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Solid-supported synthesis, molecular modeling, and biological activity of long-chain arylpiperazine derivatives with cyclic amino acid amide fragments as 5-HT$_7$ and 5-HT$_{1A}$ receptor ligands

Vittorio Canale [a], Paweł Guzik [a], Rafał Kurczab [b], Pascal Verdie [c], Grzegorz Satała [b], Bartłomiej Kubica [a], Maciej Pawłowski [a], Jean Martinez [c], Gilles Subra [c], Andrzej J. Bojarski [b], Paweł Zajdel [a,*]

[a] Department of Medicinal Chemistry, Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Kraków, Poland
[b] Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, 31-343 Kraków, Poland
[c] Department of Amino Acids, Peptides and Proteins, Institute Biomolecules Max Mousseron, University Montpellier 1, 15 Avenue Charles Flahault, 34-093 Montpellier, France

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ABSTRACT

A 47-membered library of novel long-chain arylpiperazines, which contained cyclic amino acid amides in the terminal fragment (pyrrolidine-2-carboxamide and 1,2,3,4-tetrahydroisoquinoline-3-carboxamide), was synthesized on Rink-amide resin and biologically evaluated for binding affinity for 5-HT$_7$ and 5-HT$_{1A}$ receptors. Surprisingly, members of the designed series containing piperidine-2-carboxamide fragments underwent hydrolysis, which occurred during the acidic treatment for release from the solid-support, to their respective pipecolic acid analogs. Representative compounds from the library displayed high-to-low affinity for 5-HT$_7$ (K_i = 18–3134 nM) and 5-HT$_{1A}$ (K_i = 0.5–6307 nM) sites. The possible interactions implicated in binding of the studied compounds to the 5-HT$_7$ receptor were supported by molecular modeling. Research was also applied to support the exploration of the influence of the amide fragment, the length of alkylene spacer, and arylpiperazine substituents on the receptor's affinity and selectivity.

1. Introduction

The 5-HT$_7$ receptor (5-HT$_7$R) is the latest addition to a family of serotonin receptors that are positively coupled to adenylyl cyclase through a G$_s$ protein [1]. The distribution of 5-HT$_7$Rs in several region of the brain, such as the hippocampus, hypothalamus, or thalamus, has fortified interest in these sites as potential targets for drug development. Notably, several antidepressant and antipsychotic drugs display high affinity for 5-HT$_7$Rs, and the antagonism of 5-HT$_7$Rs produces antidepressant and pro-cognitive effects [2–4]. On the other hand, the activation of 5-HT$_7$Rs produces antinociceptive effects. Potential applications of 5-HT$_7$R agonists as co-adjuvants in opioid-mediated analgesia have been proposed and could represent a new therapeutic target for the treatment of pain [5,6].

In parallel to the acquisition of more detailed insight into the function of 5-HT$_7$R pharmacology, an academic and pharmaceutical research was directed toward the development of 5-HT$_7$R ligands [7]. Several potent 5-HT$_7$R agents belong to the group of long-chain arylpiperazines (LCAP) [8]. Unfortunately, the fact that the arylpiperazine privileged core is easily recognized by other monoaminergic receptors (e.g., 5-HT$_{1A}$, 5-HT$_{2A}$, D$_2$, D$_3$, α_1, H$_1$) limits the selectivity of the LCAPs [9,10].

Some of these obstacles were recently overcome by Leopoldo et al. [11], who reported the generation of an amide series of potent 5-HT$_7$R ligands (Fig. 1). The modification of the phenylpiperazine pharmacophore and variation in the linker length were critical to achieving 5-HT$_7$/5-HT$_{1A}$ receptor selectivity.

Inspired by these findings, we continued our search for 5-HT$_7$ ligands by designing a series of LCAPs functionalized with the

* Corresponding author.
E-mail address: pawel.zajdel@uj.edu.pl (P. Zajdel).

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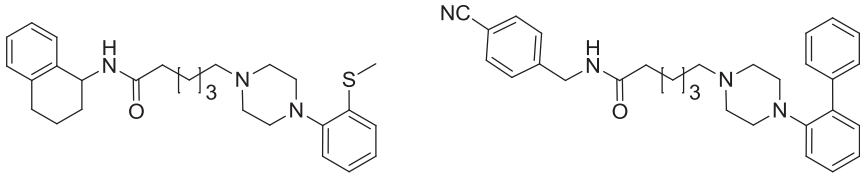


K_i (5-HT$_7$) = 0.22 nM
K_i (5-HT$_{1A}$) = 52.7 nM

K_i (5-HT$_7$) = 0.58 nM
K_i (5-HT$_{1A}$) = 188 nM

Fig. 1. LCAP examples of 5-HT$_7$R ligands.

primary amides of cyclic amino acids in the terminal fragment [12,13]. These compounds may be considered LP-44 analogs because the exocyclic amide bond was replaced with an endocyclic one and an additional primary amide group was introduced concurrently (Fig. 2). On the other hand, these studies may be regarded as an extension of our ongoing efforts toward the verification of an effect caused by an amino acid-derived terminal fragment on the affinity and selectivity of monoaminergic receptors [14]. The latter issue was extensively evaluated in a series containing *N*-acylated proline and cyclized aspartic acid moieties [15].

