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Computer-aided design of some quinazoline analogues as epidermal growth factor receptor inhibitors

Muhammad Tukur Ibrahim*, Adamu Uzairu, Gideon Adamu Shallangwa and Sani Uba

Abstract

Background: The treatment of epidermal growth factor receptor (EGFR)-muted non-small cell lung cancer (NSCLC) remains among the utmost important unachieved therapeutic need worldwide. Development of EGFR inhibitors to treat NSCLC mutations has been among the difficult tasks faced by researchers in this area. As such, there is a need to discover more EGFR inhibitors. The purpose of this work is to perform computer-aided/structure-based design of novel EGFR inhibitors, elucidate their nature of interactions with their target, and also assess their ADMET properties as well as their drug-likeness, respectively. Compound 17 with a highest binding affinity of −9.5kcal/mol was identified as the template hit compound using molecular docking virtual screening in our previous work. The compound interacted with the active site of the EGFR receptor via hydrogen bond with the following amino acid residues MET793, MET793, THR854, and ASP855 with bond distances of 2.61394 (Å), 2.18464 (Å), 2.57601 (Å), and 2.68794 (Å), respectively. It also interacted with the active site of the EGFR receptor via halogen bond (GLN791), hydrophobic bond (LEU718, CYS797, LYS745, ALA743, ALA743, and VAL726), electrostatic bond (LYS745), and others (MET766), respectively. Furthermore, from our previous study, the following descriptors (ATSC6m, ATSC8e, MATS7m, SpMax3_Bhp, SpMax5_Bhs, and MaxHBint10) contained in the reported model were found to be responsible for the inhibitory activities of the studied compounds. In this research, the template (compound 17) was modified manually by attaching halo-phenyl and halo-phenyl-amino rings on the para position of the flouro-nitro-benzamide moiety of the template compound, respectively.

Results: A computer-aided design/structure-based approach was used to design six new EGFR inhibitors using molecule 17 as the template compound for the design identified in our previously reported work. Molecular docking investigation was performed to elucidate the binding mode of these newly designed EGFR inhibitors with the binding pose of EGFR receptor (pdb code 4ZAU) and found to have better affinities which range from −9.5 to −10.4 kcal/mol than the template compound and gefitinib, the control, respectively. The ADMET property assessment of these newly designed EGFR inhibitors indicated that they were orally bioavailable with good absorption, distribution, metabolism, and excretory properties with no toxicity. And for their drug-likeness, they were seen to have a higher molecular weight which might be as a result of halo-phenyl-amino ring attachments. Based on this finding, halo-phenyl-amino rings might be responsible for the inhibitory activities of these newly designed compounds.

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Conclusion: The six newly designed EGFR inhibitors were found to have higher binding affinities toward their target EGFR receptor than the template compound and gefitinib which was used as the control in this research. They were seen to have good ADMET and drug-like properties which indicate that they might be orally bioavailable. Furthermore, according to their synthetic accessibility score, they can be easily synthesized in the laboratory because the values were found to be less than five which fall within the easy portion of the scale. Therefore, this research recommends that these newly designed EGFR inhibitors should be synthesized most especially those with higher binding affinities, good ADMET, and drug-likeness properties than the template compound.

Keywords: Computer-aided, Design, Quinazoline, EGFR, NSCLC

Background

Receptor tyrosine kinases (RTKs) belong to the ErbB family, located on cell membranes of living organisms, and played a significant role in the management of the physiological cycle of malignant tumors [1]. Epidermal growth factor receptor (EGFR) is a member of RTKs which was recognized to be one of the most significant targets for the management of malignant tumors, which plays a vital role in the control of cancer cell growth, proliferation, and differentiation [2, 3].

Among all types of cancer, lung cancer remains the foremost cause of cancer death in the globe, with about 1.4 million deaths every year [4]. Lung cancer was estimated to account for about 25% of the 7 million people that died as a result of cancer-related mortality every year in the world [5]. Lung cancer was classified traditionally into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [6]. NSCLC, the principal type of lung cancer, was reported to estimate for about over 80% of all lung cancer cases [7].

The prevalence rate of EGFR-muted NSCLC in the globe was estimated to be about 10% with roughly 30–40% in the East Asian patients [8]. The treatment of EGFR-muted NSCLC remains among the utmost important unachieved therapeutic need worldwide [9]. NSCLC with classical/activating mutations in the receptor tyrosine kinase domain of EGFR is very sensitive to management/treatment with EGFR inhibitors. These classical/activating mutations are responsible for the increase of EGFR-driven cell survival and proliferation [10]. Unluckily, successful management of EGFR-muted NSCLC with the so-called first- and second-generation EGFR inhibitors was followed by the development of resistance from a gatekeeper mutation in the EGFR binding domain [11, 12]. The discovery of third-generation EGFR inhibitors was seen to have the capacity to overcome this drug resistance by the secondary mutation (the so-called gatekeeper mutation T790M mutation) [13]. Development of EGFR inhibitors to treat non-small cell lung cancer mutation (NSCLC) has been among the difficult tasks faced by researchers in this area.

