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ORIGINAL PAPER

Molecular Dynamic Screening Sesquiterpenoid Pogostemon Herba as Suggested Cyclooxygenase Inhibitor

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ABSTRACT

Objective: Virtual molecular dynamic sesquiterpenoid Pogostemon Herba (CID56928117, CID94275, CID107152, and CID519743) have screening as cyclooxygenase (COX-1/ COX-2) selective inhibitor. **Methods:** Molecular interaction studies sesquiterpenoid compounds with COX-1 and COX-2 were using the molecular docking tools by Hex 8.0 and interactions were further visualized using by Discovery Studio Client 3.5 software tool and Virtual Molecular Dynamic 1.9.1 software. The binding energy calculation of molecular dynamic interaction was calculated by AMBER12 software. **Result:** The analysis of the sesquiterpenoid compounds showed that CID56928117, CID94275, CID107152, and CID519743 have suggested as inhibitor of COX-1 and COX-2. **Conclusion:** Collectively, the scoring binding energy calculation (with PBSA Model Solvent) sesquiterpenoid compounds: CID519743 had suggested as candidate for non-selective inhibitor; CID56928117 and CID94275 had suggested as candidate for a selective COX-1 inhibitor; and CID107152 had suggested as candidate for a selective COX-2 inhibitor.

Key words: molecular dynamic screening, scoring binding energy, sesquiterpenoid compounds, COX-1/ COX-2 inhibitor selective.

1. INTRODUCTION

Sesquiterpenoid compounds were the major of from *Pogostemon cablin* Benth, including alpha-patchouli alcohol, alpha-bulnesene (CID94275), alpha-guaiene (CID107152), and seychellene (CID519743) (1). Sesquiterpenoid compounds from patchouli oil usually use as perfume bases (fixative), but not optimize as drugs compounds material (1, 2). All sesquiterpenoid compound have not much explored of in-vivo, in-vitro, and in-silico analysis, especially COX inhibitory activity. In-silico analysis (QSAR) showed the all sesquiterpenoid compound have candidates as enzyme inhibitors, protein kinase inhibitors and inhibitors of nuclear receptors by molinspiration analysis (3). In silico analysis of alpha-patchouli alcohol isomers showed that alpha-Patchouli alcohol compounds (CID442384, CID6432585, CID3080622, CID10955174, and CID56928117) was suggested as a candidate for a selective COX-1 inhibitor and CID521903 as nonselective COX-1 / COX-2 (4). In-vitro analysis of alpha-patchouli alcohol had increase protection against influenza virus infection in mice by increasing the immune response, and attenuation of the systemic inflammatory response (5). In-vivo analysis of alpha-patchouli alcohol also had the effect of anti-inflammatory activity, by regulating the mRNA expression of the panel of inflammatory mediators, including TNF-α, IL-1β, iNOS and COX-2 (6). In-vivo analysis of alpha-bulnesene had the ability as an anti-platelet aggregation in rabbit blood by inhibiting the COX enzymes and the mechanism of PAF (Platelet Factor Activating) (7, 8).

Drugs that inhibit mechanism of isoenzymes COX (cyclooxygenase) is a NSAID. The enzymes of cyclooxygenase (COX) pathway are prostanoids, prostaglandins and thromboxane. There are two isoforms of COX enzymes, COX-1 and COX-2. Both isoforms have different regulatory functions. Since the early 1990s, research in this area has been dominated by investigations of the two COX enzymes COX-1 and COX-2, while the therapeutic market has been revolutionized by the development of drugs targeted

