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Der Pharmacia Sinica, 2013, 4(4):112-117

Der Pharmacia Sinica
ISSN: 0976-8688
CODEN (USA): PSHIBD

Synthesis and antibacterial screening of some 1-phenyl-3-aryl-5-(4-(4-butanoloxy) phenyl)-1*H*-pyrazoles

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ABSTRACT

A series of 1-phenyl-3-aryl-5-(4-(4-butanoloxy) phenyl)-1H-pyrazoles were synthesized from chalcones and screened for their in vitro antibacterial activity. Chalcones i.e.,1-aryl-3-(4-hydroxyphenyl) prop-2-en-1-ones, ***1*** *on reaction with phenyl hydrazine in presence of acetic acid and few drops of hydrochloric acid furnished the corresponding 1-phenyl-3-aryl-5-(4-hydroxyphenyl)-1H-pyrazoles* ***2*** *which on further reaction with 4-chlorobutanol yielded the title compounds* ***3****. These compounds were characterized by CHN analyses, IR, mass and* ^{1}*H NMR spectral data. All the compounds were studied for their in vitro antibacterial activity against two Gram positive strains (Bacillus subtilis and Staphylococcus aureus) and two Gram negative strains (Escherichia coli and Pseudomonas aeruginosa) and their minimum inhibitory concentration (MIC) were determined.*

Keywords: Chalcones, 1*H*-pyrazoles, antibacterial activity, minimum inhibitory concentration (MIC).

INTRODUCTION

Multi-drug resistance arises due to the extensive exploitation of chemotherapeutic drugs for the treatment of infectious diseases. This creates an alarming situation for the health of world population and also gives the opportunity to the medicinal chemists for the development of novel antimicrobial agents having a different mode of action to fight against multi-drug resistance [1]. Heterocyclic compounds continue to create a center of attention due to their various biological activities. Amongst the five membered heterocles, pyrazoles have been found to exhibit wide application in the field of medicinal and pharmaceutical chemistry. In recent years, progressively more concentration has been given to the synthesis of pyrazole derivatives for the development of new antibacterial agents. Pyrazole derivatives have been reported to possess diverse biological activities such as antibacterial [2, 3], antifungal [4, 5], herbicidal [6], insecticidal [7], anti-inflammatory [8, 9] anticonvulsant [10], anti-tumor [11], anti-oxidant [12] and so on. Further, 1*H*-pyrazoles containing phenoxy alkanol [13-17] side chain have been reported to possess antibacterial activity by us as a part of our ongoing research program in the field of synthesis and antimicrobial activity of medicinally important heterocyclic compounds [18, 19]. These reports prompted us to undertake the synthesis of some more 1*H*-pyrazoles bearing phenoxy butanol moiety. The synthesized compounds were characterized on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral data. All the compounds were screened for their *in vitro* antibacterial activity against two Gram positive strains (*Bacillus subtilis* and *Staphylococcus aureus*) and two Gram negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*), respectively.

MATERIALS AND METHODS

Chemistry. The purity of all the synthesized compounds was checked by thin layer chromatography on silica gel G as a stationary phase and different solvent systems as a mobile phase using iodine vapors as detecting agent. Melting points were determined by the Tempo melting point determination apparatus in open capillary tubes and are uncorrected. Infrared spectra were recorded on Shimadzu 8000 FTIR Spectrophotometer in KBr phase. Proton NMR spectra were done on Bruker Avance II 400 NMR Spectrometer using tetra-methyl silane as internal standard. Mass spectra of the compounds were carried out on Waters Micromass Q-Tof Micro Mass Spectrometer using electrospray ionization (ESI) technique. Elemental analyses were carried out on Perkin Elmer 2400 CHN Elemental Analyser. Chalcones **1a–g** were synthesized by a base-catalyzed Claisen-Schmidt condensation reaction of appropriately substituted acetophenones and 4-hydroxy benzaldehyde [20], and 1-phenyl-3-aryl-5-(4-hydroxyphenyl)-1*H*-pyrazoles **2a–g** were prepared from the chalcones **1a–g** following the procedure described in the literature [21].

