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Modelling of QSAR Equations for Styryl Quinolone Compound Derivatives as HIV-1 Inhibitors

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Abstract

HIV-1 (Human Immunodeficiency Virus) inhibitor compounds have been designed using a QSAR analysis approach for 33 styryl quinolone derivative compounds, with descriptors calculated using semi-empirical methods. This research aims to determine the best semi-empirical method and to obtain the best QSAR equation by comparing the Principal Component Regression method with Multiple Linear Regression, as well as modifying the structure of new styryl quinolone derivative compounds to achieve higher predicted theoretical HIV-1 integrase protein inhibitor activity. The analysis results showed that the semi-empirical MINDO3 method was the best. The QSAR MINDO3 equation with Principal Component Regression is as follows: : pIC_{50} = 5.046 + 0.515 VL1 with n = 33, r = 0.611, r^2 = 0.374, SD = 0.677, F_{count}/F_{table} = 4.45, PRESS = 20.554, Sig = <0.01. Meanwhile, with Multiple Linear Regression, the equation is as follows: pIC_{50} = -11.252 + 88.481 (qC3) + 26.667 (qC4) + 9.156 (qC5) – 1.443 (qC7) + 4.284 (qC8)-0.03 (Surface Area Approx) + 0.033 (Grid) - 0.195 (logP) – 0.007 (Mr) – 2.166 (HOMO) with n = 33; r = 0.870; r^2 = 0.758; SD =0.500; F_{count}/F_{table} =2.995; PRESS =5.505; Sig. <0.01. The design of the new compound was carried out based on the best QSAR equation, namely Multiple Linear Regression. We obtained 10 structural modifications from the equation above with the best theoretical pIC50 values from the reference ligand.

Keywords: *QSAR, styryl quinolone, Multiple Linear Regression, Principal Component Regression, MINDO3*

Introduction

HIV-1 remains a major global health problem, with more than 39.9 million people living with HIV by the end of 2023. In the same year, approximately 630,000 people died from HIV-related causes (WHO, 2021). HIV disease in Indonesia continues to increase from year to year, and from 2010 to 2020, there were 3,690 people affected by HIV cases (Mahayati et al., 2024). HIV (Human Immunodeficiency Virus) is a virus that attacks or infects white blood cells and causes a decrease in human immunity (Ministry of Health, 2016). Continuous infections due to decreased immunity will result in a malfunction of the immune system, which fights infections and diseases (Rahman et al., 2019). This virus is divided into two types, namely HIV-1 and HIV-2; HIV-1 is the leading cause of infection in the body (Gilbert et al., 2003). Although HIV-1 and HIV-2 share the same transmission pathway and both can cause immune deficiency syndrome (AIDS), there are essential differences between these two viruses in terms of epidemiology, natural history, diagnosis, and management (Campbell-Yesufu et al., 2011). HIV-1 is the most widespread type of HIV compared to HIV-2; besides that, HIV-1 is more easily

transmitted than HIV-2. Spreads through blood, semen, vaginal fluids, rectal fluids and breast milk, while HIV-2 is less easily transmitted. Requires a higher concentration of virus for transmission and is less likely to spread from mother to child, through sexual contact, or through sharing needles. Virulence and Disease Progression. HIV-1, generally more virulent, causes disease progression to AIDS more quickly if untreated, whereas HIV-2 usually has slower disease progression, and many individuals infected with HIV-2 remain asymptomatic for longer. HIV-2 is associated with a lower viral load and a slower decline in CD4 T cell numbers (Marlink R et al., 1994; Matheron S et al., 2003; Burgard M et al., 2010). This is quite worrying, so research is needed to develop compounds as anti-HIV-1 agents. Compounds that can be developed to be used as anti-HIV-1 drugs are Styryl quinolone and its derivatives.

Styryl quinolone and its derivatives are aromatic and lipophilic compounds with diverse biological activity (Wilczkiewicz et al., 2019). Styryl quinolone derivatives have been reported as antibacterial (Cieslik et al., 2012), antifungal (Musiol et al., 2006), antiviral (Mouscadet et al., 2010), anticancer (Staderini et al., 2013), and HIV integrase protein inhibitors (Musiol et al., 2010). Styryl quinolone can also act as an anti-HIV-1 virus by inhibiting the integration activity of HIV-1 (the enzyme that catalyzes viral DNA entering the host cell genome) so that HIV-1 replication will be hampered because HIV DNA cannot enter the host cell. (Mouscadet and Desmaele, 2010). Several researchers have reported that styryl quinolone and its derivatives can inhibit HIV-1 proteins, including Mekouar et al. (1998) stated that

Research on the QSAR approach of styryl quinolone derivatives was carried out by Leonard & Kunal (2008), who carried out 3D-QSAR of styryl quinolone derivatives using Cerius 2 4.8 (Accelrys) software, Goudarzi et al. (2012) predicted the anti-HIV-1 activity of styryl quinolone derivatives automatically. QSAR with Genetic Algorithm-Multi Linear regression, Mouhsin et al. (2022) examined QSAR modelling of styryl quinolone derivatives as HIV-1 inhibitors. However, some of these studies have only formulated equations and have yet to design new, theoretically better predictive compounds than existing ones. Apart from that, the existence of drug resistance against HIV can also be used as a basis for the development of new, more potential drugs.

styryl quinolone derivatives could inhibit the HIV-1 integrase protein and block the HIV-1 replicase protein in CEM cells, Zouhiri et al. al (2000) reported that styryl quinolone derivatives could be inhibitors of the HIV-1 integrase protein which was tested on HIV-1 cells, Bayle et al. (2005) stated that styryl quinolone with an aryl/acyl group at the C-7 position could inhibit the HIV replicase protein -1, substitution of the aryl/acyl group at position C-7 will increase hydrophobic interactions and π bonds with the integrase protein, thereby blocking the function of the HIV-1 integrase protein. So, research on styryl quinolone is interesting to study.

