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DISCOVERY OF NOVEL DNMT-1 INHIBITOR BY FRAGMENT-BASED DRUG DESIGN AS A POTENTIAL BREAST CANCER TREATMENT

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ABSTRACT: Breast cancer is the most common and lethal type of cancer among women in the world. Epimutation is the leading cause of the tumorigenesis of breast cancer. DNA methyltransferase 1 (DNMT1) is the key enzyme involved in the regulation of DNA methylation pattern. In this research, the fragment-based drug design approach on natural products was performed to discover a novel inhibitor of the DNMT1 as a therapeutic strategy against breast cancer. About 2,601 fragments out of 168,646 compounds were obtained from the Lipinski's Rule of Three and toxicity screening. The fragments were docked into the S-Adenosyl-L-methionine (SAM) binding site of DNMT1. The potential fragments were merged with S-Adenosyl-L-homocysteine (SAH), generating nine ligands. The ligands underwent flexible docking simulation and ADME-Tox prediction by using AdmetSAR, Toxtree, SwissADME software. Three ligands show favorable characteristics as a new drug candidate for the DNMT1 inhibitor according to the interaction of the amino acid residues, RMSD, and $\Delta G_{binding}$. MAHI1 being the best ligands in term of $\Delta G_{binding}$ -12.6300 kcal/mol, molecular interaction, and pharmacological properties.

Keywords: Breast cancer, DNA methyltransferase, Natural products, Molecular docking simulation, Fragment-based drug design

1. INTRODUCTION

Cancer is a major public health problem worldwide [1]. Breast cancer is among the leading causes of death in women [2]. It is also the current most cancer in women worldwide with 1.7 million diagnosed cases [3]. The human genome consists of genetic information and epigenetic. Epigenetics regulate how and where genetic information should be used [4]. DNA methylation is one of the essential mechanism in functional epigenetic [5]. DNA methyltransferases (DNMTs) is the leading enzyme in the epigenetic regulation of gene expression in mammalian cells [6]. DNMT1 is the most abundant DNMTs in the mammalian cells and have a role in maintaining the methylation pattern [7].

DNA methylation, whether hypomethylation or hypermethylation, affects gene expression and chromosomal instabilities. Hypomethylation causes overexpression of transcription of proto-oncogenes, and reactivation of transposable elements and demethylation of xenobiotic [8]. On the other hand, hypermethylation causes suppression of tumor suppressor genes and downregulation of DNA repair genes. DNA hypermethylation also plays an essential role in silencing the tumor suppressor genes as one of the most consistent hallmarks of human cancer [7].

Aberrant DNMT1 activity leads to local hypermethylation in DNA promoter gene and global hypomethylation which pose potential causes for the abnormal growth of cancer cells [8]. Thus, the inhibition of DNMT1 activity has been established as a possible way to reactivate gene silenced by methylation of their promoters in some disease, including breast cancer [9]

Natural products have been known as one of a candidate drug. It is a potential source of drugs due to their molecular diversity and low toxicity [9,10]. One of the methods for lead compound discovery is fragment-based drug design (FBDD). One of the advantages of FBDD is that it results in a lower molecular weight lead, that is likely to have higher oral bioavailability [11]. Fragment merging is an elaboration of the fragment which incorporates a structural portion of overlapping molecules, usually an already known substrate or inhibitor of the target protein, into a fragment [12]. Hence, preserving the essential molecular interaction of the initial substrate or inhibitor while improving the activity by the introduction of the new fragment. In this research, the fragment merging approach is utilized on the potential natural product compounds and the already known product of the DNMT1 enzymatic reaction, S-Adenosyl-L-homocysteine (SAH), to generate lead compounds as an inhibitor for DNMT1 through in silico molecular docking simulation method and pharmacological test.

2. RESEARCH METHODOLOGY

This research done through an in the silico method by employing Molecular Operating Environment (MOE) v2014.09, DataWarrior v04.07.02, ChemBioDraw Ultra v14.0, Toxtree v2.6.13, SwissADME (http://www.swissadme.ch/), and AdmetSAR (http://lmmd.ecust.edu.cn/1) software. The 3D structure of DNMT1 protein was obtained from Protein Data Bank at the Research Collaboratory for Structural Bioinformatics (RCSB PDB). The database of natural products was acquired from PubChem database.