General Procedure for the Synthesis of 1-phenyl-3-aryl-5-(4-(4-butanoloxy phenyl)-1H-pyrazoles (3a–g). 1-phenyl-3-aryl-5-(4-hydroxy phenyl)-1*H*-pyrazoles (2a–g 0.01 M) and 4-chlorobutanol (0.01 M) were refluxed in acetone (50 mL) in the presence of tri-ethylamine (0.01 M) for about four hours. Excess of solvent was removed under reduced pressure. The residue thus obtained was washed thoroughly with cold distilled water, dried, and then re-crystallized from ethanol. The physical and analytical data of the synthesized title compounds are given as follows.

1, 3-Diphenyl-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole (3a): Yield: 76%; m.p.: 81-83 ^{o}C; IR (KBr, cm^{-1}): 3340 (O–H), 3070 (aromatic C–H *str*), 2916 (C–H), 1465, (CH_2), 1255 (C–O–C), 1071 (C–O), 830, 732 & 690 (aromatic C–H *def*); ^{1}HNMR ($CDCl_3$): δ (ppm) 8.05-7.09 (m, 14H, Ar**H**), 7.02 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C$\mathbf{H_2}$–O–Ar), 3.69 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C$\mathbf{H_2}$–CH_2–CH_2–CH_2–O–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C$\mathbf{H_2}$–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–$\mathbf{CH_2}$–CH_2–CH_2–O–Ar); MS, m/z (%): 385 $[M+H]^+$ (100%). Anal.: Calcd. for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29. Found: C, 78.16; H, 2.22; N, 7.21.

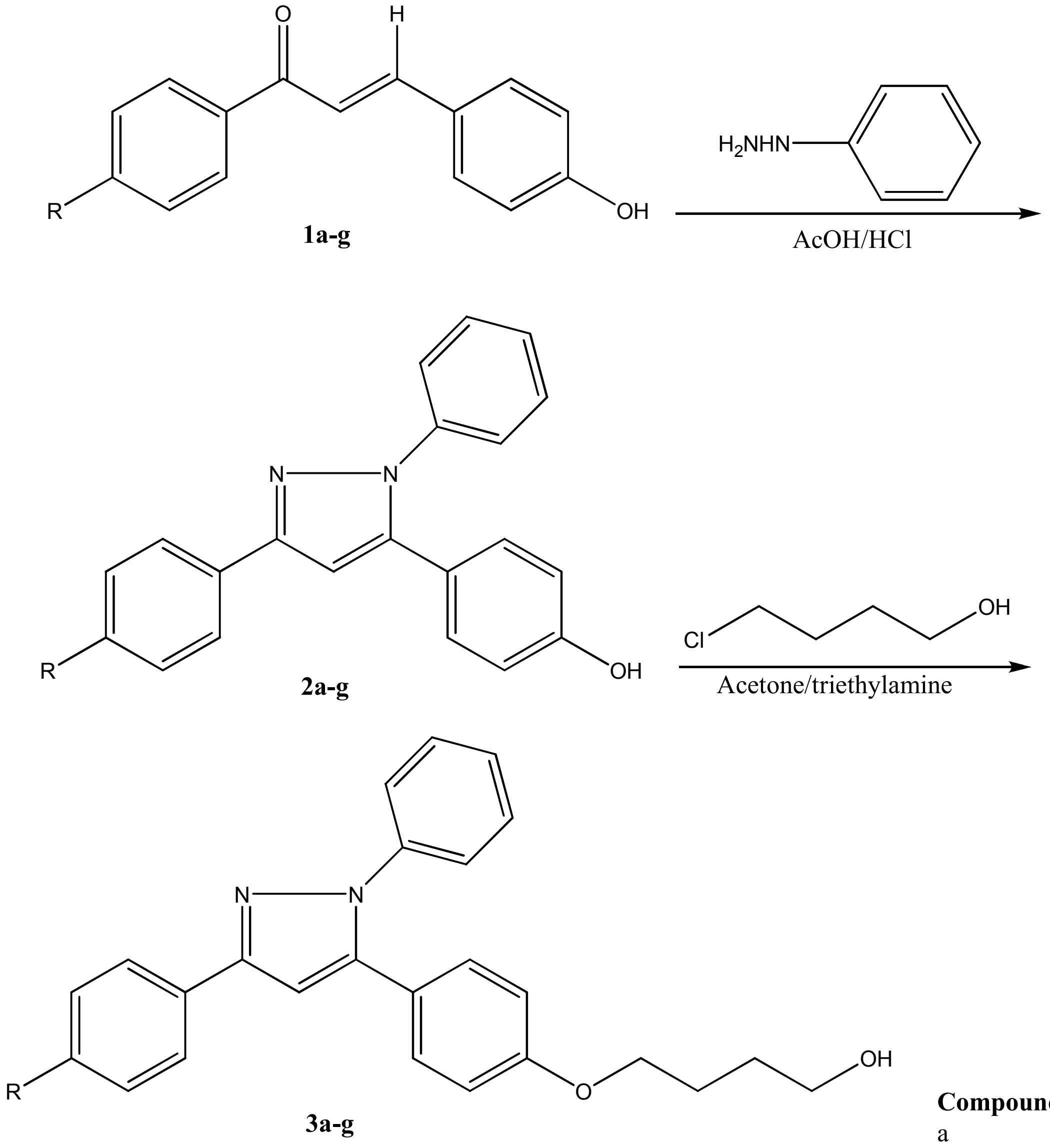
1-Phenyl-3-(4-methyl phenyl)-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole (3b): Yield: 69%; m.p.: 87-89 ^{o}C; IR (KBr, cm^{-1}): 3339 (O–H), 3065 (aromatic C–H *str*), 2919 (C–H), 1465, (CH_2), 1255 (C–O–C), 1070 (C–O), 832, 730 & 690 (aromatic C–H *def*); ^{1}HNMR ($CDCl_3$): δ (ppm) 7.67-7.08 (m, 13H, Ar**H**), 7.01 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C$\mathbf{H_2}$–O–Ar), 3.69 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C$\mathbf{H_2}$–CH_2–CH_2–CH_2–O–Ar), 2.34 (s, 3H, C$\mathbf{H_3}$–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C$\mathbf{H_2}$–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–$\mathbf{CH_2}$–CH_2–CH_2–O–Ar); MS, m/z (%): 399 $[M+H]^+$ (100%). Anal.: Calcd. for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.30; H, 6.51; N, 7.09.

