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Synthesis and Antimicrobial Activity of Some Novel Pyrazolones

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ABSTRACT

Knoevenagel condensation was carried out using heterocyclic aldehydes and pyrazolone derivatives. The structure elucidation of condensation products 1, 2, 3 and 4 was done using spectral methods like IR, ^{1}H NMR and mass spectrometry. These novel compounds were screened for antimicrobial activity.

Keywords: Pyrazolone, Knoevenagel condensation, Antimicrobial activity.

INTRODUCTION

Multi drug resistant micro-organisms and increased systemic as well as infectious diseases are the two major challenges for scientific world. Development of newer synthetic entities can offer a major solution for these problems.

Pyrazolone containing compounds are associated with antimicrobial[1], antiviral[2], antifungal[3], antioxidant[4], cytotoxic[5], analgesic[6], anti-inflammatory[7]activities.Thiophene derivatives have found very important place in the field of drug discovery because of their potential biological activities[8].

Thiazoles have found applications in drug development for treatment of HIV infections[9], hypertension[10] and as inhibitors of bacterial gyrase B[11]. Moreover pyrazole containing compounds are reported to have good biological activities like antimicrobial[12], antifungal[13], antiviral[14],analgessic[15],anti parastic[16] and antineoplastic[17].

Pyridine nucleus is important nitrogen heterocycle which exhibits antimicrobial[18], anticancer[19] and antioxidant[20] activities. Imidazole derivatives have been shown to exhibit antibacterial [21], antifungal and antioxidant[22] activity.

It has been shown that substitution pattern of bromine can alter the activity of a compound[23]. Fluorine containing compounds are associated with bioactivities such as antibacterial[24], anticancer[25] and analgesic[26].

Knoevenagel condensation [27] reaction shave occupied an important place in synthetic organic chemistry due to its efficiency in carbon-carbon bond formation. Many researchers have studied Knoevenagel condensation reactions of various aldehydes with pyrazolones[28-29].

Activities associated with pyrazolones, thiophenes, pyrazoles, imidazoles and halogens prompted us to synthesize compound containing these moieties.

EXPERIMENTAL

Physical constants were determined in open capillary. IR of the compounds were recorded using IR Affinity-1 Fourier transform infrared spectrophotometer *(Shimadzu). P*MR spectra were taken using Bruker Avance II 400 MHz NMR spectrometer. TMS was used as an internal standard and DMSO-d_6 as a solvent. The mass spectra were recorded on HP 1100 LC/MS.

(4*E*)-4-((3-(5-Bromothiophen-2-yl)-1-(2,3-dimethylphenyl)-1*H*- pyrazol-4-yl) methylene)-1-(2,3-dimethylphenyl)-3-propyl-1*H*-pyrazol-5(4*H*)-one, 1.

The mixture of 3-(5-bromothiophen-2-yl)-1-(2,3-dimethylphenyl)-1*H*- pyrazole-4-carbaldehyde A (0.01 mol) and 2-(2,3-dimethylphenyl)-5-propyl-2,4-dihydro-3*H*-pyrazol-3-one B (0.01mol) in 5 mL of glacial acetic acid was refluxed in round bottom flask for 30 min. Reaction progress was studied and confirmed using TLC at the end of reaction, reaction mixture was poured over ice. Product obtained 1 was separated using simple filtration then purified by re crystallization from ethanol. Compounds 2,3 and 4 were synthesized using same procedure. Physical data of all the synthesized compounds is given in Table 1 and spectral data as below.

