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Synthesis, anticonvulsant activity and 5-HT_{1A}/5-HT_7 receptors affinity of 1-[(4-arylpiperazin-1-yl)-propyl]-succinimides

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Abstract:
Background: Epilepsy is the most prevalent neurological disorder, affecting approximately 50 million people worldwide. Even though significant advances have been made in epilepsy research, convulsions in about 30% of epileptics are still inadequately controlled by standard drug therapy. For this reason, constant attempts are made to investigate new chemical agents and mechanisms through which epilepsy can be effectively controlled. Therefore, in the present studies, a series of sixteen new 1-[(4-arylpiperazin-1-yl)-propyl]-3-methyl-3-phenyl- and 3-ethyl-3-methylpyrrolidine-2,5-dione derivatives as potential anticonvulsant agents was synthesized.
Methods: Anticonvulsant properties were evaluated in the maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ) and psychomotor seizure (6-Hz) tests after intraperitoneal injection in mice. The acute neurological toxicity was determined in the motor impairment rotorod screen.
Results: The compounds showed activity at a dose of 30 mg/kg (**4**, **8**, **16**) or 100 mg/kg (**6**, **9**, **10**, **12**, **17**, **18**) in the MES model in mice. Four or them (**8**, **10**, **16**, **17**) were also evaluated after *po* administration in rats. In this series, the most active was 1-{3-[4-(3-chlorophenyl)-piperazin-1-yl]-propyl}-3-methyl-3-phenyl-pyrrolidine-2,5-dione (**8**) with the ED_{50} value of 28.2 mg/kg, TD_{50} value of 268.5 mg/kg and protective index of 9.52 after *po* administration in rats.
Conclusions: Taking into consideration the role of 5-HT_{1A} and 5-HT_7 receptor subtypes in relation to the control of seizures as well as the fact that all compounds obtained belong to the class of long-chain arylpiperazines, their serotonin 5-HT_{1A} and 5-HT_7 receptor affinity was determined. The most potent 5-HT_{1A} receptor ligands are 2-OCH_3 (**11**, **19**) and 3-Cl (**8**, **16**) derivatives with K_i = 72, 14 nM, and 109, 44 nM, respectively. With respect to the 5-HT_7 receptors, the best K_i values were obtained for derivatives **8** and **11** (K_i = 76 nM and 63 nM, respectively).

Key words:
anticonvulsant activity, 5-HT_{1A}/5-HT_7 receptor ligands, 3,3-disubstituted pyrrolidine-2,5-diones, arylpiperazines

Introduction

The currently available antiepileptic drugs are effective in reducing the severity and number of seizures in less than 80% of patients [3]. Moreover, their usage is associated with undesirable side-effects from cosmetic (gingival hyperplasia) to life threatening (e.g., hepatotoxicity, megaloblastic anemia) [30]. For these reasons, constant attempts are made to investigate new agents and mechanisms through which epilepsy can be effectively inhibited.

It is well known that numerous derivatives with anticonvulsant activity contain 5- or 6-membered nitrogen heterocycle rings, one or two carbonyl groups as well as an aromatic system [12]. Following these findings, in the course of the search of new anticonvulsants our attention has been focused on a group of 3-substituted pyrrolidine-2,5-diones with different substituents at the imide nitrogen atom [9, 10]. It has been shown recently a high activity in the maximal electroshock (MES) test of great number of pyrrolidine-2,5-diones with 4-arylpiperazines connected to the imide nitrogen atom by the alkylene spacer [22, 26]. Furthermore, the previous investigations proved also an essential role of aromatic moiety at position-3 of pyrrolidine-2,5-dione ring [21, 23, 25, 27]. Therefore, taking into consideration the above findings, in the present work we have synthesized a series of 1-[(4-arylpiperazin-1-yl)-propyl]-pyrrolidine-2,5-diones with two different substituents, namely methyl and phenyl (**4**–**11**) or only alkyl – ethyl and methyl groups (**12**–**19**) at the position-3 of pyrrolidine-2,5-dione. All the compounds obtained were tested for their anticonvulsant activity within the Antiepileptic Drug Development (ADD) Program in Epilepsy Branch, Neurological Disorders Program, National Institute of the Neurological and Communicative Disorders and Stroke (NIH/NINDS), Rockville, MD, USA.

The compounds synthesized may be regarded as long-chain arylpiperazines (LCAPs), that is molecules exhibiting a variety of pharmacological effects *via* interactions with several receptor types, however, the best known as ligands of different serotonin (5-HT) receptor subtypes. It is worthy of note that serotonin (5-hydroxytryptamine, 5-HT) is a major neurotransmitter involved in a large number of processes in central nervous system (CNS), including the regulation of feeding behavior, aggression, mood, perception, pain, anxiety and brain excitability. Furthermore, the wide distribution of the 5-HT receptors, both in the CNS and in the peripheral tissues, is highly associated with their implications in psychiatric and neurological disorders such as depression, anxiety and epilepsy [1, 15]. It is well known that serotonin exerts its effects *via* at least 14 different receptors subtypes, but the role of only a few of them, namely 5-HT_{1A}, 5-HT_{2C} and 5-HT_7 has been studied in relation to the control of seizures. This was the subject of several investigations and the obtained results are diversified (positive or negative role), depending on both the ligand type and the seizure model [19, 29]. Taking this into consideration, in the current studies the affinities for 5-HT_{1A} and 5-HT_7 receptor subtypes have been assessed.

Materials and Methods

Chemical syntheses

The synthesis of compounds **4**–**19** is shown in Figure 1. All the chemicals and solvents were purchased from Sigma-Aldrich. Melting points (m.p.) were determined on Büchi 353 melting point apparatus (Büchi Labortechnik, Flawil, Switzerland) and are uncorrected. The chemical structures of the obtained compounds were confirmed by elemental and spectral analyses. The ^{1}H NMR spectra were obtained using a Varian Mercury spectrometer (Varian Inc., Palo Alto, CA, USA), operating at 300 MHz. The chemical shifts were reported as parts per million (δ, ppm) with $(CH_3)_4Si$ (TMS) as an internal standard. Signal multiplicities are represented by: s (singlet), brs (broad singlet), d (doublet), t (triplet), m (multiplet).

The purity of the compounds was checked by thin-layer chromatography (TLC) performed on Merck silica gel GF_{254} aluminum sheets, using the developing system S_1 consisted of chloroform : isopropanol : 25% ammonia (9:11:2, v/v/v). Spots were detected by their absorption under UV light. Elemental analyses for C, H, and N were carried out by a micro method using the elemental Vario EI III Elemental analyzer (Hanau, Germany). The elemental analyses for C, H, N were within ± 0.4% of the theoretical values.

The starting 2-methyl-2-phenylsuccinic acid (**1**), was obtained by the method described previously [11]. The appropriately substituted 1-(3-aminopropyl)-4-arylpiperazines were synthesized based on the described method [7].