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Research Article

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3D-QSAR studies for some pyrazolones against a pathogen

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ABSTRACT

3D QSAR viz. 3 descriptor quantitative structure and activity relationship studies for a series of compounds i.e. pyrazolone derivatives using their semi-empirical quantum chemical descriptors and their laboratory reported activities against a pathogen viz. .Ralstonia solanacearum (ITCC – B1-0002) have been carried out and reported in the present paper. Graphs between observed and predicted activities, both in the terms of p(MIC)cal and p(MIC)obs. are also being reported on the basis of which this may be concluded that some parameters/descriptors effect towards the activity. The method has been proved to be useful tool for such type of studies.

Key words: Semiempirical, 3D-qsar, *Ralstonia solanacearum*, Pyrazolone compounds

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INTRODUCTION

Medicinal chemists are trying out their best to speed up the drug discovery process for finding the lead molecule by using different techniques which includes QSAR (Quantitative Structure and Activity Relationship), 3D-QSAR, CADD (Computer Aided Drug Design), Molecular Modeling, Combinatorial Chemistry and Microwave assisted synthesis. The use of these techniques has reduced the time required for primary screening of the molecule to locate the lead molecule.

QSAR (Quantitative Structure and Activity Relationship) technique has been developed as a recent and finest technique in the field of drug designing. This technique has its foundation on the statistical analysis particular regression analysis of structural descriptors of compounds under studies with their lab. reported activities. In some of the recent references scientists have even utilized electronic properties or parameters of compounds/ drugs computed on the basis of Quantum Chemical Calculation viz. *ab initio* or semi-empirical studies as descriptors for QSAR studies and correlated these descriptors with activities of the compounds against a certain micro-organism, which has been proved as a step ahead in the related field.

Pyrazoles refer to the class of compounds which are heterocyclic compounds characterized by 5-membered ring structure composed of three carbon and two nitrogen atoms in the adjacent position to the two nitrogen atoms, one is basic and second is neutral nitrogen, the aromatic nature arises from the four electrons and the unshared pair of electrons on the NH nitrogen. Pyrazoles derivative have a long history of application in agrochemicals as herbicides and insecticides and in pharmaceutical industry as antipyretic anti anti-inflammatory. Due to wide range of biological activity, pyrazoles have received a considerable interest in the field of drug discovery and therefore, pyrazole ring constitutes a relevant synthetic target in pharmaceutical industry. In fact such a heterocyclic moiety represents the core structure of a number of drugs.

Literature survey carried out in the proposed field (1-29) revealed that on one side the workers/ scientists have tried many naturally occurring and synthetic compounds to check their activities against various microorganisms while on the other QSAR studies of various series of compounds have also been carried out successfully. Some of the workers have also tried to correlate activities with 2 descriptors and 3 descriptors of the compounds pertaining to 2D- QSAR and even 3D- QSAR studies(1-25).

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. pyrazolone compounds shown in figure 1 with their activities against *Ralstonia solanacearum* (ITCC – B1-0002) are reported.

EXPERIMENTAL SECTION

Preparation of pyrazolone compounds:-

Some of the Pyrazolone compounds were prepared in the laboratory while some were obtained from standard sources as E Merck, C.D.H. and B.D.H. etc. and were used as such for further work. Processes of synthesis of synthesized pyrazolones are given below:-

3- Methyl -5- pyrazolone (MeP):-

Hydrazine hydrate (50%solution, approx. 4 ml) was taken in a beaker with diethyl ether (20 ml) and ethyl acetoacetate (8 ml) was added to it drop wise in order to avoid the vigorous reaction. White crystalline solid separated out within one minute. It was then filtered and washed with diethyl ether, 3 to 4 times. On exposing to air surface oxidation of the compound may take place and compound becomes pink (yield ~95%).

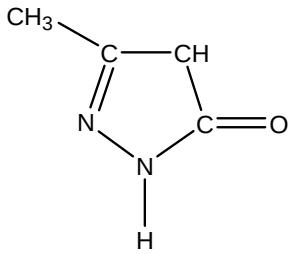
3- Methyl-4-Nitroso-5- pyrazolone (MNP):-

Above procured pyrazolone (2g) was dissolved in minimum amount of (1:1) acetic acid in a conical flask. This was then kept in an ice bath for about 15 minutes, so that the temperature of the solution was brought down to 10^0C. Solid sodium nitrite (4g) was added in portions to this solution. Precipitate was obtained immediately but the reaction mixture was kept in the ice bath with stirring for 1 hour. The product was then filtered and washed with dilute acetic acid followed by water and was re- crystallized from (1:1) aq. Methyl alcohol and yellow product was obtained(yield ~70%).

