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NEW 3-PHENYL INDOLE DERIVATIVES ASSEMBLING AS ANTITUBERCULOSIS DRUG USING QSAR AND ADMET STUDY

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Abstract

The newly designed compounds of the 3-phenyl indole derivative show great antituberculosis activities. They become a solution for MDR-TB treatment. This study was conducted to design 3-phenyl indole compounds through the QSAR approach. QSAR study used multi-linear regression (MLR) analysis. ADMET-drug likeness of new compounds investigated through in silico. The result provided the best QSAR equation, which was pMIC = 40.52 + 4.531(QC6) – 9.989(QC8) – 12.567(QC9) + 2.803(HOMO) – 166.568(LUMO). The addition of donating groups in indole compounds could enhance antituberculosis activity. ADME-drug likeness analysis revealed that newly designed compounds were good properties and were non-toxic.

Keywords: *QSAR, Indole, Antituberculosis*

INTRODUCTION

Tuberculosis (TB) is a disease caused by infection of *Mycobacterium tuberculosis*. Globally, this disease is still a serious public health problem because it can cause death [1]. In 2019, there were 10 million cases of this disease found, and 1.2 million patients were declared dead [2]. In the same year, several countries in South-East Asia (44%), Africa (25%), and western pacific (18%) regions recorded TB cases [3]. Several efforts to overcome this disease have been conducted. Isoniazid and rifampicin are known antituberculosis drugs used to reduce the number of TB cases. This treatment is given to patients regularly for up to 22 months. However, the achievement of this therapy is only 48% [4], thus only impacting a 9% decrease in TB cases [5]. One of the reasons is the downward efficacy drug and leads to multidrug resistance by *Mycobacterium tuberculosis* (MDR-TB).

For tackling this issue, the discovery of new drugs to reduce the number of TB cases becomes a solution. Computational-aided drug discovery (CADD) provides an opportunity for researchers to accelerate finding new drugs [6]. CADD offers two approaches, which are structure-based drug design (SBDD) dan ligand-based drug design (LBDD) [7]. The SBDD approach requires the 3D structure of the targeted protein to study the energy and type of interaction that occurs between the ligand and the receptor protein. When targeted protein is absent, LBDD could be an option for drug discovery purposes. Quantitative structure-activity relationship (QSAR) is one of the computational methods using the LBDD approach. The QSAR method provides a mathematical equation that describes the correlation between the physicochemical properties of the compound and its biological activity. In this way, new compounds could be designed and predicted their biological activities.

Indole is a five-ring heterocyclic compound containing nitrogen fused with a benzene ring (Figure 1). Indole compounds are known to have broad biological activities. Rathod et al [8] reported that the synthesized indole compound showed good antimycobacterial activity. This indole compound can inhibit the mycobacterial enoyl reductase (InhA) enzyme. This enzyme plays a role in mycolic acid biosynthesis for the main component of cell walls [9]. The derivative of the indole compound had also been successfully synthesized by Etchart et al [10]. In this study, indole compound was able to inhibit *M. tuberculosis* H37Rv strain with a MIC value of 8.4 mM. However, this value is not promising to be further developed in TB remedies because it could allow resistance to long-term use of this compound. The pharmacokinetic properties and toxicity of these compounds are not evaluated. Thus, it is challenging to apply directly to the treatment of TB.

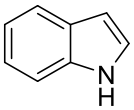


Figure 1. The chemical structure of indole ring

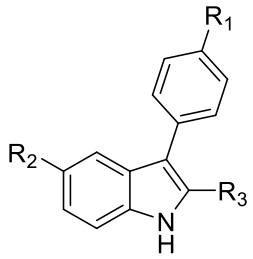
The modification of the indole ring becomes the solution to answer this problem. The insertion of new functional groups into indole rings is expected to enhance biological activity. Therefore, this study concentrates on conducting a QSAR study of indole derivatives. The absorption, distribution, metabolism, excretion, and toxicity (ADMET) and the drug-likeness of the new compounds were also studied. The newly designed compounds were expected to become a proposed compound to be studied in the laboratory.

