IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

QSAR studies of 2/3-bromo-N^0-(substituted benzylidene/3-phenylallylidene) benzohydrazides for thier affinity towards Anti Fungal activity.

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Abstract:-

In the present research Quantitative structure–activity relationship (QSAR) model for 22 compounds of 1,6-dihydro-pyrimidine derivatives analysed using multiple linear regression analysis (MLRA) followed by statistical evaluation by NCSS software (IBM). Quantitative structure activity relationship (QSAR) study remains as a very useful tool in the era of modern drug discovery to get better insights into structure activity relationships. The behavior of QSAR models developed is examined with a variety of statistical parameters and the contribution of various descriptors is analyzed. In this communication, we describe the results of QSAR studies carried out on a series of 1,6-dihydro-pyrimidine derivatives as potential antifungal agents. The best model since have the values **R = 0.8802, R^2 = 0.7748 , R^2A = 0.6997 , R^2 cv = 0.7741** are the best as compared to all the models. The calculated F value is greater than F theoretical value, the value of standard error of estimate is the lowest , **SE = 0.0398, PRESS/SSY = 0.2259** confirms that it is statistically significant and excellent model and it has been found to be having outstanding predictive power also.

Keywords:-

Quantitative structure–activity relationship (QSAR) model for 1,6-dihydro-pyrimidine derivatives , Anti Fungal activity , 2/3-bromo-N^0-(substituted benzylidene/3-phenylallylidene) benzohydrazides.

1. Introduction :-

Over the past two decades, health benefits ascribed to commercially available antimicrobials became doubtful, since many commonly used antibiotics have become less effective against certain bacterial infections; not only because of the toxic reactions they produce, but also due to emergence of drug resistant bacteria like methicillin resistant Staphylococcus aureus (MRSA) and vancomycin resistant Enterococcus faecium (VRE).[1,2] Resistance to a number of antimicrobial agents (β-lactam antibiotics, macrolides, quinolones, and vancomycin) among a variety of clinically significant species of bacteria is becoming increasingly major global problem. These pose a serious challenge to the scientific community, hence emphasis has been laid on development of new antimicrobial agents.[3,4] Moreover, there has been a rapid spread in primary and opportunistic fungal infections, particularly C. albicans, because of the increased number of immunocompromised patients suffering from AIDS, cancer, and organ transplantation.[5,6] Consequently, such types of infections continue to provide impetus for the search and discovery of novel, more potent, and selective nontraditional antimicrobial agents so that no cross-resistance with the present therapeuticals can take place. A practical synthesis of 2/3-bromo-N^0- (substituted benzylidene/3-phenylallylidene)benzohydrazides would be very helpful for chemists because it is found in many bioactive natural products and exhibits a wide range of biological properties.Quantitative structure activity relationship (QSAR) study remains as a very useful tool in the era of modern drug discovery to get better insights into structure activity relationships.[7,8,9,10] The behavior of QSAR models developed is examined with a variety of statistical parameters and the contribution of various descriptors is analyzed. In this communication, we

describe the results of QSAR studies carried out on a series of 1,6-dihydro-pyrimidine derivatives as potential antifungal agents.

2. Research Methodology :-

2.1. Data Set :-

All data of the present investigation were obtained from the reference *(* B.Narasimah et all *)*. The data set for this investigation consisted 22 compounds of 1,6-dihydro-pyrimidine derivatives as potential antifungal agents. is analysed using multiple linear regression analysis (MLRA) followed by statistical evaluation by NCSS software (IBM).The structure of parent compound is given in (Structure- 1).

2.2. Molecular Descriptor Generation :-

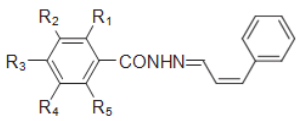
To obtain a QSAR model, compounds are often represented by the molecular descriptors. The calculation process of the molecular descriptors was described as below: The two-dimensional molecular structures for 22 compounds of 1,6-dihydro-pyrimidine derivatives were drawn by Chem Sketch 12.0 then calculated some parameters. Then this optimize structure files were exported into software Dragon 6.0 to calculate all kinds of descriptors. The software Dragon 6.0 can calculate Physicochemical parameters, constitutional, topological, geometrical, descriptors and has been successfully used in various QSAR researches. Following topological indices have been calculated using dragon software and they are reported in Table-2. (MW, Sv, Se, Sp, Mv, Pol, VDA, W, J, JhetZ, Jhetm, Jhetv, Jhete, Jhetp, BAC, Dr06, X0, X1, X2, X0A, X1A, X2A, X1v, X2v, X3v, X0sol, X1sol, X2sol, AMR, TPSA(Tot), MLOGP, ALOGP).Then value of all parameters put into NCSS statistical and data analysis software or SPSS (We can also use MSTAT instead of SPSS & NCSS) statistical and data analysis software to get data regression and correlation.

3. RESULTS AND DISCUSSION :-

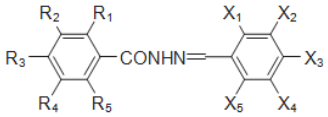
By using the multiple linear regression analysis (MLRA) method of 2D-QSAR, regression models were developed for 22 compounds. The anti fungal activity is being affected by various groups attached at x2 and x3 position and their fore dummy parameters are IP1 , IP2 and IP3. IP1 has been given value of 1

The anti fungal activity is being affected by various groups attached called indicator parameters . IP1 if it is other than (Structure – 1), It has been given value 1. IP2 when –OCH3 group at position X1 and IP2 electron releasing group is present at X3.

