SYNTHESIS, IN VITRO ACTIVITY AND CYTOTOXIC EVALUATION OF NOVEL IMIDAZOLIDINE-2,4-DIONE DERIVATIVES WITH BIPHENYLPIPERAZINYLALKYL MOIETY

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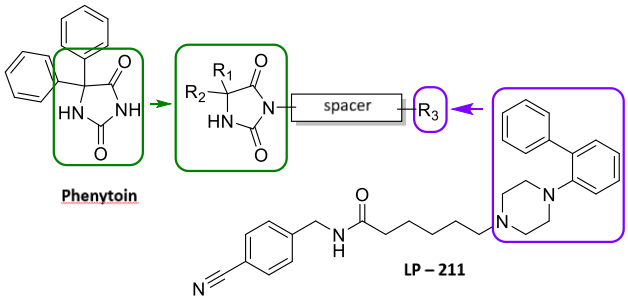
Neuropathic pain is caused by damage of the somatosensory part of the nervous system leading to hyperexcitability of neurons. In the treatment of neuropathic pain, classic analgesics are ineffective, therefore drugs from other therapeutic groups are used in the treatment, among them: tricyclic antidepressants (non-selective noradreanaline and serotonin reuptake inhibitors), selective norepinephrine and serotonin reuptake inhibitors, antiepileptic drugs (blockers of calcium and / or sodium channels). Currently available therapies provide pain relief in approximately 30% of patients. This low effectiveness of the therapy may result from the complex and still not fully understood mechanisms of the origin and development of neuropathic pain. In the case of multifactorial diseases such as neuropathic pain, designing of potential drugs that act simultaneously at several therapeutic targets seems to be a promising approach. Compounds designed in this way, combining various mechanisms of action, may contribute to increasing the effectiveness and safety of the therapy.[2]

Taking into account the complex etiology and variety of mechanisms involved in the development of neuropathic pain, compounds with an original dual mechanism of action were designed, which are serotonin 5-HT_7 receptors ligands (biphenyl-amine fragment of 5-HT_7 receptor agonist: LP-211) and sodium channel inhibitors (hydantoin moiety present in phenytoin).



The final compounds were obtained in a multi-stage synthesis using the Bucherer-Bergs reaction, alkylation, and then condensation with the appropriate biphenylpiperazine moiety. In the next step, the obtained compounds were subjected to receptor affinity and cytotoxicity studies. Then, for the most active of them, the in vitro pharmacological profile studies were conducted.

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