RESEARCH PAPER

In Silico Study Of Novel Piperazine Derivatives As Anticancer Agents Targeting Egfr

Sunildatta T Gore[1*], Abhijeet A Jondhale[2], Vijay Bhausaheb Jadhav[3], Avinash G Mansuk[4], Atul Gunjal[5], Pravin S Uttekar[6], Narender Boggula[7]

[1*]Associate Professor, Usha Dwarakadas Pathrikar Institute Of Pharmacy, Phulambri, Chatrapati Sambhajinagar, Maharashtra, 431111, India

[2]Associate Professor, Dr. Kolpe Institute Of Pharmacy Kolpewadi, Ahilyanagar, Maharashtra, 423602, India

[3]Associate Professor, Rashtrasant Janardhan Swami College Of Pharmacy, Kokamthan, Kopargaon, Ahilyanagar, Maharashtra, 423601, India

[4]Associate Professor, Dr. Ithape Institute Of Pharmacy Sangamner, Ahilyanagar, Maharashtra, 422605, India

[5]Associate Professor, Dr. Ithape Institute Of Pharmacy Sangamner, Ahilyanagar, Maharashtra, 422605, India

[6]Professor & Principal, Dnyan Kala Krida & Krushi Prathishthan'S, Late Laxmibai Phadtare College Of Pharmacy, A/P-Kalamb-Walchandnagar, Tal: Indapur Dist: Pune, 413114, India

[7]Associate Professor, Department Of Pharmaceutical Chemistry, Omega College Of Pharmacy, Edulabad, Ghatkesar, Hyderabad, Telangana, India – 501301, India

***Corresponding Author:**

Sunildatta T Gore

Associate Professor, Usha Dwarakadas Pathrikar Institute Of Pharmacy, Phulambri, Chatrapati Sambhajinagar, Maharashtra, 431111, India

ABSTRACT:

In this study, novel 1-(2-methyl)-1,3-dioxalan-2yl piperazine derivatives were designed and evaluated as potential anticancer agents. Molecular docking simulations were carried out against the Epidermal Growth Factor Receptor (EGFR) with PDB ID 1M17 using Mcule docking software. EGFR is an important therapeutic target involved in the proliferation and survival of various cancer cells. The designed compounds were docked into the active site of EGFR and compared with the standard anticancer drug Erlotinib. The docking results revealed that several derivatives such as M4, M5, M6, M7, and K6 exhibited significant binding affinity and favorable interactions with key amino acid residues in the EGFR catalytic domain. Furthermore, in silico ADME prediction indicated that the designed molecules satisfy drug-likeness criteria and possess acceptable pharmacokinetic properties. These findings suggest that the designed piperazine derivatives may serve as promising lead compounds for the development of new anticancer agents.

Keywords: Piperazine derivatives, Molecular docking, EGFR (1M17)**,** Anticancer activity,

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INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, representing a major challenge to global public health. According to the World Health Organization, cancer accounts for millions of deaths annually and its incidence continues to increase due to lifestyle changes, environmental factors, and aging populations[1]. The uncontrolled proliferation of abnormal cells, their ability to invade surrounding tissues, and metastasize to distant organs characterize this complex group of diseases. Despite significant advances in chemotherapy, radiotherapy, and targeted therapy, the development of safer and more effective anticancer drugs remains an important objective in pharmaceutical research[2, 3]. Among the various molecular targets implicated in cancer progression, the Epidermal Growth Factor Receptor (EGFR) has emerged as a crucial regulator of cellular proliferation, differentiation, migration, and survival. EGFR belongs to the ErbB family of receptor tyrosine kinases and is activated upon binding with epidermal growth factor ligands[4, 5]. Activation of EGFR triggers intracellular signaling pathways such as the MAPK signaling pathway, PI3K-Akt signaling pathway, and JAK-STAT signaling pathway, which regulate cell growth and survival[6]. Overexpression, mutation, or dysregulation of EGFR has been reported in various cancers including lung cancer, breast cancer, colorectal cancer, and head and neck cancers.

