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Original article

Synthesis and pharmacological evaluation of new 5-(cyclo)alkyl-5-phenyl- and 5-spiroimidazolidine-2,4-dione derivatives. Novel 5-HT_{1A} receptor agonist with potential antidepressant and anxiolytic activity

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ABSTRACT

The synthesis of 5-(cyclo)alkyl-5-phenyl- and 5-spiroimidazolidine-2,4-dione derivatives with an arylpiperazinylpropyl moiety (**12**–**23**) and their in vitro and in vivo pharmacological properties and molecular characteristics were described. The investigated compounds exhibited high affinity for 5-HT_{1A} (**13**–**22**) and 5-HT_{2A} (**18**, **20**, **21**, **23**) receptors and diversified pharmacological profile. Compounds **17**, **20** and **22** showed antagonistic, partial agonistic and agonistic activity, respectively, toward 5-HT_{1A} receptor and they were investigated as potential antidepressants and/or anxiolytics. The most interesting compound **22** (1-[3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl]-3′,4′-dihydro-2′H-spiro[imidazolidine-4,1′-naphthalene]-2,5-dione), a pre- and postsynaptic 5-HT_{1A} receptor agonist produced an antidepressant-like effect, which was more pronounced than that of imipramine in the forced swim test in mice, without affecting locomotor activity. Moreover, compound **22** produced a weak anxiolytic-like effect in the four-plate test in mice. Molecular docking studies of compound **22** to the homology model of the 5-HT_{1A} receptor showed that a 3′,4′-dihydro-2′H-spiro[imidazolidine-4,1′-naphthalene]-2,5-dione moiety played an important role in stabilizing the ligand–receptor complex.

1. Introduction

The role of serotonin (5-HT) in the central nervous system and its importance for the pathogenesis and treatment of mood disorders are unquestionable. 5-HT is believed to act via an interaction with 14 identified 5-HT receptor subtypes, of which 5-HT_{1A} one is the most extensively studied because of its specific connotation of affective disorders [1,2]. Despite a great number of currently marketed antidepressants and anxiolytics, continual efforts are made to develop new drugs with greater efficacy (especially in non-responders), an earlier onset of therapeutic improvement and less intensive side-effects [3]. Among the numerous potential drug candidates currently explored, 5-HT_{1A} receptor agonists are a group of high interest, which is evidenced by not only the number of scientific studies [4–6], but also the fact that some of them are currently in different phases of clinical trials for the treatment of depression and anxiety (OPC-14523, II phase, Pharmos [7]; MN-305, II/III phase, MediciNova; AP-521, II phase, Asahi Kasei Corporation; Vilazodone, III phase, PGxHealth, LLC [8]; Gepirone ER, III phase, Fabre-Kramer [9]) as well as Alzheimer's disease (Xaliproden, III phase, Sanofi-Aventis [10]).

In the course of our studies with active 5-HT_{1A} and 5-HT_{2A} ligands, a series of β-tetralinohydantoin (3′,4′-dihydro-1′H-spiro[imidazolidine-4,2′-naphthalene]-2,5-dione) derivatives were synthesized. Among them, a few compounds were especially interesting due to their 5-HT_{1A} receptor agonistic activity and potential anxiolytic/antidepressant properties [11,12]. As a continuation of our research, in the present experiment we synthesized a series with a novel terminal amide part containing 5-(cyclo)alkyl-5-phenylimidazolidine-2,4-diones (5-cyclopropyl-5-phenyl (**15**–**17**) and 5-methyl-5-phenylimidazolidine-2,4-diones (**12**–**14**)), or their counterparts with 5-spiroimidazolidino-2,4-diones (2′,3′-dihydrospiro[imidazolidine-4,1′-indene]-2,5-dione (**18**–**20**) and 3′,4′-dihydro-2′H-spiro[imidazolidine-4,1′-naphthalene]-2,5-diones (**21**–**23**)). We chose those terminal amide parts to examine the influence of structural changes at the 5-position of the imidazolidine ring on receptor affinity and pharmacological profile. The planned compounds possess an asymmetric carbon atom at

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terminal amide part which can exist in two stereoisomeric forms R or S. The racemic compounds were chosen for the synthesis with the aim to evaluate in vitro affinity at central serotonin and dopamine receptors. To explore the effect of structural modifications at terminal amide part, 5-HT_{1A}, 5-HT_{2A} and dopamine D_2 receptor affinities and in vivo intrinsic activities were determined for the newly synthesized compounds. Three compounds (**17**, **20**, **22**) with a diversified 5-HT_{1A} functional profile were chosen and examined using common behavioural tests for predicting antidepressant and/or anxiolytic like activity in mice. Furthermore, to ascertain the potential ligand binding mode of the studied compounds within the 5-HT_{1A} receptor, the most interesting one (**22**) was docked to the homology model of that receptor, and molecular interactions, potentially important to its pharmacological activity, were described.

