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Qsar And Synthesis Of Curcumin Analogues As Antibacterial

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Abstract: *This study was aimed to analyze the Quantitative Structure-Activity Relationship (QSAR) of antibacterial activity between 37 curcumin analog compounds against S. aureus, B. subtilis and K. pneumoniae. The new compound wassynthesizedbased on QSAR studiesthen evaluate its antibacterial activity compound against S. aureus, B. subtilis and K. pneumoniae.*

Structure of curcumin analogues were geometry optimized.Variable selection used Systematic Search (SS) technique with Build QSAR application. Multiple Linear Regression Analysis (MLR) techniquewas used to select the descriptors and generate the equation. The compound result from QSAR was synthesized by aldol condensation reaction. TLC, melting point and GCMS were used to confirm the purity of compound. Antibacterial activity was determined using liquid dilution towards S. aureus, B. subtilis and K. pneumoniae. The antibacterial activity was showed as inhibitory concentration 50 (IC_{50}).

From the QSAR analysis, the best equation for S. aureus was inhibition zone = -205.0479 (± 73.1584) qC11 - 287.4352 (± 67.8597) qC12 - 17.2094 (± 5.2861) E Homo - 5.1675 (± 1.3691) log P + 1.1153 (± 0.3406) Polarizability - 183.1937 (± 57.5073). The best equation for B. subtilis was inhibition zone= + 83.4420 (± 41.8871) qC14 - 8.2071 (± 18.4883) qC16 - 0.4226 (± 0.1939) EHydr + 0.0007 (± 0.0009) E Binding + 0.0139 (± 0.0145) Hf + 19.6949 (± 7.3192). However the best equation for K. pneumoniae was inhibition zone= - 38.9096 (± 27.1149) qC18 + 63.6439 (± 56.9040) qC20 - 0.7478 (± 0.3882) E Hydr + 0.0550 (± 0.0290) Surface Area + 0.0132 (± 0.0093) Hf - 20.3836 (± 13.8032). A145 was synthesized based on QSAR studies. The inhibitory Concentration 50 (IC50) of A145 against S. aureus, K. pneumoniae and B. subtilis were 386.1 μg/mL; 360 μg /mL; and 441 μg/mL respectively.

From the study we concluded that A145 had antibacterial activity against S. aureus, K. pneumoniae and B. subtilis. The best antibacterial activity of A145 was against K. pneumoniae.

Keyword: *QSAR, curcuminanalog, antibacterial activity*

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I. Introduction

Several mono-ketone analogues of curcumin that have been successfully synthesized such as Dibenzylidenecyclohexanone(HGV), Dibenzylidenecyclopentanone (PGV) and1,5-diphenyl-1,4-pentadiene-3-one (GVT) had biological activity including anti-inflammatory[1], antibacterialactivity and for treating early cervical cancer[2]. Antibacterial drugs couldbe design by computational chemistry approach due to get better biological activity with less side effect than the lead compound. One of the advantages of the computational chemistry approach of drugs design is to minimize the utilization of chemical materials.Furthermore, this methodmore efficient because it is not needed atrial and error in experiment process but still able to provide decent credibility. Quantitative Structure-Activity Relationship (QSAR) analysis is one of methodsthat can be used in drug design.QSAR analysis aimed to empirically find the consistent relation between molecular characteristics and biological activity of compounds. The structure of drug, receptor, and interaction between both of them can be analyzed to design a new drug. Based on theory, the new drug design commonly have high activity and can be recommended to be synthesized[3].

The curcumin analogueswere synthesized by modifying the curcumin structuresusing aromatic aldehyde with cyclohexanone, cyclopentanone and monoketonehas been reported and examined regarding its biological activity. Sardjiman (2000) has been previously modified the curcumin structures into three groups, includingHGV, PGV and GVT. They have mainly conducted towards the aromatic aldehyde compounds that contain hydroxide group in aromatic ring with six-cyclic ketones, five-cyclic ketones and monoketone. The compounds (HGV, PGV and GVT) with hydroxide group as essential role in their antibacterial activity[1].

This research aimed to design the curcumin analogues by QSAR, synthesis a new compound from QSAR analysis and evaluate its antibacterial assay to against*S. aureus*, *B. subtilis*, and *S. pneumoniae*.QSAR analysis assumes that there is a quantitative relationship between the microscopic characteristic (molecular structure) and macroscopic/empiric characteristic (biological activity) of a molecule[4].

METHOD

The research materials were consisted of secondary data of structures and activities from the curcumin analogues that acquired from previous study[1]. 37 analoguesof curcumin along with their inhibition zone values in several bacteria were shown at table 1.

The assessment of quantum mechanics for the atomic and molecular descriptor were conducted by utilizing the Hyperchem 7.5 program package. The prediction wasassessed through BuildQSAR and Microsoft Excel 2013 program with Intel Core i3-6006U 2.0 GHz hardware, 4 GB Ram with Windows 7 operating system.

Table 1. The curcumin analogues with their inhibition values in several bacteria.

