In silico ADMET screening & molecular docking of some 1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-3(2H)-yl) ethanone derivatives to be developed as triple mutant T790M/C797S EGFR inhibitors

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Abstract--- EGFRs' high expression and/or adaptive activation coincides with the pathogenesis and development of many tumors, making them appealing candidates for both diagnosis and therapy. Several strategies for targeting these receptors and/or the EGFR-mediated effects in cancer cells have been established. A lot of in silico models are developed for prediction of chemical ADMET properties. However, it is still not easy to evaluate the drug-likeness of compounds in terms of so many ADMET properties. In present study, we have designed some 1-(5-(4-chlorophenyl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone derivatives to be developed as potential EGFR inhibitors for the treatment of cancer. The designed derivatives were screened through Lipinski rule, Veber's rule, ADMET analysis, drug-likeness properties and molecular docking. We concluded that all the compounds sm1, sm2, sm3, sm8, sm9, sm10, sm11, sm12, sm13, sm14, sm15, sm18, and sm19 were found to possess drug-likeness properties and therefore were subjected for molecular docking studies. From molecular docking studies it was observed that Molecules Sm3, Sm8, Sm9, Sm10, Sm12, and Sm2 had formed either three or two conventional hydrogen bonds with EGFR enzyme and hence selected for synthesis which can be developed further to get more promising molecules for the treatment of cancer.

Keywords---EGFR, angiogenesis, cancer, ADMET, molecular docking.

Introduction

Radiation and chemotherapy are effective against a wide variety of malignancies, but molecular targeting medicines for cancer treatment can target specific types of tumours with greater accuracy. Progress has been achieved over the last few decades in uncovering the complex cellular, metabolic and genetic processes that lead to cancer formation and progression(1). More tumor-targeted anticancer treatments have been developed because to this improved understanding of how cancer works. Tumor development and proliferation have been linked to tyrosine kinases, which are frequent therapeutic targets. By blocking downstream signalling pathways from activating, tyrosine kinase inhibitors (TKIs) prevent the related kinases from phosphorylating their substrates' tyrosine residues(2). Over the last two decades, a number of robust and well-tolerated TKIs targeting single or multiple targets, such as EGFR, ALK, ROS1, HER2, NTRK, VEGFR, RET, MET, MEK, FGFR, PDGFR, and KIT, have been developed, advancing our understanding of precision cancer medicine based on a patient's genetic alteration profile(3). The epidermal growth factor receptor (EGFR) has been identified as a molecular target for certain potential cancer therapies. Four transmembrane tyrosine kinases (EGFR1/ErbB1, Her2/ErbB2, Her3/ErbB3, and Her4/ErbB4), as well as thirteen secreted polypeptide ligands, make up the EGFR family(4). Multiple solid tumours, including breast, pancreatic, head and neck, kidney, vaginal, renal, colon, and non-small-cell lung cancer, have overexpressed EGFRs(5). Overexpression of these genes causes cell proliferation, differentiation, cell cycle progression, angiogenesis, cell motility, and apoptosis inhibition through stimulating downstream signaling channels(6). We will be able to quantify the individual activities of EGFR signalling networks as our understanding of their involvement in tumour activity advances. The high expression and/or adaptive activation of EGFRs correlates with the pathophysiology and progression of many cancers, making them attractive candidates for diagnostics and treatment. Several techniques have been developed to target these receptors and/or the EGFR-mediated effects in cancer cells. Monoclonal antibodies (mAbs) that specifically target the EGFR extracellular domain, such as cetuximab (Erbitux), and small molecule TKIs that particularly target the EGFR catalytic domain, such as gefitinib (Iressa) and erlotinib(Tarceva), are two types of EGFRIs(7–11).
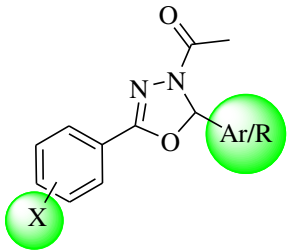
A lot of *in silico* models are hence developed for prediction of chemical ADMET properties. However, it is still not easy to evaluate the drug-likeness of compounds in terms of so many ADMET properties(21–28). In the present work we have performed *in silico* ADMET screening of designed derivatives to be developed as potential EGFR inhibitors for the treatment of cancer. All the designed derivatives were subjected for the calculations of different ADMET parameters to select most promising compound which can possess more drug-likeness properties.

Material and Methods

Designing of 1-(5-(4-chlorophenyl)-1, 3, 4-oxadiazol-3(2H)-yl)ethanone derivatives

The reaction was achieved by heating the aldehydes with 4-chlorobenzohydrazide in the presence of ethanol & sulfuric acid to form 4-chloro-N'-methylenebenzohydrazide. Further 4-chloro-N'-methylenebenzohydrazide undergoes internal cyclization when refluxed to give fused 1-(5-(4-chlorophenyl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone derivatives. This reaction will be carried out in presence of acetic anhydride. The structure of the parent compound and the substituted azole derivatives are depicted in Table 1.

