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Advances in Bioresearch

Benzimidazolo Quinoline Derivatives: A Combined Design, Docking, and Drug-Likeness Study based on Lipinski's Rule of Five

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ABSTRACT

This study designed and evaluated a series of novel benzimidazolo quinoline derivatives as potential inhibitors of PI3K and EGFR-TK receptors using molecular docking studies. Eighteen compounds were designed by modifying the aryl moiety at the C3 position of the parent nucleus. Molecular docking revealed high binding affinities of the compounds towards PI3K (-9.6 to -11.5 kcal/mol) and EGFR-TK (-9.7 to -10.8 kcal/mol), comparable to reference drugs imatinib and AMG319. Key interactions included hydrogen bonding and hydrophobic interactions with active site residues. Drug-likeness evaluation showed the compounds satisfied Lipinski's rule of five and exhibited favorable ADME properties including high GI absorption. ADMET predictions indicated most compounds are unlikely to be P-glycoprotein substrates, suggesting lower potential for drug-drug interactions. The computational studies utilized software tools including ChemSketch for design, OpenBabel for file conversion, Chimera for protein preparation, PyRx for docking simulations, and Discovery Studio for visualization. While the results are promising, further studies are needed to synthesize and experimentally evaluate the biological activity of the designed compounds. Additionally, lead optimization could potentially enhance the potency and drug-like properties of these novel benzimidazolo quinoline derivatives as PI3K and EGFR-TK inhibitors.

Keywords: Benzimmidazole Quinazoline derivatives, molecular docking, PI3K, EGFR-TK, ADME study, Lipinski's rule of five.

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INTRODUCTION

Cancer is one of the biggest killers at present, it causes incredible dangers, not only to society but also to single human lives [1,2]. Despite the advances in the treatments and continuous trials looking for cancer prevention, success in treating cancer is still having a lot of challenges [3,4]. Hence, the search for new anticancer active agents that have a broader spectrum of cytotoxicity is continuous [5]. Quinoline is a privileged scaffold in medicinal chemistry as its derivatives have shown good biological activities through different mechanisms of action such as growth inhibitors, apoptosis inducers, angiogenesis inhibitors, disruption of cell migration, and nuclear receptor modulators [6-13]. In addition, some quinoline derivatives showed activity as perspective HIV integrase inhibitors [14], antibacterial [15,16], antimalarial [17], antitumor agents [18-20], antifungal and herbicidal [21], protein tyrosine kinase inhibitors [22] and antiprotozoal [23].

Benzimidazole, the benzo derivative of imidazole, is a class of bicyclic aromatic organic compound consisting of a six-membered benzene ring fused to five-membered imidazole at 4- and 5-positions of the

imidazole ring. Its IUPAC name is 1H-benzimidazole and it is also referred to as 1H-1,3-Benzimidazole or 1H-Benzo[d]imidazole. Benzimidazole is a vital pharmacophore of many biologically active heterocyclic compounds with a variety of pharmacological activities. The NH group in benzimidazole is both highly acidic and weakly basic [24]. They also have the ability to form salts. The benzimidazole moiety is useful in the pharmaceutical field for the development of novel medicinal compounds. Therefore, the synthesis of various benzimidazole derivatives has been reported for their pharmacological activities. Over time, benzimidazole and its derivatives have evolved as vibrant heterocyclic systems due to their potency in a wide range of bioactive compounds like analgesics [25,26], antiparasitic [27], antifungals [28], anticoagulants, anti-inflammatory agents [29], antihypertensives[30], antihistaminic[31], anticonvulsants [32], antimalarial [33], antitubercular [34], anti-HIV [35], antimicrobial [36], antiprotozoal [37], antiviral [38], and so on.

Phosphorylated lipids are produced at cellular membranes during signaling events and contribute to the recruitment and activation of various signaling components. The role of phosphoinositide 3-kinase (PI3K), which catalyzes the production of phosphatidylinositol-3,4,5-trisphosphate, in cell survival pathways; the regulation of gene expression and cell metabolism; and cytoskeletal rearrangements are highlighted. The PI3K pathway is implicated in human diseases including diabetes and cancer, and understanding the intricacies of this pathway may provide new avenues for therapeutic intervention[395]. Phosphatidylinositol (PI), participates in cellular function regulation such as cell proliferation, cell differentiation, cell migration, chemotaxis, and phagocytosis. The PI3K pathway is a frequently activated pathway in human cancer. Inhibitors targeting key components in this pathway are being developed in anti-cancer studies.

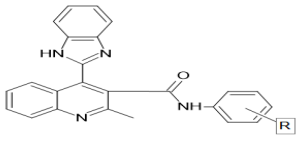
Trans-membrane receptor tyrosine kinases play an important role in the modulation of growth factor signaling. The epidermal growth factor receptor (EGFR) is a member of a family of four closely related receptors: EGFR (or erbB1), HER2/neu (erbB2), HER3 (erbB3) and HER4 (erbB4). The EGFR mediates the actions of multiple ligands including epidermal growth factor, transforming growth factor-a, amphiregulin, and heparin-binding EGF, and may also be constitutively activated by mutation. EGFR signaling has been reported to be important for tumor cell proliferation, inhibition of apoptosis, angiogenesis, metastasis, and sensitivity to chemotherapy and radiotherapy [40].

MATERIAL AND METHODS

Designing of new benzimidazolo quinoline derivatives and molecular modeling studies

In this study designing new benzimidazolo quinoline derivatives by the molecular modification approach using ACD/ChemSketch software (Advanced Chemistry Development, Inc., version 2022.1.2). The novel compounds designed in this study are summarized in Table 1. Eighteen benzimidazolo quinoline derivatives were designed by substituting the aryl moiety to the side chain at the C_3 position. Molecular modeling studies were performed on Biovia Discovery studio DS 2024 software.

Table 1: The structure of the parent nucleus and designed Benzimidazole Quinazoline derivatives.



4-(1*H*-1,3-benzimidazol-2-yl)-*N*-benzyl-2-methylquinoline-3-carboxamide derivatives.

