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MOLECULAR DOCKING STUDIES OF SUBSTITUTED QUINOLINES AGAINST ANGIOTENSIN CONVERTING ENZYME (ACE) AS POTENTIAL ANTI HYPERTENSIVE AGENT

P. Raja[1]*, P. Tarakeswara Rao[2] and Dr. D. Ravisankar Reddy[3]

[1]Department of Pharmaceutical Chemistry, College of Pharmaceutical sciences, Acharya Nagarjuna University, Guntur, Andhra Pradesh.

[2]Department of Pharmaceutical Analysis, College of Pharmaceutical sciences, Acharya Nagarjuna University, Guntur, Andhra Pradesh.

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***Corresponding Author**
P. Raja
Department of Pharmaceutical Chemistry, College of Pharmaceutical sciences, Acharya Nagarjuna University, Guntur, Andhra Pradesh.

ABSTRACT

Hypertension a prevalent cardiovascular disorder, poses significant health risks globally. Quinoline derivatives have various pharmacological properties, including anti-hypertensive potential. This present study explores the potential of quinoline compounds by performing molecular docking studies against Angiotensin Converting Enzyme. Quinolines ability to modulate various pathways implicated in hypertension, such as the renin-angiotensin-aldosterone system, sympathetic nervous system, and endothelial function, highlights their promise as anti-hypertensive agents. Furthermore, the structural versatility of quinoline scaffolds allows for rational drug design, facilitating the development of potent and selective compounds with improved efficacy and safety profiles. Despite these promising attributes, further preclinical and clinical investigations are warranted to elucidate the full therapeutic potential of quinoline derivatives in the management of hypertension. Using molecular docking techniques, ligands were designed and docked against the ACE receptor (PDB ID:7Z6Z), comparing their efficacy with standard ACE inhibitors such as Fosinopril and Enalapril. **Materials and procedures:** The ligands were initially designed in. mol format using ChemSketch software and then converted to .pdb format through Avogadro software. Molecular docking studies were performed using iGEMDOCK software, and the results were visualized using Discovery Studio Visualizer. **Findings and discussion:** The majority of the

compounds exhibited higher binding affinities for the Angiotensin-Converting Enzyme (ACE) compared to standard ACE inhibitors like Fosinopril (-106.1 kcal/mol) and Enalapril (-102.8 kcal/mol). Among these, the top two ligands, 3a8b1c (-118.4 kcal/mol) and 4a12b1c (-117.9 kcal/mol), were selected for visualization. **Conclusion**: Quinoline derivatives were docked against the Angiotensin-Converting Enzyme (ACE) and demonstrated potential as a promising class of antihypertensive drugs, owing to their higher binding affinity to ACE compared to standard inhibitors.

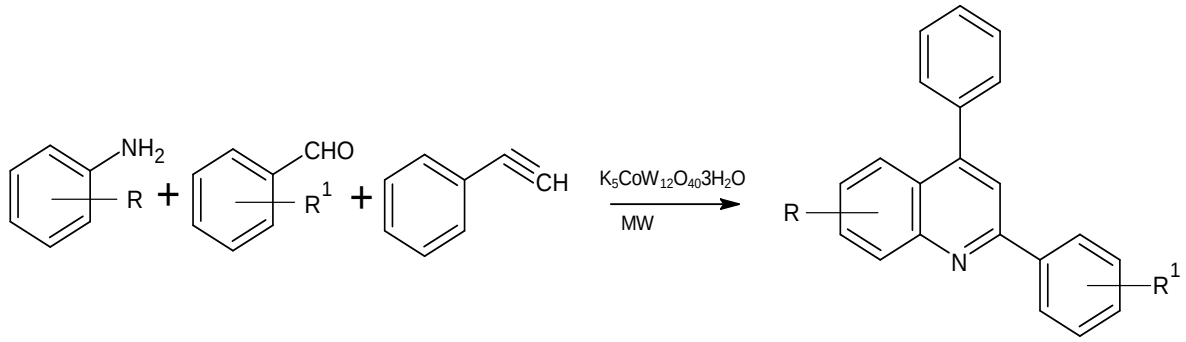
KEYWORDS: ACE inhibitors, anti-Hypertensive activity, Molecular Docking, iGEMDOCK Software, Discovery Studio Visualizer.