Table 1
1-(5-(4-chlorophenyl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone derivatives

1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-3(2H)-yl) ethanone derivatives

Code	R/Ar	Code	R/Ar
sm1	H	sm11	—3-hydroxy phenyl
sm2	—phenyl	sm12	—2,3,4-trihydroxy phenyl
sm3	—4-nitro phenyl	sm13	—3-methoxy-4-hydroxy phenyl
sm4	—4-bromo phenyl	sm14	—2-methoxy phenyl
sm5	—4-fluoro phenyl	sm15	—4-styryl
sm6	—4-chloro phenyl	sm16	—napthyl
sm7	—4-methyl phenyl	sm17	—2,4-dinitro phenyl
sm8	—4-methoxy phenyl	sm18	—4-methylsulfonyl phenyl
sm9	—4-hydroxy phenyl	sm19	—4-dimethylamino phenyl
sm10	—3-nitro phenyl	sm20	—4-trifluoromethyl phenyl

Pharmacokinetics and toxicity predictions of designed derivatives

Chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET), play key roles in drug discovery and development. A high-quality drug candidate should not only have sufficient efficacy against the therapeutic target, but also show appropriate ADMET properties at a therapeutic dose. The designed derivatives were screened for its ADME analysis, drug-likeliness and toxicity parameters. The Lipinski rule of five and the pharmacokinetic (ADME) characteristics of designed derivatives were investigated using Swiss ADME(29) servers. The toxicity of the compounds has been predicted using ProTox-II, which

is a freely accessible webserver for *in silico* toxicity predictions of new derivatives (http://tox.charite.de/protox_II)(30).

Molecular Docking

All the selected compounds and the native ligand were docked against the crystal structure of the crystal Structure of EGFR T790M mutant in complex with naquotinib using Autodock vina 1.1.2 in PyRx 0.8(1). ChemDraw Ultra 8.0 was used to draw the structures of the compounds and native ligand (mole. File format). All the ligands were subjected for energy minimization by applying Universal Force Field (UFF)(2). The crystal structure of the enzyme with PDB ID 5Y9T was obtained from RCSB Protein Data Bank (PDB) (https://www.rcsb.org/structure/5Y9T). Discovery Studio Visualizer (version-19.1.0.18287) was used to refine the enzyme structure, purify it, and get it ready for docking(3). A three-dimensional grid box (size_x=62.5293379415Å; size_y=43.0367205343Å; size_z=43.851824552Å) with an exhaustiveness value of 8 was created for molecular docking(1). BIOVIA Discovery Studio Visualizer was used to locate the protein's active amino acid residues. The approach outlined by Khan et al. was used to perform the entire molecular docking procedure, identify cavity and active amino acid residues(4–10). Fig. 1 shows the revealed cavity of enzyme with the native ligand molecule.
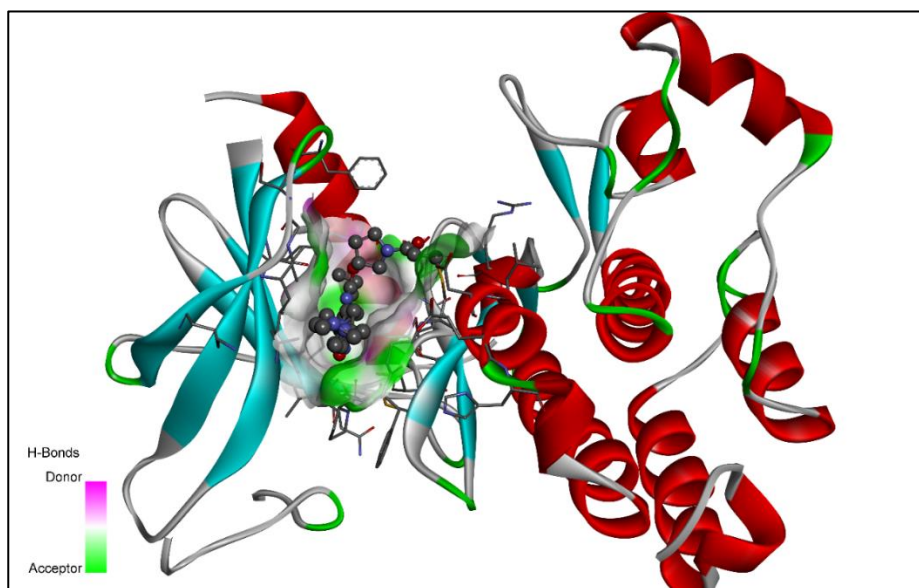

Fig. 1. The 3D ribbon view of the enzyme with native ligand in the cavity

Result and Discussion

Pharmacokinetic characteristics are critical to drug development because they enable scientists to investigate the biological impacts of possible pharmacological candidates(23). This compound's oral bioavailability was evaluated using Lipinski's rule of five and Veber's rules (Table 2). To better understand the pharmacokinetics profiles and drug-likeness properties of the proposed

compounds, the ADME characteristics of all of them were examined (Table 3). The oral acute toxicity have been predicted along with LD_{50} (mg/kg), toxicity class, hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity (Table 4). Table 5 depicts the active amino residues, bond length, bond category, bond type, ligand energies, and docking scores. The docking poses of the molecules are exemplified in Table 6.

Table 2
Lipinski rule of 5 and Veber's rule calculated for molecules

Compound Codes	Lipinski rule of five					Veber's rule	
	Log P	Mol. Wt.	HBA	HBD	Violations	Total polar surface area (Å^2)	No. of rotatable bonds
sm1	2.04	224.64	3	0	0	41.9	2
sm2	3.38	300.74	3	0	0	41.9	3
sm3	2.05	346.75	5	1	0	91.56	4
sm4	4.01	379.64	3	0	1	41.9	3
sm5	3.7	318.73	4	0	1	41.9	3
sm6	3.92	335.18	3	0	1	41.9	3
sm7	3.71	314.77	3	0	1	41.9	3
sm8	3.29	330.77	4	0	0	51.13	4
sm9	2.97	316.74	4	1	0	62.13	3
sm10	2.05	346.75	5	1	0	91.56	4
sm11	2.97	316.74	4	1	0	62.13	3
sm12	2.21	348.74	6	3	0	102.59	3
sm13	2.95	346.77	5	1	0	71.36	4
sm14	3.3	330.77	4	0	0	51.13	4
sm15	3.44	328.79	2	0	0	32.78	4
sm16	4.29	350.8	3	0	1	41.9	3
sm17	1.39	392.75	7	2	0	141.22	5
sm18	3.05	378.83	5	0	0	84.42	4
sm19	3.3	343.81	3	0	0	45.14	4
sm20	4.43	368.74	6	0	1	41.9	4

