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IN-SILICO DESIGN AND COMPUTATIONAL STUDY OF NOVEL QUINAZOLIN-4-ONE DERIVATIVES AS POTENTIAL AFFINITY WITH EGFR FOR ANTICANCER ACTIVITY

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Keywords:

Computational study, EGFR, Anticancer agents, Docking study, Quinazolinone derivatives

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ABSTRACT: Molecular object precise healing designed for the malignancy be unrelated as of the predictable therapy, as well as radio healing in conditions of selectivity and specificity target to the malignant tyrosine kinase, is well-thought-out additional shows potential molecular intention for invention and expansion of the new cytotoxic drug molecules. Epidermal growth factor receptor is overexpression irregulation or alteration are experiential in the various types of epithelial type cancer such as non-small cell lung cancer (NSCLC), carcinoma of the breast, colon, *etc*., in the present research carry out molecular modeling study approaches on quinazolinone derivatives as EGFR Inhibitors with the put of 20 drug molecules will be taken to show the relationship of the structural parameters, a drug like properties by using molinspiration technique and further, molecular docking simulation was done and find the interaction of Ligands active position of EGFR, as well as computational study, was carried out which results in the prediction of pharmacokinetic & bioactivity properties. Moreover, the results of this work afford the information related to the imperative of structure-activity relationship and structural requirements for the interface of compounds at the active location of the receptor molecule and to make available and design of new target Analogue as Epidermal Growth factor receptor of tyrosine kinase inhibitors.

INTRODUCTION: However, growth of abnormal cell by epidermal growth factor receptor (EGFR) leads to epithelial malignancies, its movement increases the tumor growth, invasion, metastasis [1] include part of a family of ErbB TK receptors, category of transmembrane TK receptor which is accountable for the inflection of expansion facet signaling [2].

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In addition ErbB family of receptor tyrosine kinase consists of four receptors as ErbB-1 (EGFR), Erbb-2(HER 2), ErbB-3, ErbB-43,4) and also these are located in the cytoplasmic membrane, which is having hydrophobic transmembrane region as well as submission intracytoplasmic membrane TKs domain [5].

Dependent and independent of ligand with both of the mechanisms which take part into significant function in overexpression of EGFR receptor in the tumor. Though EGF family growth factor binds with receptor ErbB, activation takes place, and this expansion factor was formed through the identical cell and articulate the receptor of ErbB (autocrine

secretion) or through the nearest cell (paracrine secretion) [6, 7]. EGF Growth which is alienated, keeps on mainly three types:1. EGF as well as transforming growth factor α (TGF-α) and Amphiregulin (AR), which bind with the Epidermal growth factor 8 2.EPR-Epiregulin, growth factor of heparin (HB-EGF) and betacellulin (BTC) binds to ErbB-4 along with EGFR.3. NRGs- Neuregulins which is able to bifurcate to mainly two subgroups of NRG 1 and NRG 2: Subgroup of NRG 1 and NRG 2 which binds to ErbB-3. The Sub group of NRG 3 and NRG 4 binds to the ErbB-4 receptor [9-12]. A subgroup of NRG 3, NRG 4 it binds with the over the appearance of EGF receptor is reported during many cancerous type such as epithelial as well as head and neck tumors (100% cases), carcinoma of lungs (80% cases), Glioblastoma (50% cases), colon and breast cancer [13] consequently, EGFR have be glowing studied one of the receptors of anticancer molecule. Behind the detection of EGFR as a target molecule of cancer, numeral anticancer agents acting against the EGFR receptor have been urbanized. Namely erlotinib, gefitinib, afatinib, brigatinib, vandetanib, neratinib, Lapatinib, osimertinib, icotinib *etc*, [14-20].

The approved Drugs of EGFR inhibitor present in **Fig. 1**. apart from this monoclonal antibody inhibitors like nimotuzumab, matuzumab, panitumumab, *etc.*,. be also developed [21-23]. Although the innovation progress of a number of large EGFR inhibitors, at rest inherent or acquired battles were observed in the malignancy patients who are treated in the midst of EGFR battered drugs [24]. Therefore, in attendance be a stable necessitate for the finding of original inhibitors embattled to the EGF receptor. The crystal structure of EGFR is enclosed and presented. Consequently, the drug design structure-based that is molecular docking in addition to ligand-based that is QSAR and also Pharmacophore model are potential for detection of new-fangled EGFR inhibitors. In the present reading, we comprise carry out the molecular docking and computational method for the discovery of structural obligation and association of structural constraint among its biological bustle in that order. The particular, efficient EGFR inhibitors were present in the literature [25]. In addition, ADME and the molecular belongings prediction of the selected quinazolin -4-one moiety were reported.

