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Modeling of Quinoacridinium Derivatives as Antitumor Agents using a QSAR analysis

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ABSTRACT

A QSAR analysis has been performed on a compound series of 1-11 quinoacridinium derivatives as internal test compounds, and compounds of 12-15 quinoacridinium derivatives as external test compounds. The electronic descriptors used in this study were atomic net charge (q), dipole moment (μ), E_{LUMO}, E_{HOMO}, polarizability (α), and Log P. They were calculated through HyperChem for Windows 8.0 software using semi-empirical PM3 method. The antitumor activity (IC_{50}) of quinoacridinium derivative compounds was obtained from literature. Furthermore, the model of QSAR equation was analyzed through RML method which produced the best QSAR equation model: Log IC_{50} = -13.010+15.338(qC3) - 4.31(qC4) - 155.308(qC9) + 33.626(qC11) + 26.626(qC12) + 24.631(qC14) - 0.228(μ) - 0.621(E_{LUMO}) - 0.066(α) + 0.233(Log P). The model of QSAR equation has a correlation coefficient n =11, (r) = 1.00, (r^2) =1.00, SE =0, and PRESS = 0.003. Among 28 compounds of quinoacridinium derivative which were designed, only 15 compounds, namely 16, 19-20, 22-28, 30-32, 39, and 40 compounds, have been recommended to be synthesized in the laboratory.

Key words: quinoacridinium derivatives, QSAR analysis, anti-tumor, PM3 method, MLR analysis

INTRODUCTION

Tumors and cancers still become dangerous health problem in the world because of their high morbidity and mortality. In 2012, there were 14.1 million new cancer cases, with 8.2 million cancer deaths (Torre *et al.,* 2015). In 2000, productivity costs which was lost due to cancer deaths were 115.8 billion US dollars, and by 2020, these costs are predicted to reach 147.8 billion US dollars (Bradley *et al.,* 2008). The main problems in a cancer therapy are low selectivity and high toxicity. Therefore, it is necessary to develop antitumor drugs with high selectivity as well as low toxicity, so that the therapy will be more effective. One of the antitumor compounds that has been widely studied and continuously developed by previous researchers is the derivatives of acridinium compounds.

A recent study on acridinium derivatives was conducted in 2008 (Cheng *et al.,* 2008). It was a synthesis on a series of salt-derivative compound with 8,13-dimethylquino[4,3,2-kl]acridinium as an antitumor. Derivatives of the acridinium compounds used as an antitumor have been studied (Cooksonet *et al.,* 2005). Research on the derivatives of acridine compounds has been done by various researchers since 1984. They isolated acridine compounds from plant species, *Lactariusnecator* (*Agaricales*) (Fugmann *et al.,* 1984). Furthermore, after 13 years later, the ring of acridine compounds was successfully synthesized and antitumor activity was tested (Hagan *et al.,* 1997). After that in 1998, several researchers conducted a study to convert 9-azidoacridine to 7H-pyrido [4,3,2-kl]acridine compound and succeeded in changing the pyridine ring to 7H-pyrido[4,3,2-kl]acridine compound to increase the antitumor derivative activity of acridine compounds (Hagan *et al.,* 1998; Julino & Stevens, 1998). In 2000, the ring of acridine compound was developed into *tetra-*, *penta-*, and *hexacyclic* rings in a heteroaromatic system through a cyclical process of 9-anilinoacridineto enhance antitumor activity of derivatives of acridine compounds which were synthesized in the previous years (Stanslas *et al.,* 2000; Ellis *et al.,* 2001).

