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Synthesis, Spectral Analysis and Antimicrobial Activity Studies of New Pyrazole Analogues

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ABSTRACT

An efficient procedure for the synthesis of substituted pyrazoles was developed. Claisen-Schmidt condensation of 2,4,5-trimethoxybenzaldehyde and substituted acetophenone in the presence of aqueous potassium hydroxide produced chalcones. An acid catalyzed cyclocondensation reaction of chalcones with 3-chlorophenylhydrazine hydrochloride produced substituted pyrazolines in good yields. The synthesized new compounds were characterized by spectral studies and elemental analysis; and some of the intermediate chalcones by single crystal X-ray diffraction studies and evaluated in vitro for their antimicrobial susceptibilities.

Keywords: Antibacterial, Antifungal, Cyclocondensation, Inhibition, Pyrazoline, Spectral

INTRODUCTION

Chalcone is an aromatic α, β-unsaturated ketone that forms the central core for a variety of important biological compounds. Chalcones are used as key precursors in the synthesis of biologically important heterocycles such as benzothiazepines [1], pyrazolines [2] and isoxazoles [3] which exhibit interesting pharmacological activities. A number of chalcones have been reported to possess anti-malarial [4], antimicrobial [5, 6], antioxidant [7] properties. Amongst the five membered heterocycles, pyrazoles have drawn a great deal of attention due to their contributions in biological and pharmacological fields. A survey of the literature revealed that the main routes for the construction of pyrazole rings consist of the reaction of α, β-unsaturated aldehyde and ketones with hydrazines [8] and Vilsmeier Haack formylation reaction of hydrazones [9]. However the classical method employed for the synthesis of pyrazolines and pyrazoles involves 1, 3-dipolar cycloaddition reactions of nitrile imines to alkenes and alkynes [10, 11].

Pyrazole derivatives were extensively studied and used as antimicrobial agents. In particular, 5-chloropyrazole derivatives are reported to show potential antimicrobial [12], antioxidant [13], analgesic and anti-inflammatory [14] activities. After the discovery of the natural pyrazole C-glycoside pyrazofurin; 4-hydroxy-3-β-D-ribofuranosyl-1H-pyrazole-5-carboxamide, which demonstrated a broad spectrum of antimicrobial activities, much attention was given to pyrazoles as antimicrobial agents [15]. Appreciation of these findings motivated us to synthesize pyrazoline derivatives from the chalcones hoping to discover a new lead structure that would have a significant antimicrobial activity at very small concentrations.

MATERIALS AND METHODS

Melting points were determined by an open capillary tube method and are uncorrected. Purity of the compounds was checked on Thin Layer Chromatography (TLC) plates pre-coated with silica gel using solvent system ethyl acetate: dichloromethane (1:4 v/v). The spots were visualized under Ultra Violet (UV) light. Proton Nuclear Magnetic Resonance (^{1}H-NMR) and Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR) spectra were recorded on Agilent-NMR 400 MHz and 100 MHz spectrometer respectively. The solvent Deuterated Chloroform ($CDCl_3$) with Tetramethylsilane (TMS) as an internal standard was used to record the spectra. The chemical shifts are expressed in δ ppm. Mass spectra were obtained on Mass Lynx SCN781 spectrometer TOF mode. Elemental analysis was obtained on a Thermo Finnigan Flash EA 1112 CHN analyzer. Purification of compounds was done by column chromatography on silica gel (70-230 mesh Merck).

The synthetic method involves; the synthesis of a series of chalcones, 3a-f by the reaction of 2,4,5-trimethoxybenzaldehyde, 1 with substituted acetophenone, 2a-g in the presence of base in alcohol medium. The cyclocondensation reaction of chalcones, 3a-f with 3-chlorophenylhydrazine hydrochloride, 4 and few drops of concentrated hydrochloric acid in methyl alcohol to obtain pyrazole derivatives, 5a-g in good yields.

The schematic diagram for the synthesis of chalcones and pyrazolines is outlined in Figure 1.

