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SEMI-EMPIRICAL METHODS BASED 3D-QSAR STUDIES FOR SOME SUBSTITUTED SCHIFF BASES OF PYRIDINE-2-AMINE

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ABSTRACT

3D QSAR viz. 3 descriptor quantitative structure and activity relationship studies for a series of compounds i.e. Schiff base derivatives of 4-methyl pyridine-2-amine involving their semi-empirical quantum chemical descriptors and their laboratory reported activities against pathogen viz. *P.aeruginosa* has been carried out and reported in the present paper. Graphs between observed and predicted activities, both in the terms of p(MIC) are also being reported on the basis of which this may be concluded that some parameters/descriptors have positive contribution towards the activity. The method has been proved to be a useful tool for such type of studies.

KEY WORDS: **Semiempirical/3dqsar/substituted pyridine-2-amine compounds**

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INTRODUCTION

Micro-organism viz. fungi, bacteria and viruses etc. may be harmful to mankind(1-3). Studies of nature and properties of micro-organisms were the necessity of man since past (1-3). Some of the discoveries such as penicillin, chloromycitin, sulpha drugs and antibiotics may be treated as mile stones in this regard (4-6). The studies involving antimicrobial activities of naturally occurring and/ or synthetic compounds in the laboratory which may include organic and inorganic complex compounds were of interest of many workers since past (7-18). A few years ago workers in this field have started carrying out theoretical studies in drug discovery pertaining to QSAR studies, which may prove to be a better tool and technique to save time and labor of screening of each and every compound against microbes. In some of the recent references scientists have even utilized electronic properties or parameters of compounds computed on the basis of Quantum Chemical calculations viz. ab-initio or semi-empirical studies as descriptors for QSAR studies and correlated these descriptors with activities of the compounds against microorganisms (19-29) which has been proved as a step ahead in the related field. Keeping above discussion in mind, in this present paper QSAR precisely 3D-QSAR studies which have been carried out on a new series of compounds i.e. Schiff base derivatives of 4-methyl pyridine-2-amine (E1-E10 compounds shown in figure) with their activities against *P.aeruginosa,* are reported. These compounds were procured and their activities were checked and taken into consideration for the studies according to the reported references (30-31).

Computational Details

The AM1 Hamiltonia on Hyperchem 8.0 professional version were used to calculate the QSAR related descriptors such as Hydration energy (Hyd E), log P (log P), Refractivity (REF), Polarizability (POL). mass (mass), Surface area approx (SAA), Surface area Grid (SAG), volume (Vol), Heat of formation (HF) , Zero point energy (ZPE), HOMO energy (HOMO), LUMO energy (LUMO) and dipole moment (DM). All these computations were carried out on Pentium core -2 duo machine having configuration Intel (R) core $^{(TM)}$ 2 Duo CPU T $_{5450}$@ 1.66 GHz. 982 MHz, 896 MB RAM 150 GB HDD with windows – Microsoft windows XP software as an operating system. These descriptors and the activities of the compounds against specified microbes, mentioned in the tables, were taken into consideration in terms of p (MIC) and were subjected to statistical analysis/ regression analysis to get QSAR equations. All these statistical calculations were carried out on the same machine mentioned above using EXCEL software.

RESULTS AND DISCUSSION

In the present paper, author wishes to report the semi-empirical quantum chemically computed properties viz. Hydration energy (Hyd E), log P (log P), Refractivity (REF), Polarizability (POL). mass (mass), Surface area approx (SAA), Surface area Grid (SAG), volume (Vol), Heat of formation (HF) , Zero point energy (ZPE), HOMO energy (HOMO), LUMO energy (LUMO) and dipole moment (DM) which were used as descriptors to correlate laboratory reported activities of the compounds under studies. Structures of all the compounds were drawn on HYPERCHEM 8.0 professional version and their geometries were optimized. Their quantum chemical parameters were computed semi- empirically on Pentium core -2 duo model computer whose configuration is mentioned above in the heading computational details. Compounds under studies are shown the figure 1. The physico-chemical and analytical parameters of these compounds are taken as reported and are recorded in the tables 1-2 with their reported activities against the pathogen under studies. The computed parameters which are taken into consideration as descriptors for QSAR studies are shown in tables 3-6. These descriptors were considered with the activities of the compounds under studies against the mentioned pathogens. Statistical analysis of all these parameters and activities in terms of p(MIC) were carried out to get the corresponding S.D. (standard deviation), F-test , correlation (r) and square of correlation

