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Computer-Aid Design of Novel Sulfonamide Derivatives as EGFR Kinase Inhibitors for Cancer Treatment

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Abstract

Several novel sulfonamide-derivatives were designed and studied their physicochemical properties to develop novel kinase inhibitors. Therefore, molecular docking was performed for the designed compounds against epidermal growth factor receptor (PDB ID: 2ITY) to identify new drug candidates for treating cancer. Binding free energy was calculated by Molegro virtual docker (MVD) to select the most promising hits. The corresponding docking score values into EGFR of 4b gave the best energy docking −128.819 Kcal/mol. The identified hits can serve as starting points for further chemical synthesis and optimization to develop new potent anticancer agents.

Keywords

Sulfonamide, Anticancer, EGFR, 2ITY, Kinases, Molecular Docking, Molegro Virtual Docker, MVD, MarvinSketch

1. Introduction

Cancer is a worldwide health problem and the most deadly disease in humans [1], and it is considered the second leading cause of mortality after cardiovascular diseases [2]. Various conditions and factors can turn normal cells into cancer cells by altering the normal function of a wide spectrum of apoptotic, and signal transduction pathways. This is called loss of differentiation [3]. There are several methods for treating cancer such as Surgery, Chemotherapy, Hormonal therapy, Immunotherapy [3] [4], and Phototherapy [5].

Kinase enzymes are motivated the transfer of phosphate groups from ATPs to

certain substrates, a process is called phosphorylation. Kinases are part of the phosphotransferases family which is a subclass of transferases. Kinases are used widely to control complex processes and transfer signals in cells. Protein kinases have a role in most of the signal transduction in eukaryotic cells and control many other cellular processes, including cytoskeletal rearrangement, transcription, cell cycle progression, metabolism, cell movement, apoptosis, and differentiation [6].

One of the kinase families is Protein tyrosine kinases (PTKs) that are known to be activated in cancer cells and to drive tumor growth, progression, angiogenesis, and metastasis. PTKs are involved in the transfer of phosphate in ATP to tyrosine residues on protein substrates, which is known as tyrosine phosphorylation [6]. Several TKs play essential roles in growth, cell proliferation, signaling, differentiation, survival, metabolism, and apoptosis [7] [8]. Epidermal growth factor receptor (EGFR) is a member of the tyrosine kinase family and is usually overexpressed in several types of cancer, such as non-small-cell lung cancer (NSCLC), breast, esophageal, head, cervical, and neck cancer [9] [10]. In NSCLC, studies have demonstrated that the EGFR is overexpressed in 40% to 80% of cases, depending on histology [11]. Also, mutations in epidermal growth factor receptor have been discovered in association with some lung cancers [12].

Kinase inhibitors can be classified into three classes depending on their binding mode: type I inhibitors are ATP-competitive compounds targeting the ATP binding site in the active form of a kinase, type II inhibitors are ATP-competitive compounds that also target the ATP binding site but in the inactive form of a kinase, and type III inhibitors are allosteric inhibitors that are not ATP-competitive since they bind to binding sites far from the ATP binding site [13].

EGFR-TK inhibitors are the second most main drug targets that have been approved for the therapy of non-small cell lung cancer, and this catalyzed inhibition of EGFR signaling may not only be active in anti-proliferative effects and have also been increased sensitivity to cytotoxic therapies [14]. Therefore, blocking tyrosine kinase activity represents a rational approach to cancer therapy [7].

Among the broad range of compounds tested as potential anticancer agents, derivatives of sulfamide have attracted reasonable attention [15]. Sulfonamide derivatives include an important class of drugs with different biological activities [16], and many of them are widely used in therapy as antihypertensive, antibacterial, anti-inflammatory, anti-thyroid [17] [18], and hypoglycemic [19], diuretic and receptor tyrosine kinase inhibitors [1]. Recently, a host of structurally novel sulfonamide derivatives have been reported to show anticancer activity *in vivo* and/or *in vitro* [20] [21].

