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2D-QSAR STUDIES OF SOME 1, 3, 4-THIDIAZOLE-2YL AZETIDINE 2-ONE AS ANTIMICROBIAL ACTIVITY

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In the present study quantitative structure activity relationship studies were performed on a series of 1, 3, 4-thidiazole-2yl) azetidine 2-one as antimicrobial activity using Chem Office ultra 7.01. Multiple linear regression analysis was performed to derive quantitative structure activity relationship models which were further evaluated internally as well as externally for the prediction of activity. The best quantitative structure activity relationship model was selected having a correlation coefficient (r^2) of 0.8040 and cross-validated correlation coefficient (Q^2) of 0.6189. This study indicates that thermodynamic descriptors (total energy, molar refractivity, ovality, logp and non Vander walls energy) and steric descriptors (principle moment of inertia non Vander walls energy) and play important role for the antimicrobial activity. The information generated from the present study may be useful in the design of more potent substituted compounds 1, 3, 4-thidiazole-2yl azetidine 2-one as antimicrobial activity.

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Keywords: 2D-*QSAR, 1,3,4-thidiazole-2yl azetidine 2-one, Antimicrobial activity.*

1. Introduction

The emergence and spread of antimicrobial resistance has become one of the most serious public health concerns across the world. Antimicrobial resistance refers to micro-organism that have developed the ability to inactivate, exclude or block the inhibitory or lethal mechanism of the antimicrobial agents[1-4]. Benzimidazole Compounds constitute an important class of heterocyclic aromatic organic compounds for their versatile pharmacological activities such as antibacterial, antifungal, antihelmintic, antiallergic, antineoplastic, local analgesic, antihistaminic, vasodilative, hypotensive, and spasmolytic activities[5-6]. In the present study, QSAR, analysis of some 1, 3, 4-Thidiazole-2yl Azetidine 2-One compounds with antimicrobial activity were performed by using multiple linear regression analysis. No QSAR studies have been carried out on 1, 3, 4-Thidiazole-2yl) Azetidine 2-One compounds. It appears to be interesting to perform QSAR analysis employing Chem Office ultra 7.01[7] to correlate various physiochemical parameters to the antimicrobial activity for the design of some 1, 3, 4-thidiazole-2yl azetidine 2-one compounds.

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2. Experiments

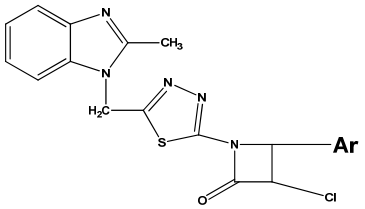
A data set of 17 molecules has been taken from published article (K.F ansari *et al.*)[8]. The Structures of reported compounds were shown in Table-1 and fig-1. All the values of biological data were shown in MIC (µg/ml), which were converted into –logMIC (µg/ml) for convenience of computational work. All structure of 1, 3, 4-Thidiazole-2yl azetidine 2-One compounds were constructed using Chem draw and transferred to chem 3D to convert them into 3D structures. The energy minimization of the molecules was done using MM2 force field followed by semi empirical AM1 (Austin model) Hamiltonian method available in MOPAC module by fixing root mean square gradient as 0.1 and 0.0001 kcal/Mol respectively for calculating partial atomic charges and electron density on various atoms. Most stable structure for each compound was generated and used for calculating various physicochemical descriptors like thermodynamic and steric. Values of descriptors, which are significant in equation, are shown in Table-2. All the calculated descriptors were considered as independent variable and biological activity as dependent variable. VALSTAT[9] software was used to generate QSAR Models by Multiple linear regression analysis. Cross validation was performed using leave-one-out method. Statistical measures used were: n- number of samples in regression, r^2-suared correlation coefficient, F-test (Fischer's value) for statistical significance, S- standard deviation, cross-validated squared correlation coefficient (Q^2), boot strapped squared correlation coefficient (bsr^2), S_{PRESS}, S_{DEP} and correlation matrix to show mutual correlation among the parameters.