values. The one descriptor QSAR equations were reported using this statistical analysis. The correlation matrices involving all these descriptors were also obtained for all the parameters that were computed using all methods viz. AM1, PM3, MNDO and ZINDO. Out of these equations appropriate equations are selected on the basis of their statistical values. Same method was adopted for getting 3D-QSAR equations also and ultimately one most appropriate equation was selected on the basis of their statistical values computed by the software EXCEL.

This final equation was used to get predicted activities for all the series of compounds and against microorganism under study. The final 3D QSAR equations are reported as under:-

P. Aeruginosa /AM1/ 3D- QSAR EQUATIONS/E1-E10 Compounds:-

p(MIC) = (-0.0059)HF – (0.4529)HOMO+ (0.012449)DM -1.975539

n = 10, SD = 0.203482, cc= 0.621409, F test =1.258117

P. Aeruginosa /PM3/ 3D- QSAR EQUATIONS/E1-E10 Compounds:-

p(MIC) = (-0.0609259)LogP – (0.00486)HF - (0.04073)DM -1.90761

n = 10, SD = 0.232725, cc= 0.443881, F test =0.490753

P. Aeruginosa /MNDO/ 3D- QSAR EQUATIONS/E1-E10 Compounds:-

p(MIC) = (0.397018)LogP + (0.001595)SAG - (0.01381)HF -2.85172

n = 10, SD = 0.172085, cc= 0.74893, F test =2.555707

P. Aeruginosa /ZINDO/ 3D- QSAR EQUATIONS/E1-E10 Compounds:-

p(MIC) = (0.000774)SAA - (0.06742)HOMO + (0.059149)LUMO – 3.78268

n = 10, SD = 0.1638885, cc= 0.775754, F test =3.022536

Graphs were also drawn between observed activities and predicted activities, both in the terms of p(MIC) form 3 D-QSAR equations for this series of compounds. These trend line graphs are shown in figure 2-5.

Table-1

Physical and analytical data of the compounds under study

Compd	R-	Mol. Formula	Mol. Wt.	% Yield (color)	M.P. (^{0} C)
E1	-H	$C_{22}H_{18}N_4$	338.40	80 Goldy	115
E2	p-Cl	$C_{22}H_{17}N_4Cl$	372.85	83 Buff	128
E3	o,p-di-Cl	$C_{22}H_{16}N_4Cl_2$	406.07	85 White	125
E4	p-CH_3	$C_{23}H_{20}N_4$	352.43	82 Musturd	118
E5	p-OCH_3	$C_{23}H_{20}N_4O$	368..43	84 Parchment	120
E6	o-OH	$C_{22}H_{18}N_4O$	354.40	81 Brown	78
E7	m-OH	$C_{22}H_{18}N_4O$	354.40	80 Dark Brown	89
E8	p-OH	$C_{22}H_{18}N_4O$	354.40	79 Brown	83
E9	m-NO_2	$C_{22}H_{17}N_5O_2$	383.40	83 Yellow	140
E10	p-NO_2	$C_{22}H_{17}N_5O_2$	383.40	85 Yellow	133

