DESIGN OF HYDROXY XANTHONES DERIVATIVES AS ANTICANCER USING QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP

EMMY YUANITA*, HARNO DWI PRANOWO, JUMINA JUMINA, MUSTOFA MUSTOFA

Department of Chemistry, Laboratory of Organic Chemistry, Universitas Gadjah Mada, Yogyakarta, Indonesia.
Email: emmy.yuanita@mail.ugm.ac.id

ABSTRACT

Objective: The objective of the research is to design a new hydroxy xanthone derivative has anticancer activity using quantitative structure-activity relationship (QSAR).

Methods: The QSAR designed new compounds were calculated by parameterized model 3 methods and analysis of multi-linear regression (MLR).

Result: The result showed that the best model as follows:
$LogIC_{50}$ = −9.132 qC1 + 28.853 qC5 + 2.456 qC6 − 7.375 qC10 − 5.112 qC11 + 3.900
This result has appropriate some statistical parameters (n=24; PRESS=0.999; r^2=0.782; SEE=0. 235; R=0. 885; F_{cal}/F_{tab}=4.68).

Conclusion: This Model could be used to design of halogen-substituted hydroxy xanthone scaffold and predict their inhibitory concentration (IC_{50}) as anticancer in the range of 0.001 - 0.484 μM.

Keywords: Anticancer, Quantitative structure-activity relationship, Xanthone.

INTRODUCTION

Cancer is the main cause of death worldwide. In 2012, there were 8.2 million to 14.1 million cases of death all over the world. The highest rate of the death is caused by an inappropriate cancer treatment. So far, the treatment requires one or more interventions such as surgery, radiotherapy, and chemotherapy [1,2]. Chemotherapy is commonly used as the treatment options. However, the low selectivity and the high toxicity of anticancer drugs compromise the beneficial treatment effects of these agents [3-5]. Therefore, development of a new chemotherapeutic agent with high selectivity and low toxicity is important to be conducted.

Xanthones, were used in this study, comprise a large number of oxygenated heterocycles planar compounds which play an important role in medicinal chemistry. Their derivatives are widely distributed in various plants, and they have a variety of biological properties such as analgesic [6], anti-oxidant [7], anti-inflammatory [8], anti-allergic [9], anti-bacterial [10], anti-tuberculosis [11], anti-fungal [12], anti-viral [13], and also as anticancer such α-mangosteen and γ-mangosteen [14,15]. The simple structural scaffold and diverse pharmacological properties of xanthone derivatives have prompted many scientists to isolate these compounds from natural resources or synthesize them as novel drug candidates. Isolation method is not recommended because it gives a low yield of the isolated compound. Synthesis is one of the recommended ways to develop a new compound that has the best activity based on the understanding of structure modification by changing the substituents on the xanthone ring. However, this method has disadvantages over the time-consuming for "trial and error" and also cost during the synthesis.

One of the promising ways to develop a new therapeutic agent is to utilize the QSAR analysis into guiding the modification structure of the effective compounds. In the last decades, QSAR has been applied in many areas, particularly in the prediction of biological activities to save time and cost during the analysis. A QSAR equation is a mathematical equation related to the biological activity and wide variety of physical or chemical parameters. There were a lot of QSAR models mentioned in the literatures which have been successfully used for the screening

of compounds and their biological activity [16-19]. The pre-requisite for developing QSAR equations is the availability of a wide range of molecular structures and their complementary activities. Nowadays, there are some researchers conducting the computational studies on xanthones, and they believe that it is critically important.

