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IN SILICO ADME AND TOXICITY STUDIES OF DERIVATIVE PHTHALIMIDE COMPOUNDS AS NON-NUCLEOSIDE HIV-1 REVERSE TRANSCRIPTASE INHIBITOR

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ABSTRACT

Phthalimide derivate compounds was reported as a new class nonnucleoside reverse tranckriptase inhibitors. The aim of this research is to determine the prediction of absorption, distribution, metabolism, and excretion (ADME) as well as the toxicity test of phthalimide-derived compounds which have the best potential as HIV-1 reverse transcriptase enzyme inhibitors. This study used an in silico approach to predict oral bioavailability and toxicity. The prediction of the ADME in this study using SwissADME which is run online where thirty-three phthalimide derivate compounds have molecular weight, hydrogen donor and acceptor bond, and log P that meet the criteria of Lipinski Rules. Prediction of toxicity in this study using in silico method with Toxtree v1.60 and it is known that phthalimide derivate compounds are not carcinogenic and mutagenic.

Keywords: HIV; phthalimide; SwissADME; toxtree

INTRODUCTION

Phthalimide derivate compounds was reported as a new class of nonnucleoside reverse tranckriptase inhibitors. The reverse transcriptase enzyme is an enzymes that have the function of reversing the normal flow of information contained in biological systems. This enzyme is responsible for transcription of viral Ribonucleic acid (RNA) to produce double-stranded Deoxyribonucleic acid (dsDNA) which can be inserted into the host genome. The HIV virus will sow their genetic material into cells after the process of merging with a cell. To overcome the problem of differences in the genetic code, where the HIV genetic code is written in RNA while the human genetic code is written in DNA, HIV makes reverse transcriptase enzymes that copy their RNA genetic code into DNA (Braz, 2010).

Antiretroviral (ARV) use is given to HIV patients with the aim of stopping the activity of the virus, restoring the immune system, reducing the occurrence of opportunistic infections and reducing disability. Non-nucleoside reverse transcriptase inhibitors are a class of ARV drugs. ARV drugs that have been circulating in the market mostly show resistance factors and side effects in the form of rashes and lesions when consumed by HIV patients, so the idea arose to look for alternative compounds that can be used for treatment.

In 2019, Listyani et al. Conducted research on phthalimide-derived compounds as Non-Nucleoside HIV-1 Reverse Transcriptase inhibitors using Molecular docking analysis to determine the affinity and interaction pattern between the above compounds and the reverse transcriptase enzyme. The interaction pattern seen from thirty-three phthalimide-derived compounds with the reverse

transcriptase enzyme showed hydrogen bonds with the amino acid Lys101 where the interaction was similar to the interaction of TIBO R 86183 which is the original ligand of the target protein. The results when compared with nevirapine as a positive comparison have more potent. This can be seen in the higher bond energy values than the positive control. This indicates that phthalimide derivatives have potential as HIV-1 reverse transcriptase inhibitors.

Prediction of pharmacokinetic parameters is carried out as an initial stage for pre-clinical trials of drugs. An in silico approach to predicting pharmacokinetic parameters (absorption, distribution, metabolism, and excretion or often shortened to ADME) was pioneered by Lipinski and team (Lipinski et al., 1997). Parameter prediction of ADME has been developed to reduce the probability of failure at the drug candidate development stage. Toxicity tests generally aim to assess the risks that may arise from a chemical or toxicant. Along with the rapid development of science, the prediction of toxicity can be done in silico and it is found that the chemical structure of the drug can explain the properties of the drug and it is seen that the molecular groups of the drug are related to their biological activity (Djalil et al., 2012).

This study aims to identify phthalimide-derived compounds that have the potential to be used as oral preparations that do not cause adverse biological effects. The prediction of ADME values in this study used the SwissADME program which was run online in which thirty-three phthalimide-derived compounds had molecular weights, hydrogen bond acceptor and donor values, and log P values that met the criteria of the Lipinski rule. Prediction of the value of toxicity in this study using the in silico method with the Toxtree v1.60 program. The results of this study are expected to be used as a basis for conducting further experimental research.