Therefore, inhibition of EGFR tyrosine kinase activity has become an important strategy in the development of targeted anticancer therapies [7]. Several EGFR inhibitors have been developed and successfully introduced into clinical practice. Small-molecule tyrosine kinase inhibitors such as Erlotinib, Gefitinib, and Afatinib act by binding to the ATP-binding pocket of the EGFR kinase domain and preventing receptor phosphorylation and downstream signaling. Although these drugs have shown significant therapeutic benefits, the emergence of drug resistance, adverse effects, and limited efficacy in certain patient populations necessitate the discovery of new molecules with improved pharmacological profiles [8, 9]. In recent years, in silico drug design approaches have gained considerable importance in the early stages of drug discovery. Computational techniques such as Molecular Docking, virtual screening, and ADME prediction allow researchers to evaluate the interaction between drug candidates and target proteins rapidly and cost-effectively. Molecular docking predicts the orientation, binding affinity, and interactions of small molecules within the active site of a protein, providing valuable insights into structure–activity relationships and guiding further optimization of lead compounds[10, 11].

Piperazine derivatives are widely recognized in medicinal chemistry due to their diverse pharmacological activities, including antimicrobial, antiviral, antifungal, and anticancer properties. The piperazine scaffold offers favorable physicochemical characteristics, structural flexibility, and the ability to form strong interactions with biological targets. Several piperazine-containing compounds have demonstrated promising inhibitory activity against various cancer-related proteins. Therefore, designing novel piperazine derivatives may provide potential candidates for anticancer drug development [12, 13].

In the present study, a series of 1-(2-methyl)-1,3-dioxolan-2-yl piperazine derivatives were designed and evaluated as potential anticancer agents. Molecular docking simulations were performed against the EGFR tyrosine kinase domain (PDB ID: 1M17) to investigate the binding affinity and interaction patterns of the designed compounds within the active site of the receptor. The docking results were compared with the standard EGFR inhibitor Erlotinib. In addition, in silico pharmacokinetic and drug-likeness properties of the compounds were predicted to assess their potential as drug candidates. The findings of this study may contribute to the identification of novel lead molecules for the development of effective anticancer agents targeting EGFR [14, 15]. Figure 1, represents Basic structure and Protein of study.

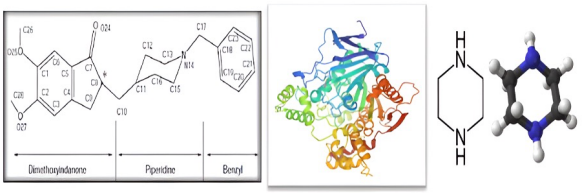


Figure 1: Basic structure and Protein of study

METHODOLOGY

Molecular Docking Procedure

1. Preparation of Target Protein: The three-dimensional crystal structure of the Epidermal Growth Factor Receptor (EGFR) tyrosine kinase domain was retrieved from the Protein Data Bank with PDB ID: 1M17. The downloaded protein structure was prepared for docking by removing water molecules, co-crystallized ligands, and other heteroatoms that may interfere with docking calculations. Missing hydrogen atoms were added, and the protein structure was optimized to ensure proper geometry and stability. The prepared protein structure was then saved in PDB format for further docking studies [16].

2. Preparation of Ligands: The chemical structures of the designed piperazine derivatives were drawn using ChemDraw software and converted into three-dimensional structures using Chem3D. The energy of each ligand molecule was minimized using the MM2 force field to obtain stable conformations. The optimized structures were saved in SDF or MOL format and uploaded to the Mcule molecular docking platform for further analysis [17].

3. Docking Protocol: Molecular docking was performed using the Mcule online docking server, which integrates AutoDock Vina as the docking engine. The prepared protein structure (PDB ID: 1M17) was uploaded to the Mcule docking interface, and the ATP-binding pocket of EGFR was selected as the active binding site. A grid box was defined around the catalytic domain of the protein to include important amino acid residues involved in ligand binding. The prepared ligand molecules were uploaded to the docking platform, and docking simulations were carried out under default parameters. The docking algorithm generated multiple binding poses for each ligand and calculated the binding affinity (kcal/mol) based on predicted interactions between the ligand and the target protein [18].

4. Analysis of Docking Results: The docking results were analyzed based on the binding energy values and interaction patterns between the ligands and the target

protein. Compounds showing lower binding energy values were considered to have stronger binding affinity toward the receptor. The binding poses were visualized to identify key interactions such as hydrogen bonding, hydrophobic interactions, and van der Waals forces between ligands and active site residues of EGFR [19].

5. Validation Using Standard Drug: To validate the docking protocol, the standard EGFR inhibitor Erlotinib was also docked into the same active site of the protein. The binding affinity and interaction profile of the designed compounds were compared with that of the reference drug to evaluate their potential anticancer activity [20].

