ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

INSILICO DRUG DESIGN AND DISCOVERY OF NOVEL PANTOPRAZOLE DERIVATES

[1]Sai Kiran Annam, [2]SK Abdul Rahaman and [3]Sundar Raj Injeti

[1,2,3] Nirmala College of Pharmacy, Atmakur, Mangalagiri, Guntur (Dt), Andhra Pradesh, India.

Corresponding Author

Dr.SK.Abdul Rahaman

Principal and Professor, Nirmala College of Pharmacy, Atmakur, Mangalagiri, Guntur(Dt), Andhra Pradesh, India.

ABSTRACT

AIM: To develop novel Pantoprazole derivatives using docking studies and determine and compare the binding efficiency of predicted molecules with standard proton pump inhibitors

MATERIALS & METHODS: ChemDraw Ultra 12.0 software, Discovery studio, software Open bable Autodock version 4.2 of pyrx software

RESULTS: Molecular docking studies of 12 Pantoprazole derivatives and isometric derivatives were carried out and the docking scores of 12 compounds fall within the range of -6.21 to -8.73 kcal/mol and the Pantoprazole derivative of compound 1 and 8 shows better binding energy i.e., -8.73 and -8.43 than the standard Pantoprazole compound

CONCLUSION: Molecular docking studies for anti-ulcer activity on H^+/K^+- ATP ase enzyme were carried out on 12 compounds of Pantoprazole derivatives and it is observed that among all derivatives compound 1 showed significant binding energy (-8.73) compared with standard Pantoprazole (-6.21).

INTRODUCTION

The completion of the human genome project has resulted in an increasing number of new therapeutic targets for drug discovery. At the same time, high-throughput protein purification, crystallography and nuclear magnetic resonance spectroscopy techniques have been developed and contributed to many structural details of proteins and protein-ligand complexes[1]. These advances allow the computational strategies to permeate all aspects of drug discovery today, such as the virtual screening (vs) techniques for hit identification and methods for lead optimization. Compared with traditional experimental high-throughput screening (hts), vs is a more direct and rational drug discovery approach and has the advantage of low cost and effective screening .vs can be classified into ligand-based and structure-based methods. When a set of active ligand molecules is known and little or no structural information is available for targets, the ligand-based methods, such as pharmacophore modeling and quantitative structure activity relationship (qsar) methods can be employed[2]. As to structure-based drug design, molecular docking is the most common method which has been widely used ever since the early 1980's. Programs based on different algorithms were developed to perform molecular docking studies, which have made docking an increasingly important tool in pharmaceutical research. Various excellent reviews on docking have been published in the past, and many comparison studies were conducted to evaluate the relative performance of the programs[3].

The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes[4]. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites (usually referred to as pose) and assessment of the binding affinity[5]. These two steps are related to sampling methods and scoring schemes, respectively, which will be discussed n the theory section. Knowing the location of the binding site before docking processes significantly increases the docking efficiency. In many cases, the binding site is indeed known before docking ligands into it[6]. Also, one can obtain information about the sites by comparison of the target protein with a family of proteins sharing a similar function or with proteins co-crystallized with other ligands. In the absence of knowledge about the binding sites, cavity detection programs or online servers, e.g. Grid, pocket, surfnet, pass andmmc can be utilized to identify putative active sites within

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

proteins. Docking without any assumption about the binding site is called blind docking[7] . The early elucidation for the ligand-receptor binding= mechanism is the lock-and-key theory proposed by fischer, in which the ligand fits into the receptor like lock and key. The earliest reported docking methods were based on this theory and both the ligand and receptor were treated as rigid bodies accordingly. Then the "induced-fit" theory created by koshland takes the lock-and-key theory a step further, stating that the active site of the protein is continually reshaped by interactions with the ligands as the ligands interact with the protein. This theory suggests that the ligand and receptor should be treated as flexible during docking. Consequently, it could describe the binding events more accurately than the rigid treatment[8].

Considering the limitation of computer resources, docking has been performed with a flexible ligand and a rigid receptor for a long time, and remains the most popular method in use recently many efforts have been made to deal with the flexibility of the receptor, however, flexible receptor[9]. Docking, especially backbone flexibility in receptors, still presents a major challenge for available docking methods[10].
In our study, I had attemped to develop novel pantoprazole derivatives using docking studies and also to determine and compare the binding efficiency of predicted molecules with standard proton pump inhibitors.