Structure (1)



(1, 20)



(2-19, 21, 22)

Table -1 Structure and substituent

S. No.	R_1	R_2	R_3	R_4	R_5	X_1	X_2	X_3	X_4	X_5
1	H	Br	H	H	H	-	-	-	-	-
2	H	Br	H	H	H	H	H	OCH_3	H	H
3	H	Br	H	H	H	H	OCH_3	OCH_3	OCH_3	H
4	H	Br	H	H	H	OH	H	H	H	H
5	H	Br	H	H	H	H	H	Br	H	H
6	H	Br	H	H	H	H	OCH_3	OCH_3	H	H
7	H	Br	H	H	H	H	OC_2H_5	OH	H	H
8	H	Br	H	H	H	H	H	$N(CH_3)_2$	H	H
9	Br	H	H	H	H	H	H	H	H	H
10	Br	H	H	H	H	H	H	Cl	H	H
11	Br	H	H	H	H	H	Cl	H	H	H
12	Br	H	H	H	H	H	H	Br	H	H
13	Br	H	H	H	H	H	H	NO_2	H	H
14	Br	H	H	H	H	H	OCH_3	OCH_3	H	H
15	Br	H	H	H	H	H	H	$N(CH_3)_2$	H	H
16	Br	H	H	H	H	H	H	CHO	H	H
17	Br	H	H	H	H	H	OC_2H_5	OH	H	H
18	Br	H	H	H	H	H	OCH_3	OCH_3	OCH_3	H
19	Br	H	H	H	H	H	H	OCH_3	H	H
20	Br	H	H	H	H	-	-	-	-	-
21	Br	H	H	H	H	H	H	CH_3	H	H
22	Br	H	H	H	H	H	OCH_3	OH	H	H

Table 2 Topological Indices Calculations of compounds.

IP1	IP2	IP3	MW	Sv	Se	Sp	Mv	Pol	VDA	W	J	JhetZ	Jhetm	Jhetv	Jhete	Jhetp	BAC	D/Dr06	X0	X1	X2	X0A	X1A	X2A	X1v	X2v	X3v	X0sol	X1sol	X2sol	AMR	TPSA(Tot)	MLOGP	ALOGP
0	0	0	250.32	22.009	32.833	23.003	0.67	22	94.947	902	1.4662	1.9775	1.9774	1.488	1.97	1.3778	2	144.115	13.339	9.36	7.5117	0.7002	0.4668	0.3133	5.9633	3.8555	2.4551	13.339	9.36	7.517	77.305	41.46	3.4436	3.044
1	0	1	333.2	22.668	33.339	23.884	0.69	26	98.2	982	1.5882	2.1773	2.1774	1.5256	2.14	1.4005	11	148.082	14.372	9.686	8.2355	0.7119	0.4661	0.3005	6.7112	4.8998	3.0776	15.372	10.263	9.052	81.831	50.69	3.631	3.415
1	1	1	393.26	26.9	41.811	28.827	0.66	36	127	1524	1.7477	2.4401	2.4402	1.6114	2.3711	1.4822	35	181.53	17.527	11.583	9.6886	0.73	0.4663	0.2944	7.77	5.5844	3.6447	18.527	12.161	10.503	94.757	69.15	2.546	3.383
1	0	0	319.17	21.088	30.511	22.088	0.7	25	85.684	814	1.6638	2.2443	2.2444	1.59	2.204	1.4663	10	137.14	13.665	9.165	7.9622	0.7119	0.4558	0.3006	6.3229	4.6844	2.8887	14.665	9.7422	8.7778	77.062	61.69	3.384	3.164
1	0	0	382.06	21.666	29.441	22.998	0.75	24	88.211	838	1.5593	2.2133	2.2144	1.5911	2.1445	1.4722	10	138.711	13.665	9.148	8.0666	0.7119	0.4557	0.31	7.0811	5.5592	3.3587	15.665	10.303	9.699	82.99	41.46	4.559	4.18
1	1	1	363.23	24.779	37.6	26.006	0.67	31	113	1243	1.6654	2.2722	2.2733	1.5558	2.2411	1.4331	21	164.806	15.949	10.635	8.9556	0.7225	0.4662	0.2999	7.2411	5.224	3.3367	16.949	11.212	9.7722	88.294	59.92	3.083	3.399
1	1	1	363.23	24.779	37.6	26.006	0.67	30	113.364	1247	1.6449	2.2544	2.2544	1.5548	2.2233	1.4233	19	164.357	15.949	10.597	9.1445	0.7225	0.4661	0.3005	7.444	5.2855	3.2443	16.949	11.174	9.962	88.273	70.92	3.083	3.497
1	0	1	346.25	24.776	37.005	26.115	0.67	28	107.429	1128	1.5889	2.1663	2.1664	1.5599	2.1332	1.4337	18	157.454	15.242	10.059	8.9665	0.7226	0.4557	0.3009	7.2177	5.6111	3.3369	16.242	10.636	9.781	89.796	44.7	3.871	3.594
1	0	0	303.17	20.557	29.188	21.163	0.71	22	79.222	713	1.5597	2.1889	2.119	1.5749	2.1449	1.445	5	129.723	12.795	8.754	7.4444	0.7111	0.4661	0.31	6.1889	4.5336	2.7559	13.795	9.3331	8.261	75.368	41.46	3.924	3.432

