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Synthesis of Novel Pyrazolines of Medicinal Interest

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ABSTRACT. Different pyrazoline derivatives (6a–h and 7a–h) were synthesized by cyclization of substituted chalcones with hydrazine hydrate in acidic as well as basic conditions. Both the reactions were performed under conventional heating and microwave irradiation and percentage yields were compared. All the reactions were accelerated in acidic and basic conditions under microwave irradiation, with higher yields. All the synthesized compounds were characterized by their spectral study (IR, MS, ^{1}H and ^{13}C NMR) and were tested for their antibacterial and antifungal activity. The compounds 6g and 7g exhibited significant activity against *S. aureu*, 7g against *E. faecalis*, 6b and 7b against *E. coli* and 6b, 6c, 7b, 7c against *S. typhi*. The compounds 6d and 7d exhibited significant activity against *C. albicans* and 6c against *M. luteus*. Rest of the synthesized compounds showed moderate to poor activity against tested species with compared to standard.

Key words: Microwave irradiation, Chalcones, Pyrazolines, Antimicrobial activity

INTRODUCTION

Pyrazolines are well known and important nitrogen containing 5-membered heterocyclic compounds and various methods have been worked out for their synthesis. The ring is quite stable and has inspired chemists to carry out various structural variations in the ring.[1] Numerous pyrazoline derivatives have been found to possess considerable biological activities, which stimulated the research activity in this field.[2–5] Amongst all the nitrogen containing five member heterocycles, it have proved to be the most useful framework for biological activities and have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activities associated with them. The dihydropyrazoles have been reported to possess some interesting biological activities such as anti-inflammatory, antimicrobial and analgesic agents,[6,7] antitumor,[8,9] cannabinoid CB1 receptor agonists,[10] BRAF inhibitors,[11] monoamine oxidase inhibitor,[12] antidepressant[13] etc.

In the last few years microwave organic reaction enhancement chemistry has gained popularity as a non-conventional technique for rapid organic synthesis and many researchers have described accelerated organic reactions[14] and a large number of research articles have proven the importance of microwave synthesis as synthetic utility for routine organic synthesis.[15,16] It can be termed as 'e-chemistry' because it is easy, effective, economical and eco-friendly and is believed to be a step towards green chemistry. Under the framework of, "Green Chemistry" we have developed an environmentally benign solvent-free approach for the synthesis of pyrazolines inspired by Loupy et al.[17,18]

Herein we report the synthesis of α, β-unsaturated ketones (chalcones), by Claisen-Schmidt condensation of different aromatic aldehydes with ketone[19–23] and their cyclization with hydrazine hydrate in acidic as well as basic conditions. Both the reactions were performed under microwave irradiation and conventional heating.

EXPERIMENTAL

Materials

Melting points were determined in open capillary on an electro thermal apparatus and were uncorrected. Samsung MW83Y Microwave Oven was modified locally to perform all the reactions. TLC was performed on silica gel PF_{254} plates (Merck).

Methods

General procedure for the synthesis of 3-(4-((4-fluorobenzyl)oxy)phenyl)-1-phenylprop-2-en-1-one (5a–h)

(**a**) A mixture of 10 mmol of p-hydroxy benzaldehyde (**1**) and 10 mmol of 1-(chloromethyl)-4-fluorobenzene (**2**) in DMF was stirred at 120 °C for 12 hours using K_2CO_3 as a catalyst. The reaction mixture was poured in crushed ice. The crude product 4-((4-fluorobenzyl)oxy) benzaldehyde (**3**) was isolated and recrystallized from absolute hot ethanol. Yield: 84% M.P: 99 °C.

(**b**) A mixture of 10 mmol of **3** and 10 mmol of substituted acetophenone (**4a–h**) in methanol (30 ml) was stirred at room temperature for 24 hours using 20% NaOH as a catalyst to make the solution alkaline. The reaction mixture was poured in ice cold water. The crude 3-(4-((4-fluorobenzyl)oxy)phenyl)-1-phenylprop-2-en-1-one (**5a–h**) was isolated and recrystallized from hot absolute ethanol.

General procedure conventional synthesis of 5-(4-((4-fluorobenzyl)oxy)phenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole derivatives (6a–h)

A mixture of 10 mmol of **5** and 50 mmol of hydrazine hydrate in 25 ml Ethanol was refluxed for under catalytic amount of KOH. The solution was poured into crushed ice and neutralize with dilute HCl solution. Product **6** was isolated and crystallized from hot ethanol. Same reaction was carried out under microwave irradiation which resulted in poor yields. The physical data are recorded in *Table* 1.

General procedure microwave assisted synthesis of 1-(5-(4-((4-fluorobenzyl)oxy)phenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone derivatives (7a–h).

A mixture of 10 mmol of **5** and 50 mmol hydrazine hydrate were dissolved in 20 ml of acetic acid which was used as self solvent. The reaction mixture was subjected to MWI for a 5–10 min. at low power (180 W). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature; separated product **7** was filter washed with methanol and crystallized from hot ethanol. The same reaction was carried out on oil bath. The **7** was also synthesized by usual acetylating process of **6**. The physical data are recorded in *Table* 2.

