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Synthesis, antitubercular and antimicrobial screening of pyrazolyl pyrazolines derivatives

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ABSTRACT

The chalcones 2 have been synthesized by the Claisan-Schmidt reaction of 1-N, 3-diphenyl-4-formyl pyrazole with different aromatic ketones. The titled compounds 3a-m and 4a-m have been undertaken by the reaction of 1-aryl-3-(1'-N,3'-diphenyl-4'-pyrazoyl)-2-propene-1-ones 2 with hydrazine hydrate and phenyl hydrazine respectively. All the synthesized products have been characterized on the basis of spectral data and elemental analysis. The compounds have been screened for their *in vitro* antitubercular, antibacterial and antifungal activities.

INTRODUCTION

The compounds bearing pyrazole nucleus have been of great interest to synthetic and medicinal chemists for a long time due to their diversified biological activities such as anticancer[1], antiviral[2], antiinflammtory[3], and cardiovascular[4]. We have reported earlier the synthesis and biological activities of pyrazoline derivatives[5-8]. Moreover pyrazoline derivatives have been also found to possess wide range of biological activities[9-16] such as antiinflammatory, anticonvulsant, antidepressant, cardiovascular and antimicrobial. In view of therapeutic activities shown by pyrazolines, it was contemplated to synthesize some novel pyrazolines in search of agents possessing higher biological activity with least side effect.

1-N,3-Diphenyl-4-formyl pyrazole[17] 1 one reaction with different arylketones yielded the corresponding 1-aryl-3-(1'N,3'-diphenyl-4'-pyrazolyl)-2-propene-1-ones 2. Compounds **(2)** on condensation with hydrazine hydrate and phenyl hydrazine afforded corresponding 3-aryl-5-(1'N,3'-diphenyl-4'-pyrazolyl)-pyrazolines **(3a-m)** and 1-N-phenyl-3-aryl-5-(1'N,3'-diphenyl-4'-pyrazolyl)-pyrazolines **(4a-m)**.

The constitution of all the synthesized products were confirmed by IR ^{1}H NMR spectra and elemental analyses and were screened for their antitubercular activity towards *Mycobacterium tuberculosis* H_{37} Rv and antimicrobial activity against different strains of bacterial and fungi.

EXPERIMENTAL

All the melting points were determined in an open capillary tube and are uncorrected. Thin layer chromatography was used for monitoring the reaction and to check purity. IR spectra (KBr disc) were recorded on Shimadzu-8400 spectrophotometer and ^{1}H NMR spectra were recorded on 300MHz spectrophotometer using TMS as internal standard. Mass spectra were recorded on 300MHz spectrophotometer using TMS as an internal standard. Mass spectra were recorded on

Full Paper

JEOL SX 102/DA 6000 spectrophotometer. All the compounds gave satisfactory elemental analysis.

1-(4-Anisyl)-3-(1'N,3'-diphenyl-4'-pyrazolyl)-2-propene-1-one (2f).

To a well stirred solution of 1N, 3-diphenyl-4-formyl pyrazole 1 (2.48g, 0.01M) and p-methoxyaceto phenone (1.5g, 0.01M) in ethanol (25ml), 40% NaOH added till the solution become basic and stirred for 24 hrs. The contents were poured onto ice and isolated by acidification and recrystallized from ethanol. Yield 3.57g, (94%), m.p. 102^{0}C. (Found: C, 78.92; H, 5.20; N, 7.32%. Calcd. from $C_{25}H_{20}N_2O_2$; C, 78.95 ; H, 5.26 ; N, 7.36%) IR (KBr) cm^{-1} : 1658 (C=O), 1596 (C=N), 1031(C-O-C), ^{1}H NMR ($CDCl_3$) d ppm : 3.88 (s, 3H, -OCH_3), 6.92-6.97 (d, 2H, Hbb', J=8.9 Hz), 7.3-7.4 (d, 2H, Hjk, J=15.5Hz), 7.45 (m, 5H, Hc), 7.7 (d, 2H, Hdh), 7.75 (d, 2H, Heg), 7.9 (d, 1H, Hf), 8.0 (d, 2H, Haa' J=8.9 Hz), 8.33 (s, 1H, Hi). In mass spectra molecular weight=380, m/z=381 (m+1). Similarly, other compounds in the series were also prepared.

