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Anti-Microbial and QSAR Studies of Some Pyrazolone Compounds

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ABSTRACT

Some novel synthetic pyrazolone compounds were evaluated for their *in-vitro* antimicrobial activity viz. antifungal activity against *Gibberella fujikuroi*. The compounds were characterized by elemental and spectral analysis. Quantitative Structure Activity Relationship (QSAR) studies were applied to find correlation between different calculated molecular descriptors of the synthesized compounds and biological activity. Four compounds viz. 3-Methyl-4-nitroso-5-pyrazolone (C-6), 4-Amino antipyrine thiosemicarbazone (C-8), 1-(2-Chloro-5-sulfophenyl)-3-methyl-5-pyrazolone (C-9) and 1-(4-Sulfoamidophenyl)-3-methyl-5-pyrazolone (C-10) showed significant activity against *Gibberella fujikuroi.*

Keywords: Antimicrobial activity, *Gibberella fujikuroi,* Pyrazolones, QSAR study.

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INTRODUCTION

The emergence and speed of antimicrobial resistance has become one of the most serious public health concerns across the world. Antimicrobial resistance refers to micro-organism that have developed the ability to inactivate, exclude or block the inhibitory or lethal mechanism of the antimicrobial agents [1-4]. Pyrazolone compounds constitute an important class heterocyclic aromatic organic compound for their versatile pharmacological activities such as anti-bacterial, anti-fungal, antihelmintic and anti-inflammatory.

The Quantitative Structure Activity Relationship (QSAR) is a mathematical model relating measured biological activity of series of structurally related compounds / pharmacological agents to the variation in their chemical structure [5].

In the present study QSAR analysis of selected ten pyrazolone compounds with antimicrobial activity viz. antifungal activity against *Gibberella fujikuroi* were performed. It appears to be interesting to perform QSAR analysis using Hyperchem 8.0 professional version software to correlate lab reported activities with computed activities for the design of some pyrazolone compounds.

EXPERIMENTAL

Selected compounds:

Ten pyrazolone compounds were selected for study. Structures of pyrazolone compounds under study were constructed using Hyperchem 8.0 professional version of software. Structures of these compounds are mentioned in **Table-1**. Compounds were characterized by elemental analysis and spectral studies [6].

Test organism:

All the synthesized compounds were screened for their antifungal activity against *Sclerotium rolfsii* by paper disc diffusion techniques [7-11] and were procured from ITCC, Division of Plant Pathology, Indian Agriculture Research Institute (IARI), New Delhi.

Preparation of Petri-plates and Media:

A well known media Potato Dextrose Agar (PDA) and Potato Dextrose Broth (PDB) were autoclaved at 121^{o}c for 15 lbs pressure for 15 min. Media were cooled and then plates were prepared by dispensing 15-20 mL medium per plate. Plates were kept in the same position for 0.5 h to solidify media and kept inverted in the incubator at 28^{o}c overnight for sterility checking.

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Inoculation and Incubation:

100 µL of test organism was used to inoculate sterile Potato Dextrose Agar plate by spread plate swab method. Whatmann paper discs were dispensed on glass plates and each was loaded with 5 µL volume of pre-designated dilution. The discs were left air dried in the laminar air flow and were then carefully transferred to inoculated plates at pre-designated positions. The plates were then incubated at 28^{o}c for 48 hrs.

RESULTS AND DISCUSSION

Antifungal activity:

Ten pyrazolone compounds viz. C-1 to C-10 as listed in **Table-1**, were tested for antifungal activity against *Gibberella fujikuroi.* Out of ten compounds, four compounds, 3-Methyl-4-nitroso-5-pyrazolone (C-6), 4- Amino antipyrine thiosemicarbazone (C-8), 1-(2-Chloro-5-sulfophenyl)-3-methyl-5-pyrazolone (C-9) and 1-(4-Sulfoamidophenyl)-3-methyl-5-pyrazolone (C-10) were found most active at the concentration of 2.0 to 5.0 mg per 10 mL against *Gibberella fujikuroi.*

All the compounds were investigated by m. pt. determination, CHN analysis, Infrared and Mass spectral studies [12-15]. The preliminary investigation of the compounds viz. m. pt. determination was carried out in research laboratory, Dept. of Chemistry, Govt. K.R.G. Auto. P.G. College, Gwalior (MP). CHN analyses of these compounds were carried out on Elemental analyzer, Elemental Vario EL III and the results of m. pt. determination are included in **Table-1**.