Research through the stages of molecular design, drug synthesis, purification, and drug identification are the steps that must be taken in the experimental development of new drugs. Initial studies to analyze the activity of new drug designs can be carried out in silico through computational chemistry approaches. New drug compounds with potential biological activity in silico can continue to be validated in the laboratory. Computational chemistry can play an important role in medicinal chemistry, especially in drug design and theoretical predictions about a molecule's chemical properties and activity (Nugraheni et al., 2004). The application of computational chemistry in medicinal chemistry uses quantitative structure-activity relationship (QSAR) studies or quantitative structure-activity relationships (HKSA) (Azizah, 2013). The quantitative relationship between structure and activity is an efficient and effective step in the search for new drug compounds (new drug discovery). It is a green chemistry concept that reduces environmental pollutants (Mestres, 2005).

Based on the description above, the research that will be carried out is to model

the QSAR equation for styryl quinolone derivative compounds to obtain the best mathematical equation prediction model as an HIV-1 inhibitor using the best semi-empirical calculation method with a comparison of Principal Component Analysis and Multi Linear Regression calculations. The descriptors used in the research are based on Hansch's theory which includes electronic descriptors (HOMO energy, LUMO energy, dipole moment, and hydration energy), steric (molecular volume and molecular surface area), and hydrophobicity. In this research, a prediction of the modification of a new styryl quinolone derivative compound will also be carried out, which is expected to theoretically have higher HIV-1 inhibitory activity so that it can be used as a reference in the synthesis of styryl quinolone.

Materials and Methods

Materials and Tools

The materials used in this research were data on 36 styryl quinolone derivative compounds and their biological activity as anti-HIV-1 inhibitory compounds. The 36 structures of styryl quinolone derivative compounds were divided into 26 fitting compounds and 10 test compounds. The division of fitting and test compounds is based on the steric hindrance of each compound (small, medium and large) (Leonard & Kunal, 2008). The equipment used in this research is an Intel Core i5 computer processor, 8 GB RAM (Random Access Memory), a Windows 10 operating system, Hyperchem version 8.0 (Hypercube, 2007), and SPSS version 25 (IBM, 2016).

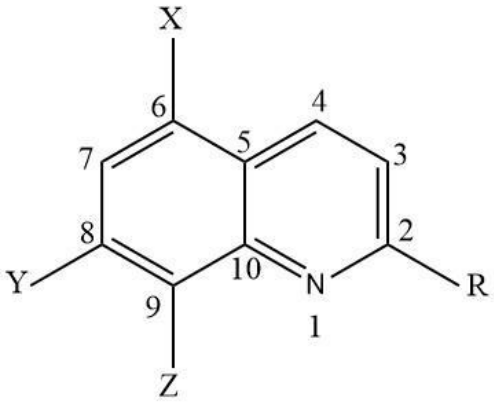


Figure 1. Structure of the parent compound of the styryl quinolone derivative

Table 1. Substituents of fitting and test compounds as well as experimental pIC_{50} of styryl quinolone derivative compounds (Leonard and Kunal, 2008)

Structure of compound no.	**R**	**X**	**Y**	**Z**	**pIC_{50}**
Fitting Compound					
2	Styr-1-yl	H	CO_2H	OH	5,28
3	-CH=CH,Furan-2-yl	H	CO_2H	OH	5,72
4	-CH=CH,Thiaphen-3-yl	H	CO_2H	OH	5,47
5	-CH=CH, Pyridin-3-yl	H	CO_2H	OH	5,39
8	4-$NHCOCH_3$-Styr-1-yl	H	CO_2H	OH	5,85
9	4-OH-Styr-1-yl	H	CO_2H	OH	5,80

Structure of compound no.	R	X	Y	Z	pIC_{50}
11	2,4-$(OH)_2$-Styr-1-yl	H	CO_2H	OH	5,43
12	3,4-$(OH)_2$-Styr-1-yl	H	CO_2H	OH	5,62
14	3-OH,4-MeO-Styr-1-yl	H	CO_2H	OH	6,05
15	2,3,4-$(OH)_3$-Styr-1-yl	H	CO_2H	OH	6,52
16	3,4-$(OH)_2$,5-OMe-Styr-1-yl	H	CO_2H	OH	6,15
17	3,5-$(OMe)_2$,4-OH-Styr-1-yl	H	CO_2H	OH	5,31
18	3,5-$(Br)_2$,4-OH-Styr-1-yl	H	CO_2H	OH	5,89
19	3,4-$(OH)_2$,5-I-Styr-1-yl	H	CO_2H	OH	5,40
20	3,4-$(OH)_2$-Styr-1-yl	H	CO_2Me	OH	4
23	-CH_3	H	H	OH	4
24	-CH_3	H	H	-OCO-3,4-$(OMe)_2$-Styr-1-yl	4
25	-CH_3	H	H	-OCO-3,4-$(OH)_2$-Styr-1-yl	4
27	Styr-1-yl	H	H	OH	4
28	-CH=CH-(8-OH)Quinolin-2-yl	H	H	OH	4
30	3,4-$(OH)_2$-Styr-1-yl	H	H	NO2	4
31	3,4-$(OH)_2$-Styr-1-yl	H	H	NH2	4
33	3,4-$(OH)_2$-Styr-1-yl	H	H	OH	5,13
34	3,4-$(OH)_2$-Styr-1-yl	H	3,4-(OH)2-styr-1-yl	OH	5,66
35	3,4-$(OH)_2$-Styr-1-yl	H	CN	OH	5,52
36	3-CO_2H,4-OH-Styr-1-yl	H	CO_2H	OH	5,57
Senyawa Uji					
1	-CH_3	H	CO_2H	OH	4
6	4-NO_2-Styr-1-yl	H	CO_2H	OH	5,92
7	4-NH_2-Styr-1-yl	H	CO_2H	OH	5,46
10	3,5-$(OH)_2$-Styr-1-yl	H	CO_2H	OH	5,49
13	3-Me, 4-OH-Styr-1-yl	H	CO_2H	OH	5,55
21	3,4-$(OH)_2$-Styr-1-yl	Cl	Cl	OH	4
22	3,4-$(OH)_2$-Styr-1-yl	H	CO_2H	OH	5,64
26	Styr-1-yl	H	H	OAc	4
29	3,4-$(OH)_2$-Styr-1-yl	H	H	H	4
32	3,4-$(OAc)_2$-Styr-1-yl	H	H	OAc	4

