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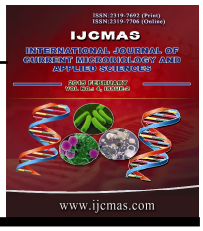

Original Research Article

Synthesis and Characterization of some new Synthesis of 1-acetyl-3-(4-nitrophenyl)-5-(substituted phenyl) pyrazoline Derivative and antimicrobial activity

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K e y w o r d s

Pyrazoline, Structure, activity relationships, Synthesis

A B S T R A C T

Pyrazolines, the well-known five-membered nitrogen-containing heterocyclic compounds, have received considerable interests in the fields of medicinal and agricultural chemistry because of their broad spectrum of biological activities. To discover more potent antifungal compounds, a series of structurally related 1,3,5-trisubstituted-2-pyrazoline derivatives have been synthesized by introducing furan rings regarded as bioactive substructure into the scaffold of pyrazolines and tested for their activities against six plant pathogenic fungi in vitro. The preliminary bioassays indicated that almost all synthesized compounds had displayed variable growth inhibitory effects on the tested pathogenic fungi. In particular 3,5-diaryl-4,5-dihydropyrazole regioisomers, and their 1-acetylated derivatives, bearing a 3,4,5-trimethoxyphenyl moiety combined with a variety of substituted phenyl rings, was synthesized and evaluated for antitumor activity. Results of the in vitro assay against a non-small cell lung carcinoma cell line (NCI-H460) showed several compounds to be endowed with cytotoxicity in micromolar to sub-micromolar range, depending on substitution pattern and position of aryl rings on 4,5-dihydropyrazole core. Potent and selective activity was also observed in the NCI 60 human cancer cell line panel

Introduction

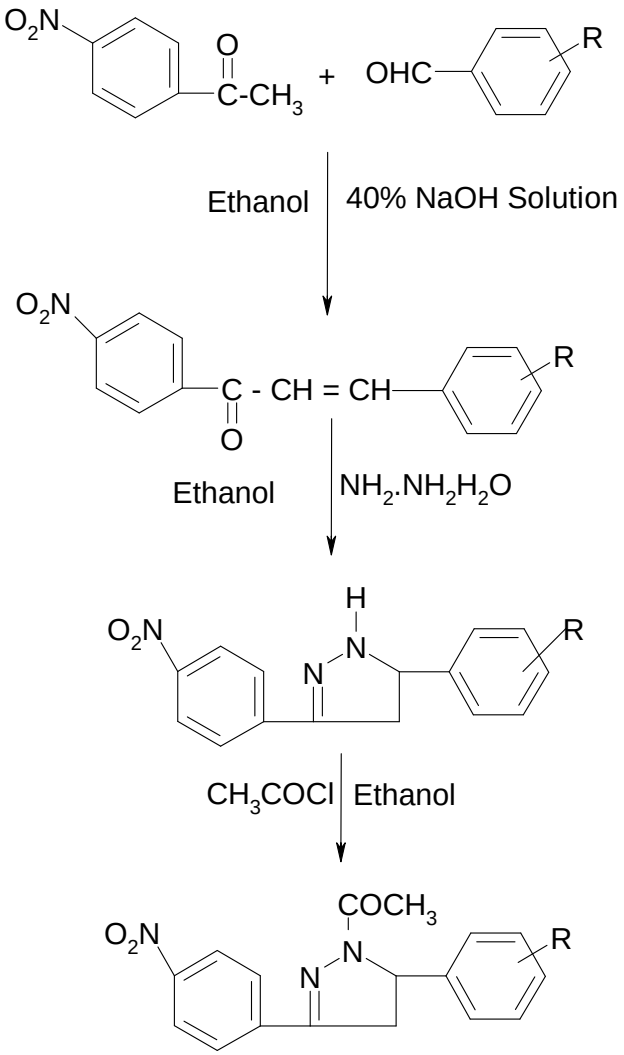
Diversely substituted pyrazolines and their derivatives embedded with variety of functional groups are important biological agents and a significant amount of research activity has been directed towards this class. In particular, they are used as antitumor, antibacterial, antifungal antiviral, antiparasitic, anti-tubercular and insecticidal agents. Some of these compounds have also anti-inflammatory, anti-diabetic, anaesthetic, analgesic, and potent selective activity such as Nitric oxide synthase inhibitor and cannobinoid CB1 receptor antagonists activity. A classical synthesis of these compounds involves the base catalyzed aldol condensation reaction of aromatic ketones and aldehydes to give unsaturated ketones (chalcones), which undergo a subsequent cyclization reaction with hydrazines affording 2-pyrazolines in this method, hydrazones are formed as intermediates, which can be subsequently cyclizing to 2-pyrazolines in the presence of