Mass spectral studies of the compounds:

Mass spectral studies of compounds were recorded on mass spectrometer, Jeol SX-102 (FAB) at SAIF, CDRI Lucknow. Study of parent ion peaks in mass spectra provide us the information of molecular weight of any compound [16-17]. Mass spectral studies of the compounds chosen for this study show that the parent ion peaks in the spectra of these compounds appear at the m/e values where these are expected to come.

The results for antimicrobial activity are shown in **Table-2.**

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Table-1: Code, Name, Molecular weight and Structures of Pyrazolone Compounds

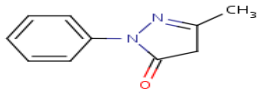
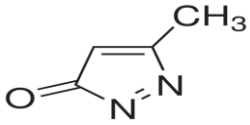
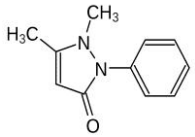
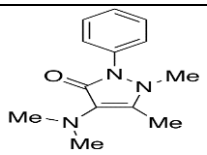
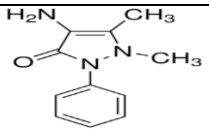
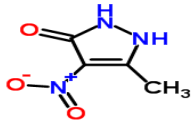
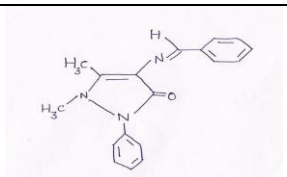
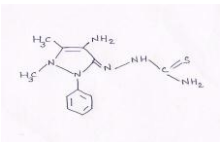
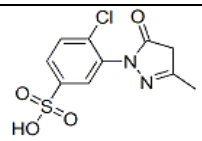
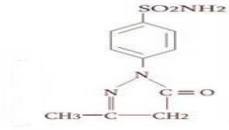
Code	Name of Compound	Molecular weights	Structure
C-1	3-Methyl-1-phenyl-5-pyrazolone	174	
C-2	3-Methyl-5- pyrazolone	72	
C-3	Antipyrine	188	
C-4	4-(Dimethyl amino) antipyrine	231	
C-5	4-Amino antipyrine	203	
C-6	3-Methyl-4-nitroso-5-pyrazolone	143	
C-7	4-Benzoyl amino antipyrine	291	
C-8	4-Amino antipyrine thiosemicarbazone	276	
C-9	1-(2-Chloro-5-sulfophenyl)-3-methyl-5-pyrazolone	288	
C-10	1-(4 -Sulfoamidophenyl)-3-methyl-5-pyrazolone	253.28	

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Table 2: Antifungal activity for pyrazolone compounds against *Gibberella fijikuroi*

Conc→ ↓Compd	10ml DMF	0.5mg/ 10ml	1.0mg/ 10ml	1.5mg/ 10 ml	2.0mg/ 10 ml	2.5mg/ 10 ml	3.0mg/ 10 ml	3.5mg/ 10 ml	4.0mg/ 10 ml	4.5mg/ 10 ml	5.0mg/ 10 ml
C1	0.0	-	-	-	-	-	-	-	-	-	-
C2	0.0	-	-	-	-	-	-	-	-	-	-
C3	0.0	-	-	-	-	-	-	-	-	-	-
C4	0.0	-	-	-	-	-	1.0	1.0	1.0	1.0	1.0
C5	0.0	-	-	-	-	1.0	1.0	1.0	1.5	1.5	1.5
C6	0.0	-	-	-	1.0	1.0	1.5	2.0	2.0	2.0	2.0
C7	0.0	-	-	-	-	-	-	-	-	-	-
C8	0.0	-	-	-	1.5	1.5	2.0	2.5	2.5	3.0	3.0
C9	0.0	-	-	1.0	1.0	1.5	2.0	2.0	2.0	2.5	2.5
C10	0.0	-	1.5	1.5	2.0	2.5	2.5	3.0	3.0	3.5	3.5

Analytical study of compounds:

Infrared spectral studies of compounds:

Infrared spectra of the compounds were recorded on Perkin-Elmer infrared spectrophotometer in the range of 4000 to 50 cm^{-1} at SAIF, CDRI Lucknow. Infrared absorption studies of pyrazolones have been assigned by a comparison of these spectra with those of pyrazole, five membered ring systems and the mono-substituted benzene ring system [18]. The strong band has been assigned to the ring stretching of 5-membered ring in pyrazolone compounds. Five membered ring hetero atomic compounds are found to have two strong bands near 1590-1560 and 1450-1430 cm^{-1} which are considered to be characteristics of five membered rings.

