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DESIGNING OF 2, 5-DISUBSTITUTED-1,3,4-THIADIAZOLE DERIVATIVES FOR THEIR ANTICONVULSANT POTENTIAL

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ABSTRACT

QSAR is the study of quantitative relationships between biological activity and the physicochemical properties of a common parent structure molecule. CS chemoffice software utilized for QSAR of series. The reported IC_{50} values were converted to negative log IC_{50} values, which were correlated with various descriptors. Upon stepwise, multiple, and sequential regression analysis of descriptor, the statistically significant QSAR equations were obtained. The correlation between the physicochemical parameters and the biological activity were found using the least squares method. The equations having good correlation coefficient (r^2), F-test value, SD values and minimum variance were validated by the cross validation method and IC_{50} and pIC_{50} values were calculated using Valstat. 5-Benzenesulphonamido-1,3,4-thiadiazol-2-sulphonamide, was designed as parent structure.

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INTRODUCTION:

With the evolution of mankind, its confrontation with newer and complex diseases has also been increased. Humanity has always been searching for new ways to overcome the disease, and one of such way is the discovery of the newer drugs for the prophylaxis and/or treating the diseases. Today medicinal chemistry has been trying to reduce the toxicity and increases the therapeutic efficacy of the existing compound by structural modification using computer aided drug design and QSAR[1]. In the early 1960s, one could expect to discover a marketable compound out of 2000-3000 tested molecules, where-as this ratio in now close to 1 in 10000 and biological testing expenses have increased dramatically. Good drug must be replaced by better one, which often seemed to result from a small change in structure of the original or "lead" compound[2]. Drug design is inherently multi-disciplinary and involves the integration of vast amount of complex information, so computational methods can aid in this process. The strategy use in the design of drugs, involved a change in shape such that the new drug had a better 'fit' for receptor. Other strategies involved the change in the physical properties of the drug such that its distribution, metabolism, or receptor binding interactions were affected[3].

The primary objective of the research is to increase the efficiency by designing new drug by making structural modification with the help of QSAR & CADD where the chemical feature of molecules or series of molecules have been correlate to biological activities[4].

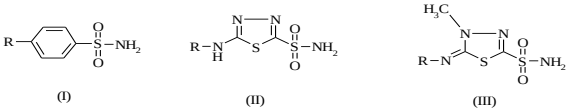
MATERIALS AND METHODS:

The workstation

All the computational studies were performed using software CS Chem. Office (Version 6.0).

QSAR analysis of 2,5-disubstituted 1,3,4-thiadiazole

QSAR analysis was carried out on all thirty compounds which are reported previously [5].



(I) (II) (III)

Figure 1: Structure of Sulphonamide and 1,3,4-Thiadiazole Derivatives which are reported as Carbonic Anhydrase Inhibitors are as follows

Upon stepwise, multiple, and sequential regression analysis of descriptor, the following statistically significant QSAR equations were obtained as follows. The correlation between the physicochemical parameters and the biological activity were found using the least squares method. The cross correlation matrix for –log IC_{50} and the various physicochemical descriptors were calculated for equation (1, 2, and 3).

- BA = [5.31643(± 0.468307)] + HLC [0.300503(± 0.103401)] + LUMO [-0.701809(± 0.384675)] + VDWE [0.083507(± 0.0521942)] **…..Equation (1)**

N = 30, r = 0.918647, r^2 = 0.843912, variance = 0.103995, std = 0.322482, F = 46.8575

- BA = [5.31042(± 0.418884)] + HLC [0.287537(± 0.0929893)] + LUMO [-0.703293(± 0.34406)] + VDWE [0.086354(± 0.0467316) **…..Equation (2)**

N = 29, r = 0.931009, r^2 = 0.866778, variance =0.0828709, std = 0.287873, F = 54.219

- BA = [5.43547(± 0.477882)] +DM [0.0686359(± 0.0675143)] +PMIY [7.44461e-005(± 5.29802e-005)] +NVDWE [-0.144571(± 0.0782467)] +LUMO [-1.06437(± 0.376148)] **…..Equation (3)**

N = 30, r = 0.904767, r^2 = 0.818604, variance = 0.125691, std = 0.354529, F = 28.2049

Out of the several models, equation (2) was selecting as the best equation on considering the criteria for QSAR equations. The equation had better statistical significance viz., r > 0.8, std. deviation (std) should be minimum, statistically significant F value and the correlation matrix was found to be in the limit.

Although the above equations are having good correlation coefficient (r^2), sequential fisher test value (F-test) and standard deviation (Std) values and minimum variance. But in equation (3) shows less correlation than in equation (2). Equations (1, 2, and 3) were validated by the cross validation method and IC_{50} and pIC_{50} values were calculated for these equations using software Valstat. The pIC_{50} calculated and predicted for the equations (1, 2, and 3) by Valstat are covered in the Table 1. Equations (1, 2, and 3) are validated by using different parameters such as cross-validated correlation coefficient, predicted sum of squares, and standard error of prediction and cross-validated equations are reported in the Table 2.