6. ADME and Drug-Likeness Prediction: The pharmacokinetic properties of the designed compounds were evaluated using in silico ADME prediction tools available in the Mcule platform. The parameters assessed included molecular weight, hydrogen bond donors and acceptors, lipophilicity (LogP), and compliance with Lipinski's Rule of Five. Compounds satisfying these criteria were considered to have favorable drug-like properties [21].

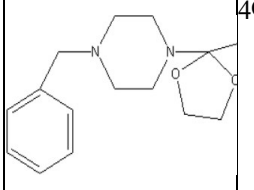
RESULTS AND DISCUSSION

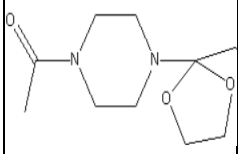
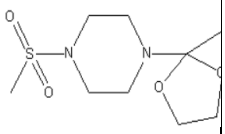
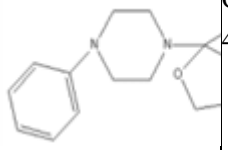
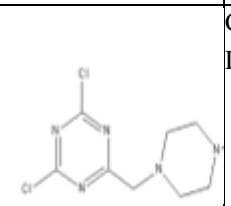
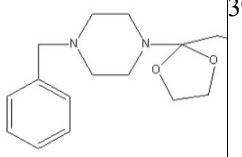
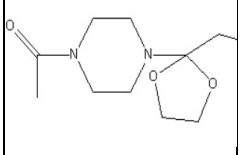
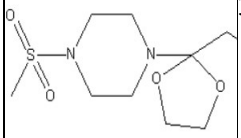
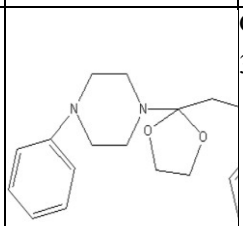
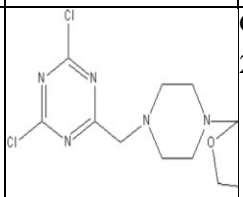
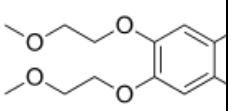
Docking studies:

The designed novel piperazine–1,3-dioxolane derivative compounds were subjected to molecular docking studies using the Mcule 1-Click Docking platform in the year 2020. The docking study was carried out to investigate the binding mode and molecular interactions between the designed compounds and the anticancer target protein Epidermal Growth Factor Receptor (EGFR).

The crystal structure of EGFR with PDB ID: 1M17 was selected as the target receptor for docking analysis. EGFR is a receptor tyrosine kinase that plays a key role in regulating cellular proliferation, differentiation, and survival. Overexpression or abnormal activation of EGFR has been reported in several types of cancers including lung cancer, breast cancer, and colorectal cancer. Therefore, inhibition of EGFR kinase activity is considered an important strategy for anticancer drug development. Molecular docking simulations were performed using the Mcule 1-Click Docking method, which integrates the docking engine AutoDock Vina. The docking procedure predicted the optimal binding orientations of the designed compounds within the ATP-binding pocket of the EGFR tyrosine kinase domain. The docking results indicated that the designed inhibitors were able to fit well within the active site cavity of EGFR, forming stable interactions with key amino acid residues responsible for kinase activity. The docking scores obtained from the Mcule platform are summarized in Table 2. Lower docking score values indicate stronger binding affinity between the ligand and the receptor protein. Among the ten designed piperazine derivatives, compounds P7, P8, P9, and P10 exhibited the most significant binding affinity toward the EGFR active site. These compounds showed strong interactions with important catalytic residues present in the EGFR binding pocket, suggesting a favorable inhibitory potential against EGFR tyrosine kinase activity. Particularly, compound P10 demonstrated the highest docking score with an average value of −10.76 kcal/mol, which is comparable to or even better than the reference anticancer drug Erlotinib (average docking score −10.16 kcal/mol). The enhanced binding affinity of compound P10 may be attributed to the presence of dichloro-triazinyl substituted piperazine moiety, which promotes strong hydrophobic and hydrogen bonding interactions within the EGFR catalytic domain. Similarly, compounds P9 (−10.33 kcal/mol) and P8 (−10.23 kcal/mol) also displayed significant binding affinity toward the receptor and showed stable interactions with residues located in the ATP-binding pocket of EGFR. These interactions may contribute to effective inhibition of EGFR kinase activity and suppression of cancer cell proliferation. Compound P7 also exhibited a promising docking score (−10.13 kcal/mol), which is comparable to the standard drug Erlotinib. The presence of a diphenylamino substituent in this compound likely enhances hydrophobic interactions within the binding pocket, thereby improving binding stability. Docking scores were displayed in **Table 1.**