Where: Mol. Wt., molecular weight; HBA, hydrogen bond acceptors; HBD, hydrogen bond donors

Table 3

The pharmacokinetics and drug-likeness properties of developed compounds

| Compound codes | Pharmacokinetics | Drug-likeness | | | | | | | | | | | |
	GI abs.	BBB pen.	P-gp sub.	CYP1A2 inhibitors	CYP2C19	CYP2C9	CYP2D6	CYP3A4	Log K_p (skin permeation, cm/s)	Ghose	Egan	Muegge	Bioavailability Score
sm1	High	Yes	No	Yes	No	No	No	No	-6.22	0	0	0	0.55
sm2	High	Yes	No	Yes	Yes	Yes	No	No	-5.6	0	0	0	0.55
sm3	High	No	No	No	No	No	No	No	-6.33	0	0	0	0.55
sm4	High	Yes	No	Yes	Yes	Yes	No	No	-5.59	0	0	0	0.55
sm5	High	Yes	No	No	Yes	Yes	No	No	-5.64	0	0	0	0.55
sm6	High	Yes	No	Yes	Yes	Yes	No	No	-5.36	0	0	0	0.55
sm7	High	Yes	No	No	Yes	Yes	No	No	-5.43	0	0	0	0.55
sm8	High	Yes	No	Yes	Yes	Yes	No	No	-5.8	0	0	0	0.55
sm9	High	Yes	No	Yes	Yes	Yes	No	No	-5.95	0	0	0	0.55
sm10	High	No	No	No	No	No	No	No	-6.33	0	0	0	0.55
sm11	High	Yes	No	Yes	Yes	Yes	No	No	-5.95	0	0	0	0.55
sm12	High	No	No	Yes	No	No	No	No	-6.65	0	0	0	0.55
sm13	High	Yes	No	Yes	Yes	Yes	No	No	-6.15	0	0	0	0.55
sm14	High	Yes	No	Yes	Yes	Yes	No	No	-5.8	0	0	0	0.55
sm15	High	Yes	No	No	Yes	Yes	No	No	-5.37	0	0	0	0.55
sm16	High	Yes	No	Yes	Yes	Yes	No	No	-5.02	0	0	0	0.55
sm17	Low	No	Yes	No	Yes	Yes	No	No	-7.06	0	1	0	0.55
sm18	High	No	No	Yes	Yes	Yes	No	No	-6.62	0	0	0	0.55
sm19	High	Yes	No	No	Yes	Yes	No	No	-5.78	0	0	0	0.55
sm20	High	Yes	No	No	Yes	Yes	No	No	-5.39	0	0	0	0.55

Where: NL, Native ligand; GI abs., gastrointestinal absorption; BBB pen., blood brain barrier penetration; P-gp sub., p-glycoprotein substrate

Table 4

The predicted acute toxicity of molecules

| Compound codes | Parameters | | | | | | | |
	LD$_{50}$ (mg/kg)	Toxicity class	Prediction accuracy (%)	Hepatotoxicity (Probability)	Carcinogenicity (Probability)	Immunotoxicity (Probability)	Mutagenicity (Probability)	Cytotoxicity (Probability)
sm1	3000	5	54.26	I (0.54)	A (0.57)	I (0.97)	I (0.61)	I (0.61)
sm2	1000	4	54.26	A (0.59)	A (0.50)	I (0.96)	I (0.72)	A (0.65)
sm3	3000	5	54.26	A (0.61)	A (0.50)	I (0.73)	I (0.71)	A (0.65)
sm4	700	4	54.26	A (0.60)	I (0.50)	I (0.76)	I (0.71)	A (0.69)
sm5	700	4	54.26	A (0.61)	I (0.50)	I (0.73)	I (0.71)	A (0.68)
sm6	1000	4	54.26	A (0.61)	A (0.50)	I (0.73)	I (0.71)	A (0.65)
sm7	1000	4	54.26	A (0.59)	I (0.51)	I (0.97)	I (0.70)	A (0.63)
sm8	1000	4	54.26	A (0.62)	I (0.53)	I (0.62)	I (0.66)	I (0.70)

sm9	550	4	54.26	A (0.65)	I (0.50)	I (0.90)	I (0.68)	I (0.55)
sm10	3000	5	54.26	A (0.65)	I (0.50)	I (0.90)	I (0.68)	I (0.55)
sm11	1000	4	23	A (0.65)	I (0.50)	I (0.77)	I (0.68)	I (0.55)
sm12	4920	5	23	A (0.63)	I (0.52)	I (0.52)	I (0.68)	I (0.69)
sm13	4920	5	54.26	A (0.64)	I (0.54)	A (0.82)	I (0.67)	I (0.73)
sm14	1000	4	23	A (0.61)	I (0.57)	A (0.53)	I (0.67)	I (0.77)
sm15	300	3	54.26	I (0.52)	I (0.50)	I (0.96)	I (0.68)	I (0.61)
sm16	1000	4	54.26	A (0.58)	I (0.53)	I (0.89)	I (0.76)	A (0.85)
sm17	2201	5	23	A (0.58)	I (0.53)	I (0.89)	I (0.76)	A (0.85)
sm18	4000	5	23	I (0.53)	I (0.59)	I (0.77)	I (0.72)	I (0.68)
sm19	5505	6	54.26	A (0.54)	I (0.62)	I (0.68)	I (0.64)	I (0.60)
sm20	700	4	54.26	A (0.63)	A (0.50)	I (0.89)	I (0.68)	A (0.61)