INTRODUCTION

Quinoline[1-2] is a heterocyclic ring consisting of a benzene ring fused to a pyridine ring which has attracted considerable attention in medicinal chemistry due to its diverse pharmacological properties and structural versatility. Originally isolated from coal tar in the 19th century, quinoline and its derivatives ever since emerged as vital scaffolds for the development of therapeutic agents targeting various diseases. Hypertension[3-4] is a prevalent cardiovascular condition affecting millions worldwide, poses a significant public health burden due to its association with increased morbidity and mortality from cardiovascular events including stroke, heart attack, and heart failure. ACE inhibitors[5-7] exert their pharmacological actions by targeting the renin-angiotensin-aldosterone system (RAAS), a pivotal pathway implicated in blood pressure regulation and cardiovascular homeostasis. Through inhibition of ACE, these agents attenuate the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, and inhibit the degradation of bradykinin, a vasodilatory peptide. Consequently, ACE inhibitors promote vasodilation, reduce systemic vascular resistance, and mitigate aldosterone-mediated sodium and water retention, collectively contributing to blood pressure reduction and cardiovascular protection. Quinoline nucleus has various biological activities like anti-hypertensive activity[8-9], anti-microbial activity[10-11], anti-cancer activity[12-13], anti-inflamatory activity[14-15], anti-oxidant activity[16-17], anti-viral activity[18-19], and anti-malarial activities.[20-21]

METERIAL AND METHODS

Scheme[22-23]



From the above-mentioned scheme[22-23] different substituted aromatic aldehydes, different substituted aromatic amines and aromatic phenyl acetylene were chosen, and the final products were designed following the proposed scheme. Designed final compounds were subjected to a toxicity screening *in silco* by utilizing TopKat software[24,29,30,31], After predicting the toxicity in silico, Swiss ADME software[25,29,30,31], was used to estimate the ADME properties like absorption distribution metabolism and excretion. The potential targets for all non-toxic compounds exhibiting favourable ADME properties were predicted using Swiss Target Prediction software.[26,29,30,31] The majority of the designed ligands identified the ACE receptor as a potential target. The ACE receptor was identified as the primary target for most of the designed ligands. The 2D structures of the ligands were constructed using the ChemSketch program and saved in. mol format. The Avogadro tool[27,29,30,31], was utilized to convert the ligand structures from the. mol format to the .pdb format. The designed final products were docked by using iGEMDOCK software.[28,29,30,31] iGEMDOCK software was used for molecular docking, screening and analysis of all the designed ligands together with the Standard ACE inhibitors Enalapril[32-33], and Fosinopril.[34-35] The orientation and interaction of the ligands with the receptor's active site were visualized using Discovery Studio Visualizer software. The structure of the protein was obtained from protein data bank, which was used to evaluate the molecular interactions between the designed ligands and standard antagonists of ACE receptor figure:1 (PDB ID: 7z6z) ACE receptor with co-crystallized ligand fosinoprilat. Accurate docking approach was followed for docking studies. The software computed the score function by combining electrostatic energy hydrogen bonding and vander waals energy. Docking simulations were used to evaluate molecular interactions and binding affinities. The software combined hydrogen bonding, electrostatic

energy, and Vander Waals energy to compute the scoring function. The top two compounds having greater binding energy were chosen for visualization.

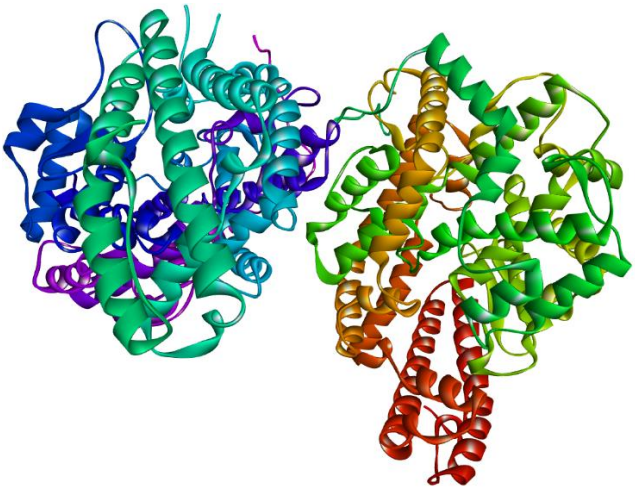


Figure 1: ACE receptor cleaned (PDB ID: 7Z6Z).

