Int J Pharm Bio Sci 2015 July; 6(3): (P) 186 - 196

**Research Article** **Pharmacology**

**International Journal of Pharma and Bio Sciences** **ISSN 0975-6299**

# BIOLOGICAL EVALUATION AND QSAR STUDIES OF SOME SYNTHETIC PYRAZOLONE COMPOUNDS

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## ABSTRACT

Some novel synthetic pyrazolone compounds were evaluated for their biological activity. Structures of these compounds have been established on the basis of their melting point and Infrared spectral data. All the compounds were screened for their antifungal activity by disc diffusion methodof measuring the zone of inhibition and found that the compounds viz. 4- Amino antipyrine thiosemicarbazone (C-8) and 1-(4-Sulfoamidophenyl)-3-methyl-5-pyrazolone (C-10) showed significant antifungal activity against *Sclerotium rolfsii.*Quantitative Structure Activity Relationship (QSAR) investigation with a stepwise linear regression analysis was applied to find a correlation between different calculated physico-chemical parameters of the compounds and biological activity.

**KEYWORDS:** **Antimicrobial activity, Pyrazolones, QSAR*, Sclerotium rolfsii.***

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# INTRODUCTION

The usage of most antimicrobial agents is limited, not only by the rapidly developing drug resistance, but also by the unsatisfactory status of present treatment of bacterial and fungal infections and drug side effect[1-3] Therefore, the development of new and different antimicrobial drugs is an important objectives and much of research program efforts are directed towards the design of new agents. Recently, substituted pyrazolones have received considerable attention due to their wide range of biological activities viz. anti-bacterial, anti-fungal, anthelmintic and anti-inflammatory.Quantitative Structure Activity Relationship (QSAR) models are nowadays regarded as a scientifically credible tool for predicting and classifying biological activities of untested chemicals. QSAR can save substantial amount of time, money and human resources.In the present study ten synthetic pyrazolone compounds were screened for their antifungal activities against *Sclerotium rolfsii* and these activities were correlated with the structure of compounds with the help of Quantitative Structure Activity Relationship (QSAR) models.

# EXPERIMENTAL

### *Synthesized compounds*

A data of ten synthetic pyrazolone compounds have been taken for study. The structures of reported compounds were shown in Table-1. The structures of these compounds were confirmed by standard analytical techniques [4-5].

### *Antimicrobial activity*

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

### *Preparation of Petri-plates and Media*

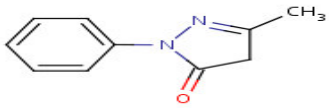
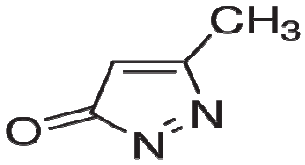
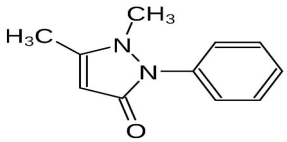
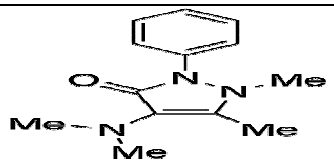
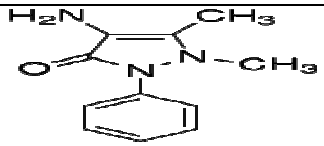
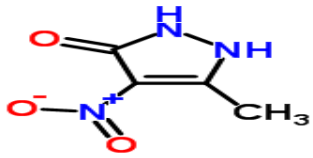
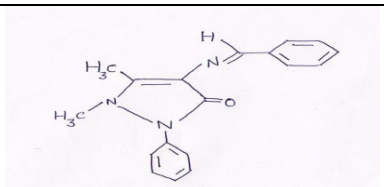
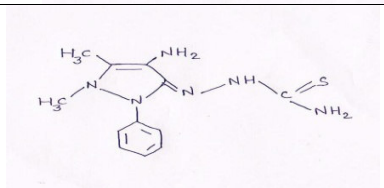
A well known media Potato Dextrose Agar (PDA) and Potato Dextrose Broth (PDB) were autoclaved at 121$^{o}$c for 15 lbs pressure for 15 min. Media were cooled and then plates were prepared by dispensing 15-20 mL medium per plate. Plates were kept in the same position for 0.5 h to solidify media and kept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

