

Ultrasound Promoted Environmentally Benign Synthesis of Some Novel Pyrazoline Derivatives

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ABSTRACT: The chalcones 1-(2-hydroxyphenyl)-3-(1-phenyl-3-(pyridin-3-yl)-1*H*-pyrazol-4-yl)prop-2-en-1-ones (3a-g) were transformed into corresponding pyrazoline derivatives by using hydrazine hydrate and some drops of glacial acetic acid in alcohol. The pyrazoline 2-(4,5-dihydro-5-(1-phenyl-3-(pyridin-3-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrazol-3-yl)phenols (4a-g) derivatives have been synthesized by using ultrasonication methods & screened for its antimicrobial activities. All these synthesized compounds have been confirmed by using FTIR, ¹HNMR and mass spectral tools.

KEYWORDS: Ultrasound, chalcones, 2-hydroxyacetophenone, pyrazoline, antimicrobial activities.

I. INTRODUCTION

Recently ultrasound method has increasingly been used in organic synthesis[1,2]. The conventional method required longer time to complete the reaction and gives low yield. The ultrasound method is more convenient as it requires shorter time for reaction completion and obtained higher yields as compare to traditional methods. Pyrazolines[3,4] and its derivatives have been found to involve a wide spectrum of biological activities such as such as anti-cancer[5], anti-tumer[6], anti-oxidant[7], anti-hypertensive[8], anti-depressant[9], anti-convulsant-[10], anti-bacterial[11,12], activities. Recently these classes of compounds were reported to involve potential anti-viral[13] against HIV[14], flavivirus[15], anti-malarial[16], anti-inflammatory[17] activity.

Recent decade have been shown several anti-bacterial and chemically semi synthetic modification of many natural compounds. It consist for example, the cephalosporins, the carbapenems and the β -lactam anti-bacterials. The other anti-bacterials for example the quinolones, the axazolidinones and the sulphonamides were synthesized solely by using chemical methods whereas the compounds which are still extracted from living organisms were the aminoglycosides. Several of the antibacterial compounds were classified on the basis of biosynthetic/ chemical origin into synthetic, semi-synthetic and natural. Further classification system was depend on biological activity; in this classification anti-bacterials were divided into two broad groups according to its biological effect on microorganisms bactericidal agents kill bacteria and bacteriastatic agents slow down or prevent bacterial growth. Resistance against bacterial infection had been resulting in the development of a wide spectrum of antibiotics, overuse of antibiotics bacteria is becoming antibiotics resistant after years of misuse, resulting in a potential global health crisis. It is already proved that antibacterial resistance is associated with an increase in mortality. Therefore to overcome this problem it was recommended to use new antibacterial agent with enhanced wide variety of potency. Due to this reason, recent efforts have been directed towards exploring novel antibacterial agents.

To overcome this very fast development of drug resistance, newly agents should preferably consist of chemical characteristic which clearly differ from those of existing agents. The synthesis of molecules in drug designing programmes an essential constituent of the search for new leads that are novel yet resemble known biologically active molecules by virtue of the presence of critical structural features. Some of the very small heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of a variety of biologically active and medicinally useful molecules. Nitrogen containing 5-membered heterocyclic compounds are pyrazolines, and number of methods have been worked out for its synthesis. Most widely used procedure were based on the reaction of α,β -unsaturated aldehyde and ketone with hydrazine hydrate.

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II. MATERIALS AND DISCUSSION

