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QSAR STUDY TO PREDICT ANTI-AMOEBIC ACTIVITIES OF PYRAZOLINE AND DIOXAZOLE DERIVATIVES WITH THE HELP OF PM5-BASED DESCRIPTORS

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ABSTRACT

In quest of better anti-amoebic agents, quantitative structure-activity relationship (QSAR) studies were performed on a series of pyrazoline & dioxazoles derivatives with the help of PM5 calculations and geometry optimizations using CAChe software. Multiple Linear Regression (MLR) analysis was performed to derive QSAR models using the descriptors, molecular weight (M_W), conformation minimum energy (ε), HOMO energy (ε_{HOMO}), shape index, basic kappa second order (k2), absolute hardness (η), electronegativity (χ), electrophilicity index (ω), molar volume (MV), molar refractivity (MR), LogP (LP), parachor (Pc) and solvent accessibility surface area (SASA). The QSAR models equations of anti-amoebic agents have been developed by using maximum of seven descriptors, in which conformation minimum energy, shape index, molar volume and parchor were present have good predictive powers of correlation coefficients. These models can successfully predict the anti-amoebic activity of any newly discovered pyrazoline and dioxazole derivatives which can later be tested in laboratory.

INTRODUCTION: Parasitic infections such as amoebiosis and other protozooses are still major threats against public health, especially in developing countries and the intestinal protozoan *Entamoeba histolytica* is a major cause of morbidity and mortality [1, 2]. Infection occurs through the oral uptake of the pathogen in its cyst form, with contaminated food or water.

Despite its socio-economic importance, intestinal and extra-intestinal amoebiasis is not yet officially listed among the "neglected infectious diseases", obviously due to difficulties in developing effective control strategies like studies involving drug molecules and hygiene management. Amoebiasis is primarily treated with the drug metronidazole which has significant side-effects [3-6].

Diloxanide furoate, a luminal amoebicide can be used for the treatment of oligosymptomatic and asymptomatic carriers of *E. histolytica* where as chloroquine is a useful support to other medications in the management of invasive amoebiasis [7].

The available anti-amoebic drugs have short-comings regarding tolerability and efficacy and the range of medicaments available for the treatment of amoebiasis has not changed over the past decade.

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Recent studies tried to improve the treatment of this infection by developing anti-amoebic therapy [8, 9], a set of dioxazoles derivatives showed better activity than the reference drug metronidazole; besides being non-toxic to human kidney epithelial cells. Recently QSAR studies have been quite helpful to identify important structural parameters responsible for anti-amoebic activity and a number of industrial research units are using classical as well as 3D QSAR techniques for contemporary drug design [10-15].

The basis of QSAR method is use of molecular descriptors which represent the structural, stereochemical and topological features of the target molecule [16-20]. Recently our group is engaged in finding new drugs using QSAR study [21, 22], herein we have taken, a series of 63 1-*N*-substituted thiocarbamoyl-3-phenyl-2-pyrazolines [23] and 3, 5-substituted-1, 4, 2-dioxazoles [8] were subjected to QSAR study by choosing appropriate molecular descriptors incorporating important structural features of the target molecule.

A multiple linear regression (MLR) analysis was executed to obtain and select best models in the form of regression equations to predict the anti-amoebic activity of chosen molecules.

MATERIALS AND METHODS: The experimental IC_{50} (µM) of anti-amoebic activities of 1-*N*-substituted thiocarbamoyl- 3- phenyl- 2- pyrazolines and 3, 5-substituted-1, 4, 2-dioxazoles are collected from recent publications [23, 8]. We have chosen the values of experimental observed activity and converted them into logarithmic scale of $-logIC_{50}$ and are placed in **Tables 1-4**.

$-logIC_{50}$ can be defined as, *"It is negative of $logIC_{50}$ value and because of negative sign, its magnitude has an inverse relationship with the biological activity or drug potency of the selected molecules".* Consequently a low magnitude of $-logIC_{50}$ predicts a higher biological value and a high magnitude of $-logIC_{50}$ indicates lower potency.

QSAR studies of the compounds listed in Tables 1-4 have been made with the help of following quantum chemical and topological descriptors-

1. Molecular weight M_W
2. Conformation minimum energy ε
3. HOMO energy ε_{HOMO}
4. Shape index, basic kappa second order k2
5. Absolute hardness η
6. Electronegativity χ
7. Electrophilicity index ω
8. Molar volume MV
9. Molar refractivity MR
10. LogP LP
11. Parachor Pc
12. Solvent accessibility surface area SASA

PM5 based calculations of the above descriptors have been made on the compounds listed in Tables 1-4 with the help of Cache Software and their relationship with the known activity of the anti-amoebic drugs have been studied by developing QSAR models. The values of the descriptors have been used to prepare Multiple Linear Regression (MLR) equations for predicted activities and compared with the known activity. The correlation coefficient and cross-validation coefficient have been evaluated to adjudge the quality of QSAR model and its predictive power.

RESULT AND DISCUSSION: Descriptors in different combinations have been used for Multiple Linear Regression (MLR) analysis. The predicted activity obtained by regression equation has been examined for selecting QSAR models, which have high degree of predictive power; the correlation coefficient and cross validation coefficient of all the regression equation have been evaluated.

