Journal of Advance Research in Science and Social Science (JARSSC)
Publisher: Indian Mental Health & Research Centre

ISSN: 2582-2004
Volume 06, Issue 01

DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

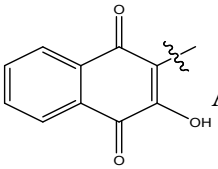
Generation of 2D-QSAR Models for Designing Potent Atovaquone Derivatives

Dr. Neerja Shukla

Assistant Professor, Department of Chemistry, NSN PG College, Lucknow

Email: neerjashuklaau2007@rediffmail.com

Atovaquone belongs to the class of naphthalenes and is mainly an anti parasite drug which selectively targets malarial parasite. It is structurally hydrophobic in nature therefore having poor water solubility and oral bioavailability. Chemically it is composed of a napthoquinonyl head, a cyclohexanyl linker and a hydrophobic 4-chlorophenyl tail, which is responsible for the hydrophobic nature of this drug. Due to the presence of naphthoquinonyl head moiety

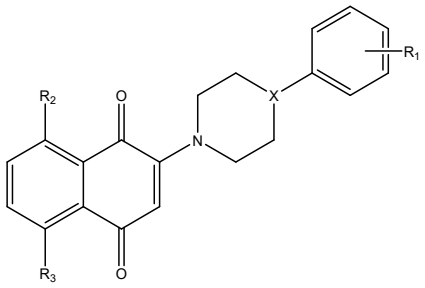


Atovaquone shows antitumor activity. The 4-chlorophenyl tail and cyclohexanyl linker provides potential sites for structural optimization. Drug designing is a crucial step for obtaining novel drugs and requires potent methodologies. In this research work, QSAR analysis of Atovaquone derivatives was performed using a number of structural parameters. The values of different physicochemical parameters are evaluated and indicator parameter I_1 for 4-F-3-Cl at R_1, I_2 for H at R_3 position and I_3 for CH groups at X position were used in present QSAR studies. In this work, the ratio PRESS/SSY for the equations 2, 17, 18, 41 and 42 are 0.190, 0.174, 0.190, 0.180, 0.179 respectively, which are less than 0.400, indicating that these models are reliable QSAR models. The PSE as well as S_{PRESS} are good parameters to be used for discussing the uncertainty in prediction. The lower the value of these parameters, the better will be the predictive ability of the model. Also, the highest R^2_{CV} (0.826) has been found for the QSAR model. no. 17 indicating that it has excellent overall predictive power. Thus from the results obtained it is clear that for getting the potent and efficient drug less Bulky groups having lesser vertices should be used, more polar, less electronegative group, more hydrophobic group is beneficial for the activity. Group H at R_3 position and CH at position X should be retained at R_2 position. The results are

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC)
Publisher: Indian Mental Health & Research Centre
ISSN: 2582-2004
Volume 06, Issue 01
DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

critically discussed on the basis of regression data and cross validation techniques. Poglani factor (Q) and the results of leave one out (LOO) method confirms the reliability and predictability of the proposed models that can be highly beneficial for future designing of new analogues with higher potency.



(**Structure of parent molecule**)

Keywords: QSAR, Atovaquone derivatives, Poglani factor (Q), leave one out (LOO), molecular descriptors

Introduction

For obtaining novel drugs drug designing is a crucial step which requires potent methodologies. One of such methods is Quantitative Structure Activity Relationship (QSAR) which is one of the widely used statistical tool that correlates the structure of a molecule to a biological activity as a function of molecular descriptors, thereby, playing an essential role in the drug designing. It must also be noted that the constructed QSAR[1] models also need to be tested and validated for their efficiency and practical usage. As the QSAR models are structure specific, they may not be universally applicable. However, because of their high precision and efficacy, they have a promising future in the world of drug design. *J. Zhou and coworkers* studied the role of Atovaquone derivatives as potent cytotoxic agents. The biological activity data reported by them has been used here. Inhibitory activity pIC_{50} against prostate Du 145 cells are reported in literature, where pIC_{50} represents the inhibition of the binding of receptor to the receptor site. In this research work, attempt has been done to obtain the QSAR models with the series of 29 Atovaquone derivatives which help in understanding and designing the structure of more potent drug.

Results and discussion

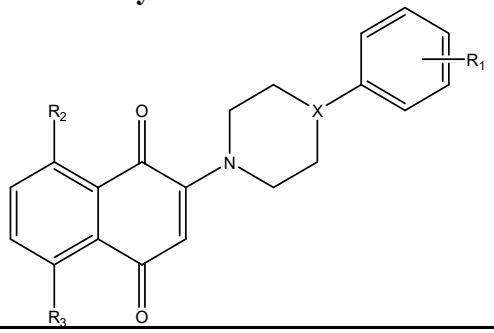
Two dimensional (2D) structures of 29 Atovaquone derivatives were drawn using ACD Lab Chem

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC)
Publisher: Indian Mental Health & Research Centre
ISSN: 2582-2004
Volume 06, Issue 01
DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

Sketch version 10 software[2] (www.acdlabs.com/acdlabs-rss-feed.xml) and some physicochemical and hydrophobic parameters such as weight (Mw), molar volume (Mv), molar refractivity (Mr), parachor (Pc), density (D), Index of refraction (IOR), surface tension (St),polarizability (Pz) and partition coefficient (Log P) were calculated with the help of this software[6]. However, most of the topological parameters such as wiener index (W), mean wiener index, (Wa) balaban indices (J), Balaban centric index (BAC) and molecular connectivity (χ); were calculated by using E Dragon software. Hansch analysis-multiparametic regression analysis [3]. Pogliani's quality factor and other statistical techniques are used in this work for investigating the predictive power of various parameters and finally cross validation technique was employed to test the validity of the models. The regression analysis used to derive the correlation was executed with SPSS 7.5 Software . The different analogues of parent structure and the values of biological activity are reported in Table 1.