QSAR study:

Quantitative Structure Activity Relationship (QSAR) study is used to find successful structure activity relationship properties, correlation and then to predict the activity or property of other compounds more accurately [19].

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Table 3: AM1 computed parameters for pyrazolone compounds

Compounds	SAA ($Å^2$)	SAG ($Å^2$)	VOL ($Å^3$)	HE (Kcal/mol)	Log P	RF ($Å^3$)	POL ($Å^3$)	Mass (amu)	TE (Kcal/mol)	EE (kcal/mol)	HF (kcal/mol)	DM (Debye)	ZPE (kcal/mol)
C-1	354.36	317.33	502.23	-4.16	0.12	46.39	17	168.15	-47433	-229739	307.92	1.96	73.28
C-2	237.23	241.26	334.2	-8.58	0.77	28.24	9.29	96.09	-29947	-105992	51.33	3.74	50.48
C-3	339.75	383.77	608.22	-1.84	0.4	61.23	21.43	188.23	-53153	-302313	63.63	4.41	135.45
C-4	419.06	439.75	732.69	-1.24	1.22	74.92	26.45	231.3	-65414	-426785	72.08	3.87	181.52
C-5	337	399.31	638.89	-6.51	-1.99	64.85	22.78	203.24	-58252	-343522	60.63	3.39	146.4
C-6	262.01	289	425.83	-21.96	-4.58	33.8	12.56	145.12	-50432	-220072	-9.58	3.39	82.74
C-7	442.46	523.41	888.29	-5.11	-0.57	98.38	34.28	293.27	-80807	-583434	94.24	3.71	216.95
C-8	328.97	520.54	853.25	-4.74	-1.34	86.56	31.41	276.36	-73459	-465295	236.13	4.43	174.31
C-9	372.62	422.1	670.98	-10.22	-0.95	70.44	25.16	2256.71	-69740	-379930	24.32	3.08	111.94
C-10	367.78	426.94	688.04	-9.88	-1.44	73.45	25.88	255.72	-67460	-378253	51.06	3.47	123.4

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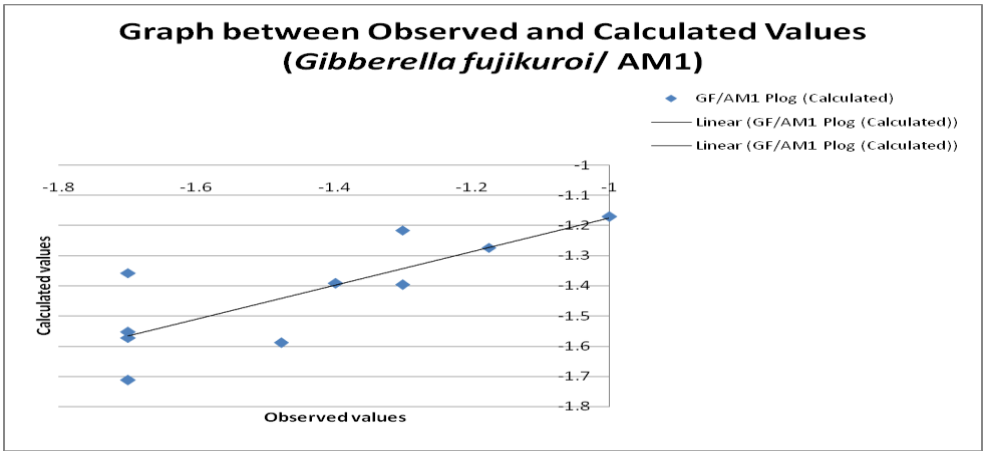
AM1/*Gibberella fujikuroi*/C-1 to C-10/3D-QSAR Equation

p(MIC) = - 0.009589 (POL) – 0.08624 (Log P) – 0.01134 (DM) – 1.69376
N = 10, SD = 0.243948, CC = 0.613918, F-test = 1.209734



p(MIC) (Observed)	p(MIC) (Calculated)
-1.69897	-1.55316
-1.69897	-1.71333
-1.69897	-1.57261
-1.477121	-1.58907
-1.39794	-1.39199
-1.30103	-1.21663
-1.69897	-1.3578
-1.30103	-1.39708
-1.176091	-1.2738
-1	-1.1706

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Table 4: PM3 computed parameters for pyrazolone compounds