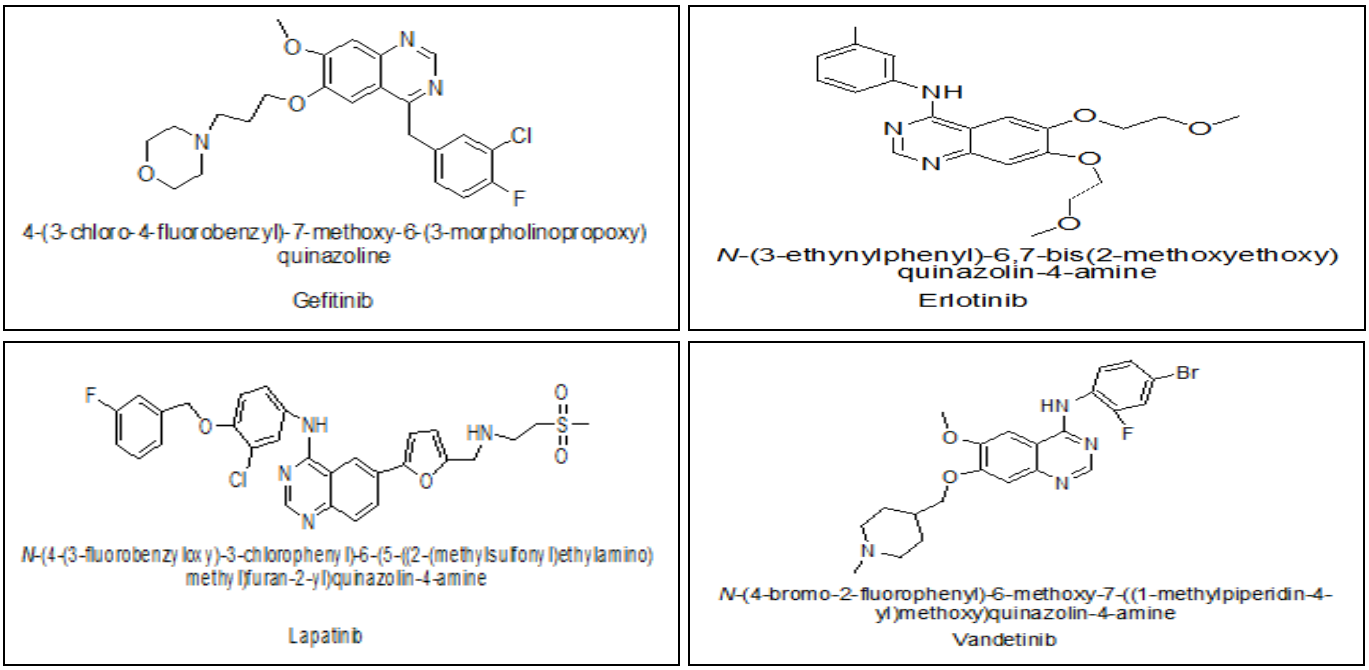


FIG: 1. CHEMICAL STRUCTURE & NAME OF APPROVED EGFR RECEPTOR INHIBITORS

Molecular Docking: Molecular docking models, the lock and key theory (in 1890) Emil Fischer introduced a model known as "lock and key model" so as to elucidate how biological systems work. A substratum slides in the active position of a macromolecule for the reason that a key is well surrounded into padlock [26]. The induced-fit theory: The induced match hypothesis, developed by

Daniel koshland at 1958 .the fundamental idea is with the aim of both the ligand and the target which can act in response to each other minor conformation shifts, awaiting an optimum fit in the appreciation cycle is reached, Also both the ligand, target will gradually change to each other via minor confirmation change awaiting most select fit is reached in the detection process.

Rigid Docking: In this docking, if we regard the molecules to be stable, we appear at a 3D space transformation of one of the molecules at that moment which will build them optimally appropriate to the other molecules in expressions of the scoring function. Confirmation of ligand might occur in the absence of a receiver or in the presence of a binding receptor.

Flexible docking: away from transformation, we look upon molecular versatility as our objective of ruling receptor and ligand molecule confirmations. In attendance, three main approaches for an investigation of molecular docking depend on ligand, receptor stability, and stiffness [27, 28].

Rigid Ligand and Receptor Docking: Both ligand as well as the receptor is a rigid body and offer minimal docking space by means of only three transitional degree of liberty within the ligand receptor composite surrounded by three rotations.

Flexible ligand and inflexible receptor docking: This is a habitually used docking progression; the ligand must connect with a more conformation–shifting unbending receptor.

Flexible Ligand and Receptor: In the region of docking, versatile receptors pose a foremost challenge. Furthermore, the essential needs for molecular docking, ligand Molecular Docking and ligand docking move towards require components of a target protein structure, exciting molecules or a database include available components of a target protein structure, Computer docking molecules and a computational mechanism which helps to and a computational mechanism that helps to be relevant the essential docking as well as scoring procedures.

The majority of docking algorithms assume the protein is rigid; usually, ligand is known as flexible. The binding of protein–binding pockets should be in use of the report in relation to the conformational degree of freedom. Docking can achieve by dense molecules or fragments into protein energetic sites by approaches different poses such as clique-searching, geometric hashing and clustering posing.

MATERIALS AND METHODS:

Molecular Docking Study: Auto Dock is a series of computerized docking tools intended to establish how the small molecules unite surrounded in target macromolecules of well-known 3D-structure. Auto Dock vina used to recognize the binding mode of proposed and selected molecules of quinazolin-4-one derivatives which are responsible for activity to identify the binding energies of those analogs in the active sites. Additionally, the site of ligand within the enzyme binding location can be sight by biovia discovery studio visualizer, which can be useful for mounting efficient and potential drug molecules for important binding nature. Selected compounds were afforded for prediction of anticancer activity on Transferase EGFR TKs (1M17) through molecular docking study [29, 30].

Software Required: In addition, Molecular graphics laboratory tools, Auto Dock vina PyRx virtual screening tool were downloaded in www. scrpps.edu, ChemDraw ultra 8.0 were used as well as biovia Discovery studio visualizer was downloaded from https://www.3dsbiovia.com/ biovia-discovery. The Mol file of Ligand to PDB format translation was carried out by Chem 3D Pro 8.0; in addition, protein to PDB format translations were done by using a Molecular operating environment (MOE).

Methodology: Nowaday, in understanding the structure-activity relationship, binding energy, the interaction between the ligand and protein, binding affinity as well as other molecular properties, the Computer-Aided drug design is one of the tools acting a crucial responsibility. On this program, Auto dock was widely used in evaluating the binding studies of our selected molecules on the embattled enzyme. The binding energy of the proposed analogs (QSD1-QSD20) on the crystal composition of EGFR TKs PDB ID: 1M17 was acquired in a protein data bank (http://www.rcsb. org/pdp) place at Brookhaven National Laboratory in 1971.