1-Phenyl-3-(4-methoxy phenyl)-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole (3c): Yield: 71%; m.p.: 93-95 ^{o}C; IR (KBr, cm^{-1}): 3343 (O–H), 3065 (aromatic C–H str), 2916 (C–H), 1465, (CH_2), 1255 (C–O–C), 1068 (C–O), 832, 735 & 693 (aromatic C–H def); ^{1}HNMR ($CDCl_3$): δ (ppm) 7.64-7.07 (m, 13H, Ar**H**), 7.02 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C$\mathbf{H_2}$–O–Ar), 3.83 (s, 3H, C$\mathbf{H_3}$O–Ar), 3.70 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C$\mathbf{H_2}$–CH_2–CH_2–CH_2–O–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C$\mathbf{H_2}$–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–$\mathbf{CH_2}$–CH_2–CH_2–O–Ar); MS, m/z (%): 415 $[M+H]^+$ (100%). Anal.: Calcd. for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75.39; H, 6.38; N, 6.71.

1-Phenyl-3-(4-chloro phenyl)-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole (3d): Yield: 77%; m.p.: 83-85 ^{o}C; IR (KBr, cm^{-1}): 3336 (O–H), 3061 (aromatic C–H *str*), 2916 (C–H), 1465, (CH_2), 1255 (C–O–C), 1066 (C–O), 832, 730 & 690 (aromatic C–H *def*); ^{1}HNMR ($CDCl_3$): δ (ppm) 8.01-7.07 (m, 13H, Ar**H**), 7.01 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C$\mathbf{H_2}$–O–Ar), 3.70 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C$\mathbf{H_2}$–CH_2–CH_2–CH_2–O–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C$\mathbf{H_2}$–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–$\mathbf{CH_2}$–CH_2–CH_2–O–Ar); MS, m/z (%): 419 $[M+H]^+$ (100%), 421 $[M+2+H]^+$ (35%).Anal.: Calcd. for $C_{25}H_{23}ClN_2O_2$: C, 71.68; H, 5.53; 8.46; N, 6.69. Found: C, 71.61; H, 5.58; N, 6.62.