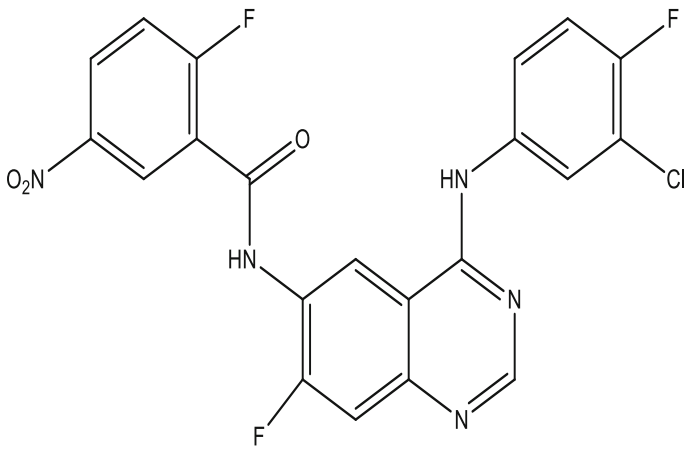
In our previously reported work titled computational modeling of novel quinazoline derivatives as potent epidermal growth factor receptor inhibitors, compound 17 with the highest binding affinity of −9.5 kcal/mol was identified as the template hit compound using molecular docking virtual screening.

The purpose of this work is to perform computer-aided/structure-based design of novel EGFR inhibitors, elucidate their nature of interactions with their target, and also assess their ADMET properties as well as their drug-likeness, respectively.

Methods

Template selection and design

Compound 17 (Fig. 1) with a binding affinity of −9.5 kcal/mol was selected and chosen as a template compound from our previous work, for the design of new EGFR inhibitors [14]. The compound interacted with the active site of the EGFR receptor via hydrogen bond with the following amino acid residues MET793, MET793, THR854, and ASP855 with bond distances of 2.61394 (Å), 2.18464 (Å), 2.57601 (Å), and 2.68794 (Å), respectively. The interaction was not only via hydrogen bond; it also interacted with the active site of the EGFR receptor via halogen bond (GLN791), hydrophobic bond (LEU718, CYS797, LYS745, ALA743, ALA743, and VAL726), electrostatic bond (LYS745), and others (MET766), respectively (Fig. 2). Furthermore, from our previous study, the following descriptors (ATSC6m, ATSC8e, MATS7m, SpMax3_Bhp, SpMax5_Bhs, and MaxHBint10) contained in the reported model were found to be responsible for the inhibitory activities of the studied compounds. Their interpretations and individual contribution in the reported model are shown in Table 1, respectively. Six new EGFR inhibitors (Table 2) were designed by carrying out structural modification on the flouro-nitro-benzamide moiety of the template compound. The structural modification was performed by attaching halo-phenyl and halo-phenyl-amino rings on the para position of the flouro-nitro-benzamide moiety of the template compound. Chemdraw software developed



N-(4-((3-chloro-4-fluorophenyl)amino)-7-fluoroquinazolin-6-yl)-2-fluoro-5-nitrobenzamide

Fig. 1 The selected template compound

by Cambridge University was used to draw the 2D structures of the newly designed EGFR inhibitors (Table 2) [15, 16]. Scheme 1 presents the flowchart of the methodology employed in the study.

Stable conformation search for the designed compounds and their preparations

Stable conformation search involved the transformation of drawn 2-dimensional structures to 3-dimensional structures of these newly designed EGFR inhibitors which was done by direct importation of the structures onto the interface of Spartan 14 software. The search was performed using Merck molecular force field (MMFF) with density functional theory (DFT) at Becke's three-parameter hybrid function utilizing LYP correlation functional using 6-311G* basis set. Then the stable conformations of these newly designed EGFR inhibitors were saved in protein data bank file format [17, 18]. The

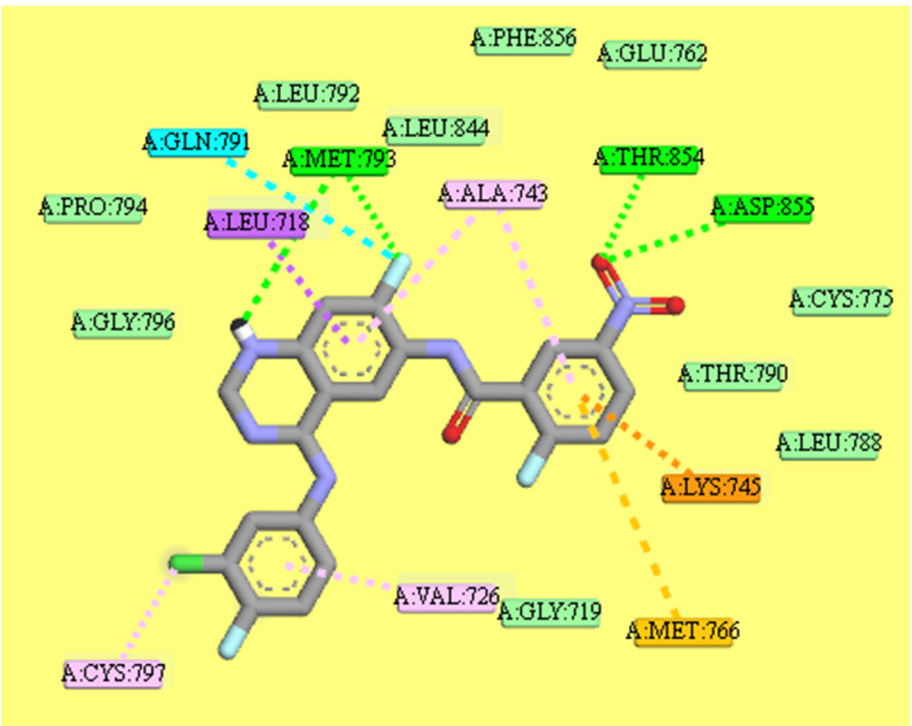


Fig. 2 The 2D interaction of compound 17 in complex with the EGFR receptor

Table 1 The interpretations and mean effect (individual contribution) of descriptors in the model

