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Anticancer activity of derivatives of 2-Mercaptobenzimidazole – Molecular docking approach

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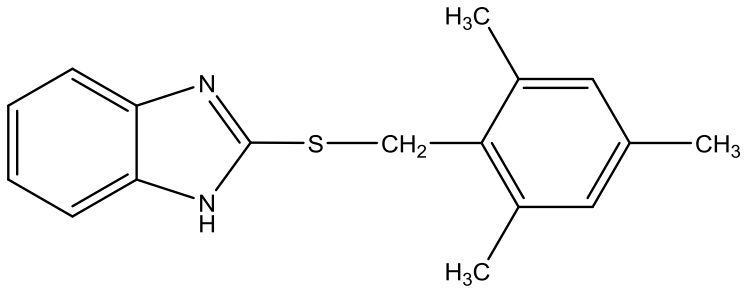
Abstract
Nowadays cancer threats everyone since it is growing with uncountable varieties. Researchers are in urge to find suitable antibodies to each case. Molecular docking is one of the best tool to carry this emergent job within short time. With the help of molecular docking theoretical approach, this present study carried by taking three derivatives of 2-mercaptobenzimidazole as anticancer dote. The molecular docking study of selected three compounds were performed by using Autodock vina against EGFR tyrosine kinase protein. The docking study revealed that synthesised compounds are potential anticancer drugs especially IMM3 shows best binding efficiencies.

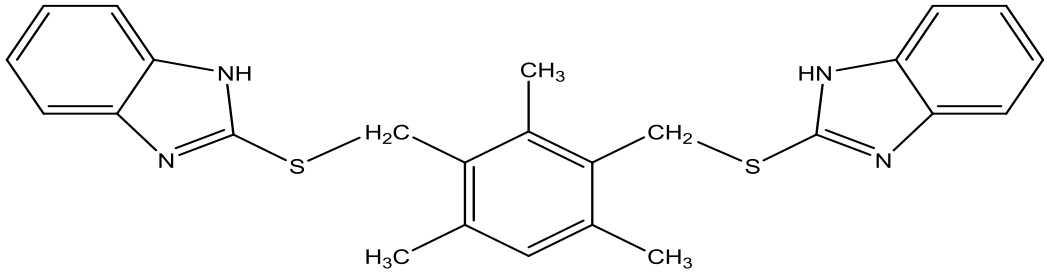
Keywords: 2-mercaptobenzimidazole, anticancer, EGFR tyrosine kinase protein, Autodock

1. Introduction
The benzo derivative of imidazole is referred to as benzimidazole [1]. Although benzimidazole is the commonest name of the parent compound of the series, other names such as benzimidazole and 1,3-benzodiazole are often used. Benzimidazole derivative are associated with various types of pharmacokinetic and pharmacodynamic properties. Benzimidazole nucleus is one of the bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, this nucleus is a constituent of vitamin B12 [2]. The pharmacological activities of the benzimidazole containing moiety have been well documented [3]. Albendazole, Mebendazole and Thiabendazole are widely used as anthelmintic drugs [4]. Literature survey reveals that the various derivatives of benzimidazole have been synthesized for their pharmacological activities. Some of the already synthesized compounds from the above mentioned field have found very strong application in medicine praxis [5]. The activity against bacteria, fungi and helminthes resulted their mode of action, which resulted in the blockage of microtubule in various nematode, trematode and cystode [6].
This present work focus on modelling of different derivatives of 2-mercaptobenzimidazole with different substituted mesitylene as shown in Figs. 1-3 and their anticancer activities against EGFR. Over expression of EGFR (Epidermal Growth Factor Receptor) results in cancer. EGFR gene encodes protein containing 1186 amino acid and 621 residues, which compromise the extra cellular domain and binding site for specific ligand amino acid residues, which server binding site for EGFR inhibitors.



