DESIGN AND FACILE SYNTHESIS OF PHENYL SUBSTITUTED PYRAZOLE DERIVATIVES AND ITS BIOLOGICAL ACTIVITIES

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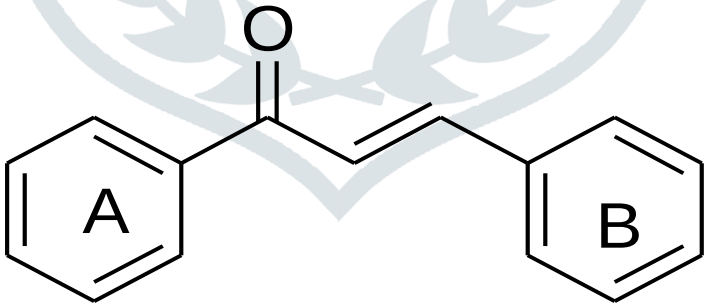
Abstract

A series of phenyl substituted pyrazole derivatives demonstrate a wide range of biological and Pharmacological activities. They are found to be as effective as local anesthetics, antibacterial, anti-malarial, anti-protozoal, anti-tubercular, anticancer, cardiovascular, antiulcer and antifungal agents. These different properties of chalcones have prompted us to synthesize them in order to study their medicinal and biological activities. In this study, a series of substituted pyrazole linked chalcones were synthesized by 4-hydroxybenzaldehyde, 4-nitroacetophenone, 4-chloroacetophenone, hydrazine hydrate and PEG-600. The synthesized compounds were characterized by FT-IR, UV-Visible, and ^{1}H NMR techniques. The purity of the synthesized compounds was monitored by TLC and tested for their antimicrobial activity by Minimum Inhibitory Concentration (MIC) method against two different microorganisms (Staphylococcus aureus and Escherichia coli. The antimicrobial activities of the synthesized compounds of pyrazole derivatives are more active than the corresponding chalcones.

Keywords: Substituted chalcone derivatives, Pyrazole, Antimicrobial activity, MIC.

1. Introduction

In the series of chemistry, Chalcones has generated intensive scientific and systematic studies throughout the universe. Especially interest has been focused on the synthesis of biodynamic and biological activities of chalcones [1]. In Chalcones, two aromatic rings are linked by an aliphatic three carbon chain and one carbonyl group is present. Chalcone bearing a very good synthon so that variety of heterocycles with good medicinal and biological profile [3] can be designed Chalcones are unsaturated ketone containing the reactive keto- ethylenic group -CO-CH=CH-. These are coloured Compounds because of the presence of the chromophores -CO-CH=CH-, which depends on the presence of other auxochromes [4].



In the past, many decades since penicillin was discovered and introduced as a powerful antibacterial agent [5], antibiotics [6] have become critical in the strong fight against infectious diseases caused by bacteria, Fungi, malarial and other microbes. However, widespread antibiotic use has promoted the emergence of antibiotic-resistant pathogens [7], including multidrug resistant strains. At present, the appearance of more and more pathogenetic bacterial species resistant to conventional antibiotics has resulted in either high expenses or failure in the treatment of infectious diseases. A causing fear increase in resistance of bacteria that cause community acquired infections has also been documented, especially in Staphylococci and Pneumococci [8], which are prevalent causes of disease and mortality. In addition, the risk of opportunistic bacterial, fungal, malarial infections increases [9] rapidly accompanied with AIDS disease, and as an obviously consequence invasive infections represent a major cause of mortality for these patients. With the emergence of new microbial strains resistant to many conventional available antibiotics there is growing interest in the drug discovery of new antibacterial agents. According to the known structure and activity relationships, it is considered that certain small heterocyclic molecules act as highly functionalized scaffolds [10] and are known pharmacophores and microphores of a number of biologically active and medicinally useful molecules.

Chalcones (1, 3-diarylpropinones) are natural substances found in a number of plants or synthetically prepared. They display many biological activities such as antimicrobial [11], anti-inflammatory [12], antiviral, antitumor, Cytotoxic [13], analgesic and antipyretic [14] properties. They also act as potential anti-ulcer, antifungal, anticancer [15] and antimalarial agents. In addition compounds are of a high interest due to their use as starting compounds in the synthesis of a series of heterocyclic compounds

like pyrazoline, imidazoline, thiadiazine, benzodiazepine, benzofuranones, benzohydroxychromens, flavones etc., Moreover, these are important precursors in many addition reactions of nucleophiles due to inductive polarization of carbonyl group at the alpha position. Several strategies for the synthesis of these systems based on the formation of carbon-carbon bond have been already reported. Among them the direct aldol condensation and Claisen-Schmidt condensation still involve prominent positions. The main method for the synthesis of Chalcones is Claisen-Schmidt condensation in the presence of aqueous alkaline bases like NaOH, KOH, and K_2CO_3.

Pyrazole derivatives have been developing to be active as pathogenic, antibiotonic agents. The pyrazole derivatives may be used as bacterial, fungicidal, Insecticidal, herbicidal activities. The pyrazole derivatives also show antitubercular, antitumor, antipyretic, antidiabetic, analgesic, antimicrobial, anti-inflammatory, antimalarial, anticancer properties. Pyrazole derivatives are extensively employed in photography as colour couplers, sensitizers, supersensitizers, colour filter antihalation agents. The most important commercial use of pyrazoles is as dyes. It is also useful for colouration of paints, lacquers, and varnishes, natural and synthetic polymers and ink, multi colour inkjet printing, hair dying creams and anti- inhalation layers of photographic materials.

2. Experimental details

2.1. Materials and characterization

3-hydroxybenzaldehyde and 4-hydroxybenzaldehyde and 4-chloro and 4-nitroacetophenone were purchased from Sigma Aldrich, India. Sodium Hydroxide and PEG-600, Ethanol, Hydrazine Hydrate was purchased from Avra, Chemicals, Hyderabad. Pre-coated Silica gel plate was purchased from Merck (TLC purpose).The melting point of the synthesized compounds was determined in open capillary tubes and were found uncorrected. IR spectra were recorded on FT-IR spectrometer (Alpha -Bruker) using KBr disc Method. UV-Visible spectra were recorded on a UV-Visible spectrometer (Alpha- Bruker) ^{1}H NMR and spectra were recorded on BRUKER F01300mHz spectrophotometer by using CDCl3 and DMSO as a solvent. The purity of the compounds is checked by TLC plates (Merck) using hexane and ethyl acetate.