Compounds	SAA $Å^2$	SAG $Å^2$	VOL $Å^3$	HE Kcal/mol	Log P	RF $Å^3$	POL $Å^3$	Mass amu	TE Kcal/mol	EE kcal/mol	HF kcal/mol	DM Debye	ZPE kcal/mol
C-1	355.76	320.1	502.45	-4.18	0.12	46.39	17	168.15	-42727	-221869	274.63	1.43	71.68
C-2	237.14	238.8	333.28	-8.59	0.77	28.24	9.29	96.09	-26557	-101377	28.65	3.74	49.1
C-3	341.87	385.24	613.47	-1.85	0.4	61.23	21.43	188.23	-48543	-293434	22.75	4.04	130.46
C-4	422.9	443.56	724.65	-1.36	-1.22	74.92	26.45	231.3	-59530	-416062	23.36	4.17	176.43
C-5	343.8	390.57	629.1	-5.59	-1.99	64.85	22.78	203.24	-52645	-333790	22.07	3.7	142.23
C-6	275.65	281.66	409.68	-13.43	-1.74	33.14	11.65	143.1	-44165	-199607	-13.77	7.58	66.01
C-7	445.68	540.81	902.51	-5.11	-0.57	98.38	34.28	293.37	-73894	-573707	46.4	3.34	209.28
C-8	-41.32	397.64	659.91	3.7	-1.32	86.56	31.41	276.36	-65062	-462886	210.67	4.66	168.53
C-9	375.37	417.82	672.39	-11.64	-0.95	70.44	25.16	256.71	-63114	-369363	-17.9	4.92	111.27
C-10	371.32	435	693.47	-10.86	-1.44	73.45	25.88	255.72	-60446	-365609	19.35	4.5	119.43

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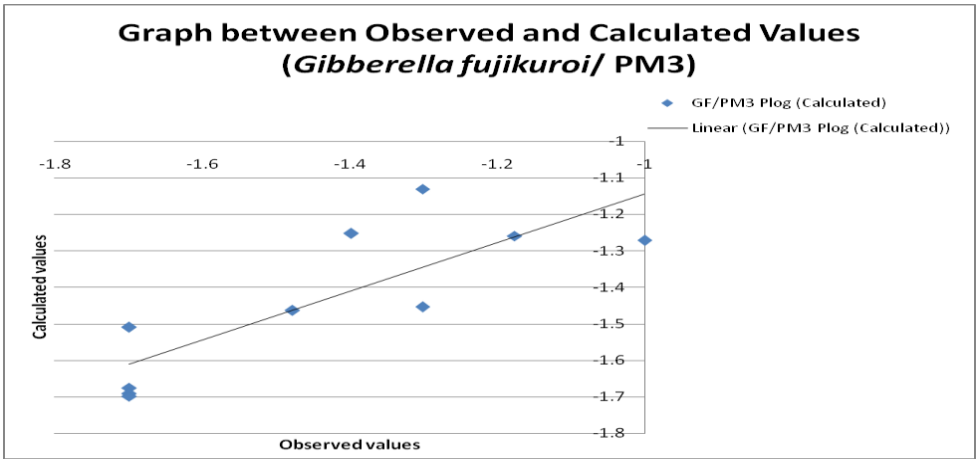
PM3/*Gibberella fujikuroi*/C-1 to C-10/3D-QSAR Equation

p(MIC) = - 0.01128 (HE) – 0.17158 (Log P) + 0.0197 (DM) – 1.73048
N = 10, SD = 0.188599, CC = 0.792193, F-test = 3.370124



p(MIC) (Observed)	p(MIC) (Calculated)
-1.69897	-1.67575
-1.69897	-1.69202
-1.69897	-1.69866
-1.477121	-1.46366
-1.39794	-1.25309
-1.30103	-1.13111
-1.69897	-1.50924
-1.30103	-1.45393
-1.176091	-1.25926
-1	-1.27225

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Table 5: MNDO computed parameters/ SAR descriptors for pyrazolone compounds

