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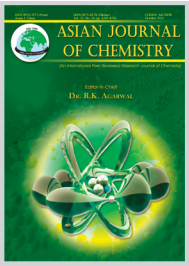

Synthesis and Antimicrobial Screening of Some Novel Pyrazoline Derivatives

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A new series of methyl-4-(4,5-dihydro-5-[(*Z*)phenyl]-1*H*-pyrazol-3-yl)-2-methylbenzohydrazide were synthesized by cyclisization of chalcones, methyl 4-((E)-3-((*Z*)phenyl)acryloyl)-2-methylbenzoate with hydrazine hydrate in presence of basic media. The chalcones were synthesized starting from 4-acetyl-2-methylbenzoic acid in 2 step. The structures of the synthesized compounds have been established on the basis of physical and spectral data and are screened for antimicrobial activity. Some of them exhibited significant activity.

Key Words: Chalcones, Pyrazolines, Antimicrobial activity.

INTRODUCTION

Chalcones constitute an important class of naturally occurring flavonoid compounds that exhibit a wide spectrum of biological activities and are well-known intermediates for the synthesis of various heterocycles. Chalcones are useful synthons in the synthesis of a large number of bioactive molecules. Amongst nitrogen containing five membered heterocycles, pyrazolines have proved to be the most useful framework for biological activities. Pyrazolines have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activities associated with them[1-5]. The discovery of this class of compounds provides an outstanding case history of modern drug development and also emphasizes the unpredictability of biological activity from structural modification of a prototype drug molecule. Considerable interest has been focused on the pyrazoline structure, which is known to possess a broad spectrum of biological activities, such as antitumor[6], immunosuppressive[7], antibacterial[8], antiinflammatory[9], anticancer[10], antidiabetic[11] and antidepressant[12]. Thus, the synthesis of the pyrazolines is always a great challenge.

EXPERIMENTAL

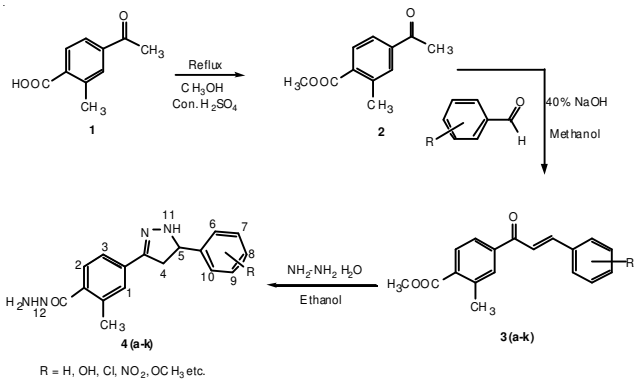
Melting points were determined in open capillary tubes in a Thomas Hoover melting point apparatus and are uncorrected. The purity of the compounds was confirmed by thin layer chromatography using silica gel glass plates. The spots were developed in iodine chamber and visualized under ultraviolet lamp. Infrared (IR) and ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded for the compounds in Shimadzu FTIR 8400 Spectrophotometer and Bruker spectrometer (300 MHz) respectively. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Elemental analysis was undertaken with Perkin Elmer 2400 instrument and the measured values agreed within 0.4 % with the calculated.

Synthesis of methyl 4-acetyl-2-methylbenzoate: To a solution of 4-acetyl-2-methylbenzoic acid (0.01 mol, 1.78 g) in methanol (20 mL), conc. sulphuric acid (0.01 mol, 0.53 mL) was added and reflux for 5 h on waterbath. Completion of the reaction was check by TLC and excess methanol was distilled off, light yellow colour oil obtained, Yield 98 %.