We present the design, which was directed by computational modeling and simulations, and solid-supported synthesis of a 47-membered library as well as the biological evaluation of selected library members for binding to 5-HT$_7$ and 5-HT$_{1A}$ receptors.

The structural modifications comprised the introduction of three cyclic amino acids to the terminal fragment, giving proline amides (Pro-amides, set **I**), piperidine-2-carboxamides (Pip-amides, set **II**), and 1,2,3,4-tetrahydroisoquinoline-3-carboxamides (Tic-amides, set **III**) as well as variation in the length of the alkylene spacer and the diversification of the aryl fragments of the N_1-piperazine moiety.

2. Results and discussion

2.1. Chemistry

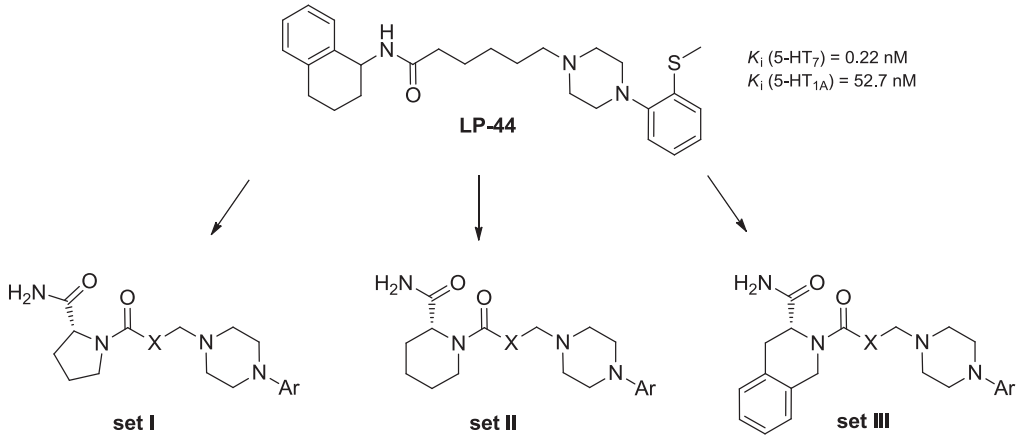
Synthesis of the designed compounds was carried out on solid support according to a six-step procedure (Scheme 1). Our workflow began with the base-mediated deprotection of a commercially available Rink-amide resin, followed by coupling with Fmoc-protected L-amino acid **2**{*1–3*} (Fig. 3) with HBTU.

After the removal of the Fmoc group, the resulting secondary amines **3**{*1–3*} were reacted with ω-bromo-acyl chlorides **4**{*1–4*} (Fig. 4) to furnish the corresponding amino acid derivatives **5**{*1–3*, *1–4*}.

The resin-bound intermediates were further submitted to a nucleophile displacement with various substituted arylpiperazine derivatives **6**{*1–10*} (Fig. 5) in DMF at 75 °C for 24 h.

The final compounds with general structures **8**–**24**{*1*, *1–4*, *1–10*}, **25**–**36**{*2*, *1–3*, *1–10*} and **37**–**54**{*3*, *1–4*, *1–10*} were released from the resin via treatment with a mixture of TFA/CH_2Cl_2 (80/20, v/v). All of the compounds were purified with a Waters preparative LC/MS apparatus. The final compounds belonging to sets **I** (**8**–**24**) and **III** (**37**–**54**) were obtained in moderate yields (33–45%) and excellent purities (97–99%). In contrast, the designed pipecolic amid derivatives (set **II**), when treated with acidic medium during cleavage from solid support, underwent hydrolysis to form carboxylic acid analogs (Table 1).

Although a similar hydrolytic process was observed for an amide bond in *N*-acylated pipecolic acid derivatives on a BAL linker [16,17], no reports concerning the hydrolysis of pipecolic amides on Rink-amide resin have been disclosed. Following our previous reports, a detailed mechanism of the unexpected amide bond cleavage was proposed (Scheme 2). First, an intramolecular tetrahedral intermediate was formed; the lone pair of electrons on the nitrogen atom was no longer conjugated with the carbonyl bond in this moiety. Consequently, a nitrogen atom became a proton acceptor, allowing for the release of the cyclic structure from the support and the formation of the oxazolinium intermediate (Muchnone). The



X = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$, *p*-C_6H_4; Ar = 2-MeS-Ph, 2-MeO-Ph, 2-OH-Ph, 2-Cl-Ph, 2-F-Ph, 3-Cl-Ph, 4-Cl-Ph, 4-F-Ph, 2,3-diCl-Ph, Benzoisoxazol-3-yl

Fig. 2. General structure of the designed pyrrolidine-2-carboxamides (set **I**), piperidine-2-carboxamides (set **II**), and 1,2,3,4-tetrahydroisoquinoline-3-carboxamides (set **III**).