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Original Article

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QSAR study of cytotoxicity of some heterocyclic compounds

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ABSTRACT

QSAR analysis on a set of Heterocyclic compounds for physiochemical activity was performed by using multiple regression procedure. The activity contributions of these compounds were determined from regression equation and the validation procedure to analyze the predictive ability of QSAR model was described. High agreement between experimental and predicted cytotoxicity values was obtained. The results of this study indicate that the parameter has a significant effect on physiochemical activity of this class of compounds, thus simplifying design of new physiochemical active molecules.

Keywards: QSAR analysis, Cytotoxicity, Heterocyclic compounds.

INTRODUCTION

Quantitative Structure activity relationships (QSAR) have been shown to be a powerful research tool two basic kinds of molecular descriptors are used in QSAR, one of them involves parameters that bear relation to free energy and usually represent some of the important physiochemical properties of the molecule (Hansch approach)[(1)], another category of molecular descriptor is the topological index which is produced directly from molecular structure (Topological approach), among many topological indices that have been proposed since 1971 by Hosoya[(2)]. In recent years, topological indices have gained attention in explaining biological activities and physical and chemical properties of organic compounds.

Hydantoin and thiohydantoin are five-member heterocyclic system containing very reactive cyclic urea and thiourea cores[(3,4)]. In recent years, heterocyclic compound and its derivatives are very familiar to their anti-inflammatory[(5)], antimicrobial[(6)], antitubercular[(7)], antipyretic[(8)], analgesic[(9)], antioxidant[(10)] and cytotoxic[(11)] activities. They are now widely used as drugs, medicines, dyes and raw materials in manufacturing industries etc. Much attention has been paid to the synthesis of nitrogen (N)-, oxygen (O)-, and sulfur (S) - containing heterocyclic compounds and their derivatives mainly due to their broad spectrum biological and pharmaceutical activities.

In this study cytotoxicity of various heterocyclic compounds is correlated with topological and physiochemical descriptors and cytotoxicity of these compounds is obtained from Elsevier Arabian J. of Chem (2014) 7, 639–646 King Saud U. Arabian J. of Chem.[(12)]

QSAR are being applied in many disciplines with much emphasis in drug design. As a well accepted technique, two dimensional quantitative structure–activity relationships (2DQSAR) was carried out to study the cytotoxicity. It is a mathematical model that was used to evaluate the toxicity of a compound from its physiochemical properties of molecular structures.

In QSAR it is a common rule that those indices should not be used together which show strong co linearity because if they will be used simultaneously, in multi-vitiate analysis they may lead to chance. But Randic gave his own explanation. According to Randic the indices having strong co linearity can be used simultaneously since each index has its own importance. If one discards one index due to co linearity he may lose certain information which that particular index contains. Hence, the Randic recommendation is quite acceptable and in this study the same will be followed.

Cytotoxic Activity

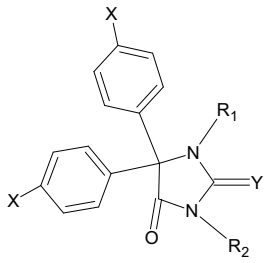
Cytotoxicity of heterocyclic compound like Hydantoin and thiohydantoin derivatives were tested, theough development of drug is laborious ,lengthy and expensive process so computer aided drug design may helpful in the development of a new drug with lesser toxic and higher biological activity ,in this study 22 heterocyclic compound are chosen the median lethal concentration LC_{50} with 95% confidence intervals of these compound where calculated using the provide analysis program by finery(1971) and Rickman et al (1974),according to research methodology all experimental LC_{50} values (µg/ µL) Were converted to logarithm of LC_{50} i.e. $\log_{10} LC_{50}$ and used as depend variable in QSAR study .

Presentation of data

In present study table-1 represents the structure of heterocyclic compounds with substitution, while table II shows the calculated physiochemical descriptors with cytotoxicity of heterocyclic compound, table III represents the correlation matrix between different physicochemical

Descriptor and cytotoxic activity table IV represents the results of regression analysis with statistical descriptor while table V represents the residual report from best model of physicochemical descriptors.

