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Opinion Article

Evaluation of Inhibitors for Nor Epinephrine and Atomoxetine

Maria Connor*

Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

DESCRIPTION

The treatment of psychiatric disorders and neurological conditions frequently targets the monoaminergic systems, particularly the transporters for neurotransmitters like norepinephrine, dopamine and serotonin. This study builds on a research that utilized Computer-Aided Drug Design (CADD) to identify potential inhibitors of the Nor Epinephrine Transporter (NET) as novel antipsychotic agents. The lead compound chosen for further design in this study was compound 2, which was selected based on key descriptors identified in Quantitative Structure-Activity Relationship (QSAR) models and molecular docking simulations.

In this study, ten new hypothetical inhibitors were designed by modifying compound 2 and their pharmacological properties were compared to atomoxetine, a widely approved drug used to treat Attention-Deficit Hyperactivity Disorder (ADHD) and other psychiatric conditions. The design strategy involved incorporating various electrophilic substituents onto the aromatic ring of compound 2, based on the findings from the previous QSAR model and docking analysis. Molecular docking simulations showed that these newly designed inhibitors had improved binding affinities with the NET receptor, ranging from -7.2 kcal/mol to -7.6 kcal/mol. For comparison, the lead compound 2 had a binding affinity of -7.1 kcal/mol, while atomoxetine showed a binding affinity of -6.5 kcal/mol. The higher binding affinities observed for the new inhibitors suggest stronger molecular interactions with the biological target, which is critical for their potential therapeutic efficacy.

In addition to improved binding affinities, the molecular docking analysis revealed that all the newly designed inhibitors formed multiple hydrogen bonds with key amino acid residues of the NET receptor. This finding highlighted the enhanced interaction between the inhibitors and the receptor when compared to compound 2, further supporting the potential of these new inhibitors as strong candidates for the treatment of psychiatric disorders.

The design of the inhibitors was primarily based on the influence of certain molecular descriptors identified in the QSAR model. The results from these models suggested that the introduction of electron-donating substituents would increase the reactivity and binding affinity of the compound, while electron-withdrawing groups would have the opposite effect.

The modifications made to compound 2 included the incorporation of both activating and deactivating groups at different positions on the aromatic ring. The electron-donating groups helped to increase the electron density on the ring, improving its interaction with the NET receptor. The electron-withdrawing groups, in contrast, reduced the reactivity of the ring, which could influence the overall activity of the inhibitors. These structural modifications allowed for the identification of inhibitors with enhanced binding affinity and potential pharmacological efficacy.

Drug-likeness and pharmacokinetic evaluations were conducted to assess the suitability of the designed inhibitors for further development. The results indicated that all of the newly designed compounds adhered to lipinski's rule of five, which is a standard criterion used to predict the oral bioavailability of drug candidates. Additionally, the Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) properties of the compounds were evaluated, revealing that the inhibitors exhibited favorable pharmacological attributes. These results suggest that the new inhibitors have the potential to be developed into viable drug candidates with optimal bioavailability and minimal side effects.

Toxicity risk assessments of some of the selected inhibitors showed great results, with most of the compounds being non-mutagenic and not classified as carcinogenic. This suggests that these compounds are safe for further development, although additional experimental testing will be necessary to fully evaluate their toxicity profiles.

Among the newly designed inhibitors, compound 2 demonstrated the strongest binding affinity and best molecular interactions with the NET receptor. This compound incorporated two electron-donating substituents at the ortho and meta positions of the aromatic ring, which enhanced the electron density of the compound and improved its reactivity.

Correspondence to: Maria Connor, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland, E-mail: maria.connor@unibas.ch

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The strong electron-donating effect of these groups likely contributed to the improved binding affinity and stronger molecular interactions with the target receptor.

CONCLUSION

In conclusion, the results of this study demonstrate that computational drug design can effectively identify potential new inhibitors of the norepinephrine transporter with enhanced pharmacological properties. The designed inhibitors showed improved binding affinity, better drug-like properties and favorable safety profiles compared to the lead compound and the reference drug atomoxetine. These findings suggest that the newly designed inhibitors could serve as potential candidates for further experimental studies and development as novel antipsychotic agents.