In Silico Study on Reverse Transcriptase Receptor for Anti-virus HIV Candidate from Secondary Metabolite *Monascus sp.*

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Abstract. HIV cases are still increasing along with the current increase in Corona Virus-19 (COVID-19) cases. HIV sufferers who also suffer from COVID-19 will experience a worsening of health status if they have comorbidities (comorbidities). The use of ARVs still has a toxic effect due to the large number of drugs consumed, so it is a reason not to continue treatment. This certainly endangers people with HIV during the pandemic because they will be more susceptible to COVID-19. Therefore, it is necessary to develop HIV antiretroviral drugs that are safe and comfortable for consumption for life, one of which is using *Monascus sp*. *Monascus sp*. have secondary metabolites that have potential as HIV antivirals. Lipinski rules have been applied, ADME and toxicity predictions have been carried out using the pkCSM application, molecular anchoring using Autodock 4.2.6 and visualized using Biovia Discovery Studio 2017 against secondary metabolites of *Monascus sp*. The results of the binding of the 40 test compounds to the HIV-1 Reverse Transcriptase (3V81) receptor showed that the best compound was Red derivate 2 at the 3V81 receptor with a higher free energy value than the original ligand (-8.16), namely (-11.93). This compound complies with Lipinski's rule, predicted ADMET. The results of this study have the potential for further development of HIV antiviral drugs.

Keywords*: antivirus HIV; Monascus sp., ADMET prediction; in silico.*

1 Introduction

Human Immunodeficiency Viruses (HIV) is a virus that attacks the immune system causing it to become susceptible to various infectious diseases. Until now, HIV is still the first deadly infectious disease, and cases in the world from year to year tend to increase. Since this case was discovered, 76 million people have been infected with the HIV virus and about 33 million of them died of HIV. In the world, as many as 38 million (31.6-44.5 million) sufferers by the end of 2019. An estimated 0.7% (0.6-0.9%) of adults aged 15-49 years worldwide are living with HIV (UNAIDS, 2020). In addition to the world, data shows that HIV cases in Indonesia also tend to increase since it was first reported in 1987. The number

of cases found until December 2020 was 496 districts/cities out of 514 districts/cities throughout Indonesia. The cumulative number of patients reported until December 2020 was 419,551 people (Ministry of Health, 2020). This increase in cases also occurred in line with the increase in cases of Corona Virus-19 (COVID-19), which is still hitting Indonesia. Basically, HIV patients who have complied with taking medication have the same chance of being exposed to COVID-19 as healthy people, but HIV sufferers who also suffer from COVID-19 will experience a worsening of health status if they have comorbidities (comorbidities). Research on the relationship between deaths of people living with HIV who also suffer from COVID-19 shows that out of the total study population of 17.3 million adults, 27,480 people with HIV and have comorbidities (0.16% of the population) have a higher chance of dying than those with HIV. do not have HIV, Khrishnan, et al., 2020 in [1].

It has long been found drugs to control the Antiretroviral Virus (ARV) virus in the body which is introduced in combination form or called Highly Active Antiretroviral Therapy (HAART). Combination of HAART can reduce the risk of transmitting HIV infection so that it can improve the quality of health that is almost the same as for individuals who are not infected with HIV Johnson et al., 2013 in [2]. However, the number of drugs consumed by patients causes increased toxicity when consuming these drugs. Data show that more than 25% of patients discontinue ARV treatment due to non-adherence during the first 8 months and the toxic effects, Lucas GM, 1999 in [6].

This is certainly dangerous for people with HIV during a pandemic like this because they will be more susceptible to COVID-19 when their immune system decreases. Therefore, it is necessary to develop HIV antiretroviral drugs that are safe and comfortable for consumption for life.

Currently the drug development center is focusing on the use of biological resources including microorganisms. One of the microorganisms that have various therapeutic activities is *Monascus sp. Monascus sp*. has long been used in the fermentation process of Angkak rice which can produce dyes in the form of pigments as secondary metabolite products, which can be useful as hypercholesterolemic and antihypertensive drugs by inhibiting the activity of the HMG-CoA enzyme in cholesterol biosynthesis, Lee et al., 2006 in [4], anti-breast cancer, Lee et al., 2013 in [5] and antiviral against Hepatitis C virus (HCV), Sun et al, 2011 in [9].

This research was conducted to determine the activity of the fungus *Monascus sp.* as a candidate for In silico HIV Antivirus. In silico has several advantages, namely it can provide modeling interactions between disease and potential

compounds so that it can be used as complementary data in in vitro and in vivo tests. This test can provide screening results for drug candidate compounds more quickly, reduce research costs, minimize the use of experimental animals, maximize effectiveness and safety in the drug development process Valerio LG., 2012 in [12].

2 Research Method

Tools

The equipment used is in the form of computer hardware and software. The device is a laptop with System specifications Windows 10 Home Single Language 64-bit (10.0, Build 19041) Intel® Core™ i3-8154 CPU @2.10GHz (4 CPUs), 2.3 Ghz, 4096 GB RAM. The software used consisted of: Marvin Sketch, Biovia Discovery Studio 2017, Autodock 4.2.6, pkCSM Pires et al., 2015 in [8], Autodock Tools 1.5.6.