Where: I, Inactive; A, Active

Table 5
The active amino residues, bond length, bond category, bond type, ligand
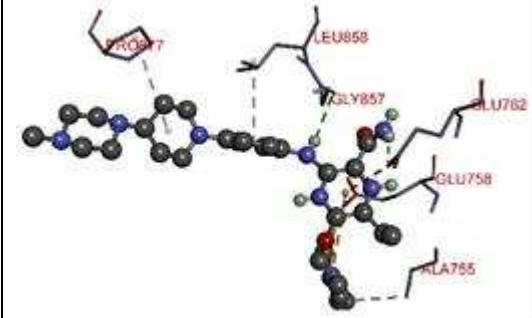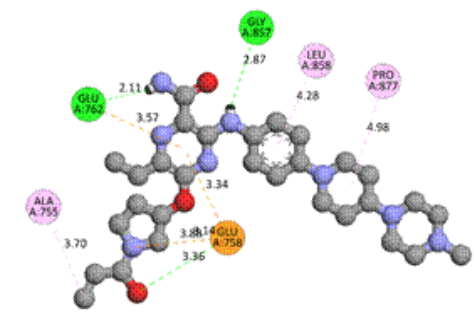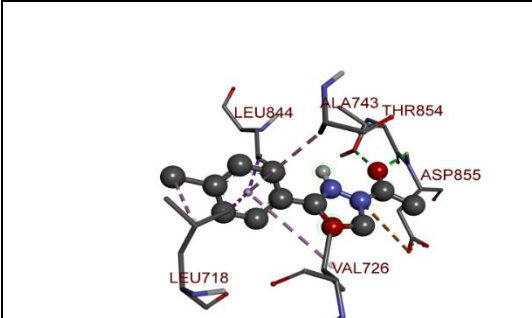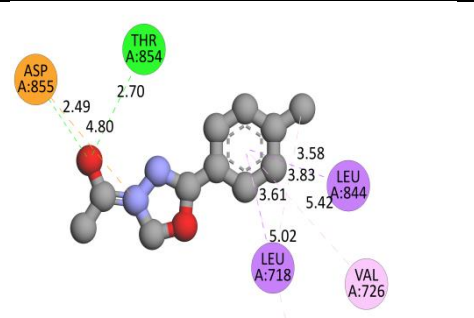energies, and docking scores
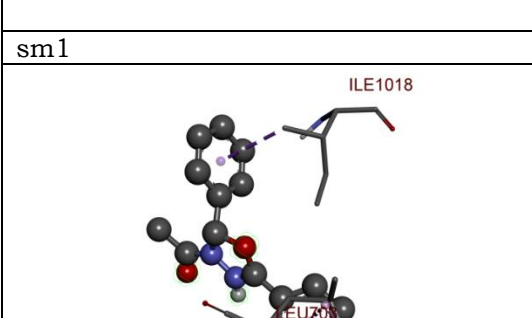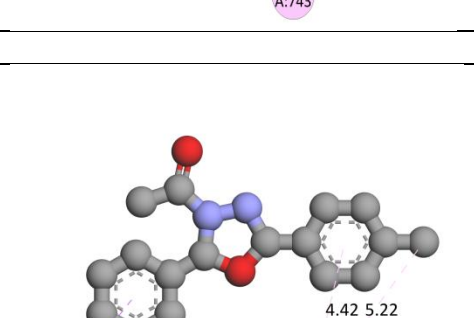
Active amino acids	Bond length	Bond type	Bond category	Ligands energy	Docking score
Native ligand					
GLU758	3.88487	Electrostatic	Attractive Charge	568.59	-8.3
GLY857	2.87344	Hydrogen Bond	Conventional Hydrogen Bond		
GLU762	2.10926				
GLU758	3.35859				
GLU758	3.13642		Carbon Hydrogen Bond		
GLU758	3.33922	Electrostatic	Pi-Anion		
GLU762	3.56702				
ALA755	3.69661	Hydrophobic	Alkyl		
PRO877	4.97918				
LEU858	4.28035		Pi-Alkyl		
sm1					
ASP855	4.80189	Electrostatic	Attractive Charge	304.76	-6
THR854	2.70059	Hydrogen Bond	Conventional Hydrogen Bond		
ASP855	2.49241				
LEU718	3.6134	Hydrophobic	Pi-Sigma		
LEU844	3.58116				
LEU718	3.82636		Alkyl		
VAL726	5.42251		Pi-Alkyl		
ALA743	5.01938				
sm2					
ILE1018	3.56188	Hydrophobic	Pi-Sigma	461.68	-8.2
LEU703	5.22421		Alkyl		
LEU703	4.42024		Pi-Alkyl		
sm3					
THR854	3.16086	Hydrogen Bond	Conventional Hydrogen Bond	449.4	-8.3
GLU762	2.44501				