2.1 Preparation of DNMT1 Protein

The 3D structure of DNMT1 with PDB ID 3AV5, 3AV6, 3PTA, 3SWR, and 4WXX were obtained from the RCSB. The chosen 3D structures were saved in PDB format. The optimization DNMT1 was done using MOE v2014.09 by removing water molecules and unnecessary metal atoms and optimizing the structure using LigX with the default setting. Lastly, all of the DNMT1 protein were saved in .moe format.

2.2 Protein-Ligand Interaction Fingerprints (PLIF)

PLIF was applied to summarize the interaction between ligands and protein using a fingerprinting scheme. This method has been done using MOE v2014.09 with potential setup AMBER10: EHT, forcefield, R-field solvation and superpose. Superpose generated sequence alignment, structure alignments, PDB coordinates, Root Mean Square Deviation (RMSD) statistics, difference distance plots, and an interactive image of the superimposed structures [13,14]. The procedure of PLIF has been done based on standard default in MOE v2014.09.

2.3 Preparation of the Natural Product Fragments

The standard ligands SAH, S-Adenosyl-L-methionine (SAM), and Sinefungin (SFG), as well as the natural products as candidate fragment, were obtained from PubChem database. The ligands were then optimized through MOE v2014.09. The MMF94x force field with RMS gradient of 0.001 was selected as the optimization parameters. Natural products of The optimized ligands were stored in .mdb format. The prepared natural products were screened to get fragments which fulfill Lipinski's Rule of Three (RO3) and Toxicity test by DataWarrior v04.07.02.

2.4 Molecular Docking of Natural Product Fragments and Fragment Merging

The selected fragments were on docked into the SAM-binding site of DNMT1 by using pharmacophore query through MOE v2014.09. The fragments with favorable Gibbs binding energy ($\Delta G_{binding}$), RMSD, and molecular interaction were selected to be merged with the standard molecule, SAH. This merging process of fragments and standards was done by utilizing MOE v2014.09 and ChemBioDraw Ultra 14.0.

2.5 Molecular Docking of Ligands

The molecular docking simulation for ligands and standard were initiated with rigid docking and followed by the flexible docking protocol. All the parameters for the molecular docking simulation were selected according to MOE v2014.09 standard protocol with AMBER10: EHT as the forcefield.

2.6 Pharmacological Properties ADME-Tox

The potential ligands from molecular docking simulation underwent pharmacological properties prediction. Toxtree v2.6.13 was used to screen the carcinogenicity and mutagenicity. The toxic properties of the ligands were analyzed using DataWarrior v04.07.02 and AdmetSAR. The health effects of the ligands on human organ were predicted using SWISSADME.

3. RESULT AND DISCUSSIONS

3.1 Preparation and Visualization of DNMT1

DNMT1 is responsible for discharging the DNA methylation during replication. DNMT1 has also been considered as an essential target for cancer therapy [15]. In this research, the 3D structures of DNMT1 were obtained from RCSB PDB. The water molecules and other unnecessary molecules were eliminated because the solvation effect is not taken into account in the molecular docking simulation [16]. Hydrogen atoms were incorporated into the protein. The protein structures from RCSB PDB is generated from X-ray crystallography which commonly does not have a hydrogen atom because of the limited resolution of the instrumentation. The presence of a complete atom on protein structures is essential because it will affect the molecular mechanics, dynamics, and electrostatic calculations involved in molecular docking simulation [16,17]. The last step of protein preparation was energy minimization to generate zero gradients of all atoms; the lowest energy and the most stable condition that can be used to investigate the mechanism of a chemical or biological process [18]. The PLIF method was employed to quantify and compare ligand-protein interactions. Through the PLIF method, the fingerprints were covered into a normalized quantitative score that expresses the similarity between the interaction profile of docking pose and that of a reference protein-ligand complex [19].

Furthermore, the pharmacophore was validated to assess its ability to distinguish active compounds that have potentially inhibit DNMT1 to the other [20]. In addition, the purpose of pharmacophore validation was to evaluate the quality of pharmacophore features which created from the previous step. Standard ligands were utilized to perform the validation test. Visualization on the binding site of DNMT1 was done with 'Surface Navigation and Maps' tools in MOE 2014.09 (Fig. 1).

