Piperidine as an Effective Catalyst for the Synthesis of Phenyl Substituted Pyrazoles Mediated as PEG - 600

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Abstract - An effective and convenient method has been developed for preparation of phenyl substituted pyrazole derivatives. The substituted pyrazoles derivatives were synthesized by two steps. In a first step, substituted chalcones were prepared by Claisen-Schmidt condensation using recyclablepolyethyleneglycol (PEG-600) asareactionmedium. This method hasthe advantages of accessible starting materials, good yields, mild reaction conditions and begin ecofriendly. In a second step, carried out to condensation between the substituted chalcones and hydrazine hydrate in the presence of piperidine.All compounds were characterized using UV-Visible, IR, [1]HNMR and MS techniques. The anti-microbial activities of compounds have also been tested using Minimum Inhibitory concentration (MIC) method with two different microorganisms Staphylococcusaureus (MTCC3381) and Escherichia coli (MTCC739). The results of the antimicrobial activity clearly shown that substituted chalcones have excellent activity than corresponding phenyl substituted pyrazole derivatives.

Keywords: Chalcones; Hydrazine Hydrate; pyrazole; piperidine; antimicrobial activity; PEG–600.

I. INTRODUCTION

Flavonoids comprise a large family of plant-derived poly-phenolic compounds classified as anthocyanidins, flavonols, chalcones, aurones, flavanones, isoflavones, flavans, flavanonols, flavanols and flavones differencing from each other in their structural group arrangements. Chalcone, an important intermediate of flavonoid synthetic pathway, has been shown to exhibit diverse biological and pharmacological activities such as anti- cancer, antioxidant, anti-inflammatory, antimicrobial, anti- allergic, and antimalarial properties [1-3].

The pyrazole ring system is a five-membered heterocyclic ring structure composed of two nitrogen atoms and used in the synthesis of pharmaceuticals. The pyrazole moiety is a versatile lead molecule in pharmaceutical development and has a wide range of biological activities. In the past few years, the therapeutic interest of pyrazole derivatives in pharmaceutical and medicinal field has been given a great attention to the medicinal chemist. Literature survey reveals that pyrazole derivatives are well known to have antibacterial [4], antifungal [5], antitubercular [6], anticancer [7], analgesic, anti- inflammatory [8], anticonvulsant [9], antidepressant [10] and anti-arrhythmic [11] activities. In recent years, the extensive studies have been focused on pyrazole derivatives because of their diverse chemical reactivity, accessibility and wide range of biological activities. The chalcones are the convenient intermediates for the synthesis five, six and seven membersheterocycles, often have exhibited diverse biological activity. Some pyrazoline derivatives were used as the bacteriostatic, fungicidal, and anticancer agents.

Recently, polyethylene glycol (PEG) has been found to be an interesting solvent system. PEG is an environmentally benign reaction solvent, it is inexpensive, potentially recyclable and water soluble, which facilitates its removal from there action product. Reducing or eliminating the use of volatile organic solvents can minimize the generation of waste, which is a requirement of one of the principles of green chemistry.Based on the careful analysis of the literature, present investigation focused on the PEG-600, the series of chalcones and diphenyl substituted pyrazoles compounds were synthesized. The synthesized compounds were characterized on the basis of UV-Visible, FTIR, [1]HNMR and mass spectral data. All the compounds were screened for their in vitro antibacterial activity against Gram positive strains (Staphylococcus aureus) and Gram negative strains (Escherichia coli) respectively.

II. EXPERIMENTAL

A. Methods and Materials

The chemicals 4-chloroacetophenone (1), 2-hydroxybenzaldehyde (2), hydrazine hydrate (3), PEG-600, sodium hydroxide and piperidine were obtained from Avra chemicals, Hyderabad and were used as such without further purification. Silica gel (TLC and Column grade) were purchased from Merck. The

solvents were purified as per the standard procedure reported elsewhere.

