RESEARCH ARTICLE

QSAR modeling on Quinazolinonyl Pyrazolines and Quinazolinoyl Isoxazolines as Anticonvulsant Agents

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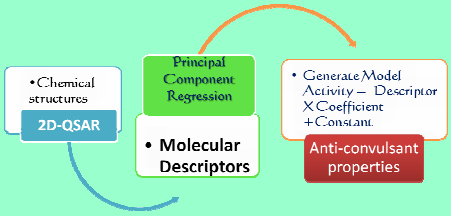
ABSTRACT

Two dimensional (2D) quantitative structure activity relationship (QSAR) analyses have been performed on a series of known quinazolinonyl derivatives as anticonvulsant agents. This study was performed on compounds having quinazolinonyl ring substituted at position 3 with pyrazoline and isoxazoline moieties to find out the structural requirements for anticonvulsant activity. Principal component regression, combined with stepwise forward-backward variable selection method resulted with r^2, q^2 and pred_r^2 values of 0.6109, 0.5487 and 0.6188, respectively. The validation of models was performed through the leave-one-out cross technique in conjunction with external validation. The results thus obtained may provide useful substitution patterns on the quinazolinonyl skeleton and may also help to design more potent compounds.



Keywords: QSAR, Principal component regression, quinazolinonyl pyrazolines, quinazolinonyl isoxazolines , MMFF

INTRODUCTION

Epilepsy is one of the most common neurological disorders, affecting about 1% of the world's population. The currently available anticonvulsants are effective in reducing the severity and number of seizures in less than 70% of patients. Moreover, their usage is associated with undesirable side effects ranging from cosmetic (gingival hyperplasia) to life threatening (hepatotoxicity, megaloblastic anemia). Therefore, the search for safe and more potent anticonvulsant remains a drug design priority and the continued search for the safer and more effective antiepileptic drugs is urgently necessary.

Literature survey reveals that various derivatives of quinazolinone, thienopyrimidine and pyridopyrimidine shown very promising anticonvulsant activity along with other pharmacological activities. Methaqualone [1] [2-methyl-3-(*o*-tolyl)-4-(3*H*) quinazolinone], is an important landmark in the field of synthetic anticonvulsant drugs. This compound possesses the potent pharmacodynamic nucleus i.e. quinazolinone. Various quinazolinone congeners possess diverse type of biological activities viz. anticonvulsant [2-4], CNS depressant [5], hypnotic [6], psychotropic [7], antiparkinsonian[8] and analgesic[9] activities. It has been shown that quinazolinone system possesses variable sites at positions 2 and 3 which can be suitably modified by the introduction of different heterocyclic moieties to yield the potential anticonvulsant agents [10,11]. Furthermore, a large number of pyrazolines [12,13] and isoxazoline [14, 15] derivatives were found to possess anticonvulsant activity. In spite of the fact that according to the literature thousands of quinazolinone, pyrazoline and isoxazoline related compounds have been synthesized and tested for a possible central nervous system depressant and anticonvulsant activity [16], there has

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been a limited attempt has been to correlate their structural parameters with the activity.

QSAR, which stands for "quantitative structure-activity relationships", is a method that relates chemical structure to biological or chemical activity using mathematical models[17]. If the activity of a set of ligands can be determined, a model can be constructed to describe this relationship. Quantifying the structure and activity of a ligand is important in the modeling process. A structure cannot be represented by a mere value. Instead, a set of properties, usually known as the "descriptors", is computed from the structure and used to quantify it. By using structural descriptors as independent variables and activity as a dependent variable, a model can be built to describe the relationship between the two [18]. After a QSAR model is built and validated, it can predict the biological activity of novel molecules from their structural properties [19].

In this work, it was envisaged to use this ligand based drug design approach to elucidate the structural correlates of reported anticonvulsant activity in the series of 30 compounds containing pyrazoline and isoxazoline moieties in the quinazolinone nucleus at position -3 ,on convulsions produced by maximal electroshock (MES) in albino rats.

MATERIALS AND METHODS

All quinazolinonyl-pyrazolines (4a-4j) and quinazolinonyl-isoxazolines (5a-5j) in this study were synthesized and pharmacologically evaluated as previously described [16]. The data Set of these derivatives (30 molecules) with known anti-convulsant activities is shown in Table 1. The parameter of biological activity [BA] data determined as % inhibition values at a dose of 100mg/kg was first transformed into log BA to get a more standardized property and used as dependent variable in the QSAR study.