Descriptors calculated for the QSAR study

S. No.	Descriptor	Type
1	Heat of Formation (HF)	Thermodynamic
2	Boiling Point (BP)	Thermodynamic
3	Critical Pressure (CP)	Thermodynamic
4	Critical Temperature (CT)	Thermodynamic
5	Critical Volume (CV)	Thermodynamic
7	Henry's Law Constant (HLC)	Thermodynamic
8	Ideal Gas Thermal Capacity (IGTC)	Thermodynamic
9	LogP	Thermodynamic
10	Melting Point (MP)	Thermodynamic
11	Molar Refractivity (MR)	Thermodynamic
12	Standard Gibbs Free Energy (SGFE)	Thermodynamic
13	Connolly Accessible Area (CAA)	Steric
14	Connolly Molecular Area (CMA)	Steric
15	Connolly Solvent-Excluded Volume (CSEV)	Steric
16	Ovality (OVA)	Steric
17	Principal Moment of Inertia - X (PMI-X)	Steric
18	Principal Moment of Inertia - Y (PMI-Y)	Steric
19	Principal Moment of Inertia - Z (PMI-Z)	Steric
20	Dipole Moment (D)	Electronic
21	Dipole Moment -X Axis (DX)	Electronic
22	Dipole Moment -Y Axis (DY)	Electronic
23	Dipole Moment -Y Axis (DZ)	Electronic
24	Electronic Energy (EE)	Electronic
25	HOMO Energy (HOMO)	Electronic
26	LUMO Energy (LUMO)	Electronic
27	Repulsion Energy (RE)	Electronic
28	Bend Energy (E_b)	Thermodynamic
29	Charge-Charge Energy (CCE)	Thermodynamic
30	Charge-Dipole Energy (CDE)	Thermodynamic
31	Dipole— Dipole Energy (DDE)	Thermodynamic
32	Non-1, 4 VDW Energy (E_v)	Thermodynamic
33	Stretch Energy (SE)	Thermodynamic
34	Stretch-Bend Energy (SEE)	Thermodynamic
35	Torsion Energy (E_t)	Thermodynamic
36	Total Energy (E)	Thermodynamic
37	Van der Waals e 1,4 Energy (VDWE)	Thermodynamic
38	VDW 1,4 Energy (VDWE)	Thermodynamic

3. Results and discussion

Acceptability of the regression model was judged by examining the correlation coefficient (r), squared correlation coefficient (r^2), fisher's value (F) and standard deviation. Performing multiple linear regression analysis results in four statistically significant QSAR models against Bacillus subtilis



3-chloro-4-methyl-1-(5-((2-methyl-1*H*-benzimidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)azetidin-2-one

Fig .1. substituted 1, 3, 4-Thidiazole-2yl) Azetidine 2-One compound used in this study

S.NO.	COMPOUND CODE NO.	Ar	MIC (µg/ml) (Bacillus subtilis)
1	5a	-C_6H_5	100
2	5b	4-Br- C_6H_4	500
3	5c	4-Cl- C_6H_4	200
4	5f	4-OCH3- C_6H_4	100
5	5g	2-CH3- C_6H_4	6.25
6	5i	2-OH C_6H_4	12.5
7	5k	4-OH C_6H_4	25
8	5l	4-NH2 C_6H_4	50
9	6a	C_6H_5	64
10	6b	2-Cl C_6H_4	6.3
11	6e	4-OCH_3 C_6H_4	100
12	6f	2-OCH_3 C_6H_4	100
13	6h	4-CH_3 C_6H_4	3.2
14	6i	2-OH C_6H_4	0.8
15	6j	3-OH C_6H_4	1.6
16	6k	4-OH C_6H_4	50
17	6l	4-NH2 C_6H_4	200

