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Research Article

TARGET-ORIENTED MOLECULAR DOCKING AND ADMET ANALYSIS OF NOVEL CHALCONE-LINKED QUINOLINE DERIVATIVES FOR CANCER THERAPY

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ABSTRACT

Objective: Molecular docking studies were carried out on 33 novel chalcone-linked quinoline derivatives to evaluate their potential as anticancer drug candidates targeting epidermal growth factor receptor (EGFR) tyrosine kinase.

Methods: The computational study was executed using the Maestro interface in Schrodinger to target the EGFR enzyme (PDB ID: 4HJO). For all the compounds, molecular docking was subjected to absorption, distribution, metabolism, and excretion (ADME) analysis using the QikProp module.

Results: A good docking score was obtained for compound TKS2-8 and TKS3-7 as (−9.221) and (−9.93), respectively, leading to promising anticancer activity prediction, whereas standard compound erlotinib scored (−9.834). Analysis of protein-ligand interactions demonstrated that the most active compounds formed stable hydrogen bonds with key residues PHE-832, THR-830, SER-676, THR-766, MET-796, CYS-751, GLN-767, and ASN-818 in the EGFR binding pocket. ADME and toxicity predictions indicated favorable drug-like properties for all compounds, with an acceptable molecular weight range of ≤500 Da, optimal lipophilicity (LogP <5), and high gastrointestinal absorption rates. The compounds showed compliance with Lipinski's rule of five and exhibited blood–brain barrier permeability.

Conclusion: The targeting of EGFR tyrosine kinase by these derivatives indicates the potential effectiveness of chalcone-linked quinoline derivatives.

Keywords: Structure-activity relationship, Molecular docking, Chalcone-lined quinolines, anticancer agents, Absorption, distribution, metabolism, excretion.

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INTRODUCTION

The human body is made up of trillions of cells, which are generally divided and grow throughout life. Cancer is something which is identified as an abnormal and uncontrolled division of cancerous cells takes place. These cancer cells grow and divide in an uncontrolled way which is further entering the normal tissues, organs, and in the end, it spreads throughout the whole body. Worldwide, every year, 1.8 million new cases of cancer are being diagnosed, and cancer is also considered one of the most dreaded diseases and a major cause of death. Development of cancerous cells takes place because of multiple changes in genes, which are due to many possible causes such as lifestyle habits, being exposed to cancer-causing substances, heredity, and many times, there is no obvious reason for cancer. The development of therapeutic tools, synthetic and natural products for cancer treatment, has advanced in the last few years. Many approaches have been made to cure cancer by the eradication of cancer cells without affecting normal cancer cells [1-4].

The development of heterocyclic moieties has been known as one of the important targets for biologically evaluating cancer treatment. Compounds with a heterocyclic core are known to play a significant role in designing and developing a new class of structural entities with anticancer potential. Few heterocyclic compounds such as quinazoline, quinoline, pyrimidines, purines, oxadiazole, oxazole, quinoxaline, pyrazole, and imidazole-based derivatives have been synthesized and biologically evaluated as potent anticancer agents by many researchers [5-10].

Chalcones, belonging to the flavonoid family, are known to have important versatile medicinal activities such as antimicrobial, anticancer, antioxidant, antimalarial, and antituberculosis. These activities are due to the presence of ketoethylenic group (-CO-CH=CH-) or reactive α, β-unsaturated keto functional group [11,12].

The strategic combination of chalcones with a quinoline pharmacophore represents an innovative approach to anticancer drug development. In observation of the biological importance of quinoline and chalcone molecules, we are selecting a few chalcone-fused quinoline-based heterocyclic derivatives for molecular docking, to know about their biological potential [13-18]. This work aims to evaluate the potential of newly designed chalcone-linked quinoline compounds as anticancer agents through molecular docking, binding mode analysis, and detailed absorption, distribution, metabolism, excretion, and toxicity (ADMET) predictions.

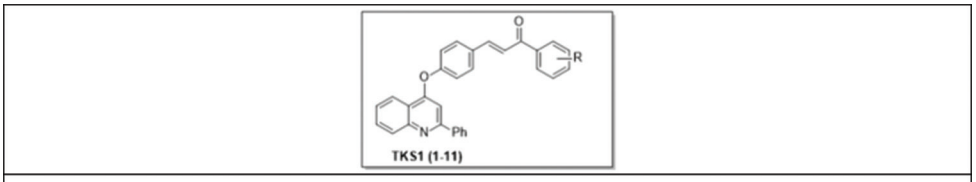
METHODS

Molecular docking studies

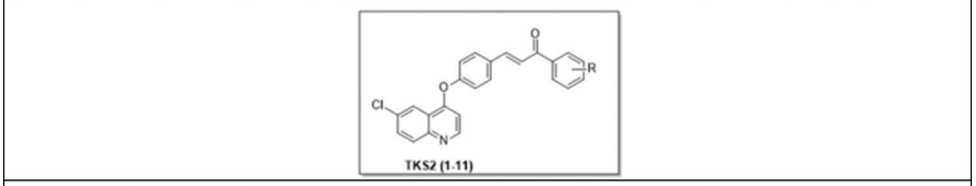
To examine the possible binding mode of chalcone-linked quinoline hybrids as tyrosine kinase inhibitors, docking studies of these 33 compounds were performed at the inactive epidermal growth factor receptor (EGFR) tyrosine kinase domain with erlotinib crystal structure (PDB ID: 4HJO) using MOE 2015 (Fig. 1).