Descriptor	Interpretation	ME
ATSC6m and **ATSC8e**	Are Moreau–Broto autocorrelation of a topological structure, ATS (The ATS descriptor is a graph invariant describing how the property considered is distributed along the topological structure). These descriptors can be seen as a special case in which other types of descriptors can also be derived from	0.360912 and −0.19827
MATS7m	Is a Moran autocorrelation which if applied to a molecular graph. Moran coefficient usually takes value in the interval [−1, +1]. Positive autocorrelation corresponds to positive values of the coefficient whereas negative autocorrelation produces negative values	0.295192
SpMax3_Bhp and **SpMax5_Bhs**	Are the maximum absolute eigenvalue of Burden modified matrix - n 3 / and - n 5 / weighted by relative I-state and relative polarizabilities, called leading eigenvalue or spectral radius; SpMaxA is the maximum absolute value of the spectrum. These kinds of functions were called by Ivanciuc matrix spectrum operators. This eigenvalue has been suggested as an index of molecular branching; this descriptor talks about branching in molecules	0.112306 and −0.35122
MaxHBint10	Is a maximum E-State descriptor of strength for potential hydrogen bonds of path length 10	0.781081

3-dimensional optimum conformation of a prepared designed EGFR inhibitor is shown in Fig. 3.

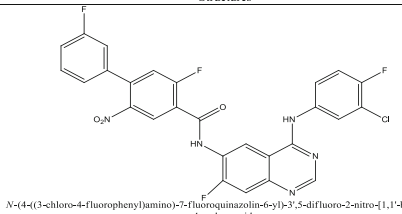
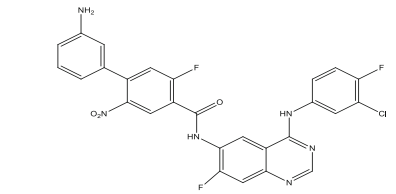
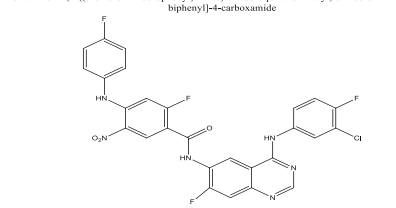
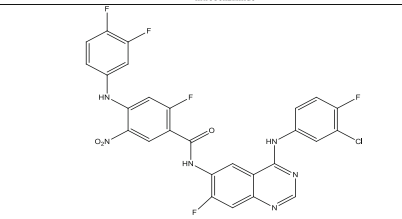
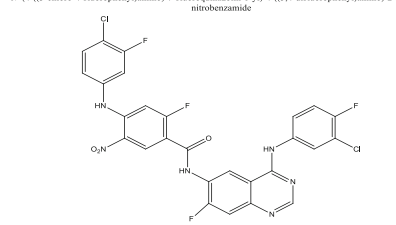
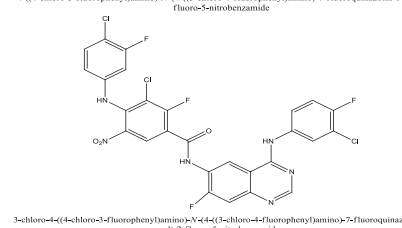
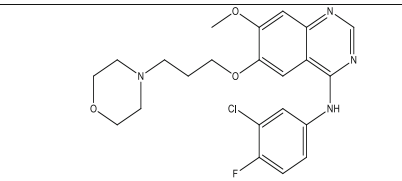
Retrieval and preparation of epidermal growth factor receptor

