Research Article Impact Factor: 4.226 ISSN: 2319-507X
N. G. Ghodile, IJPRET, 2017; Volume 6 (2): 193-199 IJPRET

INTERNATIONAL JOURNAL OF PURE AND APPLIED RESEARCH IN ENGINEERING AND TECHNOLOGY

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SPECIAL ISSUE FOR INTERNATIONAL LEVEL CONFERENCE "ADVANCES IN SCIENCE, TECHNOLOGY & MANAGEMENT" (IC-ASTM)

SYNTHESIS AND CHARACTERISATION OF SOME NEW CHLOROSUBSTITUTED ANALOGUES OF IMIDAZOLE-PYRAZOLINES AND THEIR IMPACT ON PATHOGENS RESPONSIBLE FOR *OYSTER MUSHROOM* CROP DISEASES

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Accepted Date: 05/09/2017; Published Date: 10/10/2017

Abstract: The heterocyclic compounds mainly constituted by the involvement of Nitrogen are frequently reported for their utility in the various fields *viz*. agricultural, medicinal, pharmaceutical and industrial. The heterocycles involving pyrazolines nucleus were reported for their broad spectrum of pharmacological and agricultural activities. The incorporation of an active moiety in the structure of heterocyclic compounds enhances properties associated with it. This has proven useful in the development of newer potent heterocycles possessing several activities. In this context, we have recently synthesised 1-phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-N-methyl-N-[(2'-hydroxy-5'-chlorophenyl)ethanonylamino]-4,5-dihydro-Δ^2-pyrazoline (3), 1-phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-[2-methyl -thio-4-(2'-hydroxy-5'-chlorophenyl)imidazolo]-4,5-dihydro-Δ^2-pyrazoline(4) and their acetyl analogues(5) from 1-Phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-N,N-dimethyl-amino-4,5-dihydro-Δ^2-pyrazoline (1) and studied their antipathogenic assay against the pathogens damaging *Oyster mushroom* cultivation *viz.* fungi *G. roseum*, *V. fungicola* and bacteria *P. stutzeri*, *P. alcaligens, P. fluorescene, B. gladioli.*

Keywords: Pyrazolines, α-amino ketone of pyrazolines, imidazole derivatives of pyrazolines, acetyl analogues of imidazolo-pyrazolines and antipathogenic assay.

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How to Cite This Article:

N. G. Ghodile, IJPRET, 2017; Volume 6 (2): 193-199

INTRODUCTION

The chemistry of heterocyclic compounds is as logical as that of aliphatic or aromatic compounds. Heterocyclic compounds occur widely in nature and in a variety of non-naturally occurring compounds. A large number of heterocyclic compounds are essential to life. Various components such as haemoglobins, vitamins, antibiotics, hormones, alkaloids, large number of synthetic drugs, dyes, many dyestuffs and pigments contain heterocyclic moiety. Of the twenty amino acids commonly found in proteins, three, namely histidine, proline and tryptophan, are heterocyclic. They have a wide range of applications such as pharmaceuticals, agro-chemicals and veterinary products[1].

Amongst nitrogen containing five membered azoles, pyrazolines and their analogues have seems to be most useful towards biological activities and have attracted the chemists to undertake their synthesis. Various workers have developed several procedures to find out the more convenient route for the synthesis of pyrazoline involved the treatment of α,β-unsaturated carbonyl compounds with hydrazine or phenylhydrazine proceed *via* the cyclization of intermediate hydrazone or phenylhydrazone in combination with different solvents. In some of the cases substituted hydrazine[2-4] and isatinhydrazide have also been reported in preparation of substituted Δ^2-pyrazolines.

Some of their derivatives show the fungicidal and plant growth regulatory activities[5,6]. Besides this their prominent activities are anti-epileptic[7], anti-inflammatory[8], antidepressant[9], analgesic[10], antiamoebic[11], antituberculotic[12], antioxidant[13], anticonvulsant[14], antinociceptive[15], antiproliferative[16], and antibacterial[17-18] activities.

Kumar *et al.*[19] reported the synthesis of 4-bromo-3(substituted phenyl)-5-(substitutedphenyl)-1-phenyl-2-pyrazolines by the cyclization of bromo-substituted 1,3-diphenylprop-2-en-1-one with substituted hydrazine as antioxidant and anti-inflammatory agents.

Bhoyar *et al.*[20] reported the synthesis of 3-(2-hydroxy3,5-dichloro-phenyl)-4-substituted-1-phenyl-Δ^2-pyrazolines from 3-aroyl-6,8-dichloro-flavanones and phenyl-hydrazinehydrochloride in DMF containing piperidine with good percentage of yield.