Determining the Best Semi Empirical Method (Paramitra et al, 2020)

The best optimization method was determined using Hyoperchem 8.0 software. The optimization method used is semi-empirical. The selection of the best semi-empirical method for styryl quinolone derivative compounds was carried out by comparing the calculated ^{1}H-NMR spectrum between semi-empirical methods with the experimental ^{1}H-NMR spectrum. The semi-empirical methods used are CNDO (Complete Neglect of Differential Overlap), INDO (Intermediate Neglect of Differential Overlap), MINDO3 (Modified Intermediate Neglect of Differential Overlap, Version 3), MNDO (Modified Neglect of Diatomic Overlap), AM1 (Austin Model 1), RM1 (Recife Model 1), PM3 (Parametric Method 3), ZINDO1 (Zerner's Intermediate Neglect of Differential Overlap, Version 1), and TNDO (Tight-binding Neglect of Differential Overlap). The steps are to optimize the parent compound styryl quinolone, namely quinolone, using each semi-empirical method. Single point optimization, calculate the ^{1}H-NMR spectrum by selecting all the hydrogen atoms contained in the compound, then selecting the computing menu, and selecting Invoke NMR with spectrum settings with frequencies according to experimental data and Reference Shielding 23.91 (adjusted for validation with formaldehyde). After that, select the compute menu, and in the compute menu, click the Both: I then II option in the compute menu. After obtaining the ^{1}H-NMR spectrum, the PRESS value for each method was calculated. After that, the best method will be used to determine structure optimization. The PRESS value can be calculated using Equation 1.

$$PRESS=\sum i=ln(yi-y\hat{}(i))^2$$

(Weisberg, S. 2005) (Equation 1)

Where:

- • yiy_iyi is the actual observed value of the ith data.
- • y^(i)\hat{y}_{(i)}y^(i) is the predicted value for the ith data obtained from the model formed without including the ith data.

Geometry optimization (Iswanto et al, 2007)

Geometry optimization is done by setting the method for optimization in the setup menu, clicking the semi-empirical menu, and selecting the best optimization method based on the analysis in the Determining the Best Semi-Empirical Method step. In the computing menu, select geometry optimization, then adjust the optimization conditions using the polak-Riviere algorithm, lowest state, which means it is calculated at the lowest energy or ground state and the RMS gradient is 0.001 kcal/A.mol, click ok, wait until running is complete, convergent =YES, then stop logging on the file menu.

Determining Descriptors (Miladiyah et al, 2016)

Determining descriptors is essential in determining the best QSAR equation. Some of the descriptors used in this research are descriptors representing electronic properties (atomic charge, dipole moment, HOMO and LUMO energy), steric properties (molecular weight, molecular area, molecular volume), lipophilicity (log P), hydration energy, refractivity and polarizability. According to Miladiyah et al. (2016), to create QSAR modelling and predict cytotoxic accuracy, all descriptors must be included in the preparation of the model.

Structure Optimization (Iswanto et al, 2007)

Each styryl quinolone derivative compound was made into a two-dimensional structure model using the Hyperchem application. The model is then formed into a 3D structure with the build menu (Add H and Model Build). The following process optimizes the structure's geometry by minimizing molecular energy to obtain the most stable molecular conformation. Optimization was carried out using semiempirical methods, with RHF spin pairing, state-Lowest, Polak-Ribiere

algorithm, and RMS Gardien 0.001 (Kcal/ Å.mol). The data obtained from optimization is in the form of atomic charges and bipolar moments, which QSAR will then analyze.

Determining the QSAR Equation using the Principal Component Regression Method

The determination of the QSAR equation is based on the method of Miladiyah et al. (2016). This method will select variables to select appropriate descriptors using Principal Component Analysis (PCA) or Factor Analysis with the SPSS application. PCA analysis was conducted on 26 fitting compounds to determine the values of Kaiser-Meyer-Olkin (KMO) and Bartlett. If the KMO value is <0.5, then independent variables are removed from the Anti Image Correlation data whose Measure of Sampling Adequacy (MSA) value is <0.5. The results are in the form of a principal component (Principal Component) as a latent variable, and the latent variables obtained must have Initial Eigenvalues with a total of >1. Next, the coefficient of each variable can be seen from the Component Matrix. The resulting values of the latent variables formed were then carried out by Principal Component Regression (PCR) on $\log IC_{50}$. The values of r, r^2, SD, calculated F/F table and predicted residual sum of squares (PRESS) will be assessed for each model. After getting the best equation, the same method is applied to all the fitting and test data to obtain the final QSAR equation.

Determining the QSAR Equation using the Multiple Linear Regression Method

The determination of the QSAR equation is based on the method of Iswanto et al. (2007). The analysis was carried out using the SPSS application with the backward method on 26 fitting compounds to the dependent variable in pIC_{50}. In contrast, the independent variables were descriptors obtained from optimization results in the form of atomic charge, Approx Surface Area, grid, Vvdw, logP, dipole moment, HOMO and LUMO, Energy Hydration, refractivity, polarisability and molecular weight. The selection of the equation model for the output data from the backward method analysis was analyzed statistically, including the correlation coefficient (r), partition coefficient (r2), standard deviation (SD) and Fcount/Ftable values from the models obtained, each of which was carried out by PRESS testing on 10 test compounds. The selected model is then analyzed using the enter method for all styryl quinolone derivative compounds (fitting and test compounds) to obtain the final QSAR equation.

Theoretical Modification of Styryl Quinolone Structure (Vaulina dan Ponco, 2006)

Molecular design is carried out by modifying substituents at positions R. The compound's theoretical activity (pIC_{50}) was determined using the best QSAR equation. Compounds with pIC_{50} have the highest activity, and these compounds can be proposed for synthesis in the laboratory.