ASP855	2.06482				
ASP855	4.85569	Electrostatic	Pi-Anion		
LEU718	4.78982	Hydrophobic	Alkyl		
VAL726	4.93425		Pi-Alkyl		
LEU718	3.8475				
sm4					
LEU718	3.92364	Hydrophobic	Pi-Sigma	466.2	-8.2
LEU718	4.53559		Alkyl		
VAL726	5.49873		Pi-Alkyl		
sm5					
LYS745	2.01835	Hydrogen Bond;Halogen	Conventional Hydrogen Bond;Halogen (Fluorine)	346.51	-8.1
GLU762	3.67342	Halogen	Halogen (Fluorine)		
ASP855	4.58384	Electrostatic	Pi-Anion		
LEU718	3.98999	Hydrophobic	Pi-Sigma		
LEU844	3.54568				
LEU718	4.37964		Alkyl		
VAL726	5.34235		Pi-Alkyl		
MET790	5.33612				
sm6					
LEU718:O	2.33685	Hydrogen Bond	Conventional Hydrogen Bond	359.49	-8.0
ASP855	4.48375	Electrostatic	Pi-Anion		
MET790	4.83339	Hydrophobic	Alkyl		
VAL726	4.50617		Pi-Alkyl		
VAL726	5.25874				
LEU718	3.92772				
sm7					
ASP855	4.43382	Electrostatic	Pi-Anion	322.46	-8.0
LEU718	3.9588	Hydrophobic	Pi-Sigma		
LEU844	3.5256				
LYS745	5.21002		Alkyl		
MET790	4.76992				
LEU718	4.30575				
MET790	5.39316		Pi-Alkyl		
LEU844	5.47259				
sm8					
LEU703	2.38234	Hydrogen Bond	Conventional Hydrogen Bond	494.79	-8.7
TYR827	2.52106				
ARG776	4.94776	Electrostatic	Pi-Cation		
ASP770	4.30886		Pi-Anion		
ILE1018	3.72929	Hydrophobic	Pi-Sigma		
ARG831	4.66377		Alkyl		
LEU778	5.00032				
ILE1018	4.48071				
TYR1016	4.91462		Pi-Alkyl		

sm9					
ALA767	2.31174	Hydrogen Bond	Conventional Hydrogen Bond	457.81	-8.5
ALA1013	2.51271				
TYR1016	2.03423				
ARG776	4.04585	Electrostatic	Pi-Cation		
ASP770	4.25988		Pi-Anion		
ARG776	5.36441	Hydrophobic	Pi-Alkyl		
ILE1018	4.91446				
sm10					
ASP770	4.51903	Electrostatic	Attractive Charge	774.68	-8.7
ALA1013	2.12736	Hydrogen Bond	Conventional Hydrogen Bond		
ARG776	2.23577				
A:ASP770	4.45104	Electrostatic	Pi-Anion		
ILE1018	4.57745	Hydrophobic	Pi-Alkyl		
ALA702	4.34458				
sm11					
ASP855	4.6377	Electrostatic	Pi-Anion	341.44	-8.1
LEU844	3.52938	Hydrophobic	Pi-Sigma		
LEU718	4.47331		Alkyl		
VAL726	5.16417		Pi-Alkyl		
MET790	5.37716		Pi-Alkyl		
LEU718	3.85611		Pi-Alkyl		
sm12					
GLN701	3.19535	Hydrogen Bond	Conventional Hydrogen Bond	312.33	-8.6
SER768	1.86175				
TYR827	2.39179				
TYR827	2.87448				
ASP770	4.19161	Electrostatic	Pi-Anion		
ILE1018	3.91424	Hydrophobic	Pi-Sigma		
LEU778	4.49671		Alkyl		
ILE1018	4.44808				
sm13					
LEU703	2.44512	Hydrogen Bond	Conventional Hydrogen Bond	338.83	-8.8
ARG776:	4.93935	Electrostatic	Pi-Cation		
ILE1018	3.70366	Hydrophobic	Pi-Sigma		
LEU778	5.17816		Alkyl		
ILE1018	4.38419				
TYR1016	4.85315		Pi-Alkyl		
sm14					
ARG841	3.51246	Hydrogen Bond	Carbon Hydrogen Bond	334.32	-8.2
ASN842	3.59968				
LEU718	3.91693	Hydrophobic	Pi-Sigma		
LEU718	4.49092		Alkyl		
VAL726	5.26015		Pi-Alkyl		
sm15					
ALA767	3.31618	Hydrogen Bond	Carbon Hydrogen Bond	314.49	-8.2
ASP770	3.61071				

LEU1017	3.68846		Pi-Sigma		
LEU778	4.11015		Alkyl		
ILE1018	4.65007	Hydrophobic			
ILE1018	4.87111		Pi-Alkyl		
TRP731	5.32319				
TYR1016	5.45835				
sm16					
ASP770	5.12621	Electrostatic	Attractive Charge		
:LEU703	3.00373	Hydrogen Bond	Pi-Donor Hydrogen Bond	450.85	-8.4
ILE1018	3.435		Pi-Sigma		
ILE1018	3.64982	Hydrophobic			
LEU703	5.2363		Pi-Alkyl		
LEU703	5.15416				
sm17					
LEU777	2.25265	Hydrogen Bond	Conventional Hydrogen Bond	445.15	-8.1
LEU778	2.24662				
LEU703	3.89849		Pi-Sigma		
LEU703	5.30319	Hydrophobic	Alkyl		
ILE1018	4.52615		Pi-Alkyl		
sm18					
ASP770	3.66561	Electrostatic	Attractive Charge		
ASN700	2.0857	Hydrogen Bond	Conventional Hydrogen Bond	450.16	-8.1
ASN700	2.73068				
GLN701	2.10706				
ASP770	4.17503	Electrostatic	Pi-Anion		
ILE1018	3.9243		Pi-Sigma		
LEU778	4.32332	Hydrophobic	Alkyl		
ILE1018	4.56006				
ALA702	4.58581		Pi-Alkyl		
sm19					
ASP855	2.99904	Hydrogen Bond	Conventional Hydrogen Bond	337.45	-8.3
ASP855	3.47705	Electrostatic	Pi-Anion		
LEU718	3.39223		Pi-Sigma		
LEU844	3.78158				
LEU718	3.8247	Hydrophobic	Alkyl		
LEU792	5.22053				
ALA743	5.09194		Pi-Alkyl		
PHE723	4.35843				