No.	Code	Subtituent					inhibition zones S. aureus (mm)	inhibition zones B.subtilis (mm)	inhibition zones S.pneumonia (mm)
		R1	R2	R3	R4	R5			
	A0	H	H	OH	H	H	10.3	9	0
2	A1	H	OCH_3	OH	H	H	12.7	11	11
3	A2	H	H	H	H	H	0	0	7
4	A4	H	H	OCH_3	H	H	0	0	7.1
5	A6	H	H	*t*-C_4H_9	H	H	0	0	8
6	A7	H	H	CF_3	H	H	0	0	7.2
7	A8	H	H	$N(CH_3)_2$	H	H	0	0	10.3
8	A9	H	Cl	Cl	H	H	0	0	6.9
9	A10	H	Cl	H	H	H	0	0	8.9
10	A11	H	CH_3	OH	CH_3	H	0	0	8.1
11	A15	H	OCH_3	OH	OCH_3	H	0	0	11.2
12	A16	H	Cl	OH	Cl	H	11.5	16.5	11.4
13	B0	H	H	OH	H	H	0	8.1	10
14	B1	H	OCH_3	OH	H	H	0	9.2	10.1
15	B2	H	H	H	H	H	0	7	0
16	B3	H	H	Cl	H	H	0	0	0
17	B4	H	H	OCH_3	H	H	0	0	0
18	B5	H	H	CH_3	H	H	0	0	6.5
19	B6	H	H	*t*-C_4H_9	H	H	0	7.3	6.6
20	B7	H	H	CF_3	H	H	0	7.5	6.8
21	B8	H	H	$N(CH_3)_2$	H	H	8	10	0
22	B9	H	Cl	Cl	H	H	0	7.2	0
23	B10	H	Cl	H	H	H	0	6.8	0
24	B11	H	CH_3	OH	CH_3	H	9	0	0
25	B16	H	Cl	OH	Cl	H	17.8	17	12
26	C0	H	H	OH	H	H	15.8	14.6	14.1
27	C1	H	OCH_3	OH	H	H	12.8	14	14
28	C2	H	H	H	H	H	9.5	12.2	13.8
29	C3	H	H	Cl	H	H	7	0	7
30	C4	H	H	OCH_3	H	H	0	0	8.1
31	C5	H	H	CH_3	H	H	0	0	8.2
32	C6	H	H	*t*-C_4H_9	H	H	0	6.6	0
33	C7	H	H	CF_3	H	H	7	6.8	7.2
34	C8	H	H	$N(CH_3)_2$	H	H	8	10	0
35	C9	H	Cl	Cl	H	H	7	6.7	7.2
36	C10	H	Cl	H	H	H	0	0	10
37	C11	H	CH_3	OH	CH_3	H	9.5	10	9.6
38	C15	H	OCH_3	OH	OCH_3	H	9.5	0	7.5
39	C16	H	Cl	OH	Cl	H	14	16.5	15

QSAR study

Geometric Optimization

Each compound used as the research materials (Table 1) was transformed into two dimension structures (2D) (Figure 1) by using Hyperchem program. Atom H wasadded to complete the structures and transformed into three dimension structures (3D). Later, this structures were optimized geometriesusing the AM1 method through the Polak-Ribiere algorithm. The convergence margin wasdetermined after the 0.01 kcal/A gradient is acquired[4].

Descriptor Calculation

The single point calculationwas conducted through the optimized structure to acquire electronic parameters i.e net charges of C atom, total energy (E total), Binding Energy (E Binding) and heat of formation (HF); lipophilicity parameter; and steric parameter (molecule size) for each ofthe optimized moleculeusingthe Hyperchem program[4].

QSAR Analysis

Every descriptors was analyzed using multilinear regression toevaluate the antibacterial activityusing BuildQSAR application. The best equation model from Build QSAR was chosen by considering the best statistical parameter and used to predictantibacterial activity. The statistical parameter such as the highest R (regression), the largest F ratio, the smallest s value, the smallest SPress (Predicted Residual Sum of Squares) and the lowest Q2 with the Microsoft Excel as supporting tool.

Figure 1. The numbering structure of C atom in curcumin analogues basic structure

Synthesis

0.931 mL (6.659 mol) of 2-etoxybenzaldehide, 1.1 mL (0.104 mol) of cyclohexanone, 2.0 mL THF and 0.2 mL of concentrated hydrochloric acid were heated on water bath (25-30^{o}C) with stirring for two hours.The temperature was increased to 40-45 ^{o}C, and stirring was continued for 6 hours. After standing 3 days, the mixture was treated with cold ethanol-water (1:1), filtered and the residue was dried. TLC, melting point and GCMS were used to confirm the purity of compound.

Antibacterial Assay

The antimicrobial activity was tested by the diffusion method against various bacteria such as *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 6538P, *klebsiella pneumoniae* ATCC 49619. For the analysis by the dilution method solution of the compound A145 was prepared. The final concentration of DMSO in liquid nutritious base was < 1,25 %. The compound was incubated using 96 microplate. After the incubation for 24 h at 37^{o}C, then inhibition of bacteria was read in microplate reader (595 nm).That was taken to represent IC_{50} expressed in mg/mL. The concentration of the prepared solutions were: 0,5mg/mL; 0,25 mg/mL; 0,125 mg/mL; 0,0625 mg/mL; 0,03125 mg/mL. This method was used to determine the exact concentration of the investigated compound which showed an inhibitory effect on the growth of selected microorganisms. This concentration was considered as *inhibition concentration 50 (IC_{50}).*