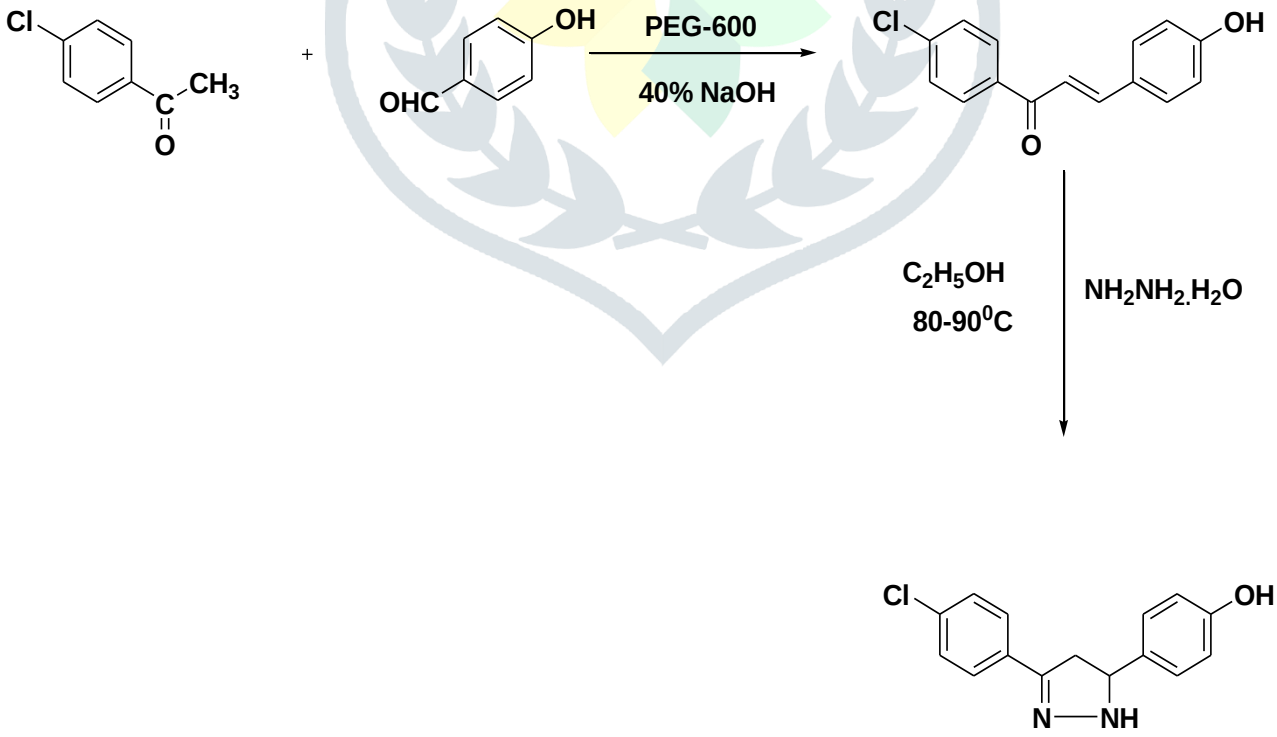
2.2. Synthesis

2.2.1. Step-1: Synthesis of chalcones by PEG-600 as recyclable solvent (RI1)

4-Chloroacetophenone (0.01mol) and 4-hydroxybenzaldehyde (0.01mol) and NaOH (0.02 mol) was stirred in PEG-600 (15 mL) for 1 hour at 65ºC. After completion of the reaction (monitored by TLC), the crude mixture was worked up in ice-cold water (100 mL). The product which separated out was filtered. The filtrate was evaporated to remove water leaving PEG behind. The same PEG was utilized to synthesize further chalcones (Yield – 95%).

2.2.2. Step-2: Synthesis of pyrazole derivatives from chalcones (RI1A)

A mixture of Chalcone (0.01 mol) in 25ml of absolute alcohol, add hydrazine hydrate (0.01 mol) was refluxed in an oil bath at a temperature 80-90ºC for 8 hours. Then the reaction mixture poured into ice. The product was isolated and crystallized from ethanol. The separated product purified by column chromatography using 60-120 silica gel mesh size using hexane and ethyl acetate as an eluent. A synthesized compound was recrystallized from ethanol. (Yield – 80%). The synthesis scheme is given below,



3. Results and discussion

The Claisen-Schmidt condensation is an important C-C bond formation for the synthesis of 1,3-diaryl-2-propane-1-ones (chalcones). It is generally carried out of the use of strong bases such as NaOH or KOH in polar solvents like Ethanol or Methanol or DMF. The aim of my present study was to develop an efficient protocol using PEG-600 as a recyclable reaction solvent to obtain chalcones with excellent yields in a short period of time without formation of any side product and the same time the solvent can be reused again and again by embrace the recycling process and environmentally safe. In the second step, Chalcones are condensed with hydrazine hydrate to produce hydrazine substituted chalcones namely phenyl substituted pyrazole. The yields of the synthesized compounds of pyrazole were finding to be significant. The structure of the synthesized compounds

was identified by IR and UV-Visible spectroscopy and confirmed by ^{1}HNMR spectroscopy. All the compounds give the characteristic IR and absorption peaks that proved that the presence of a particular functional group and ^{1}HNMR spectrum helps to find the structure of synthesized compounds.

3.1. Interpretation of 1-(4-chlorophenyl)-3-(4-hyroxyphenyl)prop-2-en-1-one

It is a crystalline yellowish solid. This compound were synthesized by mentioning the procedure of Step – I. The formation of product was confirmed by Thin-Layer chromatography. The following datas are mentioned in Table 1.