Table 1
Biological activity data with different substituents



S.No.	R_1	R_2	R_3	X	pIC_{50}
1.	*p*-Cl	H	H	N	4.530
2.	*p*-F	H	H	N	4.931
3.	*p*-MeO	H	H	N	4.336
4.	*p*-Me	H	H	N	5.086
5.	H	H	H	N	5.004
6.	*m*-Cl	H	H	N	5.080

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC)
Publisher: Indian Mental Health & Research Centre
ISSN: 2582-2004
Volume 06, Issue 01
DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

7.	*o*-Cl	H	H	N	5.537
8.	*m*-Me	H	H	N	5.130
9.	*o*-Me	H	H	N	5.244
10.	*m*-OMe	H	H	N	4.823
11.	*o*-OMe	H	H	N	5.096
12.	3,5-di Methoxyl	H	H	N	4.826
13.	3,4-di Methoxyl	H	H	N	4.749
14.	3,4,5-tri Methoxyl	H	H	N	4.935
15.	4-F-3-Cl	H	H	N	4.492
16.	H	OH	H	N	5.552
17.	H	H	OH	N	4.818
18.	4-F	OH	H	N	5.075
19.	4-F	H	OH	N	4.649
20.	*o*-Cl	OH	H	N	5.638
21.	*o*-OMe	OH	H	N	5.744
22.	*o*-Me	OH	H	N	5.638
23.	H	OH	OH	N	5.886
24.	H	H	H	CH	5.221
25.	H	OH	H	CH	5.522
26.	*p*-Cl	H	H	CH	5.136
27.	*P*-Cl	OH	H	CH	5.585
28.	*o*-Me	H	H	CH	5.214
29.	*o*-Me	OH	H	CH	5.602

The values of different physicochemical parameters[4] evaluated and indicator parameter I_1 for 4-F-3-Cl at R_1, I_2 for H at R_3 position and I_3 for CH groups at X position were used in present QSAR studies are listed in Table 2. The value 1 and 0 was assigned to this parameters depending upon the presence or absence of these groups at R_3 position and are listed in Table 2.

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC) **ISSN:** 2582-2004
Publisher: Indian Mental Health & Research Centre Volume 06, Issue 01

DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

Table 2
Physicochemical parameters for different Atovaquone derivatives

.	BAC	D	Id	IOR	J	LogP	Mr	Mv	Mw	Pc	Pz	St	W	WA	$^{0}\chi$	$^{1}\chi$	$^{2}\chi$	$^{3}\chi$	$^{4}\chi$	$^{5}\chi$	Xeq	I_1	I_2
	10.000	1.362	4.578	1.662	1.324	3.155	95.860	258.900	352.814	721.200	38.00	60.20	1574.000	5.247	17.389	12.131	11.043	9.750	8.107	6.940	2.377	0.00	1.00
	10.000	1.339	4.578	1.644	1.324	3.032	90.960	251.100	336.359	691.400	36.05	57.40	1574.000	5.247	17.389	12.131	11.043	9.750	8.107	6.940	2.388	0.00	1.00
	11.000	1.285	4.637	1.640	1.302	2.339	97.640	270.900	348.395	742.700	38.70	56.40	1791.000	5.511	18.096	12.699	11.212	10.158	8.418	7.050	2.365	0.00	1.00
	10.000	1.262	4.578	1.648	1.324	3.155	95.790	236.200	332.395	722.300	37.97	56.70	1574.000	5.247	17.389	12.131	11.043	9.750	8.107	6.940	2.348	0.00	1.00
	5.000	1.289	4.531	1.658	1.344	2.907	90.960	246.900	318.369	684.100	36.06	58.80	1382.000	5.007	16.518	11.737	10.421	9.339	7.956	6.716	2.358	0.00	1.00
	10.000	1.362	4.578	1.662	1.338	3.155	95.860	258.900	352.814	721.200	38.00	60.20	1556.000	5.187	17.389	12.131	11.055	9.666	8.259	6.940	2.377	0.00	1.00
	10.000	1.362	4.578	1.662	1.352	3.155	95.860	258.900	352.814	721.200	38.00	60.20	1538.000	5.127	17.389	12.148	10.949	9.806	8.352	6.956	2.377	0.00	1.00
	10.000	1.262	4.578	1.648	1.338	3.155	95.790	263.200	332.395	722.300	37.97	56.70	1556.000	5.187	17.389	12.131	11.055	9.666	8.259	6.940	2.348	0.00	1.00
	10.000	1.262	4.578	1.648	1.352	3.155	95.790	263.200	332.395	722.300	37.97	56.70	1538.000	5.127	17.389	12.148	10.949	9.806	8.352	6.956	2.348	0.00	1.00
	11.000	1.285	4.637	1.640	1.325	2.339	97.640	270.900	348.395	742.700	38.70	56.40	1755.000	5.400	18.096	12.669	11.224	10.090	8.482	7.173	2.365	0.00	1.00
	11.000	1.285	4.637	1.640	1.352	2.339	97.640	270.900	348.395	742.700	38.70	56.40	1719.000	5.289	18.096	12.686	11.140	10.120	8.671	7.278	2.365	0.00	1.00
	21.000	1.282	4.735	1.625	1.334	1.784	104.320	294.900	378.421	801.300	41.35	54.40	2148.000	5.683	19.673	13.601	12.039	10.783	9.018	7.778	2.371	0.00	1.00
	21.000	1.282	4.735	1.625	1.315	1.784	104.320	294.900	378.421	801.300	41.35	54.40	2180.000	5.767	19.673	13.618	11.933	10.918	9.179	7.614	2.371	0.00	1.00
	35.000	1.280	4.827	1.612	1.344	1.239	111.000	318.900	408.447	859.900	44.00	52.80	2589.000	5.952	21.250	14.566	12.663	11.631	9.949	8.294	2.376	0.00	1.00
	17.000	1.409	4.624	1.649	1.327	3.278	95.850	263.100	370.804	728.600	38.00	58.70	1751.000	5.388	18.259	12.542	11.551	10.328	8.367	7.135	2.408	1.00	1.00
	10.000	1.362	4.637	1.681	1.369	2.090	92.840	245.300	334.368	699.300	36.80	65.90	1524.000	5.080	17.389	12.148	10.958	9.744	8.430	7.000	2.376	0.00	1.00
	10.000	1.362	4.637	1.681	1.359	2.090	92.840	245.300	334.368	699.300	36.80	65.90	1536.000	5.120	17.389	12.148	10.958	9.739	8.469	6.933	2.376	0.00	0.00
	17.000	1.411	4.681	1.666	1.349	2.215	92.840	249.500	352.358	706.600	36.80	64.20	1729.000	5.320	18.259	12.542	11.580	10.155	8.582	7.224	2.406	0.00	1.00
	17.000	1.411	4.681	1.666	1.339	2.215	92.840	249.500	352.358	706.600	36.80	64.20	1742.000	5.360	18.259	12.542	11.580	10.149	8.621	7.157	2.406	0.00	0.00
	17.000	1.433	4.681	1.684	1.376	2.339	97.740	257.300	368.813	736.400	38.74	67.00	1691.000	5.203	18.259	12.559	11.486	10.211	8.827	7.240	2.395	0.00	1.00
	18.000	1.352	4.735	1.660	1.373	1.539	99.520	269.300	364.394	757.900	39.45	62.60	1884.000	5.368	18.966	13.097	11.677	10.525	9.145	7.562	2.358	0.00	1.00
	17.000	1.331	4.681	1.669	1.376	2.339	97.670	261.600	348.395	737.600	38.72	63.10	1691.000	5.203	18.259	12.559	11.486	10.211	8.827	7.240	2.365	0.00	1.00
	17.000	1.437	4.735	1.704	1.387	1.290	94.730	243.800	350.367	714.500	37.55	73.70	1683.000	5.178	18.259	12.559	11.496	10.158	8.837	7.438	2.393	0.00	0.00
	5.000	1.240	4.531	1.638	1.344	3.993	92.010	255.800	317.381	695.800	36.47	54.60	1382.000	5.007	16.518	11.737	10.421	9.339	7.956	6.716	2.343	0.00	1.00
	10.000	1.310	4.637	1.660	1.369	3.155	93.890	254.300	33.380	711.000	37.22	61.00	1524.000	5.080	17.389	12.148	10.958	9.744	8.430	7.000	2.360	0.00	1.00
	10.000	1.313	4.578	1.643	1.324	4.238	96.900	267.800	351.826	732.900	38.41	56.00	1574.000	5.247	17.389	12.131	11.043	9.750	8.107	6.940	2.361	0.00	1.00
	17.000	1.381	4.681	1.664	1.349	3.401	98.780	266.200	367.825	748.100	39.16	62.30	1729.000	5.320	18.259	12.542	11.580	10.155	8.582	7.224	2.378	0.00	1.00
	11.000	1.241	4.637	1.622	1.352	3.401	98.690	279.800	347.407	754.400	39.12	52.70	1719.000	5.289	18.096	12.686	11.140	10.120	8.671	7.278	2.351	0.00	1.00
	18.000	1.305	4.735	1.642	1.373	2.584	100.570	278.300	363.406	769.600	39.87	58.40	1884.000	5.368	18.966	13.097	11.677	10.525	9.145	7.562	2.367	0.00	1.00

