www.pharmaerudition.org

ISSN: 2249-3875

International Journal of Pharmaceutical Erudition

Research for Present and Next Generation

NOV 2024

Vol: 14 Issue:03

(60-69)

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Review Article

MOLECULAR DOCKING APPROACHES TO CHYMASE INHIBITION: ROLE OF IMIDAZOLE DERIVATIVES IN HYPERTENSION THERAPY: A REVIEW

Ajit Singh*, D B Joshi

Dept of Pharmaceutical Chemistry, Shrinathji Institute of Pharmacy, Nathdwara, Rajsamand (Raj.) 313301

The rennin-angiotensin system is closely related to hypertension, a worldwide health issue, with chymase being essential for the production of angiotensin II. This review examines the therapeutic potential of chymase inhibitors by analysing previous molecular docking and computational research, with an emphasis on imidazole derivatives. The structural variety and binding effectiveness of imidazole-based drugs are highlighted in current research as promising options for the treatment of hypertension or high blood pressure. Understanding these interactions has been greatly aided by computational methods such as molecular docking, ADMET profiling, and QSAR research. The essay highlights information gaps, summarises current developments, and explores potential future uses of imidazole derivatives in drug discovery.

KEYWORDS: Chymase inhibitors, Imidazole derivatives, Molecular Docking, Computational studies, ADMET profiling.

INTRODUCTION

Hypertension, commonly referred to as high blood pressure, is one of the leading risk factors for cardiovascular diseases, affecting millions globally. It is a silent condition that can cause severe damage to vital organs if left untreated. Despite advancements in antihypertensive therapies, a significant number of patients fail to achieve adequate blood pressure control, necessitating the search for novel therapeutic targets and drug molecules. Among the pathways contributing to hypertension, the renin-angiotensin system (RAS) is pivotal, and within this system,[1] chymase a serine protease has gained attention as a critical enzyme in angiotensin II formation. Unlike angiotensin-converting enzyme (ACE), chymase-mediated angiotensin II production remains active even when ACE inhibitors are administered, making it a compelling target for intervention.

Chymase is predominantly found in mast cells and plays an essential role in vascular remodeling, flammation, and fibrosis. These processes exacerbate hypertension and related complications, such as atherosclerosis and heart failure.[2] By inhibiting chymase, it is possible to suppress the production of angiotensin II and its harmful effects, offering a novel mechanism for blood pressure regulation and cardiovascular protection.

Imidazole derivatives, characterized by their nitrogen-containing heterocyclic structure, have shown immense potential as enzyme inhibitors. Their versatility allows them to form strong interactions with active sites of enzymes, making

them excellent candidates for chymase inhibition.[3] In recent years, several studies have highlighted the ability of imidazole-based molecules to inhibit chymase activity effectively, with promising results in preclinical settings. These derivatives also exhibit favorable pharmacokinetic properties, such as high bioavailability and metabolic stability, enhancing their potential as therapeutic agents.[4]

The advent of computational techniques, such as molecular docking and virtual screening, has revolutionized the drug discovery process. These methods enable researchers to predict the binding affinity of potential inhibitors to target enzymes with high precision, significantly reducing the time and cost associated with traditional drug development.[5] Molecular docking studies on imidazole derivatives have provided valuable insights into their interaction patterns with chymase, identifying key binding residues and optimizing structural features for improved efficacy.

This review aims to consolidate existing research on the molecular docking and computational studies of imidazole derivatives as chymase inhibitors. By analyzing recent advancements, this article seeks to highlight the therapeutic potential of these compounds for hypertension management and identify areas requiring further investigation. Such efforts are crucial for developing next-generation antihypertensive therapies that address current limitations and improve patient outcomes.[6]

Role of Chymase in Hypertension:

A serine protease called chymase cleaves angiotensin I at the same location as ACE. Because of its high affinity, it converts angiotensin I to angiotensin II much more quickly than ACE. Moreover, chymase is extremely resistant to ACE inhibitors, but serine protease inhibitors totally suppress it. ACE activity and expression are significantly decreased in diabetic kidneys, while ACE2 levels are increased, according to evidence from a thorough set of tests conducted utilising the leptin receptor-deficient db/db type II diabetes mice as a model. Furthermore, these researchers showed that ACE inhibition prevented the vasoconstriction caused by exogenously delivered angiotensin I (as a precursor to angiotensin II) in healthy mice but not in diabetic animals utilising the in vitro blood-perfused juxtamedullary nephron technique. In contrast, serine protease inhibition prevented angiotensin I-induced constriction in diabetic mice but not in control mice.[7] These findings thus support the idea that this type of diabetic nephropathy is caused by a mechanism that does not rely on ACEs to produce angiotensin II. An important line of research with significant therapeutic ramifications is the degree to which these findings can be extrapolated to other

diabetic models and species.[8]

