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Imidazole Derivatives as Anticancer Agents: A Molecular Docking Approach to Identify Potential Lead Compounds.

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ABSTRACT

EGFR Kinase domain is a crucial role player cell surface receptor protein activated by specific binding of its ligand like EGFR. Importance of this protein as a therapeutically important drug target towards treating various cancer types has been proven elsewhere in previous literature. In this present study, we have designed a novel series of 27 compounds and computationally evaluated their potential to act as inhibitors of EGFR kinase domain towards anti-cancer activity. Our docking study shows compounds have the potential to dock into the active site of the EGFR Kinase domain with a binding energy in a range of -11.2 to -9.3 Kcal/mol, among all the compounds, Compound 2l was found to be the lead like molecule with the binding energy of -11.2 kcal/mol and revealed several interesting molecular interactions with some of the important residues ASP:831, LYS:721, PHE:832 (3 Hydrogen bonds) present at the active binding site of EGFR Kinase. Designed compound 2l of the present study have shown promising anti-cancer potential worth considering for further evaluations and other compounds also showing good binding energy 2j (-10.5 Kcal/mol), 2k (-10.5 Kcal/mol), 2v (-10.5 Kcal/mol), 2y (-10.7 Kcal/mol), 3a (-10.5 Kcal/mol).

Keywords: EGFR Kinase, Molecular docking, Imidazole, anti-cancer.

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INTRODUCTION

Nowadays, major advances have been developed to take care the cancer disease; however, there are still several challenges in cancer care remains unaddressed due to lack of selectivity of conventional drugs leading to toxicity and multidrug resistance [1-6]. Therefore, the development of target based anti-cancer drugs for the reduction of cancer disease as well as this major health problem is the decisive task for the researchers working in the domain of medicinal chemistry [7-9]. Imidazole's have attracted attention since imidazole ring presents in the essential amino acid, histidine which is existed in many proteins and enzymes and plays an important role in the structure and binding function of haemoglobin. Biological studies showed great numbers of substituted imidazole's with wide spectrum of biological activities such as antitumor, antimicrobial, anti-HIV, antibacterial, antihypertensive, antifungal and anticonvulsant activity [10]. The epidermal growth factor receptor (EGFR) belongs to ErbB family of receptor tyrosine kinases. It is upregulated in many cancers such as breast cancer and head and neck squamous cell carcinoma. Moreover, in more than half of the patients with non-small cell lung cancer (NSCLC), EGFR is an attractive target for anticancer therapy and a large number of EGFR tyrosine kinase inhibitors (TKIs) have been developed [11].

Molecular docking is a kind of computational modeling, which facilitates the prediction of preferred binding orientation of one molecule (eg. ligand) to another (eg. Receptor), when both interact each other in order to form a stable complex [12]. The unique structure of imidazole ring makes great advantage of their derivatives to easily interact with diverse range of biomolecules such as enzymes, DNAs, receptors in organisms via various types of hydrogen bonding and π-π stacking interactions. The interactions are also responsible for the enhancement of water solubility of these drugs up to some extent and thus increase thepotency [13].

MATERIALS AND METHODS

Dataset ligands and Ligand Optimization

The 2D structures (figure 1) of 27 compounds were generated from the ACD-/Chemsketch software (Table 1). The generated ligands cleaned and performed 3D optimization then saved in the MDL Molfile format. The ligands were then converted to a PDBQT file format using the Open Babel chemistry toolbox.

Molecular Docking Studies

The three-dimensional structure of Pokeweed Anticancer Protein (figure2) (PDB ID: 4HJO) was downloaded from Brook heaven Protein Data Bank (https://www.rcsb.org/structure/4HJO) and saved as a RCSB'S protein data bank file and the structure were optimized by deleting unbound water molecules which are over 1 Å, adding hydrogen atoms to satisfy the valences, adding missing amino acids to stabilize side chains and energy of the whole structure was minimized using AUTODOCK suite of MGL Tools.

Auto dock Vina was used for molecular docking studies. A grid was generated around the co-crystallized ligand. The co-ordinates (x = 61.97 A^0, y =66.53 A^0, z = 59.86 A^0) were generated with the help of MGL Tools & Pharmit: interactive exploration of chemical space (http://pharmit.csb.pitt.edu/). Prepared pdbqt files for both target & ligands. Created in house batch file of ligands & amp; target and docking performed in the absence of water molecules for all 27 molecules. The molecules were analysed after docking and visualized in the discovery studio for the interactions with the active site amino acids.

