Quantitative Structure Activity Relationship of 2, 5, 6–Trisubstituted imidazo (2, 1-*b*)-1, 3, 4–Thiadiazole as Anticancer Compounds

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ABSTRACT

Imidazoles being good Pharmacophore for anticancer series were exploited for their potential in the present study. Some new 2,5,6–trisubstituted imidazo (2,1-*b*)-1,3,4–thiadiazole possesing antineoplastic potential against 3 cell lines i.e. murine leukemia cells (L1210/0) and human T- lymphocyte cells (Molt4/C8 and CEM/0) were selected for studies. The IC_{50} values were taken along with the structures and a quantitative structure activity relationship was established for these novel 2,5,6-trisubstituted imidazo(2,1-*b*)-1,3,4-thiadiazole derivatives. The descriptors were calculated with the help of Chem 3D and Dragon software. Codessa and Vlife software were used to generate QSAR models. MLRA, PCR AND PLSR are the statistical tools employed for the study. The models developed had shown good statistical correlation with $R^2 = 0.99$ and $Q^2 = 0.98$. The QSAR models generated were also validated by using test compounds which have shown comparable results to the experimental values.

Key words: Antineoplastic agent, CODESSA, Dragon, Imidazo-thiadiazole, PLSR and PCR QSAR.

INTRODUCTION

Cancer is one of the major diseases, which is the leading cause of death of the human population in some areas of the world. It is the second leading cause of death, behind cardiovascular disease [1,2]. At present, there are three main methods of cancer treatment: surgery, radiation therapy, and chemotherapy [3]. Development in the understanding of tumour biology, molecular biology and genetics together with the greater understanding of the pharmacology and pharmacokinetics of drugs have combined to open up the field of medical oncology to rapid advances in the treatment of cancer. The range of drugs that are available for any particular kind of ailment is wide; one of the primary aim of drug development is to increase the therapeutic window so that drug toxicity is minimized and the drug becomes more tolerable [4].

Drug discovery is a challenging process due to the complexity of biological system. Traditional approaches encompassing synthesis of compounds by trial and error and random screening for biological activity have proved to be quite time consuming. Accordingly, it is a dream of pharmaceutical scientist to design new molecules rationally that is to predict their activity prior to their synthesis. Apart from scientist's interest, there is economic consideration as well in using such systematic drug design approaches. Quantitative structure activity relationships have been applied for quite some time now for the development of new drugs. Although a quantitative structure activity relationship does not completely eliminate the trial and error factor involved in the development of new drug, it certainly decreases the number of compounds synthesized by facilitating the selection of most promising examples.

Interest in the QSAR for antitumor drugs has begun to develop in the past three decade. The work in this area has been

Submission Date : 16-05-2015
Revision Date : 03-08-2015
Accepted Date : 24-08-2015

DOI: 10.5530/ijper.50.1.24

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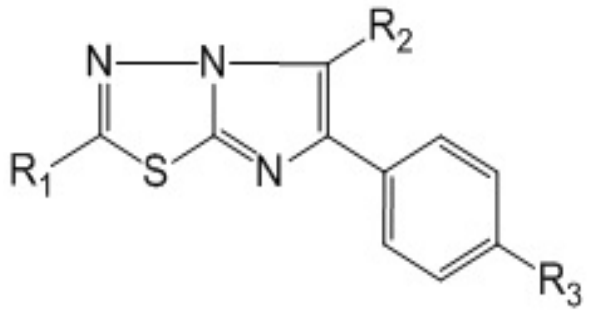


Graphical Abstract

reviewed briefly, using as examples studies on nitrosoureas, aniline mustards, and aryl triazenes. A salient conclusion from this analysis is that the present drugs in clinical use are more hydrophilic than one might expect. The reason for this may be that they have been developed using leukemia as the test system, which may in part account for the fact that while the currently used drugs are effective against leukemia, they are not effective in general against solid tumors [5].