Table-2

Physical and analytical data of the compounds under study

Compd	R-	Mol. Formula	%C Found (Calcd.)	%H Found (Calcd.)	% N Found (Calcd.)
E1	-H	$C_{22}H_{18}N_4$	77.96 78.08	5.24 5.36	16.51 16.56
E2	p-Cl	$C_{22}H_{17}N_4Cl$	70.80 70.87	4.55 4.56	14.97 15.03
E3	o,p-di-Cl	$C_{22}H_{16}N_4Cl_2$	64.79 64.88	3.83 3.96	13.63 13.76
E4	p-CH_3	$C_{23}H_{20}N_4$	78.27 78.38	5.81 5.72	16.04 15.90
E5	p-OCH_3	$C_{23}H_{20}N_4O$	75.06 74.98	5.39 5.47	15.25 15.21
E6	o-OH	$C_{22}H_{18}N_4O$	74.48 74.56	5.06 5.12	15.90 15.81
E7	m-OH	$C_{22}H_{18}N_4O$	74.50 74.56	5.09 5.12	15.88 15.81
E8	p-OH	$C_{22}H_{18}N_4O$	74.49 74.56	5.05 5.12	15.86 15.81
E9	m-NO_2	$C_{22}H_{17}N_5O_2$	68.97 68.92	4.41 4.47	18.22 18.27
E10	p-NO_2	$C_{22}H_{17}N_5O_2$	68.99 68.92	4.43 4.47	18.20 18.27

Table-3
Semi- Empirical AM1 based Computed properties of the Compounds (E1-E10) under study

SAA	SAG	Vol	HF	ZPE	HOMO	LUMO	DM
502.6	602.5	1026.5	193.262	225.42	-0.3448	0.10923	1.995
538.6	629.6	1070.4	186.523	219.55	-0.1235	0.21952	1.796
556.4	637.4	1100.7	184.739	213.653	-0.4056	0.21072	2.538
547.5	634.2	1080.3	185.265	242.731	-0.3494	0.12727	2.298
562.9	646.7	1104.4	155.396	246.27	-0.3182	0.03436	3.366
499.8	612.7	1043.8	154.559	228.21	-0.3381	0.00369	2.979
517.9	616	1048.6	149.581	228.251	-0.3896	0.08907	3.139
518.4	615.9	1048.9	149.252	228.246	-0.0495	0.29065	2.994
556.6	652.8	1111.7	169.073	241.661	-0.0709	0.28841	1.955
556.6	653.8	1111.6	168.457	241.665	-0.7528	0.0104	2.498

Compd	MIC	P(MIC) (Observed)	HE	Log P	Ref	Polar	Mass
E1	1000	-3	-5.82	2.44	115.4	40.47	338.4
E2	1000	-3	-5.47	2.22	120.2	42.4	372.8
E3	500	-2.699	-4.93	1.99	124.4	44.33	407.3
E4	500	-2.699	-4.62	2.54	119.7	42.31	352.4
E5	500	-2.699	-7.5	1.45	121.8	42.95	368.4
E6	500	-2.699	-8.63	1.41	117	41.1	354.4
E7	200	-2.301	-12.4	1.41	117	41.11	354.4
E8	1000	-3	-12.7	1.41	117	41.11	354.4
E9	500	-2.699	-20.4	1.22	122.3	43.1	385.4
E10	500	-2.699	-20.9	1.22	122.3	43.1	385.4

Table-4
Semi- Empirical PM3 based Computed properties of the Compounds (E1-E10) under study

Compd	MIC	P(MIC) (Observed)	HE	Log P	Ref	Polar	Mass
E1	1000	-3	-5.69	2.44	115.4	40.47	338.4
E2	1000	-3	-5.33	2.22	120.2	42.4	372.8
E3	500	-2.699	-4.78	1.99	124.9	44.33	407.3
E4	500	-2.699	-4.78	2.59	119.7	42.31	352.4
E5	500	-2.699	-7.33	1.45	121.8	42.95	368.4
E6	500	-2.699	-8.56	1.41	117	41.11	354.4
E7	200	-2.301	-12.42	1.41	117	41.11	354.4
E8	1000	-3	-12.55	1.41	117	41.11	354.4
E9	500	-2.699	-21.91	1.22	122.3	43.1	385.4
E10	500	-2.699	-22.32	1.22	122.3	43.1	385.4