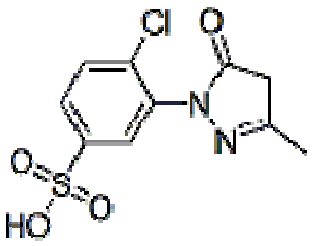
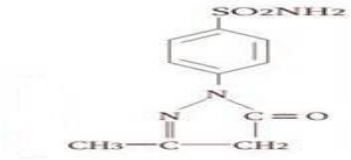
### *Inoculation and incubation*

100 µL of test organism was used to inoculate sterile Potato Dextrose Agar plate by the spread plate swab method. Whatmann paper discs were dispensed on glass plates and each was loaded with 5 µL volumes 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.

**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 |  |

## RESULTS AND DISCUSSION

***Antifungal activity of pyrazolone compounds***

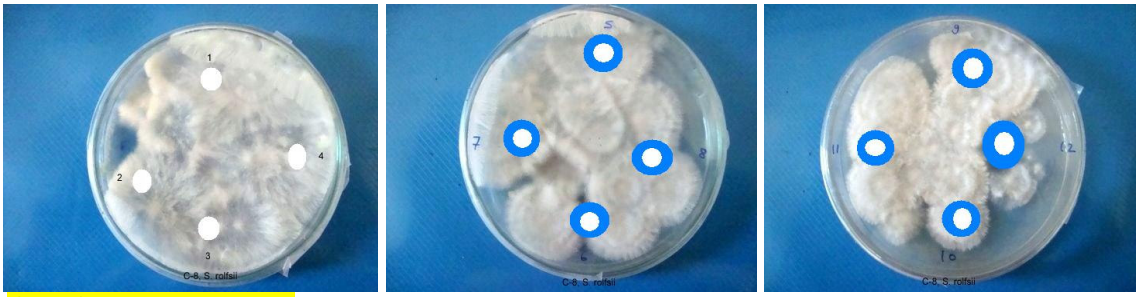
Total ten pyrazolone compounds viz. 3-Methyl-1-phenyl-5-pyrazolone (C-1), 3-Methyl-5-pyrazolone (C-2), Antipyrine (C-3), 4-(Dimethyl amino) antipyrine (C-4), 4-Amino antipyrine (C-5), 3-Methyl-4-nitroso-5-pyrazolone (C-6), 4-Benzoyl amino antipyrine (C-7), 4- Amino antipyrine thiosemicarbazone (C-8), 1-(2-Chloro-5-sulfophenyl)-3-methyl-5-pyrazolone (C-9) and 1-(4-Sulfoamidophenyl)-3-methyl-5-pyrazolone (C-10) were tested for antifungal activities against *Sclerotium rolfsii.*1-(4-Sulfoamidophenyl)-3-methyl-5-pyrazolone (C-10) was found highly active at the concentration of 1.5 to 5.0 mg and 4- Amino antipyrine thiosemicarbazone (C-8) was moderately effective at the concentration of 2.0 to 5.0 mg.

The results are presented in Table-2.

