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Quantitative Relationships Between Structure and Activity of Gamma-Carboline Derivative Compounds as Anti-Bovine Viral Diarrhea Virus (BVDV) Using Semi-Empirical AM1 Method

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Abstract

This research aims to study the quantitative structure and activity relationship (QSAR) of gamma-carboline derivative compounds as anti-BVDV agents to get an equation that can predict the value of the anti-BVDV activity of gamma-carboline derived compounds. The research material is experimental EC50 data that convert to anti-BVDB activity. 14 gamma-carboline derivative compounds are divided into 2 groups, namely, 11 fitting compounds and 3 test compounds. QSAR analysis is based on multilinear regression calculations of the fitting compound by plotting the EC50 log as the dependent variable and the descriptor as the independent variable. The used descriptors are atomic net charge (q) and dipole moment (μ), which are involved in calculations using the AM1 semiempirical quantum mechanics method. In addition, the partition coefficient of n-octanol/water (Log P), molecular polarizability (α), molecular weight (BM), Van Der Waals surface area (A vdw), Van Der Waals volume (V vdw), and index of refraction (RD) are obtained from QSAR properties. The resulting QSAR equation is:

$$Log\ pEC_{50} = -48.670 - 124.801\ (qC_{11}) - 12.661\ (\alpha) - 0.918\ (\mu) - 0.876\ (RD) - 0.999\ (Log\ P) + 1.863\ (BM) + 0.043\ (V\ vdw)$$

$$with\ n = 14;\ r = 0.937;\ r^2 = 0.878;\ SD = 0.244;\ F_{count}/F_{table} = 1.466;\ PRESS = 0.749;\ Sig. = 0.02$$

This equation can be used as an initial guide for designing the structure of new compounds of the gamma-carboline class by considering some of the most influential descriptors. Consequentially, new compounds can be designed that have a smaller predicted EC_{50} value than the known compounds derived from gamma-carboline.

Keywords: *anti-BVDV; drug design; gama-carboline; QSAR*

Introduction

Bovine Viral Diarrhea (BVD) or malignant diarrhea in cattle is caused by the bovine viral diarrhea virus (BVDV). BVDV can cause a variety of clinical symptoms in cattle, including dermatitis, gastrointestinal problems, fever, diarrhea, leukopenia, bleeding, and even death (Bianchi et al., 2019). The BVDV virus is widespread throughout the world and is also to blame for major livestock losses, which result in substantial financial losses for farmers (Houe, 2003). Worldwide reports of BVDV infection in cattle indicate a substantial prevalence (Richter et al., 2019).

Australia, which produces beef and dairy products, indicated that the prevalence of BVDV in cattle was approximately 13% (South Australia), while the prevalence of BVDV in cattle was found to be 60% in New Zealand (Reichel et al., 2018). Malaysia reported a BVDV prevalence of 33.2% in Selangor (Daves et al., 2016). In heifers in the northeast, research from Thailand found a seroprevalence of 36.1% (n = 1165) (Nilnont et al., 2016). In the north of the country, livestock had a seroprevalence of just 7.7% (n = 390), according to a Laos study (Olmo et al., 2019).

Timika, formerly known as Mimika, is a cattle ranch or cattle breeding region in southern Papua, Indonesia. Bali cattle (Bos javanicus), a breed raised in Timika, is one breeds that provide animals for Muslims during Eid al-Adha. BVDV prevalence is found to be 18.4% in the Timika cattle area (Nugroho et al., 2020). It is required to research medications that can be used to decrease the degree of risk of disease and its spread based on reports and analyses of disease risk and its dissemination.

Drug design is a process that begins with the determination of compounds that exhibit important biological properties and ends with compound optimization steps. Combining synthesizes and straight tests of a compound's activity can be more difficult and take longer before the medications are used. Utilizing computational chemistry enables the development of a theoretical strategy that can quantitatively calculate the relationship between biological activity and compound structure transformation. If a compound's harmful effect on biological activity is determined, the biological activity of similar compounds or their derivatives can be estimated (Hernandez & Shivraj, 2020). To find out new compounds, it should develop molecular designs either direct synthesis or experiments through a modeling approach using computational chemistry concepts (Genheden et al., 2017). In this study, the gamma-carboline and the pEC50 data from the research of Dai et al., (2018). Alkaloid-carboline (Figure 1) is a chemical compound with various bioactivities, including antivirus, antibacterial, antifungal, antiparasitic, antitumor, anti-inflammatory, and neuropharmacological activities (Zhang et al., 2017).

