Open Access Research Journal of
Science and Technology
Journals home page: https://oarjst.com/
ISSN: 2782-9960 (Online)

OARJ OPEN ACCESS RESEARCH JOURNALS

(Research Article)

Computational molecular modelling of proline derivatives as ACE inhibitors

VANI V [1] *, SREEJA S [1], AMRUTHA SA [2], FEBA SAJI [2], JASNI FATHIMA MS [2] and JAYALAKSHMI C [2]

[1] *Department of Pharmaceutical Chemistry, Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala, India.*
[2] *Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala, India.*

Open Access Research Journal of Science and Technology, 2023, 08(02), 064–078

Publication history: Received on 14 June 2023; revised on 17 August 2023; accepted on 19 August 2023

Article DOI: https://doi.org/10.53022/oarjst.2023.8.2.0050

Abstract

Objective: The study aims to design Proline derivatives having anti-hypertensive activity by computational molecular modelling.

Methods: Various methodology used in the study include lead identification, selecting derivatives, molecular modelling, target identification, docking and visualizing the output. The ligands that show good binding scores are selected and Captopril was selected as standard drug.

Results: In this study, we designed various derivatives of acylated proline into a ligand having ACE Inhibitor activity. All the twenty designed derivatives showed more binding affinity towards the receptor compared to the standard drug Captopril.

Conclusions: The work concluded that the designed twenty ligands are promising ACE Inhibitors which provides anti-hypertensive activity.

Keywords: Proline; Anti-hypertensive; Captopril; ACE Inhibitor

1. Introduction

Hypertension is a condition in which pressure in the blood vessels is too high. That is systolic blood pressure (SBP) of 140 mm of Hg or greater and/or diastolic blood pressure (DBP) of 90 mm of Hg or greater. There are two types of hypertension, primary and secondary. Primary or essential high blood pressure is the most common type which is caused without any specific disease. It is influenced by the activity of hormone regulating blood pressure, environmental factors like stress and lack of exercise. Secondary hypertension is caused due to another condition such as diabetes, pregnancy, obstructive sleep apnoea, etc.[1]

Hypertension is a notable health problem, with a prevalence rate of 40.8% world wide and 32.3 % control rate. It is the major cause of various health problems such as cardiovascular disease, cerebrovascular diseases, and chronic kidney disease. 9.4 million deaths were reported as a result of complications from hypertension, among this, 51% of all deaths were due to stroke and 45% of all deaths due to coronary artery disease.[2]

Hypertension can be treated by self-care such as life style modification and by taking anti-hypertensive medications. Life style modifications such as following a healthy diet, exercise and being more active help to control the blood pressure. Anti-hypertensive drugs include ACE inhibitors, diuretics, beta blockers, AR II blockers, calcium channel blockers, vasodilators. ACE inhibitors act by inhibiting angiotensin converting enzyme; which causes decrease in angiotensin II production and increases bradykinin level by inhibiting its degeneration, which leads to vasodilation.[3]

* Corresponding author: VANI V.

Our aim is to design proline derivatives using Chemsketch, AutoDock, PyMOL as ACE inhibitor in hypertension treatment. L-Proline is a secondary amino acid which is proteinogenic in nature. Its anti-hypertensive activity is exhibited when it is acylated with 3-acetylthio-2-methylpropionic acid and act by competitively inhibiting Angiotensin Converting Enzyme. The ACE inhibitor activity of acylated proline can be enhanced by attaching various heterocyclic compounds having the same activity to C-14 position of the lead.

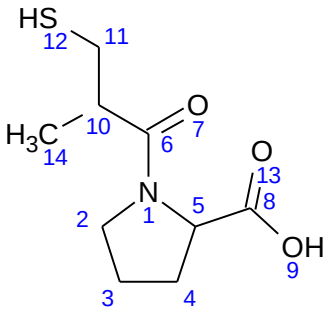


Figure 1 Structure of acylated proline

2. Materials and methods

2.1. Computational Platforms and Software Used

Table 1 Software Used in In Silico Design

Software Used	Usage
ACD Chemsketch	To draw 2-D structure
SMILES (Simplified Molecular Input Line Entry System)	To translate a chemical's 2-D structure into a string of symbols that is easily understood by computer software
Molinspiration	To calculate drug likeness property
PASS Online	To predict the activity
PDB (Protein Data Bank)	To obtain a target protein(receptor)
PubChem	To obtain the 3D structure of standard drug
NovoPro Bioscience Inc.	To convert SMILES of derivatives to PDB format
AutoDock	For Docking
PyMol	For the visualization of docked complex

ACD Chemsketch is a molecular modelling program used to create and modify images of chemical structures. It also allows molecules and molecular models displayed in two and three dimensions, to understand the structure, chemical bonds and the nature of functional groups. It has several templates with ions and functional groups with the possibility to add text and use other tools to optimize productions created by the software. This program also offers some advanced features which allow the molecule to rotate and apply colour to improve visualization. Using this program, we are able to write and perform chemical equations, SMILES notations, and chemical structures of various entities.

Molinspiration is a cheminformatics tool, supporting molecule manipulation and processing, including SMILES and SDF conversion, generation of tautomer, calculation of various molecular properties needed in QSAR, molecular modelling and drug design. It also supports fragment-based virtual screening, bioactivity prediction and data visualization. It works under the principle of Lipinski Rule of Five, which is a rule that is important to keep in mind during the drug discovery process. According to this rule, an orally active drug has no more than one violation of the following criteria. The criterias are follows:

- No more than 5 hydrogen bond donors (nHDon),
- No more than 10 hydrogen bond acceptors (nHAcc),
- No more than 10 rotational bonds (nrtob),
- A molecular mass less than 500 Daltons,
- A calculated octanol-water partition coefficient (logP) not greater than 5.

PDB (Protein Data Bank) is a database software, were structural data of macromolecules are stored. It consist of experimentally determined 3D structures which enables its exploration, visualization and analysis.

NovoPro Bioscience Inc. is a software which helps in the conversion of SMILES notation of a molecule to its 3D structure, where it can be downloaded in various formats like .sdf, .pdb, .mol etc

AutoDock is a molecular modelling simulation software. It is especially effective for protein-ligand docking. AutoDock4 is available under the GNU General Public License. AutoDock is one of the most cited docking software applications in the research community. AutoDock consist of two main programs. AutoDock for docking of the ligand to a set of grids describing the target protein; Auto Grid for pre-calculating these grids. [20,21]

PyMol is a 3D molecular visualization software, which is used for preparing high resolution and high quality 3D images of small molecules and biological macromolecules such as proteins. PyMOL is one of the few mostly open-source model visualization tools available for use in structural biology .[20,21]

Protein Preparation: The X-ray crystal structures retrieved from the PDB database as raw could not be suitable for molecular docking studies. A typical PDB structure consists of only heavy atoms, waters, co factors, metal ions and can be of multimeric. These structures do not have the information about bond orders, topologies or formal atomic charges. So, the raw PDB structure should be prepared in a suitable manner for docking. Protein preparation wizard of Glide software was used to process and prepare the protein. This also follows the OPLS-AA force fields for energy minimization.