A QSAR study conducted by Alam and Khan [20] showed the prediction for specific targets such as HeLa cell using multi-linear regression (MLR) and optimizing their structures by MM + molecular mechanics. Their study showed that five molecular descriptors - dielectric energy, group count (hydroxyl), LogP (the logarithm of the partition coefficient between n-octanol and water), shape index basic (order 3), and the solvent-accessible surface area - were significantly correlated with anticancer activity. The other QSAR model was parameterized model 3 (PM3) methods which being used to predict a series of xanthone derivatives as antimalarial compounds and showed that hydroxyl groups could influence their activity [21]. The QSAR model of a new series of xanthone derivatives against the oral human epidermoid carcinoma (KB) cancer cell was conducted by Suphavanich *et al.* [22]. They reported the combination of steric, electrostatic, hydrophobic and hydrogen-bond, which was calculated using 3D QSAR models, has satisfactory correlated to the test set activities. Practically, all of the QSAR models involved molecular descriptors. In this study, we focused on to find out the electronic descriptor which could affect the anticancer activity of xanthone derivatives.

In this study, a series of xanthone derivative compound using QSAR was carried out based on the data of the inhibitory concentration (IC_{50}, μM) of xanthone derivatives from literatures [23-25]. The aim of this work focuses on finding establish new model which has chosen from the first step of study by selecting method of calculation of nuclear magnetic resonance (NMR) properties each model austin model 1 (AM1), PM3, Hartree-Fock (HF) level of theory, and density functional theory (DFT) methods. Based on these the best QSAR models, new compounds with highly predicted anticancer activity were theoretically designed, and they are waiting for experimental verification.

METHODS

Hardware and software

This study used a PC with Intel® Core™ i3 CPU M 350 4.54 GHz; RAM 5.00 GB. The used programs were Gaussian® 09W [26], statistical SPSS® Release 17.0.0 [27].

Data set

The structures of xanthone derivative compounds and its anticancer activity were divided into two sets as listed in Table 1. Namely a training set (19 compounds) for generating QSAR models and a test set (5 compounds) for validating the quality of the models. The selected compound of the training set and test set is an important feature and key of any QSAR models. Hence, the treatment was taken in such a way by biological activities of all tests set compounds with the maximum and minimum range of biological activities of the training set and test set compounds. The maximum and minimum data of training and test set were compared with: (i) The maximum data of the log IC_{50} of test set which should be less than or equal to the maximum value of log IC_{50} of training set, (ii) the minimum data of the log IC_{50} of test set that should be higher or equal to the minimum value of log ic_{50} of the training set [28].

Computational validation and descriptor calculation

Xanthone compounds were the first modeled computationally using AM1, PM3, HF, and DFT to obtain the most suitable calculation method and using the Gaussian package to calculate their chemical shift (NMR properties). The model with the smallest difference (PRESS value) between calculated and experimental data for each method (AM1, PM3, HF, or DFT) was chosen as the statistics of the training and test sets for QSAR calculation.

The development of QSAR model

The QSAR model was generated by the MLR Backward method using the SPSS package. This method refers to the dependent variable ŷ (biological activity) with a number of independent variables xi (electronic descriptors) by using linear equations. Moreover, this regression method estimates the values of the regression coefficients by applying least square curve fitting method. The model was chosen for QSAR calculation based on some statistical parameters such as r^2, standard estimation of error (SEE), F-ratio between the variance of prediction and observation activity, and PRESS (predictive residual sum of square), where: PRESS = Σ (predicted value-observed value)^2 [29] in criteria $r^2 > 0.6$ [30]; SEE < 0.3 [31]; $F_{cal}/F_{tab} \geq 1$ [32].

The validation of QSAR model

The best-selected model obtained from the previous step was used to predict the Log IC_{50} of the test set. The model was validated by criteria $r^2_{prediction} > 0.5$ [33].

Design and activities prediction of the new compounds

The new designed and predicted xanthone derivative compounds based on the validated data with the best inhibitory activity and has lower IC_{50} value was chosen as a new candidate of the anticancer compound.

RESULT AND DISCUSSION

Validated method

The calculation of the chemical shift from each method (AM1, PM3, HF, and DFT) was compared with the experimental measurements to get the most suitable calculation method for modeling the series of xanthones derivatives with anticancer activity. The experimental measurement showed that the PM3 method gave the smallest difference (PRESS value) between calculated and experimental result. The correlation coefficient from each model was more than 0.99 (near 1) and listed in Table 2. Therefore, PM3 method has been selected as a calculation method for further modeling of anticancer activity of xanthones derivatives.