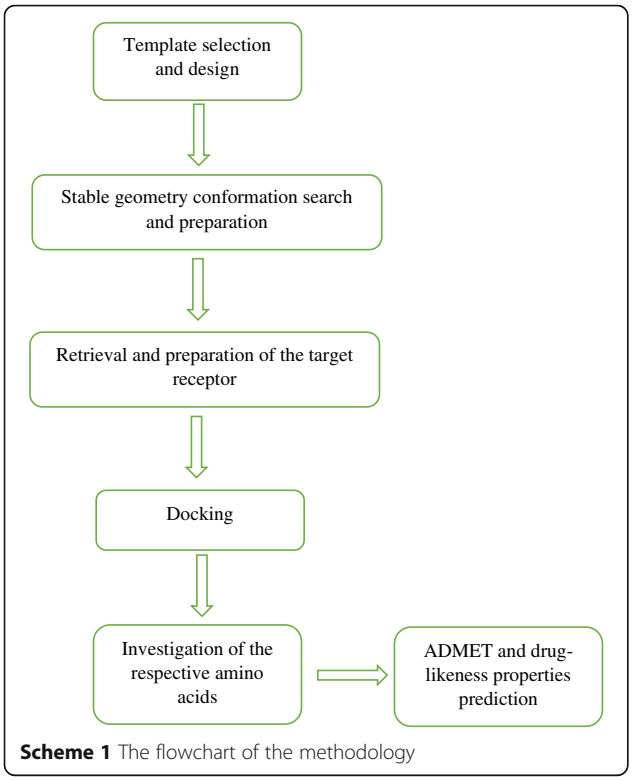
The crystal structure of the EGFR receptor in complex with AZD9291 (pdb entry: **4ZAU**) was successfully downloaded and retrieved from the RCSB protein data base and used in this study. Receptor preparation is a very vital step in any molecular docking investigation. Therefore, the receptor must be prepared before investigating its binding interactions with its ligands [19]. Discovery studio software was sued for its preparation for the docking investigation. Hydrogen was added, and AZD9291 (co-crystalized ligand) and water molecule on the crystal structure of the receptor were deleted and saved in protein data bank file format recognized by the Pyrex virtual screening molecular docking software. The prepared structure of the EGFR receptor is shown in Fig. 4.

Molecular docking investigation

Vina of Pyrex-virtual screening software was used for the docking of the newly designed EGFR

Table 2 The structures of six newly designed EGFR inhibitors and gefitinib

S/NO	Structures
SDD1	 *N*-(4-((3-chloro-4-fluorophenyl)amino)-7-fluoroquinazolin-6-yl)-3',5-difluoro-2-nitro-[1,1'-biphenyl]-4-carboxamide
SDD2	 3'-amino-*N*-(4-((3-chloro-4-fluorophenyl)amino)-7-fluoroquinazolin-6-yl)-5-fluoro-2-nitro-[1,1'-biphenyl]-4-carboxamide
SDD3	 *N*-(4-((3-chloro-4-fluorophenyl)amino)-7-fluoroquinazolin-6-yl)-2-fluoro-4-((4-fluorophenyl)amino)-5-nitrobenzamide
SDD4	 *N*-(4-((3-chloro-4-fluorophenyl)amino)-7-fluoroquinazolin-6-yl)-4-((3,4-difluorophenyl)amino)-2-fluoro-5-nitrobenzamide
SDD5	 4-((4-chloro-3-fluorophenyl)amino)-*N*-(4-((3-chloro-4-fluorophenyl)amino)-7-fluoroquinazolin-6-yl)-2-fluoro-5-nitrobenzamide
SDD6	 3-chloro-4-((4-chloro-3-fluorophenyl)amino)-*N*-(4-((3-chloro-4-fluorophenyl)amino)-7-fluoroquinazolin-6-yl)-2-fluoro-5-nitrobenzamide
Gefitinib	 *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine



Scheme 1 The flowchart of the methodology

inhibitors with the active site of the EGFR receptor [20]. UCSF chimera software was then used to re-couple the docked newly designed EGFR inhibitors with the EGFR receptor and saved in pdb format for the investigation of the respective amino acids; the newly designed EGFR inhibitors interacted within the active site of the EGFR receptor. Discovery studio and molecular operating environment (MOE) were used for the investigation of the respective amino acids; the newly designed EGFR inhibitors interacted within the active site of the EGFR kinase receptor [14].

ADMET properties and drug-likeness assessment of newly designed EGFR inhibitors

The ADMET properties of these newly designed EGFR inhibitors under investigation were determined using pkCSM an online web server (http://structure.bioc.cam.ac.uk/pkcsm), while the drug-likeness of these newly designed EGFR inhibitors were also evaluated using SWISS ADME, also an online web server (http://www.swissadme.ch/index.php). Many rules were developed to guide the choice of compounds in the early phases of drug discovery. Among the famous rules applied for compound selection based on the drug-likeness properties in the early phase of drug discovery was Lipinski's rule of five (RO5). The studied compounds would be evaluated for their drug-likeness properties based on the RO5 criteria [21, 22].

Results

Results of molecular docking investigation of the newly designed EGFR inhibitors

The results of molecular docking are presented in Table 3 and Figs. 5, 6, 7, and 8, respectively.

Results of ADMET properties and drug-likeness assessment

The results of ADMET properties and drug-likeness are presented in Tables 4 and 5, respectively.

Discussion

Molecular docking investigation of newly designed EGFR inhibitors

Molecular docking investigation was performed on the newly designed EGFR inhibitors and EGFR receptor (pdb entry: **4ZAU**). Table 3 shows the results of all newly designed compounds in the binding site of the EGFR receptor. Based on the molecular docking results, the range of binding affinities of these newly designed compounds is between −9.5 and −10.4 kcal/mol,