Ligand Preparation: Ligand preparation was done to minimize the energy of the ligand. A standard drug having selected activity and having binding properties were selected from PubChem database. The selected ligand was then downloaded in .sdf format and visualized in PyMol and then converted to .pdb format. Then it was opened in AutoDock. And then it was subjected to elimination of water, addition of polar hydrogen and addition of Kollmann charges and then saved in .pdbqt format.

Docking: The prepared target and ligand were then opened in Autodock software, then we have selected our target from grid as macromolecule and then inserted the grid box and saved the grid dimension file in .txt format. Then we have created the config file in .txt format and the command was entered into the command prompt and runned the command to obtain the docking score.

2.2. Scheme of Work

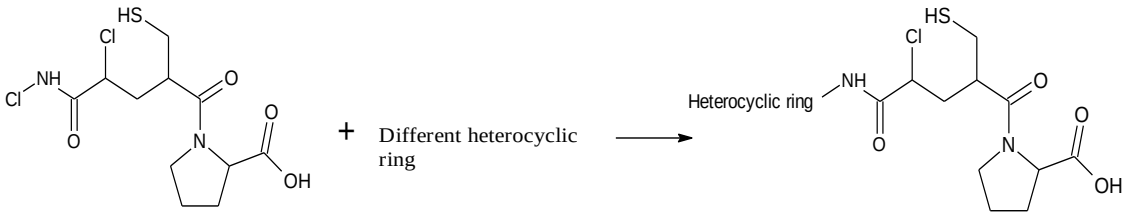


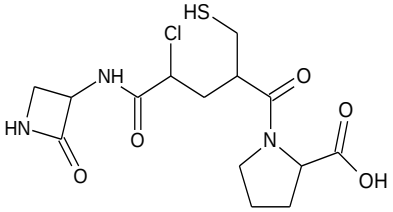
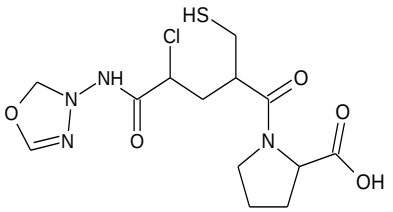
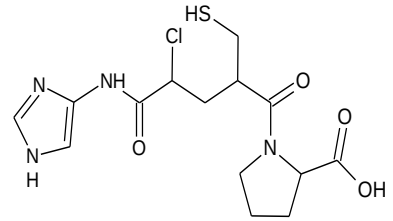
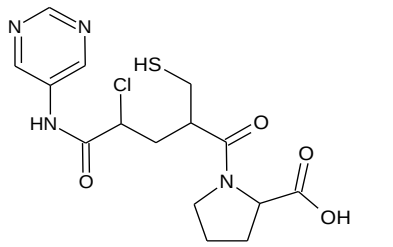
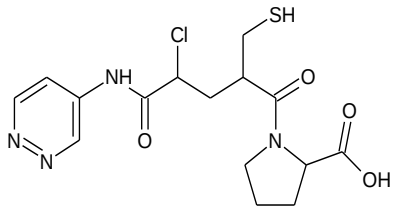
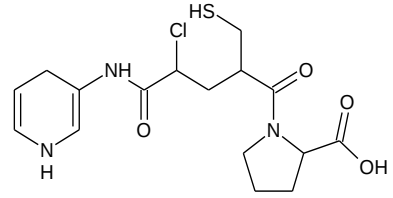
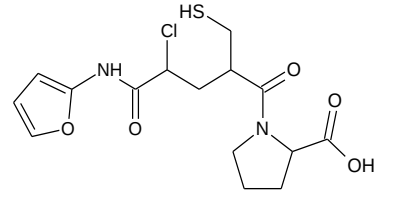
Figure 2 Scheme of Work

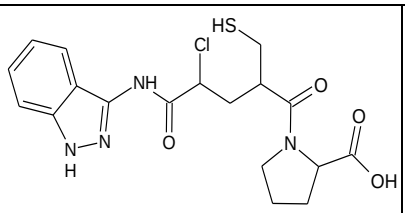
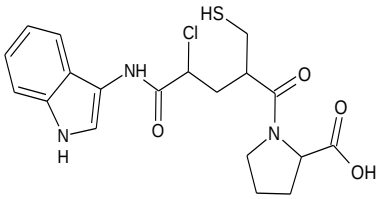
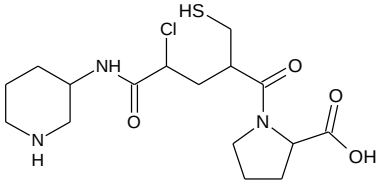
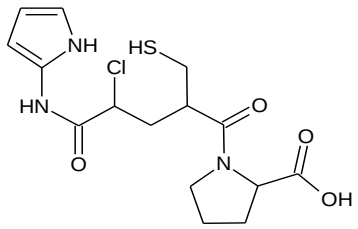
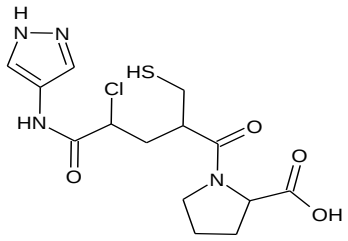
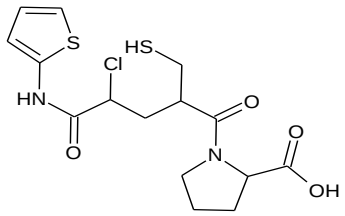
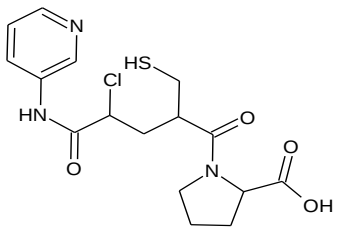
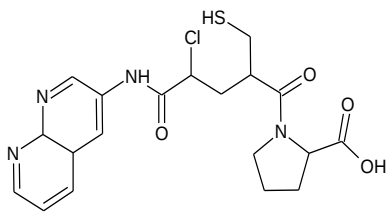
3. Results and discussion