Ingredients

There were 39 *Monascus sp* pigment test compounds in this study, including: monascin, ankaflavin, monascusone a, monascusone b, monaphilone a, monaphilone b, monaphilone c, xanthomonascin a, xanthomonascin b, monankarin a, monankarin b, monankarin c, monankarin d, monankarin e, monankarin f, monasfluore a, monasfluore b, y3, monaphilol a, monaphilol b, monaphilol c, monaphilol d, rubropunctamine, monascopyridine a, monascopyridine b, monascopyridine c, monascopyridine d, r3, pp-v rubropunctatin, red derivate 1, red derivate 2, red derivate 3, red derivate 4, red derivate 5, red derivate 6, red derivate 8, n-glucosylrubropunctamine and n-glucosylmonascorubramine. The test compound was obtained from PubChem based on experimental data from previous studies, Yuliana et al., 2017 in [13]. The test compound is downloaded and saved in *.sdf format.

The receptor file is obtained by downloading it on the website www.rscb.org in the form of a protein data file (*.pdb). The receptor used in this study is the Reverse Transcriptase Enzyme (PDB ID:3V81).

Prediction of Solubility and Permeability of Compounds using Lipinski's Rule

Physicochemical properties in the form of solubility and permeability of a compound have an important role in developing a drug, this aims to minimize the failure of a drug caused by the low quality of absorption of the compound Nursamsiar et al., 2016 in [7]. Based on the Lipinski Rules, the development of

oral drugs must meet the 5 requirements of the Lipinski rules or also known as the "Rule of Five". Lipinski's rule generally states that a drug to be administered orally will have good absorption or permeation if (1) the molecular weight is less than 500 Da (2) the log P value is less than 5, (3) the number of hydrogen bond donors is less than 5, (4) the number of hydrogen bond acceptors is less than 10 and (5) the refractive value should be between 40-130.

Prediction of Toxicity of Test Compounds

Toxicity test of the test compounds was carried out using pkCSM tools to predict the pharmacokinetic ability of the test compounds and potential toxic risks through ADMET parameters (Absorption, distribution, metabolism, excretion and toxicity). Only non-toxic compounds are continued in the molecular anchoring process.

Docking Method Validation

At this stage, redocking is carried out using a natural ligand found on the receptor, in this case the native ligand is an ARV drug that is already on the market. The re-tethering process is carried out by re-tethering the natural ligand to its receptor using AutoDock 4.2.6 software. To assess the validity of the data, the Root Mean Square Deviation (RMSD) parameter of the best redocking ligand conformation was used which was compared with the position of the crystallographic ligands. The RMSD value is declared valid if it is less than 2.0 A.

Molecular Docking

Molecular docking is carried out on prepared receptors and ligands. Gridbox locations were determined using AutoDockTools 1.5.6 software, based on the location of the test compound and the active site of the target protein (Yuliana et al., 2020). The parameters, dimensions and coordinates of the grid box are set. The dimensions of the grid box are adjusted to the size of each ligand, the coordinates of the grid box are adjusted to the coordinates of the center of the natural ligand that have been obtained from the re-tethering results, Yuliana, A., 2020 in [14]. In this study, the genetic algorithm (GA) parameter was used with the number of GA runs 100 times. The prepared ligands and receptors were then continued with the gridding and docking process. After docking the test compound molecules and receptors with various parameters, then visualization was carried out using the Biovia Discovery Studio 2017 software to see the amino acid residues and the bonds formed. The results obtained are G (Energy Gibbs) which represents the strength of the interaction between the ligand-receptors and the value of Ki (constant of inhibition) which describes the affinity of the ligand-receptors. Other parameters analyzed were the bond formed between the ligand-

receptor, and the same amino acid residue as the validated ligand. The same amino acid residue is thought to be the active site responsible for the activity of the test compound.

3 Result and Discussion

Proteins and Ligands

In this study, the protein receptor 3V81 was used (Figure 1). Both of these receptors have native ligands in the form of drugs that have been circulating in the market, namely 3V81 protein which has nevirapine natural ligand and resolutions below 2A, therefore the two receptors are used as comparisons.

