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SYNTHESIS, EVALUATION AND QSAR STUDIES OF SOME SUBSTITUTED PYRAZOLE DERIVATIVES

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Key words:

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ABSTRACT: In the present paper QSAR studies related to some novel substituted pyrazole derivatives are reported. All the compounds were evaluated for antmicrobial activity viz- antifungal activity against *A. niger*. Their reported antimicrobial activities were used for Quantitative Structure Activity Relationship (QSAR) studies to find correlation between different calculated molecular descriptor of the compounds and biological activity. It is reported that five compounds viz. A-2, A-6, A-7, A-10 and A-11 showed maximum activity against *A. niger*.

INTRODUCTION: One of the key objectives of organic and medicinal chemistry is to design and synthesize molecule that possess potent therapeutic values. The rapid development of resistance to existing antimicrobial drugs generates a serious challenge to the scientific community. Consequently, there is a vital need for the development of new antimicrobial agents with potent activity against resistant microorganism [1-17]. Pyrazole derivatives have a long history of application in agrochemicals as herbicides and insecticides and in pharmaceutical industry. Due to its wide range of biological activity, pyrazoles have received a considerable interest in the field of drug discovery and therefore pyrazole ring constitute a relevant synthetic target in pharmaceutical industry. In fact, such a heterocyclic moiety represents the core structure of a number of drugs.

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QSAR is a methodology 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 activity profile [19].

Prompted by the above facts and in continuation to our efforts in the study of novel compounds for antimicrobial infection, we hereby report the quantum chemical based QSAR studies of pyrazole compounds.

Experimental:

Twelve pyrazole derivatives have been identified for their antifungal activity against *A. niger.*

All the compounds were screened for antifungal activity at 200µg/ml concentration.

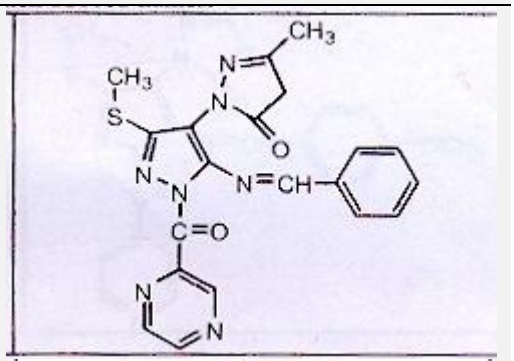
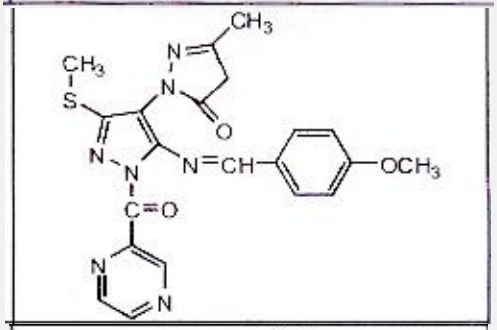
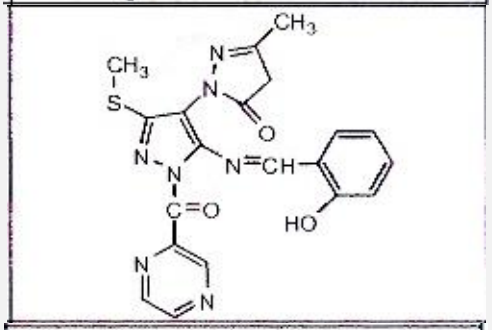
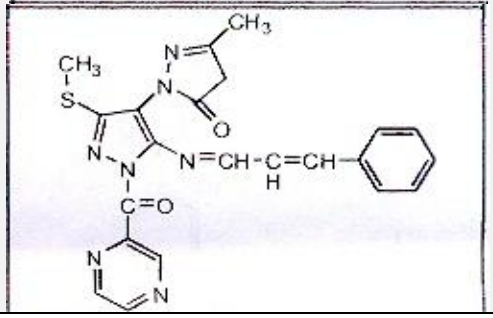
Their reported antifungal activities are mentioned in **Table 1**.

