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

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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