Table 1: Characterization of Designed Derivative Compounds

Comp. code	Structures	Mol. Formula	Mol. Weight (g/mole)	IUPAC name
P1		C21H28N4O2	368.47	N1-((2-(4-benzylpiperazin-1- yl)-1,3-dioxolan-2-yl) methyl) benzene-1,2-diamine

P2		C16H24N4O3	320.39	1-(4-(2-((2-aminophenylamino) methyl)-1,3-dioxolan-2-yl) piperazin-1-yl)ethanone
P3		C15H24N4O4S	356.44	[[amino-(1Phenylethoxyamino) methylidene]N-cyclohexylsulfamate
P4		C20H26N4O2	354.45	N1-((2-(4-phenylpiperazin-1- yl)-1,3-dioxolan-2-yl) methyl) benzene-1,2-diamine
P5		C18H23CL2N7O2	440.33	N1-((2-(4-((4,6-dichloro-1,3,5-triazin-2-yl) methyl) piperazin-1-yl)-1,3-dioxolan-2-yl) methyl) benzene-1,2- diamine
P6		C27H31N3O2	429.55	N-((2-(4-benzylpiperazin-1- yl)-1,3-dioxolan-2-yl) methyl)-N-phenylbenzenamine
P7		C22H27N3O3	381.47	1-(4-(2-((diphenylamino)methyl)-1,3-dioxolan-2-yl) piperazin-1-yl)ethanone
P8		C21H27N3O4S	417.52	(2R)-1-methylsulfonyl-?N-[(1R)-1-[3-(pyridine- 2-ylmethoxy)phenyl]ethyl]piperidine-2-carboxamide
P9		C26H29N3O2	415.53	N-phenyl-N-((2-(4-phenylpiperazin-1- yl)-1,3-dioxolan-2-yl) methyl) benzenamine
P10		C24H26Cl2N6O2	501.41	N-((2-(4-((4,6-dichloro-1,3,5-triazin-2-yl) methyl) piperazin-1-yl)-1,3-dioxolan-2-yl) methyl)-N-phenylbenzenamine
Std		C24H29NO3	379.49	2-((1-benzylpiperidin-4- yl) methyl)-2,3-dihydro-5,6-dimethoxyinden-1- one

Computational analysis of Designed Derivative Compounds

The docking results revealed that compounds P4, P5, and P1 also demonstrated moderate binding affinity toward the EGFR receptor with docking scores ranging from −9.6 to −9.8 kcal/mol. Although these compounds showed slightly lower affinity compared to the most active derivatives, they still exhibited favorable interactions within the active site region. The docking analysis suggests that the designed piperazine–1,3-dioxolane derivatives possess strong binding potential against the EGFR tyrosine kinase

receptor. Among all the compounds studied, P10, P9, P8, and P7 were identified as the most promising candidates based on their docking scores and predicted interaction profiles. Figure 2-12 represents binding interaction of design molecule with selected protein. These findings indicate that the designed derivatives may serve as potential lead molecules for the development of novel anticancer agents targeting EGFR.

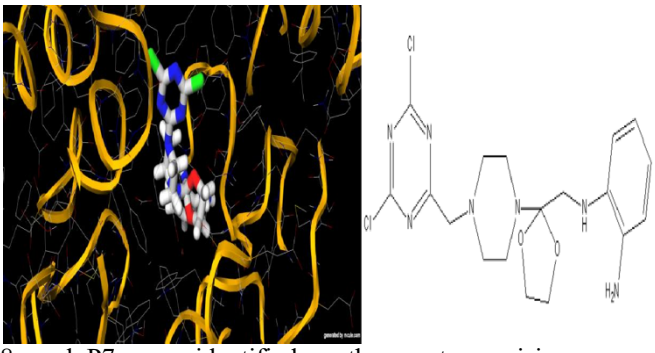


Table 2: Molecular docking results representing docking sores

Sr. No	Code	Docking score (1)	Docking score (2)	Docking score (3)	Average
1.	P1	-9.0	-8.8	-8.7	-8.83
2.	P2	-9.1	-9.0	-9.0	-9.03
3.	P3	-9.6	-8.4	-7.7	-8.56
4.	P4	-10.1	-9.5	-9.4	-9.6
5.	P5	-10.0	-9.8	-9.6	-9.8
6.	P6	-9.8	-9.7	-9.4	-9.63
7.	P7	-10.4	-10.3	-9.7	-10.13
8.	P8	-10.4	-10.4	-9.9	-10.23
9.	P9	-10.6	-10.3	-10.1	-10.33
10.	P10	-11.5	-10.6	-10.2	-10.76
11.	Std	-10.5	-10.1	-9.9	-10.16