The best QSAR model and the combination of descriptors providing that model have been identified. On the basis of such models new derivatives can be proposed which may have better anti-amoebic activity.

Cache software has been used for the calculation of descriptors of pyrazoline and dioxazole derivatives. At first, we have optimized the geometry by using PM5 Hamiltonian and then calculated the values of descriptors with the help of project leader associated with cache programme. Values of quantum chemical and topological descriptors of anti-amoebic agents are included in **Table 5**.

TABLE 1: PYRAZOLE DERIVATIVES AND THEIR OBSERVED ANTI-AMOEBIC ACTIVITIES –logIC$_{50}$

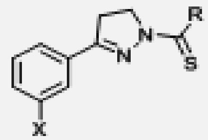
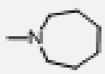
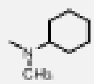
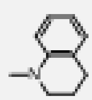
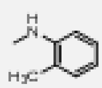
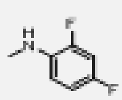
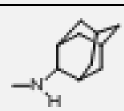
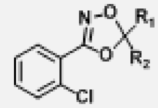
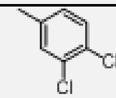
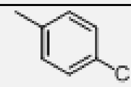
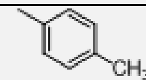
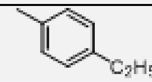
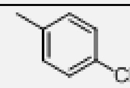
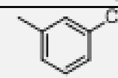
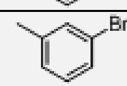
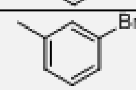
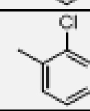
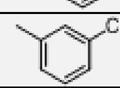
Comp	Parent Molecule 		
	X	R	-logIC$_{50}$ (obs)
1	H		0.572
2	Br		0.450
3	Cl		0.364
4	H		0.642
5	Br		0.037
6	Cl		-0.51
7	H		0.774
8	Br		0.720
9	Cl		0.569
10	H		0.864
11	Br		0.647
12	Cl		0.464
13	H		0.792
14	Br		0.444
15	Cl		0.248
16	H		0.679
17	Br		0.582
18	Cl		0.225
19	H		0.700
20	Br		0.525
21	Cl		0.449
22	H		0.980
23	Br		0.727
24	Cl		0.380
25	H		0.246
26	Br		-0.174
27	Cl		-0.292
28	H		0.253
29	Br		-0.237
30	Cl		-0.328

TABLE 2: DIOXAZOLE DERIVATIVES AND THEIR OBSERVED ANTI-AMOEBIC ACTIVITIES –logIC$_{50}$

Comp	Parent Structure 		
	R¹	R²	-logIC$_{50}$ (obs)
31	H		-0.092
32	H		-0.292
33	H		0.494
34	H		0.486
35	CH_3		0.461
36	C_2H_5		0.400
37	CH_3		0.364
38	C_2H_5		0.408
39	CH_3		0.210
40	H		-0.387
41	H		-0.143

We have also calculated the predicted activity of anti-amoebic agents PA1-PA5 by substituting the values of descriptors in MLR equations. These values are listed in **Table 6**.

Several QSAR models in different combination of descriptors have been tried and five models were chosen from best five equations, whose correlation coefficients values are above 0.80. The descriptors used in these models are presented in **Table 7** and the QSAR model equations after the table numbered as **1, 2, 3, 4 and 5** and their **graphs (1-5),** respectively.

TABLE 3: DIOXAZOLE DERIVATIVES AND THEIR OBSERVED ANTI-AMOEBIC ACTIVITIES $-logIC_{50}$

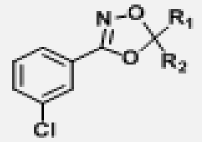
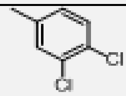
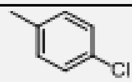
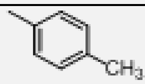
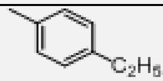
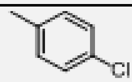
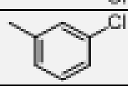
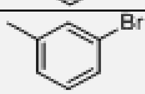
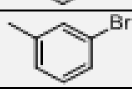
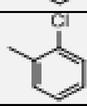
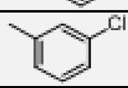
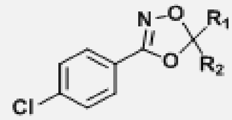
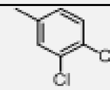
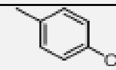
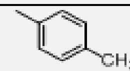
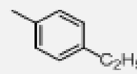
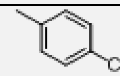
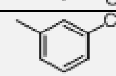
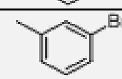
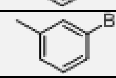
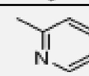
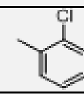
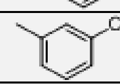
Comp	Parent Structure 		
	R^1	R^2	$-logIC_{50}$ (obs)
42	H		0.083
43	H		-0.125
44	H		0.452
45	H		0.444
46	CH_3		0.468
47	C_2H_5		0.441
48	CH_3		0.433
49	C_2H_5		0.367
50	CH_3		0.238
51	H		-0.208
52	H		-0.041

TABLE 4: DIOXAZOLE DERIVATIVES AND THEIR OBSERVED ANTI-AMOEBIC ACTIVITIES $-logIC_{50}$

Comp	Parent Structure 		
	R^1	R^2	$-logIC_{50}$ (obs)
53	H		0.053
54	H		-0.276
55	H		0.433
56	H		0.373
57	CH_3		0.433
58	C_2H_5		0.389
59	CH_3		0.417
60	C_2H_5		0.403
61	CH_3		0.199
62	H		-0.319
63	H		-0.066

MOPAC 2000 engine was used for calculating the value of descriptors of pyrazoline and dioxazole derivatives after optimizing the geometry by using PM5 Hamiltonian. These values are presented in **Table 5**.