SAA	SAG	Vol	HF	ZPE	HOMO	LUMO	DM
499	600.5	1019.3	146.914	217.327	-0.0341	0.2239	2.857
534.2	625.7	1062	140.582	211.577	-0.0669	0.1462	2.857
550.8	636.9	1091.7	137.302	206.089	-0.0742	0.1289	2.967
542.7	629.2	1071.8	137.389	234.751	-0.0213	0.2361	3.093
558	643.3	1096.3	108.811	237.432	-0.0173	0.2509	4.124
496.1	606.4	1036.1	107.036	220.965	-0.1181	0.0183	3.142
513.4	613	1040.6	102.274	220.788	-0.0321	0.2281	3.862
513.7	612	1041.7	101.847	220.789	-0.0263	0.2342	3.977
536.9	649.4	1106.9	127.832	232.851	-0.0498	0.1911	3.011
557.1	650.7	1106.7	127.573	232.692	-0.0385	0.1901	3.239

Table -5
Semi- Empirical MNDO based Computed properties of the Compounds (E1-E10) under study

SAA	SAG	Vol	HF	ZPE	HOMO	LUMO	DM
510.1	609.9	1033.1	151.3013	230.459	-0.0094	0.1141	1.956
547.6	639.4	1079.2	143.854	224.304	-0.328	0.0382	1.888
574.7	691.1	1152	125.7192	218.557	-0.1185	0.0382	1.618
555.2	644	1088.6	143.1313	248.508	-0.4149	0.0088	1.965
571.2	692.9	1151	97.976	252.376	-0.1074	0.0844	2.501
507.8	619.7	1051.3	108.6003	233.624	-0.1229	0.1645	3.001
522.3	655.9	1087.7	89.8851	234.299	-0.0172	0.1099	1.961
526.5	626.4	1056.1	103.1823	233.826	-0.1356	0.116	2.975
571.1	691.6	1154.9	108.1479	248.68	-0.1058	0.0522	1.201
556	653.8	1111.6	106.3883	248.706	-0.0506	0.0715	1.201

Table-6
Semi- Empirical ZINDO based Computed properties of the Compounds (E1-E10) under study

Compd	MIC	P(MIC) (Observed)	HE	Log P	Ref	Polar	Mass
E1	1000	-3	-4.26	2.44	115.4	40.4	338.4
E2	1000	-3	-5.1	2.22	120.2	42.4	372.8
E3	500	-2.699	-3.43	1.99	124.9	44.3	407.3
E4	500	-2.699	-4.24	2.59	119.7	42.3	352.4
E5	500	-2.699	-8.27	1.45	121.8	42.9	368.4
E6	500	-2.699	-3.34	1.41	117	41.11	354.4
E7	200	-2.301	-12.02	1.41	117	41.11	354.4
E8	1000	-3	-11.13	1.41	117	41.11	354.4
E9	500	-2.699	.17.77	-1.22	122.3	43.1	385.4
E10	500	-2.699	-18.26	-1.22	122.3	43.1	385.4

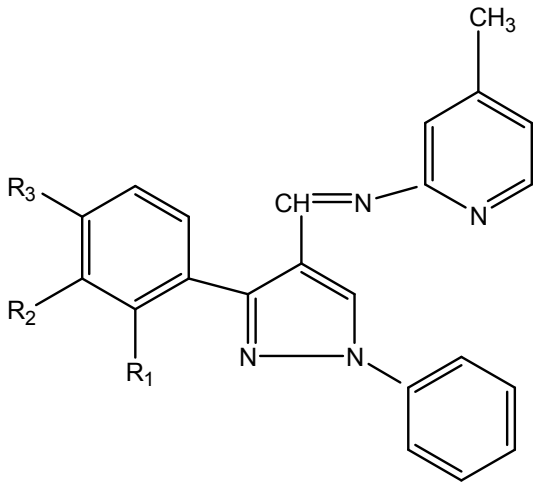
Compd	MIC	P(MIC) (Observed)	HE	Log P	Ref	Polar	Mass
E1	1000	-3	-5.86	2.44	115.4	40.47	338.4
E2	1000	-3	-5.53	2.22	120.2	42.4	372.8
E3	500	-2.699	-5.62	1.99	124.9	44.33	407.3
E4	500	-2.699	-4.65	2.59	119.7	42.31	352.4
E5	500	-2.699	-7.83	1.45	121.8	42.95	368.4
E6	500	-2.699	-8.47	1.41	117	41.11	354.4
E7	200	-2.301	-12.68	1.41	117	41.11	354.4
E8	1000	-3	-12.72	1.41	117	41.11	354.4
E9	500	-2.699	-21.74	1.22	122.3	43.1	385.4
E10	500	-2.699	-21.92	1.22	122.3	43.1	385.4