selectively against COX-2. Inhibition of COX-2 produces the analgesic, antipyretic, and anti-inflammatory effects typical of non-steroidal anti-inflammatory drugs (NSAIDs), while inhibition of COX-1 was responsible for the antithrombotic effects of aspirin and other non-selective NSAIDs, as well as many of their side effects, such as gastric ulcer formation. Many studies since the early 1990s have shown that the broad range of classical NSAIDs inhibit both COX-1 and COX-2 although with a general tendency toward COX-1 selectivity (9-15). This appears to be associated with gastrointestinal toxicity: the more COX-1-selective drugs appear to have the tendency to cause more gastrointestinal damage. This has provided the rationale for the development of selective inhibitors of COX-2 (16, 17). COX-1 and COX-2 selectivity of NSAIDs were determined by the IC_{50} value. The determination of IC_{50} analysis (in-vitro and in-vivo) performed by oxygen uptake method, peroxidase method, enzyme immunoassay, and Radioimmunological Assay (18). This study was expected to further develop ligands NSAIDs as COX selective inhibitors based on in-silico analysis by scoring of binding energy calculation. We have assessed the benefit of a virtual screening of alpha-patchouli alcohol isomer as inhibitors of only cyclooxygenase-1 (COX-1) and the also as predicted inhibitor cyclooxygenase (COX-1/ COX-2) isoenzymes. The analysis energy was use energy of hydrogen bond interaction by LeadIT2 Bisolve software [3, 19, 20]. LeadIT Biosolve software was also equipped with a predictive scoring free energy binding between the ligands and receptor. The scoring energy by LeadIT Biosolve can never be more than a rough approximation of the free energy of binding, because the scoring energy was using a simple function based on a single configuration of a receptor-ligand complex (21, 22, 23).

The development of virtual molecular dynamic method can perform to screening docking results of drug compounds (ligands) to the receptor protein to predict the position and orientation (pose) ligand interaction with the target protein that has a low molecular weight. This is a basic guideline to obtain the structure activity relationship in cases of the condition of high-resolution structure of a compound cannot be obtained. The development of virtual molecular dynamic is to perform energy calculations for the complexes, protein, and ligand, as well as using certain solvent models (23). To further explore the structural characters of the COX-1/ COX-2-sesquiterpenoid complexes, molecular docking, molecular dynamics simulations, and MM-PBSA (Molecular Mechanical and Poisson Born/Surface Accessible) model solvent, and binding-free-energy calculations were performed on COX-1 and COX-2 systems in complexes with sesquiterpenoid compounds (CID521903, CID94275, CID107152, and CID519743). Results of the study not only support the use of sesquiterpenoid from *Pogostemon cablin* Benth as a potential therapeutic agent by targeting sesquiterpenoid, also help the development of novel COX-1/ COX-2 inhibitors selective based on other natural products.

2. MATERIAL AND METHODS

2.1. Ligand sesquiterpenoid and COX protein receptor preparation:

Sesquiterpenoid compounds (CID56928117, CID94275, CID107152, and CID519743) were downloaded from pubchem.ncbi.nlm.nih.gov as 3D-SDF format, and then its energy form were minimized and converted to 3D-PDB format by Open Babel 2.3.1 in Hex.8.0 as ligand for virtual docking screening. 3D model from PDB ID: 1PTH was obtained from SWISS-MODEL repository for cyclooxgenase-1 (COX-1) and 3D model from PDB ID: 6COX for cyclooxygenase-2 (COX-2) ID: EDL_39487 (24).

2.2. Docking of Ligand-Protein, Visualization, Virtual Molecular Dynamic and Binding Energy Calculation

We used rigid docking the Hex 8.0 software to compute possible interaction COX-1 and COX-2 with sesquiterpenoid compounds (CID56928117, CID94275, CID107152, and CID519743) on its interaction site. Output of the docking was refined using Discovery Studio Client 3.5 software. We used Discovery Studio Client 3.5 to analysis 2D/3D interaction ligand sesquiterpenoid compounds binds to COX-1/ COX-2. We also use Virtual Molecular Dynamics 1.9.1 software to simulate most possible native complex structure of sesquiterpenoid compounds binds with COX-1 and COX-2 in molecular dynamic with MM-PBSA (Molecular Mechanical and Poisson Born/Surface Accessible) Model Solvent, which were include both backbone and side-chains movements. We use AMBER12 software also acquire the results of the analysis of 200 poses: the complex energy, energy ligand protein and energy. Subsequent the binding energy calculation and a standard error using the equation $\Delta G = G_{complex} - [G_{protein} + G_{ligand}]$(4, 25, 26).