3-(4-Anisyl)-5-(1'N', 3'-diphenyl-4'-pyrzolyl)-pyrazoline (3f)

A mixture of 1-(4-anisyl)-3-(1'N,3'-dipheyl-4'-pyrazolyl)-2-propene-1-one 2f (3.8g, 0.01M), hydrazine hydrate (2g, 0.04M) in 30 ml methanol was refluxed for 12 hrs. The product obtained was filtered, washed with hot methanol and crystallized from dioxen. Yield 3.2g (81%), m.p. 155^{0}C . (Found : C, 76.10 ; H, 5.53 ; N, 14.17%. Calcd from $C_{25}H_{22}N_4O$: C, 76.14; H, 5.58; N, 14.20%). IR (KBr) cm^{-1}, 3315 (-NH), 2839 (CH_2 str.), 1598 (C=N), 1548 (C=N), 1172 (C-N), ^{1}H NMR ($CDCl_3$) d ppm : 3-3.1 (q, 1H, Hk), 3.42-3.5 (q, 1H, Hj), 3.83 (s, 3H-OCH_3), 5.1-5.22 (q, 1H, Hz), 6.89-6.94 (d, 2H, Hbb'J=8.8 Hz), 7.27-7.31 (m, 1H, Hf), 7.41-7.5 (m, 5H, Hc), 7.6 (d, 2H, Haa', J=8.8Hz), 7.74 (d, 3H, Hdeg), 7.85 (M, 1H, Hh), 8.05 (S, 1H, Hi). In mass spectra, molecular weight=394, m/z=394. Other compound **(3a-m)** in the series was similarly prepared and is listed in TABLE 1.

1N-Phenyl-3-(4-anisyl)-5-(1'N, 3'-diphenyl-4'-pyrazolyl)-pyrazoline (4f)

A mixture of 1-(4-anisyl)-3-(1'N, 3'-diphenyl-4'-pyrazolyl)-2-propene-1-one 2f (3.8g, 0.01M), phenyl hydrazine (1.08g, 0.01M) in 25 ml methanol was refluxed for 12 hrs. in presence of basic catalyst piperidine. The reaction mixture was poured onto ice, crude product was isolated, crystallized from dioxan. Yield 3.8g (81%), m.p. 176^{0}C. (Found: C, 79.10; H, 5.48; N, 11.88% Calcd. from $C_{31}H_{26}N_4O$; C, 79.15; H, 5.53; N, 11.91%). IR (KBr) cm^{-1} : 2922, 2842 (-C-H str.), 1598 (C=N), 1548 (C=N), 1109 (C-N), ^{1}H NMR ($CDCl_3$) d ppm : 3.17-3.25 (q, 1H, Hr), 3.77-3.83 (q, 1H, Hq), 3.87 (s, 3H, -OCH_3), 5.44-5.50 (q, 1H, Hp), 6.76-6.81 (t, 1H Hd), 6.89-6.92 (d, 2H, Hbb', J=8.7 Hz), 7.0 (d, 2H, Hfh), 7.16-7.25 (m, 3H, Hegi), 7.34-7.4 (t, 2H, Hkm), 7.42 (d, 1H, Hl), 7.49 (t, 2H, CHjn), 7.62-7.68 (m, 4H, Hc), 7.78-7.83 (t, 3H, Haa', J=8.7 Hz). In mass spectra, molecular weight=470, m/z=470. Other compound **(4a-m)** in the series was similarly prepared and is listed in TABLE 1.

