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QSAR STUDIES ON NOVEL 1, 4-DIHYDROPYRIDINE DERIVATIVES

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ABSTRACT: QSAR studies on N^3, N^5-diphenyl-1, 4-dihydropyridine-3, 5-dicarbohydrazides [2A-2D'] and 2, 6-dimethyl-1,4-dihydro-pyridine-3, 5-yl-bis[carbonyl-2-(phenyl)]pyrazolidine-3, 5-diones] [3A -3D'] were carried out. 3D chemical structures were given as input and desired molecular attributes and molecular indices were selected. Various molecular descriptors were studied using TSAR (Tools for Structure Activity Relationship) Accelrys Discovery studio software. All the properties were calculated based on the chemical structure. Hansch equations were developed for all the above mentioned compounds against respective microorganisms and for anti-inflammatory activities, using some of the calculated descriptors. A correlation matrix was developed, which gives the inter correlation between the calculated descriptors.

INTRODUCTION: 1, 4-Dihydropyridines and their analogues are well known for their diverse activities like antibacterial, antifungal, anti-hypertensive, anticonvulsant, anti-inflammatory, anticancer etc [1-6]. The structural formula of an organic compound basically encodes within it all the information that predetermines the chemical, biological and physical properties of that compound [7].

The characteristic of various biological activities exhibited by the same basic nucleus owes to the presence of a number of varying substituents. Biological activity of a molecule is profoundly influenced by various substituents present. So, there exists a relationship between molecular structure and biological response [8].

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The biological activity of a molecule differs accordingly, with changes in the substituents. An extensive study on any class of molecules is required to develop a quantitative structure and activity relationship. This has provided us with a direction to the research.

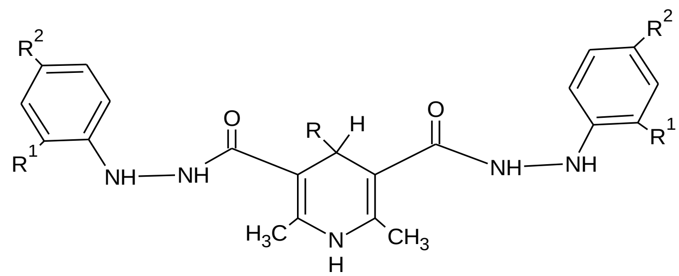
The rationale behind this project was to carry out QSAR study of N^3, N^5-diphenyl-1,4-dihydropyridine-3, 5-dicarbo hydrazides [2A-2D'] [9] and 2, 6-dimethyl-1,4-dihydropyridine-3,5-yl-bis[carbonyl-2-(phenyl)] pyrazolidine-3, 5-diones] [3A-3D'] [10] derivatives. Hansch equations for antimicrobial as well as anti-inflammatory activities were developed using Accelrys TSAR Software. Correlation matrix was also developed with the aid of this software by using the calculated molecular descriptors.

MATERIALS AND METHODS [7, 11]: Tsar is an integrated analysis package for interactive investigation of Quantitative Structure-Activity Relationships (QSARs). It is intended to provide all the functions required to carry out any QSAR investigation.

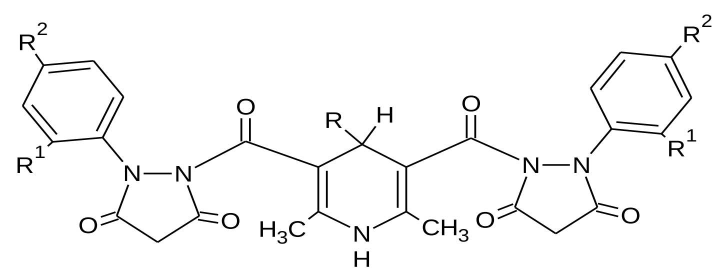
TSAR uses an integrated approach to provide all components together. It uses a chemically aware spreadsheet to store and manipulate different types of data. The main application of this software is to develop Hansch equation for a given training set compounds and this equation can be used for the future generation compounds to obtain biological activity data without being synthesized. This rational approach will allow us to synthesize compounds with good biological activity. Regression analysis module of statistical analysis tool TSAR was used to build the QSAR models.

Regression analysis was performed using zone of inhibition as independent variable and calculated descriptors as dependent variables. QSAR models were derived after ensuring reasonable correlation of zone of inhibition with individual descriptor and minimum inter-correlation among the descriptors used in the derived models. The use of more than one variable in multivariate equation was justified by autocorrelation study. In the present study various statistical measures were used such as n = number of compounds; r = coefficient of correlation; s = standard error; f = test for quality to fit.