3. RESULT

3.1. Ligand sesquiterpenoid and COX protein receptors

Ligand sequiterpenoid obtained from pubchem.ncbi.nlm.nih.gov, such as CID56928117, CID94275, CID107152, and CID519743. And both units of 3D Flat Ribbon structure protein isoforms COX-1 and COX-2, as illustrated by Discovery Studio 3.5 software.

3.2. Docking of Ligand-Protein, Visualization-Interaction and Virtual Molecular Dynamic

Next step is docking (ligand to protein) sesquiterpenoid (CID56928117, CID94275, CID107152, and CID519743) respectively to COX-1 and COX-2 using rigid docking Hex 8.0 software. The results of the docking ligand CID56928117 to COX-1 and COX-2 performed active visualization-interaction 2D and 3D using Discovery Studio 3.5 software, as presented in Figure 1 (A-1 - A-3 and B-1 - B-3). We also use Virtual Molecular Dynamics 1.9.1 to simulate most possible native complex structure of CID56928117 binds with COX-1 and COX-2 in molecular dynamic with MM-PBSA (Molecular Mechanical and Poisson Born/Surface Accessible) Model Solvent, as presented in Figure 1 (A-4 and B-4) and all active interaction ligand sesquiterpenoid with COX-1 and COX-2 the summarized on Table 1. We were using Amber 12 software using scoring binding energy calculation, as presented in Figure 2 and summarized on Table 1.

4. DISCUS SION

Major component of sequiterpenoid compounds obtained from *Pogostemon cablin* Benth were alpha-patchouli alcohol (CID56928117), alpha-bulnesene (CID94275), alpha-guaiene (CID107152), and seychellene (CID519743). Alpha-patchouli