Based on their structure and substrate selectivity, the complex family of enzymes known as chymases can be divided into two subgroups, α and β. Both subgroups have the ability to change angiotensin I into angiotensin II. It is noteworthy that the β-chymases, which seem to be mostly present in rodents, do not seem to be expressed in humans. This highlights the necessity of expanding these investigations to other species, especially humans. Chymase and renin generated from cardiac mast cells have been linked to cardiac ischemia-reperfusion injury, and vascular chymase has been implicated in the ACE-independent process for local angiotensin II production in human arteries.[9] As a result, it has also been noted that the human diabetic kidney has significantly elevated chymase expression, namely in mesangial cells and vascular smooth muscle cells. However, the functional implications of these alterations have not been well examined. Accordingly, it has been proposed that the angiotensin II produced by the chymase pathway is more likely to be engaged in the structural remodelling linked to cardiovascular illness than it is in the control of blood pressure and haemodynamics.[10] This idea is disproved by Park et al.'s current research, which shows that angiotensin II production that is not ACE-dependent is crucial for controlling renal haemodynamics as diabetic nephropathy advances. Accordingly, our work identifies chymase as a potentially significant therapeutic target for the management of nephropathy and hypertension associated with diabetes. In addition to endothelin-1, chymase has been extensively reported for its role in the synthesis of Ang II from Ang I. Chymase's ACE-independent Ang II production has been linked to the structural remodelling linked to cardiovascular illness, and research into the pathophysiological significance of chymase in cardiac disease has accelerated recently.[11] According to one recent study, up to 75% of Ang II generation in human cardiac tissue may be dependent on chymase rather than ACE. This shows that Ang II formation may be more dependent on chymase than ACE. Research using human heart coronary artery homogenates showed that, in contrast to the ACE inhibitor captopril, chymostatin could decrease the synthesis of Ang II. In animal models of cardiovascular disease, research has therefore concentrated on decreasing the enzyme's availability by using the MC stabiliser tranilast rather than chymase inhibition in and of itself. Unfortunately, despite tranilast's preclinical effectiveness, clinical studies were a failure.[12]

Imidazole Derivatives as Chymase Inhibitors

Among the practical areas of organic chemistry, nitrogen-based heterocyclic chemistry is a prominent and distinctive class, with a large portion of research devoted to the creation of

new compounds and composites. Over the past 20 years, there has been a growing interest in these compounds. They found several uses in the chemical sciences and helped establish a number of procedures for organic synthesis. The physiological and pharmacological features of numerous N-heterocyclic compounds, which are widely found in nature, make them components of numerous biologically significant molecules, such as vitamins, nucleic acids, medications, antibiotics, dyes, and agrochemicals, among many others. Additionally, they are a crucial component of numerous pharmacologically active compounds. Purines, pyrimidines, and other N-heterocyclic chemicals make up the base pairs of DNA and RNA, which are guanine, cytosine, adenine, and thymine.[13] These nitrogen-containing heterocyclic compounds have become well-known in the quickly developing domains of medicinal and organic chemistry as well as the pharmaceutical sector due to their unique properties and uses. Moreover, the electron-rich nitrogen heterocycle can easily form a variety of weak interactions in addition to being able to give or take a proton with ease. Certain intermolecular forces, like the formation of hydrogen bonds, dipole-dipole interactions, hydrophobic effects, van der Waals forces, and π-stacking interactions of nitrogen compounds, have made them more significant in the field of medicinal chemistry.[14] Because of their enhanced solubility, these compounds can bind with a wide range of enzymes and receptors in biological targets with high affinity. Their derivatives' structural characteristics are advantageous because of their wide range of bioactivities. Imidazole derivatives, characterized by their nitrogen-rich heterocyclic ring, have shown potential as effective enzyme inhibitors. Their structure allows strong binding to the chymase active site through hydrogen bonding and hydrophobic interactions, particularly with residues like Ser189 and Asp194 in the enzyme's catalytic triad. Computational docking studies indicate that these derivatives exhibit strong binding affinity with binding energies ranging from -8 to -10 kcal/mol, demonstrating high specificity and potency.[15]

According to recent developments in structure-activity relationship (SAR) research, trisubstituted imidazole derivatives are more effective since they can occupy more than one binding pocket. For example, alkyl or aryl substituents increase solubility and bioavailability, but halogenated derivatives improve specificity. Despite the paucity of direct experimental research on imidazole derivatives as chymase inhibitors, their potential is highly supported by their proven application as serine protease inhibitors.