1	0	0	337.61	21.27	29.5	22.48	0.73	24	88.211	838	1.593	2.204	2.206	1.584	2.148	1.467	10	138.711	13.665	9.148	8.066	0.719	0.457	0.31	6.666	5.113	3.082	15.165	10.014	9.291	80.172	41.46	4.438	4.096
1	0	0	337.61	21.27	29.5	22.48	0.73	24	86.947	826	1.614	2.232	2.234	1.599	2.174	1.479	10	137.865	13.665	9.148	8.078	0.719	0.457	0.311	6.666	5.117	3.044	15.165	10.014	9.303	80.172	41.46	4.438	4.096
1	0	0	382.06	21.66	29.41	22.98	0.75	24	88.211	838	1.593	2.213	2.214	1.591	2.145	1.472	10	138.711	13.665	9.148	8.066	0.719	0.457	0.31	7.081	5.592	3.358	15.665	10.303	9.699	82.99	41.46	4.559	4.18
1	0	0	348.17	21.99	32.005	22.78	0.71	28	107.429	1128	1.589	2.203	2.204	1.561	2.171	1.432	18	157.454	15.242	10.059	8.965	0.726	0.457	0.309	6.688	4.974	3.064	16.242	10.636	9.781	82.692	87.28	3.923	3.326
1	1	1	363.23	24.79	37.6	26.006	0.67	31	113	1243	1.654	2.272	2.273	1.558	2.241	1.431	21	164.806	15.949	10.635	8.956	0.725	0.462	0.299	7.241	5.24	3.367	16.949	11.212	9.772	88.294	59.92	3.083	3.399
1	0	1	346.25	24.776	37.005	26.115	0.67	28	107.429	1128	1.589	2.163	2.164	1.559	2.132	1.437	18	157.454	15.242	10.059	8.965	0.726	0.457	0.309	7.217	5.611	3.369	16.242	10.636	9.781	89.796	44.7	3.871	3.594
1	0	1	331.18	22.08	31.51	23.088	0.71	26	98.2	982	1.582	2.167	2.168	1.587	2.134	1.468	11	148.082	14.372	9.686	8.235	0.719	0.461	0.305	6.624	4.91	3.032	15.372	10.263	9.052	81.959	58.53	3.555	3.191
1	1	1	363.23	24.79	37.6	26.006	0.67	30	113.364	1247	1.649	2.254	2.254	1.548	2.223	1.423	19	164.357	15.949	10.597	9.145	0.725	0.461	0.305	7.444	5.285	3.243	16.949	11.174	9.962	88.273	70.92	3.083	3.497
1	1	1	393.26	26.9	41.81	28.27	0.66	36	127	1524	1.747	2.401	2.402	1.614	2.371	1.482	35	181.53	17.527	11.583	9.686	0.73	0.463	0.294	7.77	5.584	3.647	18.527	12.161	10.503	94.757	69.15	2.546	3.383
1	0	1	333.2	22.68	33.39	23.884	0.69	26	98.2	982	1.582	2.173	2.174	1.526	2.14	1.405	11	148.082	14.372	9.686	8.235	0.719	0.461	0.305	6.712	4.898	3.076	15.372	10.263	9.052	81.831	50.69	3.631	3.415
0	0	0	329.21	23.	33.	24.	0.7	24	103	10	1.4	2.0	2.0	1.5	2.0	1.4	5	152.	14.209	9.754	8.1	0.71	0.4	0.3	6.8	4.9	2.9	15.209	10.331	8.968	84.928	41.46	4.067	3.792

				17	06	39				30	91	34	35	25	04	17		476			51		64	14	55	15	95							
1	0	0	317.2	22.17	32.006	23.339	0.69	24	88.211	838	1.5593	2.1775	2.1776	1.5884	2.1339	1.4463	10	138.7111	13.665	9.148	8.0666	0.7119	0.4557	0.31	6.5999	5.0356	3.0337	14.665	9.725	8.882	80.409	41.46	4.17	3.918
0	1	1	349.2	23.19	34.772	24.3	0.68	29	103.81	1090	1.6643	2.2555	2.2556	1.5668	2.2222	1.4442	18	155.435	15.242	10.097	8.7665	0.7226	0.4559	0.3022	6.8652	5.0556	3.1164	16.242	10.674	9.581	83.525	70.92	2.843	3.148

Table 3: Correlation of Topological Indices Anti Fungal

	pMICaf	*IP1*	*IP2*	*IP3*	*MW*	*Sv*	*Se*	*Sp*	*Mv*	*Pol*	*VDA*	*W*
pMICaf	1											
IP1	0.053647	1										
IP2	0.02834	0.216025	1									
IP3	0.181075	0.34641	0.62361	1								
MW	0.265392	0.553415	0.543625	0.410224	1							
Sv	0.287122	0.097107	0.750473	0.754753	0.572653	1						
Se	0.25736	0.088819	0.772082	0.775303	0.474721	0.985668	1					
Sp	0.298467	0.111488	0.740496	0.748392	0.594638	0.9979	0.975592	1				
Mv	0.15958	0.09512	0.61808	0.69867	0.00783	0.78604	0.86795	0.76211	1			
Pol	0.253448	0.341821	0.82556	0.727193	0.696292	0.911802	0.914048	0.899799	0.66638	1		
VDA	0.21871	0.058363	0.759881	0.729276	0.558201	0.950884	0.950868	0.933	0.75116	0.93273	1	
W	0.21939	0.120219	0.789393	0.719836	0.600602	0.955647	0.95521	0.939556	0.73605	0.962392	0.993987	1
J	0.162598	0.672062	0.727423	0.494664	0.741797	0.614224	0.611946	0.617438	0.33967	0.82675	0.577771	0.657866
JhetZ	0.14719	0.709895	0.676821	0.421077	0.787332	0.534881	0.520335	0.54041	0.20858	0.779243	0.514774	0.597626
Jhetm	0.14789	0.711482	0.673906	0.419261	0.78779	0.53239	0.517438	0.538078	0.2051	0.777344	0.512181	0.595122

Jhetv	0.148078	0.615724	0.146903	0.08066	0.58512	0.079789	0.015847	0.100194	0.29147	0.309126	0.022057	0.110724
Jhete	0.150634	0.658258	0.736906	0.495864	0.741437	0.615407	0.617911	0.614275	0.34361	0.844986	0.604033	0.681542
Jhetp	0.140026	0.522283	0.030996	0.18675	0.518223	0.01845	0.09766	0.006959	0.400522	0.178359	0.08729	0.0039
BAC	0.285267	0.434241	0.754207	0.64683	0.742879	0.870019	0.86068	0.863333	0.57561	0.97901	0.873846	0.915335
D/Dr06	0.226526	0.090508	0.783476	0.718903	0.585634	0.954872	0.954553	0.9381	0.74197	0.954011	0.997002	0.999117
X0	0.238271	0.250894	0.811756	0.736091	0.672161	0.942121	0.939261	0.92894	0.69703	0.987866	0.973918	0.989385
X1	0.208462	0.140087	0.819728	0.730011	0.604618	0.950527	0.954029	0.934302	0.7376	0.971935	0.986645	0.997322
X2	0.264666	0.348905	0.746	0.705839	0.727804	0.905154	0.888973	0.896543	0.62229	0.95616	0.935474	0.948042
X0A	0.30764	0.715628	0.600218	0.629892	0.808814	0.668775	0.643965	0.671306	0.35404	0.828493	0.67638	0.710935
X1A	0.16794	0.64251	0.355699	0.232201	0.27866	0.347517	0.405659	0.319599	0.5321	0.215761	0.386745	0.364581
X2A	0.2192	0.43044	0.80028	0.7059	0.59749	0.73468	0.76111	0.72218	0.569076	0.89874	0.7411	0.79181
X1v	0.274822	0.353578	0.693012	0.619839	0.888037	0.861678	0.784034	0.879251	0.39748	0.84613	0.807116	0.830248
X2v	0.352131	0.559147	0.338957	0.390403	0.905289	0.548945	0.43161	0.585024	0.00738	0.561905	0.455186	0.484277
X3v	0.383908	0.522058	0.554274	0.551145	0.942772	0.738208	0.648107	0.762147	0.22636	0.784204	0.670307	0.70628