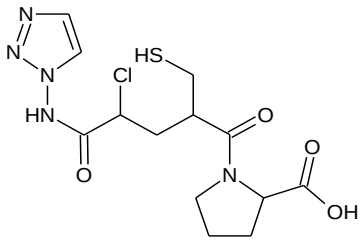
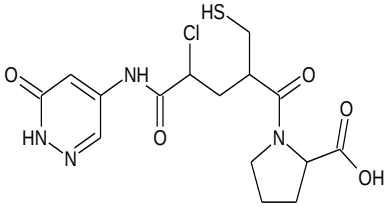
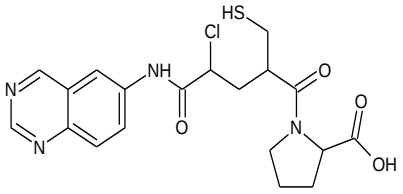
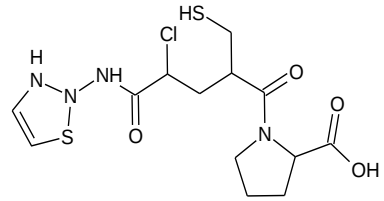
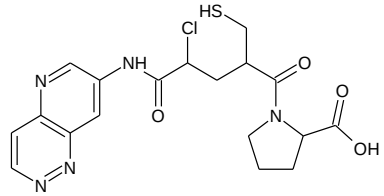
3.1. ACD/Chemsketch

The 2-D structure of proposed derivatives were drawn using ACD/Chemsketch and was shown in Table 2.

Table 2 Proline Derivatives and Their IUPAC Name with SMILES Notation

Sl No.	IUPAC Name	Proposed Ligands	SMILES Notation
1	1-{4-chloro-5-oxo-5-[(2-oxoazetidin-3-yl)amino]-2-(sulfanylmethyl)pentanoyl}pyrrolidine-2-carboxylic acid		OC(=O)C2CCCN2C(=O)C(CC(Cl)C(=O)NC1CNC1=O)CS
2	1-[4-chloro-5-(1,3,4-oxadiazol-3(2*H*)-ylamino)-5-oxo-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		O=C(NN1N=COC1)C(Cl)CC(CS)C(=O)N2CCCC2C(=O)O
3	1-[4-chloro-5-(1*H*-imidazol-4-ylamino)-5-oxo-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		O=C(O)C1CCCN1C(=O)C(CS)CC(Cl)C(=O)Nc2c[nH]cn2
4	1-[4-chloro-5-oxo-5-(pyrimidin-5-ylamino)-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		O=C(O)C1CCCN1C(=O)C(CS)CC(Cl)C(=O)Nc2cncnc2
5	1-[4-chloro-5-oxo-5-(pyridazin-4-ylamino)-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		OC(=O)C2CCCN2C(=O)C(CC(Cl)C(=O)Nc1ccnnc1)CS
6	1-[4-chloro-5-(1,4-dihydropyridin-3-ylamino)-5-oxo-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		OC(=O)C2CCCN2C(=O)C(CC(Cl)C(=O)NC1=CNC=CC1)CS
7	1-[4-chloro-5-(furan-2-ylamino)-5-oxo-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		O=C(Nc1ccco1)C(Cl)CC(CS)C(=O)N2CCCC2C(=O)O

8	1-[4-chloro-5-(1H-indazol-3-ylamino)-5-oxo-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		O=C(O)C1CCCN1C(=O)C(CS)CC(Cl)C(=O)Nc2n[nH]c3ccccc
9	1-[4-chloro-5-(1H-indol-3-ylamino)-5-oxo-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		O=C(O)C1CCCN1C(=O)C(CS)CC(Cl)C(=O)Nc2c[nH]c3ccccc
10	1-[4-chloro-5-oxo-5-(piperidin-3-ylamino)-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		OC(=O)C2CCCN2C(=O)C(CC(Cl)C(=O)NC1CCCNC1)CS
11	1-[4-chloro-5-oxo-5-(1H-pyrrol-2-ylamino)-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		OC(=O)C2CCCN2C(=O)C(CC(Cl)C(=O)Nc1cccn1)CS
12	1-[4-chloro-5-oxo-5-(1H-pyrazol-4-ylamino)-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		O=C(Nc1cnnc1)C(Cl)CC(CS)C(=O)N2CCCC2C(=O)O
13	[4-chloro-5-oxo-2-(sulfanylmethyl)-5-(thiophen-2-ylamino)pentanoyl]pyrrolidine-2-carboxylic acid		O=C(Nc1cccs1)C(Cl)CC(CS)C(=O)N2CCCC2C(=O)O
14	[4-chloro-5-oxo-5-(pyridin-3-ylamino)-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		OC(=O)C2CCCN2C(=O)C(CC(Cl)C(=O)Nc1cccnc1)CS
15	1-[5-(4a,8a-dihydro-1,8-naphthyridin-3-ylamino)-4-chloro-5-oxo-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		OC(=O)C3CCCN3C(=O)C(CC(Cl)C(=O)NC1=CC2C=CC=NC2N=C1)CS

16	1-[4-chloro-5-oxo-2-(sulfanylmethyl)-5-(1*H*-1,2,3-triazol-1ylamino)pentanoyl]pyrrolidine-2-carboxylic acid		O=C(Nn1ccnn1)C(Cl)CC(CS)C(=O)N2CCCC2C(=O)O
17	1-{4-chloro-5-oxo-5-[(6-oxo-1,6-dihydropyridazin-4-yl)amino]-2(sulfanylmethyl)pentanoyl}pyrrolidine-2-carboxylic acid		O=C(NC1=CC(=O)NN=C1)C(Cl)CC(CS)C(=O)N2CCCC2C(=O)O
18	1-[4-chloro-5-oxo-5-(quinazolin-8-ylamino)-2-(sulfanylmethyl)pentanoyl]pyrrolidine-2carboxylic acid		OC(=O)C3CCCN3C(=O)C(CC(Cl)C(=O)Nc2cccc1cncnc12)CS
19	1-[4-chloro-5-oxo-2-(sulfanylmethyl)-5-(1,2,3-thiadiazol-2(3*H*)ylamino)pentanoyl]pyrrolidine-2-carboxylic acid		O=C(NN1NC=CS1)C(Cl)CC(CS)C(=O)N2CCCC2C(=O)O
20	1-[4-chloro-5-oxo-5-(pyrido[3,2-*c*]pyridazin-7-ylamino)-2(sulfanylmethyl)pentanoyl]pyrrolidine-2-carboxylic acid		OC(=O)C3CCCN3C(=O)C(CC(Cl)C(=O)Nc1cc2nnccc2nc1)CS

2-D structure of proposed derivatives were drawn in ACD/Chemsketch.