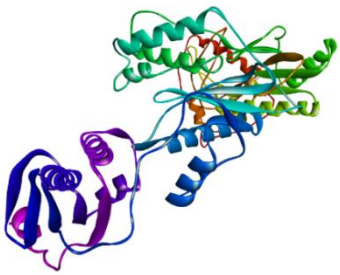
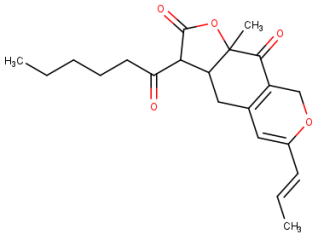
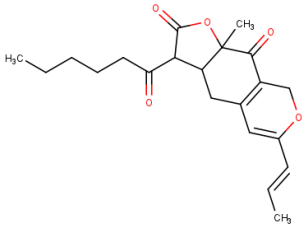
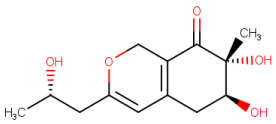
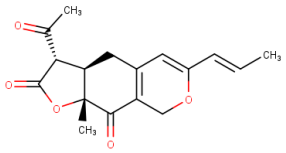
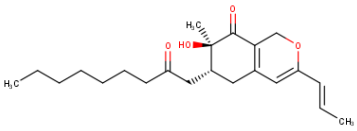
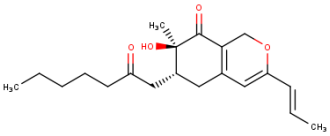
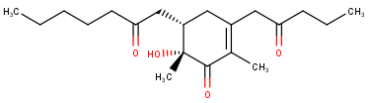
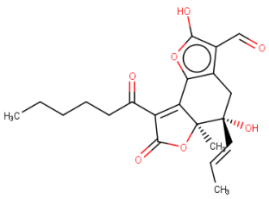
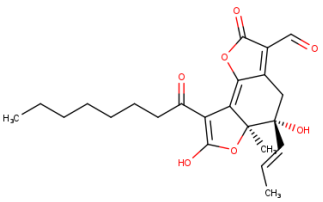
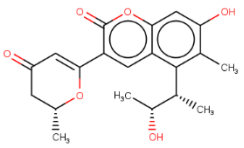
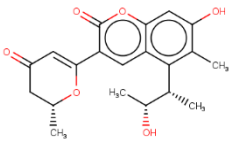
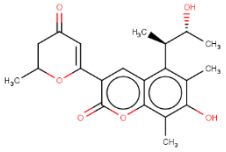
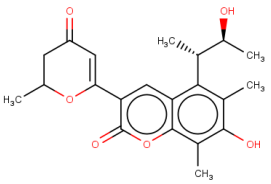
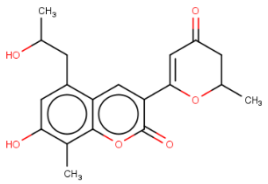
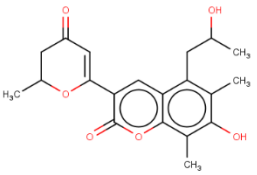


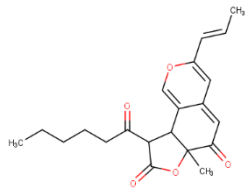
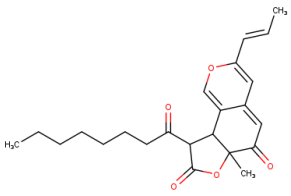
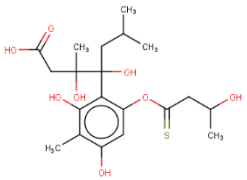
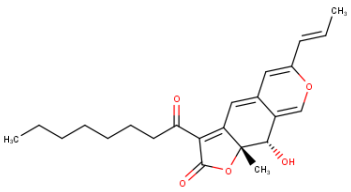
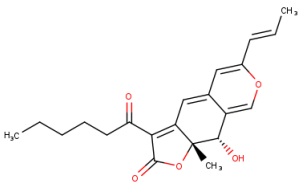
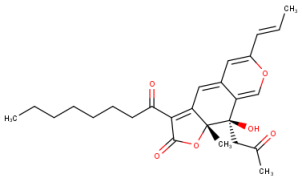
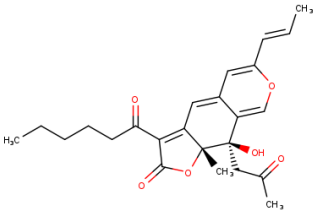
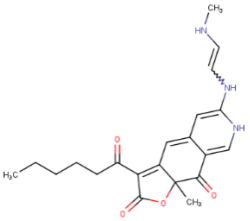
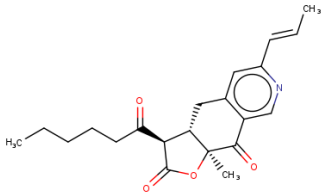
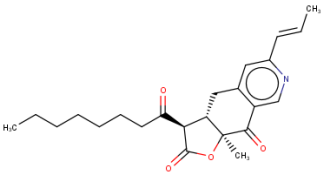
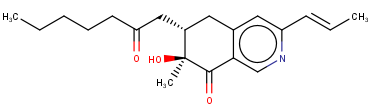
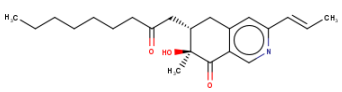
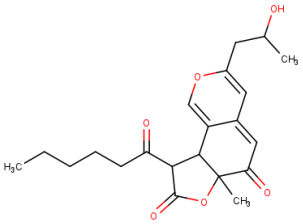
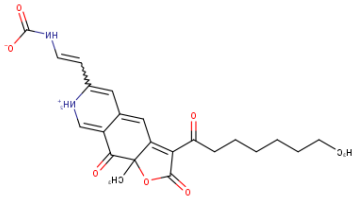
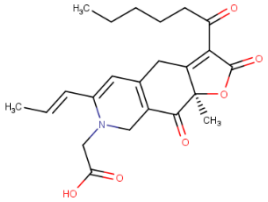
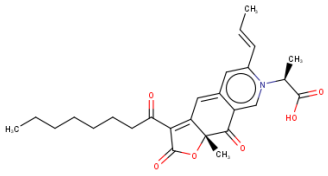
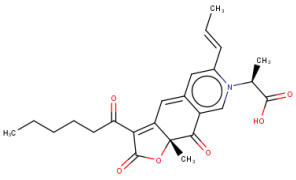
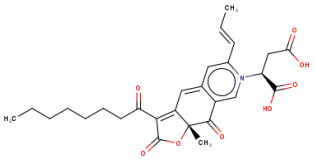
Figure 1 HIV-1 Reverse Transcriptase Receptor (3V81)

