2D QSAR Study of 1, 3, 4 – Oxdiazole Possessing Benzimidazole Moiety as Potential Anticancer Agents

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ABSTRACT

Recently Oxadiazole derivatives, such as 1, 3, 4-Oxadiazoles have been discovered as novel anti-cancer agents. Quantitative Structure Activity Relationship studies have been conducted on a series (33 compounds) of 1, 3, 4-Oxadiazoles with selective anti-cancer activity using ChemOffice v.8.0 software. The best prediction has been obtained for anti-cancer activity (R^2 = 0.941, Q^2 = 0.986). The equation emphasized the importance of (MATS5m) Moran Autocorrelation (By Atomic Masses), (GATS5m) Gaery Autocorrelation (By Atomic Masses), (GATS8e) Gaery Autocorrelation (By Atomic Sanderson Electro-negativities), (SP19) Shape Profile (Randic Molecular Profile), (MAXDN) Maximal Electrotopological Negative Variation and (Km) K Global Shape Index (By Atomic Masses) parameters on biological activity. The equation is validated by test set (8 compounds). The information obtained from this 2D- QSAR may be utilized in the design of more potent 1, 3, 4-Oxadiazole analogs and anti-cancer agents.

Keywords: 1, 3, 4-Oxadiazole, 2D-QSAR, anti-cancer agents, MATS5m, GATS5m, GATS8e, SP19, MAXDN

INTRODUCTION

Cancer chemotherapy has entered a new field of molecularly targeted therapeutics, which is highly selective and not associated with the serious toxicities of conventional cytotoxic drugs [1]. Telomerase keeps its activity in the early stages of life cycle maintaining telomere length and the chromosomal integrity of frequently dividing cells, but becomes dormant in most somatic cells during adulthood [2]. In cancer cells, however, telomerase gets reactivated and works tirelessly to maintain the short length of telomeres of rapidly dividing cells, leading to their immortality [3]. Therefore, telomerase has been proposed as a potential and highly selective target for the development of a novel class of anticancer agents [4]. Oxadiazole derivatives play a significant role in various pharmaceutical applications [5, 6]. As an important class of heterocyclic compound, 1, 3, 4-oxadiazoles show broad spectrum of bioactivities [7-12]. Among these, a few differently substituted 1, 3, 4-oxadiazoles have exhibited potent antitumor activities particularly [13-15]. Of the various human diseases, cancer has proven to be one of the most intractable diseases to which humans are subjected, and as yet no practical and generally effective drugs or methods of control are available. Therefore, identification of novel potent, selective and less toxic anti-cancer agent's remains one of the most pressing health problems [16]. Targeting tubulin in rapidly dividing tumor cells has been a well validated strategy for cancer therapy [17-19]. Benzimidazole derivatives are well known for their anti-inflammatory activity and more recently have been discovered to have anticancer effect [20]. Therefore, in the present paper we planned to incorporate the Benzimidazole moiety with 1, 3, 4-oxadiazole to combine the benefits of their effects to give a compact structure with expected anticancer activity.

MATERIALS AND METHODS

Data Set

It was reported that pharmacological evaluation of 1, 3, 4-oxadiazole derivatives in vitro against 2-cell lines MCF-7 (breast) and HEPG2 (liver) revealed them to possess high anti-tumor activities with IC_{50} values ranging from 2.67 to 20.25 (mg/mL). 1, 3, 4-Oxadiazole derivatives of 33 compounds were divided into a training set of 25 compounds (Table 1 & Figure 1) and test set of 8 compounds (Table 2 & Figure 2). The IC_{50} data were used for QSAR analysis as dependent parameters after converting them into reciprocal of the logarithm of IC_{50} (pIC_{50}). The ratio of training set to test set is approximate 3:1.