a suitable cyclizing reagent like acetic acid. In recent years, a significant portion of research in heterocyclic chemistry has been devoted to 2-pyrazolines containing different aryl group as substituent's, as evident from the literature. The preceding section of the review is focusing on the recent development on pyrazolines along with their biological properties.[8]

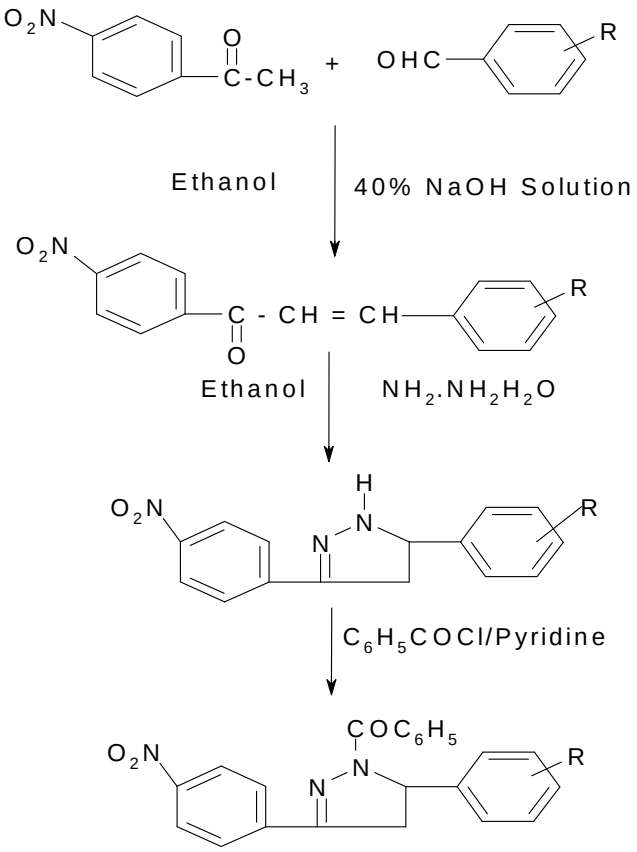
Synthesis and characterization of pyrazoline derivatives has been a developing field within the realm of heterocyclic chemistry for the past several year because of their ready accessibility and broad spectrum of biological activity Pyrazoline derivative have been found to be antitumor, and immunosuppressive agents. Survey of literature in recent past reveals that some pyrazoline derivatives possess cerebro-protective effect and CNS-depressant activity.

Synthesis of compounds involves the following steps:

Synthesis of 1-acetyl-3-(4-nitrophenyl)-5-(substituted PHENYL) pyrazoline :-

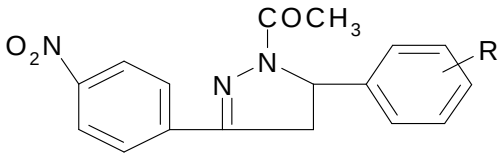


Synthesis of 1-benzoyl-3-(4-nitrophenyl)-5-(substituted phenyl) pyrazoline :-

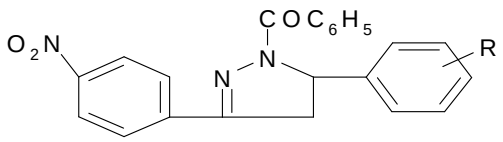


In present study pyrazolines were prepared and screened for antimicrobial, insecticidal and anthelmintic activities (given in chapter No. 5, 6, and 7). The compound were synthesized