TABLE-1: Structure of 5, 5-Diphenyl-imidazolidine-2, 4-dione moiety



Comp. No.	R_1	R_2	X	Y
1	H	H	H	O
2	H	C_6H_5	H	O
3	C_6H_5	C_6H_5	H	O
4	H	C_6H_{11}	H	O
5	C_6H_{11}	C_6H_{11}	H	O
6	H	H	Br	O
7	H	CH_3	Br	O
8	H	CH_3CH_2	Br	O
9	H	$CH_3CH_2CH_2CH_2$	Br	O
10	H	$CH_3CH_2CH_2CH_2CH_2$	Br	O
11	H	H	Cl	O
12	H	CH_3CH_2	Cl	O
13	H	$CH_3CH_2CH_2CH_2$	Cl	O
14	H	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2$	Cl	O
15	H	H	H	S
16	H	CH_3	H	S
17	CH_3	CH_3	H	S
18	H	CH_3CH_2	H	S
19	CH_3CH_2	CH_3CH_2	H	S
20	H	$CH_3CH_2CH_2CH_2$	H	S
21	$CH_3CH_2CH_2CH_2$	$CH_3CH_2CH_2CH_2$	H	S
22	H	C_6H_5	H	S

RESULT AND DISCUSSION

In order to understand experimental cytotoxicity data of 22 heterocyclic compound on theoretical basis, we established a QSAR study between toxicity and descriptor for physicochemical, topological and indicator properties of the molecules under consideration using multiple linear regression describing by Hansch and Fojity.

Developing a QSAR model requires a diverse set of a data and thereby a large number of descriptor have to be considered.

Descriptors are numerical values that encode different structural features of the molecules selection of set of appropriate descriptor from a large number of them require a method, which is able to discrimination between parameters.

The different molecular descriptors independent variables like density moral refractivity, parachor, polerizibility, index of refraction, surface tension are calculated for heterocyclic compounds presented in table II.

Preliminary analysis was carried out in terms of correlation analysis (table III). In general high co-linearity (r>8) was

observed between different parameters .the high inter relationship was observed between,

1. Molar volume and Parachor(r=0.9508)

2. Surface tension and Index of refraction (r=0.9681)

3. Polarizability and Parachor (r=0.9582)

4. Molar volume and Polarizability (0.8433) and low interrelationship is observed between density and molar volume (0.0017),

The data presented in Table III demonstrated the low co-linearity between the parameters (r<8) indicated that these parameter could be combined to get multiples regression (MLR) models. The analysis of matrix revealed physiochemical topological and indictor descriptors for the development of (MLR) models.

Validations is a crucial aspect of any QSAR analysis .the statistical quality of the resulting models and result of cross validation is depicted in table IV are determined by R^2=regression coefficient se = standard error of estimations, F ratio, (Quality factor) and cross validated regression coefficient (R^2_{cv}).

We have done the multiple regression analysis with these physiochemical descriptors. The Physiochemical data was subjected to regression analysis and the best mono parametric model v $Q=\sqrt{r2}/MSE$ cal descriptor is as follows.

The regression analysis gave mono -parametric models. Out of which one contain **Po** was found to give good results, the model obtained is as follows-

Log LC_{50} = 5.1753 - 0.1066 (±0.0139) Po ....[1]

N = 22, MSE = 0.1183, R^2= 0.7470, Ar^2 = 0.7344, Q-VALUE= 7.3059

Here n is the number of compound, MSE is the means square error of estimation, R^2 is the regression coefficient, AR^2 Is the adjusted Regression coefficient and Q-value is the Quality factor. From above mono parametric model it is clear that Polarizibility (Po) has a negative correlation influence on toxicity suggest that toxicity as expressed by log LC_{50} decreases with increase in magnitude of Polarizibility.

However to have better model we carried out several multi parametric correlations and those which are statistically significant are presented in table IV.

A perusal of table IV shows that bi parametric correlations involves the molecular refractivity and Polarizibility as-

Log LC_{50} = 5.0667 - 0.0044 (±0.0045) MR, -0.0931 (±0.0196) Po ...[2]

N=22, MSE=0.1185, R^2=0.7592, AR^2=0.7338, Q-VALUE=7.3529

In this model molecular refractivity shows also a negative influence on cytotoxicity and a slight increase from 0.747 to 0.759 in variance is observed. In an attempt to obtained still better regression expression we tried for some tri parametric correlations which are statistically significant. The best tri parametric correlation involves the surface tension, density and nominal mass as follows-

Log LC_{50} = 2.6983 - 0.0254(±0.0124) ST, 2.9786 (±0.4943) D, -0.0117(±0.0016) NM ..... [3]

N=22, MSE=0.1114, R^2=0.7856, AR^2=0.7498, Q-VALUE=7.9563

Further insure of most significant correlation we added one more physiochemical descriptor in above model as-

Log LC_{50} = -0.8149 + 0.0064 (±0.0057) P, -0.0436 (±0.0203) ST, 6.4218(±3.0882)D, -0.0250 (±0.0119) NM ..... [4]

N=22, MSE=0.1097, AR^2=0.7536, R^2=0.8005, Q-VALUE=8.1559

Finally in order to confirm out of the proposed models which is the most appropriated for modelling the toxicity? We calculated the pogliani's quality factor Q which is Ratio of R and MSE (means square error) among these Q value maximum value is found for Eq.4 as 8.1559. Result of cross validation also represents the superiority of model no.4 due to the higher value of cross validated regression coefficient as 0.7071. So Eq. 4 is the best model for modelling toxicity with physicochemical parameters and a graph (fig. 1&2) is plotted between observed vs. predicted values of cytotoxicity from Eq. 4.