General procedure for the synthesis of methyl 4-[(E)-3-(*Z*)phenyl]acryloyl-2-methylbenzoate: To a solution of methyl 4-acetyl-2-methylbenzoate (0.01 mol), aromatic aldehydes (0.01 mol) in methanol (25 mL) and 40 % NaOH solution was added till the solution become basic (pH = > 10). The reaction mixture was stirred for 3-4 h at room temperature. Reaction was monitored by TLC using mobile phase hexane: ethyl acetate - 7:3 mL. After completion of reaction the content was poured in to crushed ice. Upon neutralization the solid separated was crystallized from ethanol.

General procedure for the synthesis of 4-[5-(*Z*)phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-2-methylbenzohydrazide: A mixture of methyl 4-((E)-3-((*Z*)phenyl)acryloyl)-2-methylbenzoate (0.01 mol) and hydrazine hydrate (0.05 mol) in 25 mL Ethanol was refluxed for 10-13 h. Reaction was monitored by TLC using mobile phase dichloromethane:methanol-8:2 mL and iodine is used as visualizing agent. After completion of

reaction solution was poured into crushed ice and neutralize with dilute HCl solution. Product was isolated and crystallized from ethanol (**Scheme-I**). Physical constants for compounds (**3a-k, 4a-k**) are given in Table-1.



Scheme-I

TABLE-1
PHYSICAL CONSTANTS OF COMPOUNDS **3(a-k)** AND **4(a-k)**

Comp.	R	m.f.	m.w. (g/mol)	m.p. (ºC)	Yield (%)
3a	2-Hydroxy	$C_{18}H_{16}O$	296.32	151	92
3b	3-Nitro	$C_{18}H_{15}NO_5$	325.32	275	80
3c	4-Hydroxy	$C_{18}H_{16}O$	296.32	190	85
3d	4-*N,N*-Dimethyl	$C_{20}H_{21}NO_3$	323.39	247	82
3e	4-Hydroxy-3-methoxy	$C_{19}H_{18}O_5$	326.34	238	75
3f	4-Chloro	$C_{18}H_{15}O_3Cl$	314.76	240	90
3g	4-Nitro	$C_{18}H_{15}NO_5$	325.32	288	85
3h	H	$C_{18}H_{16}O_3$	280.32	210	80
3i	4-Methoxy	$C_{19}H_{18}O_4$	310.34	185	95
3j	2-Chloro	$C_{18}H_{15}O_3Cl$	314.76	255	92
3k	4-Fluoro	$C_{18}H_{15}O_3F$	298.31	235	95
4a	2-hydroxy	$C_{17}H_{18}N_4O_2$	310.35	173	51
4b	3-Nitro	$C_{17}H_{17}N_5O_3$	339.35	121	55
4c	4-Hydroxy	$C_{17}H_{18}N_4O_2$	310.35	217	45
4d	4-N,N-Dimethyl	$C_{19}H_{23}N_5O$	337.42	231	57
4e	4-Hydroxy-3-methoxy	$C_{18}H_{20}N_4O_3$	340.38	210	42
4f	4-Chloro	$C_{17}H_{17}N_4OCl$	328.80	195	61
4g	4-Nitro	$C_{17}H_{17}N_5O_3$	339.35	145	53
4h	H	$C_{17}H_{18}N_4O$	294.35	163	58
4i	4-Methoxy	$C_{18}H_{20}N_4O_2$	324.38	231	67
4j	2-Chloro	$C_{17}H_{17}N_4OCl$	328.80	182	63
4k	4-Fluoro	$C_{17}H_{17}N_4OF$	312.34	153	70

4-[4,5-Dihydro-5-(2-hydroxyphenyl)-1*H*-pyrazol-3-yl]-2-methylbenzohydrazide (4a): IR: (KBr, ν_{max}, cm^{-1}): 3387 (NH), 3188 (OH), 2958, 2858 (C-H), 1681(C=O), 1512 (C=N), 1201 (C-N), ^{1}H NMR (400 MHz, DMSO): 2.09 (s, 3H, CH_3), 2.51-2.54 (m, 1H, H4), 2.54-2.57 (m, 1H, H4'), 2.58-2.61 (t, 1H, H5), 5.56 (s, 1H, OH), 6.90-6.95 (m, 2H, H7, H9), 6.99-7.05 (m, 3H, H6, H8, NH11), 7.65-7.69 (m, 2H, H1, H3), 7.92-7.95 (m, 2H, H2, NH12), 12.12 (s, 2H, NH_2). Anal. calcd. for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05; Found: C, 65.80; H, 5.87; N, 18.08.