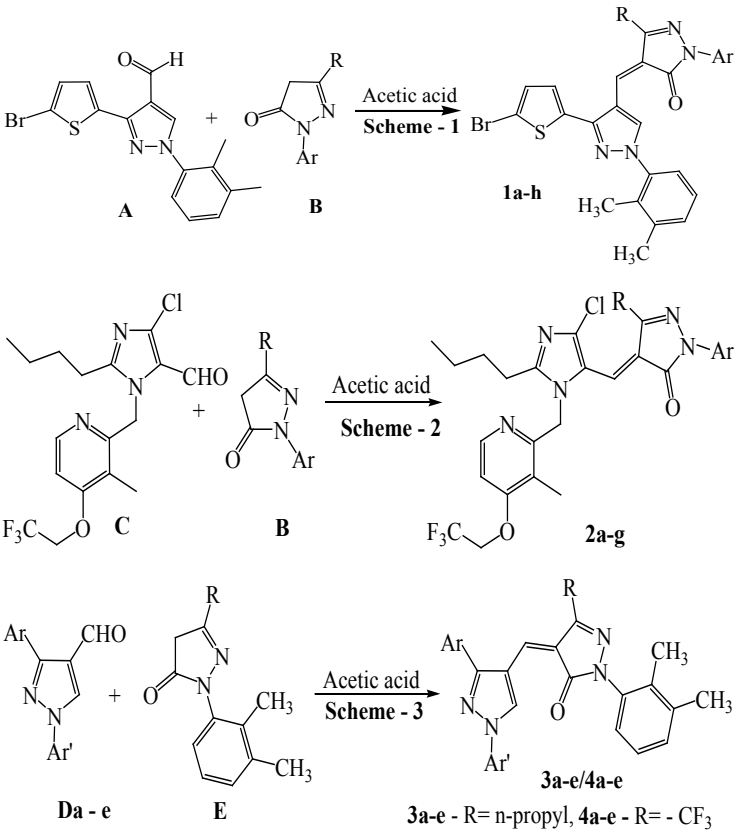
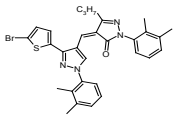
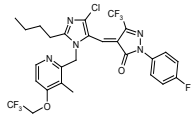
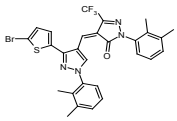
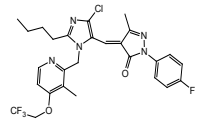
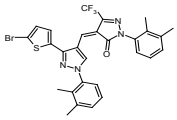
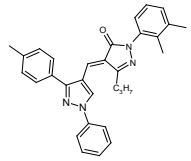
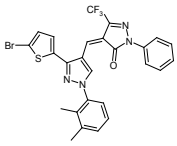
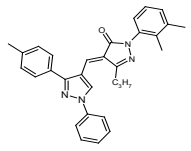
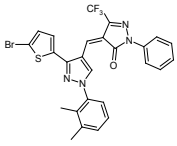
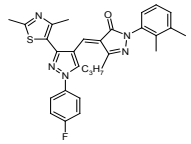
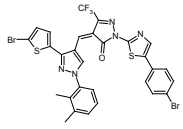
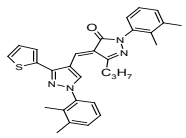
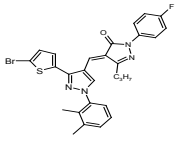
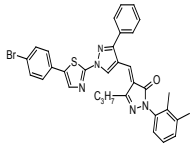
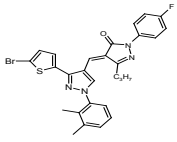
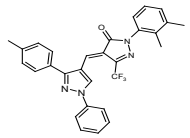
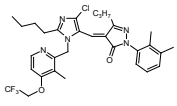
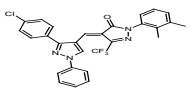
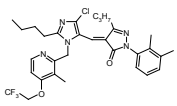
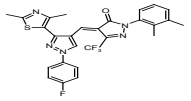
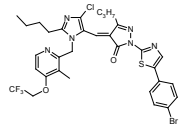
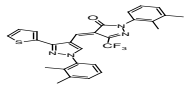
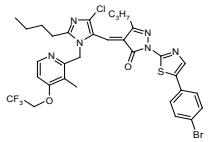
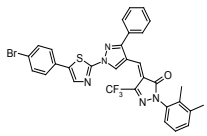
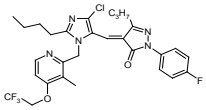


Table 1: Physical data of synthesized compounds

Compd	Structure	M.P. (°C)	% Yield	Compd	Structure	M. P. (°C)	% Yield
1a		235	77	2f		132	71
1b		218	81	2g		166	64
1c		198	74	3a		180	62
1d		223	83	3b		188	60
1e		258	75	3c		178	63
1f		227	82	3d		205	61
1g		205	72	3e		210	65
1h		224	84	4a		245	70
2a		135	60	4b		204	72
2b		140	66	4c		228	71

2c		192	63	4d		220	73
2d		184	72	4e		248	74
2e		142	61				

1a, MS: *m/z* 572 (M^+); PMR: δ 9.74 (s, 1H),7.70 (s, 1H),7.37 (d,1H, *J* = 3.8 Hz),7.32 (d, 2H, *J* = 3.8 Hz), 7.25-7.26 (m, 2H), 7.11-7.17 (m, 3H), 2.68 (t, 2H),2.36 (s, 3H), 2.31 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H),1.77 (sextet, 2H),1.04 (t, 3H); IR: 3132, 2958, 2918, 1676, 1554, 790, 754, 717, 663 cm^{-1}.