The selection method is important to improve the accuracy because the method of calculation giving smallest differences between calculated and experimental data validated method for the selection of methods of QSAR is also done in the design of new insecticide compounds have potent of organophosphate [34] with the results of AM1 method used for the analysis of advanced QSAR.

Generation and selection of QSAR model

Multiple linear regression analysis using SPSS version 17 for Windows has been performed to obtain the best model which correlates independent variables (descriptors) to a dependent variable (biological activity). QSAR analysis of this research was done to see the relationship between electronic variable against anticancer activity. Analysis of different from that done by previous researchers [10,11] that combines electronic and molecular variables. The use of electronic parameter because the electronic charge on ring xanthone can

Table 1: A series of xanthone derivatives

S. No	Compound	Log IC_{50}
1	1-hydroxy-9H-xanthen-9-one	1.635*
2	1,6-dihydroxy-9H-xanthen-9-one	1.607*
3	1,3,6-trihydroxy-9H-xanthen-9-one	1.662
4	1,3,7-trihydroxy-9H-xanthen-9-one	1.199
5	1,3,6,8-tetrahydroxy-9H-xanthen-9-one	0.963
6	9-oxo-9H-xanthene-1-yl-acetate	1.617
7	9-oxo-9H-xanthene-1,3,6-triyl triacetate	1.602
8	1- hydroxy-3-methoxy-9H-xanthen-9-one	1.617
9	1- hydroxy -3-(oxyran-2-yl methoxy) -9H-xanthen-9-one	1.15
10	1- hydroxy -3-(2-(piperidine-1-yl) ethoxy) -9H-xanthen-9-one	1.47
11	3-(2,3-di hydroxy Propoxy) -1- hydroxy -9H-xanthen-9-one	1.354*
12	1,3-di hydroxy-12H-benzo [b] xanthen-12-one	0.928
13	1,3,7-tri hydroxy -12H-benzo[b] xanthen-12-one	0.611
14	9,11-dihydroxy-12H-benzo[b] xanthen-12-one	0.838*
15	1,5,8-trihydroxy-3-methoxy-2,4-bis (3-methylbut-2-en-1-yl)-9H-xanthen-9-one	1.594
16	6,9-dihydroxy-3,3-dimethyl-8-(3-methylbut-2-en-1-yl) pyrano[2,3-c] xanthen-7 (3H)-one	1.47
17	3-(4-(dimethylamino) butoxy) -1-hydroxy-12H-benzo [b] xanthen-12-one	0.545
18	3-(4-(diethylamino) butoxy) -1-hydroxy-12H-benzo [b] xanthen-12-one	0.879
19	1-hydroxy-3-(4-(pyrrolidin-1-yl) butoxy) -12H-benzo [b] xanthen-12-one	0.61
20	11-hydroxy-3-(4-(piperidin-1-yl) butoxy) -12H-benzo [b] xanthen-12-one	0.756
21	3-(2-(dimethylamino) ethoxy) -1-hydroxy-12H-benzo [b] xanthen-12-one	0.994
22	3-(3-(dimethylamino) Propoxy) -1-hydroxy-12H-benzo [b] xanthen-12-one	0.74
23	3-((5-(dimethylamino) pentyl) Oxy) -1-hydroxy-12H-benzo [b] xanthen-12-one	0.236
24	3-((6-(dimethylamino) hexyl) Oxy) -1-hydroxy-12H-benzo [b] xanthen-12-one	0.371*

*Test set compound

describe the role or position of atoms which are the most influential on the anticancer activity. The 24 active compounds with their *in vitro* inhibition concentration were randomly divided into the training set of 19 compounds and a test set of 5 compounds. 14 independent variables for electronic descriptor was described to consist of 14 atomic nets-charges (q) of C1, C2, C3, C4, C5, C6, C7, C8, C9, C11, C12, O14, and O15. Of the 15 charges is difficult to determine the most dominant nets-atom effect, so the backward method was performed to gradually eliminate the less relevant variables from the models. This procedure has finally given 8 QSAR models as listed in Table 3. From the Table 3, it was emerged that all selected models show a good correlation ($r \approx 0.9$) between biological activity and the selected descriptors.