Computational docking studies

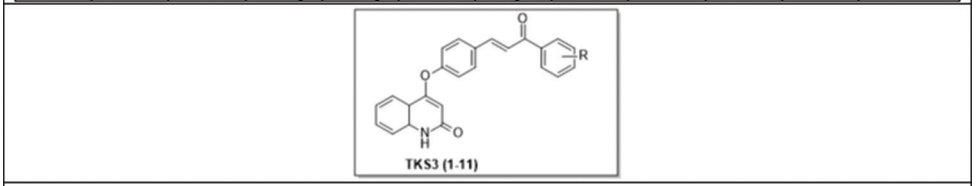
For differently substituted three series of chalcone-linked quinoline hybrids named as TKS1, TKS2, and TKS3, molecular docking calculations have been made to elucidate the various factors influencing biological activity as anticancer. For each series, TKS1, TKS2, and TKS3, 11 compounds



S.No	TKS1-1	TKS1-2	TKS1-3	TKS1-4	TKS1-5	TKS1-6	TKS1-7	TKS1-8	TKS1-9	TKS1-10	TKS1-11
R	H	3-CH_3	4-OCH_3	3,4-OCH_3	4-CH_3	3,4-CH_3	4-OH	3,4-OH	4-Cl	3,4-Cl	1,3-dioxolane



S.No	TKS2-1	TKS2-2	TKS2-3	TKS2-4	TKS2-5	TKS2-6	TKS2-7	TKS2-8	TKS2-9	TKS2-10	TKS2-11
R	H	3-CH_3	4-OCH_3	3,4-OCH_3	4-CH_3	3,4-CH_3	4-OH	3,4-OH	4-Cl	3,4-Cl	1,3-dioxolane



S.No	TKS3-1	TKS3-2	TKS3-3	TKS3-4	TKS3-5	TKS3-6	TKS3-7	TKS3-8	TKS3-9	TKS3-10	TKS3-11
R	H	3-CH_3	4-OCH_3	3,4-OCH_3	4-CH_3	3,4-CH_3	4-OH	3,4-OH	4-Cl	3,4-Cl	1,3-dioxolan

Fig. 1: Structure of 33 designed compounds

of each series were designed, and molecular stimulation studies were performed. The binding energies of all these compounds in the active site of the selected crystal structure of the inactive EGFR tyrosine kinase domain with erlotinib were determined (Table 1). Good correspondences have been observed in presenting the ligand binding docking data score in the provided computations and their crystallographic structures (Fig. 2) of the complexes for the reference protein (PDB ID: 4HJO).

ADMET studies

For all the compounds, molecular docking was subjected to absorption, distribution, metabolism, and excretion (ADME) analysis using the QikProp module. The ADME properties included number H-bond donors, number of H-bond acceptor, octanol/water partition coefficient (Qlog Po/w) aqueous solubility [Log S]), Caco-2 (human colon adenocarcinoma) permeability (QPCaco), predicted blood/brain partition coefficient (Log BB), number of likely metabolic reaction (Metab), prediction of binding to human serum albumin (Log Khsa), percent human oral absorption (HOA), polar surface area (PSA), and Lipinski rule of five were calculated. As per QikProp ADME analysis, all the compounds obey the rule (Table 2).

RESULTS AND DISCUSSION

Molecular docking analysis

Protein preparation

The crystallographic structure of the inactive EGFR tyrosine kinase domain with erlotinib was obtained from the RCSB Protein Data Bank, utilizing PDB ID: 4HJO (Fig. 2). The obtained structure (Fig. 1) was then prepared where water molecules, heteroatoms, and co-crystallized ligands were removed.

Ligand preparation

Thirty-three novel chalcone-linked quinoline derivatives (Fig. 1) were designed using ChemDraw Ultra 12.0.

Structure- activity relationship analysis

Compounds exhibited the highest binding affinity; these synthesized analogs exhibited moderate to significant cytotoxicity activity. Three series of chalcone-linked quinoline hybrids possessing different functional groups and different positions were designed, and their molecular docking was evaluated. Compounds substituted with 4-hydroxyl, 3,4-dihydroxyl, 4-chloro, 3,4-dichloro, 3-methyl, and 4-methyl in all three series containing compounds exhibited a good docking score as compared to that of standard erlotinib. The above study provides valuable information for the researcher in studying the SAR studies of fused quinoline with different chalcones. Thus, our evaluated compounds might be considered as promising new templates for future development of new improved anticancer agents, by making more chemical modifications, investigations, and docking studies. In future studies of heterocyclic compounds as anticancer, quinoline and chalcones hybrids can act as the most auspicious moieties.

Binding mode analysis

Detailed analysis of protein-ligand interactions showed consistent binding patterns across the most active compounds. The compounds substituted with 4-hydroxyl, 3,4-dihydroxyl, 4-chloro, 3,4-dichloro, 3-methyl, and 4-methyl in all three series formed hydrogen bonds with different amino acids (Table 3 and Fig. 3).

ADMET profile analysis

According to the ADMET investigations, the molecular weight is within the permissible range of ≤500 Da, which is good for permeability