Finding and Discussion

Determining the Best Semi Empirical Method

This research uses semi-empirical method calculations with electronic structure calculations, which only involve valence electrons in solving the Schrodinger equation so that the time required for optimization is shorter and is accompanied by specific parameters (Sudarmanto et al., 2002). The best semi-empirical method will be selected first before optimizing the structure of the styryl quinolone. The chosen method was carried out by describing the parent compound of styryl quinolone, namely quinolone, which was then optimized using all semi-empirical methods in Hyperchem version 8.0 software, namely Extended Hucle, CNDO, INDO, MINDO3, MNDO, MNDOd, AM1, RM1, PM3, ZINDO 1, TNDO. Optimizing the geometric structure aims to obtain the most stable molecular shape and structure with low potential energy (Widyasturi et al., 2020). The following are images before and after optimization of the quinolone structure with one of the semi-empirical methods (AM1). According to Jensen (2017), the advantages of the semi-empirical method are that generally,

calculations are faster than DFT and abinitio because the semi-empirical uses empirical parameters that have been determined from experiments and can be used on more significant compounds, including biomolecules and complex materials. The descriptors qC3, qC4, qC5, qC7, qC8, HOMO and Approx are classified into electronic groups so that this will influence stronger electrostatic interactions between the compound and the HIV-1 integrase protein. The molecular weight descriptors Approx and Grid are classified into the steric hindrance group, increasing the compound's selectivity and conformational stability. The logP descriptor is classified into the lipophilicity group to influence the water and fat solubility balance. Based on the resulting formula, the greater the log P, the smaller the value of logIC50, which theoretically increases the inhibitory activity against the HIV-1 protein integration.

Figure 2 shows that the optimized compound 1 has a different conformation from the compound before optimization. Compounds that have been optimized have a more comprehensive structure and a shifted position because atoms such as carbon, nitrogen and hydrogen in the compound tend to contain opposite charges due to the effect of the induction of electron clouds on certain atoms or groups so that they move further apart. The results of the optimization of all semi-empirical methods were then carried out with a ^{1}H-NMR test to determine the best method. The ^{1}H-NMR test is based on the absorption of radio waves by the ^{1}H atomic nuclei in organic molecules when the molecules are in a strong magnetic field (Paramita, S et al., 2020).

The spectrum analysis results in Table 2 were carried out with a frequency of 600 MHz with a reference shielding of 23.91; this is adjusted to validation with ^{1}H-NMR formaldehyde experiments (Lewicki, J. P et al., 2015). Based on the data obtained, the MINDO3 method is the most accurate method for analyzing substituted quinolone compounds. This is because it has the smallest PRESS ^{1}H-NMR value, namely 2.947474. The validation results of this method, namely the MINDO3 method, will then be calculated to obtain data on the physicochemical properties of the styryl quinolone derivative. The MINDO3 method has also been proven to be widely used as an optimization method to determine physical and chemical property descriptor data to formulate QSAR equations, including in the research of Živadinović, B. et al. (2023); Yousefi et al., (2022); and Garro Martinez et al., (2015).

Optimization of Geometric Structure and Calculation of Styryl Quinolone Derivative Compound Descriptors

Styryl quinolone derivative compounds that have been optimized, then calculate their physicochemical properties using QSAR properties in the compute menu to obtain physicochemical values in the form of area (Approx Surface Area and grid), van der Waals volume (Vvdw), hydration energy, partisan coefficient -octanol/water (log P), refractivity, polarizability, molecular weight. HOMO LUMO energy in the compute menu, then orbital and dipole moment, which can be seen in the start log calculation. In contrast, atomic charges can be seen in the optimization results log file. The determination of these descriptors represents the hydrophobic, electronic and steric parameters present in the Hansch model QSAR analysis, which are considered to influence the performance of a drug. This MINDO3 calculation cannot calculate compounds containing Br and I atoms, so compounds 18, 18,19, and 24 are removed from the calculation, and the total number of final compounds is 33. Data from descriptor calculations for the MINDO3 method can be seen in Table 3.

Table 3. Results of [1]Hydrogen Nuclear Magnetic Resonance spectrum analysis using all semi-empirical methods

Method	H1	H2	H3	H4	H5	H6	H7	PRESS
Experiment (Mitra dkk, 2002)	7.7	7.3	7.5	7.7	7.7	7.3	8.8	
CNDO	7.209	7.101	6.914	6.995	7.244	7.509	10.357	3.796969
INDO	7.25	7.143	6.95	7.027	7.301	7.542	10.412	3.798887
MINDO3	**7.342**	**7.212**	**7.05**	**7.08**	**7.469**	**7.551**	**10.252**	**2.947474**
MNDO	7.252	7.161	6.974	6.974	7.314	7.557	10.72	4.925222
MNDOd	7.252	7.161	6.974	6.974	7.314	7.557	10.72	4.925222
AM1	7.184	7.087	6.918	6.974	7.249	7.527	10.538	4.452999
RM1	6.982	6.895	6.7	6.741	7.003	7.339	10.707	6.363209
PM3	7.156	7.06	6.854	6.871	7.201	7.439	10.835	5.86764
ZINDO 1	7.19	7.088	6.881	6.909	7.221	7.48	10.608	4.844591
TNDO	7.154	7.065	6.854	6.857	7.182	7.461	10.716	5.446607

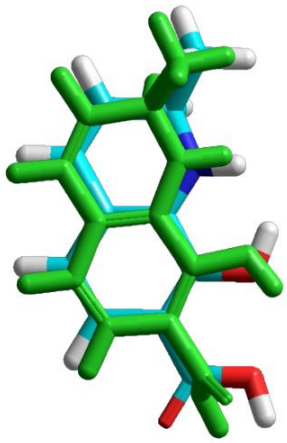


Figure 2. Structure of 1 styryl quinolone derivative before and after (green) MINDO3 optimization

