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A MOLECULAR DOCKING STUDY OF EPOXYXANTHONES TOWARD NON-SMALL AND SMALL CELL LUNG CANCER TARGET PROTEINS

M.R. Iresha[1,2], J. Jumina[1,✉], H.D. Pranowo[1,2], E.N. Sholikhah[3] and F. Hermawan[1,2]

[1]Department of Chemistry, Faculty of Mathematics and Neutral Sciences, Universitas Gadjah Mada, Sekip Utara, Yogyakarta, Indonesia, 55281.

[2]Austrian-Indonesian Centre (AIC) for Computational Chemistry, Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Gadjah Mada, Sekip Utara, Yogyakarta, Indonesia, 55281.

[3]Department of Pharmacology and Therapeutic, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Sekip Utara, Yogyakarta, Indonesia, 55281.

✉Corresponding Author: jumina@ugm.ac.id

ABSTRACT

Molecular docking studies have been used to evaluate the anticancer activity of the epoxyxanthones against non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). A series of twenty-four xanthone compounds possessing epoxy and hydroxy substituents have been designed and investigated. The epoxyxanthone derivatives were docked in the active site of EGFR and KIT tyrosine kinase proteins to examine their inhibition activity toward two types of lung cancer, i.e., NSCLC and SCLC, respectively. The xanthone derivatives were successfully docked in a similar binding mode to native ligands on EGFR and KIT proteins with free binding energies ranging from -7.51 to -6.35 and -9.58 to -7.06 kcal/mol, respectively. It was found that compound XE9 exhibited the most promising activity with a free binding energy value of -9.58 and -7.51 kcal/mol against KIT and EGFR proteins, respectively. This study discovered that XE9 has potency as a therapeutic agent used as the SCLC and NSCLC inhibitors or used in the combination of the cells found in lung cancer.

Keywords: Epoxyxanthone, Xanthone, Molecular Docking, Autodock, Lung Cancer.

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INTRODUCTION

Lung cancer is the most reported cancer case, and it is the leading cause of death in 93 countries as of today. Around 2.2 million annual new cases and 1.8 million annual deaths have been reported due to lung cancer in 2020.[1] Lung cancer can be categorized into two types, i.e., small cell lung cancer (SCLC, comprising 20% of lung cancers) and non-small cell lung cancer (NSCLC, comprising 80% of lung cancers).[2,3] The NSCLC is a lung cancer type with a high mortality rate as 75-80% of cancer cases are commonly found at an advanced stage.[4] The treatment of the disease requires further attention and development. Unfortunately, the current efficient drug treatment of NSCLC is still lacking. The epidermal growth factor receptor (EGFR) is one of the receptors belonging to RTKs. Inhibiting the EGFR receptor affects NSCLC lung cancer cells' activity.[5] EGFR is expressed in more than 60% of NSCLC cases; thus, it is chosen as a therapeutic target for curing the disease. Erlotinib and gefitinib are well-known tyrosine kinase inhibitors (TKIs) of EGFR as they have been approved as therapeutic agents for NSCLC treatment.[6] However, the 5-year survival rate has remained low (16%) in the last four decades. The efficacy of these molecule inhibitors has been caused by drug resistance.[7] In contrast to NSCLC, SCLC is a very aggressive form of lung cancer. The SCLC generally grows and spreads faster than NSCLC.[8] SCLC can be discovered as a pure SCLC or with NSCLC. SCLC combined with NSCLC was found in 28% of cases.[9] SCLC treatment is very responsive to cisplatin-based chemotherapy; however, the recorded recurrence cases frequently occur. The rapid progress of the recurred cancer resulted in a poor prognosis with a low survival rate in less than two years.[10] KIT as one of the RTK family has been reported as the primary target protein of lung cancer, especially co-expressed in