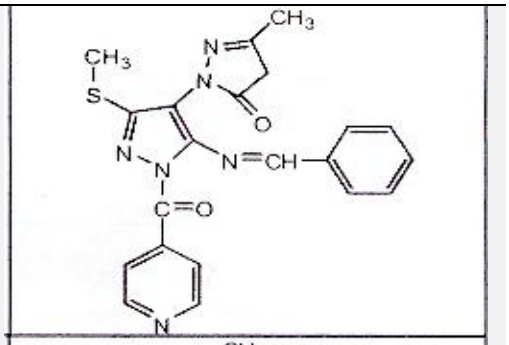
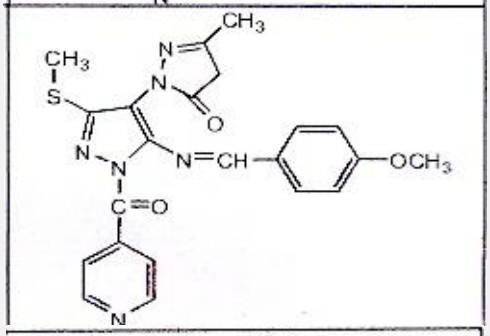
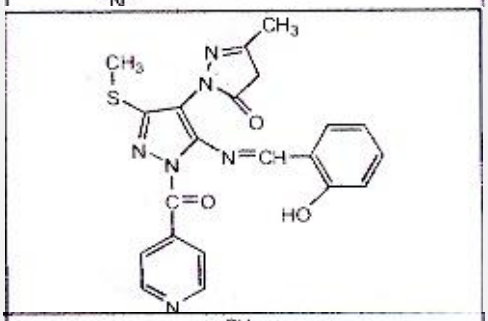
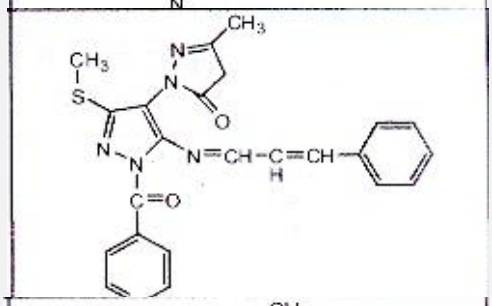
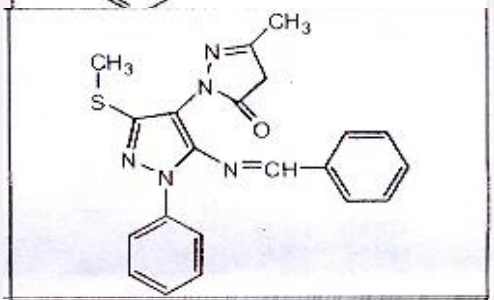
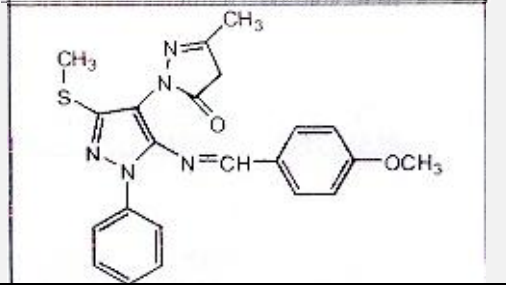
Structures of the compounds under study are mentioned in **Table 2**.

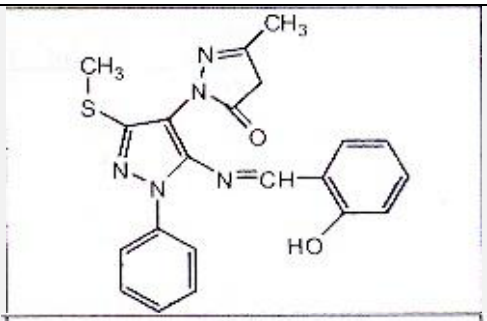
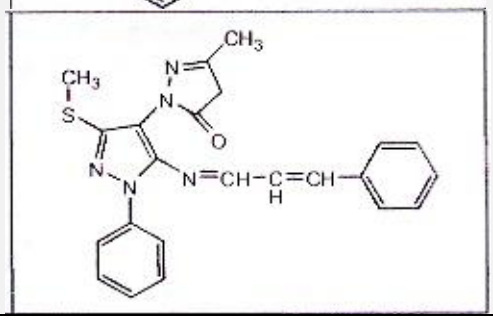
TABLE 1: ANTIFUNGAL ACTIVITY OF PYRAZOLONE COMPOUNDS

Compound	*A. niger*
A-1	12
A-2	21
A-3	21
A-4	14
A-5	16
A-6	24
A-7	23
A-8	14
A-9	12
A-10	22
A-11	20
A-12	17

