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IN-VITRO EVALUATION OF NOVEL SYNTHETIC COMPOUNDS AGAINST *FUSARIUM SACCHARI*

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ABSTRACT

A total of seven Pyrazolones and Pyridines and three Schiff bases were evaluated *in-vitro* against *Fusarium sacchari*, the causative organism of wilt disease of sugarcane. The pyridine based compounds were found superior to pyrazolone compounds. Two compounds viz., 3-methyl-1-Phenyl-5-pyrazolone (**C5**) and 2-Benzyl Pyridine (**C10**) recorded significant anti-microbial activity against *Fusarium sacchari in- vitro*.

KEY WORDS: ***Fusarium sacchari*, wilt, Pyrazolones, Pyridines and Schiff base.**

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INTRODUCTION

Plant diseases are known since ancient times and fossil evidence indicates that plants were affected by diseases 250 million years ago. There are many examples of plant diseases that have made impact on society and have changed human history (Levetin and Mc Mahon, 2003). Loss of crops from plant diseases may result in hunger and starvation, especially in less developed countries where access to disease control method is limited and annual losses of 30 to 50% are common for major crops like sugarcane in countries like India. Sugarcane (*Saccharum officinarum*) is important cash crop in India as well as world and comes under family Gramineae (Poaceae). The crop is affected by several bacterial and fungal phytopathogens. Among fungal diseases include-Banded sclerotial leaf disease (*Rhizoctonia solani*), Downy mildew (*Peronosclerospora miscanthi*), Wilt disease (*Fusarium sacchari*) Pokkh boeng disease (*Fusarium moniliforme*) Red rot of sugarcane disease (*Colletotrichum falcatum*), Seedling blight (*Curvularia lunata*) etc.

Fungal plant diseases are one of the major concerns to agricultural production. It has been estimated that total losses as consequence of plant diseases reach 25% of the yield in Western countries and almost 50% in developing countries. Of this, one third is due to fungal infection (Bowyer 1999). So there is a pressing need to control fungal diseases. (Vipul Gohel, Anil Singh, Maisuria Vimal, Phadnis Ashwini and Chhatpar H.S., 2006) In the present paper, ten novel synthetic organic compounds were screened *in-vitro* against *Fusarium sacchari* (ITCC-4208). The selection of ten novel synthetic organic compounds viz; Pyrazolones, Pyridines and Schiff bases are based on the fact that none of these compounds were not previously screened against *Fusarium sacchari*. The characterization, establishment, computational studies and Structure activity relationship (SAR) of selected ten novel synthetic organic compounds also reported in this paper (Piscopo E, Diurno MV, Gangliardi R, Mazzoni O & de Francesco FM, Parrilli C, 1989, K. Suresh Babu, Xing-Cong Li, Melissa R. Jacob, Qifeng Z. Khan, Daneel Ferreira, and Alice M. Clark, 2006). The whole *in-vitro* antifungal study was focused to find out the solution for pest management of phytopathogen - *Fusarium sacchari* on local area crop of Sugarcane.

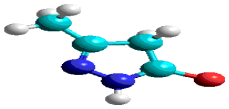
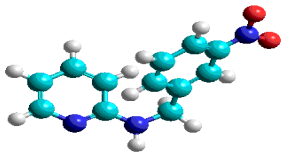
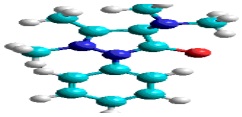
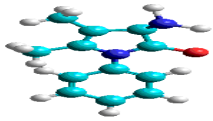
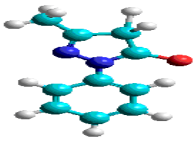
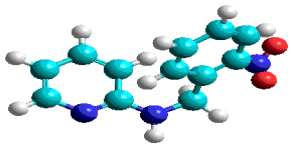
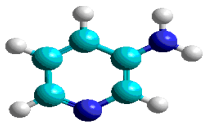
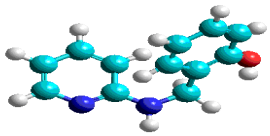
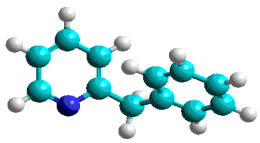
MATERIAL AND METHODS

FUNGAL CULTURE: Plant pathogen *Fusarium sacchari* (ITCC-4208) were procured from division of plant pathology, I.A.R.I. New Delhi. The test organism were cultured on Potato dextrose agar (PDA) and Potato dextrose broth (PDB) and incubated at 22-24 ºC for 5-7 days for revival and sub culturing purposes. For inoculation 100 µl. of actively growing cells of (OD 10^6–10^8 / ml.) *Fusarium sacchari* inoculated Potato dextrose broth (PDB) was used to inoculate sterile Potato dextrose agar plates through spread plate swab method.