Research on the derivatives of acridine compounds continues being developed by researchers. Some of them are the synthesis of acridine polycyclic compounds, i.e. 8,13-diethyl-6-methylquino[4,3,2-kl]acridinium iodide and 3,11-difluoro-6,8,13-trimethyl-8H-quino[4,3,2-kl]acridinium methosulfate (Missailidis *et al.,* 2002; Leonetti, 2004). The synthesis of the acrylic polycyclic derivative was intended to increase the antitumor activity and the solubility of the compound (Missailidis *et al.,* 2002; Leonetti, 2004). Efforts to obtain a more active antitumor through the derivatives of acridine compounds were continued by researchers through the synthesis of more polar and complex compounds using the alkylation method of polycyclic acridine compounds (Cookson *et al.,* 2005). The development of antitumor compounds from polycyclic acridine has been carried out (Cheng *et al.,* 2008). It is a salt compound of 8,13-dimethylquino[4,3,2-kl]acridinium and has an antitumor activity (IC_{50}) around 0.21 to 2.00 μM. The salt compound which has the highest activity is derivatives of 8,13-dimethylquino[4,3,2-kl]acridinium which is bound up both with anionic iodine and an ester functional group on C2 atom of such cyclic compound ring. Antitumor activity of salt derivatives 8,13-dimethylquino[4,3,2-kl]acridinium compound is still low when it is compared with antitumor compounds that have been circulating in the market (Cheng *et al.,* 2008). Based on the results of the research above, the efforts to develop antitumor compounds from other compounds have also been developed recently, such as o-isoselenazolon, and gallium-pyridine complexes known as metal-based drugs with a very high anticancer activity (Schmitt & Dou, 2013; Florea & Büsselberg, 2011; Luo *et al.,* 2012). However, the development of an anticancer compound from heavy metals causes many metabolic risks to the human body. Other studies on anticancer and antitumor have also been done by many researchers (Miladiyah *et al.,* 2016; Hosny *et al.,* 2012; Alam *et al.,* 2016; Reddy *et al.,* 2012; Bladt *et al.,* 2013; Heliawati *et al.,* 2015; Noolvi and Patel, 2013; Deep *et al.,* 2016; Shelton *et al.,* 2016; Tripodi *et al.,* 2012; Su *et al.,* 2011). They consecutively isolated and modified the chemical structures on the following compounds: (1) derivatives of benzoylphenylurea; (2) derivatives of *N*-benzoyl cephalexin; (3) derivatives of benzoyl paracetamol mercaptotriazoles; (4) derivatives of coumarin and quinolinyl; (5) sesqui-terpenecoumarin; (6) derivatives of tri-terpenoide saponin; (7) extracts of *Acalyphaindica leaf*; (8) derivatives of polyketide; (9) extracts of *Scaevolaspinescens*; (10) extracts from the *Coryphautan Lamk*; (11) derivatives of polyketide; (12) derivatives of 2,3,7-trisubstituted quinazoline; (13) derivatives of 2-azetidinone; (14) derivatives of glutathione; (15) derivatives of nucleoside and nucleotide; (16) derivatives of 1,4-diaryl-2-azetidinones; and (17) xanthone derivative compounds (Miladiyah *et al.,* 2016; Hosny *et al.,* 2012; Alam *et al.,* 2016; Reddy at al., 2012; Bladt *et al.,* 2013; Heliawati *et al.,* 2015; Noolvi & Patel, 2013; Deep *et al.,* 2016; Shelton *et al.,* 2016; Tripodi *et al.,* 2012; Su *et al.,* 2011). The antitumor activities of all compounds afore mentioned before are still low when they are compared with antitumor compounds that have been circulating in the market. All compounds which were isolated and modified generally have a functional group of primary amine ($-NH_2$). Based on the results of the research above, to design the structure of antitumor or anticancer molecules, it is necessary to make a model of anticancer molecules whose structures are cyclic compounds and have functional groups of amine ($-NH_2$). In this study it was attempted to synthesize quinoacridinium derivative compounds that have an amine functional group, so that they are antitumor compounds that meet this criterion.

Based on the explanation above, the effort to find an antitumor compound from the 8,13-dimethylquino[4,3,2-kl]acridinium which has a functional group $-NH_2$ is still very potential to be a candidate for antitumor drugs which are expected to have activity high and friendly to the body. Efforts to develop an antitumor drug from 8,13-dimethylquino[4,3,2-kl]acridinium derivatives need to be done through a computational chemistry approach with a Quantitative Structure-Activity Relationship (QSAR) analysis to obtain more active and body-friendly compounds. The QSAR analysis is one of the latest methods in the phases of developing new drugs. The results of QSAR analysis are generally used as a guide to design new drugs theoretically. In this study, the results of QSAR analysis are used as guidance in designing compounds of 8,13-dimethylquino[4,3,2-kl]acridinium derivatives that are potentially to be antitumor and have never been previously synthesized. The QSAR analysis approach as an effort to design drug compounds is very important because it minimizes the use of chemicals and energy. It also saves time because it can avoid trial and error experiments in laboratory.

However, it can still provide a relatively high level of confidence (Hadanu and Syamsudin, 2013). The QSAR analysis aims to find an empirically consistent relationship between the molecular properties and the biological activity of a series of homologous structural compounds of the drug. The QSAR study began to grow rapidly after1960. It was pioneered by Corwin Hansch who connected chemical structures with drug biology activities through common chemical-physical properties such as fat solubility, ionization degree, and molecular size. Later on in the last few decades, it was developed more intensively into a quantitative relationship between biological activity and various chemical-physical parameters such as net atomic charge, E_{LUMO}-E_{HOMO}, solubility in fat (polarisabilities), solubility in water and alcohol (Log P), molecular size, hydrophobic parameters, electronics and sterics in a series of molecules (Hadanu and Syamsudin, 2013). The relationship between physical as well as chemical properties and biological activity is proposed by (Ferguson *et al.,* 1997) with an equation that can be used to relate some activity data with the following parameters:

Log BR = f(P_1, P_2, P_3)……(**1**)

BR (Biological Response) is a biological activity or biological response as an algebraic function of 3 parameters P_1, P_2, and P_3 which is the nature of the structure under investigation. The development of QSAR analysis in the next period uses the net charge of the atom as an estimator and expressed by:

$$\text{Log BR} = \sum_i P_i q_i + C \quad \text{……(2)}$$

P_i is the fitting parameter for i^{th} atom, and q^i is the net charge of the atoms and other parameters for the i^{th} atom and C is constant. In the development of subsequent research, QSAR study is very helpful in the search for new drugs with greater activity, higher selectivity, toxicity or minor side effects, and greater comfort. In addition, using the QSAR equation model can save more money because to get a new drug with high activity, the experimental factor can be minimized as much as possible (Hadanu *et al.,* 2015).

Some attempts at cancer treatment have been performed in various ways such as surgery, radiation, anticancer drug treatment or chemotherapy. However, these efforts have not achieved satisfying results; even the effects of surgical failure can cause cancer to spread to other parts of the body with severe conditions (Nugraha *et al.,* 2018). This encourages the development of new medicine from 8,13-dimethylquino[4,3,2-kl]acridinium compound which is more active, friendly to the body, and expectedly to have a good therapeutic effect.

