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RESEARCH ARTICLE

In-Silico QSAR Studies of Some Pyrazolone Compounds

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ABSTRACT

***In-silico* studies are fascinating the workers/scientists working in the field of drugs designing. The present paper includes QSAR studies related to some novel substituted pyrazolone derivatives. A series of seven pyrazolone compounds is taken for these studies. All the compounds were evaluated for antimicrobial activity against six different microbes viz. bacterial and fungal microbes. Their reported antimicrobial activities were used for Quantitative Structure Activity Relationship (QSAR) studies. The correlation between different computed molecular descriptor of the compounds with their reported biological activities has also been studied and reported in the paper.**

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1. Introduction

It is one of the key objectives of organic and medicinal chemistry that workers working in these branches are extensively and actively involved in the designing and synthesis of molecule that possess potent therapeutic values and use. The rapid development of resistance towardsany present antimicrobial drugs puts a serious challenge before scientific community. Consequently, there is utmost requirement to develop new antimicrobial agents with potent activity against resistant microorganism [1]–[10].

Pyrazolone derivatives have a long history of application in pharmaceutical industry. Due to their wide range of biological activity, pyrazolones have received a considerable interest in the field of drug discovery and therefore, these ring compounds have been a relevant synthetic target in pharmaceutical industry. In fact, these heterocyclic compounds have the core structure of a number of drugs.

QSAR is one of the methods used to correlate the biological property of molecule with molecular descriptor derived from chemical structure. It is a mathematical model of a statistically validated correlation between the chemical structure and their activities [11], [12].

Keeping the above facts in mind and in continuation to the efforts in the study of novel compounds for antimicrobial infection, the author is hereby reporting the *in-silico* semi-empirical quantum chemical based QSAR studies of pyrazolone compounds in this present paper.

2. Materials And Methods

Seven pyrazolone derivatives, mentioned in Table I, have been identified and their antimicrobial activities against six different bacterial and fungal microbes have been recorded [13]. The reported antimicrobial activities of these pyrazolones derivatives against different bacterial and fungal microbes which are used for further studies are adopted as such from the literature [13] where the authors have compared these with standard viz. Chloramphenicol (for bacterial stains) and Fluconazole (for fungal stains). In this work, the reported activities are adopted for further studies as such. These activities are mentioned in Table I. The structures of these compounds (A–G) are given in the Fig. 1.

TABLE I: Antimicrobial Activity Data in MIC (μg/ml) for the Compounds under Study

Compound	Name compd.	Molecular formula	*E. coli*	*S. aureus*	*B. anthrecis*	*P. aeruginosa*	*C. albicanes*	*A. niger*
A	3-methyl-5-oxo-N-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide	$C_{11}H_{11}N_3OS$	17	19	15	16	17	16
B	3-methyl-5-oxo-N-(2-methylphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide	$C_{12}H_{13}N_3OS$	18	16	13	18	15	18
C	3-methyl-5-oxo-N-(3-methylphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide	$C_{12}H_{13}N_3OS$	18	16	14	16	17	18
D	3-methyl-5-oxo-N-(4-methylphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide	$C_{12}H_{13}N_3OS$	14	16	12	17	13	15
E	N-(2-methyoxyphenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbothioamide	$C_{12}H_{13}N_3O_2S$	15	17	15	15	16	17
F	N-(3-methyoxyphenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbothioamide	$C_{12}H_{13}N_3O_2S$	17	16	13	18	18	19
G	N-(4-methyoxyphenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbothioamide	$C_{12}H_{13}N_3O_2S$	19	19	13	20	15	14