Characterization

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 MHz FT NMR spectrometer. Chemical shifts are expressed in δ ppm downfield from internal TMS as reference. ^{1}H NMR data are reported in order: multiplicity (bs, broad singlet; s, singlet; d, doublet; t, triplet; m, multiplet). IR spectra were recorded on a Shimadzu FTIR-8400 instrument in KBr disc and only noteworthy absorption levels (cm^{-1}) are listed. Mass spectra were recorded on a GCMS QP 2010 spectrophotometer. Elemental analysis was performed on a Carlo Erba EA 1108 elemental analyzer. The results of elemental analyses (C, H, and N)

***Table* 1.** Synthesis of pyrazolines in basic condition under conventional heating and microwave irradiation **(6a–h)**

Code	R	M.F.	MW (gm/mol)	M.P. (°C)	Conventional		Microwave**	
					Time (h)	% Yield*	Time (min)	% Yield*
6a	H	$C_{22}H_{19}FN_2O$	346	135–138	16	68	11	88
6b	4-Br	$C_{22}H_{18}BrFN_2O$	424	151–154	13	71	9	85
6c	4-Cl	$C_{22}H_{18}ClFN_2O$	380	140–143	14	69	14	85
6d	4-OCH_3	$C_{23}H_{21}FN_2O_2$	376	123–125	16	64	13	90
6e	4-CH_3	$C_{23}H_{21}FN_2O$	360	129–131	17	61	12	82
6f	4-NH_2	$C_{22}H_{20}FN_3O$	361	138–141	14	70	10	86
6g	4-NO_2	$C_{22}H_{18}FN_3O_3$	391	155–157	13	69	12	84
6h	4-OH	$C_{22}H_{19}FN_2O_2$	362	137–140	17	72	13	89

*Isolated yield in ethanol.
**Continuous irradiation.

***Table* 2.** Synthesis of pyrazolines in acidic condition under conventional heating and microwave irradiation **(7a–h)**

Code	R	M.F.	MW (gm/mol)	M.P. (°C)	Conventional		Microwave**	
					Time (h)	% Yield*	Time (min)	% Yield*
7a	H	$C_{24}H_{21}FN_2O_2$	388	140–143	20	56	8.5	73
7b	4-Br	$C_{24}H_{20}BrFN_2O_2$	466	177–180	19	59	9	70
7c	4-Cl	$C_{24}H_{20}ClFN_2O_2$	422	155–158	16	61	10.5	75
7d	4-OCH_3	$C_{25}H_{23}FN_2O_3$	418	138–141	20	68	8.5	71
7e	4-CH_3	$C_{25}H_{23}FN_2O_2$	402	159–152	15	60	7.5	68
7f	4-NH_2	$C_{24}H_{22}FN_3O_2$	403	164–168	19	54	11	67
7g	4-NO_2	$C_{24}H_{20}FN_3O_4$	433	178–182	20	62	11.5	75
7h	4-OH	$C_{24}H_{21}FN_2O_3$	404	151–153	16	69	7.5	78

*Isolated yield in DMF.
**Continuous irradiation.

were within ± 0.4% of the theoretical values.

5-(4-((4-fluorobenzyl)oxy)phenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole (6a)

IR (ν_{max}, cm^{-1}): 3355 (N–H str. of Sec. Amine) 3034 (C=C–H str.), 2938 (C–H str.), 1509 (C=C– str), 1231 (C–O–C str. of ether), 1180 (C–F str); ^{1}H NMR (200 MHz, $CDCl_3$), 1.30 (1H, t, *J* = 7.00 Hz), 4.20 (1H, dd, *J* = 4.3, 15.7 Hz), 4.45 (1H, dd, *J* = 7.1, 14.8 Hz), 5.46 (2H, s, CH_2), 7.08–7.89 (m, 14H); 8.23 (1H, s, NH); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 41.4, 50.2, 72.0, 114, 125.9, 127.2, 128.2, 131.1, 136.7, 137.2, 151, 160.1,162.8; MS, *m/z* (%) = 346, 317, 251, 269, 237, 221, 201, 144, 125; Elemental Analysis: Calculated: C, 76.26; H, 5.53; N, 8.09%, Found: C, 76.22; H, 5.50; N, 8.10%.

