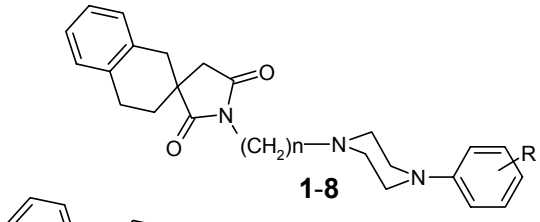
SYNTHESIS, ANTICONVULSANT ACTIVITY AND X-RAY ANALYSIS OF NEW N-(4-ARYLPIPERAZIN-1-YL)-ALKYL-3-SPIROSUCCINIMIDE DERIVATIVES

Jolanta Obniska[a], Krzysztof Kamiński[a], Ewa Tatarczyńska[b] Agnieszka Dzierżawska-Majewska[c], Janina Karolak-Wojciechowska[c]
mfobnisk@cyf-kr.edu.pl

[a] Department of Pharmaceutical Chemistry, Medical College of Jagiellonian University,Medyczna 9, 30-688 Kraków, Poland;
[b] Department of New Drugs Research, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, 31-343 Kraków, Poland;
[c] Institute of General and Ecological Chemistry, Technical University, Żwirki 36, 90-924 Łódź, Poland

In the course of our earlier research on anticonvulsant activities of 1,3-substituted pyrrolidine-2,5-diones it has been found that introduction of the 4-substituted piperazine at the imide nitrogen atom caused considerable growth of the anti-seizure activity [1, 2]. The second factor essential for the activity is an aromatic ring at a 3-position of pyrrolidine-2,5-dione. On the other hand, it was proved that many of spirosuccinimides exhibited anticonvulsant activity [3]. Based on these findings, in effort to obtained compounds with enhanced anticonvulsant activity the following modifications in the 3-position of pyrrolidine-2,5-dione ring have been performed:

- introduction of aromatic area as a distal fragment with the conformational freedom,
- introduction of rigid tetrahydronaftalene skeleton.



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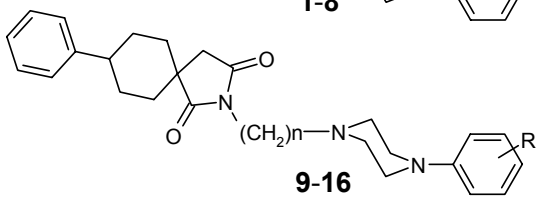

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n=2, 3
R = H, 2-OCH_3, 3-Cl, 3-CF_3

The preliminary anticonvulsant assay for all the compounds were provided by the Antiepileptic Drug Development (ADD) program using the testing procedures described elsewhere [4]. The ED_{50}=26mg/kg for N-[{4-(3-trifluoromethylphenyl)-piperazin -1-yl}-propyl]-3-spiro-β-tetralone-pyrrolidine-2,5-dione was recorded. For all derivatives we determined the lipophilicity by use of the RP-TLC method. For selected compounds the structural characterization by crystal X-ray analysis has been done.

References:

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[3] K. R. Scott, I. O Edafiogho J. A. Moore, V. A. Farrar, J. M. Nicolson: J. Med. Chem 34, 387-392, (1991)
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