TABLE 5: THE VALUES OF QUANTUM CHEMICAL AND TOPOLOGICAL DESCRIPTORS FOR ANTI-AMOEBIC AGENTS

Comp.	ε	$ε_{HOMO}$	χ	η	ω	Mw	k2	LP	MR	SASA	MV	Pc
1	63.711	-8.426	-4.365	4.061	2.345	273.395	6.635	2.86	82.66	128.891	223.5	585.9
2	67.833	-8.496	-4.5275	3.9685	2.582	352.291	6.840	3.69	90.35	143.564	236.1	629.4
3	56.235	-8.500	-4.526	3.974	2.577	307.840	6.840	3.42	87.27	139.351	232.8	614.7
4	58.698	-8.429	-4.34	4.089	2.303	301.449	8.022	3.69	91.86	137.603	255.7	663.1
5	63.650	-8.424	-4.499	3.925	2.578	380.345	8.203	4.52	99.55	150.967	268.2	706.6
6	52.055	-8.427	-4.497	3.93	2.572	335.894	8.203	4.25	96.46	146.692	265.0	691.9
7	51.028	-8.428	-4.432	3.996	2.457	315.476	8.203	4.09	96.35	143.877	270.9	694.2
8	55.061	-8.508	-4.56	3.948	2.633	394.372	8.393	4.92	104.04	160.011	283.4	737.7
9	43.463	-8.511	-4.562	3.949	2.635	349.921	8.393	4.65	100.95	155.645	280.2	723.0
10	97.659	-8.510	-4.419	4.091	2.386	323.455	8.909	4.27	99.84	152.314	287.0	732.8
11	102.88	-8.569	-4.603	3.966	2.671	402.351	9.087	5.10	107.53	164.235	299.5	776.3
12	89.974	-8.581	-4.5415	4.0395	2.552	357.900	9.087	4.83	104.44	162.516	296.3	761.6

