

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, mass spectral, 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 the synthesized compounds were characterized by IR, ¹H-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 chalcone are 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 in adjacent positions, of two nitrogen atoms one basic nitrogen and neutral nitrogen, the aromatic 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 precoated 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. ¹H & ¹³C NMR spectra were recorded on Jeol GSX (400MHz) and DPX 200 (200MHz). mass spectra were recorded on Jeol-JMS-DX 30 hf.

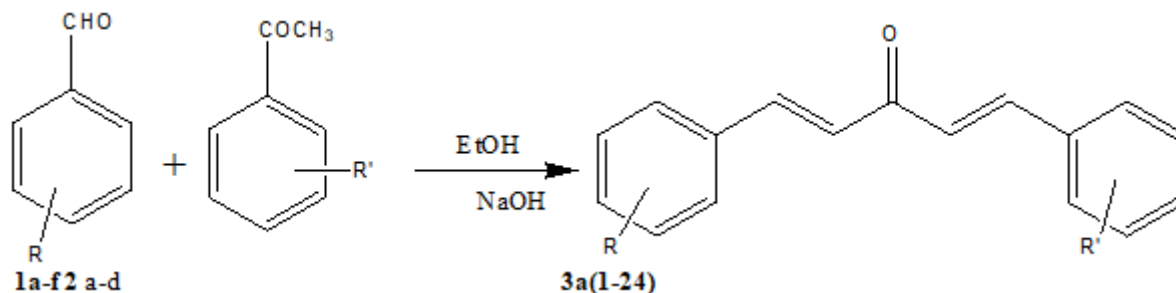
3. Result and Discussion

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.

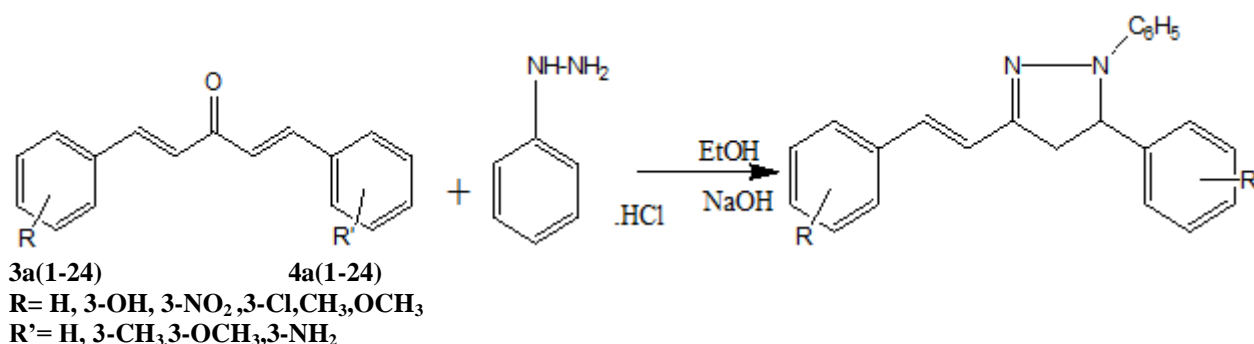


R= H, 3-OH, 3-NO₂, 3-Cl, CH₃, OCH₃
R'= H, 3-CH₃, 3-OCH₃, 3-NH₂

Synthesis of substituted pyrazole 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**).



Characterization

Synthesis of 4,5 dihydro-1,5-diphenyl-3styryl-1H-pyrazole : (**4a₁**)

Eq. moles of (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one (**3a₁**) 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 (**4a₁**) was prepared. yield: 80%, m.p : 87-90°C, ¹H NMR: δ 5.25 (t, CH₂), 6.55 (d, αCH), 6.74 (d, βCH), 7.13-7.59 (m, Ar-H), ¹³C NMR : δ 42.2 (CH₂), 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-2201 cm⁻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-1H-pyrazole : (**4a₂**)

Yield: 81%, m.p : 86-90°C, ¹H NMR: δ 5.30 (t, CH₂), 6.57 (d, αCH), 6.78 (d, βCH), 7.18-7.60 (m, Ar-H), 2.36 (methyl proton). ¹³C NMR : δ 40.9 (CH₂), 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-2270 cm⁻¹, CH-Stretch, 2945 cm⁻¹, Mass: (m/z): 338.

(E)-5-(4-methoxyphenyl)-1-phenyl-3-styryl-4,5-dihydro-1H-pyrazole : (**4a₃**)

Yield: 83%, m.p : 88-92°C, ¹H NMR: δ 5.40 (t, CH₂), 6.59 (d, αCH), 6.94 (d, βCH), 7.18-7.64 (m, Ar-H), 3.87 (methoxy proton). ¹³C NMR : δ 40.9 (CH₂), 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-2290 cm⁻¹, CH-Stretch, 2980 cm⁻¹, Mass: (m/z): 354.