Molecular docking is in silico structure-based method vastly used in drug discovery. Docking enables the identification of new compounds of therapeutic benefit, delineating structure-activity relationships (SAR), or predicting ligand-target interactions at a molecular scale, without previous information about the chemical structure of other target modulators [22] [23]. The docking

process includes two steps: prediction of the ligand conformation moreover its position and orientation within these sites (usually called as pose) and estimate the binding affinity [24]. The lock-and-key theory suggested by Fischer, which be the early explanation for the ligand-receptor binding mechanism, where the ligand suits the receptor-like lock and key.

The current study aims to design novel sulfonamide derivative EGFR inhibitors using computational drug design approaches. The identified hits can serve as starting points for further chemical synthesis and optimization to develop new potent anticancer agents.

2. Materials and Methods

Protein Data Bank (PDB), PubMed and software's like Marvin sketch version 21.2, ChemSketch version 14.01, and Molegro Virtual Docker (MVD) version 2011.4.3 were implemented to within the current study.

2.1. EGFR Structure

The 3D crystal structure of EGFR (PDB ID: 2ITY) domain was retrieved from PDB and has a resolution of 3.42 Å. The kinase domain consists of 327 residues between 696 - 1022 residues. The resolved EGFR structure was co-crystallized as holoform with a known kinase inhibitor Iressa (**Figure 1**).

The EGFR was prepared by imported in MVD, then a list of residues is shown. All residues with potential errors are highlighted on the list and emphasized in the 3D view with red or yellow spheres pointing to the two different kinds of residue errors (such as missing atoms or incorrect bonds) and corrected in those cases where it had failed, and water molecules were removed from the crystal structure of the protein.
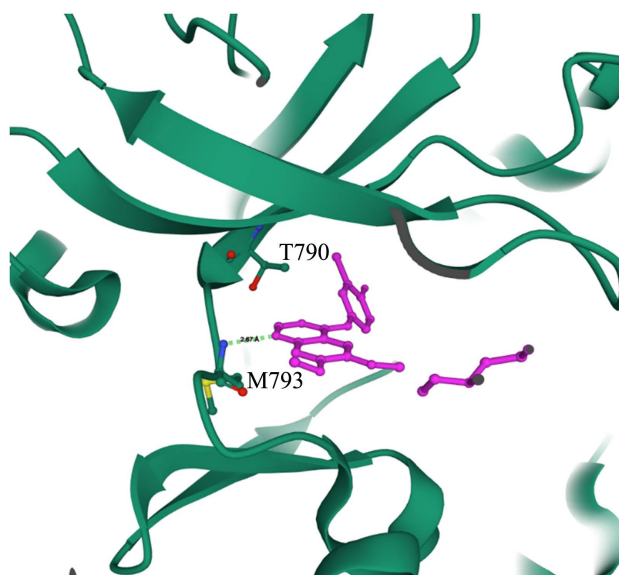

Figure 1. Co-crystal structure of the EGFR (PDB ID: 2ITY) kinase domain in complex with Iressa.

2.2. Define the Binding Pocket

The binding pocket was defined using the co-crystallized ligand as a center of the pocket, which had a volume of 241.664 Å, and fitted to the polar surface area for designed compounds, (Figure 2).

2.3. Compounds Preparation

Structures of designed compounds were drawn and optimized by using Marvin Sketch and saved as mol2. The preparation of compounds was performed using the default setting to assign bonds, assign bond orders and hybridization, create explicit hydrogens, assign charges (calculated by MVD), detect flexible torsions in ligands, and assign tripos atom types.

2.4. Molecular Docking

The Molecular Docking was performed in MVD. The following parameters were used for docking in the EGFR kinase (Figure 3).
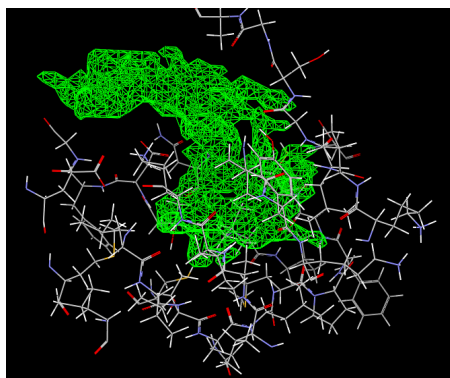

