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Note

Synthesis and characterization of some novel isoxazolines and pyrazolines as potent antimicrobial agents

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The title compounds **4a-h** and **5a-h**, have been prepared starting from chalcones **3a-h** having 5-chlorothiophene moiety. Chalcones **3a-h** react with hydroxylamine hydrochloride in presence of alkali to afford isoxazolines **4a-h**. Further **3a-h** react with hydrazine hydrate in presence of glacial acetic acid to give pyrazolines **5a-h**. The structures of newly synthesized compounds have been confirmed by elemental analysis as well as IR, ^{1}H NMR and mass spectral data. The newly synthesized compounds have been screened for their antimicrobial activity. Some of the compounds show moderate antimicrobial activity as compared to the known reference drugs Gentamycin, Cefixime and Ketoconazole.

Keywords: Isoxazolines, pyrazolines, chalcones, 5-chlorothiophene, antimicrobial activity

Chalcones are natural substances found in a number of plants or synthetically prepared. These compounds are of a high interest due to their use as starting material in the synthesis of a series of heterocyclic compounds[1-4]. Nitrogen and oxygen containing five membered heterocyclic compounds, natural as well as synthetic, have received considerable attention due to the wide range of pharmacological activities. Isoxazoline represents one of the active classes of compounds possessing a wide spectrum of biological activities. Isoxazoline have been reported to possess anti-diabetic[5], diuretic[6], analgesic[7], antihelimentic[8], hypolipaemic[9], antimicrobial[10], antiproliferative and apoptotic activities in the micro molar concentration range[11]. Various substituted pyrazolines and their derivatives are important biological agents and a significant amount of research activity has been directed towards this class of compounds. In particular, they show antimicrobial[12-15], antimycobacterial[16], anti-inflammatory, and analgesic[17-19] and antidepressant activities[20].

In view of these observations and in continuation of the research work on bioactive heterocycles[21-24], it was intended to design and synthesize some new isoxazoline and pyrazoline derivatives and evaluate them for antimicrobial activities.