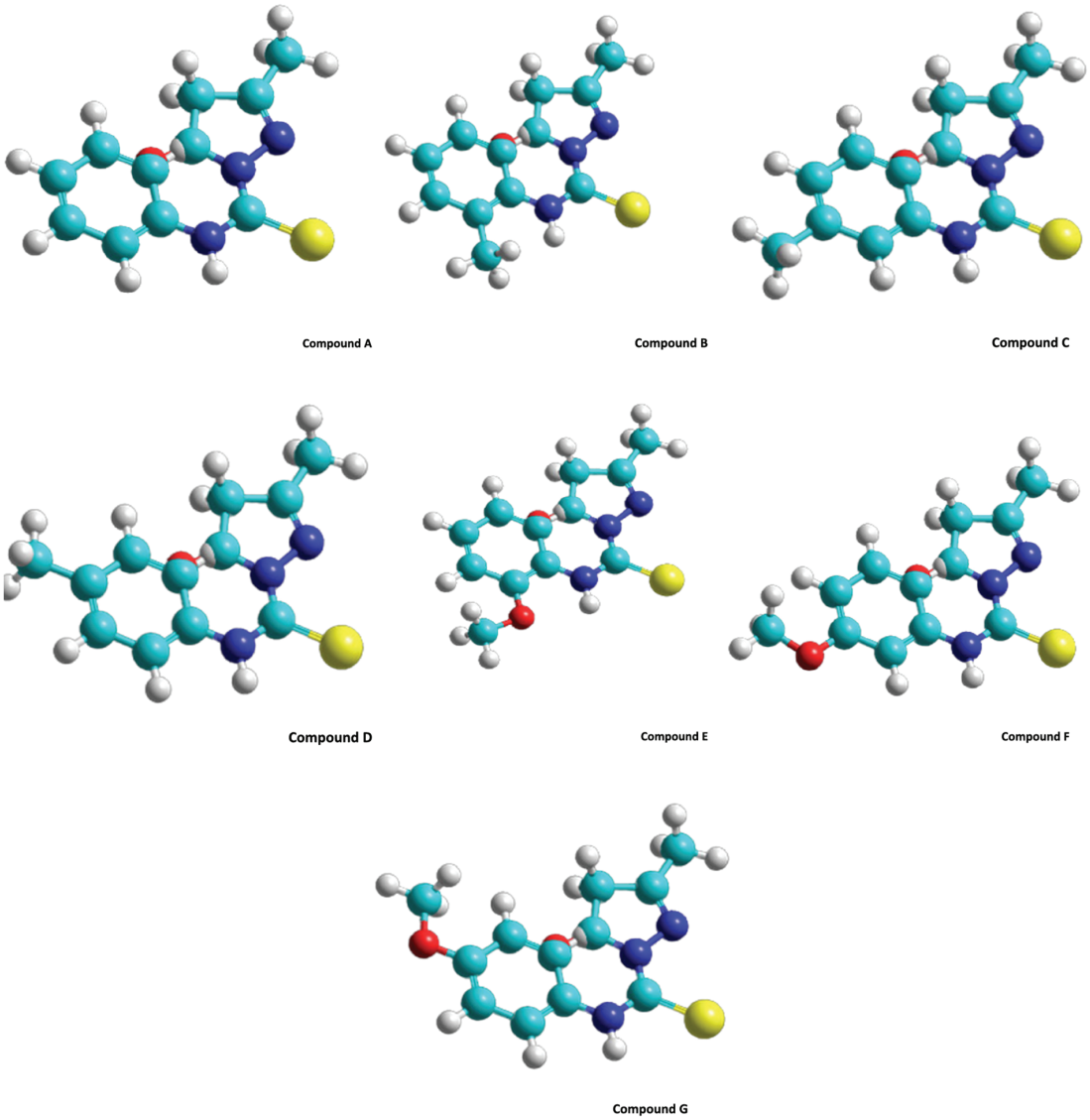


Fig. 1. Ball & stick structures of compounds under study.