All the properties are calculated based on the chemical structure and a Hansch equation is developed using some of the calculated descriptors. The following structures are first drawn using DS Viewer Pro Suite software and their smiles strings are appended into TSAR software. Substitutions for the derivatives are given in **Table 1**.



2A-2D'

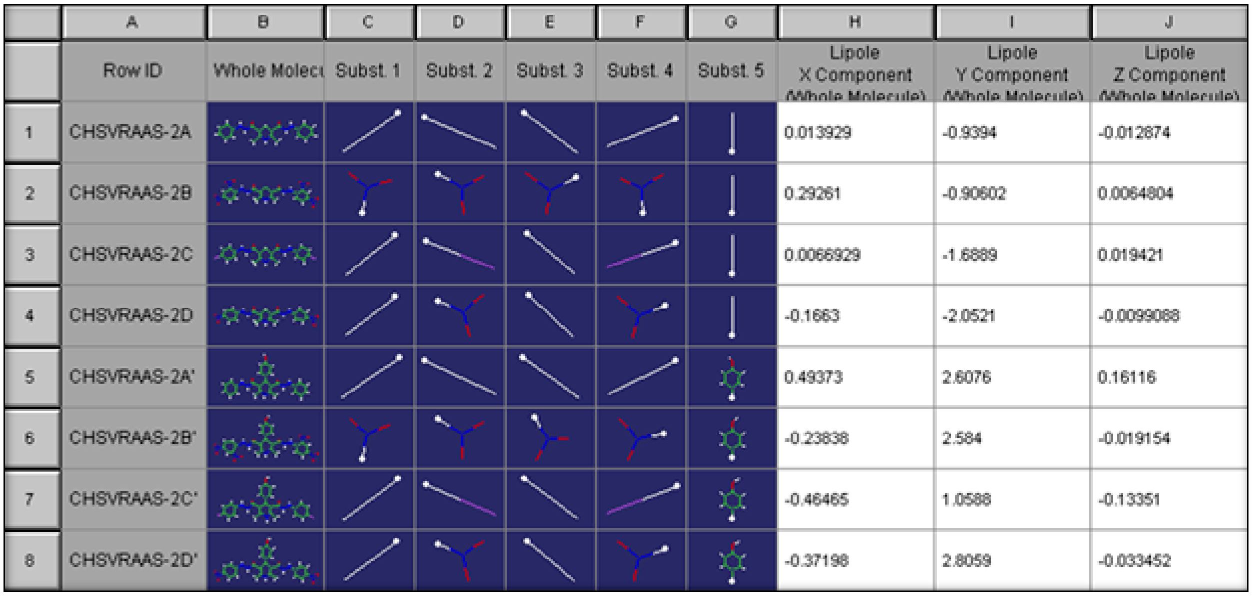


3A-3D'