3-(4-bromophenyl)-5-(4-((4-fluorobenzyl)oxy)phenyl)-4,5-dihydro-1*H*-pyrazole (6b)

IR (ν_{max}, cm^{-1}): 3355 (N-H str. of Sec. Amine) 3034 (C=C–H str.), 2938 (C–H str.), 1509 (C=C– str.), 1231 (C–O–C str. of ether), 1185 (C–F str.), 825 (C–H .p. def.) 547 (C–Br str.); ^{1}H NMR (200 MHz, $CDCl_3$), 1.35 (1H, t, *J* = 6.98 Hz), 4.14 (1H, dd, *J* = 3.5, 14.8 Hz), 4.35 (1H, dd, *J* = 7.2, 15.2 Hz), 5.46 (2H, s, CH_2), 7.08–7.89 (m, 13H); 8.20 (1H, s, NH); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 41.2, 50.4, 74.4, 114.1, 125.4, 125.9, 127.1, 128.6, 131.4, 136.8, 137, 151, 159, 161.2; MS, *m/z* (%) = 424, 405, 345,329, 326, 299, 222, 201, 144, 125; Elemental Analysis: Calculated: C, 62.13; H, 4.27; N, 6.59; %, Found: C, 62.10; H, 4.25; N, 6.60%.

3-(4-chlorophenyl)-5-(4-((4-fluorobenzyl)oxy)phenyl)-4,5-dihydro-1*H*-pyrazole (6c)

IR (ν_{max}, cm^{-1}): 3355 (N–H str. of Sec. Amine) 3034 (C=C–H str.), 2938 (C–H str.), 1509 (C=C– str.), 1231 (C–O–C str. of ether), 1185 (C–F str.), 825 (C–H .p. def.) 710 (C–Cl str.); ^{1}H NMR (200 MHz, $CDCl_3$), 1.33 (1H, t, *J* = 6.80 Hz), 4.08 (1H, dd, *J* = 4.2, 14.3 Hz), 4.25 (1H, dd, *J* = 7.1, 14.9 Hz), 5.52 (2H, s, CH_2), 7.08–7.89 (m, 13H); 8.12 (1H, s, NH); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 41.4, 50.2, 72.2, 114.1, 127.1, 127.6, 128.9, 134.5, 134.8, 151.7, 159.1, 162.8; MS, *m/z* (%) = 380, 361, 345, 326, 285, 269, 255, 201, 179, 144, 125,111; Elemental Analysis: Calculated: C, 69.38; H, 4.76; N, 7.36%, Found: C, 69.32; H, 4.74; N, 7.39%.

5-(4-((4-fluorobenzyl)oxy)phenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole (6d)

IR (ν_{max}, cm^{-1}): 3355 (N–H str. of Sec. Amine), 3034 (C=C–H str.), 2938 (C–H str.), 1509 (C=C– str.), 1231 (C–O–C str. of ether), 1184 (C–F str.), 825 (C–H .p. def.); ^{1}H NMR (200 MHz, $CDCl_3$), 1.35 (1H, t, *J* = 7.02 Hz), 3.45 (3H, s, CH_3), 4.17 (1H, dd, *J* = 3.8, 14.3 Hz), 4.39 (1H, dd, *J* = 6.9, 15.3 Hz), 5.48 (2H, s, CH_2), 7.08–7.90 (m, 13H); 8.14 (1H, s, NH); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 42.1, 51.1, 56.2, 72.0, 114.2, 128.1,128.5, 128.9, 137.1, 152.8, 158.2, 162.1, 163.4; MS, *m/z* (%) = 376, 357, 345, 281, 269, 251, 201, 175, 144, 125; Elemental Analysis: Calculated: C, 73.39; H, 5.62; N, 7.44%, Found: C, 73.42; H, 5.60; N, 7.40%

5-(4-((4-fluorobenzyl)oxy)phenyl)-3-(p-tolyl)-4,5-dihydro-1*H*-pyrazole (6e)

IR (ν_{max}, cm^{-1}): 3355 (N-H str. of Sec. Amine), 3034 (C=C–H str.), 2938 (C–H str.), 1509 (C=C– str.), 1231 (C–O–C str. of ether), 1185 (C–F str.), 825 (C–H .p. def.); ^{1}H NMR (200 MHz, $CDCl_3$), 1.89 (1H, t, *J* = 7.1 Hz), 2.1 (3H, s, CH_3), 4.23 (1H, dd, *J* = 4.3, 14.2 Hz), 4.45 (1H, dd, *J* = 7.2, 14.5 Hz), 5.21 (2H, s, CH_2), 7.08–7.98 (m, 13H); 8.22 (1H, s, NH); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 22.1, 41.4, 52.0, 71.0, 114.7, 125.8, 128.9, 135.2, 137.3, 142.5, 151.7, 158.1, 162.2; MS, *m/z* (%) = 360, 345, 341, 269, 235, 201, 159, 144, 125; Elemental Analysis: Calculated: C, 76.64; H, 5.87; N, 7.77%, Found: C, 76.61; H, 5.42; N, 7.56%.

