Article

Antimicrobial Properties Of Pyrazolone Compounds With Their Qsar Investigations

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Abstract

The present paper reports the analysis and the antimicrobial activity *viz*. antifungal activity of some pyrazolone compounds which were performed against *Alternaria solani* using disc diffusion method on nutrient agar and nutrient broth media. The compounds were characterized by elemental analysis and spectral studies. Result of antimicrobial screening indicated that compounds 4-Amino antipyrine thiosemicarbazone, 1-(2-Chloro-5-sulfophenyl)-3-methyl-5-pyrazolone and 1-(4 -Sulfoamidophenyl)-3-methyl-5-pyrazolone were found to be the most potent/active against *A. solani*. Correlation studies between different computed properties of the compounds with their biological activity, QSAR (Quantitative Structure Activity Relationship) investigations with a stepwise linear regression analysis were conducted. The studies are carried out using Hyperchem 8.0 version software using AM1, PM3, MNDO and ZINDO methods. Selected QSAR/ 3D-QSAR equations including different physical parameters of these series are reported.

Keywords

Antimicrobial Activity, *A.Solani*, Pyrazolone, QSAR Studies

1. Introduction

Fungicides have long been used to combat illness caused by plant diseases. However, plant pathogenic fungi have evolved resistance to currently available commercial fungicides, posing a significant threat to plant output and quality, prompting the development of novel antifungal medicines.

Pyrazoles are a family of five-membered heterocycles that are particularly valuable in chemical synthesis [1]. Pyrazoles are useful in drug development programmes because of their various physicochemical and pharmacological properties [2, 3]. Their ability to prevent the growth of plant diseases makes them a crucial component in the creation of fungicides (cheng et al 2016, cheng et al 2018).

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QSAR studies are computational based models studies that seek to predict complicated physicochemical / biological qualities of materials based on their simpler actual or calculated attributes. Researchers can use QSAR to generate a trustworthy logical knowledge of the structure and behavior of new compounds, which can then be used to create an *in-silico* model to predict their activity before they are synthesized [4].

The QSAR studies are based on the statistical idea's that allows changes in multiple substances, biological patterns to be computationally linked to changes in their molecular format. As a result, all biological activities and functions of the molecule are connected with a unique chemical descriptor, and biological impacts can be determined using particular regression analysis [5].

Materials and Methods

All of the chemicals used were of the highest purity & came from Aldrich and Merck Chemicals. KBr discs/nujol was used to record infrared spectra on a Perkin Elmer FT-IR spectrometer. The ^{1}H spectrum was measured in CDCl3 using tetramethylsilane as an internal standard on a Bruker spectrospin 300MHz spectrometer. In an electric melting point apparatus, melting points were measured in open capillaries.

2.1 Experimental

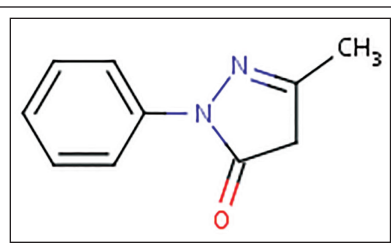
2.1.1 Pharmacological profile of Pyrazolone:

Antifungal activity against *Alternaria solani* has been discovered in five pyrazolone derivatives. At a concentration of 200 g/mL, all of the compounds were tested for antifungal activity. Table 1 shows the structures of the compounds that have been reported. Standard analytical techniques [6, 7] confirm the structures of these substances.