METHOD

Materials

The used data set was acquired from research data by Etchart et al [10]. Twenty 3-phenyl indole compounds had synthesized and evaluated for their antituberculosis activity against *Mycobacterium* tuberculosis (Mtb H37Rv). The antituberculosis activity was represented by the MIC value (mM). This value is further converted to pMIC (6-log MIC) and used for QSAR analysis, as shown in Table 1.

Table 1. The data set of 3-phenyl Indole compounds



Compound	R_1	R_2	R_3	pMIC
1	-H	-H	-H	3.888
2*	$-CH_3$	-H	-H	3.919
3	$-OCH_3$	-H	-H	4.553
4	-F	-H	-H	4.024
5	$-CF_3$	-H	-H	4.321
6	$-OCH_3$	-H	$-CH_3$	4.074
7	-F	-H	$-CH_3$	4.052
8	$-CF_3$	-H	$-CH_3$	4.740
9	-F	$-CH_3$	-H	4.353
10	$-CF_3$	$-CH_3$	-H	4.440
11	$-CH_3$	$-OCH_3$	-H	3.978
12	$-OCH_3$	$-OCH_3$	-H	4.607
13*	-F	$-OCH_3$	-H	4.081
14	$-CF_3$	$-OCH_3$	-H	4.764
15	-F	-F	-H	4.361
16*	$-CF_3$	-F	-H	4.446
17	-H	-Cl	-H	3.959
18*	$-OCH_3$	-Cl	-H	4.712
19	-F	-Cl	-H	4.693
20	$-CF_3$	-Cl	-H	5.076

*test set compound

Instrumentation

The Computing operating system used specifications as follows intel® Core™ i3-7020U CPU @ 2.3 GHz, 4 GB (RAM). The software installed were ChemDraw Professional 16, Chem 3D 16, Gaussian 09, and SPSS version 25.

Procedure

QSAR analysis

QSAR analysis began with validating the best computational method for later use as a compound's structure optimizing method. C-NMR of compound 5 was determined by semi-empirical methods, Ab initio, and DFT as validation stage. Semi-empirical methods include AM1, PM3, and PM6, while the Ab initio method used the HF method. The selected method was based on the smallest PRESS value, and then it was used to optimize all the compound structures. The optimization process was carried out to obtain electronic descriptor data such as electron charge, HOMO, and LUMO.

The data set breaks down into two categories. The first category was the training set. The training set is the data used to build the QSAR equation model using Multi Linear Regression with the backward method. The second category was the test set. The obtained QSAR equation is validated using this second category under statistical considerations. The PRESS (Predictive Residual Sum of Square) value is the summative value of the square of the difference between experimental and predictive activity. The smaller the PRESS value indicates that the selected QSAR equation is close to the actual value. The r^2 value describes the linearity of the measurement, where if the value > 0.5 means that the QSAR equation could be used as a reference to predict the activity of the new compound [11].

We also employ an Applicability Domain (AD) for evaluating the presence of outliers in the data set. AD provides an idea of whether the viability QSAR equation is able to predict new compounds [12]. The application of AD is shown through a graph between standardized residual versus leverage. Threshold value (h*) for AD uses the equation [13]:

$$h^* = 2.5 \times (k+1)/n \quad (1)$$

Where n value reflects the number of data sets in the training set group, k is the number of selected descriptors for the QSAR equation used, and the 2.5 value is the standard deviation in AD [11].

New design compound

The modification of the 3-phenyl indole structure by considering the selected QSAR equation was carried out. The insertion of new substituents on this parent structure was intended to provide a better predictive activity value. The best predictive activity is represented by the higher pMIC value. The new compounds obtained could be used as reference compounds of candidate drugs for antituberculosis (Table 5).