II. Result And Discussion

QSAR Study

The curcumin analog serial in this research is acquired from the literature[1] with lead compound serials are A2, B2, and C2 which have no substituent on their both benzene sides. The calculations of atomic and molecular descriptors have to be conducted on an optimized structure. The geometric optimization is conducted by utilizing the AM1 method to acquire molecule structure with Potential Energy Surface (PES) minimum, thus the molecule with well-defined structure can be acquired. The geometric optimization is conducted towards

those three dimensions curcumin analog compounds by using Polak-Ribiere algorithm and 0.01 kcal/mol RMS (root mean square) gradient margin. The AM1 method also reported producing better analysis of curcumin analog compound series of QSAR as the anti-oxidant compared to the PM3 method[5]. Net charge value of C atom obtain from single point calculation of structured was optimized.

Table 2. The equations model from MLR analysis of S. aureus.

No.	Descriptor	n	m	r	S	F	P	Q2	SPres	SDep	equation
1	qC_{11}, qC_{12}, EHomo, logP, Polarizability	16	5	0.954	1.19	20.469	0.0001	0.778	1.878	1.533	Inhibition zone = - 205.0479 (± 73.1584) qC11 - 287.4352 (± 67.8597) qC12 - 17.2094 (± 5.2861) E Homo - 5.1675 (± 1.3691) log P + 1.1153 (± 0.3406) Polarizability - 183.1937 (± 57.5073)
2	qC_3, EHomo, logP, Polarizability	16	4	0.931	1.386	17.972	0.0001	0.752	1.896	1.623	Inhibition zone = - 264.1788 (± 73.1121) qC5 - 18.6206 (± 6.4936) E Homo - 5.0076 (± 1.5670) log P + 1.0438 (± 0.3825) Polarizability - 185.1440 (± 67.8041)
3	qC_4, logP, Mass	16	3	0.874	1.768	12.976	0.0004	0.522	2.517	2.252	Inhibition zone = + 108.8140 (± 43.2174) qC4 - 2.3843 (± 0.9940) log P + 0.0397 (± 0.0218) Mass + 21.1744 (± 7.3080)
4	qC_4, EHydr	16	2	0.805	2.077	11.946	0.0011	0.452	2.589	2.41	Inhibition zone = + 39.6335 (± 33.5405) qC6 - 0.3243 (± 0.1569) E hydr + 11.2306 (± 3.3981)
5	EHydr	16	1	0.686	2.452	12.467	0.0033	0.336	2.747	2.654	Inhibition zone = - 0.3003 (± 0.1824) E hydr + 7.8354 (± 2.1271)

n= number of data, m= number of variable, r= correlation coefficient, s= error standard, F= Fisher coefficient, SPress= Predictive Error Sum of Squares

The descriptor of C atom net charges and molecular descriptor was obtained then correlated with antibacterial activity. The best equation was obtained from MLR analysis using systematic search (SS) in the QSAR menu of BuildQSAR program. The formulation for each variable acquired is the prediction of the inhibition zone diameter value of the curcumin analog compound. In table 2, five equations models resulted from MLR analysis by using the atomic and molecular descriptor of the AM1 method for *S.aureus.*

The first model with inhibition diameter equations = -205.0479 (± 73.1584) qC11 - 287.4352 (± 67.8597) qC12 - 17.2094 (± 5.2861) E Homo - 5.1675 (± 1.3691) log P + 1.1153 (± 0.3406) Polarizability - 183.1937 (± 57.5073). The equations was used to design the new compound of curcumin analogues with *S. aureus*antibacterial activity. Base on model 1, five variables have significantly influenced the inhibition of *S.aureus.*R value is 0.954 as the largest value and 20.460 Fisher coefficient as the best values, with 1.19 standard error value (s), 1.878 values of the Predicted Residual Sum of Squares (SPress), the smallest value of Q2 (0.078). The model 1 is the only one model in this research, that fulfills the best model criteria in accordance with Kubinyi (1993)[6].The best statistical parameter as the highest r, the largest F ratio, the smallest s, the smallest SPress (Predicted Residual Sum of Squares) and the lowest Q2.

That model 1 equations is used to calculate the prediction of the inhibition diameter value of *S. aureus*bacteria for each compound. The calculation prediction result is presented in Table 3. The correlation analysis plot between the experimental inhibition diameter zone value and the prediction of the inhibition diameter value of curcumin analog compounds are presented in figure 2.