METHOD

Ingredients

Three-dimensional structure design of the test ligands, namely thirty-three phthalimide-derived compounds using ChemOffice2004 along with data on their inhibitory activity against HIV-1 reverse transcriptase (Samee et al., 2004)
Tool

Hardware (hardware)

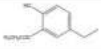
The hardware used is an Asus notebook computer model X540Y with specifications AMD E1-7010 Dual-core 1.5Ghz, 2 Giga Byte RAM, 500 Giga Byte hard disk, AMD Radeon R2 Graphics Card.

Software (software)

The software used to process the data is the operating system Windows 7 Ultimate, ChemDraw Ultra 8.0, Chem3D Ultra 8.0, SwissADME and Toxtree.

Tabel 1.

Aktivitas penghambatan senyawa derivat *phthalimide* terhadap enzim *reverse trancriptase* secara *in vitro* (Samee et al. 2004)

Senyawa No.	R	% penghambatan	Senyawa No.	R	% penghambatan
1.		43	18.		32
2.		37	19.		84 IC_{50} : 120,75 µg/mL.
3.		22	20.		61
4.		3	21.		43
5.		29	22.		43 IC_{50} : 60,90 µg/mL.
6.		21	23.		37
7.		14	24.		22
8.		8	25.		3
9.		43	26.		29 IC_{50} = 98,10 µg/mL.
10.		11	27.		21
11.		24	28.		8
12.		3	29.		43
13.		26	30.		11
14.		6	31.		24
15.		20	32.		3
16.		52	33.		26
17.		16			

ADME parameter prediction

Prediction of ADME value in this study using the SwissADME program which is run online. At first the site was opened http://www.swissadme.ch. The next step is to import the structure file of the 2D phthalimide derivative compound into the molecular sketcher field, after that the structure sketch is transferred to the SMILES list, which contains one molecule per line with optional names separated by spaces by clicking the double arrow button. When the list of molecules is ready to be submitted, the calculation can be started by clicking the "Run" button (Daina et al., 2017).

Toxicity test

Prediction of the value of toxicity in this study using the in silico method with the Toxtree v1.60 program. First, open the Toxtree program and then open the 2D phthalimide derivative structure by clicking the file button and then open. The next step is to select the parameters to be calculated by clicking the Method button, selecting parameters, clicking Estimate. The calculation results will be displayed in the Classification Area. Details of the decision tree are seen by selecting the menu Method – View decision tree (Herowati, 2015).

RESULTS AND DISCUSSION

ADME predictions

Physical chemical properties a[11]he basis for explaining the biological activity of drugs because physical chemical properties play an important role in determining the right method for the

formulation of a drug, so that an effective, stable, and safe preparation is obtained. Physical and chemical properties will also be closely related in the transport of drugs to reach the receptor. Before reaching the receptor, drug molecules must pass through various membranes, interacting with compounds in the external and internal fluids of the cell and with biopolymers. Chemical and physical properties play a role in the process of absorption and distribution of drugs so that drug levels at a certain time reach the receptors in large enough quantities. Only drugs that have a highly specific structure can interact with biological receptors, the physicochemical properties must support the unique orientation of the molecule on the receptor surface.

Lipinski's rule of five is a rule invented by Lipinski which helps to distinguish drug and non-drug compounds from the structure of the compound. This theory predicts a high probability of success or failure of a drug compound because of the similarity of the drug to a molecule that obeys 2 or more of these rules. Lipinski's rule can determine the physicochemical properties of ligands to determine the hydrophobic/hydrophilic character of a compound to pass through cell membranes by passive diffusion. The rules set by Lipinski are molecular weight (BM) which is not more than 500 g/mL, the partition coefficient value (logP associated with lipophilicity or hydrophobicity) is less than 5, has the number of hydrogen bond donors less than 5, and has the number of bond acceptors. hydrogen is less than 10.