3.2. Molinspiration

The Lipinski's rule and the drug likeness properties of proposed derivatives were analysed by Molinspiration. The properties are shown in Table 3 and 4

Table 3 Lipinski's rule analysis of proposed derivatives

Compound	Log P	Mol Wt	nHDon	nHAcc	nrtob	nViolations
1	-2.54	377.85	3	8	7	0
2	-1.83	378.84	2	9	7	0
3	-1.69	374.85	3	8	7	0
4	-1.58	386.86	2	8	7	0
5	-2.01	386.86	2	8	7	0
6	-1.12	387.89	3	7	7	0
7	-0.66	374.85	2	7	7	0

8	0.01	424.91	3	8	7	0
9	0.35	423.92	3	7	7	0
10	-1.67	391.92	3	7	7	0
11	-0.76	373.86	3	7	7	0
12	-1.49	374.85	3	8	7	0
13	-0.01	390.91	2	6	7	0
14	-0.87	385.87	2	7	7	0
15	-1.03	438.94	2	8	7	0
16	-1.98	375.84	2	9	7	0
17	-2.15	402.86	3	9	7	0
18	-0.25	436.92	2	8	7	0
19	-1.21	394.91	3	8	7	0
20	-0.97	437.91	2	9	7	0
Captopril	-1.09	217.29	1	4	3	0

The molinspiration for the above designed 20 proline derivatives along with the standard drug Captopril were done and it was found that all the 20 derivatives were found to obey the Lipinski's Rule of Five.

Table 4 Drug Likeness Properties of Proposed Ligands

Compound	**GPCR Ligand**	**Ion Channel Modulator**	**Kinase Inhibitor**	**Nuclear Receptor Ligand**	**Protease Inhibitor**	**Enzyme Inhibitor**
1	0.37	0.03	-0.17	0.02	1.28	0.41
2	0.15	-0.12	-0.39	-0.03	0.87	0.30
3	0.47	-0.04	0.08	-0.46	0.82	0.55
4	0.35	0.05	0.03	-0.03	0.87	0.36
5	0.34	0.13	-0.04	-0.15	0.81	0.36
6	0.30	-0.10	-0.32	-0.08	0.83	0.40
7	0.25	-0.37	-0.35	-0.35	0.58	0.20
8	0.40	0.10	0.28	-0.15	0.93	0.33
9	0.22	0.05	0.20	-0.03	0.68	0.09
10	0.23	-0.05	-0.05	-0.19	0.66	0.14
11	0.34	0.08	-0.09	0.03	0.89	0.38
12	0.14	-0.21	-0.17	-0.39	0.67	0.26
13	0.06	-0.23	-0.30	-0.34	0.75	0.16
14	0.27	0.06	-0.09	-0.08	0.89	0.34
15	0.22	-0.19	-0.34	-0.27	0.78	0.36
16	0.38	-0.08	-0.02	-0.15	1.04	0.46
17	0.10	-0.20	-0.18	-0.47	0.47	0.20
18	0.38	0.14	0.10	-0.15	0.80	0.42

19	0.30	-0.09	-0.10	-0.11	0.90	0.38
20	0.25	0.25	0.18	-0.06	0.71	0.33
Captopril	-0.14	-0.08	-0.98	-0.55	0.97	0.50

GPCR- G-protein Coupled Receptor

The molinspiration for the above designed 20 proline derivatives along with the standard drug Captopril were done and it was found that all the 20 derivatives were found to obey the drug likeness properties. Thus, these compounds have been selected for further steps.

3.3. PASS (Prediction of Activity Spectra for Substances)

PASS predicts the biological activity of proposed derivatives, where 'Pa' indicates the probability to be active and 'Pi' indicates the probability to be inactive.

Table 5 PASS Values of Proposed Derivatives

Sl No	PASS Values	
	Pa	Pi
1	0,164	0,008
2	0,106	0,014
3	0,078	0,023
4	0,086	0,019
5	0,098	0,016
6	0,096	0.016
7	0,091	0,018
8	0,073	0,026
9	0,110	0,014
10	0,176	0,007
11	0,088	0,019
12	0,082	0,021
13	0,109	0,014
14	0,088	0,019
15	0,069	0,029
16	0,104	0,015
17	0,074	0,025
18	0,069	0,029
19	0,119	0,012
20	0,062	0,035
Captopril	0,592	0,002

PASS for the designed 20 Proline derivatives and standard drug Captopril was done, and it was found all the derivatives possess Angiotensin Converting Enzyme Inhibitor activity similar to the standard drug Captopril.

3.4. Docking

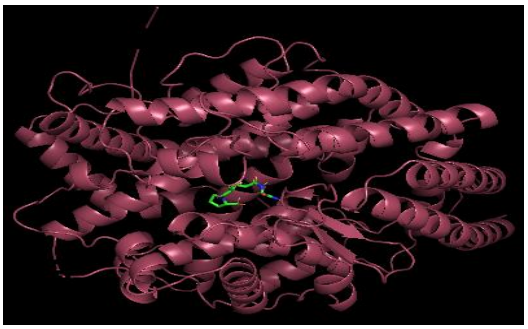
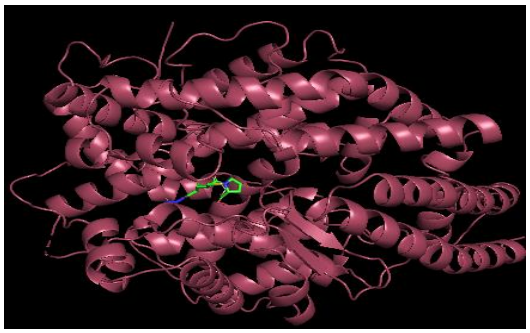
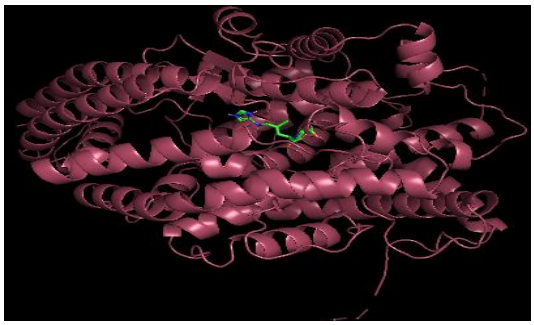
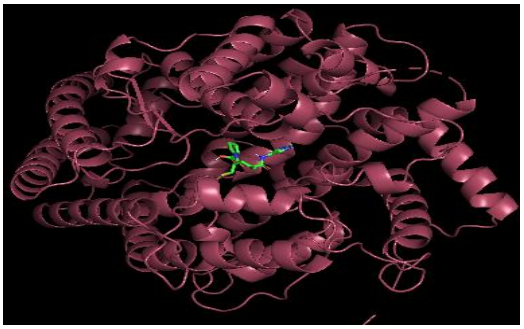
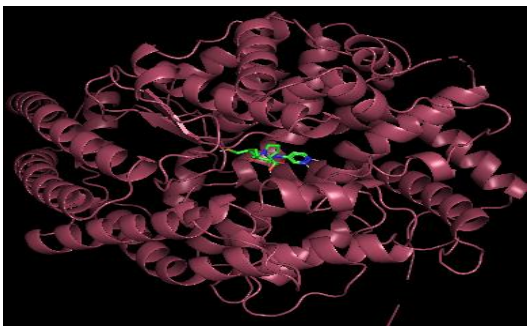
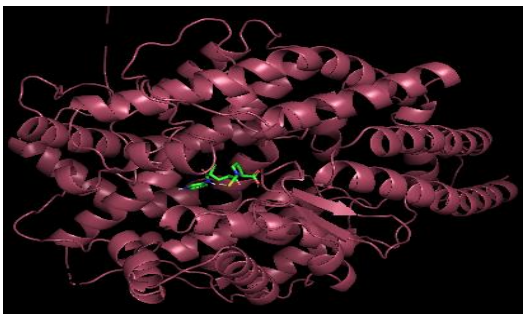
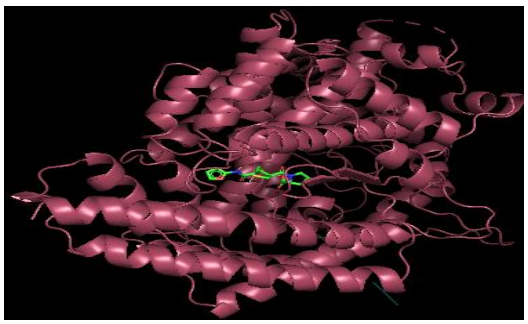
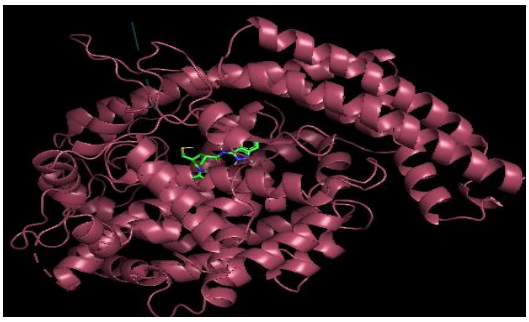
Designed ligands and standard drug metformin were docked with 1O8A (Human Angiotensin Converting Enzyme). The docking scores of analogues are shown in Table 6.