METHODOLOGY

SOFTWARES USED FOR DOCKING:

i. ChemDraw Ultra 12.0 software

ii. Discovery studio software

iii. Open bable

iv. Autodock version 4.2 of pyrx software

Molecular docking studies:

Protein-Ligand docking studies of Pantaprazole derivatives was evaluated in order to investigate the interaction between the active site of H^+/K^+-ATPase enzyme and the ligands on Hp G630 computer system, with Intel ® Core™ i3 Dual CPU, M330 @2.13 GHz 2.13 GHz, 4 GB of RAM using Auto dock vina 4.2 of pyrex virtual screening software, Chimera version 1.10.2 and open bable software.

1. Ligands preparation for docking:

The 2D structure of the compounds (pantaprazole derivatives) was drawn using ChemDraw Ultra 12.0 software, and where later converted to 3D structures for geometry optimization of the compounds, using discovery studio software

2.Preparation of receptor:

The structure of gastric proton pump inhibitors, with the PDB code 3IXZ receptor, was downloaded from Protein Databank (PDB). The 3D structure receptor was prepared by discarding water molecules and cofactors using open bable and save as Pdb (Ravinchandran et al., 2011).

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

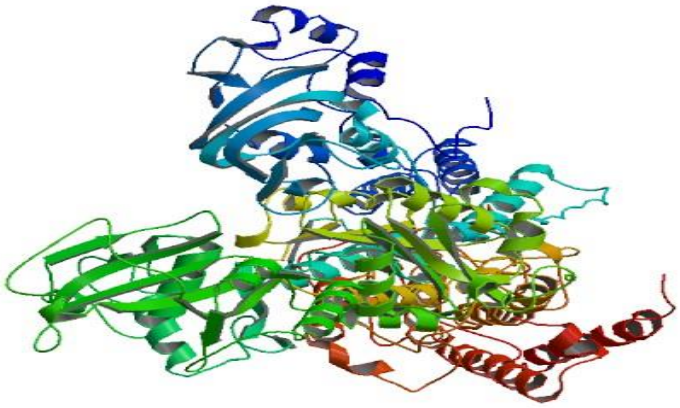


Fig1: structure of 3IXZ receptor

3.Docking of the ligands with the receptor using Autodock version 4.2 of pyrx software:

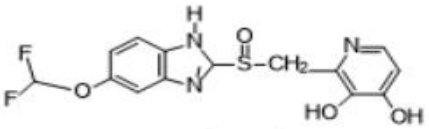
The docking of the ligands (pantaprazole derivatives) and the receptor (H^+/K^+ ATpase) was perform using Autodock version 4.2 of pyrx software (Trott and Olson,2010). Chimera 1.10.2 software was used to form the complex (ligand-receptor) since the receptor and the ligand separate after carrying out the docking with autodock vina of pyrx. The complexes were visualized to view their interactions using discovery studio software.

RESULTS:

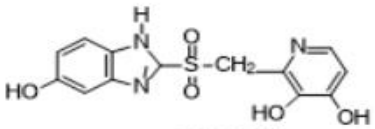
The structural derivatives of pantaprazole are given in below figure.2

Fig.2 structures of pantaprazole derivatives

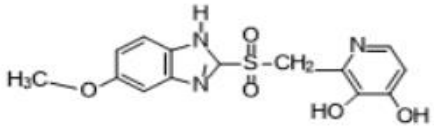
ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021