This result indicated the determination of the best model among 8 QSAR models listed in Table 3 was not adequate only by comparing the r size, while they have similar value. Therefore, other statistical parameters such as r^2, standard estimation of error (SEE<0.3), PRESS (predictive residual sum of square) and also F_{cal}/F_{tab} (≥ 1) could be taken into account. Comparison of the mentioned parameters (r^2, SEE, PRESS, and F_{cal}/F_{tab}) toward the 8 models, presented in Table 3, pointed that it was also not easy to choose the best model because their value were not significantly different. However, F_{cal}/F_{tab} considered as the most noticeable parameter which give a variety of value from 1.26 to 3.99. According to this value, model 7 and 8 were decided to be the best QSAR model because their F_{cal}/F_{tab} value was the highest among the others (>3). Furthermore, model 7 and 8 were used to search and design of new xanthones derivatives with better anticancer activity and their complete QSAR equations was, respectively, presented in Eq. 1 and Eq. 2 as below as:

Table 2: Comparison of calculated and experimental NMR chemical shift data (δ, ppm)

Number	Experiment	Calculated method			
		AM1	PM3	HF	DFT
H-8	8.03	9.00	8.81	8.41	8.88
H-5	6.85	7.52	7.48	6.60	7.04
H-4	6.40	7.17	7.14	6.29	6.78
H-7	6.93	6.25	6.16	5.71	6.09
H-2	6.21	5.04	4.97	4.44	4.88
C-1	163.90	161.96	160.00	156.53	161.85
C-2	98.10	92.60	91.44	89.32	93.65
C-3	165.10	162.81	161.72	151.63	156.30
C-4	93.90	100.14	100.34	92.26	97.19
C-4a	158.00	162.03	161.80	157.48	162.08
C-5	102.30	106.96	106.77	100.91	105.84
C-6	164.10	161.67	160.19	156.26	161.39
C-7	113.80	93.46	105.28	103.65	106.66
C-8	127.50	134.08	132.48	111.25	115.09
C-8a	113.40	112.99	112.41	103.18	106.66
C-9	179.80	180.29	174.96	177.09	187.15
C-9a	102.50	104.18	105.28	98.23	102.58
C-10a	158.00	157.77	156.88	131.46	135.04
Correlation		0.995	0.997	0.995	0.994
PRESS		585.884	297.161	1587.065	983.388

NMR: Nuclear magnetic resonance, AM1: Austin model 1, PM3: Parameterized model 3, HF: Hartree-Fock, DFT: Density functional theory

$$\text{Log IC}_{50} = -9.378 \, qC1 + 31.283 \, qC5 + 3.962 \, qC6 - 7.278 \, qC10 - 4.898 \, qC11 + 4.135 \quad (1)$$

$$\text{Log IC}_{50} = 19.633 \, qC5 + 6.458 \, qC6 - 5.731 \, qC11 + 3.986 \quad (2)$$

The two equations above can be sure yet where that will be used to design new anticancer compound xanthone, if the terms of the simplicity of electronic parameter number of influential model equation 8 or 2 the most good, but needs to be continued validation against both equations is obtained to ensure that the equation with parameters most appropriate statistics.

Validation of QSAR models

QSAR equation (1) and (2) was applied to calculate the activity of 5 test set compounds, and we could see how good these models predict the anticancer activity of the xanthone derivatives. A validation for searching the best model was performed using calculation for each equation toward the test set. The PRESS value is the amount of quadrate difference between the predicted and observed LogIC$_{50}$ value, where the equation with the smallest difference was chosen as the best equation. PRESS value from the predicted and observed LogIC$_{50}$ of model 7 and 8 were listed in Table 4.