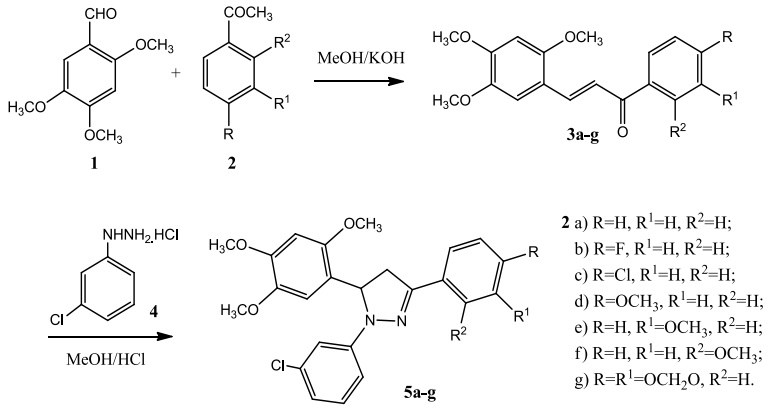

Figure 1: Schematic diagram for the synthesis of pyrazolines, 5a-g

General procedure for synthesis of chalcones, (3a-g)

The intermediate chalcones were obtained according to our reported procedure [16-19]. A mixture of 2,4,5-trimethoxybenzaldehyde, 1 (5 mmol), acetophenone, 2a-g (5 mmol) and sodium hydroxide (5 mmol) in 95% ethyl alcohol (25 mL) was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was poured in to ice cold water and kept in the refrigerator for overnight. The solid formed was filtered, and washed with cold hydrochloric acid (5%). Crude products obtained were crystallized from methyl alcohol to obtain pure chalcones 3a-g.

General procedure for the synthesis of pyrazolines, (5a-g)

To a stirred solution of chalcones, 3a-g (0.01 mol) and 3-chlorophenylhydrazine hydrochloride, 4 (0.01 mol) in methyl alcohol (15 ml), concentrated hydrochloric acid (7-8 drops) were added. The mixture was refluxed for 3-4 h and the progress of the reaction was monitored by TLC. After completion, the reaction mixture was poured in to ice cold water; solid separated was filtered, washed with ice cold water and dried. The products were purified column chromatography using silica gel (60-120 mesh) and ethyl acetate: dichloromethane (1:4 v/v) as eluent.

1-(3-Chlorophenyl)-3-phenyl-5-(2,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole, (5a)

Obtained from (E)-1-phenyl-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one, 3a (10 mmol) and (3-chlorophenyl)hydrazine hydrochloride, 4 (10 mmol) in 86% yield. ^{1}H-NMR: δ=3.441-3.532 (dd, 1H, *J= 7.7, 15.6Hz*, C_4-H_a), 3.675-3.752 (dd, 1H, *J= 6.2, 12.9Hz*, C_4-H_b), 3.891 (s, 9H, OCH_3), 4.432-4.592 (dd, 1H, *J= 7.8, 16.0Hz*, C_5-H), 6.421 (s, 1H, Ar-H), 6.509 (s, 1H, Ar-H), 6.654 (d, 1H, Ar-H), 6.876 (s, 1H, Ar-H), 6.995 (t, 1H, Ar-H), 7.100 (d, 1H, Ar-H), 7.375–8.094 (m, 5H, Ar–H);^{13}C-NMR: δ=40.31 (1C, C-4), 54.80 (1C, C-5), 56.54 (3C), 99.98 (1C),112.32 (1C), 113.21 (1C), 114.02 (1C), 119.91 (1C),122.61 (1C), 127.21 (2C), 128.62 (2C), 130.04 (1C), 131.04 (1C), 135.65 (1C), 136.54 (1C), 141.21 (1C), 144.93 (1C), 148.80 (1C), 149.43 (1C), 151.95 (1C, C-3); MS *m/z*: 424 (M^+, ^{37}Cl, 33), 422 (M^+, ^{35}Cl, 100); Anal. calcd. for $C_{24}H_{23}ClN_2O_3$ (%): C, 68.16; H, 5.48; N, 6.62; Found: C, 68.02; H, 5.34; N, 6.56.