Energy minimization and batch optimization:

The structures of all the compounds were energy minimized and batch optimization was carried out using Merck Molecular Force Field (MMFF) before carrying out the QSAR studies. In order to correlate the physiochemical parameters of these derivatives with their anti-convulsant activities, the linear free energy relationship (LFER) model described by Hansch and Fujita[20] was used. All the 2D descriptors (thermodynamic, spatial, electronic and topological parameters) were calculated for QSAR analysis using VLife Molecular Design Suite[21].Thermodynamic parameters describe free energy change during drug receptor complex formation. Spatial parameters are the quantified steric features of drug molecules required for its complimentary fit with receptor. Electronic parameters describe weak non-covalent bonding between drug molecules and receptor[22,23] .In order to establish a predictive structure–activity relationship, it is necessary to search for a subset with the best molecular descriptors that reflect the structural features of compounds that best correlate with the biological activity under study. For this, the compounds were divided into training and test set. This was achieved by setting aside nine compounds as test set (30%) which have regularly distributed activity. Selection of molecules in the training set and test is a key and important feature of any QSAR model. Therefore care was taken in such a way that biological activities of all compounds in test set lie within the maximum and minimum value range of biological activities of training set of compounds. A Uni-Column statistics for training set and test set was generated (Table 2) to check correctness of selection criteria for trainings and test set molecules. The maximum and minimum value in training and set were compared in a way that:

1. The maximum value of pMIC of test set should be less than or equal to maximum value of pMIC of training set.
2. The minimum value of pMIC of test set should be higher than or equal to minimum value of pMIC of training set.

This observation showed that test set was interpolative and derived within the minimum–maximum range of training set. The mean and standard deviation of log BA values of sets of training and test provide insights to relative difference of mean and point density distribution of two sets.

2D-QSAR models were generated for these data for training set of twenty one compounds (70%) using principal component regression (PCR) method. The main goal of QSAR model development is to find the best set of descriptors that will produce a stable QSAR model with the ability to predict properties of unknown compounds. For the PCR technique, stepwise forward-backward regression was chosen in the development of the QSAR model, in which a selection algorithm was used to select a subset of the input variables, *X*. The advantage of estimating a model with stepwise PCR is that only a few variables are needed to build the QSAR model [24]. The stepwise method combines two approaches, which are the forward and backward stepping. Cross validation provides a rigorous internal check on the models derived using multiple regression analysis, giving an estimate of the true predictive power of the model *i.e.*, how reliable are the predicted values for the untested compounds. The cross validation analysis was performed using leave-one-out [L.O.O] method where one compound is removed from data set and its activity is predicted using the model derived from the rest of the data set.

Model Validation

The last step in QSAR model development is model validation. It is important to evaluate the robustness and the predictive capacity or validity of the model before using the model to predict and interpret biological activities of compounds in the test set. When estimating the predictive ability of QSAR models, it is necessary to distinguish two classes of predictive power, namely the internal and external predictivity. Internal predictivity measures how accurately the model can predict the bioactivities of the set of compounds (training set) used to build the statistical model. External predictivity tries to measure the predictive power for molecules to which the model has not been subjected to before. Of the two, external predictivity is observed to be more accurate[25].

In the data, since there were few compounds which showed about the same percentage inhibition, but due to structural differences, the descriptor values obtained for these compounds were naturally different. So we didn't ignore any of the values in developing the models. The best QSAR model was selected on the basis of values of statistical parameters like r^2 (square of correlation coefficient for training set of compounds), q^2 (cross validated r^2), and pred_r^2 (predictive r^2 for the test set of compounds). All QSAR models were validated and tested for their predictability using an external test set of compounds. Statistical results generated by 2D-QSAR analysis showed that QSAR models have good internal as well as external predictability. The results obtained for actual and predicted activity are presented in Table 3 and the residuals were found to be minimal. The regression equations obtained for the different sets of activities are given below.

EXPERIMENTAL

For the QSAR study of all the structures were drawn in ACD Chem Sketch version 12.0 and were converted into the mol files. These were then optimized and converted into mol2 files. Optimization of the molecules was done to calculate the energies and optimize the geometry of the molecules by MMFF method with the setting of dielectric constant: 1, convergence criteria 0.01, maximum number of cycles: 1, 00,000 and gradient type as analytical.