10442
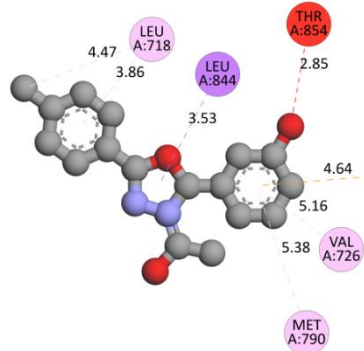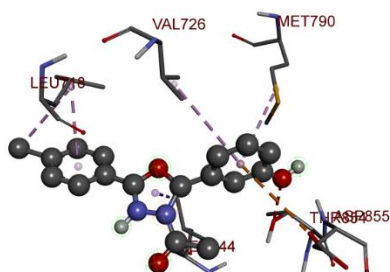
Table 6
The 3D- and 2D-docking poses of the molecules

3D-docking poses	2D-docking poses
Native ligand	
sm1	
sm2	

Sm3

Sm8

Sm9

10444

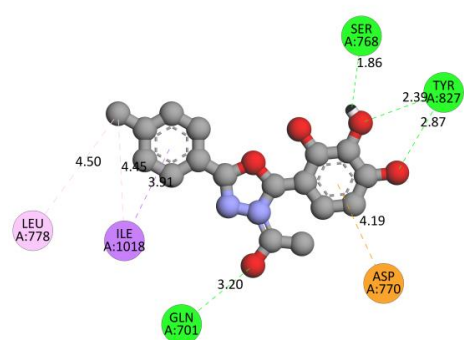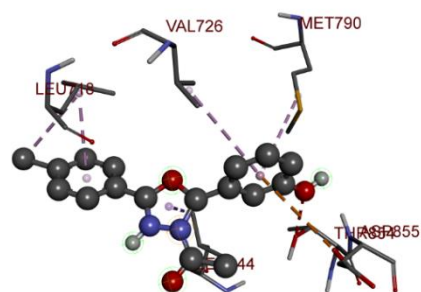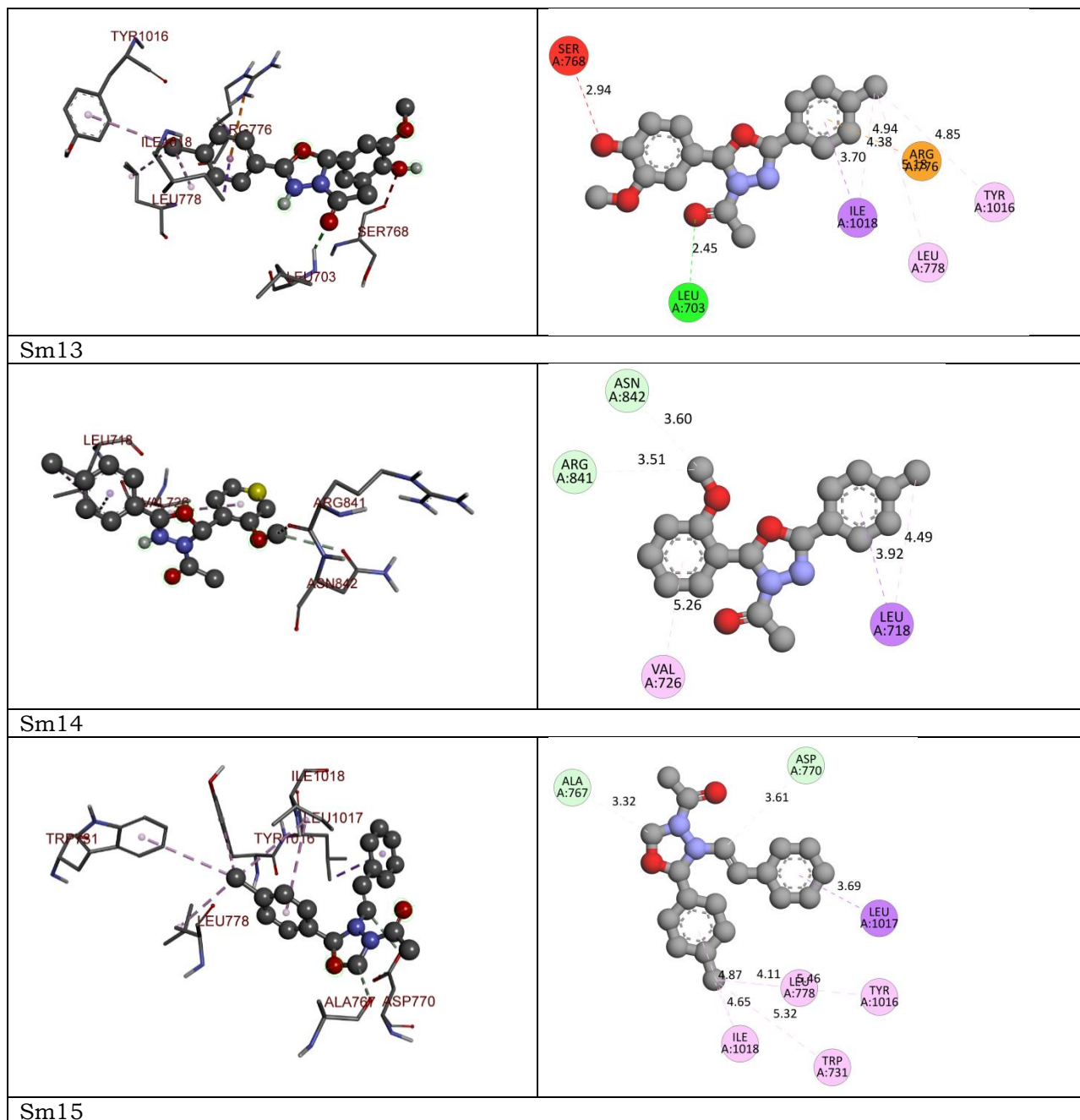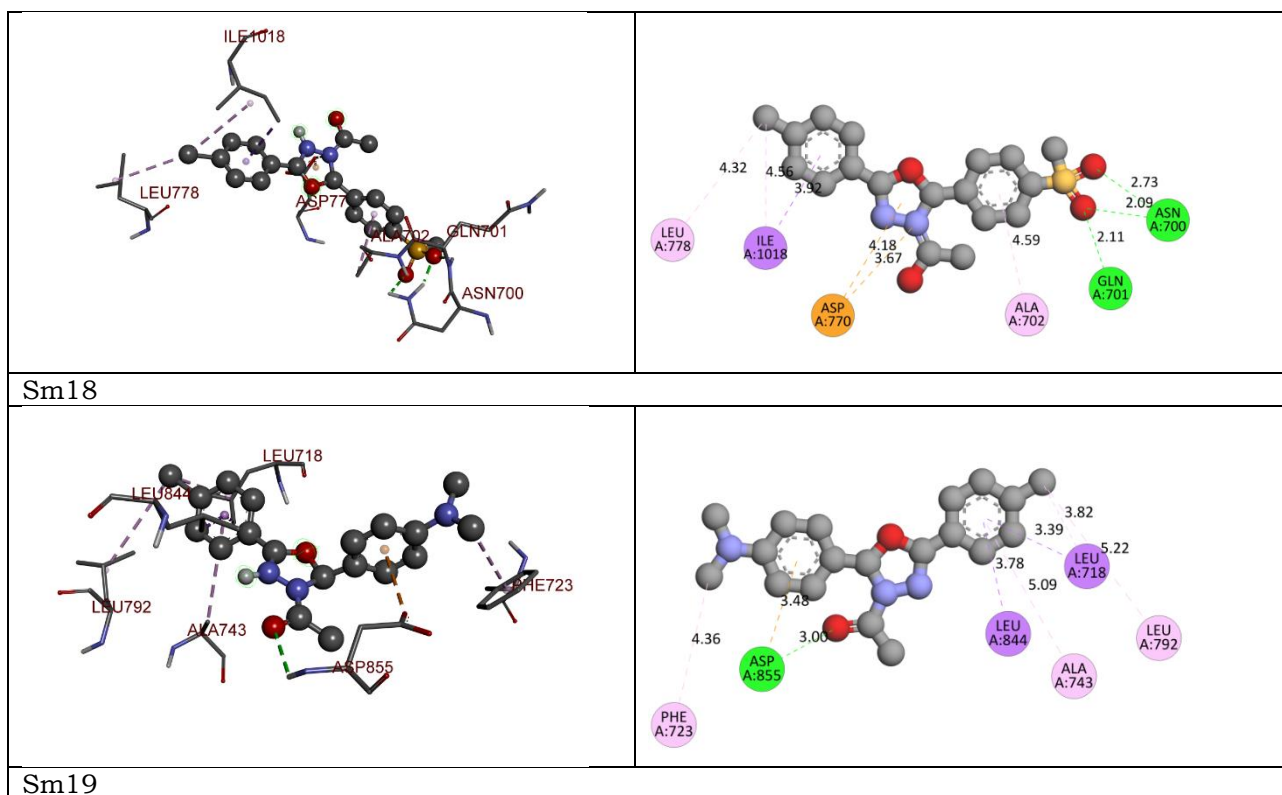|	
Sm10	
Sm11	
Sm12	

