International Journal of Research and Development in Pharmacy and Life Sciences
Available online at http//www.ijrdpl.com
April - May, 2016, Vol. 5, No.3, pp 2147-2152
ISSN (P): 2393-932X, ISSN (E): 2278-0238

Research Article

MODELING OF ANTILEUKEMIC ACTIVITY FOR CARBOQUINONES USING QSAR METHODOLOGY

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(Received: February 13, 2016; **Accepted:** March 29, 2016**)**

ABSTRACT

In the present study, Quantitative Structure Activity Relationship (QSAR) studies were performed on a series of Carboquinones derivatives as an anti-Leukemic agent. Stepwise multiple linear regression (MLR) analysis was applied to identify the structural requirement for anti-leukemic activity. The QSAR developed as a result of MLR indicate that the activity is affected by the Parachor, Refractive Index, logP and Pogliani index. The presence of Indicator parameter for amide group in the QSAR model shows the role of amide substitution on a parent structure in regulating anti – leukemic activity of the compounds. The results were further evaluated for its statistical significance and predictive power by cross validation method.

The information generated from the present study may be useful in the design of more potent carboquinones as an anti – leukemic agent.

Keywords: Modeling, QSAR, Anti-Leukemic activity, Carboquinones.

INTRODUCTION

Natural and synthetic quinoid compounds are known to be biologically active compounds with antibacterial[1,2,] antifungal [3,4,] antiprotozoal [5,6,] virus inhibitory[7,] and antitumor activities [8,9]. The biological activity of quinoid compounds has been investigated by using structure- activity relationship approaches since 1969[10]. The antileukemic activity of carboquinones expressed as the minimum effective dose (MED) and the optimum effective dose (OED) was previously modeled using the electrotopological state and the molecular connectivity indices with multiple linear regression (MLR)[11]. The General structure of Carboquinone is represented in Figure 1.

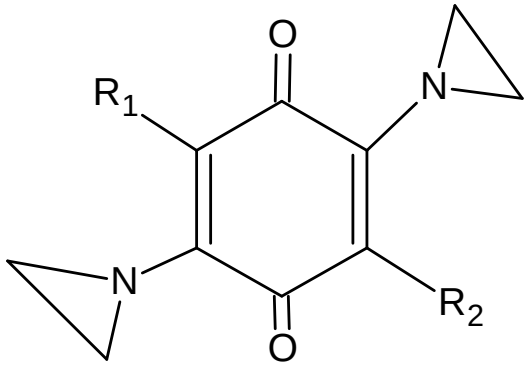

Figure 1: Parent Structure of Carboquinones

QSAR is a mathematical relationship between a biological activity of a molecular system and its geometric structural and chemical characteristics. QSAR attempts to find consistent relationship between biological activity and molecular properties, so that these "rules" can be used to evaluate the activity of new compounds. The QSAR methodology focuses on finding a model, which allows for correlating the activity to structure within a family of compounds.

QSAR studies can reduce the costly failures of drug candidates in clinical trials by filtering the combinatorial libraries. Virtual filtering can eliminate compounds with predicted toxic of poor pharmacokinetic properties[12, 13] early in the pipeline. It also allows for narrowing the library to drug-like or lead-like compounds[14] and eliminating the frequent-hitters, i.e., compounds that show unspecific activity in several assays and rarely result in leads[15]. Including such considerations at an early stage results in multidimensional optimization, with high activity as an essential but not only goal[16].

In an effort to for search of new potent anti leukemic agent, we have performed QSAR studies on Carboquinone derivatives for quantify the necessary structural and physicochemical requirement of this series of compounds as potent anti – leukemic agent.

To determine the stability and goodness of fit of predictive model, the statistical results were cross validated by a reliable validation process. The definitive validity of a model is examined with the external validation, to evaluate its efficacy.

Experimental

Biological activity data set

In this study 36 carboquinones derivatives (Table 1) were utilized to constructs QSAR model using biological activity data from literature11. In this work anti – leukemic activity is expressed as minimum effective dose (MED). The values are reported in the form of log(1/mol/kg) and shown in Table 1. The MED is defined as the lowest dose level of a pharmaceutical product that provides a clinically significant response in average efficacy. The inverse log value was adapted as dependent variable in QSAR analysis.