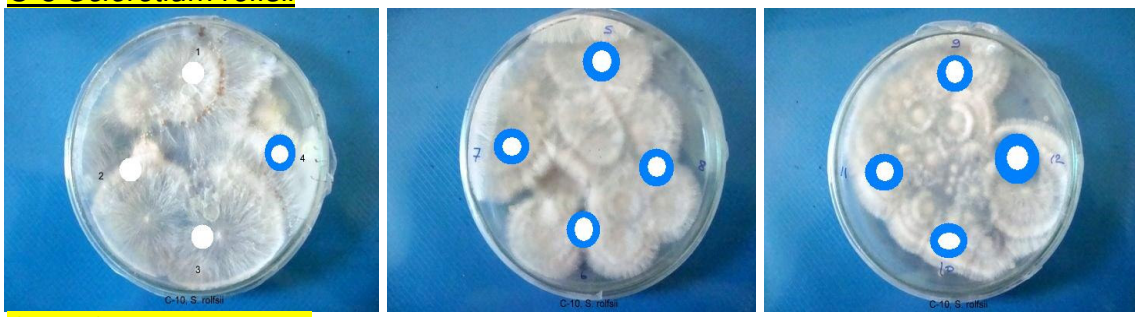
**Table 2**

***Antifungal activity for pyrazolone compounds against Sclerotium rolfsii***

| 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 |
| C5 | 0.0 | - | - | - | - | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| C6 | 0.0 | - | - | - | - | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| C7 | 0.0 | - | - | - | - | - | - | - | - | - | - |
| C8 | 0.0 | - | - | - | 1.0 | 1.0 | 1.5 | 1.5 | 2.0 | 2.0 | 2.0 |
| C9 | 0.0 | - | - | - | - | 1.0 | 1.0 | 1.5 | 1.5 | 1.5 | 1.5 |
| C10 | 0.0 | - | - | 1.0 | 1.0 | 1.5 | 1.5 | 2.0 | 2.0 | 2.0 | 2.5 |



C-8 *Sclerotium rolfsii*



C-10 *Sclerotium rolfsii*

***Analytical studies of compounds***

All the compounds were investigated by m. pt. determination, CHN analysis, Infrared and Mass spectral studies[6-7] . 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 of any compound help in the establishment of its molecular weight [8]. 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.

***Infrared spectral studies of compounds***

Infrared spectra of the compounds were recorded on Perkin-Elmer infrared spectrophotometer in the range of 4000 to 450 $cm^{-1}$ 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[9] 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 ring

***QSAR Analysis***

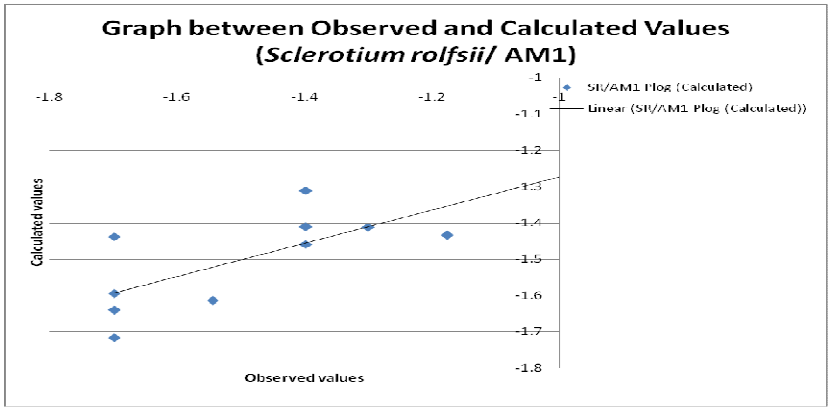
In an attempt to determine the role of structural features which appears to influence the observed activity of reported compounds, QSAR studies were undertaken using stepwise linear regression analysis [10-18]. Biological activity data determined as MIC values were first transformed to p(MIC), which has been used as dependent variable in QSAR study. These were correlated with different molecular descriptors like Surface Area Approx (SAA), Surface Area Grid (SAG), Volume (VOL), Hydration Energy (HE), Log P (Log P),

**Table 3**
***AM1 computed parameters for pyrazolone compounds***

| Compound | SAA (A²) | SAG (A²) | VOL (A³) | HE (Kcal/mol | Log P | RF (A³) | POL (A³) | 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 | 399.3 | 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 | 523.4 | 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 | 2256.7 | -69740 | -379930 | 24.32 | 3.08 | 111.94 |
| C-10 | 367.38 | 426.94 | 688.04 | -9.88 | -1.44 | 73.45 | 25.88 | 255.32 | -67460 | -378253 | 51.06 | 3.47 | 123.4 |