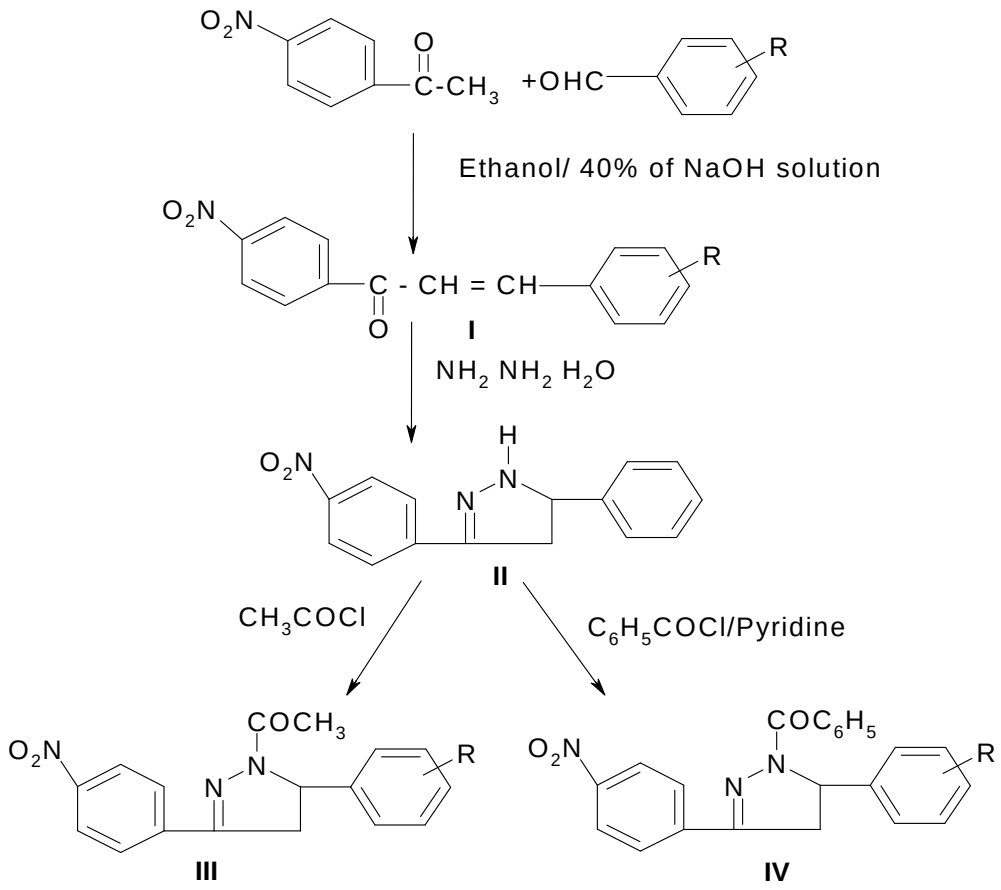
Synthesis of compounds: The compounds selected in the present study may be given general formula.



R = H, 4-OCH_3, 3-NO_2, 2-Cl, 4-Cl, 2-OH, 4-OCH_3, 3,4,5 Tri methyl, 2-NO_2, 2-OH



R = H, 4-OCH_3, 3-NO_2, 2-Cl, 4-Cl, 2-OH, 4-OCH_3, 3,4,5 Tri methyl, 2-NO_2, 2-OH



Materials and Methods

Step;-1 1-(4-nitrophenyl)-3-(substituted phenyl) prop-2-en-1-one :

p-nitroacetophenone (0.01 mol) was dissolved in ethanol. Aromatic substituted aldehyede (0.01mol) was added and the solution was heated to boiling. To this solution 40% NaOH was added with constant stirring. A yellow orange coloured mass was obtained which was kept overnight and acidified by 10% HCl washed with 10% $NaHCO_3$ followed by water and crystallized from ethanol.