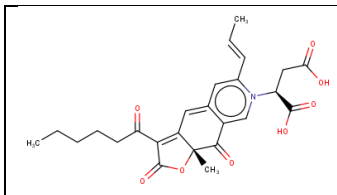
Ligand in this case Monascus sp. contains pigments and various secondary metabolites in it. The main pigments produced by Monascus sp. consist of 6 compounds, namely monascin and ankaflavin (yellow), rubropunctatin and monascorubrin (orange) and rubropunctamine and monascorubramine (red).

Along with the development of research, currently as many as 40 secondary metabolites have been found from Monascus sp. including: monascin, ankaflavin, monascusone a, monascusone b, monaphilone a, monaphilone b, monaphilone c, xanthomonascin a, xanthomonascin b, monankarin a, monankarin b, monankarin c, monankarin d, monankarin e, monanfluores a, monasfluores b, y3, monaphilol a, monaphilol b, monaphilol c, monaphilol d, rubropunctamine, monascopyridine a, monascopyridine b, monascopyridine c, monascopyridine d, r3, pp-v, glycyl-rubropunctatin, red derivate 1, red derivate 2, red derivate 3, red derivative 4, red derivative 5, red derivative 6, red derivative 8, n-glucosylrubropunctamine and n-glucosylmonascorubramine.

Tabel 1 Structure of Secondary Metabolic Compounds *Monascus sp.*

 Monascin	 Ankaflavin	 Monascusone A
 Monascusone B	 Monaphilone A	 Monaphilone B
 Monaphilone C	 Xanthomonascin A	 Xanthomonascin B
 Monankarin A	 Monankarin B	 Monankarin C
 Monankarin D	 Monankarin E	 Monankarin F

 Monasfluore A	 Monasfluore B	 Y3
 Monaphilol A	 Monaphilol B	 Monaphilol C
 Monaphilol D	 Rubropunctamine	 Monascopyridine A
 Monascopyridine B	 Monascopyridine C	 Monascopyridine D
 R3	 PP-V	 Glycyl rubropunctatin
 Red Derivat 1	 Red Derivat 2	 Red Derivat 3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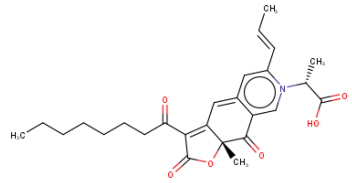
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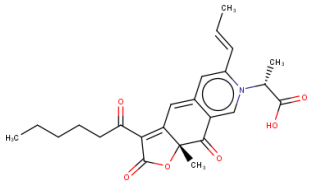
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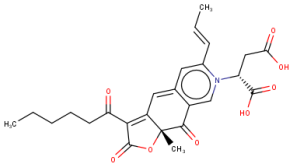
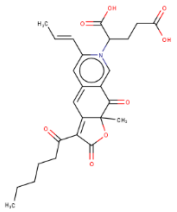

Red Derivat 8


N-Glucosylrubropunctamine

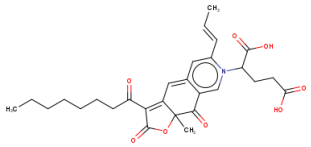

N-Glucosylmonascorubramine

Table 1 Results of screening test compounds based on the Lipinski Rule of Five

No.	Nama Senyawa	BM (g/mol)	Donor Hidrogen	Akseptor Hidrogen	Log P	Refraktifitas Molar	Ket.
1.	Monascin	358.434	0	4	3.67	100.50	Yes
2.	Ankaflavin	386.488	0	4	4.56	109.70	Yes
3.	Monascusone A	254.282	3	5	-0.99	67.08	Yes
4.	Monascusone B	302.326	0	4	1.64	82.07	Yes
5.	Monaphilone A	360.494	1	4	4.16	106.90	Yes
6.	Monaphilone B	332.440	1	4	3.27	97.70	Yes
7.	Monaphilone C	336.472	1	4	4.4	95.95	Yes
8.	Xanthomonascin A	388.416	2	5	4.0	102.20	Yes
9.	Xanthomonascin B	416.470	2	6	3.24	122.01	Yes
10.	Monankarin A	358.390	2	5	2.80	98.10	Yes
11.	Monankarin B	358.390	2	5	2.80	98.10	Yes
12.	Monankarin C	372.417	2	5	3.31	103.14	Yes
13.	Monankarin D	372.417	2	5	3.31	103.14	Yes
14.	Monankarin E	344.363	2	5	2.44	93.63	Yes
15.	Monankarin F	358.390	2	5	2.95	98.67	Yes
16.	Monasfluore A	356.418	0	4	3.38	100.67	Yes
17.	Monasfluore B	384.472	0	4	4.27	109.87	Yes
18.	Y3	430.51	6	7	2.41	111.19	No
19.	Monaphilol A	384.472	1	4	3.62	111.10	Yes
20.	Monaphilol B	356.418	1	4	2.73	101.89	Yes
21.	Monaphilol C	440.536	1	5	3.59	125.32	Yes
22.	Monaphilol D	412.482	1	5	2.70	116.12	Yes
23.	Rubropunctamine	383.448	3	6	2.28	116.86	Yes
24.	Monascopyridine A	355.434	0	4	4.23	98.81	Yes
25.	Monascopyridine B	383.488	0	4	5.12	108.01	No
26.	Monascopyridine C	329.440	1	4	3.84	96.01	Yes
27.	Monascopyridine D	357.494	1	4	4.72	105.21	Yes
28.	R3	374.433	1	5	2.05	101.41	Yes