-LogMIC = [19(± 13.3739)] +logp [-0.221371(± 0.293608)] +NVDW [0.134489(± 0.187207)] +Ovality [-8.66874(± 8.45316)] +TE [0.0501429(± 0.125823)] **(Model-1)**

n=13, r=0.804029, r^2=0.72146, variance=0.0242845, std=0.155835, F=24.586

Model-1 shows high correlation coefficient (r=0.8040) between descriptors such as thermodynamic (non-Vander walls energy, ovality, total energy and logp). Squared correlation coefficient (r^2) of 0.7214, which explains 72.1% variance in biological activity. Model-1 also indicates statistical significance >99.9% with F-values F= 24.586.Cross-validated Square correlation coefficient of the model was 0.6189, which shows good internal predictivity of the model, Fig-2 displays a plot between actual activity and predicted activity.

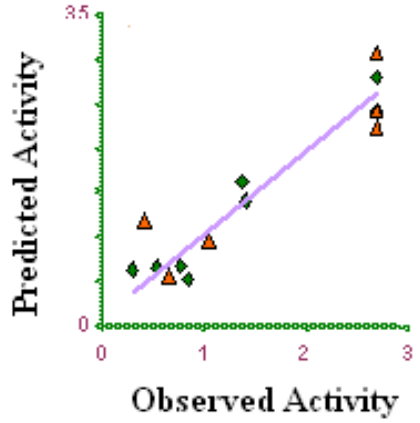


Fig. 2. A plot between observed activity and predicted activity for mode-lI

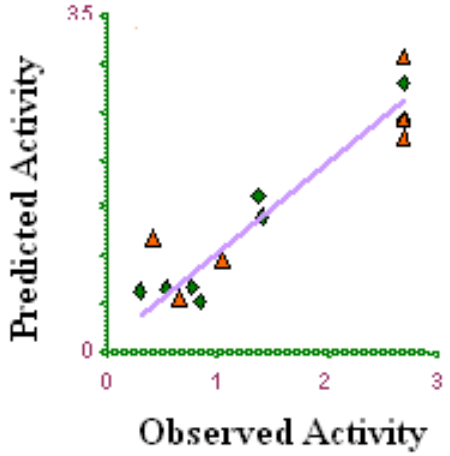


Fig. 3. A plot between observed activity activity and predicted activity for model-I

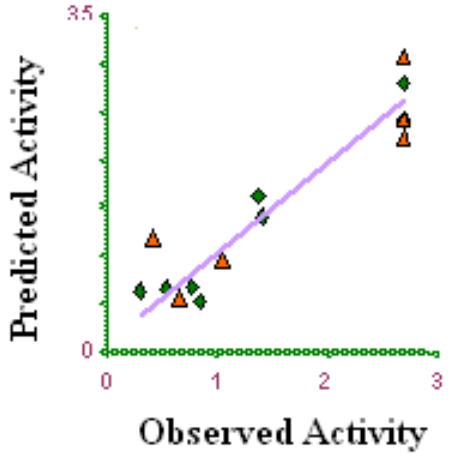


Fig. 4. A plot between observed activity and predicted activity for model-lV

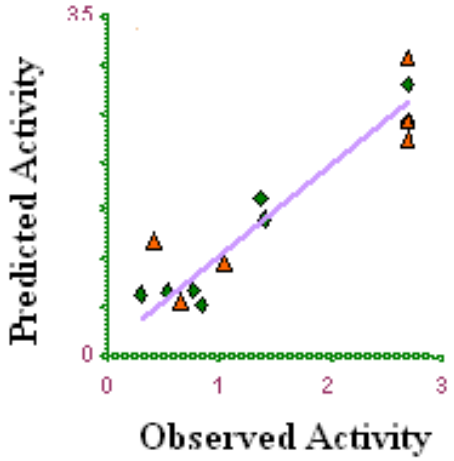


Fig. 5. A plot between observed activity and predicted activity for model-III

-LogMIC = [16.6426(± 12.4606)] +logp [-0.308519(± 0.200485)] +NVDW [0.0750929(± 0.1333)] +Ovality [-6.87904(±7.7988)] **(Model-2)**

n=13, r=0.79649, r^2=0.634396, variance=0.021008, std=0.144941, F=21.526

Model-2 shows good correlation coefficient (r=0.7964) between descriptors such as Steric Non-Vander walls energy ovality and logp). Squared correlation coefficient (r^2) of 0.6343, which explains 63.4% variance in biological activity. Model-2 also indicates statistical significance >99.9% with F-values F= 21.526 Cross-validated Square correlation coefficient of the model was 0.6026, which shows good internal predictivity of the model, Fig-3 displays a plot between actual activity and predicted activity.