FTIR spectra (KBr pellets) were measured using Alpha Bruker FTIR instrument scanning with the entire region of 4000 - 400 cm^{-1} with typical resolution of 1.0 cm^{-1}. UV-Visible spectra were also recorder using Alpha Bruker UV spectrophotometer. The NMR spectra of the compounds have been recorded on Bruker AV400 spectrometer operating at 400 MHz for recording ^{1}HNMR spectra in DMSO solvent using TMS as internal standard. Mass spectra have been recorded on SHIMADZU spectrometer using chemical ionization technique. Melting points of all synthesized compounds have been determined in open glass capillaries on Mettler FP51 melting point apparatus and are uncorrected.

B. Synthesis

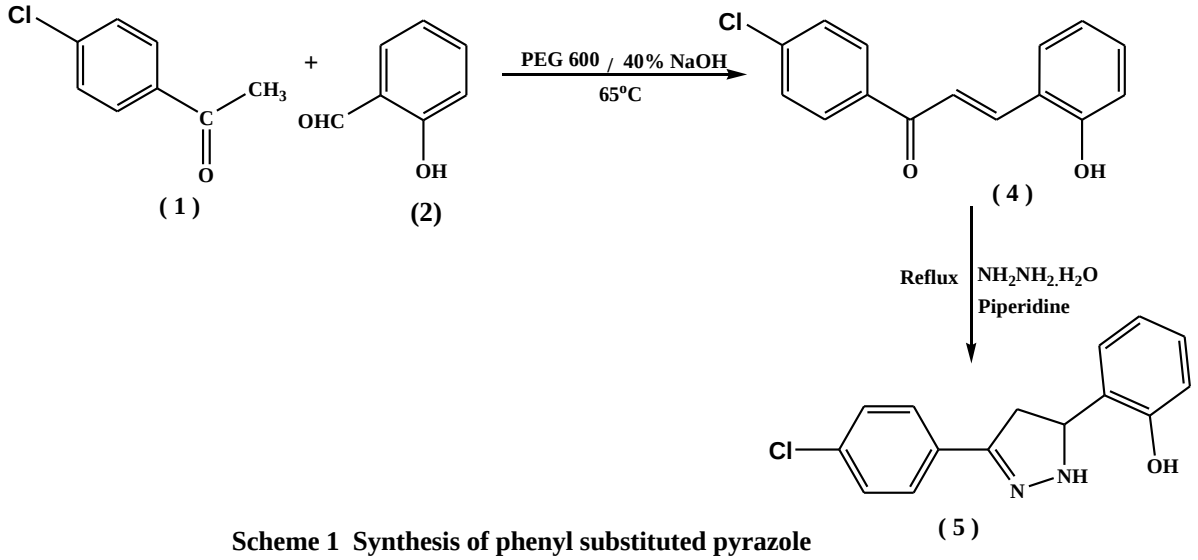
Step- 1: Synthesis of 1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (4)

A mixture of compounds 1 (1.54g, 0.01mol) and 2 (1.22g, 0.01mol) and NaOH (0.8g in 20mL, 0.02 mol) ethanol. (Yield – 85%& melting point: 145-146^{o}C) were stirred in PEG-600 (20mL) as solvent at 65^{o}C for 1 hour. The completion of the reaction was monitored by TLC and the crude mixture was worked up in ice-cold water (100mL). The product was separated out and filtered. The filtrate was evaporated to dryness to remove water leaving behind PEG-600. The recovered

PEG-600 has been utilized for the synthesis of chalcones. Synthesized compounds wererecrystallized from ethanol to afford pure compound (4). (Yield – 89%& melting point: 110-111^{o}C)

Step- 2: Synthesis of 2-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol (5)

A mixture of Compound (4) (2.58g, 0.01mol) in ethanol (20mL) was refluxed with hydrazine hydrate (0.32g, 0.01mol) in the presence of piperidine (2-3 drops) as catalyst for an hour. The completion of reaction was monitored by TLC. The reaction mixture was quenched by poured into ice-cold water. The product was separated out and filtered. A synthesized compound (5) was recrystallized from



Scheme 1 Synthesis of phenyl substituted pyrazole

III. RESULTS AND DISCUSSION

Spectral details of 1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (4)

Melting Point : 110-111^{o}C ;

UV-Visible ($\lambda_{max,}$ nm):227 ($\pi \rightarrow \pi^*$ transition), 67 ($n \rightarrow \pi^*$ transition)(Fig. 1);