(E)-4-(1-phenyl-3-styryl-4,5-dihydro-1H-pyrazole-5-yl)aniline : (**4a₄**)

Yield: 85%, m.p : 87-90°C, ¹H NMR: δ 5.19 (t, CH₂), 6.55 (d, αCH), 6.83 (d, βCH), 7.02-7.63 (Ar-H, m), 6.27 (amino proton). ¹³C NMR : δ 40.9 (CH₂), 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-2290 cm⁻¹, CH-Stretch, 2980 cm⁻¹, NH₂-1650 cm⁻¹, Mass: (m/z): 339.

(E)-4-(2-(1,5-diphenyl-4,5-dihydro-1H-pyrazol-3-yl)vinyl)phenol : (**4a₅**)

yield: 80%, m.p : 82-85°C, ¹H NMR: δ 5.19 (t, CH₂), 6.65 (d, αCH), 7.56 (d, βCH), 7.23-7.64 (Ar-H, m). ¹³C NMR : δ 40.9 (CH₂), 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-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, OH-3560 cm⁻¹, Mass: (m/z): 340.

(E)-4-(2-(1-phenyl-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-3-yl)vinyl)phenol : (**4a₆**)

Yield: 84%, m.p : 83-86°C, ¹H NMR: δ 5.19 (t, CH₂), 6.67 (d, αCH), 7.49 (d, βCH), 7.23-7.70 (m, Ar-H), 5.35 (OH proton), 2.63 (methyl proton). ¹³C NMR : δ 40.7 (CH₂), 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-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, OH-3560 cm⁻¹, Mass: (m/z): 354.

(E)-4-(2-(5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)vinyl)phenol : (4a₇)

Yield: 79%, m.p : 81-83°C, ¹H NMR: δ 5.20 (t, CH₂), 6.69 (d, αCH), 7.50 (d, βCH), 7.37-7.72 (m, Ar-H), 5.35 (OH proton), 3.83 (methoxy proton). ¹³C NMR : δ 40.5 (CH₂), 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-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, OH-3560 cm⁻¹, Mass: (m/z): 370.

(E)-4-(2-(5-(4-aminophenyl)phenyl-4,5-dihydro-1H-pyrazol-3-yl)vinyl)phenol : (4a₈)

Yield: 80%, m.p : 85-88°C, ¹H NMR: δ 5.21 (t, CH₂), 6.65 (d, αCH), 7.41 (d, βCH), 7.34-7.78 (m, Ar-H), 5.35 (OH proton), 6.27 (amino proton), ¹³C NMR : δ 41.0 (CH₂), 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-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, OH-3560 cm⁻¹, Mass: (m/z): 355.

(E)-3-(3-nitrostyryl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole : (4a₉)

Yield: 81%, m.p : 82-85°C, ¹H NMR: δ 5.19 (t, CH₂), 6.77 (d, αCH), 6.83 (d, βCH), 7.23-8.21 (m, Ar-H), ¹³C NMR : δ 41.0 (CH₂), 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-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, NO₂-1503 cm⁻¹, Mass: (m/z): 369.

(E)-3-(3-nitrostyryl)-1-phenyl-5-(p-tolyl)-4,5-dihydro-1H-pyrazole : (4a₁₀)

Yield: 83%, m.p : 83-86°C, ¹H NMR: δ 5.18 (t, CH₂), 6.75 (d, αCH), 6.85 (d, βCH), 7.25-8.20 (m, Ar-H), 2.60 (methyl proton), ¹³C NMR : δ 40.5 (CH₂), 116.5, 120.7, 123.5, 126.5, 126.7, 128.7, 129.1, 129.6, 135.9, 140.0 (Aromatic carbons), 21.5 (methyl carbon), IR: C=N-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, NO₂-1503 cm⁻¹, Mass: (m/z): 383.

(E)-5-(4-methoxyphenyl)-3-(3-nitrostyryl)-1-phenyl-4,5-dihydro-1H-pyrazole : (4a₁₁)

Yield: 84%, m.p : 86-89°C, ¹H NMR: δ 5.19 (t, CH₂), 6.77 (d, αCH), 6.82 (d, βCH), 7.27-8.19 (m, Ar-H), 3.90 (methoxy proton), ¹³C NMR : δ 40.1 (CH₂), 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-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, NO₂-1503 cm⁻¹, Mass: (m/z): 399.

(E)-4-(3-(3-nitrostyryl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)aniline : (4a₁₂)

Yield: 79%, m.p : 86-88°C, ¹H NMR: δ 5.19 (t, CH₂), 6.75 (d, αCH), 6.85 (d, βCH), 7.28-8.18 (m, Ar-H), 6.30 (amino proton), ¹³C NMR : δ 40.2 (CH₂), 116.5, 120.9, 123.7, 128.6, 127.0, 128.6, 129.7, 130.0, 135.5, 139.8 (Aromatic carbons), IR: C=N-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, NO₂-1503 cm⁻¹, Mass: (m/z): 384.

(E)-3-(4-chlorostyryl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole : (4a₁₃)

Yield: 88%, m.p : 84-86°C, ¹H NMR: δ 5.20 (t, CH₂), 6.83 (d, αCH), 6.77 (d, βCH), 7.29-7.68 (m, Ar-H), ¹³C NMR : δ 40.9 (CH₂), 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-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, Cl- 670 cm⁻¹, Mass: (m/z): 359.