Sreenivasa *et al.*[21] investigated a novel series of pyrazolines bearing imidazole moiety for analgesic and anti-inflammatory activities. The target molecules were synthesized by the cycloaddition reactions of *N*-(nitrobenzyl)-imidazole nitrile imines with different dipolarophiles.

Considering the applicability of pyrazoline in the field of agriculture, we have undertaken the synthesis of 1-phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-N-methyl-N-[(2'-hydroxy-5'-chlorophenyl)ethanonylamino]-4,5-dihydro-Δ^2-pyrazoline (3), 1-phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-[2-methylthio-4-(2'-hydroxy-5'-chlorophenyl) imidazolo]-4,5-dihydro-Δ^2-pyrazoline (4) and their acetyl analogues (5) from 1-Phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-N,N-dimethyl-amino-4,5-dihydro-Δ^2-pyrazoline (1) and screened the titled compounds against the pathogens damaging *Oyster mushroom* cultivation *viz. G. roseum*, *V. fungicola, P. stutzeri*, *P. alcaligens, P. fluorescene, B. gladioli.*

EXPERIMENTAL:

The structure of all the newly synthesised compounds was characterised on the basis UV, IR and NMR. The UV-Vis spectra were taken in ethanol solvent. IR spectra were recorded on Perkin-Elmer spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance-II 400 NMR spectrophotometer in CDCl3 using TMS as an internal standard.

Preparation of 1-phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-N-methyl-N-[(2'-hydroxy-5'-chlorophenyl)ethanonylamino]-4,5-dihydro-Δ^2- pyrazoline (3):

1-Phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-N,N-dimethyl-amino-4,5-dihydro-Δ^2-pyrazoline (1) (0.01M) was refluxed with 1-(2- hydroxy-5-chlorophenyl)-2-bromoethanone (2) (0.01M) in absolute ethanol for about 1 hour. After cooling, the reaction mixture was decomposed in ice-cold water. The product, thus separated, was filtered and crystallized from ethanol to get the compound 3.

M.F. $C_{31}H_{25}N_3O_4Cl_2$ (3): Pale yellow amorphous solid, m.p.102 ^{o}C, yield 70 %, Elemental analysis (%): **C** 64.77/64.81, **H** 4.33/4.39, **N** 7.24/7.31, **O** 11.08/11.14, **Cl** 12.27/12.34. UV (ethanol): λmax 385 nm, n→ π* transition. IR (KBr) (cm-1): 3600-2800 (-OH stret.), 3066.60 (Ar. C-H stret.), 2925.63 (Ali. C-H stret.), 1627.52 (C=O stret.), 1644.54 (C=O stret.), 1284.54 (C-O stret.), 767.47 (C-Cl stret.). ^{1}H NMR (δ ppm): 2.62 (s, 3H, -NC**H**$_3$), 6.8 (s, 2H, N-C**H**$_2$-CO), 6.87 (d, 1H, C**H**-CH-CO-Ph), 6.9 (d, 1H, CH-C**H**-CO-Ph), 7.0-8.2 (m, 16H, Ar-**H**), 1.6 (s, 1H, -N**H**), 12.13 (s, 1H, O-**H**). 10.8 (s, 1H, -O**H**), 12.8 (s, 1H, -O**H**).

Preparation of 1-phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-[2-methylthio-4-(2'-hydroxy-5'-chlorophenyl)imidazolo]-4,5-dihydro-Δ^2- pyrazoline (4):

1-Phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-N-methyl-N-[(2'-hydroxy-5'-chlorophenyl)ethanonylamino]-4,5-dihydro-Δ^2-pyrazoline (3) (0.01M) was refluxed with potassium thiocyanate (0.01M) for 4 hours in glacial acetic acid. After cooling, the reaction mixture was poured into ice-cold water and the product, thus separated, was crystallized from ethanol-acetic acid mixture to get the compound 4.