QSAR have emerged as a rational alternative in order to find new active molecules including anticancer compounds [6-8]. Several nitro compounds have been screened for carcinogenicity in rodents, but this is a lengthy and expensive process, taking two years and typically costing 2.5 million dollars, and uses large numbers of animals. There is, therefore, much impetus to develop suitable alternative methods. One possible way of predicting carcinogenicity is to use QSAR. QSAR have been widely utilized for toxicity testing, thereby contributing to a reduction in the need for experimental animals [9].

The search for anticancer drugs led to the discovery of several imidazo fused heterocycles having anticancer activity [10-13]. An early report on 2-amino-1,3,4-thiadiazole derivatives deals with the activity of these compounds against several transplanted animal tumors [14]. Recently Gadad [15] have reported on the cytotoxic effects of imidazo [2,1-*b*] [1,3,4] thiadiazoles. Andreani [16] have studied on some imidazo [2,1-*b*] thiazole guanyl hydrazones which active against various cancer cell lines.

QSAR studies has proved that 5-substituted 2,4-dihydroxyphenylo-1,3,4-thaidiazole derivatives has shown anticancer activity [17].

Thus synthesis of certain 2,5,6-trisubstituted imidazo (2,1-*b*)-1,3,4-thiadiazole derivatives were carried out, and the compounds were examined for their *in vitro* anticancer activity against a panel of 3 cell human cancer cell lines i.e. murine leukemia cells (L1210/0) and human T- lymphocyte cells (Molt4/C8 and CEM/0)[18,19]. To fulfill this objective Chem 3D, Dragon, Codessa and V life software was used to develop QSAR model. Multiple linear regression analysis (MLRA) was carried out to find out the correlation between physicochemical properties and biological activity and cross validation is done by using Leave One Out (LOO) method. Partial Least Square Regression (PLSR) and Principle Component Regression (PCR) of new chemical entities were generated using V-life molecular design suite software. Best equation was selected on the basis of validation, high R^2value, low S^2 value, high F value and low p value.

MATERIALS AND METHODS

The 2D structures of compounds were drawn using Chem Draw Ultra and with the help of CHEM 3D, the different 2D structures are converted to 3D structures. These 3D structures were at last stored in the corresponding mol file. Various descriptors (1664) were calculated with the help of DRAGON. The various 3D structure files which were saved in MDL. mol files format are provided as input file for dragon. Then DRAGON calculates all the molecular descriptors for that particular 3D compound and saves it.

Molecular descriptors

It is necessary to construct numerical descriptors of a set of molecules in order to build QSAR models. A descriptor can represent a quantitative property that depends on the structure of the molecule. An advantage of the exclusive use of theoretical descriptors is that they are free of the uncertainty of experimental measurements and can be calculated for compounds not yet synthesized. Molecular descriptors (i.e., features) were computed mainly using the *DRAGON* software of Talete Srl: Milano Chemometrics and QSAR Research Group for 12 newly synthesized 2,5,6- tri substituted-imidazo(2,1-*b*)-1,3,4-thiadiazole derivatives possessing antineoplastic activity against 3 cell lines i.e. murine leukemia cells (L1210/0) and human T- lymphocyte cells (Molt4/C8 and CEM/0). The input files for descriptor calculation, containing information on atom and bond types, connectivity, partial charges and atomic spatial coordinates, relative to the minimum energy conforma-

Table 1: Structure, molecular weight and antineoplastic activity of 2,5,6 trisubstituted imidazo (2,1-*b*)-1,3,4-thiadiazole

