

Design and Molecular Docking Studies of Quinazoline Derivatives as Antiproliferation

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Abstract

Background: Nowadays, a lot of new active substances as anticancer agents have been developed. One of the protein targets of anticancer is selective cyclooxygenase-2 (COX-2). Selective COX-2 is the regulator of cell proliferation. *Objective:* In this research, quinazoline derivatives were used to design the anticancer agent through a selective COX-2 inhibition. The potential activity of quinazoline derivatives could be increased by substitution in position 2 and 3 of quinazolinone. Molecular docking of selective COX-2 inhibition was required to predict their antiproliferation activity. *Methods:* The molecular docking of quinazoline derivatives was carried out using Molegro Virtual Docker (MVD) Ver.5.5. Twenty-one of quinazoline derivatives were docked into selective COX-2 with PDB code 3LN1. The interaction was evaluated based on the re-ranked score comparison between quinazoline derivatives with co-crystallized ligand CEL_682. Celecoxib was used as the reference to this research. *Results:* The result indicated that 18 of 21 quinazoline derivatives showed the approximately re-ranked score -131.508 to -108.418 kcal/mol. Eight of these 18 new quinazoline derivatives have re-ranked score better than Celecoxib. *Conclusions:* In conclusion, 8 of the new quinazoline derivatives are feasible to be synthesized and performed their in vitro evaluation.

Keywords: quinazoline derivative, molecular docking, selective COX-2, antiproliferation

Abstrak

Pendahuluan: Saat ini, banyak zat aktif baru sebagai senyawa antikanker telah dikembangkan. Salah satu target protein antikanker adalah siklooksigenase-2 (COX-2) selektif. COX-2 selektif adalah regulator proliferasi sel. *Tujuan:* Dalam penelitian ini, turunan kuinazolin digunakan untuk merancang senyawa antikanker melalui hambatan COX-2 selektif. Aktivitas dari turunan kuinazolin dapat ditingkatkan dengan penambahan gugus pada posisi 2 dan 3 dari kuinazolinon. Penambahan molekul penghambat COX-2 selektif diperlukan untuk memprediksi aktivitas antiproliferasinya. *Metode:* Penambahan molekul turunan kuinazolin dilakukan dengan menggunakan Molegro Virtual Docker (MVD) Ver.5.5. Dua puluh satu dari turunan kuinazolin dilakukan penambahan molekul pada COX-2 selektif dengan kode PDB 3LN1. Interaksi dievaluasi berdasarkan perbandingan nilai re-rank antara turunan kuinazolin dengan ko-kristalin ligan CEL_682. Selekoksisib digunakan sebagai acuan untuk penelitian ini. *Hasil:* Hasil penelitian menunjukkan bahwa 18 dari 21 turunan kuinazolin diketahui memiliki nilai re-rank sebesar -131,508 sampai -108,418 kkal/mol. Delapan dari 18 turunan kuinazolin yang baru memiliki nilai re-rank yang lebih baik dari Selekoksisib. *Kesimpulan:* 8 dari turunan kuinazolin yang baru pantas untuk disintesis dan dilakukan evaluasi in vitro.

Kata kunci: turunan kuinazolin, penambahan molekul, COX-2 selektif, antiproliferasi

INTRODUCTION

Cancer has caused a major problem in developed as well as undeveloped countries. In 2012, *GLOBOCAN*, *International Agency for Research on Cancer (IARC)* reported 14.1 million has been indicated as a new cancer

case and 8.2 million people have died due to cancer. Breast cancer was indicated as new higher case than another cancer disease (IARC, 2012). There are many chemotherapeutic strategies for the anticancer treatment that have been proposed and tested in some cases. The

main procedures of cancer treatment are surgery, irradiation, and chemotherapy. Although the chemotherapeutic management has been conducted and has been showed major advances for patients, the continuous research for new anticancer agent remains important (EL-Azab *et al.*, 2010).

In the field of medicinal chemistry, chemical agents are very important for designing novel agents. One of agents known as a lead compound of anticancer drug is quinazoline (Noolvi & Patel, 2011). Quinazoline is a fused bicyclic heterocyclic framework which known as benzo-1,3-diazanaphthalene. Numerous compounds of quinazolines have been reported to have biological and pharmacological activities such as antimicrobial, antitumor, antimitotic, anticancer and others (Zayed *et al.*, 2015). In the past, drug development is based on trial and error so it was very expensive and long time. Today, molecular modelling with the aid of computer hardware and software are deducted this risk, the process of discovery is more effective in cost and time (Noolvi & Patel, 2011).