Correlation of pIC_{50} with physicochemical parameters Monoparametric Models
Table 1(a)

S.No.	Equations	n	R	R^2	R^2_A	SE	$F_{(1, 27)}$
1.	pIC_{50}=0.001(±0.026) BAC + 5.119	29	0.024	0.001	-0.036	0.411	0.016
2.	pIC_{50}=1.359 (±2.679) D + 3.337	29	0.196	0.039	0.003	0.403	1.084
3.	pIC_{50} =1.044 (±2.201)Id + 0.295	29	0.184	0.034	-0.002	0.404	0.947
4.	pIC_{50} =9.039(±7.005) IOR – 9.803	29	0.454	0.206	0.177	0.366	7.010

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC) **ISSN:** 2582-2004
Publisher: Indian Mental Health & Research Centre Volume 06, Issue 01
DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

5.	pIC_{50}=16.401(±4.011) J - 16.935	29	0.850	0.723	0.712	0.216	70.376
6.	pIC_{50} =-0.033 (±0.211) LogP+ 5.229	29	0.062	0.004	-0.033	0.410	0.103
7.	pIC_{50}=-0.004 (±0.037) Mr + 5.557	29	0.046	0.002	-0.035	0.411	0.057
8.	pIC_{50}=-0.004 (0.009) Mv + 6.312	29	0.193	0.037	0.001	0.403	1.042
9.	pIC_{50}=-0.001 (±0.003) Mw + 5.560	29	0.189	0.036	0.000	0.404	0.998
10.	pIC_{50}=-8.65×10^{-4}(±4.135×10^{-3})Pc+ 5.776	29	0.080	0.006	-0.030	0.410	0.174
11.	pIC_{50}=-0.010 (± 0.094) Pz + 5.553	29	0.045	0.002	-0.035	0.411	0.056
12.	pIC_{50}=0.039 (±0.020) St + 2.809	29	0.469	0.220	0.191	0.363	7.606
13.	pIC_{50}=-2.84 × 10^{-4} (±7.16×10^{-4}) W + 5.627	29	0.176	0.031	-0.005	0.405	0.864
14.	pIC_{50}=-0.745 (±0.681) WA + 9.082	29	0.396	0.157	0.126	0.378	5.027
15	pIC_{50}=-0.022 (±0.163) $^{0}\chi$ + 5.543	29	0.054	0.003	-0.034	0.411	0.079
16.	pIC_{50}=-0.064 (±0.265) $^{1}\chi$ + 5.954	29	0.097	0.009	-0.027	0.409	0.254
17.	pIC_{50}=-0.028 (±0.343) $^{2}\chi$ + 5.468	29	0.033	0.001	-0.036	0.411	0.030
18.	pIC_{50}=-0.056 (±0.332) $^{3}\chi$ + 5.714	29	0.068	0.005	-0.032	0.410	0.125
19.	pIC_{50}=0.176 (±0.358) $^{4}\chi$ + 3.638	29	0.190	0.036	0.001	0.404	1.015
20.	pIC_{50}=0.099 (±0.470) $^{5}\chi$ + 4.428	29	0.083	0.007	-0.030	0.410	0.187
21.	pIC_{50}= -3.306(8.868) Xeq + 12.984	29	0.146	0.021	-0.015	0.407	0.585