1b, MS: *m/z* 598 (M^+); PMR: δ 9.76 (s, 1H), 7.81 (s, 1H), 7.42 (d,1H, *J* = 4 Hz),7.34 (d, 1H, *J* = 4.8 Hz), 7.27-7.31 (m, 4H),7.18 (t, 2H, *J* = 7 Hz),2.35 (s, 3H),2.32 (s, 3H), 2.11 (s, 3H),2.06 (s, 3H); IR: 3122, 2920, 1691, 1593, 1112, 794, 754, 713, 619 cm^{-1}.

1c, MS: *m/z* 544 (M^+); PMR: δ 9.71 (s, 1H),7.84-7.93 (m, 5H), 7.66 (s, 1H), 7.56-7.58 (m, 3H), 7.42 (d,1H, *J* = 3.9 Hz), 7.33 (d, 1H, *J* = 3.9 Hz),2.80 (t, 2H), 2.33 (s, 3H), 2.15 (s, 3H),1.81 (sextet, 2H), 1.08 (t, 3H); IR: 3128, 2952, 2911, 1669, 1544, 792, 758, 719 cm^{-1}.

1d, MS: *m/z* 570 (M^+); PMR: δ 9.82 (s, 1H), 8.69 (s, 1H),7.87-8.09 (m, 5H), 7.51-7.54 (m, 3H),7.42 (d, 1H, *J* = 3.8 Hz), 7.33 (d,1H, *J* = 3.8 Hz),2.38 (s, 3H), 2.12 (s, 3H); IR: 3122, 2925, 1693, 1597,1120, 790, 717, 688 cm^{-1}.

1e, MS: *m/z* 707 (M^+); PMR: δ 9.76 (s, 1H), 7.93 (d, 2H, *J* =7.8 Hz), 7.70 (s, 1H), 7.36-7.41 (m, 4H), 7.31-7.33 (m, 3H),7.16 (t, 1H), 2.71 (t, 2H, *J* =7.4 Hz), 2.39 (s, 3H), 2.14 (s, 3H), 1.81 (sextet, 2H, *J* =7.4 Hz), 1.07 (t, 3H, *J* = 7.4 Hz); IR: 3128, 2926, 1693, 1597,1120, 790, 756, 715, 629 cm^{-1}.

1f, MS: *m/z* 731 (M^+); PMR: δ 9.79 (s, 1H), 7.79 (s, 1H), 7.85 (d, 2 H, *J* =7.7 Hz),7.49 (d, 2H, *J* =7.7 Hz),7.42 (d, 1H, *J* = 3.88 Hz),7.30-7.35 (m, 5H),2.38 (s, 3H),2.14 (s, 3H); IR : 3127, 2924, 1697, 1596, 1117, 793, 757, 718, 639 cm^{-1}.

1g, MS: *m/z* 562 (M^+); PMR: δ 9.73 (s, 1H), 7.93 (dd, 2H, *J* = 9.2 & 5 Hz),7.73 (s, 1H),7.44 (d, 1H, *J* = 3.8 Hz),7.37-7.39 (m, 2H),7.30-7.33 (m, 2H),7.22 (t, 2H, *J* = 8.8 Hz),2.72 (t, 2H),2.38 (s, 3H),2.12 (s, 3H),1.78 (sextet, 2H, *J* = 7.3 Hz), 1.04 (t, 3H); IR : 3135, 2968, 2922, 1671, 1559, 788, 757, 722, 687 cm^{-1}.

1h, MS: *m/z* 588 (M^+); PMR: δ 9.82 (s, 1H), 7.88 (dd, 2H, *J* = 9.12 & 4.92 Hz),7.75 (s, 1H),7.45 (d, 1H, *J* = 3.88 Hz),7.36-7.39 (m, 2H),7.32-7.35 (m, 2H),7.22 (t, 2H, *J* = 8.8 Hz),2.38 (s, 3H),2.12 (s, 3H); IR: 3133, 2929, 1690, 1593,1123, 798, 755, 722, 689 cm^{-1}.