Calculation of molecular descriptor:

Molecular descriptors define the molecular structure and physicochemical properties of molecules by a single number. The Topological descriptors tested in present study were Wiener index, Balaban J Index, Randic Connectivity index, Pogliani index etc. these are calculated using two-dimensional representation of the molecules with the software Dragon. The physicochemical properties tested in present work were, Molar reractivity, Molar Volume, Parachor, Refractive index, surface tension, density and polarizability along with log P these properties have been calculated using software ACD Labs. Indicator parameters were also tested to describe the significance of presence and absence of some substituents. These parameters or descriptors are adapted as independent variable in QSAR analysis. The significant parameter screened by MLR is shown in Table 2.

Multiple Linear Regressions:

MLR is a method used for modeling linear relationship between a dependent variable Y (log1/C) and independent variable X (2D descriptors). MLR is based on least squares: the model is fit such that sum-of-squares of differences of observed and a predicted value is minimized. MLR estimates values of regression coefficients (r2) by applying least squares curve fitting method. The model creates a relationship in the form of a straight line (linear) that best approximates all the individual data points. In regression analysis, conditional mean of dependant variable (log1/C) Y depends on (descriptors) X. MLR analysis extends this idea to include more than one independent variable.

Regression equation takes the form

$$Y = b1 * x1 + b2 * x2 + b3 * x3 + c$$

where Y is dependent variable, 'b's are regression coefficients for corresponding 'x's (independent variable), 'c' is a regression constant or intercept[17,18].

All the calculated descriptors and indicator variables were considered as independent variable and biological activity as dependent variable. STATISTICA software was used to generate QSAR models. Statistical measures used were n-number of compounds in regression, r correlation coefficient, r2-squared correlation coefficient, F- test (Fischer's value), SEE- standard error of estimation for statistical significance, Validation parameters considered to evaluate the significance of these statistical parameters were, cross validated R2 or q2 (Adjusted R2), standard deviation based

on predicted residual sum of squares (RSS) and Total sum of square (TSS),.

Residual Sum of Squares (RSS)

It is the sum of the squared difference between the experimental response y and the response calculated by the regression model x:

$$RSS = \sum_{i=1}^{n} (Yi - \hat{Y}i)2$$

Lower the value of RSS shows better predictive ability of the model and more nearness of the calculated and experimental values.

Total Sum of Squares (TSS)

It is the total variance that a regression model can explain and is used as a reference quantity to calculate standardized quality parameters. Also denoted as SSY, it is the sum of the squared differences between the experimental responses and the average experimental response:

$$TSS = SSY = \sum_{i=1}^{n} (Yi - \bar{Y}i)2$$

Adjusted R2

Sometime the r value of a model shows regression by chance, therefore in order to validate that whether the correlation actual or by chance R2 adjusted has been shown.

RESULTS AND DISCUSSION

A data set of 36 carboquinones compounds (Table 1 and 2) for anti-leukemic activity in terms of MED is used for the present QSAR study. The QSAR studies of the carboquinones series resulted in several QSAR equations. The descriptors involved in the selected models are given in Table 2. The best pentavariate model obtained as:

MED (log1/C) = -10.71 – 0.021 (±0.0052) Pc + 11.03 (±2.7)RI – 0.282 (±0.0642) Dz – 1.11 (±0.156)logP + 0.941 (±0.170) Iam ..... Eq (1)

N = 36, r = 0.919, r^2 = 0.8445, SEE = 0.2738, F- Ratio = 32.589, R^2adj = 0.8186, RSS = 2.25, TSS = 14.47

Eq (1) is the best pentavariate model obtained in MLR analysis.

In order to improve result further, compound no 11 and 35 is removed from the regression analysis and the statistical fitness of Eq (1) has been improved and shown below in the form of Eq (2).