Maybe synthesized synthesis of quinazolines by adding substituted binding group such as phenyl ring at position 2-, imines at position 3, and chloro in position 7 of quinazoline rings (Noolvi & Patel, 2013). This substituted was used to increase the activity of cancer cells inhibition. Quinazolines works as anticancer agent through potent inhibition in various enzymes such as epidermal growth factor receptor tyrosine kinase (EGFR-TK), dihydrofolate reductase, folate thymidylate synthase, tyrosin kinase, aldose reductase, cyclic GMP phosphodiesterase and DNA repairing enzymes (Zayed *et al.*, 2015).

The discovery of quinazoline derivatives aimed to design the anticancer agent through cyclooxygenase-2 (COX-2) inhibition. COX-2 is a family of myeloperoxidase located at luminal side of reticulum and nuclear membrane. This enzyme is not detected in most normal tissue, but the increasing of COX-2 enzyme is detected in both premalignant and malignant tissues (Danneberg *et al.*, 2006). Overexpression of COX-2 has accelerated biosynthesis of prostaglandin E₂ (PGE₂) which modulates cell proliferation and apoptosis mainly in solid tumors such as colorectal, breast and prostate cancers and more recently, in hematological malignancy (Sobolewski *et al.*, 2009).

This study aims to design and discover new active substances better than previous compounds by using 1 molecular docking. Docking of ligands to the protein of interest followed by scoring to determine the binding affinity and the strength of interaction (Noolvi & Patel, 2013).

Twenty one of quinazoline derivatives were docked into COX-2 extracted from protein data bank (PDB code 3LN1), by utilizing Molegro Virtual Docker Ver. 5.5 docking software. Quinazolines were docked and scored to identify the ligands that bind similarly to the reference ligand for COX-2 (Celecoxib).

Re-rank score comparison between quinazolines with co-crystalline ligand CEL_682. The potential anticancer activity of quinazolines could be increased by substitution in position 2 and 3 (Noolvi & Patel, 2013). The substitution position 2 such as 4-nitrophenyl, 2,4-dichlorophenyl and 3,4-dichlorophenyl of quinazolinone. And then, substitution in position 3 such as 3-(substitutedbenzylideneamino) of quinazolinone.

MATERIAL AND METHODS

Design of new quinazoline derivatives

The role of the new drug development are (i) determining lead compound, (ii) manipulating the substituent of lead compound (iii) determine the list of new substituents. In this study, quinazoline is a new lead compound of anticancer agent (Noolvi & Patel, 2011). The Substituents are selected for designing new compound. These substituents are consist of -NO₂, OCH₃, -OH, -N(CH₃)₂, -Cl. They are substituted in benzylideneamino group.

Preparation of target protein x-ray structure

The crystal structure of human COX-2 (PDB ID 3LN1) was selected as the protein target downloaded from <http://www.pdb.org/>.

Ligands preparation

The structure of quinazoline derivatives were drawn by using Chem Bio Draw Ultra ver 13.0 (Cambridge Soft). The 2D structure of compounds were converted to the 3D structure utilizing ChemBio 3D 13.0. The optimization molecule and minimization geometry of the ligand were performed using MMFF 94 method and saved as an SYBYL.mol2 format, to be read by Molegro Virtual Docker program.

Molecular docking studies

Molecular docking is the computational simulation of a ligand binding to a receptor, which helps to predict binding molecule to the protein target in order to predict the affinity and activity. The study of quinazoline derivatives and cyclooxygenase-2 interaction were evaluated by using molecular docking techniques on Molegro Virtual Docker (MVD) Ver.5.5. (CLC Bio). We used the crystal structure of human COX-2 (code 3LN1, <http://www.pdb.org/>) as the protein target. Prior to screening the ligands, docking protocol was validated by re-docking 3LN1 ligand into its binding pocket within the COX-2 crystal to obtain the docked pose and RMSD. The protocol is good in reproducing the X-ray crystal structure in complex forms for further docking experiments.

RESULTS AND DISCUSSION

Virtual screening experiments are the most convenient way to incorporate protein in the docking process by performing docking using an ensemble of static receptor conformations. Molecular docking is used in modern drug design to help understand interaction ligands and receptor. These technique are support to design of novel drug which have specific activity by the mechanism of drug receptor interaction. Computer aided drug design (CAAD) helps to identify small molecules by orienting and scoring them in the active binding site a protein (Elangovan *et al.*, 2013).