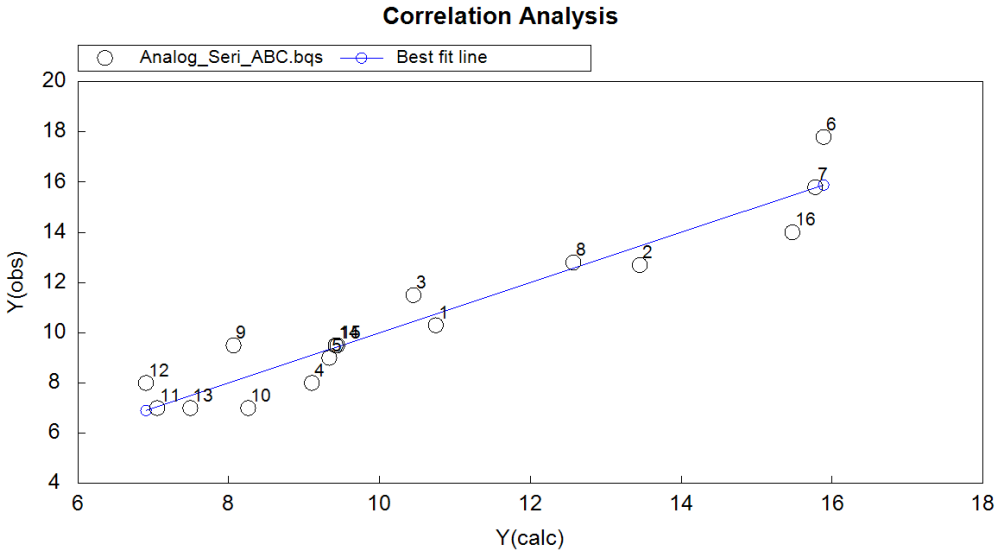

Figure 2. The correlation analysis between experimental inhibition value and the prediction inhibition value of curcumin analoguesagainstS. aureus using Build QSAR

According to the model 1 equations in table 2, the molecule designing of the new curcumin analogues compound as the antibacterial can be conducted when the variable value is dependent as the inhibition diameter will be greater. This condition can be acquired by the curcumin analogues compound that conceives net atom charge on C11 and C12 and becomes more negative (the value of C11 and C12 net atom charges become smaller), the highest value of orbital energy level, which filled with electron (E Homo) and small log P, while bigger polarizability (solubility) value.

In table 3, difference value between the calculation result of experimental inhibition value and the prediction inhibition value shows small difference value.That's not implicated much different or approaching similar value. So, the model 1 equations can be used in designing the new curcumin analogues compound with better activity in inhibiting the growth of *S. aureus.*

Table 3. The antibacterial activity against S. aureus based on experimental and prediction research

No.	Code	Inhibition $zone_{experiment}$ (mm)	Inhibition $zone_{prediction}$ (mm)	Deviation
1	A0	10.3	9.9	0.4
2	A1	12.7	14.6	-1.9
3	A16	11.5	9.8	1.7
4	B8	8.0	7.7	0.3
5	B11	9.0	9.5	-0.5
6	B16	17.8	15.2	2.6
7	C0	15.8	16.1	-0.3
8	C1	12.8	11.5	1.3
9	C2	9.5	8.6	0.9
10	C3	7.0	8.4	-1.4
11	C7	7.0	7.1	-0.1
12	C8	8.0	9.0	-1.0
13	C9	7.0	7.4	-0.4
14	C11	9.5	9.7	-0.2
15	C15	9.5	9.5	0.0
16	C16	14.0	15.4	-1.4

The design of curcumin analogues with antibacterial activity against *S.aureus*shown in table 4. The design of curcumin analoguesare divided into three series marked with A, B, and C code. A series is the curcumin analog which its two benzene groups are connected by six cyclic ketones (cyclohexanone). B series is the curcumin analogue, which its two benzene groups are connected by five cyclic ketones (cyclopentanone). C series is the curcumin analogue, which its two benzene groups are connected by aliphatic ketone.

Table 4. The calculation of curcumin analogue to predictantibacterial activityagainst S. aureues.

Code	Subtituent					Inhibition zone prediction	qC11	qC12	E Homo	log P	Polarizability
	R 1	R 2	R 3	R 4	R5						
A145	H	H	H	H	OC_2H_5	20.5	-0.037628	-0.082129	-9.140704	5.2	37.59

The calculation result is in accordance with the model 1 equationobtained to design a more active analogue compound with large inhibition diameter. The interventions of the netatom of C11 (qC11) and 12 (qC12) could not indirectly intervened, especially on the C11 (qC11). The addition of electron withdrawing groups such as $-NO_2$, -F, -Cl, -Br, -OH, $-OC_2H_5$, and $-OCH_3$ on R_1, R_2, R_3, R_4 and R_5 position are influencing of highest orbital energy value filled with electron (E Homo) and smaller log P, while the large polarizability value (solubility).

In table 5, the first model with inhibition diameter equations = + 83.4420 (± 41.8871) qC14 - 8.2071 (± 18.4883) qC16 - 0.4226 (± 0.1939) EHydr + 0.0007 (± 0.0009) E Binding + 0.0139 (± 0.0145) Hf + 19.6949 (± 7.3192). The equations was used to design the new compound of curcumin analogues with *B. subtilis* antibacterial activity. Base on model 1, five variables have significantly influenced the inhibition of *S.aureus.* R value is 0.804 as the largest value and 7.195 Fisher coefficient as the best values, with 2.234 standard error value (s), 2.978 values of the Predicted Residual Sum of Squares (SPress), the smallest value of Q2 (0.477).

That model 1 equations is used to calculate the prediction of the inhibition diameter value of *B. subtilis* bacteria for each compound. The calculation prediction result is presented in Table 6. The correlation analysis plot between the experimental inhibition diameter zone value and the prediction of the inhibition diameter value of curcumin analog compounds are presented in figure 3. In table 6, difference value between the calculation result of experimental inhibition value and the prediction inhibition value shows small difference value. That's not implicated much different or approaching similar value. So, the model 1 equations can be used in designing the new curcumin analogues compound with better activity against*B. subtilis.*

Table 5. The equations model from MLR analysis of B. subtilis.