29.	PP-V	426.469	2	5	0.43	138.67	No
30.	Glycyl-rubropunctatin	413.470	1	6	3.33	114.09	Yes
31.	Red Derivat 1	453.535	1	6	4.65	128.03	Yes
32.	Red Derivat 2	425.481	1	6	3.76	118.83	Yes
33.	Red Derivat 3	497.544	2	8	4.01	134.07	No
34.	Red Derivat 4	469.490	2	8	3.12	124.87	Yes
35.	Red Derivat 5	453.535	1	6	4.65	128.03	Yes
36.	Red Derivat 6	425.481	1	6	3.76	118.83	Yes
37.	Red Derivat 8	469.490	2	8	3.12	124.87	Yes
38.	N-glucosylrubropunctamine	483.517	2	8	3.41	129.62	Yes
39.	N-glucosylmonascorubramine	511.571	2	8	4.30	138.82	No

Physicochemical tests, in this case the solubility and permeability of compounds in the body, are important for drug development, especially for future oral drugs. This is done to prevent the failure of a drug caused by low levels of absorption and permease, Nursamsiar et al., 2016 in [7]. Based on table 2. The results of the physicochemical properties test using Lipinski's rule showed that from a total of 40 secondary metabolites of Monascus sp. There are several compounds that do not pass Lipinski's rules including: Y3, Monascopyridine B, PP-V, Red Derivat 3, N-glucosylmonascorubramine. Molecular weight of more than 500 daltons will make it difficult to penetrate through the skin and digestive membranes. Then the Log P value is important to see the toxic effect if the compound has a Log P value of more than 5, so it is difficult to be excreted and will accumulate, bound to hydrophobic targets than the intended target, making it difficult for the body to metabolize, Gao et al., 2017 in [1].

ADMET test using pkCSM app

The method used to predict and optimize related to pharmacokinetic mechanism and level of toxicity. This method develops the prediction model of ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) especially in drug development. The accuracy of this method in the mutagenicity test reached 83%. There are several parameters that can be studied from the results of this pkCSM test, including: ADMET Absorption (CaCo2 permeability, Intestinal absorption in human), Distribution (Distribution Volume in Human (VDSS), Metabolism (Substrate/inhibitor of CYP3A4), Excretion (Total Clearance, Renal OCT2 substrate), Toxicity (AMES toxicity, Hepatotoxicity, Skin Sensitization) Pires et al., 2015 in [8].

In the absorption test, the CaCo2 permeability parameter was carried out to test the drug solubility in the human intestinal mucosa to predict the absorption of

orally administered drugs. The compound can be well absorbed if it has a value above 0.90 in the CaC02-permeability parameter. In addition, the Intestinal absorption in human test was carried out to predict the ability of the test compound to be absorbed in the intestine, a value above 0.30 indicates the compound can be well absorbed.

In the distribution test, the Distribution Volume in Human (VDSS) parameter is intended to see the ability of the test compound to distribute in tissue and in blood plasma, a value above 0.15 indicates the compound is well distributed.

In the metabolism test, the substrate/inhibitor of CYP3A4, is intended to see the ability of the test compound to become a substrate or inhibitor of CYP3A4. There are no special rules for this test.

In the total clearance and renal excretion test, the OCT2 substrate is intended to see the ability of the renal clearance, which is related to the ability of the drug to be properly excreted out of the body.

In the Toxicity test, there are AMES toxicity, Hepatotoxicity, Skin Sensitization parameters to see the level of toxicity of the test compounds in the body, so that the development of medicinal compounds carried out remains safe for the body.