TABLE 1: SET OF COMPOUNDS FOR TSAR STUDY

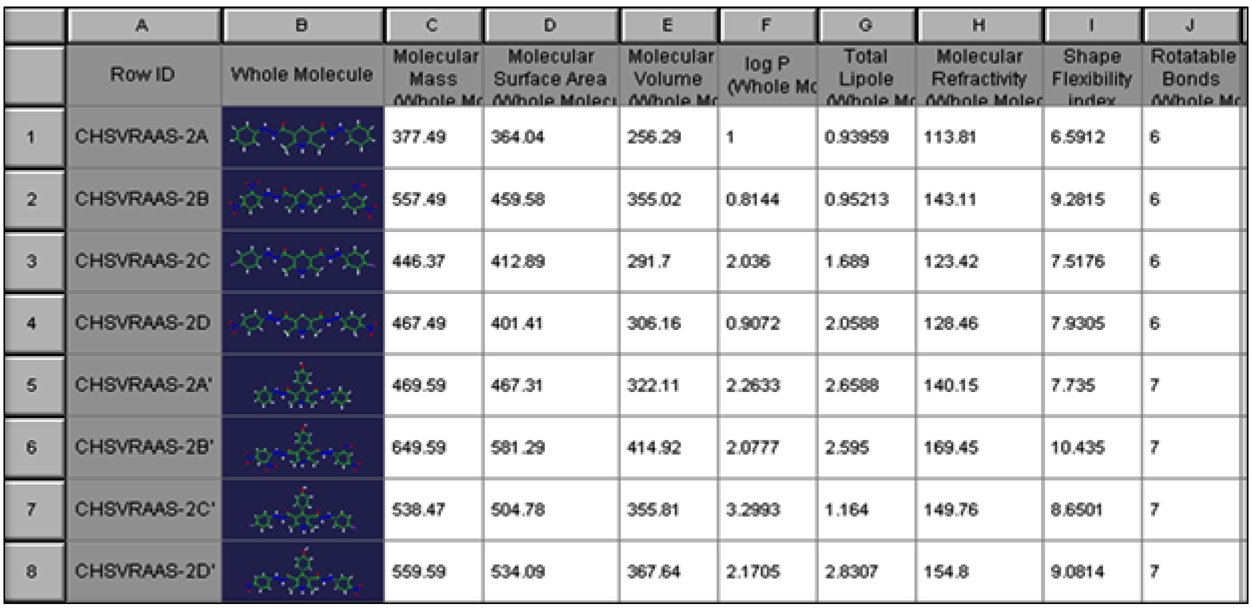
Compound	R^1	R^2	R
2A	H	H	H
2B	NO_2	NO_2	H
2C	H	Cl	H
2D	H	NO_2	H
2A'	H	H	C_6H_4OH
2B'	NO^2	NO_2	C_6H_4OH
2C'	H	Cl	C_6H_4OH
2D'	H	NO_2	C_6H_4OH
3A	H	H	H
3B	NO_2	NO_2	H
3C	H	Cl	H
3D	H	NO_2	H
3A'	H	H	C_6H_4OH
3B'	NO^2	NO_2	C_6H_4OH
3C'	H	Cl	C_6H_4OH
3D'	H	NO_2	C_6H_4OH

RESULTS AND DISCUSSION: Various Molecular attributes calculated and biological activities for the set of compounds 2A-2D' and 3A-3D' are given in the following **figures 1-10**.



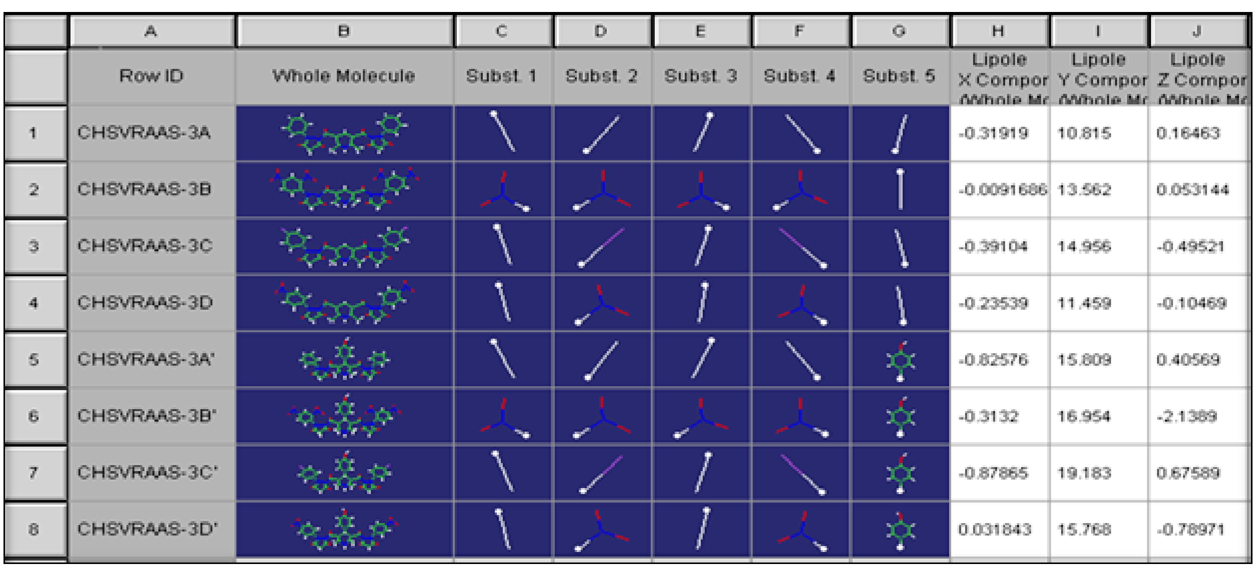
	A	B	C	D	E	F	G	H	I	J
	Row ID	Whole Molecu	Subst. 1	Subst. 2	Subst. 3	Subst. 4	Subst. 5	Lipole X Component (Whole Molecule)	Lipole Y Component (Whole Molecule)	Lipole Z Component (Whole Molecule)
1	CHSVRAAS-2A							0.013929	-0.9394	-0.012874
2	CHSVRAAS-2B							0.29261	-0.90602	0.0064804
3	CHSVRAAS-2C							0.0066929	-1.6889	0.019421
4	CHSVRAAS-2D							-0.1663	-2.0521	-0.0099088
5	CHSVRAAS-2A'							0.49373	2.6076	0.16116
6	CHSVRAAS-2B'							-0.23838	2.584	-0.019154
7	CHSVRAAS-2C'							-0.46465	1.0588	-0.13351
8	CHSVRAAS-2D'							-0.37198	2.8059	-0.033452