MED (log1/C) = -6.05 + 0.0147 (±0.0049) Pc + 8.2 (±2.52)RI – 0.208 (±0.060) Dz – 0.99 (±0.133)logP + 0.777 (±0.158) Iam .....Eq (2)

N = 34, r= 0.9456, r^2 = 0.8941, SEE = 0.225, F-Ratio = 47.3, R^2adj = 0.8752, RSS = 1.42, TSS = 13.38

Further 3 compounds (19, 20 & 36) appear as an outlier in the MLR analysis performed with set of 34 compounds. Therefore compound 19, 20 and 36 was also removed from the data set and MLR has been performed with a set of 31 carboquinones. This results in the further improvement of statistical fitness and the Eq (2) has been improved and presented as Eq (3).

MED (log1/C) = -5.25 + 0.0138 (±0.0036) Pc + 7.8 (±1.9)RI – 0.202 (±0.044) Dz – 0.92 (±0.104)logP + 0.934 (±0.120) Iam .....Eq (3)

N = 31, r= 0.9709, r^2 = 0.9426, SEE = 0.166, F – Ratio = 82.09, R^2adj = 0.9311, RSS = 0.6865, TSS = 11.96

In the QSAR model Eq (3) parachor shows positive correlation coefficient, which is responsible for direct relationship between parachor and log1/C i.e., higher the value of Pc higher will be the log1/C and results in lower MED and vice versa. Therefore a substitution which increases the parachor and hence reduce MED is favorable for the anti-leukemic activity of the carboquinones.

Refractive index is showing positive coefficient, means increase in RI increases log1/C and therefore reduces MED, therefore substitution which increases the RI of overall compound is desirable. RI is a measure of bulkiness therefore more bulk in a compound is required.

Similarly pogliani index, represent ratio of valance electron to the principal quantum number. In the Eq (3) negative coefficient of Dz shows that increase in Dz reduces the log1/C and hence increases MED value. Therefore higher Dz is not favorable, which shows that the group with less number

Table 1 : Substituents of Carboquinones, Experimental log1/C, Calculated log1/C using Eq (3) and Residual value of log1/C (Exp log1/C- Calc log1/C)

S. No	R_1	R_2	Exp log1/C	Calc.log1/C	Residue
1.	C_6H_5	C_6H_5	4.33	4.31	0.02
2.	CH_3	$(CH_2)_3C_6H_5$	4.47	4.46	0.01
3.	C_5H_{11}	C_5H_{11}	4.63	4.49	0.14
4.	$CH(CH_3)_2$	$CH(CH_3)_2$	4.77	5.03	-0.26
5.	CH_3	$CH_2C_6H_5$	4.85	4.94	-0.09
6.	C_3H_7	C_3H_7	4.92	5.00	-0.08
7.	CH_3	$CH_2OC_6H_5$	5.15	5.13	0.02
8.	$CH_2CH_2OCON(CH_3)_2$	$CH_2CH_2OCON(CH_3)_2$	5.16	5.21	-0.05
9.	C_2H_5	C_2H_5	5.46	5.37	0.09
10.	CH_3	$CH_2CH_2OCH_3$	5.57	5.75	-0.18
11.	OCH_3	OCH_3	5.59	------	-----
12.	CH_3	$CH(CH_3)_2$	5.60	5.43	0.17
13.	C_3H7	$CH(OCH_3)CH_2OCONH_2$	5.63	5.90	-0.27
14.	CH_3	CH_3	5.66	5.93	-0.27
15.	H	$CH(CH_3)_2$	5.68	5.76	-0.08
16.	CH_3	$CH(OCH_3)C_2H_5$	5.68	5.58	0.10
17.	C_3H7	$CH_2CH_2OCONH_2$	5.68	5.91	-0.23
18.	$CH_2CH_2OCH_3$	$CH_2CH_2OCH_3$	5.69	5.72	-0.03
19.	C_2H_5	$CH(OC_2H_5)CH_2OCONH_2$	5.76	--------	---
20.	CH_3	$CH_2CH_2OCOCH_3$	5.78	--------	---
21.	CH_3	C_2H_5	5.86	5.63	0.23
22.	CH_3	$CH(OCH_2CH_2OCH_3)CH_2OCONH_2$	6.03	5.82	0.21
23.	CH_3	$CH_2CH(CH_3)OCONH_2$	6.14	6.09	0.05
24.	C_2H_5	$CH(OCH_3)CH_2OCONH_2$	6.16	6.25	-0.09
25.	CH_3	$CH(C_2H_5)CH_2OCONH_2$	6.18	6.00	0.18
26.	CH_3	$CH(OC_2H_5)CH_2OCONH_2$	6.18	6.28	-0.10
27.	CH_3	$(CH_2)_3OCONH_2$	6.18	6.13	0.05
28.	CH_3	$(CH_2)_2OCONH_2$	6.21	6.34	-0.13
29.	C_2H_5	$(CH_2)_2OCONH_2$	6.25	6.09	0.16
30.	CH_3	CH_2CH_2OH	6.39	6.29	0.10
31.	CH_3	$CH(CH_3)CH_2OCONH_2$	6.41	6.15	0.26
32.	CH_3	$CH(OCH_3)CH_2OCONH_2$	6.41	6.46	-0.05
33.	H	$N(CH_3)_2$	6.45	6.37	0.08
34.	CH_2CH_2OH	CH_2CH_2OH	6.54	6.53	0.01
35.	CH_3	$N(CH_3)_2$	6.77	--------	----
36.	CH_3	$CH(OCH_3)CH_2OH$	6.90	--------	----