Molecular weight more than 500 g/mol cannot diffuse across cell membranes. The larger the log P value, the more hydrophobic the molecule. Molecules that are too hydrophobic tend to have a high level of toxicity because they will be retained longer in the lipid bilayer and distributed more widely in the body so that the selectivity of binding to the target enzyme is reduced. A log P value that is too negative is also not good because if the molecule cannot pass through the lipid bilayer membrane. The number of hydrogen bond donors and acceptors describes the higher the hydrogen bonding capacity, the higher the energy required for the absorption process to occur. In general, Lipinski's rule describes the permeability of certain compounds to penetrate cell membranes by passive diffusion.

Physical chemical properties are the basis for explaining the biological activity of drugs because physical chemical properties play an important role in determining the right method for the formulation of a drug, so that an effective, stable, and safe preparation is obtained. Physical and chemical properties will also be closely related in the transport of drugs to reach the receptor. Before reaching the receptor, drug molecules must pass through various membranes, interacting with compounds in the external and internal fluids of the cell and with biopolymers. Chemical and physical properties play a role in the process of absorption and distribution of drugs so that drug levels at a certain time reach the receptors in large enough quantities. Only drugs that have a highly specific structure can interact with biological receptors, the physical and chemical properties must support the unique orientation of the molecule on the receptor surface

Tabel 2 Lipinski *rules* senyawa derivat *phthalimide* dengan HIV-1 *reverse transcriptase* (http://www.swissadme.ch/index.php)

Ligan	Formula	Bobot Molekul	H-*bond acceptors*	H-*bond donors*	Log P	Kelarutan dalam air
Molekul 4	C9H12O2	152,19	2	2	2,.02	Larut
Molekul 6	C9H12O	136,19	1	0	2,56	Larut
Molekul 7	C10H14O2	166,22	2	0	2,36	Larut
Molekul 10	C7H10N2	122,17	1	1	1,29	Sangat Larut
Molekul 17	C14H18O4	250,29	4	0	2,98	Larut
Molekul 18	C6H8O	96,13	1	0	1,82	Larut
Molekul 22	C8H10O2	138,16	2	2	1,39	Sangat Larut
Molekul 33	C7H15NO	129,20	2	0	1,08	Sangat Larut

Based on the data from (Table 2) it can be seen that the phthalimide-derived compounds have low molecular weight, hydrogen bond donor and acceptor values, and logP values that meet the criteria of Lipinski's rule, which means that all phthalimide-derived compounds have a fairly good level of drug likeness. The logP value of phthalimide-derived compounds is less than five, this means that phthalimide-derived ligands tend to be soluble in non-polar solvents but relatively soluble in polar solvents. These properties are good candidates for absorption and permeation. A negative logP value indicates that a compound is hydrophilic. In its transportation in the body, a drug should not be too hydrophobic (logP> 5) because it can be retained in the lipid bilayer. Drug molecules that are too hydrophobic tend to have greater toxicity because they will be retained longer and are widely distributed in the body so that the selectivity of binding to the target enzyme is reduced. A negative logP value is also not recommended because if the drug compound is too hydrophilic, it cannot pass through the lipid bilayer. The phthalimide-derived ligands meet the criteria for high oral bioavailability because they have a relative molecular mass of less than 500g/mol. The relative molecular mass of less than 500g/mol makes the process of chemical synthesis and molecular design less complex and requires a longer time.