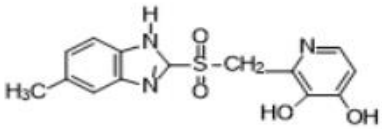
pantaprazole



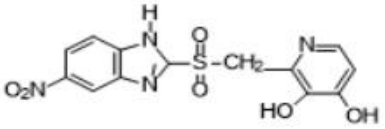
compond1



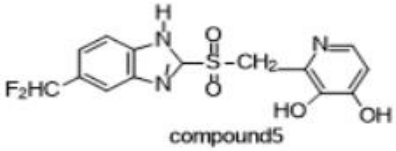
compound2



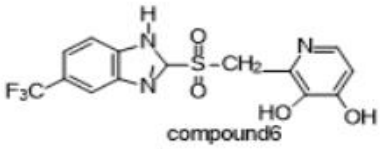
compound3



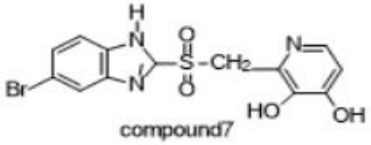
compound4



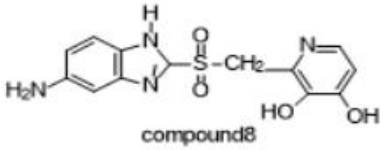
compound5



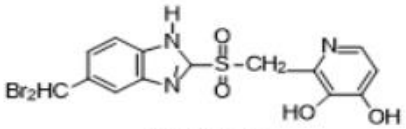
compound6



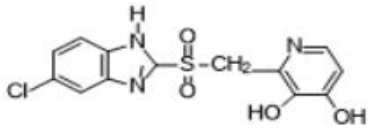
compound7



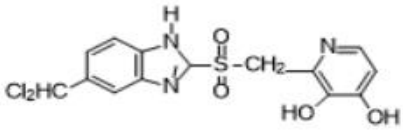
compound8



compound9



compound10



compound11

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Table-1 Results of docking structures of Pantoprazole derivatives

TARGET		H+, K+-ATPASE(PDB: 5YLV)	
Srl.No.	**LIST OF LIGANDS**	**BINDING ENERGY(KCAL/MOL)**	**KI VALUE**
1	Pantoprazole	-6.21	27.97 µM
2	**Compound 1**	**-8.73**	**398.88nM**
3	**Compound 2**	**-7.87**	**1.71µM**
4	Compound 3	-7.26	4.77µM
5	**Compound 4**	**-8.15**	**1.06µM**
6	Compound 5	-6.76	11.06 µM
7	Compound 6	-6.87	9.25 µM
8	Compound 7	-6.51	16.82 µM
9	**Compound 8**	**-8.43**	**662.33 nM**
10	Compound 9	-7.31	4.36µM
11	Compound 10	-7.34	4.14µM
12	**Compound 11**	**-8.13**	**1.09µM**
13	Compound 12	-7.07	6.55µM

DISCUSSION

- Molecular docking studies of 12 Pantoprazole derivatives and isometric derivatives were carried out and the docking scores of 12 compounds fall within the range of -6.21 to -8.73 kcal/mol.
- In Pantoprazole structure, 6-difluoromethoxy is replaced with hydroxyl group(-OH) which yield -8.73 kcal/mol with KI value 398.88nM
- In Pantoprazole structure, 6-difluoromethoxy is replaced with methoxy group(-CH3O) which yield -7.87 kcal/mol with KI value 1.71µM
- In Pantoprazole structure, 6-difluoromethoxy is replaced with nitrous oxide group (-NO2) which yield -8.15 kcal/mol with KI value 1.06µM
- In Pantoprazole structure, 6-difluoromethoxy is replaced with amine group (-NH2) which yield -8.43 kcal/mol with KI value 662.33 nm
- In Pantoprazole structure, 6-difluoromethoxy is replaced with methyl dichloro group (-CHCl2) which yield -8.13 kcal/mol with KI value 1.09µM
- All the Compounds were found to strongly inhibit the H^+/K^+-ATPase enzyme by totally inundating the efficient site in target protein, the result of docking analysis showed that all the docked ligands have lower energy value (high binding energy value) near to the standard anti-ulcer drug (Pantoprazole) with it binding energy value of -6.21 kcal/mol. Fig depict the best low binding energy (high binding energy values) for the docked ligands.
- Among the 12 ligands; that were docked with the enzyme (H^+/K^+-ATPase), compund 1 (fig 1) shows better result.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

CONCLUSION

- Molecular docking studies for anti ulcer activity on H^+/K^+- ATP ase enzyme were carried out on 12 compounds of Pantoprazole derivatives .
- It is observed that among all derivatives compound 1 showed significant binding energy (-8.73) compared with std Pantoprazole (-6.21).