The energy-minimized geometry of the compounds was used for the calculation of the various 2D descriptors (Individual, Chi, ChiV, Path count, Chi Chain, Chi V Chain, Chainpath count, Cluster, Pathcluster, Kapa, Element Count, Estate number, Estate contribution, Hydrophilic–hydrophobic and Polar surface area). The various alignment-

independent (AI) descriptors were also calculated. For calculation of alignment, the independent descriptor was assigned the utmost three attributes. The first attribute was T to characterize the topology of the molecule. The second attribute was the atom type, and the third attribute was assigned to atoms taking part in the double or triple bond. The pre-processing of the independent variables (i.e., 2D descriptors) was done by removing invariable (constant column).

Total 456 2D descriptors were calculated which remained 207 after removing the invariable columns. Random selection method was used for selection of test and training set. 2D-QSAR models were generated for these data for training set of 21 compounds using principal component regression (PCR) method. Partial least square regression method coupled with stepwise forward- backward variable selection method was used to generate QSAR equation considering log BA values as dependent variable and calculated descriptors as independent variables.

RESULTS AND DISCUSSION

Several QSAR models were generated by different methods and one significant QSAR model were finally selected on the basis of statistical parameters. Model summary of the best model is given below.

Best QSAR model for anti-convulsant activity:

log BA= (0.1138 * SssOcount) + (0.0262 * T_2_2_7) - (0.0663 * T_O_O_7) + (0.0353 * SaasCE-index) + 1.2771

n=21, s=0.07, r^2= 0.6109, r^2_se= 0.0506; q^2=0.5487, q^2_se= 0.0545, pred_r^2=0.6188, pred_r^2se=0.0514, F-Test= 34.5477

For a reliable model, the squared predictive correlation coefficient should be 0.60 [26,27]. The generated model could explain 61.09 % of variance (adjusted coefficient of variation). The leave-one-out predicted variance was found to be 54.87 %. When this model was applied for the prediction of anti-convulsant activity, the pred_r^2 was found to be 61.88 %. Hence, this model fulfilled the selection criteria with low standard error of squared correlation coefficient (r^2_se) and showed good fitness of the model (Figure-2).

Statistical analysis

The descriptors were taken as independent variables and biological activity as dependent variable. Principal component regression (PCR) method of analysis was used to derive the 2D QSAR equations. The developed QSAR models are evaluated using the following statistical measures: r^2, (the squared correlation coefficient); r^2se, (standard error of squared correlation coefficient); F test, (Fischer's value) for statistical significance; q^2, (cross-validated correlation coefficient); q^2_se, (standard error of cross-validated square correlation co-efficient); pred_r^2, (r^2 for external test set); pred_r^2se, (standard error of predicted squared regression); Z score, (Z score calculated by the randomization test); best_ran_q^2, (highest q^2 value in the randomization test). The regression coefficient r^2 is a relative measure of fit by the regression equation. It represents the part of the variation in the observed data that is explained by the regression. However, a QSAR model is considered to be predictive, if the following conditions are satisfied: r^2 >0.6, q^2 >0.6 and pred_r^2 >0.5[28,29]. The F-test reflects the ratio of the variance explained by the model and the variance due to the error in the regression. High values of the F-test indicate that the model is statistically significant. The low standard error of r^2 (r^2_se), q^2 (q^2_se) and pred_r^2 (Pred_r^2se) shows absolute quality of fitness of the model.

In order to confirm our results we predicted the anticonvulsant activities of quinazolinonyl derivatives using the model expressed by the best QSAR models (Eq. 1) and compared them with the observed values. The data presented in Table 3 and Figure 2 shows that the observed and the estimated activities are very close to each other evidenced by low values of residual activity. Further the plot of principal component regression predicted log BA values against the observed log BA values also favors the model expressed by Eq. 1 (Figure 1). The cross-validation of

the models was also done by leave one out (LOO) technique[30]. The cross-validated correlation coefficient (r^2_{cv}>0.5) values obtained for the best QSAR models indicated their reliability in predicting the anti-convulsant activity of quinazolinonyl derivatives. The model is validated by α_ran_r^2 = 0.001, α_ran_q^2 = 0.01,α_ran_ pred_r^2 = 0.01. The randomization test suggests that the developed model has a probability of less than 1% that the model is generated by chance.

The positive coefficients (45.00%) of SssOcount (Total number of oxygen connected with two single bonds), and (85 %) of T_2_2_7 (Count of number of double bounded atoms separated from any other double bonded atom by seven bonds) and 25% of SaasCE-index (Electrotopological state indices for number of carbon atom connected with one single bond along with two aromatic bonds) showed that increase in the values of this descriptor is beneficial for the anti-convulsant activity (like in compounds 4g and 5g). The next descriptor T_O_O_7 (total number of oxygen atoms separated from any other Oxygen atom by 7 bonds), indicates a negative contribution to the biologic activity.