Table 1. Interpretation of spectrum to 1-(4-chlorophenyl)-3-(4-hyroxyphenyl)prop-2-en-1-one(RI1)

UV (λ max: nm)	(CH=CH) 227 & (C=O) 269
FTIR (cm^{-1})	3107 (O-H), 744 (Aromatic C-Cl str), 2899 (C-H), 1744 (C=O), 1605 (C=C str), 856(C-H out plane bending)
^{1}H NMR (ppm)	6.25 - 6.29 (2d, 2H, -CH=CH), 6.95-8.0 (m, 8H, Ar-H),11.10 (s, 1H, Ar-OH)

3.1.1. Interpretation of UV-Visible spectrum of 1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one

UV peak appear at 227 nm (CH=CH) conforms the $\pi \rightarrow \pi^*$ transition of aliphatic double bond and peak at 269 nm (C=O) is due to $n \rightarrow \pi^*$ transition of carbonyl group. The UV-Visible spectrum of compound-C1 was shown in the Fig.1.

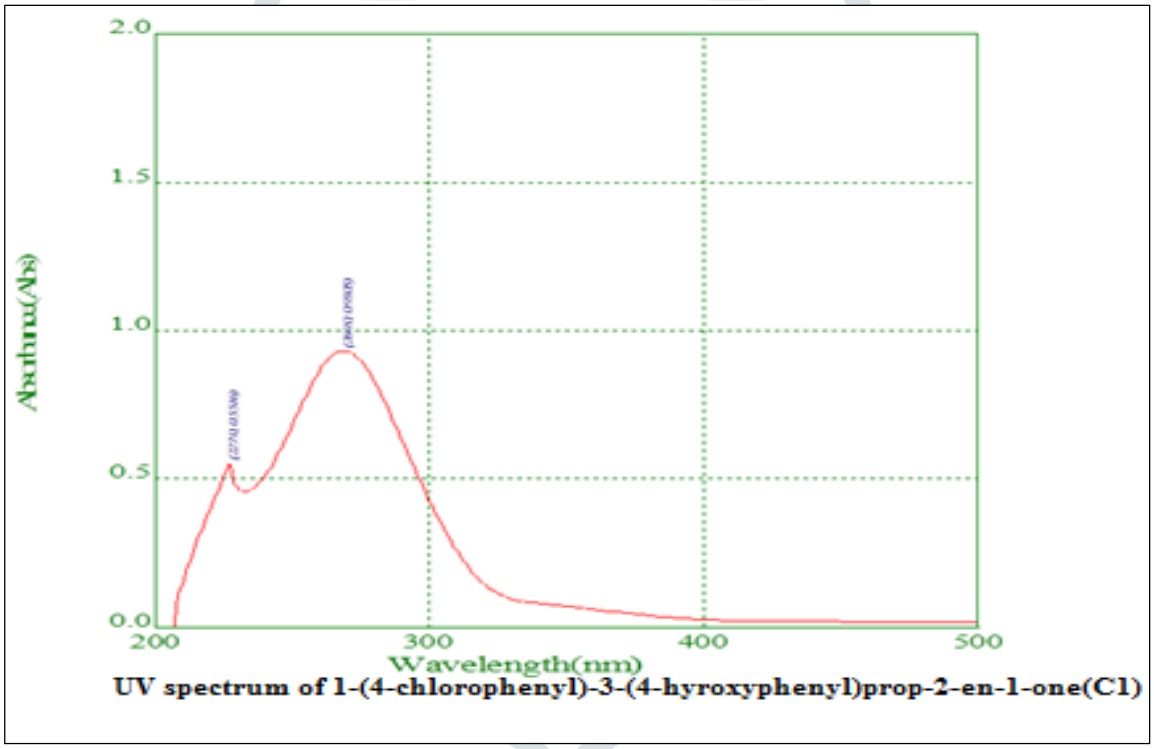


Fig. 1. UV spectrum of 1-(4-chlorophenyl)-3-(4-hyroxyphenyl)prop-2-en-1- one(RI1)

3.1.2. Interpretation of IR spectrum of 1-(4-chlorophenyl)-3-(4-hyroxyphenyl)prop-2-en-1-one

The FT-IR spectrum of the 1-(4-chlorophenyl)-3-(4-hyroxyphenyl)prop-2-en-1-one were shown in Fig. 2. The melting point of the plain chalcone is 90-92°C. A band at 3107cm^{-1} indicates the presence of the C-H aromatic stretching .A band at 1744cm^{-1} indicates the compounds which consists of carbonyl as functional group(C=O). A band at 1605cm^{-1} indicates the presence of the C=C stretching in the Aromatic ring and a band at 1253cm^{-1} indicates the presence of the C-C stretching. A band at 856cm^{-1} indicates C-H out-of-plane bending vibrations. The broad absorption peak at 3441cm^{-1} due to the OH stretching vibration. A band at 744cm^{-1} indicates C-Cl stretching vibration.

