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Research Article **QSAR Studies**

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SEMI EMPIRICAL BASED 3D-QSAR STUDIES OF SOME PHARMACOLOGICAL IMPORTANT COMPOUNDS

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ABSTRACT

3D QSAR viz. 3 descriptor quantitative structure and activity relationship studies for a series of Schiff base derivatives of 2- Methyl pyridine -2- amine involving their semi-empirical quantum chemical descriptors and their laboratory reported activities against pathogens viz. *E.coli* and *A.niger* have been carried out and reported in the present communication. 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 useful for such type of studies.

KEY WORDS: **Semiempirical/3dqsar/pharmacological compounds**

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INTRODUCTION

Microorganism viz. fungi, bacteria and viruses etc. may be harmful to mankind (1-3). Studies of the nature and properties of microorganisms have been the necessity of man since past (1-3). Discoveries such as penicillin, chloromycitin, sulpha drugs and antibiotics may be treated as milestones 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 (7-19). 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 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 (20-22) 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 Schiff base derivatives of 2- Methyl pyridine -2- amine (E1- E10 compounds shown in figures) with their activities against *A. niger* and *E. coli,* are reported.These compounds were procured and their activities were checked and taken into consideration for the studies according to the reported references (23-24).

COMPUTATIONAL DETAILS

The AM1, PM3, MNDO and ZINDO, 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), 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 STATISTICA 9.0 version software.

RESULTS AND DISCUSSION

In the present paper, the author wishes to report the semi-empirical quantum chemically computed properties viz. Hydration energy (Hyd E), log P (log P), 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 understudies. 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 in the heading computational details. Compounds under studies are shown the figure 1 with their ball and stick models. 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 pathogens understudies. 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 understudies against the mentioned pathogens. Statistical analysis of all 13 parameters activities in terms of p(MIC) was carried out to get the corresponding S.D. (Standard deviation), F-test , correlation (r) and square of correlation values. The 1D-QSAR equations were reported using this statistical analysis. The correlation matrices involving all the 13 descriptors were also obtained for all the parameters that were computed using all methods viz. AM1, PM3, MNDO and ZINDO. These matrices are also given in tables 7-10. On examination of correlation values of the correlation matrices and adopting a cross validation process 2D- i.e. 2 Descriptor QSAR equations for various parameters and their combinations were obtained by correlating these parameters with laboratory reported activities. Out of these equations appropriate equations are selected on the basis of their statistical values. The 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 STATISTICA 9.0.

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

AM1/E1- E10/*A. Niger:*
p(MIC) = -0.261 (log P) +0.529 (HOMO) +0.211(DM) – 3.733768792
r= 0.9999729 r^2 =0.9999457 r^2(adj.) = 0.99992253
SE = 0.5840697 t= 6.393 F=43025.45

AM1/E1- E10/*E.coli:*
p(MIC) = -0.07 (Hyd.E) + 0.621 (log P) + 0.451(DM)
r= 0.99994588 r^2 =0.99989177 r^2(adj.) = 0.99984538
SE = 0.3060350 t= 18.45 F=21556.24

PM3/E1- E10/*A. Niger:*
p(MIC) = -0.03 (Hyd.E) + 0.555 (log P) + 0.473(DM)-5.782432417
r= 0.99997225 r^2 =0.99994450 r^2(adj.) = 0.9992072
SE = 0.2237040 t= -25.85 F=42040.59

PM3/E1- E10/*E.coli:*
p(MIC) = 0.05 (Hyd.E) – 0.421 (log P) + 0.627(DM) -6.008535411
r= 0.99997366 r^2 =0.99994732 r^2(adj.) = 0.99992474
SE = 0.2173922 t= -27.64 F=44288.42

MNDO/E1- E10/*A. Niger:*
p(MIC) = 0.086 (log P) +0.0985 (HOMO) - 0.07(DM) – 2.652300614
r= 0.99998662 r^2 =0.99997323 r^2(adj.) = 0.99996176
SE = 0.2556331 t= -10.38 F=87175.88

MNDO/E1- E10/*E.Coli:*
p(MIC) = -0.14 (log P) +1.12 (LUMO) +0.016(DM) – 2.520404426
r= 0.99996617 r^2 =0.99993234 r^2(adj.) = 0.99990334
SE = 0.3956055 t= -6.376 F=34482.77

ZINDO/E1- E10/*A. Niger:*
p(MIC) = 0.186 (log P) +0.691 (LUMO) +0.153(DM) – 8.202752592
r= 0.99991753 r^2 =0.999983507 r^2(adj.) = 0.99976438
SE = 0.5630258 t= -14.57 F=14144.70

ZINDO/E1- E10/*E.coli:*
p(MIC) = 0.2 (log P) -0.02 (Hyd.E) +0.816(LUMO) – 8.067256515
r= 0.99992279 r^2 =0.99984558 r^2(adj.) = 0.99977941
SE = 0.4394233 t= -18.36 F=15108.35

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.