FIGURE 1: MOLECULAR ATTRIBUTES FOR THE SET 2A-2D'



	A	B	C	D	E	F	G	H	I	J
	Row ID	Whole Molecule	Molecular Mass (Whole Mo	Molecular Surface Area (Whole Molecu	Molecular Volume (Whole Mo	log P (Whole Mo	Total Lipole (Whole Mo	Molecular Refractivity (Whole Molec	Shape Flexibility index	Rotatable Bonds (Whole Mo
1	CHSVRAAS-2A		377.49	364.04	256.29	1	0.93959	113.81	6.5912	6
2	CHSVRAAS-2B		557.49	459.58	355.02	0.8144	0.95213	143.11	9.2815	6
3	CHSVRAAS-2C		446.37	412.89	291.7	2.036	1.689	123.42	7.5176	6
4	CHSVRAAS-2D		467.49	401.41	306.16	0.9072	2.0588	128.46	7.9305	6
5	CHSVRAAS-2A'		469.59	467.31	322.11	2.2633	2.6588	140.15	7.735	7
6	CHSVRAAS-2B'		649.59	581.29	414.92	2.0777	2.595	169.45	10.435	7
7	CHSVRAAS-2C'		538.47	504.78	355.81	3.2993	1.164	149.76	8.6501	7
8	CHSVRAAS-2D'		559.59	534.09	367.64	2.1705	2.8307	154.8	9.0814	7

FIGURE 2: MOLECULAR ATTRIBUTES FOR THE SET 2A-2D'



	A	B	C	D	E	F	G	H	I	J
	Row ID	Whole Molecule	Subst. 1	Subst. 2	Subst. 3	Subst. 4	Subst. 5	Lipole X Compor (Whole Mo	Lipole Y Compor (Whole Mo	Lipole Z Compor (Whole Mo
1	CHSVRAAS-3A							-0.31919	10.815	0.16463
2	CHSVRAAS-3B							-0.0091686	13.562	0.053144
3	CHSVRAAS-3C							-0.39104	14.956	-0.49521
4	CHSVRAAS-3D							-0.23539	11.459	-0.10469
5	CHSVRAAS-3A'							-0.82576	15.809	0.40569
6	CHSVRAAS-3B'							-0.3132	16.954	-2.1389
7	CHSVRAAS-3C'							-0.87865	19.183	0.67589
8	CHSVRAAS-3D'							0.031843	15.768	-0.78971

FIGURE 3: MOLECULAR ATTRIBUTES FOR THE SET 3A-3D'

	A	B	C	D	E	F	G	H	I	J
	Row ID	Whole Molecule	Molecular Mass (Whole Molecu	Molecular Surface Area (Whole Molecu	Molecular Volume (Whole Mole	log P (Whole Mole	Total Lipole (Whole Mo	Molecular Refractivity (Whole Mole	Shape Flexibility index	Rotatable Bonds (Whole Mol
1	CHSVRAAS-3A		513.55	458.02	347.96	0.093802	10.821	135.91	6.6108	4
2	CHSVRAAS-3B		693.55	502.95	413.63	-0.0918	13.562	165.21	9.2608	4
3	CHSVRAAS-3C		582.43	488.09	382.89	1.1298	14.969	145.52	7.4636	4
4	CHSVRAAS-3D		603.55	503.36	393.58	0.0010012	11.462	150.56	7.9299	4
5	CHSVRAAS-3A'		605.65	532.07	390	1.3571	15.835	162.25	7.8463	5
6	CHSVRAAS-3B'		785.65	619.58	475.72	1.1715	17.091	191.55	10.491	5
7	CHSVRAAS-3C'		674.53	548.89	419.42	2.3931	19.215	171.86	8.6973	5
8	CHSVRAAS-3D'		695.65	566.31	429.18	1.2643	15.788	176.9	9.1632	5