Carboline compounds have been identified by Salim et al., (2010) as therapeutic candidates with potent anti-BVDV action. It possesses the highest anti-BVDV activity among the carboline-derived compounds (Figure 2g), with an EC50 value of 0.26 μM (concentration induces a 50% reduction in BVDV-induced cell death) (Dai et al., 2018). Gamma-carboline, a derivative molecule, can be examined computationally to determine the best QSAR equation based on this potential. The study's objective was to determine the best QSAR equation, which may then be used to predict how effective gamma-carboline derivatives will be in preventing BVDV. The QSAR equation is an determines the characteristics that influence a compound's activity. This equation can also be utilized to construct linear equations that identify the most influential descriptors on a compound's biological activity and predict the biological activity of new compounds. So the equation can use as a reference for designing a new more potential gamma carboline-derived anti-BVDV drug. The QSAR equation involves several descriptors that have the most influence on a compound's activity value. As a result, this equation can use as a first guide for developing new gamma-carboline derivative

compounds with EC_{50} value that lower prediction than existing compounds.

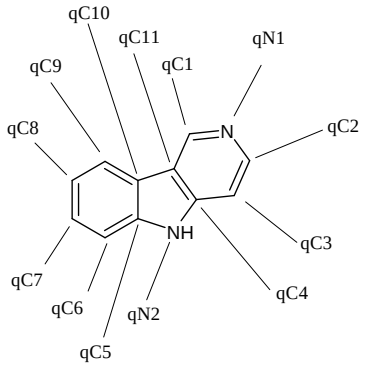


Figure 1. Gamma-carboline and the designation of the net charge of the atoms

Computational optimization of molecular modeling geometry uses quantum mechanical principles. Semiempirical Method Austin Model 1 (AM1) is a quantum mechanical method that has been widely used in chemical modeling to produce the best QSAR equations (A. Asmara et al., 2013; A. P. Asmara & Dwi, 2015; Hadanu et al., 2015; Hafshah & Karlina, 2019; Mudasir et al., 2010; Mustofa et al., 2010; Rakhman et al., 2019; Thalheim et al., 2011). The determination of the QSAR equation, besides selecting the optimization method, also needs descriptors which are parameters that influence the pEC50 value. The descriptors determined after the structure was optimized net atomic charge (q), dipole moment (μ), partition coefficient n-octanol/water (Log P), molecular polarizability (α), molecular weights (MWs), surface area of Van Der Waals (A vdW), Van Der Waals volume (V vdW), and index of refraction (IR). Determination of the most influential descriptor on the value of pEC50 is mathematically done with a correlation test. The QSAR equation is obtained through multilinear regression analysis by backward method and continues by enter method with the descriptor as the independent variable and the log pEC50 value as the dependent variable.

Research Methods

Materials

This study examined 14 Gama-carboline derivative compounds that had been synthesized and tested experimentally for anti-BVDB activity by Dai et al., (2018). The 14 gamma-carboline derivatives (Figure 2) distribute into 2 groups: 11 fitting compounds (Figures 2c–2m) and 3 test compounds (Figures 2a, 2b, and 2n). The fitting compound used for the initial analysis to determine the QSAR equation uses the *backward method*. The results of these equations are tested on test compounds whose structures are representative of all gamma-carboline derivative compounds. The determination of the test compounds is based on the steric hindrance of the variations of gamma-carboline derivatives. Compounds 2a, b, and n (Figure 2) represent the steric level of the gamma-carboline derivatives, from the least steric to the most steric.

Tools

Computational chemical calculations are carried out using a set of computers, including hardware and software. The hardware has specifications such as an Intel Core i5 processor and Random Access Memory (RAM). The software is Windows *8*, Hyperchem 8.0.8, and JASP's statistical software.

Work Procedures

Determination of descriptors

This research used Iswanto et al. (2007), which started method, started in modeling derivative compounds Gama-carboline in two dimensions using hyperChem 8.0.8. The structure was then equipped with hydrogen atoms on each of its atoms. Each structure is optimized through geometry optimization to minimize molecular energy to obtain the most stable conformation. Geometry optimization used the Polak-Ribieré algorithm, the lowest state, which means calculated at the lowest energy or ground state, and the RMS gradient was 0.001 kcal/A.mol, and the convergence limit is 0,001 kcal/A.mol. Descriptors included the et atomic charge, dipole moment, Log P, molecular polarizability, molecular weight, Van Der Waals surface area, Van Der Waals volume, and index of refraction. The data of descriptors and their calculation method are presented in Table 1.