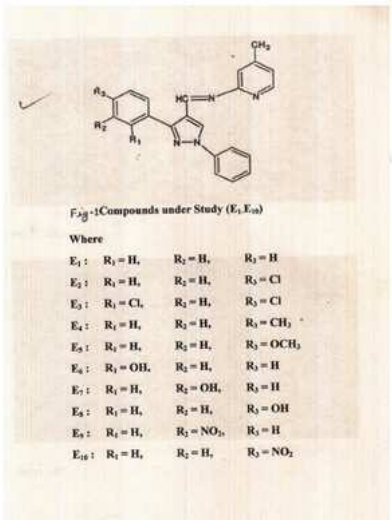

Table 1
Physical and analytical data of the compounds under study

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 1
Physical and analytical data of the compounds under study (Contd.)

Compd	R-	Mol. Formula	%C Found (Calcd.)	%H ound(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 2
Anti bacterial and anti fungal activities of the compounds under study

Compd	R-	Mol. Formula	*E.Coli* MTCC443	*A. Niger*MTCC227
E1	-H	$C_{22}H_{18}N_4$	1000	500
E2	p-Cl	$C_{22}H_{17}N_4Cl$	**1000**	1000
E3	o,p-di-Cl	$C_{22}H_{16}N_4Cl_2$	500	500
E4	p-CH_3	$C_{23}H_{20}N_4$	500	1000
E5	p-OCH_3	$C_{23}H_{20}N_4O$	100	1000
E6	o-OH	$C_{22}H_{18}N_4O$	500	1000
E7	m-OH	$C_{22}H_{18}N_4O$	200	200
E8	p-OH	$C_{22}H_{18}N_4O$	500	1000
E9	m-NO_2	$C_{22}H_{17}N_5O_2$	200	1000
E10	p-NO_2	$C_{22}H_{17}N_5O_2$	200	1000
	-	Gentamycine	0.05	-
	-	Ampicillin	100	-
	-	Chloramphenicol	50	-
	-	Nystatin	-	100
	-	Greseofulvin	-	100

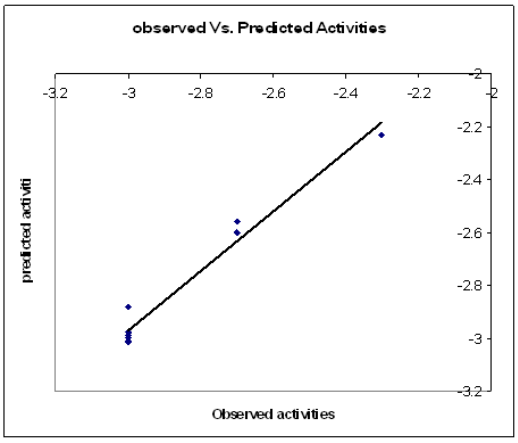

Figure 2
Trend line graph between Observed Vs. AM1 Predicted activity – E1-E10 compounds / A.niger

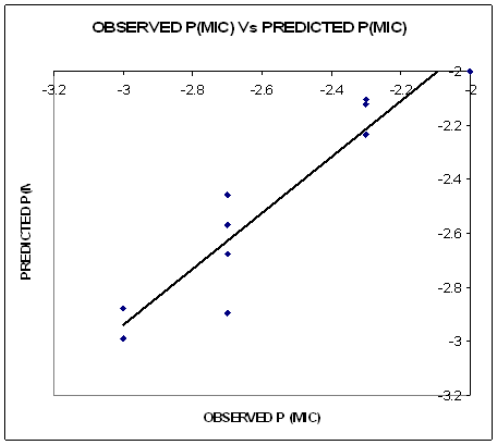

Figure 3
Trend line graph between Observed Vs. AM1 Predicted activity – E1-E10 compounds / E.coli