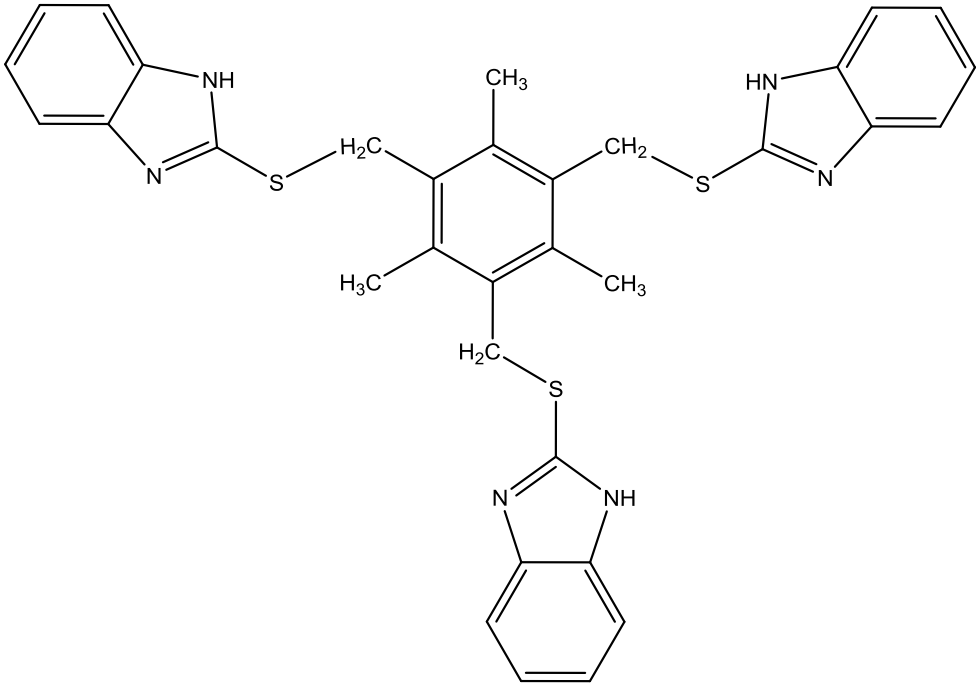
2-((2,4,6-trimethylbenzyl)thio)-1*H*-benzo[*d*]imidazole

Fig 1: Structure of monosubtituted mesitylene with 2-mercaptobenzimidazole denoted as IMM1



2,2'-(((2,4,6-trimethyl-1,3-phenylene)bis(methylene))bis(sulfanediyl))bis(1*H*-benzo[*d*]imidazole)

Fig 2: Structure of disubtituted mesitylene with 2-mercaptobenzimidazole denoted as IMM2



2,2',2''-(((2,4,6-trimethylbenzene-1,3,5-triyl)tris(methylene))tris(sulfanediyl))tris(1*H*-benzo[*d*]imidazole)

Fig 3: Structure of trisubtituted mesitylene with 2-mercaptobenzimidazole denoted as IMM3

2. Methodology

The docking was carried out in Autodock vina software. The two-dimensional (2D) chemical structures of the synthesised compound were sketched using Chemdraw ultra and converted to pdb using Chem3D Ultra. For docking study, the protein was downloaded from Protein Data Bank website and software's like Discovery studio 4.0 client and PyMol were used to find the intermolecular interaction.

2.1 Molecular Docking

Binding mode and interaction of EGFR tyrosine kinase with selected synthesised was performed using AutoDock Vina software. Docking was performed to obtain a population of possible conformations and orientations for the ligand at the binding site.

The protein data bank accession code for EGFR is 21TY with a resolution of 3.42 Å. The 'A' chain of EGFR is constituted by 327 amino acids. The Chain A was chosen for docking it contains natural ligand Iressa which is a standard anticancer drug. The binding site required for the action of EGFR kinase domain is Leu-718-THR 854.

The protein was loaded in Autodock 4.2 software, creating a PDBQT file that contains a protein structure with hydrogens in all polar residues. All bonds of ligands were set to be rotatable. The docking site on protein target was defined by establishing a grid box with the dimensions of X: 74 Y: 60 Z: 62 Å, with a grid spacing of 0.372 Å, centered on X: -52.45 Y:-0.316 Z: -21.46 Å. The best conformation was chosen with the lowest docked energy after the docking search was completed. Ten runs with AutoDock Vina were performed in all cases per each ligand structure, and for each run the best pose was saved. The interactions of complex EGFR protein-ligand conformations, including hydrogen bonds and hydrophobic interactions were analyzed using Discovery studio 4.0 client [7, 8].

3. Results and Discussion

Docking was performed to obtain a population of possible conformations and orientations for the ligand at the binding site. Docking of small molecule compounds into the binding site of a receptor and estimating the binding affinity of the complex is an important part of the structure based drug design process. AutoDock Vina [8] is an open-source program for drug discovery, molecular docking and virtual screening, offering multicore capability, high performance and enhanced accuracy and ease to use. The parameters chosen for the docking can be judged by the docking tool's ability to reproduce the binding mode of a ligand to protein, when the

structure of the ligand–protein complex is known.
The ten different orientations of the selected three compounds to the receptor EGFR tyrosine kinase protein were carried out. The binding energy of the best orientation of the synthesised compounds are presented in Table 1. The binding affinity of compound IMM3 is experimentally found to be most active and also the best docked ligand, having high score (-9.2), indicating highest binding propensity towards the enzyme. The docked compounds occupied the same binding site pocket as occupied by Iressa in the crystal structure. The binding affinity of all the synthesised compounds showed higher than that of the standard Iressa.