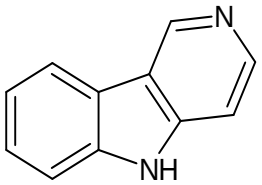
Table 1. Descriptors and how to calculate them

No	symbol	Descriptor	Unit	Calculation method
1	q	Net charge of atoms C_1–C_{11} and atoms N_1–N_2 (Figure 1)	*Coulumb*	Semiempirical *AM1, Hyperchem, and* optimization of gama-*carboline*
2	μ	moment	*Debye*	
3	Log P	n-octanol/water partition coefficient	-	*Hyperchem, QSAR properties*
4	α	molecular polarizability	$Å^3$	
5	MW	molecular weight	s.m.a	
6	A_{vdw}	Van Der Waals surface area	$Å^2$	
7	V_{vdw}	Van Der Waals volume	$Å^3$	
8	RD	Refractive Index	Å	

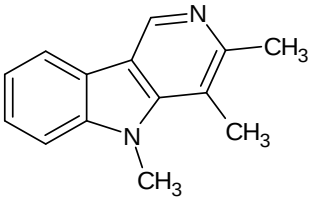
Correlation Analysis and Determination of QSAR Equations

The Correlation analysis bivariate was carried out using the two-tailed and Pearson's coefficient method (Vaulina et al., 2012). In this step, each descriptor looks for its correlation level with pEC50 activity. Then choose the atomic charge (qC_1-qC_{11} and qN_1-qN_2), dipole moment (μ), log P, polarizability (α), MW, Van der Waals surface area (A_{vdw}), volumes *Van der Waals* (V *vdw),* and index of refraction (RD). A high degree of correlation means that it has a significant effect on pEC_{50}. Furthermore, the selected descriptors use as independent variables in Multiple Linear Regression (MLR) analysis. The used of MLR method is a backward and enter method (A. Asmara et al., 2013; A. P. Asmara & Dwi, 2015; Iswanto et al., 2007; Rakhman et al., 2019; Vaulina & Iswanto, 2006).

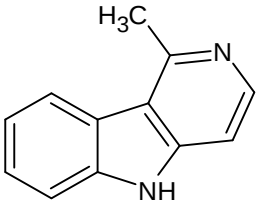
Determination of the best QSAR equation will require multilinear regression statistical analysis. The analysis was carried out using the JASP application, with the *backward* method on 11 compounds *fitting* for the dependent variable pEC50 and the independent variable result from the correlation test. The selection of the equation model for the *output* method *backward* analysis is statistically analyzed, including the correlation coefficient (r), partition coefficient (r^2), standard deviation (SD), and the F value of the model obtained each one is tested by PRESS testing on the 3 test compounds. The selected model is then analyzed using the enter method for all compounds (fitting and test compounds) to obtain the final QSAR equation.



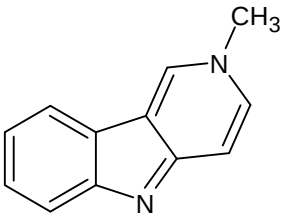
A
EC_{50} = 2.0 µM
5*H*-pyrido[4,3-*b*]indole



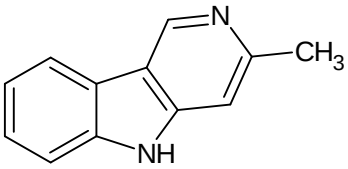
B
EC_{50} = 3.5 µM
3,4,5-trimethyl-5*H*-pyrido[4,3-*b*]indole



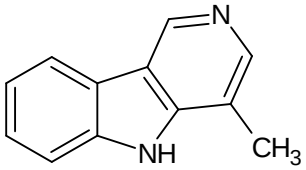
C
EC_{50} = 0.58 µM
1-methyl-5*H*-pyrido[4,3-*b*]indole