CONCLUSIONS:

The QSAR model has been successfully developed with a good correlative and predictive ability for predicting anti-convulsant activity. This QSAR model exhibiting a high degree of accuracy was then validated by predicting the anti-convulsant activity of compounds in the external test set. The 2D-QSAR results can reveal trends in the relationship between ligand structures and their activities for these set of compounds. Analysis of 2D-QSAR model has demonstrated the important role of electronic and topological features of molecules on their anticonvulsant activity and provides details on the fine relationship linking structure and activity. This also offers clues for structural modifications that can improve the activity. These trends should prove to be an essential guide for the future work.

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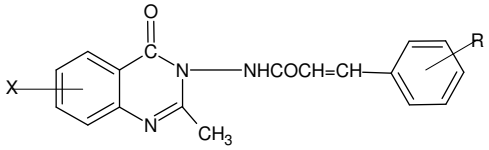

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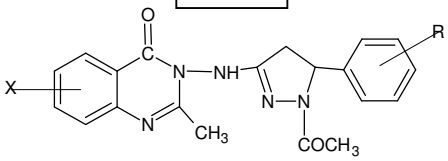

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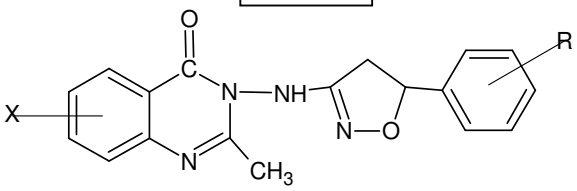

5a-j

S. No.	Compound	R	X	log BA
1	3a	H	H	1.69
2	3b	*p*-OCH_3	H	1.77
3	3c	*p*-OH	H	1.69
4	3d	*p*-$N(CH_3)_2$	H	1.69
5	3e	m-OCH_3,*p*-OH	H	1.77
6	3f	H	6-Br	1.77
7	3g	*p*-OCH_3	6-Br	1.84
8	3h	*p*-OH	6-Br	1.77
9	3i	*p*-$N(CH_3)_2$	6-Br	1.77
10	3j	*m*-OCH_3,*p*-OH	6-Br	1.69
11	4a	H	H	1.77
12	4b	*p*-OCH_3	H	1.90
13	4c	*p*-OH	H	1.77
14	4d	*p*-$N(CH_3)_2$	H	1.77
15	4e	*m*-OCH_3,*p*-OH	H	1.84
16	4f	H	6-Br	1.84
17	4g	*p*-OCH_3	6-Br	1.95
18	4h	*p*-OH	6-Br	1.90
19	4i	*p*-$N(CH_3)_2$	6-Br	1.84
20	4j	*m*-OCH_3,*p*-OH	6-Br	1.90
21	5a	H	H	1.69
22	5b	*p*-OCH_3	H	1.90
23	5c	*p*-OH	H	1.84
24	5d	*p*-$N(CH_3)$	H	1.77
25	5e	*m*-OCH_3,*p*-OH	H	1.84
26	5f	H	6-Br	1.77
27	5g	*p*-OCH_3	6-Br	1.95
28	5h	*p*-OH	6-Br	1.90
29	5I	*p*-$N(CH_3)_2$	6-Br	1.84
30	5j	*m*-OCH_3,p-OH	6-Br	1.90

Table 1: General structure of the compounds of quinazolinonyl derivatives and their biological activities

	Avg	Max	Min	Std. Dv.	Sum
Training Set	1.8104	1.9500	1.6900	0.0793	43.4500
Test Set	1.81171	1.9000	1.6900	0.0833	10.8700