4-(5-(4-((4-fluorobenzyl)oxy)phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)aniline (6f)

IR (KBr, cm^{-1}): 3450 (N-H str. of Pri. Amine), 3355 (N–H str. of Sec. Amine), 3034 (C=C–H str.), 2938 (C–H str.), 1509 (C=C– str.), 1231 (C–O–C str. of ether), 1185 (C–F str.), 825 (C–H .p. def.); ^{1}H NMR (200 MHz, $CDCl_3$), 1.56 (1H, t, *J* = 6.80 Hz), 4.15 (1H, dd, *J* = 4.6, 14.2 Hz), 4.23 (1H, dd, *J* = 6.8, 13.9 Hz), 5.42 (2H, s, CH_2), 5.9 (1H, s, NH), 7.10–7.99 (m, 13H); 8.12 (1H, s, NH); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 41.3, 52.4, 57.2, 114.2, 114.6, 126.4, 130.1, 136.7, 152.1, 158.7, 161.9; MS, *m/z* (%) = 361, 345, 342, 269, 256, 236, 201, 160, 144, 125; Elemental Analysis: Calculated: C, 73.11; H, 5.58; N, 11.63%, Found: C, 73.08; H, 5.50; N, 11.59%.

5-(4-((4-fluorobenzyl)oxy)phenyl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole (6g)

IR (ν_{max}, cm^{-1}): 3355 (N–H str. of Sec. Amine), 3034 (C= C–H str.), 2938 (C–H str.), 1540 (N=O Str.), 1509 (C=C– str.), 1231 (C–O–C str. of ether), 1185 (C–F str.), 821 (C–H .p. def.); ^{1}H NMR (200 MHz, $CDCl_3$), 1.83 (1H, t, *J* = 6.92 Hz), 4.11 (1H, dd, *J* = 4.1, 15.2 Hz), 4.21 (1H, dd, *J* = 6.8, 14.2 Hz), 5.47 (2H, s, CH_2), 7.08–7.97 (m, 13H); 8.20 (1H, s, NH); ^{13}C NMR (200 MHz, $CDCl_3$,

δ): 41.8, 51.4, 70.2, 114.1, 126.5, 128.7, 138.2, 142.5, 150.7, 152.1, 157, 162.2; MS, *m/z* (%) = 391, 372, 345, 282, 269, 266, 201, 190, 144, 125; Elemental Analysis: Calculated: C, 67.51; H, 4.64; N, 10.74%, Found: C, 67.43; H, 4.66; N, 10.78%.

4-(5-(4-((4-fluorobenzyl)oxy)phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenol (6h)

IR (ν_{max}, cm^{-1}): 3480 (−OH str. of Phenolic OH), 3355 (N−H str. of Sec. Amine), 3034 (C=C−H str.), 2938 (C−H str.), 1509 (C=C− str.), 1231 (C−O−C str. of ether), 1180 (C−F str.), 830 (C−H .p. def.); ^{1}H NMR (200 MHz, $CDCl_3$), 1.45 (1H, t, *J* = 7.2 Hz), 4.16 (1H, dd, *J* = 4.2, 14.8 Hz), 4.42 (1H, dd, *J* = 7.2, 15.6 Hz), 5.46 (2H, s, CH_2), 5.98 (1H, s, OH), 7.00−7.99 (m, 13H); 8.28 (1H, s, NH); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 42.2, 51.7, 71.1, 114, 125.4, 128.7, 135.6, 137.4, 151.9, 158.4, 162.0,162.9; MS, *m/z* (%) = 362, 345, 343, 269, 267, 201, 161, 144, 125; Elemental Analysis: Calculated: C, 72.91; H, 5.28; N, 7.73%, Found: C, 72. 88; H, 5.32; N, 7.70%.

1-(5-(4-((4-fluorobenzyl)oxy)phenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (7a)

IR (ν_{max}, cm^{-1}): 3037 (C=C−H str.), 2931 (C−H str.), 1705 (C=O str.), 1509 (C=C− str.), 1230 (C−O−C str. of ether), 1172 (C−F str.); ^{1}H NMR (200 MHz, $CDCl_3$) 2.40 (3H, s, CH_3), 2.90 (1H, dd, *J* = 5.2, 18.6 Hz), 3.10 (1H, dd, *J* = 12.3, 16.2 Hz), 5.10 (2H, s, CH_2), 5.74 (1H, dd, *J* = 3.7, 12.3 Hz), 6.90–7.85 (m, 14H); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 23.2, 40.1, 66.4, 71.1, 114.1, 127.1, 128.2, 127.6, 128.8, 131.1, 134, 136.4, 136.7, 151.9, 158.7, 161.1, 169.1; MS, *m/z* (%) = 388, 369, 345, 311, 293, 263, 201, 187, 125; Anal. cacld: C, 74.21; H, 5.45; N, 7.21%, Found: C, 74.17; H, 5.40; N, 7.25%.