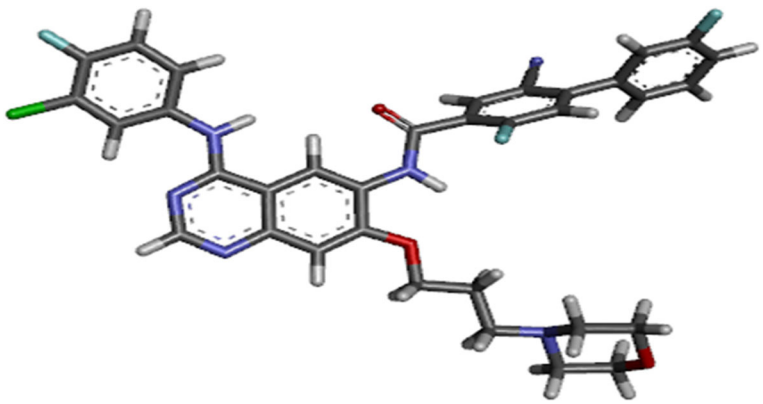


Fig. 3 The 3D optimum conformation of a prepared designed EGFR inhibitor

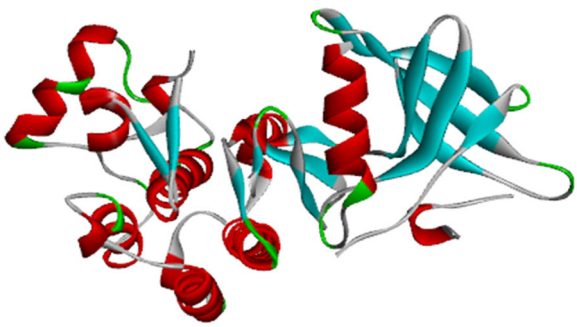


Fig. 4 The 3D prepared structure of the EGFR receptor

respectively. Compound SDD4 has the highest binding affinity of −10.4 kcal/mol followed by compounds SDD3 and SDD5, respectively.

Compound SDD3 with a binding affinity of −10.3 kcal/mol interacted with the EGFR receptor via conventional hydrogen bond with LEU778 (2.75Å), LEU703 (1.83 Å), ALA767 (2.99 Å), ASN771 (2.35 Å), and LYS852 (1.79 Å), and also halogen interaction was observed between the compound SDD3 and EGFR receptors with ASP1014 and TYR1016 amino acids. Besides the two mentioned interactions, it also interacted with ASP770 and ASP1014 amino acids via electrostatic and via hydrophobic with LEU703, ARG776, PRO772, and ALA702 amino acids, respectively.

Compound SDD4 with the highest binding affinity of −10.4 kcal/mol formed both conventional and carbon–hydrogen bonds with LEU703 (1.79 Å), LEU778 (2.79 Å), ALA767 (2.96 Å), ASN771 (2.36 Å), LYS852 (1.79 Å), and HIS850 (3.58 Å) amino acids in the binding pose of the EGFR receptor. It was seen to interact in the binding pose of the EGFR receptor with ASP1014 and TYR1016 via a halogen bond. Not only carbon–hydrogen and halogen bonds were seen in the interactions between the two, but also electrostatic with ASP770 and ASP1014 were observed between the two. Apart from the hydrogen, halogen, and electrostatic bonds, hydrophobic interactions were observed between the two with the following amino acid residues ASN771, LEU703, ALA702, ARG776, and PRO772, respectively.

Compound SDD5 with a binding affinity of −10.2 kcal/mol formed a conventional hydrogen bond with LEU703 (1.79 Å), LEU778 (2.74 Å), ALA767 (2.95 Å), ASN771 (2.38 Å), and LYS852 (1.79 Å) amino acid backbone of the receptor. Besides hydrogen bond, it formed halogen bond with ASP1014 and TYR1016 amino acids, electrostatic bond with ASP770 and ASP1014 amino acids, and hydrophobic bond with LEU703, ALA702, ARG776, and PRO772 amino acid residues of the receptor, respectively.

Compound SDD1 formed conventional and carbon–hydrogen bonds with LEU778 (2.40 Å), LEU703 (1.87 Å), ALA767 (2.79 Å), LYS852 (2.96 Å), LYS852 (2.61 Å), and PRO772 (3.32 Å) amino acid residues, respectively. On the other hand, it also formed a halogen bond with ALA1013 and TYR1016 amino acids. In addition to the halogen bond, it formed electrostatic with ASP770 and ASP1014 amino acids and hydrophobic bond with ALA702, LEU703, ARG776, LEU1017, PRO772, and ALA702 amino acid residues of the target protein, respectively.

The following amino acid residues LEU778, LEU703, ALA767, LYS852, TYR1016, ASP770, ASP1014, ALA702, ARG776, and PRO772 were common to almost all the reported compounds. The attachment of halophenyl and halo-phenyl-amino rings on the para position of the flouro-nitro-benzamide moiety of the