Based on the PRESS parameter, the smallest PRESS value was shown by model 7, with 0.51 in difference, compared with model 8 with 0.69 in value. This result indicated that it has a small difference of anticancer activity as IC$_{50}$ values within the predicted and experimental. It could be decided from PRESS value, that the model 7 was better than 8 as QSAR model to predict the anticancer activity and also it could give good structure of the predicted xanthone derivative compound.

Other parameters to convince the best model was with compared their slope and correlation coefficient (r^2). As seen in Fig. 1, it was determined that r^2 of model 7 and 8 were 0.861 and 0.556, respectively.

According to PRESS and r^2 parameters of statistical analysis, model 7 with equation 1 would be the best QSAR model to generating the validation model toward the test set. Further validation for determining the best QSAR model was evaluated using enter statistical calculation. In the end, based on the calculation toward some statistical parameters, we found out the result as follows: PRESS=0.999, r^2=0.7829, SEE=0. 235, R=0. 885, F_{Cal}/F_{Tab}=4.68. Plots of the predicted versus experimental of anticancer activity as Log IC$_{50}$ values was shown in Fig. 2.

The correlation coefficient (r^2) was 0.7829, it means there is 78.29% similarity value between predicted and experimental anticancer activity. Based on statistics obtained renewal of the parameter values of the equation 2, it could be generated the best equation model of QSAR regression as follows:

$$\text{Log IC} = -9.132 \, qC1 + 28.853 \, qC5 + 2.456 \, qC6 - 7.375 \, qC10 - 5.112 \, qC11 + 3.900 \quad (3)$$

Based on the Equation 3, electronic descriptors for electron charge of carbon atom in number 1, 5, 6, 10 and 11 (Fig. 3) Showed as the position with the most affect to the anticancer activity. The better anticancer activity as IC$_{50}$ could be given by the more negative of the

Table 3: Statistical parameters of 8 selected QSAR models of xanthones derivatives

Model	Descriptors	r	R²	Adjusted R	SEE	PRESS	F_{Calc}/F_{tab}
1	qO14, qC8, qC6, qC7, qC10, qC12, qC1, qC11, qC4, qC13, qC5	0.93	0.86	0.642	0.26	0.47	1.26
2	qO14, qC8, qC6, qC10, qC12, qC1, qC11, qC4, qC13, qC5	0.93	0.86	0.686	0.24	0.47	1.58
3	qO14, qC6, qC10, qC12, qC1, qC11, qC4, qC13, qC5	0.93	0.86	0.719	0.23	0.47	1.97
4	qO14, qC6, qC10, qC12, qC1, qC11, qC4, qC5	0.92	0.85	0.735	0.22	0.50	2.32
5	qO14, qC6, qC10, qC1, qC11, qC4, qC5	0.92	0.84	0.747	0.21	0.52	2.76
6	qO14, qC6, qC10, qC1, qC11, qC5	0.91	0.82	0.734	0.22	0.60	2.98
7	qC6, qC10, qC1, qC11, qC5	0.90	0.80	0.726	0.22	0.473	3.38
8	qC6, qC10, qC11, qC5	0.88	0.78	0.717	0.23	0.74	3.99

SEE: Standard estimation of error, QSAR: Quantitative structure-activity relationship