1-(3-(4-bromophenyl)-5-(4-((4-fluorobenzyl)oxy)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethanone (7b)

IR (ν_{max}, cm^{-1}): 3034 (C=C−H str.), 2931 (C−H str.), 1702 (C=O str.), 1505 (C=C− str.), 1231 (C−O−C str. of ether), 1175 (C−F str.), 822 (C−H .p. def.) 540 (C−Br str.); ^{1}H NMR (200 MHz, $CDCl_3$) 2.24 (3H, s, CH_3), 2.83 (1H, dd, *J* = 4.9, 18.2Hz), 2.98 (1H, dd, *J* = 11.2, 17.3 Hz), 5.25 (2H, s, CH_2), 5.70 (1H, dd, *J* = 4.2, 11.9 Hz), 6.90–7.85 (m, 13H); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 23.4, 41.2, 65.8, 71.1, 114.1, 125.4, 126.2, 127.4, 128.7, 128.9, 134.1, 136, 151.8, 158.8, 161.4, 168.7; MS, *m/z* (%) = 466, 447, 387, 368, 325, 311, 265, 201, 186, 125; Elemental Analysis: Calculated: C, 61.68; H, 4.31; N, 5.99% Found: C, 61.63; H, 4.28; N, 6.03%.

1-(3-(4-chlorophenyl)-5-(4-((4-fluorobenzyl)oxy)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethanone (7c)

IR (ν_{max}, cm^{-1}): 3034 (C=C−H str.), 2931 (C−H str.), 1710 (C=O str.), 1515 (C=C− str.), 1231 (C−O−C str. of ether), 1170 (C−F str.), 822 (C−H .p. def.) 710 (C−Cl str.); ^{1}H NMR (200 MHz, $CDCl_3$) 2.37 (3H, s, CH_3), 2.87 (1H, dd, *J* = 5.6, 17.8 Hz), 3.05 (1H, dd, *J* = 12.8, 17.7 Hz), 5.34 (2H, s, CH_2), 5.68 (1H, dd, *J* = 4.8, 12.4 Hz), 6.90–7.85 (m, 13H); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 23.1, 40.1, 65.8, 70.9, 114.1, 127.1, 128.2, 128.9, 134.5, 136.6, 136.7, 151.7, 159.1, 162.3, 168.7; MS, *m/z* (%) = 422, 403, 387, 327, 313, 297, 292, 221, 201, 178, 125; Elemental Analysis: Calculated: C, 68.17; H, 4.77 N, 6.62% Found: C, 68.16; H, 4.72; N, 6.65%.

1-(5-(4-((4-fluorobenzyl)oxy)phenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethanone (7d)

IR (ν_{max}, cm^{-1}): 3030 (C=C−H str.), 2931 (C−H str.), 1702 (C=O str.), 1508 (C=C− str.), 1240 (C−O−C str. of ether), 1181 (C−F str.), 829 (C−H .p. def.); ^{1}H NMR (200 MHz, $CDCl_3$) 2.39 (3H, s, CH_3), 2.85 (1H, dd, *J* = 3.9, 18.8 Hz), 3.01 (1H, dd, *J* = 11.9, 16.9Hz), 4.26 (3H, s, CH_3), 5.20 (2H, s, CH_2), 5.67 (1H, dd, *J* = 3.9, 12.2 Hz), 6.90–7.85 (m, 13H); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 23.4, 40.7, 55.7, 65.9, 71.7, 114.1, 114.7, 126.6, 127.1, 127.6, 128.9, 134.1, 138.2, 151.7, 158.2,161.6, 162.9, 168.7; MS, *m/z* (%) = 418, 399, 387, 311, 309, 293, 266, 217, 201, 174, 143, 125; Elemental Analysis: Calculated: C, 71.76; H, 5.54; N, 6.69% Found: C, 71.78; H, 5.52; N, 6.74%.

1-(5-(4-((4-fluorobenzyl)oxy)phenyl)-3-(p-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (7e)

IR (ν_{max}, cm^{-1}): 3034 (C=C−H str.), 2931 (C−H str.), 1712 (C=O str.), 1512 (C=C− str.), 1228 (C−O−C str. of ether), 1178 (C−F str.), 823 (C−H .p. def.); ^{1}H NMR (200 MHz, $CDCl_3$) 1.9 (3H, s, CH_3) 2.40 (3H, s, CH_3), 2.82 (1H, dd, *J* = 4.3, 17.3 Hz), 3.05 (1H, dd, *J* = 11.4, 18.2 Hz), 5.10 (2H, s, CH_2), 5.27 (1H, dd, *J* = 3.2, 12.2 Hz), 6.90–7.85 (m, 13H); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 22.7, 23.7, 40.7, 66.1, 71.1, 114.1, 126.6, 127, 129.1, 128.8, 133.4, 134, 140.7, 152.1, 158.6, 162.4, 169.7; MS, *m/z* (%) = 402, 387, 383, 368, 311, 293, 277, 201, 186, 125, 91; Elemental Analysis: Calculated: C, 74.61; H, 5.76; N, 6.96% Found: C, 74.68; H, 5.72; N, 7.00%.