FTIR (cm^{-1}):3438 (O-H), 2926 (Aromatic C-H str), 1271(-C-C str.), 1645(C=O), 1565 (C=C str), 826(C-H out plane bending. (Fig. 2);

^{1}H NMR (ppm): 6.25-6.54(dd,2H, CH=CH-)6.95-8.05 (m, 8H, Ar-H), 11.10 (s, 1H, Ar-OH)(Fig.3);

Mass (m/z): Calculated M.W 258.70, Observed M.W 259.06(M+1) (Fig. 4)

Spectral details of2-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol (5)

Melting Point :145-146^{o}C

UV-Visible ($\lambda_{max,}$ nm):229 ($\pi \rightarrow \pi^*$ transition), 269 ($n \rightarrow \pi^*$ transition)(Fig. 5)

FTIR (cm^{-1}):3337(O-H), 2911(Aromatic C-H str), 1589(C=N), 1333(-C=C-str.), 1087(C-N str.), 730(N-H bending vib.)(Fig. 6);

^{1}H NMR (ppm):2.50 to 3.01 (2H, m, -CH_2 protons-), 4.83 to 4.90 (q, 1Hmethine Protons adjacent to N-H), 6.8 to 6.89 (d, 1H, N-H), 6.87 to 7.89 (m, 8H, Ar-H), 11.11(s, 1H, Ar-OH) (Fig.7)

Mass (m/z):Calculated M.W 272.07, Observed M.W 273.3(M+1) (Fig. 8)

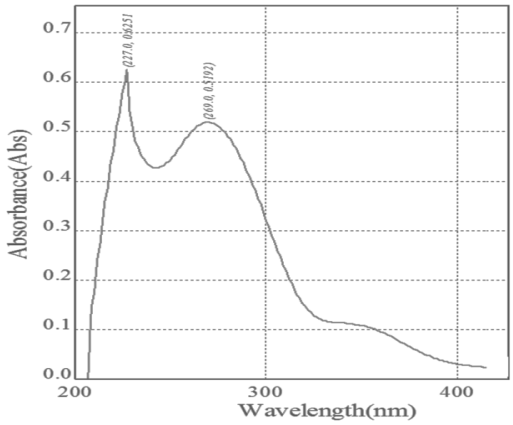


Fig. 1 UV-Vis. spectrum of 1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one

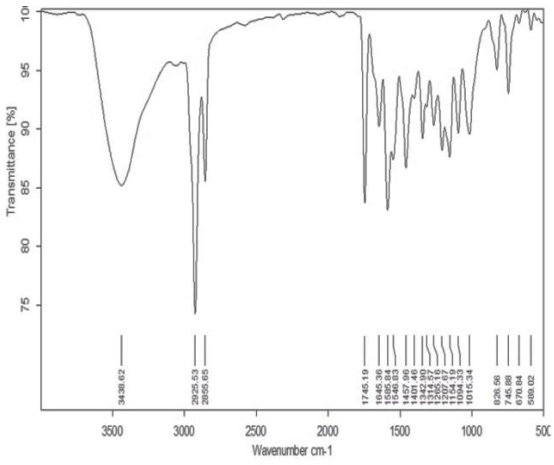


Fig. 2 FTIR spectrum of 1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one

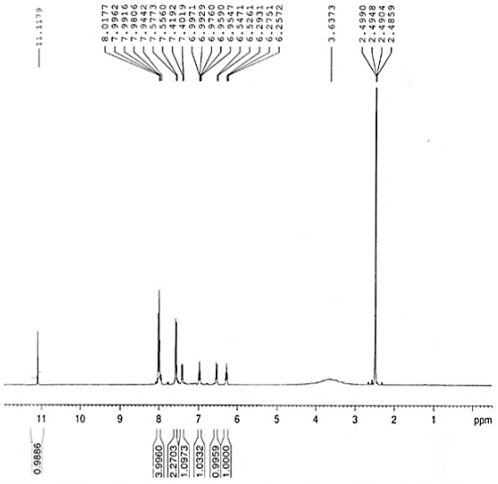


Fig. 3 ^{1}HNMR spectrum of 1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one