Preparation of Protein: The crystal structure 3D of EGFR-TKs (PDB code: 1M17) was retrieved on the RSCB protein data bank. Docking preparation tool of the molecular operating environment (MOE) used to organize enzyme for docking, and python prescription (PyRx) 0.8 were second-hand to maintain protein molecule in pdbqt build up contain hydrogen atoms at every polar residue.

Ligand Preparation: The Ligands 2D structures were equipped by chembiodraw (Cambridge, MA, USA).and converted into relevant 3D structures in open Babel of Pyrx0.8.

Validation of Docking: In Ligand, active location of the crystal structure of EGFR TKs detached from the (MOE) molecular operating environment for ligand were redocked, alignment among docked ligand in the crystal structure by means of biovia studio viewer.

Receptor Grid Generation: Here, the Receptor Lattice creation has need of an "outfitted" structure, every atom structure in proper bond array as well as proper charge. Auto Dock searches bear the binding interactions by means of one if not more ligand and also receptor fragment, typically a protein contour and property of the receptor is represented resting on grid by a plentiful, diverse set of a field which offers a more and more precise score of the ligand pose and option inside all label of the Receptor lattice building pane authorize necessary receptor makeup by limited of some co-crystallized ligand which possibly will be present, confirm location, dimension of the energetic spot will be represent by means of receptor grid, display Auto Dock constriction, A grid area were prepared at the region of binding location of the receptor.

Docking Analysis: Docking study be performed by PyRx auto dock vina. The results are measured in expressions free of binding energy mode and value of higher binding energy resultant the RMSD value zero to be consider as binding affinity interaction of Ligand, pose dock analysis done by biovia discovery studio visualizer.

The prepared crystal structures of ligand, the active site of various enzymes such as crystal structure of [PDB ID: 1M17] were subjected to Auto dock Vina for measuring binding energies. The grid box was set at approx. above 90 90 90, genetic algorithm (GA) in default setting was engaged for the studies. In investigating parameters; the quantity of runs and the other setting were left as default. The result of docked study measurements seen in output was at word format. Location, the orientation of Ligands at protein receptor, interaction in amino acids which bounce to ligand was identified, visualize in Auto Dock tool. Throughout the docking process, the top ten conformations were replicated for each of the compounds after the minimization of the energy. The binding energy of all the Ligands against EGFR-TKs macromolecule prediction done by using auto dock vina, one of the most generally used docking software in docking process, eight binding poses be produced, the binding pose with highest binding energy resultant in the RMSD value of zero measured as the binding affinity of ligand.

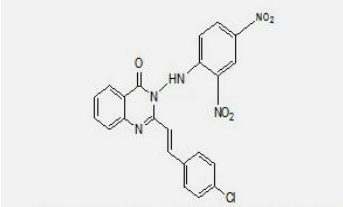
Among all the proposed analogs such as QSD16 & QSD20 (-8.9 kcal/mol) exist the highest binding energy and remaining compounds of quinazolinones; however, produced better binding energy than the 5 fluoro Uracil, which is used as reference drug I binding score (-4.5kcal/mol)& almost related affinity when compared to Gefitinib which is used as a reference drug 2 binding score (-9.1kcal/mol.) Almost all the compounds showed an excellent binding score (-6.8 to -8.9 kcal/mol) selected quinazolin-4-(3H)-ones. The amino acid residue interacting with elected quinazolin4 (3H)-one derivative and all molecules showed hydrogen bond interactions, many having Vander walls attraction in different amino acid residue at the binding site. In universal, the proposed compounds were found to include almost equal binding affinity to Gefitinib this is because of an increased number of hydrogen bonds, Vanderwall attraction at the amino acids of the binding site. The most active molecule has hydrogen bond interactions in excess of the enzyme even though pialkyl interactions, also pi-sigma interactions were identified.

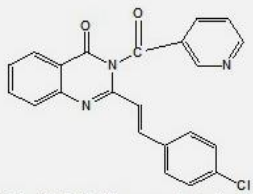
ADME Properties Prediction: Even though this analysis, A computational method in the purpose of ADME properties of selected molecules were functionalized as well as absorption percentage designed by Topological polar surface area. Among all the parameters which could exist experimentally, all the elected and proposed molecules having a better range of % ABS exclude

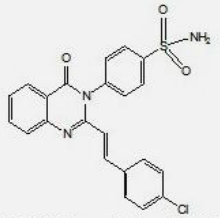
few molecules. The entire parameter deliberate with molinspiration toolkit, the outcome located at **Table 2**. The percentage of absorption quantified by % ABS = 109-(0.345×TPSA) [20].

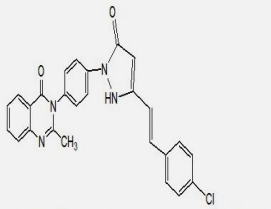
Bioactivity Prediction: Although this investigation, for the strength of mind of bioactivity properties of proposed analogs were done in the each and every one calculated parameter, which is able to experimental that all selected and proposed derivatives compared with reference drugs (1&2) Showed less affinity with G- coupled receptor kinase inhibitor, protease inhibitor, nuclear receptor ligand, as well as ion channel modulator, enzyme inhibitor, in addition, the toxicological proportional study of every selected derivative into the reference drugs.