Table 1: Training set used for anti-cancer activity

Compound No.	Observed Bio-Activity	Calculated Bio-Activity
6. I	0.818226	0.822843
6. II	0.788168	0.792342
6. III	0.762679	0.773194
6. IV	0.843855	0.844076
7. V	0.873321	0.869012
7. VI	0.895423	0.890299
7. VII	0.873321	0.867308
7. VIII	0.879669	0.875373
7. IX	0.863917	0.891129
7. X	0.859138	0.856187
7. XI	0.829304	0.849621
7. XII	0.91698	0.912308
7. XIII	0.89487	0.892472
7. XIV	0.915927	0.914315
7. XV	0.873321	0.867106
7. XVI	0.870404	0.864823
7. XVII	0.815578	0.816943
7. XVIII	0.862728	0.854653
7. XIX	0.860937	0.854127
7. XX	0.867467	0.864853
7. XXI	0.842609	0.837631
7. XXII	0.865696	0.877091
7. XXIII	0.873321	0.873067
7. XXIV	0.836324	0.83481
7. XXV	0.869818	0.863259

Table 2: Test set used for anti-cancer activity

Compound No.	Observed Bio-Activity	Calculated Bio-Activity
7. XXVI	0.863917	0.854591
7. XXVII	0.9154	0.921831
7. XXVIII	0.884795	0.889828
7. XXIX	0.884795	0.889876
7. XXX	0.856729	0.852536
7. XXXI	0.85248	0.84328
7. XXXII	0.859138	0.853893
7. XXXIII	0.913814	0.9173

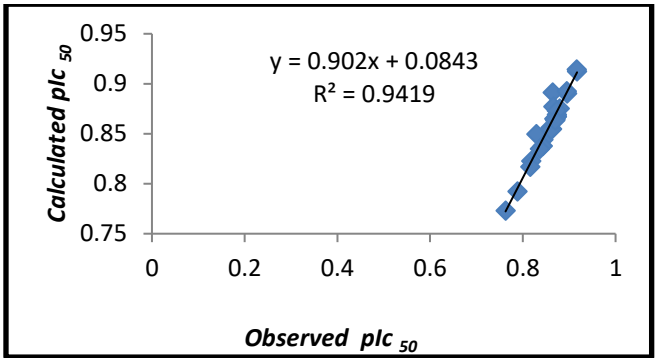


Figure 1: Plot of observed vs calculated pIC_{50} values for Training set compounds

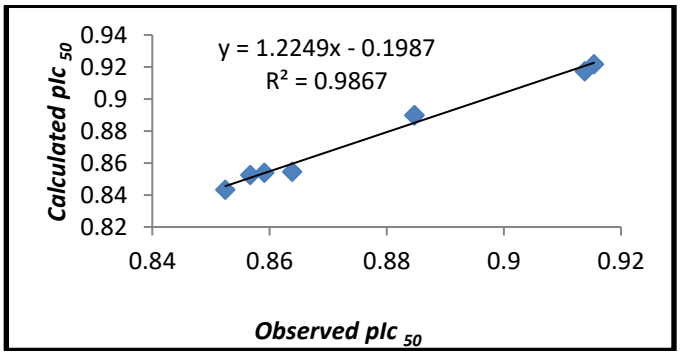


Figure 2: Plot of observed Vs calculated pIC_{50} values for Test set compounds

Energy Minimization And Geometry Optimization

The molecular structure of all 33 compound were sketched using Chem3D Ultra (version 8.0) software of Chemoffice and subjected to energy minimization technique using Allinger's Molecular Mechanics (MM_2) force fields followed by geometry optimization using semi empirical Quantum mechanics based on AM-1 (Austin

Model-1). Hamiltonian approximations method and closed shell (restricted) wave function available in MOPAC module by fixing Root Mean Square (RMS) gradient as 0.1 and 0.001 kcal/molA^0 respectively was used for calculating partial atomic charges and electronic density on various atoms. Charges were kept as mulliken and maximum numbers of iterations was set to 1000.

Various physicochemical parameters were calculated with the help of DRAGON (version 1.11 2001). Total 842 parameters were calculated. Out of these 842 parameters only 6 parameters were used in development of best equation. These 6 parameters were shown in Table 3.

Molecular Descriptors And Statistical Methods

The physicochemical parameters were taken as independent variables and biological activity (in terms of negative logarithms of biological inhibition constants) values as dependent variable. The best equation was developed with the help of best correlation matrix and regression analysis.

