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Synthesis and Characterization of Novel Trisubstituted Pyrazole Derivatives from Chalcones

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Abstract: ***Pyrazole moiety, being called as pharmacophore, plays an important role in many biologically active compounds and therefore represents an interesting template for combinatorial as well as medicinal chemistry. In addition pyrazoles are also used extensively as useful synthons in organic synthesis. These derivatives have wide spread biological activities such as anticancer, analgesic, anti-inflammatory, antimicrobial, antiviral, anticonvulsant and anti-HIV. The recent success of pyrazole COX-2 inhibitor has further highlighted the importance of these heterocycles in medicinal chemistry. These newly synthesized compounds were characterized by NMR,massspectral, IR spectral studies as well as by C,H and N analyses. Several pharmacological activities like antitubercular, analgesic, anti-cancer, anti-inflammatory, antiasthmatic, antioxidant and antibacterial activities have been attributed to pyrazoles. In the present study, a novel series of pyrazole derivatives (4a1-24) were synthesized by phenylhydrazine hydrochloride with different chalcones. The starting material, chalcones were prepared by Claisen Schmidt condensation of ketones with aldehydes in the presence of sodium hydroxide in ethanol. All thesynthesized compounds were characterized by IR, ^{1}H-NMR, and Elemental Analysis.***

Keywords: Chalcone, Phenylhydrazine hydrochloride, antimicrobial activity, Sodiumhydroxide, Pyrazoles

1. Introduction

Heterocyclic ring system containing nitrogen becomes most interesting field in research area due to their wide variety of biological activities like, antibacterial, antifungal, antitubercular, anticancer, analgesic, anti-inflammatory, anticonvulsant and antidepressant activities[1,2].

The chemistry of chalcones has generated intensive scientific interest due to their biological and industrial applications. Chalcones exhibits various biological activities, such as antioxidant, anti inflammatory, antimalarial, antileishmanial, anticancer and antitumor[3-7]. In addition to this, chalcones are very important compounds as a Michael acceptor in organic syntheses.

Chalcones have been used as intermediates for the preparation of compounds having therapeutic value. In view of the varied biological and pharmacological applications, some heterocyclic derivatives of chalconeare used for their antibacterial activity. Whereas pyrazole is a class of organic compounds, which has many applications in different field. One of the methods for the synthesis of such compound is from α, β-unsaturated carbonyl compound by the cyclization with substituted hydrazines[8-9].

Moreover, chalcones have played a crucial part in the development of theory of heterocyclic compounds, and also they used extensively in organic synthesis [10–14]. A classical synthesis of these compounds involves the base-catalyzed aldol condensation reaction of ketones and aldehydes to give α,β-unsaturated ketones (chalcones), which undergo a subsequent cyclization reaction with hydrazines affording pyrazoles[15-17]. In recent years, a significant portion of research in heterocyclic chemistry has been devoted to pyrazoles containing different aryl groups, as evident from the literature [18].Pyrazoles are the significant members of heterocyclic compounds with two neighboring nitrogens in a five-member ring system, pyrazole derivatives have given good pharmacological effect. Pyrazoles refers to the class of heterocyclic compounds characterized by 5 – membered aromatic ring structure composed of three carbon atoms and two nitrogen atoms inadjacent positions, of two nitrogen atoms one basic nitrogen and neutral nitrogen, thearomatic nature arises from the four electrons and the unshared pair of electrons on the –NH nitrogen[19].

Further, pyrazole derivatives are also used as chelating agents and inhibitors for the corrosion of the steel . Due to these interesting activities of pyrazole derivatives, considerable attention has been focused on this class of compounds. In addition, pyrazoles have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively in organic synthesis [20].