Compound code	Molecular formula	IUPAC name
Com 5	$C_{24}H_2ON_4O$	4-(1*H*-1,3-benzimidazol-2-yl)-*N*-benzyl-2-methylquinoline-3-carboxamide
Com 6	$C_{25}H_{19}F_3N_4O$	4-(1*H*-1,3-benzimidazol-2-yl)-2-methyl-*N*-[-2-trifluoromethyl)phenyl]quinoline-3-carboxamide
Com 7	$C_{25}H_{19}F_3N_4O$	4-(1*H*-1,3-benzimidazol-2-yl)-2-methyl-*N*-[-3-trifluoromethyl)phenyl]quinoline-3-carboxamide
Com 8	$C_{25}H_{19}F_3N_4O$	4-(1*H*-1,3-benzimidazol-2-yl)-2-methyl-*N*-[-4-trifluoromethyl)phenyl]quinoline-3-carboxamide
Com 9	$C_{25}H_{22}N4O_2$	4-(1*H*-1,3-benzimidazol-2-yl)-2-methyl-*N*-[-4-methoxy)phenyl]quinoline-3-carboxamide
Com 10	$C_{25}H_{22}N4O$	4-(1*H*-1,3-benzimidazol-2-yl)-2-methyl-*N*-(4-methylphenyl)quinoline-3-carboxamide

Com 11	$C_{25}H_{19}ClN_4O_3$	2-{[4-(1*H*-1,3-benzimidazol-2-yl)-2-methylquinoline-3-carbonyl]amino}-3-chlorobenzoic acid
Com 12	$C_{25}H_{19}ClN_4O_3$	2-{[4-(1*H*-1,3-benzimidazol-2-yl)-2-methylquinoline-3-carbonyl]amino}-5-chlorobenzoic acid
Com 13	$C_{25}H_{19}ClN_4O_3$	2-{[4-(1*H*-1,3-benzimidazol-2-yl)-2-methylquinoline-3-carbonyl]amino}-6-chlorobenzoic acid
Com 14	$C_{23}H_{19}N_5O$	4-(1*H*-1,3-benzimidazol-2-yl)-2-methyl-*N*-(pyridin-4-yl)quinoline-3-carboxamide
Com 15	$C_{23}H_{19}N_5O$	4-(1*H*-1,3-benzimidazol-2-yl)-2-methyl-*N*-(pyridin-3-yl)quinoline-3-carboxamide
Com 16	$C_{25}H_{20}N_4O$	3-{[4-(1*H*-1,3-benzimidazol-2-yl)-2-methylquinoline-3-carbonyl]amino}benzoic acid
Com 17	$C_{24}H_{19}FN_4O$	4-(1*H*-1,3-benzimidazol-2-yl)-*N*-(2-fluorophenyl)-2-methylquinoline-3-carboxamide
Com 18	$C_{24}H_{20}N_4O$	4-(1*H*-1,3-benzimidazol-2-yl)-2-methyl-*N*-phenylquinoline-3-carboxamide
Com 19	$C_{24}H_{19}FN_4O$	4-(1*H*-1,3-benzimidazol-2-yl)-*N*-(4-fluorophenyl)-2-methylquinoline-3-carboxamide
Com 20	$C_{26}H_{22}N_4O_3$	2-{[4-(1*H*-1,3-benzimidazol-2-yl)-2-methylquinoline-3-carbonyl]amino}-6-methylbenzoic acid
Com 21	$C_{26}H_{22}N_4O_3$	2-{[4-(1*H*-1,3-benzimidazol-2-yl)-2-methylquinoline-3-carbonyl]amino}-5-methylbenzoic acid
Com 22	$C_{26}H_{22}N_4O_4$	2-{[4-(1*H*-1,3-benzimidazol-2-yl)-2-methylquinoline-3-carbonyl]amino}-4-methoxybenzoic acid

DOCKING STUDIES

Receptor (Phosphoinositide 3-Kinase and Epidermal Growth Factor Receptor Tyrosine Kinase) Preparation

The Phosphoinositide 3-kinase (1E7V) and Epidermal growth factor receptor tyrosine kinase (1M17) crystal form shown in Figure 1 and 2. was downloaded from RCSB Protein Data Bank (http://www.rcsb.org/) [41]. All imported foreign matters like cofactors and ligands allied with the enzyme were removed using Chimera 1.17.3 software. Later on, the target protein was saved in the format in (PDB) i.e. recommended format for Discovery Studio Visualizer and Pyrx software. Thereafter, the target protein saved in PDB format was imported into the Pyrx software and converted as macromolecules [42-45].

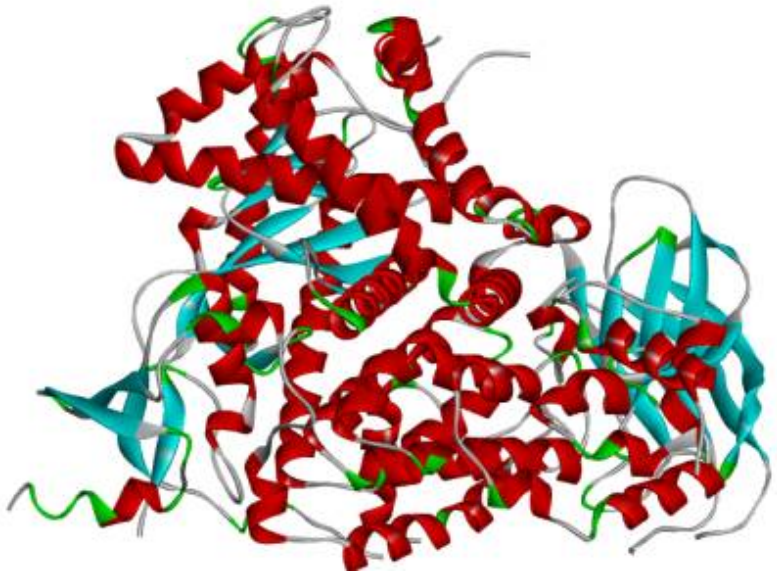


Figure 1: 3D Crystal structure of Phosphoinositide 3-kinase (1E7V).

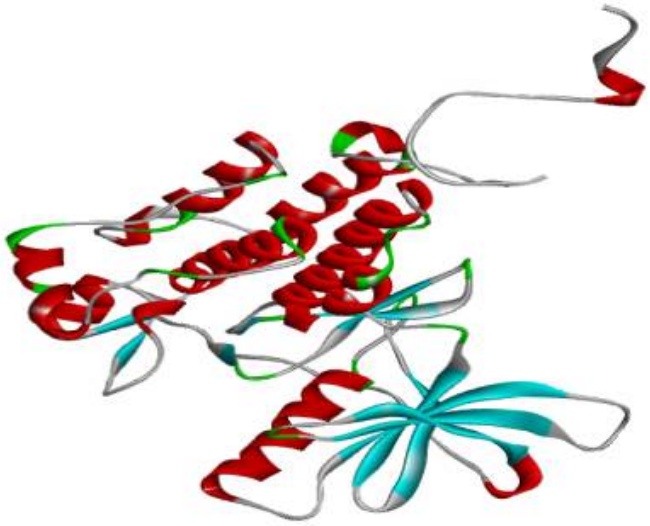


Figure 2: 3D Crystal structure of Epidermal growth factor receptor tyrosine kinase (1M17).

Ligand Preparation

The stable conformation of Benzimidazolo Quinoline derivatives at a minima energy were achieved by employing Open Babel software which serve as an optimized tool. The ligands optimized were later saved as a PDB format in order to be recognized by the Pyrx software. Later on, the ligands saved in PDB format were imported in the Pyrx software and converted as micro molecules [46,47].

