



Impact of aromatic substitution on the anticonvulsant activity of new N-(4-arylpiperazin-1-yl)-alkyl-2-azaspiro[4.5]decane-1,3-dione derivatives

Jolanta Obniska¹, Krzysztof Kamiński¹, Ewa Tatarczyńska²

¹Department of Pharmaceutical Chemistry, Medical College of Jagiellonian University, Medyczna 9, PL 30-688 Kraków, Poland

²Department of New Drugs Research, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

Correspondence: Jolanta Obniska, e-mail: mfobnisk@cyf-kr.edu.pl

Abstract:

A series of N-[(4-arylpiperazin-1-yl)-alkyl]-2-azaspiro[4.5]decane-1,3-dione derivatives were synthesized and evaluated for their anticonvulsant and neurotoxic properties. The main modifications to that series of compounds consisted in the introduction of an aromatic area to the cyclohexane ring as a flexible fragment with conformational freedom (**1a–h**), or as a rigidified skeleton (**2a–h**). Except for N-[3-(4-phenylpiperazin-1-yl)-propyl]-8-phenyl-2-aza-spiro[4.5]decane-1,3-dione derivative (**1e**), all the other compounds displayed anticonvulsant activity in the MES test, but some of them (**1c**, **2f** and **2g**) were found to be neurotoxic at a dose of 30 mg/kg, irrespective of their activity. The most potent and relatively weakly neurotoxic analogues of that series, i.e. N-[2-{4-(3-chlorophenyl)-piperazin-1-yl}-ethyl]-[7,8-f]benzo-2-aza-spiro[4.5]decane-1,3-dione (**2c**) and N-[3-{4-(3-trifluoromethylphenyl)-piperazin-1-yl}-propyl]-[7,8-f] benzo-2-aza-spiro[4.5]decane-1,3-dione (**2h**) had ED₅₀ values of 205 mg/kg (**2c**) and 23 mg/kg (**2h**) respectively, in the MES-test in mice, and showed higher protection than magnesium valproate (ED₅₀ = 211 mg/kg), used as a standard substance.

Key words:

anticonvulsant activity, 2-azaspiro[4.5]decane-1,3-diones, pyrrolidine-2,5-diones, spirosuccinimides