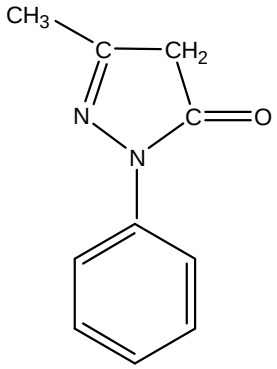
3- Methyl- 1-(2,4-di nitrophenyl)-5-pyrazolone:-

A mixture of phenyl hydrazine/ 2,4-dinitrophenyl hydrazine (0.01 mol) and thylacetoacetate (0.01 mol) were taken in absolute alcohol (30 mL) and refluxed for 12 hrs. After completion of the reaction, excess of solvent was distilled off and the resultant residue was poured on crushed ice to obtain the yellow/ orange long needle shaped crystals. Solids precipitated were filtered and re-crystallized using ethanol (yield~70%).

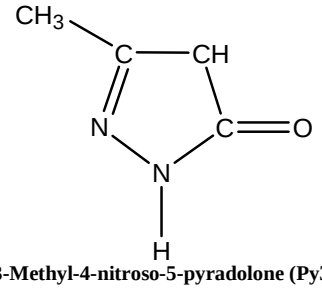
Compounds i.e. pyrazolones (Py1-Py7) are shown in the figure 1. Analytical studies were also carried out for the synthesized pyrazolone compounds under study. These are given in the tables 1 along with their melting points.



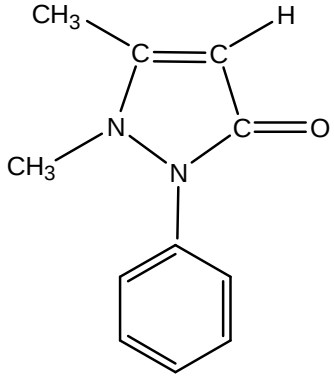
3-methyl-5-pyrazolone (PY1)



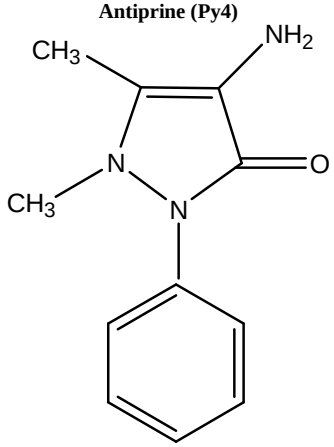
3-Methyl-l-phenyl-5-Pyrazolone (PY2)



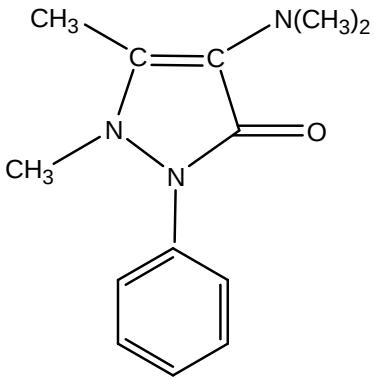
3-Methyl-4-nitroso-5-pyradolone (Py3)



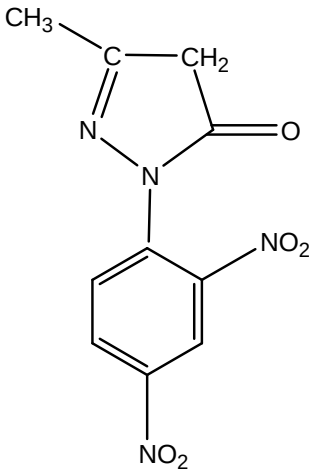
Antiprine (Py4)



4-Aminoantipyrine (PY5)



Amino Pyrine (Py6)



3-Methyl – 1 (2,4-dinitrophenyl)5-pyrazolone (Py7)