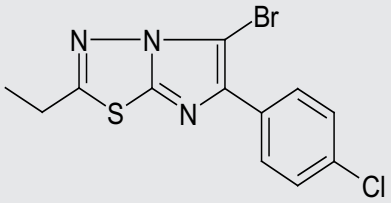
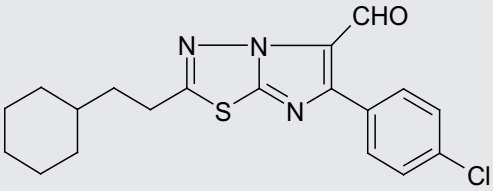
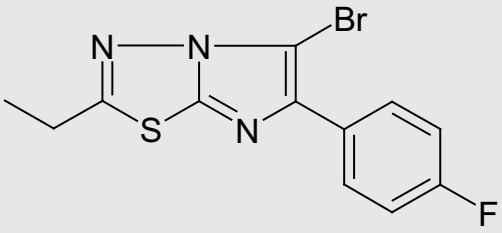
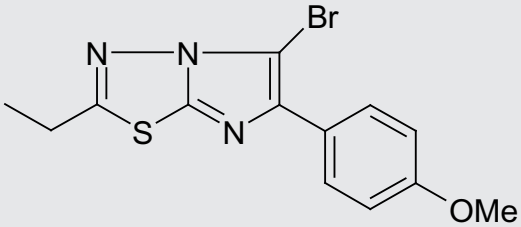
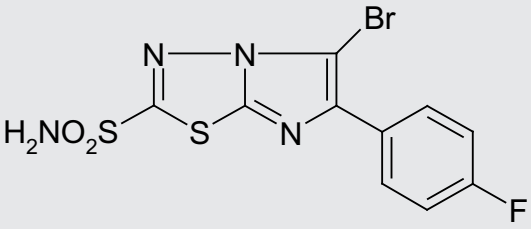
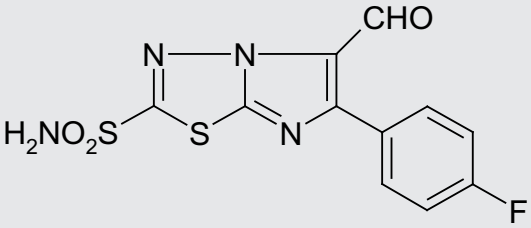
Structure	m.wt.	Activity :-IC_{50} (μM)		
		L1210/0	Molt4/c8	Molt4/c8
	342.64	500	500	414
	373.90	129	76	93
	259.33	260	270	245
	338.22	308	314	234
	377.21	6.1	1.9	1.6
Structure	**M.Wt.**	**Activity :-IC_{50} (μM)**		
		L1210/0 (MLC)	**Molt4/c8 (HTL1)**	**CEM/0 (HTL2)**
	326.33	3.2	1.8	3.7

Table 2: 2,5,6- trisubstituted-imidazo (2,1-*b*)-1,3,4-thiadiazole (L1210/0)						
ACTIVITY	**QSAR EQUATION**	**R^2**	**Q^2**	**S^2**	**F-VALUE**	**p <**
L1210/0	Activity = 10.444 + 277.50*nCp + 5622.2*Relative number of Cl atoms	0.9904	0.9820	379.7112	361.18	0.0005
	Activity = -875.46 + 6088.1*G1s – 3530.2*Relative number of S atoms	0.9877	0.9799	487.4215	280.59	0.0005
	Activity = -776.36 + 5253.4*G1s – 10.157*G(N..N)	0.9867	0.9696	527.7698	258.87	0.0005
	Activity = 589.65 + 5193.4*G1s – 380.29*Eeig02r	0.9859	0.9692	558.2017	244.57	0.0005
	Activity = -523.91–597.8*Max partial charge for a H atom [Zefirov's PC] + 4347.0*G1s	0.9857	0.9440	564.1724	241.94	0.0005
	Activity = 886.49–436.16*Eeig 08r + 06.54*Number of Cl atoms	0.9850	0.9739	593.4363	229.84	0.0005
	Activity = 953.85 + 280.74*Mor 09m – 3.5357*WNSA-1 Weighted PNSA	0.9846	0.9689	610.4225	223.35	0.0005
	Activity = 652.46 + 647.86* GATS3v – 474.08*Average Information Content (order0)	0.9841	0.9588	627.3111	217.24	0.0005
	Activity = 1143.9–48.476*G2 + 191.76*Mor09m	0.9838	0.9642	639.6663	212.98	0.0005
	Activity = 761.10 + 5226.1*G1s – 41.038*MAXDN	0.9831	0.9656	669.5578	203.31	0.0005