Future studies should concentrate on enhancing these drugs' pharmacokinetics and selectivity while confirming their effectiveness in preclinical and clinical contexts. The development of

imidazole-based chymase inhibitors for the treatment of hypertension will proceed much more quickly with the combination of computational methods and in vivo research.[16]

Molecular Docking And Computational Approaches

Drug discovery has been transformed by molecular docking and computational methods, which allow for quick screening of possible inhibitors and reduce the need for lengthy laboratory testing. These methods offer a framework for examining how tiny compounds, such as imidazole derivatives, interact with the active site of chymase inhibitors. In addition to the binding affinity, docking simulations identify the precise molecular interactions—such as hydrogen bonds, π-π stacking, and van der Waals forces—that are in charge of activity.[17]Why Molecular Docking Matters in Chymase Inhibition. An essential part of the production of angiotensin II is the serine protease chymase. Inhibiting it presents a viable strategy for treating hypertension, particularly when the renin-angiotensin system is overactive. The nitrogen-rich structure of imidazole derivatives has made them attractive candidates because it interacts well with the catalytic triad residues of chymase (Ser189, His57, Asp194). Imidazole compounds can block the active site, restricting substrate access, according to docking studies.[18] Key findings from computational studies include: Binding Affinity: Strong and stable interactions are indicated by imidazole derivatives' binding energies, which fall between -8 and -12 kcal/mol. Analysis of Interaction: Hydrophobic substituents improve binding inside the enzyme pocket, whereas electron-rich groups on the imidazole ring create hydrogen bonds with Asp194. Optimization: By enhancing hydrophobic contacts and lowering steric hindrance, halogenated and trisubstituted imidazole derivatives show increased inhibitory efficacy.[19]

Integration Of Docking With Computational Techniques

Molecular Dynamics (MD) Simulations:

By analyzing the stability of ligand-enzyme complexes over time, MD simulations supplement docking. Imidazole-based inhibitors, for instance, have been shown to preserve important interactions with active site residues while being securely bound in dynamic settings.

Structure-Activity Relationships (SARs):

By focusing on particular enzyme pockets, SAR analysis have shown that Imidazole scaffold modifications like fluorine or methoxy groups improve specificity and efficacy.

Pharmacophore Modelling:

Common characteristics of strong inhibitors, such as hydrophobic areas and hydrogen bond acceptors/donors, are extracted by computational techniques. The logical development of innovative derivatives with

enhanced efficacy is guided by these ideas. Benefits and Prospects for the Future Molecular docking prioritize lead compounds for production and testing, which speeds up the drug discovery process. However, when paired with MD, QSAR, and in silico ADME (absorption, distribution, metabolism, and excretion) assessments, its predictive power is increased. In order to create safer and more potent antihypertensive medications, imidazole-based chymase inhibitors must combine computational predictions with experimental validation.[20]

Future Perspectives

Chymase inhibition appears to have a bright future as a treatment approach for hypertension and associated cardiovascular conditions. The discovery of novel imidazole-based derivatives as possible inhibitors has already been made possible by molecular docking and computational techniques. Nonetheless, there are still a number of chances to improve these inhibitors effectiveness and broaden their therapeutic uses.

Optimization of Imidazole Derivatives:

It is essential to further optimize imidazole derivatives using molecular dynamics simulations and docking data. This involves investigating new functional groups that can improve selectivity and potency as well as optimizing the structure-activity correlations (SARs). To increase solubility and bioavailability, researchers can also investigate non-traditional replacements on the imidazole ring. The lead drugs are more likely to be used in clinical settings when absorption, distribution, metabolism, and excretion (ADME) patterns are predicted with the aid of sophisticated pharmacokinetic models.[21]

Targeting Allosteric Sites:

Allosteric inhibition of chymase may be investigated in future research. Allosteric inhibitors alter the function of the enzyme by binding to a location different from the active site, in contrast to conventional active-site inhibitors. Allosteric inhibitors might have fewer adverse effects and greater specificity. Consequently, creating imidazole compounds that attach to these locations may lead to new therapeutic opportunities.

Combination Therapies:

Imidazole derivatives and other antihypertensive drugs may be used in combination therapy that show promise. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may work in concert with chymase inhibitors to improve overall effectiveness in treating hypertension and reducing organ damage brought on by long-term high blood pressure.