MATERIAL AND METHODS

The materials used in this study were quinoacridinium derivative compounds that have been synthesized by Cheng *et al.,* (2008). Inhibition Concentration (IC_{50}) was used as the dependent variable (Table I and II) (Cheng *et al.,* 2008).

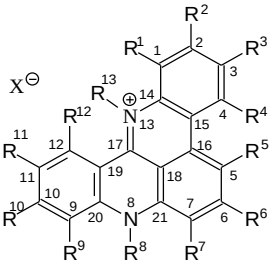
Instrumentation

In this study, the tools used for QSAR test were computer hardware devices namely a Sony Vaio Laptop with Intel® Dual Core Processor 2.20 GHz; 1 GHz RAM, and HDD 250 GB. Meanwhile, the software used in this study is HyperChem 8.0 for Windows for optimization purposes of 3D structure and geometry optimization of the chemical structure of tested compounds (compounds 1-11), external test compounds (compounds 12-15) and the structure of quinoacridinium derivative compounds (compound 16-43). For statistical analysis to obtain the QSAR equation, SPSS 19.0 for Windows was used.

Calculating the descriptors

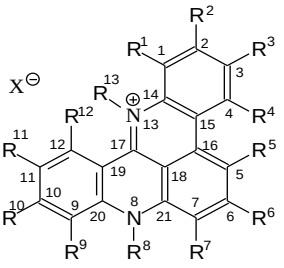
Internal fitting compounds (Table I), external fitting compounds (Table II), and modeling compounds (Table V) were constructed respectively in three-dimensional (3D) structures with the HyperChem 8.0 for Windows programming package. Furthermore, the geometric structures of all fitting compounds and model compounds were optimized to obtain more stable structural conformation using the semi-empirical PM3 method. This method is chosen because semi-empirical methods can be performed descriptor calculations quickly and accurately. The semi-empirical method is faster than the ab-initio method although it is less accurate and the semi-empirical method is more accurate than the AM1 method even though it is slower than the AM1 method. In addition, semi-empirical methods are methods that use experimental and theoretical data sets. When viewed with the molecular structure used, semi-empirical methods are suitable, because the quinoacridinium molecule have a medium molecular weight and functional groups -NH_2, -NHR, and -NR_2.

Table I. Chemical structure and activity data of antitumor compounds of quinoacridinium derivatives obtained from Cheng *et al.,* (2008)



Compounds	R^2	R^3	R^6	R^8	R^{10}	R^{11}	R^{13}	X^-	IC_{50} (μM)	Log IC_{50}
1	H	H	CH_3	C_2H_5	H	H	C_2H_5	I^-	2.00	0.30
2	H	CH_3	CH_3	CH_3	H	CH_3	CH_3	$H_3COSO_3^-$	0.25	-0.60
3	H	H	CH_3	CH_3	H	H	CH_3	$H_3COSO_3^-$	0.74	-0.13
4	H	H	H	CH_3	H	H	CH_3	I^-	1.55	0.19
5	$NHCOCH_3$	H	H	CH_3	H	H	CH_3	I^-	0.38	-0.42
6	$NHCOCF_3$	H	H	CH_3	H	H	CH_3	I^-	0.31	-0.51
7	$NHCO(CH_2)_4CO_2CH_3$	H	H	CH_3	H	H	CH_3	I^-	0.21	-0.68
8	$N(CH_3)SO_2C_6H_4$-*p*-F	H	H	CH_3	H	H	CH_3	I^-	0.73	-0.14
9	H	$NHCOCH_3$	H	CH_3	H	H	CH_3	I^-	0.41	-0.39
10	H	Cl	OCH_3	CH_3	H	H	CH_3	I^-	0.28	-0.55
11	H	$CH=CHCON(CH_2CH_2)_2O$	H	CH_3	H	H	CH_3	I^-	0.37	-0.43

Table II. The chemical structure of external standard compounds of quinoacridinium derivatives from Cheng *et al.,* (2008).



Compounds	R^2	R^3	R^6	R^8	R^{10}	R^{11}	R^{13}	X^-	IC_{50} (μM)	Log IC_{50}
12	H	F	CH_3	CH_3	H	F	CH_3	$H_3COSO_3^-$	0.33	-0.48
13	NH_2	H	H	CH_3	H	H	CH_3	I^-	1.86	0.27
14	$NHCOC(CH_3)_3$	H	H	CH_3	H	H	CH_3	I^-	0.23	-0.64
15	H	Cl	H	CH_3	H	H	CH_3	I^-	0.26	-0.59

The structural optimization was performed by using Polak-Ribiere algorithm optimization method with RMS value = 0.001 kcal/(Å.mol), which was recorded through the single point menu. Via the data fromthe single point menu, the electronic parameters such as the net atomic charge, the dipole moment (μ), the polarization (α), and the Log P were obtained. Meanwhile, the E_{LUMO} and the E_{HOMO} were obtained from compute and orbital menus which were presented (Table III and IV). The selection of descriptor type was adjusted to the type of descriptor used by Motta *et al.,* (2006) in conducting QSAR analysis. The structure of the quinoacridinium derivative compounds as the study material was calculated by involving an ion counter of salt.