Table 3 Types of interactions of newly designed EGFR inhibitors

Entry	Binding affinities (kcal/mol)	Hydrogen bond	Bond distance (Å)	Hydrophobic and other interactions
SDD1	−9.6	LEU778, LEU703, ALA767, LYS852, LYS852, and PRO772	2.40, 1.87, 2.79, 2.96, 2.61, and 3.32	ALA1013, TYR1016, TYR1016, ASP770, ASP1014, ALA702, LEU703, ARG776, LEU1017, PRO772, and ALA702
SDD2	−9.5	CYS797	2.95	LEU718, MET766, LYS728, VAL726, ALA743, LEU844, and LYS745
SDD3	−10.3	LEU778, LEU703, ALA767, ASN771, and LYS852	2.75, 1.83, 2.99, 2.35, and 1.79	ASP1014, TYR1016, ASP770, LEU703, ARG776, PRO772, and ALA702
SDD4	−10.4	LEU703, LEU778, ALA767, ASN771, LYS852, and HIS850	1.79, 2.79, 2.96, 2.36, 1.79, and 3.58	TYR1016, ASP770, ASP1014, ASN771, LEU703, ALA702, ARG776, and PRO772
SDD5	−10.2	LEU703, LEU778, ALA767, ASN771, and LYS852	1.79, 2.74, 2.95, 2.38, and 1.79	ASP1014, TYR1016, ASP770, LEU703, ALA702, ARG776, and PRO772
SDD6	−9.5	THR790, MET793, and CYS797	2.14, 2.19, and 2.95	PHE795, GLY796, CYS797, LYS745, LEU844, ALA743, LYS745, LEU718, and HIS805
Gefitinib	−7.5	GLN791 and GLY796	3.37 and 3.52	ASP855, LYS745, VAL726, LEU718, ALA743, CYS797, ARG841, LEU844, and PHE723

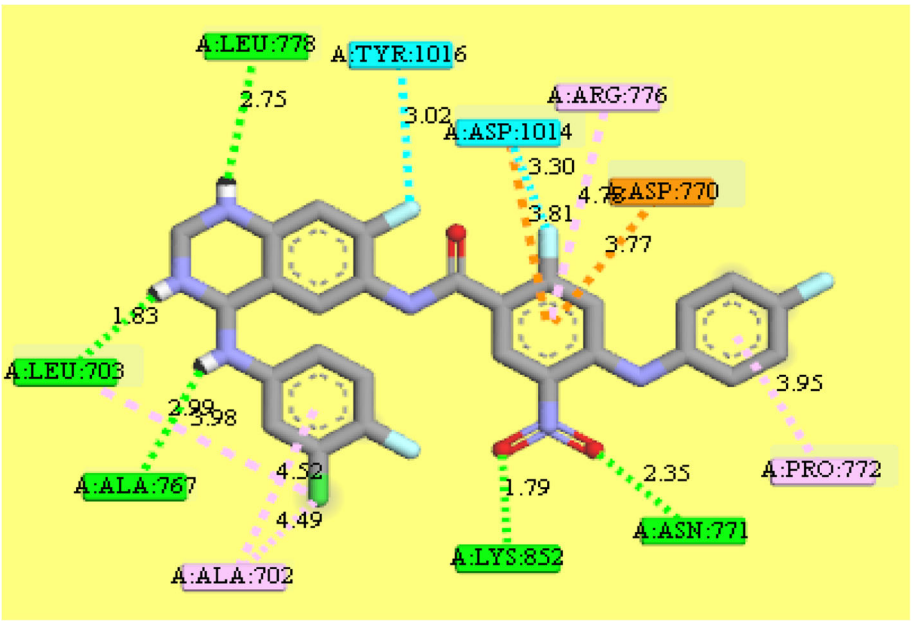


Fig. 5 2D structures of the SDD3 receptor using discovery studio

template compound might be responsible for the higher binding affinities possessed by these newly designed compounds. On comparing these newly designed compounds with the template compound and gefitinib, the control, the newly designed compounds possessed better binding affinities than the template and gefitinib. Furthermore, the visualized 2D and 3D structures of some of the docked designed compounds with higher binding affinities are presented in Figs. 5, 6, 7, and 8, respectively.