Step;-2 Synthesis of 1H-3-(4-nitrophenyl)-5-(substituted phenyl) pyrazolines :

4-nitro substituted chalcone (I) dissolved in ethanol (25 ml) and hydrazine (0.02mol) was added to it. The reaction mixture was refluxed for 2hrs, cooled concentrated and allowed to stand overnight. The resulting solid which separated out was recrystallized from ethanol.

Step;-3 Synthesis of 1-acetyl-3-(4-nitrophenyl)-5-(substituted phenyl) pyrazoline:

Compound II and acetyl chloride (10 ml) were refluxed for 4hrs. The reaction mixture was then concentrated, allowed to cool. The solid was filtered, washed with water and recrystallized from ethanol.

Reaction II

Step;-4 1-(4-nitrophenyl)-3-(substituted phenyl) prop-2-en-1-one :

p-nitroacetophenone (0.01 mol) was dissolved in ethanol. Aromatic substituted

aldehyede (0.01mol) was added and the solution was heated to boiling. To this solution 40% NaOH was added with constant stirring. A yellow orange coloured mass was obtained which was kept overnight and acidified by 10% HCl washed with 10% $NaHCO_3$ followed by water and crystalized from ethanol.

Step;-5 Synthesis of 1H-3-(4-nitrophenyl)-5-(substituted phenyl) pyrazolines :

4-nitro substituted chalcone (I) dissolved in ethanol (25 ml) and hydrazine (0.02 mol) was added to it. The reaction mixture was refluxed for 2hrs, cooled concentrated and allowed to stand overnight. The resulting solid which separated out was recrystallized from ethanol.

Step;-6 Synthesis of 1-benzoyl-3-(4-nitrophenyl)-5-(substitutedphenyl) pyrazoline

Compound II was dissolved in pyridine and benzoyl chloride stirred at room temperature for 1hr, after which the reaction mixture was treated with cold dilute HCl. The resulting solid was filtered washed successively with water, NaOH (2%) and finally crystallized from glacial acetic acid.

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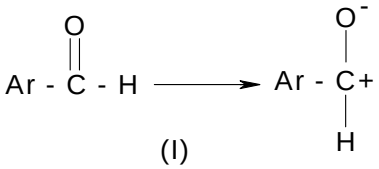
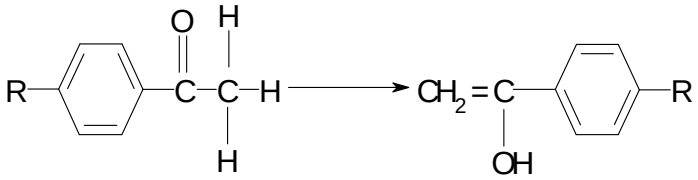
Mechanism

The mechanism involves the aromatic aldehyde rearranged into carbonium ion (I) intermediate with the negative charge on the oxygen atom.



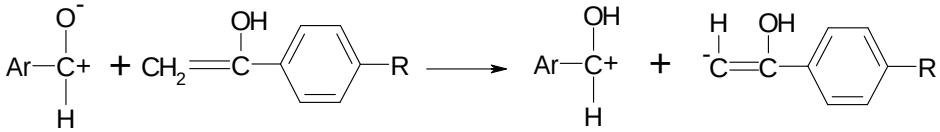
(I)

Acetophenone derivative is rearranged into its enolic form (II) in presence of strong alkali



(II)

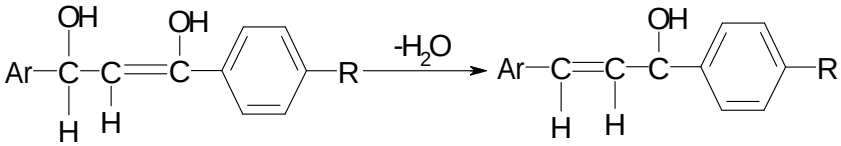
This enolic form donates a proton from the □-carbon to condense with the oxygen atom of aldehyde.