Table 2: Unicolumn Statistics

S. No.	Compound	logP	Log BA		
			Observed	Predicted	Residual
1	3a	2.72	1.69	1.713698	0.023698
2	3b	2.99	1.77	1.814383	0.044383
3	3c	2.34	1.69	1.802589	0.112589
4	3d	2.82	1.69	1.773544	0.083544
5	3e	2.31	1.77	1.835046	0.065046
6	3f	3.51	1.77	1.878127	0.108127
7	3g	3.48	1.84	1.864871	0.024871
8	3h	3.14	1.77	1.835728	0.065728
9	3i	3.62	1.77	1.736311	-0.03369
10	3j	3.10	1.69	1.734946	0.044946
11	4a	4.07	1.77	1.809997	0.039997
12	4b	4.04	1.90	1.814773	-0.08523
13	4c	3.69	1.77	1.764869	-0.00513
14	4d	4.18	1.77	1.75288	-0.01712
15	4e	3.66	1.84	1.874911	0.034911
16	4f	4.86	1.84	1.852395	0.012395
17	4g	4.83	1.95	1.940493	0.01374
18	4h	4.49	1.90	1.872084	-0.02792
19	4i	4.97	1.84	1.82257	-0.01743
20	4j	4.45	1.90	1.860875	-0.03912
21	5a	3.92	1.69	1.778904	0.088904
22	5b	3.90	1.90	1.83105	-0.06895
23	5c	3.55	1.84	1.852201	0.012201
24	5d	4.03	1.77	1.772764	0.002764
25	5e	3.52	1.84	1.795961	-0.04404
26	5f	4.72	1.77	1.817697	0.047697
27	5g	4.69	1.95	1.916042	-0.03396
28	5h	4.35	1.90	1.855904	-0.0441
29	5i	4.83	1.84	1.792647	-0.04735
30	5j	4.31	1.90	1.902007	0.002007

Table 3: Observed, predicted anticonvulsant activity (log BA) and residual values of quinazolinonyl derivatives

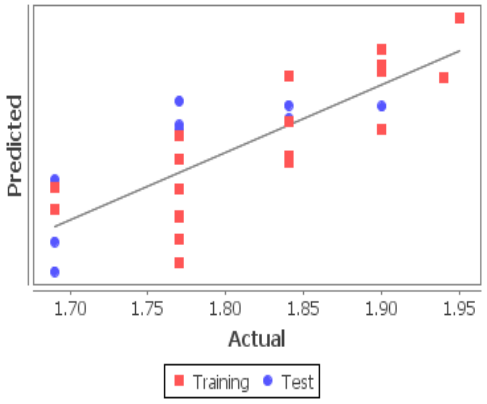

Figure 1: Plot between observed and predicted anti-convulsant activity of the compounds in the training set and test set for the principal component regression developed model.

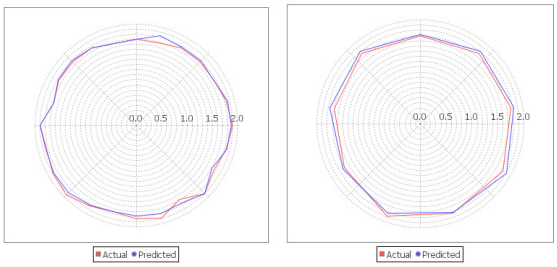

Fig. 2: Comparison of observed and predicted activity of training set and test set data

REFERENCES

1. Swift J. G., Dickens E. A., Beacker B. A. Anticonvulsant and other pharmacological activities of Tuazolone (2-methyl-3-o-tolyl-4 (3*H*) quinazolinone), *Arch. Int. Pharmacodyn.* 1960; 128: 112-125.
2. Nowrocka W., Stasko J. J. *Chem Abstr*, 2000; 132: 87507m.
3. El-Helpy A. G. Synthesis of novel-2-styryl-3-benzylidenimino- 4(3*H*)-quinazolone derivatives of expected anticonvulsant activity, *J Pharm Sci*. 1994; 14: 193-201.
4. El-Naser O. A. R., El-Sayed B. S. Synthesis and anticonvulsant activity of some new 3-(*p*-sulfamoylphenyl)-4(3*H*)-quinazolinones *Arzeim-Forsch/Drug Research*, 1994; 44: 915.
5. Ergene N., Buyuktimkin S., Capan G., Baktir G., Rollas. Synthesis and evaluation of some 3-(2-[(5-aryl-1,3,4-oxadiazole-2-yl)amino]acetamido)-2-methyl-4 (3H)-quinazolinones. *Pharmazie.* 1991; 64: 290-291.
6. Buyuktimkin S, *Chem Abstr*, 1987; 107: 51388t.
7. Lata A., Satsangi R.K., Srivastava V.K. , Kishor K. Monoamine oxidase inhibitory and CNS activities of some quinazolinones, Arzeneim Forsch. 1982; 32:1, 24-27.
8. Kumar S., Kaur H., Kumar A. Synthesis of new azetidinonyl/thiazolidinonyl quinazolinone derivatives as antiparkinsonian agents. Arab. J. Chem. 2012; 5:4, 475-484.
9. Gursoy A., Buyuktimkin S., Demirayak S., Ekinci A. C. Quinazolinones, Synthesis and Pharmacological Activities of Antipyryloxoalkylthioquinazolinones, *Arch Pharm*. 1990; 323: 623.