Figure 2. EGFR binding pocket (PDB ID: 2ITY) used to dock the designed compounds.
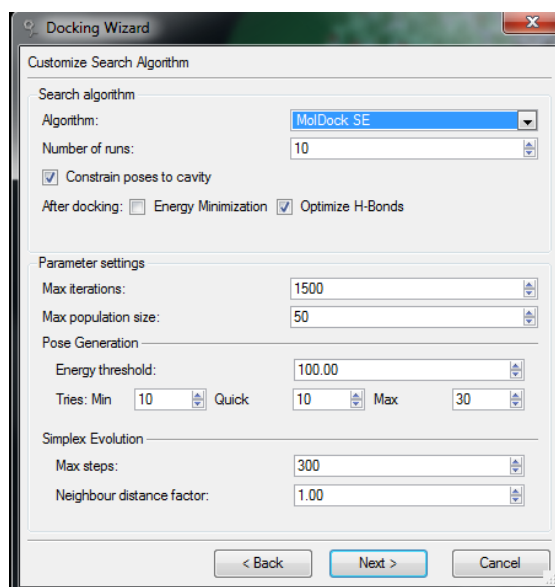

Figure 3. Parameters of Molegro Virtual Docker.

Plants score (GRID) function was used with a grid resolution of 0.30 Å and a binding site radius of 15 Å with respect to the origin of the respective cavities. The "MolDock SE" searching algorithm 10 runs using a maximum of 1500 iterations with a total population size of 50 was applied. The energy threshold used for the minimized final orientation is 100. The simplex evaluation with 300 maximum steps of neighbor distance factor 1 was completed. Docker uses the MolDock docking engine to predict ligand-protein interactions. MolDock is based on a new hybrid search algorithm called guided differential evolution [25].

The results of docking compounds with the receptors were compared with two standard compounds are shown in (**Figure 4**) that were synthesized by Ihmaid S and el, which the first standard compound

((*E*)-*N*-{*2*-[*2*-(*2,4-Dihydroxybenzylidene*)*hydrazine*-1-*carbonyl*]*phenyl*}*furan*-2-*carboxamide*), docked with EGFR receptor and had IC$_{50}$ value 85.4 ± 0.32 nM, and the second standard compound

(*N*-{*2*-[(*4-Sulfamoylphenyl*)*carbamoyl*]*phenyl*}*furan*-2-*carboxamide*), docked with tubulin receptor and had IC$_{50}$ value 31.2 ± 0.12 nM [26].

The PLANTS scoring function (PLANTS Score) used by MVD is derived from the PLANTS scoring function originally proposed by Korb *et al.*

The docking scoring function, $E_{plantsscore}$, is defined by the following energy terms:

$$E_{plantsscore} = f_{PLP} + f_{clash} + f_{tors} + c_{site} - 20$$

f_{PLP}: is a piecewise linear potential taking into account protein-ligand interactions.

f_{clash} and f_{tors} take into account internal ligand clashes and torsional contributions for the flexible bonds in the ligand.

The c_{site} term specifies a penalty that is calculated if a ligand conformation (pose) is located outside the binding site.

The −20 energy offset was originally needed for the PLANTS search algorithm and is included here in order for PLANTS scores to be comparable with the original PLANTS implementation.
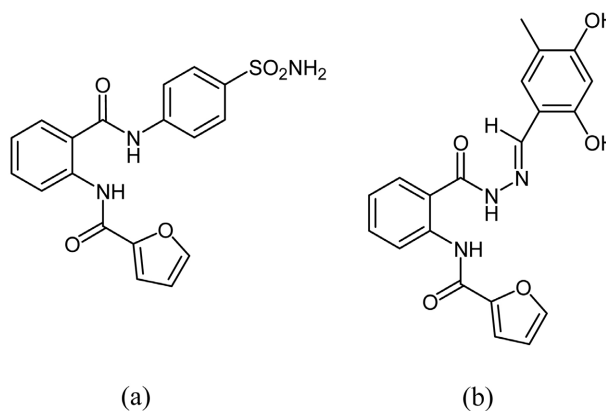

Figure 4. (a) Reference drug 1 structure, (b) reference drug 2 structure.

3. Result and Discussion

3.1. Sulfonamide Derivatives

The core scaffold of the sulfonamide shown in (Figure 5) was used to design several derivatives in the current study. Two modification sites were considered on the main scaffold represented by R_1 and R_2 (Table 1). Whereby the substituents of the R_1 were changed in order to study the role of the amine in binding with the receptor and containing aromatic rings with different substituents. As for the substituents of the R_2, the change of the aromatic ring associated with the amide group was studied.