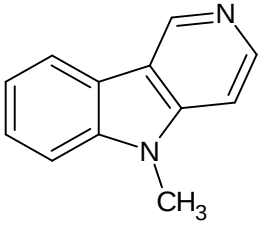
D
EC_{50} = 4.3 µM
2-methyl-2*H*-pyrido[4,3-*b*]indole



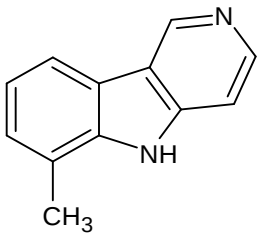
E
EC_{50} = 2.2 µM
3-methyl-5*H*-pyrido[4,3-*b*]indole



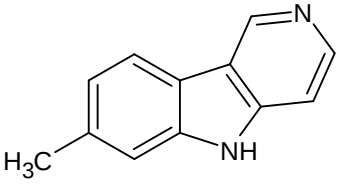
F
EC_{50} = 0.55 µM
4-methyl-5*H*-pyrido[4,3-*b*]indole



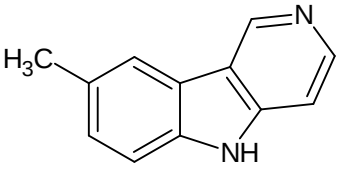
G
EC_{50} = 0.26 µM
5-methyl-5*H*-pyrido[4,3-*b*]indole



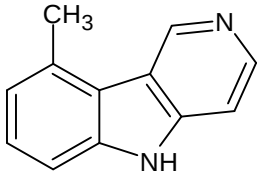
H
EC_{50} = 1.7 µM
6-methyl-5*H*-pyrido[4,3-*b*]indole



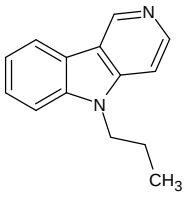
I
EC_{50} = 1.1 µM
7-methyl-5*H*-pyrido[4,3-*b*]indole



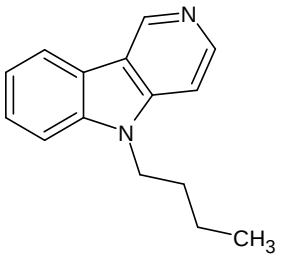
J
EC_{50} = 3.0 µM
8-methyl-5*H*-pyrido[4,3-*b*]indole



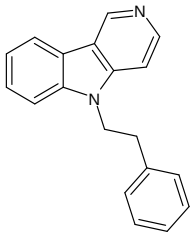
K
EC_{50} = 1.2 µM
9-methyl-5*H*-pyrido[4,3-*b*]indole



L
EC_{50} = 8.2 µM
5-propyl-5*H*-pyrido[4,3-*b*]indole



M
EC_{50} = 9.2 µM
5-butyl-5*H*-pyrido[4,3-*b*]indole



N
EC_{50} = 8.7 µ
5-(2-phenylmethyl)-5*H*-pyrido[4,3-*b*]indole

Figure 2. Gamma-carboline derivatives

Results and Discussion

This study examined the quantitative relationship between the structure of *gamma-carboline* and anti-BVDV activity. A total of 14 compounds derived *from gamma-carboline* are modeled with *Hyperchem 8.0.8,* and then geometry optimization carries out. Geometry optimization is the way to get the most stable shape and molecular structure with the lowest potential energy. Figure 3 depicts the stick and ball model of the derivative compound gamma-carboline after optimization with the AM1 method.

The derivative compound *gamma-carboline* is calculated with its physicochemical properties with *QSAR properties* to obtain the values of log P, polarizability (α), MW, area *Van der Waals* (A $_{vdw}$), volumes *Van der Waals* (V *vdw),* and index of refraction (RD), meanwhile the atomic charge and dipole moment are obtained from the log file of optimization result. Descriptor calculation data for the *AM1* method can be seen in Table 2.

