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Research paper

Design, synthesis and biological activity of new amides derived from 3-methyl-3-phenyl-2,5-dioxo-pyrrolidin-1-yl-acetic acid

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ABSTRACT

A series of new 3-methyl-3-phenyl-2,5-dioxo-pyrrolidin-1-yl-acetamides (**6**–**23**) has been synthesized and evaluated for their anticonvulsant activity in the maximal electroshock (MES) and subcutaneous pentylenetetrazole (*sc*PTZ) seizure tests after intraperitoneal injection in mice. The acute neurological toxicity was determined using the rotarod test. The *in vivo* preliminary pharmacological results showed that in the whole series only two compounds (**15**, **21**) were devoid of activity, whereas other molecules revealed protection in at least one animal model of epilepsy (MES or/and *sc*PTZ). The *in vivo* quantitative studies in mice showed that in the MES test the most active were 1-{2-[4-(2-methoxyphenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-methyl-3-phenyl-pyrrolidine-2,5-dione (**17**), 1-{2-[4-(4-fluorophenyl)-piperazin-1-yl]-2-oxo-ethyl}-3-methyl-3-phenyl-pyrrolidine-2,5-dione (**8**), and its 2-fluorophenyl analog (**7**) with ED_{50} values of 97.51 mg/kg (**17**), 104.11 mg/kg (**8**), and 114.68 mg/kg (**7**), respectively. In the *sc*PTZ screen the most potent were compound **6** with an $ED_{50} = 40.87$ mg/kg, and 4-benzylpiperidine derivative **22** – $ED_{50} = 60.00$ mg/kg. Furthermore, selected compounds **8**, **14**, **17**, and **23** were tested in the psychomotor seizure 6-Hz test. Compounds **7**, **8**, and **17** revealed significant analgesic activity in the formalin model of tonic pain in mice, without impairment of the motor coordination in the chimney test. The *in vitro* binding studies showed that the mechanism of anticonvulsant activity may be partially related with the influence on the voltage-gated sodium and calcium channels. The mutagenic and antimutagenic effects of **13**, **17**, and **22** were evaluated using the novel *Vibrio harveyi* assay.

1. Introduction

Epilepsy is a chronic medical disorder or condition, usually resulting in unpredictable, unprovoked recurrent seizures that affect a variety of mental and physical functions. Treatment of epilepsy often imposes an exposure to various antiepileptic drugs (AEDs) and requires long term commitment and compliance from the patient. The vast majority of patients are maintained through chronic medical management for appropriate seizure control. Despite the advent of new AEDs over the past 25 years, approximately 30% of epileptics experience recurrent seizures as well as many undesirable side effects most notably related to CNS exposure like diminished attention, executive function, intelligence, language skills, memory and processing speed [1–3]. Therefore, there remains a substantial need for the development of more efficacious AEDs especially for patients with refractory seizures.

Numerous compounds are synthesized and screened for their anticonvulsant activities each year. To make the discovery of new anticonvulsants more rational, several investigators identified chemical fragments which presence in the structure may enhance anticonvulsant properties. One of the structural features that play a significant role in relation to antiepileptic activity is an amide function. This moiety may be the part of heterocyclic ring e.g. ethosuximide, phenytoin or may appear as linear as amide bond e.g. levetiracetam, and its analogs brivaracetam or seletracetam [4–6] (Fig. 1).

The previous research from our laboratory have demonstrated diversified anticonvulsant activity of differently substituted pyrrolidine-2,5-diones [7–15]. Among these compounds the most promising were *N*-Mannich bases derived from 3,3-disubstituted-

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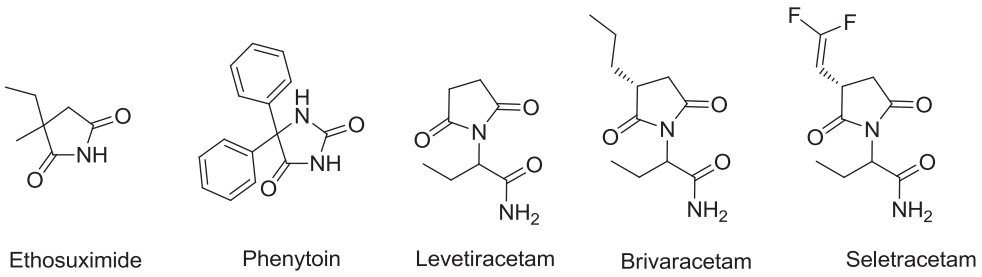