1-Phenyl-3-(4-bromo phenyl)-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole(3e): Yield: 76%; m.p.: 95-97 ^{o}C; IR (KBr, cm^{-1}): 3337 (O–H), 3066 (aromatic C–H *str*), 2919 (C–H), 1465, (CH_2), 1256 (C–O–C), 1072 (C–O), 832, 732 & 695 (aromatic C–H *def*); ^{1}HNMR ($CDCl_3$): δ (ppm) 7.79-7.08 (m, 13H, Ar**H**), 7.01 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C$\mathbf{H_2}$–O–Ar), 3.68 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C$\mathbf{H_2}$–CH_2–CH_2–CH_2–O–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C$\mathbf{H_2}$–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–$\mathbf{CH_2}$–CH_2–CH_2–O–Ar); MS, m/z (%): 463 $[M+H]^+$ (100%), 465 $[M+2+H]^+$ (98%). Anal.: Calcd. for $C_{25}H_{23}BrN_2O_2$: C, 64.80; H, 5.00; N, 6.05. Found: C, 64.87; H, 5.06; N, 6.10.

1-Phenyl-3-(4-fluoro phenyl)-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole (3f): Yield: 74%; m.p.: 91-92 ^oC; IR (KBr, cm^{-1}): 3340 (O–H), 3073 (aromatic C–H *str*), 2917 (C–H), 1465, (CH_2), 1255 (C–O–C), 1070 (C–O), 830, 730 & 692 (aromatic C–H *def*); ^{1}HNMR ($CDCl_3$): δ (ppm) 8.15-7.08 (m, 13H, Ar**H**), 7.02 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C**H_2**–O–Ar), 3.69 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C**H_2**–CH_2–CH_2–CH_2–O–Ar), 1.89-1.87 (quin, 2H, HO–CH_2–CH_2–C**H_2**–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–**CH_2**–CH_2–CH_2–O–Ar); MS, m/z (%): 403 $[M+H]^+$ (100%). Anal.: Calcd. for $C_{25}H_{23}FN_2O_2$: C, 74.61; H, 5.76; N, 6.96. Found: C, 74.67; H, 5.71; N, 6.90.



Compound	R
a	H
b	CH_3
c	OCH_3
d	Cl
e	Br
f	F
g	NO_2

Scheme 1: Synthesis of1-Phenyl-3-aryl-5-(4-(4-butanoloxy)phenyl-1*H*-pyrazoles

1-Phenyl-3-(4-nitrophenyl)-5-(4-(4-butanoloxy) phenyl)-1H-pyrazole (3g): Yield: 72%; m.p.: 87-88 ^oC; IR (KBr, cm^{-1}): 3342 (O–H), 3065 (aromatic C–H *str*), 2918 (C–H), 1465, (CH_2), 1255 (C–O–C), 1070 (C–O), 832, 735 & 690 (aromatic C–H *def*); ^{1}HNMR ($CDCl_3$): δ (ppm) 8.35-7.08 (m, 13H, Ar**H**), 7.01 (s, 1H, =C**H**–), 4.08-4.06 (t, 2H, HO–CH_2–CH_2–CH_2–C**H_2**–O–Ar), 3.70 (s, 1H, O–**H**), 3.53-3.51 (t, 2H, HO–C**H_2**–CH_2–CH_2–CH_2–O–Ar), 1.89-1.87

(quin, 2H, HO–CH_2–CH_2–C**H_2**–CH_2–O–Ar), 1.57-1.53 (quin, 2H, HO–CH_2–**CH_2**–CH_2–CH_2–O–Ar); MS, m/z (%): 430 $[M+H]^+$ (100%). Anal.: Calcd. for $C_{25}H_{23}N_3O_4$: C, 69.92; H, 5.40; N, 9.78. Found: C, 69.98; H, 5.47; N, 9.72.