FIGURE 4: MOLECULAR ATTRIBUTES FOR THE SET 3A-3D'

	A	B	C	D	E	F	G	H	I	J	K	L	M
	Row ID	Whole Molecule	Subst. 1	Subst. 2	Subst. 3	Subst. 4	Subst. 5	S.Aureus	B.Subtilis	E.Coli	P.Vulgaris	A.Niger	C.Albicans
1	CHSVRAAS-2A							11	10	7	12	12	12
2	CHSVRAAS-2B							14	11	14	14	17	17
3	CHSVRAAS-2C							13	13	16	15	11	13
4	CHSVRAAS-2D							8	9	10	16	14	14
5	CHSVRAAS-2A'							10	14	11	17	9	8
6	CHSVRAAS-2B'							11	13	15	14	10	10
7	CHSVRAAS-2C'							15	12	14	13	8	9
8	CHSVRAAS-2D'							12	14	6	15	11	11

FIGURE 5: OBSERVED BIOLOGICAL ACTIVITY FOR THE SET 2A-2D'

	A	B	C	D	E	F	G	H	I	J	K	L	M
	Row ID	Whole Mo	Subst. 1	Subst. 2	Subst. 3	Subst. 4	Subst. 5	B.Subtilis	P.Vulgaris	E.Coli	S.Aureus	C.Albicans	A.Niger
1	CHSVRAAS-2A							9.8694	13.179	9.9038	10.496	14.773	14.524
2	CHSVRAAS-2B							10.977	13.469	11.462	11.935	13.577	13.468
3	CHSVRAAS-2C							11.344	14.157	10.93	11.334	12.428	12.051
4	CHSVRAAS-2D							10.962	14.542	9.903	9.3741	13.393	13.349
5	CHSVRAAS-2A'							12.679	15.398	11.471	11.062	10.624	10.364
6	CHSVRAAS-2B'							13.86	15.626	13.219	12.781	9.352	9.2246
7	CHSVRAAS-2C'							12.867	13.881	13.82	15.334	10.094	9.4284
8	CHSVRAAS-2D'							13.441	15.749	12.292	11.685	9.7589	9.5916

FIGURE 6: PREDICTED BIOLOGICAL ACTIVITY FOR THE SET 2A-2D'

	A	B	C	D	E	F	G	H	I	J	K	L	M
	Row ID	Whole Molecule	Subst. 1	Subst. 2	Subst. 3	Subst. 4	Subst. 5	S.Aureus	B.Subtilis	E.Coli	P.Vulgaris	A.Niger	C.Albicans
1	CHSVRAAS-3A							9	11	11	13	11	12
2	CHSVRAAS-3B							10	14	13	10	12	14
3	CHSVRAAS-3C							12	13	12	14	13	15
4	CHSVRAAS-3D							11	8	10	15	12	13
5	CHSVRAAS-3A'							12	10	15	11	15	12
6	CHSVRAAS-3B'							11	11	12	12	16	15
7	CHSVRAAS-3C'							14	15	14	11	11	16
8	CHSVRAAS-3D'							10	12	13	7	14	14

