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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of 1,3,5-trisubstituted pyrazoline nucleus containing compounds and screening for antimicrobial activity

Manish Agrawal · Pankaj Kumar Sonar · Shailendra K. Saraf

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Abstract In this study, a novel series of heterocyclic compounds containing pyrazoline nucleus has been synthesized. The compounds were synthesized in two steps. Chalcone was synthesized in the first step by Claisen-Schmidt reaction, using 1-acetylnaphthalene and p-nitro benzaldehyde as reactants. In the second step, the chalcone was cyclized in an acidic medium with some hydrazine derivatives to form pyrazolines. All the compounds were characterized by physical, chromatographic, spectroscopic, and elemental analysis and evaluated in vitro for antimicrobial activity against nine microorganisms by cup-plate method. The minimum inhibitory concentration of all the compounds was determined by tube dilution method. All the compounds exhibited higher antibacterial activity as compared to the antifungal activity. Compound **5g** (3-Naphthalen-1-yl-1-(2-nitro-phenyl)-5-(4-nitro-phenyl)-4,5-dihydro-1H-pyrazole) exhibited maximum antibacterial and antifungal activity and may be designated as the most potent member of the series, with 2-nitrophenyl group at N-1 position of the 2-pyrazoline ring.

Keywords Pyrazoline · Chalcone · Antimicrobial activity · Claisen-Schmidt reaction

Introduction

Heterocyclic compounds are well known for their wide range of biological applications and pyrazolines occupy a unique position due to dominant applications. Pyrazolines have played a crucial role in the development of theory in heterocyclic chemistry and are also used extensively as agents in organic synthesis. A classical synthesis of these compounds involves the base-catalyzed aldol condensation reaction of aromatic ketones and aldehydes to give α, β-unsaturated ketones (chalcones), which undergo a subsequent cyclization reaction with hydrazines affording 2-pyrazolines. In this reaction, hydrazones are formed as intermediates which can be subsequently cyclized to 2-pyrazolines in the presence of a suitable cyclizing reagent like acetic acid (Azarifar and Ghasemnejad, 2003). Electron-rich nitrogen heterocyclics play an important role in diverse biological activities. Pyrazoline nucleus is a privileged pharmacophore for various pharmacological activities, such as antimicrobial (Ozdemir *et al.*, 2007a; Azarifar and Shaebanzadeh, 2002; Ashok and Holla, 2006; Kumar *et al.*, 2005; Abunada *et al.*, 2008; Abdel-Wahab *et al.*, 2009; Rai *et al.*, 2009; Prakash *et al.*, 2009), analgesic and anti-inflammatory (Sahu *et al.*, 2008; Venkataraman *et al.*, 2010; Girisha *et al.*, 2010; Bashir *et al.*, 2011), antinociceptive (Kaplancikli *et al.*, 2009), antidepressant and anticonvulsant (Ozdemir *et al.*, 2007b; Palaska *et al.*, 2001) and anti-amoebic (Bhat *et al.*, 2009). Recently, 5-(substituted) aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines have been utilized as versatile templates for synthesizing compounds that act as potential anti-inflammatory and analgesic agents (Khode *et al.*, 2009). Some pyrazoline derivatives have shown anticancer activity against leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancer cell lines (Havrylyuk *et al.*, 2009; Rostom *et al.*, 2011; Havrylyuk *et al.*, 2011). Thus, pyrazoline moiety has attracted considerable interest in the development of biologically active compounds.

M. Agrawal · P. K. Sonar · S. K. Saraf (✉)
Faculty of Pharmacy, Northern India Engineering College, Sec-II, Dr. Akhilesh Das Nagar, Faizabad Road, Lucknow 227105, Uttar Pradesh, India
e-mail: dirpharmniec@gmail.com

Materials and methods

Chemistry

All the chemicals used in this study were procured as LR grade reagents from S. D. Fine Chem. Ltd., Mumbai and Sigma–Aldrich Chemie, Germany. The melting points were determined by open capillary method and are uncorrected. Purity of the compounds was checked by TLC on precoated silica gel G plates using chloroform: methanol, ethyl acetate: n-hexane and diethyl ether: n-hexane as solvent systems. The IR spectra were recorded on Shimadzu FTIR-8400S and Perkin Elmer Spectrum RX1 FTIR spectrophotometers. Mass spectra were recorded on JEOL-Accu TOF JMS-T100LC spectrometer and Micromass Quattro II triple quadrupole mass spectrometer. NMR spectra were recorded on Bruker DRX-300 spectrometer and elemental analysis was performed on Elemental Vario EL III analyzer from Central Drug Research Institute, Lucknow, India.