RESULTS AND DISCUSSION

All the ligands exhibited higher binding energies compared to standard ACE inhibitors, such as Fosinopril (-106.1 kcal/mol) and Enalapril (-102.8 kcal/mol). The top two compounds having greater binding energies, Compounds 3a8b1c (-118.4 K. Cal/mol) and compound 4a12b1c (117.9 K. Cal/mol) were selected for Visualization.

TOP 2 compounds 3a8b1c, 4a12b1c

3a8b1c 4a12b1c

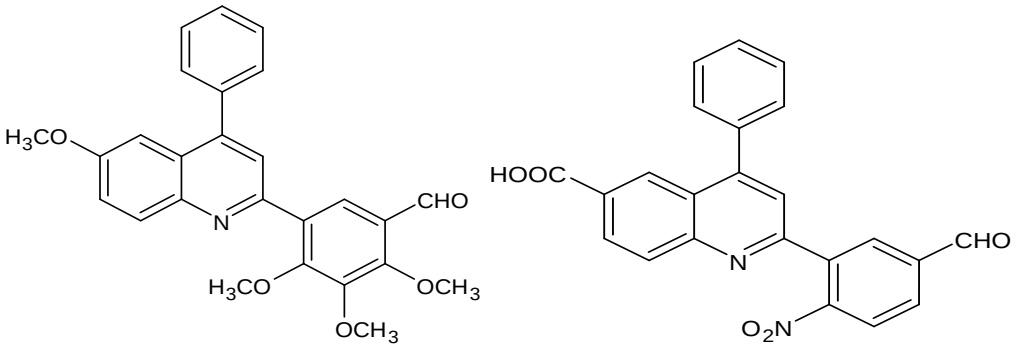
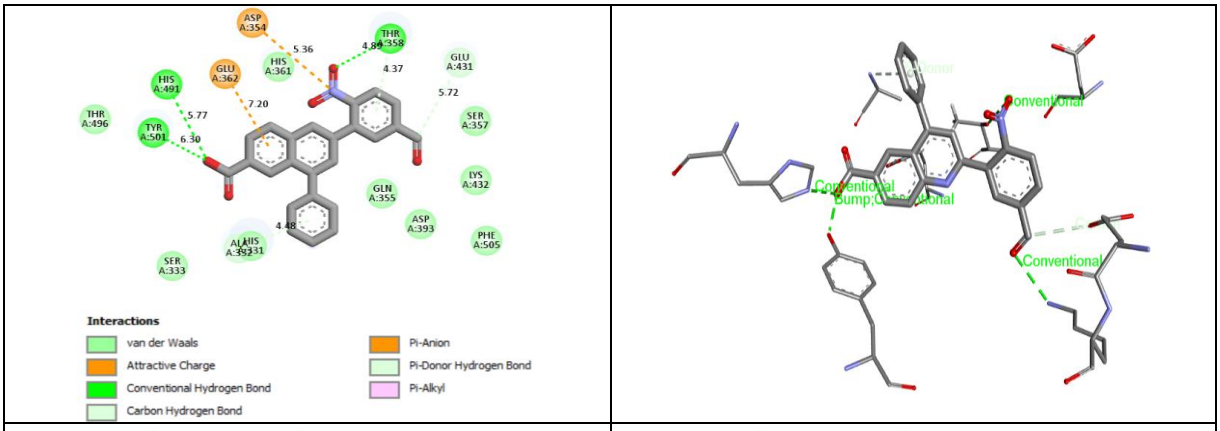


Table 1: The interacting amino acid residues and the binding energies of top ten compounds towards the ACE- Receptors.