AMDET and Drug-likeness analysis

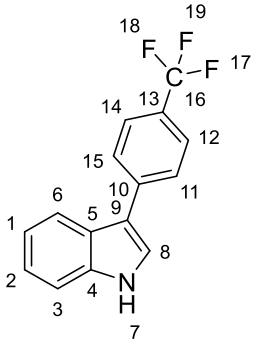
The new compounds from the QSAR analysis were screened for pharmacokinetic properties in silico. The pkCSM is a web-based tool for evaluating the pharmacokinetic properties of new compounds [14], while their drug-likeness properties were determined using the SwissAdme tool [15] and Molsoft tool by inputting the SMILE code from the new compound's design.

RESULT AND DISCUSSION

QSAR Analysis

Built the QSAR equation began with determining the best computational method. This step was one of the crucial stages. For compound 5, computational analysis was carried out to obtain the chemical shift data from C-NMR. Compound 5 was selected as the validation compound because it had the highest yield on the experimental data. Furthermore, the analysis involved the AM1, PM3, PM6, HF, and DFT methods using Gaussian 09 software. It produces a chemical shift (Table 2). Table 2 showed that the PM6 method had the smallest PRESS value. The smallest PRESS value characterized the results of the computational method analysis had the similarity with the experimental data.

Table 2. Optimization of several computational methods based on C-NMR calculations



Position	δ experiment (ppm)	AM1	PM3	PM6	HF	DFT
C3	111.6	96.58	95.83	96.31	93.336	96.071
C9	117.1	104.00	101.65	104.84	101.33	103.02
C1	119.6	104.45	103.78	104.71	102.10	105.24
C8	120.9	111.57	111.22	110.55	104.56	108.94
C6	122.6	101.66	103.32	102.07	100.63	103.34
C2	122.8	105.70	105.23	106.33	104.02	106.75
C16	124.5	128.17	122.83	120.09	125.18	132.46
C12	125.5	110.27	108.71	110.28	107.00	110.65
C14	125.7	110.81	109.89	111.68	108.12	110.73
C11, C15	127.3	110.81	108.03	111.51	109.38	110.57
C5	127.6	108.95	107.09	109.00	105.98	108.37
C10	127.8	119.88	119.16	121.63	120.07	122.56
C13	136.8	109.21	108.83	109.12	107.98	109.37
C4	139.4	120.65	119.16	120.52	113.46	117.29
PRESS		3706.83	4105.34	3609.47	4994.08	3843.32

The PM6 method was then used to measure the descriptor value of the entire data set compounds. The descriptor used in this research was the electronic descriptor. The total charge of the atoms in each compound was determined. The value of HOMO and LUMO were also measured using the PM6 method. Every descriptor of the compounds was then tabulated on excel and was analyzed using the Multi Linear regression (MLR) with the backward method. This method was selected because it is simple and eliminates descriptors that do not significantly affect the regression equation. The elimination stage was carried out until the largest F_{cal}/F_{table} ratio value was obtained.

Table 3. QSAR equation from the MLR analysis

Model	Descriptor	r	r^2	Adjusted r^2	SEE	F_{cal}/F_{table}	PRESS
1	LUMO, QC6, QC9, QC13, HOMO, QC3, QC14, QC8	0.941	0.886	0.755	0.174	1.82	0.212
2	LUMO, QC6, QC9, QC13, HOMO, QC3, QC8	0.924	0.853	0.724	0.185	1.89	0.272
3	LUMO, QC6, QC9, QC13, HOMO, QC8	0.918	0.842	0.737	0.181	2.37	0.293

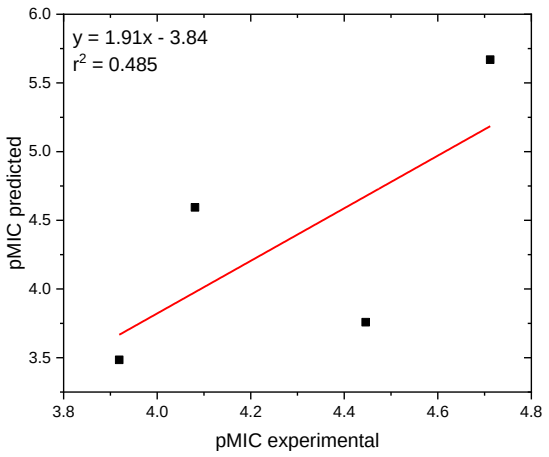
Table 3 provides three equation models based on MLR analysis. All equations had good r values where the values were close to 1. It means that every descriptor selected had a strong correlation. Table 3 also showed that the r square value was in the range of 0.80-0.90. These values were fairly good to be used as a model for the QSAR equation and indicated that each descriptor (independent variable) from each equation had a major influence on biological activity (dependent variable) with a confidence level