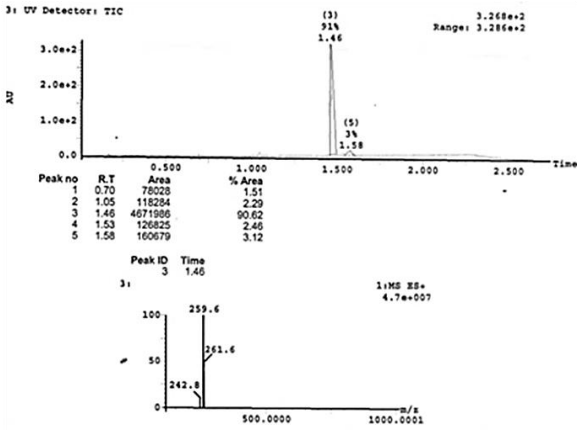


Fig. 4 Mass spectrum of 1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one

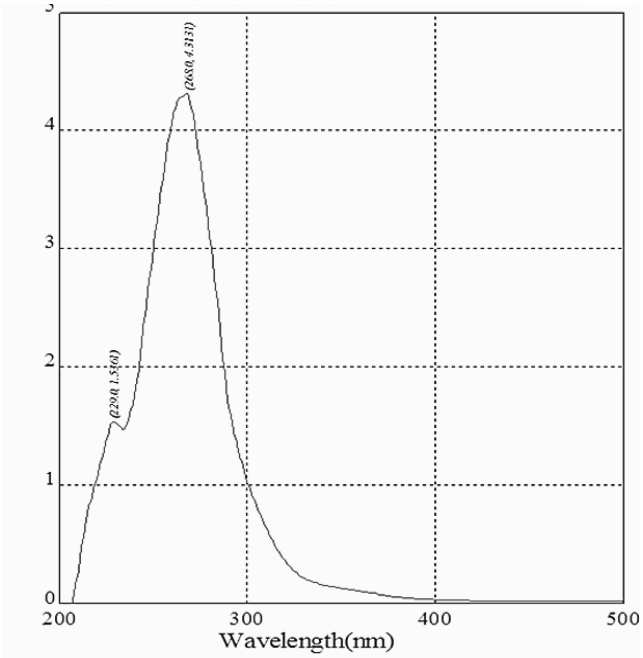


Fig. 5 UV-Vis. spectrum of 2-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol

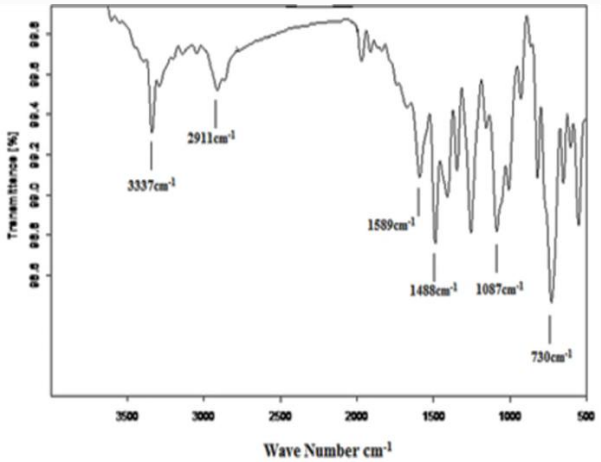


Fig. 6 FTIR spectrum of 2-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl) phenol

