Research in Pharmaceutical Sciences, 2012;7(5)
School of Pharmacy and Pharmaceutical Sciences
Isfahan University of Medical Sciences

Synthesis and docking studies of new 4-oxo-1,3-thiazolidine derivatives as potential anticonvulsant agents

M. Ghadimi[1,*], A. Almasirad[1], H. Azizian[1], S. Mirahmadi[1], A. Shafiee[2]

[1]Department of Medicinal Chemistry,Pharmaceutical Sciences Branch, Islamic Azad University,Tehran, Iran
[2]Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences,Tehran University of Medical Sciences,Tehran, Iran

Background and Aims: Prompted by reports on potent anticonvulsant activity of phenoxy phenyl derivatives and thiazolidinone ring, a series of 15 new hybrid molecules with both of these nucleus having 2-(2-flurophenoxy)-4-chloro-N-(4-oxo-2-(aryl) thiazolidin-3-yl) benzamide structures were synthesized and their binding properties with epilepsy molecular targets; GABA-aminotransferase (GABA AT), NMDA receptor, AMPA receptor and sodium channel were investigated in order to compare the binding energy of these compounds with the standard reference inhibitors of related targets and propose the most favorable target which interfere with these structures.
Methods: Title compounds were obtained by starting from 2, 4-dichlorobenzoic acid and 2-fluorophenol following by the reaction of hydrazide intermediates with various substituted aromatic aldehydes and finally with thioglycolic acid. For molecular modeling study, the crystal structure of GABA AT and NMDA and AMPA receptors were extracted from Protein Data Bank (PDB). Modeler v 9.0 and autodock 4.2 were used to construct 3D structure of sodium channel and docking investigations, respectively.
Results: The structure of synthesized compounds was confirmed by 1H-NMR, IR and Mass spectra. The docking studies showed all compounds exhibited good binding properties with all molecular targets rather than the reference standard compounds. The result is more significant with GABA AT. Also docking energy of compounds was compared in order to identify nonbonded and electrostatic interactions with the targets that corresponded to the differences in compounds affinity, eg; electron withrawing substitution on aryl has lower electrostatic energy.
Conclusions: Computational studies were carried on 2-(2-flurophenoxy)-4-chloro-N-(4-oxo-2-(aryl) thiazolidin -3-yl) benzamide structures which exhibited good binding properties on epilepsy molecular targets in the Lamarckian genetic algorithm based on flexible docking studies. GABA AT was proposed as more probable mechanism of these derivatives. Further studies need to be carried out the precise mechanism of these molecules.

Keywords: Thiazolidinone; Anti-convulsant activity; Docking; GABA-aminotransferase