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Synthesis, and anticonvulsant activity of new amides derived from 3-methyl- or 3-ethyl-3-methyl-2,5-dioxo-pyrrolidin-1-yl-acetic acids

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ABSTRACT

This paper describes the synthesis of the library of 22 new 3-methyl- and 3-ethyl-3-methyl-2,5-dioxo-pyrrolidin-1-yl-acetamides as potential anticonvulsant agents. The maximal electroshock (MES) and the subcutaneous pentylenetetrazole (*sc*PTZ) seizure models were used for screening all the compounds. The 6 Hz model of pharmacoresistant limbic seizures was applied for studying selected derivatives. Six amides were chosen for pharmacological characterization of their antinociceptive activity in the formalin model of tonic pain as well as local anesthetic activity was assessed in mice. The pharmacological data indicate on the broad spectra of activity across the preclinical seizure models. Compounds **10** (ED_{50} = 32.08 mg/kg, MES test) and **9** (ED_{50} = 40.34 mg/kg, *sc*PTZ test) demonstrated the highest potency. These compounds displayed considerably better safety profiles than clinically relevant antiepileptic drugs phenytoin, ethosuximide, or valproic acid. Several molecules showed antinociceptive and local anesthetic properties. The in vitro radioligand binding studies demonstrated that the influence on the sodium and calcium channels may be one of the essential mechanisms of action.

1. Introduction

The past decades have demonstrated many attempts to identify the structural features of compounds crucial for anticonvulsant activity. It is well documented that important core fragment of anticonvulsants is defined by nitrogen heteroatomic system, usually an imide, with at least one carbonyl group and phenyl or alkyl groups attached to the heterocyclic system.[1–3] This common template is present in the structures of old-generation, however, well-established antiepileptic drugs (AEDs) such as ethosuximide and phenytoin as well as levetiracetam, brivaracetam, or seletracetam, e.g., among the newest drugs (Fig. 1). In the previous studies, we have found the pyrrolidine-2,5-diones differently substituted at position-1 and -3 as targets for new AEDs. Many of these compounds were effective in the MES and *sc*PTZ tests that are still recognized as the 'gold standard' in the early stages of testing new drug candidates.[4–8]

Recent studies on the structure–activity relationship (SAR) demonstrated the potent anticonvulsant activity of the *N*-(4-arylpiperazin-1-yl)-methyl-3,3-disubstituted-pyrrolidine-2,5-dio-nes among which the most active were 1-[{4-(3-chlorophenyl)-piperazin-1-yl}methyl]-3-methyl-3-phenyl-pyrrolidine-2,5-dione (**I**) and its 3,4-dichloro analog (**II**), showing protection exclusively in the MES test.[9] Further SAR analysis revealed that exchange of the methylene linker between imide and amine function into acetamide moiety yielded compounds active in both MES and PTZ seizure models or predominantly in the PTZ test—compound **III** (Fig. 2).[10]

Considering the aforementioned results, as part of our efforts to design new anticonvulsant agents, in the present study, we have synthesized a new series of analogs in which we introduced one methyl or ethyl and methyl substituents at position-3 of imide ring. The proposed structural modifications enable to assess the influence of alkyl groups on anticonvulsant properties in this series of derivatives. With the aim of ensuring the reliable SAR discussion as an amine function, variously substituted 4-arylpiperazines have been introduced.

Note that several AEDs such as pregabalin, gabapentin, phenytoin, lacosamide, and topiramate are clinically effective for the treatment of certain kinds of pain (neuropathic pain, migraine prophylaxis).[11] Using different models of pain, studies performed by various groups found that AEDs can inhibit sensitized signaling associated with allodynia and hyperalgesia.[12–14] Moreover, local anesthetics, which act by blocking nerve conduction by altering the function of voltage-gated sodium channels, are used as

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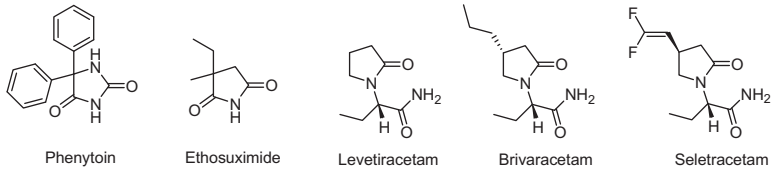


Figure 1. Structures of ADEs with five-member heterocyclic ring.

