Molecular Docking and ADMET Prediction Of Quinazoline Derivates As Potential Anti Cancer

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ABSTRACT

Objective: The objective of this study is to design some dimethyl amino substituent quinazoline derivatives as an anticancer with a computational method to obtain the interaction of the compound with tyrosine kinase as a protein target, as well as data related to ADMET of the compounds. **Methods:** A set of Compounds are designed and stabilized using ChemDraw and Chembio3D, docking and visualization using Molegro Virtual Docker, ADME prediction using pkCSm Tool online. Toxixcity prediction using Protox Online II. Molecular Docking Studies Were Carried Out On Tyrosine Kinase Protein In Order To Assesses Binding Affinity **Results:** Sixteen compounds of dimethyl amino substituent quinazolin derivatives docked with tyrosine kinase receptor (PDB ID: 1M17).Compound DAQ-2, DAQ-3 and DAQ-6 have rerank score at -99,70; -96,30;-99,30 lower than erlotinib which rerank score at -95,62. Compunds additionally evaluated from ADME predition and toxicity **Conclusion:** This study indicates that dimethyl amino quinazoline-3 (DAQ-3) has potential Tyrosine kinase inhibitor as anti cancer activity with lower toxicity

Keywords: Molecular Docking, Tyrosine kinase, Molegro Virtual Docker, Rerank Score

INTRODUCTION

Tumor cell growth and metastasis require a supply of nutrients and oxygen from the blood vessels, then the growth of these cells will also be followed by blood vessel growth. Angiogenesis is a process of formation of new blood vessels. This phase of angiogenesis occurs due to activation of receptors tyrosine kinases, such as VEGFR, PDGFR-β and EGFR (Lugano, 2019). Activation carried out by Proangiogenic growth factors such as VEGF, PDGF, and EGF. Interventions at this stage can be used as the basis for the development of chemotherapy new, namely receptor tyrosine kinase (RTK) inhibitors [1].

Inhibition of one of the receptor tyrosine kinases has been shown to inhibits angiogenesis, but mutations and upregulation of -type Other receptor tyrosine kinases can thwart therapeutic efforts. So Multiple receptor tyrosine kinase inhibition offers advantages in overcome the resistance mechanism of cancer cells [2]. Therefore, The use of multi-RTK inhibitors has been recognized as an important approach in cancer chemotherapy and validated by the approval of multiple multi-RTK . Inhibitors such as axitinib (PDGFR, VEGFR and c-kit), pazopanib (PDGFR, FGFR, VEGFR and c-kit), vandetanib (EGFR, VEGFR, RET kinase), sunitinib (VEGFR, PDGFR and c-kit) and sorafenib (VEGFR-2, PDGFRβ an Raf kinase) [3].

The quinazoline heterocyclic ring skeleton RTK inhibitor compound used as a support compound followed by the addition of a functional group to the positions 4, 6, and 7. This was demonstrated in erlotinib (EGFR), gefitinib (EGFR) and vandetanib (EGFR, VEGFR-2, and VEGFR-3). If, the similarity of the presence of a quinazolin ring is found to have inhibitory activity RTK, then this framework can be further explored as a guide compound to be modified into a drug candidate.

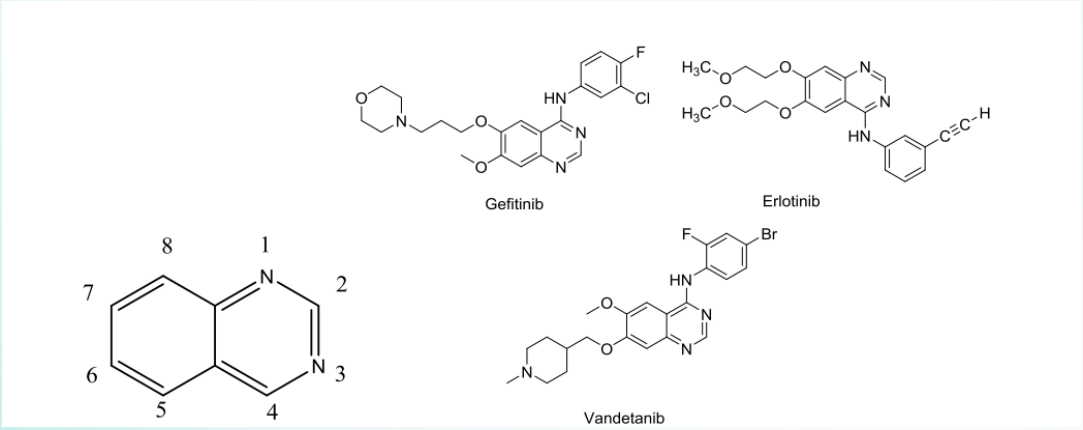

Figure 1: The quinazoline ring and structure of the Receptor Tyrosine Kinase inhibitor gefitinib, erlotinib, and vandetinib.