Docking of Receptor and Ligand

Ligand-receptor interactions between Benzimidazolo Quinoline derivatives and the receptor (Phosphoinositide 3-kinase and Epidermal growth factor receptor tyrosine kinase) was carried out using molecular docking technique by employing the PyRx virtual screening software. The PyRx software [https://pyrx.sourceforge.io/], is software used for execution virtual screening. PyRx uses AutoDock Vina and AutoDock 4.2 as docking software. Discovery Studio Visualizer software version DS2024 was used to visualized and analyzed the docked results [48-50]. All docked poses were scored and ranked. The binding affinities of docked compounds were predicted by analysing interactions of receptor-ligand complexes. The binding modes of the best-docked pose were analyzed using the 2D receptor-ligand complex. Different nonbonding interactions (hydrogen bonding, hydrophobic, etc.) were also analyzed using the 2D diagram of receptor-ligand complexes. The docking results of the test compounds were compared with Imatinib and AMG319 against Phosphoinositide 3-kinase and Epidermal growth factor receptor tyrosine kinase respectively.

Drug-Likeness Study

Drug-likeness properties of the compounds 7,8,10,11,12,16,19, and 21 were studied in this part and the drug-likeness results were tabulated as in Table 3. These parameters were taken from the SwissADME web page [51]. Because these parameters are very crucial in drug design and its potential to be a drug. According to the Lipinski rules, the candidate molecules must have 5 important properties in literature as follows [52]:

MlogP ≤ 5

Molecular weight (MW) ≤ 500 g/mol

Number of H-bond acceptors (HBA) ≤ 10 and number of H-bond donors (HBD) ≤ 5

Number of rotatable bonds (n_{Rot}) ≤ 10

Topological Polar Surface Area (TPSA)< 140 $Å^2$

From the results, we can say that all the designed compounds are in accordance with the criteria defined by Lipinski rules above and there are no violations. Furthermore, the bioavailability radars and predicted[51].

ADMET Prediction

The ADME-Toxicity (ADMET) parameters were calculated using the ADMET descriptor protocol of DS 2020 software. Six mathematical models (aqueous solubility, blood-brain barrier penetration, cytochrome P450 (CYP) 2D6 inhibition, hepatotoxicity, intestinal absorption, and plasma protein binding) were used for quantitative prediction of properties related to ADMET characteristics or pharmacokinetics (PKs) of drug molecules [52-54].

RESULTS AND DISCUSSION

Molecular Docking Studies

Molecular docking studies were performed to evaluate the interactions and binding affinities of the suggested benzimidazole quinoline compounds with PI3K and EGFR-TK. The results are summarized in Table 2. The docking scores revealed that compounds 5-22 exhibited high binding affinity towards PI3K, with scores ranging from -9.6 to -11.5 kcal/mol. Similarly, compounds 5-22 showed high binding affinity towards EGFR-TK, with scores ranging from -9.7 to -10.8 kcal/mol. All 18 compounds, showed the highest binding affinity against 1E7V and 1M17. Along with a few secondary interactions including hydrophobic interactions, the 2D interaction diagram showed that the main interactions between the receptor and ligand molecule were polar hydrogen bonding interactions. There were clear molecular interactions between the complementary ligand moieties/atoms and the binding site residues of the receptor molecule.

Table 2: Docking scores of the designed Benzimidazole quinoline Com5 to Com22 and Co-crystal ligand like AMG319 AND Imatinib against PI3K (1E7V) and EGFR-TK (1M17).

Ligands	1M17	1E7V
Com5	-10.4	-10.6
Com6	-10.2	-10.1
Com7	-10.2	-11.5
Com8	-10.2	-9.9
Com9	-10.1	-9.6
Com10	-10.7	-10.9
Com11	-10.2	-10.9
Com12	-10.6	-10.5
Com13	-10.3	-9.9
Com14	-9.9	-10.7
Com15	-9.9	-9.7
Com16	-10.3	-10.8
Com17	-10.3	-10.8
Com18	-10.3	-10.1
Com19	-10.4	-11
Com20	-10.3	-10
Com21	-10.8	-10.8
Com22	-9.7	-10.1
Imatinib	-9.5	-
AMG319	-	-9.5

The higher the number of hydrogen bonds, the higher the binding affinity. eight potent compounds, namely com7, com8, com10, com11, com12, com16, com19 and com21 interacted with different active site residues such as GLN291, GLN295, ARG690, ARG849 and TYR787 with 1E7V and LYS721, ASP831, ARG817 and THR766 with 1M17 predominantly by hydrogen bond formation are summarized in Table 3 and 4. A comparative analysis revealed that the co-crystal ligands AMG319 and Imatinib exhibited similar binding interactions with the amino acid residues of 1E7V and 1M17, respectively, as observed with the designed ligands. The details of 2D interaction diagrams of five compounds and the co-crystal inhibitor AMG319 and five compounds and the co-crystal inhibitor Imatinib are shown in Figure 3 and Figure 4.

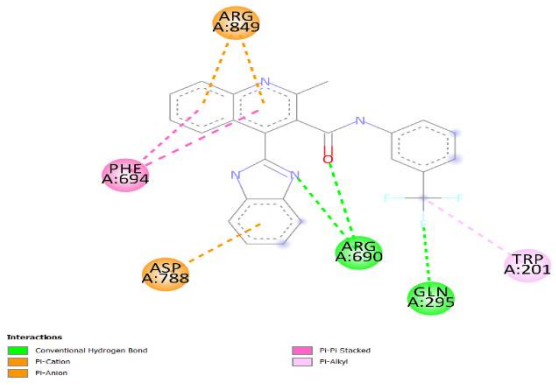
Table 3: Molecular Docking interactions formed between prominent ligands and co-crystal ligand AMG319 with 1E7V.

Sr. NO	LIGAND	TYPE OF INTERACTION	CONTACTING RECEPTOR RESIDUES	BOND LENGTH (Å)
1	C7	Conventional Hydrogen Bond	GLN295	2.35
		Conventional Hydrogen Bond	ARG690	2.89
		Conventional Hydrogen Bond	ARG690	2.53
		Pi -cation	ARG849	3.05
		Pi-cation	ARG849	3.92
		Pi-Pi stacked	PHE694	4.50
		Pi-Pi stacked	PHE694	4.56
2	C10	Conventional Hydrogen Bond	ARG690	2.18
		Pi-cation	ARG849	3.91
		Pi-cation	ARG849	3.58
		Pi-Pi stacked	PHE694	4.54