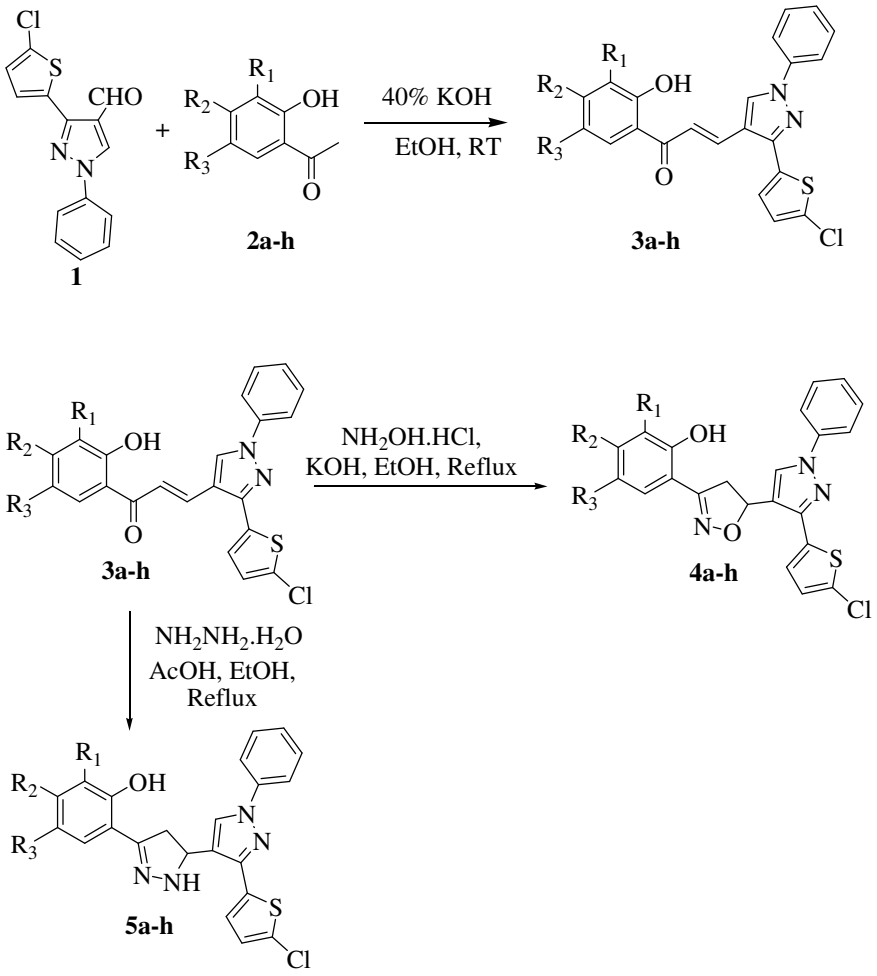
Results and Discussion

The experimental work was started from the Claisen-Schimdt condensation[25] of substituted 2-hydroxyacetophenones **2a-h** with 3-(5-chlorothiophen-2-yl)-1-phenyl-1*H*-pyarazole-4-carbaldehyde **1** to give corresponding (*E*)-3-(3-(5-chlorothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)-1-(2-hydroxyphenyl)-prop-2-en-1-one **3a-h** in dilute ethanolic solution of potassium hydroxide at RT.

Further 2-(5-(3-(5-chlrothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydroisoxazol-3-yl)phenols **4a-h** were prepared by reacting (*E*)-3-(3-(5-chlorothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one **3a-h** with hydroxyl amine hydrochloride in alcoholic KOH.

The reaction of(*E*)-3-(3-(5-chlorothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one **3a-h** with hydrazine hydrate in presence of catalytic amount of acetic acid in ethanol led to 2-(5-(3-(5-chlrothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenols **5a-h** in fairly good yields **(Scheme I)**. Structural assignments to the newly synthesized compounds were based on their elemental analysis as well as IR, ^{1}H NMR and mass spectral data.

The IR spectrum of **4f** shows typical absorption bands at 3290 (-OH), 1633 (-C=N) and 1230 cm^{-1} (C-O). The ^{1}H NMR spectrum shows a singlet at δ 2.25 due to methyl proton, three doublet of doublets at δ 3.47, 3.81 and 5.92 due to two -CH_2 (distereotopic protons) and one -CH proton of isoxazoline ring respectively. Mass spectrum of **4f** shows (M+) peak at *m/z* 469, (M+2) at 471 and (M+4) at 473. The synthesis of **5a-h** from **3a-h** was confirmed by spectral analysis. IR spectrum of compound **5b** shows typical absorption bands at 3350, 3131 and 1625 cm^{-1} due to -OH, -NH, and -C=N stretching vibrations respectively. Compound **5b** shows singlets at δ 2.31 and 11.78 which indicate the



Scheme I

presence of methyl and hydroxyl group. The appearance of three doublet of doublets at δ 3.25, 3.45 and 5.21 indicating the two CH_2 (distereotopic protons) and one CH proton of pyrazoline ring. The NH proton of pyrazoline appears at δ 6.08 as a singlet. Compound **5b** shows (M+) peak at *m/z* 434 and (M+2) at 436. Physical characterization data and elemental analysis of compounds **3a-h**, **4a-h**, and **5a-h** are listed in **Table I**.

Synthesized compounds **4a-h** and **5a-h** were evaluated for their antibacterial activities against different strains of bacteria such as *E. coli, Pseudomonas aeruginosa*, *Staphylococcus aureus* and antifungal activity against *Candida albicans* which are listed in **Table II**. Compounds **5a, 5d** and **5h** show excellent antibacterial activity against the bacterial strain *Staphylococcus aureus*, whereas compounds **4d, 4e, 4g, 4h, 5c, 5e** and **5g** show moderate activity against *Staphylococcus aureus* as compared to reference drugs.