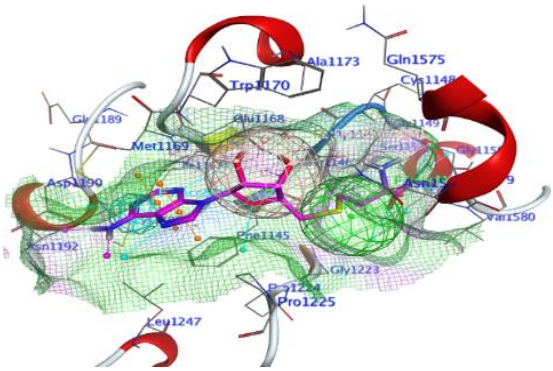

Fig. 1. Binding site visualization of DNMT1 with pharmacophore, the green, pink, and blue color is HydA, Don&Acc, and Acc, respectively.

3.2 Preparation of Natural Product Fragments

About 168,646 compounds of natural products were obtained from PubChem database. It was screened by RO3 which has parameters such as, molecular weight lower than 300 Da, LogP lower than 3.0, the number of hydrogen donor less than 3, and the number of hydrogen acceptor less than 3, which suitable for the screening of small compound for fragment development [21]. The natural products also screened based on the veber rule [22], rotatable bond no more than 3 and topological polar surface area (TPSA) lower than 60 Á. Natural products which drug-likeness lower than 0, and shows the toxicity potential such as mutagenic, tumorigenic, reproductive effective and irritant were also eliminated. From the initial screening, 2,601 compounds were saved in a .mdb format as the fragment for the next experiment.

3.3 Analysis of Molecular Docking Simulation of DNMT1 Protein and Fragments

Molecular docking simulation has become an irreplaceable tool in drug design and discovery to predict the conformation of small molecule ligands with compatible target binding site and define binding affinity of the ligand to form a stable complex structure [23,24]. The selected fragments from the previous step were further screened molecular docking simulation. In the first molecular docking simulation, only 543 compounds bind to the pharmacophore points in the binding pocket. Then, the second molecular docking simulation produced only 282 compounds that bind to the pharmacophore points. Only 77 compounds fulfilled the RMSD value lower than 2.0. The $\Delta G_{binding,}$ the number of a hydrogen bond between the ligand and the protein, and the position of the fragment in the binding site were determined to choose the best fragments (Table 1).

3.4 Preparation of Natural Product Ligands

The fragment merging was performed by deploying MOE v2014.09. The fragments were connected to the part of the lead compound (SAH) by building a bond and replace the overlap part. New ligands were generated based on Lipinski's Rule of Five (RO5) and Veber rule which include molecular weight lower than 500 Da, TPSA lower than 140 Á, logP between -0.5 and 5.6, number of hydrogen donor no more than 5, and number of hydrogen acceptor no more than 10 [25]. The produced ligands must underwent the ADME-Tox screening following drug-likeness and toxicity prediction test (carcinogenic, mutagenic, irritant, and reproductive effect risks); a total of 9 ligands selected from this process. The best ligands through this process were shown in Fig. 2.

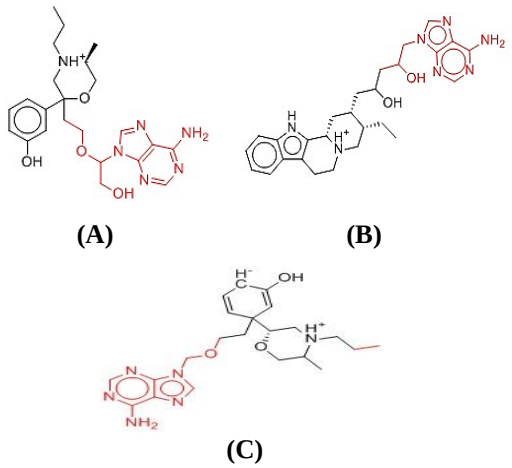

Fig. 2. The Selected Fragments and the merging position (A) MAHI1. (B) MAHI2. (C) MAHI3. The red and black color is the part of the lead compounds and the fragment, respectively.