TABLE 2: NAMES AND STRUCTURES OF THE COMPOUNDS USED FOR STUDY

Code	Compound	Structure
A-1	1-(5-benzylideneamino)-3-(methylthio)-1-(pyrazine-2-carbonyl)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-2	1-(5-(4-benzylideneamino)-3-(methylthio)-1-(pyrazine-2-carbonyl)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-3	1-(5-(2-benzylideneamino)-3-(methylthio)-1-(pyrazine-2-carbonyl)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-4	3-methyl-1-(3-(methylthio)-5-(3-phenylallylideneamino)--1-(pyrazine-2-carbonyl)-1H-pyrazole-4-yl)-1H-pyrazole-5(4H)-one	

A-5	1-(5-(benzylideneamino)-1-isonicotinoyl-3-(methylthio)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-6	1-(1-isonicotinoyl-5-(4-methoxybenzylideneamino)-3-3-(methylthio)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-7	1-(5-(2-hydroxybenzylideneamino)-1-isoncotinoyl-3-(methylthio)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-8	1-(1-isonicotinoyl-3-(methylthio)-5-(3-phenylallylideneamino)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-9	1-(5-(benzylideneamino)-3-(methylthio)-1-phenyl-1H-pyrazole-4-yl)-1H-pyrazole-5(4H)-one	
A-10	1-(5-(4-methoxybenzylideneamino)-3-(methylthio)-1-phenyl-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	

A-11	1-(5-(2-hydroxybenzylideneamino)-3-(methylthio)-1-phenyl-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-12	3-methyl-1-(3-(methylthio)-5-(3-phenylallylideneamino)--1-phenyl-1H-pyrazole-4-yl)-1H-pyrazole-5(4H)-one	

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Computational details:

AM1 and PM3 Hamiltonia were studied for these compounds to develop one dimensional and later three dimensional descriptors. The structures of compounds were drawn using professional version of Hyperchem software 8.0. the descriptors studied were Surface Area (SAA), Surface Area Grid (SAG), Volume (VOL), Hydration Energy (HE), Refractivity (REF), Polarisibility (POL), Total Energy (TE), Electronic Energy (EE), Heat of Formation (HF), Dipole Moment (DM), Zero Point Energy (ZPE). The calculations were conducted with the aid of Pentium core-2 duo machine with the following configuration

Intel ® core TM 2 Duo CPU

T5450@1.66GHz

982 MHz 896 MB RAM

Windows - Microsoft windows XP software as an operating system. Regression analyses to get QSAR equations were performed and statistical calculations were done with the help of MS EXCEL software.

RESULTS AND DISCUSSION:

Analytical studies of compounds:

The compounds taken for the studies were reported earlier and their structural viz. analytical spectral and other studies were also reported. Their structures were established and taken as such for the studies in the present paper. The analytical studies related to these compounds are reported in **Table 3.**

TABLE 3: PHYSICAL DATA OF THE COMPOUNDS UNDER STUDY

Compound	Mol. formula	Mol. wt.	m. p. (^{o}c)	Yield (%)
A-1	$C_{20}H_{17}N_7O_2S$	419.46	140-142	71
A-2	$C_{21}H_{19}N_7O_3S$	449.49	143-145	67
A-3	$C_{20}H_{17}N_7O_3S$	435.46	152-154	63
A-4	$C_{22}H_{19}N_7O_2S$	445.5	194-196	79
A-5	$C_{21}H_{17}N_6O_2S$	418.47	178-180	58
A-6	$C_{22}H_{20}N_6O_3S$	448.5	145-147	56
A-7	$C_{21}H_{18}N_6O_3S$	434.47	146-148	65
A-8	$C_{23}H_{20}N_6O_2S$	444.51	186-188	70
A-9	$C_{21}H_{19}N_5OS$	389.47	126-128	63
A-10	$C_{22}H_{21}N_5O_2S$	419.5	139-141	64
A-11	$C_{21}H_{19}N_5O_2S$	405.47	146-148	68
A-12	$C_{23}H_{21}N_5OS$	415.51	165-167	72

Antifungal activity:

All the compounds were screened for antifungal activity. However, compound A-2, A-6, A-7, A-10 and A-11 have showed maximum activity, while the remaining compounds have also shown moderate antifungal activity, when compared with standard Griseofulvin against *Aspergillus niger* [18].

QSAR Study:

In order to identify substituent effect of antimicrobial activity, we established a Quantitative Structure Activity Relationship (QSAR) between in-vitro antimicrobial activity and descriptors coding for electronic properties of the molecule under consideration using linear regression analysis [20-21].