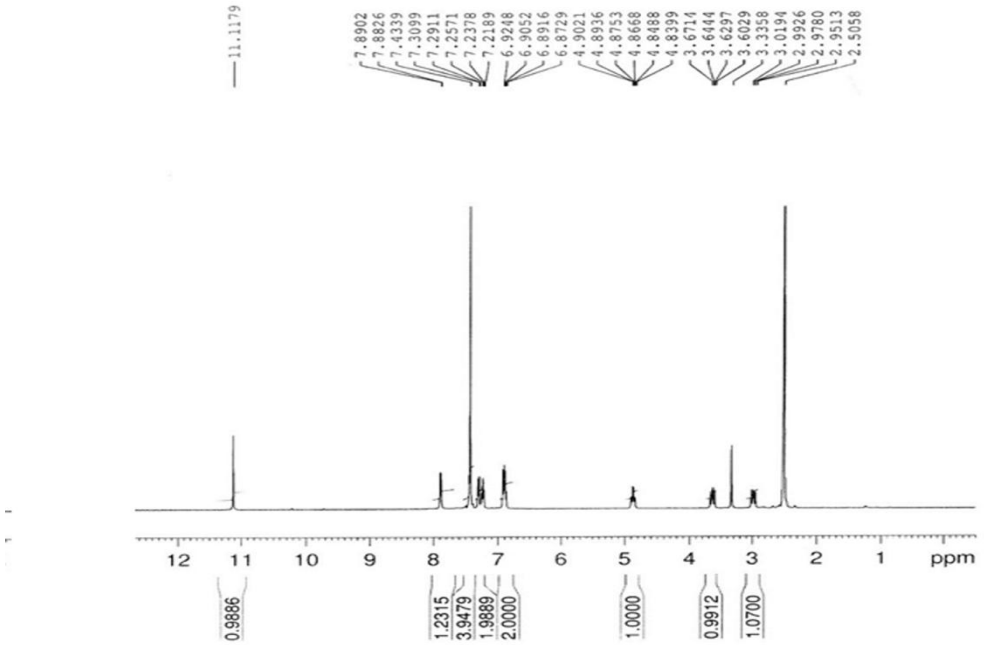


Fig. 7 ^{1}HNMR spectrum of 2-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol

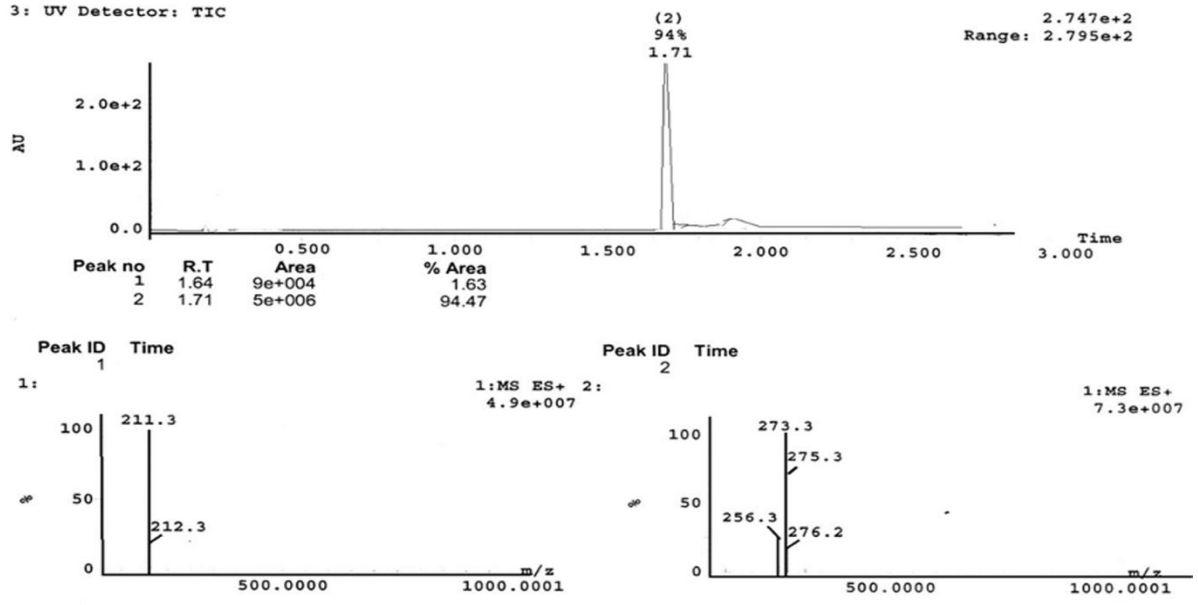


Fig. 8 Mass spectrum of 2-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol

Figure (1-4) revealed the UV absorption, FTIR, ^{1}HNMR and Mass spectra of 1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one(4)respectively using compound 1, and 2 in the presence of sodium hydroxide has been shown in the scheme 1. Figure(5-8) revealed the UV absorption, FTIR, ^{1}HNMR and Mass spectra of2-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol(5)respectively using compound 4 with compound 3 in the presence of piperidine as catalyst has also been presented in the scheme 1.