QSAR equation analysis by using a linear regression method

The dependent variable in this study was the antitumor activity with IC_{50}value based on experiment (Table I), while the independent

Table III. Log IC_{50} experiments and Log IC_{50} calculated of external test compounds

Compounds	Log IC_{50} experiments	Log IC_{50} calculated
12	-0.48	-0.359
13	0.27	0.166
14	-0.64	-0.602
15	-0.59	-0.589

Table IV. Descriptors/independent variables used for QSAR analysis of antitumor compounds of quinoacridinium derivatives calculated by the semi-empirical PM3 method

Comp.	Atomic net charges (Coulomb)												
Number	qC1	qC2	qC3	qC4	qC5	qC6	qC7	qN8	qC9	qC10	qC11	qC12	qN13
1	-0.075	-0.060	-0.077	-0.083	-0.160	0.033	-0.193	0.200	-0.179	-0.015	-0.112	-0.039	0.200
2	-0.056	-0.072	-0.038	-0.095	-0.153	0.023	-0.187	0.188	-0.165	-0.034	-0.062	-0.054	0.523
3	-0.069	-0.067	-0.073	-0.090	-0.155	0.024	-0.189	0.188	-0.182	-0.025	-0.114	-0.073	0.491
4	-0.019	-0.077	-0.064	-0.098	-0.145	-0.015	-0.179	0.170	-0.170	-0.030	-0.124	-0.046	0.573
5	-0.139	-0.014	-0.126	-0.054	-0.153	0.001	-0.187	0.194	-0.175	-0.017	-0.115	-0.042	0.458
6	-0.052	-0.058	-0.104	-0.066	-0.146	-0.010	-0.179	0.175	-0.170	-0.026	-0.124	-0.044	0.558
7	-0.152	-0.015	-0.131	-0.050	-0.144	-0.017	-0.178	0.187	-0.173	-0.031	-0.115	-0.057	0.420
8	-0.207	0.087	-0.138	-0.042	-0.156	0.002	-0.187	0.189	-0.176	-0.017	-0.115	-0.029	0.453
9	-0.065	-0.095	-0.043	-0.131	-0.138	-0.022	-0.171	0.187	-0.170	-0.033	-0.111	-0.060	0.432
10	-0.003	-0.081	-0.099	-0.101	-0.191	0.178	-0.264	0.171	-0.168	-0.030	-0.122	-0.045	0.562
11	-0.086	-0.074	-0.038	-0.064	-0.139	-0.020	-0.174	0.189	-0.172	-0.032	-0.111	-0.060	0.416

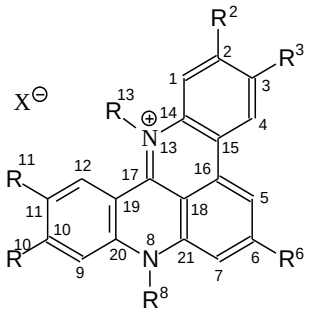
Comp.	Atomic net charges (Coulomb)								μ	E_{LUMO}	E_{HOMO}	α	Log P
Number	qC14	qC15	qC16	qC17	qC18	qC19	qC20	qC21	(Debye)	(ev)	(ev)	(Å^3)	
1	-0.126	-0.052	0.067	0.073	-0.145	-0.145	-0.019	0.012	20.946	-2.563	-4.236	46.27	2.12
2	-0.161	-0.025	0.052	0.017	-0.127	-0.120	-0.043	0.003	18.287	-2.291	-8.730	45.49	0.94
3	-0.154	-0.040	0.057	0.037	-0.136	-0.141	-0.031	0.005	16.840	-2.252	-8.784	41.82	0.63
4	-0.124	-0.033	0.056	0.000	-0.113	-0.119	-0.025	-0.010	13.352	-2.078	-5.712	40.77	1.28
5	-0.115	-0.079	0.070	0.049	-0.135	-0.139	-0.022	-0.003	15.507	-2.541	-4.590	45.88	-0.61
6	-0.098	-0.049	0.060	0.018	-0.119	-0.124	-0.024	-0.008	14.899	-2.311	-5.323	45.60	0.50
7	-0.094	-0.065	0.048	-0.005	-0.100	-0.112	-0.029	-0.015	12.513	-2.478	-5.327	55.77	0.00
8	-0.083	-0.084	0.077	0.074	-0.134	-0.139	-0.022	0.001	15.889	-2.456	-4.310	54.66	-0.56
9	-0.149	-0.008	0.028	-0.014	-0.091	-0.107	-0.031	-0.017	14.072	-2.604	-5.459	45.88	-0.61
10	-0.121	-0.028	0.087	0.016	-0.150	-0.117	-0.028	0.031	15.096	-2.151	-5.098	45.17	0.06
11	-0.127	-0.033	0.035	-0.007	-0.094	-0.108	-0.030	-0.017	15.213	-2.558	-5.367	54.72	0.36

variables used were net atomic charges, dipole moment (μ), E_{LUMO}, E_{HOMO}, polarizability (α), and Log P (Tables III and IV). All variables were analyzed using enter method through MLR to find out which sequence of independent variables influenced the antitumor activity value of quinoacridinium derivative compounds. The result generated QSAR equations as well as statistical parameters such as r, r^2, SE, and PRESS values. In addition to the statistical parameters, the calculation result also obtained the constant value and the coefficient value of each independent variable involved in the equation result. The obtained coefficient value was used to calculate the theoretical antitumor activity (IC_{50} theoretical value) toward quinoacridinium derivative compounds. Furthermore, after finding out the square difference betweenthe IC_{50} experimental value andthe IC_{50} theoretical value, the PRESS value can be calculated to know the quality and prediction ability of the best equation of the QSAR model.