Synthetic compounds: The ten novel *synthetic compounds of three groups viz:* Pyrazolones, Pyridines and Schiff bases (C1-C10) as listed out in Table 1 synthesized in the laboratory and their structures were confirmed by standard analytical techniques (Gurdip Singh, Om Prakash Singh, G.P. Rao and S.R. Sharma, 2002). The Structures and some physical properties of Pyrazolones, Pyridines and Schiff bases compounds are listed out in Table.1

Table 1

Structures and some physical properties of Pyrazolones, Pyridines and Schiff bases compounds are listed below.

Codes	Name of compounds	Molecular Weights	M. pt. / b. pt. 0ºc	Structures (Ball and Stick models)
1	2	3	4	5
C1 (MeP)	3-Methyl-5-Pyrazolone	70	224 - 226	
C2 (3-N-BAPy)	2-N-[3 Nitrobanzalidene] amino Pyridine	227	202 - 205	
C3 (AMPy)	Amino Pyrine	231	107 - 108	
C4 (4-AAPy)	4-Amino anti-Pyrine	203	107 - 109	
C5 (MPP)	3-Methyl-1-Phenyl-5-pyrazolone	174	124 - 126	
C6 (2-N-BAPy)	2-N-[Benzalidene] amino pyridine	227	172 - 177	
C7 (3-AMPy)	3-Amino Pyridine	94	60 - 63	
C8 (4-AMPy)	4-Amino Pyridine	94	157 - 160	
C9 (2-N-SAPy)	2-N-[Salysaldehyde] amino pyridine	198	190 - 192	
C10 (2-BzPy)	2-Benzyl Pyridine	169	140 - 143	

PREPARATION OF INOCULUM: After 5-7 days of incubation at 22-24 ºc, the test organism *Fusarium sacchari*, was revived. A loopful of culture was taken and dispensed in 50 ml. of Potato dextrose broth (PDB) in a conical flask and kept at 22-24 ºc for further 5-7 days for the preparation of inoculum (Park, Cheol Nam, Jung Min Lee, Dongho Lee and Beom Seok Kim, 2008, Maurizio Del Poeta, Wiley A. Schell, and John R. Perfect, 1997, Dong-Sun Jung, Yeo-Jung NA, and Ki Hyun Ryu, 2002, Babu Joseph, Muzafar Ahmad Dar and Vinod Kumar, 2008).

Preparation of Petri plates and media: Potato Dextrose Agar (PDA), Potato Dextrose Broth (PDB) was used. Media were cooled and then plates were prepared by dispensing 15-20 ml. media per plate. Plates were kept in the same position for ½ hour for solidification to take place and kept inverted in the incubator at 22-24 ºc over night for sterility checking.

Preparation of antimicrobial discs: Whatmann 1 filter paper discs of 6 mm. diameter were punched out from barge sheet and were autoclaved at 121ºC, at 15 lbs for 15 minute (Abdul Rashid and Narendra Singh 2002).

Preparation of serial dilutions of compounds: Each compound was 10 times serially diluted (50mg.→05mg.) in DMF (Table-2) and each dilution of each compound was tested against *Fusarium sacchari*.

Table 2
Concentrations of the test compounds used in the study.

Dilutions	Test tube No.	Concentration of Compound
D0	1	Negative control
D1	2	5 mg.
D2	3	10 mg.
D3	4	15 mg.
D4	5	20 mg.
D5	6	25 mg.
D6	7	30 mg.
D7	8	35 mg.
D8	9	40 mg.
D9	10	45 mg.
D10	11	50 mg.

Inoculation and incubation: 100 µl of actively growing cells of (OD 10^6-10^8/ml.) *Fusarium sacchari* ITCC-4208, inoculated Potato Dextrose Broth (PDB) was used to inoculate sterile Potato Dextrose Agar (PDA) plates through spread plate swab method. The whatman paper discs were dispensed on glass plates and each was load with 5µl. volume of pre designated dilution (C1→C10). 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 22-24 ºC for 5-7 days

(Bauer AW, Kirby WM, Sherris J C, Turck M, 1966).