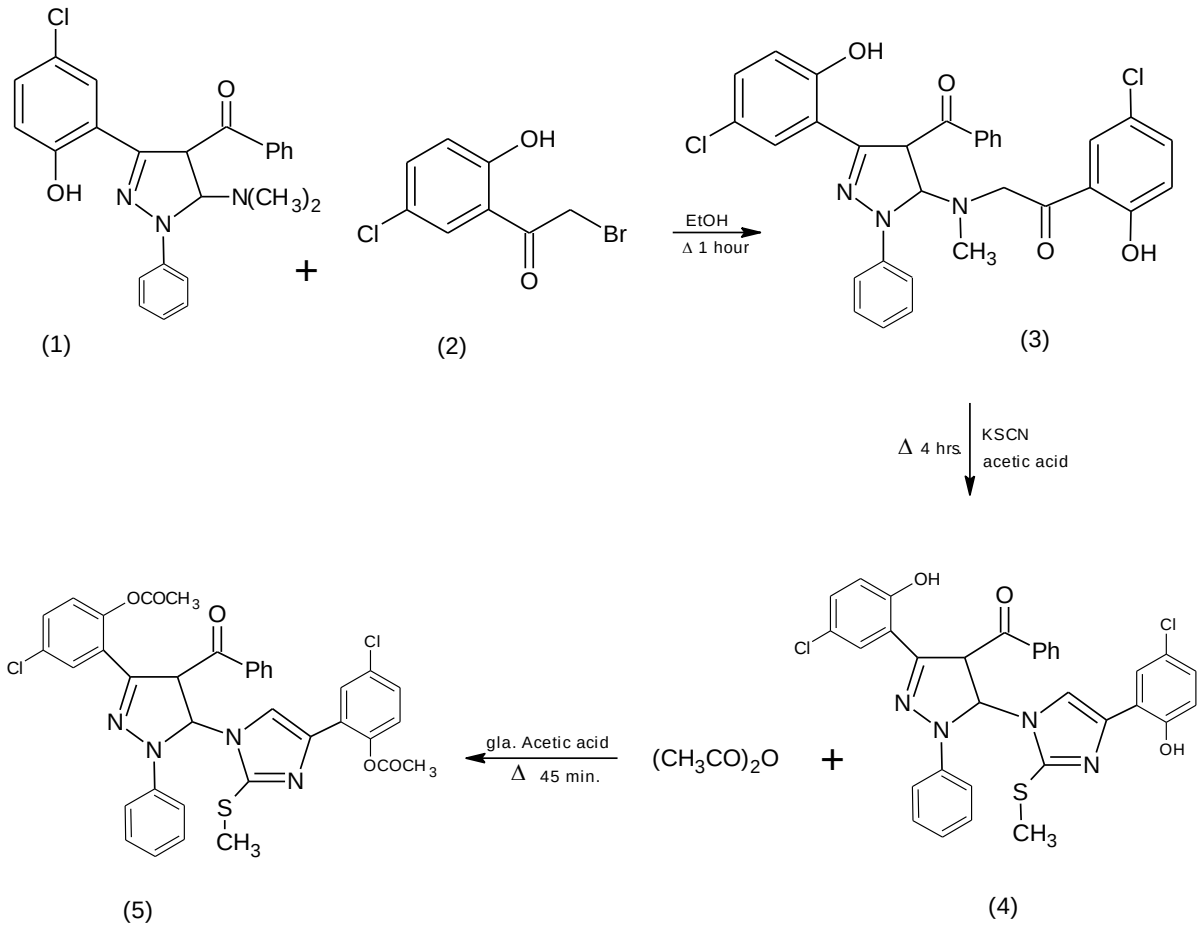
M.F. $C_{32}H_{24}N_4O_3SCl_2$ (4): Yellow amorphous solids, m.p. 38^{o}C, yield 73 %; Elemental analysis (%): **C** 62.36/62.44, **H** 3.88/3.93, **N** 9.06/9.10, **O** 7.72/7.80, **S** 5.14/5.21, **Cl** 11.44/11.52; UV (ethanol): λmax 390 nm, n→ π* transition, IR (KBr) (cm^{-1}): 3500-2400 (-OH stret.), 3064.35 (Ar. C-H stret.), 2923.40 (Ali. C-H stret.), 1646.23 (C=O stret.), 1604.34 (C=N stret.), 1283.23 (C-O stret.), 768.18 (C-Cl stret.), ^{1}H NMR (δ ppm): 2.6 (s, 3H, -C**H**$_3$), 6.81 (d, 1H, C**H**-CH-CO-Ph), 6.95 (d, 1H, CH-C**H**-CO-Ph), 7.01-8.18 (m, 16H, Ar-**H**), 10.85 (s, 1H, -O**H**), 12.14 (s, 1H, -O**H**).

Preparation of 1-phenyl-3-(2-acetyloxy-5-chlorophenyl)-4-benzoyl-5-[2-methylthio-4-(2'-acetyloxy-5'-chlorophenyl)imidazolo]-4,5-dihydro-Δ^2- pyrazoline (5):

1-Phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-[2-methylthio-4-(2'-hydroxy-5'-chlorophenyl)imidazolo]-4,5-dihydro-Δ^2-pyrazoline (4) (0.01M) was refluxed with acetic anhydride for 45 min. in glacial acetic acid. After cooling, the reaction mixture was decomposed in water and the product, thus separated, was crystallized from ethanol-acetic acid mixture to get the compound 5.