After obtaining several drug candidate structures, the next approach is to perform virtual screening by means of docking or in silico study. The in silico test itself is using computational chemistry as a test tool. In Silico study in drug development is needed to know the description of the compound in interacting with the receptor. In silico study is activity prediction prior to compound synthesis. The purpose of this in silico test is to reduce the trial and error factor so that drug development is carried out more effective and efficient. Testing is done using a computer program virtual docking [4].

MATERIALS AND METHODS

The research was conducted in the form of a computational *In silico* test for quinazoline derivatives at the Tyrosine Kinase Receptor (PDB code: 1M17). The preparation of the ligand structure was carried out by downloading the ligand-receptor 1M17 via the RCSB website in PDB format. The structure of 16

compounds of dimethyl amino substituent quinazolin derivatives was drawn in 2D using ChembioDraw Ver.13. The 2D structure was then converted into a 3D structure using Chembio 3D ultra Ver.13 and minimized the energy stored in the form of SYBYL.mol2. The docking process uses the Molegro Virtual Docker 5.5 program. The results obtained are the rank score (RS). Docking validation by determining the RMSD score. Root Mean Square Deviation) which has a conditional value of 2 (Angstrom).

Prediction of ADME (Absorption, Metabolism, Distribution, Excretion) and prediction of *ames toxicity* using the pkCSM tool (http://biosig.unimelb.edu.au/pkcsm/). pkCSM Tool is a new method for predicting and optimizing the pharmacokinetic properties and toxicity of small molecules. pkCSM Tool is a web service that can be used for the analysis and optimization of the pharmacokinetic properties (Absorption, Distribution, Metabolism, and Excretion) of a compound and its toxicity properties [5]. Prediction of toxicity value using Protox II (https://tox-new.charite.de/protox_II/). ProTox-II is a free web service and users can make toxicity predictions for the test compound. Prediction of compound toxicity in the form of toxicity class classification based on the Globally Harmonized System (GHS). Use of the app starts by getting the compound SMILE code from ChembioDraw Ver.13. then the SMILE code is copied into the column listed on the web which will be processed and data related to the ADMET value is obtained.

RESULT AND DISCUSSION

The structure of scaffold is given in figure. Total sixteen derivatives of the designed scaffold were prepared using ChemDraw and their structures are given in figure.

