler apparatus and are uncorrected. IR spectra were recorded on Specord 75 IR spectrophotometer (Zeiss, Jena) in KBr pellets. ^{1}H NMR spectra were recorded with a Tesla 567A 100 MHz apparatus; TMS was used as internal reference. The results of elemental analyses (C, H, N) were within ±0.4 of theoretical values.

4.1.1. 3-(4-Chlorobutyl)-7,8-benzo-1,3-diazaspiro[4,5]-decane-2,4-dione (2)

A mixture of 0.01 mol (2.16 g) of 7,8-benzo-1,3-diazaspiro[4,5]decane-2,4-dione (**1**), 100 ml acetone, 0.25 g KI and 0.01 mol (1.71 g) 1-bromo-4-chlorobutane was refluxed for 50 h. After cooling, the formed precipitate was filtered off and washed with cool benzene yielding **2**.

4.1.2. General method of preparing 3-[4-(4-aryl-1-piperazinyl)butyl)-7,8-benzo-1,3-diazaspiro[4,5]decane-2,4-diones (3–8)

A mixture of 0.01 mol (3.07 g) of compound **2** and 0.015 mol of amine in 30 ml acetonitrile was refluxed in the presence of 2 g anhydrous K_2CO_3 for 30 h. The hot mixture was filtered and the solvent was removed on a rotary evaporator. The solid obtained was crystallized from the appropriate solvent yielding compounds **3–8**.

4.1.3. 3-(4-Bromobutyl)-7,8-benzo-1,3-diazaspiro[4,5]-decane-2,4-dione (9)

A mixture of 0.01 mol (2.16 g) of imide **1** and 0.05 mol (10.75 g) of 1,4-dibromobutane in 100 ml of acetone was refluxed in the presence of 15 g K_2CO_3 for 30 h. The hot mixture was filtered and the solvent was removed on a rotary evaporator. The residue was crystallized from 60% EtOH.

^{1}H NMR ($CDCl_3$): 7.62–7.12 m, arom. 4H; 5.99 s, NH 1H; 3.69 m, CH_2N+CH_2Br 4H; 3.58**, 3.40**, 2.90*, 2.72*dd ($J^*=2$ Hz), CH_2 2H; 3.21–2.96 m, CH_2 2H; 2.50–1.99 m, $3\times CH_2$ 2H; 1.87 m, $(CH_2)_2$ 4H; $J_{gem}CH_2{}^{**}=18$ Hz.

4.1.4. Pyrimidinyl 3-{4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl}-7,8-benzo-1,3-diazaspiro[4,5]decane-2,4-dione (3)

A mixture of 0.01 mol (3.71 g) of compound **9** and 0.015 mol of amine in 30 ml acetonitrile was refluxed in the presence of 2 g anhydrous K_2CO_3 for 50 h. The hot mixture was filtered, and the solvent was removed on a rotary evaporator. The solid obtained was crystallized from heptane yielding compound **3**.

^{1}H NMR ($CDCl_3$): 8.56 d, α-pyrim. 2H; 7.62–7.20 m, arom. 4H; 6.69 t, β-pyrim. 1H; 5.92 s, NH 1H; 3.98 t, pyrim. N-$(CH_2)_{2pip}$ 4H; 3.70 t, $CONCH_2$ 2H; 3.42**, 3,60**, 2.74*, 2.82* dd, CH_2 2H ($J^*=2$ Hz); 3.25–2.97 m, CH_2 2H; 2.60 t, $N(CH_2)_{2pip}$ 4H; 2.52–1.42 m, $N_{pip}CH_2+CH_2$ 8H, $J_{gem}CH_2{}^{**}=18$ Hz; Jα-βpyrim = 4.5 Hz.

4.2. Pharmacology

4.2.1. Receptor binding determinations

Binding reaction was performed according to the method described by Pazos et al. [7] using anterior parts of the rat brain stem and [^{3}H] 8-OH-DPAT (specific activity 183 Ci/mM) as a specific ligand for serotonin (5-HT_{1A}) receptors. The compounds were tested in concentrations ranging from 3×10^{-10} to 3×10^{-3} M. Samples were counted on a Betamatic II (scintillating Kontron β-counter). Results were expressed as mean values of at least 5 independent experiments as K_i calculated according to the program set up by Munson [8] using an IBM PC/AT machine.