Table 2. Calculated value of descriptors of given series of compounds

Compound No.	[a]NVDW	[b]Ovality	[c]logp	[d]BE	[e]TE	[f]PMIX
1	-5.315	1.59534	4.869	71.1508	-7.35	1845.79
2	-5.95	1.61192	5.698	69.138	-10.33	3974.37
3	-4.34	1.57739	5.427	72.492	-7.57	2026.09
4	-4.21	1.63236	4.743	79.453	-7.79	2673.84
5	-3.77	1.59147	5.356	73.819	-7.08	1886.02
6	-3.65	1.58694	4.479	75.722	-6.92	2068.56
7	-5.6	1.60011	4.479	75.969	-8.07	2189.74
8	-5.91	1.60496	4.066	70.339	-11.5	2513.58
9	-5.31	1.59534	4.869	71.15	-7.35	1845.79
10	-4.34	1.57739	5.427	72.492	-7.57	2026.09
11	-4.45	1.6298	4.743	79.731	-7.39	2732.63
12	-3.77	1.59147	5.356	73.819	-7.08	1886.02
13	-5.71	1.62224	5.356	69.918	-8.47	2452.87
14	-3.65	1.58694	4.479	75.722	-6.92	2069.56
15	-5.84	1.60366	4.479	74.346	-9.64	2314.38
16	-5.6	1.60011	4.479	75.969	-8.07	2189.74
17	-5.91	1.60499	4.066	70.339	-9.87	2513.58

A= Non- Vander walls energy, b= Ovality, c= logp, d= Bend energy, e= Total energy, f= principle moment of inertia

-LogMIC= [4.8338(± 0.811715)] +PMI [-0.000209802(± 0.000254797)] +NVDW [0.112248(±0.16506)] **(Model-3),**

n=13, r=0.75128, r^2=0.651794, variance=0.0397372, std=0.199342, F=31.251

Model-3 shows good correlation coefficient (r=0.7512) between descriptors such as Steric (Principle moment of inertia, non-Vander walls energy,). Squared correlation coefficient (r^2) of 0.6517, which explains 65.1% variance in biological activity. Model-3 also indicates statistical significance >99.9% with F-values F= 31.251.Cross-validated Square correlation coefficient of the model was 0.5869, which shows good internal predictivity of the model. Fig-4 displays a plot between actual activity and predicted activity.

Table 3. Predicted activity data

Sr.no.	Comp.no.	Actual act. (MIC)	Obs.act (-PMIC).	Pred. act Model-1	Pred. act Model-2	Pred. act Model-3	Pred. act Model-4
1	5a	100	4	3.35458	3.34658	3.33658	3.3058
2	5b	500	3.30103	3.31218	3.33118	3.32118	3.3418
3	5c	200	3.69897	3.32418	3.36518	3.35518	3.3618
4	5f	100	4	4.5269	4.5679	4.5479	5.2134
5	5g	6.25	5.20412	3.5960	3.6079	3.5779	3.4879
6	5i	12.5	4.90309	3.7869	3.8059	3.8249	3.883
7	5k	25	4.60206	4.5896	5.5876	5.5376	5.7346
8	5l	50	4.30103	3.6740	3.5740	3.5840	3.4840
9	6a	64	4.19382	5.6982	5.7082	5.7482	5.6482
10	6b	6.3	5.200659	3.8456	3.7446	3.4746	3.3746
11	6e	100	4	4.20386	4.19486	5.2036	5.2236
12	6f	100	4	3.3856	3.4146	3.4258	3.4958
13	6h	3.2	5.49485	5.50486	4.60886	4.50236	4.52236
14	6i	0.8	6.09691	3.7546	3.6376	3.6893	3.8546
15	6j	1.6	5.79588	3.7269	3.8149	3.7139	3.7139
16	6k	50	4.30103	3.51238	3.42468	3.5346	3.5346
17	6l	200	3.69897	3.48690	3.6890	3.9120	3.9120