1-(3-(4-aminophenyl)-5-(4-((4-fluorobenzyl)oxy)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethanone (7f)

IR (ν_{max}, cm^{-1}): 3405 (N−H str.), 3034 (C=C−H str.), 2931 (C−H str.), 1701 (C=O str.), 1500 (C=C− str.), 1228

(C–O–C str. of ether), 1172 (C–F str.), 820 (C–H .p. def.); ^{1}H NMR (200 MHz, $CDCl_3$) 2.35 (3H, s, CH_3), 2.70 (1H, dd, *J* = 5.2, 17.8 Hz), 3.13 (1H, dd, *J* = 9.9, 18.1 Hz), 5.32 (2H, s, CH_2), 5.70 (1H, dd, *J* = 3.2, 12.1 Hz), 5.95 (2H, s, NH_2), 6.90–7.96 (m, 13H); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 23.1, 40.1, 65.9, 71.6, 114.1, 114.3, 126.6, 130, 134.1, 136.7, 150.7, 158.6, 161.9, 168.7; MS, *m*/*z* (%) = 403, 387, 384, 368, 308, 311, 278, 202, 186, 125; Elemental Analysis: Calculated: C, 71.45; H, 5.50; N, 10.42% Found: C, 71.48; H, 5.54; N, 10.43%.

1-(5-(4-((4-fluorobenzyl)oxy)phenyl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethanone (7g)

IR (ν_{max}, cm^{-1}): 3039 (C=C–H str.), 2931 (C–H str.), 1702 (C=O str.), 1540 (N=O Str.), 1504 (C=C– str.), 1228 (C–O–C str. of ether), 1170 (C–F str.), 825 (C–H .p. def.); ^{1}H NMR (200 MHz, $CDCl_3$) 2.20 (3H, s, CH_3), 2.67 (1H, dd, *J* = 4.6, 17.4 Hz), 2.98 (1H, dd, *J* = 12.1, 17.9 Hz), 4.90 (2H, s, CH_2), 5.10 (1H, dd, *J* = 3.9, 12.2 Hz), 6.90–8.50 (m, 13H); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 22.7, 39.9, 70.1, 114.1, 126.6, 127.0, 127.7, 134.9, 142.7, 151.1, 157.9, 162.1, 168.7; MS, *m*/*z* (%) = 433, 414, 387, 368, 324, 262, 232, 219, 189, 125; Elemental Analysis: Calculated: C, 66.51; H, 4.65; N, 9.69% Found: C, 66.52; H, 4.61; N, 9.73%.

1-(5-(4-((4-fluorobenzyl)oxy)phenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethanone (7h)

IR (ν_{max}, cm^{-1}): 3494 (–OH str. of Phenolic OH), 3034 (C=C–H str.), 2931 (C–H str.), 1708 (C=O str.), 1540 (N=O Str.), 1504 (C=C– str.), 1228 (C–O–C str. of ether), 1185 (C–F str.), 825 (C–H .p. def.); ^{1}H NMR (200 MHz, $CDCl_3$) 2.04 (3H, s, CH_3), 2.97 (1H, dd, *J* = 4.2, 17.8 Hz), 3.43 (1H, dd, *J* = 10.8, 17.1 Hz), 5.05 (1H, s, OH), 5.20 (2H, s, CH_2), 5.42 (1H, dd, *J* = 4.9, 14.5 Hz), 6.90–7.85 (m, 13H); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 23.4, 40.4, 65.9, 70.7, 114.1, 116.0, 126.6, 129.1, 134.0, 157.7, 161.4, 162.9, 168.9; MS, *m*/*z* (%) = 404, 387, 385, 309, 292, 279 236, 203, 186, 160, 125; Elemental Analysis: Calculated: C, 71.27; H, 5.23; N, 6.93% Found: C, 71.23; H, 5.24; N, 7.00%.

Biological Activity

The antibacterial activity was determined applying the cup-plate agar-diffusion method[24] and antifungal activity was determined applying the agar plate technique method.[25] Results were obtained in duplicate, and results with differences higher than 5% were discarded and the measurement repeated.

RESULTS AND DISCUSSION

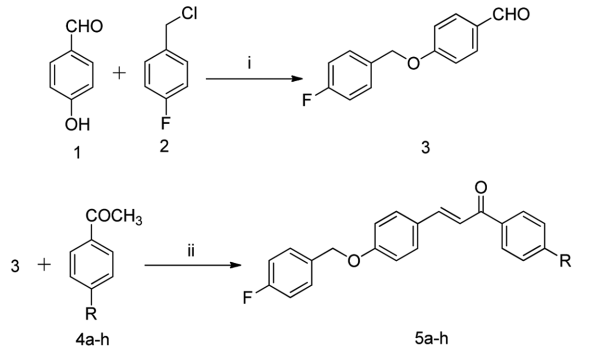
Chemistry

In the initial step 4-((4-fluorobenzyl)oxy) benzaldehyde **(3)** was synthesized by reacting 4-hydroxy benzaldehyde **(1)** and benzyl chloride **(2)** using K_2CO_3 as catalyst. Chalcone **(5a–h)** were synthesized by condensing **3** with appropriate para substituted acetophenones (**4a–h**) in ethanolic NaOH solution at room temperature (*Scheme* 1).