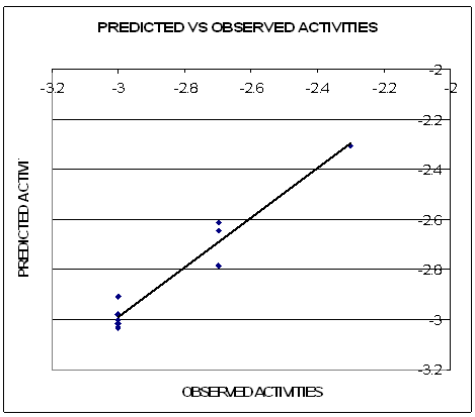

Figure 4
Trend line graph between Observed Vs. PM3 Predicted activity – E1-E10 compounds / A.niger

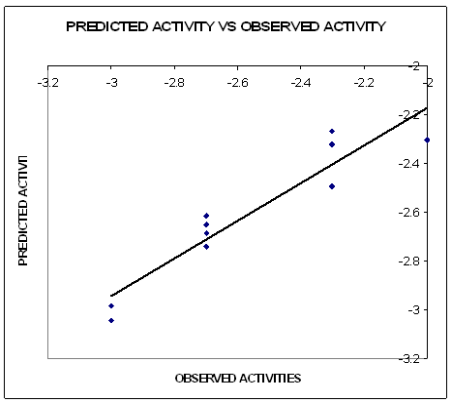

Figure 5
Trend line graph between Observed Vs. PM3 Predicted activity – E1-E10 compounds / E.coli

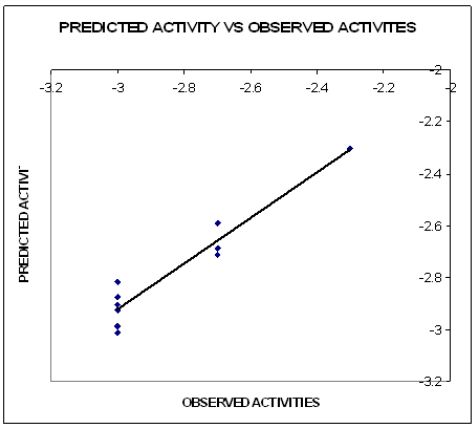

Figure 6
Trend line graph between Observed Vs. MNDO Predicted activity – E1-E10 compounds / A.niger

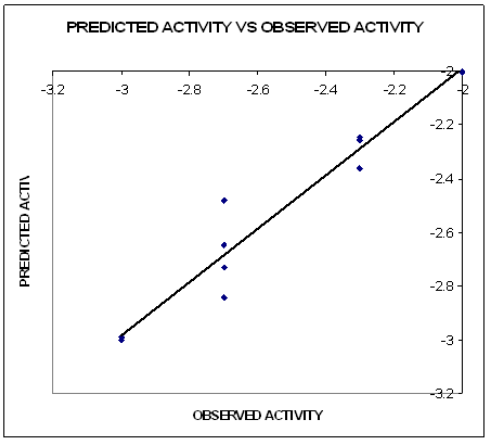

Figure 7
Trend line graph between Observed Vs. MNDO Predicted activity – E1-E10 compounds / E.coli

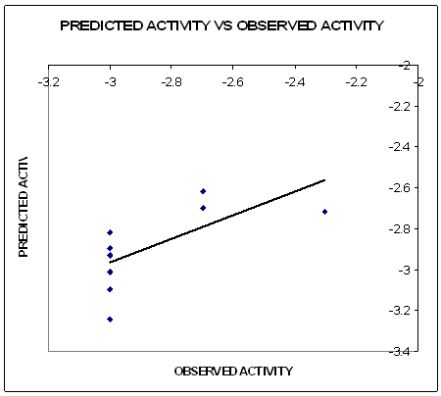

Figure 8
Trend line graph between Observed Vs. ZINDO Predicted activity – E1-E10 compounds / A.niger

