

Design, Synthesis and Evaluation of New Hetroaryl Compounds having 5HT_{1A/2A} Receptor Affinity

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Purpose:

The study was aimed to design, synthesize and evaluation of some heteroaryl compounds and screened by *In-silico* ADME study for anticonvulsant activity.

Methods:

Twenty-two derivatives were synthesized to evaluate anticonvulsant activity. The synthesis of title compounds has been realized in two steps (scheme: 1). In the first step N-3 alkylation of phenytoin was done by reacting phenytoin with 1-bromo-2-chloro-ethane (n=2) and 1-bromo-3-chloro- propane (n=3) respectively. In the second step these intermediate were converted into respective derivatives by reacting with 1-aryl-piperazine and aniline derivatives in DMF/DMSO according to the method reported by Zha et al.2004. All synthesized compounds were purified, analyzed and evaluated for anticonvulsant activity by using the maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ) screens. Their neurotoxicity was determined applying the rotarod test. *In-silico* ADME studies were also performed for preliminary screening. Ligands were built using Maestro 8.5 build panel and prepared by LigPrep 2.2 version v22208 (Schrödinger, LLC., USA) application that uses OPLS 2005 force field. The QikProp program was used to obtain the ADME properties of the analogues. The best-fit ligands were neutralized before being used by QikProp.

Results:

Structure of all the synthesized compounds were confirmed by spectral analysis: IR, ¹H and ¹³C NMR, Mass spectroscopy. Reactions were optimized with different solvents and bases that yielded a compound good to moderate. *In-silico* ADME studies were also performed for preliminary screening. This also shows good to moderate results. Preliminary screening results indicated that the title compounds have pronounced anti-MES activity. A series of new hetroaryl derivatives of 5,5-diphenylhydantoin showed Anticonvulsant activity. According to the rotarod test none of the compounds showed neurotoxicity at the applied dose. 1-aryl piperazine derivatives were found to have more active then aniline derivatives.

Conclusion:

Hetroaryl derivatives were successfully synthesized with good yield and screened compound showed anticonvulsant activity against phenytoin. The obtained results suggested that to conduct the binding assay for 5-HT_{1A/2A} receptor affinity in future.