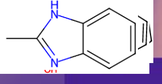

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Benzimidazoles-Based Antioxidants: A Computational Study on Lipoxygenase Inhibition

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INTRODUCTION & AIM

Oxidative stress is an observable fact resulting from an imbalance between the generation and accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in cells and tissues and the ability of cellular machineries to eliminate these by-products. It arises due to agitations between the ROS and the antioxidant defense system in the body. Both ROS and RNS are by-products of cellular respiration [1]. Cumulative oxidative stress is known to bring about cellular damage, impairment of the DNA repair system [2,3] and mitochondrial dysfunction. All of these have been reported to accelerate aging process and the development of neurodegenerative disorders and other diseases including atherosclerosis, chronic obstructive pulmonary disease (COPD), and cancer [4–6].

Lipoxygenase is a family of non-heme iron-containing enzyme that catalyzes formation of hydroperoxides via oxidation of polyunsaturated fatty acids (PUFAs) [7]. The enzymes are known to be seven hundred (700) amino acid long and classified into 5(S), 8(S), 12(S), and 15(S). Metabolites of PUFAs profoundly impact the progression of inflammation and cancer. Therefore, inhibition of PUFAs metabolizing enzymes such as LOX could have a therapeutic connection against such diseases [8]. For these reasons, there have been continuing efforts to find agents that can protect against oxidative damage and potentially treat neurodegenerative diseases.

Benzimidazoles are a class of heterocyclic, aromatic compounds that share a fundamental structural characteristic of six-membered benzene fused to five-membered imidazole moiety [9]. The pharmacological application of benzimidazole analogs found potent inhibitors of various enzymes involved and therapeutic uses including as antioxidant, antidiabetic, anticancer, antimicrobial, antiparasitic, analgesics, antiviral, antihistamine, and also neurological, endocrinological, and ophthalmological drugs [9,10]. This study aims to design benzimidazole derivatives and evaluate their antioxidant activity using an insilico approach.

METHOD

Ligand preparation

The 2D structures were generated using ChemDraw ultra version 12.0.2 and Spartan 14v 114 was used to convert the 2D structure to 3D structures. The ligands were optimized and saved as mol2 files.

Receptor preparation

The crystal structure of lipoxygenase enzyme (PDBs: 1N8Q) protein was downloaded from Protein Data Bank (PDB, http://www.rcsb.org). The enzyme was prepared by removing all non-residues followed by the addition of hydrogen atoms and Gasteiger charges to the amino acid residues, using UCFS chimera version 1.17.3 [11].

Molecular docking

Both the prepared 3D ligands and the receptor were converted to pdbqt by utilizing AutoDockTool version 1.5.6 [12]. The molecular docking of the ligands and target enzyme was carried out using Autodock Vina [13] with the aid of Cygwin64 terminal. The docking calculations were viewed using UCFS chimera version 1.17.3 [11] and were saved in pdb format. The saved pdb files were viewed using Discovery Studio visualizer version 20.1.0 for receptor-ligand interactions.

Theoretical Oral Bioavailability

The oral bioavailability prediction was done using an online web server (ADMETlab 2.0).

RESULTS & DISCUSSION

Table 1: IUPAC Name, Chemical Structure, and Synthetic Accessibility (SA) of Designed Ligands

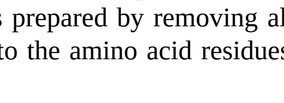
S/No	Code	IUPAC Name	Chemical Structure	SA Score
1	L1	2-allyl-1H-benzo[d]imidazole		2.20
2	L11	2-ethyl-1H-benzo[d]imidazole		1.86
3	L12	2-butyl-1H-benzo[d]imidazole		1.81
4	L20	2-methyl-1H-benzo[d]imidazole		1.85

Table 2: Insilico theoretical oral bioavailability of the designed benzimidazole derivatives

S/No	Code	Mw (g/mol)	GI Absorption	LogP	n-HA	n-HD	Lipinski's Violation	Inference
1	L1	158.08	High	2.4	2	1	0	Pass
2	L11	210.08	High	3.28	3	2	0	Pass
3	L12	146.08	High	2.28	2	1	0	Pass
4	L20	132.07	High	1.34	2	1	0	Pass

Mw: Molecular weight; GI: Gastrointestinal; n-HA: Number of hydrogen bond acceptor; n-HD: Number of hydrogen bond donor