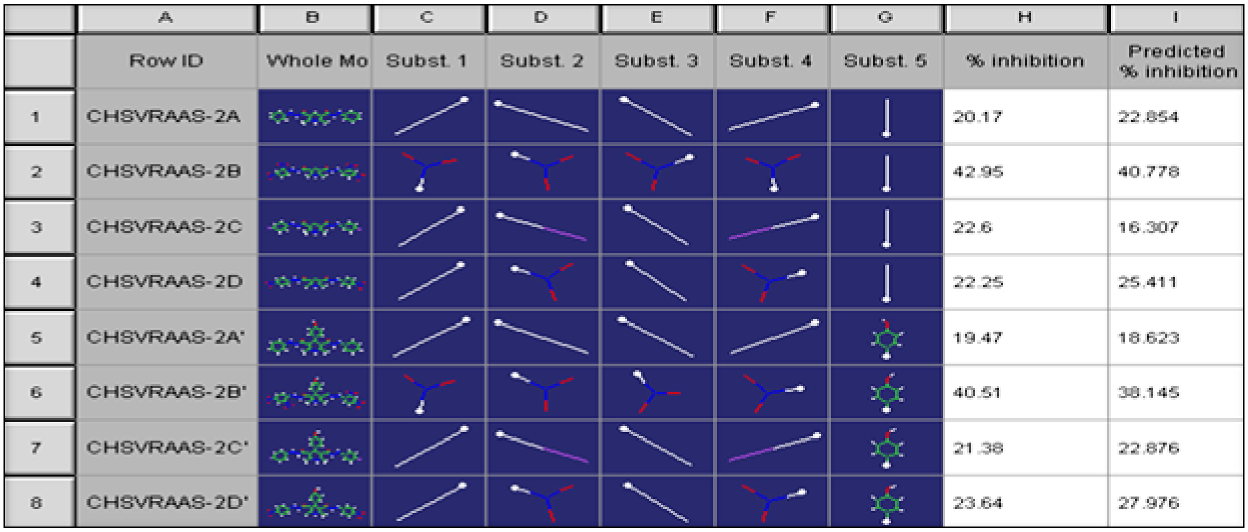
FIGURE 7: OBSERVED BIOLOGICAL ACTIVITY FOR THE SET 3A-3D’

	A	B	C	D	E	F	G	H	I	J	K	L	M
	Row ID	Whole Mo	Subst. 1	Subst. 2	Subst. 3	Subst. 4	Subst. 5	B.Subtilis	P.Vulgaris	E.Coli	S.aureus	C.Albicans	A.Niger
1	CHSVRAAS-3A							9.8321	13.542	11.252	10.084	12.478	11.312
2	CHSVRAAS-3B							14.087	12.187	11.575	9.7997	13.335	12.555
3	CHSVRAAS-3C							12.599	12.257	12.867	11.902	13.557	12.325
4	CHSVRAAS-3D							9.0354	12.796	11.121	9.6417	12.921	12.077
5	CHSVRAAS-3A'							11.959	11.342	13.041	11.828	14.15	13.199
6	CHSVRAAS-3B'							10.593	9.8737	12.79	10.953	15.018	14.698
7	CHSVRAAS-3C'							14.764	10.245	14.545	13.521	15.08	14.028
8	CHSVRAAS-3D'							11.131	10.759	12.807	11.27	14.462	13.806

FIGURE 8: PREDICTED BIOLOGICAL ACTIVITY FOR THE SET 3A-3D’

	A	B	C	D	E	F	G	H	I
	Row ID	Whole Mo	Subst. 1	Subst. 2	Subst. 3	Subst. 4	Subst. 5	% inhibition	Predicted % inhibition
1	CHSVRAAS-2A							20.17	22.854
2	CHSVRAAS-2B							42.95	40.778
3	CHSVRAAS-2C							22.6	16.307
4	CHSVRAAS-2D							22.25	25.411
5	CHSVRAAS-2A'							19.47	18.623
6	CHSVRAAS-2B'							40.51	38.145
7	CHSVRAAS-2C'							21.38	22.876
8	CHSVRAAS-2D'							23.64	27.976

FIGURE 9: OBSERVED AND PREDICTED % INHIBITION OF ALBUMIN DENATURATION FOR THE SET 2A-2D’



	Row ID	Whole Mo	Subst. 1	Subst. 2	Subst. 3	Subst. 4	Subst. 5	% inhibition	Predicted % inhibition
1	CHSVRAAS-2A							20.17	22.854
2	CHSVRAAS-2B							42.95	40.778
3	CHSVRAAS-2C							22.6	16.307
4	CHSVRAAS-2D							22.25	25.411
5	CHSVRAAS-2A'							19.47	18.623
6	CHSVRAAS-2B'							40.51	38.145
7	CHSVRAAS-2C'							21.38	22.876
8	CHSVRAAS-2D'							23.64	27.976

FIGURE 10: OBSERVED AND PREDICTED % INHIBITION OF ALBUMIN DENATURATION FOR THE SET 3A-3D'

Totally 14 Hansch equations were developed based on the above molecular descriptors, observed and predicted biological activities which are given in the following **tables 2 and 3**.