3.2. Physicochemical Properties of Designed Sulfonamide Derivatives

The physicochemical properties were predicted using Marvin Sketch from chemical structures and placed in (Table 2). The Calculators and predictors in Marvin Sketch generate values for properties of a particular chemical structure. A calculation is something that generates a value for that structure (e.g. number or atoms, molecular weight) whereas a prediction generates an estimated value for a property that cannot be precisely determined, except by experimental methods (e.g. logP, pKa, solubility), though this distinction is often somewhat blurred. There are usually multiple ways to generate a prediction (e.g. different computer algorithms and/or different parameters) and different ways will generate different values.

Rule of five (ROF) is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule describes molecular properties important for a drug's absorption, distribution, metabolism and excretion in the human body [27]. Therefore, to analyze the drug-like characteristics, Lipinski's rule of five was considered, molecules were evaluation using Lipinski's rule of five was considered, which specifies that a probable drug molecule should have molecular weight $\leq$ 500, logP $\leq$ 5, polar surface area $\leq$ 140 Å, hydrogen bond acceptors $\leq$ 10, and donor $\leq$ 5 [28]. As the rule of five compliance ensures bioavailability, the designed library molecules were assumed to have better intestinal permeability. Several pharmacophores were proposed on the scaffold by introducing different function groups as hydrogen donors/acceptors. The lipophilicity of the compounds log P has a significant impact on the permeability of the cell membrane. The intermediate polar surface area (PSA) of compounds plays a role in cell internalization. Therefore,
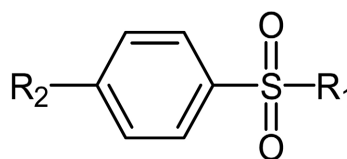
Figure 5. Scaffold of sulfonamide.

Table 1. R_1 and R_2 substitutions on sulfonamide scaffold considered in the study.

	R_2	R_1		R_2	R_1
1a	Ph–C(=O)–NH–	OH	5a	(C_4H_9)Ph–CH(CH$_3$)–C(=O)–NH–	OH
1b	Ph–C(=O)–NH–	5-methyl-3-(methylamino)isoxazole	5b	(C_4H_9)Ph–CH(CH$_3$)–C(=O)–NH–	5-methyl-3-(methylamino)isoxazole
1c	Ph–C(=O)–NH–	(HO)Ph–C(=O)–NH– → Ph–C(=O)–NH–	5c	(C_4H_9)Ph–CH(CH$_3$)–C(=O)–NH–	(C_4H_9)Ph–CH(CH$_3$)–C(=O)–NH–
2a	(HO)Ph–C(=O)–NH–	OH	6a	(C_2H_6)Ph–NH–Ph–C(=O)–NH–	OH
2b	(HO)Ph–C(=O)–NH–	5-methyl-3-(methylamino)isoxazole	6b	(C_2H_6)Ph–NH–Ph–C(=O)–NH–	5-methyl-3-(methylamino)isoxazole
2c	(HO)Ph–C(=O)–NH–	(HO)Ph–C(=O)–NH–	6c	(C_2H_6)Ph–NH–Ph–C(=O)–NH–	(C_2H_6)Ph–NH–Ph–C(=O)–NH–
3a	phthalimido–	OH	7a	Ph–C(=O)–NH–CH$_2$–C(=O)–NH–	OH
3b	phthalimido–	5-methyl-3-(methylamino)isoxazole	7b	Ph–C(=O)–NH–CH$_2$–C(=O)–NH–	5-methyl-3-(methylamino)isoxazole
3c	phthalimido–	phthalimido–	7c	Ph–C(=O)–NH–CH$_2$–C(=O)–NH–	Ph–C(=O)–NH–CH$_2$–C(=O)–NH–
3d	phthalimido–	NH$_2$			
4a	(Cl_2)Ph–NH–Ph–C(=O)–NH–	OH	8a	–NH–C(=O)–Ph–C(=O)–OCH$_3$	OH
4b	(Cl_2)Ph–NH–Ph–C(=O)–NH–	5-methyl-3-(methylamino)isoxazole	8b	–NH–C(=O)–Ph–C(=O)–OCH$_3$	5-methyl-3-(methylamino)isoxazole
4c	(Cl_2)Ph–NH–Ph–C(=O)–NH–	(Cl_2)Ph–NH–Ph–C(=O)–NH–	8c	–NH–C(=O)–Ph–C(=O)–OCH$_3$	NH$_2$

Table 2. Physicochemical properties of designed compounds.