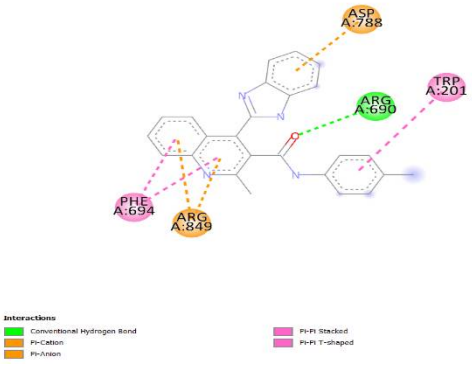
		Pi-Pi stacked	PHE694	4.50
3	C11	Conventional Hydrogen Bond	ARG690	2.05
		Conventional Hydrogen Bond	ARG849	2.41
		Pi-cation	ARG849	3.53
		Pi-cation	ARG849	4.02
		Pi-Pi stacked	PHE694	4.44
		Pi-Pi stacked	PHE694	4.60
4	C16	Conventional Hydrogen Bond	GLN291	2.44
		Conventional Hydrogen Bond	ARG690	2.23
		Conventional Hydrogen Bond	ARG690	2.00
		Conventional Hydrogen Bond	ARG849	3.00
		Conventional Hydrogen Bond	TYR787	1.93
		Pi-cation	ARG690	3.86
		Pi-cation	ARG849	4.07
		Pi-cation	ARG849	4.04
		Pi-cation	ARG849	4.03
		Pi-Pi stacked	PHE694	3.82
		Pi-Pi stacked	PHE694	4.73
5	C19	Conventional Hydrogen Bond	GLN291	2.94
		Conventional Hydrogen Bond	ARG690	2.09
		Pi-cation	ARG849	3.57
		Pi-cation	ARG849	3.90
		Pi-Pi stacked	PHE694	4.47
		Pi-Pi stacked	PHE694	4.59
6	AMG319	Conventional Hydrogen Bond	ARG849	3.49
		Pi-cation	ARG690	3.84
		Pi-cation	ARG849	3.74
		Pi-cation	ARG849	4.04
		Pi-cation	HIS658	4.85
		Pi-Pi stacked	PHE694	4.86
		Pi-Pi stacked	PHE694	4.20

Table 4: Molecular Docking interactions formed between prominent ligands and co-crystal ligand Imatinib with 1M17

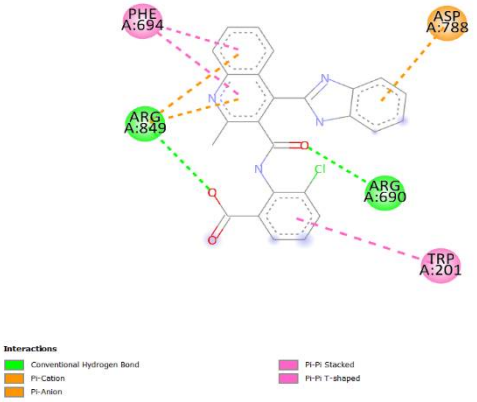
Sr. NO	LIGAND	TYPE OF INTERACTION	CONTACTING RECEPTOR RESIDUES	BOND LENGTH(Å)
1	Com11	Carbon Hydrogen Bond	LYS721	2.01
		Pi-cation	LYS721	4.65
		Pi-Pi Stacked	PHE699	4.42
2	Com12	Conventional Hydrogen bond	ASP831	2.81
		Conventional Hydrogen bond	ARG817	2.11
		Pi-cation	LYS721	4.37
		Pi-Pi Stacked	PHE699	4.28
3	Com13	Conventional Hydrogen bond	LYS721	2.38
		Carbon Hydrogen Bond	LYS721	2.02
		Pi-cation	LYS721	4.70
		Pi-Pi Stacked	PHE699	4.32
4	Com16	Conventional Hydrogen bond	LYS721	2.79
		Conventional Hydrogen bond	ALA719	2.15
		Conventional Hydrogen bond	THR766	2.59
5	Com21	Conventional Hydrogen bond	ASP831	2.90
		Conventional Hydrogen bond	ARG817	2.23
		Pi-Pi cation	LYS721	4.38
		Pi-Pi stacked	PHE699	4.23
6	Imatinib	Conventional Hydrogen bond	LYS721	2.56
		Conventional Hydrogen bond	ASP831	2.79
		Carbon Hydrogen Bond	PRO770	3.58
		Pi-Pi stacked	PHE699	5.07



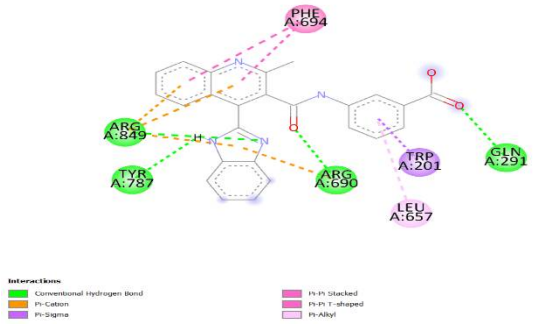
The 2D model of the binding pose with bond length and interacting amino acid of docked Com 7 with 1E7V Protein



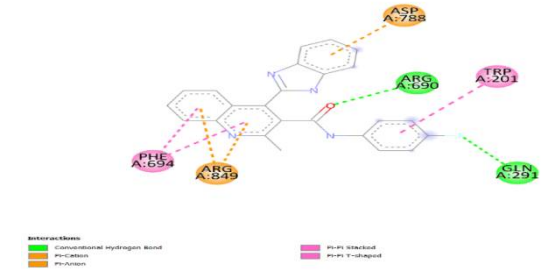
The 2D model of the binding pose with bond length and interacting amino acid of docked Com 10 with 1E7V Protein



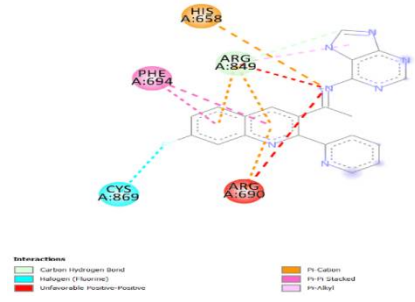
The 2D model of the binding pose with bond length and interacting amino acid of docked Com 11 with 1E7V Protein



The 2D model of the binding pose with bond length and interacting amino acid of docked Com 16 with 1E7V Protein

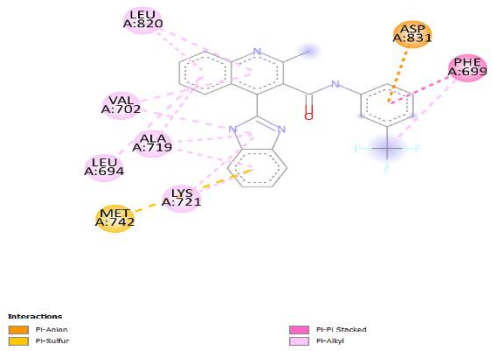


The 2D model of the binding pose with bond length and interacting amino acid of docked Com 19 with 1E7V Protein

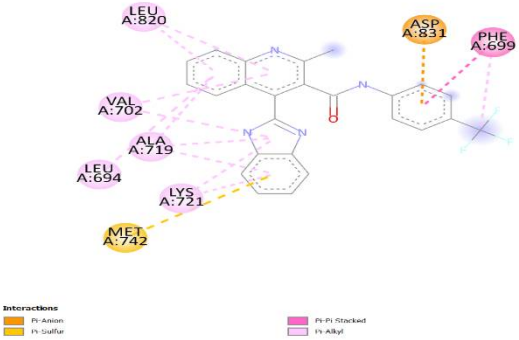


The 2D model of the binding pose with bond length and interacting amino acid of docked co-crystal ligand (AMG319) with 1E7V Protein

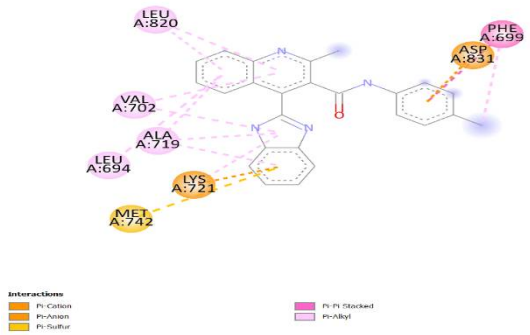
Figure 3: 2D interactions with binding modes and docking interactions diagrams of prominent ligands and the co-crystal ligand AMG319 against PI3K enzyme (1E7V); dotted green lines indicate conventional H-bonding interactions and dotted yellow and purple lines indicate different types of hydrophobic interactions.