M.F. $C_{36}H_{28}N_4O_5SCl_2$ (5): Yellowish crystalline solids, m.p.98°C, yield 67 %, Elemental analysis (%): **C** 61.77/61.80, **H** 3.89/4.03, **N** 7.97/8.01, **O** 11.36/11.43, **S** 4.50/4.58, **Cl** 10.04/10.14; UV (ethanol): λmax 410 nm, n→ π* transition, IR (KBr) (cm^{-1}): 3065.54 (Ar. C-H stret.), 2927.87 (Ali. C-H stret.), 1640.89 (C=O stret.), 1601.28 (C=N stret.), 1271.13 (C-O stret.), 765.22 (C-Cl stret.), ^{1}H NMR (δ ppm): 2.6 (s, 3H, -C**H**$_3$), 6.85 (d, 1H, C**H**-CH-CO-Ph), 6.93 (d, 1H, CH-C**H**-CO-Ph), 7.07-8.23 (m, 16H, Ar-**H**).

SCHEME:



ANTIMICROBIAL SCREENING:

The Pyrazolines (1), α-amino ketone of pyrazolines (3), imidazole derivatives of pyrazolines (4) and their acetyl analogues (5) were essayed for their antifungal and antibacterial efficacy by cup plate method against causal organisms responsible for *Oyster mushroom* crop diseases *viz.* some fungi *Gliocladium roseum (Link) Bainier*, *Verticillium fungicola* and some bacteria *Pseudomonas stutzeri*, *Pseudomonas alcaligens, Pseudomonas fluorescene, Burkholderia gladioli.*

The petriplates were prepared with 25 ml sterile medium using potato carrot agar for fungal organisms and nutrient agar for bacterial organisms. In each plate 8 mm wells were made using sterile cork borer and the bottom of the wells were seal by adding single drop of melted agar. 1 ml suspension was allowed to inoculate over the agar medium to form a uniform distribution of test organism culture. Followed by 100µl test solution of 0.01 mol concentration prepared in appropriate solvent was added into the wells. The bacterial petriplates were then incubated at 37°C for 24 hrs. and fungal petriplates at 27°C for 48 hrs. Between this time period activity exhibited with the development of the zone of inhibition at the peripheral of the well. The discs of *Carbendizium* (10mcg/disc), and *Gentamycine* (10mcg/disc) were used as positive control. The zones of inhibition were measured in mm by using Himedia Zone Reader Scale. The inhibitory effects of compounds against these organisms are given in Table-1.

TABLE-1: Antimicrobial screening of titled compounds against *Oyster mushroom* crop pathogens.

S.N.	Compounds	Zone of inhibition (mm)					
		Fungal pathogens		Bacterial pathogens			
		G. roseum	*V.fungicola*	*P. stutzeri*	*P. alcaligens*	*P. fluorescene*	*B. gladioli*
1.	1	11	09	10	12	11	09
2.	3	09	08	10	10	13	12
3.	4	18	16	13	20	18	22
4.	5	12	11	14	13	15	22
5.	*Carbendizium*	09	09	--	--	--	--
6.	*Gentamycine*	--	--	08	08	08	08

RESULTS AND DISCUSSION:

The antimicrobial activity reported in this study reveals that the newly synthesised compounds 1-phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-N,N-dimethyl-amino-4,5-dihydro-Δ^2-pyrazoline (1), 1-phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-N-methyl-N-[(2'-hydroxy-5'-chlorophenyl)ethanonylamino]-4,5-dihydro-Δ^2-pyrazoline (3), 1-phenyl-3-(2-hydroxy-5-chlorophenyl)-4-benzoyl-5-[2-methylthio-4-(2'-hydroxy-5'-chlorophenyl) imidazolo]-4,5-dihydro-Δ^2-pyrazoline (4) and 1-phenyl-3-(2-acetyloxy-5-chlorophenyl)-4-benzoyl-5-[2-methylthio-4-(2'-acetyloxy-5'-chlorophenyl)imidazolo]-4,5-dihydro-Δ^2- pyrazoline (5) found to be effective against pathogenic fungi *G. roseum*, *V. fungicola* and bacteria *P. stutzeri*, *P. alcaligens, P. fluorescene, B. gladioli.*

The results obtained was compared with the activities of standard antifungal and antibacterial agents like *Carbendizium* and *Gentamycine* and appreciate that the imidazole blend of pyrazolines shows greater efficacy toward the test organism. Also showed prominent activity that pyrazoline and their derivatives.

ACKNOWLEDGEMENT:

We are thankful to Central Instrumentation Laboratory and SAIF, Panjab University, Chandigarh for their consultancy in providing the UV, IR and NMR spectrum. We highly acknowledged to NCIM, NCL, Pune and MTCC, CSIR, Chandigarh for supply of microorganism. We also thanks to the faculty of Department of Microbiology, Shankarlal Khandelwal College, Akola for their help during the study of antimicrobial screening of titled compounds of the present work.

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