*1-Naphthalen-1-yl-3-(4-nitro-phenyl)-propenone (**3**)*

A solution of sodium hydroxide (0.5 g, 0.012 mol), water (5 ml), and ethanol (3 ml) was poured over 1-acetylnaphthalene (1.519 ml, 0.01 mol) in a 50 ml round bottom flask and the reaction mixture was stirred by a magnetic stirrer at room temperature. Then, 4-nitro benzaldehyde (1.51 g, 0.01 mol) was added to the above mixture and a thick paste was formed after 6 h. The progress of the reaction was monitored by TLC. The reaction mixture was kept in a refrigerator overnight. The product was filtered and washed with cold water, followed by cold ethanol and recrystallized from chloroform (Furniss *et al.*, 2007) as pale yellow solid (Scheme 1), yield 73.06%, melting range 114–118°C; IR (KBr) 1658.67, 1589.23, 1514.02, and 1340.43 cm^{-1}; ms: m/z 304.10 (100).

*General procedure for the synthesis of pyrazoline derivatives (**5a**–**e**)*

An equimolar mixture of (**3**) and hydrazine derivatives in 4–6 ml of glacial acetic acid was refluxed for the respective time period as given in the Scheme 2. The progress of the reaction was monitored by TLC. The reaction mixture was cooled and poured into ice water. Crude product was filtered, washed with cold water and recrystallized with chloroform.

*3-Naphthalen-1-yl-5-(4-nitro-phenyl)-4,5-dihydro-1H-pyrazole (**5a**)*

A red solid, yield 47.35%, melting range 104–108°C; IR (KBr) 1660.60, 1514.02, 1344.29, and 1108.99 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ, ppm): 7.26–8.25 (m, 11H), 7.0 (s, H), 4.02 (s, H) 2.54 (s, 2H); ms: m/z 360.09 (100). *Anal.* Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 70.92; H, 4.82; N, 12.18.

*3-Naphthalen-1-yl-5-(4-nitro-phenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**5b**)*

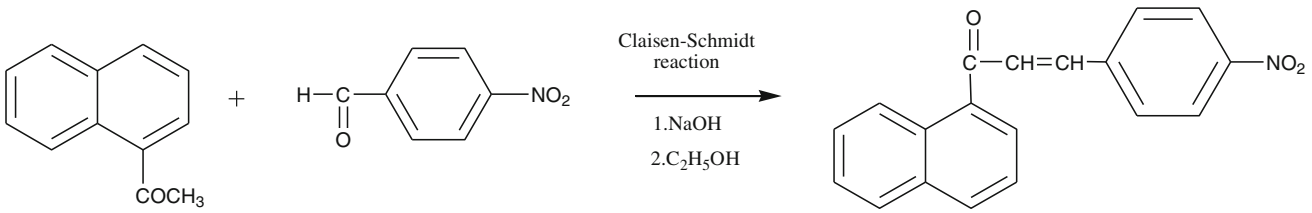
A yellow solid, yield 48.34%, melting range 132–136°C; IR (KBr) 1647.10, 1107.06, 1508.23, and 1340.43 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ, ppm): 6.5–8.4 (m, 16H), 4.4 (s, H), 1.25 (d, 2H); ms: m/z 393.10 (100). *Anal.* Calcd. for $C_{25}H_{19}N_3O_2$: C, 76.32; H, 4.87; N, 10.68. Found: C, 75.46; H, 4.50; N, 10.63.