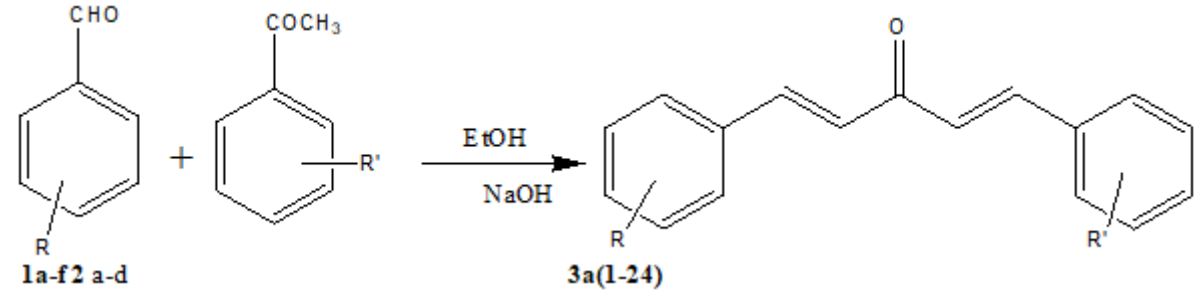
2. Material and Methods

All the chemicals and the reagents used in the study were of synthesis grade purity. Aldehydes, Ketones. All compounds prepared for studies were purified by crystallization using appropriate solvents and established procedures. Melting points are noted on a sigma melting point apparatus using capillary tubes. Analytical TLC was performed on a procoated sheets of silica gel to monitor the process of the reaction as well as to check the purity. The spots were visualized by using iodine vapour. IR spectra were recorded on FTIR-8300 shimadzu spectrometer. H^1& C^{13} NMR spectra were recorded on Jeol GSX (400MHz) and DPX 200 (200MHz). mass spectra were recorded on Jeol-JMS-DX 30 hf.

3. Result and Discussion

Synthesis of substituted Chalcones:
Equal moles (0.1 mol) of substituted aldehydes (10.6g, 0.1 mol) and substituted ketones(12g, 0.1 mol) were mixed and dissolved in minimum amount (30 ml)of ethanol. Sodium hydroxide solution (60%) was poured gradually with constant stirring and continued the stirring for 1.5hrs. After adding , the mixture of sodium salt of chalcone was kept for

14-16 hrs at room temperature. The sodium salt of chalcone was separated in ice-cold condition**(3a1-24).** The separated solid was filtered and washed with ice-cold water till the washing was neutral. Recrystallised the compound with ethanol and dried at room temperature and melting point is noted.

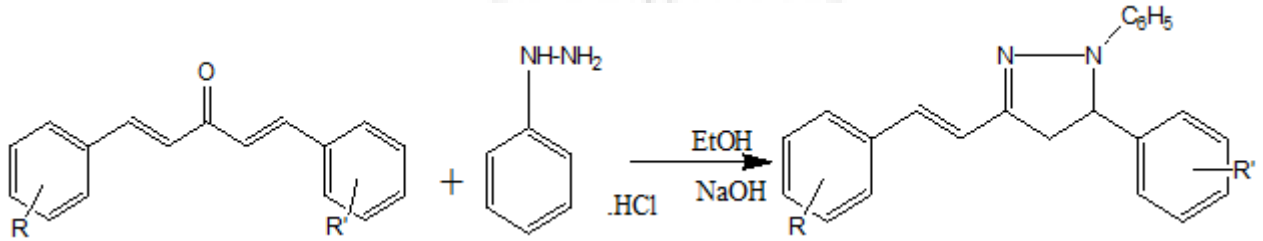


1a-f2 a-d **3a(1-24)**

R= H, 3-OH, 3-NO_2 ,3-Cl,CH_3,OCH_3
R'= H, 3-CH_3,3-OCH_3,3-NH_2

Synthesis of substitutedpyrazole derivatives

A mixture of chalcone (0.01 mol), hydrazine hydrochloride (0.01) and Sodium hydroxide (10 ml) in ethanol was refluxed for 8 hrs. The reaction mixture was cooled and poured over ice cold water. The solid separated was filtered, washed with water, dried and recrystallized from ethanol gave yellow crystals and then recrystallized from ethanol **(4a1-24).**



3a(1-24) **4a(1-24)**

R= H, 3-OH, 3-NO_2 ,3-Cl,CH_3,OCH_3
R'= H, 3-CH_3,3-OCH_3,3-NH_2

Characterization

Synthesis of 4,5 dihydro-1,5-diphenyl-3styryl-1H-pyrazole : ($4a_1$)