2.2 Computational Details:

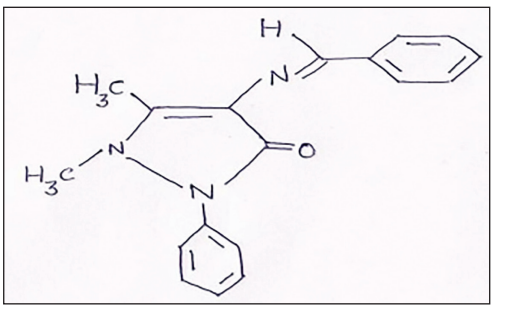
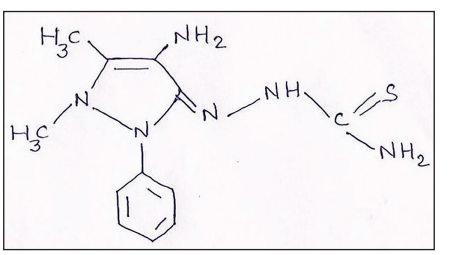
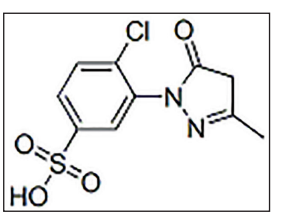
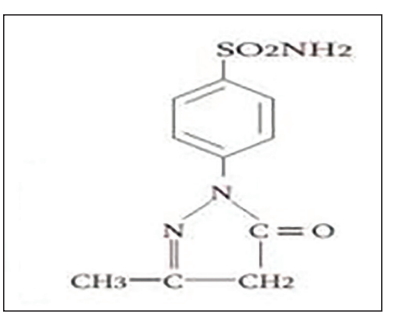
These compounds were examined using Hyperchem 8.0 professional version with AM1, PM3, MNDO and ZINDO methods in order to develop one dimensional and then three-dimensional descriptors. The structures of compounds were drawn using the HYPERCHEM Software 8.0 professional version followed by computations of descriptors viz. Surface Area Approx (SAA), Volume (VOL), Hydration

Table 1. Details of Pyrazolone Compounds

Code	Name	Structure
C-1	**3-methyl-1-Phenyl-5-pyrazolone**	

(Table 1 continued)

(Table 1 continued)

Code	Name	Structure
C-2	**4-Benzoyl amino antipyrine**	
C-3	**4-Amino antipyrine thiosemicarbazone**	
C-4	**1-(2-Chloro-5-sulfophenyl)-3-methyl-5-pyrazolone**	
C-5	**1-(4 -Sulfoamidophenyl)-3-methyl-5-pyrazolone**	

energy (HE), Refractivity (REF), Polarizability (POL), Total Energy (TE), Electronic Energy (EE), Heat of Formation (HF), Dipole Moment (DM) and Zero Point Energy (ZPE) after optimization of the geometries of the compounds under investigation. The calculations/ computations were carried out using a Pentium Core-2 duo computer with the following settings.

Intel (R) core ™ 2 Duo CPU
T_{5450} @ 1.66 GHZ
2 GB RAM
250 GB HDD

With the addition of windows as an operating system, Microsoft Windows XP is used. MS EXCEL software was used to perform regression studies and statistical computations in order to get QSAR equations.

3. Results and Discussion

3.1 Analytical studies of compounds

Melting point, CHN analysis, IR, and Mass Spectrum analyses were used for investigation and structural establishment purpose of all of the compounds. The early researches were carried out in the Research Laboratory of Govt. Kamla Raja Girls Post-Graduate Autonomous College Gwalior's Department of Chemistry (M.P.). On the Elemental Vario EL III, CHN analyses of these chemicals were performed at SAIF, CDRI Lucknow, and the findings are tabulated in Table-2.

3.1.1 Mass spectral studies of the compounds

Mass spectral investigations of the compounds were also recorded on Jeol SX-102 (FAB) mass spectrometers at SAIF CDRI Lucknow. Mass spectral investigations of chemicals aid in the identification of compounds through fragmentation studies. Apart from that, examinations of the parent ion peak in mass spectra of any chemical aid in the determination of its molecular weight [8]. Mass spectral studies