2a, MS: *m/z* 601 (M^+); PMR: δ 8.18 (d,1H, *J* = 5.7 Hz), 7.48 (s, 1H),7.45 (t, 1H, *J* = 8Hz),7.09-7.18 (m, 2H),7.02 (d, 1H, *J* = 5.7 Hz),5.46 (s, 2H),4.81 (q, 2H),2.67 (t, 2H),2.61 (t, 2H),2.33 (s, 3H),2.22 (t, 3H),2.12 (t, 3H),1.78 (sextet, 2H),1.59(quintet, 2H),1.32 (sextet, 2H),1.05 (t, 3H),0.84 (t, 3H, *J* = 7.32 Hz); IR:2928, 1656, 1623, 1558, 1234, 1126, 967, 769, 754, 711 cm^{-1}.

2b, MS: *m/z* 627 (M^+); PMR: δ 8.16 (d,1H, *J* = 5.7 Hz), 7.50 (s, 1H), 7.43 (t, 1H, *J* = 8 Hz),7.09-7.20 (m, 2H),7.04 (d, 1H, *J* = 5.7 Hz),5.45 (s, 2H),4.80 (q, 2H),2.62 (t, 2H),2.32 (t, 3H),2.21 (t, 3H),2.14 (t, 3H),1.57 (quintet, 2H),1.33 (sextet, 2H),0.85 (t, 3H, *J* = 7.4 Hz); IR: 2958, 2920, 1655, 1620, 1524, 1231, 1120, 967, 788cm^{-1}

.

2c, MS: *m/z* 734 (M^+); PMR: δ 8.20 (d,1H, *J*= 5.7 Hz), 8.07 (s, 1H),7.93 (d, 2H, *J* = 7.7 Hz),7.50 (d, 2H, *J*= 5.8Hz),7.47 (s, 1H),7.05 (d, 1H, *J*= 5.7 Hz),5.47 (s, 2H),4.80 (q, 2H),2.68 (t, 2H),2.62 (t, 2H),2.24 (s, 3H),1.77 (sextet, 2H),1.60 (quintet, 2H),1.34 (sextet, 2H),1.07 (t, 3H),0.87 (t, 3H, *J* = 7.4 Hz); IR: 2927, 2918, 1676, 1622, 1525, 1231, 1123, 966cm^{-1}.

2d, MS: *m/z* 760 (M^+); PMR: δ 8.16 (d, 1H, *J*= 5.7 Hz), 8.06 (s, 1H), 7.91 (d, 2H, *J* = 7.8 Hz),7.49 (d, 2H, *J* = 7.8 Hz),7.48 (s, 1H),7.05 (d, 1H, *J*= 5.7 Hz),5.48 (s, 2H),4.81 (q, 2H),2.63 (t, 2H),2.22 (t, 3H),1.62 (quintet, 2H),1.32 (sextet, 2H),0.88 (t, 3H, *J* = 7.3 Hz); IR: 2925, 2916, 1652, 1626, 1554, 790, 1233, 1126, 963, 755 cm^{-1}.

2e, MS: *m/z* 591 (M^+); PMR: δ 8.20 (d, 1H, *J* = 5.5 Hz), 7.85-7.91 (m, 2H),7.48 (s, 1H),7.20 (t, 2H, *J* = 8.8 Hz),7.03 (d, 1H, *J* = 5.5Hz),5.47 (s, 2H),4.78 (q, 2H),2.66 (t, 2H),2.62 (t, 2H),2.21 (t, 3H),1.76 (sextet, 2H),1.57 (quintet, 2H),1.33 (sextet, 2H),1.05 (t, 3H),0.84 (t, 3H, *J* = 7.4 Hz); IR: 2928, 2915, 1656, 1622, 1524, 1230, 1123, 966, 786cm^{-1}.

2f, MS: *m/z* 617 (M^+); PMR: δ 8.19 (d,1H, *J*= 5.5 Hz), 7.84-7.90 (m, 2H),7.47 (s, 1H),7.19 (t, 2H, *J*= 8.76 Hz),7.01 (d, 1H, *J*= 5.6Hz),5.47 (s, 2H),4.83 (q, 2H),2.63 (t, 2H),2.21 (s, 3H),1.60 (quintet, 2H),1.32 (sextet, 2H),0.85 (t, 3H, *J* = 7.34 Hz); IR: 2938, 2913, 1666, 1622, 1521, 1233, 1120, 966, 789 cm^{-1}.