of 80-90%. This was also in line with another parameter of the statistical analysis result, namely the value of the F_{cal}/F_{table} ratio, which described the significance of an equation model. The three equations had a large F_{cal}/F_{table} ratio value and tend to increase in equation 3, therefore the three equation models offered could be used to predict the activity of the design compound. Table 3 also showed the PRESS value of the three equations which were fairly low, therefore it means that these equations were close to the true value. Although the values shown by the parameters above were fairly good, if only referring to these parameters, it would be difficult to select the best equation model. Therefore, external validation was carried out.

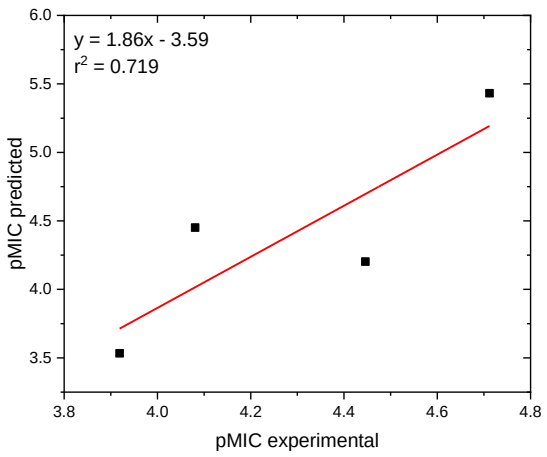
Table 4. External validation of the QSAR equation from the MLR analysis

Test Compound	pMIC experimental	Predicted pMIC Calculation		
		Model 1	Model 2	Model 3
2	3.919	3.484	3.533	3.546
13	4.081	4.594	4.451	4.464
16	4.446	3.758	4.203	4.204
18	4.712	5.669	5.432	5.341
PRESS		1.841	0.862	0.739
r^2		0.485	0.719	0.707

External validation was determined by the PRESS and the r square values for all equation models offered (Table 4). Furthermore, the three equation models were used to determine the value of the predictive activity. These values were then evaluated by regression analysis and provided to the graph as presented in Figure 1. The best r square value was owned by the equation model 2, which was slightly larger than model 3. Based on the PRESS value perspective, equation model 3 had a larger value than model 2. Therefore, equation 3 suggested the best equation model. This was because it had a better close to the true value.



(a)



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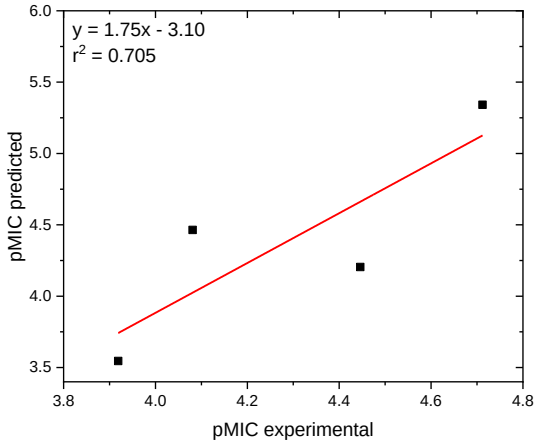


(c)

Figure 1. Linear regression graph of a) model 1, b) model 2, and c) model 3.