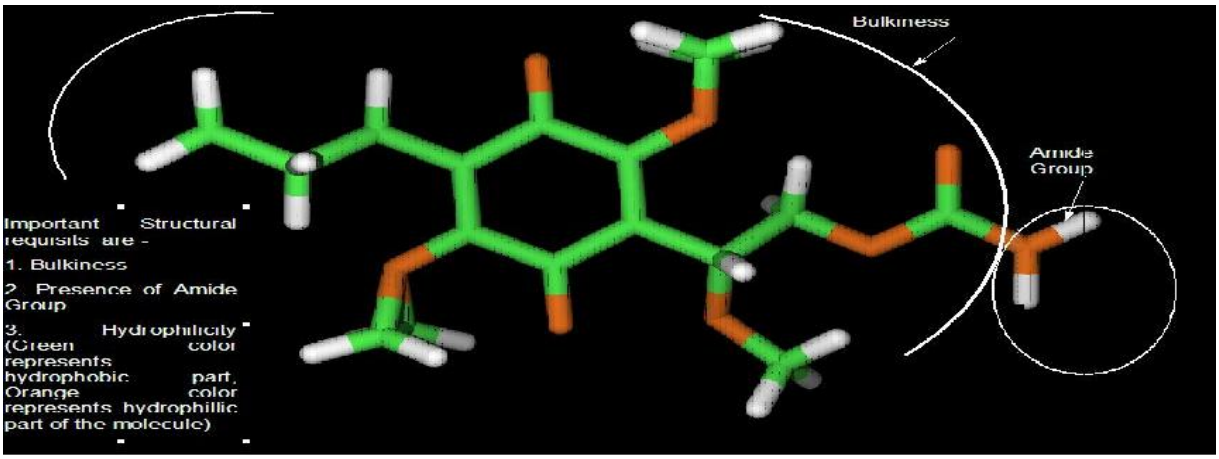

Figure 2 : The diagramatic representation of structural requisits of Carboquinones

Table 2: Structural and physicochemical Parameters present in QSAR models

S. No	Pc	RI	Dz	logP	I_{am}
1.	712.9	1.739	55	2.987	0
2.	699.4	1.661	51	2.839	0
3.	766	1.575	51	3.079	0
4.	601.6	1.618	43	2.138	0
5.	619.2	1.707	47	2.379	0
6.	605.7	1.607	43	2.138	0
7.	639.6	1.68	50	1.591	0
8.	789.5	1.618	64	1.168	1
9.	525.5	1.632	39	1.632	0
10.	545.9	1.63	42	0.845	0
11.	486.1	1.619	41	-0.463	0
12.	523.5	1.644	39	1.632	0
13.	744.2	1.626	58.5	1.013	1
14.	445.4	1.68	35	1.097	0
15.	487.1	1.668	37	1.369	0
16.	583.9	1.623	44	1.101	0
17.	660.9	1.634	51.5	1.361	1
18.	646.4	1.598	49	0.578	0
19.	679.2	1.635	54.5	0.612	1
20.	580.8	1.668	47.5	0.855	1
21.	485.5	1.653	37	1.369	0
22.	784.9	1.621	64.5	0.356	1
23.	618.8	1.65	49.5	1.111	1
24.	679.2	1.635	54.5	0.612	1
25.	658.9	1.644	51.5	1.316	1
26.	679.2	1.639	54.5	0.612	1
27.	620.9	1.652	49.5	1.111	1
28.	580.8	1.668	47.5	0.855	1
29.	620.9	1.647	49.5	1.111	1
30.	502.5	1.686	40	0.518	0
31.	618.8	1.658	49.5	1.111	1
32.	639.2	1.652	52.5	0.363	1
33.	475.4	1.654	37.5	0.309	0
34.	559.6	1.692	45	0.073	0
35.	511.8	1.635	39.5	0.581	0
36.	560.8	1.666	45	0.073	0