The cyclization of **5a–5h** with hydrazine hydrate in presence of KOH and ethanol as a solvent and with hydrazine hydrate in presence of glacial acetic acid as self solvent led to the compounds **6a–6h** and **7a–7h** respectively. Both the reactions were performed in conventional heating and microwave irradiation. The cyclization took place via nucleophillic attack of hydrazine hydrate on carbonyl carbon of **5a–h** with removal of water molecule followed by inter molecular cyclization reaction to afford products **6a–6h** and **7a–7h** respectively.

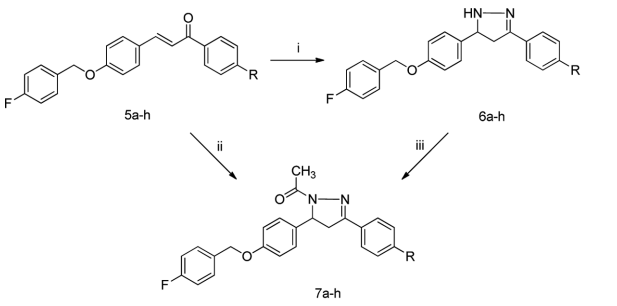
The products **7a–h** were than synthesized from **6a–h** by usual acetylation process using acetic anhydride (*Scheme* 2).

All the reactions were accelerated in acidic and basic conditions under microwave irradiation with slightly better percentage yields. The reaction time was up to ten times



Reagents and conditions: i: K_2CO_3, DMF, reflux, 120°C; ii: 20% NaOH, Methanol

***Scheme* 1.** Synthesis of Chaclones.



Reagents and conditions: i: $NH_2NH_2.H_2O$, CH_3CH_2OH, KOH, reflux, 12-16hr; ii: $NH_2NH_2.H_2O$, Glacial CH_3COOH, 180 MW, 5-10min; iii. CH_3COOH, $(CH_3CO)_2O$, reflux 6-8hr.

***Scheme* 2.** Synthesis of dihydropyrazoles.

shorter than for comparable reactions under conventional heating. There was a clear improvement in using microwave heating over conventional heating in the acidic condition for all of our studied substrates (*Table* 1, 2).

The structures of the products (**6a–h** and **7a–h**) were determined by spectroscopic as well as elemental analytical data. The compounds **6a–6h** showed IR absorption bands at 3355 cm^{-1} of cyclic secondary amine (–NH) stretching of pyrazoline ring system and **7a–7h** showed 1710 cm^{-1} of acetyl group stretching. The ^1H NMR spectra of all the synthesized compounds (**6a–h** and **7a–h**) showed characteristic doublet of doublet at 4.10–4.50 ppm for substituted pyrazol ring system. Measured chemical shift and coupling constant values unequivocally proved the pyrazoline structure. Moreover the etheric protons (–O–CH_2) showed singlet at 5.40–5.50 ppm. The aromatic ring protons and *J* value were found to be in accordance with substitution pattern on phenyl ring.

Biological Activity

Lack of development of new antimicrobial agents is a serious problem these days because the microorganisms are getting more and more 'use to' to the drugs available in the market.[26] The wide range of activity profile of pyrazole probes us to test and study the biological activities of some of the synthesized novel analogues. The newly synthesized compounds **6a–h** to **7a–h** were tested in vitro for their antibacterial activity against two gram positive bacteria *Staphylococcus aureus, Enterococcus faecalis* and two gram negative bacteria *Escherichia coli*, *Salmonella typhi* by the cup-plate agar-diffusion method. DMSO was used as a control solvent, Sparfloxacin and Benzyl Penicillin as standard drugs.

After 24 h incubation at 37 °C, the zone of inhibition was measured in mm. The results are depicted in *Table* 3. The results showed that almost all compounds were active against the microorganism tested. It is worth noting here that compounds **6g** and **7g** exhibited significant activity against *S. aureu,* **7g** against *E. faecalis,* **6b** and **7b** against *E. coli* and **6b**, **6c**, **7b**, **7c** against *S. typhi* The other compounds showed moderate-to-low activity. Over all, in both the series conpounds with R = NO_2 (**6g**, **7g**) found to be more active against the gram positive bacteria and compounds with R = Cl, Br (**6b**, **6c**, **7b** and **7c**) were found to be more active against the gram negative bacteria. Compounds with R = H, NH_2, OH (**6a**, **6f**, **6h**, **7a**, **7f** and **7h**) were found to be least active against all the tested bacterial species with respect to standard (*Fig.* 1).