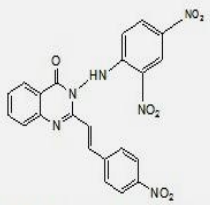
TABLE 1: LIST OF PROPOSED MOLECULE OF QUINAZOLIN-4-ONE DERIVATIVES

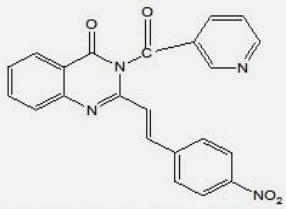

QSD1:-(*E*)-2-(4-chlorostyryl)-3-(2,4-dinitrophenylamino) quinazolin-4(3*H*)-one

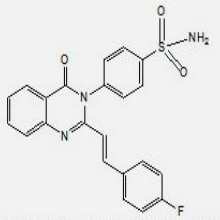

QSD6:-(*E*)-2-(4-chlorostyryl)-3-nicotinoyl quinazolin-4(3*H*)-one

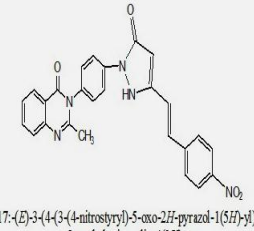

QSD11:-(*E*)-4-(2-(4-chlorostyryl)-4-oxoquinazolin-3(4*H*)-yl) benzenesulfonamide

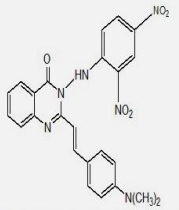

QSD16:-(*E*)-3-(4-(3-(4-chlorostyryl)-5-oxo-2*H*-pyrazol-1(5*H*)-yl)phenyl) -2-methylquinazolin-4(3*H*)-one

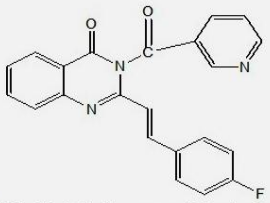

QSD2:-(*E*)-2-(4-nitrostyryl)-3-(2,4-dinitrophenylamino) quinazolin-4(3*H*)-one

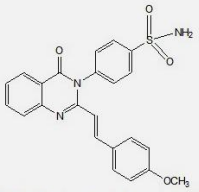

QSD7:-(*E*)-2-(4-nitrostyryl)-3-nicotinoyl quinazolin-4(3*H*)-one

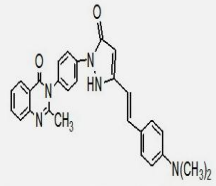

QSD12:-(*E*)-4-(2-(4-fluorostyryl)-4-oxoquinazolin-3(4*H*)-yl) benzenesulfonamide

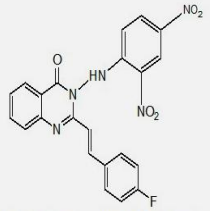

QSD17:-(*E*)-3-(4-(3-(4-nitrostyryl)-5-oxo-2*H*-pyrazol-1(5*H*)-yl)phenyl) -2-methylquinazolin-4(3*H*)-one

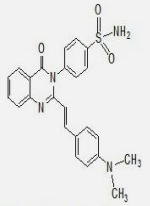

QSD3:-(*E*)-2-(4-(dimethylamino)styryl)-3-(2,4-dinitrophenylamino) quinazolin-4(3*H*)-one

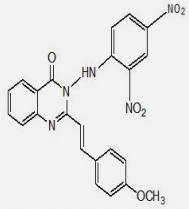

QSD8:-(*E*)-2-(4-fluorostyryl)-3-nicotinoyl quinazolin-4(3*H*)-one

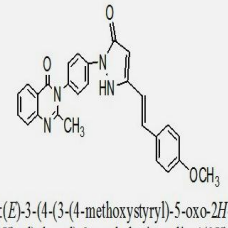

QSD13:-(*E*)-4-(2-(4-methoxystyryl)-4-oxoquinazolin-3(4*H*)-yl) benzenesulfonamide

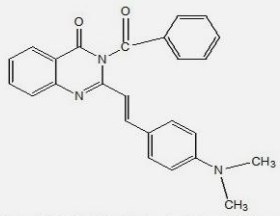

QSD18:-(*E*)-3-(4-(3-(4-(dimethylamino)styryl)-5-oxo-2*H*-pyrazol-1(5*H*)-yl)phenyl)-2-methylquinazolin-4(3*H*)-one

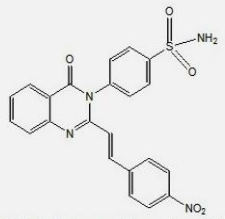

QSD4:-(*E*)-2-(4-fluorostyryl)-3-(2,4-dinitrophenylamino) quinazolin-4(3*H*)-one

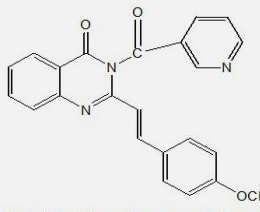

QSD9:-(*E*)-4-(2-(4-(dimethylamino)styryl)-4-oxoquinazolin-3(4*H*)-yl) benzenesulfonamide


QSD14:-(*E*)-2-(4-methoxystyryl)-3-(2,4-dinitrophenylamino) quinazolin-4(3*H*)-one


QSD19:(*E*)-3-(4-(3-(4-methoxystyryl)-5-oxo-2*H*-pyrazol-1(5*H*)-yl)phenyl)-2-methylquinazolin-4(3*H*)-one


QSD5:-(*E*)-2-(4-(dimethylamino)styryl)-3-benzoyl quinazolin-4(3*H*)-one


QSD10:-(*E*)-4-(2-(4-nitrostyryl)-4-oxoquinazolin-3(4*H*)-yl) benzenesulfonamide


QSD15:-(*E*)-2-(4-methoxystyryl)-3-nicotinoyl quinazolin-4(3*H*)-one

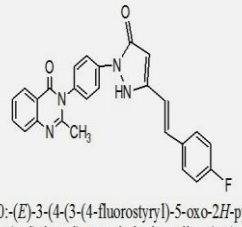

QSD20:-(*E*)-3-(4-(3-(4-fluorostyryl)-5-oxo-2*H*-pyrazol-1(5*H*)-yl)phenyl)-2-methylquinazolin-4(3*H*)-one