Where, Pc = Parachor, RI = Refractive index, Dz = Pogliani index, logP = Octanol water partition coefficient, I_{am} = Indicator parameter for amide functional group.

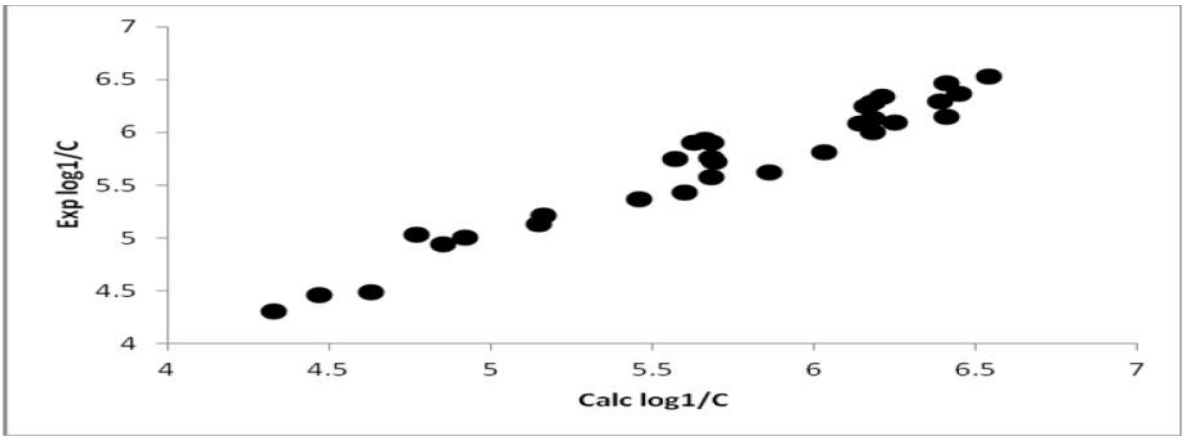

Figure 3: Graph obtained between Experimental log1/C and Calculated log1/C

of valance electron and with higher principal quantum number is beneficial for the biological activity.

logP is also showing inverse relationship, ie.., higher logP reduces log1/C and in turn increases MED. Therefore lower hydrophobicity in the compound is needed. All the structural requisites are also represented in the form of Figure 2.

Positive correlation coefficient of indicator parameter Iam, shows that presence of amide group at the chain terminal of R2, increase the value of log1/C, which reduces the MED of the compounds hence presence of amide group at the chain terminal of R2 is desirable.

The statistical results shows continues improvement in the statistical parameter, Cross validation parameters were also showing continues improvement, and hence justifying the removal of outliers from the MLR analysis. The regular improvement in R2adj from 0.8186 to 0.9311 justifying the outlier of compounds in each step and assure that the regression is not by chance.

Similarly regular lowering of RSS from 2.25 to 0.6865 and lowering of TSS from 14.47 to 11.96 proves the fitness of model at par.

The experimental MED and calculated MED from Eq (3) has been shown in Table 1 along with their residual values.

The graph between observed and calculated MED is also represented in Figure 3.

CONCLUSION:

In the present study, on the basis of QSAR obtained , it has been concluded that the substituents which increases parachor and refractive index of the overall substituted carboquinones, shows improved anti-leukemic activity. On the other hand substituents which reduces hydrophobicity and pogliani index of overall compound, shows improved antileukemic activity. Presence of –CONH2 group at the chain terminal of R2 is also favorable factor in terms of anti leukemic activity.

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