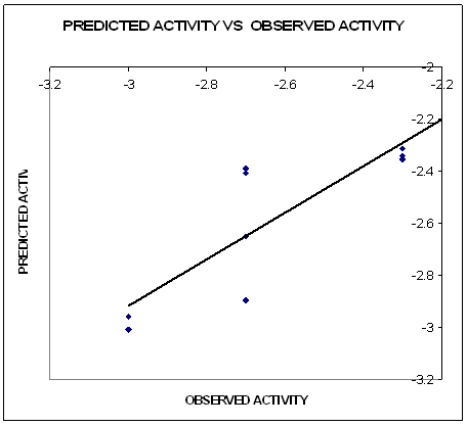

Figure 9
Trend line graph between Observed Vs. ZINDO Predicted activity – E1-E10 compounds / E.coli

Table 3
AM1 computed properties /QSAR descriptors of Compounds (E1- E10) under study

Compd	HYD.E	Log p	REF	polar	Mass	SAA	SAG	VOL	HF (kCal/mol)	ZPE (kCal/ mol)	HOMO	LUMO	DM (D)
E1	-5.82	2.44	115.4	40.47	338.4	502.6	602.5	1026.5	193.262	225.420	-0.3448	0.10923	1.995
E2	-5.47	2.22	120.2	42.4	372.8	538.6	629.6	1070.4	186.523	219.550	-0.1235	0.21952	1.796
E3	-4.93	1.99	124.4	44.33	407.3	556.4	637.4	1100.7	184.739	213.653	-0.4056	0.21072	2.538
E4	-4.62	2.54	119.7	42.31	352.4	547.5	634.2	1080.3	185.265	242.731	-0.3494	0.15727	2.298
E5	-7.50	1.45	121.8	42.95	368.4	562.9	646.7	1104.4	155.396	246.270	-0.3182	0.03436	3.366
E6	-8.63	1.41	117.0	41.11	354.4	499.8	612.7	1043.8	154.559	228.210	-0.3351	0.00369	2.979
E7	-12.4	1.41	117.0	41.11	354.4	517.9	616.0	1048.6	149.581	228.251	-0.3896	0.08907	3.139
E8	-12.7	1.41	117.0	41.11	354.4	518.4	615.9	1048.9	149.242	228.246	-0.0495	0.29065	2.994
E9	-20.4	1.22	122.3	43.10	385.4	556.6	652.8	1111.7	169.073	241.661	-0.0709	0.28841	1.955
E10	-20.9	1.22	122.3	43.10	385.4	556.0	653.8	1111.6	168.457	241.665	-0.7528	0.01040	2.498

Table 4
PM3 computed properties /QSAR descriptors of Compounds (E1- E10) under study

Compd	HYD.E	Log p	REF	polar	Mass	SAA	SAG	VOL	HF (kCal/mol)	ZPE (kCal/mol)	HOMO	LUMO	DM (D)
E1	-5.69	2.44	115.4	40.47	338.4	499.0	600.5	1019.3	146.914	217.327	-0.0341	0.2239	2.857
E2	-5.33	2.22	120.2	42.40	372.8	534.2	625.7	1062.7	140.582	211.577	-0.0669	0.1462	2.637
E3	-4.78	1.99	124.9	44.33	407.3	550.8	636.9	1091.7	137.302	206.089	-0.0742	0.1289	2.967
E4	-4.48	2.59	119.7	42.31	352.4	542.7	629.2	1071.8	137.389	234.751	-0.0213	0.2361	3.093
E5	-7.33	1.45	121.8	42.95	368.4	558.0	643.3	1096.3	108.811	237.432	-0.0173	0.2509	4.124
E6	-8.56	1.41	117.0	41.11	354.4	496.1	606.4	1036.1	107.036	220.965	-0.1181	0.0183	3.142
E7	-12.42	1.41	117.0	41.11	354.4	513.4	613.0	1040.6	102.274	220.788	-0.0321	0.2281	3.862
E8	-12.55	1.41	117.0	41.11	354.4	513.7	612.0	1041.7	101.847	220.789	-0.0263	0.2342	3.977
E9	-21.91	1.22	122.3	43.10	385.4	536.9	649.4	1106.9	127.832	232.851	-0.0498	0.1911	3.011
E10	-22.32	-1.22	122.3	43.10	385.4	557.1	650.7	1106.7	127.573	232.692	-0.0385	0.1901	3.239

Table 5
MNDO computed properties /QSAR descriptors of Compounds (E1- E10) under study