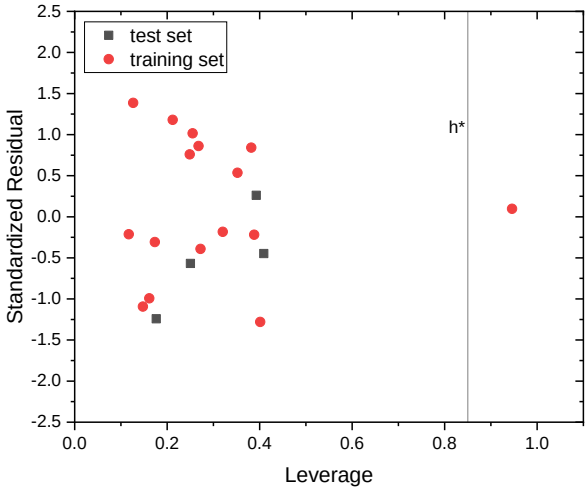


Figure 2. William's graph plots the selected QSAR model

The selected QSAR equation model was also evaluated using the Applicability Domain (AD). The Applicability Domain was applied to detect outliers' presence in the data set, shown as *William* plot graph (Figure 2) by plot standard value versus leverage. Furthermore, the threshold value (h*= 0.875) describes that compounds located at the right-handed threshold have low reliability for predicting new compounds. In Figure 2, compound 1, belonging to a data set, was founded as an outlier while several compounds in the test set did not contain outliers. Thus, the selected QSAR equation model is still allowed as guidance in designing and predicting new compounds.

New Compound Design

The selected QSAR equation was used as a guide for designing new compounds. That equation contained several important descriptors which affect predictive activity. The selected descriptors include the QC6, QC8, QC9, QC13, HOMO, and LUMO with the QSAR equation as follows:

$$pMIC = 40.52 + 4.531(QC6) - 9.989(QC8) - 12.567(QC9) + 2.803(QC13) + 126.833(HOMO) - 166.568(LUMO) \quad (2)$$

Some of the charges contained in the QSAR equation could be used as guidance to increase predictive antituberculosis activity. Based on figure 3, the C6, C8, and C13 were modifiable carbons to enhance antituberculosis activity, while the C9 included the quaternary carbon cannot add substituents. For this purpose, the pMIC value should make high value. C6 and C13 had positive signs, so these carbons need to insert an electron-donating substituent. On the other hand, C8 preferred electron-withdrawing substituent. This was because this substituent could attract electrons from the benzene nucleus so that the QC8 value becomes negative. Consequently, a positive value contribution to the QSAR equation occurred

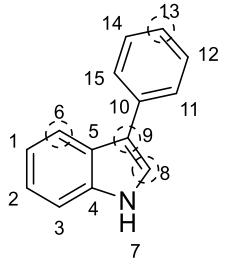
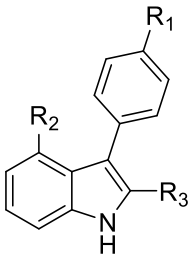


Figure 3. 3-phenyl indole structure

Table 5. The newly designed compound of 3-phenyl indole



Compound	R_1	R_2	R_3	pMIC prediction
20	$-CF_3$	-Cl	-H	5.08
I1	-OH	-OH	$-NH(CO)CH_3$	6.95
I2	-OH	-OH	-COOH	9.03
I3	-OH	$-OCH_3$	-I	11.38
I4	$-OCH_3$	$-OCH_3$	-I	11.38
I5	-OH	$-OCH_2CH_3$	-I	11.39
I6	-OH	$-N(CH_3)_2$	-I	11.61

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) also contributed to the predictive antituberculosis activity. These descriptors are responsible for the reactivity and stability of a compound [16]. The positive sign of the HOMO descriptor suggested the modification of a new compound by adding substituents that could improve the electrophilic properties of the compound. Moreover, the LUMO descriptor indicated that the nucleophilic character of a compound also needed to be considered. The negative sign of the LUMO descriptor preferred to modify structure which decreases the value of LUMO, so it contributed positively to the predictive antituberculosis activity.

Based on the interpretation of the selected QSAR equation, then modification of the 3-phenyl indole compound was carried out. Table 5 depicts several new compounds that had been designed. Compound 20 was used as a reference compound to modify a new compound. At R_1, this position adored electron-donating groups such as hydroxyl groups (-OH). The change of the hydroxyl to methoxy ($-OCH_3$) group has not significantly changed activity. However, this modification yielded a high impact on the R_2 position with the improvement predictive pMIC value from 9 to 11.