SAA	SAG	Vol	HF	ZPE	HOMO	LUMO	DM
421.7	576.8	977.43	10147.38	306.43	-3.3308	4.7229	7.255
52	622.1	1058	10083.44	297.39	-6.4405	5.7524	5.638
469.4	625.6	1060.8	10207.73	291.4	-6.3312	5.8534	8.778
532.8	623.5	1065.5	10622.03	330.23	-6.059	6.1045	3.353
557.2	665.8	1107.2	10747.01	334.42	-5.9857	6.3585	2.161
411.5	590.8	1011.3	10318.82	311.93	-3.9144	5.4422	4.699
502.9	618.3	1051.4	10204.94	309.97	-6.4244	6.1035	3.993
437.4	588.7	999.73	10285.67	309.42	-3.3267	4.7533	6.279
466.7	637.4	1072.5	10840.31	329.88	-6.0091	6.4703	3.815
469.7	635.1	1072.7	10815.97	330	-4.9475	6.4178	1.946

Table-7
Reported activities of the compounds against pathogen P.aeruginosa

Compd	R-	Mol. Formula	MIC	P(MIC) (Observed)
E1	-H	$C_{22}H_{18}N_4$	1000	-3
E2	p-Cl	$C_{22}H_{17}N_4Cl$	1000	-3
E3	o,p-di-Cl	$C_{22}H_{16}N_4Cl_2$	500	-2.699
E4	p-CH_3	$C_{23}H_{20}N_4$	500	-2.699
E5	p-OCH_3	$C_{23}H_{20}N_4O$	500	-2.699
E6	o-OH	$C_{22}H_{18}N_4O$	500	-2.699
E7	m-OH	$C_{22}H_{18}N_4O$	200	-2.301
E8	p-OH	$C_{22}H_{18}N_4O$	1000	-3
E9	m-NO_2	$C_{22}H_{17}N_5O_2$	500	-2.699
E10	p-NO_2	$C_{22}H_{17}N_5O_2$	500	-2.699

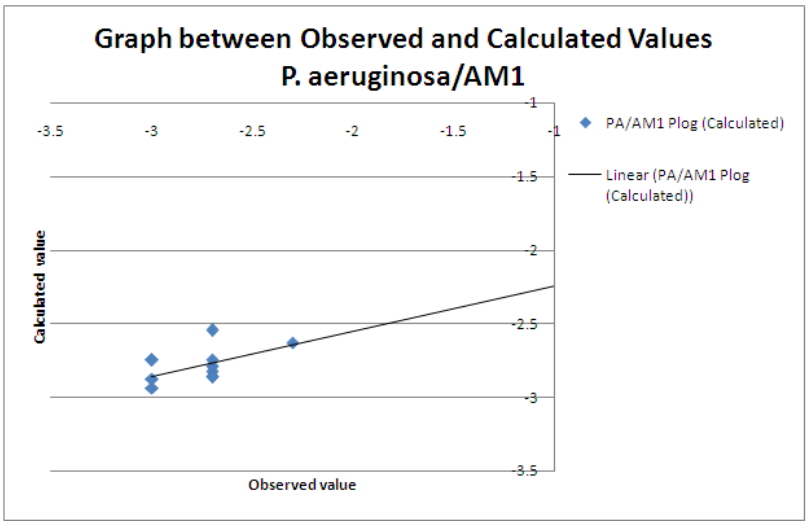
Figure-1
Compounds Under Study (E_1 – E_{10})