log IC$_{50}$. To get the most negative value of logIC$_{50}$, it was ordered by the negative net atomic charge of qC5 and qC6 and the positive net atomic charge of qC1, qC10, and qC11. From the Equation 3, qC5 and qC6 have positive value 28.853 and 2.456, respectively, so to make an electron net charge becoming negative, the C5 and C6 or neighbor's position should be occupied with electron donating groups (EDG) such as hydroxy and methoxy group to make the π system more nucleophile. Meanwhile, the other positions such as C1, C10, and C11 were supposed to fill up with electron withdrawing groups (EWG) such as nitro (–NO$_2$) and also halogen (–X) to remove the electron density from the π system and make it less nucleophile or to make the net charge become positive. In other word, to make the net charge become negative, it is important to consider for adding the EDG and EWG groups on the best position to predict a series of xanthones derivatives with the best activity. Based on previous reports [35], it showed that the halohydrin (bromo and chloro) xanthones where the most effective inhibitors for Topo II, similar with doxorubicin as commercial cancer therapy, which has same inhibition activity. So in this study, it has been conducted to design a new hydroxy xanthone

by modification of hydroxy xanthone scaffold with halogen groups, such as bromo, chloro and iodo, to look out their predicted anticancer activity, as listed as Table 5.

This research showed that there was a significant difference in the value of predicted Log IC$_{50}$ compared with doxorubicin as commercial cancer therapy. This result indicates that the halogen-substituted hydroxy xanthone has potential to be developed as anticancer drugs, especially for HepG2 (human liver cancer) with predicted IC$_{50}$ in the range of 0.001 - 0.484 μM, wherein it was lower than IC$_{50}$ of doxorubicin at 3.83 μM [24]. Compounds predicted to also differ from other types of cancer as a result of the prediction by Alam and Khan [10] for HeLa cell cancer design derivatives of xanthone compounds hydroxy, methoxy, epoxy, and prenyl. While the special halogen compound bromo, and chloro is not done. Hence, the design of compound analysis results QSAR is a new xanthone derivative hydroxy compound with activity better value when compared to the values of IC50 cancer drug doxorubicin.

CONCLUSION

Study of the correlation between electronic parameters, atomic net charge, and the anticancer activity of xanthones has been performed using semi-empirical molecular orbital calculation PM-3. This study found out that the descriptors of atomic net charges: qC1, qC5, qC6, qC10, and qC11, were hypothetically active at the molecular site of xanthone derivatives and seem to be the most responsible for their pharmacological activity. The best QSAR regression equation from this study was revealed to be: Log IC$_{50}$ = –9.132 qC$_1$ + 28.853 qC$_5$ + 2.456 qC$_6$ - 7.375 qC$_{10}$ - 5.112 qC$_{11}$ + 3. 900. n=24, PRESS=0.999, r^2=0.7829, SEE=0.235, R=0.885 and F$_{cal/}$F$_{table}$=4.68. This QSAR model could predict a good inhibition activity (IC$_{50}$) value of halogen-substituted hydroxy xanthone derivatives within the range 0.001-0.484 μM.

Table 4: The comparison between predicted and experimental anticancer activity (Log IC$_{50}$) of 5 test set selecting calculated by selected model 7 and 8

Compounds of test sets	Experimental Log IC$_{50}$	Predicted Log IC$_{50}$	
		Model 7 (Eq. 1)	Model 8 (Eq. 2)
1	0.37	0.70	0.75
2	0.84	0.99	0.72
11	1.35	1.21	1.37
14	1.61	1.29	1.22
24	1.64	1.12	1.02
PRESS		0.51	0.69

Table 5: New designed xanthones derivatives as anticancer and their predicted IC$_{50}$ calculated using the best QSAR model