Table 1: Binding affinity of synthesised compounds with EGFR tyrosine kinase protein

Compound	Binding affinity (kcal/mol)
IMM3	-9.2
1MM2	-9.1
IMM1	-7.3
Standard (Iressa)	-7.2

Table 2: Hydrogen bonding interactions of synthesised compounds with EGFR tyrosine kinase protein

Compound	IMM2
Atom of compound involving interaction	Nitrogen
Amino acid residue involving interaction	CYS797
Atom of Amino acid residue involving interaction	Hydrogen
Type of Interaction	Direct interaction
Distance (Å)	2.98

Weak intermolecular interactions such as hydrogen bonding and hydrophobic interactions are key players in stabilizing energetically-favored ligands, in an open conformational environment of protein structures
The hydrogen bonding and hydrophobic interactions [9, 10] of the best orientations are presented in Table 2 and Table 3 respectively and in Fig. 4.
The hydrogen bonding interaction is the most important interaction because the binding energy is very high than hydrophobic and other interaction. Out of three synthesised compound only IMM2 shows one hydrogen bond with protein interacting site. Even the standard natural ligand Iressa also does not any have hydrogen bonding. It may be due to the binding site have more hydrophobic amino acids than hydrophilic amino acids.
The protein does not have the water moiety in the binding site, so there are no water mediated hydrogen bonding interaction between the protein and ligand.

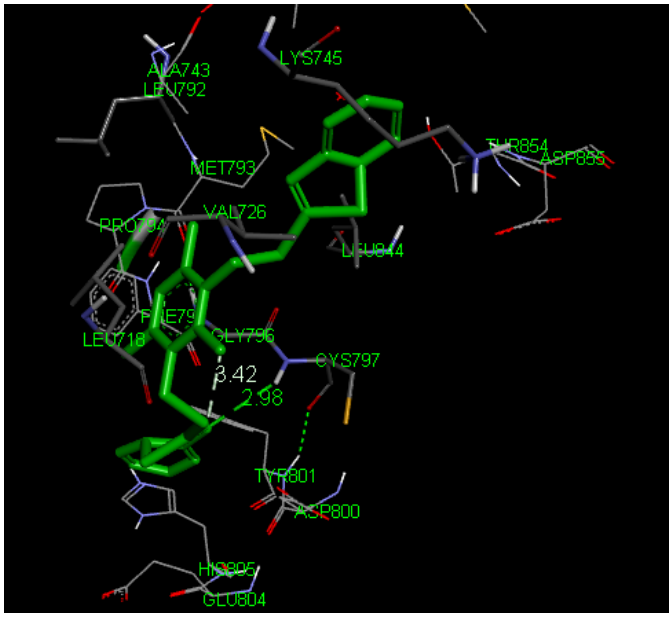


Fig 4: Hydrogen bonding interaction of synthesised compounds with EGFR tyrosine kinase IMM2

Table 3: Hydrophobic interactions of synthesised compounds with EGFR tyrosine kinase protein

Compound	Hydrophobic interaction of compounds with EGFR tyrosine kinase protein (Distance A°)
IMM3	LEU718(4.23, 3.45), VAL726(5.49,4.89,4.93,5.19,4.89), THR790(3.71),LYS745(4.20,4.78,5.18,5.46), LEU747(5.18), MET766(5.23), CYS797(3.88), PHE723(4.21,5.33)
IMM2	LEU718(4.38, 3.69,5.17,4.91), VAL726(4.88), LYS745(4.61), LEU844(4.87)
IMMI	LEU718(4.09, 3.87), LEU792(4.43), VAL726(4.27), LYS745(4.31,3.13, 5.07), LEU844(4.55), ALA743(3.91), MET793(4.59, 5.23)
Standard (iressa)	LEU747(4.41), VAL726(3.96,4.62,5.35), LYS745(4.45, 2.87), ASP855(3.51,3.74), GLY721(3.30),PHE723(3.75,4.79)

The compound IMM3 shows seventeen hydrophobic interactions and have the highest binding affinity (-9.2). The compound IMM2 shows only seven hydrophobic interaction with four amino acids but it has high binding affinity (-9.1) due to one hydrogen bonding since hydrogen bonding and hydrophobic interactions are major contributors for binding

affinity. Similarly compound IMMI and standard Iressa also have low biding affinity because it does not have interaction with important LEU718.

Thus hydrophobic interaction was predominant and made major contribution. The overall strengths of these bonds determine the degree of affinity between the drug and the receptor. Thus, the study provide a theoretical way by which new hypothetical EGFR tyrosine kinase inhibitors can be developed prior to their synthesis only by introducing effective hydrophobic substituents at specific sites.