Tabel 3 Nilai parameter farmakokinetika senyawa derivat *phthalimide* terbaik (http://www.swissadme.ch/index.php)

Molecule	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Bioavailability Score
Molecule 4	High	Yes	No	Yes	No	No	No	No	0.55
Molecule 6	High	Yes	No	Yes	No	No	No	No	0.55
Molecule 7	High	Yes	No	Yes	No	No	No	No	0.55
Molecule 10	High	Yes	No	No	No	No	No	No	0.55
Molecule 17	High	Yes	No	Yes	Yes	No	No	No	0.55
Molecule 18	High	Yes	No	No	No	No	No	No	0.55
Molecule 22	High	Yes	No	No	No	No	No	No	0.55
Molecule 33	Low	No	No	No	No	No	No	No	0.55

The pharmacokinetic phase includes the process of absorption in the digestive tract, distribution through the blood, metabolized into the form of active metabolites and excreted out of the body (ADME). This phase plays a role in the availability of drugs to reach the target tissue (target) or receptors so that they can cause a biological response. To give a biological effect, the compound must go through an absorption process to produce bioavailability of the drug (bioavailability), namely the active compound in blood fluids (pH = 7.4) which will be distributed to tissues or organs of the body.

ADME prediction results showed that the selected ligand showed a high absorption rate through the gastrointestinal tract (except compound 33) but the bioavailability value was not good, which was 0.55. The small value of bioavailability is not the basis for the effectiveness of the compound in the target tissue. The phase that involves the distribution, metabolism and excretion of the drug, is to determine the level of the active compound in the compartment where the receptor is located. The drug in its active form must interact with the receptor or site of action or target cells, at a sufficiently high level. The blood brain barrier (BBB) is an essential diffusion layer that functions as a barrier to the central nervous system. BBB endothelial cells differ from endothelial cells in other parts of the body by the absence of penetration, the connection between cells using tight junctions (TJ), and transport using pinocytosis. Endothelial cell tight junctions restrict the flow of hydrophilic compounds to penetrate into the BBB. The results of the calculation of ADME parameters showed that compound 33 was the only best phthalimide derivative that could not penetrate the brain barrier.

The metabolic process of drug compounds is generally metabolized in the liver (liver). Cytochrome P450 enzymes are found primarily in the liver, although some (eg CYP3A4) are also found in large amounts in the intestine. These enzymes are often involved in the metabolism of most drugs and are the most important mechanisms in drug pharmacokinetics. Cytochrome P450 3A4 (CYP3A4) often receives attention because the majority of drugs are metabolized by CYP3A4. In the prediction of ADME, the CYP3A4 enzyme cannot catalyze the metabolic reactions of most of the ligands that are the best candidates as inhibitors. Judging from the structure of the best phthalimide derivative which, according to ADME predictions, is a water-soluble structure, it is possible that there is a polarity effect on the metabolism of the CYP3A4 enzyme. The characteristics of the substrate that can be in CYP3A4 are large molecules and are lipophilic. Generally, more than 50% of drugs are lipophilic, so that before further analysis, drugs are often predicted to be able to act as substrates for CYP3A4 enzymes. Another important CYP450 enzyme is CYP1A2, which can catalyze Compound 4, Compound 6, Compound 7 and Compound 17. The substrate characteristics of CYP1A2 enzymes are planar, aromatic, polyaromatic, heterocyclic amide and amine compounds.

However, ADME predictions show that Compound 10, Compound 18, Compound 22 and Compound 33 are not inhibitors of this enzyme. CYP1A2 is present on the endoplasmic reticulum and its expression is induced by several polycyclic aromatic hydrocarbons (PAHs), some of which are found in cigarette smoke. The endogenous substrate of the enzyme is unknown but is capable of metabolizing some PAHs into carcinogenic intermediates.The CYP2C19 enzyme is characterized by neutral or weak base compounds or amides with 2 to 3 hydrogen bond acceptors, generally proton pump inhibitors. The pharmacokinetic effects of this enzyme have been reported to metabolize several antidepressants, antifungals and antimalarials. ADME predictions showed Compound 17 was the only inhibitor of the CYP2C19 enzyme. The CYP2C9 enzyme has the characteristics of weak acid compounds with hydrogen bond acceptors such as NSAID compounds. In some studies this enzyme can metabolize sulfonyl urea compounds such as glibenclamide, tolbutamide, and glimepiride. ADME predictions show that the CYP2C9 enzyme is an enzyme that cannot be inhibited by all the best phthalimide-derived compounds. CYP2D6 enzyme is an enzyme that functions as a catalysis of basic compounds with a protonated nitrogen atom of 4-7Å, common examples are plant compounds containing alkaloids and antidepressants. ADME predictions show that all the best phthalimide-derived compounds do not show potential as inhibitors of this enzyme.