Biomarker Identification:

Finding trustworthy biomarkers for chymase activity will be crucial for tracking how well

imidazole-based treatments are working. Proteomics and genomics developments can assist in locating putative biomarkers that may direct individualized care, enabling medical professionals to customize treatments according to the unique characteristics of each patient.[22]

Artificial Intelligence and Machine Learning:

The process of finding new drugs can be sped up by machine learning (ML) and artificial intelligence (AI). The most promising compounds for chymase inhibition can be predicted with the use of AI and ML by utilizing extensive chemical databases and experimental data. The drug development process can be improved by these technologies since they can also reveal hidden patterns in data that conventional approaches might miss.[23]

Challenges

Even with these encouraging viewpoints, there are still a number of obstacles to overcome in the creation and use of imidazole-based chymase inhibitors:

Off-Target Effects:

Reducing off-target impacts is a significant task. Like many tiny compounds, imidazole derivatives have the potential to attach to unexpected sites and cause unwanted side effects. To reduce these hazards, sophisticated in silico screening techniques that anticipate off-target interactions will be crucial.[24]

Bioavailability and Drug Delivery

Numerous imidazole derivatives have issues with their low bioavailability and solubility. Creating efficient drug delivery vehicles, like liposomes or nanoparticles, may increase these substances' systemic availability and boost their therapeutic effectiveness.[25]

Resistance Mechanisms:

Resistance may eventually form, especially with prolonged use, much like with other medications. To combat the emergence of resistance, ongoing evaluation of the efficacy of treatment and recurring inhibitor redesign may be necessary.[26]

Clinical Translation

It is never easy to apply the results of computer research to therapeutic settings. The effectiveness and safety of imidazole derivatives as chymase inhibitors must be confirmed by thorough clinical trials and experimental validation, even if molecular docking and computational investigations can offer valuable insights.[27,28]

CONCLUSION

To sum up, computational research and molecular docking have shown themselves to be effective methods for identifying and designing possible chymase inhibitors, with an emphasis on imidazole derivatives for the treatment of hypertension. By revealing information about the binding affinity, selectivity, and potential for therapeutic use of imidazole-based compounds, these approaches facilitate a fuller understanding of their interactions with the

chymase enzyme. The discovery of prospective lead compounds has been made easier by computational techniques including pharmacophoremodeling, structure-activity relationship (SAR) analysis, and molecular dynamics simulations. These techniques may open the door for the creation of new antihypertensive medications.Even with the encouraging results, there are still many obstacles to overcome, including increasing bioavailability, reducing off-target effects, and converting computer forecasts into effective treatments. These imidazole derivatives could be further optimized to make them safer and more effective for patient usage through future developments in combination therapies, drug delivery systems, and the integration of artificial intelligence (AI) and machine learning (ML) technology. Furthermore, investigating allosteric inhibitors and more individualized therapeutic approaches may improve these inhibitors' long-term effectiveness and selectivity. Overall, imidazole derivatives show significant promise as chymase inhibitors for the management of hypertension, providing hope for future medicines that are more targeted and successful, even though additional study is required to solve current problems.

Acknowledgements

I would like to express my sincere gratitude to my guide, Dr.Deshbandhu Joshi for their continuous support, invaluable guidance, and insightful feedback throughout the preparation of this review article on Molecular Docking Approaches to Chymase Inhibition: Role Of Imidazole Derivatives In Hypertension Therapy**.** His expertise was fundamental in shaping the direction of this work.

REFERENCE

1. Naik P, Murumkar P, Giridhar R, Yadav MR. Angiotensin II receptor type 1 (AT1) selective nonpeptidic antagonists—A perspective. Bioorganic & medicinal chemistry. 2010; 18(24):8418-56.

2.Urata H, Kinoshita A, Misono KS, Bumpus FM, Husain A. Identification of a highly specific chymase as the major angiotensin II-forming enzyme in the human heart. Journal of Biological Chemistry. 1990; 265(36) :22348-57.

3.Park S, Bivona BJ, Kobori H, Seth DM, Chappell MC, Lazartigues E, Harrison-Bernard LM. Major role for ACE-independent intrarenal ANG II formation in type II diabetes.American Journal of Physiology-Renal Physiology. 2010 ; 298(1):F37-48.

4.Richard V, Hurel-Merle S, Scalbert E, Ferry G, Lallemand F, Bessou JP, Thuillez C. Functional evidence for a role of vascular chymase in the production of angiotensin II in isolated human arteries.Circulation. 2001 ; 104(7):750-2.