Figure-1: Pyrazolone Compounds under study

Table 1:- Analytical studies for the Pyrazolone compounds under study

Compound	M. Pt. (^{0}C)	C Found (Calcd.)	H Found (Calcd.)	N Found (Calcd.)
Py-1	224-226	49.85 (49%)	6.04 (5.1%)	28.20 (28.8%)
PY-2	124-126	71.59 (69%)	5.65 (5.7%)	16.32 (16.0%)
PY-3	229-231	39.88 (42.0%)	2.899 (4.0%)	32.97 (33.0%)
PY-4	110-115	71.50 (70.2%)	6.43 (6.3%)	14.73 (14.8%)
PY-5	105-110	66.97 (65.0%)	6.32 (6.4%)	19.64 (20.69%)
PY-6	107-108	67.59 (67.5%)	7.24 (7.3%)	17.52 (18.1%)
PY-7	81-88	57.49 (48.0%)	6.35 (4.9%)	20.04 (20.0%)

These compounds were also established on the basis of modern spectroscopic studies viz. i.r. spectral studies. N.M.R. spectral and Mass spectral studies for some of the representative compounds were also carried out. Analysis of the studies is given below:-

I.R. spectral studies:-
Assignments of peaks are given in the table -2 for pyrazolone compounds. I.R. spectral analysis shows that (C=O) Stretching is the predominant peak in the case of pyrazolone compounds under study. It appears ca 1660-1610 cm^{-1}. Apart from these peaks some other notable peaks are ring stretching of 5 membered ring, Ring stretching, CH out of plane deformation of pyrazolone ring, C=O in plane bending and out of plane bending etc. These are reported in the table 2.

NMR spectral studies:-
NMR spectral studies are of less interest for the compounds under study. However, these spectra were also recorded for some representative compounds on NMR spectrometer Bruker DRX-300 with due acknowledgement to C.D.R.I. Lucknow. Some notable peaks in these spectra are listed below:-

Py1: 1.150-1.105 (t);2.430-2.011 (q); 3.997-3.974 (d);5.140-(s);6.005 (s); 10.277(s).

Py2:- 2.110 (s); 2.500 (s); 3.329 (s); 3.327-3.696 (d); 5.349 (s); 7.817-7.174 (multiplet).

Py5:-2.083 (S); 2.723-2.489(d); 3.333(s); 3.842 (s); 7.4445-7.219 (q).

MASS spectral studies:-
Mass spectral studies of some representative Schiff base compounds have been carried out. Notable peaks in different compounds are:- base peaks at , Py-1:- 79, Py-2 :-175, Py-3:- 127 and Py-5:-203 with parent ion peaks at Py-1:- 98, Py-2 :-174, Py-3:- 127 and Py-5:-203.. These parent peaks confirm the mol. weights of the compounds under study

Antimicrobial activities of the compounds under study:-
Procurement of pathogen:-ITCC certified Pathogen viz. *Ralstonia solanacearum* (ITCC – B1-0002) was procured from plant pathology division, I.A.R.I., New Delhi with due acknowledgement. Their sub- cultures have been made and the anti-microbial studies of the compounds under study were carried out against these pathogens at Birla Institute of Professional Studies with due acknowledgements. MIC (minimum inhibitory concentration) have been recorded which is then subjected to further studies to get QSAR equations. Experimental procedures that have been adopted for anti microbial studies are mentioned below:

Experimental procedure for Anti bacterial studies:-
Pure cultures that were obtained from IARI were revived. Fresh inoculation of *Ralstonia solanacearum* was done by taking a loopful from IARI culture tube and streaking was done on sterile nutrient agar petri plate and slant and incubated at 28^0c for 48 hrs to revive the culture. After 48 hrs on revival of test organism, a loopful this has been taken and dispensed in 50 mL of medium in a conical flask and kept for further 48 hrs for the preparation of inoculum. Culture media were autoclaved at 121^0c for 15 lbs pressure for 15 minutes. Plates were made by dispensing the media approx 15-20 mL in each plate. Plates were kept inverted in the incubator at 28^0c overnight for sterility checking. Whatmann 1 filter paper discs of 6 mm diameter were punched out from barge sheet and were autoclaved for 15 minutes. About 100µL of actively growing pathogen inoculated nutrient broth was used to inoculate sterile nutrient agar plates through spread plate method. The whatmann paper discs were dispensed on glass plates and each was loaded with about 5 µL. Volume of pre designated dilutions were used for analysis. The discs were left air dried in the laminar air flow and were then carefully transferred to inoculated positions. The plates were then inoculated at 28^0c for 48 minimum hrs.