Compounds	SAA Å^2	SAG Å^2	VOL Å^3	HE Kcal/mol	Log P	RF Å^3	POL Å^3	Mass amu	TE Kcal/mol	EE kcal/mol	HF kcal/mol	DM Debye	ZPE kcal/mol
C-1	356.68	321.7	506.12	-4.18	0.12	46.39	17	168.15	-47472	-228849	291.38	1.09	74.32
C-2	237.6	242.64	334.3	-8.56	0.77	28.24	9.29	96.09	-30047	-106208	17.61	3.6	52.65
C-3	340.55	392.42	620.67	-1.83	-0.4	61.23	21.43	188.23	-53297	-302001	28.81	3.71	139.85
C-4	423.24	461.04	759.23	-1.26	-1.22	74.92	26.45	231.3	-65604	-426490	39.68	3.34	187.01
C-5	339.34	415.13	658.53	-6.43	-1.99	64.85	22.78	203.24	-58408	-343088	28.77	2.87	151.05
C-6	278.99	288.33	416.15	-13.34	-1.74	33.14	11.65	143.1	-49945	-207139	10.5	6.5	71.32
C-7	440.29	534.89	917.75	-4.9	-0.57	98.38	34.28	293.37	-80986	-591131	59.57	2.58	223.36
C-8	-41.32	397.64	659.91	-3.7	-1.32	86.56	-31.44	276.36	-74378	-456409	230.21	2.8	181.98
C-9	390.91	442.86	694.31	-11.72	-0.95	70.44	25.16	256.71	-70251	-377400	-14.43	3.38	119.6
C-10	380.47	451.86	708.67	-10.74	-1.44	73.45	25.88	255.72	-67932	-376391	25.75	3.04	127.58

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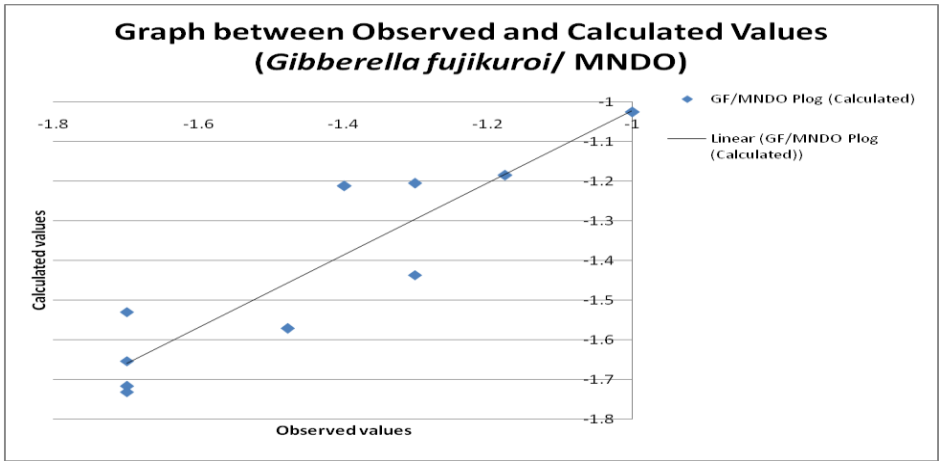
MNDO/*Gibberella fujikuroi*/C-1 to C-10/3D-QSAR Equation

p(MIC) = - 0.03547 (HE) – 0.1965 (Log P) – 0.05222 (DM) – 1.68128
N = 10, SD = 0.155699, CC = 0.863813, F-test = 5.879357



p(MIC) (Observed)	p(MIC) (Calculated)
-1.69897	-1.65352
-1.69897	-1.71695
-1.69897	-1.73151
-1.477121	-1.57127
-1.39794	-1.21204
-1.30103	-1.20563
-1.69897	-1.5302
-1.30103	-1.43688
-1.176091	-1.1854
-1	-1.02612

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Table 6: ZINDO computed parameters/ SAR descriptors for pyrazolone compounds

Compounds	SAA Å^2	SAG Å^2	VOL Å^3	HE Kcal/mol	Log P	RF Å^3	POL Å^3	Mass amu	TE Kcal/mol	EE kcal/mol	HF kcal/mol	DM Debye	ZPE kcal/mol
C-1	339.01	322.6	492.53	0.35	0.12	46.39	17	168.15	-66169	-278099	-4133.4	6.17	100.03
C-2	235.87	238.28	330.45	-8.67	0.77	28.24	9.29	96.09	-41929	-129187	-2117.6	4.71	69.33
C-3	333.46	370.99	592.48	-1.86	-0.4	61.23	21.43	188.23	-74016	-354456	-5450.6	7.09	184.89
C-4	422.9	443.56	724.65	-1.36	-1.22	74.92	26.45	231.3	-91086	-493720	-6820	5.86	249.13
C-5	332.57	389.92	622.96	-6.59	-1.99	64.85	22.78	203.24	-81172	-400070	-5727	6.4	199.12
C-6	274.94	280.08	403.32	-12.94	-1.74	33.14	11.65	143.1	-70596	-249055	-2845.1	10.92	92.37
C-7	445.68	540.81	902.51	-5.11	-0.57	98.38	34.28	293.37	-112180	-662184	-8687.9	4.21	290.62
C-8	253.93	442.53	738.14	-9.06	-1.32	86.56	31.41	276.36	-102800	-609648	-7076.6	12.05	246.95
C-9	375.37	417.82	672.39	-11.64	-0.95	70.44	25.16	256.71	-95269	-441882	-5087.1	9.5	155.84
C-10	348.71	416.91	671.69	-10.31	-1.44	73.45	25.88	255.72	-91772	-437150	-5240.2	8.03	166.75