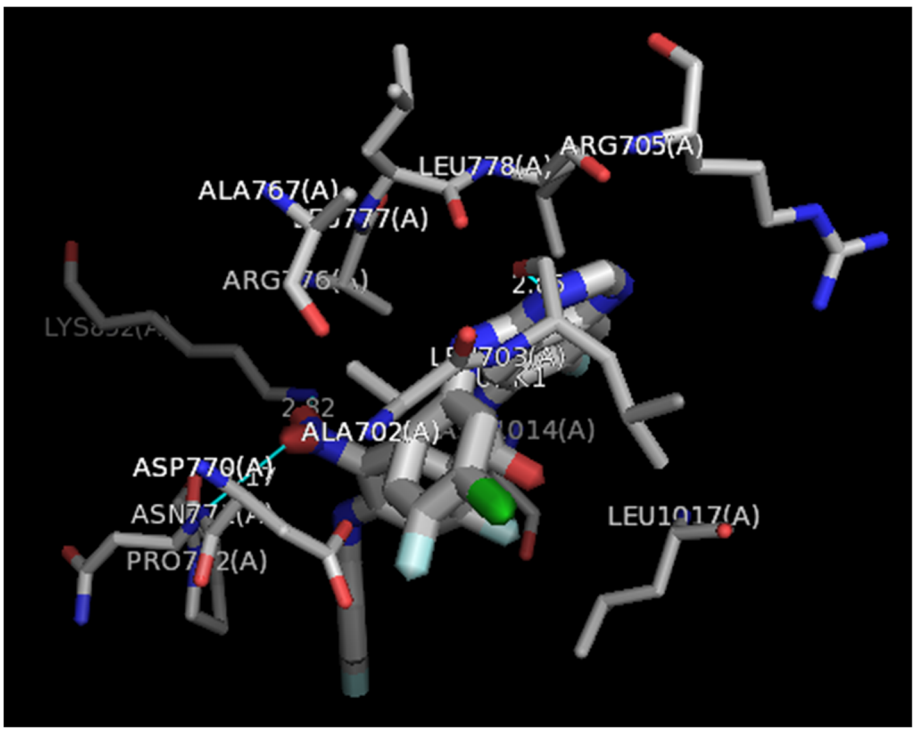


Fig. 6 Siteview 3D structure of the SDD3 receptor using MOE

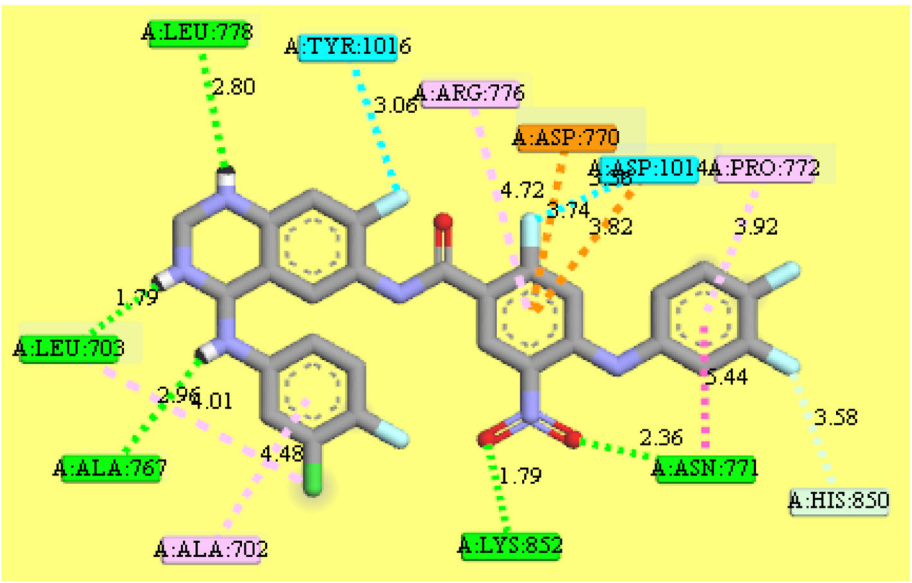


Fig. 7 2D structures of the SDD4 receptor using discovery studio

ADMET properties and drug-likeness assessment of newly designed EGFR inhibitors

The predicted ADMET properties of these newly designed compounds are represented in Table 4. The intestinal absorption values for these compounds range from 89.054 to 100% which have passed the threshold value of 30%; this clearly shows that these newly designed compounds have high human intestinal absorption properties. Their BBB permeability (Log BB) values range from −1.929 to −3.391, which implies that all of them would be better distributed through the brain. Their CNS permeability (Log PS) values were >

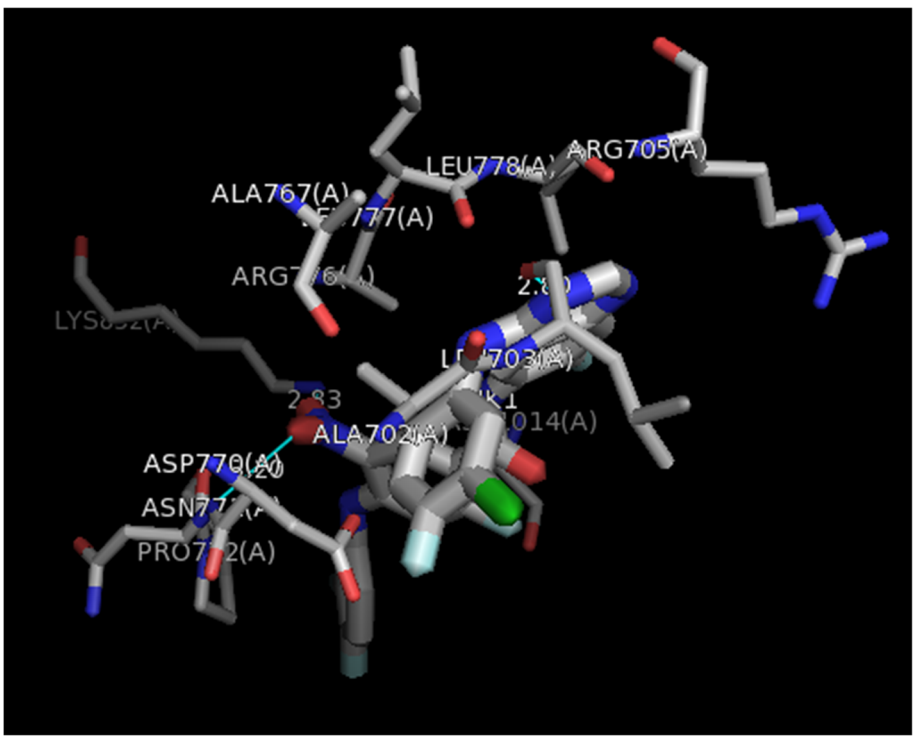


Fig. 8 Siteview 3D structure of **A** SDD4 receptor and **B** SCD4 receptor using MOE

