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Short communication

Synthesis, anticonvulsant activity and 5-HT_{1A}, 5-HT_{2A} receptor affinity of new *N*-[(4-arylpiperazin-1-yl)-alkyl] derivatives of 2-azaspiro[4.4]nonane and [4.5]decane-1,3-dione

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Abstract

The synthesis, physicochemical and pharmacological properties of new *N*-[(4-arylpiperazin-1-yl)-alkyl]-2-azaspiro[4.4]nonane- (**8a–c, 10a–d**) and [4.5]decane-1,3-dione (**9a–c, 11a–d**) derivatives were described. The antiepileptic effects of those compounds were examined by a maximal electroshock (MES) and a pentylenetetrazole (*sc*. PTZ) tests, and their neurotoxicity was determined using a rota-rod test. Compounds **8c, 9c, 10c, d, 11c, d** with a CF_3 group at the 3-position of the 4-arylpiperazine fragment exhibited anti-seizure properties in the MES model; in contrast, their 2-CH_3 and 2-OCH_3 analogues were inactive in both the tests used. Moreover, since the investigated compounds belong to the class of long-chain arylpiperazines, their serotonin 5-HT_{1A} and 5-HT_{2A} receptor affinity was determined. The relationship between the length of alkylene spacer and 5-HT_{1A}/5-HT_{2A} receptor activity was observed. Compounds with an ethylene and a propylene bridge (**10a–d** and **11a–d**) were 3–80-fold more potent (K_i ranged from 3.1 to 94 nM for 5-HT_{1A} and 32–465 nM for 5-HT_{2A}) than their methylene analogues (**8a–c** and **9a–c**; K_i ranged from 81 to 370 nM for 5-HT_{1A} and 126–1370 nM for 5-HT_{2A}). The highest 5-HT_{1A} receptor affinity was displayed by 2-OCH_3 and 3-CF_3 phenyl derivatives (**10b**, **11b**: $K_i = 6.8$ and 5.7 nM, respectively, and **10c, 11c**: $K_i = 6.0$ and 3.1 nM, respectively), while in the case of 5-HT_{2A} receptor the highest affinity was observed for the 3-CF_3 phenyl derivatives **10c, d, 11c, d** (K_i ranged from 32 to 86 nM).

Keywords: 2-Azaspiro[4.4]nonane- and [4.5]decane-1,3-diones; 4-Arylpiperazine derivatives; Anticonvulsant activity; 5-HT_{1A}, 5-HT_{2A} receptor affinity

1. Introduction

Epilepsy is one of the most frequent neurological disorders characterized by spontaneous recurrent seizures arising from excessive electrical activity in some portion of the brain. Uncontrolled electrical activity in the central nervous system may occur via either a reduction in inhibitory neurotransmission or an increase in excitatory transmission. Changes in ionic conductance through neuronal membranes may underlie the above-mentioned abnormalities [1].

Additionally, there has been a growing evidence that serotoninergic neurotransmission modulates a wide variety of experimentally induced seizures and is involved in the enhanced seizure susceptibility observed in some genetically prone rats [2–5]. Furthermore, the experimental data obtained with animals show that 5-HT_{1A} receptors are predominantly located in limbic areas and they suggest that serotonin mediates the anticonvulsant effect via these receptors [6–8]. On the other hand, following the findings of Stean et al. [9], the mixed 5-$HT_{1A, 1B, 1D}$ receptor agonists SFK 99101 and RU 24969 produce marked increases in the seizure threshold. It has also been found that stimulation of 5-HT_2 receptors is linked to the anticonvulsant action of trifluoromethylphenylpiperazine (5-HT_{2A}/5-HT_{2C}) and *m*-chlorophenylpiperazine (5-HT_{2A}/5-HT_{2C}) in an animal maximal electroshock test [10,11].

In the course of developing new potential anticonvulsant agents and 5-HT_{1A}/5-HT_{2A} receptor ligands we focused our attention on a group of 1,3-substituted pyrrolidine-2,5-diones (succinimides) with a piperazin-1-yl-alkyl fragment at the imide nitrogen atom. In that series of derivatives, anticonvulsant activity was observed for compounds with an aromatic

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ring at the 3-position of pyrrolidine-2,5-dione and 4-aryl or 4-methyl-piperazin-1-yl alkyl moiety at the imide nitrogen atom [12,13]. Prompted by the fact that the series of pyrrolidine-2,5-diones containing at the 3-position cycloalkyl moiety connected by a spiro carbon atom showed potent anticonvulsant activity [14–17], we replaced the 3-aryl ring with a spirocycloalkyl fragment thus obtaining a series of *N*-[(4-arylpiperazin-1-yl)-alkyl]-2-azaspiro[4.4]nonane- and [4.5]decane-1,3-dione derivatives. In that series of azaspiranes connected to the arylpiperazine moiety with a propylene chain, we identified several compounds displaying activity in an *sc*. PTZ test [18]. As shown in Fig. 1, some of them exhibited high 5-HT_{2A} receptor affinity and were also found to be fairly potent 5-HT_{1A} receptor ligands [18,19]. Introduction of a spirocycloalkyl fragment into the 3-position of the pyrrolidine-2,5-dione ring significantly enhanced 5-HT_{1A}/5-HT_{2A} receptor affinity, in contrast to 3-phenyl analogues which were only slightly active (K_i > 200 nM for both receptor subtypes) [20].