Table 3: 2,5,6-trisubstituted-imidazo (2,1-b)-1,3,4-thiadiazole (Molt4/c8)						
ACTIVITY	**QSAR EQUATION**	**R^2**	**Q^2**	**S^2**	**F-VALUE**	**p <**
Molt4/c8	Activity = 670.99–109.08*MAXDP + 1031.6*Min partial charge for a O atom [Zefirov's PC]	0.9823	0.9375	678.5072	194.09	0.0005
	Activity = 594.72–78.150*MAXDP + 170.54*Mor09 m	0.9704	0.9389	1134.771	114.64	0.0005
	Activity = 918.27–573.02*GATS7e–46.069*RDF125 m	0.9661	0.9114	1297.338	99.84	0.0005
	Activity = 313.32–88.942*MAXDP + 9669.0*R7v+	0.9607	0.9266	1504.663	85.60	0.0005
	Activity = 745.72–395.66*GATS8v–20.413*RDF060 m	0.9594	0.9134	1555.449	82.69	0.0005
	Activity = 957.53–507.03*GATS7e–1764.2*GGI8	0.9583	0.8725	1599.160	80.33	0.0005
	Activity = 448.55 + 60.57*MATS7m–30.207*RDF060 m	0.9579	0.8849	1613.165	79.61	0.0005
	Activity = -346.12 + 04.00*GATS2v + 550.21*Mor09p	0.9543	0.8996	1749.207	73.14	0.0005
	Activity = 1156.7–412.13*Topogr- aphic electronic index (all bonds) [Zefirov'sPC]–446.90*GATS7e	0.9533	0.8548	1790.493	71.38	0.0005
	Activity = -1110.7 + 980.0*GATS2e–242.67*GATS8p	0.9527	0.9182	1810.929	70.53	0.0005

tion of the molecule, were obtained after full geometry optimization by the *DFT* quantum-chemical method. A total of 1664 molecular descriptors of different kinds (2D and 3D) were used to describe chemical diversity of the compounds. The descriptor typology is: a) constitutional (atom and group fragments), b) functional groups, c) atom centered fragments, d) empirical, e) topological, f) walk counts, g) various autocorrelations from the molecular graph, h) Randic molecular profiles from the geometry matrix, i) geometrical, j) WHIMs, k) GETAWAYs descriptors and various indicator descriptors. The meaning of these molecular descriptors and the calculation procedure are summarized in the manual to the *DRAGON* software.

A large number (>400) of molecular descriptors can be calculated on the basis of geometrical or electronic structure of the molecules were calculated by using CODESSA software. The descriptors which are calculated by Dragon along with the descriptors, which are collected from literature, are loaded with file path into the CODESSA software. The molecular descriptors calculated in CODESSA are divided into six groups; constitutional, topological, geometrical, electrostatic, quantum-chemical and thermodynamic. As a final result, the heuristic method yields a list of the best ten correlations each with the highest R^2 and F-values. Many such attempts were carried out to obtain significant correlations for each congeneric series. Then regression plots of each correlation thus attempted were examined.