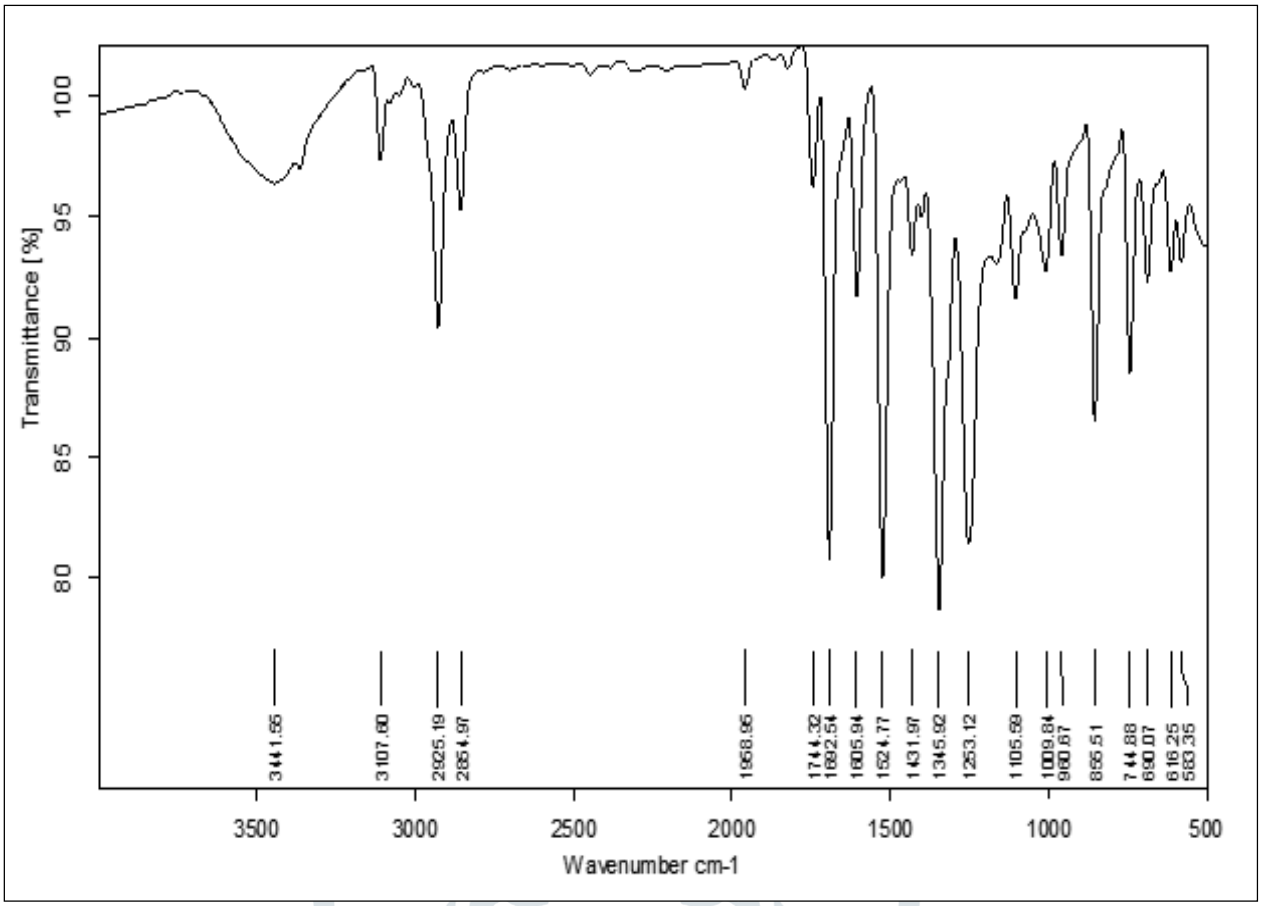


Fig. 2. FTIR Spectrum of1-(4-chlorophenyl)-3-(4-hyroxyphenyl)prop-2-en-1- one(RI1)

3.1.3. Interpretation of proton NMR spectrum of 1-(4-chlorophenyl)-3-(4-hyroxyphenyl)prop-2-en-1-one)

The ^{1}HNMR spectrum of 1-(4-chlorophenyl)-3-(4-hyroxyphenyl)prop-2-en-1-one was shown in Fig. 3. The DMSO or $CDCl_3$ is used as a solvent and TMS used as internal standard. The protons in the vast majority of organic compounds resonated at a low field than the protons of TMS. Therefore, by arbitrarily assigning TMS is zero; it is possible to device δ scale. The ^{1}H NMR spectrum shows that the peak at δ value 11.10 is singlet is assigned to the Phenolic O-H proton of chalcone. Two Doublet,(2H) CH=CH group attached with adjacent to the Carbonyl and aromatic ring 6.25 to 6.29 and 6.52 to 6.54 respectively. Multiplet, (8H) Aromatic Protons lies on the both side of the CO –CH=CH group has assigned for 6.95 to 8.0δ value.

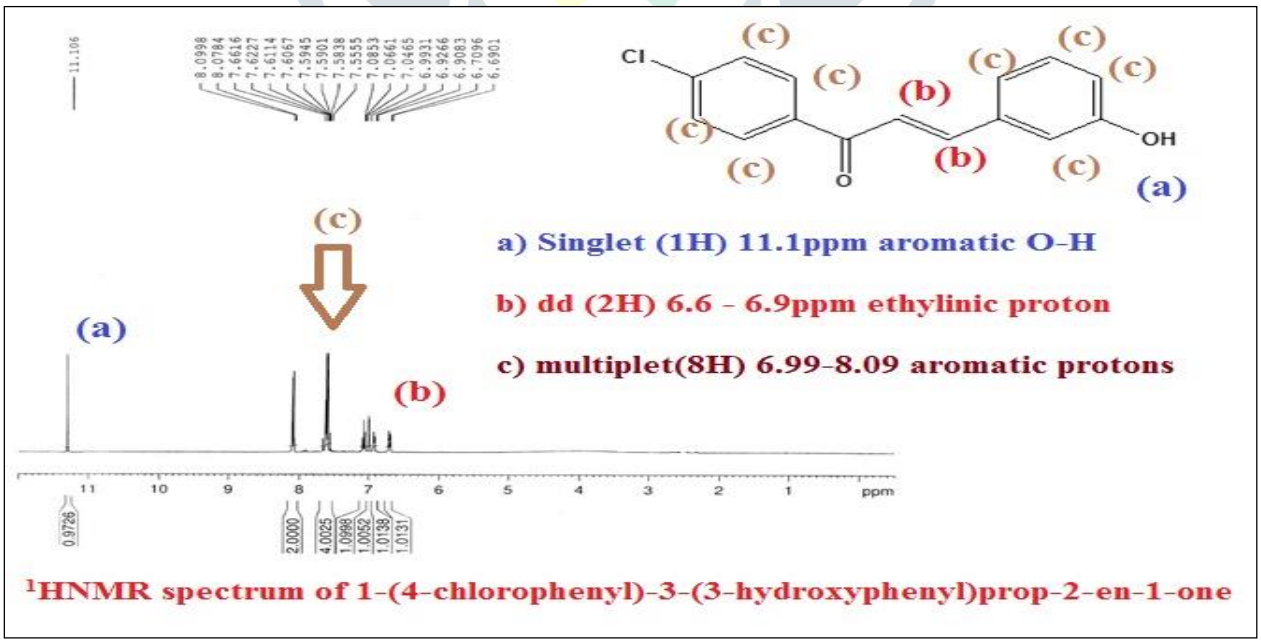


Fig. 3. ^{1}H NMR Spectrum of 1-(4-chlorophenyl)-3-(4-hyroxyphenyl)prop-2-en-1-one(RI1)

3.2. Interpretation of 4-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol

It is a crystalline yellowish white solid. This Compound were synthesized by mentioning the procedure of Step –II. The formation of product was confirmed by Thin-Layer chromatography. The following data were mentioned in Table 2.