Table-3:-Antibacterial analysis of pyrazolone compounds under study against *Ralstonia solanacearum* (ITCC NO –B1- 0002)

Compounds under study	Concentrations Of compounds/10 ml			
	10 mg	20 mg	30 mg	40 mg
PY1	34mm	38 mm	-------	-----
PY2	-------	----------	-------	03 mm
PY3	--------	----------	-------	02 mm
PY4	--------	----------	13 mm	14 mm
PY5	--------	29 mm	30 mm	31 mm
PY6	--------	28 mm	16 mm	22 mm
PY7	--------	----------	15 mm	30 mm

Computational Details for the computational work:-
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 (™) 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

The *in-vitro* anti bacterial studies of the pyrazolone compounds were carried out as per experimental procedure mentioned in the experimental section at Birla Institute of Professional Studies, Gwalior with due acknowledgement. The activities of the compounds were recorded in terms of Minimum Inhibitory Concentration (MIC). Some of the compounds have shown notable activities against the specified pathogen under study while other do not show any activity. The activities are recorded and reported here in the table 3. Photographs of some of the plates were also taken showing growth of the pathogens, (figure 2).

The lab. reported activities of the pyrazolone compounds under study in terms of p(MIC) have been subjected to QSAR studies with Semi-empirical quantum chemical based certain parameters of the compounds. These parameters/ descriptors are hydration energy (HE), logP (logP), Refractivity(RF), Polarizaility (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).

These parameters are computed on HYPERCHEM 8.0 version software after geometry optimization of the compounds under study as mentioned in the experimental section above. The computed parameters/ descriptors are reported in the tables 4-7. The correlation matrices are also computed using Excel software and are reported in tables 8-11.

The methods adopted here in this project are AM1, PM3, MNDO and ZINDO respectively. All methods are proved to be good to give optimized geometry and minimized energy for the compounds under study. This fact can also be proved as IR studies which are observed experimentally for the compounds under study match well with the computed IR spectral frequencies using Hyperchem 8.0 professional software especially on the basis of AM1 and PM3 method. The fact of authenticity of AM1 and PM3 may prove to be appropriate in this study, so far as software is concerned (26-33).

Table-4 : Semi- Empirical AM1 based Computed properties of the Compounds (Py1-Py7) under study and their antibacterial results p(MIC) on *Ralstonia solanacearum* (ITCC NO –B1- 0002)

Compd	MIC	P(MIC)Obs.	SAA	SAG	HE	Log P	RF
Py-1	50	-1.699	231.64	256.11	-5.19	0.2	24.82
Py-2	50	-1.699	310.59	365.51	-2.13	0.94	54.3
Py-3	50	-1.699	258.75	274.11	-11.31	0.17	29.75
Py-4	50	-1.699	339.82	385.49	-1.84	-0.4	61.23
Py-5	25	-1.3979	336.88	399.17	-6.51	-1.99	64.85
Py-6	15	-1.1761	448.38	474.55	-1.58	-1.22	74.92
Py-7	20	-1.301	393.51	449.94	-10.14	-2.03	73.66

POL	Mass	VOL	HF	ZPE	HOMO	LUMO	DM
9.71	98.1	351.97	4.99398	64.831	-9.5347	0.19945	2.617
19.37	174.2	565.04	44.6349	117.65	-8.6403	0.09622	2.781
10.92	127.1	391.94	19.26134	641.09	-0.1633	0.8305	2.298
21.4	188.23	608.04	63.6532	135.458	-0.1844	0.48155	4.438
22.78	203.24	640.43	60.5788	161.421	-0.0912	0.4694	3.423
26.45	231.3	770.61	73.3708	179.1184	-0.04307	0.44813	10.224
24.86	278.22	730.57	146.1111	139.8278	-0.1687	0.1007	10.819

The software Hyperchem 8.0 version was quite fast and provides reasonably good results regarding all parameters viz. physical parameters, spectroscopic parameters and SAR related parameters.