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70% of SCLC cell lines.[11] KIT activation in SCLC has also been shown to stimulate cell proliferation.[12] Extensive studies on the xanthones derivatives' effect on lung cancer cells have been reported and showed improved *in vitro* activity and drug-like properties.[13-14] Xanthone has a simple and interesting structural scaffold with diverse biological profiles.[15] Introducing new substituents to the xanthone core has been carried out to broaden its pharmacological activity. Xanthones containing epoxy group were reported to have inhibition ability of DNA chains of Topoisomerase II-α. Xanthone with two 2,3-epoxypropoxy substituents at the 3 and 5 positions gave high anticancer activity, as reported previously.[16] Molecular docking has been widely used to predict the therapeutic agent activity of xanthone derivatives.[17] However, an extensive study regarding the effect of varying epoxy substituents on the bioactivity of xanthone compounds has not been carried out, especially for its potential usage as a chemotherapy agent for lung cancer. In this report, an investigation of the free binding energy and inhibition activity of epoxyxanthone derivatives against EGFR and KIT proteins has been carried out to investigate its inhibition activity toward two types of lung cancer, i.e., NSCLC and SCLC.

EXPERIMENTAL

Materials

The crystal structures of active EGFR in the complex with erlotinib (PDB ID: 1M17) and wild-type KIT in the complex with sunitinib (PDB ID: 3G0E) were obtained from the Protein Data Bank (www.rcsb.org). Erlotinib was used as EGFR native ligand, and sunitinib was used as KIT native ligand. Twenty-four epoxyxanthone derivatives (XE1-XE24) were designed and used as drug candidates. The chemical structures of epoxyxanthones are shown in Fig.-1 and Table-1.

Proteins and Ligands Preparation

Proteins and native ligands were prepared by using Chimera software. The three-dimensional structures of native ligands were obtained from the crystal structures. The proteins and ligands structures were saved in .pdb format. The three-dimensional structure of 24 epoxyxanthone derivatives (XE1-XE24) was prepared and optimized in Gaussian 09 using DFT (B3LYP/6-31G) prior to the molecular docking study.

Molecular Docking Studies

The molecular docking simulations were performed similarly to the previously reported study.[18] The grid box was defined using a 60 Å box (x, y, and z) with 0.375 Å of spacing. All parameters were kept as default. Afterward, the binding energy of epoxyxanthone derivatives and native ligands that interacted with protein targets were calculated using AutoDock 4.2 software. The program used the calculated interaction energy to score and rank each evaluated compound. Then, the docking results were visualized using Discovery Studio Visualizer 2019.

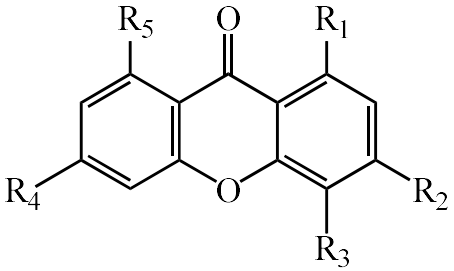


Fig.-1: The Core Structure of Xanthone

Table-1: List of Epoxyxanthone Derivatives with Different Associated Substituents

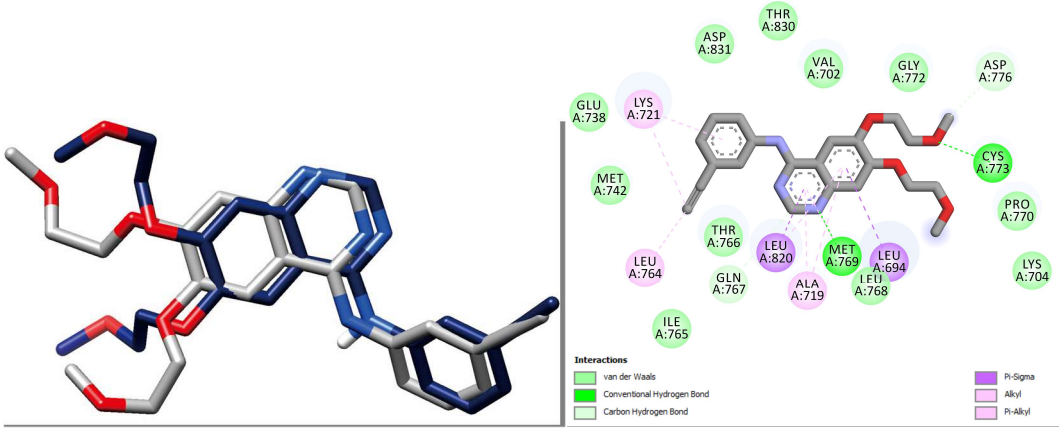
Compound	R_1	R_2	R_3	R_4	R_5
XE1	E	E	H	H	OH
XE2	E	E	H	H	E
XE3	H	E	E	H	OH
XE4	H	E	E	H	E
XE5	H	E	E	OH	H
XE6	H	E	E	E	H
XE7	E	E	H	E	H