1-(3-Chlorophenyl)-3-(4-fluorophenyl)-5-(2,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole, (5b)

Obtained from (E)-1-(4-fluorophenyl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one, 3b (10 mmol) and (3-chlorophenyl)hydrazine hydrochloride, 4 (10 mmol) in 87% yield. ^{1}H-NMR: δ=3.365-3.483 (dd, 1H, *J= 6.6, 13.0Hz*, C_4-H_a), 3.621-3.721 (dd, 1H, *J= 6.1, 13.5Hz*, C_4-H_b), 3.921 (s, 9H, OCH_3), 4.456-4.520 (dd, 1H, *J= 7.2, 14.3Hz*, C_5-H), 6.311 (s, 1H, Ar-H), 6.587 (s, 1H, Ar-H), 6.699 (d, 1H, Ar-H), 6.806 (s, 1H, Ar-H), 6.954 (t, 1H, Ar-H), 7.100 (d, 1H, Ar-H), 7.409–7.991 (m, 4H, Ar–H). ^{13}C-NMR: δ=40.33 (1C, C-4), 53.43 (1C, C-5), 56.50 (3C), 100.07 (1C), 112.42 (1C), 113.32 (1C), 114.43 (1C), 115.43 (2C), 120.07 (1C),122.32 (1C), 128.23 (2C), 130.32 (1C), 132.31 (1C), 136.40 (1C), 141.93 (1C), 145.21 (1C), 148.80 (1C), 149.82 (1C), 151.71 (1C, C-3), 163.24 (1C). MS *m/z*: 442 (M^+, ^{37}Cl, 34), 440 (M^+, ^{35}Cl, 100); Anal. Calcd. For $C_{24}H_{22}ClFN_2O_3$ (%): C, 65.38; H, 5.03; N, 6.35; Found: C, 65.31; H, 5.00; N, 6.25.

1-(3-Chlorophenyl)-3-(4-chlorophenyl)-5-(2,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole, (5c)

Obtained from (E)-1-(4-chlorophenyl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one, 3c (10 mmol) and (3-chlorophenyl)hydrazine hydrochloride, 4 (10 mmol) in 84% yield. ^{1}H NMR: δ=3.312-3.389 (dd, 1H, *J= 6.5, 13.0Hz*, C_4-H_a), 3.631-3.743 (dd, 1H, *J= 7.9, 14.5Hz*, C_4-H_b), 3.920 (s, 9H, OCH_3), 4.454-4.499 (dd, 1H, *J= 7.1, 14.3Hz*, C_5-H), 6.323 (s, 1H, Ar-H), 6.507 (s, 1H, Ar-H), 6.631 (d, 1H, Ar-H), 6.798 (s, 1H, Ar-H), 6.876 (t, 1H, Ar-H), 7.012 (d, 1H, Ar-H), 7.403–8.043 (m, 4H, Ar–H). ^{13}C-NMR: δ=40.31 (1C, C-4), 52.93 (1C, C-5), 56.15 (3C), 100.12 (1C), 112.42 (1C), 113.02 (1C), 114.34 (1C), 120.07 (1C), 121.76 (1C), 127.21 (2C), 128.92 (2C), 130.32 (1C), 133.21 (1C), 135.04 (1C), 136.40 (1C), 140.76 (1C), 144.85 (1C), 148.80 (1C), 149.82 (1C), 151.71 (1C, C-3). Anal. Calcd. For $C_{24}H_{22}Cl_2N_2O_3$ *m/z*: 452 (%): C, 63.03; H, 4.85; N, 6.13; Found: C, 63.08; H, 4.76; N, 6.04.

1-(3-Chlorophenyl)-3-(4-methoxyphenyl)-5-(2,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole, (5d)