UV absorption and FTIR spectra of compound 4 has been provided a preliminary idea in confirmation the formation of product. According to the UV spectrum, represented in Figure (1), presence of peaks at 227 and 267 nm clearly showed that the compound (4) has -CH=CH- group and hetero atom respectively. According to the FTIR, represented in Figure (2), presence of peak at 1580 cm^{-1} has clearly noticed the utilization of starting materials transforms into the product. Further, the corresponding peaks at 3438, 2926, 1645, 1565 and 826cm^{-1} have been related to –OH, aromatic C-H, carbonyl (C=O), C=C stretching and C-H out of plane bending vibrations respectively in the compound 4. The concerned mass of compound 4is in good agreement with the observed (258.708m/z) and

calculated value (259.06 m/z) were mentioned in the figure (4). Similarly, proton NMR strongly empowered for the formation of the product by its δ value at 11.10, 6.95-8.05, and 6.25-6.54 ppm corresponding to the O-H, Ar-H and CH=CH protons of compound 4 were mentioned in Figure (3).

UV absorption and FTIR spectra of compound 5 has provided a preliminary idea in confirmation the formation of product. According to the UV spectrum of compound 5, presence of peaks at 229 and 269 nm has been related to aromatic double bond and hetero atom respectively shown in Figure (5). According to the FTIR, represented in Figure (5), absence of peak at 1645 cm^{-1} clearly observed the complete utilization of starting materials transformed into the product. Further, the corresponding peaks at 3337, 2911, 1589, 1333 and 824 cm^{-1} for –OH, C-H aromatic stretching, C=N stretching, C=C stretching and N-H bending vibrations respectively in the compound 5. All such stretching and bending peaks have also been supported for the formation of the product. The concern mass of compound 5 are in good agreement with the observed (272.07 m/z) and calculated value (273.3 m/z) were mentioned in the Figure (8). Similarly, proton NMR strongly empowered for the formation of the product by its δ value at 11.11, 6.87-7.89, 6.8-6.689, 4.83 - 4.90 and 2.50-3.01 ppm corresponding to the O-H, Ar-H, N-H, C-H and CH_2 protons of compound 5 were mentioned in Figure (7).

IV. ANTIMICROBIAL ACTIVITY

The minimum inhibitory concentration (MIC), which is considered as the least concentration of the sample which inhibits the visible growth of a microbe was determined by the broth dilution method. The compounds 5 and 6 were adopted for broth dilution method to evaluate the MIC values. The MIC values are given in the following table.

Table – 1: Minimum Inhibiting Concentration (MIC) (μg/ml) of the synthesized compounds

Compounds	Staphylococcus aureus (S. a)	Escherichia coli (E. c)
4	15.63	31.25
5	31.25	62.50

V. CONCLUSIONS

In the present work phenyl substituted pyrazole derivatives were prepared successfully by Claisen-Schmidt condensation using PEG 600 as solvent. Generally most of the researchers have been synthesized chalcones using alcohol as solvent and catalyst like KOH or NaOH. While synthesizing the chalcones alcohol as solvent which is generated as organic waste. But, in our work the chalcones have been synthesized using PEG-600 as solvent, which is, eco-friendly,and non-toxic, inexpensive, water soluble and recyclable. Hence, chalcones were synthesized via green chemistry protocol (Step1).

In the Step 2, the chalcones were condensed with hydrazine hydrate in presence of piperidine as catalyst has shown in scheme. Use of piperidine as catalyst in the synthesis the phenyl substituted pyrazole derivatives have been achieved by shorter reaction time, whereas without the catalyst, the reaction was progressed more than eight hours. The chemical structures of compounds 4and 5 have been confirmed using various spectral techniques viz., FTIR, UV-Visible, Mass and ^{1}H-NMR spectra and were found to be in agreement with the chemical structures expected.

The microbial activities substituted chalcones and phenyl substituted pyrazole derivatives were checked against the two microbes Staphylococcus aureus and Escherichia coli.The report of antimicrobial activity clearly shown that, the synthesized compound 4has excellent inhibiting activity against both bacterial strains than the corresponding chalcones.

VI. REFERENCES

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