Antibacterial Activity. All the title compounds were screened for their *in vitro* antibacterial activity against two Gram positive strains, that is, *Bacillus subtilis* (MTCC 121) and *Staphylococcus aureus* (MTCC 96) and two Gram negative strains, that is, *Escherichia coli* (MTCC 40) and *Pseudomonas aeruginosa* (MTCC 2453), respectively. Ciprofloxacin was used as the standard drug for the present study. Serial two-fold dilution technique was used for the study of antibacterial activity [22]. A stock solution (10 µg/mL) of all the title compounds and standard drug was prepared in dimethyl sulfoxide. Sterilized double-strength nutrient broth (DSNB) was used as a growth media. The stock solution was serially diluted by DSNB aseptically to give concentrations of 5.0–0.01 µg/mL into a series of sterilized culture tubes. All the tubes were inoculated by bacterial strain. The inoculum's size was approximately 10^6 colony forming units (CFU/mL). The inoculated tubes were incubated for 24 h at 37(±1)◦C. After 24 h, the inoculated culture tubes were macroscopically examined for turbidity. The culture tube showing turbidity (lower concentration) and the culture tube showing no turbidity (higher concentration) gave the minimum inhibitory concentration (MIC) for the compound. The MIC for the title compounds and the standard drug, that is, ciprofloxacin are presented in Table 1.

RESULTS AND DISCUSSION

Chemistry. The syntheses of 1-phenyl-3-aryl-5-(4-(4-butanoloxy) phenyl) 1*H*-pyrazoles were achieved following the steps outlined in the scheme 1. Chalcones *i.e.*, 1-aryl-3-(4-hydroxyphenyl) prop-2-en-1-ones, **1** were prepared by the reaction of 4-hydroxy benzaldehyde with substituted acetophenones following the Claisen-Schmidt reaction. The chalcones **1** then on refluxing with phenyl hydrazine in the presence of acetic acid and few drops of hydrochloric acid furnished 1-phenyl-3-aryl-5-(4-hydroxyphenyl)-1*H*-pyrazoles **2**. 4-Chlorobutanol reacted with **2** in the presence of triethyl amine to give the **3**. All the compounds were obtained in good yield. These compounds were characterized on the basis of elemental and spectral analyses. IR spectra of each compound showed a band for O–H stretching vibrations for intermolecular hydrogen bonding near 3340 cm^{-1} while the C–O stretching vibrations for primary alcohols were observed in the range of 1075-1066 cm^{-1}. C–O–C stretching vibrations for aryl alkyl ether were appeared at 1255 cm^{-1}. The C–H stretching vibrations for methylene groups were appeared in the range of 2916-2919 cm^{-1} whereas bending vibrations for methylene scissoring were observed constantly at 1465 cm^{-1}. Aromatic C–H stretching vibrations were observed in the range of 3073-3061 cm^{-1} whereas aromatic C–H bending vibrations were appeared below 900 cm^{-1}. In case of ^1H NMR, the chemical shift value for the O–**H** group was observed in the range of 3.70-3.68 δ (ppm) and appeared as singlet (s). Aromatic protons appeared as multiplet (m) in the range of 8.35-7.07 δ (ppm). The methine proton of the pyrazole nucleus absorbed at 7.02-7.01 δ (ppm) and appeared as singlet (s). The methylene protons adjacent to the O–H group [HO–C**H_2**–CH_2–CH_2–CH_2–O–Ar] were appeared as triplet (t) in the range of 3.53-3.51 δ (ppm) whereas the methylene protons adjacent to the O–Ar group [HO–CH_2–CH_2–CH_2–C**H_2**–O–Ar] were observed at 4.08-4.06 δ (ppm) and appeared as triplet (t). The central methylene protons which are nearer to the O–H group appeared as quintet (quin) at 1.57-1.53 δ (ppm) and those are nearer to O–Ar group appeared at 1.89-1.87 δ (ppm) respectively. Aromatic methyl and methoxy protons were observed at 2.34 δ (ppm) and 3.83 δ (ppm) respectively as singlet (s). All the title compounds showed $[M+H]^+$ of 100% intensity as the molecular ion peak. Compound containing chlorine showed isotopic peak at $[M+2+H]^+$ of about 35% intensity to that of parent ion peak whereas bromo derivative showed isotopic peak at $[M+2+H]^+$ of about equal intensity. The results of elemental analyses were found in good agreement with the calculated values.