Sm13

Sm14

Sm15

Sm18

Sm19

In present study we have designed and developed some 1-(5-(4-chlorophenyl)-1, 3, 4-oxadiazol-3(2*H*)-yl)ethanone derivatives as potential EGFR inhibitors. In accordance with Lipinski's and Veber's rule (Table 2). The log P values of all the molecules were between the ranges 1.39 to 4.43 which indicates optimum lipophilicity. Lipophilicity is a significant feature of the molecule that affects how it works in the body(27). It is determined by the compound's Log P value, which measures the drug's permeability in the body to reach the target tissue(31,32). The molecular weight of all the molecules was around 500 Da which indicates active better transport of the molecules through biological membrane. Fortunately, the Lipinski rule of 5 had not been compromised by the compounds(23,24). All the compounds except sm4, sm5, sm6, sm7, sm16, sm20 violated the Lipinski rule of 5 .The total polar surface area (TPSA) and the number of rotatable bonds have been found to better discriminate between compounds that are orally active or not. According to Veber's rule, TPSA should be ≤ 140 and number of rotatable bonds should be ≤ 10. It was observed that, compound sm17 violated the Veber's rule, as it has TPSA 141Å^2.

In order to further optimize the compounds, pharmacokinetics and drug-likeness properties were calculated for each one. All the compounds showed no penetration to the blood-brain barrier (BBB). The log *Kp* (skin penetration, cm/s) and bioavailability values of all the compounds were within acceptable limits. (Table 3).The GI absorption of all the compounds was found to be high except for sm17. In acute toxicity predictions, class-III i.e. toxic if swallowed ($50 < LD_{50} \leq 300$), toxicity class-IV which means harmful if swallowed ($300 < LD_{50} \leq 2000$), class-V

which indicate may be harmful if swallowed ($2000 < LD_{50} \le 5000$)(30). From this virtual screening, it was concluded that all the compounds fall in class IV, V &VI of toxicity, which means they possess drug-like properties and hence were subjected to molecular docking studies. Out of 20 screened molecules through ADMET analysis, compound sm17 displayed low absorption and toxicity class-II therefore eliminated from further screening. The binding affinities of the derivatives have been compared with the binding mode of native ligand present in the crystal structure of EGFR enzyme (PDB ID: 5Y9T).