Where n is the number of data points, R is the coefficient of correlation[5], R^2 is the coefficient of determination, SE is the standard error of estimate, R^2_A represents adjusted R^2 or explained variance which when multiplied by 100 gives the percentage of variance in the activity that can be accounted for the equations. F is the variance ratio between observed and calculated activities and the data within the parenthesis are confidence interval at 95%. All the above statistical parameters show that all the equations in their present form are statistically insignificant. All the physicochemical parameters (equations 1-21) and their square term were taken together to test the parabolic relationship, which was found to be absent. In multiparametric modeling[6], a statistically significant model one must investigate to find out whether or not any collinearity exists between the parameters used. This is achieved by obtaining correlation matrix, such a matrix obtained in the present case is shown in Table- 3 and it is clear that each pair parameter in correlation matrix

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC) **ISSN:** 2582-2004
Publisher: Indian Mental Health & Research Centre Volume 06, Issue 01

DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

for which 'R' > 0.5 cannot be taken together due to collinearity.

Table 3
Correlation matrix demonstrating correlation between physicochemical parameters with indicator parameter

	BAC	D	Id	IOR	J	LogP	Mr	Mv	Mw	Pc	Pz	St	W	WA	$^{0}\chi$	$^{1}\chi$	$^{2}\chi$	$^{3}\chi$	$^{4}\chi$	$^{5}\chi$	Xeq	I_1	I_2	I_3
BAC	1.000																							
D	0.193	1.000																						
Id	0.913	0.216	1.000																					
IOR	-0.234	0.767	-0.087	1.000																				
J	0.126	0.351	0.320	0.573	1.000																			
LogP	-0.651	-0.251	-0.791	-0.143	-0.295	1.000																		
Mr	0.802	-0.276	0.725	-0.577	-0.087	-0.430	1.000																	
Mv	0.684	-0.408	0.594	-0.749	-0.209	-0.295	0.920	1.000																
Mw	0.388	0.121	0.266	-0.153	-0.204	-0.267	0.382	0.328	1.000															
Pc	0.820	-0.287	0.747	-0.616	-0.107	-0.446	0.995	0.936	0.374	1.000														
Pz	0.802	-0.276	0.725	-0.577	-0.087	-0.429	1.000	0.920	0.381	0.995	1.000													
St	-0.005	0.835	0.167	0.962	0.633	-0.345	-0.423	-0.607	-0.085	-0.447	-0.423	1.000												
W	0.923	-0.095	0.858	-0.514	-0.115	-0.634	0.910	0.856	0.405	0.937	0.910	-0.294	1.000											
WA	0.825	-0.150	0.728	-0.608	-0.380	-0.524	0.860	0.836	0.436	0.891	0.860	-0.415	0.959	1.000										
$^{0}\chi$	0.957	0.015	0.922	-0.400	0.027	-0.679	0.891	0.807	0.398	0.914	0.891	-0.167	0.985	0.913	1.000									
$^{1}\chi$	0.916	-0.100	0.888	-0.488	-0.023	-0.669	0.915	0.857	0.386	0.941	0.915	-0.263	0.992	0.929	0.990	1.000								
$^{2}\chi$	0.977	0.191	0.919	-0.263	0.046	-0.650	0.813	0.695	0.411	0.833	0.813	-0.031	0.935	0.870	0.971	0.929	1.000							
$^{3}\chi$	0.953	0.020	0.910	-0.406	0.018	-0.664	0.886	0.806	0.403	0.910	0.886	-0.176	0.980	0.911	0.995	0.985	0.962	1.000						
$^{4}\chi$	0.913	0.049	0.955	-0.237	0.317	-0.748	0.826	0.723	0.304	0.841	0.826	-0.004	0.896	0.748	0.943	0.932	0.896	0.937	1.000					
$^{5}\chi$	0.935	-0.002	0.936	-0.357	0.166	-0.701	0.876	0.784	0.361	0.897	0.875	-0.120	0.952	0.840	0.979	0.973	0.936	0.968	0.963	1.000				
Xeq	0.392	0.867	0.337	0.421	0.066	-0.338	-0.095	-0.140	0.239	-0.071	-0.095	0.547	0.189	0.188	0.253	0.157	0.403	0.264	0.187	0.195	1.000			
I_1	0.107	0.268	-0.054	-0.040	-0.174	0.160	-0.042	-0.006	0.093	-0.029	-0.042	-0.035	0.033	0.085	0.044	0.002	0.108	0.102	-0.084	-0.025	0.390	1.000		
I_2	-0.058	-0.449	-0.195	-0.519	-0.258	0.360	0.267	0.344	-0.028	0.254	0.267	-0.596	0.074	0.119	0.024	0.069	-0.042	0.041	-0.066	0.002	-0.391	0.064	1.000	
I_3	-0.158	-0.259	-0.079	-0.214	0.145	0.560	0.001	0.101	-0.366	0.014	0.002	-0.224	-0.150	-0.181	-0.141	-0.126	-0.169	-0.144	-0.092	-0.089	-0.338	-0.097	0.173	1.000

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC) **ISSN:** 2582-2004
Publisher: Indian Mental Health & Research Centre Volume 06, Issue 01

DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

Multiparametric modeling using indicator parameter along with physicochemical parameters

Table – 1(b)