No.	Descriptor	n	m	r	S	F	P	Q2	SPres	SDep	Persamaan
1	qC_{14}, qC_{16}, EHydr, EBinding, Hf	21	5	0.840	2.234	7.195	0.0013	0.477	2.978	2.579	Diameter Hambat = + 83.4420 (± 41.8871) qC14 - 8.2071 (± 18.4883) qC16 - 0.4226 (± 0.1939) E Hydr + 0.0007 (± 0.0009) E Binding + 0.0139 (± 0.0145) Hf + 19.6949 (± 7.3192)
2	qC_{14}, EHydr, EBinding, Hf	21	4	0.830	2.226	8.828	0.0006	0.517	2.771	2.478	Diameter hambat = + 85.1844 (± 41.3510) qC14 - 0.4458 (± 0.1851) E Hydr + 0.0005 (± 0.0009) E Binding + 0.0161 (± 0.0135) Hf + 20.1966 (± 7.1704)
3	qC_5, qC_{14}, EBinding,	21	3	0.817	2.231	11.364	0.0002	0.504	2.723	2.511	Diameter hambat = - 132.2543 (± 55.7450) qC5 + 73.6072 (± 38.5416) qC14 + 0.0017 (± 0.0008) E Binding + 16.4145 (± 6.7272)
4	qC_4, qC_{14}	21	2	0.745	2.509	11.199	0.0007	0.418	2.868	2.721	Diameter hambat = + 137.9855 (± 62.3770) qC4 + 25.9457 (± 35.8479) qC14 + 26.1950 (± 7.7613)
5	qC_4	21	1	0.705	2.594	19.788	0.0004	0.394	2.847	2.775	Diameter hambat = + 131.8082 (± 63.6454) qC4 + 22.5521 (± 6.0855)

N= jumlah data, m= jumlah variable, r= koefisien korelasi, s= standard error, F= coefficient Fisher, spares= *Predictive Error Sum of Squares*

The design of curcumin analogues with antibacterial activity against *B. subtilis* shown in table 7. The calculation result is in accordance with the model 1 equation obtained to design a more active analogue compound with large inhibition diameter. The interventions of the netatom of C14 (qC14). When net atom C16

was substituted with electron withdrawing groups such as -OH, $-OC_2H_5$, $-OCH_3$ on R_1, R_2, R_3, R_4 and R_5 position are influencing of hydration energy and binding energy (E Binding) to become smaller and the heat of formation value becomes large.

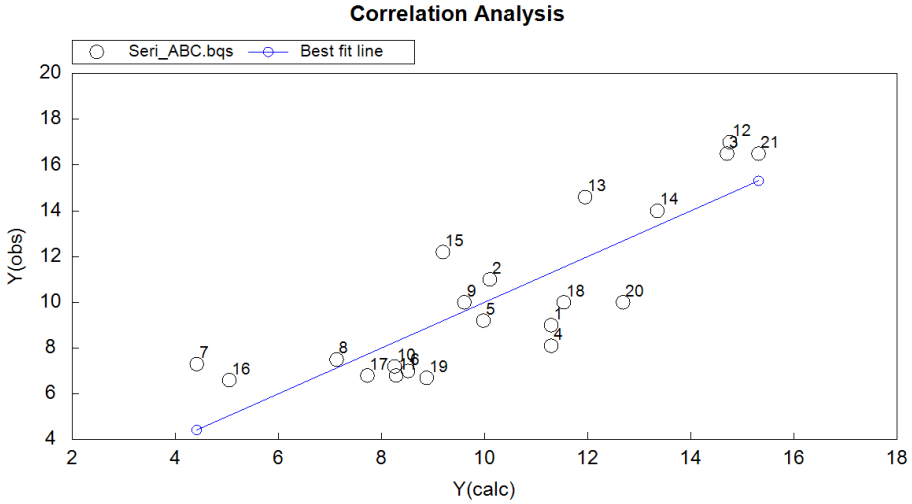

Figure 3. The correlation analysis between experimental inhibition value and the prediction inhibition value of curcumin analoguesagainstB. subtilis using Build QSAR.

Table 6. The antibacterial activity against B. subtilis based on experimental and prediction research

No.	Code	Inhibition zoneexperiment (mm)	Inhibition zoneprediction (mm)	Deviation
1	A0	9.0	11.2	-2.2
2	A1	11.0	10.0	1.0
3	A16	16.5	14.6	1.9
4	B0	8.1	11.2	-3.1
5	B1	9.2	9.9	-0.7
6	B2	7.0	8.4	-1.4
7	B6	7.3	4.3	3.0
8	B7	7.5	7.0	0.5
9	B8	10.0	9.5	0.5
10	B9	7.2	8.2	-1.0
11	B10	6.8	8.2	-1.4
12	B16	17.0	14.7	2.3
13	C0	14.6	11.9	2.7
14	C1	14.0	13.3	0.7
15	C2	12.2	9.1	3.1
16	C6	6.6	4.9	1.7
17	C7	6.8	7.6	-0.8
18	C8	10.0	11.4	-1.4
19	C9	6.7	8.8	-2.1
20	C11	10.0	12.6	-2.6
21	C16	16.5	15.2	1.3

Table 7. The calculation of curcumin analogue to predictantibacterial activityagainst B. subtilis.