Table 2. Analytical Data for Pyrazolone Compounds

			Elemental analysis		
			C	**H**	**N**
code	**Compounds**	**m.pt.(oc)**	**Found (Calculated)**	**Found (Calculated)**	**Found (Calculated)**
C-1	**3-methyl-1-Phenyl-5-pyrazolone**	127-130	63.44 (68.96)	5.17 (5.74)	14.34 (16.09)
C-2	**4-Benzoylamino antipyrine**	159-162	72.88 (73.11)	6.52 (6.09)	14.41 (15.05)
C-3	**4-Amino antipyrine thiosemicarbazone**	101-106	51.75 (52.17)	5.98 (5.79)	29.82 (30.43)
C-4	**1-(2-chloro-5-sulfophenyl)-3-methyl-5-pyrazolone**	341-344	41.12 (41.66)	3.42 (3.12)	8.91 (9.72)
C-5	**1(4-Sulfoamidophenyl)- 3-(methyl-5-pyrazolone**	246-250	47.01 (47.43)	4.71 (4.34)	15.75 (16.60)

of the compounds chosen for this study reveal that the parent ion peak in their spectra appears at the m/e values expected.

3.1.2 Infrared spectral studies

Infrared spectral investigations of the compounds were also conducted using a Perkin-Elmer infrared spectrophotometer in the range 4000 to 50 cm-1 that too at SAIF CDRI Lucknow. A comparison of these spectra with those of pyrazole, five membered ring systems, mono-substituted benzene ring systems, and those previously reported has been used to assign infrared absorption studies of pyrazolones [9]. The ring stretching of 5 membered rings in pyrazolone compounds has been given the name "strong band." Two strong bands about 1590-1560 and 1450-1430 cm-1 are detected in five membered ring hetero atomic compounds, which are regarded to be diagnostic of five membered rings.

3.2 Antifungal Activity

The antifungal efficacy of five pyrazolone compounds under study viz. 3-methyl-1-phenyl-5-pyrazolone (C-1), 4-Benzoyl amino antipyrine (C-2), 4-Amino antipyrine thiosemicarbazone (C-3), 1-(2-Chloro-5-sulfophenyl)-3-methyl-5-pyrazolone (C-4) and 1-(4-Sulfoamidophenyl)-3-methyl-5-pyrazolone (C-5) were tested. Out of these five compounds 1-(4 -Sulfoamidophenyl)-3-methyl-5-pyrazolone (C-5) was extremely active against the pathogen at concentrations of 1.0 to 5.0 mg/10mL, C-3 and C-4 were moderately effective at 1.5 to 5.0 mg/mL, and C-1 and C-2 had least or not appreciable antifungal activity against the pathogen viz. *Alternaria solani*. The MIC results are shown in Table-3. Figure 1 exhibits the t actual plates showing activities of C-5 viz. 1(4-Sulfoamidophenyl)- 3-(methyl-5-pyrazolone) against the pathogen *Alternaria solani*.

3.3 QSAR Analysis

Surface Area Approximation (SAA), Volume (VOL), Hydration Energy (HE), Refractivity (REF), Polarisability (POL), Total Energy (TE), Electronic Energy (EE), Heat of Formation (HF), Dipole Moment (DM), and Zero Point Energy (ZPE) were chosen as potential parameters in QSAR (Quantitative Structural Activity Relationship) studies of a series of these compounds and these are correlated with experimentally observed MIC (Minimum Inhibitory Concentration). AM1, PM3, MINDO and ZINDO