*3-Naphthalen-1-yl-1,5-bis-(4-nitro-phenyl)-4,5-dihydro-1H-pyrazole (**5c**)*

A dark brown solid, yield 13.74%, melting range 174–178°C; IR (KBr) 1593.09, 1517.87, 1342.36 and 1099.35 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ, ppm): 7.40–8.45 (m, 16H), 2.06 (s, 2H), 2.74 (s, H); ms: m/z 438 (20). *Anal.* Calcd. for $C_{25}H_{18}N_4O_4$: C, 68.49; H, 4.14; N, 12.78. Found: C, 71.62; H, 3.95; N, 12.23.

*3-Naphthalen-1-yl-5-(4-nitro-phenyl)-4,5-dihydro-pyrazole-1-carbothioic acid amide (**5d**)*

A yellow solid, yield 57.84%, melting range 157–161°C; IR (KBr) 1660.90, 1517.90, 1343.40, and 1105.40 cm^{-1};

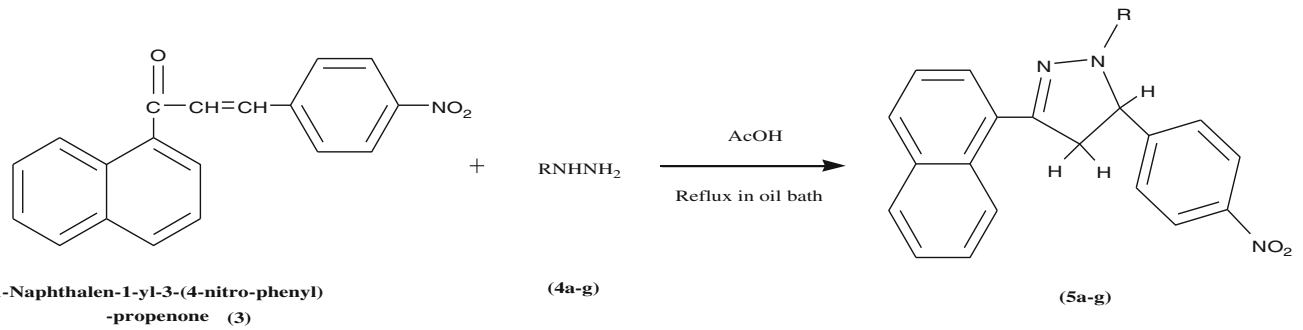


1-acetylnaphthalene (**1**)

4-nitro benzaldehyde (**2**)

1-Naphthalen-1-yl-3-(4-nitro-phenyl) -propenone (**3**)

Scheme 1 Synthesis of chalcone (**3**)



1-Naphthalen-1-yl-3-(4-nitro-phenyl) -propenone (3)

(4a-g)

(5a-g)

Compounds	R	Refluxing time	Solvent system for TLC
5a-	-H	34-hrs	Chloroform:MeOH (99:1)
5b-	$-C_6H_5$	8-hrs	Chloroform:MeOH (99:1)
5c-	$-C_6H_4(p)NO_2$	46-hrs	n-Hexane:Ethyl acetate (60:40)
5d-	$-CSNH_2$	28-hrs	Chloroform:MeOH (99:1)
5e-	$-C_6H_3(o, p)(NO_2)_2$	12-hrs	n-Hexane:Diethyl ether (60:40)
5f-	$-CONH_2$	5-6-hrs	Chloroform:MeOH (99:1)
5g-	$-C_6H_4(o)NO_2$	8-hrs	Chloroform:MeOH (99:1)

Scheme 2 Synthesis of pyrazoline derivatives (**5a–g**)

^{1}HNMR ($CDCl_3$, δ, ppm): 7.35–8.45 (m, 12H), 4.01 (s, H), 2.2 (s, 2H), 1.35 (s, H); ms: m/z 377 (20). *Anal.* Calcd. for $C_{20}H_{16}N_4O_2S$: C, 63.81; H, 4.28; N, 14.88. Found: C, 64.69; H, 3.93; N, 13.77.

*1-(2,4-Dinitro-phenyl)-3-naphthalen-1-yl-5-(4-nitro-phenyl)-4,5-dihydro-1H-pyrazole (**5e**)*

A yellow solid, yield 60.31%, melting range 204–208°C; IR (KBr) 1665.80, 1519.90, 1343.20, and 1106.30 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ, ppm): 7.40–8.45 (m, 14H), 1.65 (s, 2H), 2.80 (s, H); ms: m/z 484 (10). *Anal.* Calcd. for $C_{25}H_{17}N_5O_6$: C, 62.11; H, 3.54; N, 14.49. Found: C, 60.04; H, 2.75; N, 11.76.