Code	Subtituen					Diameter hambat prediksi	qC14	qC16	E hydr	E Binding	Hf
	R1	R2	R3	R4	R5						
A145	H	H	H	OC_2H_5	OH	18.1	-0.011768	-0.134481	-10.18	-5887.80944650	-134.00244650

Table 8. The equations model from MLR analysis of K. pneumonia

No.	Descriptor	n	m	r	S	F	P	Q2	SPres	SDep	Persamaan
1	qC_{18}, qC_{20}, EHydr, Surface area, Hf	11	5	0.960	0.717	11.864	0.0084	0.656	1.507	1.066	Diameter Hambat = - 38.9096 (± 27.1149) qC18 + 63.6439 (± 56.9040) qC20 - 0.7478 (± 0.3882) E hydr + 0.0550 (± 0.0290) Surface Area + 0.0132 (± 0.0093) Hf - 20.3836 (± 13.8032)
2	EHomo, EHydr, Surface area, Hf	11	4	0.899	1.025	6.357	0.0238	0.398	1.821	1.411	Diameter Hambat = - 2.9348 (± 3.8220) E Homo - 0.3382 (± 0.2121) E hydr + 0.0275 (± 0.0188) Surface Area + 0.0103 (± 0.0124) Hf - 34.6393 (± 43.3048)
3	qC_{10}, EHydr, Polarizability	11	3	0.871	1.066	7.361	0.0144	0.391	1.696	1.419	Diameter Hambat = + 57.6382 (± 108.9715) qC10 - 0.2016 (± 0.1218) E hydr + 0.2164 (± 0.1473) Polarizability + 7.7409 (± 16.3287)
4	EHydr, Polarizability	11	2	0.840	1.103	9.583	0.0075	0.449	1.509	1.350	Diameter Hambat = - 0.1973 (± 0.1227) E hydr + 0.1923 (± 0.1413) Polarizability - 0.2701 (± 6.1564)
5	qC_2	11	1	0.591	1.546	4.830	0.0555	0.053	1.864	1.769	Diameter Hambat = + 10.9530 (± 11.2731) qC2 + 8.8834 (± 1.0558)

N= jumlah data, m= jumlah variable, r= koefisien korelasi, s= standard error, F= coefficient Fisher, spares= *Predictive Error Sum of Squares*

In table 8, the first model with inhibition diameter equations = - 38.9096 (± 27.1149) qC18 + 63.6439 (± 56.9040) qC20 - 0.7478 (± 0.3882) E hydr + 0.0550 (± 0.0290) Surface Area + 0.0132 (± 0.0093) Hf - 20.3836 (± 13.8032). The equations was used to design the new compound of curcumin analogues with *K. pneumonia* antibacterial activity. Base on model 1, five variables have significantly influenced the inhibition of *S.aureus.* R value is 0.960 as the largest value and 11.864 Fisher coefficient as the best values, with 0.717 standard error value (s), 1.507 values of the Predicted Residual Sum of Squares (SPress), the smallest value of Q2 (1.656).

The model 1 equations in table 8 are used to calculate the predictive inhibition diameter value of *K. pneumoniae* bacteria for each compound. The calculation result is presented in table 9, while the plot of correlation analysis between experimental inhibition diameter value and predictive inhibition diameter value of curcumin analog compounds is presented in figure 4. The difference value between experimental inhibition diameter value and predictive diameter value resulted from the calculation process by using model 1 equations provide the range of difference, value that has no significant difference thus the model 1 equations can be used to design the new curcumin analogue compound with better activity against*K. pneumoniae*.

Table 9. The antibacterial activity against K. pneumoniae based on experimental and prediction research

No	Code	Inhibition zoneexperiment (mm)	Inhibition zoneprediction (mm)	Deviation
1	A1	11	11.1	-0.1
2	A2	7	7.1	-0.1
3	A4	7.1	6.6	0.5
4	A6	8	7.6	0.4
5	A7	7.2	7.2	0.0
6	A8	10.3	10.4	-0.1
7	A9	6.9	7.8	-0.9
8	A10	8.9	8.4	0.5
9	A11	8.1	9.0	-0.9
10	A15	11.2	11.1	0.1
11	A16	11.4	10.9	0.5

In millimeter The design of curcumin analogues with antibacterial activity against *K. pneumoniae* shown in table 10. The calculation result is in accordance with the model 1 equation obtained to design a more active analogue compound with large inhibition diameter. The interventions of the netatom of C18 (qC18) with –Cl and -OH will becomes smaller or more negative. The interventions of the netatom of C20 (qC20) with electron donor group (qC20 value becomes bigger or more positive) such as -NO_2, -F, -Cl, -Br, -OH,-OC_2H_5, -OCH_3 or -COOH that influence the value of hydration energy (E Hydr) and binding energy (E Binding) to become smaller and the heat of formation value becomes large.