Native ligand (naquotinib) displayed -8.3 kcal/mol binding affinity with EGFR and formed three conventional and one carbon-hydrogen bond with Gly857, Glu762, and Glu758. It has developed electrostatic (Pi-anion, attractive charge) and hydrophobic bonds (alkyl and Pi-alkyl) with Glu758, Glu762, Ala755, Pro877, and Leu858. All the designed molecules displayed most potent interactions than the native ligand. Many derivatives exhibited more than two hydrogen bonds with the target. The compounds which have formed three or more hydrogen bonds have been selected for the synthesis and biological activity. The formation of hydrogen bonds with target can effectively modulate the activity of enzyme and exhibit potent pharmacological response. There are many compounds which exhibited more binding affinity but did not formed more than three hydrogen bonds, in that case some more derivatives selected for the synthesis. The compound sm1, sm2, sm3, sm8, sm9, sm10, sm11, sm12, sm13, sm14, sm15, sm18, and sm19 has been selected as most potent molecules from virtual screening.

Compound sm1 exhibited -6 kcal/mol binding affinity and formed two conventional hydrogen bonds with Thr854 and Asp855.It displayed many hydrophobic interactions (pi-sigma, alkyl and Pi-alkyl) with Leu718, Leu844, Val726 & Ala743. Compound sm2 showed -7.6 kcal/mol binding affinity and it also displayed many hydrophobic interactions (pi-sigma, alkyl and Pi-alkyl) with Ile1018 & Leu703. Compound sm3 displayed -7.7 kcal/mol binding affinity and it also formed three conventional hydrogen bonds with Thr854, Glu762 and Asp855. It also showed pi-anion type of electrostatic interactions with Asp855.It displayed many hydrophobic interactions (alkyl and Pi-alkyl) with Leu718 & Val726. Compound sm8 exhibited -8.3 kcal/mol binding affinity and it formed two conventional hydrogen bonds with Leu703 and Tyr827.It has developed one Pi-donor hydrogen bond with Trp22 and one electrostatic (Pi-anion) bond with Asp770. It displayed many hydrophobic interactions (alkyl and Pi-alkyl) with Arg831, Leu778, Ile 1018 & Tyr1016.

Compound sm9 showed -7.8 kcal/mol binding affinity and it formed three conventional hydrogen bonds with Ala767, Ala1013 and Tyr1016. It has developed two electrostatic (Pi-cation,Pi-anion) bonds with Asp776 & Asp770. It displayed hydrophobic interactions (Pi-alkyl) with Arg776 & Ile1018. Compound sm10 displayed -7.8 kcal/mol binding affinity and it formed two conventional hydrogen bonds with Arg776 & Ala1013. It has developed one electrostatic (Pi-anion) bond with Asp770. It displayed hydrophobic interactions (Pi-alkyl) with Arg776 & Ile1018. Compound sm11 exhibited -7.1 kcal/mol binding affinity and it has developed one electrostatic (Pi-anion) bond with Asp855. It displayed hydrophobic interactions (Pi-sigma, alkyl,Pi-alkyl) with leu718, Val726 & Met790. Compound sm12 exhibited -7.6 kcal/mol binding affinity and it has developed

one electrostatic (Pi-anion) bond with Asp770. It displayed hydrophobic interactions (Pi-sigma, alkyl,) with Ile1018 & leu778.

Compound sm13 exhibited -7.8 kcal/mol binding affinity and it has developed one electrostatic (Pi-anion) bond with Asp855. It displayed hydrophobic interactions (Pi-sigma, alkyl,Pi-alkyl) with leu778, Ile1018 & Tyr1016. Compound sm14 exhibited -7.5 kcal/mol binding affinity and formed two hydrogen bonds with Arg841 & Asn842.It displayed hydrophobic interactions (Pi-sigma, alkyl, Pi-alkyl) with leu718 & Val726. Compound sm15 exhibited -7.2 kcal/mol binding affinity and formed two hydrogen bonds with Ala767 & Asp770.It displayed hydrophobic interactions (Pi-sigma, alkyl, Pi-alkyl) with leu1017, Leu778, Ile1018, Trp731 & Tyr1016. Compound sm18 displayed -7.1 kcal/mol binding affinity and it also formed three hydrogen bonds with Asn700 & Gln701. It has developed hydrophobic interactions (Pi-sigma, alkyl, Pi-alkyl) with Leu778, Ile778 & Ile1018. Compound sm19 exhibited -7.3 kcal/mol binding affinity and it has developed one electrostatic (Pi-anion) bond with Asp855. It displayed hydrophobic interactions (Pi-sigma, alkyl, Pi-alkyl) with leu718, Leu844, Leu792, Ala743 & Phe723. From above screening it was observed that native ligand formed three conventional hydrogen bonds therefore, the molecules which formed two or more conventional hydrogen bonds with enzyme are considered as most potent and selected for wet lab synthesis followed by biological evaluation. Molecules Sm3, Sm8, Sm9, Sm10, Sm12, and Sm2 had formed either three or two conventional hydrogen bonds with EGFR enzyme and hence selected for synthesis.

Conclusion

A lot of *in silico* models are developed for prediction of chemical ADMET properties. However, it is still not easy to evaluate the drug-likeness of compounds in terms of so many ADMET properties. In present study, we have designed some 1-(5-(4-chlorophenyl)-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone derivatives to be developed as potential EGFR inhibitors for the treatment of cancer. The designed derivatives were screened through Lipinski rule, Veber's rule, ADMET analysis, drug-likeness properties and molecular docking. We concluded that all the compounds sm1, sm2, sm3, sm8, sm9, sm10, sm11, sm12, sm13, sm14, sm15, sm18, and sm19 were found to possess drug-likeness properties and therefore were subjected for molecular docking studies. From molecular docking studies it was observed that Molecules Sm3, Sm8, Sm9, Sm10, Sm12, and Sm2 had formed either three or two conventional hydrogen bonds with EGFR enzyme and hence selected for synthesis which can be developed further to get more promising molecules for the treatment of cancer.

Acknowledgments

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