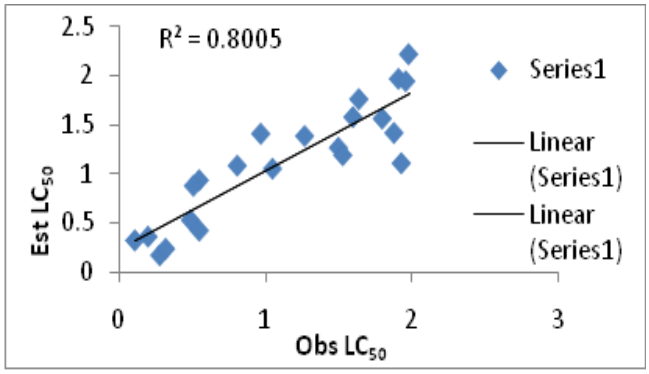


Fig. 1. Plot of observed LC_{50} Versus experimentally LC_{50}

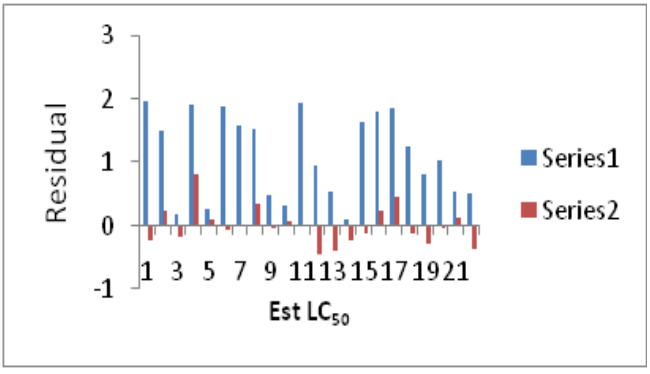


Fig. 2. Plot of Estimated LC50 Versus Residual.

TABLE II. Calculated Physiochemical descriptors and Cytotoxicity of Compounds

Comp No.	$\log_{10}(LC_{50})$	MR	MV	P	IR	ST	D	Pol	NM
1	1.98	69.58	200.5	531.3	1.61	49.2	1.257	27.58	252
2	1.5	94.24	259.7	703.2	1.645	53.6	1.263	37.36	328
3	0.2	118.91	319	875.1	1.668	56.6	1.267	47.14	404
4	1.93	95.51	275.7	738.2	1.609	51.4	1.212	37.86	334
5	0.28	121.45	350.8	945.2	1.608	52.6	1.187	48.14	416
6	1.91	4.96	232.9	633.4	1.65	54.6	1.76	33.68	408
7	1.6	89.89	247.9	671.5	1.644	53.7	1.71	35.63	422
8	1.53	94.51	265.5	711.6	1.63	51.5	1.649	37.46	436
9	0.49	103.77	298.5	791.7	1.611	49.4	1.561	41.14	464
10	0.32	108.41	315	831.8	1.604	48.5	1.524	42.97	478
11	1.96	79.37	224.4	605.5	1.625	52.9	1.43	31.46	320
12	0.97	88.92	257	683.7	1.608	50	1.358	35.25	348
13	0.55	98.18	290	763.9	1.592	48	1.3	38.92	376
14	0.11	112.08	339.6	884.1	1.574	45.9	1.234	44.43	418
15	1.64	77.78	198.8	572.7	1.711	68.8	1.34	30.86	268
16	1.8	82.71	213.9	610.9	1.7	66.5	1.31	32.78	282
17	1.88	87.57	228.9	649	1.69	64.5	1.29	34.71	296
18	1.27	87.34	230.1	650.9	1.683	64	1.28	34.62	296
19	0.81	96.83	261.4	729.2	1.662	60.5	1.24	38.38	324
20	1.05	96.6	262.6	731.1	1.657	60	1.23	38.29	324
21	0.55	115.35	326.1	889.4	1.625	55.3	1.16	45.73	380
22	0.51	102.79	256.8	744.6	1.732	70.7	1.34	40.75	344

MR = Molar Refractivity, MV = Molar Volume, P = Parachor, IR = Index of Refraction,
ST = Surface tension, D = Density, Pol = Polarizibility, NM = Nominal mass

TABLE III. Correlation matrix

	$\log_{10}(LC_{50})$	MR	MV	P	IR	ST	D	Pol	NM
$\log_{10}(LC_{50})$	1								
MR	-0.6871	1							
MV	-0.8394	0.6733	1						
P	-0.8613	0.7049	0.9855	1					
IR	0.2699	-0.1915	-0.5467	-0.4029	1				
ST	0.2204	-0.1132	-0.4968	-0.3459	0.9687	1			
D	0.2540	-0.5161	-0.2123	-0.2648	-0.0258	-0.1828	1		
Pol	-0.8642	0.7045	0.9560	0.9893	-0.2820	-0.2434	-0.2457	1	
NM	-0.5796	0.2669	0.7329	0.6830	-0.4986	-0.5656	0.5038	0.6715	1