Eq. moles of (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one **($3a_1$)** and phenylhydrazine hydrochloride in ethanol were refluxed for 8 hrs in presence of 10% NaOH produced 4,5 dihydro-1,5-diphenyl-3styryl-1H-pyrazole **($4a_1$)** was prepared. yield: 80%,m.p : 87-90^{0}C,^{1}H NMR: δ 5.25 (t,CH_2), 6.55 (d,αCH), 6.74(d,βCH), 7.13-7.59(m,Ar-H),^{13}C NMR : δ42.2(CH_2), 105,113.4,120.45,121.6,125.1,125.8,126.5,127.4,128.3,128.7,129.1,130.4,132.6 (Aromatic carbons), IR: C=N-2201cm^{-1}, CH-Stretch,2925 cm^{-1}, Mass: (m/z): 324.

Spectral details of other compounds:

(E)-1-phenyl-3-styryl-5-(*p*-tolyl)-4,5-dihydro-1-H-pyrazole : ($4a_2$)

Yield: 81%,m.p : 86-90^{0}C,^{1}H NMR: δ 5.30(t,CH_2), 6.57 (d,αCH), 6.78(d,βCH), 7.18-7.60(m,Ar-H), 2.36(methyl proton).^{13} C NMR : δ40.9(CH_2), 21.7(methyl carbon),110,116.7,120.8,127.5,128.6,129.5,130.4,132.6,140.5 (Aromatic carbons), IR: C=N-2270cm^{-1}, CH-Stretch,2945 cm^{-1}, Mass: (m/z): 338.

(E)-5-(4-methoxyphenyl)-1-phenyl-3-styryl-4,5-dihydro-1H-pyrazole : ($4a_3$)

Yield: 83%,m.p : 88-92^{0}C, ^{1}H NMR: δ 5.40(t,CH_2), 6.59 (d,αCH), 6.94(d,βCH), 7.18-7.64(m,Ar-H), 3.87(methoxy proton). ^{13}CNMR : δ40.9(CH_2) ,60.7(methoxy carbon),114.1,116.7,120.8,127.9,126.6,129.5,130.6,128.6,135.2,135.6,135.9 (Aromatic carbons),IR: C=N-2290cm^{-1}, CH-Stretch,2980 cm^{-1},Mass: (m/z): 354.

(E)-4-(1-phenyl-3-styryl-4,5-dihydro-1-H-pyrazole-5-yl)aniline : ($4a_4$)

Yield: 85%,m.p : 87-90^{0}C, ^{1}H NMR: δ 5.19(t,CH_2), 6.55(d,αCH), 6.83(d,βCH), 7.02-7.63(Ar-H,m), δ6.27(amino proton). ^{13}C NMR : δ40.9(CH_2),115,116.7,120.8,127.9,128.5,128.6,129.5,130.4,132.6,132.7,135.9 (Aromatic carbons),IR: C=N-2290cm^{-1}, CH-Stretch,2980 cm^{-1},NH_2-1650cm^{-1},Mass: (m/z): 339.

(E)-4-(2-(1,5-diphenyl-4,5-dihydro-1H-pyrazol-3-yl)vinyl)phenol : ($4a_5$)

yield: 80%,m.p : 82-85^{0}C,^{1}H NMR: δ 5.19 (t,CH_2), 6.65 (d,αCH), 7.56(d,βCH), 7.23-64(Ar-H,m). ^{13}C NMR : δ40.9(CH_2), 107,113.6,120.4,122.8,124.3,125.8,126.9,127.7,128.9,129.5,129.8,130.7,132.4 (Aromatic carbons),IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1} , OH-3560cm^{-1},Mass: (m/z): 340.

(E)-4-(2-(1-phenyl-5-(*p*-tolyl)-4,5-dihydro-1H-pyrazol-3-yl)vinyl)phenol : ($4a_6$)

Yield: 84%,m.p : 83-86^{0}C, H^1 NMR: δ 5.19 (t,CH_2), 6.67 (d,αCH), 7.49(d,βCH), 7.23-7.70(m,Ar-H), 5.35(OH proton), 2.63(methyl proton). ^{13}C NMR : δ40.7(CH_2), 107.3,113.8,120.5,122.6,124.8,125.6,126.7,127.9,128.6,129.8,130.4,132.6 (Aromatic carbons), 25.5(methyl carbon),IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1},OH-3560cm^{-1},Mass: (m/z): 354.