TABLE 2: HANSCH EQUATIONS FOR ANTIMICROBIAL AND ANTI-INFLAMMATORY ACTIVITIES FOR THE SET OF COMPOUNDS 2A-2D'

Equation	Organism
BA = 0.0086299218*X1+1.2655897*X2-1.5737636*X3+0.02968015*X4+4.1891551	*Staphylococcus aureus*
BA = 0.006181885*X1+0.54577816*X2+0.54216611*X3+0.020884452*X4+4.1868463	*Bacillus subtillus*
BA = 0.0077026109*X1+0.77354515*X2-0.62876654*X3+0.033232186*X4+3.1347725	*E. Coli*
BA= 0.0011946505*X1+0.034694269*X2+1.1057063*X3+0.0057437047*X4+11.016533	*Proteus vulgaris*
BA= -0.0072026318*X1-1.3829733*X2-0.64852422*X3-0.021038659*X4+21.532642	*Aspergillus niger*
BA=-0.0073520811*X1-1.1386263*X2-0.77155095*X3-0.023709919*X4+22.011187	*Candida albicans*
BA=0.050122123*X1-2.6390998*X2-0.72661674*X3+0.23514506*X4-23.568424	Anti-inflammatory

(BA=Biological activity, X1= Molecular surface area, X2=LogP, X3=Total Lipole, X4=molar refractivity)

TABLE 3: HANSCH EQUATIONS FOR ANTIMICROBIAL AND ANTI-INFLAMMATORY ACTIVITIES FOR THE SET OF COMPOUNDS 3A-3D'

Equation	Organism
BA=0.0031962923*X1+0.53791922*X2+0.152889*X3+0.0076855812*X4+5.429121	*Staphylococcus aureus*
BA = 0.00090397045*X1+0.46999887*X2+0.17540462*X3+0.01102224*X4+6.448936	*Bacillus subtillus*
BA =0.003513477*X1+0.40956402*X2+0.13441697*X3+0.012577558*X4+6.2336264	*E. Coli*
BA = -0.006993338*X1-0.29975083*X2-0.12470307*X3-0.025773037*X4+21.625942	*Proteus vulgaris*
BA = 0.00897035*X1+0.1751522*X2+0.085003294*X3+0.021848412*X4+3.2972562	*Aspergillus niger*
BA = 0.0044008382*X1+0.31588811*X2+0.11829211*X3+0.013429222*X4+7.327291	*Candida albicans*
BA=0.030168224*X1-2.571876*X2-0.35131389*X3+0.086893067*X4+6.0124087	Anti-inflammatory

(BA=Biological activity, X1= Molecular surface area, X2=LogP, X3=Total Lipole, X4=molar refractivity)

For all the above equations given in tables 2 and 3, the positive values of the descriptors X1, X2, X3, X4 implies that they contribute positively to the antimicrobial activity against corresponding microorganism or anti-inflammatory activity against % inhibition of albumin denaturation. The Negative values of the descriptors X1, X2, X3, X4 implies that they contribute negatively to the antimicrobial activity against corresponding microorganism or anti-inflammatory activity against % inhibition of albumin denaturation. By selecting various molecular attributes, correlation matrix is obtained which gives the inter correlation between the chosen calculated descriptors. Correlation matrix for the set of compounds 2A-2D' and 3A-3D' are shown in **figures 11 and 12**.

	Molecular Mass (Whole Molecule)	Molecular Surface Area (Whole Molecule)	Molecular Volume (Whole Molecule)	log P (Whole Molecule)	Total Lipole (Whole Molecule)	Lipole X Component (Whole Molecule)	Lipole Y Component (Whole Molecule)	Lipole Z Component (Whole Molecule)	Molecular Refractivity (Whole Molecule)	Shape Flexibility Index	Rotatable Bonds (Whole Molecule)
Molecular Mass (Whole Molecule)	1	0.92785	0.99239	0.32254	0.38589	-0.34689	0.5795	-0.28137	0.96212	0.99527	0.58229
Molecular Surface Area (Whole Molecule)	0.92785	1	0.96043	0.57235	0.55168	-0.38167	0.81994	-0.2086	0.98724	0.89196	0.82783
Molecular Volume (Whole Molecule)	0.99239	0.96043	1	0.39701	0.44296	-0.33898	0.66726	-0.24524	0.98769	0.97795	0.67474
log P (Whole Molecule)	0.32254	0.57235	0.39701	1	0.27586	-0.41524	0.6115	-0.25825	0.48535	0.23162	0.78821
Total Lipole (Whole Molecule)	0.38589	0.55168	0.44296	0.27586	1	-0.072668	0.66277	0.39364	0.51349	0.35733	0.6121
Lipole X Component (Whole Molecule)	-0.34689	-0.38167	-0.33898	-0.41524	-0.072668	1	-0.13262	0.87029	-0.35088	-0.31885	-0.29833
Lipole Y Component (Whole Molecule)	0.5795	0.81994	0.66726	0.6115	0.66277	-0.13262	1	0.11876	0.76949	0.52052	0.94943
Lipole Z Component (Whole Molecule)	-0.28137	-0.2086	-0.24524	-0.25825	0.39364	0.87029	0.11876	1	-0.21292	-0.27202	-0.046324
Molecular Refractivity (Whole Molecule)	0.96212	0.98724	0.98769	0.48535	0.51349	-0.35088	0.76949	-0.21292	1	0.93558	0.77939
Shape Flexibility Index	0.99527	0.89196	0.97795	0.23162	0.35733	-0.31885	0.52052	-0.27202	0.93558	1	0.50816
Rotatable Bonds (Whole Molecule)	0.58229	0.82783	0.67474	0.78821	0.6121	-0.29833	0.94943	-0.046324	0.77939	0.50816	1