Where

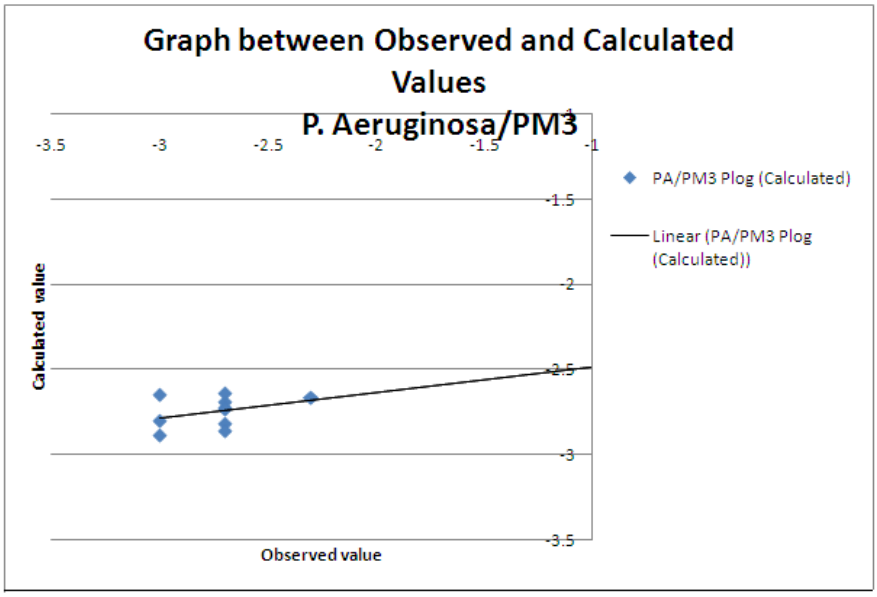
E_1	:	R_1 = H;	R_2 = H;	R_3 = H;
E_2	:	R_1 = H;	R_2 = H;	R_3 = Cl;
E_3	:	R_1 = Cl;	R_2 = H;	R_3 = Cl
E_4	:	R_1 = H;	R_2 = H;	R_3 = CH_3
E_5	:	R_1 = H;	R_2 = H;	R_3 = OCH_3
E_6	:	R_1 = OH;	R_2 = H;	R_3 = H
E_7	:	R_1 = H;	R_2 = OH;	R_3 = H
E_8	:	R_1 = H;	R_2 = H;	R_3 = OH
E_9	:	R_1 = H;	R_2 = NO_2;	R_3 = H
E_{10}	:	R_1 = H;	R_2 = H;	R_3 = NO_2

Figure-2
Graph between p(MIC) observed and p(MIC) calculated for P. Aeruginosa on the basis of selected 3D QSAR equation based on AM1 method



P.aeruginosa/AM1	
p(MIC) (Observed)	p(MIC) (Calculated)
-3	-2.8747
-3	-2.9398
-2.699	-2.7928
-2.699	-2.8242
-2.699	-2.858
-2.699	-2.7423
-2.301	-2.6323
-3	-2.75
-2.699	-2.8641
-2.699	-2.545

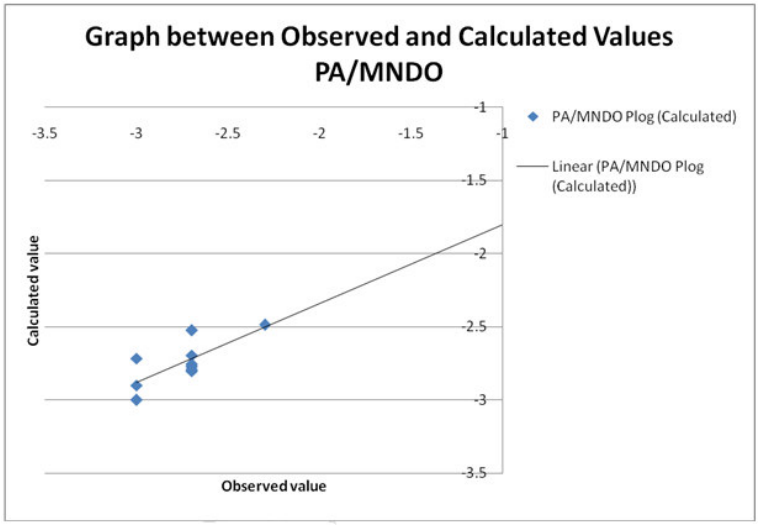
Figure-3
Graph between p(MIC) observed and p(MIC) calculated for P. Aeruginosa on the basis of selected 3D QSAR equation based on PM3 method



