Anticonvulsant properties of N-(4-methylpiperazin-1-yl)- and N-[3-(4-methylpiperazin-1-yl)-propyl] derivatives of 3-aryl- and 3-spirocycloalkyl-pyrrolidine-2,5-dione

Jolanta Obniska1, Sławomir Jurgczyk1, Alfred Zejc1, Krzysztof Kamiński1, Ewa Tatarczynska2, Katarzyna Stachowicz2

1 Department of Pharmaceutical Chemistry, Collegium Medicum of the Jagiellonian University, Medyczna 9, PL 30-688 Kraków, Poland
2 Department of New Drugs Research, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

Correspondence: Jolanta Obniska

Abstract:
Two series of N-(4-methylpiperazin-1-yl)- and N-[3-(4-methylpiperazin-1-yl)-propyl]-3-aryl- (3–10) and 3-spirocycloalkyl-pyrrolidine-2,5-dione (11–14) derivatives were synthesized and tested for anticonvulsant activity in the maximum electroshock (MES) seizure and pentetrazole (sc PTZ) seizure threshold tests. Compounds 3–10 with an aromatic ring at position-3 of pyrrolidine-2,5-dione exhibited anticonvulsant activity in the MES test. For that series of compounds, ED50 values were determined. The most potent in the series were derivatives 5, 6 and 9, 10 with a chlorine atom at position-3 or 4 of the aromatic ring. Those compounds exhibited strong anticonvulsant activity, and their ED50 values ranged from 29 to 48 mg/kg. Introduction of the spirocycloalkyl ring into the position-3 of pyrrolidine-2,5-dione (11–14) made those compounds inactive.

Key words:
anticonvulsant activity, 4-methylpiperazine derivatives, 3-arylpyrrolidine-2,5-diones, 3-spirocycloalkylpyrrolidine-2,5-diones

Introduction

Epilepsy is one of the most frequent neurological disorders characterized by spontaneous recurrent seizures arising from excessive electrical activity in a portion of the brain. Clinically available antiepileptic drugs exert satisfactory control in 60%–70% of patients, however, many of these drugs also produce undesirable side-effects, such as drowsiness, mental dullness, ataxia, hepatotoxicity, megaloblastic anemia. Therefore, there is a growing demand for new antiepileptic drugs with novel therapeutic targets, enhanced efficacy and minimal side-effects [2].

At present, the majority of currently available antiseizure drugs fall into one of the four pharmacological classes which can be characterized as follow: (i) the use-dependent blockade of voltage-sensitive sodium channels (e.g. phenytoin, carbamazepine, zonisamide, lamotrigine); (ii) the enhancement of the inhibitory activity of GABAergic neurotransmission (e.g. vigabatrine, tiagabine, gabapentin); (iii) the interaction