The predictive power of equation was validated by LOO cross validation equation Predicted residual sum of square [PRESS], cross validated correlation co-efficient r^2 (Q^2) and SDEP were considered for validation of this equation. The result from cross validated analysis were expressed as the cross validated squared correlation co-efficient Q^2.

$$\mathbf{Q^2 = 1-\Sigma(Y_{pred} - Y_{act})^2 / \Sigma (Y_{act} - Y_{mean})^2}$$

Where Ypred, Yact, Ymean are predicted, actual, and mean values of the target property (pIC_{50}) respectively. $\mathbf{\Sigma (Y_{pred} - Y_{act})^2}$ is the Predictive Residual Error Sum of Squares (PRESS).

PRESS is an important cross validation parameter as it is a good approximation of the real predictive error of the equations. To further assess the robustness and statistical confidence of the derived equations, bootstrapping analysis was performed

Table 3: List of parameters used for developing QSAR equation

Compd No.	MATS 5m	GATS 5m	GATS 8e	SP19	MAXDN	Km
6.I	-0.04	1.93	2.22	11.55	2.48	0.66
6.II	0.01	1.85	2.01	10.06	2.48	0.61
6.III	0.06	1.84	2.13	10.41	2.51	0.58
6.IV	-0.03	1.79	2.17	11.75	2.48	0.70
7.V	-0.05	1.86	2.42	10.31	2.47	0.75
7.VI	-0.02	1.80	2.46	11.38	2.46	0.79
7.VII	-0.03	2.06	2.49	10.26	2.46	0.75
7.VIII	-0.01	1.51	2.36	11.17	2.46	0.76
7.IX	0.01	1.49	2.24	10.20	1.22	0.82
7.X	0.00	1.49	2.33	11.12	2.47	0.72
7.XI	0.05	1.85	2.26	10.24	2.49	0.72
7.XII	-0.01	1.54	2.51	11.57	2.46	0.83
7.XIII	0.01	0.80	2.49	11.27	2.46	0.79
7.XIV	-0.03	1.56	2.49	12.44	2.45	0.82
7. XV	-0.03	2.08	2.52	10.27	2.45	0.75
7. XVI	-0.04	2.00	2.34	10.49	2.46	0.74
7.XVII	0.01	2.14	2.33	10.97	2.54	0.65
7.XVIII	0.06	1.40	2.40	10.35	2.48	0.73
7.XIX	0.02	1.91	1.92	10.88	2.89	0.73
7.XX	-0.02	1.72	2.41	11.44	2.47	0.74
7.XXI	0.01	2.22	2.09	11.70	2.51	0.70
7.XXII	0.07	2.43	1.70	12.32	5.75	0.73
7.XXIII	-0.07	1.90	2.07	12.50	2.61	0.75
7.XXIV	0.05	1.79	2.53	11.33	2.48	0.69
7.XXV	0.01	1.86	2.26	11.46	2.46	0.74
7.XXVI	0.05	1.84	2.01	11.72	2.46	0.73
7.XXVII	0.01	0.82	2.64	14.77	2.46	0.82
7.XXVIII	-0.07	2.02	2.55	14.00	2.47	0.77
7.XXIX	-0.17	2.30	2.46	12.36	2.49	0.77
7.XXX	0.06	1.84	1.87	12.45	2.98	0.72
7.XXXI	0.07	1.84	1.68	12.75	2.46	0.71
7.XXXII	0.01	1.86	2.26	11.45	2.46	0.72
7.XXXIII	-0.06	2.03	2.74	13.74	2.46	0.82

The r^2_{bs} is an average squared correlation co-efficient calculated during validation, which is computed from a subset ofvariables used one at a time for validation. The statistical parameters considered to compare and select the generated QSAR equations were correlation co-efficient(r), standard deviation (s), sequential Fischer (F) test, cross validated correlation co-efficient (Q^2). To validate the derived equation, the overall predictive ability of that analysis was evaluated by the terms r^2_{pred} and calculated using this formula [22, 23]

$$\mathbf{r^2_{pred} = SD - PRESS/SD}$$

Where SD is the sum of the squared deviation between the biological activities of the test set molecules and the mean activity value of the training set molecules. PRESS is the predictive error sum of squares derived from Leave-One-Out methods.

RESULTS AND DISCUSSIONS

Among the several generated QSAR equation; the best equation was selected on Standard deviation (S), sequential Fischer test (F), bootstrapping (r^2), chance, cross validated correlation co-efficient (Q^2) value, S_{PRESS}, standard deviation of error prediction (SDEP) and predictive squared correlation co-efficient of the test set (r^2_{pred}).