Design of new antitumor molecules

The design of new antitumor drug molecules in this study was aimed to discover novel

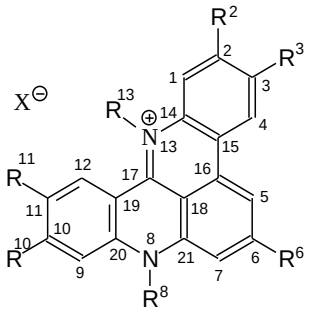
Table VI. The New designed quinoacridinium derivatives as antitumor compounds



Compounds	Substituents				
	R²	**R³**	**R⁶**	**R⁸**	**R¹⁰**
16	H	Cl	CH_3	CH_3	H
17	$NHCH_3$	H	H	CH_3	H
18	$N(CH_3)_2$	H	H	CH_3	H
19	$NHCOC_4H_9$	H	H	CH_3	H
20	$NHCOC_{11}H_{23}$	H	H	CH_3	H
21	$NHCO_2C_2H_5$	H	H	CH_3	H
22	NHCOPh	H	H	CH_3	H
23	H	H	OCH_3	CH_3	Cl
24	H	H	OCH_3	CH_3	$CH{=}CHCON(CH_2CH_2)_2O$
25	H	H	OCH_3	CH_3	$CH{=}CHCO_2CH_3$
26	H	H	$(CH2)_3OCOCH_3$	CH_3	$(CH2)_3OCOCH_3$
27	H	Cl	$CH{=}CHCON(CH_2CH_2)_2O$	CH_3	H
28	H	$CH{=}CHCON(CH_2CH_2)_2O$	OCH_3	CH_3	H
29	H	$CH{=}CHCON(CH_2CH_2)_2O$	$(CH_2)_3OCOCH_3$	CH_3	H
30	H	$(CH_2)_3OCOCH_3$	$(CH_2)_3OCOCH_3$	CH_3	H
31	H	Cl	CH_3	CH_3	H
32	H	Cl	CH_3	C_2H_5	H
33	$N(C_2H_5)_2$	H	H	CH_3	H
34	$N(C_2H_5)_2$	H	H	C_2H_5	H
35	$NHCOC_3H_7$	H	H	C_3H_7	H
36	$NHCOC_2H_5$	H	H	C_2H_5	H
37	$NHCOC_{11}H_{23}$	H	H	C_2H_5	H
38	NHCOPh	H	H	C_2H_5	H
39	H	H	$(CH2)_3OCOCH_3$	C_2H_5	$(CH2)_3OCOCH_3$
40	H	Cl	$CH{=}CHCON(CH_2CH_2)_2O$	C_2H_5	H
41	H	$CH{=}CHCON(CH_2CH_2)_2O$	OC_2H_5	C_2H_5	H
42	H	$CH{=}CHCON(CH_2CH_2)_2O$	$(CH_2)_3OCOCH_3$	C_2H_5	H
43	H	$(CH_2)_3OCOC_2H_5$	$(CH_2)_3OCO\ C_2H_5$	C_2H_5	H

compounds of quinoacridinium derivatives which have higher antitumor activity than previously synthesized compounds. The molecular design was performed by varying the type and position of substituent or functional group positions in the main framework structure of quinoacridinium derivative compounds. The substituent position was focused on the active center area by considering the feasibility of synthesis in the laboratory. The substituent or functional group is the dominantly responsible atoms of the antitumor activity of the quinoacridinium derivatives. After finding out the quinoacridinium molecular sequence series, the next step is calculating the descriptor of the new compound of modeling design (Table VI and VII) by using the semi-empirical method of PM3 using HyperChem 8.0 for Windows. Based on the best QSAR equations, we can calculate the theoretical antitumor activity of the design compounds (Table VI and VII).

Table VII. Predicted Log IC_{50} calculated using the best QSAR model



Compounds	Substituents			Predicted Log IC_{50}	Predicted IC_{50}
	R^{11}	R^{13}	X^-		
16	Cl	CH_3	$H_3COSO_3^-$	-5.692	0.000002
17	H	CH_3	I^-	-0.111	0.775149
18	H	CH_3	I^-	0.080	1.201752
19	H	CH_3	I^-	-0.901	0.125555
20	H	CH_3	I^-	-0.760	0.173970
21	H	CH_3	I^-	-0.315	0.484069
22	H	CH_3	I^-	-0.894	0.127722
23	H	CH_3	I^-	-1.036	0.091970
24	H	CH_3	I^-	-3.928	0.000118
25	H	CH_3	I^-	-3.400	0.000398
26	H	CH_3	I^-	-1.743	0.018086
27	H	CH_3	I^-	-1.254	0.055728
28	H	CH_3	I^-	-0.910	0.122898
29	H	CH_3	I^-	-0.040	0.912860
30	H	CH_3	I^-	-1.460	0.034668
31	Cl	C_2H_5	$H_5C_2OSO_3^-$	-5.414	0.000004
32	Cl	C_2H_5	$H_5C_2OSO_3^-$	-1.745	0.017990
33	H	C_2H_5	I^-	0.522	3.327068
34	H	C_2H_5	I^-	0.955	9.013149
35	H	C_3H_7	I^-	-0.329	0.468765
36	H	C_2H_5	I^-	0.847	7.031945
37	H	C_2H_5	I^-	0.001	1.001424
38	H	C_2H_5	I^-	-0.113	0.770079
39	H	C_2H_5	I^-	-1.391	0.040617
40	H	C_2H_5	I^-	-0.805	0.156537
41	H	C_2H_5	I^-	2.139	137.657528
42	H	C_2H_5	I^-	-0.699	0.200199
43	H	C_2H_5	I^-	0.093	1.237455