QSAR Equation Analysis with Principal Component Regression

Principal Component Analysis (PCA) is carried out before the Principal Component Regression (PCR) analysis of the QSAR equation, and this is to simplify the initial descriptor into several main components called latent variables (Miladiyah, I et al., 2016). A total of 21 initial descriptors of fitting compounds were subjected to PCA analysis, and the KMO and MSA value requirements were then examined. From the results of the initial analysis, it turns out that several variables do not meet the KMO (<0.5) (Table 4) and MSA (<0.5) (Table 5), so descriptors that do not meet the Anti Image Correlation value > 0.5 must be removed in the PCA analysis. Then, the same analysis is carried out on descriptors that meet the Anti Image Correlation requirements > 0.5, resulting in KMO and MSA values > 0.5. KMO and MSA values greater than 0.5 indicate that the data is suitable for factor analysis (Kaiser, H. F (1974); Field, A. (2009); Hair, J. F et al. (2010). Descriptors that meet these requirements are qC5, qC7, qC8, qC9 and qC10 with Kaiser Meyer Olkin values and Bartlett's values as in Table 4. The results of the PCA analysis produce one latent variable, which can be seen in Table 6.

Table 4. KMO and Bartlett's Test values for fitting compounds

Kaiser-Meyer-Olkin sampling size		0.690
Bartlett's Test of Sphericity	Chi-Square	269.586
	Df	10
	Sig.	0.000

Table 5. Anti Image Matrices values

		QC5	QC7	QC8	QC9	QC10
Anti-image Covariance	QC5	0.005	-0.004	0.001	0.005	0.005
	QC7	-0.004	0.007	0.006	-0.001	-0.002
	QC8	0.001	0.006	0.013	0.009	0.004
	QC9	0.005	-0.001	0.009	0.014	0.008
	QC10	0.005	-0.002	0.004	0.008	0.006
Anti-image Correlation	QC5	0.675[a]	-0.673	0.142	0.621	0.894
	QC7	-0.673	0.781[a]	0.597	-0.110	-0.345
	QC8	0.142	0.597	.731[a]	0.661	0.513
	QC9	0.621	-0.110	0.661	0.681[a]	0.874
	QC10	0.894	-0.345	0.513	0.874	0.604[a]

a. Measures of Sampling Adequacy (MSA)

Table 6. Latent Variable Results of PCA analysis of compound fitting

Compound	Latent Variables	Compound	Latent Variables
2	0.461	20	0.44862
3	0.55571	23	-0.03513
4	0.54384	25	-3.205
5	0.54582	27	-0.07153
8	0.55195	28	-0.08135
9	0.53937	30	-2.78888
11	0.42187	31	-0.39001
12	0.45762	33	-0.08135
14	0.45762	34	-0.37548
15	0.43586	35	-0.06497
16	0.56318	36	0.55649
17	0.55475	36	0.55649

Table 7. Results of principal component analysis extraction of fitting compounds

Component	*Eigen values*		
	Total	Difference %	Cumulative %
1	4.580	91.593	91.593
2	0.359	7.188	98.780
3	0.054	1.072	99.853
4	0.005	0.104	99.957
5	0.002	0.043	100.000

The results of the PCA analysis obtained Eigenvalues from PCA calculations, as shown in Table 7. From Table 7, it can be seen that the Eigenvalue is more than 1 ((Kaiser, H. F (1974); Field, A. (2009); Hair, J . F et al. (2010)). Only one component represents 91,593 total populations. Furthermore, the value resulting from the PCA analysis is the Component matrix, which can be seen in Table 8. This process will clarify the coefficient values of each variable combined into one latent variable.

Table 8. Component matrix of fitting compounds

Descriptor	Component
qC5	0.983
qC7	0.974
qC8	-0.920
qC9	0.981
qC10	-0.924

The latent variables resulting from PCA were then subjected to regression analysis using PCR between the values of the latent variables and pIC_{50}. The PCR analysis method is commonly used for QSAR studies, with n = 33, r = 0.611, r^2 = 0.374, SD = 0.677, F value/F table = 4.45, PRESS = 20.554, Sig = <0.01

Table 10 shows experimental PIC_{50} and predicted PIC_{50} data for 33 styryl quinolone derivative compounds calculated using Equation 1. The correlation graph of predicted and experimental pIC50 shown in including Xanthon derivative compounds (Miladiyah, I et al., 2016) and naphthoquinone derivatives (Saputra et al.; T., 2013). This regression analysis produces 1 equation model with values for r, r2, F calculated/ F table and PRESS values for the fitting compound and test compound as listed in Table 9

Table 9. Compound fitting QSAR equation model

Variable	**Nominal**
Model	1
Latent Variables	VL1
r	0.572
r^2	0.327
SD	0.699
F value/F table	2.357
PRESS *Fitting*	14.165
PRESS test	8.551

Using the enter method, the final QSAR equation (Equation 2) was formulated for 33 compounds (fitting and testing). One latent variable from the PCA of 33 compounds (fitting and testing) was correlated with each compound's pIC_{50}.

$$pIC_{50} = 5.046 + 0.515\ VL1 \quad \text{(Equation 2)}$$

Figure 3 shows that the data points are on the trend line. The resulting equation can provide a reasonably good prediction level, but several points are outside the regression line. Even though the Fvalue/ Ftable value is more than 1 in the resulting equation, the prediction accuracy is still unsatisfactory. This can be seen from the correlation coefficient (r) value of 0.611