REFERENCES

1. Vishwanadham Yerragunta, Pratima patil, S. Srujana, Roopa Devi, R.Gayathri, Srujana, Aary Divya, BENZIMIDAZOLE DERIVATIVES AND ITS BIOLOGICALIMPORTANCE: A REVIEW 2014, 2(3), 109-113
2. Singh G, Singh A, Verma RK, Mall R, Azeem U. Synthesis, biological evaluation and molecular docking studies of novel benzimidazole derivatives. Comput Biol Chem. 2018 Feb; 72:45-52.
3. Kumaraswamy Gullapelli , G. Brahmeshwari , M. Ravichander , Uma Kusuma , Synthesis, antibacterial and molecular docking studies of new benzimidazole derivatives, Egyptian Journal of Basic and Applied Sciences 4 (2017) 303–309
4. Poonam M More , Rishikesh V Antre , Tushar T Shelke , Madhavi M Mutha , Sahar M Badr , Hassan M Eisa and Pradeep V Kore1, Docking Studies of Benzimidazole Derivatives as Coenzyme-A Carboxylase (ACCase) Inhibitor, Volume 1 • Issue 9 • 2012, 1-6.
5. EmreMenteşe[a]FatihYılmaz[b]MustafaEmirik[a]SerdarÜlker[ab]BahittinKahveci[c], Synthesis, molecular docking and biological evaluation of some benzimidazole derivatives as potent pancreatic lipase inhibitors, Volume 76, February 2018, Pages 478-486
6. V.Chidambaranathan, C.M.Mahalakshmi, Synthesis, Antimicrobialand Molecular docking studies of novel Benzimidazole derivatives, Volume 8, Issue 3 Ver. I. (Mar. 2015), PP 28-33.
7. Awais Shaukat,Hira M. Mirza,Amna H. Ansari,Masoom Yasinzai, Benzimidazole derivatives: synthesis, leishmanicidal effectiveness, and molecular docking studies, August 2013, Volume 22, **Issue 8**, pp 3606–3620.
8. Pallav D. Patel, Maulik R. Patel, Neerja Kaushik-Basu, and Tanaji T. Talele, 3D QSAR and Molecular Docking Studies of Benzimidazole Derivatives as Hepatitis C Virus NS5B Polymerase Inhibitors, *J. Chem. Inf. Model.*, 2008, *48* (1), pp 42–55.
9. G.H.ANURADHA and MANASA REDDY GUMMI, Homology Modeling of Inactive Ubiquitin Thioesterase FAM105A and Molecular Docking Studies of Benzimidazole Derivatives, Chem Sci Trans., 2016, 5(4), 979-985.
10. M. Sai Harika , T. Raj Kumar and L. Siva Sankar Reddy, DOCKING STUDIES OF BENZIMIDAZOLE DERIVATIVES USING HEX 8.0, INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH, 2016, 8(4).1677-88.
11. *K. Hemalatha, V. Chakkaravarthi, K. Ganesa Murthy, R. Kayatri, K. Girija*, Molecular Properties and Docking Studies of Benzimidazole Derivatives as Potential Peptide Deformylase Inhibitors, Asian Journal of Research in Chemistry , 20144,7(7): 644-648
12. Rezk R Ayyad, Helmi M Sakr, Kamal M El-Gamal, Ibrahim H Eissa, Ahmad HA Tita, Adel S Abd El-Raheim, Farag F Sherbini and Ahmad M MansourAnti-Inflammatory, Proton Pump Inhibitor and Synthesis of Some New Benzimidazole Derivatives, Der Chemica Sinica, 2017, 8(1):184-197
13. Ankita Rathore, Raja Sudhakar, Mohamed Jawed Ahsan, Abuzer Ali, Naidu Subbarao, Surender Singh Jadav, Sadiq Umar, M. Shahar Yar, In vivo anti-inflammatory activity and docking study of newly synthesized benzimidazole derivatives bearing oxadiazole and morpholine rings, Bioorganic ChemistryVolume 70, February 2017, Pages 107-117
14. Abdulaziz Hammad G. Alanazi , Md. Tauquir Alam and Mohd. Imran, Design, Molecular Docking Studies, in Silico Drug Likeliness Prediction and Synthesis of Some Benzimidazole Derivatives As Antihypertensive Agents, IAJPS 2017, 4 (04), 926- 936

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

15. Nik Khairunissa Nik AbdullahZawawi[ab]MuhammadTaha[ab]NorizanAhmat[ab]Nor HadianiIsmail[ab]AbdulWadood[c] FazalRahim[d], Synthesis, molecular docking studies of hybrid benzimidazole as α-glucosidase inhibitor, Bioorganic ChemistryVolume 70, February 2017, Pages 184-191.