(III)

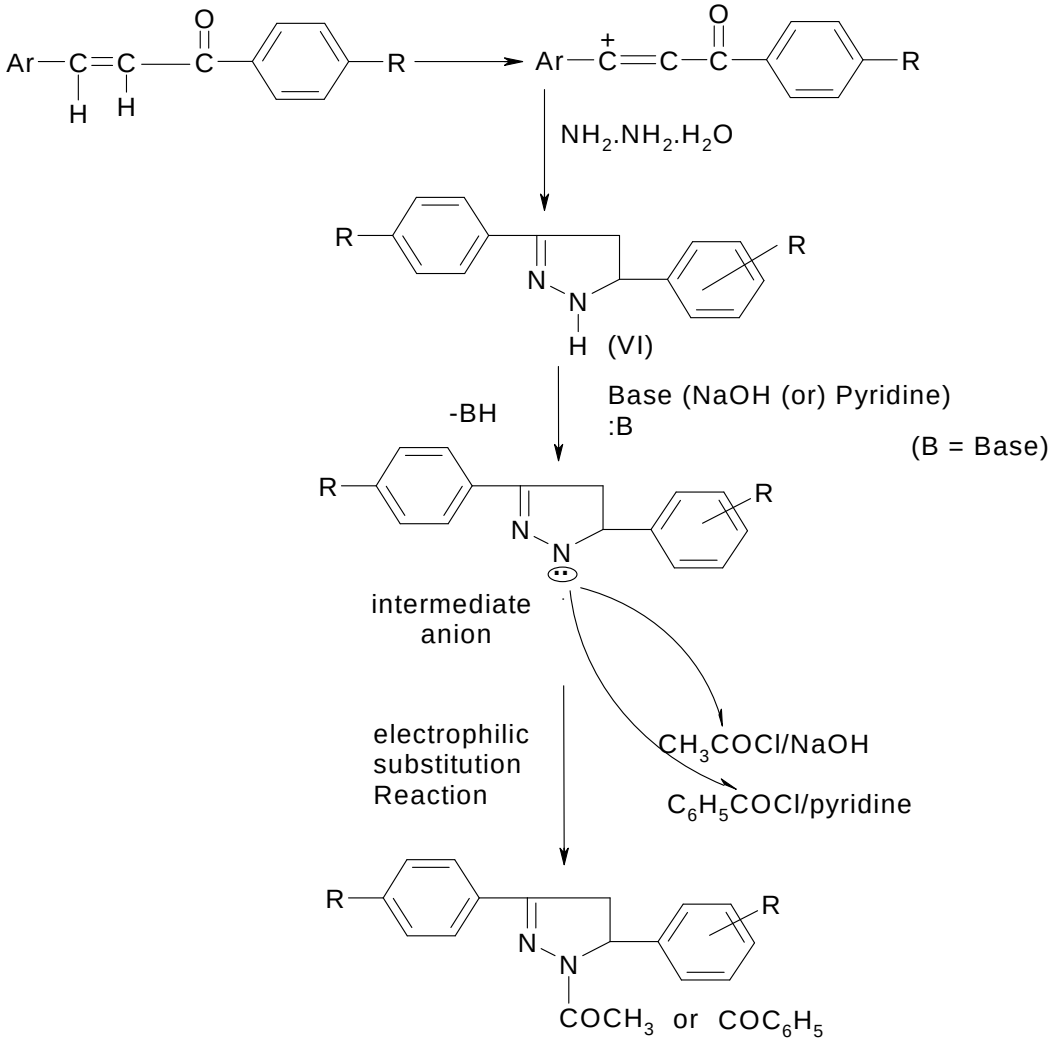
The carbanion ion (III) which condenses with the aromatic carbonium ion gives a diol (IV)

which again rearranged by elimination of water molecule to form chalcones (V).



(IV) (V)

These chalcone derivatives (V) cyclised on reacting with hydrazine hydrate to give substituted pyrazoline (VI).