Ligand	Molecular weight	LogP	Log D	Polar surface area	Molecular surface area	H donor	H acceptor	Rotatable bonds	Lipinski's rules violation
1a	277	1.9	−0.36	91.85	322.98	2	4	3	0
1b	357	2.88	1.88	109.68	423.51	2	5	4	0
1c	376	5.42	5.42	66.58	463	2	2	5	1
2a	273	1.62	−0.76	112.08	341.99	3	5	3	0
2b	373	2.6	1.48	129.91	433.91	3	6	4	0
2c	412	3.55	2.25	141.18	470.22	4	6	4	1
3a	321	1.42	−4.46	129.15	352.68	3	5	4	0
3b	383	2.09	1.07	117.96	425.3	1	6	3	0
3c	468	2.5	−5.66	175.32	510.51	4	8	6	1
3d	302	1.18	1.18	97.54	375.86	1	4	2	0
4a	450	4.49	4.49	92.34	497.92	2	7	6	0
4b	530	6.11	5.11	109.68	605.78	2	7	7	1
4c	728	8.27	7.13	124.78	798.4	4	10	10	1
5a	361	4.17	1.91	91.85	473.42	2	4	6	0
5b	441	5.15	4.55	109.68	572.36	2	5	7	1
5c	548	8	6.88	100.72	744.84	2	4	10	1
6a	396	5.39	3.13	103.88	488.65	3	5	5	1
6b	476	6.37	5.36	121.71	587.5	3	6	6	1
6c	618	10.44	9.3	124.78	781.3	4	6	8	1
7a	334	0.83	−1.44	120.95	387.35	3	5	5	0
7b	414	1.81	0.8	138.78	488.23	3	6	6	0
7c	494	1.31	0.17	158.92	579.77	4	6	8	1
8a	335	2.25	−0.13	109.77	434.89	1	5	5	0
8b	416	2.71	1.86	127.6	548.54	1	6	6	0
8c	334	1.67	1.67	115.56	441.42	2	4	5	0

results showed that most of the designed ligands are not violating the rule of five and may be developed as potential drug candidates. The partial charge of designed compounds was calculated to each atom by Marvin Sketch, (Figure 6).

3.3. Molecular Docking Results

The list of compounds was docked into the EGFR receptor binding pocket using the validated docking methods. Docking results tabulated between The EGFR binding pocket and the derivatives of sulfonamide are shown (Table 3).