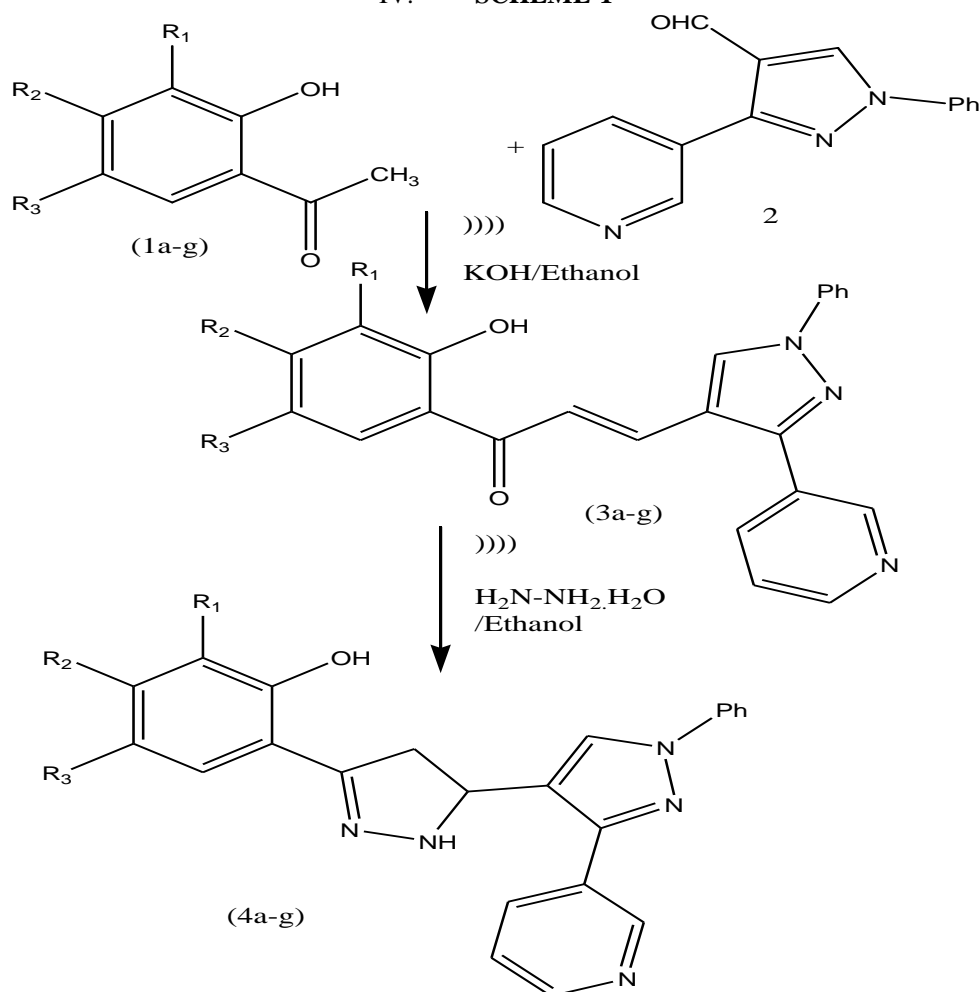
The starting material required for the synthesis of chalcone was 2-hydroxyacetophenone which were prepared by using conventional methods. The 99.99% pure chemical were used for this synthesis. The purity of the chemicals were checked by using TLC, melting point, and mixed melting point. The chemicals for this synthesis were purchased from local dealers with s d fine and Aldrich.

III. RESULT AND DISCUSSION

For the synthesis of chalcone and pyrazoline derivatives all the experiments under ultrasonication were carried out in bath type ultrasonicator model EN-20U-S manufactured by Entertech Electronica Pvt. Ltd. Mumbai, India having maximum power out put of 100w and 33kHz frequency. The synthesized compounds were evaluated for its in vitro antifungal activity against candida sp. using Ketoconazole as a standared drug. Antibacterial activity against pseudomonus aeruginasa, straphylococcus aureus and E. coli using Gentamicin and tetracycline as a reference standared by paper disc diffusion method.

All the tested compounds were evaluated at 100ug/ml concentration. Few of the compound had indicate moderate antimicrobial activities.