XE8	E	E	H	OH	H
XE9	E	OH	H	E	H
XE10	OH	E	H	E	H
XE11	OH	E	H	H	E
XE12	E	OH	H	H	E
XE13	H	OH	E	H	E
XE14	H	E	OH	H	E
XE15	H	OH	E	E	H
XE16	H	E	H	E	H
XE17	OH	E	H	H	H
XE18	H	E	H	H	H
XE19	E	E	H	H	H
XE20	E	OH	H	H	H
XE21	H	E	OH	H	H
XE22	E	H	H	H	H
XE23	H	E	E	H	H
XE24	H	OH	E	H	H

E: epoxy group (-CH_2CHCH_2O)

RESULTS AND DISCUSSION

This present study investigated epoxyxanthone's interaction with EGFR and KIT proteins to find the best position for the ligand in the receptor-binding site. Epoxyxanthone derivatives were designed through a chemical modification by combining the xanthone structure and epoxy group. The correlation between epoxy group number and positions in the xanthone core (XE1-XE24) to their inhibitory activity was observed. This study also inspected hydroxy group addition (XE1, XE3, XE5, XE8, XE9, XE10, XE11, XE12, XE13, XE14, XE15, XE17, XE20, XE21, and XE24) and its effect on epoxyxanthones inhibition activity toward EGFR and KIT proteins. The redocking process was used to validate native ligand binding mode back into their corresponding crystal structures and adjust the docking parameters. Our previous study carried out the redocking of sunitinib to the KIT binding site.[18] Erlotinib was successfully docked to the EGFR binding site with root means square deviation (RMSD) and energy binding values of 1.56 Å and -7.08 kcal/mol, respectively. The RMSD value less than 2 Å was used as a parameter of the success of docking analysis.[19] Erlotinib compound is classified as a competitive inhibitor that can interact in a similar binding spot as ATP-EGFR.[20] The erlotinib as the native ligand of EGFR was docked into the active site of EGFR (Fig.-2). Erlotinib interaction with the EGFR protein was stabilized by two hydrogen bonds between the nitrogen atom with MET769 and the oxygen atom with CYS773. It also possessed two carbon-hydrogen bonds (GLN767 and ASP776), and six hydrophobic interactions (LEU694, LEU820, ALA719, GLN767, LEU764, and LYS721) were observed with the amino acid residues of EGFR protein.



(a) (b)

Fig.-2: (a) 3D Structure of Erlotinib from X-Ray Crystal (grey) Overlapped with Erlotinib from Redocking Results (navy); (b) 2D Redocking Results of Erlotinib in Activated EGFR (PDB: 1M17)

Molecular Docking Study of Epoxyxanthones in the Active Site of EGFR

Molecular docking of 24 epoxyxanthone derivatives was conducted using the resulting binding site from the redocking analysis of the erlotinib-EGFR binding pose. The epoxyxanthone derivatives (compounds XE1-XE24) have a similar binding orientation when docked into the ATP binding site of EGFR. This result was shown by a hydrogen bond with MET769 amino acid residue of EGFR protein. The epoxyxanthone ligands were docked to obtain 100 predicted possible conformations that are grouped by their conformation similarities. The ligand conformation with the lowest free binding energy and the most similar binding pose with the reference was chosen as the most preferred ligand pose.[21] The negative energy score indicates a higher possibility for this compound to interact with the targeted protein.[22] The inhibition constant (Ki) value is also an important parameter in which a lower Ki value indicates a higher rate of ligand inhibition to the protein target.[23] The free binding energy, Ki, and intermolecular interaction of epoxyxanthone derivatives with EGFR protein are summarized in Table-2.