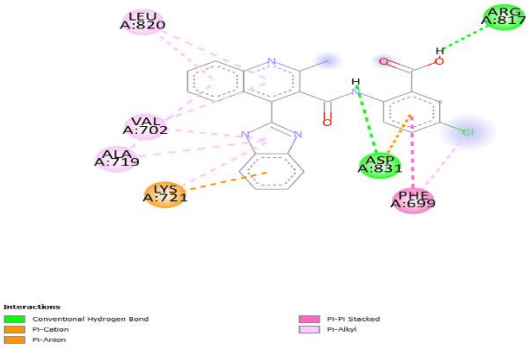
The 2D model of the binding pose with bond length and interacting amino acid of docked Com 7 with 1M17 Protein.



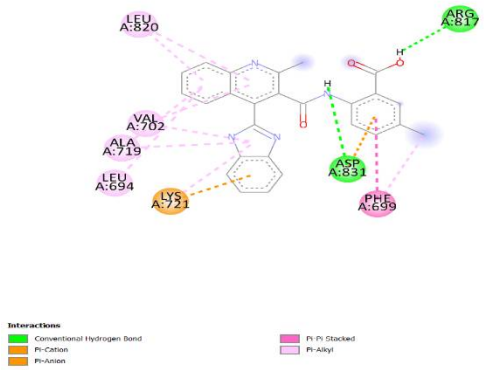
The 2D model of the binding pose with bond length and interacting amino acid of docked Com 8 with 1M17 Protein.



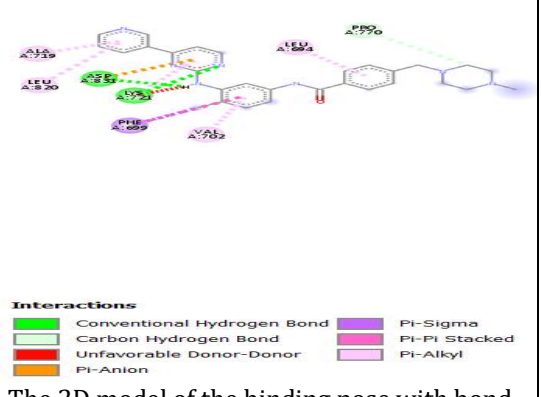
The 2D model of the binding pose with bond length and interacting amino acid of docked Com 10 with 1M17 Protein.



The 2D model of the binding pose with bond length and interacting amino acid of docked Com 12 with 1M17 Protein.



The 2D model of the binding pose with bond length and interacting amino acid of docked Com 21 with 1M17 Protein.



The 2D model of the binding pose with bond length and interacting amino acid of docked reference drug (Imatinib) with 1M17 Protein.

Figure 4: 2D interactions with binding modes and docking interactions diagrams of prominent ligands and the co-crystal ligand Imatinib against EGFR-TK enzyme (1M17); dotted green lines indicate conventional H-bonding interactions, and dotted yellow and purple lines indicate different types of hydrophobic interactions.

Lipinski's Rule of Five

The drug-likeness of the designed compounds was evaluated using Lipinski's rule of five. The results are summarized in Table 5. The results revealed that all the compounds showed good drug-like properties based on Lipinski's rule of five with additional parameters of drug-likeness. In our study, all the compounds exhibited satisfactory molecular properties and Lipinski's parameters. The parameters LogP, MW, and molecular PSA indicate good membrane permeability, intestinal absorption, and oral bioavailability, respectively, whereas the other parameters nHBAs, nHBDs, nR, and Rotb bonds facilitate to produce well-defined drug-receptor interactions for optimal drug action. None of the compounds violated the Lipinski's rule of 5. Compounds showed drug likeness scores in the range of 0.15 to 1.09 as seen from the calculations of the Molsoft program. The drug-likeness scores were within the acceptable range (0-1) [51, 52].

Table 5: Drug likeness of the designed Benzimidazole Quinoline derivatives.

Compounds	Molecular properties and Lipinski's parameters						DL score
	MW	nHBD	nHBA	QPlogP o/w	N of Violations	Nrb	
Com 5	380.44	3	2	3.81	0	4	0.34
Com 6	44.844	3	5	4.85	1	5	0.40
Com 7	448.44	3	5	4.80	0	5	0.23
Com 8	448.44	3	5	4.83	0	5	0.29
Com 9	410.47	3	3	3.81	0	5	0.53
Com 10	394.47	3	2	4.14	0	4	0.26
Com 11	458.90	4	4	3.88	0	5	1.09
Com 12	458.90	4	4	3.95	0	5	0.52
Com 13	458.90	4	4	3.97	0	5	1.00
Com 14	381.43	3	3	3.08	0	4	0.68
Com 15	381.43	3	3	3.07	0	4	0.75
Com 16	424.45	4	4	3.35	0	5	0.46
Com 17	398.43	3	3	4.13	0	4	0.54
Com 18	380.44	3	2	3.81	0	4	0.34
Com 19	398.43	3	3	4.12	0	4	0.69
Com 20	438.48	4	2	3.81	0	5	0.67
Com 21	438.48	4	4	3.81	0	5	0.15
Com 22	438.48	4	4	3.40	0	6	0.88

LogP – log of octanol/water partition coefficient; MW – molecular weight; nHBA –number of hydrogen bond acceptor(s); nHBD – number of hydrogen bond donor(s); nRotB – number of rotable bond(s) and DL score-drug-likeness score.

ADME Prediction

The ADME properties of the designed compounds were predicted using SwissADME. The results are summarized in Table 6. all the compounds show Pharmacokinetics parameters and bioavailability of the benzimidazole quinoline derivatives. Eighteen compounds had high values of GI absorption. Moreover, the analysis provided insights into the probability of some compounds crossing the blood brain barrier (BBB), although experimental studies are necessary to validate these predictions. Interestingly all the results indicated that almost all derivatives are not P-glycoprotein (P-gp) inhibitors, implying that they are unlikely to be substrates for the efflux pump and may exhibit lower potential for drug-drug interactions.