IV. SCHEME-1



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IV. EXPERIMENTAL SECTION

Liquid paraffin bath were used to determine the melting points in open capillaries of the synthesized compounds and are uncorrected. Thin Layer Chromatography was used to monitor the progress of the reactions by using silica gel-G (Merck). FTIR spectra has been recorded on a Perkin Elmer Spectrum Version 10.4.2 IR spectrometer. ¹HNMR spectra has been recorded on Bruker Avance-II 400 MHz NMR spectrometer by using CDCl₃ as a solvent and TMS as internal standard reference. Chemical shift values have been indicated in δ (ppm). ¹NMR data were reported in order; multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet). The mass spectra has been recorded on a waters, Q-TOF micromass (LC-MS) mass spectrometer. The antimicrobial activities of some representative synthesized compounds have been tested by using disc diffusion method.

By ultrasound method:

General procedure for the synthesis of 1-(2-hydroxyphenyl)-3-(1-phenyl-3-(pyridine-3-yl)-1H-pyrazol-4-yl)prop-2-en-1-ones(**3a-g**): Equimolar amount of compounds **1**(0.001 mol) & **2** (0.001 mol) were dissolved in 20 ml of ethanol in a 100 ml round bottom flask. To this reaction mixture (40%) also. KOH (10 ml) solution in water was added. Reaction mixture was subjected to ultrasonication for 80-120 minutes. Progress of the reaction was monitored with the help of TLC. After completion of reaction the contents were then poured into crushed ice and neutralized with hydrochloric acid. The yellow solid thus obtained was filtered and crystallized from ethanol. The compounds synthesized by the above procedure are shown in table-1.

3a : IR (cm⁻¹): 3141 (-OH), 1681 (-C=O), 1490 (C=O).

¹HNMR(CDCl₃) (δ): 6.9 (d, 1H, ethylene proton), 7.26-8.78 (m, 13H, Ar-H), 8.77 (s, 1H, pyrazole proton), 12.70 (s, 1H, -OH), 7.10 (d, 1H, ethylene proton).

Mass (m/z) : (m + 1) : 368.

3b : IR (cm⁻¹): 3222 (-OH), 1685 (-C=O), 1482 (C=O).

¹HNMR(CDCl₃) (δ): 6.82 (d, 1H, ethylene proton), 7.15-8.52 (m, 11H, Ar-H), 8.80 (s, 1H, pyrazole proton), 12.62 (s, 1H, -OH), 2.35 (s, 3H, -CH₃), 7.0 (d, 1H, ethylene proton).

Mass (m/z) : (m + 1) : 416.5.

3c : IR (cm⁻¹): 3225 (-OH), 1678 (-C=O), 1480 (C=O).

¹HNMR(CDCl₃) (δ): 6.8 (d, 1H, ethylene proton), 7.20-8.25 (m, 12H, Ar-H), 8.50 (s, 1H, pyrazole proton), 12.40 (s, 1H, -OH), 2.37 (s, 3H, -CH₃), 7.0 (d, 1H, ethylene proton).

Mass (m/z) : (m + 1) : 382.

General procedure for the synthesis of 2-(4,5dihydro-5-(1-phenyl-3-(pyridin-3-yl)-1H-pyrazol-4-yl)-1H-pyrazol-3-yl)phenols(**4a-g**): In a 100 ml RBF the compounds **3a** (0.001 mol) was dissolved in 20 ml ethanol. To this reaction mixture (2 ml) hydrazine hydrate was added. Reaction mixture was subjected to ultrasonication for 60-80 minutes. Progress of the reaction was monitored with the help of TLC. After completion of reaction the product obtained was separated by filtration. These products were purified by recrystallization from ethanol to afford pure compound **4a**. The compounds synthesized by the above procedure are shown in table-I.

4a : IR (cm⁻¹) : 3150 (-OH), 3240 (-NH), 1440 (C=N).

¹HNMR (CDCl₃) (δ) : 3.65 (dd, 1H, pyrazoline proton), 3.20 (dd, 1H, pyrazoline proton), 5.20 (dd, 1H, pyrazoline proton), 6.4 (s, 1H, -NH), 8.52 (s, 1H, pyrazole proton), 7.18-8.34 (m, 13H, Ar-H), 12.20 (s, 1H, -OH).

Mass : (m/z) : (m+1) : 382.