Binding interactions and efficiency of the binding were calculated in terms of dock Score, which is a combination of hydrophilic, hydrophobic, metal binding groups, Van der Waals energy, freezing rotatable bonds and polar interactions with receptor.

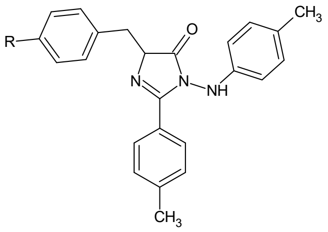


Figure 1: Lead compound containing Imidazole derivatives

Sl No	S. CODE	R
1	2a	p-OCH3
2	2b	o-OH
3	2c	o-Cl
4	2d	o-NO2
5	2e	4-CH_3NH_2
6	2f	p-OH
7	2g	p-NO2
8	2h	m-Cl
9	2i	p-Br
10	2j	m-Br
11	2k	m-NO2
12	2l	m-SO3H
13	2m	o-CHO
14	2n	m-OCH3, p-OH
15	2o	2,3-OH
16	2p	2,4-OH
17	2q	2,3,4-OH
18	2r	3,5-OH
19	2s	p-cl
20	2t	2,5-CH3
21	2u	m-F
22	2v	p-F
23	2w	o, p-OCH3
24	2x	2-Cl,5-NO2
25	2y	3-Cl,5-CH3
26	2z	3-CH3
27	3a	m-Cl

Table 1: Ligands used in the study

RESULTS AND DISCUSSION

Molecular docking studies were performed in order to find the possible protein ligand interactions of the dataset ligands. The potential active site amino acids of 4HJO) complex were predicted using EGFR kinase protein. The target protein and inhibitors were geometrically optimized. All the 27 compounds were docked against active site of target protein using AUTODOCK VINA. Additionally, these also assisted in identifying the conformational changes of the ligand in the protein environment. About 100 different protein-ligand complex conformations for each docked complex were generated through AUTODOCK suite of MGL Tools, the confirmation with highest binding energy was displayed as the best binding energy. Binding energy of the dataset ligands were shown in Table 2 along with the interaction amino acids and number of amino acids.

Table 2: Binding Energy, No of H-bonds, Interacting amino acids

COMPOUND NAME	BINDING ENERGY K cal /mol	NO OF H-BONDS	INTERACTING AMINO ACID
2a	-10.1	1	LYS:721
2b	-10	2	LEU:764 ALA:719
2c	-10.1	1	LYS:721
2d	-9.6	4	ASP:813 TYR:867 LYS:851 ARG:865
2e	-10	1	ASP:831
2f	-10.1	2	ASP:813 LYS:851
2g	-10.3	4	ASP:813 ARG:865 LYS:851 ALA:847
2h	-10.3	2	ASP:813 LYS:851
2i	-10.2	2	LYS:721 SER:696
2j	**-10.5**	**4**	**ASP:813** **LYS:851** **TYR:867** **ARG:865**
2k	**-10.5**	**4**	**ARG:865** **ALA:847** **LYS:851** **ASP:813**
2l	**-11.2**	**3**	**ASP:831** **LYS:721** **PHE:832**
2m	-9.3	2	ASP:831 PHE:832
2n	-10.3	2	PHE:832 LYS:721
2o	-9.9	3	ASP:831 LYS:851 ALA:840
2p	-9.9	3	ASP:831 ALA:851 TYR:867
2q	-10	2	LYS:721

			ARG:817
2r	-9.9	1	PHE:832
2s	-10.1	2	LYS:851 ASP:813
2t	-10.2	1	ASP:831
2u	-10.3	2	LYS:851 ASP:813
2v	**-10.5**	**1**	**LYS:721**
2w	-8.7	2	LYS:721 SER:696
2x	-10.4	3	ASP:831 GLY:700 PHE:699
2y	**-10.7**	**2**	**ASP:813** **LYS:851**
2z	-10.3	2	ASP:813 LYS:851
3a	-10.5	1	LYS:721
Native ligand	-10.0	5	LEU:694 SER:696 ASN:818 LYS:721 THR:830