Yellow crystals, yield: 84.2%; M.p.: 156–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 3.12 (dd, 1H, J_1 = 4.4 Hz, J_2 = 18.0 Hz), 3.80 (dd, 1H, J_1 = 12.0 Hz, J_2 = 17.6 Hz), 5.66 (dd, 1H, J_1 = 4.8 Hz, J_2 = 12.0 Hz), 6.54 (t, 1H, J = 0.8 Hz), 6.78 (d, 1H, J = 3.6 Hz), 7.50–7.59 (m, 3H), 8.09–8.15 (m, 2H) p.p.m.; ^{13}C NMR (600 MHz, $CDCl_3$): δ = 168.99, 148.56, 146.29, 145.29, 144.97, 143.46, 131.94, 129.95, 122.78, 120.77, 112.98, 112.04, 58.82, 41.80, 21.87 p.p.m.; MS (EI): m/z = 299

(M+).1-(3-(furan-2-yl)-5-(2-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (2)Green crystals, yield: 87.1%; M.p.: 158–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3H), 3.10 (dd, 1H, J_1 = 4.8 Hz, J_2 = 18.0 Hz), 3.99 (dd, 1H, J_1 = 12.0 Hz, J_2 = 18.4 Hz), 6.12 (dd, 1H, J_1 = 4.8 Hz, J_2 = 12.0 Hz), 6.51–6.52 (m, 1H), 6.75 (d, 1H, J = 3.6 Hz), 7.44–7.46 (m, 1H), 7.56–7.60 (m, 3H), 8.11–8.13 (m, 1H) p.p.m.; ^{13}C NMR (600 MHz, $CDCl_3$): δ = 168.74, 146.87, 146.36, 145.99, 144.90, 136.60, 134.33, 128.49, 126.31, 125.41, 113.12, 111.95, 56.57, 42.16, 21.76 p.p.m.; MS (EI): m/z = 299

(M+).**1-(5-(4-bromophenyl)-3-(furan-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (3)**Light yellow crystals, yield: 88.4%; M.p.: 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 3.06 (dd, 1H, J_1 = 4.4 Hz, J_2 = 17.6 Hz), 3.70 (dd, 1H, J_1 = 12.0 Hz, J_2 = 17.6 Hz), 5.51 (dd, 1H, J_1 = 4.8 Hz, J_2 = 12.0 Hz), 6.51–6.53 (m, 1H), 6.75 (d, 1H, J = 3.2 Hz), 7.09–7.12 (m, 2H), 7.43–7.46 (m, 2H), 7.56 (s, 1H) p.p.m.; ^{13}C NMR (600 MHz, $CDCl_3$): δ = 168.66, 146.48, 145.33, 144.74, 140.41, 131.87, 127.28, 121.44, 112.72, 111.89, 58.82, 41.74, 21.83 p.p.m.; MS (EI): m/z = 332

(M+).**1-(5-(4-chlorophenyl)-3-(furan-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (4)**Light yellow crystals, yield: 87.3%; M.p.: 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 3.06 (dd, 1H, J_1 = 4.8 Hz, J_2 = 18.0 Hz), 3.70 (dd, 1H, J_1 = 12.0 Hz, J_2 = 18.0 Hz), 5.53 (dd, 1H, J_1 = 4.4 Hz, J_2 = 11.6 Hz), 6.52–6.53 (m, 1H), 6.74–6.75 (m, 1H), 7.15–7.18 (m, 2H), 7.26–7.30 (m, 2H), 7.56–7.57 (m, 1H) p.p.m.; ^{13}C NMR (600 MHz, $CDCl_3$): δ = 168.54, 146.52, 145.38, 144.80, 139.95, 133.42, 129.01, 127.01, 112.73, 111.94, 58.83, 41.86, 21.91 p.p.m.; MS (EI): m/z = 288

Results and Discussion

The reaction of p-nitroacetophenone and aromatic substituted aldehyde in ethanol gave 1-(4-nitrophenyl)-3-substituted phenyl) prop-2-en-1-one (I). In this step chalcones are formed. Further, the compound on treatment with hydrazine hydrate in ethanol gave 1H-3-(4-nitrophenyl)-5-(substituted phenyl) pyrazoline that refluxed in acetyl chloride has given 1-acetyl-3-(4-nitrophenyl)-5-substituted phenyl) pyrazoline . Compound (II) was stirred with benzoyl chloride in pyridine at room temperature which gave 1-benzoyl-3-(4-nitrophenyl) 5-(substituted phenyl) pyrazoline.