Table-2: Free Binding Energy, Ki, and Interaction of 24 Epoxyxanthone Derivatives and Native Ligand against EGFR and KIT Tyrosine Kinase Proteins

Compound	ΔG (kcal/mol) EGFR	Ki (μM)	Hydrogen bond interaction	ΔG (kcal/mol) KIT	Ki (μM)	Hydrogen bond interaction
XE1	-7.34	4.15	GLN767, MET769, GLY772, CYS773	-8.49	0.59	LYS593, GLU671, CYS673, GLY676, ASP677
XE2	-6.96	7.92	LYS721, MET769, CYS773	-8.77	0.37	LYS593, CYS673, ASP677
XE3	-6.89	8.95	LYS721, MET769	-8.55	0.54	LYS593, GLU671, CYS673, ASP677
XE4	-7.02	7.16	LYS721, MET769, ASP831	-7.29	4.68	CYS673, ASP677
XE5	-6.95	8.05	LYS721, MET769, ASP831	-8.30	0.82	LEU595, LYS623, CYS673, ALA814
XE6	-7.20	5.32	LYS721, MET769, CYS773	-8.24	0.92	LYS593, LYS623, CYS673
XE7	-7.10	6.20	THR766, MET769, CYS773, THR830	-9.22	0.17	LYS593, LYS623, CYS673, ASP677
XE8	-7.40	6.20	LYS721, MET769, PRO770, THR830	-8.44	0.62	LYS593, THR670, CYS673, ASP677
XE9	-7.51	3.13	LYS704, LYS721, GLN767, MET769	-9.58	0.10	LYS593, LEU595, LYS623, CYS673
XE10	-7.41	3.70	LYS721, GLN767, MET769, CYS773	-9.22	0.17	LYS623, CYS673, ASP677

XE11	-7.25	4.87	LYS721, GLN767, MET769, GLY772	-9.13	0.17	LYS623, GLU671, CYS673, GLY676
XE12	-6.85	9.55	LYS721, THR766, GLN767, MET769, CYS773	-8.08	1.19	CYS673, ASP677
XE13	-6.86	9.36	LYS721, THR766, MET769, THR830	-8.20	0.97	LYS593, CYS673, THR670
XE14	-7.30	4.44	GLN767, MET769, CYS773	-9.12	0.21	LYS593, CYS673, CYS809, ASP810
XE15	-6.35	22.23	LYS721, CYS773, MET769	-8.25	0.90	LEU595, LYS623, CYS673
XE16	-6.65	13.30	CYS773, MET769, ASP831	-8.17	1.03	LYS623, CYS673, ASP677
XE17	-6.91	8.56	THR766, GLN767, MET769, ASP831	-8.65	0.45	LYS623, GLU671, CYS673
XE18	-6.65	13.28	MET769, ASP831	-7.97	1.44	LYS593, CYS673
XE19	-6.87	9.27	MET769, LYS828	-7.47	0.68	LYS593, CYS673, ASP677
XE20	-6.81	10.21	LYS721, GLN767, MET769	-8.05	1.25	LYS593, LEU595, CYS673
XE21	-7.11	6.15	THR766, GLN767, MET769	-8.10	1.16	LYS593, CYS673
XE22	-6.70	12.17	LYS721, MET769	-7.81	1.90	LYS593, CYS673
XE23	-7.18	5.43	LYS721, MET769, ASP831	-8.23	0.93	LYS593, CYS673, ASP677
XE24	-6.37	21.54	MET769	-7.06	6.63	CYS673, ASP677
Sunitinib	-	-	-	-8.25	0.89	GLU671, CYS673, ASP677
Erlotinib	-7.08	6.46	MET769, CYS773	-	-	-