Obs = observed activity, Pred= Predicted activity

Continue……

Cal act Model-1	Cal act Model-2	Cal act Model-3	Cal act Model-4	Res. act Model-1	Res. act Model-2	Res. act Model-3	Res. act Model-4
3.8663	3.76731	3.7458	3.62544	0.1337	0.1226	0.1336	0.1446
3.78907	3.75932	3.64306	3.61263	-0.48804	-0.40569	-0.5469	-0.6598
3.80474	3.90361	3.67825	3.92071	-0.10577	-0.20569	-0.4793	-0.5479
3.78907	3.90382	4.01494	3.79008	0.21093	0.3698	0.2698	0.3698
3.96875	3.7906	3.92157	3.62013	1.23537	1.5879	1.2546	1.4569
3.74699	3.34943	3.9899	3.91958	1.1561	1.2156	1.1546	1.25698
3.59382	3.79147	3.69271	3.91958	1.00824	1.00256	1.002569	1.002698
3.92055	4.07007	3.80026	3.89848	1.280109	1.32569	1.4589	1.3698
3.74631	3.83304	3.76099	3.79269	0.25369	0.5869	0.6987	0.3698
3.8456	3.76693	3.3321	4.0062	0.1544	0.1546	0.1569	0.1146
4.20386	4.19486	3.84995	3.80774	1.29099	1.23698	1.26954	1.4698
3.8663	3.63371	3.4258	3.99985	2.23061	2.32897	2.3695	2.3698

3.88676	3.79147	3.92157	3.58173	1.90912	1.21569	1.34965	1.36987
3.40835	3.6376	3.6893	3.8546	0.89268	0.23898	0.4569	0.2569
3.7269	3.8149	3.7139	3.7139	-0.02793	-0.03659	-0.03698	-0.0.398
4.10783	3.42468	3.5346	3.5346	0.17659	0.16987	0.17896	0.1897
3.48690	3.6890	3.9120	3.9120	0.5692	0.5698	0.6987	0.7893

Res = Residual activity, Cal = Calculated activity

-LogMIC= [4.1239(± 3.45587)] +NVDW [0.234309(± 0.214998)] +Ovality [-0.00394477(± 0.044348)] +TE [0.00169275(± 0.0444036)] +BE [0.135918(± 0.145357)] **(Model-4),**

n=13, r=0.78143, r^2=0.710289, variance=0.0336384, std=0.183408, F=28.246

Model-4 shows good correlation coefficient (r=0.7143) between descriptors such as Steric (Principle moment of inertia, non-Vander walls energy, Ovality, Bend energy and total energy). Squared correlation coefficient (r^2) of 0.7102, which explains 71.0% variance in biological activity. Model-4 also indicates statistical significance >99.9% with F-values F= 28.246.Cross-validated Square correlation coefficient of the model was 0.6785, which shows good internal predictivity of the model. Fig-5 displays a plot between actual activity and predicted activity.

Predicted activity data of model-1, 2, 3 and 4 were shown in Table-3 and results of the leave-one-out cross validation for model-1, 2, 3 and 4 are shown in Table-4. Out of the four models, model-1 was selected on the basis of statistical criteria; r^2=0.646463, variance=0.0242845 and standard deviation = 0.155835. Model-1 shows high statistical significance >99.9% with F-values F= 24.586. The internal predictivity of the model was assessed by cross-validated squared correlation coefficient (Q^2= 0.6189), which shows good correlation between predicted activity and actual activity (Fig-2). The boot strapped r2 (bsr^2= 32.0042), values reflect the accuracy of the models. Correlation matrix shows poor correlation between descriptors for model-1 shown in (Table-5). Correlation matrix shows poor correlation between descriptors for model-2 shown in (Table-6). Correlation matrix shows poor correlation between descriptors for model-3 shown in (Table-7). Correlation matrix shows poor correlation between descriptors for model-4 shown in (Table-8).