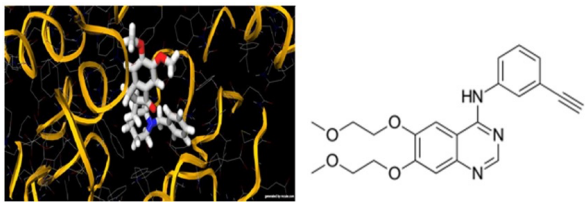


Figure 2: Binding interaction of Standard (Erlotinib) with 1M17

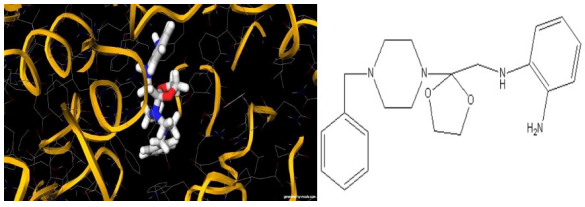


Figure 3: Binding interaction of P1 with 1M17

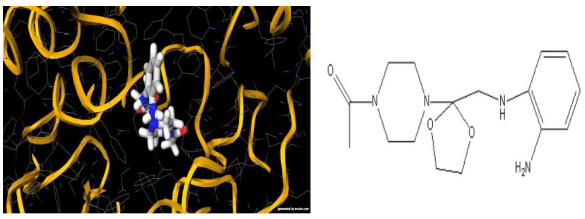


Figure 4: Binding interaction of P2 with 1M17

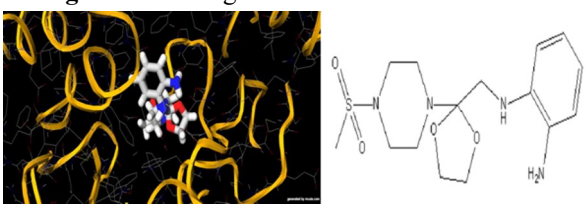


Figure 5: Binding interaction of P3 with 1M17

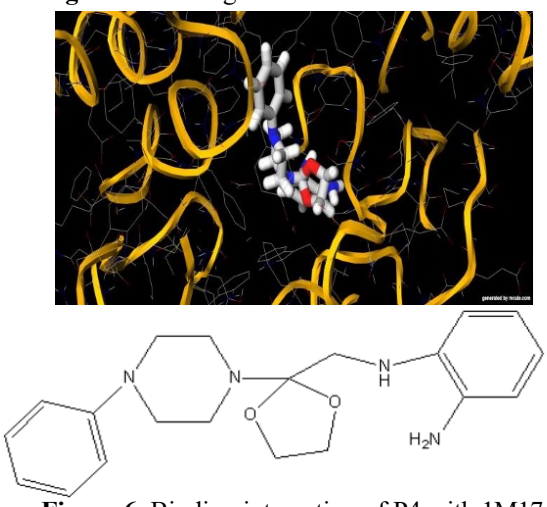


Figure 6: Binding interaction of P4 with 1M17

Figure 7: Binding interaction of P5 with 1M17

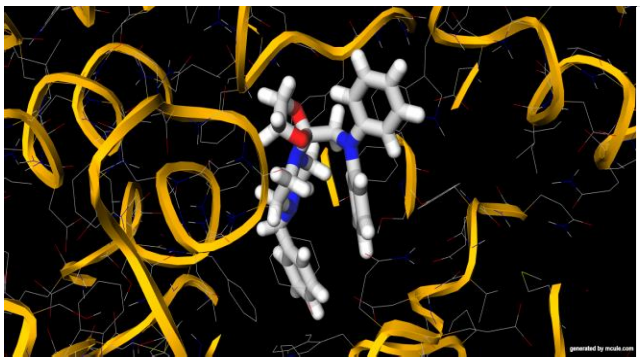
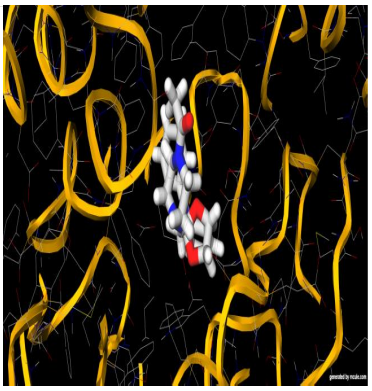