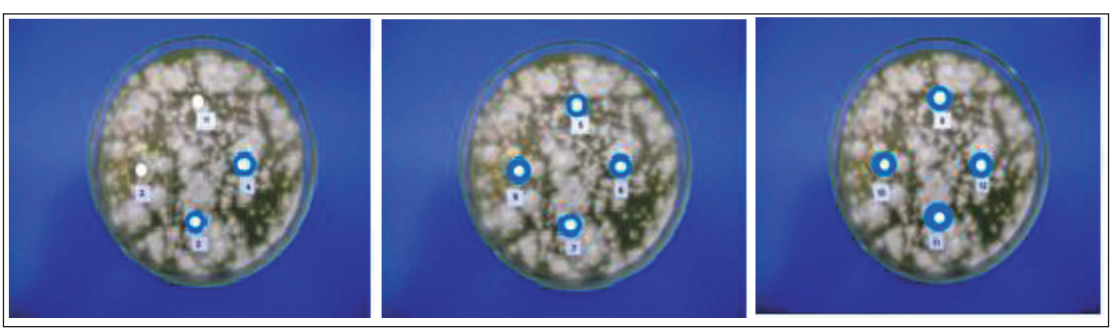


Figure-1. C-5 Alternaria solani

Table 3. Antifungal activity of pyrazolone compounds against the pathogen under study viz. Alternaria solani

Conc→ ↓Compd	10ml DMF	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
C-1	0	-	-	-	-	-	-	-	-	-
C-2	0	-	-	-	-	-	-	-	-	-
C-3	0	-	-	-	1.5	1.5	2	2.5	2.5	2.5
C-4	0	-	-	-	1	1	1.5	1.5	2	2
C-5	0	-	2	2	2	2	2.5	2.5	3	3

Note: The figures given are zone of inhibition (ZOI) in mm.

are the methods in semi- empirical studies which were employed to compute these parameters. Several tests, such as the Standard Error (SD) and the Fischer test (F-test) were used to determine the QSAR model and QSAR equations were produced following a thorough linear regression study [10–16]. The best-fit QSAR equations were chosen, and graphs with their equations were created based on plots of observed and expected fungal activities (Graphs 1–4).

The semi-empirical quantum chemically calculated attributes were used to examine the 3D quantitative structure activity relationship of synthesized compounds against the laboratory activities of mentioned fungi. The values were utilized as descriptors and fungus activities in the lab were linked to them. On the Hyperchem 8.0 professional edition, compound structures were drawn and their geometries were optimized.

Table 4–7 shows many computed parameters as one-dimensional descriptors that have been developed into three-dimensional descriptors. The activities of these compounds were compared to the descriptors. The standard deviation F-test correlation (r) and square of correlation were used to calculate the values of these parameters and the effectiveness of synthesized compounds in terms of MIC. With the use of correlation, the QSAR equations were created and presented. For various parameters and their combinations, a one-dimensional QSAR equation was obtained. The relevant equation was chosen from this group based on the statistical data generated using EXCEL. These three-dimensional equations are used to assess the efficacy of synthesized chemicals as antifungal agents. Table 4–7 includes the computed parameters for these compounds under study on the baiss of AM1, PM3, MNDO and ZINDO methods.