Table 2: Binding affinities of the docked ligands against LOX Enzyme (1N8Q)

S/No	Ligand Code	Binding affinity (Kcal/mol)
1	DHB[a]	-5.8
2	Lig1	-5.2
3	Lig11	-5.8
4	Lig12	-3.9
5	Lig20	-6.0
6	Ascorbic acid[b]	-5.4

[a] Native ligand (DHB: Dihydroxybenzoic acid, [b]Standard drug

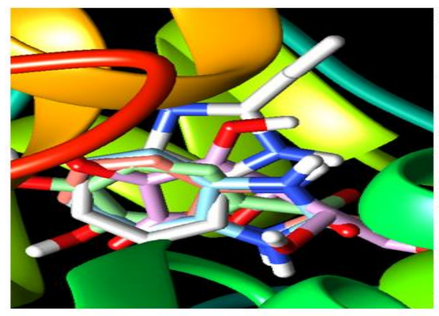


Figure 2: All docked ligands at the enzyme's active site

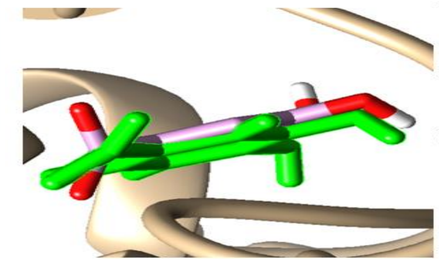
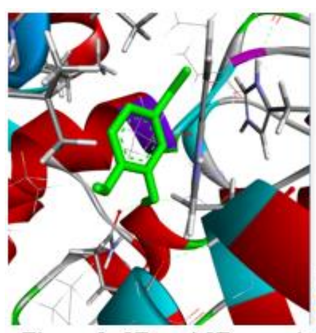


Figure 1: Docking validation (re-docked ligand superimposed on co-crystallized ligand)



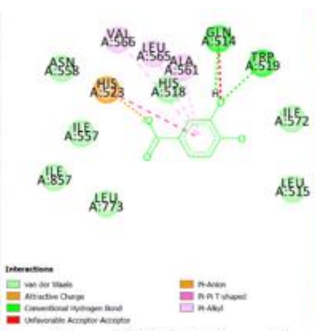


Figure 3: 3D and 2D pose interaction of DHB at the active site of LOX enzyme

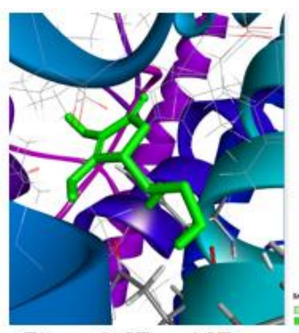


Figure 4: 3D and 2D pose interaction of Ascorbic acid at the active site of LOX enzyme