It was found that xanthones with hydroxy substituent have lower energy than compounds without hydroxy substituent in the xanthone core. A drastic change in the free binding energy value was observed between XE9 and XE12 from -7.51 to -6.85 kcal/mol, respectively. This result indicated that epoxy group positions influence anticancer activity. The number of epoxy substituents also affects the activity of these compounds, where the presence of one epoxy substituent provides a lower free binding energy value than native ligands. The same result was found in xanthones containing three epoxy substituents, where the amount caused a decrease in xanthone activity. The difference in substituent position would affect the ability of the epoxyxanthone compound to access the active site of the protein. The results showed that 10 epoxyxanthones were predicted to have promising inhibitory activity with lower binding energies (-7.51 to -7.1 kcal/mol) than erlotinib (-7.08 kcal/mol) when interacted with EGFR, which is remarkable. Among 24 epoxyxanthones, compound XE9 gave the most promising activity as it exhibited the lowest free binding energy value of -7.51 kcal/mol (Fig.-3). This result showed that epoxyxanthone with substituents in R_1, R_2, and R_4 had indicated a more stable conformation than the erlotinib-EGFR complex.

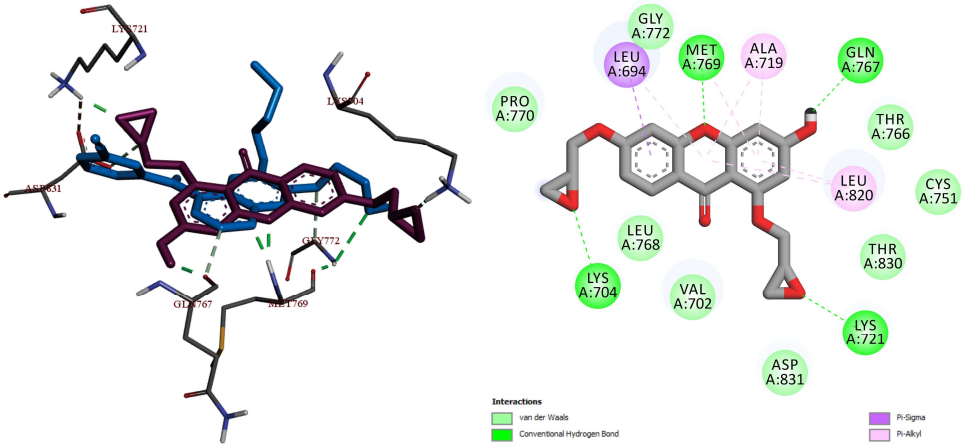


Fig.-3**:** 3D and 2D Docking Results of XE9 Compound against EGFR Protein

Molecular Docking Study of Epoxyxanthone in the Active Site of KIT

KIT gene in complex with SCF ligand is expressed in SCLC.[24] With the success of imatinib to inhibit KIT expressed gastrointestinal stromal tumors, its use in the SCLC therapeutic approach was then considered.[25] As a tyrosine kinase inhibitor, imatinib failed to exhibit any anticancer activity when used for treating SCLC patients in a clinical trial.[26] The lack of efficacy was observed among untreated patients and sensitive relapse patients.[27] The low activity of imatinib in the KIT is correlated with exons 9 and 11 mutations, thus reducing its efficacy to SCLC.[28] Sunitinib has been classified as an ATP-competitive inhibitor. Sunitinib treatment resulted in more significant tumor growth inhibition than imatinib treatment. The combination of sunitinib and cisplatin significantly delayed tumor growth. A recent *in vitro* study has shown the capability of sunitbeforereduce KIT phospho-tyrosine levels in SCLC cancers. The study showed that sunitinib holds the inactivated KIT by blocking its auto-activation.[29]