Antimicrobial activity

The antimicrobial activity was assayed using cup-plate diffusion method[18] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activity against bacterial strains like Bacillus megaterium, staphylococcus aureus,

TABLE 1: Physical constant of (3a-m) and (4a-m)

Sr. no.	R	Molecular formula	Molecular weight	M.P. °C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
3a	C_6H_5-	$C_{24}H_{20}N_4$	364	140	70	15.37	15.36
3b	4-Br-C_6H_4-	$C_{24}H_{19}N_4Br$	443	198	73	12.64	12.60
3c	4-Cl-C_6H_4-	$C_{24}H_{19}N_4Cl$	398.5	198	80	14.05	14.03
3d	4-F-C_6H_4-	$C_{24}H_{19}N_4F$	382	86	85	14.65	14.61
3e	4-CH_3-C_6H_4-	$C_{25}H_{22}N_4$	378	210	72	14.80	14.76
3f	4-OCH_3-C_6H_4-	$C_{25}H_{22}N_4O$	394	155	81	14.20	14.17
3g	2-OH-C_6H_4-	$C_{24}H_{20}N_4O$	380	>230	77	14.73	14.69
3h	4-OH-C_6H_4-	$C_{24}H_{20}N_4O$	380	208	73	14.73	14.71
3i	4-NH_2-C_6H_4-	$C_{24}H_{21}N_5$	379	148	90	18.46	18.43
3j	3-NO_2-C_6H_4-	$C_{24}H_{19}N_5O_2$	409	130	75	17.10	17.12
3k	4-NO_2-C_6H_4-	$C_{24}H_{19}N_5O_2$	409	166	69	17.10	17.13
3l	2-C_4H_3O-	$C_{22}H_{18}N_4O$	354	79	82	15.81	15.83
3m	2-C_4H_3S-	$C_{22}H_{18}N_4S$	370	97	80	15.12	15.10
4a	C_6H_5-	$C_{30}H_24N_4$	440	156	76	12.72	12.70
4b	4-Br-C_6H_4-	$C_{30}H_{23}N_4Br$	519	146	80	10.79	10.77
4c	4-Cl-C_6H_4-	$C_{30}H_{23}N_4Cl$	474.5	124	81	11.80	11.77
4d	4-F-C_6H_4-	$C_{30}H_{23}N_4F$	458	218	70	12.22	12.20
4e	4-CH_3-C_6H_4-	$C_{31}H_{26}N_4$	454	115	77	12.33	12.30
4f	4-OCH_3-C_6H_4-	$C_{31}H_{26}N_4O$	470	176	81	11.91	11.88
4g	2-OH-C_6H_4-	$C_{30}H_{24}N_4O$	456	193	84	12.27	12.29
4h	4-OH-C_6H_4-	$C_{30}H_{24}N_4O$	456	208	78	12.27	12.28
4i	4-NH_2-C_6H_4-	$C_{30}H_{25}N_5$	455	217	82	15.37	15.33
4j	3-NO_2-C_6H_4-	$C_{30}H_{23}N_5O_2$	485	196	79	14.42	14.40
4k	4-NO_2-C_6H_4-	$C_{30}H_{23}N_5O_2$	485	179	79	14.42	14.43
4l	2-C_4H_3O-	$C_{28}H_{22}N_4O$	430	110	80	13.01	13.03
4m	2-C_4H_3S-	$C_{28}H_{22}N_4S$	446	124	81	12.55	12.53

Escherichia coli, Proteus vulgaris and fungi, Aspergillus niger at a concentration 40mg. Known antibiotics like ampicillin (15-21mm), amoxycillin (18-23mm), norfloxacin (17-24mm), Penicillin (19-25mm) and greseofulvin (25mm) were used for comparison purpose.

Antitubercular activity

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF) USA. Primary screening of the compounds for antitubercular activity have been conducted at 6.25mg/ml against *Mycobacterium tuberculosis* H_{37} Rv in BACTEC 12B medium using the BACTEC 460 radiometric system. Most of the compound showed moderate activity recorded in TABLE 2.

A synthetic perusal of date presented in TABLE 2 reveals that the tested compounds showed antibacterial activity without very specific preference to among the tested bacterial strains caride spectrum of action **(4)**.

Looking to the structure activity relationship, it can be concluded that the presence of halogen group at **(4)** position. i.e. **(3b, 3d, 4b and 4d)** showed good activity towards the tested bacteria. Presence of methyl or methoxy group at **(4)** position i.e. **(3e)** and **(4f)** displayed good activity against both the types of bacterial strain. In case of fungus, *A.niger* all the compounds exhibited moderate activity.