TABLE 2: ADME PROPERTIES OF PROPOSED COMPOUNDS WITH REFERENCE DRUGS

C. code	M Log P	TPSA	n atoms	H. acceptor(n-ON	H-donor	n violations	n. rotb	MV	MW	%ABS(%)f absorption)
QSD1	5.52	138.57	33	10	1	1	6	371.07	463.84	61.19
QSD2	4.86	184.40	35	13	1	1	7	380.87	474.39	45.38
QSD3	4.94	141.81	35	11	1	1	7	403.44	472.46	60.08
QSD4	5.00	138.57	33	10	1	1	6	362.46	447.38	61.19
QSD5	3.87	68.10	30	6	0	0	4	359.20	396.45	85.50
QSD6	4.45	64.86	28	5	0	0	3	326.83	387.83	86.62
QSD7	2.90	64.86	28	5	0	0	3	322.98	352.37	86.62
QSD8	3.94	64.86	28	5	0	0	3	318.22	371.37	86.62
QSD9	3.61	98.30	32	7	2	0	5	387.09	446.53	75.09
QSD10	3.46	140.89	32	9	2	0	5	364.52	448.46	60.39
QSD11	4.18	95.06	30	6	2	0	4	354.72	437.91	76.20
QSD12	3.67	95.06	30	6	2	0	4	346.12	421.45	76.20
QSD13	3.56	104.30	31	7	2	0	5	366.73	433.49	73.02
QSD14	4.89	147.81	34	11	1	1	7	383.08	459.42	58.00
QSD15	3.83	74.09	29	6	0	0	4	338.84	383.41	83.44
QSD16	4.88	72.69	33	6	1	0	4	389.31	454.92	83.92
QSD17	4.16	118.52	35	9	1	0	5	399.10	465.47	68.11
QSD18	4.30	75.93	35	7	1	0	5	421.68	463.54	82.80
QSD19	4.26	81.93	34	7	1	0	5	401.31	450.50	80.73
QSD20	4.37	72.69	33	6	1	0	4	380.70	438.46	83.92
Ref1(FU)	-0.59	65.72	9	4	2	0	0	96.91	130.08	86.33
Ref2 (GB)	4.19	68.75	31	7	1	0	8	385.07	446.91	85.28

TABLE 3: BIOACTIVITY SCORE OF PROPOSED MOLECULE WITH REFERENCE DRUG

C. code	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
QSD1	-0.14	-0.23	-0.21	-0.45	-0.53	-0.16
QSD2	-0.13	-0.23	-0.19	-0.41	-0.47	-0.13
QSD3	-0.12	-0.24	-0.17	-0.39	-0.49	-0.13
QSD4	-0.13	-0.24	-0.18	-0.42	-0.52	-0.15
QSD5	0.05	-0.16	0.10	-0.15	-0.26	0.05
QSD6	0.06	-0.15	0.06	-0.19	-0.29	0.05
QSD7	0.06	-0.14	0.08	-0.17	-0.25	0.08
QSD8	0.06	-0.16	0.11	-0.15	-0.27	0.07
QSD9	-0.08	-0.04	-0.13	-0.42	-0.20	-0.05
QSD10	-0.20	-0.07	-0.27	-0.51	-0.29	-0.12
QSD11	-0.08	-0.03	-0.18	-0.47	-0.22	-0.06
QSD12	-0.07	-0.03	-0.13	-0.44	-0.20	-0.04
QSD13	-0.12	-0.08	-0.19	-0.45	-0.23	-0.07
QSD14	-0.17	-0.28	-0.22	-0.43	-0.53	-0.17
QSD15	0.01	-0.21	0.04	-0.17	-0.29	0.04
QSD16	-0.12	-0.20	-0.20	-0.34	-0.32	-0.24
QSD17	-0.22	-0.24	-0.29	-0.39	-0.39	-0.29
QSD18	-0.11	-0.21	-0.16	-0.31	-0.30	-0.22
QSD19	-0.14	-0.24	-0.21	-0.33	-0.33	-0.24
QSD20	-0.11	-0.20	-0.17	-0.31	-0.31	-0.23
Ref1(FU)	-2.60	-1.95	-2.62	-3.04	-3.15	-1.56
Ref2 (GB)	0.12	-0.04	0.66	-0.21	-0.30	-0.03