The final selected 3D equations are reported as-

1. **AM1/C1 - C5/A.solani**

   p(MIC) = 0.01188 (POL) – 0.09427(Log P) + 0.00479 (DM) – 1.76706128

   N = 10, SD = 0.25927953, CC = 0.63624118, F-test = 1.360231

2. **PM3/ C1 - C5/A.solani**

   p(MIC) = - 0.00502 (HE) – 0.23333 (Log P) + 0.006534 (DM) – 1.64467

   N = 10, SD = 0.181835, CC = 0.840989, F-test = 4.832041

3. **MNDO/ C1 - C5/A.solani**

   p(MIC) = - 0.02969 (HE) – 0.2601 (Log P) + 0.06596 (DM) – 1.61046

   N = 10, SD = 0.150952, CC = 0.893452, F-test = 7.913558

4. **ZINDO/C-1 to C-5/3D-QSAR Equation**

   p(MIC) = - 0.01928 (HE) – 0.19676 (Log P) + 0.012419 (DM) – 1.79686

N = 10, SD = 0.160801, CC = 0.878106, F-test = 6.736269

Table 4. AM1 computed parameters for pyrazolone compounds

Compd	SAA	VOL	HE	Log P	RF	POL	Mass	TE	EE	HF	DM	ZPE
C-1	354.36	502.23	-4.16	0.12	46.39	17	168.15	-47433	-22973	307.92	1.96	73.28
C-2	442.46	888.29	-5.11	-0.57	98.38	34.28	293.27	-80807	-58343	94.24	3.71	216.95
C-3	328.97	853.25	-4.74	-1.34	86.56	31.41	276.36	-73459	-46529	236.13	4.43	174.31
C-4	372.62	670.98	-10.22	-0.95	70.44	25.16	2256.71	-69740	-37993	24.32	3.08	111.94
C-5	367.78	688.04	-9.88	-1.44	73.45	25.88	255.72	-67460	-37825	51.06	3.47	123.4

p(MIC) (Observed)	p(MIC) (Calculated)
-1.69897	-1.56689
-1.69897	-1.28803
-1.1760913	-1.24611
-1.1760913	-1.36364
-1	-1.20702

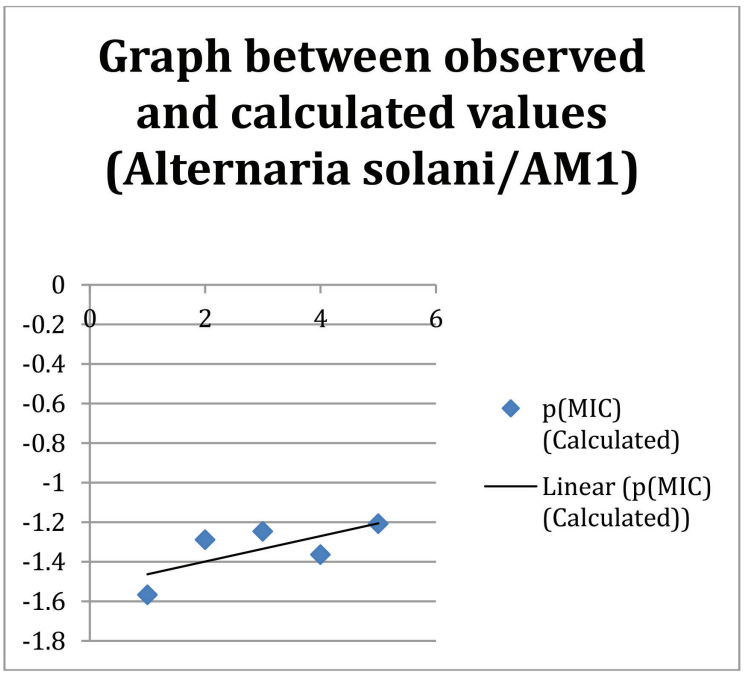


Table 5. PM3 computed parameters for pyrazolone compounds

Compd	SAA	VOL	HE	Log P	RF	POL	Mass	TE	EE	HF	DM	ZPE	C-1	355.76
502.45	-4.18	0.12	46.39	17	168.15	-42727	-221869	274.63	1.43	71.68	**C-2**	445.68	902.51	-5.11
-0.57	98.38	34.28	293.37	-73894	-573707	46.4	3.34	209.28	**C-3**	-41.32	659.91	3.7	-1.32	86.56
31.41	276.36	-65062	-462886	210.67	4.66	168.53	**C-4**	375.37	672.39	-11.64	-0.95	70.44	25.16	256.71
-63114	-369363	-17.9	4.92	111.27	**C-5**	371.32	693.47	-10.86	-1.44	73.45	25.88	255.72	-60446	-365609
19.35	4.5	119.43												

p(MIC) (Observed)	p(MIC) (Calculated)
-1.69897	-1.61234
-1.69897	-1.4642
-1.1760913	-1.2348
-1.1760913	-1.33243
-1	-1.22475