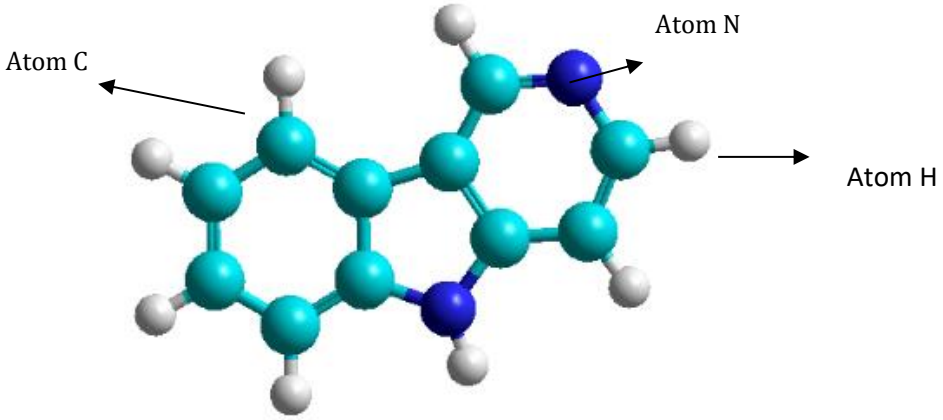


Figure 3. The *stick and balls* compound the *gamma-carboline* optimization *AM1*

The obtained data of descriptors calculation is then carried out a correlation test to determine the relationship between the variable and the pEC_{50} of derivative compound gamma-carboline. The twin-tailed and Pearson correlation coefficient is used for correlation analysis. The results of the correlation analysis were used to select the descriptors as independent variables in the calculation of *MLR (*Multiple Linear Regression*)* statistics. This is because the Backward Method only requires n-2 independent variables, which n is the number of *fittings* used (Iswanto et al., 2007; Vaulina & Iswanto, 2006). The *fitting* data in this study has as many as 11 variables, therefore the required independent variables are 9 descriptors. Based on the correlation values between variables shown in Table 3, the most influential variables to pEC_{50} are qN2, qC11, log P, RD, MW, V vdw, and A vdw.

The nine descriptors selected based on correlation analysis are then used as independent variables in the *multilinear model* of the pEC50 value as the dependent variable. Regression analysis *Multilinear* is carried out using the *backward* method first on 11 *fittings*. Therefore, it produces the three equation models presented in Table 4.

Table 2. Data for descriptor calculations of the AM1

Fitting compounds

Struktur	qC1	qN1	qC2	qC3	qC4	qN2	qC5	qC6	qC7	qC8	qC9	qC10	qC11	α (Å)	μ (Debye)	RD (Å)	Log P	BM (amu)	Vvdw (Å)	Avdw (Å)	pEC50
C	0.046	-0.168	0.04	-0.22	0.071	0.229	0.032	-0.155	-0.182	-0.157	-0.081	-0.063	-0.137	21.8	2.673	62.7	-0.46	182.22	577	264.56	-0.2366
D	0.034	-0.175	-0.044	-0.153	0.028	-0.147	-0.017	-0.106	-0.124	-0.149	-0.097	-0.083	-0.167	21.8	6.506	62.05	-0.11	182.22	588.64	291.79	0.63347
E	-0.011	-0.166	-0.015	-0.217	0.07	-0.228	-0.031	-0.154	-0.103	-0.156	-0.078	-0.063	-0.14	21.8	2.794	64.02	-1.39	182.22	587.65	282.45	0.34242
F	-0.021	-0.161	-0.047	-0.149	-0.063	-0.225	-0.031	-0.154	-0.102	-0.157	-0.077	-0.066	-0.13	21.8	3.123	62.51	-1.27	182.22	583.19	270.35	-0.2596
G	-0.018	-0.164	-0.048	-0.21	-0.071	-0.185	-0.038	-0.153	-0.102	-0.157	-0.077	-0.066	-0.134	21.8	3.317	63.12	-1.17	182.22	580.29	273.5	-0.585
H	-0.017	-0.164	-0.048	-0.212	-0.066	-0.226	-0.031	-0.093	-0.101	-0.153	-0.08	-0.063	-0.134	21.8	3.268	62.51	-1.27	182.22	581.7	268.86	0.23045
I	-0.018	-0.164	-0.048	-0.212	-0.066	-0.229	-0.037	-0.156	-0.039	-0.159	-0.072	-0.071	-0.132	21.8	3.268	62.51	-1.27	182.22	586.58	282.13	0.04139
J	-0.017	-0.164	-0.048	-0.212	-0.066	-0.227	-0.027	-0.15	-0.103	-0.095	-0.077	-0.063	-0.134	21.8	3.032	62.51	-1.27	182.22	585.72	281.76	0.47712
K	-0.02	-0.164	-0.048	-0.212	-0.066	-0.23	-0.03	-0.161	-0.097	-0.159	-0.013	-0.069	-0.131	21.8	2.775	62.51	-1.27	182.22	575.51	264.88	0.07918
L	-0.019	-0.165	-0.049	-0.211	-0.073	-0.181	-0.038	-0.153	-0.103	-0.157	-0.077	-0.066	-0.135	25.47	3.457	72.4	-0.36	210.28	680.56	325.59	0.91381
M	-0.019	-0.164	-0.05	-0.208	-0.068	-0.177	-0.034	-0.151	-0.104	-0.156	-0.078	-0.065	-0.133	27.3	3.43	77	-0.03	224.31	725.16	341.53	0.96379