S. No.	Equations	n	R	R^2	R^2_A	SE	$F_{(5,23)}$
1.	pIC_{50}= 15.797 (±3.914) J+0.877 (±1.586) D-0.441(±0.421) I_1 + 0.358 (±0.262) I_2 + 0.152 (±0.184) I_3 - 17.623	29	0.915	0.837	0.801	0.180	23.568
2.	pIC_{50}= 16.304 (±3.591) J-0.002 (±0.005) Mv-0.362(±0.383) I_1 + 0.349 (±0.249)I_2 + 0.133 (±0.176) I_3 - 16.386	29	0.917	0.840	0.806	0.178	24.214
3.	pIC_{50}= 16.693 (±3.987) J-0.003 (±0.019) Mr+0.471(±1.641) D - 0.429 (±0.444) I_1 + 0.388 (±0.280) I_2 - 17.931	29	0.904	0.817	0.778	0.190	20.597
4.	pIC_{50}= 17.129 (±3.746) J-0.004 (±0.018) Mr -1.147(±5.118) Xeq - 0.332 (±0.459) I_1 + 0.329 (±0.287) I_2 - 15.053	29	0.904	0.816	0.776	0.191	20.449
5.	pIC_{50}=16.785(±3.971)J-0.004 (±0.013) BAC+0.595(±1.617) D - 0.418 (±0.442) I_1 + 0.381 (±0.274) I_2 - 18.509	29	0.906	0.820	0.781	0.189	20.958
6.	pIC_{50}=16.693 (±3.987) J + 0.471 (±1.641) D -0.003(±0.019) Mr - 0.429 (±0.444) I_1 + 0.388 (±0.280) I_2 - 17.931	29	0.904	0.817	0.778	0.190	20.597
7.	pIC_{50}=16.600(±3.910) J + 0.291 (±1.652) D – 0.002(±0.005) Mv - 0.415 (±0.436) I_1 + 0.403 (±0.275) I_2 - 17.309	29	0.908	0.825	0.786	0.186	21.612
8.	pIC_{50}= 16.694 (±3.987) J + 0.471 (±1.641) D – 0.009 (±0.046) Pz - 0.429 (±0.444) I_1 + 0.388 (±0.280) I_2 - 17.932	29	0.904	0.817	0.778	0.190	20.597
9.	pIC_{50}= 16.535 (±3.930) J + 0.488 (±1.592) D – 1.39 × 10^{-4} (±1.39 × 10^{-4}) W - 0.423 (±0.437)I_1 + 0.381 (±0.272) I_2 – 17.852	29	0.907	0.823	0.785	0.187	21.442
10.	pIC_{50}= 16.054 (±4.162) J + 0.513 (±1.593) D – 0.164 (±0.370) WA - 0.424 (±0.438)I_1 + 0.380 (±0.272) I_2 - 16.605	29	0.907	0.823	0.784	0.187	21.331
11.	pIC_{50}= 16.733 (±3.938) J + 0.528 (±1.596) D – 0.031 (±0.076) $^0\chi$ - 0.421 (±0.439)I_1 + 0.381 (±0.272) I_2 - 17.835	29	0.907	0.822	0.783	0.188	21.245
12.	pIC_{50}= 16.713 (±3.914) J + 0.461 (±1.593) D – 0.060 (±0.122) $^1\chi$ - 0.423 (±0.436)I_1 + 0.381 (±0.271) I_2 - 17.542	29	0.908	0.824	0.786	0.187	21.533
13.	pIC_{50}= 16.664 (±3.967) J + 0.604 (±1.629) D – 0.048 (±0.163) $^2\chi$ - 0.423 (±0.443)I_1 + 0.381 (±0.275) I_2 - 17.867	29	0.905	0.819	0.780	0.189	20.827
14.	pIC_{50}= 16.745 (±3.939) J + 0.523 (±1.596) D – 0.065 (±0.154) $^3\chi$ - 0.411 (±0.440)I_1 + 0.383 (±0.273) I_2 - 17.764	29	0.907	0.822	0.783	0.188	21.244
15.	pIC_{50}= 17.288 (±4.107) J + 0.479 (±1.590) D – 0.087 (±0.177) $^4\chi$ - 0.430 (±0.436)I_1 + 0.377 (±0.271) I_2 - 18.339	29	0.908	0.824	0.786	0.187	21.551
16.	pIC_{50}= 16.931 (±4.017) J + 0.494 (±1.605) D – 0.081 (±0.222) $^5\chi$ -	29	0.906	0.821	0.782	0.188	21.029

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC) **ISSN:** 2582-2004
Publisher: Indian Mental Health & Research Centre Volume 06, Issue 01

DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

S. No.	Equations	n	R	R^2	R^2_A	SE	$F_{(5,23)}$
	0.425 (±0.441)I_1 + 0.380 (±0.274) I_2 - 18.047						
17.	pIC_{50}=14.534(±4.062) J + 3.328 (±2.876) D-10.247(±9.071) Xeq - 0.321 (±0.412) I_1 + 0.344 (±0.251) I_2 + 5.170	29	0.923	0.851	0.819	0.171	26.347
18.	pIC_{50}=16.168(±3.640)J+0.031 (±0.042) Mr – 0.010(±0.011) Mv - 0.371 (±0.383) I_1 + 0.400 (±0.246) I_2 - 17.397	29	0.916	0.840	0.805	0.178	24.114
19.	pIC_{50}=16.529(±3.717)J - 0.013 (±0.021) Pc + 0.281(±0.444) Pz - 0.354 (±0.397) I_1 + 0.326 (±0.254) I_2 - 18.327	29	0.910	0.829	0.791	0.184	22.236
20.	pIC_{50}=16.785(±3.971)J-0.004(±0.013)BAC + 0.595(±1.617) D - 0.418 (±0.442) I_1 + 0.381 (±0.274) I_2 - 18.509	29	0.906	0.820	0.781	0.189	20.958
21.	pIC_{50}=16.555(±4.009)J- 0.154 (±0.388) WA - 0.612(±5.280) Xeq - 0.344 (±0.457) I_1 + 0.327 (±0.277) I_2 - 15.158	29	0.905	0.820	0.780	0.189	20.903
22.	pIC_{50}=17.024(±4.069) J + 0.575 (±1.608) D - 0.405(±1.105) Id - 0.434 (±0.441) I_1 + 0.371 (±0.275) I_2 - 16.974	29	0.906	0.821	0.782	0.188	21.033
23.	pIC_{50}=17.459(± 3.902) J - 0.321 (±1.187) Id - 0.687(±5.451) Xeq - 0.343 (±0.464) I_1 + 0.314 (±0.277) I_2 - 15.509	29	0.904	0.817	0.777	0.190	20.511
24.	pIC_{50}=0.671(±1.521)D+0.092(±0.102)LogP+ 7.206(±3.776) J - 0.485 (±0.420) I_1 + 0.321 (±0.266) I_2 - 19.425	29	0.917	0.840	0.805	0.178	24.187
25.	pIC_{50}=0.006(±0.021)Mr+0.112(±0.130)LogP+7.963(±3.664) J - 0.410 (±0.387) I_1 + 0.234 (±0.282) I_2 - 20.157	29	0.915	0.837	0.802	0.179	23.662
26.	pIC_{50}=0.112(±0.130)LogP+0.016(±0.053)Pz+ 7.962(±3.664) J - 0.410 (±0.388) I_1 + 0.234 (±0.282) I_2 - 20.154	29	0.915	0.837	0.802	0.179	23.662
27.	pIC_{50}= 0.196 (± 5.153) Xeq + 0.089 (±0.110) LogP + 17.757 (±3.631) J - 0.418 (±0.451) I_1 + 0.278 (±0.266) I_2 - 19.698	29	0.913	0.834	0.798	0.181	23.189
28.	pIC_{50}= 0.002 (± 0.019) Mr + 0.181 (±1.634) D + 16.974(±4.126) J + 0.314 (±0.287) I_2 + 0.143 (±0.203) I_3 - 18.019	29	0.897	0.804	0.761	0.197	18.851
29.	pIC_{50}= -0.002 (± 0.019) Mr - 2.021 (±4.864) Xeq + 17.159 (±3.838) J + 0.265 (±0.285) I_2 + 0.111 (±0.200) I_3 - 13.138	29	0.900	0.810	0.768	0.194	19.550
30.	pIC_{50}= 0.282 (± 1.600) D - 0.004 (±0.013) BAC + 17.073(±4.113) J + 0.312 (±0.281) I_2 + 0.137 (±0.203) I_3 - 18.467	29	0.898	0.807	0.764	0.196	19.176
31.	pIC_{50}= -0.018 (± 1.619) D - 0.002 (±0.005) Mv + 16.829 (±4.018) J + 0.337 (±0.281) I_2 + 0.145 (±0.197) I_3 - 17.120	29	0.902	0.814	0.773	0.192	20.106
32.	pIC_{50}= 0.181 (± 1.634) D - 0.006 (±0.048) Pz + 16.975(±4.127) J + 0.314 (±0.287) I_2 + 0.143 (±0.203) I_3 - 18.018	29	0.897	0.804	0.761	0.197	18.852
33.	pIC_{50}= 0.172 (±1.589) D + 16.890 (±4.078) J-1.14×10^{-4} (±1.14×10^{-4})	29	0.899	0.808	0.766	0.195	19.359