Tabel 2 pkCSM Results

No.	Pigment Color	Compound Name	Absorption		Distribution	Metabolism	Excretion		Toxicity		
			$CaCo_2$ permeability (log Papp in 10-6cm/s)	Intestinal absorption in human (%)	Distribution Volume in Human (VDSS) (log L/Kg)	Substrate/ inhibitor of CYP3A4	Total Clearance	Renal OCT2 substrate	AMES toxicity	Hepatotoxicity	Skin Sensitisation
			0.90: Well Absorbed	> 30%: Perfectly Absorbed	>0.15: Normal Distribution	-	-	-	No	No	No
1.	Yellow	Monascin	-0.289	38.514	-0.704	Yes/No	1.011	No	No	Yes	No
2.	Yellow	Ankaflavin	0.928	97.464	0.817	Yes/No	1.376	Yes	No	No	No
3.	Yellow	Monascusone A	0.496	66.15	0.12	No/No	1.282	No	No	No	No
4.	Yellow	Monascusone B	1.228	99.536	0.129	Yes/No	0.128	No	Yes	No	No
5.	Yellow	Monaphilone A	0.733	93.879	0.092	Yes/No	1.555	Yes	No	No	No
6.	Yellow	Monaphilone B	1.078	94.586	0.113	Yes/No	1.504	Yes	Yes	No	No
7.	Yellow	Monaphilone C	1.098	94.822	-0.123	No/No	1.672	Yes	No	No	No
8.	Yellow	Xanthomonascin A	0.923	86.393	0.166	Yes/No	1.027	No	No	Yes	No
9.	Yellow	Xanthomonascin B	0.872	70.198	0.19	No/No	1.374	No	No	No	No
10.	Yellow	Monankarin A	0.723	93.425	0.206	Yes/No	0.664	No	No	No	No
11.	Yellow	Monankarin B	0.723	93.425	0.206	Yes/No	0.664	No	No	No	No
12.	Yellow	Monankarin C	1.077	93.286	0.324	Yes/No	0.727	No	No	No	No
13.	Yellow	Monankarin D	1.077	93.286	0.324	Yes/No	0.727	No	No	No	No
14.	Yellow	Monankarin E	1.105	74.041	0.16	No/No	0.764	No	No	Yes	No
15.	Yellow	Monankarin F	1.055	91.555	0.184	No/Yes	0.737	No	Yes	Yes	No
16.	Yellow	Monasfluore A	1.472	98.131	0.223	Yes/No	1.355	Yes	No	No	No
17.	Yellow	Monasfluore B	0.99	97.424	0.181	Yes/No	1.404	Yes	No	No	No
18.	Yellow	Y3	-0.527	36.077	-0.322	No/No	0.277	No	No	No	No
19.	Orange	Monaphilol A	0.696	94.503	0.073	Yes/No	1.485	Yes	No	No	No
20.	Orange	Monaphilol B	1.076	95.21	0.109	Yes/No	1.436	Yes	No	No	No
21.	Orange	Monaphilol C	0.826	95.474	-0.075	Yes/No	1.12	Yes	No	No	No
22.	Orange	Monaphilol D	1.304	96.181	-0.014	Yes/No	1.464	Yes	No	No	No
23.	Red	Rubropunctamine	0.833	94.204	0.234	Yes/No	1.063	No	No	Yes	No
24.	Red	Monascopyridine A	1.149	98.26	0.159	Yes/No	1.257	No	No	Yes	No

25.	Red	Monascopyridine B	0.714	97.554	0.249	Yes/Yes	1.307	No	No	Yes	No
26.	Red	Monascopyridine C	0.988	94.947	0.201	No/No	1.318	No	No	Yes	No
27.	Red	Monascopyridine D	0.622	94.24	0.288	Yes/No	1.374	No	No	No	No
28.	Red	R3	1.462	96.659	0.101	Yes/No	1.285	No	No	No	No
29.	Red	PP-V	0.592	55.94	-0.576	No/No	0.99	No	No	Yes	No
30.	Red	Glycyl-rubropunctatin	0.748	58.421	-0.769	Yes/No	1.367	No	No	Yes	No
31.	Red	Red Derivat 1	0.672	61.024	-0.621	Yes/No	1.086	No	No	Yes	No
32.	Red	Red Derivat 2	0.693	59.622	-0.584	Yes/No	1.468	No	No	No	No
33.	Red	Red Derivat 3	-0.347	28.624	-0.473	Yes/No	1.006	No	No	No	No
34.	Red	Red Derivat 4	-0.32	27.221	-0.436	Yes/No	1.417	No	No	No	No
35.	Red	Red Derivat 5	0.672	61.024	-0.621	Yes/No	1.086	No	No	Yes	No
36.	Red	Red Derivat 6	0.693	59.622	-0.584	Yes/No	1.468	No	No	No	No
37.	Red	Red Derivat 8	-0.32	27.221	-0.436	Yes/No	1.417	No	No	No	No
38.	Red	N-glucosylrubropunctamine	0.451	41.34	-0.344	No/No	1.118	No	No	No	No
39.	Red	N-glucosylmonascorubramine	0.48	36.7	-0.292	No/No	1.031	No	No	Yes	No

Based on the pharmacokinetic and toxicity test data using the pkCSM application, it was found that from a total of 39 test compounds there were only 26 compounds that passed the pharmacokinetic and toxicity test

Redocking Results with Native Ligands

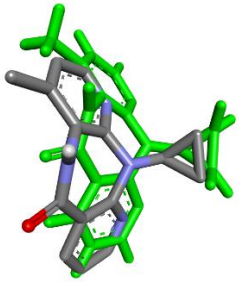


Figure 2 Redocking Results with Native Ligands

The results of natural ligand redocking give RMSD results of 1.83 (less than 2 A) so that the redocking test can be accepted for its validity value.

Results of docking test compounds and visualization

In this study, docking of 26 compounds contained in Monascus sp. with the HIV-1 Reverse Transcriptase (3V81) receptor using the Autodock 4.2.6 software. The results obtained are in accordance with table 3. The Ki value indicates the inhibitory ability of a compound at its receptor, this shows that the smaller the value, the stronger the inhibitory strength Umamaheswari et al., 2013 in [10]. The Ki value that can be seen in table 3 shows that there are several test ligands that have the potential as HIV antiviral drugs with the most potential being Red Derivat 2 with a Ki value of 1.81 which has better potential at the 3V81 receptor.