Table 1: Docking score, GLE, and glide energy of proposed compounds

S. No.	Compound name	MW	Docking score	Glide ligand efficiency	Glide energy	Interactions
1.	Standard molecule (ERLOTINIB)	446.908	−9.834	−0.317	−58.856	LEU 694, LEU768, MET 769, PRO 770, CYS773, LEU764, ALA 719, CYS 751, LEU 753, LEU 834, PHE 832, MET 742, LEU 820, VAL 702
2.	TKS1-1	427.501	−6.038	−0.183	−54.974	ASN 818, THR 830, THR 766, GLN 767
3.	T2S1-2	441.528	−6.155	−0.181	−48.842	THR 766, GLN 767, ASN 818, THR 830
4.	TKS1-3	457.528	−5.884	−0.168	−50.433	HIS 781, ASN 818, THR 830, THR 766
5.	TKS1-4	487.554	−4.986	−0.135	−46.637	ASN 818, SER 696, THR 830, THR 766,
6.	TKS1-5	441.528	−0.485	−0.014	−51.472	ASN 818, THR 830, GLN 767, THR 766
7.	TKS1-6	455.555	−5.951	−0.17	−49.071	THR 766, GLN 767, THR 830, ASN 818
8.	TKS1-7	443.501	−5.918	−0.174	−50.856	SER 696, THR 766, THR 830, ASN 818
9.	TKS1-8	459.5	−8.94	−0.255	−59.045	SER 696, THR 766, ASN 818, THR 830
10.	TKS1-9	461.946	−4.824	−0.142	−58.045	SER 696, THR 766, THR 830, ASN 818
11.	TKS1-10	496.392	−6.356	−0.182	−51.816	ASN 818, THR 830, THR 766, GLN 767
12.	TKS1-11	471.511	−3.882	−0.108	−45.062	SER 696, ASN 818
13.	TKS2-1	385.849	−7.51	−0.268	−47.794	THR 830, THR 766, GLN 767
14.	TKS2-2	399.876	−5.444	−0.188	−46.375	PHE832
15.	TKS2-3	415.875	−5.412	−0.18	−41.513	CYS 773, PHE 832, THR 766, THR 830
16.	TKS2-4	445.901	−5.315	−0.166	−45.859	APG 817, ASP 831
17.	TKS2-5	399.876	−4.884	−0.168	−43.203	LYS 721, SER 696
18.	TKS2-6	413.902	−4.954	−0.165	−50.25	LYS 721, LEU764
19.	TKS2-7	401.848	−7.71	−0.266	−48.272	CYS 751
20.	TKS2-8	417.848	−9.221	−0.307	−53.725	PHE 832, CYS 751
21.	TKS2-9	420.294	−6.828	−0.235	−45.31	CYS 773, LYS 721
22.	TKS2-10	454.739	−7.369	−0.246	−54.329	PHE 832, MET 742
23.	TKS2-11	429.859	−6.903	−0.223	−43.41	ASP 831, PHE 832
24.	TKS3-1	367.403	−9.247	−0.33	−47.821	MET 796
25.	TKS3-2	381.43	−6.557	−0.226	−48.638	MET 796
26.	TKS3-3	397.429	−5.412	−0.18	−41.513	MET 796
27.	TKS3-4	427.456	−6.308	−0.197	−51.099	LYS 796
28.	TKS3-5	381.43	−8.542	−0.295	−46.809	MET 796
29.	TKS3-6	395.457	−5.129	−0.171	−44.64	PHE 832, LEU 820
30.	TKS3-7	383.403	−9.93	−0.342	−50.372	CYS 751, MET 796
31.	TKS3-8	399.402	−9.057	−0.302	−51.128	MET 796, CYS 751
32.	TKS3-9	401.848	−8.58	−0.296	−51.537	MET 796, MET 742
33.	TKS3-10	436.293	−8.695	−0.29	−53.554	MET 796, PHE 832
34.	TKS3-11	411.413	−6.515	0.21	−40.055	LUE 694, ASP 831

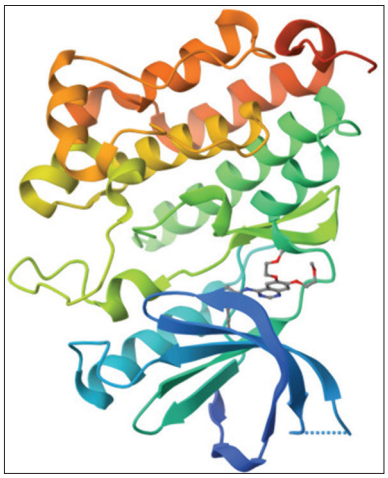


Fig. 2: Crystal structure of the inactive epidermal growth factor receptor tyrosine kinase domain with standard erlotinib

and absorption. Supporting transmembrane diffusion and probable penetration of the blood–brain barrier (BBB), the PSA stays at or below 140 Å^2. A higher solvent-accessible surface area (SASA) indicates a more robust interaction with aquatic environments, which in turn affects solubility and permeability. Solubility and permeability are greatly affected by hydrogen bonding properties, which are described by hydrogen bond donors (≤5) and hydrogen bond acceptors (≤10). Lipophilicity, which impacts bioavailability and membrane permeability, is determined by the logP value, which ideally falls between -0.4 and 5.6. The ideal range for aqueous solubility, as measured by logS, is -6 to 0, which guarantees sufficient dissolution for systemic absorption. Oral absorption efficiency is affected by permeability, which is characterized as high when >500 nm/sec and poor when <25 nm/sec, as measured by Caco-2 permeability. A considerable level of BBB permeability is defined as >0.3, while values < −1 indicate little penetration into the central nervous system (CNS). The distribution of drugs throughout the body and the availability of free drugs are impacted by serum protein binding, where high binding is defined as >1.5 and low binding as <0.5. The fact that HOA is at its highest at 100% suggests efficient uptake, and the fact that it complies with Lipinski's rule (≤1 violation) implies that it has drug-like qualities that are applicable to future research.

Standard(Erlotinib) has promising drug-like characteristics in its ADMET analysis, which complies with Lipinski's rule of five without any infractions. An excellent oral bioavailability is supported by the molecular weight (446.908 Da) and PSA (60.271 Å^2), both of which are within optimum ranges. Intestinal permeability is high (QPP Caco-2: 1115.548 nm/s) and solubility is modest (QPlogS: −4.445) for this chemical, suggesting the necessity for techniques to improve its solubility. Effective membrane penetration is supported by the logP value of 4.211, which indicates balanced lipophilicity. Protein binding to serum (QPlogKhsa: 0.327) and BBB permeability (QPlogBB: 0.361) both point to effective systemic distribution and moderate CNS penetration, respectively. The chemical is also well-suited for oral delivery because it is completely absorbed when taken orally by humans. The pharmacokinetic profile of standard is supported by these features, which allow for effective systemic exposure and therapeutic potential.

