Ashish A. Gawai et al., Drug Des 2017, 6:5 (Suppl)
DOI: 10.4172/2169-0138-C1-020

Homology modeling, docking, synthesis and pharmacological evaluation of new chromen-2-one derivatives with atypical antipsychotic activity

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Statement of the Problem: Schizophrenia is a chronic mental illness commonly with hallucinations, delusions, disorganized speech and disorganized thinking. Schizophrenia is a complex disorder whose etiology and pathogenesis is not completely understood. Schizophrenia is associated with the increased activity of dopaminergic and serotoninergic receptor sites. The purpose of this work is to discover new derivatives by homology modeling, design, synthesis and preliminary pharmacological studies of synthesized compounds with minimum side effects and better pharmacological action. Methodology & Theoretical Orientation: A Homology modeling and simulation was carried out by using Modellar 9v8 software followed by template identification and its alignment with target structure. The analysis of protein receptor structures for Dopamine (D_2) and Serotonin ($5HT_{2A}$) receptors and validation was performed on Exome Horizon 1.3 software. Docking studies were performed on same software and some selected active chromen-2-one derivatives were synthesized (B4a-B4k). Preliminary pharmacological screening such as Apomorphine induced climbing behavior i.e predictive of Dopaminergic (D2) antagonistic activity and 5HTP induced head twitches i.e predictive of serotonergic (5-HT) antagonistic activity were performed. Support of docking and preliminary pharmacological results gives lead for identification of final active molecules. Conclusion & Significance: All the synthesized compounds possessed dopaminergic antagonist and also possessed significant antagonistic activity at serotonin (5-HT) receptor (5HTP induced head twitches) which is an index of hypothesized atypical antipsychotic profile. The compounds which were substituted with Chloro ortho and Meta position showed significant dopamine D2 receptor antagonistic activity & the compounds which were substituted with Chloro at ortho position and Chloro and Fluoro at Meta position showed significant 5HT receptor antagonistic activity. From this data, we can conclude that compound (B4e) has better atypical antipsychotic profile.

Recent Publications

1.Sandhya K (2011) Interaction of novel hybrid compounds with the D3 dopamine receptor: site-directed mutagenesis and homology modeling studies. Biochem Pharmcol 81:157-163.

2.Morris G (1998) Automated Docking Using a Lamarckian Genetic Algorithm and Empirical Binding Free Energy Function. J Comput Chem 19:1639-1662.

3.Hrib NJ (1994) Benzisoxazole and Benzisothiazole-3- carboxamides as potential atypical antipsychotic agents. J Med Chem 37: 2308-2314.

4.Davis AS (1986) A comparison of motor behaviours in groups of rats distinguished by their climbing response to apomorphine. Br J Pharmacol 87:1:129-137

5.Chung WJ (2002) Behavioural pharmacology of polygalasaponins indicates potential antipsychotic efficacy. Pharmacol Biochem Behav 71:191-195.

Biography

Dr. Ashish Ashok Gawai has experienced in drug design, multi-step synthesis and Analysis, also have a passion to resolve complicated problem in synthesis and habitual to computer based software for molecular modeling or docking studies. His research work was based on Homology modeling of Dopamine (D2) and Serotonin (5HT) receptors, a complicated receptor site that will creates new pathways for docking and pharmacological studies. This work is complete research work for design of new molecules/compounds in search of promising molecule for Atypical antipsychotic agents. This work is based on Receptor creation, validation, energy minimization, selection of specific active moieties for synthesis, preliminary pharmacological screening and finding of promising compounds with lesser side effect and maximum pharmacological activity.

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