4-[4,5-Dihydro-5-(3-nitrophenyl)-1*H*-pyrazol-3-yl]-2-methylbenzohydrazide (4b): IR: (KBr, ν_{max}, cm^{-1}): 3415 (NH), 2967, 2861 (C-H), 1691 (C=O), 1522 (C=N), 1211 (C-N), ^{1}H NMR (400 MHz, DMSO): 2.04 (s, 3H, CH_3), 2.41-2.43 (m, 1H, H4), 2.44-2.48 (m, 1H, H4'), 2.53-2.56 (t, 1H, H5), 7.05 (s, 1H, NH11), 7.38-7.42 (m, 2H, H6, H7), 7.60-7.65 (m, 2H, H1, H3), 7.90-7.94 (m, 2H, H2, NH12), 8.00-8.06 (m, 2H, H8, H10), 13.02 (s, 2H, NH_2). Anal. calcd. for $C_{17}H_{17}N_5O_3$: C, 60.17; H, 5.05; N, 20.64; Found: C, 60.20; H, 5.07; N, 20.68.

4-[4,5-Dihydro-5-(4-hydroxyphenyl)-1*H*-pyrazol-3-yl]-2-methylbenzohydrazide (4c): IR: (KBr, ν_{max}, cm^{-1}) : 3397 (NH), 3195 (OH), 2956, 2847 (C-H), 1690 (C=O), 1515 (C=N), 1200 (C-N), ^{1}H NMR (400 MHz, DMSO): 2.10 (s, 3H, CH_3), 2.50-2.52 (m, 1H, H4), 2.54-2.58 (m, 1H, H4'), 2.60-2.63 (t, 1H, H5), 5.61 (s, 1H, OH), 6.70-6.74 (m, 2H, H7, H9), 6.95-7.00 (m, 3H, H6, H10, NH11), 7.61-7.65 (m, 2H, H1, H3), 7.95-8.00 (m, 2H, H2, NH12), 13.14 (s, 2H, NH_2). Anal. calcd. for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05; Found: C, 65.81; H, 5.89; N, 18.05.

4-[5-(4-(Dimethylamino)phenyl]-4,5-dihydro-1*H*-pyrazol-3-yl)-2-methyl benzohydrazide (4d): IR: (KBr, ν_{max}, cm^{-1}): 3390 (NH), 2965, 2855 (C-H), 1698 (C=O), 1535 (C=N), 1220 (C-N). ^{1}H NMR (400 MHz, DMSO): 2.30 (s, 3H, CH_3), 2.41-2.44 (m, 1H, H4), 2.45-2.49 (m, 1H, H4'), 2.88 (s, 6H, $(NCH_3)_2$), 3.01-3.04 (t, 1H, H5), 6.61-6.66 (m, 2H, H7, H9), 6.92-6.96 (m, 3H, H6, H10, NH11), 7.58-7.63 (m, 2H, H1, H3), 7.88-7.93 (m, 2H, H2, NH12), 13.00 (s, 2H, NH_2). Anal. calcd. for $C_{19}H_{23}N_5O$: C, 67.63; H, 6.87; N, 20.76; Found: C, 67.66; H, 6.90; N, 20.77.