X0sol	0.266482	0.400422	0.768513	0.662671	0.861972	0.871835	0.829024	0.872293	0.47267	0.954456	0.887611	0.915745
X1sol	0.241972	0.290491	0.80023	0.678056	0.808208	0.908108	0.872377	0.904847	0.53753	0.966282	0.929469	0.952912
X2sol	0.282314	0.544603	0.607177	0.525223	0.948106	0.709971	0.634161	0.723081	0.21857	0.812418	0.712879	0.743562
AMR	0.32681	0.195575	0.67027	0.688537	0.743738	0.955799	0.899912	0.96281	0.58749	0.891616	0.914123	0.920787
TPSA(Tot)	0.007212	0.307008	0.641098	0.440243	0.4045	0.456508	0.519544	0.413218	0.42783	0.700151	0.652169	0.663494
MLOGP	0.11524	0.06666	0.82162	0.70226	0.23362	0.73256	0.81417	0.70082	0.826564	0.79977	0.7693	0.78826
ALOGP	0.000319	0.125891	0.33576	0.4635	0.299478	0.2752	0.41072	0.22257	0.666693	0.34376	0.38883	0.37208

	J	*JhetZ*	*Jhetm*	*Jhetv*	*Jhete*	*Jhetp*	*BAC*	*D/Dr06*	*X0*	*X1*	*X2*	*X0A*	*X1A*	*X2A*	*X1v*	*X2v*	*X3v*	*X0sol*	*X1sol*	*X2sol*	*AMR*	*TPSA(Tot)*	*MLOGP*	*ALOGP*
J	1																							
JhetZ	0.988317	1																						
Jhetm	0.987789	0.999981	1																					
Jhetv	0.680178	0.728263	0.730616	1																				
Jhete	0.995549	0.988618	0.988036	0.655613	1																			
Jhetp	0.556502	0.611995	0.614764	0.98394	0.526504	1																		
BAC	0.870698	0.836111	0.83476	0.448287	0.88464	0.321765	1																	
D/Dr06	0.631367	0.570264	0.567745	0.082903	0.656169	0.0292	0.90233	1																

X0	0.743889	0.691366	0.689216	0.209707	0.763961	0.086359	0.954728	0.985032	1														
X1	0.689975	0.629731	0.62719	0.128912	0.713241	0.011141	0.921025	0.9954	0.990713	1													
X2	0.735391	0.693288	0.691666	0.262349	0.749985	0.140858	0.94698	0.942693	0.975068	0.940261	1												
X0A	0.823013	0.818314	0.818475	0.512481	0.8261	0.389382	0.872784	0.966119	0.799537	0.711788	0.882286	1											
X1A	0.09583	0.17069	0.17435	0.449182	0.06689	0.503886	0.077099	0.377593	0.253267	0.381177	0.055263	0.35487	1										
X2A	0.86275	0.8261	0.82457	0.367	0.88243	0.23645	0.86857	0.77879	0.83316	0.82799	0.74561	0.70351	0.282335	1									
X1v	0.714505	0.69705	0.695941	0.359709	0.706024	0.281676	0.852546	0.820913	0.861991	0.825398	0.898975	0.802226	0.00857	0.65666	1								
X2v	0.5937	0.622137	0.623394	0.556466	0.56791	0.526994	0.642006	0.471383	0.55669	0.469656	0.670334	0.787685	0.47475	0.38548	0.856886	1							
X3v	0.748667	0.759163	0.759488	0.537559	0.740026	0.464808	0.833592	0.693965	0.766148	0.703558	0.814494	0.855514	0.21882	0.66101	0.941681	0.937987	1						
X0sol	0.810017	0.793575	0.792442	0.391716	0.82311	0.282465	0.954109	0.906625	0.953235	0.917801	0.962028	0.878635	0.04554	0.80406	0.947192	0.751696	0.905483	1					
X1sol	0.774223	0.747788	0.746175	0.311432	0.791292	0.204292	0.946156	0.946252	0.972463	0.956394	0.953607	0.809068	0.188238	0.82262	0.93234	0.674398	0.860238	0.98948	1				
X2sol	0.765306	0.782506	0.782601	0.515607	0.76777	0.402743	0.854455	0.731428	0.809185	0.737554	0.883718	0.918659		0.6282	0.934439	0.901655	0.949172	0.940663	0.873846	1			

													0.26931										
AMR	0.629002	0.582548	0.581083	0.229319	0.628385	0.147378	0.882201	0.918496	0.924178	0.907313	0.930884	0.757956	0.143935	0.67176	0.949667	0.745271	0.873589	0.931994	0.940456	0.852994	1			
TPSA(Tot)	0.577739	0.560563	0.558152	0.131197	0.626033	0.009	0.652608	0.65866	0.695332	0.674163	0.694428	0.632399	0.108403	0.62059	0.411703	0.147976	0.323952	0.630572	0.629105	0.528368	0.423434	1		
MLOGP	0.611033	0.51785	0.51421	0.018056	0.630559	0.14737	0.70449	0.78607	0.77999	0.81782	0.66449	0.45611	0.57486	0.834124	0.45657	0.02593	0.31769	0.61522	0.67876	0.34738	0.55928	0.69446	1	
ALOGP	0.11564	0.02465	0.02134	0.338446	0.15093	0.440632	0.23409	0.37941	0.33544	0.38939	0.22608	0.00536	0.55861	0.431855	0.12347	0.460312	0.22317	0.09138	0.1602	0.16984	0.06506	0.56719	0.75822	1

A close look at this Table reveals that- x3v is highly correlated with MW, BAC, X1v, X2v, X3v, X0sol, X1sol, X2sol, AMR, and moderately correlated with MW, Sv, Se, Sp, Mv, Pol, VDA, W, J, JhetZ, Jhetm, Jhetv, Jhete, Jhetp, X2A,

MW is moderately correlated with JhetZ, Jhetm,X2, AMR and highly correlated with X0A, X1A, X2A, X1v, X2v, X3v, X0sol, X1sol, X2sol.