*3-Naphthalen-1-yl-5-(4-nitro-phenyl)-4,5-dihydro-pyrazole-1-carboxylic acid amide (**5f**)*

Semicarbazide hydrochloride (0.111 g, 0.001 mol) was added to the suspension of **3** (0.303 g, 0.001 mol) and sodium hydroxide (0.01 g, 0.0025 mol) in ethanol (5 ml). The mixture was refluxed for 5–6 h. The progress of the reaction was monitored by TLC using the solvent system methanol: chloroform (1:99). The reaction mixture was cooled and poured on to crushed ice. Crude product was filtered, washed with cold water, and recrystallized with ethanol as black solid, yield 44.24%, melting range 173–176°C; IR (KBr) 3021.9, 2359.3, 1522, 1426, 1216, and 1027.2 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ, ppm): 7.04–8.70 (m, 12H), 5.45 (s, 2H), 4.94 (s, H), 1.30 (s, H); ms: m/z 360 (50). *Anal.* Calcd. for $C_{20}H_{16}N_4O_3$: C, 66.66; H, 4.48; N, 15.55. Found: C, 65.85; H, 4.10; N, 15.12.

*3-Naphthalen-1-yl-1-(2-nitro-phenyl)-5-(4-nitro-phenyl)-4,5-dihydro-1H-pyrazole (**5g**)*

A mixture of the **(3)** (0.606 g, 0.002 mol) and 2-nitro-phenyl hydrazine (0.306 g, 0.002 mol) in 4–6 ml of glacial acetic acid was refluxed for 8 h. The progress of the reaction was monitored by TLC using solvent system methanol: chloroform (1:99). The reaction mixture was cooled and poured into ice water. Crude product was filtered, washed with cold water and recrystallized with chloroform as red solid, yield 36.57%, melting range 183–187°C; IR (KBr) 3021.7, 2363.7, 1659.2, 1605.1, 1516.1, 1342.1, 1220.2, 1138.7, and 1105.5 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ, ppm): 6.81–8.40 (m, 15H), 2.75 (s, H), 1.65 (s, 2H); ms: m/z 439 (60). *Anal.* Calcd. for $C_{25}H_{18}N_4O_4$: C, 68.49; H, 4.14; N, 12.78. Found: C, 70.89; H, 3.68; N, 11.34.

Microbiological activities

Test microorganisms

Nine microorganisms *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 1430), *Pseudomonas aeruginosa* (MTCC 424), *B. pumilus* (MTCC 1456), *P. fluorescens* (MTCC 2421), *Aspergillus niger* (MTCC 2546), *Penicillium chrysogenum* (MTCC 161), *Escherichia*

Table 1 Mean diameter of zone of inhibition (mm) of synthesized compounds (**5a–g**), standard and control against various microorganisms