Table 2: ADMET parameters of docked compounds

S. No.	Donor HB	Acceptor HB	QPlogPo/w	QPlogS	QPPCaco	QPlogBB BB	#metab	QPlog Khsa	%HOA	PSA	Rule of five
Standard	1	7.7	4.211	4.445	1115.548	0.361	5	0.327	100	60.271	0
TKS1-1	0	3.5	7.255	−8.316	3176.297	−0.455	0	1.466	100	43.526	1
T2S1-2	0	3.5	7.568	−8.892	3173.994	−0.467	1	1.636	100	43.59	1
TKS1-3	0	4.25	7.313	−8.459	3181.802	−0.527	1	1.44	100	51.687	1
TKS1-4	0	5	7.382	−8.665	3172.832	−0.606	2	1.418	100	59.144	1
TKS1-5	0	3.5	7.57	−8.9	3182.009	−0.467	1	1.636	100	43.54	1
TKS1-6	0	3.5	7.858	−9.349	3181.143	−0.473	2	1.785	100	43.523	1
TKS1-7	1	4.25	6.534	−8.092	968.275	−1.147	1	1.328	100	66.037	1
TKS1-8	2	5	5.781	−7.673	343.286	−1.766	2	1.107	93.217	87.897	1
TKS1-9	0	3.5	7.76	−9.083	3171.626	−0.291	0	1.595	100	43.535	1
TKS1-10	0	3.5	8.196	−9.716	3169.835	−0.156	0	1.71	100	43.542	1
TKS1-11	0	5	6.678	−7.623	3183.923	−0.441	0	1.168	100	62.298	1
TKS2-1	0	3.5	5.949	−6.935	2305.675	−0.338	1	0.947	100	46.059	1
TKS2-2	0	3.5	6.292	−7.613	2305.525	−0.363	2	1.127	100	46.039	1
TKS2-3	0	4.25	6.033	−7.168	2306.854	−0.422	2	0.931	100	54.201	1
TKS2-4	0	5	6.052	−7.2	2300.467	−0.493	3	0.891	100	61.79	1
TKS2-5	0	3.5	6.276	−7.549	2304.457	−0.358	2	1.122	100	46.064	1
TKS2-6	0	3.5	6.559	−7.987	2304.657	−0.365	3	1.269	100	46.062	1
TKS2-7	1	4.25	5.29	−6.886	699.947	−1.01	2	0.851	95.884	68.556	1
TKS2-8	2	5	4.536	−6.412	249.192	−1.578	3	0.643	96.397	90.344	0
TKS2-9	0	3.5	6.454	−7.702	2305.677	−0.178	1	1.075	100	46.058	1
TKS2-10	0	3.5	6.879	−8.296	2304.665	−0.041	1	1.187	100	46.123	1
TKS2-11	0	5	5.361	−6.202	2305.679	−0.318	1	0.646	100	64.837	1
TKS3-1	1	5	4.427	−6.178	560.026	−1.238	0	0.628	100	76.009	0
TKS3-2	1	5	4.748	−6.778	559.17	−1.278	1	0.792	100	76.034	0
TKS3-3	1	5.75	4.534	−6.434	559.437	−1.337	1	0.638	100	84.188	0
TKS3-4	1	6.5	4.616	−6.646	558.815	−1.432	2	0.637	100	91.66	0
TKS3-5	1	5	4.753	−6.79	559.966	−1.278	1	0.794	100	76.141	0
TKS3-6	1	5	5.02	−7.197	558.824	−1.293	2	0.93	92.554	76.153	1
TKS3-7	2	5.75	3.683	−5.911	169.824	−1.922	1	0.456	88.425	98.694	0
TKS3-8	3	6.5	2.974	−5.579	60.492	−2.526	2	0.27	76.249	120.26	0
TKS3-9	1	5	4.94	−6.967	559.992	−1.097	0	0.753	100	76.149	0
TKS3-10	1	5	5.376	−7.594	559.213	−0.974	0	0.863	94.644	76.026	1
TKS3-11	1	6.5	3.946	−5.686	560.198	−1.199	0	0.423	100	94.767	0

ADMET: Absorption, distribution, metabolism, excretion, and toxicity, HOA: Human oral absorption, PSA: Polar surface area

Table 3: Binding of compounds with maximum score from three series and standard, Erlotinib

Standard Erlotinib	**LEU 694, LEU768, MET 769, PRO 770, CYS773, LEU764, ALA 719, CYS 751, LEU 753, LEU 834, PHE 832, MET 742, LEU 820, VAL 702**		
Compound with substitution	**TKS1**	**TKS2**	**TKS3**
3-CH_3	THR 766, GLN 767, ASN 818, THR 830	PHE832,	MET 796
4-CH_3	HIS 781, ASN 818, THR 830, THR 766	CYS 773, PHE 832, THR 766, THR 830	MET 796
4-OH	SER 696, THR 766, THR 830, ASN 818	CYS 751	CYS 751, MET 796
3,4-OH	SER 696, THR 766, ASN 818, THR 830	PHE 832, CYS 751	MET 796, CYS 751
4-Cl	SER 696, THR 766, THR 830, ASN 818	CYS 773, LYS 721	MET 796, MET 742
3,4-Cl	ASN 818, THR 830, THR 766, GLN 767	PHE 832, MET 742	MET 796, PHE 832