JHETZ is highly correlated with Jhete, BAC, x1a, x1v, and moderately coreelated with X0, X1, X2.

TPSA(tot) is moderetly correlated with MV, vda, w, jhetz, x0sol.

X0 and x1 is highly correlated with IP2, sv, se, sp, pol, vda, w and modertly with jhetz, j.

The data was subjected to regression analysis and the result obtained are discussed below,

Result and discussion: Modeling with Topological parameters: The Topological parameters have been subjected regression analysis for modeling pMIC activity for the compounds listed in Table-4.The resulting models obtained are summarized in Table-5. The quality of models has been reported in terms of statistical parameters viz. Se, R^2 ,R^2A, F-ratio and Q.

Table 4: Regression of Anti Fungal Topological Indices Mono Parametric

Model No	Parameter Used	R	R2	R2A	F Ratio	Q=r/se
1	IP1	0.0536	0.0029	0.0470	0.0577	0.3674
2	IP2	0.0283	0.0008	0.0492	0.0161	0.1937
3	IP3	0.1811	0.0328	0.0156	0.6780	1.2603
4	MW	0.2654	0.0704	0.0240	1.5154	1.8836
5	Sv	0.2871	0.0824	0.0366	1.7969	2.0507
6	Se	0.2574	0.0662	0.0195	1.4186	1.8229
7	Sp	0.2985	0.0891	0.0435	1.9559	2.1398
8	Mv	0.1596	0.0255	0.0233	0.5226	1.1060
9	Pol	0.2534	0.0642	0.0174	1.3729	1.7921
10	VDA	0.2187	0.0478	0.0002	1.0047	1.5337
11	W	0.2194	0.0481	0.0005	1.0113	1.5386
12	J	0.1626	0.0264	0.0222	0.5431	1.1276
13	JhetZ	0.1472	0.0217	0.0273	0.4429	1.0187
14	Jhetm	0.1479	0.0219	0.0270	0.4472	1.0235
15	Jhetv	0.1481	0.0219	0.0270	0.4484	1.0249
16	Jhete	0.1506	0.0227	0.0262	0.4643	1.0422
17	Jhetp	0.1400	0.0196	0.0294	0.4000	0.9675
18	BAC	0.2853	0.0814	0.0354	1.7717	2.0364
19	Dr06	0.2265	0.0513	0.0039	1.0818	1.5917
20	X0	0.2383	0.0568	0.0096	1.2038	1.6794
21	X1	0.2085	0.0435	0.0044	0.9086	1.4591
22	X2	0.2647	0.0700	0.0236	1.5065	1.8786
23	X0A	0.3076	0.0946	0.0494	2.0907	2.2129
24	X1A	0.1679	0.0282	0.0204	0.5805	1.1652
25	X2A	0.2192	0.0481	0.0005	1.0095	1.5372
26	X1v	0.2748	0.0755	0.0293	1.6340	1.9559
27	X2v	0.3521	0.1240	0.0802	2.8309	2.5738
28	X3v	0.3839	0.1474	0.1048	3.4573	2.8458
29	X0sol	0.2665	0.0710	0.0246	1.5288	1.8928
30	X1sol	0.2420	0.0586	0.0115	1.2438	1.7066
31	X2sol	0.2823	0.0797	0.0337	1.7321	2.0136
32	AMR	0.3268	0.1068	0.0621	2.3915	2.3664
33	TPSA(Tot)	0.0072	0.0001	0.0499	0.0010	0.0493
34	MLOGP	0.1152	0.0133	0.0361	0.2692	0.7934
35	ALOGP	0.0003	0.0000	0.0500	0.0000	0.0021

Bi Parametric

Model No	Parameter Used	AI	B	SE	R	R2	R2A	F Ratio	Q=r/se
36	X3V X2V	0.2320(±0.3177) 0.0223 (±0.2051)	0.8981	0.1384	0.3846	0.1479	0.0582	1.6491	2.7789
37	X3V AMR	0.2161(±0.2264) 0.0010 (±0.0116)	0.9161	0.1384	0.3843	0.1477	0.0580	1.6462	2.7767
38	X3V X0A	0.2342(±0.2126) 1.6507 (±8.6970)	1.9672	0.1383	0.3860	0.1490	0.0594	1.6633	2.7910
39	X3V BAC	0.2491(±0.1990) 0.0019 (±0.0064)	0.7588	0.1381	0.3890	0.1513	0.0620	1.6942	2.8168
40	X3V J	0.3103(±0.1627) 0.6278 (±0.6915)	1.5476	0.1355	0.4276	0.1828	0.0968	2.1256	3.1557
41	X3V MV	0.1907(±0.1127) 0.3923 (±1.1103)	1.1871	0.1380	0.3911	0.1530	0.0638	1.7154	2.8341
42	X3V JHETZ	0.3341(±0.1643) 0.5172 (±0.4799)	1.6043	0.1344	0.4433	0.1965	0.1119	2.3233	3.2984
43	X3V JHETM	0.3338(±0.1645) 0.5146 (±0.4792)	1.6001	0.1344	0.4429	0.1962	0.1116	2.3184	3.2954
44	X3V JHETV	0.2226(±0.1303) 0.3738 (±1.1422)	1.3994	0.1380	0.3901	0.1522	0.0629	1.7050	2.8268
45	X3V JHETE	0.3132(±0.1600) 0.4586 (±0.4781)	1.5239	0.1352	0.4322	0.1868	0.1012	2.1817	3.1967

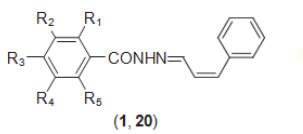
Tri Parametric

Model No	Parameter Used	AI	B	SE	R	R2	R2A	F Ratio	Q=r/se
46	X3V JHETZ JHETM	0.3287(±0.1688) 20.3136 (±52.4077) 19.7659 (±52.3246)	1.6710	0.1375	0.4504	0.2028	0.0700	1.5266	3.2756
47	X3V JHETZ X2A	0.3241(±0.1676) 0.7973 (±0.6518) 6.1672 (±9.5277)	4.1429	0.1365	0.4634	0.2148	0.0839	1.6412	3.3949
48	X3V JHETZ X0A	0.2816(±0.2156) 0.6278 (±0.5673) 3.8877 (±9.9900)	0.7872	0.1375	0.4508	0.2032	0.0704	1.5302	3.2785
49	X3V JHETZ IP1	0.3325(±0.1686) 0.4264 (±0.5963) 0.0391 (±0.1452)	1.4445	0.1378	0.4469	0.1997	0.0664	1.4975	3.2431
50	X3V JHETZ IP2	0.3483(±0.1647) 0.2546 (±0.5439) 0.0856 (±0.0838)	1.0060	0.1342	0.4905	0.2406	0.1140	1.9005	3.6550
51	X3V JHETZ IP3	0.3462(±0.1834) 0.5168 (±0.4927) 0.0119 (±0.0708)	1.5716	0.1380	0.4447	0.1978	0.0641	1.4791	3.2225