13	96.678	-8.216	-4.3355	3.8805	2.421	335.466	8.131	5.01	104.28	150.461	275.4	724.1
14	100.83	-8.271	-4.44	3.831	2.572	414.362	8.347	5.84	111.97	166.591	287.9	767.7
15	89.233	-8.275	-4.4405	3.8345	2.571	369.911	8.347	5.57	108.88	161.515	284.7	753.0
16	88.005	-8.443	-4.462	3.981	2.500	309.428	8.203	4.32	96.76	146.571	264.8	679.8
17	92.048	-8.503	-4.578	3.925	2.669	388.324	8.393	5.14	103.45	162.659	277.4	723.4
18	80.256	-8.571	-4.61	3.961	2.682	343.873	8.393	4.87	100.37	158.425	274.1	708.7
19	87.129	-8.514	-4.501	4.013	2.524	309.428	8.203	4.32	95.76	149.831	264.8	679.8
20	91.258	-8.573	-4.6145	3.9585	2.689	388.324	8.393	5.14	103.45	165.406	277.4	723.4
21	79.664	-8.577	-4.6145	3.9625	2.686	343.873	8.393	4.87	100.37	161.054	274.1	708.7
22	87.006	-8.492	-4.486	4.006	2.511	309.428	8.203	4.32	95.76	149.586	264.8	679.8
23	91.128	-8.549	-4.5995	3.9495	2.678	388.324	8.393	5.14	103.45	165.999	277.4	723.4
24	79.534	-8.552	-4.5985	3.9535	2.674	343.873	8.393	4.87	100.37	161.261	274.1	708.7
25	5.538	-8.815	-4.8175	3.9975	2.902	331.382	8.393	4.14	90.68	147.693	255.4	649.1
26	9.579	-8.870	-4.897	3.973	3.018	410.279	8.590	4.97	98.37	164.307	267.9	692.6
27	-1.730	-8.929	-4.9	4.029	2.979	365.828	8.590	4.70	95.28	159.197	264.7	677.9
28	24.846	-8.463	-4.4235	4.0395	2.422	353.524	7.197	4.17	105.86	152.285	256.8	677.9
29	28.845	-8.527	-4.554	3.973	2.609	432.421	7.438	5.00	113.56	167.926	269.4	737.1
30	17.249	-8.531	-4.553	3.978	2.605	387.970	7.438	4.73	110.47	163.785	266.1	722.4
31	2.602	-9.573	-5.208	4.365	3.106	328.582	6.406	6.11	78.34	143.051	218.1	575.1
32	7.331	-9.571	-5.1725	4.3985	3.041	294.137	6.185	5.55	73.74	133.980	208.7	546.2
33	6.801	-9.355	-5.005	4.35	2.879	273.718	6.185	5.48	75.03	129.452	214.7	548.5
34	1.763	-9.408	-5.0325	4.3755	2.894	287.745	6.840	5.90	79.63	136.298	230.7	587.1
35	-1.862	-9.510	-5.122	4.388	2.989	308.163	6.012	5.91	78.6	139.078	229.3	592.2
36	-6.680	-9.487	-5.1065	4.3805	2.976	322.190	6.630	6.48	83.2	142.524	245.4	630.8
37	10.179	-9.581	-5.1265	4.4545	2.949	352.614	6.012	6.18	81.68	143.245	232.6	606.9
38	4.877	-9.514	-5.119	4.395	2.981	366.641	6.630	6.75	86.28	146.642	248.7	645.5
39	15.494	-9.425	-5.0415	4.3835	2.899	274.706	5.780	4.44	71.51	127.523	208.6	544.5
40	8.720	-9.485	-5.1285	4.3565	3.018	294.137	6.185	5.55	73.74	130.971	208.7	546.2
41	7.490	-9.585	-5.179	4.406	3.043	294.137	6.185	5.55	73.74	133.111	208.7	546.2
42	0.226	-9.613	-5.2935	4.3195	3.24	328.582	6.406	6.11	78.34	145.859	218.1	575.1
43	4.920	-9.608	-5.261	4.347	3.183	294.137	6.185	5.55	73.74	136.144	208.7	546.2
44	4.309	-9.405	-5.1015	4.3035	3.023	273.718	6.185	5.48	75.03	132.120	214.7	548.5
45	-0.727	-9.455	-5.127	4.328	3.036	287.745	6.840	5.90	79.63	138.786	230.7	587.1
46	-3.891	-9.585	-5.21	4.375	3.102	308.163	6.012	5.91	78.60	141.216	229.3	592.2
47	-8.567	-9.550	-5.1835	4.3665	3.076	322.190	6.630	6.48	83.20	146.494	245.4	630.8
48	7.751	-9.573	-5.1975	4.3755	3.086	352.614	6.012	6.18	81.68	146.328	232.6	606.9
49	2.993	-9.547	-5.1805	4.3665	3.073	366.641	6.630	6.75	86.28	151.105	248.7	645.5
50	12.879	-9.477	-5.1245	4.3525	3.016	274.706	5.780	4.44	71.51	130.273	208.6	544.5
51	6.145	-9.547	-5.215	4.332	3.138	294.137	6.185	5.55	73.74	134.069	208.7	546.2
52	5.069	-9.619	-5.2635	4.3555	3.180	294.137	6.185	5.55	73.74	135.937	208.7	546.2
53	-0.265	-9.572	-5.2855	4.2865	3.258	328.582	6.406	6.11	78.34	145.586	218.1	575.1
54	4.422	-9.519	-5.2295	4.2895	3.187	294.137	6.185	5.55	73.74	136.002	208.7	546.2
55	3.809	-9.372	-5.099	4.273	3.042	273.718	6.185	5.48	75.03	131.919	214.7	548.5
56	-1.226	-9.391	-5.1085	4.2825	3.046	287.745	6.840	5.9	79.63	138.346	230.7	587.1
57	-4.378	-9.473	-5.1685	4.3045	3.103	308.163	6.012	5.91	78.60	140.977	229.3	592.2
58	-9.058	-9.439	-5.144	4.295	3.080	322.190	6.630	6.48	83.20	146.508	245.4	630.8
59	7.272	-9.460	-5.155	4.305	3.086	352.614	6.012	6.18	81.68	146.170	232.6	606.9
60	2.502	-9.436	-5.141	4.295	3.076	366.641	6.630	6.75	86.28	151.643	248.7	645.5
61	12.386	-9.371	-5.0845	4.2865	3.015	274.706	5.780	4.44	71.51	129.978	208.6	544.5
62	5.641	-9.439	-5.1755	4.2635	3.141	294.137	6.185	5.55	73.74	134.161	208.7	546.2
63	4.578	-9.517	-5.2255	4.2915	3.181	294.137	6.185	5.55	73.74	135.821	208.7	546.2

Com = Compound, ε = Conformation minimum energy (kcal/mole), LP = LogP, Mw = Molecular weight, k2 = Shape Index (basic kappa, order 2), ε_{HOMO} = HOMO energy, χ = Electronegativity, η = Absolute hardness, ω = Electrophilicity index, MR = Molar refractivity, SASA = Solvent accessibility surface area, MV = Molar volume, Pc = Parachor