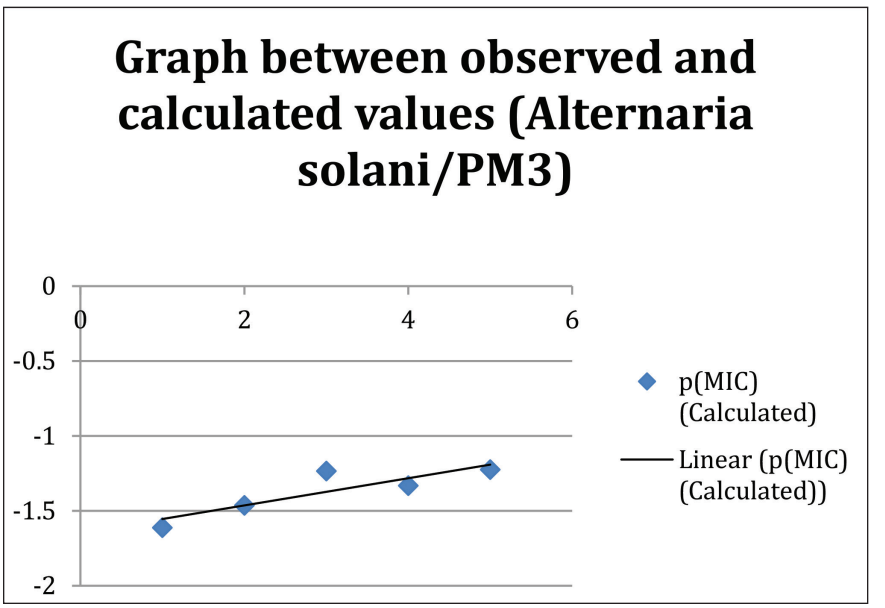


Table 6. MNDO computed parameters for pyrazolone compounds

Compd	SAA	VOL	HE	Log P	RF	POL	Mass	TE	EE	HF	DM	ZPE
C-1	356.68	506.12	-4.18	0.12	46.39	17	168.15	-47472	-228849	291.38	1.09	74.32
C-2	440.29	917.75	-4.9	-0.57	98.38	34.28	293.37	-80986	-591131	59.57	2.58	223.36
C-3	-41.32	659.91	-3.7	-1.32	86.56	-31.44	276.36	-74378	-456409	230.21	2.8	181.98
C-4	390.91	694.31	-11.72	-0.95	70.44	25.16	256.71	-70251	-377400	-14.43	3.38	119.6
C-5	380.47	708.67	-10.74	-1.44	73.45	25.88	255.72	-67932	-376391	25.75	3.04	127.58

p(MIC) (Observed)	p(MIC) (Calculated)
-1.69897	-1.64946
-1.69897	-1.4869
-1.1760913	-1.34196
-1.1760913	-1.17834
-1	-1.01756