2g, MS: *m/z* 563 (M^+); PMR: δ 8.18 (d,1H, *J* = 5.6 Hz), 7.85-7.89 (m, 2H),7.45 (s, 1H),7.19 (t, 2H, *J* = 8.76 Hz), 7.03 (d, 1H, *J* = 5.7Hz), 5.49 (s, 2H),4.81 (q, 2H, *J* = 8.52 Hz),2.61 (t, 2H),2.21 (s, 6H), 1.58 (quintet, 2H), 1.30 (sextet, 2H),0.84 (t, 3H, *J* = 7.32 Hz); IR:2922, 2918, 1651, 1622, 1523, 1230, 1122, 964, 781cm^{-1}.

3a, MS: *m/z* 474 (M^+); PMR: δ10.21 (s, 1H), 7.89-7.92 (m, 2H), 7.83 (m, 1H),7.57-7.61 (m, 4H), 7.42-7.47 (m, 3H), 7.32 (d, 1H, *J* = 7Hz),7.21-7.24 (m, 2H),2.68 (t, 2H), 2.45 (s, 3H), 2.34 (s, 3H), 2.08 (s, 3H),1.77 (q, 2H), 1.04 (t, 3H); IR: 3136, 2972, 2929, 2872, 1678, 1598, 1508, 1500, 763cm^{-1}.

3b, MS: *m/z* 494 (M^+); PMR: δ 9.78 (s, 1H), 7.91 (d, 2H, *J* = 7.5 Hz),7.70-7.75 (m, 2H),7.60-7.63 (m, 2H), 7.58 (t, 2H, *J* = 8 Hz),7.56 (s, 1H),7.46 (t, 1H, *J* =7.5 Hz), 7.30 (d, 1H, *J* = 7 Hz), 7.18-7.24 (m, 2H),2.72 (t, 2H), 2.35 (s, 3H), 2.09 (s, 3H), 1.72 (sextet, 2H), 1.09 (t, 3H); IR: 3125, 2926, 1697, 1588, 1508, 1503, 1165, 835, 748cm^{-1}.

3c, MS: *m/z* 515 (M^+); PMR: δ 9.43 (s, 1H), 7.89-7.95 (m, 2H), 7.50 (s, 1H),7.27-7.43 (m, 5H), 2.72 (s, 3H), 2.70 (t, 2H), 2.43 (s, 3H), 2.35 (s, 3H), 2.06 (s, 3H),1.76 (sextet, 2H), 1.02 (t, 3H); IR: 3120, 2922, 1695, 1598, 1508, 1500, 1155,833, 738cm^{-1}.

3d, MS:*m/z* 494 (M^+); PMR: δ 9.74 (s, 1H), 7.78 (s, 1H), 7.72 (dd, 1H, *J*=1.0 & 5.1 Hz),7.57 (dd, 1H, *J* =1.0 & 3.6 Hz),7.34 (dd, 1H, *J* = 1.4 & 7Hz),7.23-7.30 (m, 3H),7.08-7.19 (m, 3H),2.66 (t, 2H, *J* = 7.4 Hz), 2.34 (s, 3H),2.29 (s, 3H),2.11 (s, 3H), 2.06 (s, 3H), 1.75 (sextet, 2H, *J* = 7.4 Hz),1.01 (t, 3H, *J* =7.4 Hz); IR: 3128, 2958, 1681, 1610, 1502, 786, 717 cm^{-1}.

3e, MS: *m/z* 621 (M^+); PMR:δ 10.41 (s, 1H), 8.14 (s, 1H), 7.94 (d, 2H, *J* = 8.5 Hz),7.78 (s, 1H),7.68-7.70 (m, 2H),7.63-7.66 (m, 5H),7.36 (d, 1H, *J* = 7Hz),7.21-7.27 (m, 2H),2.66 (t, 2H, *J*= 7.4 Hz),2.38 (s, 3H),2.11 (s, 3H),1.75 (sextet, 2H, *J* = 7.4 Hz),1.01 (t, 3H,*J* = 7.4 Hz); IR: 3132, 2925, 1678, 1600, 1596, 1130, 814, 758 cm^{-1}.

4a, MS: *m/z* 500 (M^+); PMR: δ10.23 (s, 1H), 7.90-7.92 (m, 2H),7.82 (s, 1H),7.56-7.60 (m, 4H),7.41-7.47 (m, 3H),7.30 (d, 1H, *J* = 7 Hz),7.19-7.26 (m, 2H),2.45 (s, 3H),2.35 (s, 3H),2.09 (s, 3H); IR : 3134, 2920, 1687, 1598, 1498, 1122, 839 cm^{-1}.