RESULT AND DISCUSSION

The stages of quantitative relationship analysis of structures carried out in this study were (a) determining series of quinoacridinium compounds which had IC_{50} values based on experiment in the laboratory Cheng *et al.,* (2008); (b) optimizing the basic structural framework of the most stable quinoacridinium derivative as the initial compound in the process of optimizing the test compound for further analysis; (c) determining descriptor (independent variable); (d) calculating descriptor through optimization structure of tested compounds (optimization of derivative structure of tested compound) (Table I and II); (e) performing correlation analysis between variables through bivariate correlation method; (f) performing multilinear regression analysis to obtain the model of QSAR equation; (g) determining the best QSAR equation model (Hadanu and Syamsudin, 2013; Hadanu *et al.,* 2015) and (h) designing a new compound of quinoacridinium derivatives based on the best QSAR equation model.

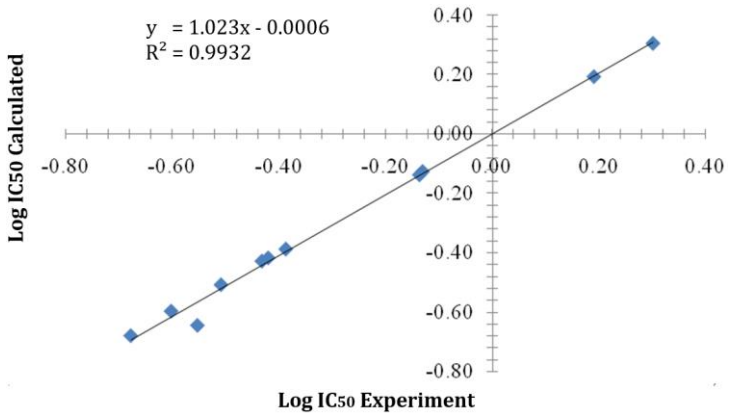


Figure 1. Correlation between Log IC_{50} calculated from the internal test compound and Log IC_{50} experiment

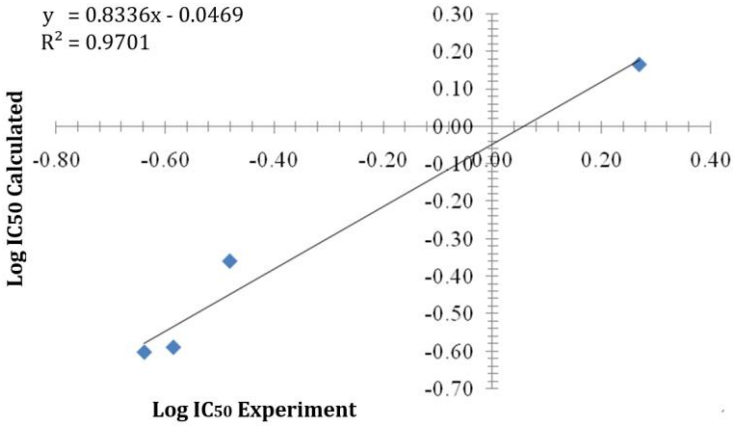


Figure 2. Correlation between Log IC_{50} of the external test compound and Log IC_{50} experiment

The quinoacridinium derivative compounds as the materials in this study has the following requirements: (1) the basic framework structure of the homologous compound should be possessed by all fittings compounds, external test compounds, and the modeled compound; (2) the fitting compound; and (3) the external test compound should have IC_{50} value which is experimented in a laboratory. The optimization of the structures of all fitting compounds, external test compounds, and the modeled compounds was carried out by the same method to obtain the most stable structural compound with the lowest energy profile. When all of compound structures are at the lowest profile energy, they are in the most stable condition. In that condition, the descriptor (independent variable) required in the next stage of QSAR analysis can be obtained.

By bivariate correlation analysis, it is clear that the variables of atomic net charge, dipole moment (μ), $E_{HOMO-ELUMO}$, polarisabilities (α), and Log P showed a very close correlation. This is indicated by the absolute value of the correlation which is closer to 1 or -1. The evidence of such close correlation can be seen in some of the relationships between descriptors that have a high correlation, for example: the correlation between variables QC1-QC2 (-0.893), qC6-qC5 (-0.898), QC2-qC4 (0.774), qC7-qC5 (0.994), qC5-QC10 (-0.754), qC6-qC7 (-0.920), QC1-qC15 (0.823), QC2-qC15 (-0.865), QC3-qC14 (-0.825), QC3-qC15 (0.831), qC4-qC14 (0.773), qC4-qC15 (-0.897), qN8-qN13 (-0.837), qC5-qC16 (-0.820), qC5-qC17 (-0.913), qC5-qC18 (0.961), qC5-qC19 (0.910), qC6-qC17 (0.724), qC6-qC18 (-0.863), qC6-qC19 (-0.766), qC7-qC16 (-0.791), qC7-qC17 (-0.890),

qC7-qC18 (0.963), qC7-qC19 (0.906), QC1-α (-0.759), qC5-qC21 (-0.961), qC5-μ (-0.764), qC6-qC21 (0.968), qC6-μ (0.903), qC7- qC21 (-0.967), qC7-μ (-0.778), and qN8-E_{LUMO} (-0.768). The negative value of such correlation does not indicate whether the substituent influence on antitumor activity is strong or not, but it only shows the direction of the effect. A negative value indicates correlation of a negative association, which means that the effect of one variable is inversely proportional to other variables. The relationship between the smallest independent variables is the qN8-qN13 (0.001) variable, which indicates that the qN8 variable and qN13 have a weaker relationship than other independent variables. Meanwhile, the relationship between the largest independent variables is variable qC7-qC5 (0.994) which shows that between variables qC7 and qC5, there is stronger relationship than other independent variables. Based on the bivariate correlation analysis, it can be concluded that between the independent variable and dependent variable, there is a significant relationship. Thus, MLR analysis can be performed on a group of the data in this research.