The modification was further on the R_3 position. Although the insertion of electron-withdrawing groups was necessary to improve pMIC predictions based on QSAR guidance, we found that the donating group was surprised to up the activity. The insertion of the carboxylic group (-COOH) on the R3 position increased the pMIC value up to 9. However, the insertion of electron-donating groups increased the pMIC significantly until 11. We found that the insertion of iodo (-I) gave a remarkable increase in pMIC and was also nontoxic compared to other halogen groups.

AMDET and Drug-likeness analysis

The pharmacokinetic character of designed compounds was also studied. There are absorption, distribution, metabolism, elimination, and toxicity (ADMET), as shown in Table 6. Analysis of the

pharmacokinetic properties needs to ensure that the efficacy and safety of new compounds (drug candidates) could be expected [17]. Table 6 showed that all compounds have a range of intestinal absorption values between 60-90%. This was included in the good category, where a compound is said to have poor absorption if its value is below 30% [18]. The best absorption properties were shown by compounds I1, I4, and I5, with absorption values reaching 90%, which is an ideal criterion regarding the bioavailability of a drug [18].

Table 6. ADMET character of the newly designed compound

Id Comp	Absorption	Distribution			Metabolism				Excretion	Toxicity
	Intestinal absorption	VDss	BBB permeability	CNS permeability	Substrate CYP		Inhibitor		Total clearance	AMES toxicity
					2D6	3A4	2D6	3A4		
	%	Log L Kg^{-1}	(log BB)	(log PS)	Categorial				Log mL min^{-1} Kg^{-1}	Categorial
20	89.93	0.29	0.56	-0.97	Yes	Yes	Yes	Yes	0.13	Yes
I1	90.57	-0.14	-1.03	-2.13	Yes	No	No	No	0.23	No
I2	69.11	-1.02	-1.15	-2.24	No	No	No	No	0.53	No
I3	89.98	0.09	0.16	-1.61	No	Yes	Yes	No	0.19	No
I4	95.49	0.68	0.18	-1.77	Yes	Yes	No	No	0.35	No
I5	89.12	0.12	0.17	-1.63	No	Yes	Yes	Yes	0.14	No
I6	90.35	0.23	0.25	-1.56	No	Yes	Yes	Yes	-0.01	No

The distribution Volume (Vdss) describes how much a drug is distributed in the body or blood plasma, a high Vdss value indicates that a compound is distributed more in body tissues than blood plasma and vice versa. A compound has a low volume of distribution (Vdss) if the value < -0.15, on the other hand, is said to have a high Vdss if the value > 0.45 [18]. Table 6 showed that the predicted values of Vdss for all new compounds were varied, which were between -0.1 – 0.68. Compounds I1 and I2 with Vdss values were -0.14 and -1.02, respectively, were predicted more widely distributed in blood plasma, but only a low amount could be distributed in body tissues. While compound I4 had the largest Vdss value, it means more distribution in the body tissues.

Compounds I1 and I2 had low BBB permeability values (Log BB), which were -1.03 and -1.15, respectively. These values indicated the inability of these two compounds to cross the blood-brain barrier. Compounds I3, I4, I5, and I6 also had a low ability to be distributed to the brain, unlike compound 20, with a log value of 0.56, which can penetrate the blood-brain barrier. A compound is considered not to be distributed to the brain if the log BB value is < -1 and could be well distributed if the log BB value is > 0.3 [18,19].