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC) **ISSN:** 2582-2004
Publisher: Indian Mental Health & Research Centre Volume 06, Issue 01
DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

S. No.	Equations	n	R	R^2	R^2_A	SE	$F_{(5,23)}$
	W + 0.312 (±0.280) I_2 + 0.133 (±0.203) I_3 - 17.933						
34.	pIC_{50}= 0.195 (± 1.587) D + 16.495 (±4.286) J - 0.133(±0.390) WA + 0.311 (±0.280) I_2 + 0.134 (±0.202) I_3 - 16.919	29	0.899	0.807	0.766	0.195	19.289
35.	pIC_{50}= 0.210 (±1.585) D + 17.041 (±4.093) J – 0.026 (±0.080) $^0\chi$ + 0.312 (±0.280)I_2 + 0.134 (±0.202) I_3 - 17.901	29	0.899	0.807	0.765	0.195	19.276
36.	pIC_{50}= 0.148 (±1.593) D - 0.049 (±0.130) $^1\chi$ + 17.041 (±4.080) J + 0.312 (±0.279)I_2 + 0.132 (±0.203) I_3 - 17.683	29	0.899	0.808	0.767	0.195	19.407
37.	pIC_{50}= 0.282 (±1.611) D + 16.962 (±4.104) J – 0.041 (±0.170) $^2\chi$ + 0.312 (±0.282)I_2 + 0.139 (±0.203) I_3 - 17.909	29	0.897	0.805	0.763	0.196	19.032
38.	pIC_{50}= 0.218 (±1.580) D + 17.042 (±4.392) J – 0.062 (±0.162) $^3\chi$ + 0.315 (±0.279)I_2 + 0.133 (±0.202) I_3 - 17.765	29	0.899	0.809	0.767	0.195	19.441
39.	pIC_{50}= 0.159 (±1.595) D - 0.064 (±0.188) $^4\chi$ + 17.473 (±4.362)J + 0.308 (±0.280) I_2 + 0.133 (±0.204) I_3 - 18.341	29	0.899	0.807	0.766	0.195	19.293
40.	pIC_{50}= 0.184 (±1.597) D + 17.186 (±4.196) J – 0.063 (±0.234) $^5\chi$ + 0.310 (±0.281)I_2 + 0.137 (±0.203) I_3 - 18.089	29	0.898	0.806	0.764	0.196	19.095
41.	pIC_{50}= 3.400 (±2.917) D - 11.201 (±9.002) Xeq + 14.455 (±4.149) J + 0.287 (±0.250)I_2 + 0.119 (±0.179) I_3 - 7.457	29	0.920	0.847	0.814	0.174	25.512
42.	pIC_{50}= 0.047 (±0.043) Mr - 0.014 (±0.011) Mv + 15.565 (±3.652) J + 0.345 (±0.243)I_2 + 0.201 (±0.179) I_3 - 17.115	29	0.921	0.848	0.814	0.174	25.586
43.	pIC_{50}= 0.408 (±0.450) Pz - 0.019 (±0.021) Pc + 16.128 (±3.775) J + 0.251 (±0.260)I_2 + 0.171 (±0.184) I_3 - 18.512	29	0.911	0.831	0.794	0.183	22.546
44.	pIC_{50}= 0.282 (±1.600) D - 0.004 (±0.013) BAC + 17.073 (±4.113) J + 0.312 (±0.281)I_2 + 0.137 (±0.203) I_3 - 18.467	29	0.898	0.807	0.764	0.196	19.176
45.	pIC_{50}= 16.788 (±4.077) J – 0.105 (±0.395) WA - 1.716 (±4.976) Xeq + 0.264 (±0.278)I_2 + 0.109 (±0.200) I_3 - 13.090	29	0.901	0.811	0.770	0.193	19.750