It has been observed that native ligand (Doxorubicin) present in the crystal structure of 4HJO mutant EGFR exhibited -10.0 kcal/mol binding affinity. Binding affinity of native ligand was considered as standard for the validation of the novel molecules. All the designed molecules have exhibited very good binding affinity with EGFR Kinase compared to native ligand. The Compound 2l exhibited most potent binding affinity i.e. -11.2 kcal/mol and stable interactions with critical residues such as ASP831, PHE832 and LYS721, indicating its potential as a lead compound other compounds having good binding affinity such as Compound 2y (-10.7 Kcal/mol), 2j (-10.5 Kcal/mol),2k (-10.5 Kcal/mol),2v (-10.5 Kcal/mol),3a (-10.5 Kcal/mol). Apart from this, many molecules showed binding affinity between -9.3 to -11.1 kcal/mol.

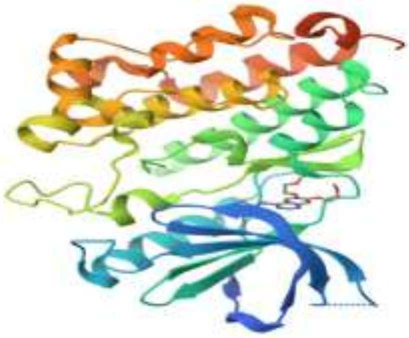
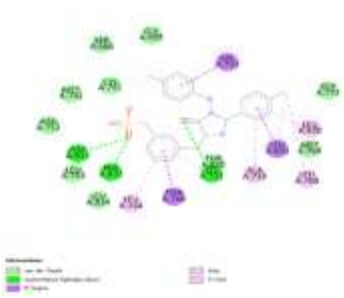
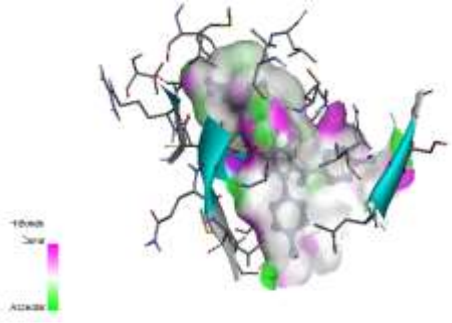


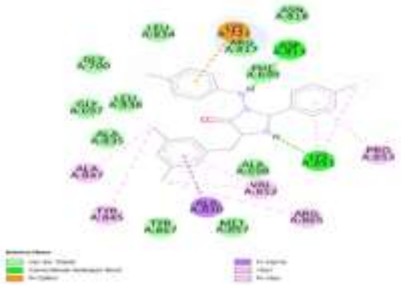
Figure 2: 3D structure of Pokeweed Anticancer Protein (PDB ID: 4HJO)