CONCLUSION

This study designed and assessed a number of benzimidazolo quinoline derivatives as possible inhibitors of the PI3K and EGFR-TK receptors using molecular docking experiments. The findings showed encouraging interactions and binding affinities with the target receptors when compared to the reference medications imatinib and AMG319. ChemSketch was used for the drug design process, and OpenBabel made file conversion easier. Chimera was used to purify proteins having PDB IDs that were obtained from the RCSB Protein Data Bank. Additionally, SwissADME was used to evaluate drug-likeness properties and conduct ADME studies. PyRx was used for molecular docking simulations, BIOVIA Discovery Studio was used for visualization, and MolSoft was used for further drug-likeness assessment. Further studies are needed to synthesize and evaluate the biological activity of the designed compounds. Additionally, the optimization of the lead compounds to improve their potency and selectivity towards PI3K and EGFR-TK is warranted.

Table 6: Pharmacokinetic parameters of the designed Benzimidazole Quinazoline derivatives

Compounds	GI absorption	BBB permeant	P-Gp substrate	CYP1A2inhibitor	CYP2C19inhibitor	CYP2C9inhibitor	CYP2D6inhibitor	CYP3A4inhibitor	Log Kp(cm/s)
Com5	High	Yes	Yes	No	Yes	Yes	Yes	Yes	-5.22
Com6	High	No	Yes	Yes	Yes	No	Yes	Yes	-5.00
Com7	High	No	Yes	Yes	Yes	No	Yes	Yes	-5.00
Com8	High	No	Yes	Yes	Yes	No	Yes	Yes	-5.00
Com9	High	Yes	Yes	No	Yes	Yes	Yes	Yes	-5.42
Com10	High	Yes	Yes	No	Yes	Yes	Yes	Yes	-5.04
Com11	High	No	No	No	No	Yes	Yes	Yes	-5.19
Com12	High	No	No	No	No	Yes	Yes	Yes	-5.19
Com13	High	No	No	No	No	Yes	Yes	Yes	-5.19
Com14	High	Yes	Yes	No	Yes	Yes	Yes	Yes	-5.09
Com15	High	Yes	Yes	No	Yes	Yes	Yes	Yes	-5.99
Com16	High	No	No	No	No	Yes	Yes	Yes	-5.82
Com17	High	Yes	Yes	No	Yes	Yes	Yes	Yes	-5.26
Com18	High	Yes	Yes	No	Yes	Yes	Yes	Yes	-5.22
Com19	High	Yes	Yes	No	Yes	Yes	Yes	Yes	-5.26
Com20	High	No	No	No	No	Yes	Yes	Yes	-5.25
Com21	High	No	No	No	No	Yes	Yes	Yes	-5.25
Com22	High	No	No	No	No	Yes	Yes	Yes	-5.64

REFERENCES

1. Bisharat H, Ahmad Z, Azam T, Ahmad F. (2025). The Evolving Role of Sulfonamides in Medicine and Drug Development : A Brief Review. Adv J Chem B Nat Prod Med Chem.;7(2):130–50.
2. Kawade DP, Raut SM, Lokhande AS, Ikhanker MA. (2022). a Review : Pharmacological Potential of Indole Derivatives. Adv J Chem B Nat Prod Med Chem.;9(1):41–8.
3. Achar, K. C. S., Hosamani, K. M., & Seetharamareddy, H. R. (2010). In-vivo analgesic and anti-inflammatory activities of newly synthesized benzimidazole derivatives. European Journal of Medicinal Chemistry, 45(5), 2048–2054. https://doi.org/10.1016/j.ejmech.2010.01.029
4. Adeniji, S. E., Adamu Shallangwa, G., Ebuka Arthur, D., Abdullahi, M., Mahmoud, A. Y., & Haruna, A. (2020). Quantum modelling and molecular docking evaluation of some selected quinoline derivatives as anti-tubercular agents. Heliyon, 6(3), e03639. https://doi.org/10.1016/j.heliyon.2020.e03639
5. Adeniji, S. E., Uba, S., & Uzairu, A. (2018a). QSAR Modeling and Molecular Docking Analysis of Some Active Compounds against Mycobacterium tuberculosis Receptor (Mtb CYP121). Journal of Pathogens, 2018, 1–24. https://doi.org/10.1155/2018/1018694
6. Adeniji, S. E., Uba, S., & Uzairu, A. (2018b). Theoretical modeling and molecular docking simulation for investigating and evaluating some active compounds as potent anti-tubercular agents against MTB CYP121 receptor. Future Journal of Pharmaceutical Sciences, 4(2), 284–295. https://doi.org/10.1016/j.fjps.2018.10.003
7. Afzal, O., Kumar, S., Haider, M. R., Ali, M. R., Kumar, R., Jaggi, M., & Bawa, S. (2015). A review on anticancer potential of bioactive heterocycle quinoline. European Journal of Medicinal Chemistry, 97(1), 871–910. https://doi.org/10.1016/j.ejmech.2014.07.044
8. Andrzejewska, M., Yepez-Mulia, L., Tapia, A., Cedillo-Rivera, R., Laudy, A. E., Starościak, B. J., & Kazimierczuk, Z. (2004). Synthesis, and antiprotozoal and antibacterial activities of S-substituted 4,6-dibromo- and 4,6-dichloro-2-mercaptobenzimidazoles. European Journal of Pharmaceutical Sciences, 21(2–3), 323–329. https://doi.org/10.1016/j.ejps.2003.10.024
9. Bakker, P. A. H. M., Ran, L. X., & Mercado-Blanco, J. (2014). Rhizobacterial salicylate production provokes headaches! Plant and Soil, 382(1–2), 1–16. https://doi.org/10.1007/s11104-014-2102-0
10. Camacho, J., Barazarte, A., Gamboa, N., Rodrigues, J., Rojas, R., Vaisberg, A., Gilman, R., & Charris, J. (2011). Synthesis and biological evaluation of benzimidazole-5-carbohydrazide derivatives as antimalarial, cytotoxic and antitubercular agents. Bioorganic and Medicinal Chemistry, 19(6), 2023–2029. https://doi.org/10.1016/j.bmc.2011.01.050
11. Cantley, L. C. (2002). The phosphoinositide 3-kinase pathway. Science, 296(5573), 1655–1657. https://doi.org /10.1126/science.296.5573.1655
12. Thenmozhi V, Santhanakumar M, Venkateshan N, Prasanthi G, Sarangi RR, Nayak SK, et al. (2025). Investigation of N-(5-nitrothiazol-2-yl)-2-((4-oxo-3,4-Dihydroquinazolin-2-yl) Thio) Acetamide Derivatives as Potential EGFR Kinase Inhibitors. Adv J Chem Sect A.;8(8):1398–430.