TABLE 6: CALCULATED PREDICTED ACTIVITIES FROM REGRESSION EQUATIONS PA1 TO PA5

Comp	PA1	PA2	PA3	PA4	PA5	Obs. Activity
1	0.561	0.597	0.570	0.552	0.541	0.572
2	0.332	0.248	0.298	0.329	0.273	0.45
3	0.353	0.315	0.371	0.331	0.340	0.364
4	0.421	0.545	0.436	0.461	0.418	0.642
5	0.190	0.171	0.154	0.247	0.144	0.037
6	0.221	0.240	0.235	0.257	0.220	-0.051
7	0.693	0.730	0.693	0.717	0.689	0.774
8	0.501	0.466	0.477	0.518	0.465	0.72
9	0.527	0.542	0.552	0.525	0.537	0.569
10	0.843	0.938	0.865	0.853	0.852	0.864
11	0.583	0.618	0.538	0.622	0.543	0.647
12	0.677	0.695	0.712	0.673	0.693	0.464
13	0.505	0.603	0.506	0.540	0.540	0.792
14	0.315	0.344	0.296	0.344	0.320	0.444
15	0.337	0.423	0.361	0.353	0.384	0.248
16	0.739	0.736	0.720	0.740	0.747	0.679
17	0.563	0.501	0.531	0.556	0.538	0.582
18	0.556	0.541	0.571	0.531	0.577	0.225
19	0.730	0.711	0.744	0.707	0.750	0.7
20	0.552	0.475	0.538	0.525	0.537	0.525
21	0.571	0.534	0.607	0.525	0.602	0.449
22	0.740	0.714	0.754	0.718	0.759	0.98
23	0.568	0.486	0.562	0.536	0.556	0.727
24	0.585	0.547	0.625	0.537	0.617	0.38
25	0.204	0.172	0.180	0.204	0.175	0.246
26	0.051	0.034	0.013	0.038	-0.007	-0.174
27	0.072	0.037	0.076	0.047	0.056	0.292
28	0.454	0.421	0.409	0.417	0.459	0.253
29	-0.291	-0.332	-0.295	-0.304	-0.282	-0.237
30	-0.270	-0.264	-0.221	-0.303	-0.215	-0.328
31	-0.188	-0.237	-0.179	-0.183	-0.181	-0.092
32	-0.079	-0.133	-0.082	-0.067	-0.076	-0.292
33	0.473	0.393	0.439	0.483	0.470	0.494
34	0.390	0.324	0.378	0.406	0.407	0.486
35	0.484	0.470	0.497	0.477	0.488	0.461
36	0.439	0.454	0.449	0.463	0.451	0.40
37	0.462	0.376	0.422	0.476	0.420	0.364
38	0.408	0.383	0.365	0.454	0.374	0.408
39	0.230	0.213	0.240	0.234	0.215	0.21
40	-0.062	-0.099	-0.085	-0.028	-0.070	-0.387
41	-0.091	-0.143	-0.102	-0.071	-0.091	-0.143
42	-0.244	-0.215	-0.221	-0.258	-0.228	0.083
43	-0.143	-0.105	-0.138	-0.145	-0.133	-0.125
44	0.406	0.376	0.384	0.399	0.412	0.452
45	0.324	0.305	0.322	0.323	0.349	0.444
46	0.422	0.459	0.442	0.402	0.434	0.468
47	0.401	0.439	0.435	0.397	0.428	0.441
48	0.420	0.387	0.398	0.411	0.389	0.443
49	0.386	0.381	0.373	0.399	0.369	0.367
50	0.175	0.185	0.198	0.160	0.169	0.238
51	-0.118	-0.097	-0.124	-0.105	-0.115	-0.208
52	-0.146	-0.110	-0.143	-0.146	-0.137	-0.041
53	-0.242	-0.150	-0.220	-0.254	-0.226	0.053

54	-0.121	-0.056	-0.112	-0.123	-0.110	-0.267
55	0.405	0.401	0.381	0.399	0.410	0.433
56	0.333	0.335	0.330	0.335	0.357	0.373
57	0.452	0.515	0.476	0.431	0.463	0.433
58	0.430	0.495	0.471	0.425	0.459	0.389
59	0.451	0.445	0.433	0.442	0.420	0.417
60	0.420	0.426	0.417	0.427	0.406	0.403
61	0.202	0.232	0.229	0.188	0.197	0.199
62	-0.087	-0.032	-0.088	-0.077	-0.083	-0.319
63	-0.119	-0.055	-0.111	-0.119	-0.108	-0.066

PA = Predicted activity derived from various QSAR model equations

Examination of **Table 6** suggests that compounds No. **1**, **3**, **7**, **9**, **10**, **11**, **17**, **19**, **20** and **21** of pyrazoline group show predicted activity almost at par with the observed activity in all the five selected models (PA1 to PA5).

The same is true for compounds No. **33**, **35**, **46**, **47**, **49**, **55**, **56**, **57**, **60** and **61** of dioxazole group which show highly comparable predicted activity with observed activity in all the selected five models (PA1 to PA5).

TABLE 7: VALUES OF CROSS VALIDATION AND CORRELATION COEFFICIENTS OF BEST FIVE QSAR MODELS

PAE	rCV^2	r^2	Variable counts	Descriptors used in QSAR models
PA1	0.756404	0.806883	7	Conformation Minimum Energy, Electronegativity, Molecular Weight, Shape Index (2), SASA, Molar Volume, Parachor
PA2	0.729243	0.806268	7	Conformation Minimum Energy, Electronegativity, Absolute Hardness, Electrophilicity Index, Shape Index (2), Molar Volume, Parachor
PA3	0.747698	0.804047	7	Conformation Minimum Energy, Electronegativity, Shape Index (2), Molar Refractivity, SASA, Molar Volume, Parachor
PA4	0.760651	0.803411	7	Conformation Minimum Energy, Electronegativity, Molecular Weight, Shape Index (2), LogP, Molar Volume, Parachor
PA5	0.750508	0.802723	7	Conformation Minimum Energy, Electronegativity, Shape Index (2), LogP, SASA, Molar Volume, Parachor