Figure 8: Binding interaction of P6 with 1M17



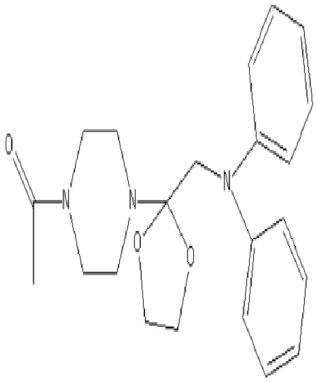


Figure 12: Binding interaction of 10 with 1M17

Figure 9: Binding interaction of P7 with 1M17

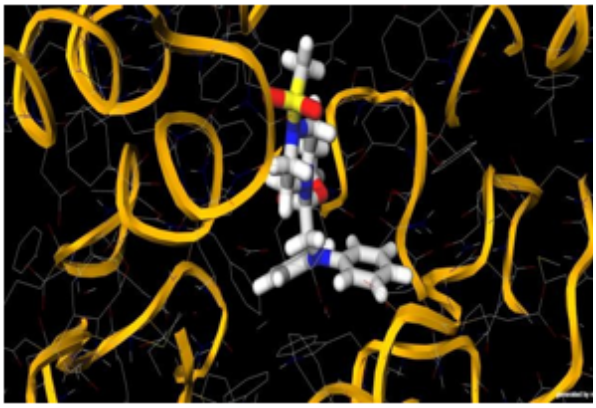


Figure 10: Binding interaction of P8 with 1M17

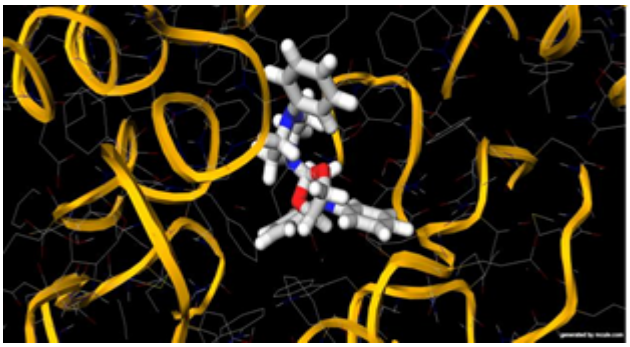
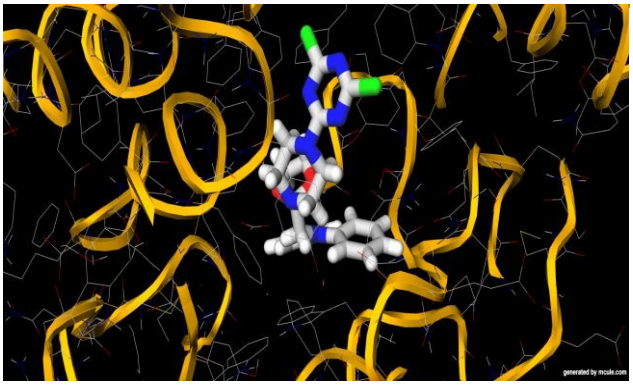
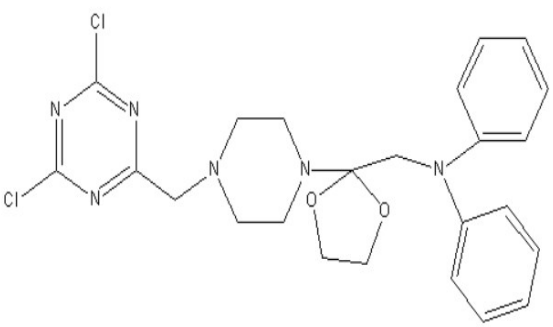


Figure 11: Binding interaction of P9 with 1M17





ADME studies:

To Predict the *In-silico* ADME profile of synthesized molecules was done by using the SWISS ADME programme physically significant descriptors and pharmacologically relevant properties of these compounds were predicted. Fundamental physiochemical features of CNS drugs are mainly related to their ability to penetrate the blood-brain barrier (BBB) and exhibit CNS activity. Our results indicated that compounds from all the series (P1 to P10**)** showed drug like characteristics based on Lipinski's rule of five (Mol MW<500, logP<5, donor HB<5, acceptor HB<10). All the synthesized derivative compounds were showed very low permeability for Caco-2, displayed good oral absorption, indicate their moderate binding with plasma protein and presented moderate in silico possible toxicity risks. The predicted ADMET properties revealed that all compounds fulfil drug-like

criteria and could be considered as good candidate for drug development. All the synthesized compound derivatives have Standard Drug (Erlotinib) like ADMET properties. ADME properties were calculated using SWISSADME server and results were displayed in **Table 3, 4.**

Table 3: In-silico Absorption and Distribution studies of Designed Derivative Compounds

Comp. Code	**Absorption**						**Skin permeation CM/S**
	Human Intestinal (HIA)	Aqueous Solubility (logS)	CaCO-2 Permeability (LogP cm/s)	P-glycoprotein		Blood Brain Barrier Penetration (BBB)	
				Substrate	Inhibitor		
P1	HIGH	YES	NO	YES	NO	YES	-7.04
P2	HIGH	YES	NO	YES	NO	NO	-8.64
P3	HIGH	YES	NO	YES	NO	NO	-8.56
P4	HIGH	YES	NO	YES	NO	YES	-6.75
P5	HIGH	YES	NO	YES	NO	NO	-6.97
P6	HIGH	NO	NO	YES	NO	YES	-5.73
P7	HIGH	YES	NO	YES	NO	YES	-6.87
P8	HIGH	YES	NO	YES	NO	YES	7.24
P9	HIGH	NO	NO	YES	NO	YES	-5.43
P10	HIGH	NO	NO	NO	NO	YES	-5.65
Std	HIGH	NO	NO	YES	YES	YES	-5.60
LIMIT	1.0000	1-7.5	4.0000	1.0000			1.0000

*=Inhibitor/Substrate

Table 4: In-Silico Metabolism Studies of Designed Derivative Compounds

Comp. Code	**CYP450 Inhibitor**					**Lipinski**
	1A2	2C9	2D6	2C19*	3A4	
P1	NO	NO	YES	NO	NO	YES 0 Violation
P2	NO	NO	NO	NO	NO	YES 0 Violation
P3	NO	NO	NO	NO	NO	YES 0 Violation
P4	NO	NO	YES	NO	NO	YES 0 Violation
P5	YES	NO	YES	NO	YES	YES 0 Violation
P6	NO	YES	YES	NO	YES	YES 0 Violation
P7	NO	NO	YES	YES	YES	YES 0 Violation
P8	NO	YES	YES	YES	YES	YES 0 Violation
P9	YES	YES	YES	NO	YES	YES 0 Violation
P10	YES	YES	YES	YES	YES	YES 0 Violation
Std	YES	NO	YES	NO	YES	YES 0 Violation

*=Inhibitor/Substrate

CONCLUSION:

All the designed derivative compounds of novel 1,4-disubstituted piperazine derivatives were evaluated through physical and spectral characterization along with computational analysis. The molecular docking results were compared with the standard anticancer drug Erlotinib, a known inhibitor of Epidermal Growth Factor Receptor. The docking study revealed that the synthesized derivative compounds P7, P8, P9, and P10 exhibited significant binding interactions within the active binding pocket of the EGFR receptor. These compounds demonstrated favorable binding affinity and interaction patterns with key amino acid residues of the EGFR catalytic domain, suggesting their potential inhibitory activity against EGFR-mediated signaling pathways involved in cancer cell proliferation. Furthermore, the predicted ADME properties indicated that all the designed compounds satisfied the essential drug-likeness criteria and showed pharmacokinetic profiles comparable to the standard drug Erlotinib. The in-silico results suggest that the designed molecules possess favorable absorption, distribution, metabolism, and excretion characteristics, supporting their potential as orally active drug candidates. Therefore, the designed 1, 4-disubstituted piperazine derivatives may serve as promising lead molecules for the development of novel anticancer agents targeting EGFR. However, further investigation including in vitro cytotoxicity studies and in vivo pharmacological evaluation is required to confirm their therapeutic potential and to identify the most active candidate for

future drug development.

DECLARATIONS:

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All the authors approved the manuscript for publication.

Competing interests:

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