2.1. Computational Details

AM1, PM3, MNDO and ZINDO Hamiltonia were used for studies of these compounds to develop one dimensional and later three descriptors 3D-QSAR equations. The structures of compounds were drawn using a professional version of HYPERCHEM software 8.0. The different descriptors studied were Surface Area (SAA), Surface Area Grid (SAG), Volume (VOL), Hydration Energy (HE), Refractivity (REF), Polarizability (POL), Total Energy (TE), Electronic Energy (EE), Heat of Formation (HF), Dipole Moment (DM) and Zero Point Energy (ZPE). All the computations using above mentioned software were done with the aid of Pentium core-2 duo machine with the following configuration

Intel ® core TM 2 Duo CPU
T5450@1.66 GHz
982 MHz 896 MB RAM
150 GB HDD

Windows-Microsoft windows XP software as an operating system were used to perform regression analyses to get QSAR equations. The statistical calculations were done with the help of MS EXCEL software [14].

3. Results and Discussion

The results are obtained for different descriptors after computing as mentioned in the experimental section above. Out of these results, the selected descriptors are used which provide the nearly perfect QSAR equations. The p(MIC) and Computed p(MIC) values on the basis of these framed QSAR equations are mentioned in the Tables II–V.

The QSAR equations that are obtained after computation as explained in the above section are 3D-QSAR equations. These equations for different pathogens using different methods correlating different descriptors are mentioned below:

3.1. QSAR Equations Applying AM1 Method

AM1/*E. coli*

p(MIC) = 0.024476974 (Hyd E) + 0.001535544 (Vol) − 0.002059239 (SAG) − 1.28758951

n = 7

AM1/*P. aeruginosa*

p(MIC) = 0.063609 (logP) − 0.01189 (Hyd E) + 0.001282 (SAG) − 1.98186

n = 7;

AM1/*A. niger*

TABLE II: p(MIC) and Computed p(MIC) on the Basis of Framed QSAR Equations Using AM1 Methods

E. coli		*S. aureus*		*B. anthrecis*		*P. aeruginosa*		*C. albicanes*		*A. niger*	
p (MIC)	C P (MIC)	P(MIC)	CP(MIC)	P(MIC)	C P(MIC)	P(MIC)	c p(MIC)	p(MIC)	C P (MIC)	p(Mic)	c p (MIC)
−1.23045	−1.31811	−1.27875	−1.27512	−1.17609	−1.18026	−1.20412	−0.69287	−1.23045	−1.23728	−1.20412	−1.21792
−1.25527	−1.31816	−1.20412	−1.19992	−1.11394	−1.12531	−1.25527	−0.61671	−1.17609	−1.19854	−1.25527	−1.23516
−1.25527	−1.31717	−1.20412	−1.21347	−1.14613	−1.11983	−1.20412	−0.71754	−1.23045	−1.17974	−1.25527	−1.20843
−1.14613	−1.31619	−1.20412	−1.20215	−1.07918	−1.09053	−1.23045	−0.91478	−1.11394	−1.13626	−1.17609	−1.19696
−1.17609	−1.31785	−1.23045	−1.25182	−1.17609	−1.18169	−1.17609	−0.58928	−1.20412	−1.21814	−1.23045	−1.22975
−1.23045	−1.31767	−1.23045	−1.24347	−1.17609	−1.17243	−1.25527	−0.62031	−1.25527	−1.20765	−1.27875	−1.23293
−1.27875	−1.3178	−1.27875	−1.24491	−1.17609	−1.17359	−1.30103	−0.62469	−1.17609	−1.2087	−1.14613	−1.23045

TABLE III: p(MIC) and Computed p(MIC) on the Basis of Framed QSAR Equations Using PM3 Methods