4-[4,5-Dihydro-5-(4-hydroxy-3-methoxyphenyl]-1*H*-pyrazol-3-yl)-2-methylbenzohy- drazide (4e): IR: (KBr, ν_{max}, cm^{-1}): 3420 (NH), 2522-3195 (OH), 2970, 2867 (C-H), 1698 (C=O), 1501 (C=N), 1223 (C-N), ^{1}H NMR (400 MHz, DMSO): 2.33 (s, 3H, CH_3), 2.58-2.60 (m, 1H, H4), 2.62-2.66 (m, 1H, H4'), 3.20-3.23 (t, 1H, H5), 4.12 (s, 3H, OCH_3), 5.45 (s, 1H, OH), 6.50-6.58 (m, 3H, H6, H7, H10), 7.01 (s, 1H, NH11), 7.63-7.68 (m, 2H, H1, H3), 7.93-7.98 (m, 2H, H2, NH12), 13.23 (s, 2H, NH_2). Anal. calcd. for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46; Found: C, 63.52; H, 5.94; N, 16.46.

4-[5-(4-Chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-2-methylbenzohydrazide (4f): IR: (KBr, ν_{max}, cm^{-1}): 3401 (NH), 2960, 2855 (C-H), 1687 (C=O), 1519 (C=N), 1208 (C-N), ^{1}H NMR (400 MHz, DMSO): 2.22 (s, 3H, CH_3), 2.48-2.50 (m, 1H, H4), 2.52-2.56 (m, 1H, H4'), 2.78-2.81 (t, 1H, H5), 6.90-6.95 (m, 3H, H6, H10, NH11), 7.15-7.20 (m, 2H, H7, H9), 7.65-7.69 (m, 2H, H1,H3), 7.97-8.02 (m, 2H, H2, NH12), 13.11 (s, 2H, NH_2). Anal. calcd. for $C_{17}H_{17}N_4OCl$: C, 62.10; H, 5.21; N, 17.04; Found: C, 62.11; H, 5.23; N, 17.05.

4-(4,5-Dihydro-5-(4-nitrophenyl)-1*H*-pyrazol-3-yl)-2-methylbenzohydrazide (4g): IR: (KBr, ν_{max}, cm^{-1}): 3410 (NH), 2963, 2858 (C-H), 1695 (C=O), 1530 (C=N), 1228 (C-N), ^{1}H NMR (400 MHz, DMSO): 2.00 (s, 3H, CH_3), 2.38-2.41 (m, 1H, H4), 2.43-2.47 (m, 1H, H4'), 2.56-2.58 (t, 1H, H5), 7.00 (s, 1H, NH11), 7.32-7.36 (m, 2H, H6, H10), 7.64-7.67 (m, 2H, H1, H3), 7.93-7.98 (m, 2H, H2, NH12), 8.12-8.17 (m, 2H, H7,H9), 13.15 (s, 2H, NH_2). Anal. calcd. for $C_{17}H_{17}N_5O_3$: C, 60.17; H, 5.05; N, 20.64; Found: C, 60.17; H, 5.04; N, 20.67.

4-(4,5-Dihydro-5-phenyl-1*H*-pyrazol-3-yl)-2-methylbenzohydrazide (4h): IR: (KBr, ν_{max}, cm^{-1}): 3396 (NH), 2954, 2843 (C-H), 1680 (C=O), 1515 (C=N), 1210 (C-N), 1H NMR (400 MHz, DMSO): 2.28 (s, 3H, CH_3), 2.43-2.48 (m, 1H, H4), 2.49-2.53 (m, 1H, H4'), 2.71-2.74 (t, 1H, H5), 7.01-

7.04 (m, 2H, H8, NH11), 7.12-7.17 (m, 2H, H6,H10), 7.20-7.25 (m, 2H, H7,H9), 7.42-7.48 (m, 2H, H1, H3), 7.62-7.69 (m, 2H, H2, NH12), 13.00 (s, 2H, NH_2). Anal. calcd. for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03; Found: C, 69.35; H, 6.22; N, 19.05.