Table 1: Predicted Activity Data of Earlier Synthesized Compounds

Compd. No.	IC_{50}*	Equation (1)		Equation (2)		Equation (3)	
		pIC_{50}** Cal.	pIC_{50} ** Pred.	pIC_{50}** Calc.	pIC_{50} ** Pred.	pIC_{50}** Cal.	pIC_{50} ** Pred.
(Ia)	3.228892	7.65354	7.67835	7.61418	7.63532	7.51513	7.53411
(Ib)	2.656621	6.62968	6.64967	6.60267	6.61773	6.41428	6.39318
(Ic)	2.734382	6.83843	6.84394	6.80039	6.80293	6.82511	6.83221
(Id)	2.756201	6.83114	6.83419	6.79324	6.79301	6.82664	6.82997
(Ie)	1.930475	6.95766	6.98075	6.92539	6.94687	6.62471	6.62666
(If)	1.737577	6.9574	6.96279	6.92513	6.92846	6.62468	6.59319
(Ig)	1.95221	6.93711	6.95869	6.90509	6.92483	6.61923	6.61737
(Ih)	1.953405	6.90713	6.92897	6.87545	6.89504	6.61699	6.61371
(Ii)	1.951018	6.97728	6.99903	6.94487	6.9654	6.69369	6.70419
(Ij)	1.588046	6.69372	6.69668	6.66516	6.66461	6.73768	6.74897
(Ik)	1.610167	6.71378	6.72227	6.68507	6.6904	6.7148	6.72738
(Il)	1.440459	6.981	6.96894	6.94855	6.93426	6.79528	6.76165
(Im)	1.271854	6.85372	6.53771	6.82119	6.47087	7.33379	7.60966
(In)	1.652787	7.12452	7.10433	7.09076	7.06773	7.07325	7.0487
(Io)	1.762105	8.035	8.13625	7.98791	8.0725	8.44837	8.57969
(Ip)	0.889326	7.30917	7.35963	7.27296	7.32215	7.40561	7.46131
(Iq)	1.25642	7.34023	7.4013	7.29577	7.35054	7.3543	7.45399
(IIa)	1.278754	7.01245	7.00672	6.97175	6.96356	7.22887	7.24159
(IIb)	2.440922	7.06207	7.02058	7.06207	7.02058	7.55027	7.39195
(IIc)	1.66227	7.31066	7.31070	7.2739	7.27228	7.16904	7.15532
(IId)	1.771029	7.26035	7.24107	7.21692	7.19093	7.46718	7.47505
(IIe)	1.963489	7.23979	7.17812	7.19688	7.12543	7.53781	7.53395
(IIf)	2.344829	7.52942	7.48820	7.48955	7.44369	7.74769	7.7162
(IIg)	2.25329	8.1305	8.20568	8.08186	8.1297	8.387	8.54984

(IIh)	2.134695	6.95684	6.94726	6.91702	6.90466	7.73489	8.00052
(IIi)	2.476107	8.5579	8.56907	8.57619	8.59324	8.10879	8.07261
(IIIa)	2.698101	8.86932	8.83303	8.88264	8.85001	8.52344	8.45435
(IIIb)	2.698101	8.90283	8.87316	8.91858	8.89367	8.56855	8.49718
(IIIc)	2.298853	9.03929	9.16298	9.0572	9.1877	8.75267	8.76483
(IIId)	2.476107	8.10072	8.04244	8.09029	8.03088	8.31289	8.08426

IC_{50} =Biological activity, pIC_{50} = Negative log of IC_{50} value, * Determined from systat, ** Determined from validated model in valstat, Cal. = Calculated, Pred. = Predicted

RESULTS AND DISCUSSION:

The study of Equation (2) revealed that thermodynamic (HLC, VDWE) and electronic (LUMO) parameters are associates with anticonvulsant activity. The HLC and VDWE contributed positively where as LUMO contributed negatively to biological activity. The equation suggested that HLC of molecule and VDWE are of significance, they are having better correlation with biological activity and have minimum standard deviation. The results shows overall significance level better than 99.9% as it exceeded the tabulated F value (54.219,$F_{3,15}$). The Equation (3) revealed that all three parameters viz., thermodynamic (NVDWE), spatial (PMIY) and electronic (DM, LUMO) are associated with anticonvulsant activity. The PMIY and DM have better correlation with biological activity and have low value of standard deviation. The data showed overall significant level greater than a 99.9% as it exceeded the tabulated F value (28.2049F3.15). Both of above equation was validated by leave one out cross validation method and bootstrapping method which give statistically significant values of internal equation where as Q^2 was found to be greater than 0.5 also statistically significant.

Table 2: Cross Validation with Different Parameters

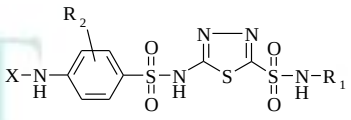
Sr. No.	Parameters	Equations		
		20	21	22
1	Q^2	0.766858	0.806632	0.719494
2	S_{PRESS}	0.394122	0.363346	0.440867
3	S_{DEP}	0.366908	0.337359	0.402455

Q^2 : Cross validated correlation coefficient[21], S_{PRESS} : Predicted sum of squares, S_{DEP} : standard error of prediction

This statistical parameter represents a high level of significance having high Q^2 values (0.719494). PMIY is depends on the total mass of molecule, mass distribution within molecule and position of the axis of rotation of the molecule equation shows direct relationship between PMIY of molecule and biological activity, whereas DM is an indication of strength and orientation behavior in electrostatic field and shows direct correlation. NVDWE and LUMO energy is directly correlated to stability of molecule.

CONCLUSION:

On the basis of QSAR study and nucleus present in the reported series, the parent structure was selected. In the series; compounds (Ia-q, IIa-i, IIIa-d), 1,3,4-thiadiazole, benzene and sulphonamide moieties are present and thus, 5-benzenesulphonamido-1,3,4-thiadiazol-2-sulphonamide (IV), was selected as parent structure which contains all three aforesaid moieties.



(IV)

On the basis of results and discussion theiron, the parent structure (IV) 1,3,4-thiadiazole will substituted at different position as represented R_1, R_2 and X .The bulkier substitution at R_1 and electronegative group at R_2 will play a significant role. However, X can be either hydrogen or acetyl group.

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