Table 10. Data for predicted pIC_{50} and experimental pIC_{50} for PCR method

Compound	pIC_{50} Prediction	pIC_{50} Experiment	PRESS	Compound	pIC_{50} Prediction	pIC_{50} Experiment	PRESS
2	5.426	5.28	0.021	30	4.882	4	0.777
3	5.418	5.72	0.091	31	5.229	4	1.510
4	5.416	5.47	0.003	33	5.319	5.13	0.036
5	5.416	5.39	0.001	34	5.275	5.66	0.148
8	5.416	5.85	0.188	35	5.315	5.52	0.042
9	5.416	5.8	0.147	36	5.416	5.57	0.024
11	5.423	5.43	0.000	1	5.420	4	2.016
12	5.425	5.62	0.038	6	5.418	5.92	0.252
14	5.425	6.05	0.390	7	5.415	5.46	0.002
15	5.424	6.52	1.202	10	5.416	5.49	0.005
16	5.418	6.15	0.536	13	5.416	5.55	0.018
17	5.417	5.31	0.011	21	5.005	4	1.009
20	5.424	4	2.029	22	5.417	5.64	0.050
23	5.322	4	1.749	26	5.278	4	1.634
25	4.813	4	0.661	29	4.919	4	0.845
27	5.320	4	1.742	32	5.279	4	1.636
28	5.319	4	1.738				
	∑ PRESS				**20.554**		

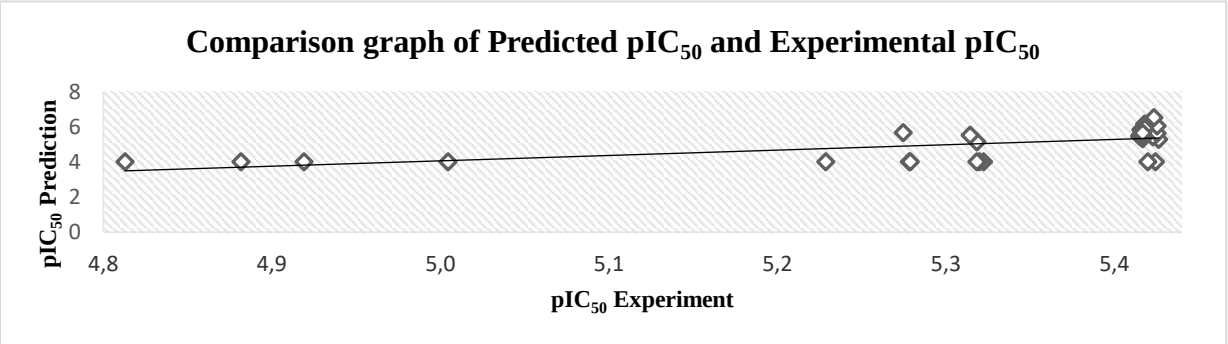


Figure 3. Correlation graph between experimental pIC_{50} and predicted pIC_{50}

Analysis of QSAR Equations using the Multiple Linear Regression Method

QSAR equation analysis uses the backward and enter methods by comparing all descriptors with pIC_{50}. The MLR method is also often used in QSAR equation analysis, such as estradiol derivatives (Iswanto, P., Isnaeni, T. R., and Iqmal, T., 2007) and kalanon derivatives (Vaulina, E. Y. D., Chasani, M., and Abdulghani, M., 2012). This research divides the styryl quinolone compound derivatives into two parts, namely fitting compounds and test compounds. The MLR calculation is carried out for compound fitting using the backward method to eliminate independent variables that have little influence on the dependent variable. Based on statistical analysis using SPSS, 11 QSAR equation models for the MINDO3 method were obtained, listed in Table 11. The criteria for the best equation recommended in the QSAR method are that the correlation coefficient (r) must be greater than 0.8 and the calculated F / F table must be greater than 0.8. of 1 for a 95% confidence level (Hafshah, M., Firdaus. I. M., and Suratno, 2022).

Table 11 shows that models 1 and 2 were eliminated because F count < F table. Meanwhile models 3-11 met statistical tests from both r, r^2, SD and F value/F table with a

confidence level of 95%. This research chose the 10th model as the best backward model among the nine models that passed. This is due to considering the calculated F/F table, which is more than 1, namely models 3 to 11. Then, it is analyzed again by comparing the PRESS values. Small PRESS values were obtained from models 10 and 11. The final stage was selected by analyzing the most significant r and r2 models or those closest to 1 and obtained model 10 as the best model using the backward method. Next, the variables in model 10 were tested for the final QSAR equation for all styryl quinolone derivative compounds with multiple linear regression (MLR) analysis using the enter method, and the results obtained are shown in Table 12.

Based on Table 12, it can be seen that the correlation coefficient (r) > 0.8, which can then be used to predict a new compound with the Fcount/Ftable statistic > 1 with a confidence level of 95% and a sig value. <0.01. Enter method calculations obtained the final QSAR equation (Equation 3). Table 13 shows experimental PIC_{50} and predicted PIC_{50} data for 33 styryl quinolone derivative compounds calculated using Equation 2. The experimental and predicted pIC50 correlation graph shown in Figure 4 shows the position of the data points on the trend line. This means that the resulting equation can provide a relatively good level of prediction.

Table 11. QSAR MINDO3 equation model results of multiple linear regression analysis using the backward method