Compound TKS1-1 ADMET study indicates some limited but favorable pharmacokinetic features. Based on Lipinski's rule of five, the molecular weight (427.501 Da) is within the permissible range for oral bioavailability. The fact that the PSA (PSA: 43.526 $Å^2$) is significantly lower than the 140 $Å^2$ criterion suggests that there is remarkable oral absorption and intestinal permeability. Nevertheless, the extremely low solubility (QPlogS: −8.316) indicates that it has poor solubility in water and may necessitate formulation efforts to improve it. There is a possibility of metabolic instability and poor solubility due to the high hydrophobicity, as indicated by the lipophilicity (QPlogPo/w: 7.255), which is greater than the ideal range (≤5). This chemical has a very high intestinal permeability (QPP Caco-2: 3176.297 nm/s), which means that it is very bioavailable when taken orally.

Because of its low permeability across the BBB (QPlogBB: −0.455), it cannot be used to target the CNS. Free medication availability may be affected by the plasma protein binding, which indicates a strong affinity for serum proteins (QPlogKhsa: 1.466). The fact that the medicine is completely absorbed when taken orally by humans (PercentHu: 100%) proves that. Nevertheless, difficulties in drug-like behavior may arise from a single infraction of Lipinski's rule of five, which is most likely caused by excessive lipophilicity.

Compound TKS1-8 exhibits a moderate pharmacokinetic profile according to its ADMET characteristics, accompanied by several obstacles. The molecular weight of 459.5 Da is beneath the Lipinski threshold (≤500 Da), suggesting enhanced oral bioavailability. The PSA (PSA: 87.897 $Å^2$) is under 140 $Å^2$, indicating effective membrane permeability and favorable intestinal absorption. Its aqueous solubility (QPlogS: −7.673) is markedly below the optimal range (−6–0), signifying inadequate solubility, which may need formulation approaches such as prodrugs or nanoparticle-based delivery methods.

The lipophilicity (QPlogPo/w: 5.781) above the ideal range (≤5), potentially resulting in inadequate aqueous solubility and a risk of

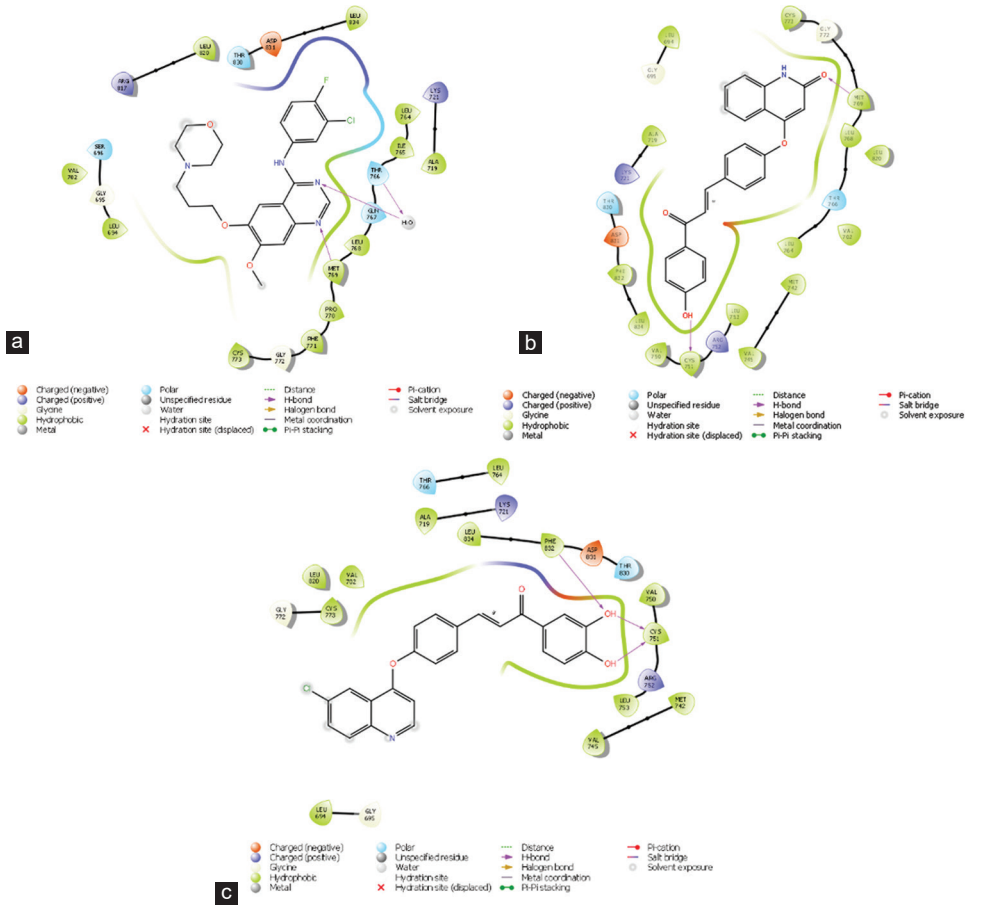


Fig. 3: 2D interactions of (a) standard erlotinib, (b) TKS3-7, (c) TKS2-8

bioaccumulation due to heightened hydrophobicity. The intestinal permeability (QPP Caco-2: 343.286 nm/sec), while moderate, falls short of the high permeability threshold (>500 nm/s), indicating certain constraints in passive absorption. The low BBB penetration (QPlogBB: −1.766) signifies limited CNS access, rendering the chemical inappropriate for neurological applications. The serum protein binding (QPlogKhsa: 1.107) is classified as moderate-to-high (>1.0), indicating that a substantial fraction of the drug will be associated with plasma proteins, potentially influencing free drug availability and systemic circulation. The HOA rate (93.217%) is elevated, indicating effective gastrointestinal uptake, but variations in absorption may occur. Notwithstanding these advantageous factors, a single Lipinski violation (presumably because of high lipophilicity) indicates possible drug-likeness difficulties that may necessitate structural optimization.