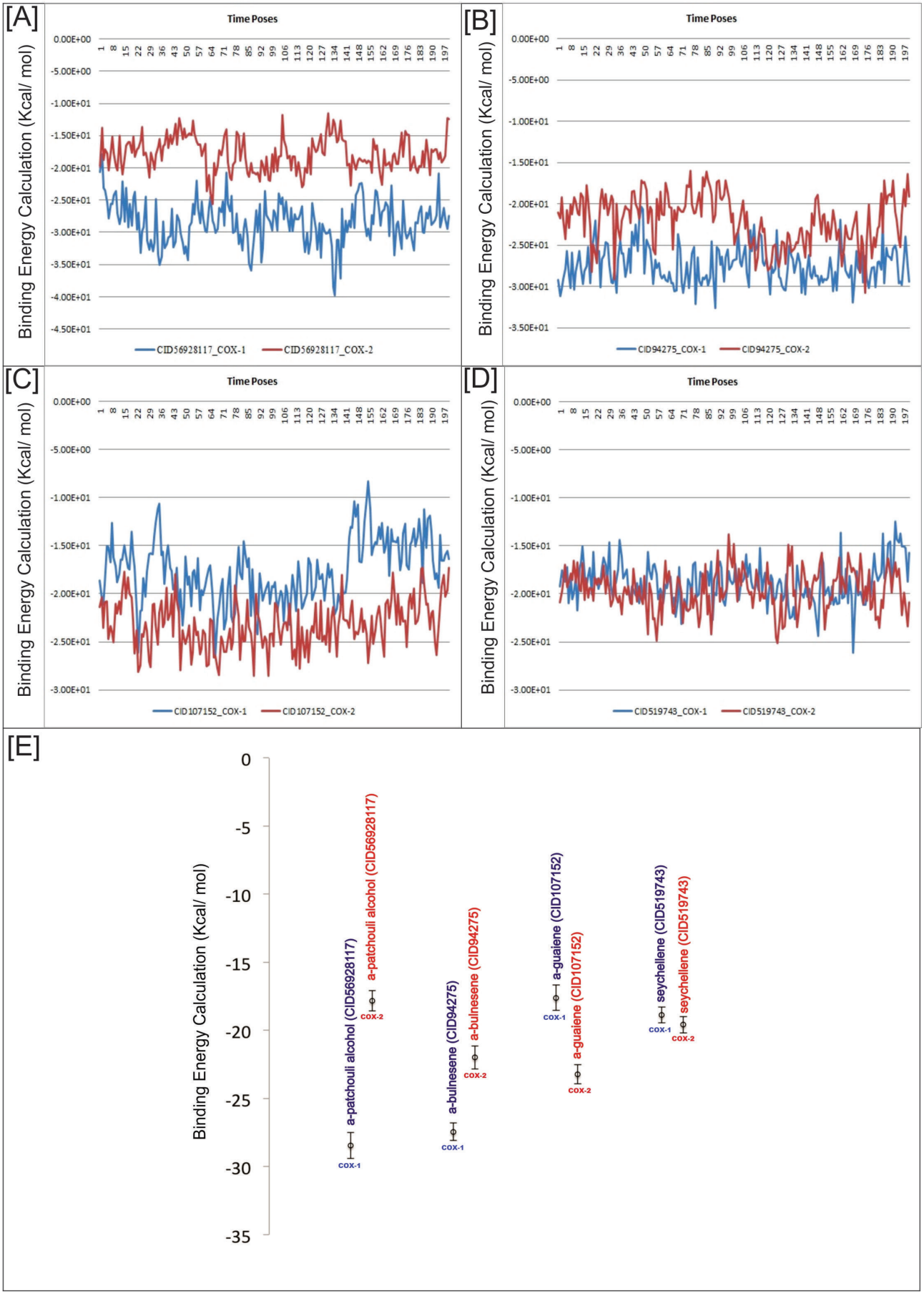

Figure 1. Modeling analyses, Shape Chemical Complementary Scores and Empirical Scoring of CID56928117-COX-1/ COX-2 complexes by Discovery Studio 3.5