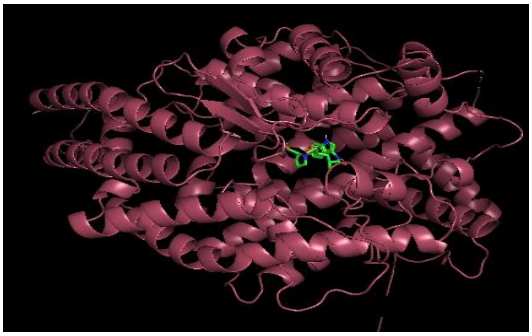
Table 6 Docking Score of Proposed Analogues and Standard with 1O8A

Sl No	Compound	Docking Score
1	1	-7.3
2	2	-7.4
3	3	-7.4
4	4	-7.5
5	5	-7.6
6	6	-7.3
7	7	-7.4
8	8	-8.9
9	9	-8.0
10	10	-7.2
11	11	-6.6
12	12	-6.7
13	13	-6.8
14	14	-6.9
15	15	-7.6
16	16	-6.9
17	17	-7.9
18	18	-7.9
19	19	-6.9
20	20	-8.0
21	Captopril	-5.4

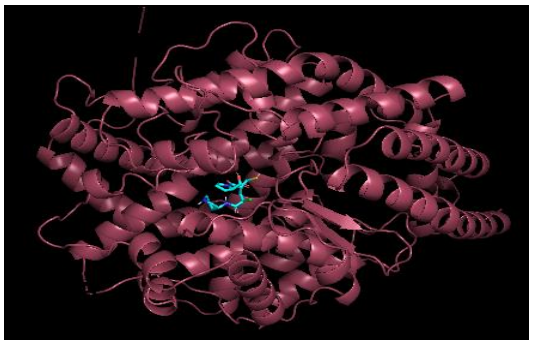
Based on the docking score, it was found that the designed proline derivatives showed higher docking score than the standard drug Captopril.

Table 7 Table Showing Images of Docked Complex

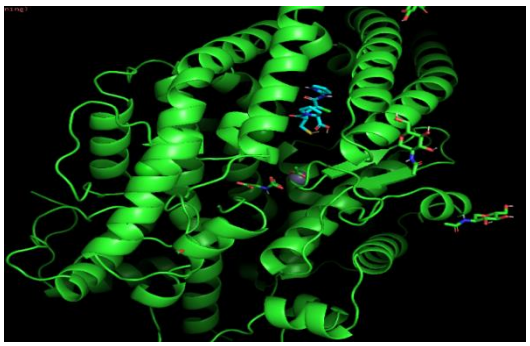
 Docked complex of 1O8A with Compound 1	 Docked complex of 1O8A with Compound 2
 Docked complex of 1O8A with Compound 3	 Docked complex of 1O8A with Compound 4
 Docked complex of 1O8A with Compound 5	 Docked complex of 1O8A with Compound 6
 Docked complex of 1O8A with Compound 7	 Docked complex of 1O8A with Compound 8