S. no.	Compounds	Concentration (μg/ml)	Gram +ve strains				Gram −ve strains			Fungal strains	
			BS	SA	BP	ML	PA	EC	PF	AN	PC
1	**5a**	100	10	9	8	9	9	–	–	8	8
		250	12	10	9	10	10	10	9	9	9
		500	13	11	10	11	11	11	11	10	10
		750	15	13	14	12	12	13	14	14	14
		1000	16	14	17	13	13	15	15	16	15
		1250	19	16	22	15	15	18	17	18	17
2	**5b**	100	12	–	–	–	9	9	8	10	10
		250	14	10	9	8	10	10	9	12	12
		500	15	11	10	9	12	11	10	13	13
		750	17	12	14	11	14	13	13	18	15
		1000	19	15	16	13	17	15	16	21	16
		1250	21	18	18	17	20	18	19	23	18
3	**5c**	100	11	–	–	–	9	10	9	12	9
		250	12	9	8	9	10	11	10	13	10
		500	13	10	10	11	11	12	11	14	12
		750	15	11	15	12	13	13	14	16	14
		1000	17	12	18	13	16	15	18	20	15
		1250	19	13	20	15	19	17	21	25	17
4	**5d**	100	9	–	10	–	10	8	8	10	10
		250	11	9	11	9	11	9	10	11	11
		500	12	10	16	11	12	11	18	17	16
		750	16	11	18	14	16	14	22	22	19
		1000	19	12	19	16	19	16	23	24	21
		1250	22	14	21	19	22	18	24	26	23
5	**5e**	100	11	–	10	8	10	9	–	–	–
		250	12	8	11	9	11	10	–	–	–
		500	13	9	18	10	12	11	18	16	18
		750	14	10	20	11	13	12	21	20	22
		1000	15	12	22	12	14	14	22	21	24
		1250	16	14	24	14	17	17	25	23	26
6	**5f**	100	10	–	–	–	9	9	8	10	8
		250	12	9	8	–	10	10	9	11	9
		500	13	10	9	–	11	11	10	13	10
		750	14	11	10	9	12	12	11	15	11
		1000	15	12	11	10	13	13	12	17	12
		1250	16	14	12	11	15	15	14	19	13
7	**5g**	100	12	–	10	–	13	9	10	10	13
		250	13	9	11	8	14	10	11	11	14
		500	14	10	12	9	15	11	13	12	15
		750	15	12	18	13	16	13	18	19	20
		1000	16	13	23	15	17	17	21	23	24
		1250	17	15	25	17	18	20	24	25	26
8	**Norfloxacin**	10	25	28	27	32	24	27	27	–	–
9	**Fluconazole**	10	–	–	–	–	–	–	–	24	25
10	**Control (DMSO)**	–	–	–	–	–	–	–	–	–	–

BS Bacillus subtilis, *SA Staphylococcus aureus, BP Bacillus pumilus, ML Micrococcus luteus, PA Pseudomonas aeruginosa, EC Escherichia coli, PF Pseudomonas fluorescens, AN Aspergillus niger,* PC *Penicillium chrysogenum*

Table 2 Minimum inhibitory concentration of synthesized compounds (**5a–g**)

Strains	MIC (μg/ml)						
	5a	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**
Bacillus subtilis	30	50	50	30	50	50	50
Staphylococcus aureus	50	150	200	150	150	200	150
Pseudomonas aeruginosa	30	50	30	50	50	50	30
Bacillus pumilus	30	150	50	30	30	200	30
Pseudomonas fluorescens	150	30	30	30	150	50	30
Aspergillus niger	50	30	30	30	150	50	30
Penicillium chrysogenum	50	30	50	30	50	50	30
Escherichia coli	200	50	50	50	150	30	30
Micrococcus luteus	30	200	150	150	150	400	150

coli (MTCC 1573), and *Micrococcus luteus* (MTCC 1538) were procured from the Institute of Microbial Technology, Chandigarh, India.

Screening for antimicrobial activity

Nutrient broth suspension of test microorganism (10 ml) was added to 100 ml of sterile molten nutrient agar growth media (cooled to 45°C), mixed well and poured into sterile Petri plates. The agar was allowed to solidify and was then punched to make six wells/cups using a 6 mm sterile cork borer (separate borer for each organism) to insure proper distribution of wells in periphery and one in center. Agar plugs were removed and 50 μl solution of test samples (each compound in six concentrations) was poured into corresponding marked well by micropipettes. Triplicate plates of each organism were prepared. The plates were left at room temperature for 2 h to allow diffusion of samples and incubated face upward at corresponding temperature of each organism for 48 h. (Gautam *et al.*, 2010). The diameters of zone of inhibition were measured to the nearest millimeters (the cup size also included) and are presented in the Table 1.

Determination of minimum inhibitory concentrations (MICs)

A series of glass tubes containing different concentrations of the synthesized compounds (in dimethyl sulphoxide) with nutrient broth was inoculated with the required amount of the inoculum to obtain a suspension of microorganism, which contains 10^5 colony forming units per milliliter. Norfloxacin and Fluconazole were used as standard drugs for antibacterial and antifungal activities, respectively. One tube was prepared with the addition of the solvent (DMSO) and one blank tube was prepared without the addition of microorganism. The tubes were incubated at 37°C for 24–48 h. The turbidity produced in each tube was recorded by using a UV–visible spectrophotometer (Pandey *et al.*, 2011). The observed MICs (μg/ml) are presented in Table 2.