RESULTS AND DISCUSSION

Antifungal activity of Pyrazolones and Pyridines:

A total of seven Pyrazolones and Pyridines viz; 3-Methyl-5-Pyrazolone (C1), Amino Pyrine (C3), 3-methyl-1-Phenyl-5-Pyrazolone (C5), 3-Amino Pyridine (C7), 4-Amino Pyridine (C8), 4-Amino anti-pyrine (C4) and 2-Benzyl Pyridine (C10) were tested for anti-fungal activity against *Fusarium sacchari.* Of the seven compounds tested, 2-Benzyl Pyridine (C10) was found highly effective at the higher concentrations tested (5.0 mg to 50 mg.), 3-methyl-1-Phenyl-5-pyrazolone (C5) and 4-Amino anti-pyrine (C4) were moderately effective at higher concentration i.e. 40-50 mg., and Amino Pyrine (C3) were least effective against *Fusarium sacchari*, while 3-Methyl-5-Pyrazolone (C1), 3-Amino Pyridine (C7) and 4-Amino Pyridine (C8) did not show antifungal activity against *Fusarium sacchari.*

Antifungal activity of Schiff bases:

A total of three Schiff bases viz; 2-N-[3-Nitrobanzalidene] amino Pyridine (C2), 2-N-[2 nitrobenzalidene] amino pyridine (C6) and 2-N-[Salysaldehyde] amino pyridine (C9) were tested for anti-fungal activity against *Fusarium sacchari.* Of the three Schiff bases tested only 2-N-[2 nitrobenzalidene] amino pyridine (C6) was moderately effective, at higher concentration i.e. 40-50 mg. While 2-N- [3-Nitrobanzalidene] amino Pyridine (C2) and 2-N-[Salysaldehyde] amino pyridine (C9) did not show antifungal activity against *Fusarium sacchari.* The present *in-vitro* antifungal investigation clearly demonstrates the significant antifungal activity of 2-Benzyl Pyridine (C10) and 3-methyl-1-Phenyl-5-pyrazolone (C5) [Table-3] against soil born plant pathogens *Fusarium sacchari.* The results of *in-vitro* antifungal study indicate potential use of these compounds in management of soil born fungal diseases caused by *Fusarium sacchari* since phytopathogenic fungi cause diseases in many important crop plants such as Sugarcane. There is no study available in literature on these synthetic Compounds with anti-fungal activity against *Fusarium sacchari.* This is the first study evaluating the anti-fungal activity of Pyrazolones, Pyridines and Schiff bases Compounds. The study however needs to be substantiated further in field conditions to fully elucidate its potential against plant pathogen.

Table 3

Antifungal activities of Pyrazolones and Pyridines against Fusarium sacchari.

Concen.→ / ↓Compd.	10ml DMF	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg	35 mg	40 mg	45 mg	50 mg
C1	0.0	-	-	-	-	-	-	-	-	-	-
C3	0.0	-	-	-	-	-	-	-	1. 0	1. 0	1. 0
C5	0.0	-	-	1. 0	1. 0	1. 0	1. 0	1. 0	**1. 5**	**1. 5**	**3. 5**
C7	0.0	-	-	-	-	-	-	-	-	-	-
C8	0.0	-	-	-	-	-	-	-	-	-	-
C4	0.0	-	0. 5	0. 5	0. 5	0. 5	0. 5	0. 5	0. 5	**1. 5**	**1. 5**
C10	0.0	1. 5	**4. 0**	**5. 0**	**8. 0**	**10.0**	**11.0**	**11.0**	**11.0**	**11.0**	**11.0**

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

ANALYSIS AND CHARACTRIZATION OF COMPOUUNDS

Analytical studies of Compounds:

Establishment of these compounds was carried out on some physicochemical studies viz: melting point (M. pt.) determination, CHN analysis spectral studies including IR, Mass and NMR spectral studies (R.K. Agarwal, P.C. Jain, V. Kapur & T.N. Srivastava, 1980). The preliminary investigation of the compounds viz: m. pt. / b. pt. determination, elemental analysis viz: CHN analysis of Compounds noted on usual methods in Chemistry Research Laboratory, Department of Chemistry, Govt. K.R.G. P.G. Autonomous college Gwalior M.P. CHN analysis of these compounds were carried out on Elemental analyzer Elemental Vario EL III, IR - Perkin Elmer Infrared Spectrophotometer in the range 4000 to 50m-¹, Mass - Mass Spectrometers Jeol SX-102 (FAB) and NMR spectral studies recorded on NMR Spectrometer Bruker DRX-300 at SAIF CDRI Lucknow. (R.K. Agarwal, Kishor Arora, Miss Priyanka & I. Charovati, 1993, R.K. Agarwal, Kishor Arora, & Prashant Dutt, 1994, Kishor Arora, K. P. Sharma & A.R. Khan; 2004).

Mass spectral studies of the Compounds:

Mass spectral studies of the compounds help in establishing the compounds by means of into fragmentation studies (R.M. Silverstein, C.A. Basaler and T.C. Morrell, 1997). Apart from it studies of parent ion peak in mass spectra of any compound help in the establishment of into molecular weight (P.S. Kalsi, 2002, Irving Sunshine 2002). 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 parent ions peaks for C1, C2, C3, C4, C5, C6, C7, C8, C9, C10 appears at ca 98, 231, 203, 174, 95 , 95, 170, 228, 228, 199. This confirms the molecular weights of the compounds C1, C2, C3, C4, C5, C6, C7, C8, C9, & C10 as compared to their formula weights (R.K. Agarwal and Kishor Arora, 1993, A.R. Khan, Kishor Arora and K.P. Sharma, 2004).

Infrared spectral studies of the Compounds:

Infrared absorption studies of Pyrazolones have been assigned by a comparison of these spectra with those of Pyrazole, five membered ring systems (Ram K Agarwal, Himanshu Agarwal, 1994), the mono-substituted benzene ring system (L. R. Bellamy, 1964), and with those already reported. (D.N. Sathyanarayan and C.C. Patel 1966, R.K. Agarwal, Kishor Arora and R.K. Sarin, 1994, Ram K. Agarwal and Surendra Prasad 2006). The C=O stretching frequencies occur at 1614.3, 1661, 1665 & 1598 respectively in case of MeP, AmPy, 4-AAPy & MPP (D.N. Sathyanarayan and C.C. Patel 1966, Aarti gupta, Kishor Arora and D. D. Agarwal, 2004). The strong band at ca 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 characteristic of five membered ring (R.K. Agarwal and Kishor Arora, 1993, Ram K. Agarwal and Surendra Prasad, 2006). The bands assigned to the benzene several other absorptions associated with C-H out of plane deformation modes appear in the region 980-840 Cm-¹ in Pyrazolones (Kishor Arora, K. P. Sharma & A.R. Khan; 2004, Kishor Arora, D.D. Agarwal and Aarti Gupta 2005, & Aarti gupta, Kishor Arora and D.D. Agarwal, 2004).Infrared absorption of all Schiff bases have been assigned by comparison of their spectra with those of the five membered Pyrazole ring system (Ram K Agarwal, Himanshu Agarwal, 1994), the mono substituted benzene ring system (Agarwal R.K., Kishor arora, Priyanka and Chakrovorti I, 1993), and substituted anti-pyrines [Aarti gupta, Kishor Arora and D.D. Agarwal, 2004, Kishor Arora, K.P. Sharma and A.R. Khan, 2003, R.K. Agarwal, K. Arora,

Himanshu Agarwal and R.K. Sarin, 1995, M.J.S. Dewer, E. G. Zoebisch, E.F. Healy and J.J.P. Stewart, 1994, Animesh Pathak, 2002). The notable peaks in case of Schiff base appear at ca 1604-1598 Cm-1 which are attributed to (C=N-) the azomethenic group frequencies. All other diagnostic peaks such as ring stretching, N- phenyl stretching ν (C-N), ring breathing of benzene, C-N-C bending and other deformation peaks matched well with the previous observations (K. Arora, R.K. Agarwal and G. Singh, 1995, R.K. Agarwal, K. Arora and P. Dutt., 1997, R.K. Agarwal, K. Arora, Himanshu Agarwal and R.K. Sarin, 1995).