In line with the above findings, in the present study we obtained two series of *N*-[(4-arylpiperazin-1-yl)-alkyl]-2-azaspiro [4.4]nonane- and [4.5]decane-1,3-dione derivatives with different length of alkyl spacer and two kinds of substituent: the electron-attracting CF_3 and the electron–donating OCH_3 and CH_3 at the 4-arylpiperazine moiety. All the above-mentioned compounds were tested in vivo for their anticonvulsant activity through the Anticonvulsant Screening Program (ASP), and in vitro for their affinity towards 5-HT_{1A} and 5-HT_{2A} receptors.

2. Chemistry

The synthesis of compounds **8a–c**, **9a–c**, **10a–d** and **11a–d** is shown in Scheme 1. The starting 1-carboxy-1-cyclopentane- (**4**) and 1-carboxy-1-cyclohexane-acetic acids (**5**) were prepared from related cycloalkyl ketones according to the previously described procedure [14]. The synthesis of 2-azaspiro [4.4]nonane- (**6**) and 2-azaspiro[4.5]decane-1,3-dione (**7**) (spirosuccinimide) had been described in a separate publication [21]. Compounds **8a–c** and **9a–c** were prepared by the Mannich-type reaction from the appropriately 3-substituted spirosuccinimide (**6, 7**), formaldehyde and the corresponding 4-arylpiperazine to obtain the designed derivatives. The reaction was carried out in ethanol at a room temperature for ca. 6–12 h and was eventually refluxed for 30 min. The synthesis of compounds **10a–d** and **11a–d** were prepared using a one-pot cyclization reaction of the obtained acids **4** or **5** and appropriately substituted 1-amino-alkyl-4-arylpiperazine.

All compounds **8a–c, 9a–c, 10a–d** and **11a–d** were isolated as the hydrochloride salts and were recrystallized from anhydrous ethanol. Their molecular formulas were established on the basis of elemental (C, H, N) analyses (data not shown). The structures of **8a–c, 9a–c, 10a–d** and **11a–d** as well as their physicochemical data are presented in Table 1.

The structures of the investigated compounds were confirmed by the examination of their ^{1}H NMR and MS spectra (Tables 2–4).

The ^{1}H NMR spectra of the investigated compounds revealed characteristic chemical shifts agreed with their proposed structures. In all derivatives (**8a, c, 9a, c, 10a–d** and **11a–d**) the signal due to pyrrolidine-2,5-dione ring CH_2 protons appeared at about δ 2.57–2.88 ppm, as singlets. The chemical shifts of the cyclopentane and cyclohexane rings were observed as multiplets within the range of δ 1.66–2.23 ppm (**8a, c, 10a–d**), and δ 1.21–1.93 ppm (**9a, c, 11a–d**). Appearance of a sharp singlet at about δ 4.55–4.81 ppm, due to the two protons of methylene group confirms the formation of compounds **8a, c** and **9a, c**. The piperazine protons of compounds **8a, c** and **9a, c** were observed as two multiplets in the range of δ 2.77–2.80 ppm and δ 2.90–3.24 ppm (**8a, c**), and δ 2.75–3.46 ppm and δ 3.20–3.73 ppm (**9a, c**).

The ^{1}H NMR spectra of compounds **10a–d** in general were almost similar to compounds **11a–b**. The difference was only in chemical shift of two piperazine protons, for compounds **10b, 11b,** which were shifted considerably down field and were observed as a triplets at δ 5.09 ppm (*J* ca.12 Hz). The

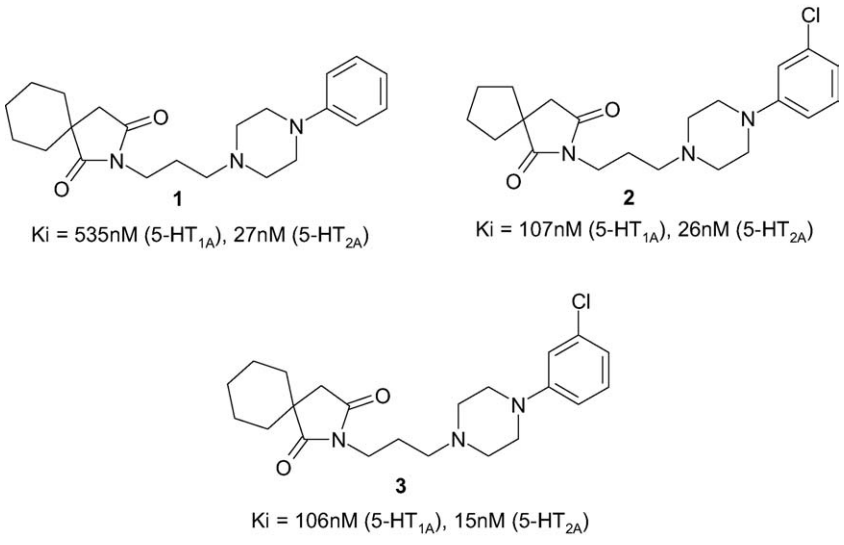

Fig. 1. Chemical structure of compounds **1**–**3**.