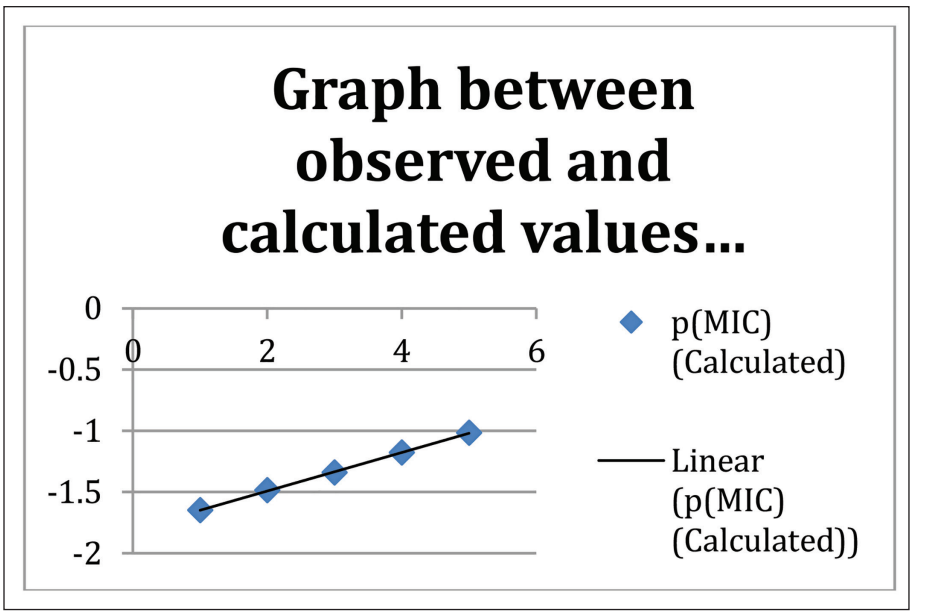
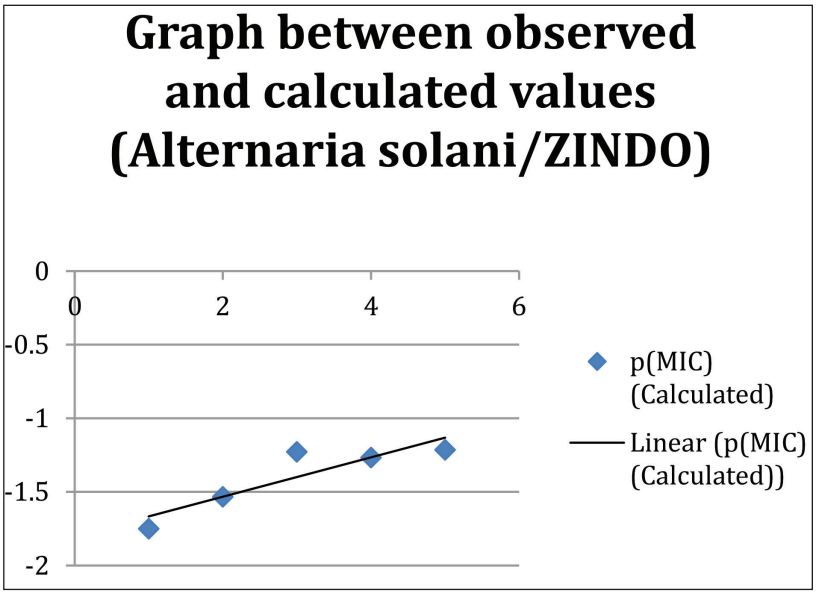


Table 7. ZINDO computed parameters for pyrazolone compounds

Compd	SAA	VOL	HE	Log P	RF	POL	Mass	TE	EE	HF	DM	ZPE
C-1	339.01	492.53	0.35	0.12	46.39	17	168.15	-6616	-2780	-4133.4	6.17	100.03
C-2	445.68	902.51	-5.11	-0.57	98.38	34.28	293.37	-11218	-6621	-8687.9	4.21	290.62
C-3	253.93	738.14	-9.06	-1.32	86.56	31.41	276.36	-10280	-6096	-7076.6	12.05	246.95
C-4	375.37	672.39	-11.64	-0.95	70.44	25.16	256.71	-9526	-4418	-5087.1	9.5	155.84
C-5	348.71	671.69	-10.31	-1.44	73.45	25.88	255.72	-9177	-4371	-5240.2	8.03	166.75

p(MIC) (Observed)	p(MIC) (Calculated)
-1.69897	-1.75059
-1.69897	-1.5339
-1.1760913	-1.2281
-1.1760913	-1.26754
-1	-1.21502



4 Conclusions

The current work entails testing some of the pyrazoles compounds (C-1 to C-5) for their antifungal effectiveness against *Alternaria solani* using QSAR investigations. The compounds C-3, C-4, and C-5 demonstrated comparatively significant antifungal activity against the pathogen, according to investigation which has been carried out. The current research paper also analyses the Quantitative Structure Activity Relationship equation. So far among the investigated parameters are concerned, it

may be inferred that three parameters viz. HE (Hydration Energy), Log P and DM (Dipole Moment) shows some significant contribution towards p (MIC). So, far as the employed methods are concerned this may be concluded that AM1 method shows some significant results.

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