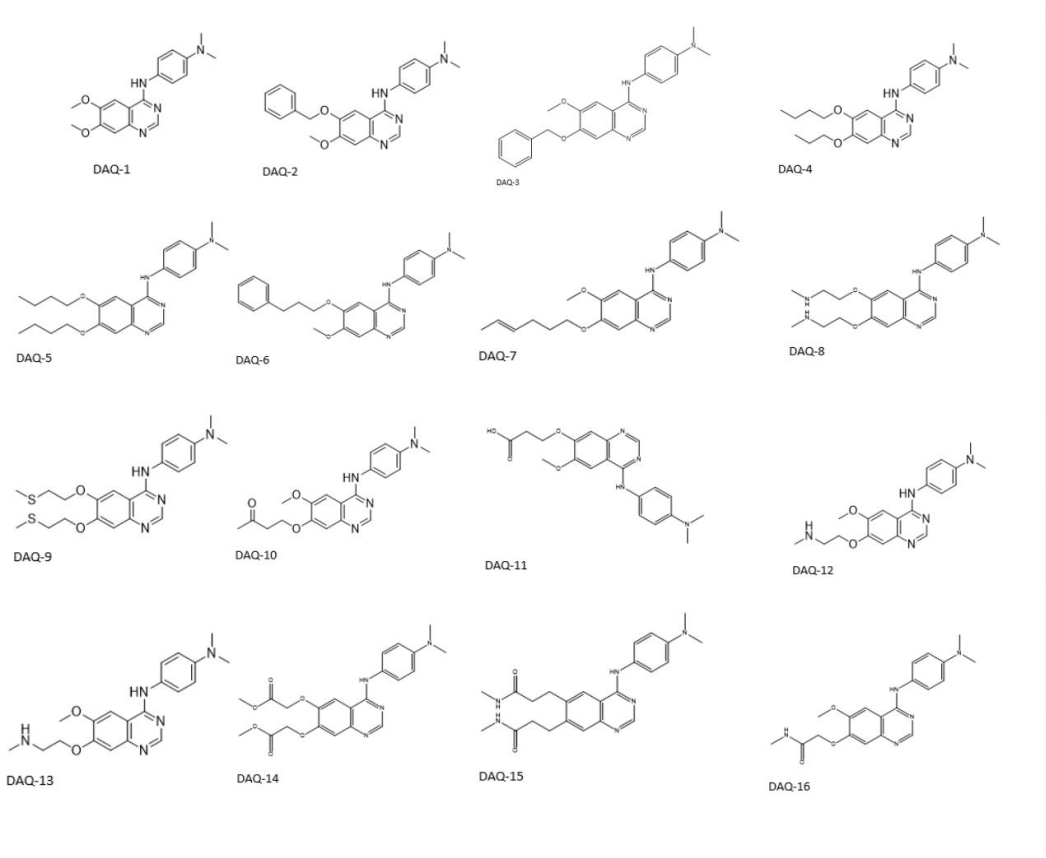

Figure 2. structure compounds of **dimethyl amino substituent quinazoline derivatives**

In Silico Computational drug design is a molecular modeling in order to design, discovering, and optimizing bioactive compounds for drug development processes. In silico study is carried out by docking the compound molecules to be predicted on the cell the chosen target . In this study, docking First, native ligands use Molegro Virtual Docking. Results of docking native ligand is the value of Root Mean Square Deviation (RMSD). Score RMSD is used as validation of the method used. RMSD is a measurement of two poses through comparison the structure that is docked on the protein with the atomic position between the structure experimental. The RMSD value 2Å indicates that the method used is has been valid. In addition, the smaller the resulting RMSD value indicates the pose of the ligand is getting closer to the conformation of the native ligand so that it shows better results [6].

Table 1: Docking scores of erlotinib as native ligand with Tyrosine Kinase as Protein Target

COMPUND	RERANK SCORE (kcal/mol)	RMSD
ERLOTINIB	-95,62	1,51

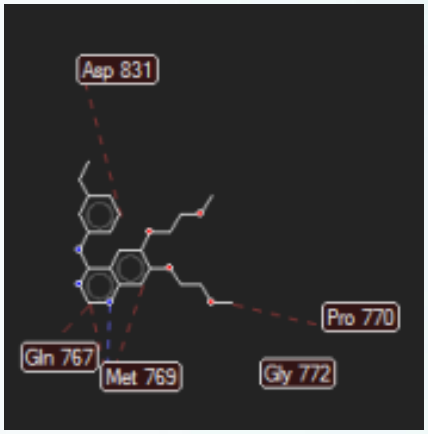

Figure 2. Interaction Erlotinib (native ligand) with Tyrosine Kinase as Protein Target

Furthermore, docking of control compounds and test compounds on native ligands and obtained the Rerank Score of each compound. Rerank Score (RS) is the bond energy which indicates the energy required to form a bond between the receptor and the ligand. The smaller the Rerank Score indicates the more stable the resulting bond. Bond stability of a ligand with the receptor indicating the greater the activity produced [6].