All the proposed QSAR models were statistically significant at 95% confidence interval[7]. Fcal is also greater than F_{theo} which is ($F_{(5,23)}$ = 2.64). The coefficient of steric parameters Mr, Mv and Pc were found to be negative which implies that these parameters have negative influence in determining the activity. In QSAR models these parameter represents good correlation of activity as well as indicator variables. The negative coefficient of topological parameters BAC, W, WA, $^0\chi$ - $^5\chi$ and Id indicates that they also exert negative influence upon activity. Negative coefficients of steric and topological parameters indicate that the less bulky group having lesser vertices may

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC)
Publisher: Indian Mental Health & Research Centre
ISSN: 2582-2004
Volume 06, Issue 01
DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

be conducive toward the activity. The coefficient of electronic parameter Xeq was found to be negative this indicate that these parameters also have negative influence in determining the activity. The sign of coefficient of Pz was found to be positive which clearly shows that this parameter has positive influence on the activity. In order to examine the relative potential of proposed models, predictive correlation coefficient (R^2_{pred}) were estimated by plotting graph between observed and calculated pIC_{50} values obtained with the help of equation 17 and 42 (Table – 1b). The comparison between observed and calculated activities is listed in Table 4. Such correlations are shown in figure 1. From the fig. 1 R^2_{pred} values obtained for equation 17 and 42 (Table -1b) are 0.8514 and 0.8476. They are fairly high indicating the good quality of model. Cross – validation method was used to evaluate predictive power [8]of all the models[9-12]. Various cross-validation parameters calculated for the proposed models are presented in Table 6.

Table 4
Comparison between observed and calculated values of substituted pyrimidines and purines for Eq. No. 17 and Eq. No. 42

1.	4.530	4.928	-0.398	4.813	-0.283
2.	4.931	4.735	0.196	4.688	0.243
3.	4.336	4.475	-0.139	4.389	-0.053
4.	5.086	4.891	0.195	5.127	-0.041
5.	5.004	5.171	-0.167	5.058	-0.054
6.	5.080	5.131	-0.051	5.031	0.049
7.	5.537	5.335	0.202	5.249	0.288
8.	5.130	5.095	0.035	4.968	0.162
9.	5.244	5.298	-0.054	5.186	0.058
10.	4.823	4.809	0.014	4.747	0.076
11.	5.096	5.201	-0.105	5.167	-0.071
12.	4.826	4.869	-0.043	4.872	-0.046
13.	4.749	4.593	0.156	4.576	0.173
14.	4.935	4.956	-0.021	5.012	-0.077

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC)
Publisher: Indian Mental Health & Research Centre

ISSN: 2582-2004
Volume 06, Issue 01

DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

15.	4.492	4.492	0.000	4.801	-0.309
16.	5.552	5.592	-0.040	5.559	-0.007
17.	4.818	5.103	-0.285	5.058	-0.240
18.	5.075	5.157	-0.082	5.189	-0.114
19.	4.649	4.668	-0.019	4.688	-0.039
20.	5.638	5.736	-0.098	5.735	-0.097
21.	5.744	5.795	-0.051	5.606	0.138
22.	5.638	5.703	-0.065	5.672	-0.034
23.	5.886	5.581	0.305	5.606	0.280
24.	5.221	5.164	0.057	5.185	0.036
25.	5.522	5.579	-0.057	5.685	-0.163
26.	5.136	4.928	0.208	4.941	0.195
27.	5.585	5.338	0.247	5.442	0.143
28.	5.214	5.201	0.013	5.295	-0.081
29.	5.602	5.553	0.049	5.732	-0.130

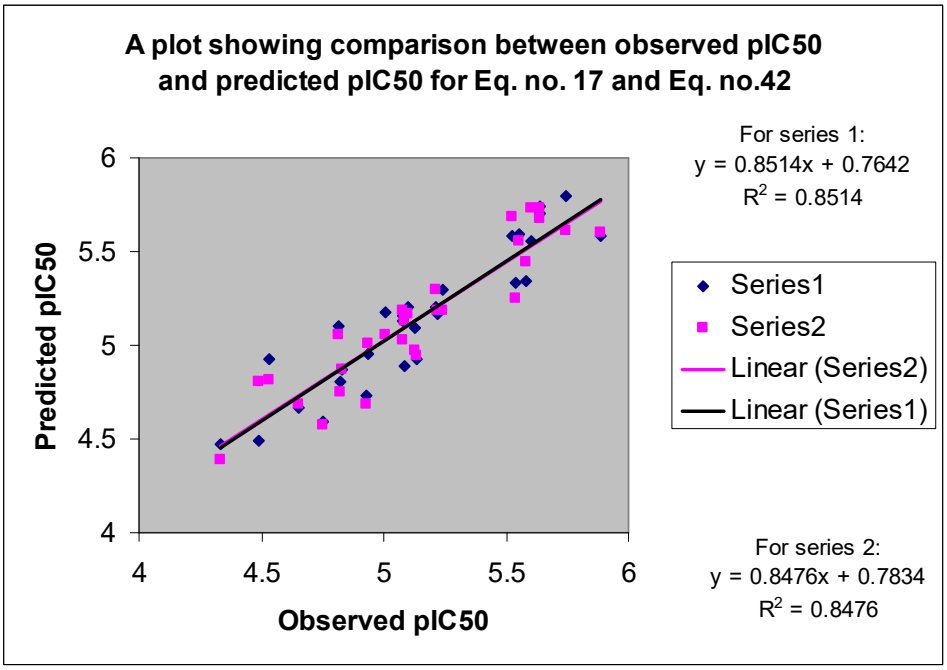


Fig.1

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC)
Publisher: Indian Mental Health & Research Centre
ISSN: 2582-2004
Volume 06, Issue 01
DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

Table 5
Some statistical techniques proves predictive ability for the proposed models

S.No.	Model No.	Q	E	K	PE	6PE
1.	2	5.151	60.00	0.400	0.019	0.114
2.	17	5.397	61.40	0.386	0.018	0.108
3.	18	5.146	60.00	0.400	0.019	0114
4.	41	5.287	60.90	0.391	0.018	0.108
5.	42	5.293	61.10	0.389	0.018	0.108

Table 6
Cross Validation parameters for proposed models

S.No.	Model No.	n	PRESS	SSY	PRESS/SSY	R^2_{cv}	PSE	S_{PRESS}
1.	2	29	0.731	3.846	0.190	0.810	0.158	0.162
2.	17	29	0.680	3.896	0.174	0.826	0.153	0.156
3.	18	29	0.733	3.843	0.190	0.810	0.158	0.162
4.	41	29	0.699	3.877	0.180	0.820	0.155	0.159
5.	42	29	0.697	3.879	0.179	0.821	0.155	0.158

As it is clear from the table 6 that the ratio PRESS/SSY for equation 2, 17, 18, 41 and 42 are 0.190, 0.174, 0.190, 0.180, 0.179 respectively, which are less than 0.400, indicating that these models are reliable QSAR models. The PSE as well as S_{PRESS}[13] are good parameters to be used for discussing the uncertainty in prediction. The lower the value of these parameters, the better will be the predictive ability of the model. Also the highest R^2_{CV} (0.826) has been found for the QSAR model.