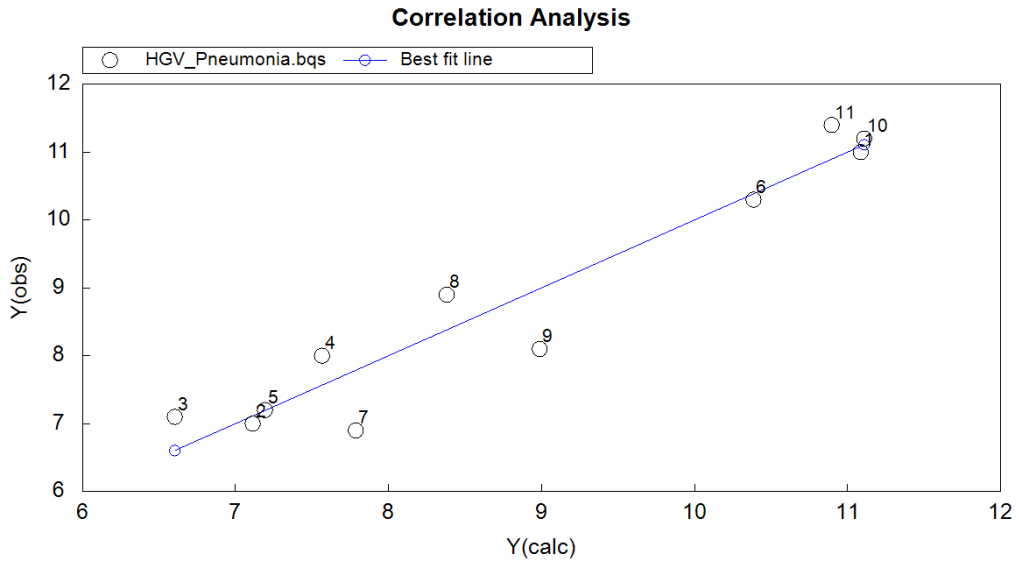

Figure 4. The correlation analysis between experimental inhibition value and the prediction inhibition value of curcumin analoguesagainstK. pneumoniae using Build QSAR

Table 10. The calculation of curcumin analogue to predictantibacterial activityagainst B. subtilis.

Code	Subtituen					Inhibition zone prediction	qC18	qC20	E Hydr	Surface Area	Hf
	R1	R2	R3	R4	R5						
A145	H	H	H	H	OC_2H_5	12.3	-0.11715	-0.11621	-3.3	612.19	-44.3940836

Synthesis A145

Experimental data of the synthesis of the A145 are compiled in table11. The purity of A145 was examined using thin layer chromatography and melting point.Thin layer chromatography is a method that can be used for measuring the polarity of the compound. Result is shown in table 11. A145 using EtOAc:$CHCl_3$=1:4 as mobile phase with Rf = 0.725.

Comp.	**R_1**	**R_2**	**R_3**	**R_4**	**R_5**	**Yield, %**	**m.p.,°C**	**Formula**	**Determined MW**	**Rf TLC**
A145	H	H	H	H	OC_2H_5	90.57	151.2 – 152.2	$C_{24}H_{28}O_3$	362.47	0.725

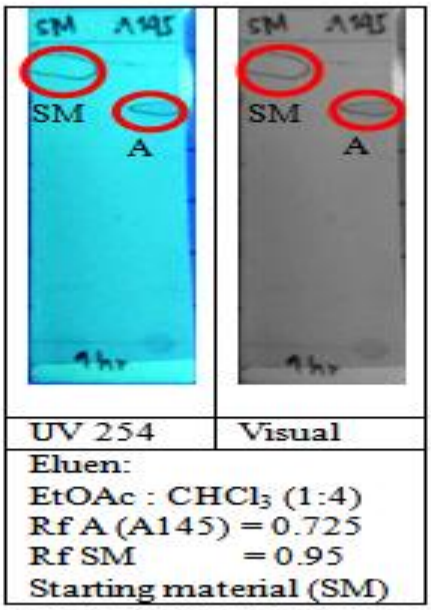

Figure 5. TLC Profi of A145

Concerning the mass spectra, hypothetically A145 have a peak m/z 363 as molecule weight A145. Fragmentation from A145 shown m/z 317 as best peak and m/z 39 shown last fragmentation.

As first impression, fragmenting a molecule with huge excess of energy would seems a brute-force approach to molecular structure. The rationalizations used to correlate spectral patterns with structure, however, can only be described as elegant. Generally, the tendency has been to represent the molecular ion with a possibility of low-energy transitions, and to the stability of the fragments both charged and uncharged formed in fragmentation process. Concepts of physical organic chemistry can be used for writing and rationalizing in predicting prominent peaks in electron impact spectra (Silverstein, 1981).

Generally, the largest substituent at a branch is eliminated most readily as a radical, presumably because of the stability of the long chain radical that is released.