Furthermore, the metabolism and inhibition by new compounds were also investigated and presented in Table 6 above. The inhibitory of Cytochrome P450 is very important to discuss because this could affect the drug interactions, especially in concurrent use (co-administration), where metabolism failure could occur therefore causing the accumulation of the drug in the blood to toxic levels [19]. Predictive analysis of metabolism activity in Table 6 was performed using two enzymes, namely CYP2D6 and CYP3A4, which are the two largest cytochrome P450 enzymes in drug metabolism. CYP2D6 enzymes play a key role in the metabolism of 15-25% of drugs from almost all therapeutic categories, while CYP3A4 metabolizes 30% of the drug [20]. Unlike compound 20, compound I2 did not even act as a substrate or inhibitor of the two enzymes. Although compound I1 was predicted to be metabolized by CYP2D6, compounds I3, I5, and I6 could inhibit the activity of the CYP2D6 enzyme well. These compounds were predicted to act as substrates for CYP3A4.

The excretory activity of these new compounds was also carried out, which was indicated by the log total clearance (Log $mL.min^{-1}.Kg^{-1}$) value where this value represented the combination of the clearance rate in the liver (liver and bile) with excretion by the kidneys [18]. Table 6 depicted that the new compounds had total clearance values ranging from -0.01 – 0.5. All the new compounds except compound I6 had a higher excretion rate than compound 20, where the largest elimination rate was predicted to be found in compound I2.

The newly designed compounds were compounds predicted to be safe or non-toxic through the Ames toxicity test in silico, unlike compound 20, which was predicted to be toxic. Ames test is a method to measure the toxicity of a compound using bacteria, where the results could show that a compound is classified as carcinogenic or not [18].

Table 7. Drug-likeness analysis of new compounds

Compound	MW[a]	Log P[a]	HBA[a]	HBD[a]	PSA[a] (A^2)	Violation of Lipinski rule[b]	Drug-likeness score[a]	Synthetic accessibility[b]
20	295.04	5.64	0	1	9.84	1	-1.28	2.11
I1	282.10	2.29	3	4	67.38	0	0.63	2.42
I2	269.07	2.37	4	4	72.66	0	0.15	2.24
I3	364.99	4.09	2	2	34.80	0	-0.26	2.63
I4	379.01	4.61	2	1	24.73	0	-0.38	2.74
I5	379.01	4.51	2	2	34.38	0	-0.00	2.71
I6	378.02	4.37	1	2	29.67	0	-0.46	2.67

[a]analysis using molsoft tool; [b]analysis using SwissAdme tool

The drug-likeness of new compounds is executed in silico, as shown in Table 7. The parameter of the *Lipinski* rule, such as molecular weight (MW), log P, Hydrogen Bonding acceptor (HBA), and Hydrogen Bonding Donor (HBD), was evaluated for all compounds. Table 7 showed that all the new compounds had a molecular weight (MW) lower than 500 and good absorption [21]. Furthermore, the lipophilicity character is represented by the log P-value. For the new compound, the log P value ranges from 2-4, while compound 20 (reference compound) had a log P value >5. This showed that the new compound tends to be polar, therefore it had a low ability to pass through the cell membrane. These results confirmed the drug distribution capability likely shown in Table 6.

The PSA value describes the ability of drug transport properties [22]. The results showed that the design of the new compound improved the PSA value, and compound I2 exhibited the higher PSA value. The higher PSA value allows a compound to be easily distributed and has good bioavailability. Furthermore, Drug-likeness scores for all new compounds were determined with the molsoft tool. This analysis showed that new compounds had a fairly good drug-likeness score, even better than compound 20. Based on this parameter, compound I1 had the best drug-likeness value. This compound could be used as a proposed compound for the antituberculosis candidate. In the synthetic accessibility parameter, all new compounds tend to have the same value, namely 2. Hadni & Elhallaoui [11] reported that if the value of synthetic accessibility is low, then it has high accessibility to be synthesized. Therefore, these new compounds were probability to be synthesized and then studied further their activity in the laboratory.

CONCLUSION

QSAR analysis of twenty 3-phenyl indole compounds provided the best QSAR equation model based on statistical parameters consideration. This equation model was used as a guide for designing new 3-phenyl indole compounds that had better predictive activity. Based on the results of ADMET analysis, all new compounds showed good pharmacokinetic characters and were non-toxic. The results of the drug-likeness analysis also gave good outcomes. So it could be proposed to be synthesized and studied further as an antituberculosis drugs candidate.

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