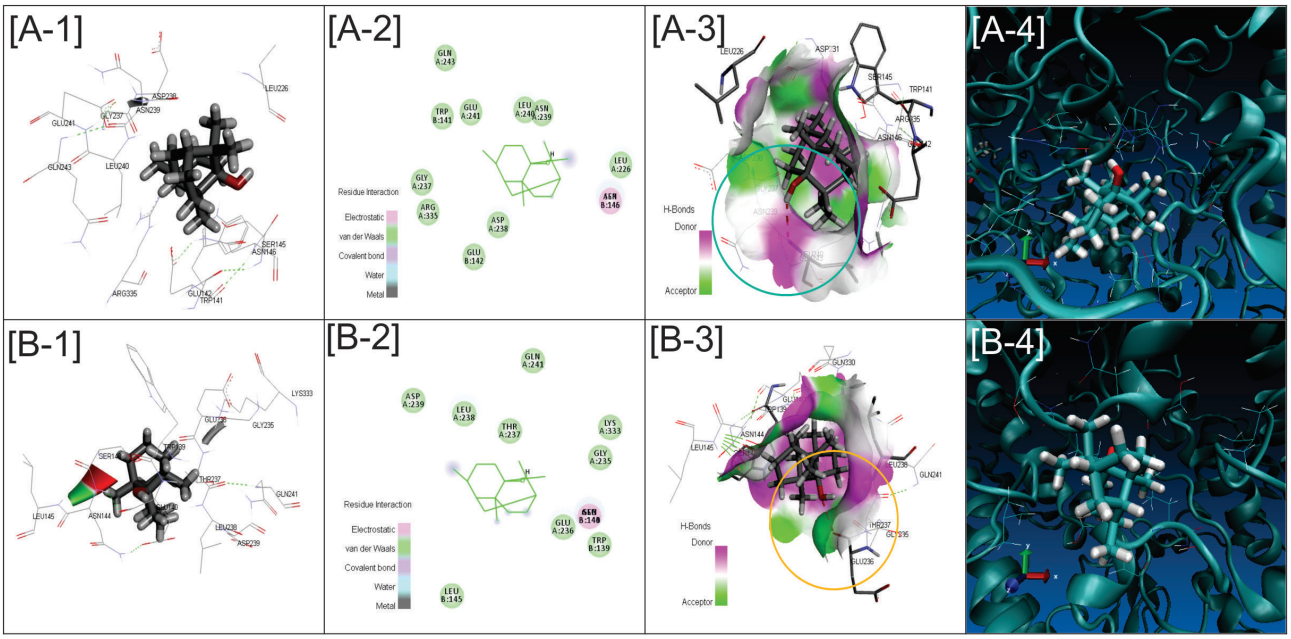

Figure 2. Binding energy calculation of sesquiterpenoid compounds (CID56928117, CID94275, CID107152, and CID519743) binds to COX-1/ COX-2. [A, B, C and D] Compare of Binding energy calculation of sesquiterpenoid-COX-1 (blue) and COX-2 (red) complexes. [E] Histogram binding energy calculation of COX-1_sesquiterpenoid complexes (blue) and COX-2_sesquiterpenoid complexes (red).

No.	Ligand	Ligand and Protein Interaction Category (by Discovery Studio 3.5)		Binding Energy Calculation ($\Delta E_{binding}$ (kcal/ mol)) ($\Delta E_{complex}$-$\Delta E_{protein}$-ΔE_{ligand}) Poses 200		Suggestion of Selectivity
		COX-1	COX-2	COX-1	COX-2	
1.	alpha-Patchouli alcohol CID56928117	Electrostatic: ASN146B Van der Walls: LEU226B, GLY237A, ASP238A, ASN239A, GLU241A, GLN243A, ARG335A, TRP141B, GLU142B Covalent bond: SER145B	Electrostatic: SER143B Van der Walls: GLY235A, GLU236A, THR237A, LEU238A, ASP239A, GLN241A, LYS333A, TRP139B, GLU142B Covalent bond: GLU140B, ASN144B	-28.448 ± 0.955 (VAR=11.339, SD=3.376, SE=0.239)	-17.833 ± 0.737 (VAR=6.755, SD=2.606, SE=0.184)	Selective of COX-1
2.	alpha-bulnesene CID94275	Van der Walls: VAL147A, LYS224A, ALA225A, LEU226A, GLY227A, ASP231A, GLY233A, GLY237A, ASP238A, ASN239A, LEU240A, ARG335A, TRP141B, GLU142B, SER145B, ASN146B, VAL147B	Van der Walls: GLY225A, ASP229A, GLY235A, GLU236A, LEU238A, GLN241A, GLN330A, THR237A, LYS333A, SER143B, TRP139B, GLU140B, ASN144B, LEU145B	-27.437 ± 0.641 (VAR=5.114, SD=2.267, SE=0.160	-21.985 ± 0.848 (VAR=8.950, SD=2.999, SE=0.212)	Selective of COX-1
3.	alpha-guaiene CID107152	Van der Walls: TRP141A, GLU142A, SER145A, ASN146A, LEU226B, GLY227B, ASP231B, GLY237B, ASN239B, ASP238B, LEU240B, GLU241B, GLN243B, ARG335B	Van der Walls: GLY225A, ASP229A, ASN231A, GLY235A, GLU236A, THR237A, GLN241A, GLN330A, LYS333A, TRP139B, GLU140B, SER143B, ASN144B, LEU145B, LEU238A	-21.724 ± 0.802 (VAR=7.996, SD=2.835, SE=0.200)	-23.213 ± 0.708 (VAR=6.232, SD=2.503, SE=0.177)	Selective of COX-2
4.	seychellene CID519743	Van der Walls: PRO544A, GLU545A, SER123B, ASN124B, LEU125B, ILE126B, PRO127B, SER128B, PHE373B, GLN372B, GLN374B, LYS534B	Van der Walls: ASP213A, HIS214A, LYS215A,LYS211A, THR212A, ARG222A, ILE274A, GLN289A, GLU290A, VAL291A, HEM682A	-18.864 ± 0.596 (VAR=4.415, SD=2.106, SE=0.149)	—19.588 ± 0.599 (VAR=4.460, SD=2.117, SE=0.150)	Non-selective COX