TABLE 4: PHYSIOCHEMICAL PROPERTIES OF PROPOSED COMPOUNDS

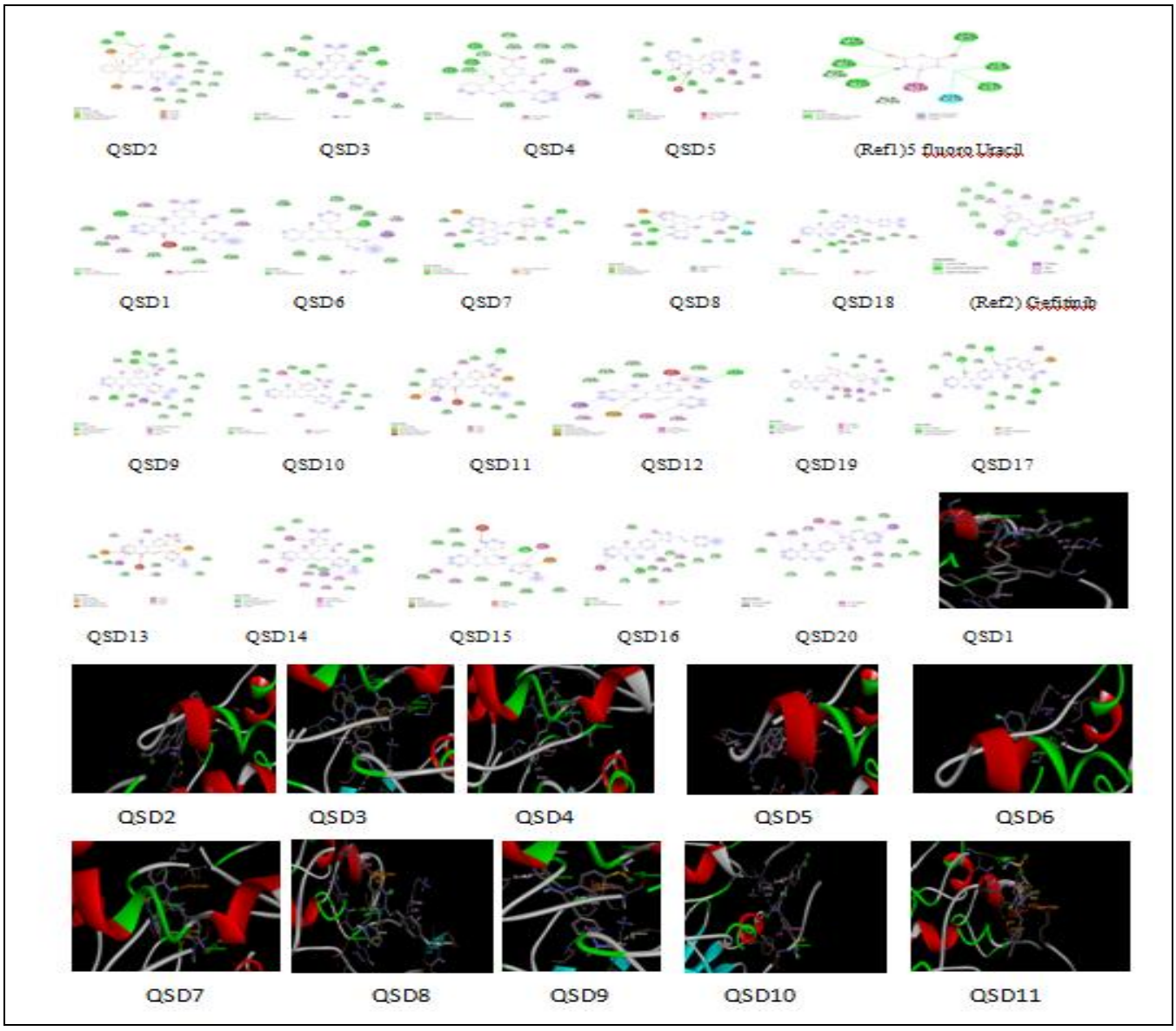
Code	Molecular formula	Binding affinity	Elemental analysis				
			C	H	N	O	X
QSD1	$C_{22}H_{14}ClO_5N_5$	-7.1	56.97	3.04	15.10	17.25	7.64
QSD2	$C_{22}H_{14}N_6O_7$	-7.1	55.70	2.97	17.72	23.61	---
QSD3	$C_{24}H_{20}N_6O_5$	-8.7	61.01	4.27	17.79	16.93	---
QSD4	$C_{22}H_{14}FN_5O_5$	-8.7	59.06	3.15	15.65	17.88	4.25

QSD5	$C_{25}H_{21}N_3O_2$	-7.0	75.93	5.35	10.63	8.09	---
QSD6	$C_{22}H_{14}ClN_3O_2$	-7.0	68.13	3.64	10.83	8.25	9.14
QSD7	$C_{22}H_{14}N_4O_4$	-8.7	66.33	3.54	14.06	16.06	
QSD8	$C_{22}H_{14}FN_3O_2$	-7.4	71.15	3.80	11.32	8.62	5.12
QSD9	$C_{24}H_{22}N_4O_3S$	-8.6	64.56	4.97	12.55	10.75	7.18
QSD10	$C_{22}H_{16}N_4O_5S$	-6.8	58.92	3.60	12.49	17.84	7.15
QSD11	$C_{22}H_{16}ClN_3O_3S$	-7.2	60.34	3.68	9.60	10.96	8.10
QSD12	$C_{22}H_{16}$ FN_3O_3S	-7.1	62.70	3.83	9.97	11.39	4.51
QSD13	$C_{23}H_{19}N_3O_4S$	-7.1	63.73	4.42	9.69	14.76	7.40
QSD14	$C_{23}H_{17}N_5O_6$	-8.7	60.13	3.73	15.24	20.90	---
QSD15	$C_{23}H_{17}N_3O_3$	-7.7	72.05	4.47	10.96	12.52	---
QSD16	$C_{26}H_{19}ClN_4O_2$	-8.9	68.65	4.21	7.79	12.32	7.03
QSD17	$C_{26}H_{19}N_5O_4$	-7.8	67.09	4.11	15.05	13.75	---
QSD18	$C_{28}H_{25}N_5O_2$	-8.7	72.55	5.44	15.11	6.90	---
QSD19	$C_{27}H_{22}N_4O_3$	-8.5	71.99	4.92	12.44	10.65	---
QSD20	$C_{26}H_{19}FN_4O_2$	-8.9	71.22	4.37	12.78	7.30	4.33
Ref1(FU)	---------	-4.5					
Ref2 (GB)	---------	-9.1					