13. Deokar SC, Pendalwar SS, Nalwar YS, Bhusare SR. (2025). Designing, Synthesis, and Anticancer Evaluation of Some New Quinoline and Benzothiazole Containing Schiff's Bases. Asian J Green Chem.;9(2):139–50.
14. Chang, P. T., Kung, F. L., Talekar, R. S., Chen, C. S., Lai, S. Y., Lee, H. Y., & Chern, J. W. (2009). An improved screening model to identify inhibitors targeting zinc-enhanced amyloid aggregation. Analytical Chemistry, 81(16), 6944–6951. https://doi.org/10.1021/ac901011e
15. Correia, M., Rodrigues, M., Paíga, P., & Delerue-Matos, C. (2015). Fungicides. Encyclopedia of Food and Health, 169–176. https://doi.org/10.1016/B978-0-12-384947-2.00342-1
16. Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports, 7(January), 1–13. https://doi.org/10.1038/srep42717
17. Duan, Y. C., Zheng, Y. C., Li, X. C., Wang, M. M., Ye, X. W., Guan, Y. Y., Liu, G. Z., Zheng, J. X., & Liu, H. M. (2013). Design, synthesis and antiproliferative activity studies of novel 1,2,3-triazole-dithiocarbamate-urea hybrids. European Journal of Medicinal Chemistry, 64, 99–110. https://doi.org/10.1016/ j.ejmech. 2013.03.058
18. Fakhfakh, M. A., Fournet, A., Prina, E., Mouscadet, J. F., Franck, X., Hocquemiller, R., & Figadère, B. (2003). Synthesis and biological evaluation of substituted quinolines: Potential treatment of protozoal and retroviral co-infections. Bioorganic and Medicinal Chemistry, 11(23), 5013–5023. https://doi.org/10.1016/j.bmc.2003.09.007
19. Firestone, G. L., & Sundar, S. N. (2009). Anticancer activities of artemisinin and its bioactive derivatives. Expert Reviews in Molecular Medicine, 11(October), 1–15. https://doi.org/10.1017/S1462399409001239
20. Gaba, M., Gaba, P., Uppal, D., Dhingra, N., Bahia, M. S., Silakari, O., & Mohan, C. (2015). Benzimidazole derivatives: Search for GI-friendly anti-inflammatory analgesic agents. Acta Pharmaceutica Sinica B, 5(4), 337–342. https://doi.org/10.1016/j.apsb.2015.05.003
21. Gaba, M., Singh, S., & Mohan, C. (2014). Benzimidazole: An emerging scaffold for analgesic and anti-inflammatory agents. European Journal of Medicinal Chemistry, 76, 494–505. https://doi.org/10.1016/j.ejmech.2014.01.030
22. Ghosh, S., Chetia, D., Gogoi, N., & Rudrapal, M. (2021). Design, molecular docking, drug-likeness, and molecular dynamics studies of 1,2,4-trioxane derivatives as novel plasmodium falciparum falcipain-2 (Fp-2) inhibitors. Biotechnologia, 102(3), 257–275. https://doi.org/10.5114/bta.2021.108722
23. Gu, W., Jin, X. Y., Li, D. D., Wang, S. F., Tao, X. B., & Chen, H. (2017). Design, synthesis and in vitro anticancer activity of novel quinoline and oxadiazole derivatives of ursolic acid. Bioorganic and Medicinal Chemistry Letters, 27(17), 4128–4132. https://doi.org/10.1016/j.bmcl.2017.07.033
24. Ilango, K., Valentina, P., Subhakar, Kathiravan, M., & Design. (2015). Design, Synthesis and Biological Screening of 2, 4-Disubstituted Quinolines. Austin J Anal Pharm Chem. Austin J Anal Pharm Chem, 2(2), 1048–4. http://d.researchbib.com/f/3nLKImqTyhpUIvoTymnTyhM2qlo3IjYzAioF9uozSfrKEcL2SfYKObLKWgLJAyqKEcL2SfYJAbMJ1cp3ElrF9xo3qhoT9uMP5jnUN_MzyfMG1zqJkfqTI4qP9unzSjLl12Zv1cMQRjAQthpTEz.pdf
25. Ingle, R. G., & Magar, D. D. (2011). Heterocyclic Chemistry of Benzimidazoles and Potential Activities of Derivatives. International Journal of Drug Research and Technology, 1(1), 26–32.
26. Iqbal, H., Verma, A. K., Yadav, P., Alam, S., Shafiq, M., Mishra, D., Khan, F., Hanif, K., Negi, A. S., & Chanda, D. (2021). Antihypertensive Effect of a Novel Angiotensin II Receptor Blocker Fluorophenyl Benzimidazole: Contribution of cGMP, Voltage-dependent Calcium Channels, and BKCa Channels to Vasorelaxant Mechanisms. Frontiers in Pharmacology, 12(March), 1–17. https://doi.org/10.3389/fphar.2021.611109
27. Jampilek, J., Dolezal, M., Kunes, J., Buchta, V., Silva, L., & Kralova, K. (2005). Quinaldine Derivatives: Preparation and Biological Activity. Medicinal Chemistry, 1(6), 591–599. https://doi.org/10.2174/157340605774598108
28. Keri, R. S., Rajappa, C. K., Patil, S. A., & Nagaraja, B. M. (2016). Benzimidazole-core as an antimycobacterial agent. Pharmacological Reports, 68(6), 1254–1265. https://doi.org/10.1016/j.pharep.2016.08.002
29. Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2012). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews, 64(SUPPL.), 4–17. https://doi.org/10.1016/j.addr.2012.09.019
30. Lu, J. J., Meng, L. H., Cai, Y. J., Chen, Q., Tong, L. J., Lin, L. P., & Ding, J. (2008). Dihydroartemisinin induces apoptosis in HL-60 leukemia cells dependent of iron and p38 mitogen-activated protein kinase activation but independent of reactive oxygen species. Cancer Biology and Therapy, 7(7), 1017–1023. https://doi.org/10.4161/cbt.7.7.6035
31. Ma, L. Y., Wang, B., Pang, L. P., Zhang, M., Wang, S. Q., Zheng, Y. C., Shao, K. P., Xue, D. Q., & Liu, H. M. (2015). Design and synthesis of novel 1,2,3-triazole-pyrimidine-urea hybrids as potential anticancer agents. Bioorganic and Medicinal Chemistry Letters, 25(5), 1124–1128. https://doi.org/10.1016/j.bmcl.2014.12.087
32. Migahed, M. A., Negm, N. A., Shaban, M. M., Ali, T. A., & Fadda, A. A. (2016). Synthesis, Characterization, Surface and Biological Activity of Diquaternary Cationic Surfactants Containing Ester Linkage. Journal of Surfactants and Detergents, 19(1), 119–128. https://doi.org/10.1007/s11743-015-1749-8
33. Monforte, A. M., Ferro, S., De Luca, L., Lo Surdo, G., Morreale, F., Pannecouque, C., Balzarini, J., & Chimirri, A. (2014). Design and synthesis of N1-aryl-benzimidazoles 2-substituted as novel HIV-1 non-nucleoside reverse transcriptase inhibitors. Bioorganic and Medicinal Chemistry, 22(4), 1459–1467. https://doi.org/10.1016/j.bmc.2013.12.045
34. Montoya, A., Quiroga, J., Abonia, R., Derita, M., Sortino, M., Ornelas, A., Zacchino, S., & Insuasty, B. (2016). Hybrid molecules containing a 7-Chloro-4-Aminoquinoline nucleus and a substituted 2-Pyrazoline with antiproliferative and antifungal activity. Molecules, 21(8). https://doi.org/10.3390/molecules21080969
35. Moret, V., Laras, Y., Cresteil, T., Aubert, G., Ping, D. Q., Di, C., Barthélémy-Requin, M., Béclin, C., Peyrot, V., Allegro, D., Rolland, A., De Angelis, F., Gatti, E., Pierre, P., Pasquini, L., Petrucci, E., Testa, U., & Kraus, J. L. (2009). Discovery

