Studies of 3,5 Diphenylpyrazoles using Piperidine as Catalyst –Synthesis and Characterisation

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ABSTRACT**: An efficient and convenient synthesis of 3,5-diphenylpyrazoles from chalcones using piperidine catalyst is reported in two stages. First stage was achieved through Claisen-Schmidt condensation using green approach. The second stage was dedicated to the condensation among chalcones and hydrazine hydrate in the presence of piperidine as catalyst. The progress of the reaction was monitored by TLC and separated the compound using column chromatography. The synthesized compounds were subjected to various characterization viz., UV-Visible, FT-IR, ^{1}H-NMR and Mass spectra. The anti-microbial activities of compounds have also been tested using Minimum Inhibitory concentration (MIC) method with two different microorganisms (*Staphyloccocous aures* (MTCC3381), and *Escheriochia coli* (MTCC739). The results of the antimicrobial activity revealed that the 3, 5-diphenyl substituted pyrazole derivatives have moderate inhibiting nature against both types of bacteria than corresponding chalcones (Gram-positive and Gram-negative).**

KeyWords: Chalcones; pyrazol; piperidine; antimicrobial activity; PEG–600; Hydrazine Hydrate

I. INTRODUCTION

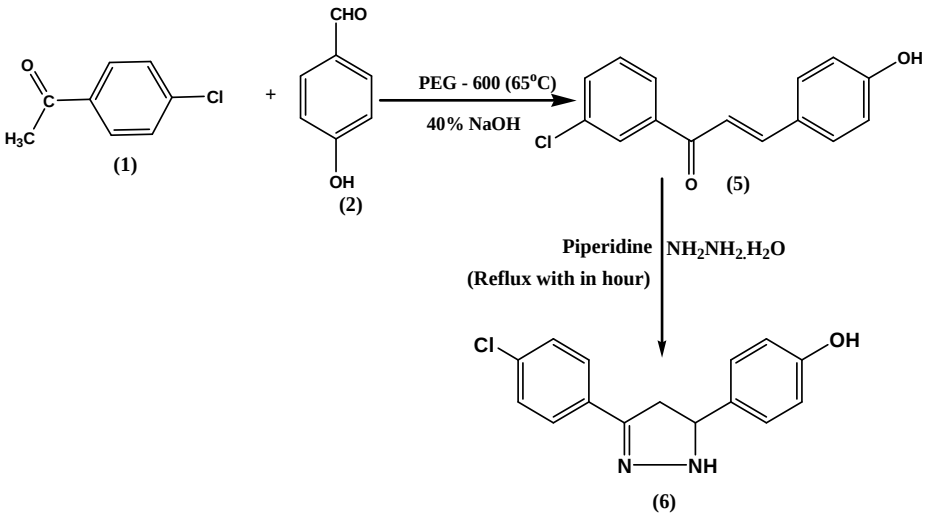
Chalcones comprise a class of compounds with important therapeutic potential. The ease of preparation, the potential of oral administration [1-2] and safety [3] also support the feasibility of chalcone-based compounds as therapeutic agents. Compounds with chalcone-based structure have shown an array of pharmacological activities, such as antiprotozoal [4-5], antifungal [6], anti-inflammatory [7], antileishmanial [8-9], nitric oxide inhibition [10], inhibition of the production of interleukin-1 [11], and anticancer activities [12]. Pyrazoles [13] are also important heterocyclic compounds due to their biological activities [14]. They have been reported to show anti-tumor activity [15], ACE-Inhibitory activity [16], antimicrobial [17] and anti-inflammatory [18], along with other biological activities.

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. Recently, polyethylene glycol (PEG) has been found to be an interesting solvent system. PEG is an environmentally benign reaction solvent, it is an inexpensive, potentially recyclable and water soluble, which facilitates its removal from there action product. Based on the careful analysis of the literature, present investigation focused on the PEG-600 mediated synthesis of chalcone which on further cyclization with hydrazine hydrate resulting substituted 3,5-diphenyl pyrazole.