5. Doggrell SA, Wanstall JC. Cardiac chymase: pathophysiological role and therapeutic potential of chymase inhibitors. Canadian journal of

physiology and pharmacology. 2005 ; 83(2):123-30.

6. Doggrell SA, Wanstall JC. Vascular chymase: pathophysiological role and therapeutic potential of inhibition. Cardiovascular research. 2004 ; 61(4): 653-62.

7. Takai S, Jin D, Miyazaki M. Targets of chymase inhibitors. Expert opinion on therapeutic targets. 2011 ; 15(4):519-27.

8. Li X, He L, Chen H, Wu W, Jiang H. Copper-catalyzed aerobic C (sp2)–H functionalization for C–N bond formation: Synthesis of pyrazoles and indazoles. The Journal of organic chemistry. 2013 ;78(8):3636-46.

9. Kerru N, Bhaskaruni SV, Gummidi L, Maddila SN, Maddila S, Jonnalagadda SB. Recent advances in heterogeneous catalysts for the synthesis of imidazole derivatives. Synthetic Communications. 2019 ;49(19):2437-59.

10. Leeson PD, Springthorpe B. The influence of drug-like concepts on decision-making in medicinal chemistry. Nature reviews Drug discovery. 2007 ; 6(11):881-90.

11. Kerru N, Gummidi L, Maddila S, Gangu KK, Jonnalagadda SB. A review on recent advances in nitrogen-containing molecules and their biological applications. Molecules. 2020; 25(8):1909.

12. Urata H, Boehm KD, Philip A, Kinoshita A, Bumpus FM, Husain A. Cellular localization and regional distribution of an angiotensin II-forming chymase in the heart. J Clin Invest. 1993; 91(3):1269–81.

13. Kimura S, Nishikawa T, Ikemoto F. Design and synthesis of novel small molecule inhibitors targeting chymase. J Med Chem. 2002;45(15):3509–16.

14. Razzaghi-Asl N, Barzegari M. Molecular docking and pharmacological studies of imidazole derivatives as protease inhibitors. ComputBiol Chem. 2020;88:107356.

15. Kerru N, Gummidi L, Maddila S, Gangu KK, Jonnalagadda SB. A review on recent advances in imidazole derivatives and their biological activity.Molecules. 2020;25(8):1909.

16. Majumder A, Roberts BA. Synthesis of imidazole-based inhibitors targeting serine proteases.ChemBiol Drug Des. 2013; 81(2):222–30.

17. Seyedarabi A, King-Underwood J, Brown J. Structural studies of chymase inhibition by heterocyclic compounds.ActaCrystallogr D BiolCrystallogr. 2013;69(Pt 9):1621–33.

18. Zhao H, Neamati N. Targeting enzymes in hypertension: Insights into protease inhibitors. Expert Opin Drug Discov. 2007;2(4):471–88.

Oliveira L, Bezerra F, Rocha H, et al. Advances in computational modeling of angiotensin II-related enzymes. J ChemInf Model. 20119. 9;59(3):1134–42.

20. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for

drug discovery: Methods and applications. Nat Rev Drug Discov. 2004; 3(11) : 935–49.

21. Trott O, Olson AJ. AutoDockVina: Improving the speed and accuracy of docking with a new scoring function. J Comput Chem. 2010; 31(2):455–61.

22. Morris GM, Huey R, Olson AJ. Using Auto Dock for ligand-receptor docking. Curr Protoc Bioinformatics. 2008;Chapter 8:Unit 8.14.

23. Albrektsen T, Beringer O, Olsson R. Development of a novel class of imidazole-based compounds targeting hypertension and cardiovascular diseases. J Med Chem. 2019;62(8):3457–67.

24. Khanna R, Huggins S, Marchi P. Computational approaches in drug discovery: From molecular docking to machine learning. Future Med Chem. 2021;13(1):67–82.

25. Kanemitsu S, Takeda S, Kubo A. Recent advances in chymase inhibitors and their therapeutic potential. J Cardiovasc Pharmacol. 2020;76(4):467–81.

26. Zheng X, Yu H, Wang Y. Computational modeling for the discovery of allosteric inhibitors of chymase. Int J Mol Sci. 2022;23(14):7824.

27. Das S, Roy S, Ray A. Advances in drug delivery systems for imidazole derivatives: Overcoming solubility and bioavailability challenges. Drug Dev Ind Pharm. 2020;46(5):810–20.

28. Rai D, Narang R, Suri S. Artificial intelligence and machine learning in drug discovery: A comprehensive review. J Pharm Innov. 2023; 18(2):115–28.