Table 1. Analysis interaction and binding energy calculation of COX-1/ COX-2-sesquiterpenoid compounds complexes.

alcohol has molecular weight: 222.36634 g/ mol; molecular formula: $C_{15}H_{26}O$; XLogP3-AA: 4.1; H-Bond Donor: 1; and H-Bond Acceptor: 1; Gibbs energy = -32.0 [kcal/mol]. Alpha-bulnesene, alpha-guaiene and sychellene have molecular weight 204 g/mol; molecular formula: $C_{15}H_{24}$; XLogP3-AA: 4.6; 4.6; and 5.1; also H-Bond Donor: 0; and H-Bond Acceptor: 0; as well as Gibbs energy = 77.7 (kcal/mol) respectively (1-3, 14).

The repeat rigid docking using Hex 8.0 software to compute possible interaction COX-1 and COX-2 with sesquiterpenoid compounds (CID56928117, CID94275, CID107152, and CID519743) on its interaction site and the data are represented by Discovery Studio 3.5 software. The position of interaction site all ligand sesquiterpenoid with COX-1/ COX-2 were analyzed Receptor-Ligand Interaction, as Table 1. The interactions active site of all ligand sesquiterpenoid with

COX-1 and COX-2 protein receptor showed the differences in the position active site and the active site also shows all ligand sesquiterpenoid compounds are in the catalytic domain. Thus all the compounds have the capability of blocking oxygenated reaction and reaction peroxides currently substrate arachidonic acid to become PGH2 (20). The analysis of active site all ligand alpha-patchouli alcohol isomers interact with receptor proteins COX-1 and COX-2 shows the differences of the active site. The difference position active site the complexes have led to interaction types, such as electrostatic, van Der Wall, and covalent bond. The different of electrostatic interaction was illustration hydrogen-bond analysis on Shape Chemical Complementary Scores and Empirical Scoring by Discovery Studio 3.5, as shown in Figure 1 (A-3 and B-3). Hydrogen bond analysis showed ligand CID56928117 acts as a hydrogen bond donor on COX-1-CID56928117 complexes, but ligand CID56928117 acts as a hydrogen bond acceptor on COX-2-CID56928117. The different types of interactions in this complex will certainly affect its binding free energy (3).

The binding free energy calculation model solvent MM-PB/SA method is characterized by the use of Poisson-Boltzmann (PB) model to compute the electrostatic component of the solvation free energy. MMPBSA has consistently been shown to be a good method for comparing binding energies of similar ligands as it is case. MMPBSA computes the binding free energy by using a thermodynamic cycle that combines the molecular mechanical energies with the continuum solvent approaches (27). The calculation of binding free energy is computed as:

$$\Delta G = G_{complex} - [\, G_{protein} + G_{ligand} \,] \quad (1)$$

In equation 2, $G_{complex}$ is the absolute free energy of the complex, $G_{protein}$ is the absolute free energy of the protein, and G_{ligand} is the absolute free energy of the ligand) (25, 26, 27).

The free energy of each term was estimated as a sum of the three terms:

$$[G] = [E_{MM}] + [G_{SOL}] - T.[S] \quad (2)$$

where E_{MM} is the molecular mechanics energy of the molecule expressed as the sum of the internal energy (bonds, angles and dihedrals) (E_{int}), electrostatic energy (E_{ele}) and van der waals term (E_{vdw}):

$$[E_{MM}] = [E_{int}] + [E_{ele}] + [E_{vdw}] \quad (3)$$

$[G_{SOL}]$ accounts for the solvation energy which can divide into the polar and nonpolar part. The polar part accounts for the electrostatic contribution to solvation and is obtained by solving the linear Poisson Boltzmann equation in a continuum model of the solvent. On the other hand, the other part accounts for the nonpolar contribution to solvation and represents the cost of creation a cavity inside the solvent. This is related linearly to the solvent accessible surface area. $[G_{SOL}]$ implicitly includes the entropy unlike $[E_{MM}]$. Finally, configurationally entropies were computed by diagonalization of the cartesian coordinate covariance matrix following the method described by Schlitter and extensively tested in protein systems (27).