(E)-3-(4-chlorostyryl)-1-phenyl-5-(p-tolyl)-4,5-dihydro-1H-pyrazole : (4a₁₄)

Yield: 86%, m.p : 80-83°C, ¹H NMR: δ 5.19 (t, CH₂), 6.85 (d, αCH), 6.79 (d, βCH), 7.30-7.70 (m, Ar-H), 2.45 (methyl proton), ¹³C NMR : δ 40.5 (CH₂), 116.5, 119.7, 123.5, 126.1, 126.3, 127.8, 129.8, 130.5, 134.7, 137.9 (Aromatic carbons), 21.9 (methyl carbon), IR: C=N-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, Cl- 670 cm⁻¹, Mass: (m/z): 373.

(E)-3-(4-chlorostyryl)-5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole : (4a₁₅)

Yield: 81%, m.p : 82-84°C, ¹H NMR: δ 5.20 (t, CH₂), 6.87 (d, αCH), 6.73 (d, βCH), 7.31-7.69 (m, Ar-H), 3.85 (methoxy proton), ¹³C NMR : δ 40.5 (CH₂), 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 (methoxy carbon), IR: C=N-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, Cl- 670 cm⁻¹, Mass: (m/z): 388.

(E)-4-(3-(4-chlorostyryl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-yl)aniline : (4a₁₆)

Yield: 85%, m.p : 82-85°C, ¹H NMR: δ 5.18 (t, CH₂), 6.85 (d, αCH), 6.78 (d, βCH), 7.29-7.70 (m, Ar-H), 6.39 (amino proton), ¹³C NMR : δ 40.1 (CH₂), 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-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, Cl- 670 cm⁻¹, Mass: (m/z): 373.

(E)-3-(4-methylstyryl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole : (4a₁₇)

Yield: 85%, m.p : 82-85°C, ¹H NMR: δ 5.20 (t, CH₂), 6.75 (d, αCH), 6.95 (d, βCH), 7.27-7.59 (m, Ar-H), 2.19 (methyl proton), ¹³C NMR : δ 41.2 (CH₂), 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-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, Mass: (m/z): 338.

(E)-3-(4-methylstyryl)-1-phenyl-5-(p-tolyl)-4,5-dihydro-1H-pyrazole : (4a₁₈)

Yield: 85%, m.p : 82-85°C, ¹H NMR: δ 5.19 (t, CH₂), 6.71 (d, αCH), 7.0 (d, βCH), 7.29-7.60 (m, Ar-H), 2.23 (methyl proton), ¹³C NMR : δ 41.0 (CH₂), 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-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, Mass: (m/z): 352.

(E)-5-(4-methoxyphenyl)-3-(4-methylstyryl)-1-phenyl-4,5-dihydro-1H-pyrazole : (4a₁₉)

Yield: 85%, m.p : 82-85°C, ¹H NMR: δ 5.18 (t, CH₂), 6.71 (d, αCH), 6.97 (d, βCH), 7.28-7.54 (m, Ar-H), 2.23 (methyl proton), 5.65 (methoxy proton), ¹³C NMR : δ 41.1 (CH₂), 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-2210 cm⁻¹, CH-Stretch, 2920 cm⁻¹, Mass: (m/z): 368.

(E)-4-(3-(4-methylstyryl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)aniline : (4a₂₀)

Yield: 85%, m.p : 82-85°C, ¹H NMR: δ 5.19 (t, CH₂), 6.75(d, αCH), 6.98(d, βCH), 7.30-7.60(m, Ar-H), 2.23(methyl proton), ¹³C NMR : δ 41.0(CH₂), 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 : (4a₂₁)

Yield: 85%, m.p : 82-85°C, ¹H NMR: δ 5.23 (t, CH₂), 6.71(d, αCH), 6.91(d, βCH), 7.27-7.64(m, Ar-H), 5.36(methoxy proton), ¹³C NMR : δ 42.5(CH₂), 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 : (4a₂₂)

Yield: 85%, m.p : 82-85°C, ¹H NMR: δ 5.27 (t, CH₂), 6.73(d, αCH), 6.93(d, βCH), 7.28-7.63(m, Ar-H), 5.36(methoxy proton), 3.86(methyl proton), ¹³C NMR : δ 42.5(CH₂), 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 : (4a₁₃)

Yield: 85%, m.p : 82-85°C, ¹H NMR: δ 5.25 (t, CH₂), 6.73(d, αCH), 6.93(d, βCH), 7.29-7.60(m, Ar-H), 5.36(d, methoxy proton), ¹³C NMR : δ 42.9(CH₂), 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-pyrazol-5-yl)aniline : (4a₂₄)

Yield: 85%, m.p : 82-85°C, ¹H NMR: δ 5.27 (t, CH₂), 6.75(d, αCH), 6.95(d, βCH), 7.24-7.64(m, Ar-H), 5.36(methoxy proton), 6.27(amino proton), ¹³C NMR : δ 42.1(CH₂), 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 trisubstituted pyrazole 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, ¹H NMR, ¹³C NMR, Mass. Biological studies are carried out in future studies.

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