Table 4 ADMET properties of newly designed EGFR inhibitors

S/N	Absorption	Distribution		Metabolism							Excretion	Toxicity
	Intestinal absorption	BBB permeability	CNS permeability	CYP Substrate		CYP Inhibitors					Total clearance	AMES toxicity
		Log BB	Log PS	2D6	3A4	1A2	2C19	2C9	2D6	3A4		
1	100	−2.07	−3.198	No	Yes	No	No	Yes	No	Yes	0.157	No
2	92.949	−1.929	−3.28	No	Yes	No	No	Yes	No	Yes	0.31	No
3	93.109	−2.188	−3.27	No	Yes	No	No	Yes	No	Yes	0.302	No
4	89.054	−2.391	−3.317	No	Yes	No	No	Yes	No	Yes	0.275	No
5	97.349	−2.314	−3.09	No	Yes	No	No	Yes	No	Yes	0.313	No
6	94.285	−2.352	−3.209	No	Yes	No	No	Yes	No	Yes	0.324	No
Gefitinib	92.84	−2.737	−1.337	No	Yes	No	No	No	No	Yes	0.778	No

BBB blood–brain barrier, *CNS* central nervous system, *CYP* cytochrome

−3 which are considered to penetrate the central nervous system. They were found to be both substrate and inhibitors of CYP3A4, respectively, thereby affirming their metabolic properties. The total clearance for these newly designed compounds was within the accepted values. All these newly designed compounds were found to be non-toxic. As such, they are said to have high absorption value, low/high toxicity level, and good permeability across the cell membrane [4, 23]. On comparing the ADMET properties of these newly designed compounds with that of the control, they were found to agree with one another except in the case of CNS permeability which the control has CNS permeability of −1.337, respectively.

The drug-likeness properties of these newly designed compounds were also predicted following Lipinski's rule of five (Table 5). No designed compound was found to violate more than the permissible limit set by Lipinski's rule of five filters for small molecules. Their molecular weight was greater than 500, and this was attributed to the attachment of halon-phenyl and halon-phenyl amino rings on the template compound (according to R05, a small molecular whose molecular weight is greater than 500 might have a problem with its bioavailability which does not mean it will be completely not active). More so, even with a higher molecular weight, they were found to have high absorption value, low toxicity level, and good permeability across the cell membrane. The number of hydrogen bond donors for all was less than 5 and the number of hydrogen bond acceptors for all was 10 except compounds SDD2 and SDD5, respectively. Their WLOGP value was greater than 5 except for compounds SDD2 and SDD3, respectively. All these newly designed compounds have good synthetic accessibility score of less than five (< 5) which indicates that they can be easily synthesized in the laboratory. From these predicted parameters, these newly designed compounds are said to be orally active and orally bioavailable most especially SDD2 and SDD3. In the case of drug-likeness, these newly designed compounds have their molecular weight greater than that of the control. For the WLOGP value, their values were greater than that of the control and the threshold value of 5 except for SDD2 and SDD3, respectively.

From our findings, the most important part of these newly designed compounds that might be responsible for the activity is the halo-phenyl-amino ring.

Table 5 Drug-likeness of newly designed EGFR inhibitors

Entry	MW	WLOGP	No. of H-bond donors	No. of H-bond acceptors	RO5 violations	Synthetic accessibility
SDD1	673.08	8.03	2	10	2	4.25
SDD2	670.11	4.06	3	9	1	4.36
SDD3	688.1	4.1	3	10	1	4.36
SDD4	706.09	8.66	3	10	2	4.37
SDD5	739	8.85	3	9	2	4.33
SDD6	722.54	8.76	3	10	2	4.34
Gefitinib	446.9	4.32	1	7	0	3.26

MW molecular weight, *TPSA* total polar surface area, *H-bond* hydrogen bond, *RO5* rule of five

Conclusion

The newly designed EGFR inhibitors were found to have higher binding affinities toward their target EGFR receptor than the template compound and gefitinib, the control in this research. They were seen to have good ADMET properties and none of them was found to be toxic. More so, they were also seen to possess drug-like properties by non-violating more than the permissible limit set by the filtering criterion used (Lipinski's rule of five) which indicates that they might be orally bioavailable. Furthermore, according to their synthetic accessibility score, they can be easily synthesized in the laboratory because the values of their synthetic accessibility score were found to be less than 5 which fall within the easy portion of the scale. Therefore, this research recommends that these newly designed EGFR inhibitors should be synthesized most especially those with higher binding affinities and good ADMET and drug-likeness properties than the template compound and gefitinib, the control, among them.

Abbreviations

ADMET: Absorption, distribution, metabolism, excretion, and toxicity; DFT: Density function theory; B3LYP: Becke's three-parameter read-Yang-Parr hybrid; PDB: Protein data bank; NSCLC: Non-small cell lung cancer agents; EGFR: Epidermal growth factor receptor; BBB: Blood–brain barrier; CNS: Central nervous system; CYP: Cytochrome; MW: Molecular weight; TPSA: Total polar surface area; H-bond: Hydrogen bond; RO5: Rule of five; RTK: Receptor tyrosine kinase

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Authors' contributions

MTI contributed throughout the research work. AU gives directives and technical advices. GAS partakes in technical activities. SU also partakes in technical activities. All authors have read and approved the final manuscript.

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Availability of data and materials

All data and materials are available upon request.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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