With certain solubility constraints, compound TKS2-1 ADMET profile emphasizes great pharmacokinetic potential, especially in intestinal permeability and oral absorption. The high probability of favorable oral bioavailability is shown by the molecular weight (385.849 Da) staying within the Lipinski threshold (≤500 Da). With a PSA (PSA: 46.059 Å^2) much below 140 Å^2, the membrane permeability is guaranteed to be effective, and intestinal absorption is fast. The low water solubility (QPlogS: −6.935) yet falls below the advised range (−6–0); hence, formulation changes may be necessary to increase dissolution and bioavailability. The lipophilicity (QPlogPo/w: 5.49) is somewhat beyond the optimum range (≤5), thereby perhaps compromising solubility and maybe affecting metabolic stability. It is remarkably high intestinal permeability (QPP Caco-2: 2305.675 nm/s); however, it confirms fast and effective absorption in the gastrointestinal system, thereby helping to offset its solubility constraints. The BBB penetration (QPlogBB: −0.338) indicates modest CNS accessibility, so the molecule might show partial brain penetration but is not very CNS-active.

Remaining in the moderate range (0.5–1.5), the serum protein binding (QPlogKhsa: 0.947) shows a balanced distribution in plasma, therefore guaranteeing an optimal percentage of the free drug for therapeutic activity. Excellent gastrointestinal absorption is confirmed by the HOA rate (100%); hence, this molecule is a strong candidate for oral treatment. One Lipinski violation (probably resulting from too high lipophilicity) may provide difficulties in formulation stability and metabolic processing, even with its great permeability and oral absorption efficiency.

With high permeability and oral absorption and a modest ADMET profile, TKS2-7 shows minimal CNS penetration and solubility problems. Lipinski's rule of five (≤500 Da) is well within the molecular weight (401.848 Da), so it guarantees good oral bioavailability. With a PSA (PSA: 68.556 Å) much below the 140 Å^2 barrier, the membrane permeability is clearly efficient and intestinal absorption has great promise. Its aqueous solubility (QPlogS: −6.886) is below the optimal range (−6–0), hence indicating poor solubility which could affect dissolution and absorption efficiency. With a lipophilicity (QPlogPo/w: 5.29) somewhat outside the ideal range (≤5), solubility may be lowered and probable bioaccumulation could arise. Strong intestinal absorption is confirmed by the intestinal permeability (QPP Caco-2: 699.947 nm/s) which exceeds the high-permeability threshold (>500 nm/s). However, the BBB permeability (QPlogBB: −1.01) points to limited CNS penetration, so this molecule is not fit for neurological uses. Maintaining the moderate range (0.5–1.5), the serum protein binding (QPlogKhsa: 0.851) guarantees sufficient systemic circulation with a balance between free and bound drug fractions. Good bioavailability is indicated by the HOA rate (95.884%) upon oral dosing. One Lipinski violation, presumably resulting from high logP, nevertheless points to possible problems with metabolic stability and solubility, which might call for formulation optimization.

With good oral absorption and conformity with Lipinski's rule of five, compound TKS2-8 shows modest pharmacokinetic properties but some limits in solubility and permeability. Maintaining the reasonable range (≤500 Da), the molecular weight (417.848 Da) supports drug-like characteristics and oral bioavailability. Under the 140 Å^2 threshold, the PSA (PSA: 90.344 Å^2) is less than required for optimal intestine absorption and membrane permeability. Its aqueous solubility (QPlogS: −6.412) is below the optimal range (−6–0), thereby indicating poor solubility which can call for formulation optimization or solubilization techniques to enhance dissolution. With a lipophilicity (QPlogPo/w: 4.536) within the ideal range (−0.4–5.6), the solubility and membrane penetration are in good balance, therefore lowering the risk of too great bioaccumulation or metabolic instability. The modest and below the high-permeability threshold (>500 nm/s) intestinal permeability (QPP Caco-2: 249.192 nm/s) suggests poor passive absorption efficiency, nonetheless. Low BBB permeability (QPlogBB: −1.578) indicates that the molecule is unlikely to penetrate the CNS, hence inappropriate for neurological therapeutic uses.

With a moderate serum protein binding (QPlogKhsa: 0.643), the drug distribution in plasma seems to be balanced, therefore guaranteeing a reasonable free drug concentration for therapeutic efficacy. Strong candidate for oral medication development, the HOA rate (96.397%) shows effective absorption from the gastrointestinal system. Moreover, the molecule follows Lipinski's rule of five (0 violations), so verifying good drug-like properties and a strong likelihood of oral bioavailability.

Although compound TKS2-10 has great solubility problems, it has tremendous pharmacokinetic potential with great permeability and oral absorption. Maintaining good oral bioavailability, the molecular weight (454.739 Da) stays within the Lipinski threshold (≤500 Da). With a PSA (PSA: 46.123 Å^2) much below the 140 Å^2 barrier, the fast intestinal absorption and effective transmembrane permeability are suggested. Its water solubility (QPlogS: −8.296) is rather poor, much below the optimal range (−6–0), so solubilization techniques such as prodrugs or nanotechnology-based delivery may be needed to improve dissolution. Higher above the advised range (≤5), the lipophilicity (QPlogPo/w: 6.879) may affect solubility, metabolic stability, and possible bioaccumulation. However, the very high intestinal permeability (QPP Caco-2: 2304.665 nm/s) guarantees great oral absorption, which may offset its solubility restrictions. The BBB penetration (QPlogBB: −0.041) is modest, suggesting partial CNS penetration, thus a possible option for both systemic and CNS-targeted treatments. With a moderate-to-high binding range (>1.0), the serum protein binding (QPlogKhsa: 1.187) falls within the drug may be bound to plasma proteins, therefore possibly influencing the free drug concentration in circulation. This molecule is a great option for oral delivery since the HOA rate (100%) validates robust gastrointestinal absorption. One Lipinski violation, however, (probably from too high lipophilicity) could affect medication metabolism and complicate formulation.