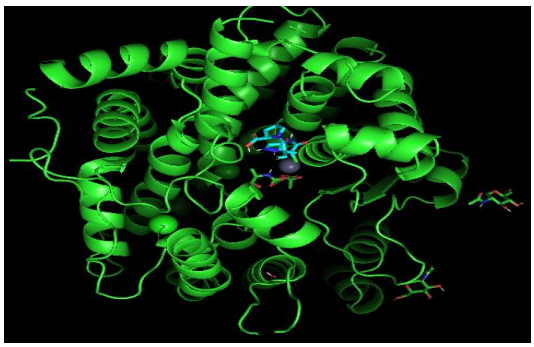
Docked complex of 1O8A with Compound 9



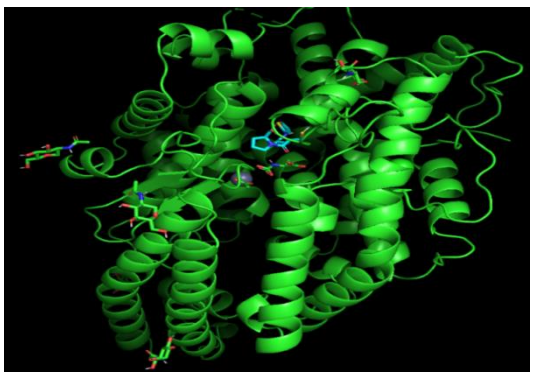
Docked complex of 1O8A with Compound 10



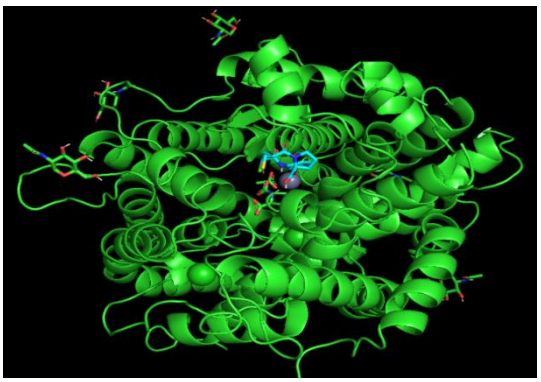
Docked complex of 1O8A with Compound 11



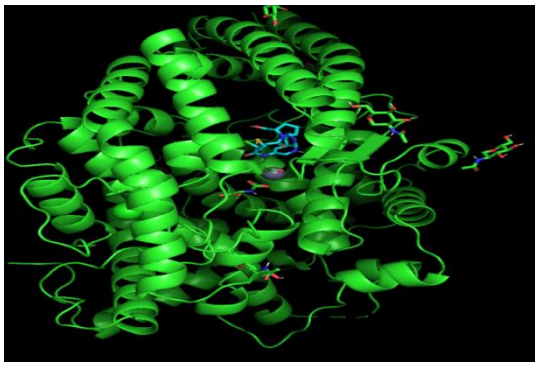
Docked complex of 1O8A with Compound 12



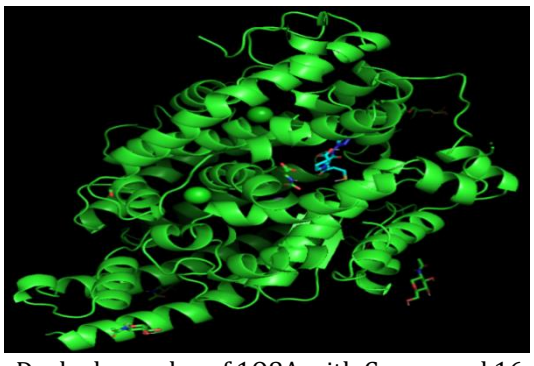
Docked complex of 1O8A with Compound 13



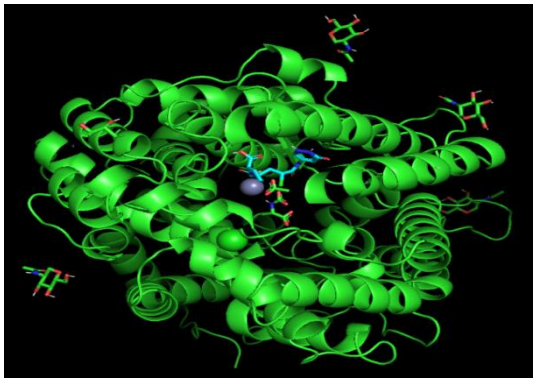
Docked complex of 1O8A with Compound 14



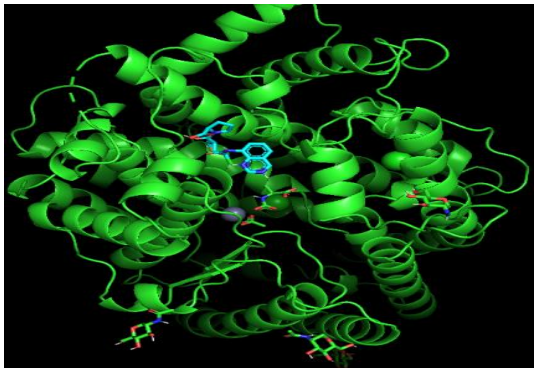
Docked complex of 1O8A with Compound 15



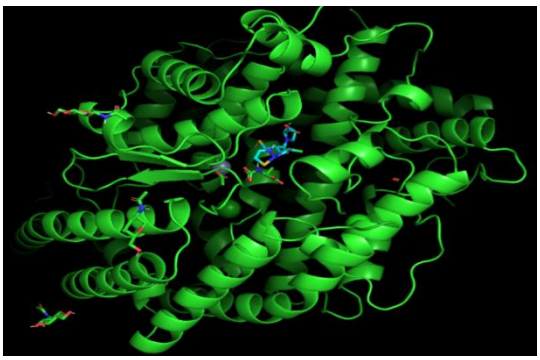
Docked complex of 1O8A with Compound 16



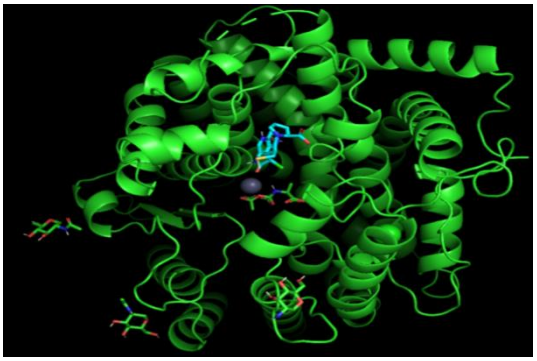
Docked complex of 1O8A with Compound 17



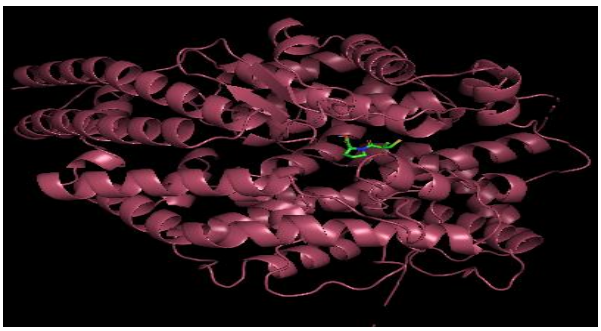
Docked complex of 1O8A with Compound 18



Docked complex of 1O8A with Compound 19



Docked complex of 1O8A with Compound 20



Docked complex of 1O8A with Captopril

The images of docked complex with the target 1O8A with the proposed derivatives and standard drug Captopril were obtained.

4. Conclusion

From the docking study, it was found that the designed Proline derivatives possess more anti-hypertensive activity than the standard drug Captopril. Captopril has a docking score of -5.4 and the designed proline derivatives possess least binding energy, because the ligands are having heterocyclic ring and they are more electronegative because of the inductive, field and mesomeric effect. The electronegativity facilitate the binding interaction with the receptor. Here, the linker used is CHCl-NH-C=O group, which links the basic nucleus with the derivative. The linker helps to increase the binding affinity towards the binding pockets residing in the receptor. In these compounds, the use of an oxygen atom as a bioisosteric linker which has smaller bond angle and greater electronegativity results in analogues with increased potency. The difference in the force field energy of the analogues varies the binding score of proposed ligands.