II. Experimental

A. Methods and Materials

The chemicals 4-chloroacetophenone **1,** 4-hydroxybenzaledehyde **2,** PEG-600 **3**, hydrazine hydrate **4**, 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 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 1H 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.



Scheme - 1 : Piperidine catalysed synthesis of 3,5-diphenylpyrazoles

B. Preparation of (E)-1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5)

A mixture of 4-chloroacetophenone (0.01mol) and 4-hydroxy benzaldehyde (0.01mol) and NaOH (0.02 mol) 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 (100 mL). 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 were recrystallized from ethanol to afford pure compound (5). (Yield – 95% & melting point: 92-93^{o}C).

C. Preparation of 4-(3-(3-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol (6)

A mixture of Compound (5) (0.01mol) in ethanol (20mL) was refluxed with hydrazine hydrate (0.01mol) in the presence of piperidine 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 (6) was recrystallized from ethanol. (Yield – 90% & melting point: 110-111^{o}C)

III. Results and Discussion

Spectral details of (E)-1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5)

UV (λmax: nm): 230 (* transition), 345 (* transition) **(Figure – 1)**

FTIR (cm^{-1}): 3222 (O-H), 3029 (Aromatic C-H str), 2899 (C-H), 1677 (C=O), 1580 (C=C str), 1089 (C-Cl chloro aromatic), 815 (C-H out plane bending) **(Figure – 2)**

1H NMR (ppm): 6.8 - 6.9 (2d, 2H, -C**H**=C**H**-), 7.41-8.08 (m, 8H, Ar-**H**), 10.45 (s, 1H, Ar-O**H**) **(Figure – 3)**

Mass (m/z): Calculated M.W 258.0448.402, Observed M.W 259.6 (M+1)

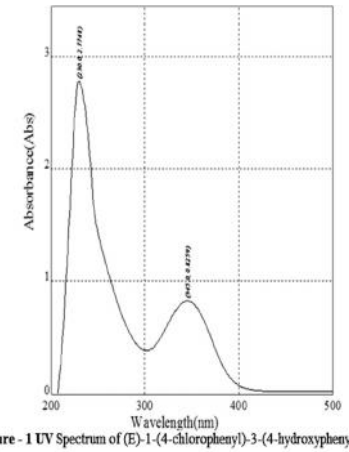


Figure - 1 UV Spectrum of (E)-1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one

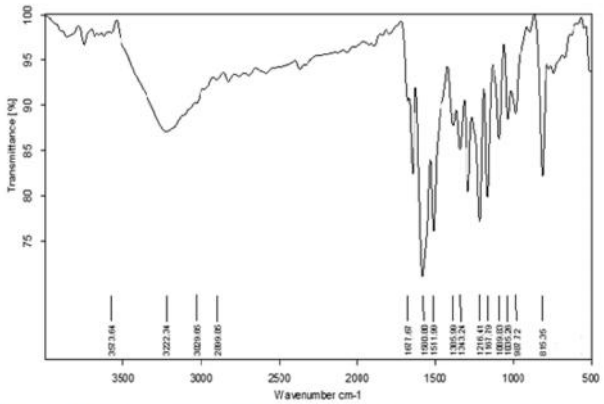


Figure - 2 FTIR Spectrum of (E)-1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one