4b, MS: *m/z* 520 (M^+); PMR: δ 10.22 (s, 1H), 7.91 (d, 2H, *J* =7.5 Hz),7.75 (s, 1H),7.71-7.74 (m, 2H),7.65-7.67 (m, 3H),7.58 (t, 2H, *J*= 8 Hz),7.45 (t, 1H, *J*= 7.5 Hz),7.18-7.25 (m, 2H),2.34 (s, 3H),2.08 (s, 3H); IR: 3120, 2922, 1687, 1602, 1496, 1124, 840, 756 cm^{-1}.

4c, MS: *m/z* 541 (M^+); PMR: δ 9.46 (s, 1H),7.89-7.95 (m, 2H),7.50 (s, 1H),7.26-7.45 (m, 5H), 2.71 (s, 3H), 2.43 (s, 3H),2.36 (s, 3H), 2.08 (s, 3H); IR: 3120, 2916, 2848, 1693, 1600, 1155, 1124, 833, 738 cm^{-1}.

4d, MS: *m/z* 520 (M^+); PMR: δ 9.78 (s, 1H), 7.81 (s, 1H), 7.78-7.79 (m, 1H),7.48-7.49 (m, 1H),7.26-7.37 (m, 5H),7.15-7.22 (m, 2H),2.35 (s, 3H),2.31 (s, 3H),2.12 (s, 3H),2.06 (s, 3H); IR: 3107, 2951, 2920, 1685, 1598, 1120, 819, 786, 717 cm^{-1}.

4e, MS: *m/z* 647 (M^+); PMR: δ10.42 (s, 1H), 8.12 (s, 1H), 7.92 (d, 2H, *J* = 8.5 Hz),7.76 (s, 1H),7.69-7.70 (m, 2H),7.62-7.64 (m, 5H),7.33 (d, 1H, *J* = 7 Hz),7.23-7.25 (m, 2H), 2.36 (s, 3H), 2.09 (s, 3H); IR: 3132, 2925, 1678, 1600, 1596, 1130, 814, 758 cm^{-1}.

RESULTS AND DISCUSSION

Pyrazolone derivatives were condensed with various aldehydes to obtain the products 1, 2, 3 and 4. Compound **1a** in its IR spectrum shows carbonyl frequency band at 1676 cm^{-1} of pyrazolone ring. PMR spectrum of the compound exhibited signals of propyl side chain, a triplet at δ1.04 due to methyl group, sextet for methylene at δ1.77 and triplet at δ 2.68 for another methylene. Compound 2g, in its IR spectrum exhibited band at 1651cm^{-1} for C=O group. PMR spectrum showed singlet at δ 7.45 for 1H due to olefinic proton and a doublet at δ 8.18 for 1H with *J* = 5.6 Hz for pyridine ring proton. Compound 3d, exhibited a band due to carbonyl group at 1681 cm^{-1}. PMR spectrum of 3d showed the signals at δ 1.01 triplet for 3H with *J* =7.4 Hz, δ1.75 sextet for 2H with *J* = *7.*4 Hz and δ 2.66 triplet for 2H with *J* = 7.4 Hz corresponding to propyl group. Signals at δ 7.57, dd, 1H, *J* =1.0 & 3.6 Hz, δ 7.72 dd, 1H, *J* = 1.0 & 5.1 Hz are due to thiophene ring. Olefinic proton is observed at δ 7.78 as a singlet. Singlet at δ 9.74 is due to proton on pyrazole ring. Compound 4a, showed band due to carbonyl group at 1687cm^{-1}. PMR spectrum of the compound exhibited three singlets at δ 2.09, 2.35 and 2.45 due to three methyl groups. Singlets at δ 7.82 and 10.23 are due to olefinic proton and pyrazole ring proton respectively.

Antimicrobial activity

The antimicrobial activity of synthesized compounds 1a-h, 2a-g, 3a-e and 4a-e was determined *in vitro* against three bacterial strains *Bacillus subtilis, Escherichia coli*, *Salmonella typhi* and two fungal strains *Alternaria alternata* and *F. Oxisporum*. The antimicrobial activity of compounds against test fungi and bacteria by using well diffusion technique. Ciprofloxacin was used as reference compound for bacteria and ketoconazole for fungi. All the experiments were performed in triplicate.

From seen activities for tested micro-organisms are not observed for our compounds.

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