Compounds **6a–h** to **7a–h** were also screened in vitro for their antifungal activity against four species using the agar plate technique. The linear growth of the fungus was obtained by measuring the diameter of the fungal colony after 7 days. The amount of growth inhibition in each case was calculated as percentage inhibition. The results shown in *Table* 4 indicated that **6d** and **7d** exhibited significant activity against *Candida albicans* and **6c** against *Micrococcus luteus*. Moreover no compound exhibited significant activity against *Trichphyton longifusus.* It is worth noting that compounds with R = OCH_3 and Cl (**6d**, **7d** and **6c** respectively) showed good antifungal activities, rest of the compounds showed poor activity against the fungal

***Table* 3.** Antimicrobial activity of pyrazoline derivatives (**6a–h** and **7a–h**)

Code	R	Gram (+)		Gram (–)	
		S.a	E.f	E.c	S.t
6a	H	06	08	06	–
6b	4-Br	15	12	**21**	**16**
6c	4-Cl	14	16	12	**17**
6d	4-OCH_3	17	09	05	12
6e	4-CH_3	16	11	07	06
6f	4-NH_2	08	09	–	–
6g	4-NO_2	18	–	06	–
6h	4-OH	07	06	08	09
7a	H	06	09	08	–
7b	4-Br	15	–	**20**	**15**
7c	4-Cl	16	16	07	**17**
7d	4-OCH_3	16	13	12	09
7e	4-CH_3	11	–	–	–
7f	4-NH_2	07	–	07	09
7g	4-NO_2	**19**	**18**	11	07
7h	4-OH	09	–	06	10
Sparfloxacin		26	18	22	16
Benzyl Penicillin		18	19	22	18

Zone diameter of growth inhibition (mm) after 24 h, ≤ 05 mm (–), Concentration 1 mg/mL in DMSO. Microorganisms selected are as follows: S.a, *Staphylococcus aureus*; E.f, *Enterococcus faecalis*; E.c, *Escherichia coli*; S.t, *Salmonella typhi*.

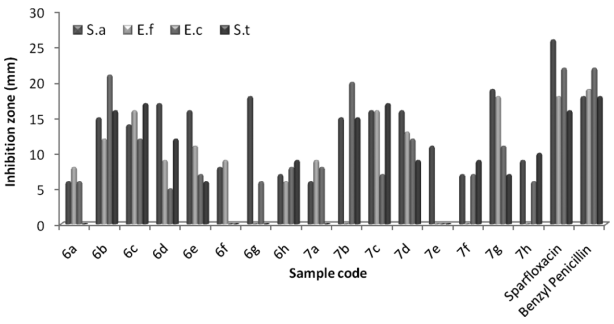


***Figure* 1.** Antimicrobial activity of **6a–h** and **7a–h**.

***Table* 4.** Antifungal activity of pyrazoline derivatives (**6a–h** and **7a–h**)

Code	R	T.l	C.a	M.c
6a	H	20	34	–
6b	4-Br	–	–	–
6c	4-Cl	58	48	**88**
6d	4-OCH_3	67	**82**	40
6e	4-CH_3	25	–	–
6f	4-NH_2	–	–	–
6g	4-NO_2	–	42	–
6h	4-OH	75	–	–
7a	H	22	24	–
7b	4-Br	–	–	13
7c	4-Cl	47	60	37
7d	4-OCH_3	76	**90**	62
7e	4-CH_3	45	–	–
7f	4-NH_2	–	23	–
7g	4-NO_2	–	–	–
7h	4-OH	67	38	27
Fluconazole		100	90	90

Conc. of sample 200 lg/mL in DMSO at 27 °C, Incubation period 7 days. Microorganisms selected are as follows: T.l, *Trichphyton longifusus*; C.a, *Candida albicans*; M.c, *Microsporum canis.*

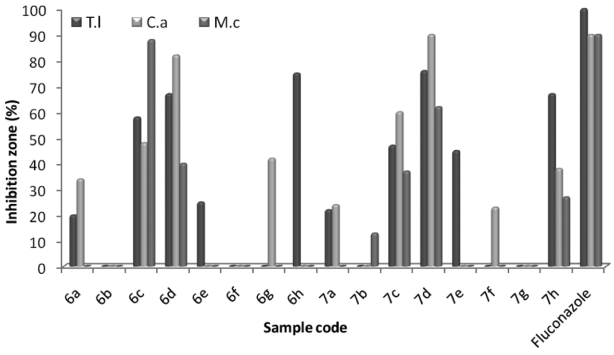


***Figure* 2.** Antifungal activity of **6a–h** and **7a–h**.

species tested with respect to standard (*Fig*. 2).

CONCLUSION

In the present article, we report the synthesis, spectral studies, antibacterial and antifungal activities of a novel series of substituted pyrazoles. These were characterized by IR, NMR, mass spectrometry study and elemental analyses. The substrates were obtained in good yield in acidic and basic conditions. Moreover microwave conditions gave advantages in terms of short reaction time and slight higher yield when compared to usual conventional methods. The compounds **6g** and **7g** exhibited significant (maximum) antibacterial activity against gram positive bacterial species, **6b**, **6c**, **7b**, **7c** against gram negative bacterial species and **6c**, **6d** and **7d** exhibited significant (maximum) antifungal activities, which may develop into the potential class of antimicrobial agents.

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