Table 3 : Docking scores of dimethyl amino quinazoline derivates with Tyrosine Kinase as Protein Target

NO	COMPOUND	RERANK SCORE (kcal/mol) (TYROSINE KINASE; PDB: 1M17)
1	DAQ-1	-81,68
2	DAQ-2	-99,70
3	DAQ-3	-96,30
4	DAQ-4	-89,71
5	DAQ-5	-81,93
6	DAQ-6	-99,30
7	DAQ-7	-72,05
8	DAQ-8	-78,44
9	DAQ-9	-92,60
10	DAQ-10	-85,41
11	DAQ-11	-61,33
12	DAQ-12	-74,63
13	DAQ-13	-85,41
14	DAQ-14	-81,93
15	DAQ-15	-86,18
16	DAQ-16	-87,19

Lipinski's rule is used to describe the solubility of a certain compounds that can penetrate cell membranes by passive diffusion. It can determine the physicochemical properties of the ligands, namely the hydrophobic or character hydrophilicity of a compound through docking simulation. Based on Lipinski's Rule in the development and discovery of a candidate If a drug is used orally, it must meet the following five requirements: known as the "Rule of Five" includes a molecular weight of not more than 500 daltons, have good lipophilicity (expressed with a log P of not more than 5), no more than 5 hydrogen bond donors, no more than 5 hydrogen bond acceptors than 10 and the rotatable bond is less than 10 [7].

Table 4 : Prediction physicochemical properties of dimethyl amino quinazoline derivates

NO	COMPOUND	Molecular weight (≤500 Dalton)	LogP (1 < Log P < 5)	Rotatable Bonds (<10)	Acceptors (<10)	Donors (<5)
1	DAQ-1	328,384	3.4566	5	6	1
2	DAQ-2	400,482	5,027	7	6	1
3	DAQ-3	400,482	5,027	7	6	1
4	DAQ-4	400,482	5,027	7	6	1
5	DAQ-5	408,546	5,797	11	6	1
6	DAQ-6	400,482	5,027	7	6	1
7	DAQ-7	392,503	5,183	9	6	1
8	DAQ-8	410,522	2,636	11	8	3
9	DAQ-9	444,626	4,923	11	8	1
10	DAQ-10	380,448	3,806	8	7	1
11	DAQ-11	382,420	3,302	8	7	2
12	DAQ-12	367,453	3,046	8	7	2
13	DAQ-13	382,42	2,999	7	8	1
14	DAQ-14	440,456	2,543	9	10	1
15	DAQ-15	434,544	2,7966	9	6	3
16	DAQ-16	381,436	2,573	7	7	2
17	Erlotinib (native Ligand)	393,443	3,405	10	7	1

The pharmacokinetic parameter of absorption prediction is based on the permeability of CaCo2. The permeability value of Caco-2 can predict drug absorption in humans through the intestinal epithelial cell barrier. The pharmacokinetic parameters of the predicted distribution are based on VDss, BBB permeability, CNS permeability. The volume of distribution (VDSS) is the theoretical volume that the total dose of drug needs to be distributed evenly to provide the same concentration as in blood plasma. The higher the VD value, the more drug is distributed in the tissues rather than the plasma.

It is generally known that most of the metabolic reactions involve oxidation processes. Cytochrome P450 is an important detoxifying enzyme in the body, mainly found in the liver. Works by oxidizing foreign organic compounds, including drugs, and facilitating the excretion of these compounds. Therefore it is important to assess the ability of the compounds to inhibit cytochrome P450, which in this study is represented by the cytochrome CYP3A4 isoform.

To predict the excretion process of compounds can be done by measuring the Total Clearance constant (CLTOT) and Renal Organic Cation Transporter 2 (OCT2) substrate. CLTOT is a combination of hepatic clearance (metabolism in the liver and bile) and renal clearance (excretion through the kidneys). This is related to bioavailability, and is important for determining the dose level in achieving steady-state concentrations

Table 5 : Prediction of ADME properties of dimethyl amino quinazoline derivates

NO	COMPOUND	**Absorption** (Cao-2 permeability log Papp in 10^{-6} cm/s)	**Distribution** VDss (human) (log L/kg)	**Metabolism** CYP3A4 substrate	**Excretion** Total Clearance (log ml/min/kg)
1	DAQ-1	**1.312**	**0.019**	Yes	**0.4**
2	DAQ-2	**1.193**	**-0.097**	Yes	**0.325**
3	DAQ-3	**1.657**	**-0.564**	Yes	**0.418**
4	DAQ-4	**1.142**	**0.497**	**Yes**	**0.461**
5	DAQ-5	**1.139**	**0.579**	**Yes**	**0.483**
6	DAQ-6	**1.209**	**-0.094**	Yes	**0.358**
7	DAQ-7	**1.699**	**0.111**	Yes	**0.525**
8	DAQ-8	**1.048**	**1.798**	Yes	**0.811**
9	DAQ-9	**1.133**	**0.505**	Yes	**0.4**
10	DAQ-10	**1.203**	**0.048**	Yes	**0.503**
11	DAQ-11	**0.309**	**-0.797**	No	**0.454**
12	DAQ-12	**1.108**	**1.079**	Yes	**0.881**
13	DAQ-13	**1.242**	**-0.106**	Yes	**0.54**
14	DAQ-14	**0.126**	**-0.298**	Yes	**0.613**
15	DAQ-15	**0.323**	**0.076**	Yes	**0.523**
16	DAQ-16	**1.139**	**0.041**	Yes	**0.465**
17	Erlatinib (native Ligand)	**1.238**	**-0.053**	Yes	**0.591**