2. Chemistry

The compounds were synthesized according to Scheme 1. The appropriate 5-(cyclo)alkyl-5-phenyl- and 5-spiroimidazolidine-2,4-diones (**4**–**7**) were prepared from a ketone by means of the Bucherer–Bergs reaction with modifications described by Goodson et al. [11,13]. Compounds **12**–**23** were obtained by a two-step procedure involving alkylation of imidazolidino-2,4-diones at N3 position (intermediate compounds **8**–**11**) with 1-bromo-3-chloropropane and condensation of intermediates with the appropriate arylpiperazine (final bases **12**–**23**). The structures of the compounds were established using spectral ^{1}H NMR spectra and an elemental analysis. The detailed spectral data of each molecule are presented in experimental section. For further pharmacological in vitro and in vivo studies, bases **12**–**23** were transformed into water-well-soluble hydrochlorides.

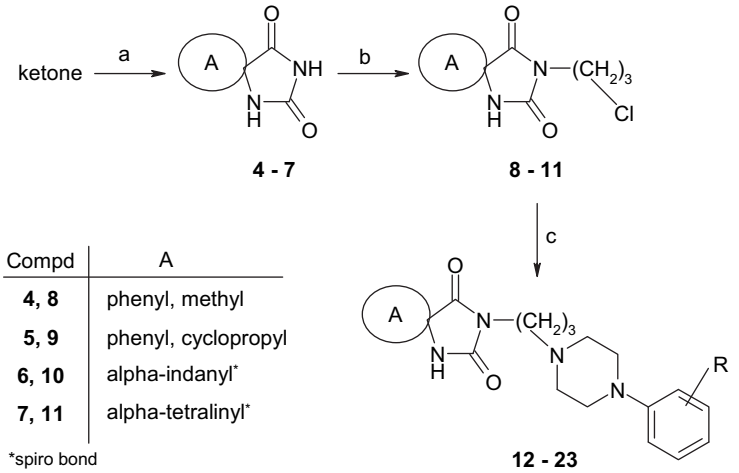
3. Pharmacology

3.1. In vitro tests

The affinities of all the synthesized compounds (**12**–**23**) for central serotonin 5-HT_{1A} and 5-HT_{2A} and dopamine D_2 receptors were evaluated on the basis of their ability to displace [^{3}H]-8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin), [^{3}H]-ketanserin and [^{3}H]-spiperone, respectively. Radioligand binding studies were conducted on rat brain using the cerebral cortex (5-HT_{1A}, 5-HT_{2A}) and the striatum (D_2) [14–16].

3.2. In vivo tests

Compounds with the highest affinities for 5-HT_{1A} (**13**, **14**, **15**, **16**, **17**, **19**, **20**, **22**) and 5-HT_{2A} (**18**, **20**, **21**, **23**) receptors were investigated in in vivo models to establish their 5-HT_{1A} and/or 5-HT_{2A} intrinsic activity.



Compd	A
4, 8	phenyl, methyl
5, 9	phenyl, cyclopropyl
6, 10	alpha-indanyl*
7, 11	alpha-tetralinyl*

*spiro bond

Compd	A	R	Compd	A	R
12	phenyl, methyl	H	**18**	α-indanyl*	H
13	phenyl, methyl	2-OCH_3	**19**	α-indanyl*	2-OCH_3
14	phenyl, methyl	3-Cl	**20**	α-indanyl*	3-Cl
15	phenyl, cyclopropyl	H	**21**	α-tetralinyl*	H
16	phenyl, cyclopropyl	2-OCH_3	**22**	α-tetralinyl*	2-OCH_3
17	phenyl, cyclopropyl	3-Cl	**23**	α-tetralinyl*	3-Cl

*spiro bond

Reagents, reaction conditions:

(a) KCN, $(NH_4)_2CO_3$, 50% ethyl alcohol;

(b) $Br(CH_2)_3Cl$, K_2CO_3, acetone, reflux;

(c) 1-phenylpiperazine derivative, anhydrous ethyl alcohol, reflux;

Scheme 1. The synthesis pathways of the investigated compounds.