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TABLE 2: Antimicrobial and antitubercular activity of (3a-m) and (4a-m)

Sr.no.	R	Antimicrobial activity Zone of inhibition (mm)				Antifungal activity Zone of inhibition (mm)	Antitubercular activity
		B.mega	*S.aureus*	*P.vulgaris*	*E.coli*	*A.niger*	% inhibition
3a	C_6H_5-	11	12	13	20	15	39
3b	4-Br-C_6H_4-	20	18	18	17	17	53
3c	4-Cl-C_6H_4-	14	11	14	12	19	16
3d	4-F-C_6H_4-	16	22	12	14	21	57
3e	4-CH_3-C_6H_4-	11	20	20	21	11	32
3f	4-OCH_3-C_6H_4-	21	13	15	13	13	33
3g	2-OH-C_6H_4-	12	19	17	11	14	56
3h	4-OH-C_6H_4-	18	23	13	12	16	45
3i	4-NH_2-C_6H_4-	13	15	16	13	18	40
3j	3-NO_2-C_6H_4-	22	16	15	21	20	39
3k	4-NO_2-C_6H_4-	17	12	16	14	23	35
3l	2-C_4H_3O-	15	11	17	14	18	23
3m	2-C_4H_3S-	13	13	18	19	15	53
4a	C_6H_5-	17	20	11	15	18	18
4b	4-Br-C_6H_4-	13	18	16	20	16	36
4c	4-Cl-C_6H_4-	17	12	19	19	17	43
4d	4-F-C_6H_4-	20	21	12	20	22	55
4e	4-CH_3-C_6H_4-	14	14	18	14	17	30
4f	4-OCH_3-C_6H_4-	15	19	20	18	13	03
4g	2-OH-C_6H_4-	12	13	19	14	18	-
4h	4-OH-C_6H_4-	15	11	15	19	23	69
4i	4-NH_2-C_6H_4-	12	16	11	21	15	18
4j	3-NO_2-C_6H_4-	17	19	13	16	19	-
4k	4-NO_2-C_6H_4-	12	14	19	11	14	22
4l	2-C_4H_3O-	22	17	12	11	23	-
4m	2-C_4H_3S-	18	13	12	13	14	-
4K	4-NO_2-C_6H_4-	12	14	19	11	14	22
41	2-C_4H_3O-	22	17	12	11	23	-
4M	2-C_4H_3S-	18	13	12	13	14	-

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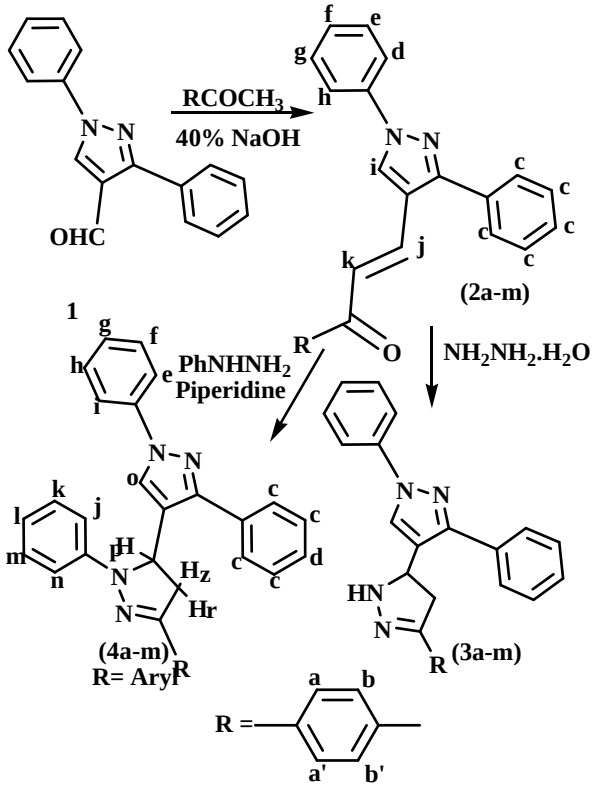

SCHEME 1

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