TABLE 5: DOCKING RESULTS WITH VARIOUS INTERACTIONS OF PROPOSED COMPOUNDS ON 1M17 TRANSFERASE

Code	Vander Waals	H.bond	Pi -alkyl	Pi-sigma
QSD1	GLUA:844,805,860,HISA:864,LYSA:936, GLNA:870,SERA:871	ASP A:932	LYSA:843,HISA:869 , ILEA:866,ALA A:931	---
QSD2	SER A:888,ILE A:914,894, PROA:890,910,912,913,LEU A:909,TRP A:881,LYS A:889	TYRA:891,ASPA:89 2,GLY A:893	---	THR A:885
QSD3	LYSA:851,ASPA:813,META:769,742,GLN A:767,CYSA:751,ALAA:719,THRA:766,830,GL U A:738,LEU A:764	ARG A:817,ASN A:818,GLY A:833,LEU A:834	LEU A:820, LYS A:721,	VAL A:702,
QSD4	ASP A:813,831,GLU A:734,738,GLY A:833,ILE A:735,LEU A:834,LYS A:721	LYSA:851,ASN A:818,ARG A:817	LEU A:820,VAL A:702	---
QSD5	PRO A:890,910,SER A:888,ILE A:894,GLU A:907	GLY A:893,TYR A:891,ASP A:892	PRO A:912,913	---
QSD6	PRO A:890,910,LEU A:909,SER A:888,ASP A:892,GLY A:893,GLU A:907	TYR A:891	ILE A:902	ILE A:894
QSD7	LEU A:834,GLU A:738,LYS A:721,PHE A:699,ASP A:831,ARG A:817,TRP A:856	ASN A:818,GLY A:833	PRO A:853	---
QSD8	GLU A:841,842,LEU A:838,ARG A:808,LYS A:936,THR A:868	GLN A:870,HIS A:869,GLU A:805	LYSA:843,ALA A:931.	---
QSD9	PHE A:699,LEU A:820,764,834,THR A:766,830,MET A:742,769,ALA A:719,GLN A:767,GLU A:738,ASN A:818,HIS A:817	ASP A:813,831,ARG A:817	CYS A:773,LYS A:721	VAL A:702
QSD10	PRO A:675,ARG A:807,SER A:744,VAL A:741,ASP A:737,LYS A:733,ALA A:840,GLU A:673,GLY A:839,LEU A:838	ASN A:676	LYS A:836,LEU A:837	
QSD11	LYS A:843,936,HIS A:864,869,GLU A:805,860,SER A:871,GLN A:870	ASP A:930	ALA A:931	ILE A:866
QSD12	ASP A:930,932,GLU A:860,SER A:871,GLN A:870	ILE A:929	LYS A:843,ILE A:866	THR A:868
QSD13	LYS A:843,936,HIS A:864,869,GLU A:805,860,SER A:871,GLN A:870		HIS A:869	ALA A:931,IL E A:866
QSD14	ASP A:813,831,LEU A:820,834,THR A:830,MET A:769	THR A:766	LEU A:753,764,LYS A:721,MET A:742,CYS A:773	VAL A:702
QSD15	GLY A:695,772,SER A:696,LEU A:820,ARG A:817,ASN A:818,ASP A:813	CYS A:773	VAL A:702,LEU A:694	---
QSD16	GLY A:695,772,ASN A:818,LYS A:721,ARG	ASP A:831	LEU A:694,820	---

	A:817,CYS A:773,PRO A:770,PHE A:771			
QSD17	ARG A:962,HIS A:781,PHE A:771,TYR A:789,ILE A:785,GLU A:780,980,LEU A:977,MET A:978	TYR A:777,ASP A:783,979	MET A:963,PROA:824	---
QSD18	GLY A:695,772,ASN A:818,ARG A:817,LYS A:721,CYS A:773,PRO A:770,GLU A:780	ASP A:831	LEU A:694,820,VAL A:702,HIS A:781	---
QSD19	TRP A:856,ASP A:831,THR A:830,MET A:769,CYS A:773	THR A:766	ARG A: 817, PRO A: 853, LEU A: 820, 764, 753, LYSA:721.	VAL A:702
QSD20	ASP A:776,831,MET A:742,769,LEU A:753,775,TRP A:856,THR A:766,GLU A:738	---	CYS A:773,751,LYS A:721,889,VAL A:702,ARG A:817,LEU A:820	THR A:830
REF1	ASPA:746,ALAA:743	TYRA:803,ARCA:807,ALAA:678,GLNA:677,VALA:745	---	---
REF2	GLNA:767,LEUA:753,THRA:766,ALA A:719,GLUA:738,CYSA:751,THRA:830,GLYA:697, SERA:696,LEUA:694,GLYA:695,META:769,GLYA:772,PHEA:699	ASPA:831	LYSA:721 METAA:742 LEUA:764	VAL A:702