Table-5 : Semi- Empirical PM3 based Computed properties of the Compounds (Py1-Py7) under study and their antibacterial results p(MIC) on *Ralstonia solanacearum* (ITCC NO –B1- 0002)

Compd	MIC	P(MIC)Obs.	SAA	SAG	HE	Log P	RF
Py-1	50	-1.699	231.61	253.25	-5.27	0.2	24.82
Py-2	50	-1.699	311.61	367.05	-2.12	0.94	54.3
Py-3	50	-1.699	260.44	275.75	-11.48	0.17	29.75
Py-4	50	-1.699	341.81	393.51	-1.85	-0.4	61.23
Py-5	25	-1.3979	338.91	403.98	-6.64	-1.99	64.85
Py-6	15	-1.1761	450.08	479.24	-1.53	-1.22	74.92
Py-7	20	-1.301	392.41	453.99	-10.28	-2.03	73.66

POL	Mass	VOL	HF	ZPE	HOMO	LUMO	DM
9.71	98.1	349.99	10.0348	61.83218	-0.0272	1.0386	2.46
19.37	174.2	565.41	20.69754	112.6618	-0.1096	0.1388	2.607
10.92	127.1	392.83	11.62258	61.7474	-0.3937	0.3769	2.112
21.43	188.23	613.4	22.7265	130.4475	-0.2538	0.2318	4.053
22..78	203.24	644.42	21.3358	141.3387	-0.2158	0.2368	3.336
26.45	231.3	770.89	51.0475	173.459	-0.0148	1.1074	10857
24.36	278.22	737.64	1.2.26173	133.1422	-0.2813	0.04362	10.665

Table-6 : Semi- Empirical MNDO based Computed properties of the Compounds (Py1-Py7) under study and their antibacterial results p(MIC) on *Ralstonia solanacearum* (ITCC NO –B1- 0002)

Compd	MIC	P(MIC)Obs.	SAA	SAG	HE	Log P	RF
Py-1	50	-1.699	231.86	255.82	-5.15	0.2	24.82
Py-2	50	-1.699	312.51	367.73	-2.01	0.94	54.3
Py-3	50	-1.699	260.81	278.31	-11.36	0.17	29.75
Py-4	50	-1.699	340.57	398.37	-1.84	-0.4	61.23
Py-5	25	-1.3979	339.38	414.33	-6.4	-1.99	64.85
Py-6	15	-1.1761	454.12	483.23	-1.58	-1.22	74.92
Py-7	20	-1.301	386.92	458.83	-9.7	-2.03	73.66

POL	Mass	VOL	HF	ZPE	HOMO	LUMO	DM
9.71	98.1	352.87	18.9028	67.243	-9.7772	0.0215	2.153
19.37	174.2	569.02	16.0375	121.0237	-0.0345	0.14629	2.261
10.92	127.1	395.23	7.4868	66.9777	-0.3169	0.6199	1.963
21.43	188.23	621.48	28.7572	139.841	-0.2134	0.1405	3.706
22.78	203.24	658.47	28.6354	151.104	-0.2951	0.0574	2.868
26.45	231.3	784.55	70.6098	184.9554	-0.4308	0.36126	10.653
24.86	278.22	753.34	118.9328	143.7598	-0.07829	0.01692	9.536

Table-7 : Semi- Empirical ZINDO based Computed properties of the Compounds (Py1-Py7) under study and their antibacterial results p(MIC) on *Ralstonia solanacearum* (ITCC NO –B1- 0002)

Compd	MIC	P(MIC)Obs.	SAA	SAG	HE	Log P	RF
Py-1	50	-1.699	231.39	252.79	-5.33	0.2	24.82
Py-2	50	-1.699	306.03	360.91	-2.13	0.94	54.3
Py-3	50	-1.699	229.25	264.75	-7.42	0.17	29.75
Py-4	50	-1.699	333.51	377.65	-1.85	-0.4	61.23
Py-5	25	-1.3979	332.91	392.87	-6.54	-1.99	64.85
Py-6	15	-1.1761	368.17	438.18	-4.37	-1.22	74.92
Py-7	20	-1.301	393.59	427.05	-10.08	-2.03	73.66

