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School of Pharmacy and Pharmaceutical Sciences
Isfahan University of Medical Sciences

Design and synthesis of isoindole derivatives as new anticonvulsant agents

A. Saadabadi*, A. Davood

Department of Medicinal Chemistry, Pharmaceutical Sciences branch, Islamic Azad University

Background and Aims: Epilepsy is a common neurological condition, affecting 0.5 to 1 % of the population worldwide. Current treatments involve seizure suppression antiepileptic drugs (AEDs), however AEDs that are presently used in clinical practice show a broad range of adverse effects. Consequently, there is a great need for the continued development of new AEDs with greater efficacy for pharmacoresistant seizures and improved side effect profiles. Recently, isoindole derivatives were designed based on ameltolide and thalidomide as they possess a similar degree of anticonvulsant potency due to their phenytoin-like profile. Therefore in the present study, a series of (1H) isoindole-1, 3(2H) dione derivatives were designed and synthesized in order to inhibit voltage-gated sodium channel.

Methods: The chemical structures of (1H) isoindole-1, 3(2H) dione derivatives were constructed by using Hyperchem software (version 7). Semiempirical molecular orbital calculations (PM3) of the structure were performed and, among all energy-minimal conformers, the global minimum compounds were considered in docking calculations. Docking calculations were performed using Autodock software (version 4.2). The designed compounds were synthesized by condensation of the respective aromatic amine with phthalic anhydride and nitrophthalic anhydride in acetic acid at reflux temperature. The product of this reaction was precipitated by addition of water, filtered, dried, and recrystallized from appropriate solvent to give the desired isoindole derivatives.

Results: 9 derivatives of N-aryl isoindole and 4-nitrophthalimide analogs were synthesized in good yields (40-60%). All of compounds were characterized by TLC, followed by IR and proton NMR. Our docking studies have revealed all of isoindole derivatives, were interacted mainly with the domain I and II in the Na channel's inner pore.

Conclusions: All of synthesized compounds were interacted with voltage-gated Na channel. Based on our previous in vivo screening studies this pharmacophore has the ability to protect against pentylenetetrazole-induced seizure.

Keywords: Anticonvulsant; Isoindole; Na channel; Phenytoin