4-(4,5-Dihydro-5-(4-methoxyphenyl)-1*H*-pyrazol-3-yl)-2-methylbenzohydrazide (4i): IR: (KBr, ν_{max}, cm^{-1}): 3390 (NH), 2950, 2842 (C-H), 1694 (C=O), 1510 (C=N), 1212 (C-N), ^{1}H NMR (400 MHz, DMSO): 2.31 (s, 3H, CH_3), 2.42-2.47 (m, 1H, H4), 2.48-2.51 (m, 1H, H4'), 3.10-3.13 (t, 1H, H5), 3.89 (s, 3H, OCH_3), 6.72-6.77 (m, 2H, H7,H9), 6.99-7.03 (m, 3H, H6, H10, NH11), 7.57-7.62 (m, 2H, H1, H3), 7.91-7.95 (m, 2H, H2, NH12), 13.12 (s, 2H, NH_2). Anal. calcd. for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27; Found: C, 66.69; H, 6.21; N, 17.26.

4-(5-(2-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-2-methylbenzohydrazide (4j): IR: (KBr, ν_{max}, cm^{-1}): 3410 (NH), 2962, 2845 (C-H), 1682 (C=O), 1522 (C=N), 1209 (C-N), ^{1}H NMR (400 MHz, DMSO): 2.24 (s, 3H, CH_3), 2.44-2.47 (m, 1H, H4), 2.50-2.55 (m, 1H, H4'), 2.79-2.82 (t, 1H, H5), 6.99-7.05 (m, 4H, H6, H7,H8, NH11), 7.20-7.24 (m, 1H, H9), 7.62-7.66 (m, 2H, H1, H3), 7.93-7.97 (m, 2H, H2, NH12), 13.05 (s, 2H, NH_2). Anal. calcd. for $C_{17}H_{17}N_4OCl$: C, 62.10; H, 5.21; N, 17.04; Found: C, 62.14; H, 5.22; N, 17.04.

4-(5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-2-methylbenzohydrazide (4k): IR: (KBr, ν_{max}, cm^{-1}): 3387 (NH), 2958, 2858 (C-H), 1681 (C=O), 1512 (C=N), 1201 (C-N), ^{1}H NMR (400 MHz, DMSO): 2.09 (s, 3H, CH_3), 2.50-2.53 (m, 1H, H4), 2.53-2.56 (m, 1H, H4'), 2.56-2.61 (t, 1H, H5), 7.15 (s, 1H, NH11), 7.29-7.32 (t, 2H, H7, H9), 7.45-7.47 (m, 2H, H6, H10), 7.75-7.78 (m, 1H, H1), 7.82-7.85 (m, 1H, H3), 7.86-7.92 (m, 1H, H2), 7.94 (s, 1H, NH12), 13.61 (s, 2H, NH_2). Anal. calcd. for $C_{17}H_{17}N_4OF$: C, 65.37; H, 5.49; N, 17.94; Found: C, 65.40; H, 5.51; N, 17.95.

RESULTS AND DISCUSSION

Biological activity: Minimum inhibitory concentration (MIC) of all the synthesized compounds was determined against four different strains, *viz.,* two Gram positive bacteria (*S. aureus* and *S. pyogenes* and two Gram negative bacteria, *E. coli* and *P. aeruginosa*) compared with standard drugs gentamycin, ampicillin, chloramphenicol, ciprofloxacin and norfloxacin by broth dilution method[13]. Antifungal activities against *C. albicans*, *A. niger* and *A. clavatus* organisms were compared with standard drugs nystatin and greseofulvin by same method.