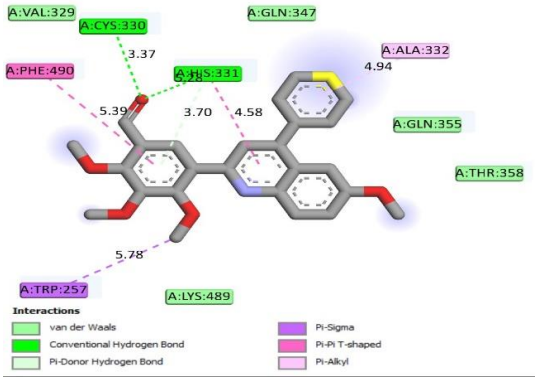
Ligand code	Binding energy (K. Cal/mol)	Active site amino acid residues involved in interactions
3a8b1c	-118.4	HIS:491, THR:358, LYS:432, TYR:501, GLU:362, HIS:361, ASP:354, SER:357, GLU:431, PHE:505,

		GLN:355, ASP:393, HIS:331, ALA:332
4a12b1c	-117.9	CYS:330, HIS:331, PHE:490, ALA:332, TRP:257
3a9b1c	-114.2	ALA:332, TYR:501, HIS:491, HIS:361, HIS:331, GLU:362, HIS:361, THR:358, GLN:355, GLU:262, SER:260, ASP:354, PHE:435, PHE:505, ASP:393, GLN:259, TYR:498
3a11b1c	-113.2	TYR:501, ALA:332, GLU:362, SER:333, HIS:331, THR:358, GLN:355, GLU:262, GLU:431, HIS:361, PHE:435, ASP:393, PHE:505, TYR:498
2a8b1c	-112.2	HIS:331, TYR:501, HIS:491, THR:358, HIS:361, GLU:362, ASP:354, SER:357, GLU:431, ALA:332
3a10b1c	-108.0	HIS:491, GLU:362, THR:358, GLU:431, ALA:332, TYR:501
1a12b1c	-107.8	CYS:330, HIS:331, ALA:332, TRP:257, PHE:490
5a8b1c	-107.5	THR:358, GLN:355, ALA:332, HIS:361, GLU:262, ASP:354
6a9b1c	-106.7	GLN:355, THR:358, SER:357, ALA:332
6a1b1c	-106.7	ASP:393, GLU:362, ALA:332, HIS:361, THR:358, PHE:505, LYS:432, GLU:431, SER:260, GLU:262, ASP:354, ASP:255, HIS:331
Cocrystal	-119.3	TYR:498, GLN:259, HIS:361,
Fosininopril	-106.1	HIS:331, ALA:332, LYS:489, THR:358
Enalapril	-102.8	THR:358, GLN:431, LYS:432, ALA:396

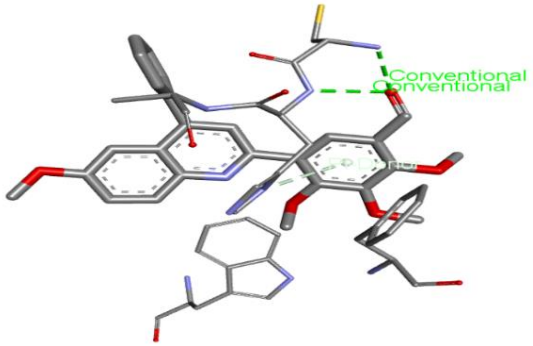
Table 2: 2D And 3D Image visualization data of the top Two Ligands 3a8b1c, 4a12b1c and Standard Antagonists Fosinopril and Enalapril.



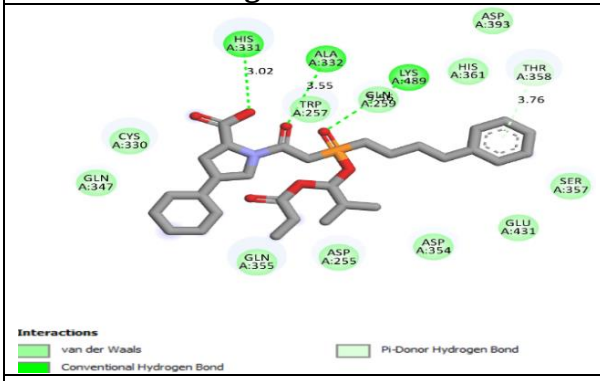
3a8b1c Ligand 2D Interaction | **3a8b1c Ligand 3D Interaction**