Toxicity prediction

Toxicity tests were carried out on the phthalimide derivatives that had the best Gbind using the Toxtree program. The parameters seen in this toxicity test are the predictions of the Chammer rules, Carcinogenicity (genotox and nongenotox) and mutagenecity rulebase by ISS and In vitro mutagenicity (Ames test) alerts alerts by ISS parameters.

Tabel 4 Hasil prediksi toksisitas derivat *phthalimide* terbaik

Ligan	Parameter		
	Chammer rules	*Carcinogenicity and mutagenecity*	*In vitro mutagenicity*
Senyawa 22	*High (class III)*	*negative for genotoxic carcinogenicity negative for nongenotoxic carcinogenicity*	*No alerts for S. Typhimurium mutagenicity*
Senyawa 18	*High (class III)*	*negative for genotoxic carcinogenicity negative for nongenotoxic carcinogenicity*	*No alerts for S. Typhimurium mutagenicity*
Senyawa 33	*High (class III)*	*negative for genotoxic carcinogenicity negative for nongenotoxic carcinogenicity*	*No alerts for S. Typhimurium mutagenicity*
Senyawa 6	*High (class III)*	*negative for genotoxic carcinogenicity negative for nongenotoxic carcinogenicity*	*No alerts for S. Typhimurium mutagenicity*
Senyawa 17	*High (class III)*	*negative for genotoxic carcinogenicity negative for nongenotoxic carcinogenicity*	*No alerts for S. Typhimurium mutagenicity*
Senyawa 7	*High (class III)*	*negative for genotoxic carcinogenicity negative for nongenotoxic carcinogenicity*	*No alerts for S. Typhimurium mutagenicity*
Senyawa 10	***High (class III)***	***structural alert for genotoxic carcinogenicity negative for nongenotoxic carcinogenicity***	***Structural alerts for S. Typhimurium mutagenicity***
Senyawa 4	*High (class III)*	*negative for genotoxic carcinogenicity negative for nongenotoxic carcinogenicity*	*No alerts for S. Typhimurium mutagenicity*

Based on the parameters of the Cramer Rules, all the best phthalimide derivative compounds are included in the third category, namely high toxicity (High Class). This shows that the best phthalimide-derived compounds include compounds with chemical structures that are considered unsafe or have significant toxicity or have reactive functional groups. Based on the Carcinogenicity (genotox and nongenotox) and mutagenecity rulebase by ISS parameters, all of the best phthalimide derivative compounds were not carcinogenic with observations showing negative for genotoxic and nongenotoxic carcinogenic, except for compound 10 which showed positive for carcinogenic genotoxicity. Based on the parameters of in vitro mutagenicity (Ames test) alerts by ISS, all the best phthalimide derivatives were not mutagenic with observations showing no warnings for S.Typhimurium mutagenicity, except for compound 10 which showed warnings for S.Typhimurium mutagenicity. Compound 10 has an NH_2 group which has a lone pair of electrons that are reactive to other compounds, making compound 10 easy to modify and has mutagenic properties. The amine group (NH_2) which serves to help adsorb heavy metals so that compound 10 can be more toxic.

CONCLUSION

Phtalimide-derived compounds have molecular weights, hydrogen bond donor and acceptor values, and logP values that meet the criteria of Lipinski's rule. Phtalimide derivative compounds are not carcinogenic and mutagenic.

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