(E)-4-(2-(5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)vinyl)phenol :($4a_7$)
Yield:79%,m.p : 81-83^{0}C, ^{1}H NMR: δ 5.20 (t,CH_2), 6.69 (d,αCH), 7.50(d,βCH), 7.37-7.72(m,Ar-H),5.35(OH proton), 3.83(methoxy proton). ^{13}CNMR : δ40.5(CH_2), 107.5,113.6,120.4,122.4,124.3,125.1,126.8,127.3,128.2,129.5,130.1,132.8 (Aromatic carbons), 60.0(methoxy carbon), IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1} ,OH-3560cm^{-1},Mass: (m/z): 370.

(E)-4-(2-(5-(4-aminophenyl)phenyl-4,5-dihydro-1H-pyrazol-3yl)vinyl)phenol :($4a_8$)
Yield: 80%,m.p : 85-88^{0}C, ^{1}H NMR: δ 5.21 (t,CH_2), 6.65 (d,αCH), 7.41(d,βCH), 7.34-7.78(m,Ar-H), 5.35(OH proton), 6.27(amino proton),^{13}C NMR : δ41.0(CH_2), 106.9,113.5,120.1,122.5,124.1,125.3,126.9,127.5,128.1,129.4,130.3,132.5 (Aromatic carbons), IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1} ,OH-3560cm^{-1}, Mass: (m/z): 355.

(E)-3-(3-nitrostyryl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole :($4a_9$)
Yield: 81%,m.p : 82-85^{0}C,^{1}H NMR: δ 5.19 (t,CH_2), 6.77 (d,αCH), 6.83(d,βCH), 7.23-8.21(m,Ar-H),^{13}C NMR : δ41.0(CH_2), 116.7,120.8,123.8,126.7,126.9,128.5,129.0,129.5,135.8,141.0(Aromatic carbons),IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1}, NO_2-1503cm^{-1}, Mass: (m/z): 369.

(E)-3-(3-nitrostyryl)-1-phenyl-5-(*p*-tolyl)-4,5-dihydro-1H-pyrazole :($4a_{10}$)
Yield: 83%,m.p : 83-86^{0}C, ^{1}H NMR: δ 5.18 (t,CH_2), 6.75 (d,αCH), 6.85(d,βCH), 7.25-8.20(m,Ar-H), 2.60(methyl proton),^{13}C NMR : δ40.5(CH_2), 116.5,120.7,123.5,126.5,126.7,128.7,129.1,129.6,135.9,140.0Aromatic carbons), 21.5(methyl carbon),IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1},NO_2-1503cm^{-1}, Mass: (m/z): 383.

(E)-5-(4-methoxyphenyl)-3-(3-nitrostyryl)-1-phenyl-4,5-dihydro-1H-pyrazole : ($4a_{11}$)
Yield: 84%,m.p : 86-89^{0}C,^{1}H NMR: δ 5.19 t,(CH_2), 6.77(d,αCH), 6.82(d,βCH), 7.27-8.19(m,Ar-H), 3.90(methoxyproton),^{13}CNMR : δ40.1(CH_2), 116.3,120.5,123.1,126.6,126.9,128.5,129.3,129.8,135.3,139.9(Aromatic carbons), 55.9(methoxy carbon),IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1},NO_2-1503cm^{-1}, Mass: (m/z): 399.

(E)-4-(3-(3-nitrostyryl-1phenyl-4,5-dihydro-1H-pyrazol-5-yl)aniline :($4a_{12}$)
Yield: 79%,m.p : 86-88^{0}C,^{1}HNMR: δ 5.19 (t,CH_2), 6.75(d,αCH), 6.85(d,βCH), 7.28-8.18(m,Ar-H), 6.30(amino proton), C^{13} NMR : δ40.2(CH2), δ116.5,120.9,123.7,128.6,127.0,128.6,129.7,130.0,135.5,139.8 (Aromatic carbons),IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1} ,NO_2-1503cm^{-1}, Mass: (m/z): 384.