**AM1/*Sclerotium rolfsii*/C-1 to C-10/3D-QSAR Equation**

p(MIC) = 0.007669 (POL) – 0.07222 (Log P) + 0.017009 (DM) – 1.79526
N = 10, SD = 0.174728, CC = 0.674454, F-test = 1.668968




| p(MIC) (Observed) | p(MIC) (Calculated) |
|---|---|
| -1.69897 | -1.64022 |
| -1.69897 | -1.71601 |
| -1.69897 | -1.59479 |
| -1.544068 | -1.6147 |
| -1.39794 | -1.45918 |
| -1.39794 | -1.311051 |
| -1.69897 | -1.4381 |
| -1.30103 | -1.41225 |
| -1.39794 | -1.41131 |
| -1.176091 | -1.43377 |

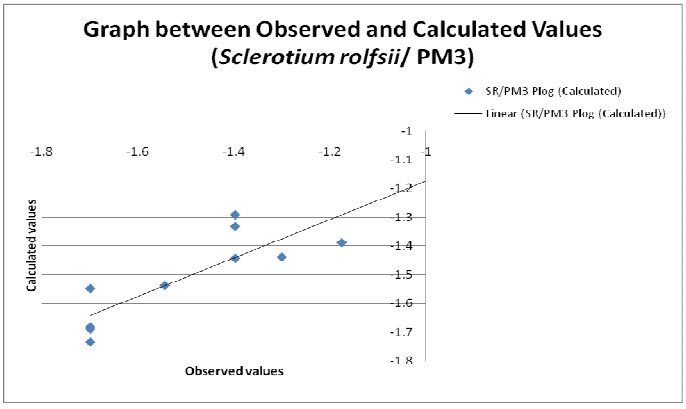
## Table 4
### *PM3 computed parameters for pyrazolone compounds*

| Compounds | SAA Å² | SAG Å² | VOL Å³ | HE Kcal/mol | Log P | RF Å³ | POL Å³ | 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 |

***PM3/Sclerotium rolfsii/C-1 to C-10/3D-QSAR Equation***

p(MIC) = - 0.00225 (HE) – 0.14866 (Log P) + 0.015387 (DM) – 1.6971

N = 10, SD = 0.139048, CC = 0.809189, F-test = 3.793512




| 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 |

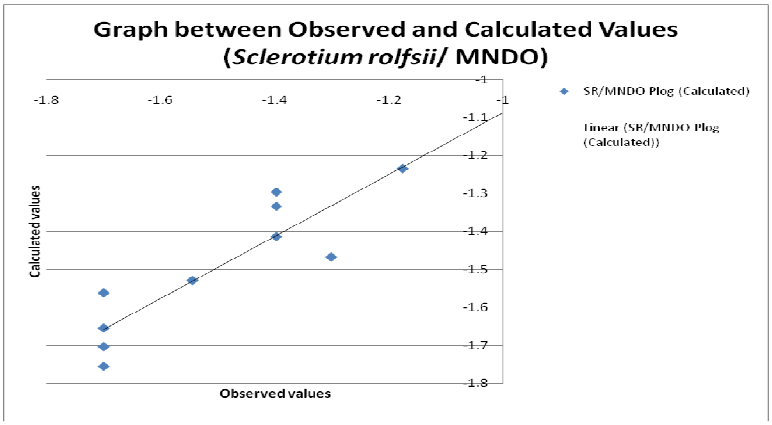
## Table 5
### *MNDO computed parameters/ SAR descriptors for pyrazolone compounds*

| Compounds | SAA Å² | SAG Å² | VOL Å³ | HE Kcal/mol | Log P | RF Å³ | POL Å³ | 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 |

***MNDO/Sclerotium rolfsii/C-1 to C-10/3D-QSAR Equation***

p(MIC) = - 0.02148 (HE) – 0.17182 (Log P) – 0.04097 (DM) – 1.65959

N = 10, SD = 0.118844, CC = 0.864765, F-test = 5.930781




| p(MIC) (Observed) | p(MIC) (Calculated) |
|---|---|
| -1.69897 | -1.65508 |
| -1.69897 | -1.75551 |
| -1.69897 | -1.70355 |
| -1.544068 | -1.52974 |
| -1.39794 | -1.29714 |
| -1.39794 | -1.334039 |
| -1.69897 | -1.5621 |
| -1.30103 | -1.46803 |
| -1.39794 | -1.41309 |
| -1.176091 | -1.234602 |