Table 4: 2,5,6- trisubstituted-imidazo (2,1-*b*)-1,3,4-thiadiazole (CEM/0)						
ACTIVITY	**QSAR EQUATION**	**R^2**	**Q^2**	**S^2**	**F-VALUE**	**p <**
CEM/0	Activity = -290.47 + 182.1*GATS4e–81.315*Kier and Hall index (order1)	0.9907	0.9813	238.99	373.91	0.0005
	Activity = -339.30 + 136.4*GATS4e–112.82*Kier and Hall index (order3)	0.9839	0.9577	414.74	213.99	0.0005
	Activity = -320.90 + 060.7*GATS4e–77.775*Kier and Hall index (order2)	0.9782	0.9300	562.95	156.73	0.0005
	Activity = -1469.6 + 310.1*GATS2e + 646.31*GATS4e	0.9727	0.9136	702.35	124.93	0.0005
	Activity = -239.54 + 114.9*GATS4e–46.699*Kier shape index (order1)	0.9713	0.9447	740.62	118.29	0.0005
	Activity = 767.91–85.334*MAXDP + 2120.1*Min partial charge (Q min)	0.9704	0.9397	761.72	114.92	0.0005
	Activity = -1150.9 + 605.4*GATS2e + 4700.8*Relative number of Cl atoms	0.9691	0.9512	795.69	109.86	0.0005
	Activity = 550.07–88.781*MAXDP + 842.12*Min partial charge for a O atom [Zefirov,s PC]	0.9682	0.9031	820.31	106.46	0.0005
	Activity = 803.52 – 500.94*GATS7e–2.6680*G (N..O)	0.9672	0.9361	846.57	103.05	0.0005
	Activity = -724.83 + 84.32*GATS4e–43.163*Qindex	0.9099	0.8306	2032.84	80.74	0.0005

Table 5: A comparison of predicted and experimentally calculated activity of test set 54, 55.						
Compound Number	**Predicted value**			**Experimental value**		
	L1210/0	**Molt4/c8**	**CEM/0**	**L1210/0**	**Molt4/c8**	**CEM/0**
54	287.9427	283.9947	146.2257	304	252	243
55	10.4438	0.4909	6.5024	8.1	5.0	5.3

Table 6: Partial Least Square Regression (PLSR) and Principle Component Regression (PCR) of L1210/0		
	Partial Least Square Regression (PLSR)	**Principle Component Regression (PCR)**
QSAR equation	-4.7934-2.0485* SssSE-index	-4.7934-2.0485* SssSE-index
N (train/test)	10/2	10/2
R^2	0.8926	0.8926
Q^2	0.8474	0.8474
F test	66.5069	66.5069
Descriptor	SssSE-index	SssSE-index

Table 7: Partial Least Square Regression (PLSR) and Principle Component Regression (PCR) of Molt4/c8.		
	Partial Least Square Regression (PLSR)	**Principle Component Regression (PCR)**
QSAR equation	-4.7020-2.0834* SssSE-index	-4.7020-2.0834* SssSE-index
N (train/test)	10/2	10/2
R^2	0.8637	0.8637
Q^2	0.8043	0.8043
F test	50.6826	50.6826
Descriptor	SssSE-index	SssSE-index

Table 8: Partial Least Square Regression (PLSR) and Principle Component Regression (PCR) of (CEM/0)

	Partial Least Square Regression (PLSR)	Principle Component Regression (PCR)
QSAR equation	-4.5296-1.9970* SssSE-index	-4.5296-1.9970* SssSE-index
N (train/test)	10/2	10/2
R^2	0.8484	0.8484
Q^2	0.7768	0.7768
F test	44.7623	44.7623
Descriptor	SssSE-index	SssSE-index

Residual plots were also examined for absence of randomization and distinct patterns in order to eliminate chance correlations. The statistical significance of each correlation was determined on the basis of the value of F-criterion and magnitude of cross-validated R^2. The values of computed F-ratio were compared with the critical values tabulated in statistical texts and level of significance discerned. The correlation found to be statistically significant were compiled from CODESSA software.

Principle component regression (PCR) and partial least square regression (PLS) were calculated by using V life sciences software.

RESULTS

A series of 2,5,6-trisubstituted imidazo(2,1-*b*)-1,3,4-thiadiazole derivatives possessing antineoplastic activity against 3 cell lines i.e. murine leukemia cells (L1210/0) and human T- lymphocyte cells (Molt4/C8 and CEM/0) were taken for the study.[18,19] QSAR studies were performed on these 12 newly synthesized molecules. The structures and their activity are reported in Table 1.

The final QSAR equations for each anticancer cell line, along with their respective Q^2, R^2, S^2, F-value and p-value is given in Table 2, 3 and 4.

Partial Least Square Regression (PLSR) and Principle Component Regression (PCR) for each cell line are given in Table 6, 7 and 8.