3.5 Analysis of Molecular Docking Simulation of DNMT1 Protein and the Ligands

Nine ligands and standards underwent molecular docking simulation using MOE v2014.09. 'Rigid Receptor' protocol was used for first and second

simulation with the retain of 1 and 30 repetitions, respectively. In the first step, only 7 ligands bind to the site and have RMSD value lower than 2.0. Only 6 ligands have potential properties such as $\Delta G_{binding}$ lower than standard. The 6 ligands were docked with 'Induced Fit' protocol, and retain the value of 100. The most potential ligands were obtained by examining the molecular interaction of the ligands with the binding pocket of DNMT1. The result of the best three ligands along with the standards from flexible molecular docking simulation is shown in Table 2.

Table 1. List of the best natural product fragments

No	Compound Name	logP	TPSA	Weight	H-Acc	H-Don
1	2-hydroxy-1-methoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]guinolin-6-ium	2.69	46.07	268.34	3	2
2	2-(3-hydroxyphenyl)-4-propylmorpholin-4-um	-0.25	33.90	222.31	3	2
3	2-(3-hydroxyphenyl)-5-methyl-4-propylmorpholin-4-ium	0.08	33.90	236.33	3	2
4	(Z)-1-((1-hydroxy-2-methylbutylidene)amino)octahydropyrrolizin-4-ium	-0.47	37.03	211.33	3	2
5	1-(hydroxymethyl)octahydropyrrolizin-4-ium	1.26	40.46	299.44	3	3
6	(E)-1,3-bis(2-hydroxyphenyl)prop-2-en-1-one	2.61	57.53	240.26	3	2
7	(E)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one	2.96	37.30	224.26	2	1

Table 2. The $\Delta G_{binding}$, RMSD value, and molecular properties of ligands

Ligand	$\Delta G_{binding}$	RMSD	logP	TPSA	Weight	H-Acc	H-Don
MAHI1	-12.6301	0.4025	-0.49	132.98	457.55	10	4
MAHI2	-12.7872	1.6431	0.57	130.31	490.63	9	5
MAHI3	-11.6353	1.0117	-0.46	112.15	428.54	9	3
SAM*	-11.2605	1.3306	-3.94	187.08	399.45	11	4
SAH*	-11.2323	1.8644	-3.73	212.38	384.47	11	4
SFG*	-10.9262	1.6747	-3.96	214.72	382.40	12	5

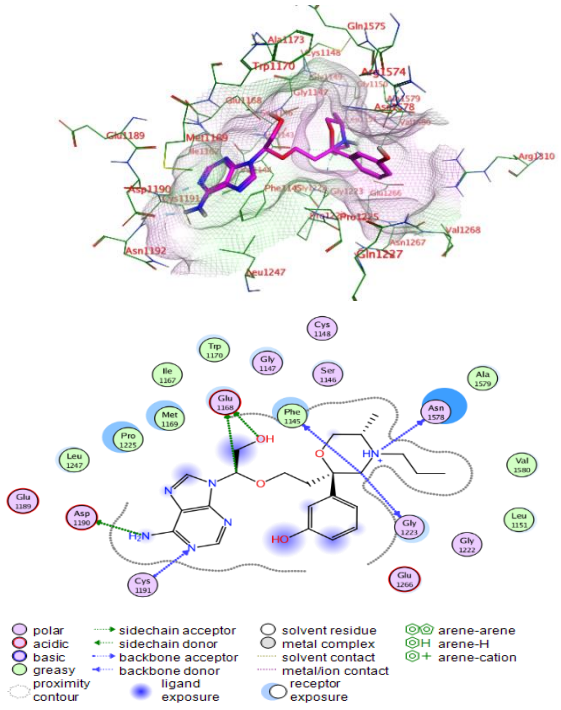

Fig. 3. Interaction of SAMI1 ligand with Amino acid residue (A) in 3D and (B) in 2D visualization.