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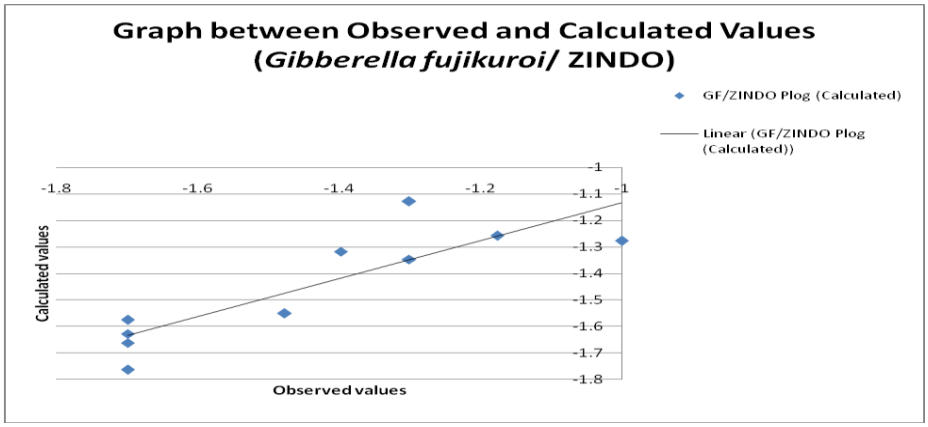
ZINDO/*Gibberella fujikuroi*/C-1 to C-10/3D-QSAR Equation

p(MIC) = - 0.0234 (HE) – 0.1326 (Log P) + 0.016168 (DM) – 1.83921
N = 10, SD = 0.162382, CC = 0.850832, F-test = 5.244161



p(MIC) (Observed)	p(MIC) (Calculated)
-1.69897	-1.76356
-1.69897	-1.66228
-1.69897	-1.62801
-1.477121	-1.55087
-1.39794	-1.31765
-1.30103	-1.12914
-1.69897	-1.57599
-1.30103	-1.34735
-1.176091	-1.25727
-1	-1.27718

In this study semi-empirical quantum chemically computed properties viz. Surface Area Approx (SAA), Surface Area Grid (SAG), Volume (VOL), Hydration Energy (HE), Log P (Log P), Refractivity (RF), Polarizability (POL), Mass (Mass), Total Energy (TE), Electronic Energy (EE), Heat of Formation (HF), Dipole Moment (DM), Zero Point Energy (ZPE) were used as descriptors to correlate lab reported activities of pyrazolone compounds under study using AM1, PM3, MNDO and ZINDO methods and are mentioned in Table-3 to Table-6. The reported activities of the compounds understudy against *Gibberella fujikuroi* are then correlated with the computed parameters to get QSAR equations, with all the 13 parameters / descriptors with their corresponding SD (Standard Error), F-test (Fischer-test) and CC (Correlation Coefficient) value [20]. These values are shown along with the computed QSAR equation. Correlation matrices

between all the 13 parameters / descriptors were obtained using AM1, PM3, MNDO and ZINDO methods.

Graphs plotted between observed and predicted activities and equation are mentioned here along with their observed and predicted values.

CONCLUSION

The present study involves some pyrazolone compounds (C-1 to C-10) to check their antifungal activity against *Gibberella fujikuroi*. From the results and discussion made above we conclude that the 3-Methyl-4-nitroso-5-pyrazolone (C-6), 4- Amino antipyrine thiosemicarbazone (C-8), 1-(2-Chloro-5-sulfophenyl)-3-methyl-5-pyrazolone (C-9) and 1-(4-Sulfoamidophenyl)-3-methyl-5-pyrazolone (C-10) showed significant antifungal activity against *Gibberella fujikuroi*. The present paper also discusses Quantitative Structure Activity Relationship with some significant QSAR equations.

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