Table 2.Interpretation of spectrum to 4-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol(RI1A)

UV (λ max: nm)	(CH=CH) 239 & N(or)O Hetero atom 312
FTIR (cm^{-1})	3416 (O-H), 2889 (Aromatic C-H str), 2899 (C-H), 1744 (C=O), 1602 (C=C str), 835(N-H out plane bending),701(C-Cl str)
^{1}H NMR (ppm)	2.95 - 2.97 (2d, 2H, -CH=CH), 6.87-7.89 (m, 8H, Ar-H),11.11 (s, 1H, Ar-OH), 4.83 to 4.90 (d,1H,-CH-NH)

3.2.1. Interpretation of UV-Visible spectrum 4-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol

The UV peak appear at 239nm (CH=CH) conforms the $\pi \rightarrow \pi^*$ transition of aromatic double bond and peak at 312nm is due to $n \rightarrow \pi^*$ transition of hetero atom present in the molecule (N or O). The UV-Visible Spectrum of compound-C1A were shown in the Fig. 4.

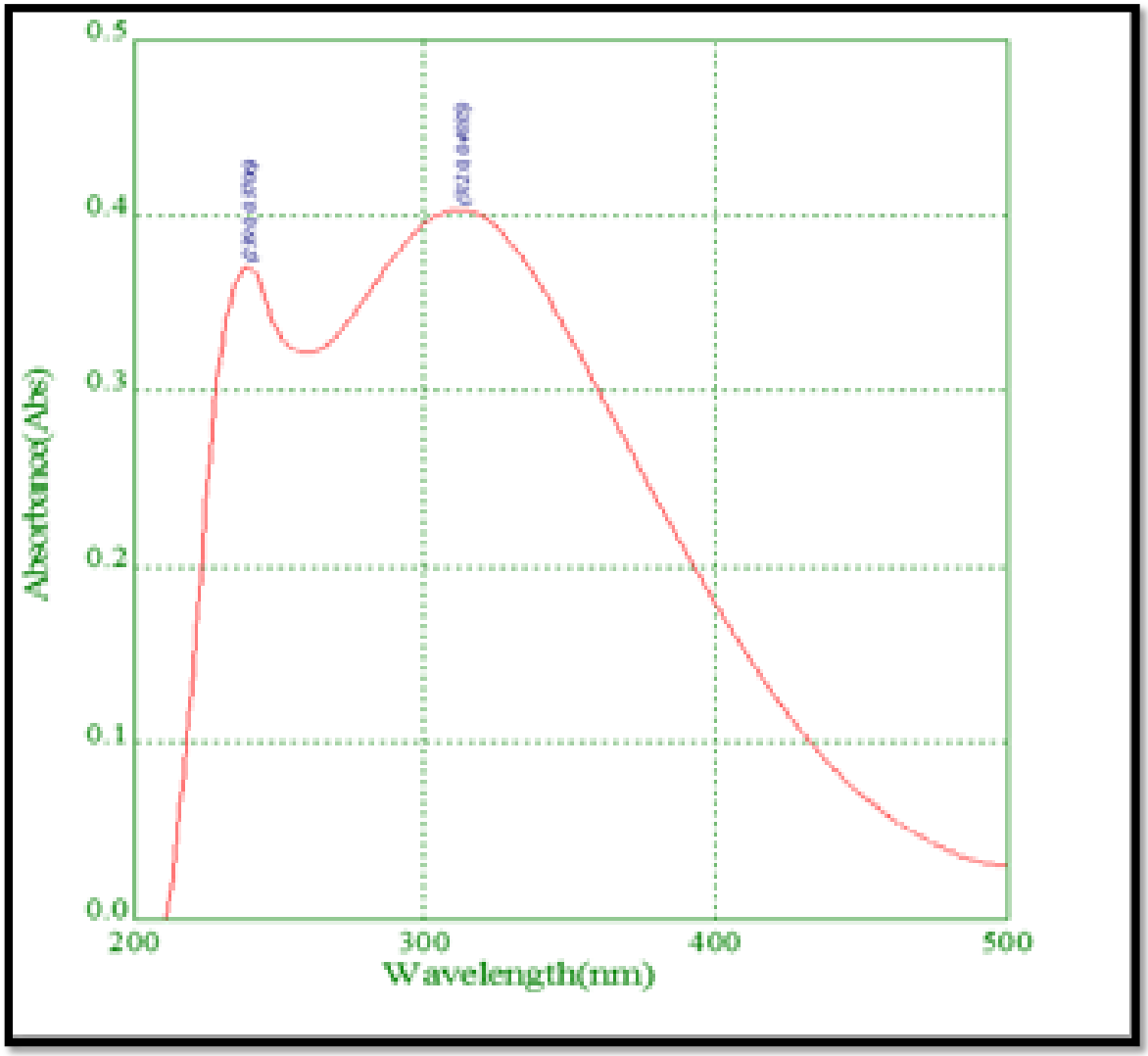


Fig. 4. UV Spectrum of 4-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5- yl)phenol(Compound – RI1A)

3.2.2. Interpretation of IR spectrum to 4-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol

The FT-IR spectrum of the 4-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol was shown in the Fig. 5.. The melting point of the substituted pyrazole is 110-111°C. The IR Spectrum showed the characteristic bands for Aromatic C-H at 2889, -C=C- stretching vibration at 1602, A strong bond due to C=N 1512, A broad peak due to – OH group 3416, The band due to – CH_2 bridge 2825 whereas-NH out plane bending vibration band appeared at 835 cm^{-1}.