As the best ligand, MAHI1 has lower $\Delta G_{binding}$ value than standards and bound on the best position in the binding site. As shown in Fig. 3, MAHI1 has 20 interaction with the amino acids residue in the binding site. Seven hydrogen bonds are binding the ligands in the pocket binding such as Asp1190, Cys1191, Gly1223, Phe1145, Asn 1578, and Glu1168.

3.6 Analysis of Molecular Docking Simulation and ADME-Tox the Ligands

The ADME-Tox analysis of the best ligands that have been obtained from the molecular docking simulation was performed by employing admeSAR [26], and SwissADME [27] software. Determining the pharmacological properties is essential because not all of the best ligands may be ready to prepare as drug candidates due to its toxicity and low ADME properties that may reduce the efficiency of the ligands to served as a drug in the human body. The result of the ADME-Tox analysis using admeSAR and SwissADME is shown in Table 3. The gastrointestinal (GI) absorption and Cytochrome P450 (CYP) inhibitors parameters were analyzed using SwissADME software, and the subcellular localization, organic cation transporter, AMES toxicity, carcinogens, and biodegradation parameters

were checked using the admetSAR software. Two of the best ligands have subcellular localization in lysosome and the other one is in the nucleus. The ADME-Tox properties should be the same for all of the best ligands. Besides, standard ligands have several bad ADME-Tox properties. For example, SFG has low GI absorption compared to other ligands.

The drug-likeness and the medicinal chemistry properties of the best and standard ligands were obtained by using SwissAdme software. The drug-likeness based on Veber's and Egan's rule was determined, and the bioavailability value was obtained. Furthermore, the Pan-assay interference compounds (PAINS), Brenk, and synthetic accessibility value were also predicted. The result is shown in Table 4. Based on this test, all of the best ligands have good drug-likeness according to both Veber's and Egan's Rule. All of the ligands shown the same bioavailability value (0.55). According to the result of analysis from SwissADME software, the bioavailability of all the best ligands was at a similar level. The synthetic accessibility score of the ligands was relatively the same as well, varying from 4.82 (MAHI1) to 5.13 (MAHI2). Furthermore, MAHI1 and MAHI3 were not determined to have any Brenk fragments. However, some of the best ligands were obtained to have one molecular fragment that contains PAINS property. In addition, MAHI1 were not predicted to have PAINS property.

Table 3. ADME-Tox prediction using admetSAR and SwissADME software

Ligand	GI Absorption	Subcellular Localization	CYP Inhibitor	Organic Cation Transporter (SLC22A2)	AMES toxicity	Carcinogens	Biodegradation
MAHI1	High	Lysosome	None	Non-inhibitor	No	No	No
MAHI2	High	Lysosome	None	Non-inhibitor	No	No	No
MAHI3	High	Nucleus	None	Non-inhibitor	No	No	No
SAM*	High	Nucleus	None	Non-inhibitor	No	No	No
SAH*	High	Nucleus	None	Non-inhibitor	No	No	No
SFG*	Low	Nucleus	None	Non-inhibitor	No	No	No

Note: *Standard Ligand

Table 4. The drug-likeness and medicinal chemistry properties of selected and standards compounds using SwissADME software

Ligand	Drug-likeness			Medicinal Chemistry		
	Veber	Egan	Bioavailability score	PAINS	Brenk	Synthetic accessibility
MAHI1	Yes	Yes	0.55	0 alert	0 alert	4.82
MAHI2	Yes	Yes	0.55	1 alert	0 alert	5.13
MAHI3	Yes	Yes	0.55	0 alert	1 alert	5.05
SAM*	No	No	0.55	1 alert	1 alert	4.94
SAH*	No	No	0.55	0 alert	0 alert	4.69
SFG*	No	No	0.55	0 alert	0 alert	4.78

Note: *Standard Ligand

4. CONCLUSION

MAHI1, MAHI2, and MAHI3 have lower $\Delta G_{binding}$ energy and better interaction with DNMT1 compared to the standards. After all analysis, the selected ligands, MAHI1, shows the best conformation and interaction in the binding site of DNMT1 and have better ADME-Tox properties than the other ligands. The result indicates that fragment-based drug design can be an essential method to discovered in developing a new drug for inhibiting the DNMT1. Finally, our result must be examined through *in vitro* and *in vivo* methods to determine its potential in the biological condition.

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