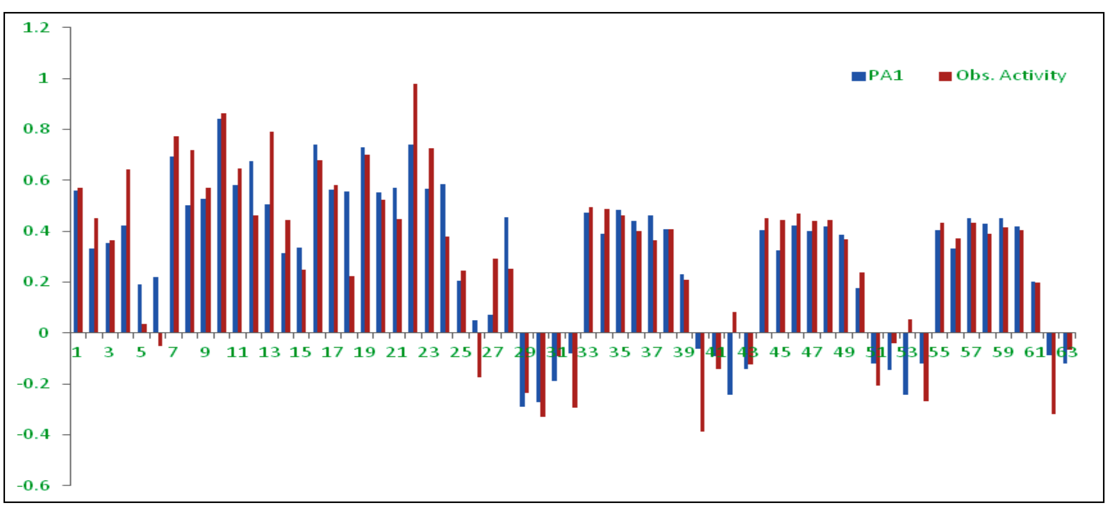
PAE = Predicted activity equations, rCV^2 = Cross validation coefficient, r^2 = Correlation coefficient

QSAR MODEL EQUATION-1

$$PA1= 0.00417292*\varepsilon+0.802645*\chi+0.00181302*Mw-0.51571*k2+0.00797046*SASA+0.0951141*MV-0.0337697*Pc+4.22522$$

rCV^2 = 0.756404 ----(1)

r^2 = 0.806883



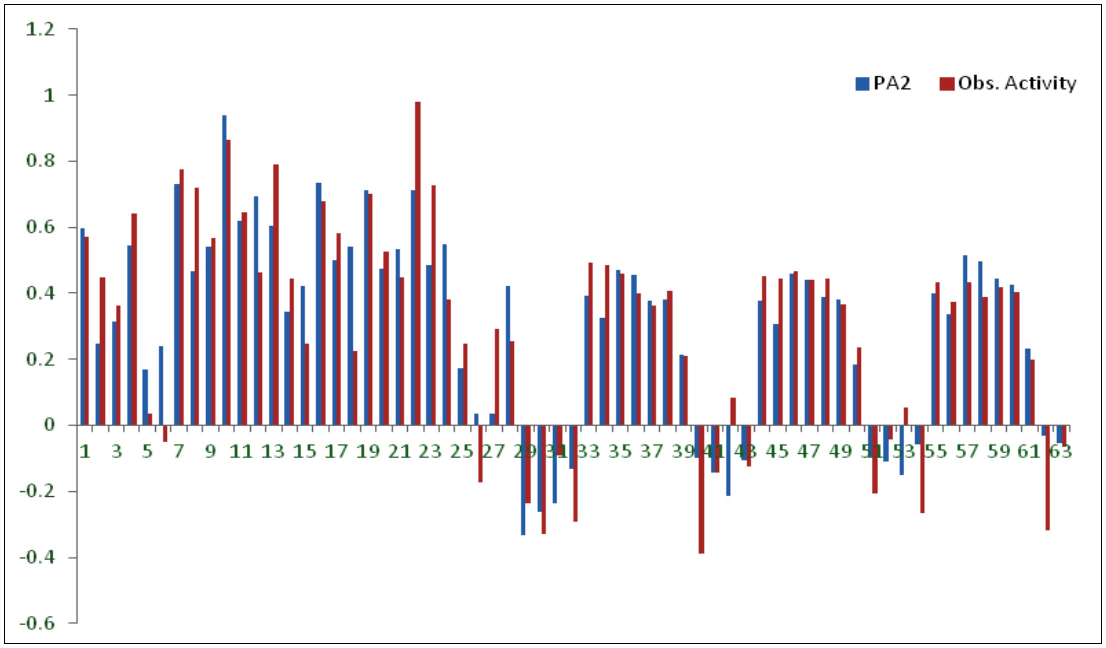
GRAPH 1: CORRELATION BETWEEN OBSERVED ACTIVITY AND PREDICTED ACTIVITY DERIVED FROM REGRESSION MODEL PA1

QSAR MODEL EQUATION- 2

$$PA2 = 0.00447077*\varepsilon+12.1849*\chi+6.49678*\eta+10.2269*\omega-0.556798*k2+0.0870785*MV-0.0274321*Pc+3.43851$$

$rCV^2 = 0.729243$ ---(2)