Model	Variable	r	r^2	SD	F value	F table	F h/F t	PRESS
1	dipol, qC4, Refractivity, logP, HOMO, qN1, qC6, qC2, LUMO, E. Hydrate , qC10, Surface Area Approx , qC8, qC3, qC9, Mr, Grid, qC7, qC5	0.971	0.944	0.53548	2.643	8.667	0.305	-
2	dipol, qC4, Refractivity, logP, HOMO, qC6, qC2, LUMO, E. Hydrate , qC10, Surface Area Approx , qC8, qC3, qC9, Mr, Grid, qC7, qC5	0.971	0.944	0.46376	3.719	5.821	0.639	-
3	dipol, qC4, Refractivity, logP, HOMO, qC6, qC2, E. Hydrate , qC10, Surface Area Approx , qC8, qC3, qC9, Mr, Grid, qC7, qC5	0.971	0.944	0.41513	4.914	4.59	1.070	50.38
4	dipol, qC4, logP, HOMO, qC6, qC2, E. Hydrate , qC10, Surface Area Approx , qC8, qC3, qC9, Mr, Grid, qC7, qC5	0.971	0.943	0.37941	6.249	3.922	1.593	52.29
5	dipol, qC4, logP, HOMO, qC2, E. Hydrate , qC10, Surface Area Approx , qC8, qC3, qC9, Mr, Grid, qC7, qC5	0.971	0.943	0.35319	7.688	3.511	2.190	62.31
6	dipol, qC4, logP, HOMO, qC2, E. Hydrate , Surface Area Approx , qC8, qC3, qC9, Mr, Grid, qC7, qC5	0.970	0.942	0.33363	9.219	3.237	2.848	79.16
7	dipol, qC4, logP, HOMO, qC2, E. Hydrate , Surface Area Approx , qC8, qC3, Mr, Grid, qC7, qC5	0.969	0.939	0.32167	10.650	3.048	3.495	70.94
8	dipol, qC4, logP, HOMO, qC2, Surface Area Approx, qC8, qC3, Mr, Grid, qC7, qC5	0.967	0.935	0.31503	11.978	2.913	4.112	67.00
9	dipol, qC4, logP, HOMO, Surface Area Approx , qC8, qC3, Mr, Grid, qC7, qC5	0.960	0.923	0.32774	11.913	2.818	4.228	63.90
10	qC4, logP, HOMO, Surface Area Approx , qC8, qC3, Mr, Grid, qC7, qC5	0.951	0.904	0.34891	11.333	2.753	4.116	55.31
11	logP, HOMO, Surface Area Approx , qC8, qC3, Mr, Grid, qC7, qC5	0.947	0.897	0.34833	12.528	2.714	4.615	58.28

Tabel 12. *Output* metode *enter* MINDO3

MODEL	r	r^2	SD	F value/F table	SIG	PRESS
qC4, logP, HOMO, Surface Area Approx, qC8, qC3, Mr, Grid, qC7, qC5	0.870	0.758	0.500	6.88/2.2966 = 2.995	<0.01	5.505

pIC_{50} = -11.252 + 88.481 (qC3) + 26.667 (qC4) + 9.156 (qC5) – 1.443 (qC7) + 4.284 (qC8) - 0.03 (Surface Area Approx) + 0.033 (Grid) - 0.195 (logP) – 0.007 (Mr) – 2.166 (HOMO)

(Equation 3)

With n = 33; r = 0.870; r^2 = 0.758; SD =0.500; Fvalue/Ftable =2.995; PRESS =5.505; Sig. <0.01

Table 13. Data for predicted pIC_{50} and experimental pIC_{50} for the MLR method

Compound	pIC_{50} Prediction	pIC_{50} Experiment	PRESS	Compound	pIC_{50} Prediction	pIC_{50} Experiment	PRESS
2	5.228	5.28	0.003	30	4.297	4	0.088
3	5.535	5.72	0.034	31	3.881	4	0.014
4	5.477	5.47	0.000	33	4.694	5.13	0.190
5	5.661	5.39	0.074	34	6.050	5.66	0.152
8	5.591	5.85	0.067	35	4.908	5.52	0.375
9	5.470	5.8	0.109	36	5.747	5.57	0.031
11	5.546	5.43	0.014	1	5.087	4	1.182
12	5.435	5.62	0.034	6	5.513	5.92	0.165
14	5.516	6.05	0.286	7	5.157	5.46	0.092
15	6.054	6.52	0.217	10	5.736	5.49	0.061
16	5.805	6.15	0.119	13	5.274	5.55	0.076
17	5.472	5.31	0.026	21	3.914	4	0.007
20	5.098	4	1.207	22	5.811	5.64	0.029
23	3.742	4	0.066	26	3.905	4	0.009
25	4.119	4	0.014	29	3.593	4	0.165
27	4.286	4	0.082	32	4.256	4	0.065
28	4.671	4	0.450				
	∑ PRESS				**5.505**		

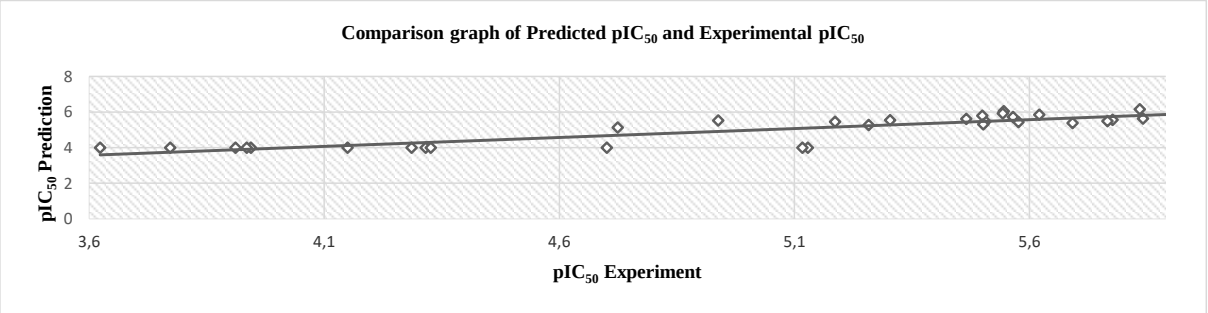


Figure 4. Correlation graph between experimental pIC_{50} and predicted pIC_{50}

Selecting the Best Equation and Styryl quinolone Derivative Structure Modification

QSAR equations are considered adequate in drug design because they can produce equation models that can be used to

accurately predict the activity of new drug compounds (Muranaka, K., 2001). To choose the best QSAR equation, comparing the output produced by the PCR and MLR methods is necessary. Table 14 shows the output results from the two methods. The results from Table 14 show that the QSAR equation using the MLR method will be chosen as the best QSAR equation for predicting new compounds derived from styryl quinolone. This is because the PRESS value of the MLR method is smaller than that of the PCR method, and the correlation coefficient and coefficient of determination values of the MLR method are higher than those of the PCR method. This is in accordance with research conducted by Sholihah, M (2020). Prediction of new drug compounds derived from styryl quinolone is carried out by taking into account the final QSAR equation, namely qC3, qC4, qC5, qC7, qC8, Approx Surface Area, Grid, logP, Mr and HOMO. The results of the descriptor for modifying the new styryl quinolone compound derivative can be seen in Table 15. The design of the drug compound in this research also considers the possibility that it can be synthesized based on the simple reactions that can occur. The compounds resulting from the structural modification of new styryl quinolone derivatives can be seen in Table 16, where the ten compounds have pIC_{50} values that are smaller than the 33 styryl quinolone derivative compounds resulting from research by Leonard & Kunal (2008). As seen in Table 1, the lowest PIC50 value is 4, while the ten compounds resulting from the design have PIC_{50} values respectively from compounds 1 to 10, namely 2.368; 2,572; 2,372; 2,518; 2,443; 2,336; 0.971; 1,039; 3,448; 2,388 (Table 16).