E. coli		*S. aureus*		*B. anthrecis*		*P. aeruginosa*		*C. albicanes*		*A. niger*	
p (MIC)	C P (MIC)	P (MIC)	C P (MIC)	P(MIC)	C P (MIC)	P(MIC)	C P (MIC)	p(MIC)	C P (MIC)	p(Mic)	C P (MIC)
−1.23045	−1.96554	−1.27875	−1.27876	−1.17609	−0.32346	−1.20412	−1.26911	−1.23045	−1.23046	−1.20412	−1.20501
−1.25527	−2.02622	−1.20412	−1.20721	−1.11394	−0.19879	−1.25527	−1.31315	−1.17609	−1.19924	−1.25527	−1.23535
−1.25527	−1.97328	−1.20412	−1.2038	−1.14613	−0.1822	−1.20412	−1.30382	−1.23045	−1.17074	−1.25527	−1.22541
−1.14613	−1.90583	−1.20412	−1.20139	−1.07918	−0.17044	−1.23045	−1.26899	−1.11394	−1.15052	−1.17609	−1.19472
−1.17609	−1.94751	−1.23045	−1.24614	−1.17609	−0.79562	−1.17609	−1.28845	−1.20412	−1.20831	−1.23045	−1.25052
−1.23045	−1.99739	−1.23045	−1.24662	−1.17609	−0.79797	−1.25527	−1.32976	−1.25527	−1.21235	−1.27875	−1.2107
−1.27875	−1.98096	−1.27875	−1.24692	−1.17609	−0.79943	−1.30103	−1.31068	−1.17609	−1.21485	−1.14613	−1.21582

TABLE IV: p(MIC) and Computed p(MIC) on the Basis of Framed QSAR Equations Using MNDO Methods

E. coli		*S. aureus*		*B. anthrecis*		*P. aeruginosa*		*C. albicanes*		*A. niger*	
p (MIC)	C P (MIC)	p(MIC)	C P (MIC)	P(MIC)	C P (MIC)	P(MIC)	C P (MIC)	p(MIC)	C P (MIC)	p(Mic)	C P (MIC)
−1.23045	−1.21546	−1.27875	−1.27898	−1.17609	−1.17608	−1.20412	−1.20797	−1.23045	−1.23045	−1.20412	−1.21249
−1.25527	−1.26776	−1.20412	−1.2043	−1.11394	−1.11905	−1.25527	−1.25556	−1.17609	−1.19445	−1.25527	−1.24515
−1.25527	−1.20913	−1.20412	−1.20432	−1.14613	−1.1109	−1.20412	−1.22876	−1.23045	−1.16589	−1.25527	−1.23144
−1.14613	−1.18663	−1.20412	−1.20432	−1.07918	−1.10926	−1.23045	−1.20703	−1.11394	−1.16015	−1.17609	−1.16732
−1.17609	−1.20002	−1.23045	−1.24683	−1.17609	−1.17415	−1.17609	−1.21845	−1.20412	−1.20508	−1.23045	−1.25245
−1.23045	−1.25631	−1.23045	−1.24682	−1.17609	−1.17803	−1.25527	−1.27448	−1.25527	−1.21866	−1.27875	−1.21367
−1.27875	−1.2258	−1.27875	−1.24682	−1.17609	−1.17606	−1.30103	−1.24312	−1.17609	−1.21175	−1.14613	−1.20331

TABLE V: p(MIC) and Computed p(MIC) on the Basis of Framed QSAR Equations Using ZINDO Methods