Validation docking method

Validation of docking was used to ensure orientation and position of ligand
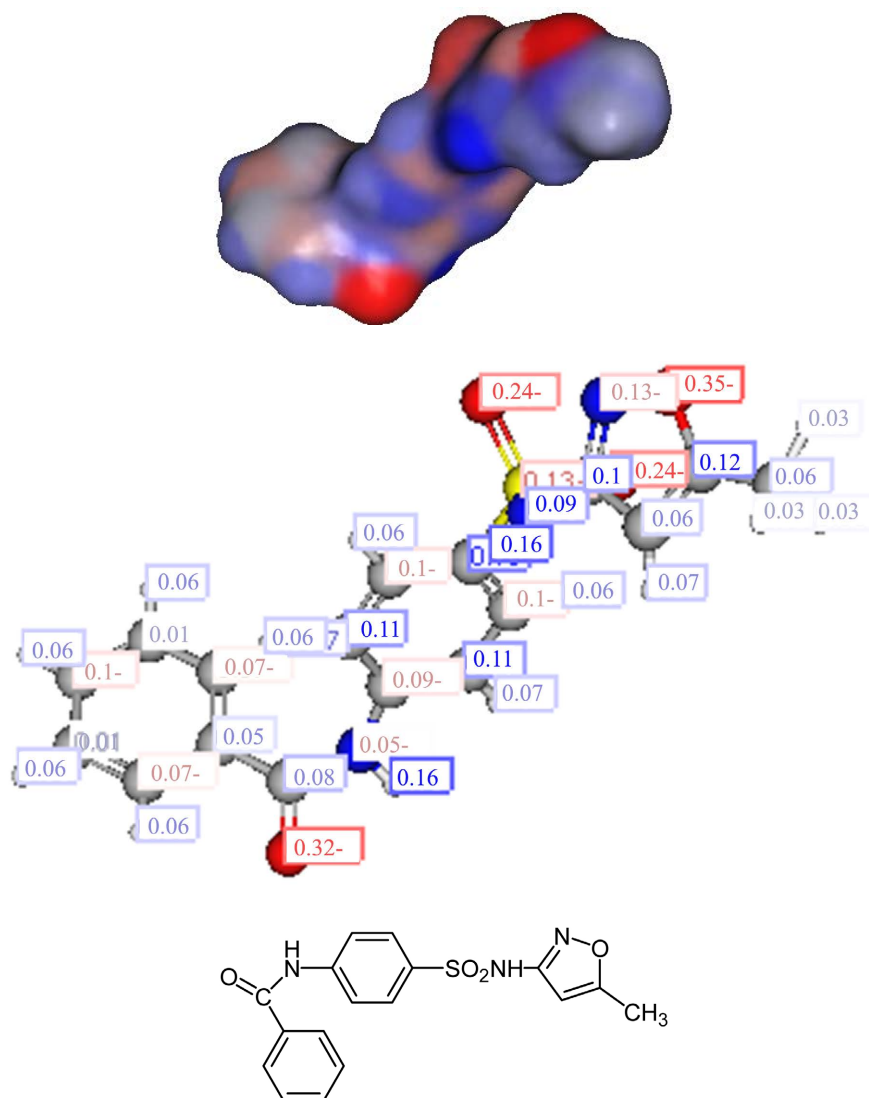
Figure 6. Partial charges of 1b compound which studied by Marvin sketch.

binding obtained from docking studies by MVD program. Therefore, the parameters must be validated by re-dock the native ligand into the crystal structure (PDB ID: 2ITY). After that, it was extracted and re-docked into the binding pocket to generate the X-ray binding mode. The ability of the docking algorithm to generate the active biding mode of the ligands was evaluated by calculating the RMSD (Root Mean Square Deviation) between the docking solutions and the X-ray binding mode. RMSD < 2 Å considered as a threshold in the computer-aided drug design.

The RMSD value for the top-ranked docking solution of ligand was 1.17949. Thus, the applied docking methods were able to generate the X-ray binding mode of the ligand.

The interactions between the binding pocket residues of the EGFR receptor and the sulfonamide derivatives together with energy docking are shown in Table 4.

Table 3. The energy docking of ligands with receptors.

Ligand	Energy docking with 2ITY (Kcal/mol)
4b	−128.819
7b	−127.523
6c	−121.849
6b	−117.124
5c	−112.43
4c	−111.427
3b	−108.688
5b	−108.364
3c	−104.139
3d	−103.186
4a	−102.175
8b	−100.42
Standard 2	−99.6243
Iressa	−98.8651
7c	−98.4738
Standard 1	−93.5665
3a	−93.0394
1b	−91.9394
2b	−88.2345
6a	−87.3354
1a	−82.1471
2c	−81.6785
8a	−80.8588
1c	−80.2854
8c	−79.8328
5a	−78.3595
7a	−74.1276
2a	−72.206

Table 4. Interaction of the amino acids in 2ITY with ligands.

ligand	Residue	Interaction	Distance (Å)	Energy	Van der Waals interaction
1a	Met793	O-H	3.1	−2.5	-
	Asp855	O-H	3.04	−2.5	
	Asp855	O-H	2.91	−1.55509	
	Thr854	O-H	2.9	−2.5	
1b	Met793	O-H	2.66	−2.5	Pro794
	Pro794	N-H	3.057	−0.701673	