(E)-3-(4-chlorostyryl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole : ($4a_{13}$)
Yield: 88%,m.p : 84-86^{0}C, ^{1}H NMR: δ 5.20 (t,CH_2), 6.83(d,αCH), 6.77(d,βCH), 7.29-7.68(m,Ar-H),^{13}C NMR : δ40.9(CH_2), 116.1,119.9,123.1,126.2,127.1,128.3,129.5,130.1,134.3,137.6,139.0 (Aromatic carbons),IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1} , Cl- 670cm^{-1}, Mass: (m/z): 359.

(E)-3-(4-chlorostyryl)-1-phenyl-5-(*p*-tolyl)-4,5-dihydro-1H-pyrazole : ($4a_{14}$)
yield: 86%,m.p : 80-83^{0}C,,^{1}H NMR: δ 5.19 (t,CH_2), 6.85(d,αCH), 6.79(d,βCH),7.30-7.70(m,Ar-H),2.45(methyl proton),
C^{13} NMR : δ40.5(CH2), δ116.5,119.7,123.5,126.1,126.3,127.8,129.8,130.5,134.7,137.9 (Aromatic carbons), δ21.9(methyl carbon),IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1},Cl- 670cm^{-1}, Mass: (m/z): 373.

(E)-3-(4-chlorostyryl)-5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole : ($4a_{15}$)
Yield: 81%,m.p : 82-84^{0}C,^{1}H NMR: δ 5.20 (t,CH_2), 6.87(d,αCH), 6.73(d,βCH),7.31-7.69(m,Ar-H),3.85(methoxy proton). ^{13}C NMR : δ40.5(CH_2), 116.9,119.9,123.8,126.5,127.1,127.9,128.1,129.7,130.6,134.9,138.0 (Aromatic carbons), 60.8(methoxycarbon), IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1},Cl- 670cm^{-1}, Mass: (m/z): 388.

(E)-4-(3-(4-chlorostyryl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-yl)aniline : ($4a_{16}$)
Yield: 85%,m.p : 82-85^{0}C, ^{1}H NMR: δ 5.18 (t,CH_2), 6.85(d,αCH), 6.78(d,βCH),7.29-7.70(m,Ar-H),6.39(amino proton),^{13} C NMR : δ40.1(CH_2), 117.0,119.8,123.7,126.1,126.8,127.3,128.5,129.8,130.0,134.8,136.7 (Aromatic carbons), IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1} ,Cl- 670cm^{-1}, Mass: (m/z): 373.

(E)-3-(4-methylstyryl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole : ($4a_{17}$)
Yield: 85%,m.p : 82-85^{0}C, ^{1}H NMR: δ 5.20 (t,CH_2), 6.75(d,αCH), 6.95(d,βCH), 7.27-7.59(m,Ar-H),2.19(methyl proton),^{13}C NMR : δ41.2(CH_2), 21.9(methyl carbon),109.0,117.4,122.6,124.7,125.7,126.7,128.5,128.8,129.0,129.5,130.5,133.7 (Aromatic carbons), IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1} , Mass: (m/z): 338.

(E)-3-(4-methylstyryl)-1-phenyl-5-(*p*-tolyl)-4,5-dihydro-1H-pyrazole : ($4a_{18}$)
Yield: 85%,m.p : 82-85^{0}C, ^{1}H NMR: δ 5.19 (t,CH_2), 6.71(d,αCH),7.0(d,βCH),7.29-7.60(m,Ar-H),2.23(d,methyl proton),^{13}C NMR : δ41.0(CH_2), 22.7(methyl carbon),109.5,117.1,122.3,124.5,126.9,127.0,128.1,128.7,129.1,129.6,130.1,134.1 (Aromatic carbons), IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1}, Mass: (m/z): 352.

(E)-5-(4-methoxyphenyl)-3-(4-methylstyryl)-1-phenyl-4,5-dihydro-1H-pyrazole : ($4a_{19}$)
Yield: 85%,m.p : 82-85^{0}C, ^{1}H NMR: δ 5.18 (t,CH_2), 6.71(d,αCH), 6.97(d,βCH), 7.28-7.54(m,Ar-H),2.23(methyl proton),5.65(methoxy proton). ^{13}C NMR : δ41.1(CH_2), 22.7(methyl carbon), 60.3(methoxy carbon), 109.3,117.5,122.4,124.7,126.7,127.3,128.5,128.9,129.6,130.0,130.8,134.5 (Aromatic carbons), IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1}, Mass: (m/z): 368.