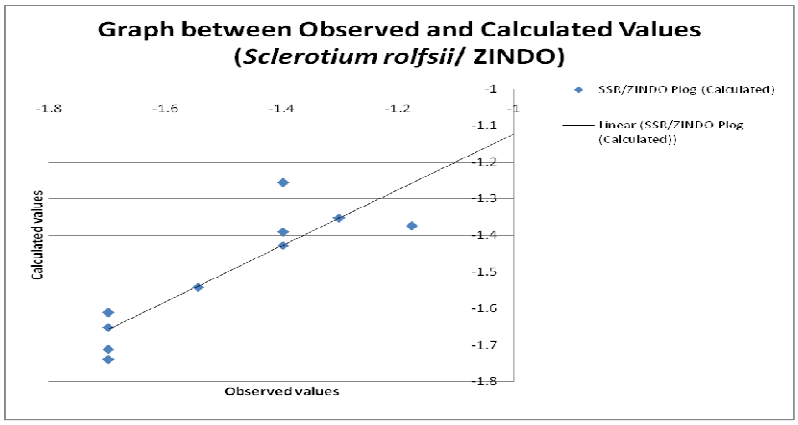
## Table 6
### *ZINDO computed parameters/ SAR descriptors for pyrazolone compounds*

| Compounds | SAA Å² | SAG Å² | VOL Å³ | HE Kcal/mol | Log P | RF Å³ | POL Å³ | Mass amu | TE Kcal/mol | EE kcal/mol | HF kcal/mo | 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 | -1.34 | 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 |

***ZINDO/Sclerotium rolfsii/C-1 to C-10/3D-QSAR Equation***

p(MIC) = - 0.01416 (HE) – 0.11809 (Log P) + 0.01591 (DM) – 1.81866

N = 10, SD = 0.112277, CC = 0.880295, F-test = 6.88569




| p(MIC) (Observed) | p(MIC) (Calculated) |
|---|---|
| -1.69897 | -1.73962 |
| -1.69897 | -1.71189 |
| -1.69897 | -1.65228 |
| -1.544068 | -1.5421 |
| -1.39794 | -1.42852 |
| -1.39794 | -1.25622 |
| -1.69897 | -1.61201 |
| -1.30103 | -1.35278 |
| -1.39794 | -1.39051 |
| -1.176091 | -1.37486 |

Refractivity (RF), Polarizability (POL), Mass (Mass), Total Energy (TE), Electronic Energy (EE), Heat of Formation (HF), Dipole Moment (DM), Zero Point Energy (ZPE). The computed values for these descriptors using AM1, PM3, MNDO and ZINDO methods are mentioned in Table-3 to Table-6. Statistical parameters such as Correlation Coefficient (CC), Standard Error (SD) and Fischer-test (F-test) etc were considered to select best QSAR model [19-20]. Correlation matrices between all the 13 parameters / descriptors were obtained using all the methods viz. AM1, PM3, MNDO and ZINDO methods [21-25]. Graphs are also drawn between observed activities and predicted activities from 3D-QSAR equation for all the compounds under study. Selected best QSAR equations are mentioned below.

## CONCLUSION

Ten pyrazolone compounds (C-1 to C-10) were tested for their *in vitro* antifungal activity against *Sclerotium rolfsii*. The results of anti-microbial activity indicated that compounds viz. 4- Amino antipyrine thiosemicarbazone (C-8) and 1-(4-Sulfoamidophenyl)-3-methyl-5-pyrazolone (C-10) showed significant activity. QSAR analysis was also performed on these compounds using Hyperchem 8.0 professional version computer software. The information generated from the present study may be useful in the design of more potent substituted pyrazolone compounds as antimicrobial agent.

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