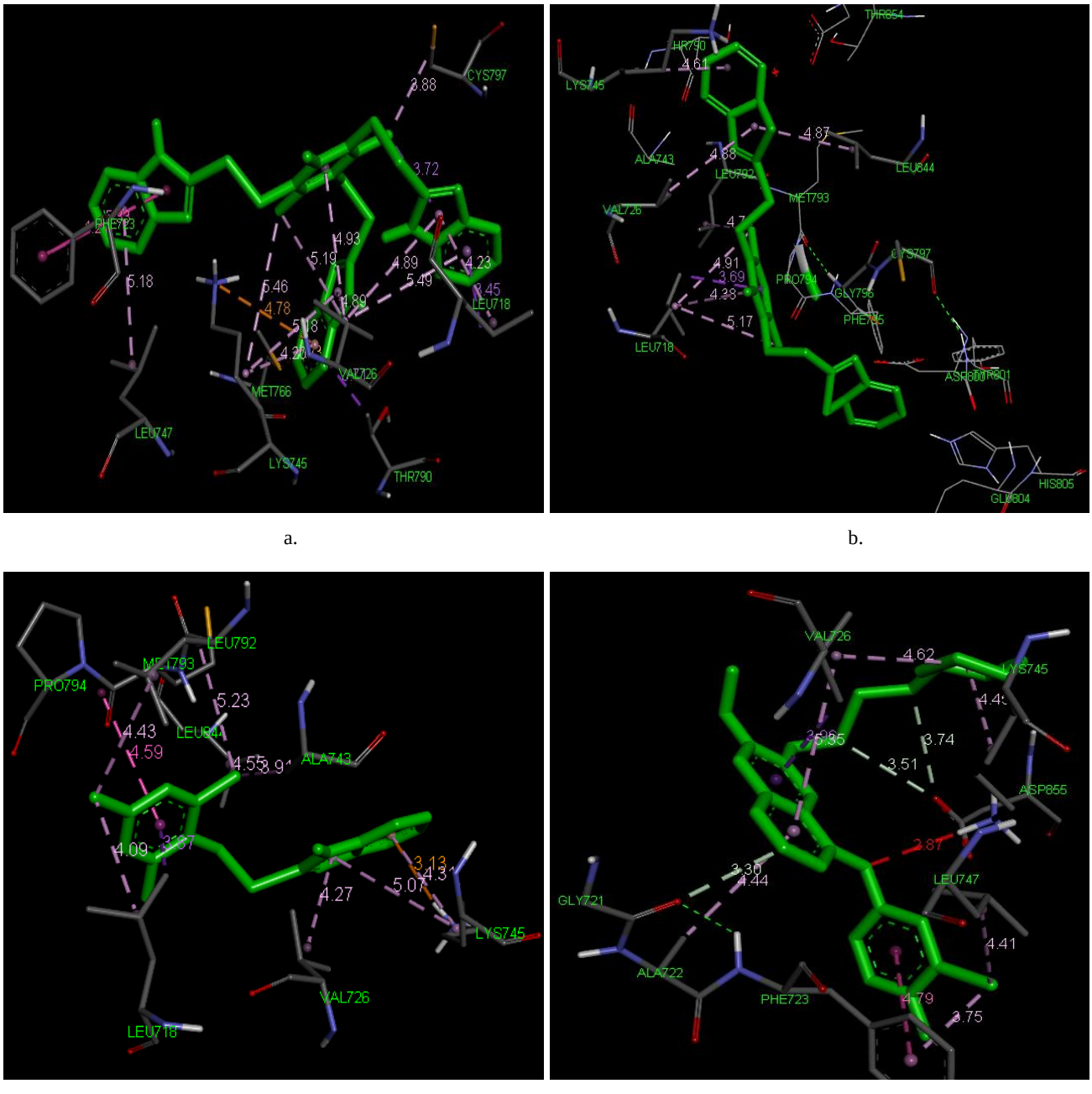


Fig 5: Hydrophobic interaction of synthesised compounds with EGFR tyrosine kinase a) IMM3; b) IMM2; c) IMM1 and d) standard Iressa

The hydrophobic phenyl ring and benzoimidazole ring of the synthesised compounds were surrounded by active site amino acid residues HIS207, LEU391, PHE 404, LEU408, HIS 386, LEU 294, HIS 388, VAL 447, VAL 444, VAL 295, LEU 294, VAL291, HIS 214.

The hydrophobic interactions of the synthesised compounds is very higher than that of hydrogen bonding interaction.

4. Conclusions

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure. The present study concludes that IMM3 is found to be most active against EGFR tyrosine kinase protein. The results indicate that the molecular modeling is a valuable tool for predicting the biological activity of synthesised compounds. The analysis of the docking result allowed us to know the efficiency of the synthesised compounds to control cancer.

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