(E)-4-(3-(4-methylstyryl)-1-phenyl-4,5-dihydro-1H-pyrazol-5yl)aniline :($4a_{20}$)
Yield: 85%,m.p : 82-85^{0}C,^{1}H NMR: δ 5.19 (t,CH_2), 6.75(d,αCH), 6.98(d,βCH), 7.30-7.60(m,Ar-H),2.23(methyl proton),^{13}C NMR : δ41.0(CH_2), 22.7(methyl carbon), 109.5,118.1,122.6,124.9,126.8,127.4,129.1,129.9,130.3,131.1,134.9 (Aromatic carbons), IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1}, Mass: (m/z): 353.

(E)-3-(4-methoxystyryl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole : ($4a_{21}$)
Yield: 85%,m.p : 82-85^{0}C,^{1}H NMR: δ 5.23 (t,CH_2), 6.71(d,αCH), 6.91(d,βCH),7.27-7.64(m,Ar-H),5.36(methoxy proton),^{13}C NMR : δ42.5(CH_2), 60.5(methoxy carbon), 107.3,114.5,121.6,122.5,126.3,126.9,127.5,128.4,129.3,129.7,130.2,130.8,133.1 (Aromatic carbons),IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1}, Mass: (m/z): 354.

(E)-3-(4-methoxystyryl)-1-phenyl-5-(*p*-tolyl)-4,5-dihydro-1H-pyrazole : ($4a_{22}$)
Yield: 85%,m.p : 82-85^{0}C, ^{1}H NMR: δ 5.27 (t,CH_2), 6.73(d,αCH), 6.93(d,βCH),7.28-7.63(m,Ar-H),5.36(methoxy proton),3.86(methyl proton),^{13}C NMR : δ42.5(CH_2), 60.5(methoxy carbon), 21.9(methyl carbon),107.5,114.7,121.6,122.5,126.4,127.0,127.7,128.5,129.7,130.1,130.5,130.9,133.5 (Aromatic carbons), IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1}, Mass: (m/z): 368.

(E)-5-(4-methoxyphenyl)-3-(4-methoxystyryl)-1-phenyl-4,5-dihydro-1H-pyrazole : ($4a_{13}$)
Yield: 85%,m.p : 82-85^{0}C,^{1}H NMR: δ 5.25 (t,CH_2), 6.73(d,αCH), 6.93(d,βCH), 7.29-7.60(m,Ar-H),5.36(d,methoxy proton),^{13}C NMR : δ42.9(CH_2), 60.5(methoxy carbon), 107.1,114.8,121.7,122.6,126.8,127.3,127.9,128.7,129.9,130.3,130.7,133.7 (Aromatic carbons), IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1}, Mass: (m/z): 384.

(E)-4-(3-(4-methoxystyryl)-1-phenyl-4,5-dihydro-1H-pyraol-5-yl)aniline : ($4a_{24}$)
Yield: 85%,m.p : 82-85^{0}C, ^{1}H NMR: δ 5.27 (t,CH_2),6.75(d,αCH),6.95(d,βCH),7.24-7.64(m,Ar-H),5.36(methoxy proton),6.27(amino proton),^{13}C NMR : δ42.1(CH_2), 60.5(methoxy carbon), 107.3,114.3,121.1,122.3,126.3,127.1,127.8,128.3,129.1,130.2,130.9,134.1 (Aromatic carbons), IR: C=N-2210cm^{-1}, CH-Stretch,2920 cm^{-1}, Mass: (m/z): 369.

4. Conclusion

Chalcones are prepared from substituted aldehydes and ketones yields from aromatic using the catalytic system NaOH/ EtOH. The substituted chalcones are treated with phenylhydrazine hydrochloride in ethanol were refluxed 8 hrs in the presence of 10% NaOH produced trisubstitutedpyrazole derivatives (3a-d). The compounds are purified and recrystallised from ethanol. The recrystallised compound are further purified with column chromatography. The characterisation of the compounds are done using IR,H^1 NMR,C^{13} NMR, Mass. Biological studies are carried out in future studies.

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