Strong pharmacokinetic characteristics, good permeability, good oral absorption, and compliance with Lipinski's rule of five define compound TKS3-1 as a very interesting oral medication candidate. Reiterating good oral absorption, the molecular weight (367.403 Da) is much below the Lipinski criterion (≤500 Da). Within the suitable range (≤140 Å^2), the PSA (PSA: 76.009 Å2) guarantees effective transmembrane diffusion and excellent intestinal absorption. Its water solubility (QPlogS: −6.178) is quite below the optimal range (−6–0), suggesting intermediate solubility, which would profit from solubilizing agents or formulation changes to improve dissolution. With a lipophilicity (QPlogPo/w: 4.427) that falls within the ideal range (−0.4–5.6), the hydrophobicity is balanced and allows effective cell membrane penetration free from too strong bioaccumulation. Excellent oral absorption and fast absorption in the gastrointestinal system are confirmed by the intestinal permeability (QPP Caco-2: 560.026 nm/s), above the high-permeability threshold (>500 nm/s). This chemical is therefore inappropriate for neurological uses since the BBB penetration (QPlogBB: −1.238) is poor, implying restricted CNS accessibility.

With a moderate serum protein binding (QPlogKhsa: 0.628), the plasma drug concentration is kept in balance, therefore optimizing therapeutic action without too high circulation retention. The HOA rate (100%) validates effective gastrointestinal absorption, thereby supporting its great potential as an orally delivered medicine. Lipinski's rule compliance (0 infractions) also shows positive drug-like characteristics, which supports its fit for clinical development even more.

Compound TKS3-5 has great pharmacokinetic properties, including good permeability, excellent oral absorption, and compliance with Lipinski's rule of five, making it an attractive oral medication candidate. Remarkably well within the Lipinski threshold (≤500 Da), the molecular weight (381.43 Da) guarantees good oral absorption. With a PSA (PSA: 76.141 Å) below the 140 Å^2 criterion, the intestinal absorption and membrane permeability seem to be good. Its aqueous solubility (QPlogS: −6.79) is modest to low, somewhat below the optimum range (−6–0), hence minimal solubility increases may be needed to maximize dissolution and bioavailability. The lipophilicity (QPlogPo/w: 4.753) falls within the reasonable range (−0.4–5.6), thereby guaranteeing a balance between solubility and membrane permeability and so preventing too strong bioaccumulation and metabolic instability. Strong intestinal absorption is confirmed by the intestinal permeability (QPP Caco-2: 559.966 nm/s), over the high-permeability threshold (>500 nm/sec), therefore offsetting their modest solubility. The limited BBB penetration (QPlogBB: −1.278) indicates, however, that the substance is unlikely to penetrate the CNS, therefore unfit for neurological use.

Within the moderate binding range (0.5–1.5), the serum protein binding (QPlogKhsa: 0.794) guarantees balanced systemic distribution without too high retention, hence optimizing therapeutic efficacy. Supporting its possible efficacy as an oral medication candidate, the HOA rate (100%) further guarantees strong gastrointestinal absorption. Lipinski's rule compliance (0 breaches) also supports its significant drug-like properties, so it is ideal for additional pharmacological research.

Compound TKS3-7 has intermediate pharmacokinetic potential, with decent solubility, tolerable oral absorption, and adherence to Lipinski's rule of five, making it a viable oral medication candidate with some permeability constraints. The molecular weight (383.403 Da) falls inside the Lipinski threshold (≤500 Da), indicating good oral bioavailability. The PSA (PSA: 98.694 Å^2) is below the 140 Å^2 threshold, maintaining acceptable membrane permeability. However, it is somewhat higher than optimum for passive diffusion, potentially impacting intestinal absorption efficiency. This compound's aqueous solubility (QPlogS: −5.911) is superior to several other compounds in the dataset, remaining within an acceptable range (−6–0), indicating improved dissolution in aqueous conditions and, most likely, greater bioavailability. The lipophilicity (QPlogPo/w: 3.683) falls within the recommended range (−0.4–5.6), achieving a balance between membrane penetration and solubility while lowering the danger of bioaccumulation or metabolic instability. However, intestinal permeability (QPP Caco-2: 169.824 nm/s) is quite low (<500 nm/s), implying that passive absorption may be limited, necessitating permeability enhancers or prodrug modifications to boost uptake. The BBB penetration (QPlogBB: −1.922) is extremely low, indicating that the chemical is unlikely to pass into the CNS and hence unsuitable for neurological therapeutic applications. The serum protein binding (QPlogKhsa: 0.456) is on the low end of the moderate range (0.5–1.5), indicating a higher free drug fraction in plasma, which may lead to improved systemic availability but may also result in a shorter half-life due to faster clearance. The HOA rate (88.425%) is moderate, showing good gastrointestinal uptake but not as high as other contenders. Furthermore, Lipinski's rule compliance (0 breaches) enhances drug-like characteristics and oral bioavailability.