Experimental Section

Melting points were recorded in open capillary tube and are uncorrected. IR spectra were recorded on KBr disc on Perkin-Elmer BX-series FT-IR spectrophotometer and ^{1}H NMR spectra on Bruker Advance 400 MHz spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. Mass spectra were scanned on a Shimadzu GC-MS-QP 2010 instrument. TLC was performed on Merck silica gel 60 F_{254} layer using hexane-ethyl acetate (4:1 v/v) as eluent. Elemental analyses were performed on Perkin-Elmer EAL-240 elemental analyzer.

Procedure for synthesis of (*E*)-3-(3-(5-chlorothiophene-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)-(2-hydroxyphenyl)prop-2-en-1-one, 3a

KOH (0.004 mol) was added to a suspension of 1-(2-hydroxyphenyl) ethanone **2a** (0.002 mol) and 3-(5-

Table I — Physical characterization data and elemental analysis of the compounds **3a-h**, **4a-h** and **5a-h**

Compd	R_1	R_2	R_3	m.p. (°C)	Yield (%)	Calcd % (Found) C	H	N	S
3a	H	H	H	220-21	75	64.88 (64.94	3.75 3.72	6.83 6.88	7.81 7.88)
3b	H	H	CH_3	236-37	78	65.66 (65.63	4.10 4.07	6.60 6.66	7.58 7.62)
3c	CH_3	H	CH_3	210-11	80	66.32 (66.28	4.43 4.40	6.41 6.44	7.29 7.37)
3d	H	H	Cl	228-29	65	59.93 (59.87	3.24 3.20	6.31 6.35	7.19 7.27)
3e	Cl	H	Cl	146-47	67	61.05 (61.10	3.36 3.54	6.27 6.30	7.18 7.21)
3f	H	CH_3	Cl	160-61	73	60.73 (60.67	3.58 3.54	6.11 6.15	6.99 7.04)
3g	H	H	Br	159-60	75	54.50 (54.39	2.94 2.90	5.72 5.77	6.57 6.60)
3h	H	H	OCH_3	180-81	60	63.41 (63.23	2.96 3.92	6.37 6.41	7.29 7.34)
4a	H	H	H	92-93	68	62.72 (62.63	3.87 3.82	9.91 9.96	7.56 7.60)
4b	H	H	CH_3	130-31	71	63.42 (63.37	4.19 4.16	9.91 9.94	7.32 7.36)
4c	CH_3	H	CH_3	127-28	80	64.12 (64.06	4.51 4.48	9.30 9.34	7.15 7.13)
4d	H	H	Cl	96-97	82	57.98 (57.90	3.34 3.31	9.17 9.21	6.97 7.03)
4e	Cl	H	Cl	112-13	77	53.91 (53.84	2.91 2.88	8.51 8.56	6.46 6.53)
4f	H	CH_3	Cl	130-31	73	58.77 (58.73	3.67 3.64	8.87 8.93	6.79 6.82)
4g	H	H	Br	114-15	67	52.81 (52.76	3.05 3.02	8.32 8.39	6.34 6.40)
4h	H	H	OCH_3	180-82	65	61.20 (61.13	4.04 4.01	9.21 9.30	7.04 7.10)
5a	H	H	H	165-66	66	62.82 (62.78	4.11 4.07	13.27 13.31	7.52 7.62)
5b	H	H	CH_3	120-21	67	63.56 (63.51	4.37 4.40	12.82 12.88	7.29 7.37)
5c	CH_3	H	CH_3	170-71	85	64.16 (64.20	4.74 4.71	12.44 12.48	7.13 7.14)
5d	H	H	Cl	180-81	79	58.11 (58.03	3.59 3.54	12.25 12.30	6.98 7.04)
5e	Cl	H	Cl	134-35	66	54.07 (53.95	3.12 3.09	11.40 11.44	6.44 6.55)
5f	H	CH_3	Cl	144-45	68	58.92 (58.85	3.93 3.87	11.87 11.94	6.77 6.83)
5g	H	H	Br	150-51	76	52.95 (52.87	3.27 3.23	11.16 11.12	6.33 6.42)
5h	H	H	OCH_3	210-11	66	61.37 (61.26	4.31 4.25	12.39 12.42	7.06 7.11)