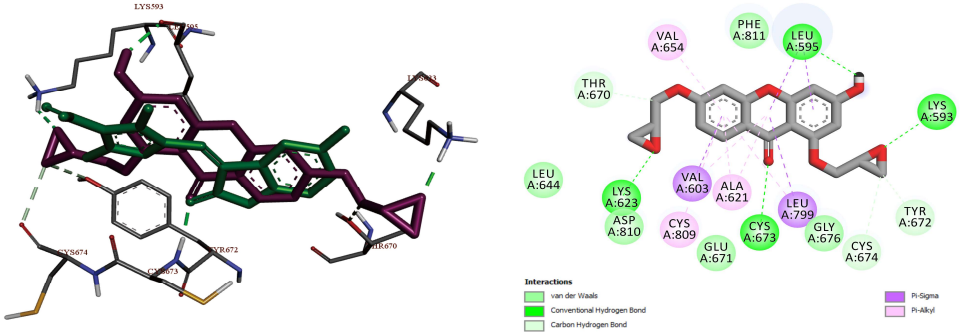


Fig.-4: 3D and 2D Docking Results of XE9 Compound against KIT Protein

Molecular docking of epoxyxanthone has been done in the same position as sunitinib in the KIT kinase domain. The epoxyxanthone derivatives (XE1-XE24) were successfully docked into the A-loop pocket in

the kinase domain of KIT and predicted to have preferable inhibitory activity. The docking results were proved by the hydrogen bond between epoxyxanthone and CYS673 amino acid residue of KIT, similar to the sunitinib-KIT complex. The free binding energy values of 12 epoxyxanthones (-9.58 to -8.25 kcal/mol) were lower than that of sunitinib (-8.25 kcal/mol) in its interaction with KIT (Table-2). It indicates that the inhibition ability of epoxyxanthone compounds in the ATP-binding pocket was better than sunitinib. The epoxyxanthones were expected to stabilize the KIT protein conformation in its inactive state, thus leading to apoptosis of targeted cancer cells. Hydrogen bonds involving oxygen atoms from the xanthone ring, as well as epoxy and hydroxy groups of xanthone substituent provide a strong bond of the compound to the binding site. The binding modes of xanthone compounds were also stabilized by hydrophobic interactions between aromatic rings and the KIT protein. The free binding energy, Ki, and intermolecular interaction of epoxyxanthone derivatives with KIT protein are summarized in Table-2. In general, epoxyxanthone compounds with two epoxy substituents and one hydroxy group gave good inhibitory activity. Meanwhile, epoxyxanthone with one epoxy substituent decreased the inhibitory ability of xanthone compounds. Among the evaluated epoxyxanthone compounds, the XE9 exhibited the best free binding energy values of -9.58 kcal/mol, which is much lower than sunitinib. The lowest free binding energy value of XE9 indicated the most stable interaction with the protein's binding site. The 3D and 2D docking results of XE9 against KIT protein are shown in Fig.-4. This result summarized that XE9 could bind strongly to both KIT and EGFR proteins. With the KIT and EGFR genes expressed possibility in the cancer cell, XE9 is expected to act as a new therapeutic agent targeting this SCLC/NSCLC combination. Further experimental studies on the XE9 were suggested to confirm the activity of this compound as a lung cancer therapeutic agent.

CONCLUSION

The present docking study estimates the inhibitory activities of 24 epoxyxanthone compounds. These epoxyxanthones were successfully docked in a similar binding mode to native ligands with free binding energies ranging from -7.51 to -6.35 and -9.58 to -7.06 kcal/mol against EGFR and KIT tyrosine kinase proteins, respectively. The results showed that compound XE9 fitted well in the active site of EGFR protein, and its ability to interact with the inactivated KIT binding pocket, which has a significant key in SCLC and NSCLC activities. From the docking results, XE9 has potency as an SCLC and NSCLC inhibitor agent or is used in the SCLC/NSCLC combination of the cells found in lung cancer. Therefore, the XE9 compound is recommended as a new anticancer drug candidate to be further evaluated in the future.

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