Testing Compounds

Struktur	qC1	qN1	qC2	qC3	qC4	qN2	qC5	qC6	qC7	qC8	qC9	qC10	qC11	α (Å)	μ (Debye)	RD (Å)	Log P	BM (amu)	Vvdw (Å)	Avdw (Å)	pEC50
A	-0.016	-0.165	-0.011	-0.145	-0.078	-0.184	-0.035	-0.154	-0.104	-0.157	-0.078	-0.065	-0.138	19.96	3.037	58.23	-1.42	168.2	532.74	238.67	0.30103
B	-0.016	-0.165	-0.011	-0.145	-0.078	-0.184	-0.035	-0.154	-0.104	-0.157	-0.078	-0.065	-0.138	25.47	3.213	73.19	-0.99	210.28	667.03	333.81	0.54407
N	-0.018	-0.164	-0.049	-0.215	-0.071	-0.17	-0.041	-0.148	-0.103	-0.156	-0.078	-0.066	-0.131	31.46	3.386	91.88	-0.16	258.32	780.5	333.99	0.93952

Table 3. A correlation value of the descriptor for pEC_{50}

No	Descriptor	Nilai Korelasi dengan pEC_{50}
1.	qC_1	-0.071
2.	qN_2	-0.273*
3.	qC_2	-0.236
4.	qC_3	-0.021
5.	qC_4	-0.220
6.	qN_2	0.452
7.	qC_5	-0.267
8.	qC_6	0.214
9.	qC_7	0.084
10.	qC_8	0.214
11.	qC_9	-0.173
12.	qC_{10}	0.276
13.	qC_{11}	-0.297*
14.	A	0.694*
15.	μ	0.349*
16.	Log P	0.572*
17.	RD	0.678*
18.	BM	0.694*
19.	V *vdw*	0.729*

Note: *9 descriptors chosen based on the highest correlation value

Table 4. Analysis result of Equation model by a backward method

Model	Equations	r	r^2	SD	F_{count}/F_{table}	PRESS
1	pEC_{50} = 126,17 – 1,318 (qN2) + 77,482 (α) – 0,899 (RD) – 1,361 (Log P) – 9,798 (BM) + 0,014 (Vvdw) + 0,003 (Avdw) – 0,838 (μ) – 138,448 (qC11)	0,999	0,998	0,983	64,468/241= 0,2675	538,0755
2	pEC_{50} = 125,608 – 0,549 (qN2) + 77,209 (α) – 0,925 (RD) – 1,385 (Log P) – 9,768 (BM) + 0,019 (Vvdw) – 0,875 (μ) – 141,445 (qC11)	0,999	0,998	0,991	134,225/19,37=6,9295	224420,94
3	pEC_{50} = 122,986 + 75,892 (α) – 0,943 (RD) – 1,397 (Log P) – 9,593 (BM) + 0,02 (Vvdw) – 0,903 (μ) – 143,028 (qC11)	0,999	0,998	0,994	224,933/8,89 =25,3017	558,573

Based on the data in Table 4, the r and r^2 of the three equation models are the same, namely 0.999 and 0.998. These two values indicate that the three equation models are accepted based on the values of r and r^2 because the good values of r and r^2 are close to 1. The SD value interprets the standard deviation value; the smaller the value, the better the equation model. Based on the SD value, model equation 2 is the best model because the SD value is the smallest than the other two equations, which are 0.991. In addition to the SD value, the F_{count}/F_{table} value also affects the selection of the best equation model. The F_{count}/F_{table} value of an equation can be accepted if the value is greater than 1, so the equation 1 model cannot be accepted because the value is 0.2675. Model equations 1, 2, and 3 then apply to the 3 test compounds, obtaining PRESS values. The PRESS value is the square of the difference between the observed EC_{50} value and the value obtained from calculations using the QSAR equation. The better the equation model, the

lower the PRESS value. Based on the PRESS values in Table 4, the equation 3 model was chosen as the best equation model because the PRESS value was smaller than equation 2. The equation 3 model results from the backward method and is then analyzed further with the *entry* derivative compound *gamma-carboline* listed in Table 5.