QSAR equation for Anti-Cancer activity of the 1, 3, 4-Oxadiazole derivative is

B.A. = - 0.42173 + (0.060597*MATS5m) + (0.004561*GATS5m) - (0.00852*GATS8e) - (0.00241*SP19) - (0.00801*MAXDN) - (0.51844* Km)

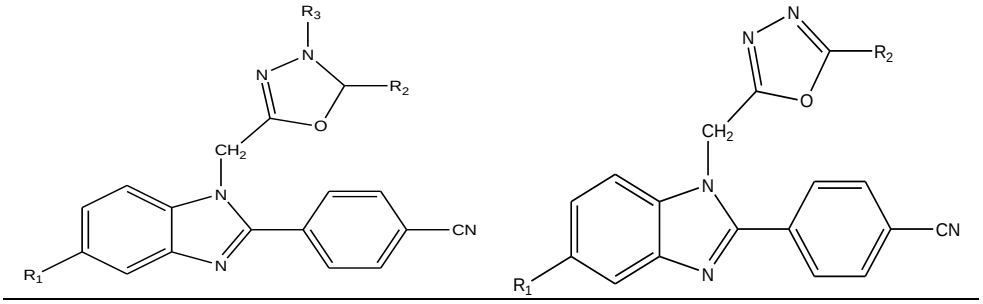
[n=25, r^2= 0.941, variance=0.0550818, s.d. = 0.0380, F = 71.422, Bootstrapping r^2 = 0.9428, chance < 0.001, Q^2= 0.986, S_{PRESS}. = 0.3424114, S_{DEP} = 0.2012605, $r^2_{pred.}$ = 0.6750]

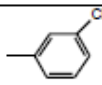
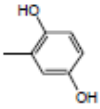
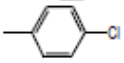
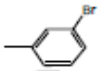
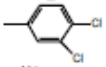
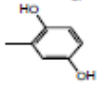
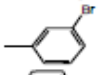
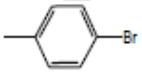
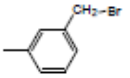
On the basis of various significant statistical parameters; best equation was selected as a representation to explore the factors responsible for anticancer activity. Equation for anticancer activity shows better correlation co-efficient which accounts for more than 80% of the variance in the activity (Table 4). The intercorrelation among parameters is less than (0.3), indicating orthogonality among the descriptors used for deriving the equations. In multivariable equation, the dependent variables can be predicted from a linear combination of the independent variables. The data showed an overall internal statistical significance better than 99.9% as it exceeded the tabulated F value (71.422). The equation was further tested for outlier by the Z-score method and no compound was found to be an outlier; suggesting that the equation is able to explain the structurally diverse analogs and is helpful in designing more potent compound using physicochemical parameters. The predictive power of the equation was validated by Leave-One-Out cross validation method. The cross validated square correlation co-efficient (Q^2= 0.986); predictive residual sum of square (Spress=0.3424114); standard deviation error of prediction (SDEP=0.2012605) suggested a good internal consistency as well as predictive ability of the equation. The bootstrapping r^2 is at par with conventional squared correlation co-efficient (r^2). The robustness and applicability for further optimization of the molecule was explained by significant r^2_{pred} value. The selected equation fulfills the statistical validation criteria to a significant extent to be useful as theoretical basis for proposing more potent compounds.

Equation for anti-cancer activity shows that parameters like Moran Autocorrelation (influence by atomic mass), Gaery Autocorrelation (By Atomic Masses), Gaery Autocorrelation (influence by electro negativity), Shape Profile, and Maximal Electrotopological Negative Variation contributed in biological activity negatively while Km contributed positively towards biological activity.