POL	Mass	VOL	HF	ZPE	HOMO	LUMO	DM
9.71	98.1	349.67	-2425.099	89.403	-6.7886	6.9301	3.918
19.37	174.2	557.74	-4915.264	160.01	-6.063	6.84	4.398
10.92	127.1	372.98	-2738.509	89.95	-6.8543	6.1565	6.832
21.43	188.23	592.26	-5450.551	184.983	-5.8917	6.6588	7.057
22.78	717.28	626.64	-5727.0466	199.149	-5.5803	6.6033	5.953
26.45	231.3	717.28	-6723.9806	248.19	-5.3664	7.3694	7.905
24.86	278.22	689.05	-6433.8554	193.0471	-3.2596	4.1054	19.919

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

AM1/Pyrazolones compounds (Py1-Py7)/Antibacterial *Ralstonia solanacearum* (ITCC NO –B1- 0002) **/3D-equation**

P(MIC) = -0.008249159(SAG)+0.004708556(VOL)+0.039448387(DM)-1.390975381
N = 7, SD = 0.14823059, r = 0.886988475, F test = 3.68929998

PM3/Pyrazolones compounds (Py1-Py7)/Antibacterial *Ralstonia solanacearum* (ITCC NO –B1- 0002) **/3D-equation**

P(MIC) = -0.05576(SAG)+0.025894(VOL)+0.010351(SAA)+0.887878
N = 7, SD = 0.0839842, r = 0.9651652, F test = 13.60791163

MNDO/Pyrazolones compounds (Py1-Py7)/Antibacterial *Ralstonia solanacearum* (ITCC NO –B1- 0002 **/3D-equation**

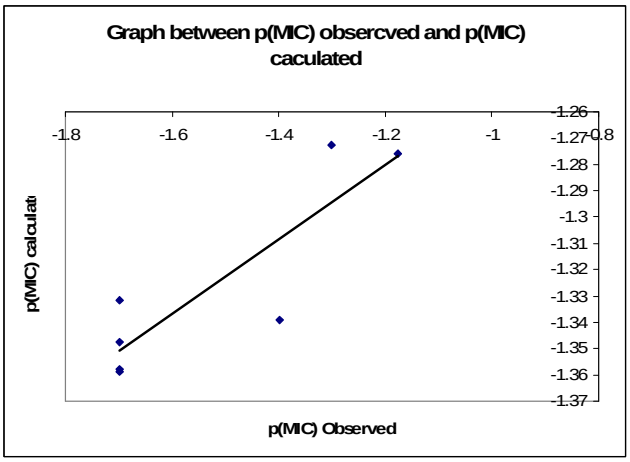
P(MIC) = -0.083211294(LogP)-0.090069921(POL)+0.015433871(ZPE)-1.761162134
N = 7, SD = 0.139293742, R = 0.900936838, F test = 4.31013

ZINDO/Pyrazolones compounds (Py1-Py7)/Antibacterial *Ralstonia solanacearum* (ITCC NO –B1- 0002 **/3D-equation**

P(MIC) = -0.076530237(POL)+0.000604852(MASS)+0.010056714(ZPE)-1.872914629
N = 7, SD = 0.097346524, r = 0.952904817, F test = 9.872825978

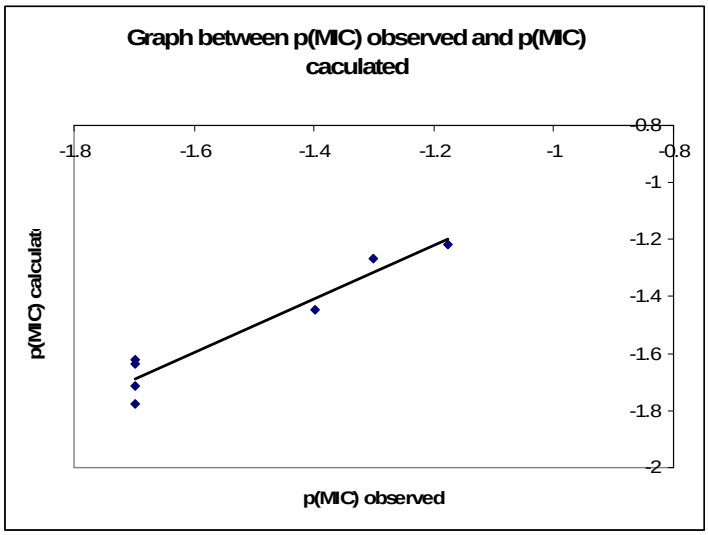
Graphs were also drawn between observed activities and predicted activities, both in the terms of p(MIC) form 3 D-QSAR equations for this series of compounds. These trend line graphs are shown in figure 3-6.