P. Aeruginosa /PM3	
p(MIC)(Observed)	p(MIC) (Calculated)
-3	-2.8866
-3	-2.8
-2.699	-2.817
-2.699	-2.8591
-2.699	-2.6927
-2.699	-2.6417
-2.301	-2.6679
-3	-2.6505
-2.699	-2.7258
-2.699	-2.7339

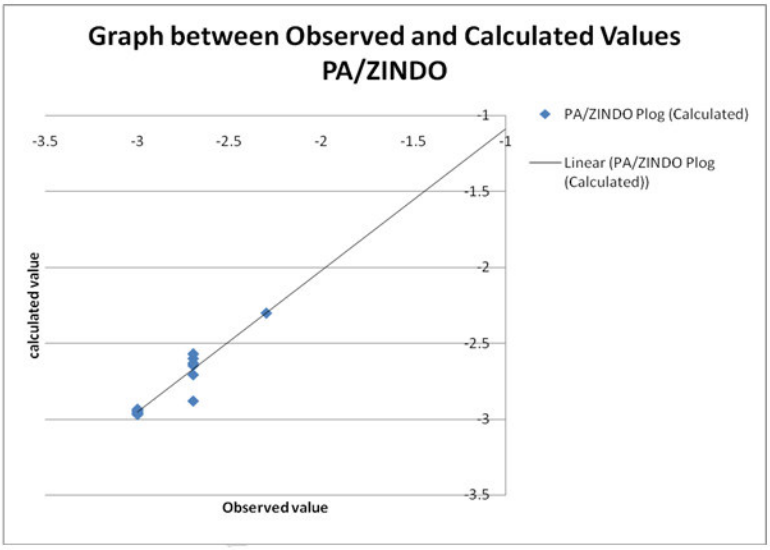
Figure -4

Graph between p(MIC) observed and p(MIC) calculated for P. Aeruginosa on the basis of selected 3D QSAR equation based on MNDO method



P. Aeruginosa /MNDO	
p(MIC) (Observed)	p(MIC) (Calculated)
-3	-2.9997
-3	-2.9
-2.699	-2.6955
-2.699	-2.7729
-2.699	-2.5239
-2.699	-2.8033
-2.301	-2.4871
-3	-2.7178
-2.699	-2.7578
-2.699	-2.7938

Figure -5
Graph between p(MIC) observed and p(MIC) calculated for P. Aeruginosa on the basis of selected 3D QSAR equation based on ZINDO method



P. Aeruginosa /ZINDO	
p(MIC)(Observed)	p(MIC) (Calculated)
-3	-2.9524
-3	-2.968
-2.699	-2.6463
-2.699	-2.6007
-2.699	-2.5718
-2.699	-2.8784
-2.301	-2.3
-3	-2.9387
-2.699	-2.6336
-2.699	-2.706

CONCLUSION

This method has once again proved to be useful for this type of studies. The parameters/ descriptors which contribute positively to p (MIC) in final 3D QSAR equations are listed below:-

AM1/E1-E10/*P.aeruginosa:* HF, HOMO and DM
PM3/E1-E10/ *P.aeruginosa:* logP, HF and DM
MNDO/E1-E10/ *P.aeruginosa:* logP, SAG and HF
ZINDO/E1-E10/ *P.aeruginosa:* SAA, HOMO and LUMO

In conclusion this may be said that these parameters / descriptors have more impact on p(MIC) over all other descriptors computed and reported.

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