Antibacterial Activity. All the synthesized title compounds were screened for their *in vitro* antibacterial activity against and two Gram positive bacterial strains, that is, *Bacillus subtilis* (MTCC 121) and *Staphylococcus aureus* (MTCC 96) and two Gram negative bacterial strains, that is, *Escherichia coli* (MTCC 40) and *Pseudomonas aeruginosa* (MTCC 2453), respectively, and their minimum inhibitory concentration (MIC) was determined. A perusal of the Table 1 shows that all the title compounds were found to be active against all the bacterial strains used in this study. However, they showed more activity against the Gram negative than the Gram positive bacterial strains. Out of the two Gram negative bacterial strains, *E. coli* (MTCC 40) was found to be more susceptible than *P. aeruginosa* (MTCC 2453) against all the title compounds. The minimum inhibitory concentration (MIC) of the title compounds **3a–g** was found to be 0.75–0.65 µg/mL, 0.80–0.70 µg/mL, 0.60–0.50 µg/mL, and 0.65–0.55 µg/mL against *B. subtilis* (MTCC 121), *S. aureus* (MTCC 96), *E. coli* (MTCC 40) and *P. aeruginosa* (MTCC 2453) respectively. The MICs of the title compounds containing electron withdrawing groups like fluoro, chloro, bromo, or nitro were found somewhat less than the compounds containing electron releasing groups like methyl and methoxy. Compound **3g** which contains nitro group was found to be most active amongst the title compounds. The reference standard ciprofloxacin inhibited Gram negative bacteria namley, *E. coli* and *P. aeruginosa* at a MIC of 0.01 µg/mL and 0.25 µg/mL, respectively, whereas against Gram positive bacteria namley, *S. aureus* and *B. subtilis* MIC was found to be 0.15 µg/mL and 0.12 µg/mL, respectively. The results of the MIC for the standard drug, ciprofloxacin, against the bacterial strains used were found to be within the range as reported in the literature [23-25].

TABLE 1: *In-vitro* antibacterial activity of 1-phenyl-3-aryl-5-(4-(4-butanoloxy) phenyl)-1*H*-pyrazoles

Compound	Minimum inhibitory concentration µg/mL			
	***B. subtilis* (MTCC 121)**	***S. aureus* (MTCC 96)**	***E. coli* (MTCC 40)**	***P. aeruginosa* (MTCC 2453)**
3a	0.75	0.80	0.60	0.65
3b	0.75	0.80	0.60	0.65
3c	0.80	0.85	0.65	0.70
3d	0.70	0.75	0.55	0.60
3e	0.70	0.75	0.55	0.60
3f	0.70	0.75	0.55	0.60
3g	0.65	0.70	0.50	0.55
Ciprofloxacin (standard drug)	0.12	0.15	0.01	0.25

CONCLUSION

Present study describes the synthesis of a series of 1-phenyl-3-aryl-5-(4-(4-butanoloxy) phenyl)-1*H*-pyrazoles starting from the chalcones. The compounds were characterized by modern analytical techniques such as CHN analyses, IR, Mass and proton NMR spectra. All the title compounds were screened for their *in vitro* antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus* (Gram positive) and *Escherichia coli*, *Pseudomonas aeruginosa* (Gram negative) and their minimum inhibitory concentration (MIC) were determined. The results of antibacterial activity showed that compounds containing electron withdrawing groups e.g., chloro, bromo, fluoro or nitro were found to be more active than the compounds containing electron releasing groups such as methyl and methoxy. These results suggest that some more compounds using different aromatic or heteroaromatic aldehydes, ketones, and haloalkanols should be synthesized and screened for their antibacterial activity to explore the possibility of 1-phenyl-3-aryl-5-(4-(alkanoloxy) phenyl) 1*H*-pyrazoles as a novel series of antibacterials.

Acknowledgments
The authors are thankful to the chairman of the Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar, India, for providing necessary facilities to carry out this work. Our sincere thanks are due to Department of SAIF, P.U. Chandigarh for elemental and spectral analysis. The director of IMTECH, Chandigarh, is also duly acknowledged for providing bacterial strains.

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