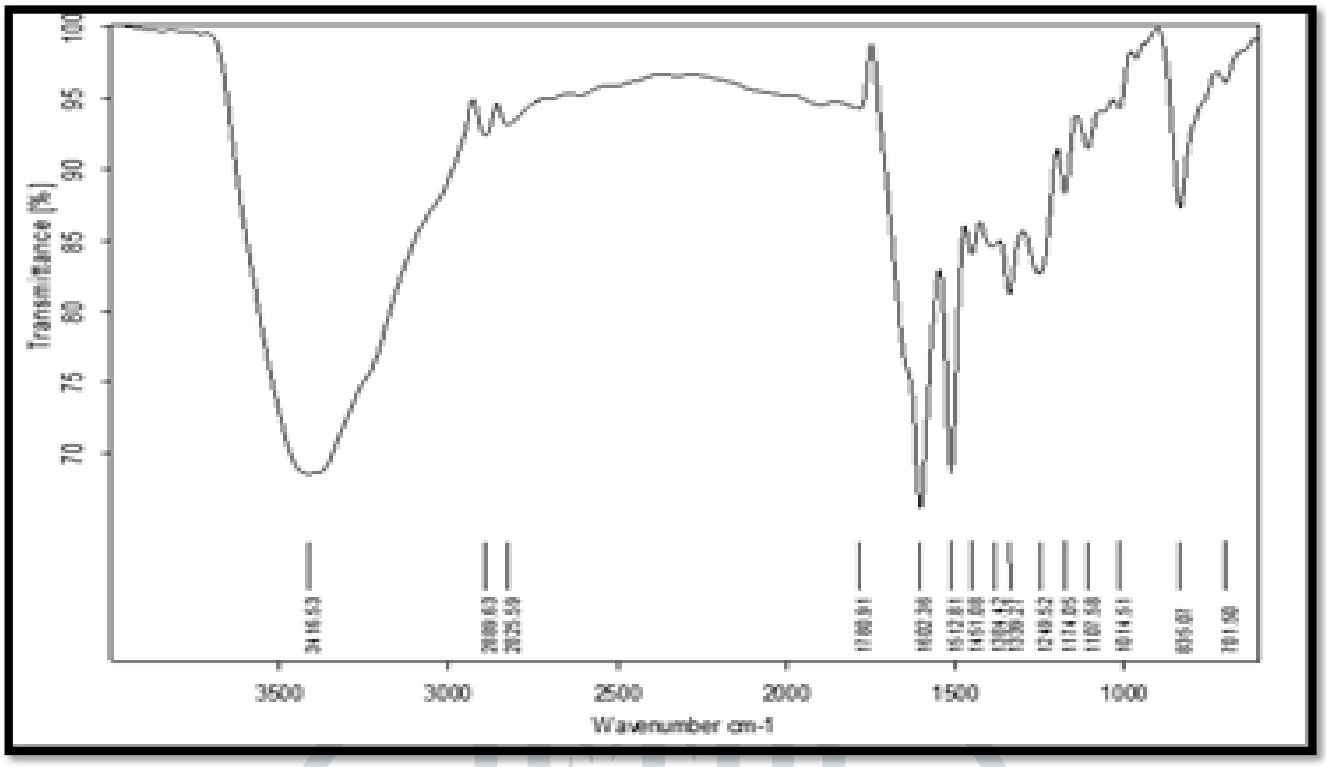


Fig. 5. FTIR Spectrum of 4-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol(Compound – RI1A)

3.2.3. Interpretation of proton NMR spectrum of 4-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol

The ^{1}HNMR spectrum of 4-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenol was shown in Fig. 6. The ^{1}H-NMR spectra for the following signals: A singlet(1H) at δ = 11.11 ppm characteristic for the Aromatic –OH protons. A Doublet (2H) attached with – CH proton at δ = 2.95 to 2.97 ppm characteristic for CH2 protons, a Multiplet (8H) at δ = 6.87 to 7.89 ppm characteristic for the aromatic protons. The methine protons of the pyrazole ring appeared as a Quintet(1H) at δ = 3.0 to 3.67 ppm. In the case of another Doublet(1H) appeared at δ = 4.83 to 4.90 ppm characteristic for -NH Proton attached with adjacent – CH proton.

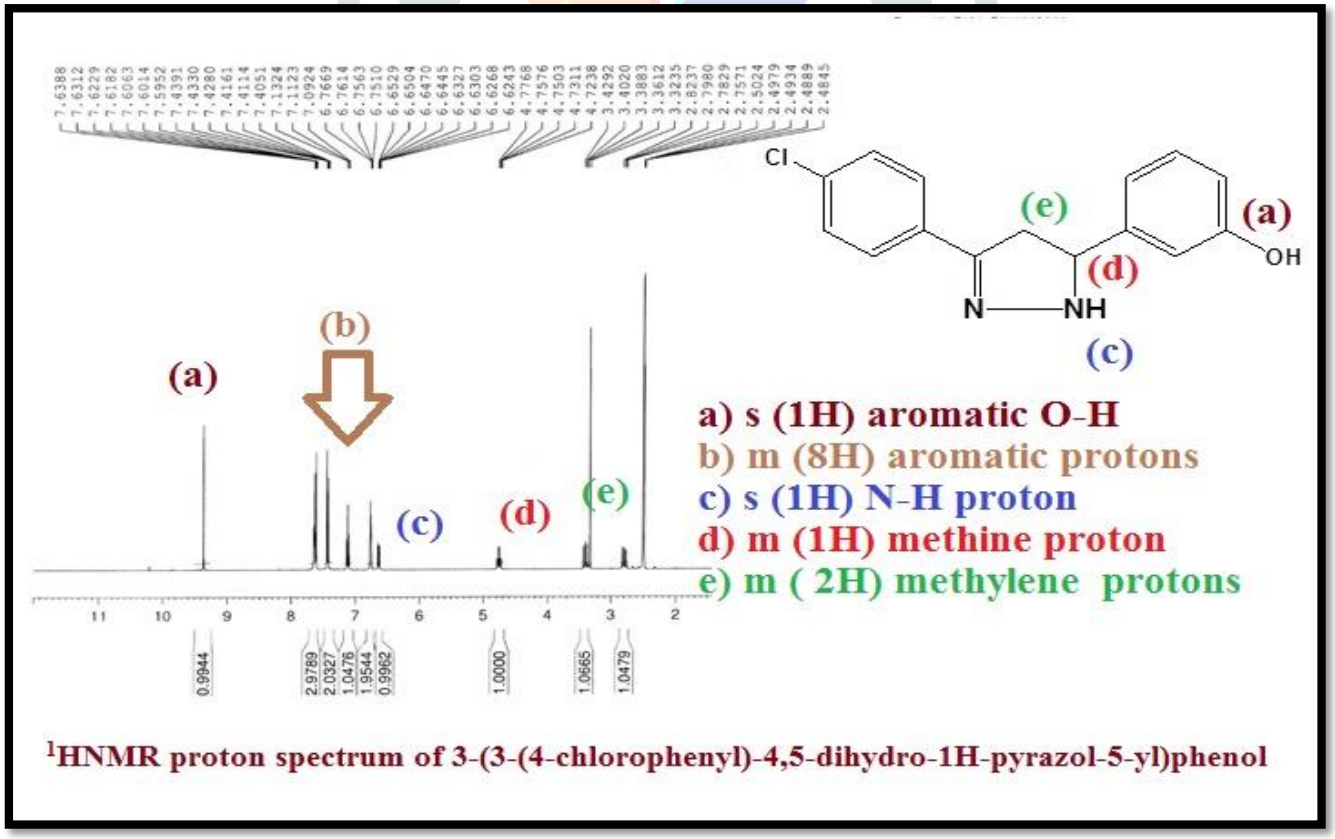


Fig.6. ^{1}H NMR Spectrum of 4-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-yl)phenol(Compound – RI1A)