Table 5: the results of the enter method analysis

Variable	r	r^2	SD	F_{count}/F_{table}	PRESS
qC_{11}, α, μ, RD, Log P, BM, V vdw	0,937	0,878	0,244	6,171/4,21 = 1,466	0,749

Table 5 shows that the values of r and r^2 are closer to 1, and the standard deviation is 0.244, meaning that the equation has a small error. The value of F-count/F-table is more than 1, which means that the equation can accept based on a 95% statistical confidence level. A small PRESS value of 0.749 indicates that the result of the predicted pEC_{50} is close to the observation pEC_{50}. The results of the *calculation* obtain the final equation for QSAR (Equation 1).

pEC_{50} = -48.670 – 124.801 (qC_{11}) – 12.661 (α) – 0.918 (μ) – 0.876 (RD) – 0.999 (log P) + 1.863 (BM) + 0.043 (V vdw)
with n = 14; r = 0.937; r^2 = 0.878; SD = 0.244; F_{count}/F_{table} = 1.466; PRESS = 0.749; Sig. = 0.02

(Equation 1)

Table 6. The last equation of PRESS value QSAR using the enter method

Compound	pEC_{50} Observation	pEC_{50} Prediction	PRESS
C	-0,2365	-0,214677	0,000479
D	0,6334	0,511149	0,014962
E	0,3424	0,279348	0,003978
F	-0,2596	-0,259584	0,0001
G	-0,5850	-0,697432	0,012635
H	0,2304	0,04244	0,035347
I	0,0413	0,002678	0,001499
J	0,4771	0,431948	0,002041
K	0,0791	-0,145559	0,050508
L	0,9138	0,481899	0,18655
M	0,9637	0,723933	0,05753
A	0,3010	-0,275468	0,33235
B	0,5440	0,435834	0,011715
N	0,9395	0,740143	0,039751
∑ PRESS = 0,749			

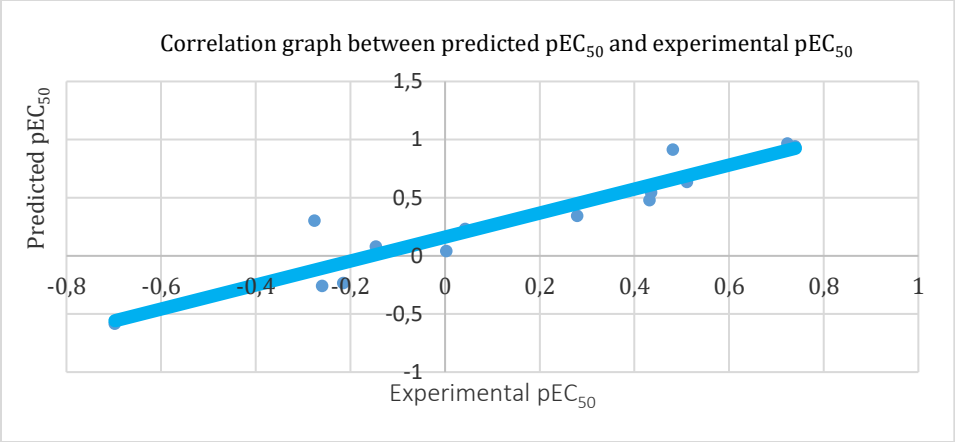


Figure 4. Correlation graph between predicted pEC_{50} and experimental pEC_{50}

The correlation graph between predicted pEC_{50} and experimental pEC_{50}, shown in Figure 4, shows a *slope* close to number 1. It means that the resulting equation can provide a fairly good level of prediction.

Conclusion

The analysis of gamma-carboline derivatives as anti-BVDV using the AM1 semi-empirical optimization method with multilinear regression analysis through the backward and enter procedures produced the optimal QSAR equation, which is provided in equation 1. This equation can be used as an initial point for designing new gamma-carboline group compounds. By considering some of the most influential descriptors, new compounds can be designed which have lower predicted EC50 values than known gamma-carboline derivatives.

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