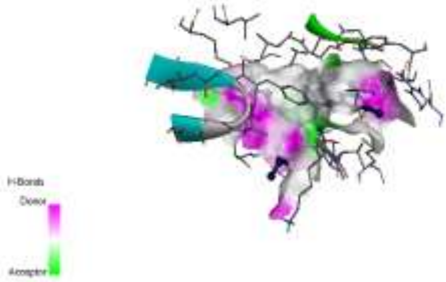
2l-2D



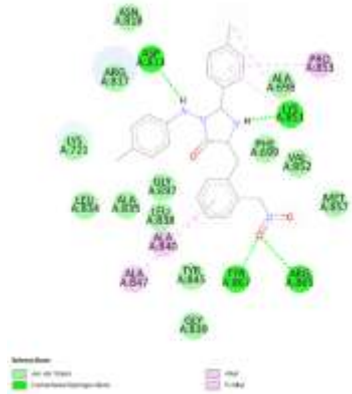
2l-3D



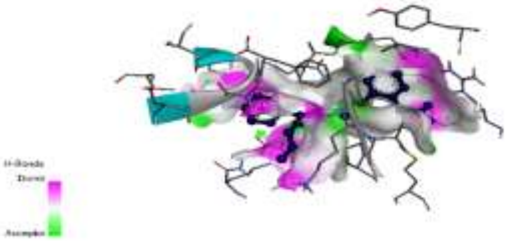
2y-2D



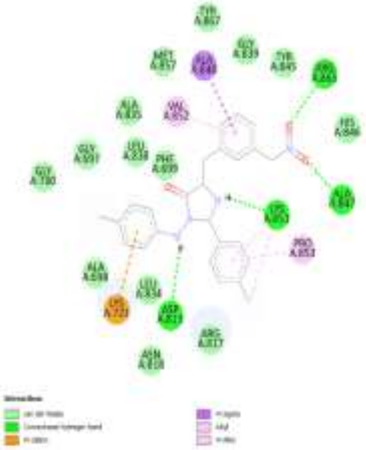
2y-3D



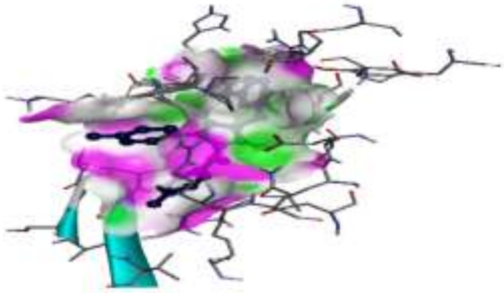
2j-2D



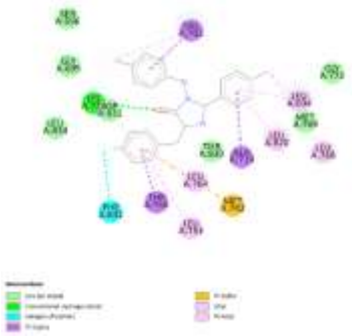
2j-3D



2k-2D

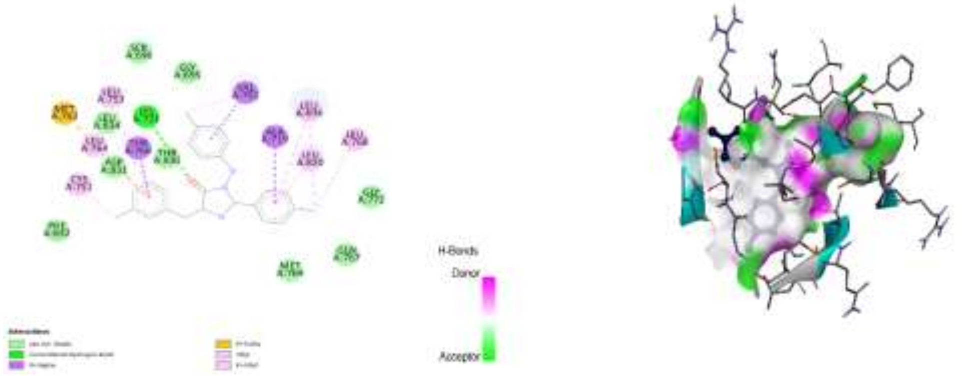


2k-3D



2v-2D

2v-3D



3a-2D **3a-3D**

Figure 3: 2D and 3D interaction of ligand with target protein according to Highest binding energy of compounds 2l (-11.2), 2y (-10.7), 2j (-10.5), 2k (-10.5), 2v (-10.5) and 3a (-10.5).

CONCLUSION

The molecular docking studies conducted on a series of imidazole derivatives targeting the epidermal growth factor receptor (EGFR) kinase have demonstrated promising anticancer potential. Several derivatives exhibited strong binding affinities with key amino acid residues within the ATP-binding site of EGFR, comparable to or surpassing that of standard inhibitor such as Doxorubicin. Compound 2l showed the highest docking score and stable interactions with critical residues such as ASP 831, PHE 832 and LYS 721, indicating its potential as a lead compound. The *in-silico* results were further supported by ADME and drug-likeliness analyses, which confirmed favorable pharmacokinetic profiles for the top candidates. These findings suggest that imidazole-based scaffolds can serve as effective EGFR kinase inhibitors and could be further optimized for enhanced anticancer activity. Future work should include *in-vitro* validation of the top-performing compounds to confirm their efficacy and safety profiles. Overall, this study highlights the potential of imidazole derivatives as promising leads for the development of novel anticancer agents targeting EGFR.

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