$r^2 = 0.806268$



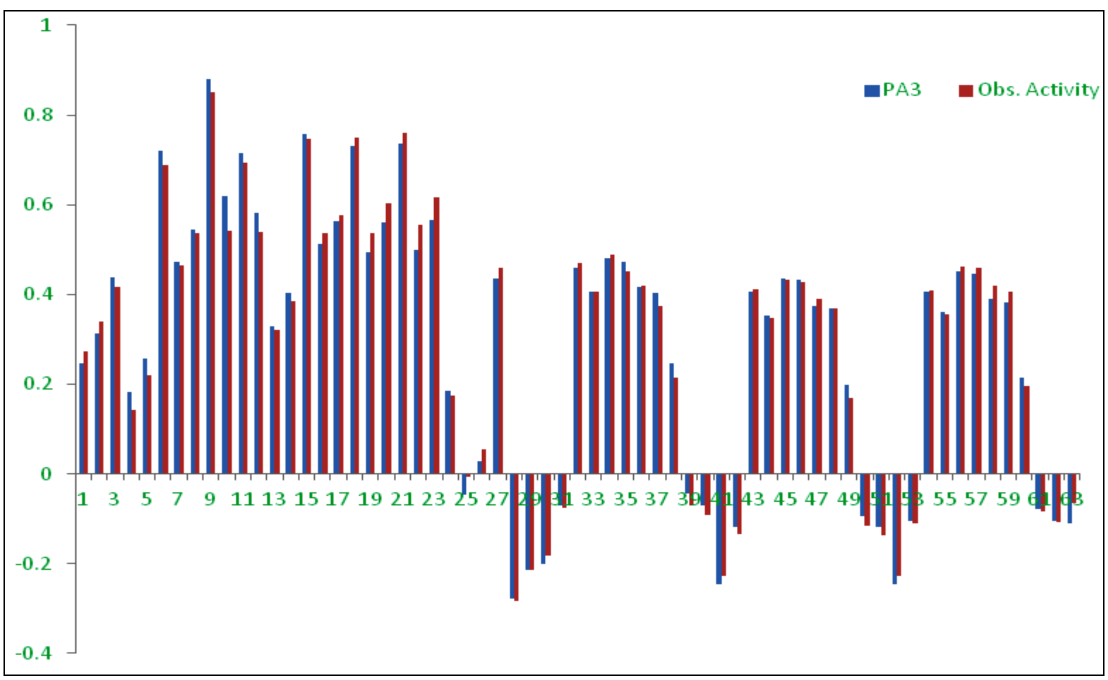
GRAPH 2. CORRELATION BETWEEN OBSERVED ACTIVITY AND PREDICTED ACTIVITY DERIVED FROM REGRESSION MODEL PA2

QSAR MODEL EQUATION-3

$$PA3 = 0.00337618*\varepsilon+0.932314*\chi-0.517113*k2-0.0115611*MR+0.0161658*SASA+0.0869679*MV-0.0292388*Pc+4.42091$$

$rCV^2 = 0.747698$ ----(3)

$r^2 = 0.804047$



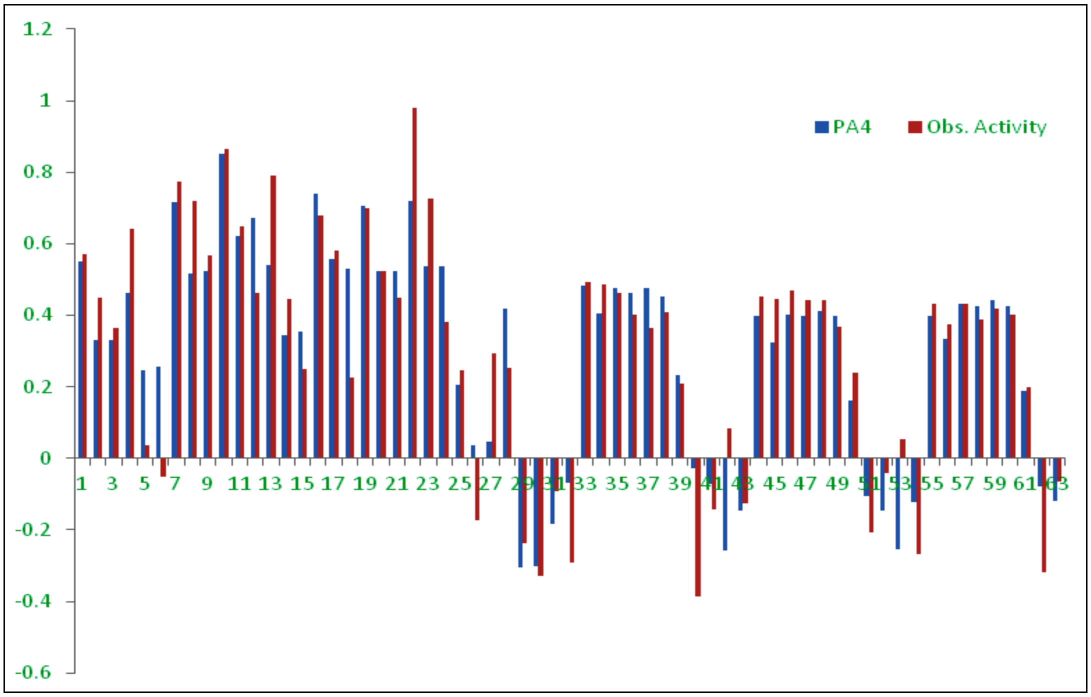
GRAPH 3. CORRELATION BETWEEN OBSERVED ACTIVITY AND PREDICTED ACTIVITY DERIVED FROM REGRESSION MODEL PA3