The docking simulation technicque was performed by using Molegro Virtual Docker (MVD) Ver.5.5. with quinazoline derivatives and they were docked with cyclooxygenase-2 as protein target. This program selected the best docked based on two criteria such as ligand binding position and fitness function scores comparison. The parameter to identify the best ligand binding

position was the root-mean square distance (RMSD). The interaction between quinazolines and CEL_682 with COX-2 is shown in Figure 1.

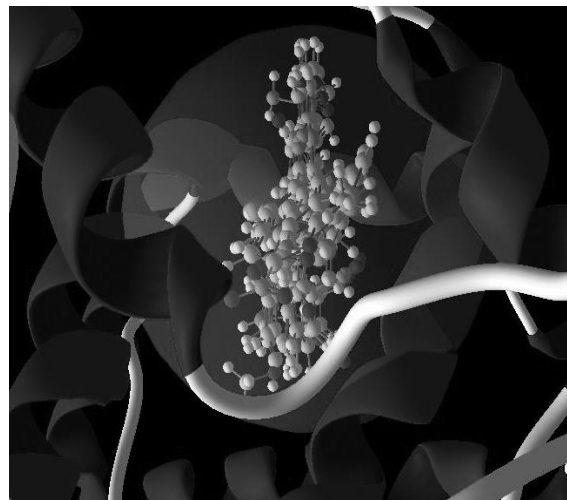


Figure 1. 3D Structure of quinazoline derivatives and CEL_682[A] interact with COX-2

Re-rank score is a value that reflects the binding energy required to form a bond between the ligand and receptor, which predict the activity of compounds. It also causes the bond between the ligand and receptor be more stable. The binding energy value of quinazolines is shown in Table 1. Generally, the obtained eighteen of twenty-one quinazoline derivatives showed the approximate re-rank score -131.508 to -108.418 kcal/mol. In the Table 2 shows that there are eight quinazoline compounds which value that have greater re-rank score compared to celecoxib. Compound 2 had higher binding energy than other quinazoline derivatives because it has the smallest re-rank score (-131.508 kcal/mol) but it was not similar with CEL_682[A]. Otherwise, the molecule 1, 15 and 17 from 8 compounds occupied all the three pocket regions and similar binding modes as observed with CEL_682[A].

Table 1. Re-rank Score of Quinazoline Derivatives with COX-2

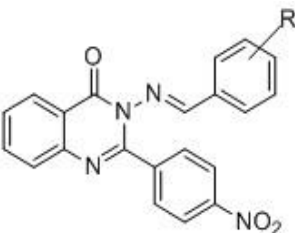
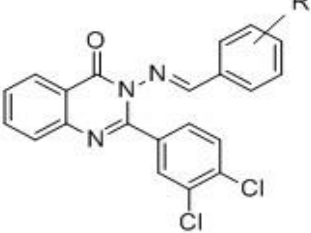
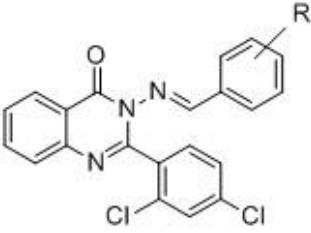
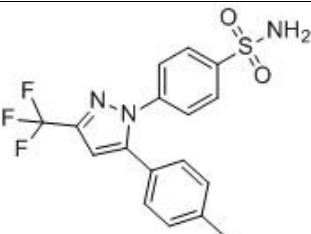
Serial No.	Chemical Structure	R ₁	Re-rank Score	Docked Pose
1		H	-127.35	√
2		2-NO ₂	-131.51	x
3		3-NO ₂	-120.20	x
4		4-NO ₂	-121.90	x
5		4-OCH ₃	-129.56	x
6		4-OH, 3-OCH ₃	-119.88	√
7		4-N(CH ₃) ₂	202.41	x
8		H	-120.96	√
9		2-NO ₂	-128.41	x
10		3-NO ₂	-121.50	√
11		4-NO ₂	-115.55	x
12		4-OCH ₃	-113.12	x
13		4-OH, 3-OCH ₃	-117.01	x
14		4-N(CH ₃) ₂	34.94	x
15		H	-121.65	√
16		2-NO ₂	-123.22	x
17		3-NO ₂	-122.56	√
18		4-NO ₂	-108.42	x
19		4-OCH ₃	-113.54	x
20		4-OH, 3-OCH ₃	-114.14	x
21		4-N(CH ₃) ₂	131.51	x
Celecoxib			-121.51	