E. coli		*S. aureus*		*B. anthrecis*		*P. aeruginosa*		*C. albicanes*		*A. niger*	
p (MIC)	C P (MIC)	p(MIC)	C P (MIC)	P(MIC)	C P (MIC)	P(MIC)	C P (MIC)	p(MIC)	C P (MIC)	p(Mic)	C P (MIC)
−1.23045	−1.22116	−1.27875	−1.28834	−1.17609	−1.17663	−1.20412	−1.18354	−1.23045	−1.23024	−1.20412	−1.08387
−1.25527	−1.21228	−1.20412	−1.20774	−1.11394	−1.11076	−1.25527	−1.22779	−1.17609	−1.18385	−1.25527	−1.18217
−1.25527	−1.22864	−1.20412	−1.22728	−1.14613	−1.11711	−1.20412	−1.23624	−1.23045	−1.16445	−1.25527	−1.23823
−1.14613	−1.22323	−1.20412	−1.21824	−1.07918	−1.11067	−1.23045	−1.24457	−1.11394	−1.17343	−1.17609	−1.23931
−1.17609	−1.22769	−1.23045	−1.2667	−1.17609	−1.1848	−1.17609	−1.2273	−1.20412	−1.20557	−1.23045	−1.31815
−1.23045	−1.22027	−1.23045	−1.24473	−1.17609	−1.16689	−1.25527	−1.25142	−1.25527	−1.22744	−1.27875	−1.34077
−1.27875	−1.23819	−1.27875	−1.26859	−1.17609	−1.17616	−1.30103	−1.25743	−1.17609	−1.20374	−1.14613	−1.39615

$p(MIC) = 0.012788\ (Hyd\ E) + 0.002262\ (SAG) - 0.0013\ (Vol) - 1.23802$
$n = 7;$

AM1/*C. albican*

$p(MIC) = 0.024755\ (Hyd\ E) + 0.008081\ (logP) - 0.002486\ (ZPE) - 1.45128$
$n = 7;$

AM1/*B. antherus*

$p(MIC) = 0.015109\ (Hyd\ E) + 0.042314\ (logP) - 0.002744\ (ZPE) - 1.53894$
$n = 7;$

AM1/*S. aureus*

$p(MIC) = 0.041091\ (log\ P) + 0.00339\ (ZPE) - 0.002406\ (Hyd\ E) - 1.78223$
$n = 7;$

3.2. QSAR Equations Applying PM3 Method

PM3/*E. coli*

$p(MIC) = 0.068015\ (Hyd\ E) - 0.13352\ (logP) - 0.00142\ (Vol) - 0.3731211$
$n = 7;$

PM3/*P.aeruginosa*

$p(MIC) = 0.036733\ (Hyd\ E) - 0.00134\ (Vol) - 0.08456\ (logP) + 069417$
$n = 7;$

PM3/*A. niger*

$p(MIC) = 0.010543\ (Hyd\ E) + 0.006917\ (SAG) - 0.0042\ (Vol) - 1.23791$
$n = 7;$

PM3/*C. albican*

$p(MIC) = 0.019254\ (Hyd\ E) + 0.018832\ (logP) + 0.017841\ (Pol) - 1.61703$
$n = 7;$

PM3/*B. antherus*

$p(MIC) = 0.011206\ (Hyd\ E) + 0.053223\ (logP) - 0.02936\ (Pol) - 1.80016$
$n = 7;$

PM3/*S. aureus*

$p(MIC) = 0.0023\ (Hyd\ E) + 0.52942\ (logP) + 0.034585\ (Pol) - 2.252248$
$n = 7;$

3.3. QSAR Equations Applying MNDO Method

MNDO/*E. coli*

$p(MIC) = 0.041759\ (Hyd\ E) - 0.00086\ (Vol) - 0.08402\ (logP) - 0.25849$
$n = 7;$

MNDO/*P.aeruginosa*

p(MIC) = 0.037992 (Hyd E) − 0.08924 (logP) − 0.00131(Vol) + 0.062422
n = 7;
MNDO/*A. niger*
p(MIC) = 0.01879 (Hyd E) + 0.004444 (SAG) − 0.00236 (Vol) − 1.4261
n = 7;
MNDO/*C. albican*
p(MIC) = 0.011706 (Hyd E) + 0.030577 (logP) + 0.023333 (Pol) − 1.83279
n = 7;
MNDO/*B. antherus*
p(MIC) = 0.065228 (logP) + 0.003341 (Hyd E) − 0.027155 (Pol) − 1.97735
n = 7;
MNDO/*S. aureus*
p(MIC) = 0.056513 (logP) − 5.7×10^{-5} (Hyd E) + 0.03567 (Pol) − 2.29989
n = 7