of a new family of bis-8-hydroxyquinoline substituted benzylamines with pro-apoptotic activity in cancer cells: Synthesis, structure-activity relationship, and action mechanism studies. European Journal of Medicinal Chemistry, 44(2), 558–567. https://doi.org/10.1016/j.ejmech.2008.03.042
36. Partap, S., Yar, M. S., Hassan, M. Z., Akhtar, M. J., & Siddiqui, A. A. (2017). Design, Synthesis, and Pharmacological Screening of Pyridazinone Hybrids as Anticonvulsant Agents. Archiv Der Pharmazie, 350(10), 1–14. https://doi.org/10.1002/ardp.201700135
37. Piton, J., Petrella, S., Delarue, M., André-Leroux, G., Jarlier, V., Aubry, A., & Mayer, C. (2010). Structural insights into the quinolone resistance mechanism of Mycobacterium tuberculosis DNA gyrase. PLoS ONE, 5(8). https://doi.org/10.1371/journal.pone.0012245
38. Ranson, M. (2004). Epidermal growth factor receptor tyrosine kinase inhibitors. British Journal of Cancer, 90(12), 2250–2255. https://doi.org/10.1038/sj.bjc.6601873
39. Sharp, M. (1997). Chapter 8 Benzimidazoles. Pharmacochemistry Library, 25(C), 195–238. https://doi.org/10.1016/S0165-7208(97)80030-X
40. Shaw, A. Y., Chang, C. Y., Hsu, M. Y., Lu, P. J., Yang, C. N., Chen, H. L., Lo, C. W., Shiau, C. W., & Chern, M. K. (2010). Synthesis and structure-activity relationship study of 8-hydroxyquinoline- derived Mannich bases as anticancer agents. European Journal of Medicinal Chemistry, 45(7), 2860–2867. https://doi.org/10.1016/j.ejmech.2010.03.008
41. Starčević, K., Kralj, M., Ester, K., Sabol, I., Grce, M., Pavelić, K., & Karminski-Zamola, G. (2007). Synthesis, antiviral and antitumor activity of 2-substituted-5-amidino-benzimidazoles. Bioorganic and Medicinal Chemistry, 15(13), 4419–4426. https://doi.org/10.1016/j.bmc.2007.04.032
42. Synthesis, spectroscopic characterization, DFT, molecular docking and. (n.d.).
43. Tahlan, S., Ramasamy, K., Lim, S. M., Shah, S. A. A., Mani, V., & Narasimhan, B. (2019). 4-(2-(1H-Benzo[d]imidazol-2-ylthio) acetamido)-N-(substituted phenyl)benzamides: Design, synthesis and biological evaluation. BMC Chemistry, 13(3), 1–16. https://doi.org/10.1186/s13065-019-0533-7
44. Rezaeianzadeh O, Asghari S, Tajbakhsh M, Mohseni M, Khalilpour A. (2024). Synthesis, Molecular Docking, and Anticancer Evaluation of New Azo-Based Sulfonamides against MCF-7 Human Breast Cancer Cell Line. Chem Methodol.;8(5):329–50.
45. Dabhade PS, Dabhade MP, Dhawale SA, Rathod LS, More SA, Mokale SN. (2025). Diaryl Pyrazole-Chalcone Hybrids as Novel ER-α Modulators: Docking, Synthesis and Anti-Breast Cancer Activity Evaluation. Adv J Chem Sect A.;8(2):341–60.
46. V. Kouznetsov, V., A. Rojas Ruiz, F., Y. Vargas Mendez, L., & P. Gupta, M. (2012). Simple C-2-Substituted Quinolines and their Anticancer Activity. Letters in Drug Design & Discovery, 9(7), 680–686. https://doi.org/10.2174/157018012801319544
47. Wang, X. J., Xi, M. Y., Fu, J. H., Zhang, F. R., Cheng, G. F., Yin, D. L., & You, Q. D. (2012). Synthesis, biological evaluation and SAR studies of benzimidazole derivatives as H 1-antihistamine agents. Chinese Chemical Letters, 23(6), 707–710. https://doi.org/10.1016/j.cclet.2012.04.020
48. Weinberg, E. D., & Moon, J. (2009). Malaria and iron: History and review Malaria and iron Eugene D. Weinberg and Jym Moon. Drug Metabolism Reviews, 41(4), 644–662. https://doi.org/10.1080/03602530903178905
49. Zhuang, L., Wai, J. S., Embrey, M. W., Fisher, T. E., Egbertson, M. S., Payne, L. S., Guare, J. P., Vacca, J. P., Hazuda, D. J., Felock, P. J., Wolfe, A. L., Stillmock, K. A., Witmer, M. V., Moyer, G., Schleif, W. A., Gabryelski, L. J., Leonard, Y. M., Lynch, J. J., Michelson, S. R., & Young, S. D. (2003). Design and synthesis of 8-hydroxy-[1,6]naphthyridines as novel inhibitors of HIV-1 integrase in vitro and in infected cells. Journal of Medicinal Chemistry, 46(4), 453–456. https://doi.org/10.1021/jm025553u
50. Zwick, E., Bange, J., & Ullrich, A. (2001). Receptor tyrosine kinase signalling as a target for cancer intervention strategies. Endocrine-Related Cancer, 8(3), 161–173. https://doi.org/10.1677/erc.0.0080161
51. Nakkala, R.K., Maddiboyina, B., Bolisetti, S.C., & Roy, H. (2023). Duloxetine hydrochloride enteric-coated pellets in capsules with delayed release: formulation and evaluation. Smart Science, 11(3), 434–446.
52. Singh, P., Singh, S., Maddiboyina, B., Kandalam, S., Walski, T., & Bohara, R. A. (2024). Hybrid silver nanoparticles: Modes of synthesis and various biomedical applications. Electron, 2(2), e22.
53. Muralidharan V, Sachdeo RA, Singh LP, Haque MA, Panigrahy UP, Mishra AK, et al. (2025). Molecular Docking and Dynamic Simulation with ADMET Exploration of Natural Products Atlas Compound Library to search for Potential Alpha Amylase Inhibitors for the T2DM Treatment. Chem Methodol.;9(2):81–102.
54. Kumar Reddy KT, Naga Venkata Arjun UV, Alhmoud JF, Reddy SM, Dhillishree D, Tambe VB, et al. (2025). In Depth in Silico Exploration of Some Natural Indole Alkaloids as Potential Plasmepsin II Inhibitors: ADMET Calculations, Molecular Docking Analysis, Molecular Dynamics Simulation, and DFT Studies. Chem Methodol.;9(4):277–300.