References

[1a] T. Zawadowski, J. Kossakowski, S. Rump, I. Jakowicz, A. Płaźnik, Synthesis and anxiolitic activity of N-substituted cyclic imides; *N*-{4-[(4-aryl)-1-piperazinyl]alkyl}-5,7-dioxabicyclo[2.2.2]octane-2,3-dicarboximide, Acta Polon. Pharm. 52 (1995) 43–46.

[1b] T. Zawadowski, J. Kossakowski, S. Rump, I. Jakowicz, A. Płaźnik, Synthesis and anxiolitic activity of N-substituted cyclic imides; *N*-{4-[(4-aryl)-1-piperazinyl]alkyl}-5,7-dioxabicyclo[2.2.2]octane-2,3-dicarboximide, Chem. Abstr. 123 (1995) 285901n.

[2a] J. Turło, T. Zawadowski, S. Rump, I. Jakowicz, T. Gidyńska, E. Gałecka, Synthesis and pharmacological screening of some *N,N'*-bis-[4-(4-aryl-1-piperazinyl)butyl]-substituted derivatives of 1,8-dimethyl-bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxydiimide, Pol. J. Pharmacol. 46 (1994) 451–455.

[2b] J. Turło, T. Zawadowski, S. Rump, I. Jakowicz, T. Gidyńska, E. Gałecka, Synthesis and pharmacological screening of some *N,N'*-bis-[4-(4-aryl-1-piperazinyl)butyl]-substituted derivatives of 1,8-dimethyl-bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxydiimide, Chem. Abstr. 122 (1995) 265332d.

[3a] T. Zawadowski, A. Skowron, S. Suski, S. Rump, I. Jakowicz, Synthesis and pharmacological profile of bicyclo[2.2.2]octane derivatives: *N*-(1-aryl-4-piperazinylbutyl) derivatives of 7-isopropyl-6-methyl- and 1-isopropyl-4-methylbicyclo[2.2.2]oct-5-ene-2,3-dicarboximide, Acta Polon. Pharm. 52 (1995) 129–132.

[3b] T. Zawadowski, A. Skowron, S. Suski, S. Rump, I. Jakowicz, Synthesis and pharmacological profile of bicyclo[2.2.2]octane derivatives: *N*-(1-aryl-4-piperazinylbutyl) derivatives of 7-isopropyl-6-methyl- and 1-isopropyl-4-methylbicyclo[2.2.2]oct-5-ene-2,3-dicarboximide, Chem. Abstr. 123 (1995) 340034j.

[4a] T. Zawadowski, J. Kossakowski, A. Skowron, S. Rump, I. Jakowicz, Preparation of *N*-(4-piperazinobutyl)-1-isopropyl-4-methylbicyclo-[2.2.2]oct-5-ene-2,3-dicarboximides, Patent No. PL 168594.

[4b] T. Zawadowski, J. Kossakowski, A. Skowron, S. Rump, I. Jakowicz, Preparation of *N*-(4-piperazinobutyl)-1-isopropyl-4-methylbicyclo-[2.2.2]oct-5-ene-2,3-dicarboximides, Chem. Abstr. 125 (1996) 86685m.

[5a] T. Zawadowski, J. Kossakowski, A. Skowron, S. Rump, I. Jakowicz, Preparation of *N*-(4-piperazinobutyl)-5,7-dioxobicyclo[2.2.2]-octane-2,3-dicarboximides, Patent No. PL 168608.

[5b] T. Zawadowski, J. Kossakowski, A. Skowron, S. Rump, I. Jakowicz, Preparation of *N*-(4-piperazinobutyl)-5,7-dioxobicyclo[2.2.2]-octane-2,3-dicarboximides, Chem. Abstr. 125 (1996) 86686n.

[6] K. Ishizumi, A. Kojima, F. Antoku, Synthesis and anxiolytic activity of N-substituted cyclic imides (*1R*,2S*,3R*,4S**)-*N*-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-2,3-bicyclo[2.2.1]heptanedicarboximide (Tandospirone) and related compounds, Chem. Pharm. Bull. 39 (9) (1991) 2288–2300.

[7] A. Pazos, D. Hoyer, J.M. Palacios, The binding of serotonergic ligands to the porcine choroid plexus: characterisation of a new type of serotonin recognition site, Eur. J. Pharmacol. 106 (1984) 539–546.

[8] P.J. Munson, Ligand: data analysis and curve-fitting for ligand binding experiments, National Institutes of Health, Bethseda, 1987.