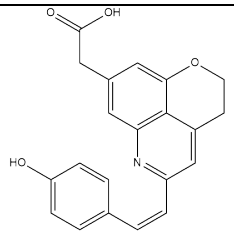
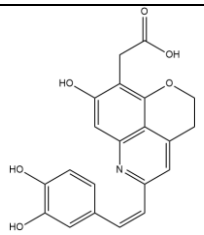
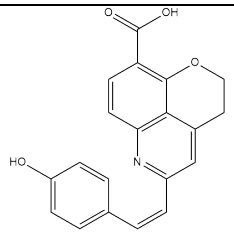
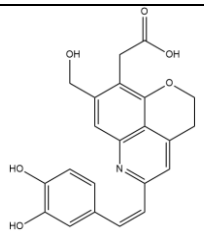
Table 14. QSAR equation output for PCR and MLR methods

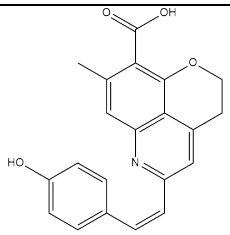
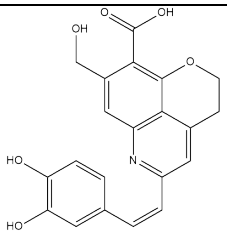
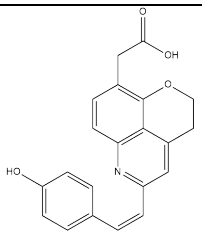
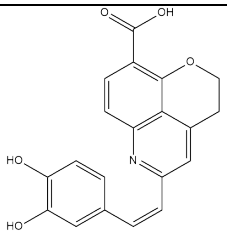
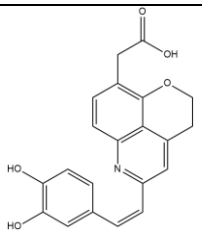
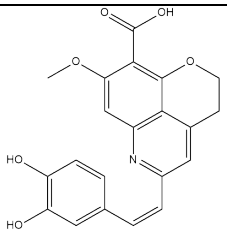
Methods	Formula	r	r^2	F_{value}/F_{table}	PRESS	Sig.
PCR	pIC50 = 5.046 + 0.515 VL1	0.611	0.374	4.45	20.554	<0.01
MLR	pIC_{50} = -11.252 + 88.481 (qC3) + 26.667 (qC4) + 9.156 (qC5) – 1.443 (qC7) + 4.284 (qC8) - 0.03 (Surface Area Approx) + 0.033 (Grid) - 0.195 (logP) – 0.007 (Mr) – 2.166 (HOMO)	0.870	0.758	2.995	5.505	<0.01

Table 15. Descriptors of Styryl Quinolone Derivative Modified Compounds

qC3	qC4	qC5	qC7	qC8	Surface Area Approx	Grid	logP	Mr	HOMO
0.106	0.102	-0.198	-0.194	0.12	471.16	615.29	-0.1	347.37	-8.00973
0.112	0.111	-0.215	-0.279	0.126	431.28	582.82	-0.03	333.34	-8.15172
0.111	0.111	-0.212	-0.291	0.131	460.7	603.66	0.12	347.37	-8.1316
0.108	0.105	-0.197	-0.141	0.087	452.29	615.93	-0.1	347.37	-7.95185
0.108	0.106	-0.197	-0.141	0.087	458.54	615.59	-1.13	363.37	-7.95444
-0.13	0.126	-0.252	-0.232	0.456	466.39	620.36	-2.15	379.37	-7.99323
0.109	0.105	-0.195	-0.14	0.044	512.81	646.37	-1.46	391.38	-7.73941
0.112	0.111	-0.213	-0.278	0.077	491.58	619.66	-1.39	377.35	-7.8159
0.102	0.111	-0.212	-0.294	0.162	435.31	584.43	-1.15	349.34	-8.03506
0.133	0.132	-0.268	-0.372	0.504	485.97	630.86	-2.05	379.37	-8.06257

Table 16. Results of structure modification of new styryl quinolone compound derivatives and pIC_{50} predicted by MINDO3

Compound Modification Structure	pIC_{50} prediction	Compound Modification Structure	pIC_{50} Prediction
 Prediction 1	2.368	 Prediction 6	2.336
 Prediction 2	2.572	 Prediction 7	0.971

Compound Modification Structure	pIC_{50} prediction	Compound Modification Structure	pIC_{50} Prediction
 Prediction 3	2.372	 Prediction 8	1.039
 Prediction 4	2.518	 Prediction 9	3.448
 Prediction 5	2.443	 Prediction 10	2.388

Conclusion

The analysis showed that the semi-empirical MINDO3 method was the best optimization method for determining the descriptor value used as an independent variable in formulating the QSAR equation for derivatives of the styryl quinolone compound as an HIV-1 inhibitor.

Statistical analysis found that the multiple linear regression method was the best compared to PCA for formulating the QSAR equation. Ten modified compounds from the MLR equation have been successfully designed, and they have theoretically more potent HIV-1 inhibitor activity than 33 styryl quinolone derivative compounds.

Suggestion

It is necessary to carry out molecular docking and dynamics simulation studies to prove the ability of 10 new modified styryl quinolone derivative compounds with HIV-1 virus inhibitory activity.

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