In the present study, we have screened 6 preselected descriptors for 33 of 1, 3, 4-Oxadiazole derivatives multiple linear regression analysis (Table 3). The inter-correlation of the descriptors used in the selected models was very low. The correlation matrix for the descriptors used is shown in Table 5

Table 4: Data set used for 2D-QSAR Study of 1, 3, 4-Oxdiazole



Compound No.	R^1	R^2	R^3	IC_{50}
1	$-NO_2$		$-COCH_3$	6.58
2	$-NO_2$		$-COCH_3$	6.14
3	$-NO_2$		$-COCH_3$	5.79
4	$-NO_2$		$-COCH_3$	6.98
5	$-NO_2$		-	7.47
6	$-NO_2$		-	7.86
7	$-NO_2$		-	7.47
8	$-NO_2$		-	7.58
9	-Cl		-	7.31
10	$-NO_2$		-	7.23
11	$-NO_2$		-	6.75
12	$-NO_2$		-	8.26
13	$-NO_2$		-	7.85
14	$-NO_2$		-	8.24
15	$-NO_2$		-	7.47
16	$-NO_2$		-	7.42
17	$-NO_2$		-	6.54

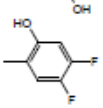
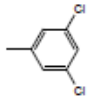
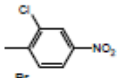
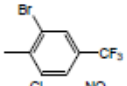
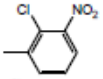
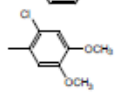
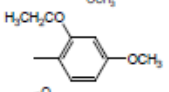
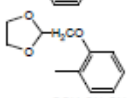
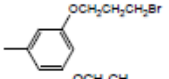
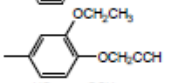
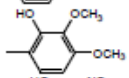
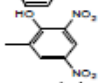
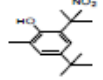
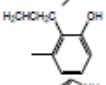
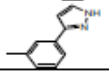
Compound No.	R^1	R^2	R^3	IC_{50}
18	$-NO_2$		-	7.29
19	$-NO_2$		-	7.26
20	$-NO_2$		-	7.37
21	$-NO_2$		-	6.96
22	$-NO_2$		-	7.34
23	$-NO_2$		-	7.47
24	$-NO_2$		-	6.86
25	$-NO_2$		-	7.41
26	$-NO_2$		-	7.31
27	$-NO_2$		-	8.23
28	$-NO_2$		-	7.67
29	$-NO_2$		-	7.67
30	$-NO_2$		-	7.19
31	$-NO_2$		-	7.12
32	$-NO_2$		-	7.23
33	$-NO_2$		-	8.2

Table 5: Correlation Study of anti-cancer agents by using different QSAR parameters

	MATS5m	GATS5m	GATS8e	SP19	MAXDN	Km	Observed B.A.
MATS5m	1						
GATS5m	-0.21277	1					
GATS8e	-0.49684	-0.32859	1				
SP19	-0.20173	-0.09857	0.111386	1			
MAXDN	0.269386	0.377375	-0.44415	0.19143	1		
Km	-0.35045	-0.35654	0.485366	0.41323	-0.12358	1	
Observed B.A.	0.390345	0.308327	-0.48602	0.49486	0.014817	0.956474	1

CONCLUSION

The fundamental properties of the molecule that are overwhelmingly involved in selective activity of 1, 3, 4-Oxadiazole derivatives are geometrical, electronic, topological and thermodynamic parameters. It is apparent from selected QSAR equation that the geometric (MATS5m, SP19) electronic, (GATS5m) electronic, (GATS8e), topological (MAXDN), and thermodynamic (Km) play an important role in the selective inhibition of anti-cancer activity. Based on understanding from selected equation, it may be concluded that 1, 3, 4-Oxadiazole derivatives having larger geometry or bulky group decrease the anti-cancer activity. Derivatives which are having smaller shape & bearing electronegative substituent improve the anti-cancer activity.

REFERENCES

[1]. L. Seymore, Novel anti-cancer agents in development: exciting prospects and new challenges, Cancer Treat. *Rev*. 1999, *25*, 301-312.

[2]. Wright WE, JW Shay, Cellular senescence as a tumor-protection mechanism: the essential role of counting, Curr Opin Genet Dev. 2001;11(1):98-103.

[3]. WE Wright, JW Shay, Cellular senescence as a tumor-protection mechanism: the essential role of counting, Curr Opin Genet Dev. 2001;11(1):98-103.

[4]. A G Bodnar, M Ouellette, M Frolkis, S E Holt, C P Chiu, G B Morin, et al; Extension of Life-Span by Introduction of Telomerase into Normal Human Cells, *Science*. 1998, *279*, 349-352.

[5]. LR Kelland, Small molecule anticancer drugs, IDrugs. 1999;2(6):550-2.