Figure -3 Trend line Graph between p(MIC) observed and AM1 computed p(MIC) calculated for the pyrazolone compounds (Py1-Py7)under study for their antibacterial activities on *Ralstonia solanacearum* (ITCC NO –B1- 0002



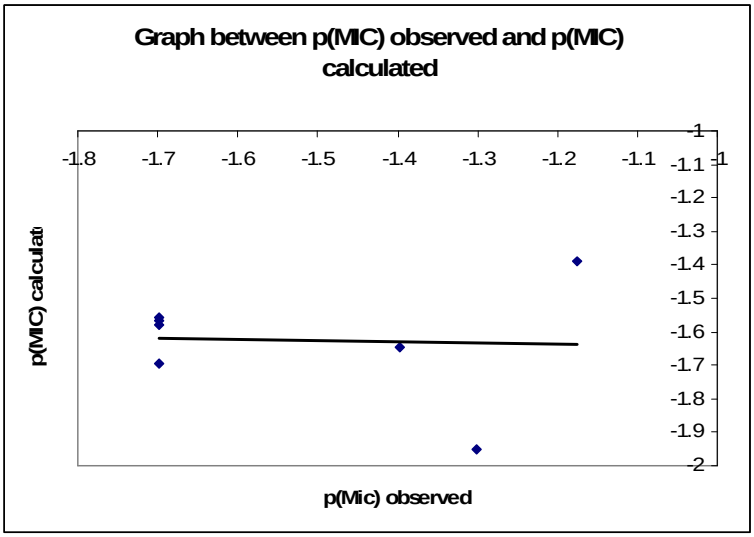
p(MIC) Observed	p(MIC) calculated
-1.699	-1.358
-1.699	-1.347
-1.699	-1.359
-1.699	-1.332
-1.398	-1.339
-1.176	-1.276
-1.301	-1.273

Figure 4 Trend line Graph between p(MIC) observed and PM3 computed p(MIC) calculated for the pyrazolone compounds (Py1-Py7)under study for their antibacterial activities on *Ralstonia solanacearum* (ITCC NO –B1- 0002)



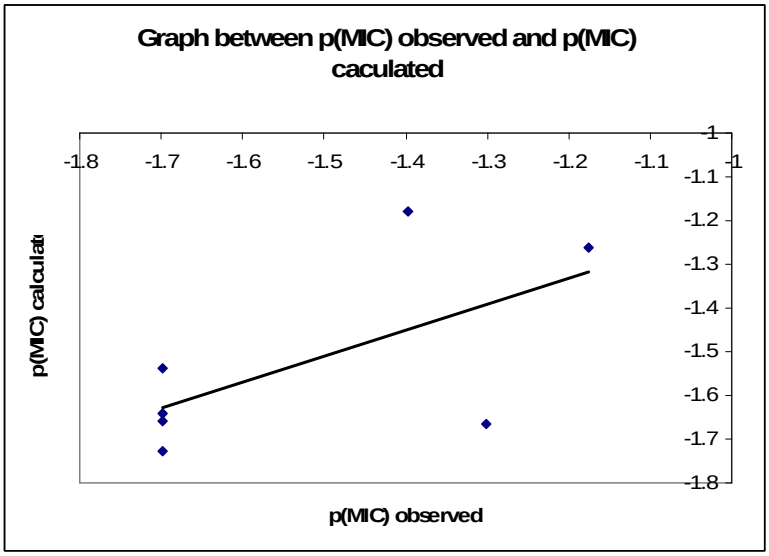
p(MIC) Observed	p(MIC) calculated
-1.699	-1.774
-1.699	-1.714
-1.699	-1.621
-1.699	-1.634
-1.398	-1.445
-1.176	-1.216
-1.301	-1.266

Figure -5 Trend line Graph between p(MIC) observed and MNDO computed p(MIC) calculated for the pyrazolone compounds (Py1-Py7)under study for their antibacterial activities on *Ralstonia solanacearum* (ITCC NO –B1- 0002)



p(MIC) Observed	p(MIC) calculated
-1.699	-1.581
-1.699	-1.56
-1.699	-1.697
-1.699	-1.566
-1.398	-1.646
-1.176	-1.39
-1.301	-1.95