Reported antimicrobial activity data in terms of MIC values were first converted into p(MIC) values and used as a dependent variable in the QSAR study. The different molecular descriptors (independent variable) like Surface Area Approximation (SAA), Surface Area Grid (SAG), Volume (VOL), Hydration Energy (HE), Log P, Refractivity (REF), Polarizability (POL), Mass, Total Energy (TE), Electronic Energy (EE), Heat of Formation (HF), Dipole Moment (DM) and Zero Point Energy (ZPE), calculated for synthesized compounds.

The generated QSAR model was selected on the basis of various statistical parameters such as correlation coefficient which is relative measure of quality of fit, Fischer's value (F-test) which represent F-ratio between the variance of calculated and observed activity, standard error, representing absolute measure of quality of fit respectively.

The best QSAR equations are discussed below:-

***A. niger*/AM1**

p(MIC) = 0.030552(HE) + 0.001631(Mass) + 1.65E-05(TE) + 0.300051

N=12, SD = 0.067833, R = 0.84592, F = 6.703166517

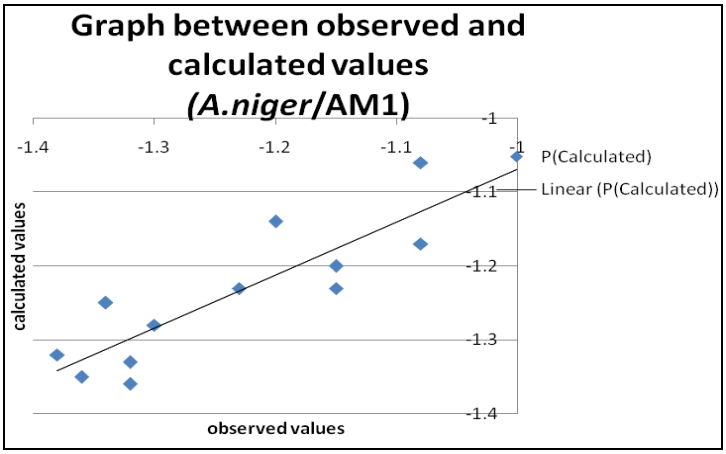


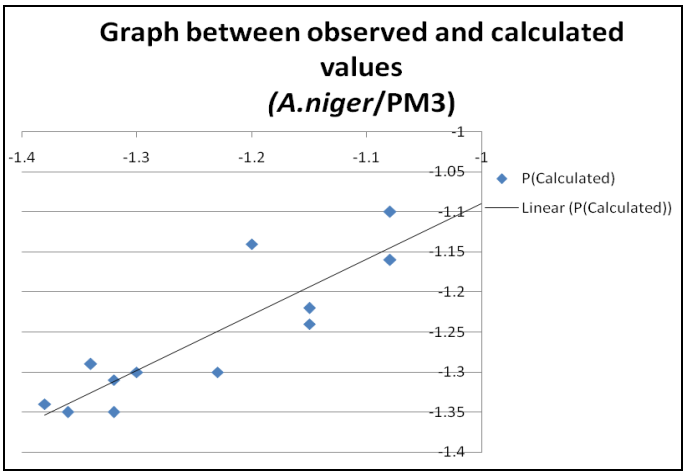
FIG. 1: LINEAR REGRESSION LINE COMPUTED AND OBSERVED P(MIC) VALUES

p(MIC) (Observed)	p(MIC) (Calculated)
-1.08	-1.17
-1.32	-1.36
-1.32	-1.33
-1.15	-1.23
-1.2	-1.14
-1.38	-1.32
-1.36	-1.35
-1.15	-1.2
-1.08	-1.06
-1.34	-1.25
-1.3	-1.28
-1.23	-1.23

***A.niger*/PM3**

p(MIC) = 0.020164(HE) + 1.45E-05(TE) + 0.000394 (HF) + 0.469788

N=12, SD = 0.068445, R = 0.84287, F = 6.542376283



p(MIC) (Observed)	p(MIC) (Calculated)
-1.08	-1.16
-1.32	-1.35
-1.32	-1.31
-1.15	-1.22
-1.2	-1.14
-1.38	-1.34
-1.36	-1.35
-1.15	-1.24
-1.08	-1.1
-1.34	-1.29
-1.3	-1.3
-1.23	-1.3

CONCLUSION: The present study involves some pyrazoles compounds (A-1 to A-12) to check their QSAR studies pertaining to their antifungal activity against *A. niger*. This may be concluded form the studies that the compounds A-2, A-6, A-7, A-10 and A-11 showed significant antifungal activity against *A. niger*. The present paper also discusses Quantitative Structure Activity Relationship equation. In conclusion this may be concluded that following parameters shows positive contributions towards p(MIC).