3.4. QSAR Equations Applying ZINDO Method

ZINDO/*E. coli*
p(MIC) = 0.000667 (Hyd E) − 0.003653 (log P) + 0.000254 (SAG) − 1.33166
n = 7;
ZINDO/*P.aeruginosa*
p(MIC) = 0.002923 (Hyd E) − 0.02142 (logP) − 0.000281 (Vol) − 1.00658
n = 7;
ZINDO/*A. niger*
p(MIC) = −0.0063 (Hyd E) + 0.001001 (REF) − 0.00463 (ZPE) − 0.14658
n = 7;
ZINDO/*C. albican*
p(MIC) = 0.065576 (logP) − 0.00016 (SAA) + 0.059963 (Pol) − 2.91461
n = 7;
ZINDO/*B. antherus*
p(MIC) = 0.061931 (logP) + 0.00011 (SAA) − 0.0008 (Hyd E) − 1.26357
n = 7;
ZINDO/*S. aureus*
p(MIC) = 0.00016 (SAA) + 0.037396 (logP) + 2.17×10^{-5} (Vol) − 1.33564
n = 7;

The correlation coefficient (cc) for these 3D-QSAR equations ranges from 0.670 to 0.999. This shows the nearly perfect correlation between parameters under study. Similarly, standard error (SE) for the above 3D-QSAR equations ranges from 0.020 to 0.060 which is indicative of nearly perfect equations which are selected and presented above from these studies. Some of the correlation diagrams between observed and computed values of p (MIC) on the basis of above computed 3D-QSAR equations are shown in the Figs. 2A–2F below.

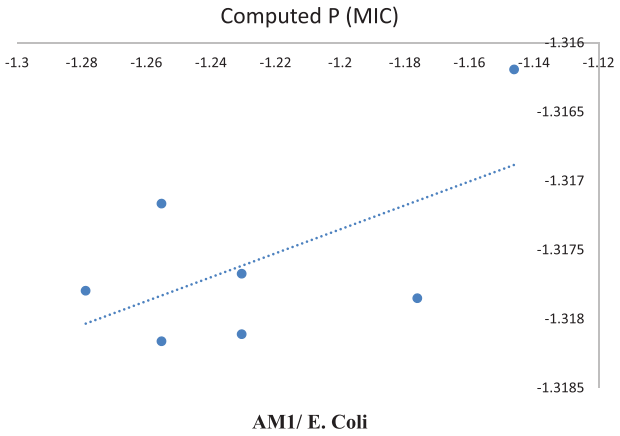
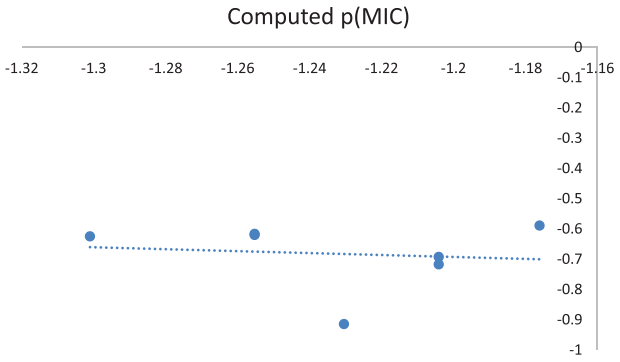
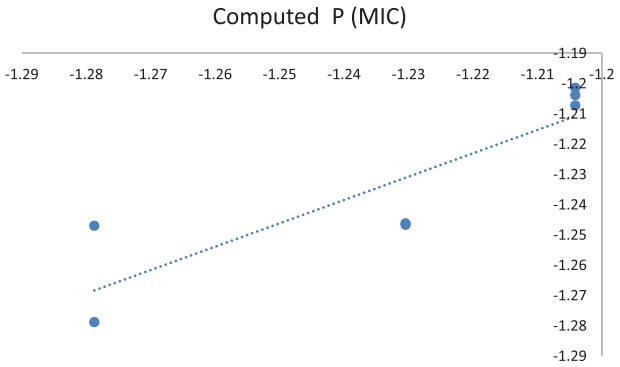


Fig. 2. (A) Correlation graph between p(MIC) and computed p(MIC).