Table II — Antimicrobial activities of the synthesized compounds **4a-h** and **5a-h**

Compd	*E. coli* (ATCC25922)	*Pseudomonas arruginosa* (ATCC278530)	*Staphylococcus aureus* (ATCC25953)	*Candida albicans* (ATCC90028)
4a	–	–	5 mm	–
4b	–	–	9 mm	–
4c	–	–	7 mm	–
4d	–	–	8 mm	–
4e	–	–	9 mm	–
4f	–	–	6 mm	–
4g	–	–	8 mm	–
4h	–	–	8 mm	–
5a	–	–	12 mm	–
5b	–	–	7 mm	–
5c	–	–	9 mm	–
5d	–	–	10 mm	–
5e	–	–	8 mm	–
5f	–	–	7 mm	–
5g	–	–	9 mm	–
5h	–	–	11 mm	–
Gentamicin	20 mm	20 mm	15 mm	–
Cefixime	28 mm	–	25 mm	–
Ketoconazole	–	–	–	23 mm

chlorothiophen-2-yl)-1-phenyl-*1H*-pyarazole-4-carbaldehyde **1** (0.002 mol) in 30 mL ethanol. The mixture was stirred at RT overnight. The completion of reaction was monitored by TLC. After competition of reaction, the contents were poured into ice cold water and acidified with HCl (2M) till *p*H 4. Yellow solid thus obtained was filtered, dried and purified by recrystallization from ethanol to obtain the chalcone **3a**. Compounds **3b-h** were also prepared in a similar manner.

3d: m.p. 228-29°C; IR (KBr): 3315 (-OH), 1660 (-C=O), 1590 (-C=C-), 1230 (-C-O), 666 (-C-S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.79 (1H,s, $OH_)$, 8.42 (1H, s, pyrazole proton), 8.09 (1H, d, olefinic proton, *J* =15.87 Hz), 6.09 to 8.19 (10H, m, Ar-H), 7.43 (1H, d, olefinic proton, *J* =15.87 Hz); MS: *m/z* 441(M+), 443(M+2) and 445(M+4).

3g: m.p. 159-60°C; IR (KBr): 3350 (-OH), 1655 (-C=O), 1578 (-C=C-), 1242 (-C-O), 637 (-C-S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.80 (1H, s, OH), 8.35 (1H, s, pyrazole proton), 8.10 (1H, d, olefinic proton, *J*-=15.50 Hz), 6.96 to 8.12 (10H, m, Ar-H), 7.42 (1H, d, olefinic proton, *J*-=15.50 Hz); MS: *m/z* 485(M+), 487(M+2) and 489(M+4).

Procedure for the synthesis 2-(5-(3-(5-chlorothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydroisoxazol-3-yl) phenol, 4a

Compound **3a** (0.001 mole), hydroxylamine hydrochloride (0.001 mole) and 0.5 g KOH were taken in 15 mL ethanol. The reaction mixture was heated at reflux for 3 hr. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured over crushed ice and neutralized with acetic acid. The precipitates were separated by filtration, washed with water and purified by recrystallization from methanol to obtain the isoxazoline **4a**. Compounds **4b-h** were also prepared in a similar manner.

4a: m.p. 92-93°C; IR (KBr): 3374 (-OH), 1653 (-C=N), 1232 (-C-O), 655 (-C-S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.02 (1H, s, -OH), 7.80 (1H, s, pyrazole proton), 6.80 to 7.79 (11H, m, Ar-H), 5.80 (1H, dd, -CH, isoxazoline proton, *J* = 10.45 and 3.77 Hz), 3.86 (1H, dd, $-CH_2$, isoxazoline proton, *J* = 10.45 and 16.50 Hz), 3.37 (1H, dd, $-CH_2$, isoxazoline proton, *J* = 3.77 and 16.50 Hz); MS: *m/z* 421(M+), 423(M+2).