Table 2 Results of Docking Test Compounds with 3V81 . Receptors

No	Compound Name	Run	Binding Affinity (kcal/mol)	Inhibition Constant (nM)	Hydrogen Bond	Amino Acid (Residue Contact)
	Nevirapine	92	-8,16	1,05	LYS101	LYS101, LYS102, LEU100, VAL106, PRO236, GLY190, LYS103, VAL179, VAL189, TYR181, PHE227, TYR188, TRP229, LEU234, HIS235, TYR318
1.	Ankaflavin	33	-11.02	8.39	LYS101, TYR181	LYS101, TYR181, PRO95, VAL179, HIS235, VAL106,

						TYR318, PRO236, LYS102, PHE227, LEU234, LEU100, LYS103, TYR188, TRP229
2.	Monascusone A	87	-7.50	3.17	PRO236, TYR188	PRO236, TYR188, TRP229, TYR181, LYS101, TYR318, LYS103, LYS102, LEU100, VAL106, HIS235, PHE227, LEU234
3.	Monaphilone A	31	-9.92	80.03	TYR188, TYR181	TYR188, TYR181, LYS103, VAL189, GLY190, VAL179, LYS101, TRP229, PHE227, LEU234, HIS235, VAL106, LYS102, TYR318, LEU100, ILE180, PRO236
4.	Monaphilone C	57	-9.24	168.53	VAL179, TYR181	VAL179, TYR181, PRO95, VAL189, GLY190, ILE180, LYS101, LYS102, HIS235, PRO236, PHE227, LEU234, TRP229, TYR188, LEU100, VAL106, LYS103, TYR318
5.	Xanthomonascin B	9	-10.21	32.75	TYR188, VAL179, LYS103, PRO236, TYR318	TYR188, VAL179, LYS103, PRO236, TYR318, PRO95, TRP229, TYR181, ILE180, VAL189, LYS101, GLY190, LYS102, LEU2234, PHE227, VAL106, LEU100
6.	Monankarin A	28	-10.25	30.64	PRO236	PRO236, HIS235, PRO225, PHE227, LEU234, TYR188, VAL106, LYS103, TYR181, ILE180, VAL179, VAL189, GLY190, LYS101, LEU100, LYS102, TYR318
7.	Monankarin B	37	-11.26	5.62	LYS103, PRO236, LYS101,	LYS103, PRO236, LYS101, TYR188, TRP229, PRO95, PRO97, LEU100,

					TYR188, TRP229	GLY190, VAL179, TYR318, LYS102, ASP237, VAL106, PHE227, LEU234
8.	Monankarin C	1	-9.34	142.17	HIS235, TYR318, LYS101, TYR181	HIS235, TYR318, LYS101, TYR181, LYS103, PRO236, VAL179, ASP237, PHE227, LEU234, TYR188, VAL106, TRP229, LEU100
9.	Monankarin D	31	-9.10	212.03	LYS101, LEU234	LYS101, LEU234, VAL106, LEU100, PHE227, TYR188, VAL179, ILE180, TYR181, PRO95, GLY190, LYS103, LYS102, TYR318, HIS235, PRO236
10.	Monasfluore A	48	-9.82	63.18	-	TYR318, LYS102, LYS103, LYS101, PRO236, TYR181, VAL179, TRP229, TYR188, GLY190, LEU234, VAL106, PHE227, LEU100
11.	Monasfluore B	31	-10.43	22.79	-	TYR318, LYS103, PRO236, LYS102, LYS101, GLY190, VAL179, TYR181, LEU100, TRP229, PRO95, TYR188, LEU234, PHE227, VAL106
12.	Y3	63	-8.18	1.01	HIS235, LYS101	HIS235, LYS101, TYR188, TYR181, VAL106, LYS102, LEU100, PRO95, TYR318, LEU234, LYS103, PRO236, TRP229, PHE227, VAL179, GLY190
13.	Monapurone B	50	-8.54	771.89	VAL189	VAL189, TYR188, GLY190, PHE227, LEU234, PRO236, HIS235, VAL106, LYS103, TYR318, LYS101, VAL179, LEU100, TYR181
14.	Monapurone C	53	-8.67	442.39	ILE180	ILE180, PRO95, TYR181, TRP229, LYS101, LEU100,