4b : IR (cm⁻¹) : 3220 (-OH), 3310 (-NH), 1430 (C=N).

¹HNMR (CDCl₃) (δ) : 3.60 (dd, 1H, pyrazoline proton), 3.25 (dd, 1H, pyrazoline proton), 5.10 (dd, 1H, pyrazoline proton), 6.4 (s, 1H, -NH), 8.52 (s, 1H, pyrazole proton), 7.15-8.20 (m, 13H, Ar-H), 2.35 (s, 3H, -CH₃), 12.20 (s, 1H, -OH).

Mass : (m/z) : (m+1) : 429.5.

4c : IR (cm⁻¹) : 3216 (-OH), 3250 (-NH), 1470 (C=N).

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¹HNMR (CDCl₃) (δ) : 3.55 (dd, 1H, pyrazoline proton), 3.20 (dd, 1H, pyrazoline proton), 5.15 (dd, 1H, pyrazoline proton), 6.5 (s, 1H, -NH), 8.40 (s, 1H, pyrazole proton), 7.12-8.25 (m, 12H, Ar-H), 12.20 (s, 1H, -OH).
Mass : (m/z) : (m+1) : 395.

VI. TABLE-1

Characterization data of synthesized compounds (3a-g) and (4a-g)

Compound	R ₁	R ₂	R ₃	M.P. (°C)	Yield (%)
3a	H	H	H	186	90
3b	H	CH ₃	Cl	102	84
3c	H	H	CH ₃	213	77
3d	H	H	Br	178	72
3e	CH ₃	CH ₃	H	133	74
3f	Cl	H	Cl	300	78
3g	H	H	Cl	172	77
4a	H	H	H	121	88
4b	H	CH ₃	Cl	140	80
4c	H	H	CH ₃	93	82
4d	H	H	Br	150	78
4e	CH ₃	H	CH ₃	140	79
4f	Cl	H	Cl	138	80
4g	H	H	Cl	122	84

VII. ANTIMICROBIAL ACTIVITY

The synthesized compounds had been screened for its in vitro antibacterial activity against gram negative organism *E. coli* and gram positive organism *pseudomonas aeruginosa* and *staphylococcus aureus* using Gentamycin as a reference standard by paper disc diffusion method. Antifungal activity has been evaluated with *Candida sp* against Ketokonazole as a reference standard. The tested compounds have been evaluated at 100 µg/ml concentration. The Muller Hinton agar used as a culture media. The zone of inhibition was measured in mm after 24 hrs of incubation at 37°C. Microbial data of synthesized compounds are summarized in Table-2.

Compounds 3c, 4b, 4c were found to be moderate antifungal activity for *candida sp.* (12-15mm). An observation of data showed that 4b and 4c have shown moderate activity for gram positive bacteria *Staphylococcus aureus* ATCC 25923 (10-14mm).

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VIII. TABLE-2

Antibacterial and Antifungal activities of some representative compounds

Compounds	<i>E-Coli</i> ATCC 25922	<i>Pseudomonas</i> <i>arruginosa</i> ATCC27853	<i>Staphylococcus</i> <i>aureus</i> ATCC 25923	<i>Candida</i> <i>sp.</i>
3a	--	--	--	--
3b	--	--	--	--
3c	--	--	12mm	10mm
3d	--	--	--	--
3e	--	--	--	--
3f	--	--	--	--
3g				--
4a	--	--	--	--
4b	--	--	13mm	14mm
4c	--	--	14mm	15mm
4d	--	--	--	--
4e	--	--	--	--
4f	--	--	--	--
4g	--	--	--	--
Gentamycin	23mm	24mm	23mm	--
Cefixime	28mm	--	15mm	--
Ketoconazole	--	--	--	23mm

IX. CONCLUSION

The procedure using ultrasound is very convenient, shortens the reaction time. That is 20 minutes in comparison to four to six hours by the usual procedure. Also the reaction proceeds in much cleaner way and afford higher purity of the products.

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