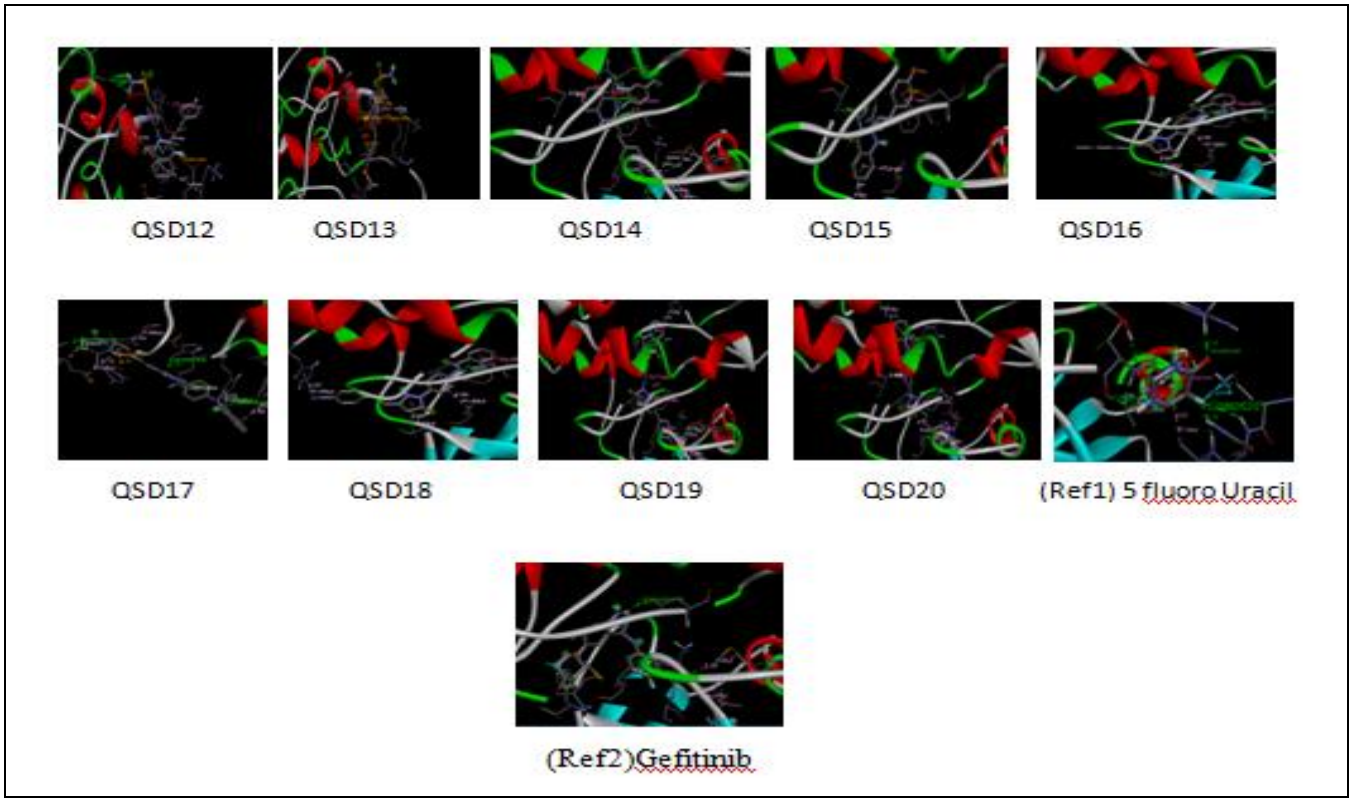


FIG. 2: 2D & 3D STEREO VIEW OF COMPOUND QSD1 TO QSD20 ON ENZYME IMI7 TKS

RESULTS AND DISCUSSION: The docking poses were obtained according to their docking parameters and their corresponding binding pockets. These evaluations should be helpful for understanding the binding interactions over the targeted enzyme. Molecular docking studies of quinazoline- 4- one derivative be carried away and in addition, docked binding scores of proposed derivatives resulting within the value of -6.8 -8.9 kcal/mol which showed at table -4.

Each and every one of the selected molecules be established towards powerfully restrain the EGFR TKs Transferase as a result of fully the proficient location into intention protein, the outcome of docking investigation be showed to every one of the docked molecules encompass lower energy value (high binding energy value) compared towards the reference 1 drug as Fluorouracil & reference 2 drugs as gefitinib with it binding energy value of -4.5 kcal/mol & -9.1 kcal/mol.

Moreover the various interaction value of QSD1 to QSD20 & REF Drugs which showed at **Table 4** and **Fig. 2**. Illustrate the most excellent low binding energy (high binding energy values) for the docked compounds. Along with 20 Ligands so as to be docked by the enzyme EGFR TKs, the substituted chlorine & fluorine group with pyrazolone moiety of ligand QSD16 & QSD20 showed the majority effective in the midst of a high binding score of -8.9kcal/mol. The substituted ligand methyl group exhibits the best-docked score of -8.7 & methoxy group of pyrazolone ligand score of -8.5 kcal/mol while the ligand QSD17 -7.8 kcal/mol with 68% ABS based on the ligand (QSD16-QSD20) no violation exhibits drug-likeness properties.

Further, the substituted electron-donating methyl group with sulphonamide moiety of ligand QSD9 the best-docked score of -8.6 kcal/mol while substituted electron-donating methoxy group with sulphonamide ligand QSD13 -7.1 kcal/mol and ligand sulphoamide moiety with Electron withdrawing group QSD10, QSD11 & QSD12 with docked score of -6.8 kcal/mol, 7.2 kcal/mol, 7.1 kcal/mol respectively with no violation and possess drug-likeness properties.

Moreover, the substituted electron-withdrawing nitro group include nictinamide moiety of ligand QSD7 with best-docked score -8.7 kcal/mol while other electro donating methoxy group contains nictinamide moiety QSD15 with docked score of -7.7 kcal/mol and others were QSD5, QSD6 & QSD8 having binding score of -7.0 kcal/mol &-7.4

kcal/mol with no violations, present in drug likeness properties. Therefore, the docked among 20 quinazolin-4-one with 2,4 dinitro phenyl hydrazine moiety of ligand QSD1-QSD4 & QSD14 with violations and binding score of -7.1 kcal/mol, 8.7 kcal/mol & 7.7 kcal/mol, which possess (45-61) %ABS Properties. Accordingly, the proposed different 2 substituted sulphonamide, nictinamide and pyrazolone moiety of quinazolin-4-one when compared with reference drugs fluorouracil, gefitinib (1&2) possess good binding interaction & good ADME with drug-likeness properties. The docked ligand configuration display Hydrogen bond and electrostatic interaction, Pi alkyl & Pi sigma interactions present in **Table 5**. These interactions indicated that Ligands bind deep in the core of the active site where the reference ligand binds.

CONCLUSION: In the present work, include and preferred compound quinazolin -4- one followed by exploring EGFR TKs binding interaction by docking study using PDB ID: 1M17. A number of quinazolin-4- one with a better range of binding score were detected. *In-silico* study data shows the most potent with the high docking score of -8.9 kcal/mol. Depending upon the docking scores of the compound were selected and further study moreover this research suggests with the purpose of the selected Compounds reveal the substantial action against EGFR TKs enzyme, which may be useful to develop better inhibitory quinazolin-4-one derivatives.

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