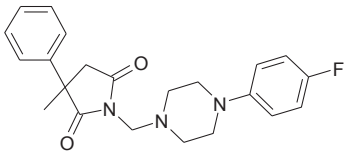
Fig. 1. Structures of known AEDs containing five-member heterocyclic ring and amide function.

pyrrolidine-2,5-diones with 4-phenylpiperazine as a basic fragment. The structure–anticonvulsant activity relationship studies (SAR) revealed that their efficiency was highly dependent on the substitution mode of the phenylpiperazine moiety thus the most favorable was the presence of electron-withdrawing chlorine, fluorine atoms or trifluoromethyl group [15]. These molecules were especially effective in the maximal electroshock seizure test (MES). Among aforementioned derivatives the most active were compounds **1**–**3** depicted in Fig. 2.

The subsequent SAR discussion revealed high anticonvulsant protection for analogs of *N*-Mannich bases containing in their structures an alkylamide moiety between the pyrrolidine-2,5-dione ring and the amine function [13,14]. Following these findings, in aim to search for new effective anticonvulsants as well as to continue systematic SAR studies among these series of derivatives, in the current work we have synthesized a new series of 3-methyl-3-phenyl-2,5-dioxo-pyrrolidine-1-yl-acetamides (**6**–**23**). These compounds have been designed as analogs of model compounds **1**–**3** in which methylene spacer has been replaced for acetamide moiety. The proposed structural modification enables to assess the influence of the presence of aforementioned amide function on anticonvulsant properties in this group of derivatives. With the aim of ensuring the reliable SAR discussion as an amine function variously substituted piperazines, benzylpiperidine or morpholine have been introduced.

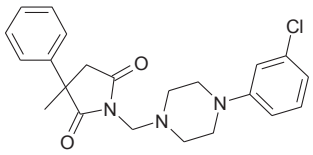
Pharmacological and clinical studies on epilepsy and neuropathic pain have documented, that both of them are chronic neurological disorders arising from an excessive neuronal activity and hypersynchronous neuronal firing [16,17]. Thus, nowadays antiepileptic drugs such as valproic acid, carbamazepine, gabapentin, pregabalin or lamotrigine are the first-line treatment of neuropathic pain. In view of the above facts, many candidates on new AEDs are often evaluated for their effectiveness in the neuropathic pain models [18]. Bearing in mind the aforementioned facts, several compounds with the most potent activity in the maximal electroshock seizures (MES) were subsequently tested for their antinociceptive activity in the formalin model of tonic pain in mice.

Taking into consideration that mutagenic activity is one of the most important endpoints for risk assessment of chemical compounds including drugs and drug candidates [19,20], the *Vibrio harveyi* assay was used to evaluate the mutagenic properties of selected 3-methyl-3-phenyl-2,5-dioxo-pyrrolidin-1-yl-acetamides. In addition, the antimutagenic potential of these compounds was also tested, in order to identify agents that can protect the genetic material against damage.



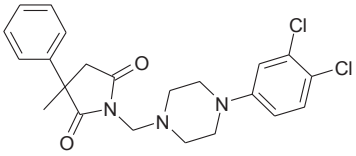
1

ED_{50} = 120.15 mg/kg (MES, mice *i.p.)*
TD_{50} > 500 mg/kg (MES, mice *i.p.*)
PI (TD_{50}/ED_{50}) > 4.16



2

ED_{50} = 41.10 mg/kg (MES, mice *i.p.*)
TD_{50} = 496.38 mg/kg (MES, mice *i.p.*)
PI (TD_{50}/ED_{50}) = 12.08



3

ED_{50} = 37.27 mg/kg (MES, mice *i.p.*)
TD_{50} > 500 mg/kg (MES, mice *i.p.*)
PI (TD_{50}/ED_{50}) > 13.41

Fig. 2. Structures of model compounds **1**–**3** obtained in the previous studies.