| No.	Compound	Predicted IC$_{50}$ (μM)
25	2,4-dibromo-3-hydroxy-9H-xanthen-9-one	0.068
26	2,4-dichloro-3-hydroxy-9H-xanthen-9-one	0.207
27	2,4-diiodo-3-hydroxy-9H-xanthen-9-one	0.019
28	4-bromo-1,3-dihydroxy-9H-xanthen-9-one	0.003
29	4-chloro-1,3-dihydroxy-9H-xanthen-9-one	0.005
30	4-iodo-1,3-dihydroxy-9H-xanthen-9-one	0.001
31	4,7-dibromo-1,3,6-trihydroxy-9H-xanthen-9-one	0.013
32	4,7-dichloro-1,3,6-trihydroxy-9H-xanthen-9-one	0.035
33	4,7-diiodo-1,3,6-trihydroxy-9H-xanthen-9-one	0.003
34	2,4-dibromo-3,5,6,7-tetrahydroxy-9H-xanthen-9-one	0.147
35	2,4-dichloro-3,5,6,7-tetrahydroxy-9H-xanthen-9-one	0.484
36	2,4-diiodo-3,5,6,7-tetrahydroxy-9H-xanthen-9-one	0.038
37	1,5-dibromo-2,3,4,6,8-pentahydroxy-9H-xanthen-9-one	0.029
38	1,5-dichloro-2,3,4,6,8-pentahydroxy-9H-xanthen-9-one	0.264
39	1,5-diiodo-2,3,4,6,8-pentahydroxy-9H-xanthen-9-one	0.036
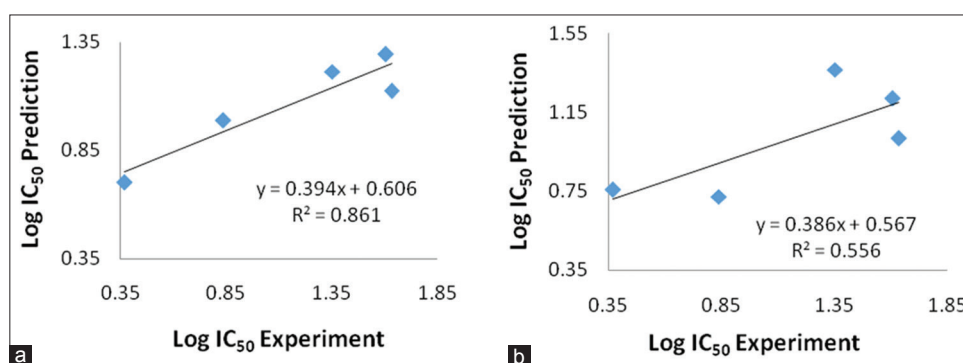
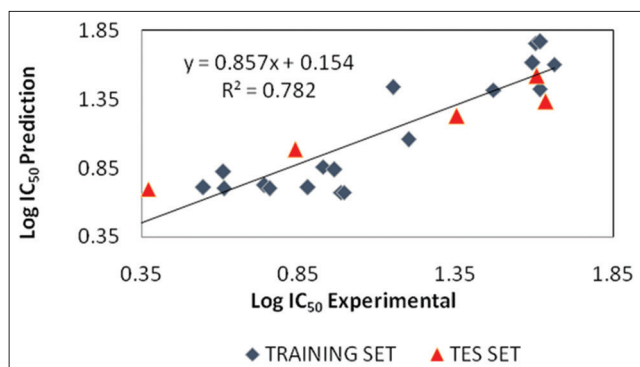**Fig. 1: Plot of prediction versus experiment anticancer (Log IC50) of model 7 (a) and 8 (b)**

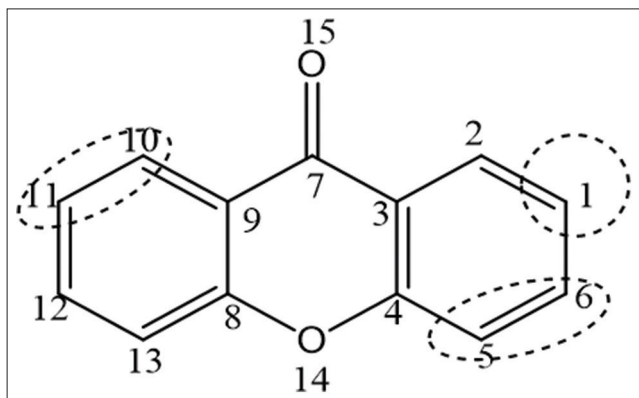**Fig. 2: Plot of predicted versus experimental anticancer activity values of model 7**

Fig. 3: Structure of xanthone

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