10. Usifoh C.O., Scriba G.K. Synthesis and anticonvulsant activity of acetylenic quinazolinone derivatives. *Arch Pharm (Weinheim),* 2000; 333:8, 261-266.
11. Archana S.V.K., Kumar A. Synthesis of newer thiadiazolyl and thiazolidinonyl quinazolin-4(3*H*)-ones as potential anticonvulsant agents. *Eur. J. Med. Chem*., 2002; 37:782–873
12. Soni N., Pande K., Kalsi R., Gupta T. K., Parmar S. S., Barthwal J. P. Inhibition of rat brain monoamine oxidase and suc-cinic dehydrogenase by anticonvulsant pyrazolines*, Res Commun Chem Pathol Pharmacol*. 1987; 56: 129-132.
13. Tripathi S., Pandey B. R., Barthwal J. P., Kishor K., Bhargava K. P. Indolylpyrazolines as monoamine oxidase inhibitors, *Indian J. Physiol Pharmacol*. 1980; 24: 155.159.
14. Lepage F., Hublot B. *Chem Abstr*, 1990; 113: 211964g.
15. Falch E., Perregaard J., Kristian S., Arne K. L. P. Froslund B; Moltzen L, *Chem Abstr*, 1996; 125: 275857e.
16. Archana, S.V.K., Chandra R., Kumar A. Synthesis of potential quinazolinonyl pyrazolines and quinazolinyl isoxazolines as anticonvulsant agents, *Indian journal of Chemistry*, 2002; 41B: 2371-2375.
17. Esposito E. X., Hopfinger A. J., Madura J. D. Methods for applying the quantitative structure-activity relationship paradigm, *Methods Mol.Bio.* 2004; 275: 131-214.
18. Bradbury S. P. Quantitative structure–activity relationships and ecological risk assessment: an overview of predictive aquatic toxicology research, *Toxicol. Lett*. 1995; 79: 229-237.
19. Lee C-H., Huang H-C., Juan H-F. Reviewing Ligand-Based Rational Drug Design: The Search for an ATP Synthase Inhibitor, *Int J. Mol.Sci.* 2011; 12: 5304-5318.
20. Hansch C., Fujita T. Method for Correlation of Biological Activity + Chemical Structure, *J. Am. Chem. Soc* 1964; 86: 1616-1626.
21. V-Life Molecular Design Suite 4.3.0, VLife Sciences Technologies Pvt. Ltd.; www.Vlifesciences.com
22. Balaban A. T. Highly discriminating distance–based topological index, *Chem. Phys. Lett.* 1982; 89: 399-404.
23. Plavsic D., Soskic M., Lers N. J. On the Calculation of the Molecular Descriptor, *Chem. Inf. Comput. Sci*. 1998; 38: 889-892.
24. Beebe K. R., Pell R. J., Seasholtz M. B. in *Chemometrics*, *a Practical Guide*; Wiley Interscience: New York, NY, USA, 1998.
25. Consonni V., Ballabio D., Todeschini R. Comments on the definition of the Q 2 parameter for QSAR validation, *J. Chem. Inf. Model.* 2009; 49: 1669–1678.
26. Dureja H., Kumar V., Gupta S., Madan A.K. Topochemical Models for the Prediction of Lipophilicity of 1,3-Disubstituted Propan-2-One Analogues *J. Theor. Comput. Chem.* 2007; 6: 435–448.
27. Wold S. Automatic search for maximum similarity between molecular electrostatic potential distributions*, Quant. Struct. Act. Relatsh.* 1991; 10: 191–193.
28. Abdel-Aziz A-M., Al-Agamy M. H. Design, synthesis and antibacterial activity of fluoroquinolones containing bulky arenesulfonyl fragment: 2D-QSAR and docking study, *Eur J. Med. Chem*. 2011; 46: 5487-5497.
29. Golbraikh A., Tropsha A. Protein tyrosine phosphatase 1B inhibitors for diabete. *J. Mol. Graph. Model.* 2002; 20: 269-276.
30. Wold S., Erikkson L. in, Waterbeemd H. van-de *Statistical validation of QSAR results, Chemometrics Methods in Molecular Design;* New York : VCH Publishers, 1995; pp 309-312.

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