4b: m.p.130-31°C; IR (KBr): 3380 (-OH), 1645 (-C=N), 1258 (-C-O), 647 (-C-S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.78 (1H, s, -OH), 7.89 (1H, s, pyrazole proton), 6.94 to 7.90 (10H, m, Ar-H), 5.93 (1H, dd, -CH, isoxazoline proton, *J* = 10.70 and 3.38 Hz), 3.82 (1H, dd, $-CH_2$, isoxazoline proton, *J* = 10.70 and 16.80 Hz), 3.48 (1H, dd, $-CH_2$, isoxazoline proton, *J* = 3.38 and 16.80 Hz), 2.18 (3H, s, $-CH_3$); MS: *m/z* 434(M+), 436(M+2).

4e: m.p.112-13°C; IR (KBr): 3399 (-OH), 1660 (-C=N), 1230 (-C-O), 643 (C-S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.02 (1H, s, -OH), 7.78 (1H, s, pyrazole proton), 6.65 to 7.95 (9H, m, Ar-H), 5.98 (1H, dd, -CH, isoxazoline proton, *J* = 10.20 and 4.10 Hz), 3.83 (1H, dd, $-CH_2$, isoxazoline proton, *J* = 10.20 and 16.95 Hz), 3.42 (1H, dd, $-CH_2$, isoxazoline proton, *J* = 4.10 and 16.95 Hz), 2.28 (3H, s, $-CH_3$); MS: *m/z* 490(M+), 492(M+2), 494(M+4) and 496(M+6).

4f: m.p.220-21°C; IR (KBr): 3290 (-OH), 1633 (-C=N), 1230 (-C-O), 680 (-C-S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.64 (1H, s, -OH), 7.98 (1H, s, pyrazole proton), 6.99 to 7.78 (11H, m, Ar-H), 5.92 (1H, dd, -CH, isoxazoline proton, *J* = 9.90 and 3.60 Hz), 3.81(1H, dd, $-CH_2$, isoxazoline proton, *J* = 9.90 and 17.07 Hz), 3.47 (1H, dd, $-CH_2$, isoxazoline proton, *J* = 3.60 and 17.07 Hz), 2.25 (3H, s, $-CH_3$); MS: *m/z* 469(M+), 471(M+2) and 473(M+4).

4h: m.p.180-82°C; IR (KBr): 3325 (-OH), 1646 (-C=N), 1252 (-C-O), 676 (-C-S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.64 (1H, s, -OH), 7.96 (1H, s, pyrazole proton), 6.69 to 7.80 (10H, m, Ar-H), 5.97 (1H, dd, -CH, isoxazoline proton, *J* = 10.25 and 3.88 Hz), 3.85(1H, dd, $-CH_2$, isoxazoline proton, *J* = 10.25 and 16.77 Hz), 3.51 (1H, dd, $-CH_2$, isoxazoline proton, *J* = 3.88 and 16.77 Hz), 2.29 (3H, s, $-CH_3$); MS: *m/z* 451(M+), 453(M+2).

Procedure for the synthesis of 2-(5-(3-(5-chlorothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-3-yl) phenol, 5a

Chalcone **3a** (0.002 mol) was dissolved in 10 mL of ethanol. To this hydrazine hydrate (0.003 mol) was added. The reaction mixture was heated at reflux for 3 hr and then 1 mL glacial acetic acid was added and heating was continued for further 2 hr. After completion of reaction (monitored by TLC), the reaction mixture was cooled to RT. At the end 50 mL cold water was slowly added in to the flask and the separated product was filtered off and washed with cold water several times. The crude product was purified by recrystallization from ethanol to obtain pyrazoline **5a**. Compounds **5b-h** were also prepared in a similar manner.

5a: m.p.165-66°C; IR (KBr): 3290 (-NH), 3120 (C-H), 1630 (-C=N), 655 (-C-S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.30 (1H, s,-OH), 7.80 (1H, s, pyrazole proton), 6.85 to 7.85 (11 H, m, Ar-H), 6.09 (1H, s, -NH), 5.18 (1H, dd, -CH, pyrazoline proton, *J*-= 9.10 and 3.56 Hz), 3.58 (1H, dd, $-CH_2$, pyrazoline proton, *J*-= 9.10 and 16.11 Hz), 3.20 (1H, dd, $-CH_2$, pyrazoline proton, *J*-= 3.56 and 16.11 Hz); MS: *m/z* 420(M+), 422(M+2).