The MLR analysis on a group of independent variables as descriptor and dependent variable or antitumor activity (Log IC_{50}) produced a model of QSAR equation which is the best model of QSAR equation. The best QSAR model built using MLR method is represented by the following equation:

$$\text{Log } IC_{50} = -13.010 + 15.338(qC3) - 4.31(qC4) - 155.308(qC9) + 33.626(qC11) + 26.626(qC12) + 24.631(qC14) - 0.228(\mu) - 0.621(E_{LUMO}) - 0.066(\alpha) + 0.233(\text{Log P}) \quad (3)$$

The statistical significance of the best QSAR models has coefficient correlation n=11, (r)=1.00, (r^2)=1.00, SE=0, and PRESS = 0.003.

To test the accuracy of the model of the obtained QSAR equation, it is necessary to calculate the IC_{50} prediction value of the internal test compound (Table I). The proof of the accuracy of the model of QSAR equation can be seen on the graph of Log IC_{50} value of prediction with an IC_{50} value of the experimental internal test (compounds **1-11**) (Figure 1). The graph shows the relationship between the Log IC_{50} prediction value of the internal test compound and Log IC_{50} experiment with obtained value r^2 = 0.993. The value of r^2 is close to 1, which indicates that the internal test model of QSAR equation has a very high level of trust.

To test the validity of the model of QSAR equation, a validity test has been performed by using external test compounds (compounds **12-15**). The external test compound is a quinoacridinium compound derivative which has been known as IC_{50} experimental value, but it is not included in the calculation process in determining QSAR equation model. This is intended to validate the QSAR model more accurately since it is validated with internal test compounds and external test compounds. The IC_{50} value of external compound test (Table III).

The graphic of correlation between Log IC_{50} calculated and Log IC_{50} experiments value has r^2=0.9701 (Figure 2). It shows that the QSAR equation model obtained in this research is the best QSAR equation for determining the IC_{50} value of compound derivative quinoacridinium. The high value of r^2 (close to 1) displayed in the correlation graph between Log IC_{50} calculated from the external test compound and the Log IC_{50} value of the experiments reinforces the QSAR model as an equation with high validity.

Based on the value of r^2 = 0.9701 obtained from the correlation between Log IC_{50} of calculated from external test compound and Log IC_{50} experiment, it proves that the relationship between calculated IC_{50} value of external test compound and Log IC_{50} value of experiment is very strong. Thus, it can be concluded that the model of QSAR equation obtained by using MLR analysis is very significant to determine the value of Log IC_{50} compounds models of quinoacridinium derivatives.

Design of new antitumor quinoacridinium derivative compounds

The molecular design of the quinoacridinium derivative remains concerned with the active side of the homologous and atomic frameworks or the functional groups bound to the basic framework structure of the compound. The differences of atoms or functional groups bound to the basic frameworks of homologous compounds of quinoacridinium derivatives may cause different charges of atoms and differences in physical and chemical properties. In addition, it also causes differences in antitumor activity of such compounds (Hadanu *et al.,* 2015). The obvious that compounds which have different structures can produce different antitumor activity (Table I-V). Based on this fact, it can be concluded that different structures have electronic properties and molecular properties (different net charge of atoms and other descriptors). Compounds that have

Table V. Descriptors/independent of external standard for QSAR analysis of antitumor compounds of quinoacridinium derivatives calculated by the semi-empirical PM3 method

Comp. Number	Atomic net charges (Coulomb)												
	qC1	qC2	qC3	qC4	qC5	qC6	qC7	qN8	qC9	qC10	qC11	qC12	qN13
12	-0.032	-0.091	0.103	-0.136	-0.147	0.024	-0.182	0.188	-0.152	-0.062	0.059	-0.113	0.527
13	-0.083	-0.043	-0.112	-0.060	-0.152	-0.011	-0.185	0.171	-0.170	-0.030	-0.125	-0.045	0.565
14	-0.154	-0.011	-0.132	-0.050	-0.145	-0.017	-0.179	0.187	-0.173	-0.032	-0.115	-0.057	0.418
15	-0.002	-0.083	-0.096	-0.105	-0.142	-0.014	-0.176	0.172	-0.169	-0.029	-0.123	-0.045	0.577

Comp. Number	Atomic net charges (Coulomb)								μ (Debye)	E_{LUMO} (ev)	E_{HOMO} (ev)	α (Å³)	Log P
	qC14	qC15	qC16	qC17	qC18	qC19	qC20	qC21					
12	-0.184	-0.006	0.047	0.013	-0.126	-0.104	-0.045	0.001	17.825	-2.485	-8.947	41.64	-0.57
13	-0.083	-0.076	0.072	0.011	-0.122	-0.121	-0.024	-0.007	12.141	-2.084	-5.097	42.12	-0.44
14	-0.093	-0.067	0.049	-0.005	-0.100	-0.111	-0.029	-0.015	12.211	-2.446	-5.288	51.38	1.24
15	-0.128	-0.020	0.053	0.005	-0.112	-0.120	-0.025	-0.010	13.966	-2.229	-5.155	42.70	1.05

different electronic and molecular properties absolutely produce different antitumor activity.