[6]. P Conti, C Dallanoce, M De Amici, C De Micheli, KN Klotz, Synthesis of new delta 2-isoxazoline derivatives and their pharmacological characterization as beta-adrenergic receptor antagonists, Bioorg Med Chem. 1998;6(4):401-8.

[7]. YK Kang, KJ Shin, KH Yoo, KJ Seo, SY Park, DJ Kim, et al; Synthesis and biological evaluation of novel 1beta-methylcarbapenems having a new moiety at C-2, Bioorg Med Chem Lett. 1999;9(16):2385-90.

[8]. SJ Dolman, F Gosselin, PD O Shea, IW Davies, Superior reactivity of thiosemicarbazides in the synthesis of 2-amino-1,3,4-oxadiazoles, J Org Chem. 2006;71(25):9548-51.

[9]. CJ Chen, BA Song, S Yang, GF Xu, PS Bhadury, LH Jin, et al. Synthesis and antifungal activities of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole and 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives, Bioorg Med Chem. 2007;15(12):3981-9.

[10]. A Zarghi, SA Tabatabai, M Faizi, A Ahadian, P Navabi, V Zanganeh, Synthesis and anticonvulsant activity of new 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles, Bioorg Med Chem Lett. 2005 Apr 1;15(7):1863-5.

[11]. YP Luo, GF Yang, Discovery of a new insecticide lead by optimizing a target-diverse scaffold: tetrazolinone derivatives, Bioorg Med Chem. 2007 Feb 15;15(4):1716-24..

[12]. MT Khan, MI Choudhary, KM Khan, M Rani, Atta-ur-Rahman, Structure-activity relationships of tyrosinase inhibitory combinatorial library of 2,5-disubstituted-1,3,4-oxadiazole analogues, Bioorg Med Chem. 2005;13(10):3385-95.

[13]. JT Palmer, BL Hirschbein, H Cheung, J McCarter, JW Janc, ZW Yu, et al. Keto-1,3,4-oxadiazoles as cathepsin K inhibitors, Bioorg Med Chem Lett. 2006;16(11):2909-14.

[14]. C Loetchutinat, F Chau, S Mankhetkorn, Synthesis and evaluation of 5-Aryl-3-(4-hydroxyphenyl)-1,3,4-oxadiazole-2-(3H)-thiones as P-glycoprotein inhibitors, Chem Pharm Bull (Tokyo). 2003;51(6):728-30.

[15]. AH Abadi, AA Eissa, GS Hassan, Synthesis of novel 1,3,4-trisubstituted pyrazole derivatives and their evaluation as antitumor and antiangiogenic agents, Chem Pharm Bull (Tokyo). 2003;51(7):838-44.

[16]. BG Szczepankiewicz, G Liu, HS Jae, AS Tasker, IW Gunawardana, TW von Geldern, et al. New antimitotic agents with activity in multi-drug-resistant cell lines and in vivo efficacy in murine tumor models, J Med Chem. 2001;44(25):4416-30.

[17]. S Eckhardt, Recent progress in the development of anticancer agents, Curr Med Chem Anticancer Agents. 2002;2(3):419-39..

[18]. D Bray, Cell Movements: From Molecules to Motility, second ed. Garland Publishing, New York, 2001.

[19]. MA Jordan, L Wilson, Microtubules as a target for anticancer drugs, Nat. Rev. Cancer. 2004, 4, 253–265.

[20]. AS Kiselyov, K Balakin, SE Tkachenko, AV Ivachtchenko, Recent developments in discovery and development of antimitotic agents, Anti-Cancer Agents Med. Chem. 2007, 7, 189–208.

[21]. T Yamori, A Matsunaga, S Sato, K Yamazaki, A Komi, K Ishizu, et al. Potent antitumor activity of MS-247, a novel DNA minor groove binder, evaluated by an in vitro and in vivo human cancer cell line panel, Cancer Res. 1999 Aug 15;59(16):4042-9.

[22]. M Jaiswal, PV Khadikar, A Scozzafava, CT Supuran, Carbonic anhydrase inhibitors: the first QSAR study on inhibition of tumor-associated isoenzyme IX with aromatic and heterocyclic sulfonamides, Bioorg Med Chem Lett 2004; 14: 3283-3290.

[23]. PP Roy, K Roy, On some aspects of variable selection for partial least squares regression models, QSAR Comb Sci 2007; 27: 302-313.