TABLE IV. Statistical and Cross- Validation descriptors Physiochemical

M no	n	Intercept	R^2	F-Ratio	PRESS	R^2_{cv}	R^2_{ADJ}
1	22	5.1753	0.7470	59.054	6.9522	0.7055	0.7344
2	22	5.0667	0.7592	29.946	362.54	0.0000	0.7338
3	22	2.6983	0.7856	21.981	6.7439	0.6857	0.7498
4	22	-0.8149	0.8005	17.057	6.1163	0.7071	0.7536

TABLE V. Residual Report

Comp no	Obs LC_{50}	Est LC_{50}	Residual
1	1.980	2.218	-0.238
2	1.5	1.267	0.233
3	0.2	0.364	-0.164
4	1.93	1.11	0.82
5	0.28	0.174	0.106
6	1.91	1.968	-0.058
7	1.6	1.58	0.02
8	1.53	1.192	0.338
9	0.49	0.532	-0.042
10	0.32	0.24	0.08
11	1.96	1.944	0.016
12	0.97	1.409	-0.439
13	0.55	0.938	-0.388
14	0.11	0.326	-0.216
15	1.64	1.762	-0.122
16	1.8	1.564	0.236
17	1.88	1.418	0.462
18	1.27	1.387	-0.117
19	0.81	1.085	-0.275
20	1.05	1.055	-0.005
21	0.55	0.425	0.125
22	0.51	0.881	-0.371

CONCLUSIONS

The following conclusions are obtained from this analysis:

(1) Physiochemical parameters may be used for modelling of these compounds.

(2) Physiochemical are more effective parameters in this QSAR study.

(3) Molar Refractivity, Molar Volume, Parachor, Index of Refraction, Surface tension, Density, Polarizibility, and Nominal mass parameters are used.

(4) Presence of Halogens decreases cytotoxicity while presence of Oxygen increases the cytotoxicity of these heterocyclic compounds.

REFERENCE

1. Hansch, C., 1994. International commission for protection against environmental mutagens and carcinogens.
2. H. Hosoya, Tables of Non–Adjacent Numbers, Characteristic Polynomials and Topological Indices. II. Mono– and Bicyclic Graphs, Natl. Sci. Rept. Ochanomizu Univ. 1971, 22, 181–214.
3. Lo´ pez, C.A., Trigo, G.G., 1985. The chemistry of hydantoins. Adv. Heterocycl. Chem. 38, 177–228.
4. Meusel, M., Gu¨ tschow, M., 2004. Recent developments in hydantoin chemistry: a review. Org. Prep. Proced. Int. 36, 391–443.
5. Ghate, M., Manohar, D., Kulkarni, M.V., Shoba, R., Kattimani, S.Y., 2003. Synthesis of vanillin ethers from 4-(bromomethyl) coumarins as anti-inflammatory agents. Eur. J. Med. Chem. 38, 297–302.
6. Khan, I.A., Kulkarni, M.V., Gopal, M., Shahabuddin, M.S., Sun, C.M., 2005. Synthesis and biological evaluation of novel angularly fused polycyclic coumarins. Bioorg. Med. Chem. Lett. 15, 3584–3587.
7. Gupta, A.S., Prabhu, B.S., 2005. Synthesis of new benzopyrones with possible bacteriostatic activity. Indian J. Heterocycl. Chem. 13, 391–392.
8. Shastri, L.A., Ghate, M.D., Kulkarni, M.V., 2004. Dual fluorescence and biological evaluation of paracetamol ethers from 4-bromomethylcoumarins. Indian J. Chem. 43B, 2416–2422.
9. Ghate, M., Kusanur, R.A., Kulkarni, M.V., 2005. Synthesis and in vivo analgesic and anti-inflammatory activity of some bi heterocyclic coumarin derivatives. Eur. J. Med. Chem. 40, 882–887.
10. Torres, R., Faini, F., 2006. Antioxidant activity of coumarins and flavonols from the resinous exudate of Haplopappus multifolius. Phytochemistry 67, 984–987.
11. Kostava, I., Momekov, G., 2008. New cerium (III) complexes of coumarins synthesis, characterization and cytotoxicity evaluation. Eur. J. Med. Chem. 43, 178–188.
12. Liton MAK, Salma U, Bhowmick AC Cytotoxicity and 2D-QSAR study of some heterocyclic compounds Elsevier Arabian J Chem (2014) 7, 639–646.