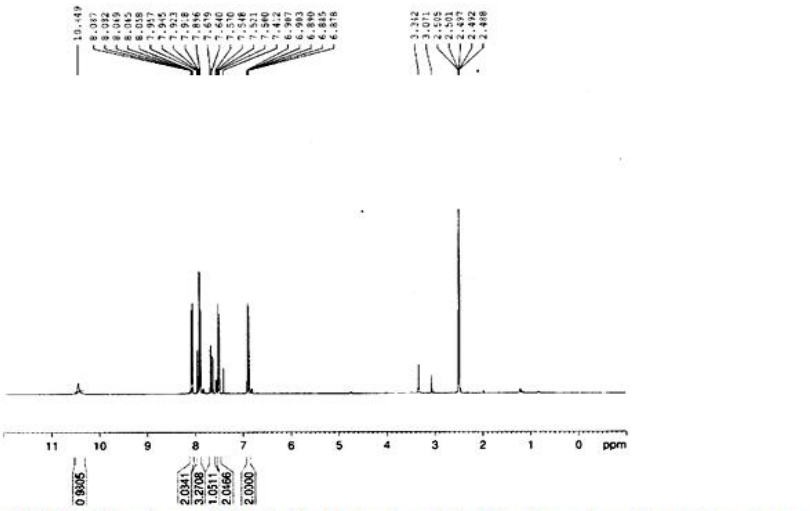


Figure - 3 1HNMR Spectrum of (E)-1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one

<u>Spectral details of 4-(3-(3-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol (6)</u>

UV (λmax: nm): 229, 268 **(Figure – 4)**

FTIR (cm^{-1}): 3284(O-H), 2938(Aromatic C-H str), 1652(C=N),
1091(C-Cl chloro aromatic), 824(N-H bending vib) **(Figure – 5)**

1H NMR (ppm): 2.48 to 3.42 (2H, (m, -C**H**$_2$ protons-), 4.7 to 4.77 (q, 1H C-**H** Protons adjacent to N-H), 6.62 to 6.626 (d, 1H, N-**H**) 6.72 to 7.63 (m, 8H, Ar-**H**), 9.35(s, 1H, Ar-O**H**) **(Figure – 6)**

Mass (m/z): Calculated M.W 272.07, Observed M.W 273.2 (M+1)

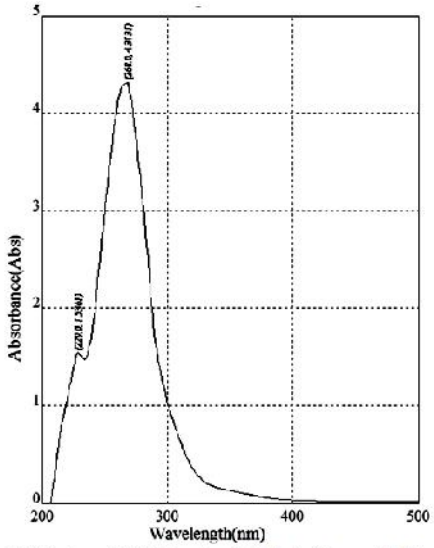


Figure - 4 UV Spectrum of 4-(3-(3-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol

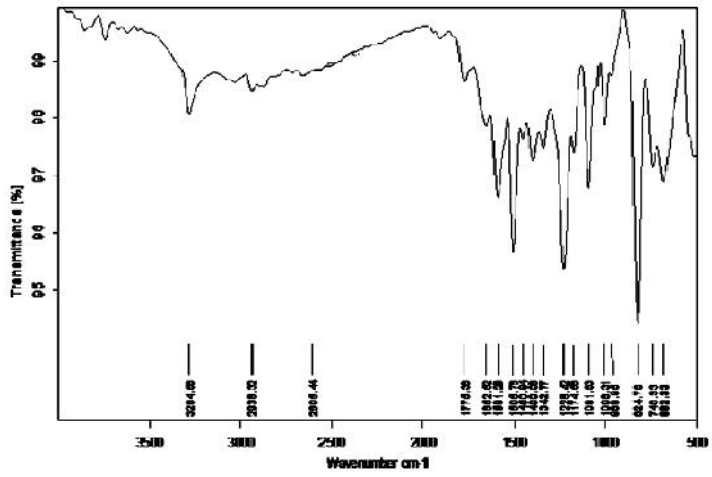


Figure -5 FTIR Spectrum of 4-(3-(3-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol

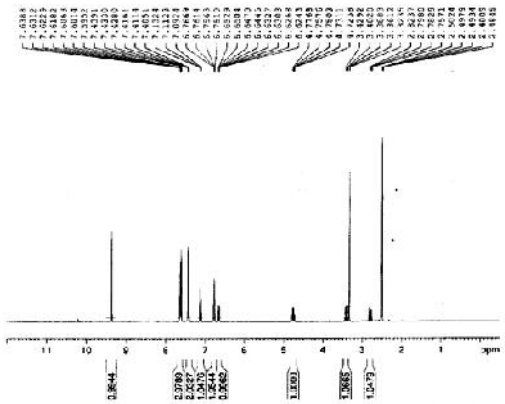


Figure -6 1HNMR Spectrum of 4-(3-(3-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol

Figure (**1-3**) revealed the UV absorption, FTIR and 1HNMR spectra of (E)-1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one respectively using compound **1,** and **2** with compound **3** in the presence of sodium hydroxide has been shown in the scheme 1. **Figure** (4-6) revealed the UV absorption, FTIR and 1HNMR spectra of 4-(3-(3-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol respectively using compound **5** with compound **4** in the presence of piperidine as catalyst has also been presented in the scheme 1.

UV absorption and FTIR spectra of compound **5** 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 230 and 345 nm clearly showed that the compound (**5**) 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 3222, 3029 and 2899, 1677 cm^{-1} have been related to –OH, C-H aromatic stretching and aliphatic C-H stretching respectively in the compound **5**. The concerned mass of compound **5** is in good agreement with the observed (258.0448m/z) and calculated value (259.2 m/z). Similarly, proton NMR strongly empowered for the formation of the product by its δ value at 10.45, 7.41-8.8, and 6.8-6.9 ppm corresponding to the O-H, Ar-H and –CH=CH- protons of compound 5 were mentioned in Figure (**3**).

UV absorption and FTIR spectra of compound **6** 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 268 nm has been related to aromatic double bond and hetero atom respectively (shown in Figure (**4**)). According to the FTIR, represented in Figure (**5**), absence of peak at 1677 cm^{-1} clearly observed the complete utilization of starting materials transformed into the product. Further, the corresponding peaks at 3284, 2938, 1652 and 824 cm^{-1} for –OH, C-H aromatic stretching, C=N stretching and N-H bending vibrations respectively in the compound **6**. All such stretching and bending peaks have also been supported for the formation of the product. The concern mass of compound **6** are in good agreement with the observed (272.07 m/z) and calculated value (273.2 m/z). Similarly, proton NMR strongly empowered for the formation of the product by its δ value at 9.35, 6.72-7.63, 6.62-6.626, 4.7 - 4.77 and 2.48-3.42 ppm corresponding to the O-H, Ar-H, N-H, C-H and CH_2 protons of compound **6** were mentioned in Figure (**6**).

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: Sample Minimum Inhibiting Concentration **(MIC)** (μg/ml)

Compounds	***Satphylococcus aureus (S. a)***	***Escherichia coli (E. c)***
5	**7.81**	**15.63**
6	15.63	31.25

V. CONCLUSIONS

In the present work 3,5-diphenyl substituted pyrazol derivatives were prepared successfully by Claisen-Schmidt condensation using green synthetic method. Generally most of the researchers have been synthesized chalcones using alcohol as solvent and catalyst like NaOH or KOH. Synthesis of chalcones by using alcohol has generated vast organic solvent as waste and which cannot reuse again. But, in our work the chalcones have

been synthesized using PEG-600 as solvent, which is non-toxic, eco-friendly, inexpensive, water soluble and potentially recyclable. Hence, chalcones were synthesised via green approach (Stage I).

In the Stage 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 pyrazole is a time consuming process whereas without the catalyst, the reaction was progressed more than eight hours. The chemical structures of compounds **5** and **6** have been confirmed using various spectral techniques viz., FTIR, UV-Visible, Mass and 1H-NMR spectra and were found to be in agreement with the chemical structures expected.