Figure -6 Trend line Graph between p(MIC) observed and ZINDO computed p(MIC) calculated for the pyrazolone compounds (Py1-Py7)under study for their antibacterial activities on *Ralstonia solanacearum* (ITCC NO –B1- 0002 **)**



p(MIC) Observed	p(MIC) calculated
-1.699	-1.658
-1.699	-1.641
-1.699	-1.727
-1.699	-1.539
-1.398	-1.18
-1.176	-1.261
-1.301	-1.666

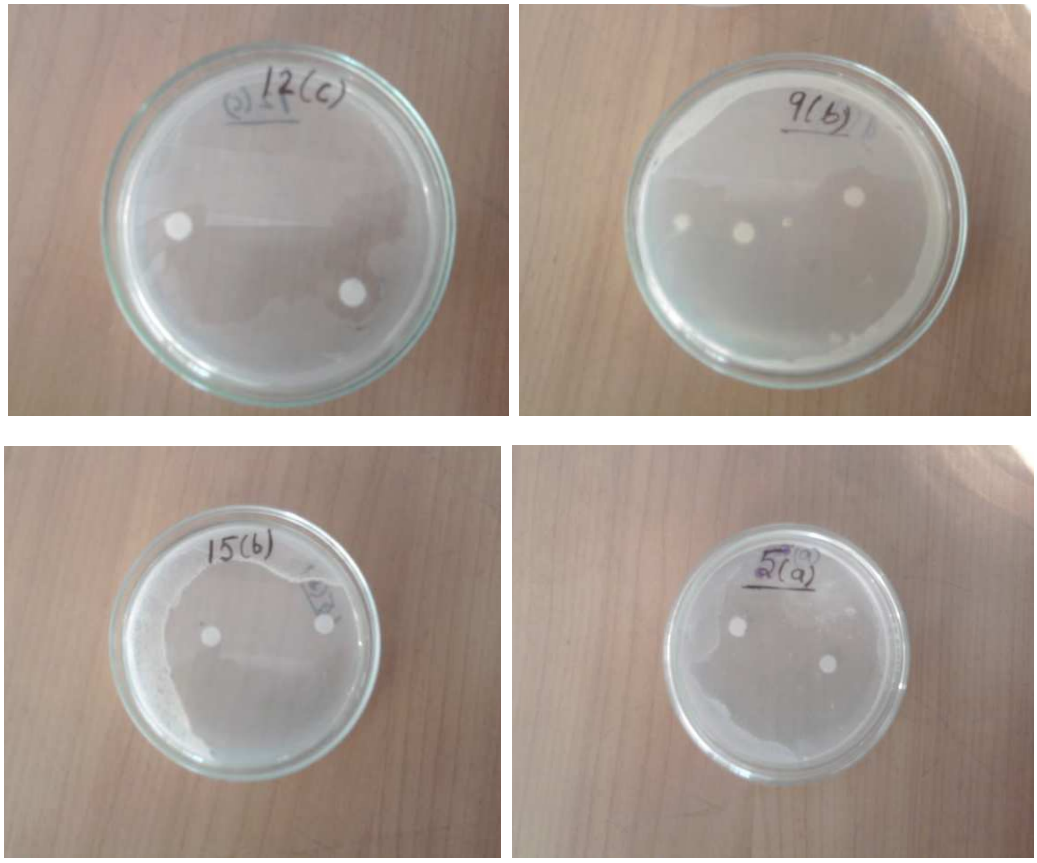


Figure 2 : Some notable photographs for anti bacterial studies of compounds under study

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/ Pyrazolones (Py1-Py7)/ *Ralstonia solanacearum* (ITCC NO –B1- 0002) **: -** SAG, VOL and DM
PM3/ Pyrazolones (Py1-Py7)/ *Ralstonia solanacearum* (ITCC NO –B1- 0002) **: -** SAG, VOL and SAA
MNDO/ Pyrazolones (Py1-Py7)/ *Ralstonia solanacearum* (ITCC NO –B1- 0002) **: -** Log P, POL and ZPE
ZINDO/ Pyrazolones (Py1-Py7)/ *Ralstonia solanacearum* (ITCC NO –B1- 0002) **: -** POL, MASS and ZPE

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

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