Continued

1c	Asp855	N-H	2.94	−2.5	Asp855, Pro794
2a	Met793	O-H	2.8	−2.5	-
	Asp855	O-H	3.05	−1.90438	
	Thr854	O-H	2.9	−2.5	
	Lys745	O-H	3	−2.5	
2b	Gln791	O-H	2.6	−2.5	-
	Met793	O-H	2.98	−1.3688	
	Met793	O-H	2.9	−2.5	
2c	Ser720	O-H	3.04	−0.750539	-
	Gly719	O-H	2.86	−2.5	
3a	Met793	O-H	2.8	−2.5	-
	Thr854	O-H	3.03	−2.5	
	Asp855	O-H	2.92	−1.56838	
	Lys745	O-H	3	−2.5	
3b	Gly724	N-H	3.16	−1.74979	Gly719
	Gly724	O-H	2.85	−1.35909	
	Ser720	N-H	2.8	−2.5	
3c	Lys745	O-H	3.1	−2.5	Val726, Arg841, Gly721
	Val726	O-H	3.3	−0.757545	
	Phe723	O-H	3	−2.5	
	Gly724	O-H	2.65	−2.5	
	Asp855	O-H	2.7	−2.5	
3d	Met793	O-H	2.8	−2.5	-
	Thr854	O-H	2.95	−2.5	
	Lys745	O-H	2.8	−2.5	
4a	Phe795	O-H	3	−2.5	-
4b	Lys745	O-H	2.77	−2.5	Leu788, Thr790, Lys745, Asp855
	Cys797	N-H	3.1	−2.5	
4c	Lys745	O-H	3.1	−0.195019	Glu762, Lys745, Gly719, Asp855
5a	Thr854	O-H	3.17	−2.10359	Leu844
5b	Ser720	N-H	2.7	−2.5	Glu762
	Lys745	N-H	2.7	−1.08594	
	Lys745	O-H	2.8	−2.08639	
5c	Met793	O-H	3	−2.38289	Val726, Leu747,
6a	Thr854	O-H	3	−1.74103	Leu792, Gly796, Pro794, Leu844
6b	Leu718	N-H	3	−2.5	-

Continued

6c	Thr854	O-H	2.7	−2.5	Lys745, Met793, Val726
7a	Gly719	N-H	2.85	−1.99386	Phe723
	Lys745	O-H	3.2	−1.95469	
	Cys797	O-H	3.3	−1.34206	
	Asp800	O-H	3.06	−2.49205	
7b	Gly719	N-H	3.06	−0.808774	Ser720
	Gly721	N-H	3.1	−0.651249	
	Ser720	N-H	2.6	−2.42948	
	Gly724	N-H	3.17	−1.54498	
	Gly724	O-H	3	−1.1997	
7c	Met793	O-H	2.93	−2.36929	Lys745, Ala743
	Asp855	N-H	3.1	−0.133077	
8a	Met793	O-H	3.3	−1.22411	-
	Thr854	O-H	2.8	−2.5	
	Lys745	O-H	3	−2.5	
8b	Ser720	N-H	2.6	−1.84127	Met793
8c	Thr854	O-H	2.84	−2.5	-
	Lys745	O-H	2.94	−2.5	

From the results, the -SO_2NH_2 group was essential for binding with the receptor. The oxazole ring in R_1 gave high binding energy in comparison with other substitutes. The benzene ring in R_2, which contains different substitutions such as chloro, methyl, and hydroxyl, was necessary for binding with the receptor. If the amine N_2 group was free, it led to low binding energy. The absence of the amine group in R_1 resulted in less binding.

All the designed compounds were bound to receptors and given energy docking, and the polar surface area represents the binding pocket of the EGFR receptor. Few compounds showed higher docking scores toward the receptor than the reference ligand, Table 3. The compounds 4b, 7b, and 6c were shown higher energy binding with EGFR binding pocket than other compounds.

Most of the compounds were given hydrogen bonds and van der Waals bonds to receptors with different bond lengths and binding energies. The ligand displayed hydrogen bonds with 15 amino acid residues of 2ITY: Met793, Pro794, Lys745, Cys797, Gly719, Gly721, Ser720, Gly724, Leu718, Gln791, Asp855, Thr854, Val726, Phe723, Asp800. The majority of compounds displayed van der Waals interactions between the amino acid residues and the ligands, which stabilized the compounds in the binding pocket.