Computational Studies of Compounds:

The most common and popular Computational (Semi-empirical) methods used today in the field of Chemi-informatics are MNDO, ZINDO, MNDO/3 AM1 and PM3 etc. In this paper we wish to report AM1, PM3, MNDO and ZINDO calculations for compounds under study. The AM1, PM3, MNDO and ZINDO, Hyperchem 8.0 software package were used to calculate the structure activity relationship (SAR) related parameters such as Heat of formation (HF), Zero point energy (ZPE) Dipole moment (DM), Hydration energy (HE), Refractivity (RF), Polarizability (PZ), Surface area (approx) (SAA), Surface area (Grid), (SAG) and Volume (VOL). All these calculations were carried out on Pentium core-2 Duo machine configuration with windows-Microsoft windows XP (K.B. Lipkowitz and D. B. Boyd, J.J. P Stewart, 1990, M.J.S. Dewer, E. G. Zoebisch, E.F. Healy and J.J.P. Stewart, 1994, Animesh Pathak, 2002).

Table 4

ntifungal activities of Schiff bases against Fusarium sacchari.

Concen.→ / ↓Compd.	10 ml DMF	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg	35 mg	40 mg	45 mg	50 mg
C2	0.0	-	-	-	-	-	-	-	-	-	-
C6	0.0	-	-	-	-	-	-	-	**1. 0**	**1. 0**	**1. 0**
C9	0.0	-	-	-	-	-	-	-	-	-	-

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

Figure 1

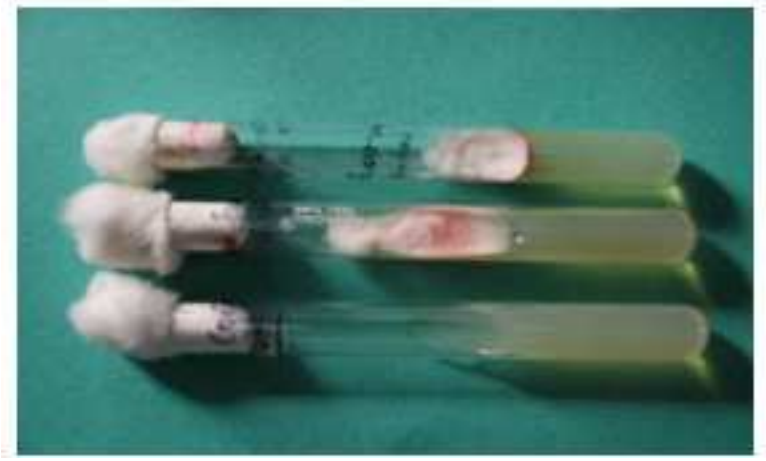


Figure 2

Figure 3

Figure 4

Figure legends:

Fig. 1, 2 Fusarium sacchari (ITCC-4208) in Petri plates and slants.
Fig. 3 Anti-microbial activity of 3-Methyl-1-Phenyl-5-pyrazolone (C-5) against Fusarium sacchari.
Fig. 4 Antimicrobial Activity of 2-Benzyl Pyridine (C-10) against Fusarium sacchari.

CONCLUSIONS

The lab reported antimicrobial data have been converted into Log values for SAR analysis (p MIC). All the computed parameters / descriptors were taken as dependent variable step wise regression analysis method (B Narasimhan, UR Kothawade, DS Pharande, VK Mourya and AS Dhake, 2003, C. Hansch, 1990, H.J. Smith and H. Willium, 1983, Kishor Arora, 2008, Dheeraj mandloi, Sheela Joshi, padmakar V. Khadikar & Navita Khosla, 2005, Sheela Joshi, & Navita Khosla, 2003, Piscopo E, Diurno MV, Gangliardi R, Mazzoni O & de Francesco FM, Parrilli C, 1989, K. Suresh Babu, Xing-Cong Li, Melissa R. Jacob, Qifeng

Z. Khan, Daneel Ferreira, and Alice M. Clark, 2006), was used to develop the SAR equation statistical parameters such as Correlation coefficient (CC), Standard error (SD), and Fischer test (F-test) etc. were considered to select best SAR Model. When set of parameters / descriptors were subjected to stepwise linear regression analysis in order develop the SAR equations with different values of CC, SD and F-test. In present study following significant SAR equation were obtained.

p (MIC) = (-0.15691) DM + 0.399992
N =7, SD = 1.613348, CC = 0.85493,
F-test = 0.025967
p (MIC) = (7.52374E-05) HF + 0.192542604
N =7, SD =1741.265352,
CC = 0.999997629,
F-test = 2.48397E-21

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