Table 5: Regression Model

Model No	Parameter Used	AI	B	SE	R	R2	R2 A	F Ratio	Q=r /se
28	X3v	0.1997 (±0.1074)	0.8866	0.1349	0.3839	0.1474	0.1048	3.4573	2.8458
42	X3V-JHETZ	0.3341(±0.1643), -0.5172 (±0.4799)	1.6043	0.1344	0.4433	0.1965	0.1119	2.3233	3.2984
50	X3V-JHETZ-IP2	0.3483(±0.1647), -0.2546 (±0.5439) ,-0.0856 (±0.0838)	1.0060	0.1342	0.4905	0.2406	0.1140	1.9005	3.6550

The anti Fungal activity is being affected by various groups attached called indicator parameters . IP1 .If it is other than



(1, 20)

Has been given value 1. IP@ when –OCH3 gp at position X1 and IP2 electron releasing group

Is present at position X3.It is taken as one for presence of that group or substitution at particular site and zero for all all such cases where it is absent.

Out of 35 mono parametric model the best parametric model contains X3V (R2=0.1474).

The Model are as follow:

Mono Parametric Model

pMIC = 0.1997 (±0.1074) x3v + 0.8866

N=22, SE=0.1349, R=0.3839,R2=0.1474, R2A=0.1048, F Ratio=3.4573, Q=2.8458

Bi Parametric Model :

Out of 10 the best model contains x3v, JhetZ as correlation parameters (R2=0.1965).

The Model Is As follow.

pMIC = 0.3341(±0.1643)x3v -0.5172 (±0.4799) JhetZ + 0.1643

N=22, SE=0.1344, R=0.4433,R2=0.1965, R2A=0.1119, F Ratio=2.323, Q=3.2984

Tri-Parametric Model :

Out of 6 the best model contains x3v, JhetZ and IP2 as correlation parameters (R2=0.2406).

The Model Is As follow.

pMIC = 0.3483(±0.1647)x3v -0.2546 (±0.5439) JhetZ -0.0856 (±0.0838), IP2+ 1.0060

n=22, SE=0.1342, R=0.4905, R2=0.2406, R2A=0.1140 F RATIO=1.9005, Q=3.6550

On the basis of Tri Parametric model pMIC values have been estimated for the compounds under present investigation and they are demonstrated in table 6 the predicted power of the model is also Shown in figure 1.

Table 6: Observed and Estimated Model of Anti Fungal Topological Indices

SN	Observed pMICaf	*Predicted pMICaf*	*Residuals*
1	1.42	1.357002137	0.062997863
2	1.58	1.524310252	0.055689748
3	1.65	1.57958429	0.07041571
4	1.71	1.440655274	0.269344726
5	1.49	1.612359043	0.122359043
6	1.61	1.514887995	0.095112005
7	1.31	1.476276218	0.166276218
8	1.59	1.628918745	0.038918745
9	1.23	1.4098143	0.1798143
10	1.58	1.518508924	0.061491076
11	1.28	1.498144424	0.218144424
12	1.64	1.612359043	0.027640957
13	1.44	1.512493408	0.072493408
14	1.31	1.514887995	0.204887995
15	1.74	1.628918745	0.111081255
16	1.42	1.51051076	0.09051076
17	1.46	1.476276218	0.016276218
18	1.65	1.57958429	0.07041571
19	1.58	1.524310252	0.055689748
20	1.57	1.531478724	0.038521276
21	1.55	1.510215969	0.039784031
22	1.6	1.448502994	0.151497006

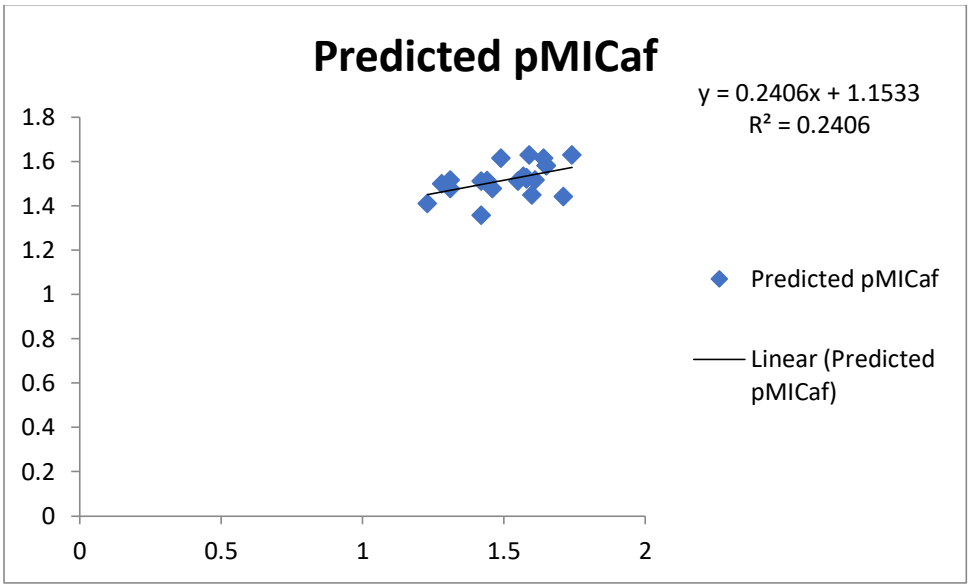


Figure 1 : The cross validated parameters have been calculated for these models and recorded in table 7 on the basis of cross validated parameters The Tri parametric model discussed above has been formed to be the best model.