Based on the above explanation and QSAR model equations (3), atomic charge values of qC3, qC4, qC9, qC11, qC12, qC14, μ, E_{LUMO}, α, and Log P for respective designed compounds are variables influencing the value of antitumor activity (IC_{50}) of quinoacridinium derivatives. In designing the molecule, it is necessary to consider the attachment of the atom or functional groups to the main framework of quinoacridinium derivatives which can cause the change of atomic charge value of qC3, qC4, qC9, qC11, qC12, qC14, μ, E_{LUMO}, α, and Log P, so that it can cause different predictions of IC_{50} value (Table V). The calculation of atomic charges and other descriptors obtained from each of the new compounds is incorporated into the QSAR model of equation (3) in order to obtain theoretical IC_{50} values of the novel compound derived from the modeling design. Compounds that have a small IC_{50} value are antitumor compounds that have the highest antitumor activity. The smaller IC_{50} value of a quinoacridinium derivative compound is, the higher the chances of the compound as an antitumor drug is and it may be proposed for synthesis in the laboratory.

The calculated IC_{50}value of new molecules from the quinoacridinium derivatives design (Table VI and VII). Some compounds from quinoacridinium (Table VI and VII) derivative design are proposed for synthesis, in which they have an IC_{50} value smaller than IC_{50} of fifteen quinoacridinium derivatives (Tables I and II). Thus the quinoacridinium derivatives compounds derived from the recommended modeling design are: compounds 16 (IC_{50}=0.000002μM), 19 (IC_{50}=0.125555μM), 20 (IC_{50}=0.173970μM), 22 (IC_{50}=0.127722μM), 23 (IC_{50}=0.091970μM) 24 (IC_{50}=0.000118μM), 25 (IC_{50}=0.000398μM), 26 (IC_{50}=0.018086μM), 27 (IC_{50}=0.055728μM) 28 (IC_{50}=0.122898μM), 30 (IC_{50}=0.034668μM) 31 (IC_{50}=0.000004μM), 32 (IC_{50}=0.017990μM), 39 (IC_{50}=0.040617 μM), and 40 (IC_{50}=0.156537 μM). Theoretically, they can be proposed for synthesis in the laboratory. Certainly, in the synthesis process in the laboratory, it is prioritized to synthesize compounds that have smaller IC_{50} values and compounds that have the easy synthesis pathways in the laboratory, as well as the availability of chemicals (Hadanu and Syamsudin, 2013; Hadanu *et al.,* 2015). The theoretical IC_{50} value of the quinoacridinium derivatives is less than the IC_{50} value determined by the National Cancer Institute (NCI) for the compounds extracted from the natural material. According to the National Cancer Institute (NCI), an extract is considered to have an active anticancer activity if its IC_{50} value is <30 μg/mL, moderate active anticancer activity if its IC_{50}value is ≥ 30 μg/mL, IC_{50}<100 μg/mL, and inactive anticancer activity if its IC_{50} value is >100 μg/mL.[2]

Based on the structure model of the QSAR analysis recommended for synthesis in the laboratory, it can be concluded that the quinoacridinium derivatives which have high and potential antitumor activities are quinoacridinium derivatives which have functional groups as follows: -Cl is bound to C3 and C11 atoms; the -CH_3 function group is bound to C6, C8, and C13 atoms, anion $H_3COSO_3^-$;-OCH_3 functional group is bound to C6 atom, anion iodide (I^-); functional group of -$CH{=}CHCON(CH_2CH_2)_2O$ is bound to C6 and C10 atoms; the functional group of-$(CH_2)_3OCOCH_3$ is bound to C3, C6, and C10;–C_2H_5 functional group is

bound to C13 atom, anion $H_5C_2OSO_3^-$. Those all are bound to the main framework of quinoacridinium compounds. Nearly all compounds modeled according to Lipinski's Rule are quinoacridinium derivative compounds having fewer than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms), less than 10 hydrogen bond acceptors (nitrogen or oxygen atoms), and having an octanol-water partition coefficient (Log P) is less than 5.

CONCLUSION

Based on the results and discussion, it can be concluded that the best model of QSAR equation which shows the relationship between antitumor activity and latent variables to 11 compounds of quinoacridinium derivatives is: Log IC_{50} = -13.010 + 15.338(qC3) - 4.31(qC4) - 155.308(qC9) + 33.626(qC11) + 26.626(qC12) + 24.631(qC14) - 0.228(μ) - 0.621(E_{LUMO}) - 0.066(α) + 0.233(Log P); n = 11, (r) = 1.00, (r^2) = 1.00, SE = 0, and PRESS = 0.003. A good correlation was observed between the experimental and predicted values of the anticancer activity (R=0.993), which indicated the validity and quality of the QSAR model developed in this work. Therefore, we conclude that the descriptors studied (e.g., atomic charge values qC3, qC4, qC9, qC11, qC12, qC14, μ, E_{LUMO}, α, and Log P), which influenced the structural features of the quino-acridinium, can be used in tandem with other topological descriptors for the development of predictive QSAR models. The design of quinoacridinium derivative compounds which have high theoretical antitumor activity and are recommended for synthesizing in the laboratory are 16 of 28 compounds. Such designed compounds are 16, 19, 20, 22 to 28, 30, 32, 39, and 40.

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