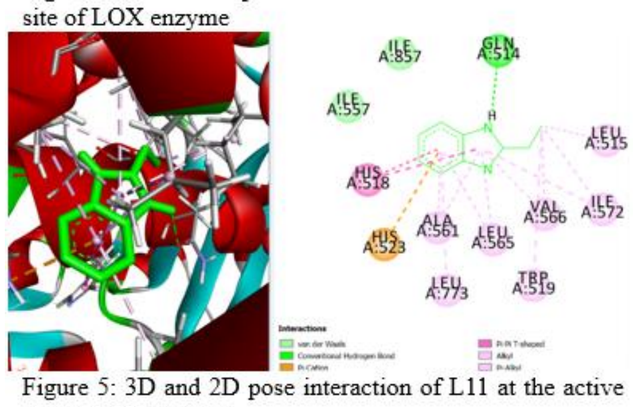


Figure 5: 3D and 2D pose interaction of L11 at the active site of LOX enzyme

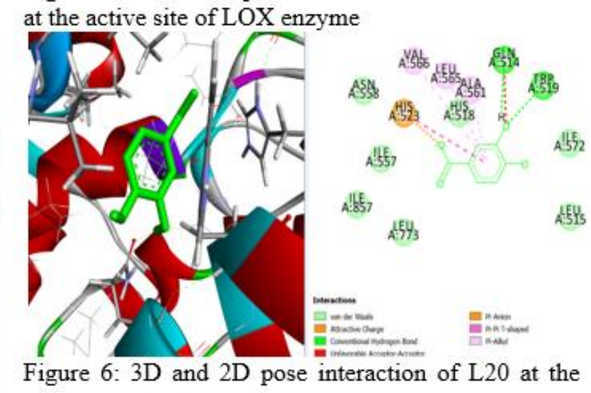


Figure 6: 3D and 2D pose interaction of L20 at the active site of LOX enzyme

The theoretical oral bioavailability result in Table 2 showed that all the designed ligands passed Lipinski's rule of five, meaning they are all druggable. All the ligands have a good synthetic accessibility score (< 6). This is in agreement with the work of Gidado et al., 2024 which reveals that benzimidazoles have good pharmacokinetic properties. The docking results showed that the ligands have a good binding affinity to the target, the LOX enzyme (1N8Q), with L20 having the best binding affinity (-6.0 Kcal/mol), followed by L11 (-5.8 Kcal/mol), L1 (-5.2 Kcal/mol), and L12 (-3.9 Kcal/mol). The native ligand (DHB: 3,4-DIHYDROXYBENZOIC ACID) has a binding score of -5.7 Kcal/mol. Ascorbic acid was used as a reference drug and has a binding score of -5.4 Kcal/mol. The results indicated that ligands interacted with the binding pockets of the enzyme's active site through conventional hydrogen bond, hydrogen bond, Van der Waals, Pi-Pi, Pi-alkyl, pi-anion, and alkyl interactions. The interacting amino acid residues responsible for the scavenging activity are HIS518, GLN514, LEU515, HIS523, ALA561, TRP519, and ILE572. All the ligands interacted with the aforementioned residues (Figure 3, 4, 5, and 6) and it corresponds to the work of Rajak et al., 2023.

CONCLUSION

The designed ligand interacts with amino acid residues at the enzyme's active site which is responsible for Lipoxygenase enzyme inhibition. This suggests that the designed benzimidazole ligands have the potential to scavenge free radicals.

REFERENCES

[1] Olufunmilayo EO, Gerke-duncan MB, Holsinger RMD. Oxidative Stress and Antioxidants in Neurodegenerative Disorders 2023:1–30.

[2] Park S, Park S-Y. Can antioxidants be effective therapeutics for type 2 diabetes? Yeungnam Univ J Med 2021;38:83–94. https://doi.org/10.12701/yujm.2020.00563.

[3] Abdali D, Samson SE, Grover AK. How effective are antioxidant supplements in obesity and diabetes? Med Princ Pract 2015;24:201–15. https://doi.org/10.1159/000375305.

[4] Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39:44–84. https://doi.org/10.1016/j.biocel.2006.07.001.

[5] Federico A, Cardaioli E, Da Pozzo P, Formichi P, Gallus G, Radi E. Mitochondria, oxidative stress and neurodegeneration. J Neurol Sci 2012;322:254–62.

[6] Gandhi S, Abramov A. Mechanism of oxidative stress in neurodegeneration. Oxid Med Cell Longev 2012;3:428010.

[7] Brash AR. Lipoxygenases: occurrence, functions, catalysis, and acquisition of substrate. J Biol Chem 1999;274:23679–23682. https://doi.org/10.1074/jbc.274.34.23679.

[8] Rajak P, Ganguly A, Mandi M, Dutta A, Sarkar S, Nanda S, et al. Advances in Redox Research In silico targeting of lipoxygenase , CYP2C9 , and NAD (P) H oxidase by major green tea polyphenols to subvert oxidative stress. Adv Redox Res 2023;7:100061. https://doi.org/10.1016/j.arres.2023.100061.

[9] Kamanna K. Synthesis and Pharmacological Profile of Benzimidazoles. Chem Appl Benzimidazole Its Deriv 2019. https://doi.org/10.5772/intechopen.85229.

[10] Gidado I, Idris AY, Hamza AN, Abdullahi M, Jibril A, Hassan LA, et al. Oxidative Stress and Insulin Resistance: Correlation, In-silico Design, and Alpha- Glucosidase Inhibition of Benzimidazole Derivatives. Niger Res J Chem Sci 2024;12:261–77.

[11] Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, et al. UCSF Chimera--a visualization system for exploratory research and analysis. J Comput Chem 2004;25:1605–12.

[12] Sanner MF. Python: A Programming Language for Software Integration and Development. J Mol Graph Mod 1999;17:57–61.

[13] Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem 2010;31:455– 461.