Antibacterial activity: From screening results, substituted chalcones **3f** (R = -4-Cl) and **3h** (R = H) against *S. aureus* and **3a** (R = -2-OH) against *E. coli* possesses very good activity compared with ampicillin while **3c** (R = -4-OH) against *S. aureus*, **3a** (R= -2-OH) and **3g** (R= -4-NO_2) against *S. pyogenus* and **3c** (R = -4-OH) against *P. aeruginosa* possesses moderate activity as compared with ampicillin where as substituted pyrazolines **4g** (R= -4-NO_2) against *S. aureus* and **4a** (R = -2-OH) against *P. aeruginosa* possesses good activity compared with ampicillin while **4f** (R= -4-Cl) against *S. aureus*, **4a** (R = -2-OH), **4e** (R = -4-OH-3-OCH_3) against *S. pyogenus* while **4b** (R= -3-NO_2) against *E. coli* and also against *P. aeruginosa* possesses good activity as compared with ampicillin. The results are recorded in Table-2.

TABLE- 2
ANTIBACTERIAL ACTIVITY OF COMPOUNDS **3(a-k)** AND **4(a-k)**

Compound code	Antibacterial activity (µg/mL)			
	Gram +*ve* Bacteria		Gram –*ve* Bacteria	
	S. aureus	*S. pyogenus*	*E. coli*	*P. aeruginosa*
3a	500	100	50	1000
3b	1000	500	1000	250
3c	100	1000	500	100
3d	500	1000	1000	500
3e	1000	250	200	1000
3f	62.5	500	500	200
3g	1000	100	200	1000
3h	50	1000	500	200
3i	200	1000	1000	1000
3j	1000	500	250	250
3k	250	250	250	250
4a	250	100	500	50
4b	500	500	100	100
4c	100	250	1000	500
4d	1000	500	250	500
4e	200	100	250	250
4f	100	250	500	200
4g	62.5	500	250	500
4h	250	1000	500	1000
4i	250	200	1000	250
4j	500	1000	1000	1000
4k	250	200	500	500
Standard drugs				
Gentamycin	0.25	0.5	0.05	1.0
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25
Norfloxacin	10	10	10	10

Antifungal activity: Antifungal screening data showed that substituted chalcones **3b** (R = -3-NO_2) and **3h** (R = H) show highly promising activity against *C. albicans* as compare to standard drug Greseofulvin while **3c** (R = -4-OH) and 3d (R = -4-*N,N*(CH_3)$_2$) against *A. niger* and also **3e** (R = -4-OH-3-OCH_3) and **3i** (R = -4-OCH_3) against *A.clavatus* show good activity compare with standard drug. While substituted pyrazoline **4h** (R= H) and **4i** (R = -4-OCH_3) show highly promising activity against *C. albicans* as compare to greseofulvin while **4a** (R = -2-OH) & **4f** (R = -4-Cl) against *A. niger* and also **4e** (R = -4-OH-3-OCH_3) and **4j** (R = -2-Cl) against *A. clavatus* show good activity compare with standard drug. The results are recorded in Table-3.

Conclusion

Compounds having such as hydroxyl, nitro group showed better antibacterial activity than the others not having such groups. Compounds having pharmacophores such as chloro or methoxy groups have exhibited more antifungal activity on all the three fungi than the others. These results suggest that the pyrazolines derivatives have excellent scope for further development as commercial antimicrobial agents. Further experiments were needed to elucidate their mechanism of action.

TABLE- 3
ANTIFUNGAL ACTIVITY OF COMPOUNDS **3(a-k)** AND **4(a-k)**

Compound code	Antifungal activity (µg/mL)		
	C. albicans	*A. niger*	*A. clavatus*
3a	500	1000	500
3b	250	>1000	>1000
3c	500	250	1000
3d	1000	250	500
3e	500	500	250
3f	500	500	500
3g	1000	1000	500
3h	200	>1000	>1000
3i	>1000	1000	250
3j	500	500	1000
3k	500	1000	500
4a	1000	250	1000
4b	500	500	500
4c	500	500	>1000
4d	>1000	1000	200
4e	500	500	250
4f	1000	250	500
4g	500	500	500
4h	200	>1000	1000
4i	200	1000	500
4j	500	500	250
4k	1000	500	1000
Standard drugs			
Nystatin	100	100	100
Greseofulvin	500	100	100

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