FIGURE 11: CORRELATION MATRIX FOR THE SET 2A-2D'

	Shape Flexibility Index	Rotatable Bonds (Whole Molecule)	Molecular Mass (Whole Molecule)	Molecular Surface Area (Whole Molecule)	Molecular Volume (Whole Molecule)	log P (Whole Molecule)	Total Lipole (Whole Molecule)	Lipole X Component (Whole Molecule)	Lipole Y Component (Whole Molecule)	Lipole Z Component (Whole Molecule)	Molecular Refractivity (Whole Molecule)
Shape Flexibility Index	1	0.54126	0.99703	0.87242	0.97737	0.25041	0.57325	0.24635	0.56689	-0.63098	0.94867
Rotatable Bonds (Whole Molecule)	0.54126	1	0.58229	0.82794	0.62484	0.78821	0.81367	-0.41207	0.81116	-0.22115	0.77939
Molecular Mass (Whole Molecule)	0.99703	0.58229	1	0.89149	0.98479	0.32254	0.63288	0.19128	0.62685	-0.61484	0.96212
Molecular Surface Area (Whole Molecule)	0.87242	0.82794	0.89149	1	0.9401	0.54605	0.73031	-0.058479	0.72303	-0.64296	0.96164
Molecular Volume (Whole Molecule)	0.97737	0.62484	0.98479	0.9401	1	0.37649	0.65274	0.13998	0.64564	-0.68515	0.9637
log P (Whole Molecule)	0.25041	0.78821	0.32254	0.54605	0.37649	1	0.92055	-0.66383	0.92244	0.029046	0.48535
Total Lipole (Whole Molecule)	0.57325	0.81367	0.63288	0.73031	0.65274	0.92055	1	-0.50061	0.99991	-0.15132	0.73509
Lipole X Component (Whole Molecule)	0.24635	-0.41207	0.19128	-0.058479	0.13998	-0.66383	-0.50061	1	-0.5028	-0.45289	0.027624
Lipole Y Component (Whole Molecule)	0.56689	0.81116	0.62685	0.72303	0.64564	0.92244	0.99991	-0.5028	1	-0.14006	0.72942
Lipole Z Component (Whole Molecule)	-0.63098	-0.22115	-0.61484	-0.64296	-0.68515	0.029046	-0.15132	-0.45289	-0.14006	1	-0.55324
Molecular Refractivity (Whole Molecule)	0.94867	0.77939	0.96212	0.96164	0.9637	0.48535	0.73509	0.027624	0.72942	-0.55324	1

FIGURE 12: CORRELATION MATRIX FOR THE SET 3A-3D'

CONCLUSION: Various molecular attributes were calculated for the 16 above mentioned derivatives. Using which, Correlation matrix was obtained. Observed Biological activities were given as input and then using TSAR software predicted biological activities were calculated. Using these results Hansch (QSAR) equations were developed. From the equations it can be concluded that almost all of the equations shows positive contribution towards the selected microorganism for antibacterial activity and % inhibition of albumin denaturation for anti-inflammatory activity.

By using regression analysis of zone of inhibition as independent variable, QSAR equations were developed for the activity against each of the microorganism studied as well as for the % inhibition of albumin denaturation. Using this data promising leads can be obtained and the biological activity data for which can be calculated without the compound being synthesized.

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