The microbial activities substituted chalcones and 3,5-diphenyl substituted pyrazole derivatives were checked against the two microbes ***Staphylococcus aureus and Escherichia coli.*** The report of antimicrobial activity clearly showed that, the synthesized compounds of 5 and **6** has moderate activities towards the tested bacterial strains of both gram positive and gram negative than the corresponding chalcones.

VI. REFERENCES

[1] L.W. Wattenberg, J. B. Coccia, A. R. Galbraith, Cancer Lett., Vol. 83, pp. 165–169, 1994.
[2] M. Baba, R. Asano, I. Takigami, T. Takahashi, M. Ohmura, Y. Okada, H. Sugimoto, T. Arika, H. Nishino, T. Okuyama, Biol. Pharm. Bull. 25, pp.247-25, 2002.
[3] R. J. Phillpotts, G. Higgins, J. S. Willman, D.A. Tyrrell, I. Lenox-Smith, J. Antimicrob.Chemother, 14, pp. 403-409, 1984
[4] R. Li, G. L. Kenyon, F. E. Cohen, X. Chen, B. Gong, J. N. Dominguez, E. Davidson, G .Kurzban, R. E. Miller, E. O. Nazum, P. J. Rosenthal, J. H. McKerrow, *J. Med.Chem.*, 38, pp.5031-5037, 1995
[5] M. Liu, P. Wilairat, M. L. Go, *J. Med. Chem.*, 44, pp. 4443-4452, 2001
[6] S. N. Lopez, M. V. Castelli, S. A. Zacchino, J. N. Dominguez, G. Lobo, C. C. Jaime, J. C. G. Cortes, Ribas, J. C Devia, M. R. Ana, D. E. Ricardo, *Bioorg. Med.Chem.*, 9, pp. 1999-2013, 2001
[7] S. J. Won, C. T. Liu, L. T. Tsao, J. R. Weng, H. H . Ko, J. P. Wang, C. N. Lin, *Eur.J. Med. Chem.*, 40, pp. 103-112, 2005.
[8] M. Chen, S. B. Christensen, T. G. Theander, A. Kharazmi, , *Antimicrob. AgentsChemother.*, 38, pp. 1339-1344, 1994.
[9] O.Kayser, A. F. Kiderlen, *Phytother. Res.*, 15, pp. 148-152, 2001.
[10] J.Rojas, J. N. Dominguez, J. E. Charris, G. Lobo, M. Paya, M. L Ferrandiz., *Eur. J.Med. Chem.*, , 37, pp. 699-705, 2002.
[11] D. G. Batt, R. Goodman, D. G .Jones, J. S. Kerr, L. R. Mantegna, C .McAllister,R.. C .Newton, S. Nurnberg, P. K.Welch, M. B. Covington, *J. Med. Chem.*, 36, pp. 1434-1442, 1993.
[12] S. Shibata, *Stem Cells*, 12, pp. 44-52, 1994.
[13] A. Schmidt, A. Dreger, *Curr. Org. Chem.*, 15, pp. 1423-1463, 2011.
[14] A. Hauhan, P. K. Sharma, N. Kaushik, *Int. J. Chem.Tech. Res.*, 3, pp. 11-17, 2011.
[15] P.–C. Lv, H.-Q. Li, J. Sun, H.-L. Zhou, *Bioorg. Med. Chem* , 18, pp. 4606-4614, 2010.
[16] M .Bonesi, M. R. Loizzo, G. A. Statti, S. Michel, F. Tillequin, F. Menichini, *Bioorg.Med. Chem. Lett.*, 20, pp.1990-1993, 2010
[17] S. Sahu, M. Banerjee, A. Samantray, , C. M. BeheraAzam, *Trop. J. Pharm. Res.*, 7, pp. 961-968, 2008
[18] A. K. Tewari, P. Srivastava, V. P . Singh, A. Singh, R. K. Goel, C. G. Mohan, *Chem.Pharm. Bull.*, 58, pp. 634-638, 2010.