3.3. Antimicrobial activity

All synthesized compounds were screened for their antibacterial activity by MIC method the following bacterial strains and procedure were used.

S. a – Staphylococcus aureus(MTCC3381)
E. c – Escherichia coli(MTCC739)

3.3.1. Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC), which is considered the least concentration of the sample which inhibits the visible growth of a microbe was determined by the broth dilution method.

3.3.2. Preparation of innocula

Organisms were subcultured on nutrient agar, followed by incubation for 24h at 37°C. Innocula were prepared by transferring several colonies of microorganisms to the sterile nutrient broth. The suspensions were mixed for 15sec and incubated for 24h at 37 °C. The required volume of suspension culture was diluted to match the turbidity of 0.5 McFarland standard (1.5x108CFU/mL)

3.3.3. Preparation of sample

Samples were prepared in dimethyl sulphoxide (DMSO) at the concentration of 2 mg/ml.

3.3.4. Broth dilution assay

A series of 15 tubes were filled with 0.5ml sterilized nutrient broth. Sequentially, test tubes 2–14 received an additional 0.5 ml of the sample serially diluted to create a concentration sequence from 500 – 0.06µg. The first tube served as the control. All the tubes received 0.5ml of inoculum. The tubes were vortexed well and incubated for 24h at 37°C. The resulting turbidity was observed, and after 24 h MIC was determined to be where growth was no longer visible by assessment of turbidity by optical density readings at 570nm. No chemicals were used experiment were triplicated. The MIC values reported in Table 3 and illustrated in Fig.7 shows that all the synthesized compounds of RI1, RI1A, RI2, RI2A, RI3 and RI3A have tested against one gram-positive and one gram-negative bacterial strains namely Staphylococcus aureus and Escherichia coli respectively. Among the synthesized compounds RI2A and RI3A show excellent activity towards two tested bacterial strains especially towards Staphylococcus aureus with the lowest value of 15.63 (µg/mL). All other synthesized compound possess significant activity against tested bacterial strains. The very good activity of the RI2A and RI3A against Staphylococcus aureus is due to the presence of heterocyclic compounds in between the two phenyl rings and the presence of hydroxyl and nitro group also responsible for the excellent activity of RI2A and RI3A.

Table 3. Minimum inhibiting concentration (MIC) values of the synthesized compounds

Compounds	Minimum Inhibiting Concentration (µg/ml)	
	***Staphylococcus aureus* (S.a)**	***Escherichia coli* (E.c)**
RI1	62.50	125.00
RI1A	15.63	31.25
RI2	15.63	125.00
RI2A	15.63	31.25
RI3	15.63	62.50
RI3A	62.50	250

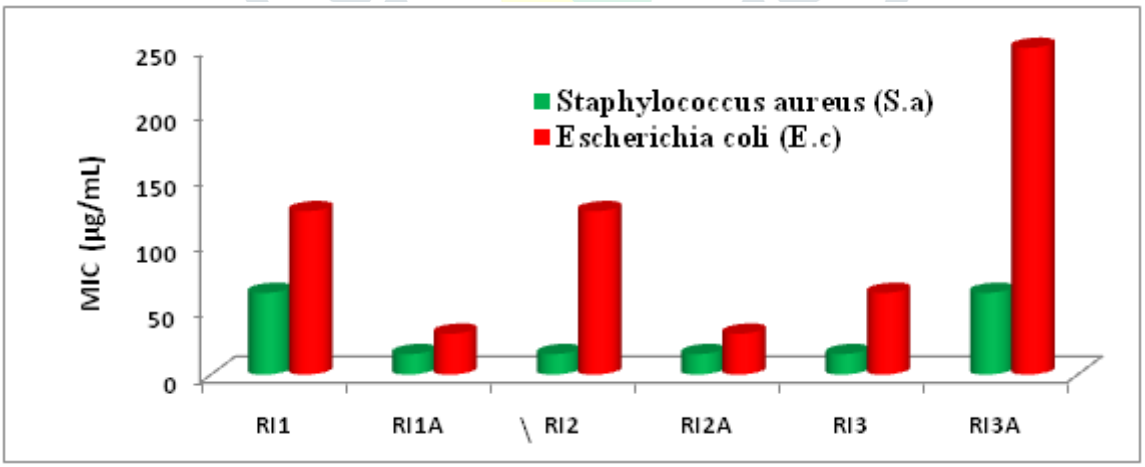


Fig.7. The comparison MIC values of all synthesized compounds

4. Conclusions

Four types of phenyl substituted pyrazole derivatives were prepared successfully by Claisen-Schmidt condensation using the green synthetic method. Totally six compounds were synthesized successfully. But, in our work, the chalcones have been synthesized using PEG-600 as a solvent, which is eco-friendly, non-toxic, inexpensive, potentially recyclable and water soluble. So, chalcones were synthesized by a green chemistry approach in the first step. In the second step, the chalcones were condensed with hydrazine hydrate as mentioned in the schemes. The Chemical structures of compounds RI1, RI1A, RI2, RI2A, RI3 and RI3A were confirmed by FT-IR, UV-Visible, and ^{1}H-NMR spectra and were found to be in agreement with the chemical structures expected. Simultaneously, in our work, the microbial activities four substituted chalcones and phenyl substituted pyrazole derivatives were checked against the two microbes staphylococcus aureus and Escherichia coli. The report of antimicrobial activity clearly shows that the synthesized compounds of RI1, RI3, and RI3A show excellent activity towards two tested bacterial strains especially towards Staphylococcus aureus with the lowest value of 15.63(µg/mL).