Table 7: Cross validation of Anti Fungal Topological Indices

Model No	Parameter Used	press	ssy	Press/SSY	R²CV	PSE	Spress
28	X3v	0.3641	0.4271	0.852494	0.147506	0.128647	0.134926
42	X3V JHETZ	0.3431	0.4271	0.803325	0.196675	0.124882	0.13438
50	X3V JHETZ IP2	0.3243	0.4271	0.759307	0.240693	0.121412	0.134226

Among all the triparametric models listed in table 5 models 28, 42 and 50 gave quite improved results. The significance and quality of these models was checked on the basis of the values of " R ", " R2", "R2A ", quality factor "Q", standard error of estimate "SE", "R2 CV", "PSE", and PRESS/SSY ratio of these equations. The squared correlation coefficient (R2) is a measure of the fit of the regression model correspondingly; it represents the part of variation in the observed data explained by the model. Study of these models shows that while carrying out the triparametric regression analysis, R2A goes on increasing while SE goes on decreasing and it means that statistically the quality of models goes on increasing. All the equations have higher Q value . Q is the quality factor estimated to determine the predictive value of the model.

QSAR MODEL DEVELOPMENT AND VALIDATION

The data set was split in two subsets the training set and test. The training set of 13 compounds is used in building the QSAR model and 9 compounds is for the test set that was used to evaluate the predictive ability of the model

Predictive ability was evaluated by the LOO (Leave one out method) cross validation procedure. This method systematically removes one data point at a point and then a model is constructed on the basis of the reduced data set which is then used to predict the activity of the removed sample. This procedure was repeated for all points until a complete set of predicted values were obtained. It was noted that the predicted activities were very close to the respective experimental values. Various cross- validation parameters calculated for the proposed models are presented in Table -8

The MLR methods are applied to generate and you Qsar model for the prediction of pMIC activities of the training and test compounds for the training set these models are reported in table 8 and they show much improvement in R square values these models are as below

Table 8: Topological Indices Regression of Training Set of Anti Fungal

Model No	Parameter Used	AI	B	SE	R	R2	R2A	F Ratio	Q=r/se
28	X3V	0.1951 (±0.0373)	0.9720	0.0406	0.8444	0.7129	0.6869	27.3205	20.7980
42	X3V JHETZ	0.2906(±0.0708) 0.2885 (±0.1857)	1.3010	0.0383	0.8768	0.7688	0.7225	16.6235	22.8930
50	X3V JHETZ IP2	0.2781(±0.0779) 0.2010 (±0.2633) 0.0192 (±0.0393)	1.1545	0.0398	0.8802	0.7748	0.6997	10.3189	22.1156

Mono Parametric Model:

pMIC = 0.1951 (±0.0373) x3v + 0.9720
N=13, SE=0.0406, R = 0.8444, R2=0.7129, R2A=0.6869, F RATIO=27.3205 Q=20.7980

Bi Parametric Model :

Out of 10 the best model contains x3v, JhetZ as correlation parameters (R2=0.1965).

The Model Is As follow.

pMIC = 0.2906(±0.0708)x3v 0.2885 (±0.1857)Jhetz + 1.3010
N=13, SE=0.0383, R=0.8768, R2=0.7688, R2A=0.7225, F RATIO=16.6235, Q=22.8930

Tri-Parametric Model :

Out of 6 the best model contains x3v, JhetZ and IP2 as correlation parameters (R2=0.2406).

The Model Is As follow.

pMIC = 0.3483(±0.1647)X3V, -0.2546 (±0.5439)JHETZ ,-0.0856 (±0.0838)IP2+ 1.0060
n=13, SE=0.1342 R=0.4905 R2=0.2406 R2A=0.1140 F RATIO=1.9005 Q=3.6550

Observed and estimated activities for the compounds using the best model is recorded in table 9 and cross validated parameters of training set have been calculated for various model and they are reported in table 10.

on the basis of value for different cross validated parameter it is observed that model containing x3v, jhetz and ip2 is the the best model with predicted power of 0.7748 the predictive power of the model is also shown in the figure 2.

Table 9: Topological Indices Observed and Estimated of Training Set of Anti Fungal

Sn	Observed pMICaf	*Predicted pMICaf*	*Residuals*
1	1.4200	1.4390	0.0190
2	1.5800	1.5730	0.0070
3	1.6500	1.6667	0.0167
4	1.6100	1.6148	0.0048
5	1.5900	1.6565	0.0665
6	1.5800	1.5684	0.0116
7	1.6400	1.6434	0.0034
8	1.7400	1.6565	0.0835
9	1.6500	1.6667	0.0167
10	1.5800	1.5730	0.0070
11	1.5700	1.5784	0.0084
12	1.5500	1.5618	0.0118
13	1.6000	1.5618	0.0382

Figure 2:

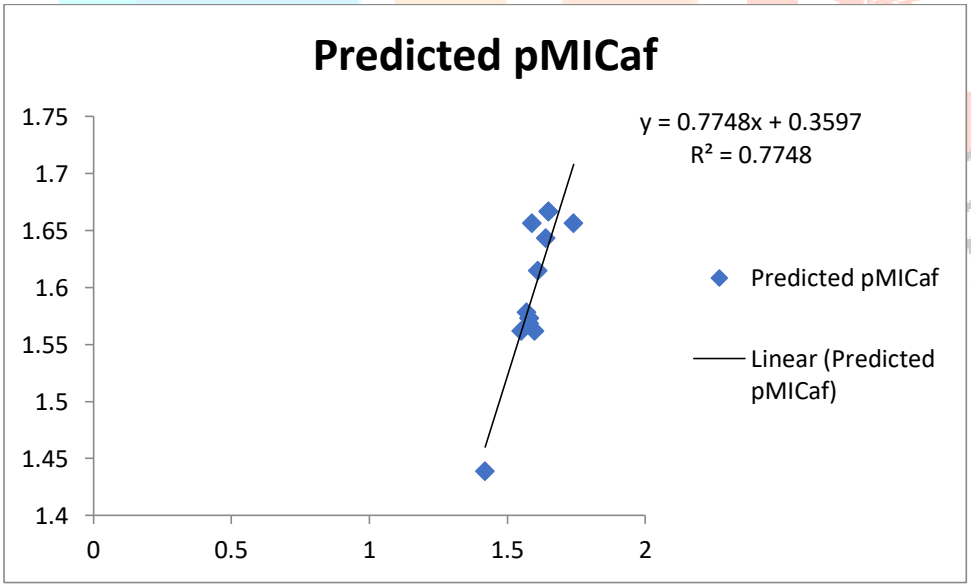


Table 10: Topological Indices Crossed validation of Training Set of Anti Fungal

Model No	Parameter Used	press	ssy	Press/SSY	R²CV	PSE	Spress
1	X3V	0.0182	0.0633	0.28752	0.71248	0.037417	0.040676
2	X3V JHETZ	0.0146	0.0633	0.230648	0.769352	0.033512	0.03821
3	X3V JHETZ IP2	0.0143	0.0633	0.225908	0.774092	0.033166	0.039861