The predicted binding modes of 4b and 7b and their interactions with the residues in the EGFR binding pocket are shown in (Figure 7).
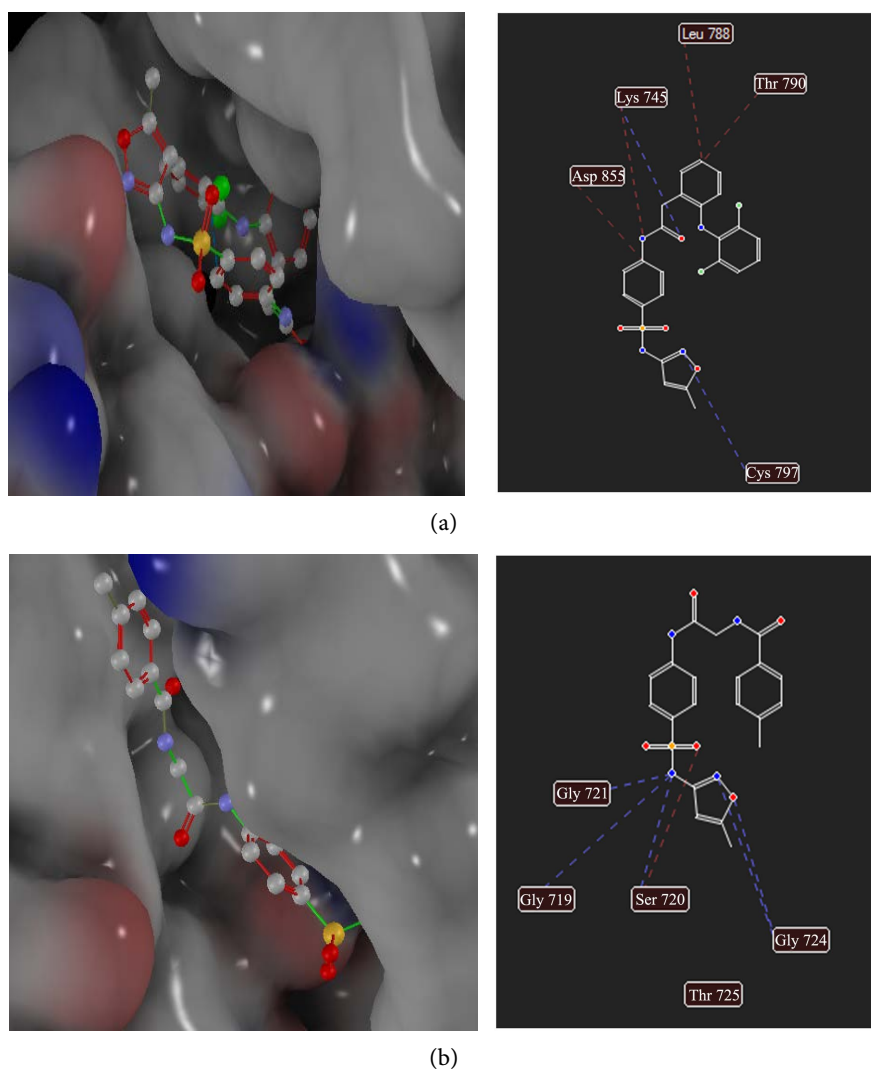
(a)

(b)

Figure 7. (a) docking solution of compound (4b) and the interactions with residues of amino acid in the EGFR binding pocket; (b) docking solution of compound (7b) and the interactions with residues of amino acid in the EGFR binding pocket. Blue bonds indicate hydrogen bonds, and red bonds indicate van der Waals.

4. Conclusion

Several sulfonamide derivatives were docked into the EGFR binding pocket using the Molegro Virtual Docker software. The binding free energy was calculated to predict their affinity toward EGFR kinase to select novel candidates as EGFR inhibitors for treating cancer. The results showed that 4b, and 7b gave the highest energy docking −128.819, −127.523 Kcal/mol toward the EGFR receptor. Their corresponding binding modes were predicted. The obtained results suggested that these compounds may be novel candidates in NSCLC lung cancer treatment by targeting EGFR tyrosine kinase; which associated with increased EGFR receptor expression in 75% of cases. More research in this area is being studied, and some designed compounds as anti-cancer agents will be synthesized.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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