Table 2. Hydrogen Bond Interaction of Quinazoline Derivatives with COX-2

Serial. No.	Re-rank Score	Hydrogen bond	Docked Pose
1	-127.345	No	√
2	-131.508	Arg 106, Ser 506, Tyr 341, Tyr 371	x
4	-121.902	Arg 106, Tyr 371	x
5	-129.558	Ser 516, Tyr 341, Tyr 371	x
9	-128.405	Arg 106, Tyr 341	x
15	-121.651	Tyr 341	√
16	-123.224	Arg 106, Tyr 341	x
17	-122.560	Tyr 341	√
Celecoxib	-121.506	Tyr 371	

The hydrogen bond interaction of 8 compounds from quinazolines is showed in Table 2. Compound 1 has no hydrogen bond interaction with protein residues. The molecules of compound 2, 4 and 5 have similar interaction with celecoxib in hydrogen bond with protein

residue (Tyr 37). The 4-nitrophenyl ring in position 2 of quinazolinone has similar interaction with Tyr 371 in compound 2 and 5. However different with compound 2, the interaction with Tyr 371 was known in position 4 of benzyledenamino quinazolinone ring. One of them which

has the lower re-rank score is compound 2. Compound 2 was substituted 4-nitrophenyl moiety at C-2 and 4-nitrobenzylideneamino at N-3. This means it has

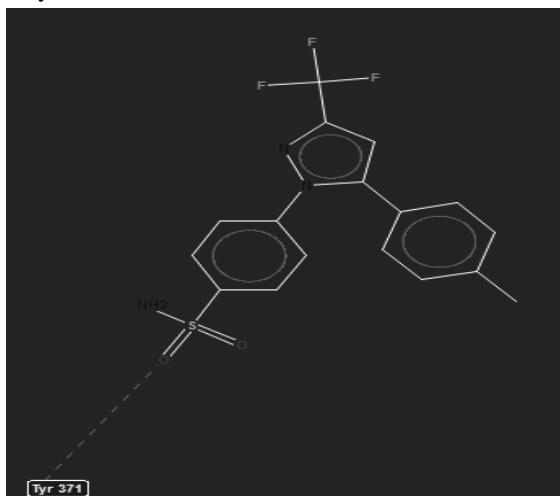


Figure 2. 2D Structure of CEL_682[A] interact

higher binding energy to interact with target receptor. The interaction compound 2 and hydrogen bond is showed in Figure 3 and celecoxib in Figure 2.

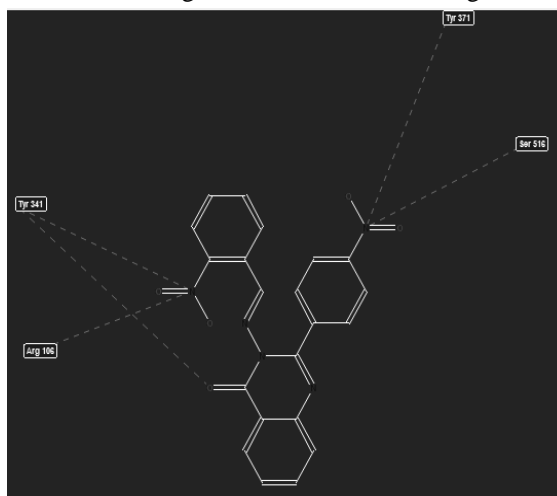


Figure 3. 2D Structure of substance with COX-2 with COX-2

CONCLUSION

Twenty-one molecular structure of 2,3-disubstituted-4-3(H)-quinazolinones possessing, phenyl moiety bound in position 2 and substitutedbenzylideneamino in position 3 have been docked and score obtained identify the ligands that bind similar orientation as observed with CEL_682 binding for COX-2. The result shows that 2,3-disubstituted-4-3(H)-quinazolinones possessing 4-nitrophenyl moiety at C-2 and 4-nitrobenzylideneamino at N-3 showed lower re-rank score than other quinazolines and celecoxib. It means it has higher binding energy interaction with target receptor. The molecule 1, 15 and 17 were occupied all the three pocket regions and similar binding modes as observed with CEL_682[A]. Therefore, these compounds could be considered as potent COX-2 inhibitor. For further investigation, synthesis and *in vitro* evaluation are required to get activity against cancer cell.

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