						VAL106, TYR318, PRO236, HIS235, LEU234, PHE227, LYS103, TYR188, GLY190, VAL189, VAL179
15.	Monaphilol A	73	-10.43	22.50	TYR188	TYR188, TRP229, LEU234, PHE227, VAL106, HIS235, PRO236, LYS102, TYR318, LEU100, VAL179, LYS103, LYS101, TYR181
16.	Monaphilol B	76	-9.65	84.98	TYR188	TYR188, TRP229, PHE227, HIS235, PRO236, TYR318, VAL106, LYS101, VAL179, LYS103, LEU100, LEU234, TYR181
17.	Monaphilol C	25	-7.22	5.06	TYR339, LYS350, GLY352	TYR339, LYS350, GLY352, SER268, THR351, ARG356, TYR354, ALA355, LYS374, LYS353, GLY262, ASN265, TRP266, HIS96, GLN269, GLU378
18.	Monaphilol D	84	-9.91	244.49	LYS101, LYS103	LYS101, LYS103, ILE180, VAL189, GLY190, LEU100, LEU234, VAL106, TRP229, TYR188, VAL179, PRO95, TYR181
19.	Monascopyridine D	59	-9.79	66.15	ILE180, LYS101	ILE180, LYS101, VAL179, VAL106, TYR318, PHE227, PRO236, LYS103, LEU234, LYS102, HIS235, TYR188, TRP229, PRO95, TYR181, LEU100
20.	R3	10	-9.18	185.85	LYS101	LYS101, VAL179, TYR318, ILE180, LYS102,LYS103, PRO236, VAL106, HIS235, LEU234, PHE227, TRP188, TYR181, PRO95, TRP229, LEU100

21.	Red Derivat 2	77	-11.93	1.81	LYS101, LEU100	LYS101, LEU100, LYS103, VAL179, TYR188, TYR318, PHE227, VAL106, HIS235, PRO236, PRO97, TYR181, TRP229, PRO95, LEU234, ILE180
22.	Red Derivat 3	43	-11.84	2.11	LYS101	LYS101, LEU234, PRO95, TRP229, PRO97, TYR188, PHE227, LYS102, PRO236, HIS235, VAL106, LYS103, TYR318, LEU100, TYR181, VAL179
23.	Red Derivat 4	66	-7.57	2.81	ALA355, LYS353, SER268, GLN269	ALA355, LYS353, SER268, GLN269, TYR339, THR351, GLY352, ASN265, LYS350, ILE94, TRP266, TYR232, HIS96, LYS374, ARG356, TYR354
24.	Red Derivat 6	71	-11.90	1.89	LYS101, LEU100	LYS101, LEU100, PRO95, TYR181, PRO97, TRP229, LEU234, TYR188, PHE227, HIS235, PRO236, TYR318, VAL106, VAL179, LYS103
25.	Red Derivat 8	79	-11.85	2.05	LYS101, ILE180	LYS101, ILE180, LYS103, VAL179, TYR318, TYR181, VAL106, LEU100, LYS102, PRO236, PHE227, TYR188, PRO97, LEU234, PRO95, TRP229
26.	N-glucosylrubropunctamine	4	-11.73	2.53	GLY99, ILE180	GLY99, ILE180, LYS101, TRP229, PRO95, LEU234, PRO97, TYR188, PHE227, VAL106, LYS102, PRO236, HIS235, TYR318, LEU100, TYR181, VAL179, LYS103

In addition to the value of the inhibitory constant that can be analyzed, there is a value of G which indicates the amount of energy released by a compound to be able to interact or form a bond with its receptor. The smaller the energy number, the greater the energy used to form a stronger bond Umamaheswari et al., 2013 in [10]. The G value that can be seen in table 3 shows that there are several test ligands that have the potential as HIV antiviral drugs with the most potential being Red Derivat 2 with energy binding -11.93 when compared to the native ligand 8.16 then Red Derivat 2 has more potential. at the 3V81 receptor as a candidate for HIV antiviral drugs.

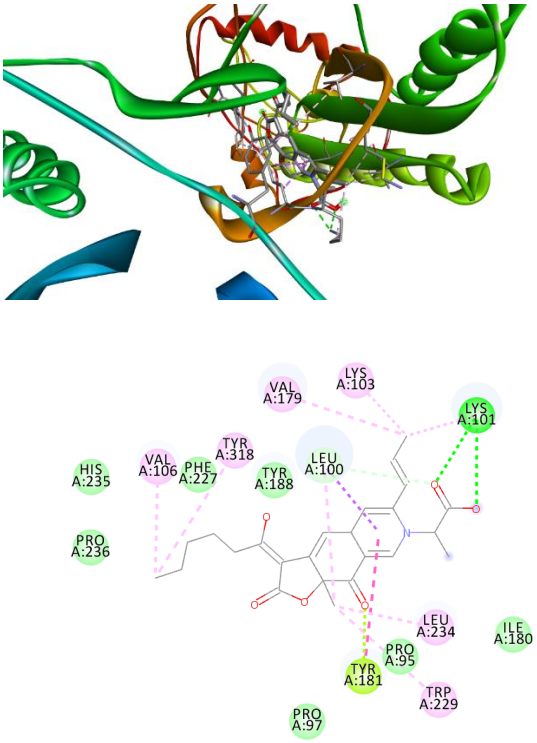


Figure 3 Visualization of red derivate 2 docking results (a) Visualization of red derivate 2 docking results and the amino acids involved

Conclusion

Based on the results of virtual screening using a computational chemistry approach with the in silico method on 39 derivative metabolites of Monascus sp. The results showed that the compound red derivate 2 has a higher binding energy

value than the native ligand and has a smaller inhibition constant, so that the compound red derivate 2 has the potential to be a candidate for HIV antiviral drugs, which have met the ADMET and Lipinksi rules tests. But still requires further research, including In vitro and Invivo test.

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