References

1. Essam Mohamed Sharshira[1], Nagwa Mohamed Mahrous Hamada[2,*], Synthesis, Antibacterial and Antifungal Activities of Some Pyrazole-1-Carbothioamides and Pyrimidine-2(1H)-Thiones, *American Journal of Organic Chemistry* (2012), 2(2): 26-31; **doi: 10.5923/j.ajoc.20120202.05**

2. Roberta K. F. Marra 1, Alice M. R. Bernardino [1,*], Tathiane A. Proux [2], Karen S.Charret[3],Marie-Luce F. Lira [2], Helena C. Castro [2,*], Alessandra M. T. Souza [4], Cesar D.Oliveira [1],Júlio C. Borges [1], Carlos R. Rodrigues [4], Marilene M. Canto-Cavalheiro [3], Leonor L. Leon [3] and Veronica F. Amaral [2,*], 4-(1H-Pyrazol-1-yl) Benzenesulfonamide Derivatives: Identifying New Active Antileishmanial Structures for Use against a Neglected Disease, *Molecules* , (2012), *17*, 12961-12973; **doi:10.3390/molecules171112961**

3. Ramanjaneyulu Unnava and Anil K. Saikia*[a], Synthesis of Substituted Pyrazole N-Oxide and Pyrazole from Propargyl Amine, *Chemistry Select (2016*), 1, 1816 – 1823; **doi: 10.1002/slct.201600528**

4. Mayur K. Vekariya+ , [a] ,Rajesh H. Vekariya,[b] Kinjal D. Patel,[a] Nirav P. Raval,[c] Prapti U. Shah,[c] Dhanji P. Rajani,[d] and Nisha K. Shah+ * [a], Pyrimidine-Pyrazole Hybrids as Morpholinopyrimidine-Based Pyrazole Carboxamides: Synthesis, Characterisation, Docking, ADMET Study and Biological Evaluation, *ChemistrySelect* (2018), 3, 6998 – 7008, **doi: 10.1002/slct.201801011**

5. Zi-Li Ren[1†] | Hao Liu[1†] | Di Jiao[1] | Hao-Tian Hu[1] | Wei Wang[1] | Jie-Xiu Gong[1] | Ai-Li Wang[1] | Hai-Qun Cao[2] | Xian-Hai Lv[1,3], Design, synthesis, and antifungal activity of novel cinnamon–pyrazole carboxamide derivatives. *Drug Dev Res.* (2018);1–6. **doi: 10.1002/ddr.21469**

6. S.R. Ubaradkaa , A.M. Isloorb*, P. Shettyc , K.S.R. Pai d, and H.K. Fune, Synthesis and in vitro biological evaluation of new pyrazole chalcones and heterocyclic diamides as potential anticancer agents, *Arabian Journal of Chemistry* (2014), **doi: 10.1016/j.arabjc.2014.01.018**

7. Khan NR, Rathod VK, Enzyme catalyzed synthesis of cosmetic esters and its intensification: a review, *Process Biochemistry* (2015), **doi:10.1016/j.procbio.2015.07.014**

8. S. Arunkumar,[1] K. Ilango,[1] R. S. Manikandan,[1] and N. Ramalakshmi[2] , Synthesis and Anti-inflammatory Activity of Some Novel Pyrazole Derivatives of Gallic Acid, *E-Journal of Chemistry*, Volume 6, S1, Pages S123-S128, **doi: 10.1155/2009/128586**

9. Urmila Gupta, Vineeta Sareen, Vineeta Khatri, Sanjana Chugh, Synthesis and antifungal activity of new Fluorine containing 4- (substituted Phenyl azo) Pyrazoles and Isoxazoles, *Indian J. of Het.Chem.*, 2005; 14: 265-266; **doi: 10.3390/molecules17054962**

10. Abdou O. Abdelhamid[1*], Hussien F. Zohdi[2], Mohamed M. M. Sallam[1] and Nagla A.Ahmed[1], Reactions with Hydrazonoyl Halides. 31. Synthesis of Some New Pyrrolidino[3,4 *c*]pyrazolines, Pyrazoles, and Pyrazolo[3,4-*d*]pyridazines† , *Molecules* (2000), 5, 967-973; **doi:10.3390/50700967**

11. Venkatapuram Padmavathi*, Boggu Jagan Mohan Reddy, Akula Balaiah, Katta Venugopal Reddy and Dandu Bhaskar Reddy, Synthesis of Some Fused Pyrazoles and Isoxazoles, *Molecules*, (2000), 5, 1281–1286, **doi: 10.3390/51201281**

12. Munusamy Saravanabhavan[a], Krishnan Sathya[a], Vedavati G. Puranikb Marimuthu Sekar[a*], Synthesis, spectroscopic characterization and structural investigations of new adduct compound of carbazole with picric acid: DNA binding and antimicrobial studies, Spectrochimica Acta Part A: Molecular and *Biomolecular Spectroscopy* (2013), **doi: 10.1016/j.saa.2013.08.115**

13. Abdullah Sulaiman Al-Ayed *, Synthesis of New Substituted Chromen[4,3-c]pyrazol-4-ones and Their Antioxidant Activities, *Molecules* (2011), *16*, 10292-10302; **doi:10.3390/molecules161210292**

14. Abdel-Sattar S. Hamad Elgazwy[1]*, Ekhlass Nassar[2] and Myssoune Y. Zaki[3], Synthesis, Biological Evaluation of Some 2,3-dihydropyrazoles and Thiazoles as Anti-inflammatory and Antibacterial Agents, *Organic Chem Curr Res* (2012), 1:5,**doi:10.4172/2161-0401.1000112**

15. Wan-Sin Loh [1], Ching Kheng Quah [1], Tze Shyang Chia [1], Hoong-Kun Fun[1,2,*], Majal Sapnakumari [3], Badiadka Narayana [3] and Balladka Kunhanna Sarojini[4], Synthesis and Crystal Structures of *N*-Substituted Pyrazolines, *Molecules* 2013, *18*, 2386-2396; **doi:10.3390/molecules18022386**