DISCUSSION

The results obtained in Table 2 shows that the antineoplastic activity on L1210/0 cell line of 2,5,6- trisubstituted imidazo(2,1-*b*)-1,3,4-thiadiazole depends positively on relative number of Cl atoms, 2D (GATS3v) and 3D (Mor09m) autocorrelation and negatively on relative number of S atoms, geometrical (G2), topological (MAXDN), eigen value (Eeig) and whem (G1s) descriptors. The activity is inversely dependent on the geometric distance between nitrogen atoms. Thus it can be said that multiple substitution of the benzene ring with chlorine atom and absence of sulphonamide group are good of this kind of activity.

The results of Molt4/c8 (Table 3) activity shows a negative dependence on topological (MAXDP), radical distribution function (RDF) and 2D autocorrelation (GATS), where as 3D Morse (Mor) and Getaway ($R7v^+$) descriptors are showing positive correlation thus they are directly proportional to the activity.

The results of CEM/0 (Table 4) show that MAXDP descriptor is inversely proportional to the activity. If the distance between nitrogen and oxygen increases [G (N..O)] activity decreases. The GATSe 2D autocorrelation shows a positive high dependence on Sanderson electro negativity.

A further validation of QSAR models was done by using two test set compounds (54, 55). The predicted activity of these two compounds using the most suitable equation which is giving the best predicted activity from each cell line i.e. equation 1 (for L1210/0), equation 7 (for Molt4/c8), equation 10 (for CEM/0); is given in Table 5. This suggested that the numbers of Cl atoms, functional group count (nCp) and 2D autocorrelation (MATS7m, GATS4e) descriptors are positively contributing towards the activity, where as RDF (RDF060m) and topological (Qindex) descriptors are negatively contributing towards the activity.

The results of PLSR and PCR (Table 6, 7 and 8) show that the presence of descriptor SssSE-index shows the importance of electronic of Sulphur atom (bonded with two single non-hydrogen atoms) in the molecule and is inversely proportional to the activity. This also suggested that the increase in electronegative atom environment adjacent to indicated Sulphur atom (SssS type) would result in increase in the activity.

CONCLUSION

The final mathematical models furnished significant statistical correlations, possessing good R^2=0.99 and Q^2= 0.98 values. The models generated where subjected to

validation using test set compounds which are showing good predictive ability.

An important and common inference, which can be drawn from both the QSAR studies (Codessa and V life) is that, that the electronegative sulphur is important atom in the molecule and has major role to play in the activity of their 2,5,6- trisubstituted imidazo (2,1-*b*)-1,3,4-thiadiazole derivatives. Using these models further designing of trisubstituted imidazo-thiadiazoles can be done, which will have higher probability of being active molecules.

ACKNOWLEDGEMENT

We are grateful to Dr. S.K. Karki for providing us the data of the compounds pertaining to anticancer activity and his support in the work.

CONFLICT OF INTEREST

Authors declare no conflict of interest in this research work

SUMMARY

- Imidazoles being good pharmacophore for anticancer series were exploited for their potential in the present study.
- Some new 2,5,6–trisubstituted imidazo(2,1-b)-1,3,4–thiadiazole possesing antineoplastic potential against 3 cell lines i.e. murine leukemia cells (L1210/0) and human T- lymphocyte cells (Molt4/C8 and CEM/0) were selected for studies.
- Codessa and Vlife software were used to generate QSAR models. MLRA, PCR AND PLSR are the statistical tools employed for the study.
- The models developed had shown good statistical correlation with $R^2 = 0.99$ and $Q^2 = 0.98$. The QSAR models generated were also validated by using test compounds which have shown comparable results to the experimental values.

About Author

Dr Sonal Dubey: Is presently working as Professor, Vice Principal and HOD Dept. of Pharm. Chemistry, Krupanidhi College of Pharmacy. She has 12 years of teaching and 19 years of research experience. Her field of interest are computer aided drug designing and synthetic chemistry in the area of anti cancer, anti HIV and anti TB compounds. She has 37 research papers and one book to her credit.

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