Obtained from (E)-1-(4-methoxyphenyl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one, 3d (10 mmol) and (3-chlorophenyl)hydrazine hydrochloride, 4 (10 mmol) in 81% yield. ^{1}H-NMR: δ=3.302-3.309 (dd, 1H, *J= 6.5, 13.2Hz*, C_4-H_a), 3.634-3.690 (dd, 1H, *J= 7.5, 16.4Hz*, C_4-H_b), 3.923 (s, 12H, OCH_3), 4.451-4.501 (dd, 1H, *J= 7.6, 15.2Hz*, C_5-H), 6.323 (s, 1H, Ar-H), 6.507 (s, 1H, Ar-H), 6.631 (d, 1H, Ar-H), 6.798 (s, 1H, Ar-H), 6.876 (t, 1H, Ar-H), 7.012 (d, 1H, Ar-H), 7.243–8.045 (m, 4H, Ar–H). ^{13}C-NMR: δ=40.31 (1C, C-4), 52.93 (1C, C-5), 55.81 (1C), 56.15 (3C), 100.10 (1C), 112.42 (1C), 113.00 (1C), 114.34 (2C), 114.81 (1C), 120.07 (1C), 122.23 (1C), 128.12 (2C), 128.72 (1C), 130.32 (1C), 135.71 (1C), 140.76 (1C), 144.85 (1C), 148.80 (1C), 149.82 (1C), 151.71 (1C, C-4), 161.87 (1C); Anal. Calcd. For $C_{25}H_{25}ClN_2O_4$ (%): C, 66.29; H, 5.56; N, 6.18; Found: C, 66.20; H, 5.44; N, 6.07.

1-(3-Chlorophenyl)-3-(3-methoxyphenyl)-5-(2,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole, (5e)

Obtained from (E)-1-(3-methoxyphenyl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one, 3e (10 mmol) and (3-chlorophenyl)hydrazine hydrochloride, 4 (10 mmol) in 87% yield. ^{1}H NMR: δ=3.312-3.387 (dd, 1H, *J= 7.7, 13.2Hz*, C_4-H_a), 3.634-3.690 (dd, 1H, *J= 7.8, 14.0Hz*, C_4-H_b), 3.831 (s, 12H, OCH_3), 4.492-4.543 (dd, *1H, J= 7.4, 15.2Hz*, C_5-H), 6.323 (s, 1H, Ar-H), 6.512 (s, 1H, Ar-H), 6.609 (d, 1H, Ar-H), 6.798 (s, 1H, Ar-H), 6.816 (t, 1H, Ar-H), 7.012 (d, 1H, Ar-H), 7.345–7.982 (m, 4H, Ar–H). ^{13}C-NMR: δ=40.31 (1C, C-4), 52.93 (1C, C-5), 55.81 (1C), 56.15 (3C), 100.10 (1C), 112.42 (1C), 113.00 (1C), 113.34 (1C), 114.30 (1C), 116.93 (1C), 120.50 (1C), 120.67 (1C), 122.23 (1C), 128.81 (1C), 130.34 (1C), 134.10 (1C), 135.71 (1C), 140.76 (1C), 144.85 (1C), 148.80 (1C), 149.82 (1C), 151.70 (1C, C-4), 160.07 (1C); MS *m/z*: 454 (M^+, ^{37}Cl, 32), 452 (M^+, ^{35}Cl, 100); MS *m/z*: 454 (M^+, ^{37}Cl, 32), 452 (M^+, ^{35}Cl, 100); Anal. Calcd. For $C_{25}H_{25}ClN_2O_4$ (%): C, 66.29; H, 5.56; N, 6.18; Found: C, 66.18; H, 5.48; N, 6.12.

1-(3-Chlorophenyl)-3-(2-methoxyphenyl)-5-(2,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole, (5f)

Obtained from (E)-1-(2-methoxyphenyl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one, 3f (10 mmol) and (3-chlorophenyl)hydrazine hydrochloride, 4 (10 mmol) in 91% yield. ^{1}H-NMR: δ=3.321-3. (dd, 1H, *J= 6.0, 12.9Hz*, C_4-H_a), 3.567-3.612 (dd, *1H, J= 6.6, 14.1Hz*, C_4-H_b), 3.830 (s, 12H, OCH_3), 4.493-4.521 (dd, 1H, *J= 7.6, 15.1Hz*, C_5-H), 6.234 (s, 1H, Ar-H), 6.456 (s, 1H, Ar-H), 6.567 (d, 1H, Ar-H), 6.712 (s, 1H, Ar-H), 6.810 (t, 1H, Ar-H), 7.172 (d, 1H, Ar-H), 7.206-7.865 (m, 4H, Ar–H). Anal. Calcd. For $C_{25}H_{25}ClN_2O_4$ (%): C, 66.29; H, 5.56; N, 6.18; Found: C, 66.22; H, 5.45; N, 6.10.