QSAR Model Equation-4

$$PA4 = 0.00423129*\varepsilon+0.761142*\chi+0.00256411*Mw-0.477313*k2+0.0198134*LP+0.0920914*MV-0.0321332*Pc+4.25876$$

$rCV^2 = 0.760651$ ----(4)

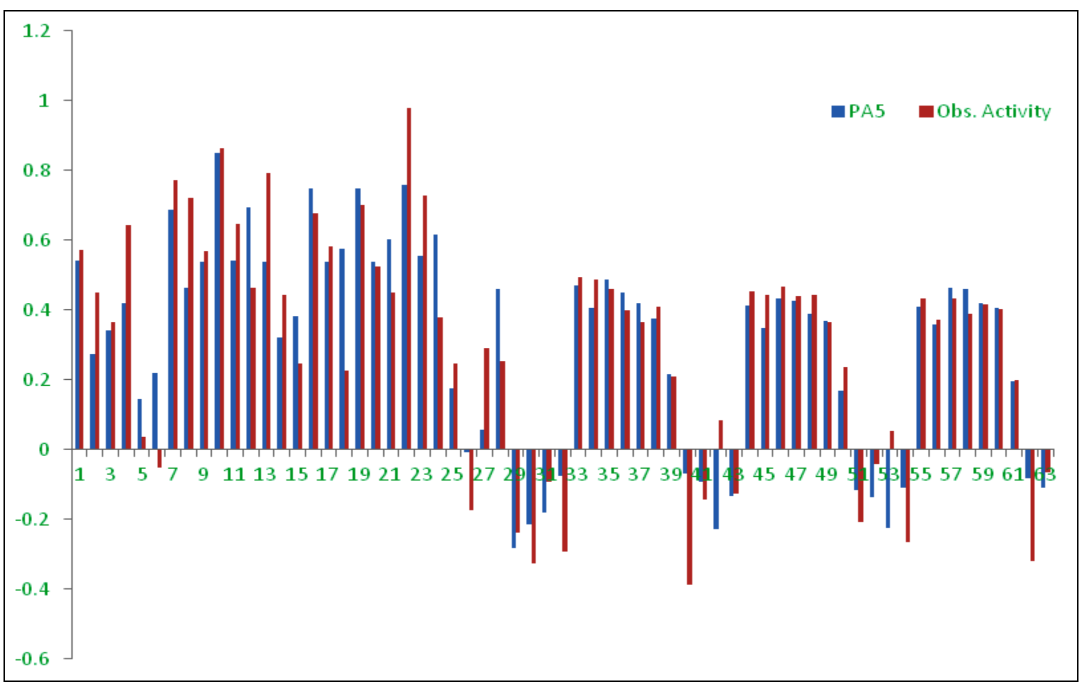
$r^2 = 0.803411$



GRAPH 4. CORRELATION BETWEEN OBSERVED ACTIVITY AND PREDICTED ACTIVITY DERIVED FROM REGRESSION MODEL PA4

QSAR MODEL EQUATION-5

PA5 = 0.00379732*ε+0.824393*χ-0.508899*k2+0.0200405*LP+ 0.0118551*SASA+ 0.0895119*MV-0.0313529*Pc+4.05228
rCV^2 = 0.750508 ---(5)
r^2 = 0.802723



GRAPH 5. CORRELATION BETWEEN OBSERVED ACTIVITY AND PREDICTED ACTIVITY DERIVED FROM REGRESSION MODEL PA5

These equations contain various descriptors in different combinations and each descriptor has a positive or negative co-efficient attached to it. These coefficients along with the value of descriptor have a significant role in deciding the overall biological activity of the molecule as discussed below. Examination of selected equation shows that coefficients of each parameter play an important role in deriving the biological activity. From the point of view of potency or biological activity of the drug molecule in terms of -logIC_{50} values, the weight of a negative co-efficient is very significant because it contributes towards a decreased value of -logIC_{50}, meaning increased value of biological activity. So the parameters with a negative co-efficient are most important followed by parameters with low weight positive coefficients and lastly the parameters with high weight positive coefficients.

On the basis of values of these coefficients, the associated descriptors are arranged in a sequence pertaining to their contribution towards overall biological activity of the molecule, in following decreasing order of biological activity of anti amoebic agents;

Shape Index (k2) > Parachor (Pc) > Conformation Minimum Energy (ε) and/or Molecular Weight (Mw) and/or Molecular Refractivity (MR) > Solvent Accessibility Surface Area (SASA) > LogP > Molar Volume (MV) > Electronegativity (χ), εHOMO, Electrophilicity Index (ω), Absolute Hardness (η)

CONCLUSION: The QSAR models developed by us in this paper represent some of the easiest ways of determining the biological activity of anti-amoebic agents. All the models are highly predictive and provides good values for cross validation coefficient (rCV^2) and correlation coefficient (r^2). Study and analysis of these models reveal that negative coefficients of regression model are most significant followed by positive coefficients of low weight and finally positive coefficients of high weight. The whole intention behind this was to facilitate the designing of new anti-amoebic drugs for the treatment against *E. histolytica*.

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