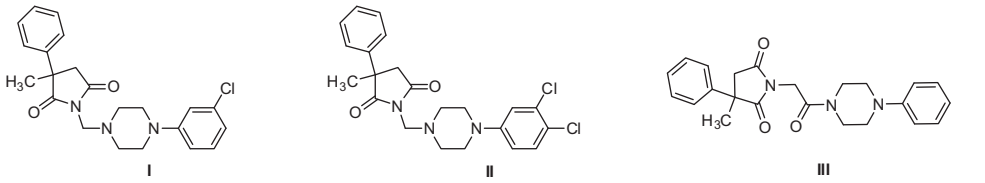


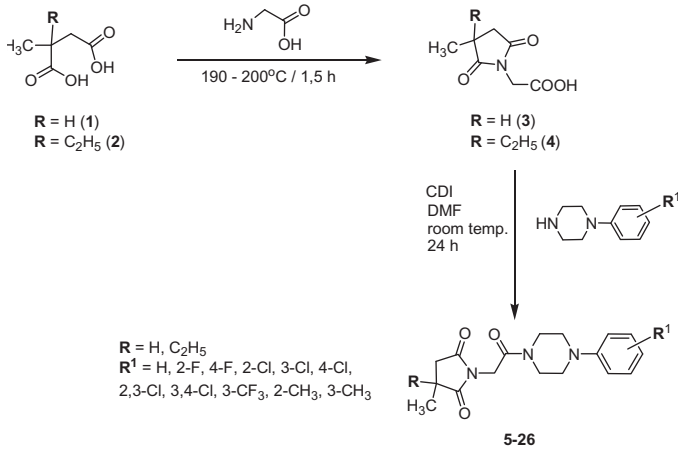
Figure 2. Anticonvulsants obtained in the previous studies.

adjuvant analgesics for the treatment of neuropathic pain.[15] Therefore, selected compounds were examined toward their antinociceptive as well as local anesthetic activity.

2. Results and discussion

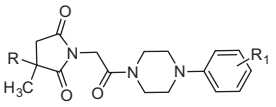
2.1. Chemistry

The final compounds **5**–**26** were synthesized according to Scheme 1. The starting material 3-methylsuccinic acid (**1**) was commercially purchased from Merck (Darmstadt, Germany) whereas 3-ethyl-3-methyl-succinic acid (**2**) was prepared as previously reported.[16] In the next step, the condensation reaction of **1** or **2** with aminoacetic acid yielded in 3-methyl- or 3-ethyl-3-methyl-2,5-dioxo-pyrrolidin-1-yl-acetic acids (**3**, **4**). These intermediates were converted to final compounds **5**–**26** in the coupling reaction with equimolar amounts of appropriate 4-phenylpiperazines in the presence of carbonyldiimidazole (CDI). The reaction was carried out at room temperature in dry DMF for 24 h. The crude products were crystalized from 2-propanol. Their purity and homogeneity were assessed by TLC and gradient HPLC chromatography. The structures of compounds synthesized were confirmed by both spectral (^{1}H NMR, LC–MS) and elemental analyses. The detailed physical and analytical data are listed in the experimental section.



Scheme 1. Synthetic protocol of the target compounds **5**–**26**.

Table 1
Anticonvulsant activity MES, *sc*PTZ, and rotarod test in mice ip



Compd	R	R^1	MES[a]		*Sc*PTZ[b]		NT[c]	
			0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
5	H	H	300	–	300	300	300	–
6	H	2-F	300	300	–	–	300	–
7	H	4-F	300	100	–	–	–	–
8	H	2-Cl	300	–	300	–	300	–
9	H	3-Cl	100	300	100	–	–	–
10	H	4-Cl	100	30	–	–	–	300
11	H	2,3-Cl	–	–	100	100	–	–
12	H	3,4-Cl	300	100	100	100	–	–
13	H	3-CF_3	100	100	300	–	300	300
14	H	2-CH_3	300	–	100	–	300	–
15	H	3-CH_3	300	–	100	–	300	–
16	C_2H_5	H	–	–	–	–	–	–
17	C_2H_5	2-F	–	–	–	–	–	–
18	C_2H_5	4-F	100	–	100	–	300	–
19	C_2H_5	2-Cl	100	–	–	–	300	–
20	C_2H_5	3-Cl	–	–	–	–	–	–
21	C_2H_5	4-Cl	–	–	100	–	300	–
22	C_2H_5	2,3-Cl	–	–	–	–	–	–
23	C_2H_5	3,4-Cl	–	–	–	–	–	–
24	C_2H_5	3-CF_3	100	100	–	–	300	–
25	C_2H_5	2-CH_3	100	–	100	–	300	–
26	C_2H_5	3-CH_3	–	–	–	–	–	–
ETX[d]	–	–	–	–	100	300	–	–
PHT[d]	–	–	30	30	–	–	100	100
VPA[d]	–	–	300	–	300	–	–	–

Doses of 100, and 300 mg/kg were administered intraperitoneally (ip). The data indicate the minimum dose whereby anticonvulsant activity was demonstrated. A dash indicates the absence of anticonvulsant activity and neurotoxicity at the maximum dose administered (300 mg/kg).

[a] Maximal electroshock test.
[b] Subcutaneous pentylenetetrazole test.
[c] Neurotoxicity screening—rotarod test.
[d] Reference drugs, data for ethosuximide (ETX), phenytoin (PHT), and valproic acid (VPA) from Ref. 20.

2.2. Anticonvulsant activity

The preclinical development of new chemical agents for the treatment of epilepsy is based on the use of predictable animal seizure models, which correspond to different types of human