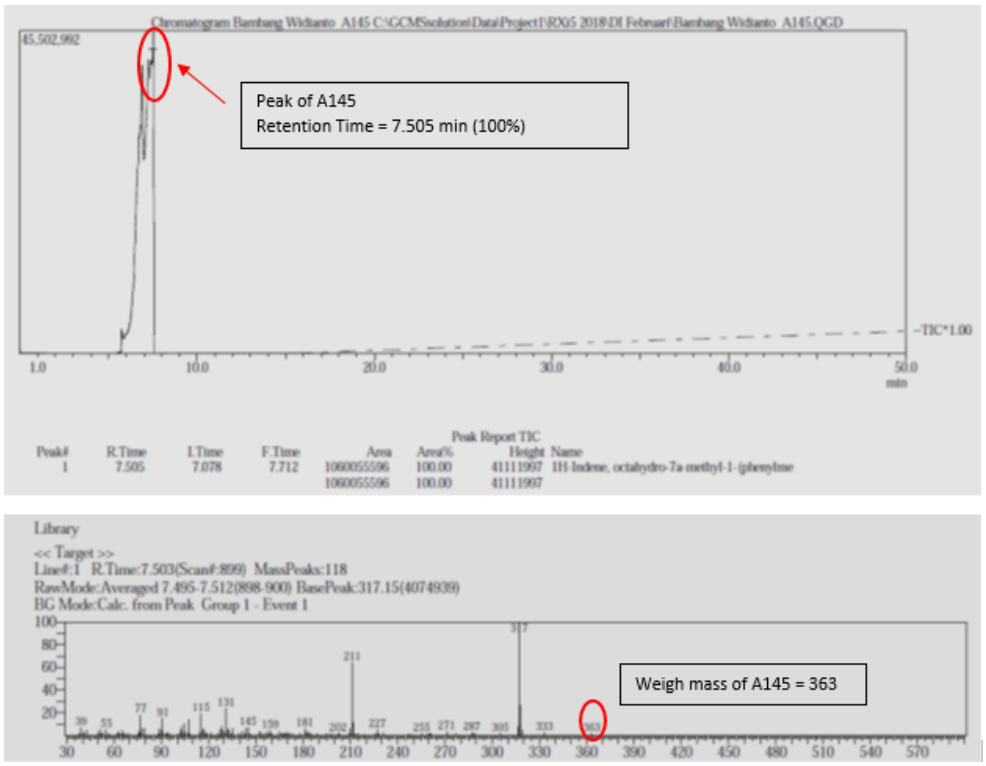

Figure 6. Mass Spectra and Kromatogram of A145

Antibacterial Assay

From table 12 can be shown A145 did against *S. aureus, B. subtilis* and *K. pneumoniae*.Inhibitory Concentration 50 (IC50) of A145 to against *S. aureus, K. pneumoniae* and *B. subtilis* were 386.1 µg/mL; 360 µg /mL; 441 µg/mL respectively. A145 is the promising compound for further research. A145 have inhibition of bacterial better than compound that only have mono substitution. The compound with mono substitution almost shew no inhibition at all in bacteria (Sardjiman, 2000). The OH group is very important in its activity. However, if the OH in para position is accompanied with two electron donating groups in ortho position there was no inhibition at all. That was opposite to the antioxidative activity. That's active as antioxidant, but did not have antibacterial properties. On the other hand the phenolic groups that can act as potent protein denaturant at the cell wall of bacteria. When one metoxy (OCH_3) group is present in every phenyl ring, the antibacterial activity was increasing. But when two metoxy (OCH_3) groups are present, the antibacterial activity was decreasing, probably caused by two positive resonance factors leading to the high density of electrons in every phenyl ring[1].

Table 12. IC_{50} value of A145 against *S. aureus, B. subtilis* and *K. pneumoniae.*

Bacteria	IC_{50} (µg/mL)
Staphylococcus aureus	386.1
Bacillus subtilis	441.0
Klebsiella pneumoniae	360.0

A145 are active to inhibit K.pneumoniae but not higher activity to inhibit S. aureus and B. subtilis. So, we concluded that A145 more active against bacteria gram negative.The important functional group as antibacterial activity was α, β unsaturated[7].

III. Conclusion

1. The QSAR analysis by utilizing Multilinear regression (MLR) analysis with BuildQSAR program can be used to acquire the best equations in designing the new compound of curcumin analog with the activity of S. aureus, B. subtilis, and S. pneumoniabacteria.
2. Inhibition diameter = -205.0479 (± 73.1584) qC11 - 287.4352 (± 67.8597) qC12 - 17.2094 (± 5.2861) E Homo - 5.1675 (± 1.3691) log P + 1.1153 (± 0.3406) Polarizability - 183.1937 (± 57.5073) is the best equations that can be used in designing the new compound of the curcumin analogagainst S. aureus.
3. Inhibition diameter = + 83.4420 (± 41.8871) qC14 - 8.2071 (± 18.4883) qC16 - 0.4226 (± 0.1939) E Hydr + 0.0007 (± 0.0009) E Binding + 0.0139 (± 0.0145) Hf + 19.6949 (± 7.3192), is the best equations that can be used in designing the new compound of the curcumin analogagainst inhibitorB. subtilis.
4. Inhibition diameter = - 38.9096 (± 27.1149) qC18 + 63.6439 (± 56.9040) qC20 - 0.7478 (± 0.3882) E hydr + 0.0550 (± 0.0290) Surface Area + 0.0132 (± 0.0093) Hf - 20.3836 (± 13.8032), is the best equations that can be used in designing the new compound of the curcumin analogagainstK. pneumoniae.
5. A145 have antibacterial activity to against gram negative bacteria.

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