Compd	HYD.E	Log p	REF	polar	Mass	SAA	SAG	VOL	HF (kCal /mol)	ZPE (kCal/mol)	HOMO	LUMO	DM (D)
E1	-5.86	2.44	115.4	40.47	338.4	510.1	609.9	1033.1	151.3013	230.459	-0.0094	0.1141	1.956
E2	-5.53	2.22	120.2	42.4	372.8	547.6	639.4	1079.2	143.8540	224.304	-0.3280	0.0382	1.888
E3	-5.62	1.99	124.9	44.33	407.3	574.7	691.1	1152.0	125.7192	218.557	-0.1165	0.0382	1.618
E4	-4.65	2.59	119.7	42.31	352.4	555.2	644.0	1088.6	143.1313	248.508	-0.4149	0.0088	1.965
E5	-7.83	1.45	121.8	42.95	368.4	571.2	692.9	1151.0	97.9760	252.376	-0.1074	0.0844	2.501
E6	-8.47	1.41	117.0	41.11	354.4	507.8	619.7	1051.3	108.6003	233.624	-0.1229	0.1645	3.001
E7	-12.68	1.41	117.0	41.11	354.4	522.3	655.9	1087.7	89.8851	234.299	-0.0172	0.1099	1.961
E8	-12.72	1.41	117.0	41.11	354.4	526.5	626.4	1056.1	103.1823	233.826	-0.1356	0.1160	2.975
E9	-21.74	1.22	122.3	43.10	385.4	571.1	691.6	1154.9	108.1479	248.680	-0.1058	0.05222	1.201
E10	-21.92	1.22	122.3	43.10	385.4	556.0	653.8	1111.6	106.3883	248.706	-0.0506	0.07150	1.201

Table 6
ZINDO computed properties /QSAR descriptors of Compounds (E1- E10) under study

Compd	HYD.E	Log p	REF	polar	Mass	SAA	SAG	VOL	HF (kCal/ mol)	ZPE (kCal/mol)	HOMO	LUMO	DM (D)
E1	-4.26	2.44	115.4	40.4	338.4	421.7	575.8	977.43	10147.38	306.43	-3.3308	4.7229	7.255
E2	-5.10	2.22	120.2	42.4	372.8	52.0	622.1	1058.0	10083.44	297.99	-6.4405	5.7524	5.638
E3	-3.43	1.99	124.9	44.3	407.3	469.4	625.6	1060.8	10207.73	291.40	-6.3312	5.8534	8.778
E4	-4.24	2.59	119.7	42.3	352.4	532.8	623.5	1065.5	10622.03	330.23	-6.0590	6.1045	3.353
E5	-8.27	1.45	121.8	42.95	368.4	557.2	665.8	1107.2	10747.01	334.42	-5.9857	6.3585	2.161
E6	-3.34	1.41	117.0	41.11	354.4	411.5	590.8	1011.3	10318.82	311.93	-3.9144	5.4422	4.699
E7	-12.02	1.41	117.0	41.11	354.4	502.9	618.3	1051.4	10204.94	309.47	-6.4244	6.1035	3.993
E8	-11.13	1.41	117.0	41.11	354.4	437.4	588.7	999.73	10285.67	309.92	-3.3267	4.7533	6.279
E9	-17.77	-1.22	122.3	43.1	385.4	466.7	637.4	1072.5	10840.31	329.88	-6.0091	6.4703	3.815
E10	-18.26	-1.22	122.3	43.1	385.4	469.7	635.1	1072.7	10815.97	330.00	-4.9475	6.4178	1.946

CONCLUSIONS

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/*A. Niger:* log P, HOMO and DM
AM1/E1- E10/*E.coli:* Hyd. E, log P and DM
PM3/E1- E10/*A. Niger:* Hyd. E, log P and DM
PM3/E1- E10/*E.coli:* Hyd. E, log P and DM
MNDO/E1- E10/*A. Niger:* log P, HOMO and DM
MNDO/E1- E10/*E.Coli:* log P, LUMO and DM
ZINDO/E1- E10/*A. Niger:* log P, LUMO and DM
ZINDO/E1- E10/*E.coli:* Hyd. E, log P and LUMO

This may be concluded that semi-empirical quantum chemically calculated parameters listed above may be considered as positive descriptors to p(MIC). On this basis one may conclude that if compounds of the same series with altered values of above parameters with some different substitution are prepared and checked against the antimicrobial activities of the pathogens stated above, will prove to be more effective.

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