Results and discussion

In this study, chalcone (**3**) was synthesized by stirring 4-nitro benzaldehyde with 1-acetyl naphthalene in the presence of ethanolic sodium hydroxide solution. Synthesis of intermediate-chalcone was confirmed on the basis of its IR and mass spectra. The IR spectra of chalcone displayed peak at 1658.67 cm^{-1} indicating the presence of a conjugated carbonyl group (C=O). Mass spectra showed the [M + 1] peak. The chalcone was then reacted with hydrazines (**4a–g**) to give 2-pyrazoline derivatives (**5a–g**) (Scheme 2). This reaction probably takes place through modification of an appropriate α, β-unsaturated carbonyl group, which cyclizes to give pyrazoline compounds in the presence of a suitable cyclizing agent (glacial acetic acid) under prolonged refluxing condition.

All the synthesized compounds were characterized by physical, spectral, and elemental analysis. The IR spectra in pyrazoline derivatives exhibited C=N stretching vibrations in the range of 1522–1665.8 cm^{-1}. $[M]^+$ or [M + 1] peaks were observed for the various compounds synthesized. In all the ^{1}H-NMR spectra, a multiplet indicating various naphthyl and aromatic protons appears at the δ values of ≈6.5–8.5 ppm. The synthesized pyrazoline derivatives were evaluated for antimicrobial activity against bacterial and fungal strains by cup-plate method. The microorganisms selected for antibacterial activity were *B. subtilis*, *S. aureus*, *P. aeruginosa*, *B. pumilus*, *P. fluorescens*, *E. coli*, *M. luteus*. *A. niger*, and *P. chrysogenum* were selected for antifungal activity. The MIC was determined by tube dilution method for the said microorganisms. Four compounds (**5b**, **5d**, **5e**, and **5g**) exhibited good antimicrobial activity. MIC of these compounds was found to be 30 μg/ml against most of the strains. Compounds (**5d**) and (**5g**) exhibited potent activity against two Gram-positive bacterial strains (*B. pumilus*, *B. subtilis*), three Gram-negative bacterial strains (*E. coli*, *P. aeruginosa*, *P. fluorescens*) and two fungal strains (*A. niger*, *P. chrysogenum*). All the compounds were active against one Gram-positive strain (*B. subtilis*) and one Gram-negative (*P. aeruginosa)* at all concentrations. Compounds (**5b–f**) and (**5g**) were active against one Gram-negative strain (*E. coli*). Thus, it can be concluded that all the compounds exhibited higher antibacterial activity as compared to the antifungal activity. Also, it is evident that compounds (**5e**) and (**5g**) exhibited maximum antibacterial activity and compound (**5g**) exhibited maximum antifungal activity. Compound (**5g**) (3-naphthalen-1-yl-1-(2-nitro-phenyl)-5-(4-nitro-phenyl)-4,5-dihydro-1H-pyrazole) may thus be

designated as the potent member of the series. The 2-nitrophenyl group at N-1 position of the 2-pyrazoline ring offers not only the potent compound in the series but also wide spectrum of activity.

Conclusion

In this study, a series of 1,3,5-trisubstituted compounds containing a pyrazoline nucleus were synthesized. The compounds were characterized using spectral techniques. The antimicrobial activities of the compounds were determined using the cup-plate method and tube dilution method. Most of the compounds exhibited potent antimicrobial activity, which was also found to be concentration dependent. The compounds exhibited higher antibacterial activity as compared to the antifungal activity. The compounds **5d, 5e**, and **5g** exhibited potent broad spectrum antimicrobial activity. The compound **5g** was the most promising in the series as it was not only active against the bacteria but also the fungi. It may also be deduced that the presence of a 2-nitrophenyl group at N-1 position of the 2-pyrazoline ring offers a potent agent which is, very interestingly, capable of inhibiting bacteria as well as fungi. From the biological point of view, all the compounds in the series offer novel leads to a new generation of antimicrobial agents. Thus, it can be concluded that 1,3,5-trisubstituted pyrazoline derivatives are capable of exhibiting potent antimicrobial activity.

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