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC)
Publisher: Indian Mental Health & Research Centre
ISSN: 2582-2004
Volume 06, Issue 01
DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

no. 17 (Table – 1b) this indicates that it has excellent overall predictive power.

Conclusions

The above results make it clear that for designing drugs of this series with reference to their activity pIC_{50}, the following points may be kept in mind: Less Bulky groups having lesser vertices should be used. More polar and less electronegativeand more hydrophobic group is beneficial for the activity. In addition to this the presence of Hydrogen at R_3 position and CH at position X is highly favourable for the activity. *J. Zhou and coworkers* reported that compound no.1 which is structurally close derivative of Atovaquone has almost identical anti-tumor activity as Atovaquone. When the Cl group was removed (compound no.5) or replaced with F, methyl groups (compound no.2 and 4) the activity was found to be improved by 3-4 folds. But the methoxy group substituted derivatives (compound no.3) was very less active and also decreased the activity. Compounds with multiple substitutions (compound no. 12, 13, 14 and 15) were less potent but it was found that the introduction of 8-dydroxyl analogues (compound no. 18, 20, 21 and 22) displayed good anti-tumor activity. These findings are similar to the predicted values obtained from model no. 17 and 42. The 2-piperidinyl naphthoquinones (compound no. 24-29) also displayed good anti-tumor activity. Thus the results obtained based on QSAR are in nice agreement with the result obtained experimentally.

References

1. Srivastava A. K., Shukla N. and Pathak V. K., Quantitative Structure Activity Relationship (QSAR) Studies on a series of off-target ion channel selective diltiazem sodium derivatives., *J. Indian Chem. Soc*., 2010, 87,1-7.
2. John A. Yagiela, Frank J. Dowd, Bart Johnson, Angelo Mariotti, Enid A. Neidle. Pharmacology and Therapeutics for Dentistry. Chapter 23, Drugs for Treating Orofacial Pain Syndromes. 384-385
3. Srivastava A.K., Shukla N., Pandey A. and Srivastava A., QSAR Based Modeling on a series of alpha-Hydroxy amides as a novel class of Braykinin B1 selective antagonists., *J. Saudi Chem. Soc*., 15, 2011, 215-220.

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC) **ISSN:** 2582-2004
Publisher: Indian Mental Health & Research Centre Volume 06, Issue 01
DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

4. SrivastavaA.K., Pandey A., Srivastava A.and Shukla N., QSAR based modeling of hepatitis C virus NS5B inhibitors ., *J. Saudi Chem. Soc*., 15, 2011, 25-28
5. Srivastava A. K., Shukla N., Quantitative structure activity relationship (QSAR) studies on a series of imidazole derivatives as novel ORL1 receptor antagonists, Journal of Saudi Chemical Society, 2013, 17 (3), 321-328

6 (a) Vaidya M., Phytochemical Screening & Antibacterial activity of aqueous & methanolic extract of Young & Mature leaves of Psidium guajava L. (guava), International Journal of Green and Herbal Chemistry, 2012, 1, 211-216.

(b)Srivastava A. K., Shukla N., QSAR based modeling on a series of lactam fused chroman derivatives as selective 5-HT transporters, , Journal of Saudi Chemical Society, 2012, 16 (4), 405-412

(c) Sharma D., Shukla S. D., Neuroprotection: It's Phytoremediation (Theoretical Perspective), International Journal of Green and Herbal Chemistry, 2013,2,1118-1131.

7. Shukla N. , Srivastava A. K.QSAR based modeling on a novel series of 2-chlorobenzamide derivatives as potent P2X (7) receptor antagonist, Oxidation Communications, 2014, 37 (1), 290-300
8. Srivastava A. K., Shukla N., Pathak V. K. Quantitative Structure ActivityRelationship(QSAR) Studies on a series of carbamate appended N-alkylsulfonamides as inhibitors of peptide amyloid-β (Aβ), , Oxidation Communications, 2013, 36 (4), 1090-1101
9. Shukla N., Srivastava A. K., QSAR studies on a novel cyclohexanamine class of human serotonin transporter (hSERT) inhibitory activities , Oxidation Communications, 2013, 36 (1), 133-142
10. Srivastava A. K., Shukla N., QSAR-based Modelling on a Novel Series of Pyrimidine-4-carboxamides as Antagonists of the Human A1 Receptor, , Oxidation Communications 35 (2), 423-437
11. Diudea, M.V., 2000. QSPR/QSAR Studies for Molecular Descriptors. Nova Science, Huntington, New York.

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023

Journal of Advance Research in Science and Social Science (JARSSC)
Publisher: Indian Mental Health & Research Centre
ISSN: 2582-2004
Volume 06, Issue 01
DOI: 10.46523/jarssc.06.01.06
Multidisciplinary, Open Access
Impact Factor: 3.612

12. QSAR methods & applications, GYANDHARA INTERNATIONAL ACADEMIC PUBLICATIONS, THANE, MUMBAI, INDIA, ISBN No. 978-93-83006-83-0
13. Sahu R., Yadav P. K., Mishra P., Shukla N., Identification and characterization of a novel therapeutic drug target in Mycobacterium abscessus by in silico method, International Journal of Green and Herbal Chemistry, 2019, 8, 091-107.

Received: 16.12.2022 **Accepted:** 12.01.2023 **Published**: 12.01.2023