PRESS (predicted residual sum of squares) appears to be the most important crossvalidation parameters accounting for good estimate of the real predictive error of the models. In case its value is less than SSY(sum of the square of all response value), it will mean that the predictive power of the model is good and is not based upon chance therefore, can be considered statistically significant

To be a reasonable QSAR model , PRESS/SSY should be smaller than 0.400. In our case , the ratio PRESS/SSY ranges between 0.2875 – 0.2259 indicating that all proposed models (eqns. 28, 42 and 50) are reliable. The PSE and SPRESS are good parameters to discuss the uncertainty in prediction. The lower the value of these parameters , the better will be the predictive ability of the model. The indication of the performance of the model is obtained from R2 CV (the overall predictive ability) higher R2 CV shows that the model is good. In order to examine the relative potential of models , predictive correlation coefficient (R2 pred) were estimated by plotting graphs between observed and calculated pMIC values obtained with the help of eqn 50. The comparison between observed and predicted activities is listed in Table-9. Such correlations are shown in figure 2. From the fig 2, R2 pred values obtained for equation 50 is 0.7748 is fairly high indicating the good quality of models.

Amongst all these statistically significant three models discussed above model 50 is the best model since the values R = 0.8802, R2 = 0.7748 , R2 A = 0.6997 , R2 cv = 0.7741 are the best as compared to all the models. The calculated F value is greater than F theoretical value, the value of standard error of estimate is the lowest , SE = 0.0398, PRESS/SSY = 0.2259 confirms that it is statistically significant and excellent model and it has been found to be having outstanding predictive power also.

The generated QSAR model was employed to predicted pMIC activities of the test (Prediction) molecules and the outcome is displayed in table 11-13 the predictive power is also shown in the figure3.

Table11: Topological Indices Regression of Test Set of Anti Fungal

Model No	Parameter Used	AI	B	SE	R	R2	R2A	F Ratio	Q=r/s e
50	X3V JHETZ IP2	0.0236(±0.6517) 2.3073 (±2.8687) 0.1710 (±0.2862)	3.6058	0.1827	0.4132	0.1707	0.4512	0.2745	2.2616

Table12: Topological Indices Observed and Estimated of Test Set of Anti Fungal

Sn	Observed pMICaf	*Predicted pMICaf*	*Residuals*
4	1.71	1.440655	0.269345
5	1.49	1.612359	0.12236
7	1.31	1.476276	0.16628
9	1.23	1.409814	0.17981
11	1.28	1.498144	0.21814
13	1.44	1.512493	0.07249
14	1.31	1.514888	0.20489
16	1.42	1.510511	0.09051
17	1.46	1.476276	0.01628

Figure 3:

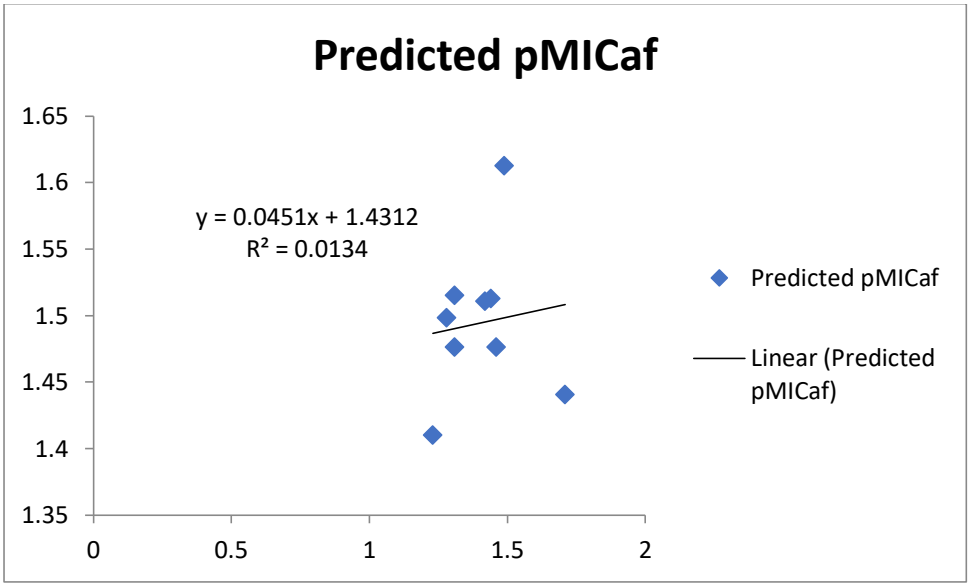


Table 13: Topological Indices Crossed validation of Test Set of Anti Fungal

Model No	Parameter Used	press	ssy	Press/SSY	R²CV	PSE	Spress
1	X3V JHETZ IP2	0.1335	0.161	0.829193	0.170807	0.121792	0.138099

The pridected pMIC values of test set is within the range of 1.4406 to 1.5148. hence model is validated.

4. Conclusions :-

On the basis of data and subsequent discussion presented in this section it may be suggested that in future designing of this class of drug with reference to their activity *pIMIC* the following points may be kept in mind.

(1). X3v, Jhet Z and IP2 has positive coefficient suggesting that these topological parameters are suitable for the modeling of pMIC.

(2) the compound no 5,8,12 and 15 (pMIC 1.6123-1.6289) were found to be most potent antifungal agents.

(3) the electron withdrawing groups increases the antifungal property.

B. Narasimhan has reported that electron withdrawing group increase the antifungal property. the activity obtained from the above proposed models (28,42&50) are in agreement. The present finding based on QSAR are in excellent agreement with the results obtained experimentally by B.Narasimah etall.

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