Table.1 Physical Data of Synthesized Pyrazoline Derivatives

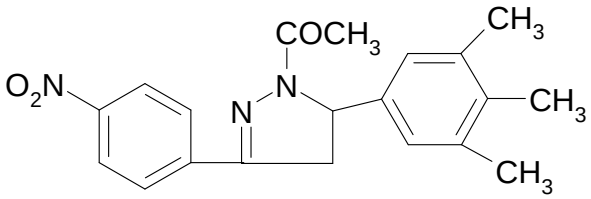
Compound	**DKI**					
Name	1-acetyl-3-(4-nitrophenyl)-5-(3',4',5', tri methyl phenyl) pyrozoline					
M.F.	$C_{20}H_{21}N_3O_5$					
M.Wt.	351.379					
M.P.	178					
Yield %	73					
Elemental	C%		H%		N%	
	Calc.	Found	Calc	Found	Calc.	Found
Analysis	68.36	68.34	6.02	6.00	11.95	11.93

Table.2 Infrared Spectral Data of Synthesized Pyrazoline Derivatives

Type of vibration	Vibration mode	Frequency in cm^{-1}
Aromatic	Ar-H str	3055.64
CH_2	C-H-str.	2951.66
C=N	C=N str	1538.14
C-N	C-N str.	1319.16
N-N	N-N bending	846.19
Pyrazoline ring breathing mode	C-H bending	835.42
COC_6H_5	C-O-C bending	1056.92
Disubstituted aromatic	Ar-H bending	752.34
NO_2 group	N=O str	1321.45
	N-O bending	696.46

Table.3 H NMR Spectral Data of Synthesized Pyrazoline Derivatives

Type of vibration	Vibration mode	Frequency in cm^{-1}
Aromatic	Ar-H str	3076.56
CH_2	C-H-str.	2939.61
Pyrazoline C=N	C=N str	1518.03
C-N	C-N str.	1340.57
N-N	N-N bending	881.5
Pyrazoline ring breathing mode	C-H bending	860.28
COC_6H_5	C-O-C bending	1109.11
Disubstituted aromatic	Ar-H bending	740.69
NO_2 group	N=O str	1340.50
	N-O bending	671.25

Table.4 Antibacterial Activity of the Synthesized Heterocyclic Pyrazoline Derivatives

Comp. Code	***Bacillus subtilis***		***Escherichia coli***		***Klebsiella pneumoniae***		***Staphylococcus aureus***	
	2%	**4%**	**2%**	**4%**	**2%**	**4%**	**2%**	**4%**
DK I1	12	18	12	18	12	19	12	13
DK I2	11	22	11	24	11	22	11	24
DK I3	09	10	09	11	09	13	09	15
DK I4	10	15	10	15	10	15	10	15
DK I5	11	14	11	14	11	14	11	14
DK I6	13	12	13	12	13	12	13	12
DK I7	08	14	08	14	08	14	28	14
DK I8	17	19	17	19	17	19	17	19
DK I9	13	15	11	15	14	15	13	15
Sts:	16	22	16	12	16	12	15	22

Table.5 Antifungal Activity of the Synthesized Heterocyclic Pyrazoline Derivatives

Comp. Code	*Aspergillus Niger*		*Aspergillus flavus*		*Trichoderma viride*		*Cadida albicans*	
	2%	**4%**	**2%**	**4%**	**2%**	**4%**	**2%**	**4%**
DK I1	12	17	11	17	10	15	12	16
DK I2	11	22	11	22	11	21	11	21
DK I3	09	12	09	11	08	12	19	12
DK I4	10	15	10	15	10	15	10	15
DK I5	11	14	12	14	13	14	16	14
DK I6	13	12	13	12	14	12	13	12
DK I7	11	14	08	14	08	14	08	14
DK I8	17	19	17	19	17	19	17	19
DK I9	13	15	13	15	13	15	13	15
Sts:	10	23	16	25	16	25	16	23

Acknowledgement

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