Compound TKS3-8 has moderate pharmacokinetic features, including good solubility, conformity with Lipinski's rule of five, and adequate oral absorption, but severe restrictions in permeability and CNS accessibility. The molecular weight (399.402 Da) falls inside the

Lipinski threshold (≤500 Da), indicating good oral bioavailability. The PSA (PSA) of 120.26 Å^2 is close to the maximum limit (≤140 Å^2), indicating moderate membrane permeability. However, its relatively high value may limit passive diffusion over biological barriers. This molecule has a higher aqueous solubility (QPlogS: −5.579) than many other compounds in the dataset, but it still falls within an acceptable range (−6–0), indicating appropriate dissolving in aquatic settings and a lower risk of solubility-limited absorption. The lipophilicity (QPlogPo/w: 2.974) is within the ideal range (−0.4–5.6), achieving a balance between membrane penetration and solubility while reducing concerns about bioaccumulation or metabolic stability.

However, intestinal permeability (QPP Caco-2: 60.492 nm/s) is relatively low (<500 nm/s), indicating that passive absorption is considerably constrained. This may need permeability enhancers, different formulation procedures, or prodrug changes. The BBB permeability (QPlogBB: −2.526) is extremely low, indicating that the chemical is unlikely to penetrate the CNS and hence unsuitable for neurological therapeutic uses. The serum protein binding (QPlogKhsa: 0.27) is low (optimal range: 0.5–1.5), implying that a greater proportion of the medication remains free in plasma, which may improve bioavailability but also raise clearance rates. HOA (76.249%) is lower than most other options, indicating inadequate gastrointestinal uptake that may impact systemic medication levels. Nonetheless, Lipinski's rule compliance (0 breaches) supports its drug-like characteristics and oral bioavailability.

Compound TKS3-9 has a remarkable pharmacokinetic potential, with exceptional permeability, high oral absorption, and compliance with Lipinski's rule of five, making it a very promising oral medication candidate. The molecular weight (401.848 Da) is beneath the Lipinski threshold (≤500 Da), indicating good oral bioavailability. The PSA (PSA: 76.149 Å^2) is less than the 140 Å^2 criterion, indicating effective membrane permeability and adequate intestinal absorption. However, its aqueous solubility (QPlogS: −6.967) falls below the optimum range (−6–0), indicating poor solubility that may necessitate formulation strategies such as solubilizers or sophisticated drug delivery approaches to improve dissolution.

The lipophilicity (QPlogPo/w: 4.94) falls within the recommended range (−0.4–5.6), ensuring a balance between solubility and membrane permeability while reducing concerns about excessive bioaccumulation or metabolic instability. The intestinal permeability (QPP Caco-2: 559.992 nm/s) exceeds the high-permeability threshold (>500 nm/sec), indicating significant passive absorption and oral bioavailability. However, the BBB permeability is poor (QPlogBB: −1.097), indicating minimal CNS penetration and making it inappropriate for neurological applications.

The serum protein binding (QPlogKhsa: 0.753) is moderate (0.5–1.5), resulting in balanced systemic drug distribution without excessive retention, hence improving therapeutic efficacy. The HOA rate (100%) shows great gastrointestinal uptake, indicating that it has considerable potential as an orally administered medication. Furthermore, Lipinski's rule compliance (0 breaches) confirms its significant drug-like properties and favorable pharmacokinetic profile.

Compound TKS3-10 has significant pharmacokinetic properties, including good permeability, high oral absorption, and moderate drug-likeness, but has low solubility and one Lipinski violation. The molecular weight (436.293 Da) is beneath the Lipinski threshold (≤500 Da), indicating good oral bioavailability. The PSA (PSA: 76.026 Å^2) is below the 140 Å^2 threshold, indicating effective transmembrane permeability and adequate intestinal absorption. However, its aqueous solubility (QPlogS: −7.594) is less than the optimum range (−6–0), indicating low solubility, which may demand solubilization techniques or formulation optimization for improved dissolution. The lipophilicity (QPlogPo/w: 5.376) is somewhat over the acceptable limit (≤5), indicating strong hydrophobicity. This may result in lower solubility and metabolic instability. The intestinal permeability (QPP Caco-2: 559.213 nm/s) exceeds the high-permeability threshold (>500 nm/s), indicating substantial passive absorption and good oral bioavailability. However, the BBB permeability (QPlogBB: −0.974) is poor, indicating limited CNS penetration and rendering the molecule inappropriate for neurological therapeutic applications. The serum protein binding (QPlogKhsa: 0.863) is moderate (0.5–1.5), resulting in balanced systemic drug distribution without excessive retention, hence improving therapeutic efficacy. The HOA rate (94.644%) confirms significant gastrointestinal uptake, indicating great potential as an orally administered medication. However, one Lipinski violation (presumably due to high logP) indicates possible problems with metabolic stability and solubility, necessitating structural or formulation changes.

CONCLUSION

The molecular docking studies of the 33 novel chalcone-linked quinoline derivatives revealed promising potential as anticancer agents by inhibiting inactive EGFR tyrosine kinase. Compounds TKS3-7 and TKS2-8 demonstrated superior binding affinities compared to the standard erlotinib drug, with stable molecular dynamics profiles and favorable ADMET properties. These results provide a strong foundation for further experimental studies and highlight the potential of these compounds as lead candidates for anticancer agent development.

AUTHOR'S CONTRIBUTION

Tejinder Kaur: Conceptualized the study design, analyzed the data, and drafted the manuscript. Shubham Das: Performed molecular docking studies, conducted ADMET predictions, and molecular dynamics simulations. Divya Dhawal Bhandari, Rajiv Sharma, and Yash Pal Singh: Contributed to data interpretation, manuscript revision, and provided critical feedback.

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CONFLICT OF INTEREST

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