3-(Benzo[d][1,3]dioxol-5-yl)-1-(3-chlorophenyl)-5-(2,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole, (5g)

Obtained from (E)-1-(benzo[d][1,3]dioxol-5-yl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one, 3g (10 mmol) and (3-chlorophenyl)hydrazine hydrochloride, 4 (10 mmol) in 94% yield. ^{1}H-NMR: δ=3.312-3.387 (dd, 1H, *J= 6.9, 15.1Hz*, C_4-H_a), 3.634-3.690 (dd, 1H, *J= 6.7, 14.3Hz*, C_4-H_b), 3.833 (s, 9H, OCH_3), 4.492-4.543 (dd, 1H, *J= 7.3, 15.0Hz*, C_5-H), 6.071 (s, 2H), 6.421 (s, 1H, Ar-H), 6.674 (s, 1H, Ar-H), 6.812 (d, 1H, Ar-H), 6.855 (s, 1H, Ar-H), 6.912 (d, 1H, Ar-H), 7.121 (d, 1H), 7.171 (t, 1H, Ar-H), 7.398 (s, 1H, Ar-H)), 7.612 (d, 1H, Ar–H). ^{13}C-NMR: δ=40.31 (1C, C-4), 52.93 (1C, C-5), 56.15 (3C), 100.10 (1C), 101.21 (1C), 111.35 (1C), 112.42 (1C), 113.34 (1C), 114.31 (1C), 114.9 (1C), 120.98 (1C), 121.10 (1C), 122.65 (1C), 127.54 (1C), 130.91 (1C), 135.32 (1C), 141.12 (1C), 145.22 (1C), 148.82 (1C), 148.99 (1C), 148.32 (1C), 150.98 (1C), 151.70 (1C, C-3); MS *m/z*: 468 (M^+, ^{37}Cl, 32), 466 (M^+, ^{35}Cl, 100); Anal. Calcd. For $C_{25}H_{23}ClN_2O_5$ (%): C, 64.31; H, 4.97; N, 6.00; Found: C, 64.23; H, 4.88; N, 5.90.

RESULTS AND DISCUSSION

Amongst the series of compounds, 3a-g the structures of 3d and 3g were confirmed by single crystal x-ray diffraction studies as depicted in ORTEP diagram (Figure 2).