In general, toxicity tests can be grouped into toxicity tests short-term/acute and long-term/chronic toxicity tests. LD50 used to assess the potential short-term toxicity of a substance. LD50 defined as a statistical sign on the administration of

a substance as a single dose which can cause 50% death in test animals [8]. The classification of compound toxicity classes is based on on the Globally Harmonized System are as follows.

Table 6: Toxicity class based on Globally Harmonized System (GHS)

Class	Description	LD50 Dose
I	fatal if swallowed	LD50 ≤ 5
II	fatal if swallowed	5 < LD50 ≤ 50
III	toxic if swallowed	50 < LD50 ≤ 300
IV	harmful if swallowed	300 < LD50 ≤ 2000
V	may be harmful if swallowed	2000 < LD50 ≤ 5000
VI	non-toxic	LD50 > 5000

To determine the level of toxicity, the test compounds will be categorized based on the class of toxicity through the LD50 value. Predicted LD50 value and grade the toxicity of the test compounds was obtained through prediction using the Protox Online Tool. Based on the prediction results, the LD50 value and toxicity class for each each test compound. *Ames toxicity* test is a test used to determine the presence of mutagenic potential in a compound. If a positive test result is obtained, it indicates that the compound is mutagenic and can act as a carcinogen [6].

Table 7 : Toxicity prediction of dimethyl amino quinazoline derivates

NO	COMPOUND	LD_{50}	Class	AMES TOXICITY
1	DAQ-1	1190mg/kg	4	NO
2	DAQ-2	125mg/kg	3	YES
3	DAQ-3	1190mg/kg	4	NO
4	DAQ-4	125mg/kg	3	NO
5	DAQ-5	125mg/kg	3	NO
6	DAQ-6	3550mg/kg	5	YES
7	DAQ-7	125mg/kg	3	NO
8	DAQ-8	125mg/kg	3	NO
9	DAQ-9	1190mg/kg	4	NO
10	DAQ-10	125mg/kg	3	NO
11	DAQ-11	1190mg/kg	4	NO
12	DAQ-12	1190mg/kg	4	NO
13	DAQ-13	1190mg/kg	4	NO
14	DAQ-14	125mg/kg	3	NO
15	DAQ-15	1190mg/kg	4	YES
16	DAQ-16	125mg/kg	3	NO
17	Erlotinib (native Ligand)	125mg/kg	3	NO

Docking study showed some compound have lower binding affinity rather than erlotinib as native ligan. Erlotinib has rerank score at -95,62. Compound DAQ-2, DAQ-3 and DAQ-6 have rerank score at -99,70; -96,30;-99,30 lower than erlotinib. Although the rerank score is better, the value of drug likeness of the three compounds has a log P value slightly higher than 5, which is based on Lipinski's rule, the log P value is not greater than 5.
Toxicity prediction based on LD50 of DAQ-2 in class 3, DAQ-3 in class 4, DAQ-6 in class 4, while erlotinib itself has a poor predictive value for toxicity, namely in class 3. Prediction of ames toxicity give result that DAQ-3 was NO potential to be mutagencic, meanwhile DAQ-2 and DAQ-6 give YES result, which propbably had potential tobe mutagenic. From a review of several parameters, the DAQ-6 compound is the most designed result well, So that possible quinazoline derivates can be potential Tyrosine Kinase Inhibitor as anti cancer

CONCLUSION

This study indicates that dimethyl amino quinazoline-3 (DAQ-3) has potential Tyrosine kinase inhibitor as anti cancer activity with lower toxicity

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest regarding the publication of this paper

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