AM1/ *A .niger*:- HE, Mass, TE

PM3/ *A. niger*:-HE, TE, HF

TABLE 5: VARIOUS COMPUTED PARAMETERS

Compd	SAA		SAG		VOL		HE		Log P	
	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
A-1	542.45	544.31	666.28	672.93	1152.3	1161.82	-7.52	-7.69	-0.82	-0.82
A-2	599.46	588.85	709.75	699.53	1231.41	1211.02	-9.28	-8.83	-1.81	-1.41
A-3	526.83	530.08	671.28	673.12	1164.56	1167.43	-9.49	-9.99	-1.84	-1.84
A-4	559.03	559.2	720.27	713.79	1233.66	1228.91	-7.28	-7.47	-0.41	-0.41
A-5	552.17	552.13	677.77	680.99	1161.71	1170.39	-6.98	-7.09	-0.32	0.32
A-6	610.13	610.46	719.62	730.67	1240.43	1248.46	-8.66	-8.74	-0.68	-0.68
A-7	552.62	556	677.99	687.46	1180.24	1190.42	-10.88	-11.54	-0.71	-0.71
A-8	528.44	537.77	683.14	696.56	1202.3	1219.59	-5.43	-5.5	-0.66	-0.66
A-9	564.69	567.71	674.02	684.52	1172.57	1181.96	-5.31	-5.43	1.79	1.79
A-10	622.33	624.01	723.77	735.72	1251.39	1258.79	-7.02	-7.09	0.8	0.8
A-11	552.64	554.53	680.73	695.22	1182.47	1194.59	-9.33	-9.31	0.76	0.76
A-12	374.81	542.62	657.73	717.88	1139.15	1243.63	-2.1	-4.83	2.2	2.2

TABLE 5: VARIOUS COMPUTED PARAMETERS (Cont'd)

Compd	RF		POL		Mass		TE		EE	
	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
A-1	120.24	120.24	43.96	43.96	419.46	419.46	-116722	-104613	-933098	-891930
A-2	126.62	126.52	46.43	46.43	449.43	449.49	-127947	-114833	-1E+06	-1E+06
A-3	121.85	121.85	44.6	44.6	435.46	435.46	-124364	-111391	-986335	-960788
A-4	130.49	130.49	47.44	47.44	445.5	445.5	-123459	-110732	-999302	-981066
A-5	122.39	122.39	44.67	44.67	418.47	418.47	-115478	-103965	-912033	-892043
A-6	128.76	128.76	47.14	47.14	448.5	448.5	-126452	-114179	-1E+06	-994683
A-7	123.99	123.99	45.31	45.31	434.47	434.47	-122870	-110741	-976927	-955952
A-8	132.65	132.65	47.85	47.85	447.51	447.51	-124879	-113471	-1E+06	-1E+06
A-9	125.96	125.96	45.38	45.38	417.49	417.49	-113980	-103314	-909874	-888750
A-10	132.33	132.33	47.85	47.85	447.51	447.51	-124955	-113528	-1E+06	-992207
A-11	127.56	127.56	46.02	46.02	433.48	433.48	-121106	-110093	-1E+06	-960111
A-12	136.2	136.2	48.86	48.86	443.52	443.52	-132217	-109384	-1E+06	-962773

TABLE 5: VARIOUS COMPUTED PARAMETERS (CONT'd)

Compd	HF		DM		ZPE	
	AM1	PM3	AM1	PM3	AM1	PM3
A-1	423.45	112.18	1.77	0.615	226.12	216.56
A-2	134	68.03	1.57	2.07	246.98	237.55
A-3	130.81	67.02	1.82	2.18	228.83	219.92
A-4	229.87	172.52	3.05	3.58	246.72	238.14
A-5	158.6	102.15	2.25	2.2	233.82	224.29
A-6	120.15	63.13	3.35	3.17	254.72	244.37
A-7	115.61	58.59	3.47	3.59	236.67	227.72
A-8	184.81	113.49	4.62	4.5	256.33	247.46
A-9	147.45	95.18	0.52	1.18	241.45	232.01
A-10	108.59	68.28	1.07	0.51	262.36	252.09
A-11	370.42	47.7	2.07	2.1	284.24	236.1
A-12	474.93	203.85	2.45	8.76	330.07	251.48

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