Table 4. Validated parameters of model-1, 2, 3 and 4.

	[a]bsr^2	[b]Q^2	[c]S_{PRESS}	[d]SDEP
Model-1	32.0042	0.6189	0.274136	0.21505
Model-2	0.704906	0.6026	0.220071	0.18311
Model-3	0.479955	0.6517	0.242476	0.212666
Model-4	0.709989	0.5102	206.023	161.617

[a]boot strapped squared correlation coefficient, [b]cross-validated squared correlation coefficient, [c]Standard deviation of sum of squared error of prediction, [d] Standard deviation of error of prediction.

Table 5. Correlation matrix of model-1

Parameters	[a]**NVDW**	[b]**Ovality**	[c]**Tot. energy**	[d]**logp**
NVDW	1.0000			
Ovality	0.22164	1.0000		
Tot. energy	0.651751	0.729153	1.0000	
logp	0.4403	0.422649	0.306134	1.0000

[a]NVDW= Non Vander walls energy, b= Ovality, c= Total energy, d= logp

Table 6. Correlation matrix of model-2

Parameters	[a]NVDW	[b]Ovality	[c]logp
NVDW	1.0000		
Ovality	0.395950	1.0000	
logp	0.323234	0.446623	1.0000

[a]NVDW= Non Vander walls energy, b= Ovality, c= logp

Table 7. Correlation matrix of model-3

Parameters	[a]NVDW	[b]PMI
NVDW	1.0000	
PMI	0.40010	1.0000

[a]NVDW= Non Vander walls energy, b= Principle moment of inertia

Table 8. Correlation matrix of model-4

Parameters	[a]NVDW	[b]Ovality	[c]Tot. energy	[d]Bend. energy
NVDW	1.0000			
Ovality	0.100010	1.0000		
Tot. energy	0.112945	0.990155	1.0000	
Bend. energy	0.743702	0.162643	0.166949	1.0000

[a]NVDW= Non Vander walls energy, b= Ovality, c= Total energy, d= Bend energy

It is evident from the QSAR studies that in model-1, thermodynamic descriptors ((total energy, molar refractivity, ovality, logp and non Vander walls energy) and steric descriptors (principle moment of inertia non Vander walls energy) are responsible for the activity. Negative contribution of non-Vander walls energy (attractive forces between active substituents and enzyme-binding sites) in biological activity indicates that minimizing parameters with suitable substituents enhances the activity. Negative contribution of total energy (electron density in the enzyme cavity) to the biological activity indicates that minimizing the total energy of the molecule increases the activity. Based on the QSAR model obtained from series, for the design of the new molecules.

4. Conclusions

QSAR analysis was performed of series of 1, 3, 4-thidiazole-2yl) azetidine 2-one as antimicrobial activity using molecular modeling program Chem Office ultra 7.01.QSAR models were proposed for antimicrobial activity using chem. SAR descriptors employing sequential multiple regression analysis method. The selected models were checked for multicollinearity and auto correlation with NVDW, Ovality Total energy, Principle moment of inertia, and $\log^p$ statistics respectively. The predictive power of each model was estimated with boot strapping method and leave-one-out cross validation method. It was observed from the selected models that biological activity of azetedine-2 one derivatives are governed by thermodynamic, Electronic and steric properties of the molecules. The models also provide valuable insight into the mechanism of action of these compounds. The result of the study suggests involvement of dipole-dipole interaction in the mechanism of microbial action of less bulky substituents are undesirable due to steric hindrance. Additionally, presence of groups contributing to the flexibility of the molecule will increase microbial potency of azetidine derivatives.

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