Therefore, the work concluded that the proposed ligands are promising ACE-Inhibitors which provides anti-hypertensive activity.

Compliance of ethical standard

Acknowledgement

We would like to express our sincere gratitude to Mrs. Vani V., Associate Professor, and Dr. Sreeja S., HOD, Department of Pharmaceutical Chemistry, Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala for their valuable suggestions and remarkable encouragement.

Disclosure of Conflict of interest

No Conflict of interest.

References

[1] Beevers DG, Lip GY, O'Brien ET. ABC of Hypertension: The pathophysiology of hypertension. British Medical Journal. 2014; 322(7291):912-916.

[2] Shafi ST, Shafi T. A survey of hypertension prevalence, awareness, treatment, and control in health screening camps of rural central Punjab, Pakistan. Journal of Epidemiology and Global Health. 2017;7(2):135-40.

[3] Herman LL, Padala SA, Ahmed I, Bashir K. Angiotensin converting enzyme inhibitors (ACEI). StatPearls. 2023;PMID:28613705

[4] Petrillo Jr EW, Ondetti MA. Angiotensin-converting enzyme inhibitors: Medicinal chemistry and biological actions. Medicinal Research Reviews. 1982;2(1):1-41.

[5] Regulska K, Stanisz B, Regulski M, Murias M. How to design a potent, specific, and stable angiotensin-converting enzyme inhibitor. Drug Discovery Today. 2014;19(11):1731-43.

[6] Krapcho J, Turk C, Cushman DW, Powell JR, DeForrest JM, Spitzmiller ER et al. Angiotensin-converting enzyme inhibitors: Mercaptan, carboxyalkyl dipeptide, and phosphinic acid inhibitors incorporating 4-substituted prolines. Journal of Medicinal Chemistry. 1988;31(6):1148-60.

[7] Venkatesh R, Kasaboina S, Gaikwad HK, Janardhan S, Bantu R, Nagarapu L et al. Design and synthesis of 3-(3-((9H-carbazol-4-yl) oxy)-2-hydroxypropyl)-2-phenylquinazolin-4 (3H)-one derivatives to induce ACE inhibitory activity. European Journal of Medicinal Chemistry. 2015;96:22-29.

[8] Auwal SM, Zainal Abidin N, Zarei M, Tan CP, Saari N. Identification, structure-activity relationship and in silico molecular docking analyses of five novel angiotensin I-converting enzyme (ACE)-inhibitory peptides from stone fish (Actinopyga lecanora) hydrolysates. PLoS One. 2019;14(5):e0197644.

[9] Mukhlif MG, Hameed AS, Algburi FS. Design, Synthesis And Molecular Docking Of L-Prolinamide Containing Thiazolidine-4-One Ring System As (ACE Inhibitors). Natural Volatiles and Essential Oils Journal. 2022;8(4):15390-415.

[10] Hai-Bang T, Shimizu K. Potent angiotensin-converting enzyme inhibitory tripeptides identified by a computer-based approach. Journal of Molecular Graphics and Modelling. 2014;53:206-11.

[11] Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry. 2010;31(2):455-61.

[12] Lionta E, Spyrou G, K Vassilatis D, Cournia Z. Structure-based virtual screening for drug discovery: Principles, applications and recent advances. Current Topics in Medicinal Chemistry. 2014;14(16):1923-38.

[13] Saeid H, Al-sayed H, Bader M. A Review on Biological and Medicinal Significance of Furan. AlQalam Journal of Medical and Applied Sciences. 2023;6(1)44-58.

[14] Makkar F, Chakraborty K. Novel furanyl derivatives from the red seaweed Gracilaria opuntia with pharmacological activities using different in vitro models. Medicinal Chemistry Research. 2018;27:1245-59.

[15] Ismail MA, Aboul-Enein MN, Abouzid KA, Abou El Ella DA, Ismail NS. ACE inhibitors hypothesis generation for selective design, synthesis and biological evaluation of 3-mercapto-2-methyl-propanoyl-pyrrolidine-3-imine derivatives as antihypertensive agents. Bioorganic & Medicinal Chemistry. 2009;17(10):3739-46.

[16] Honma T, Tada Y, Adachi I, Igarashi K. On pyrrolidine derivatives I. An efficient synthesis of 3-substituted (2S, 5S)-pyrrolidine-2, 5-dicarboxylic acids. Journal of Heterocyclic Chemistry. 1989;26(3):629-634.

[17] Nicolai E, Cure G, Goyard J, Kirchner M, Teulon JM, Versign A et al. Synthesis and angiotensin II receptor antagonist activity of C-linked pyrazole derivatives. Chemical and Pharmaceutical Bulletin. 1994;42(8):1617-30.

[18] Datta S, Kavitha PN, Singh A. Synthesis, characterization and docking studies of some new thiophene derivatives and their in-vitro anti-microbial screening. International Journal of Pharmacology. 2014;2(3):10-7.

[19] Poojari S, Krishnamurthy G, KS JK, Kumar S, Naik S. Anti-inflammatory, antibacterial and molecular docking studies of novel spiro-piperidine quinazolinone derivatives. Journal of Taibah University for science. 2017;11(3):497-511.

[20] Seeliger D, de Groot BL. Ligand docking and binding site analysis with PyMOL and Autodock/Vina. Journal of Computer-Aided Molecular Design. 2010;24(5):417-22.

[21] Rauf MA, Zubair S, Azhar A. Ligand docking and binding site analysis with pymol and autodock/vina. International Journal of Basic and Applied Sciences. 2015;4(2):168.

[22] El-Enany WA, Gomha SM, El-Ziaty AK, Hussein W, Abdulla MM, Hassan SA, et al. Synthesis and molecular docking of some new bis-thiadiazoles as anti-hypertensive α-blocking agents. Synthetic Communications. 2020;50(1):85-96.

[23] Hassall CH, Kröhn A, Moody CJ, Thomas WA. The design and synthesis of new triazolo, pyrazolo-, and pyridazo-pyridazine derivatives as inhibitors of angiotensin converting enzyme. Journal of the Chemical Society, Perkin Transactions 1. 1984;155-64.

[24] Xu, Z., Wu, C., Sun-Waterhouse, D., Zhao, T., Waterhouse, G.I., Zhao, M. and Su, G., 2021. Identification of post-digestion angiotensin-I converting enzyme (ACE) inhibitory peptides from soybean protein Isolate: Their production conditions and in silico molecular docking with ACE. Food Chemistry. 2021;345:128855 .

[25] Salah BB, Hamzaoui S, Krichen F, Saadaoui I, Mansour RB, Miled N et al. Design, synthesis of novel Triazolones and bis-Triazolones derivatives under ultrasound irradiation and evaluation as potent angiotensin converting enzyme (ACE) inhibitors. Bioorganic Chemistry. 2018;76:147-53.

