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Computer-Aided Design and Synthesis of N-Aryl and Heteroarylpiperazine Derivatives as Dual Serotonergic Antagonists for Autism Treatment

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Background and Objective

Autism Spectrum Disorders (ASD) are characterized by abnormalities in social interaction and communication skills, in addition to stereotypic behaviors and restricted activities and interests. Autism prevalence has dramatically increased from 1 case per 5000 children in the early 1980's to1 case per 68 children as of 2015. A recent pilot study on the demographic distribution of children with autism in Qatar showed a preliminary ratio of 1 child with autism per 500 school children. Currently, It is widely accepted that abnormalities in serotonin (5-HT) neurotransmission is one of the most important reasons for ASD. Consequently, Selective Serotonin Reuptake Inhibitors (SSRIs) have been utilized to target various symptoms of the disorders by their ability to increase 5-HT in synaptic clefts. Unfortunately, it was observed that there is a delay in the therapeutic effect of about 4–6 weeks that may be attributed to the time needed for 5-HT autoreceptor (5-HT1B/1D) desensitization. This delay adversely affects child compliance. Accordingly co-administration of SSRIs with 5-HT1B/1D antagonists would increase serotonin levels in the brain. It was then proposed that a "hybrid" drug that can act on both receptors would have the advantage of low cost and better compliance. In the presented study, we report the design of a dual pharmacophore model for binding with serotonin transporter and 5-HT1B/1D receptors, followed by the microwave-assisted synthesis of structurally diverse N-aryl and heteroarylpiperazines as dual antagonists at reuptake transporter and 5-HT autoreceptors.

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Method

Molecular Modeling

All compounds with IC50 value < 10 nm against serotonin transporter were retrieved from ChEMBLdb database (Version 20, 1,463,270 molecules) and filtered using Lipinski's rule of five, which led to 367 inhibitors. The retrieved compounds were then clustered into 15 cohorts using FCFP_6 fingerprints implemented in Accelrys Discovery Studio software. The most active compound of each cohort was picked and used to build the pharmacophore model using Common Feature Pharmacophore Generation module of Discovery Studio. The pharmacophore hypotheses were evaluated, ranked and validated using a set of mixed actives and decoys.

Chemistry and Biology

The first reaction of the scheme was a modified Buchwald-Hartwig amination, in which different aryl and heteroaryl bromo-derivatives were coupled with 1-Boc-piperazine utilizing microwave energy. Deprotection was then performed to remove the Boc group from the synthesized compounds and liberate the free amine that was coupled with the activated acid that mimics the SSRI Fluoxetine. The Synthesized compounds obey Lipinski rule of five and pharmacophoric features were mapped using molecular modeling studies.

Results

The proposed compounds were successfully synthesized and purified using flash chromatography. The chemical structures were confirmed with mass spectrometry and NMR. The binding affinity was then tested at 5-HT1B/1D receptors and 5-HT reuptake transporter. Some of the compounds showed promising activity and further in-vivo assay will be performed.

Conclusion

A molecular modeling study was successfully performed to generate a hypothetical pharmacophore model. A microwave-assisted synthetic scheme was accomplished and all final compounds were purified. Chemical structures were confirmed using different spectroscopic techniques. Biological in-vitro testing was conducted and all relevant data will be presented.