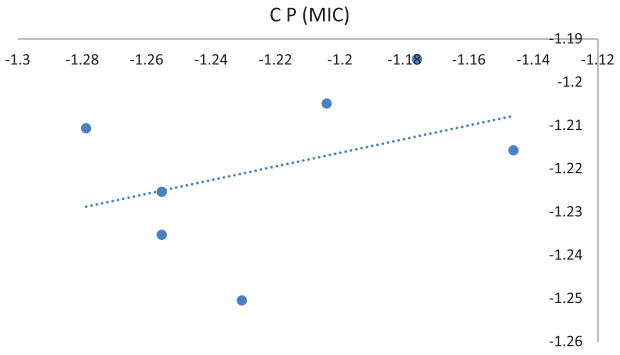
AM1/ P. Aeruginosa

Fig. 2. (B) Correlation graph between p(MIC) and computed p(MIC).



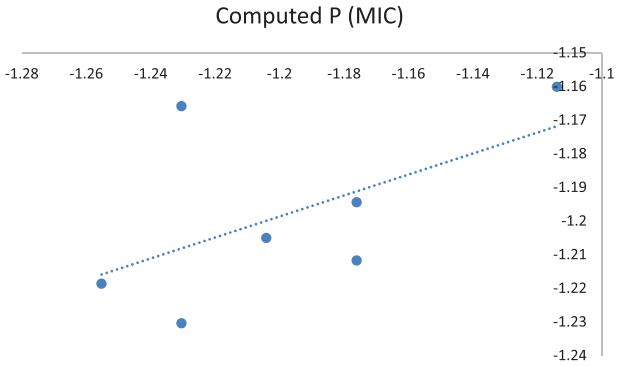
PM3/ S. Aureus

Fig. 2. (C) Correlation graph between p(MIC) and computed p(MIC).



PM3/ A. Niger

Fig. 2. (D) Correlation graph between p(MIC) and computed p(MIC).



MNDO/ C. Albican

Fig. 2. (E) Correlation graph between p(MIC) and computed p(MIC).

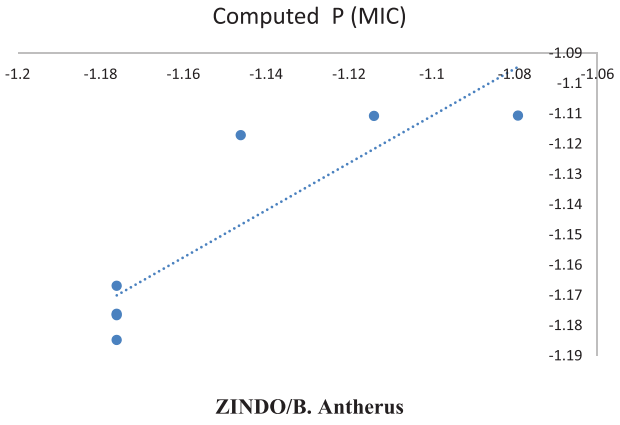


Fig. 2. (F) Correlation graph between p(MIC) and computed p(MIC).

4. Conclusions

In-silico studies are studies of interest among workers. Scientists are using different methods and software for these studies [14]–[28]. Studies present in this paper are *In-silico* studies using different semi-empirical methods viz. AM1, PM3, MNDO and ZINDO are somehow useful, reasonable and less time consuming in establishing the QSAR models for the pyrazolone compounds taken for studies for which results are reported in this paper. Among the methods employed, AM1 method comparatively provides reasonably good results.

Conflicts of Interest

The Author has no conflict of Interest.

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