[26] Choudary J, Kini SG, Karkala SR, Mubeen M. Docking studies and biological activity of fosinopril analogs. International Journal of Medicinal Chemistry. 2014;2014(6-7):721834.

[27] Qian B, Yu L, Tian C, Huang S, Huo J, Villarreal OD et al. Citrullyl-hydroxyprolyl-proline (ChPP): An artificially synthesized tripeptide as potent ACE inhibitor. International Journal of Peptide Research and Therapeutics. 2021;27:967-76.

[28] Tan C, Yang SJ, Zhao DH, Li J, Yin LQ. Antihypertensive activity of indole and indazole analogues: A review. Arabian Journal of Chemistry. 2022;103756.

[29] Tyrkov AG, Tyurenkov IN, Timchenko MV, Perfilova VN. Hypertensive activity of 3-aryl-5-nitromethyl-1, 2, 4-oxadiazoles and their alkyl substituted derivatives. Pharmaceutical Chemistry Journal. 2006;40(5):240-2.

[30] Zhu W, Bao X, Ren H, Liao P, Zhu W, Yan Y et al. Design, synthesis, and pharmacological evaluation of 5-oxo-1, 2, 4-oxadiazole derivatives as AT1 antagonists with antihypertension activities. Clinical and Experimental Hypertension. 2016;38(5):435-42.

[31] Hossain M, Thomas R, Mary YS, Resmi KS, Armaković S, Armaković SJ et al. Understanding reactivity of two newly synthetized imidazole derivatives by spectroscopic characterization and computational study. Journal of Molecular Structure. 2018;1158:176-96.

[32] Zebbiche Z, Şekerci G, Boulebd H, Küçükbay F, Tekin S, Tekin Z et al. Preparation, DFT calculations, docking studies, antioxidant, and anticancer properties of new pyrazole and pyridine derivatives. Journal of Biochemical and Molecular Toxicology. 2022;36(9):e23135.

[33] Winters G, Sala A, Barone D, Baldoli E. Synthesis, in vitro [3H] prazosin displacement, and in vivo activity of 3-aryl-4, 5, 6, 7-tetrahydropyrazolo [4, 3-c] pyridines, a new class of antihypertensive agents. Journal of medicinal chemistry. 1985;28(7):934-40.

[34] Banerjee R, Kumar HK, Banerjee M. Medicinal significance of furan derivatives: a review. International Journal of Research in Phytochemistry and Pharmacology. 2015;5(3):48-57.

[35] Shaik M, Ahmed SM. Synthesis of 6-chloro-4-(furan-2-ylmethyleneamino)-2, 2-dimethyl-2H-chromen-3-ol for antihypertensive activity. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2012;3(4):569-77.

[36] Jays J, Mohan S, Saravanan J. Molecular Docking Studies of Novel Furan-azetidinone Hybrids as Potential Inhibitors of Escherichia coli. Indian Journal of Pharmaceutical Education and Research. 2019;53(3):S325-31.

[37] Dhakad A, Sharma MC, Chaturvedi SC, Sharma S. 3D-QSAR studies, biological evaluation studies on some substituited 3-chloro-1-[5-(5-chloro-2-phenyl-benzimidazole-1-ylmethyl)-[1,3,4] thiadiazole-2-yl]-azetidin-2-one as potential antimicrobial activity. Digest Journal of Nanomaterials & Biostructures (DJNB). 2009;4(2).

[38] Farghaly AM, AboulWafa OM, Elshaier YA, Badawi WA, Haridy HH, Mubarak HA. Design, synthesis, and antihypertensive activity of new pyrimidine derivatives endowing new pharmacophores. Medicinal Chemistry Research. 2019;28:360-79.

[39] Gil-Longo J, Laguna MD, Verde I, Castro ME, Orallo F, Fontenla JA et al. Pyridazine derivatives. XI: Antihypertensive activity of 3-hydrazinocycloheptyl [1, 2-c] pyridazine and its hydrazone derivatives. Journal of Pharmaceutical Sciences. 1993;82(3):286-90.

[40] Lehmann HU, Witt E, Hochrein H. Evaluation of a pyridopyridazine as a drug with marked antihypertensive properties. Clinical Medicine Journal. 1977;72(28-29):1203-8.

[41] Siddiqui AA, Mishra R, Shaharyar M. Synthesis, characterization and antihypertensive activity of pyridazinone derivatives. European Journal of Medicinal Chemistry. 2010;45(6):2283-90.

[42] Demirayak S, Karaburun AC, Beis R. Some pyrrole substituted aryl pyridazinone and phthalazinone derivatives and their antihypertensive activities. European Journal of Medicinal Chemistry. 2004;39(12):1089-95.

[43] Caballero J. Considerations for docking of selective angiotensin-converting enzyme inhibitors. Molecules. 2020;25(2):295.

[44] Muhammad SA, Fatima N. In silico analysis and molecular docking studies of potential angiotensin-converting enzyme inhibitor using quercetin glycosides. Pharmacognosy Magazine. 2015;11(Suppl 1):S123.

[45] Goshain O, Ahmed B. Antihypertensive activity, toxicity and molecular docking study of newly synthesized xanthon derivatives (xanthonoxypropanolamine). PLoS One. 2019;14(8):e0220920.

[46] Mishra R, Siddiqui AA, Husain A, Rashid M, Goda C. Design, synthesis and antihypertensive screening of novel pyridazine substituted s-triazin-2-imine/one/thione derivatives. Journal of Enzyme Inhibition and Medicinal Chemistry. 2013;28(3):552-9.

[47] Sharifi N, Souri E, Ziai SA, Amin G, Amini M, Amanlou M. Isolation, identification and molecular docking studies of a new isolated compound, from Onopordon acanthium: A novel angiotensin converting enzyme (ACE) inhibitor. Journal of ethnopharmacology. 2013;148(3):934-9.

[48] Wu Q, Du J, Jia J, Kuang C. Production of ACE inhibitory peptides from sweet sorghum grain protein using alcalase: Hydrolysis kinetic, purification and molecular docking study. Food Chemistry. 2016;199:140-9.

[49] Al-Saad HN, Kubba AA. Evaluation of new Thiosemcarbazides derived from captopril as angiotensin-converting enzyme inhibitors with docking study, and predicted-ADMET analysis. Research Journal of Pharmacy and Technology. 2020;13(6):2733-41.

[50] Khatun S. Probing of the binding profile of anti-hypertensive drug, captopril with bovine serum albumin: a detailed calorimetric, spectroscopic and molecular docking studies. The Journal of Chemical Thermodynamics. 2018;126:43-53.