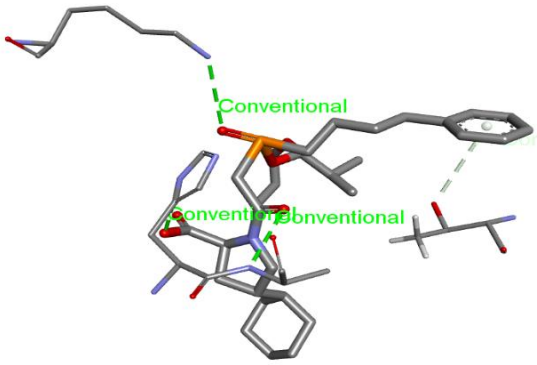
4a12b1c Ligand 2D Interaction



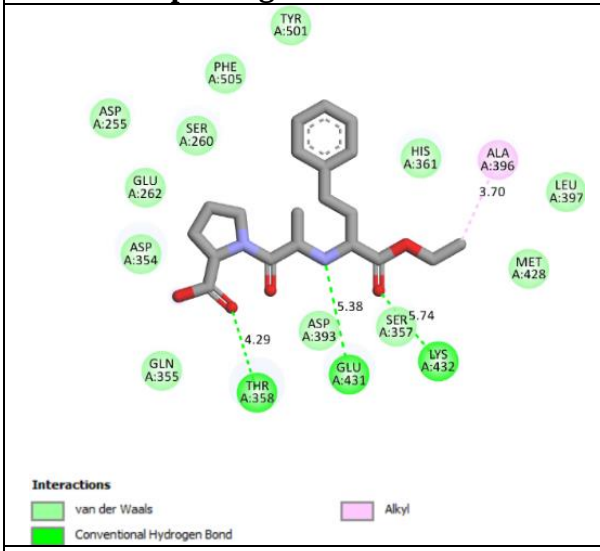
4a12b1c Ligand 3D Interaction



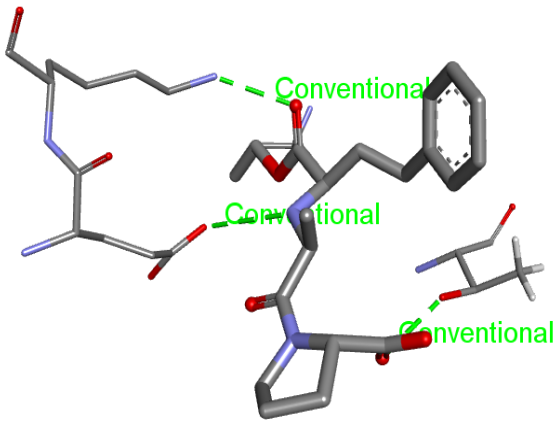
Fosinopril Ligand 2D Interaction



Fosinopril Ligand 3D Interaction

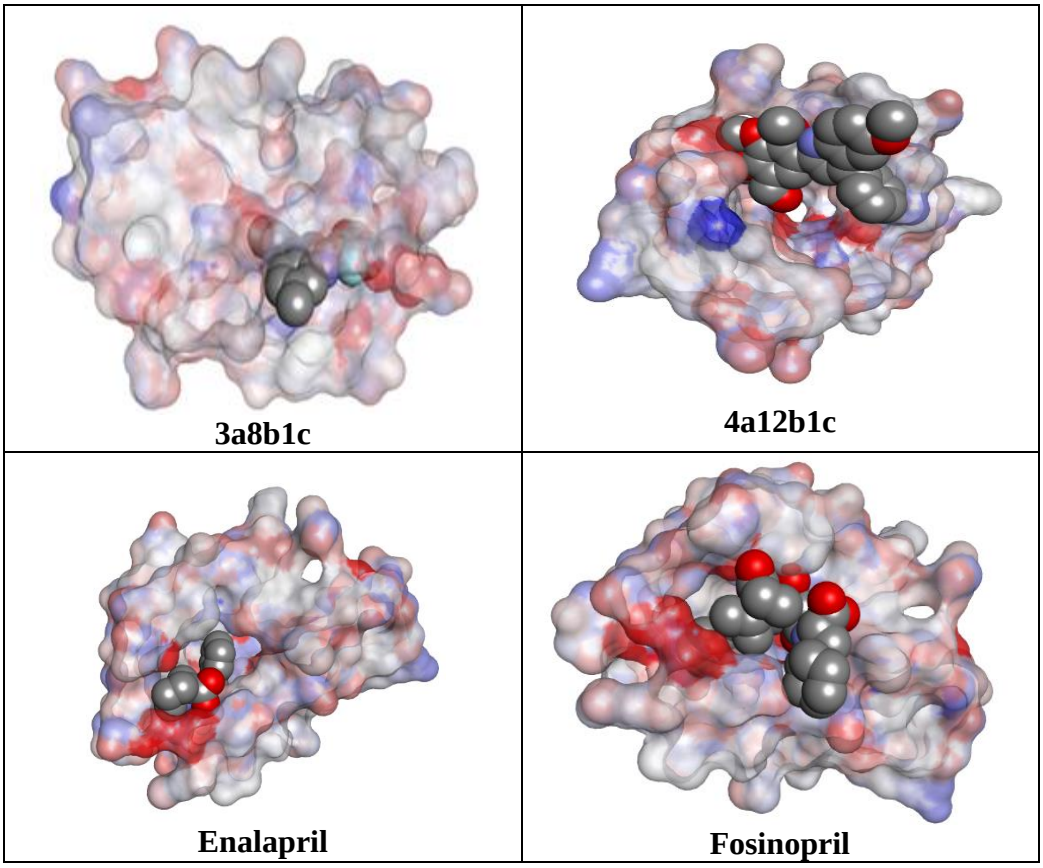


Enalapril Ligand 2D Interaction



Enalapril 3D Interaction

Table 3: Surface pocket analysis of top 2 compounds 3a8b1c,4a12b1c and standard ACE antagonists Fosinopril, Enalapril.



DISCUSSION

(Table:1) Nearly all of the top 10 compounds demonstrated higher binding energies than the standard ACE inhibitors. Top 2 ligands 3a8b1c and 4a12b1c have greater binding energies of -118.4 K. Cal/mol and -117.9 K. Cal/mol respectively. These binding energies are superior to those of standard ACE inhibitors like Fosinopril (-106.1 kcal/mol) and Enalapril (-102.8 kcal/mol). The 3D interactions revealed the number of conventional hydrogen bonds, while the 2D interactions provided a clear understanding of the amino acid residues involved in the interactions. **(Table:2)** Compound 3a8b1c forms three conventional hydrogen bonds and Compound 4a12b1c forms two conventional hydrogen bonds with ACE recpetors binding pocket. Fosinopril and Enalapril forms three conventional hydrogen bonds with ACE-receptor. Four amino acid residues **HIS:331, ALA:332, LYS:489, THR:358** are common in Fosinopril and 3a8b1c. Seven amino acids residues **CYS:330, HIS:331, PHE:490, ALA:332, TRP:257 ILE:66 GLU:169** are common in Fosinopril and 4a12b1c. Four amino acid residues **THR:358, GLN:431, LYS:432, ALA:396** are Common in Enalapril and

3a8b1c. Five amino acid residues **CYS:330, HIS:331, PHE:490, ALA:332**, **TRP:257** are common in 4a12b1c and Enalapril.

Binding pocket analysis

The pocket analysis of the top compounds 3a8b1c, 4a12b1c and the standard ligands Fosinopril and Enalapril reveals that they bound to the centre of the pocket. The higher binding energy of the 3a8b1c compound may be attributed to the presence of electron-withdrawing groups, such as a CHO, NO_2, and COOH, on the quinoline ring. Similarly, the increased binding energy of the 4a12b1c compound could be due to the presence of an electron-withdrawing CHO group and four OCH_3 groups on the quinoline ring. These observations like common amino acid residues and the functional groups present on the quinoline ring might be the reason to exhibit higher binding affinity of 3a8b1c and 4a12b1c than the standard ACE receptor inhibitors like Fosinopril and Enalapril.

CONCLUSION

As the top ligands 3a8b1c and 4a12b1c were non-toxic, having better ADME, better binding affinities than the standard ACE inhibitors and common amino acid residue interactions with that of the standard ACE inhibitors, they can be synthesized further and utilized for in vivo studies.

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