5b: m.p. 120-21°C; IR (KBr): 3350 (-NH), 3131 (C-H), 1625 (-C=N), 665 (-C-S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.78 (1H, s,-OH), 7.85 (1H, s, pyrazole proton), 7.63 to 7.94 (10 H, m, Ar-H), 6.08 (1H, s, -NH), 5.21 (1H, dd, -CH, pyrazoline proton, *J*-= 10.10 and 3.89 Hz), 3.45 (1H, dd, $-CH_2$, pyrazoline proton, *J*-= 10.14 and 16.11 Hz), 3.25(1H, dd, $-CH_2$, pyrazoline proton, *J*-= 3.89 and 16.11 Hz), 2.31 (3H, s, $-CH_3$); MS: *m/z* 434(M+), 436(M+2).

5c: m.p. 170-71°C; IR (KBr): 3245 (-NH), 3120 (C-H), 1648 (-C=N), 670 (-C-S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.50 (1H, s,-OH), 7.75 (1H, s, pyrazole proton), 6.70 to 7.72 (9 H, m, Ar-H), 6.19 (1H, s, -NH), 5.18 (1H, dd, -CH, pyrazoline proton, *J*= 10.55 and 3.92 Hz), 3.48 (1H, dd, $-CH_2$, pyrazoline proton, *J*-= 10.55 and 17.12 Hz), 3.15 (1H, dd, $-CH_2$, pyrazoline proton, *J*-= 3.92 and 17.12 Hz), 2.30 (3H, s, $-CH_3$), 2.24 (3H, s, $-CH_3$); MS: *m/z* 448(M+), 450(M+2).

5f: m.p. 144-45°C; IR (KBr): 3280 (-NH), 3135 (C-H), 1636 (-C=N), 640 (-C-S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.16 (1H, s,-OH), 7.94 (1H, s, pyrazole proton), 7.69 to 7.94 (9H, m, Ar-H), 6.04 (1H, s, -NH), 5.20 (1H, dd, -CH, pyrazoline proton, *J*-= 9.07 and 4.21 Hz), 3.49 (1H, dd, $-CH_2$, pyrazoline proton, *J*-= 9.07 and 16.22 Hz), 3.10 (1H, dd, $-CH_2$, pyrazoline proton, *J*-= 4.21 and 16.22 Hz), 2.28(3H, s, $-CH_3$); MS: *m/z* 469(M+), 471(M+2) and 473(M+4).

5h: m.p. 210-11°C; IR (KBr): 3310 (-NH), 3150 (-C-H), 1642 (-C=N), 655 (-C-S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.45 (1H, s, -OH), 7.70 (1H, s, pyrazole proton), 7.45 to 7.66 (10H, m, Ar-H), 6.12 (1H, s, -NH), 5.17 (1H, dd, -CH, pyrazoline proton, *J*-= 9.67 and 3.68 Hz), 3.58 (1H, dd, $-CH_2$, pyrazoline proton, *J*-= 9.70 and 16.22 Hz), 3.12 (1H, dd, $-CH_2$, pyrazoline proton, *J*-= 3.68 and 16.22 Hz), 2.38 (3H, s, $-OCH_3$); MS: *m/z* 450(M+), 452(M+2).

Antimicrobial activity

Newly synthesized compounds were screened for their antibacterial activity against various strains of bacteria such as *E. coli, Pseudomonus aeruginosa, Staphylocous aureus* and antifungal activity against *Candida albicans* using disc diffusion method and Muller Hinton agar as culture medium. After 24 hr of incubation at 37°C, the zone of inhibition were measured in mm. Compounds **5a, 5d** and **5h** show moderate antibacterial activity against the bacterial strain *Staphylococcus aureus*, whereas compounds **4d, 4e, 4g, 4h, 5c, 5e** and **5g** show moderate activity. The activities were compared with known reference drugs Gentamicin, Cefixime and Ketoconazole.

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