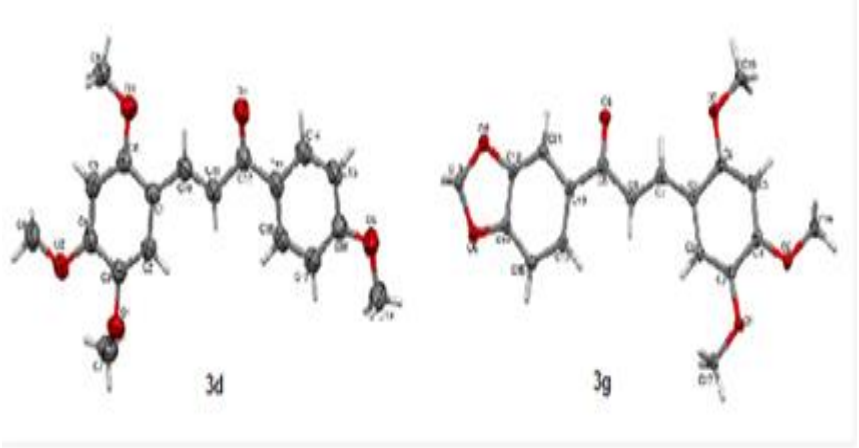

Figure 2: ORTEP diagram of 3d and 3g with 50% probability ellipsoids

Structure proof of synthesized compounds, 5a-g were, provided by ^{1}H-NMR, ^{13}C-NMR, mass spectral studies and elemental analysis. The structural assignments were made by NMR analysis by considering compound, 5c as the representative compound among the series. In ^{1}H-NMR spectra, two methylene protons designated as C_4-H_a and C_4-H_b of the newly formed pyrazoline ring is diastereotopic. The C_4-H_a, C_4-H_b and C_5-H protons appeared as a doublet of doublets. The doublet of doublet for C_4-H_a appeared in the region δ 3.312.3.389 (*J=6.5, 13.0Hz*) ppm; doublet of doublet for C_4-H_b appeared in the region δ 3.631-3.743 (*J=7.9, 14.5Hz*) ppm; and that of C_5-H in the region δ 4.454-5.499 (*J=7.1, 14.3Hz*) ppm. Among C_4-H_a, C_4-H_b and C_5-H protons, C_5-H is the most deshielded due to its close proximity to benzene ring and electronegative nitrogen. A collection of signal observed singlet for nine protons at δ=3.920 ppm and as multiplet for 10 protons in the region δ=6.323-8.043 ppm were assigned to OCH_3 and aromatic protons respectively.

In ^{13}C-NMR spectrum, compound 5c showed a signal at δ=40.31, 52.93 and 151.71 ppm due to C-4, C-5 and C-3 carbons of the pyrazole ring. A signal appeared for three carbons at δ=56.15 ppm was assigned to 3-OCH_3 carbons. An array of signals appeared at δ=100.12, 112.42, 113.02, 114.34, 120.07, 121.76, 127.21, 128.92, 130.32, 133.21, 135.04, 136.40, 140.76, 144.85, 148.80 and 149.82 ppm were ambiguously assigned to aromatic carbons. Compound 5c showed M+ ion peak corresponding to its molecular mass and a base peak corresponds to m/z (M-1). Further elemental analysis showed that the analytical data obtained for the compound were in good agreement with theoretically calculated values. Similar and consistent pattern signals were observed in the ^{1}H-NMR, ^{13}C-NMR and mass spectra of the synthesized series of compounds 5a-g, which strongly supports the structure proof for the synthesized compounds.

Antimicrobial activity

Antimicrobial studies of synthesized compounds 5a-g were, assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method [20,21]. The compounds were screened for their antimicrobial activities against Gram-negative bacteria *Escherichia coli*, Gram-positive bacteria *Staphylococcus aureus*, fungi species *Aspergillus nigar* and *Aspergillus flavus*. The experiments were carried out in triplicate; the results were taken as a mean of three determinations. The antibiotics ciprofloxacin and nystatin were used as standard drugs for antibacterial and antifungal studies respectively. The results of MIC's were tabulated in Table 1.

Table 1: Antimicrobial activities of the compounds 5a-g against bacterial and fungal stains

Compound	Minimum Inhibitory Concentration (MIC's) in µg/ml*			
	Staphylococcus aureus	***Escherichia coli***	***Aspergillus niger***	***Aspergillus flavus***
5a	50	100	100	50
5b	25	25	12.5	25
5c	25	6.25	12.5	12.5
5d	50	25	25	50
5e	50	25	25	50
5f	25	50	25	50
5g	25	25	25	25
Ciprofloxacin	25	12.5	-	-
Nystatin	-	-	12.5	25

*The results are expressed as mean of three determinations (n=3)

The synthesized pyrazoles 5a-g exerted a wide range of in vitro antimicrobial activities against the tested organisms. Results of the study reveal that, the target pyrazole derivatives 5a-g exerted increased antimicrobial susceptibilities in comparison to their intermediate chalcones against all the tested organisms. Among the synthesized series, compound 5c having chloro substitution showed excellent antimicrobial activity by inhibiting spore germination of all the tested organisms. Compounds 5d, 5e and 5f with methoxy substitutions in the aromatic ring found moderately active; while compound 5g showed good activities and compound 5b having fluoro substitution exhibited promising inhibitory activities against the testes organisms. Compounds 5a without any substitution exhibited poor inhibitory effect on the organisms.

CONCLUSION

In order to develop antimicrobial molecules, we have synthesized pyrazole analogues via Claisen-Schimidt condensation of aromatic aldehydes and ketones by the simple easy accessible procedure. Synthesized compounds were evaluated for antimicrobial activity. Among the series, compound 3c and 5c demonstrated potent antibacterial and antifungal activities.

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