The stages the binding energy calculation by AMBER12 includes: preparation, minimization, heating and energy calculations (complex, protein and ligand). We extracted 200 snapshots (at time intervals of 2 ps) for each species (complex, protein and ligand). Furthermore, the binding energy calculation be obtained from the data ligand energy, protein energy and complex energy by AMBER12, 200 times/poses respectively, the next, the analysis of binding energy calculate of sesquiterpenoid compounds-COX-1 and COX-2 complexes as shown Figure 2 (A, B, C, D and E). Binding energy calculation showed that COX-1_56928117 complexes more binding energy than COX-2_CID56928117 complexes. This is according to the illustration interaction active site that the electrostatic interaction COX-1_CID56928117 complexes come about hydrogen bond donor, whereas COX-2_CID56928117 complexes occurs hydrogen bond acceptor interaction. It is also influenced by van der Waals interactions and covalent bond, according to the explanation of the equation (3). Similarly, the binding energy calculation COX-1_CID94275 complexes more than COX-2_CID94275 complexes, but the binding energy calculation of COX-2_CID107152 complexes more than COX-1_CID107152 complexes, and the binding energy calculation of COX-1_CID519743 complexes similarity with COX-2_CID519743 complexes. In COX-1/ COX-2_CID94275, CID107152, and CID519743 complexes show the interaction of active side only influenced by van Der walls interactions, but all three showed differences in binding energy. This is due to the amount of the active site interaction of the van Der walls interactions and amino acid residues. The similar research, docking studies ligand salicin compound from *D. gangeticum* to COX-1 and COX-2 protein receptor, showed high binding affinity COX-2 protein (-5 Kcal/ mol) and lesser interaction with COX-1 (-3.79 Kcal/ mol), so that salicin as predictive COX-2 inhibitor selective (28). The previously our research, the scoring binding energy calculation (PBSA Model Solvent) alpha-patchouli alcohol compounds (CID442384, CID6432585, CID3080622, CID10955174, and CID56928117) suggested as candidate for a selective COX-1 inhibitor and CID521903 as non-selective COX-1/ COX-2 (4). Collectively, our results predictive that alpha-Patchouli alcohol (CID56928117) and alpha-bulnesene (CID94275) were predictive an inhibitor of COX-1 selective, alpha-guaiene (CID107152) was predictive an inhibitor of COX-2 and seychellene (CID519743) was predictive non-selective COX inhibitor. The suggested were alpha-patchouli alcohol (CID56928117) and alpha-bulnesene (CID94275) as candidate for a selective COX-1 inhibitor novelty, alpha-guaiene (CID107152) as candidate for a selective COX-2 inhibitor, and seychellene (CID519743) as suggest candidate non-selective inhibitor COX. These *in silico* analysis data await conformation by IC_{50} value and the biological activity analysis.

5. CONCLUSION

Exploration of the sesquiterpenoid compounds showed that (CID56928117, CID94275, CID107152, and CID519743) had suggested as inhibitor of COX-1 and COX-2. Collectively, the scoring binding energy calculation (PBSA Model Solvent) sesquiterpenoid compounds: CID519743 had suggested as candidate for non-selective inhibitor; CID56928117 and CID94275 had suggested as candidate for a selective COX-1 inhibitor; and CID107152 had suggested as candidate for a selective COX-2 inhibitor.

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- **Conflict of Interests:** The authors declare no conflict of interest.
- **Abbreviations::** CID: Chemical Information Data, COX: cyclooxygenase, QSAR: Quantitative approaches structure relationship Activity, mRNA: messenger-ribonucleic acid, TNF-α: Tumor necrosis factor-alpha, IL-6: Interleukin-6, iNOS: Inducible nitric oxide synthase, PAF: Platelet Factor Activiting, NSAID: non-steroidal anti-inflammatory drugs, PDB: Protein Database.

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