Research Article

Synthesis and Characterization of 2-(1-Benzoyl-5-Phenyl-4, 5-Dihydro-1h-Pyrazol-3-Yl)-6-Chloro-4-Methoxyphenol Derivatives

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Accepted on: 16-10-2014; **Finalized on:** 31-12-2014.

ABSTRACT

In the present study, pyrazoline derivatives were synthesized. Pyrazolines are well known and important nitrogen containing five-membered heterocyclic compounds. Pyrazoline derivatives have been extensively studied because of their ready accessibility through synthesis, diverse chemical reactivity, various biological activities and variety of industrial applications. Hence two compounds Benzaldehyde substituted pyrazoline, 2-(1-benzoyl-5-phenyl-4, 5-dihydro-1h-pyrazol-3-yl)-6-chloro-4-methoxyphenol and Fluoro benzaldehyde substituted pyrazoline, 2-[1-benzoyl-3-(3-fluorophenyl)-4, 5-dihydro-1H-pyrazol-5-yl]-6-chloro-4-methoxyphenol were synthesized and the structures of all these compounds have been established on the basis of analytical and spectral data and structural elucidations were done using IR, ^{1}H-NMR, ^{13}C-NMR, LCMS, GCMS spectral and elemental analysis. The recovery of the final compound was in the range from 95% to 100%.

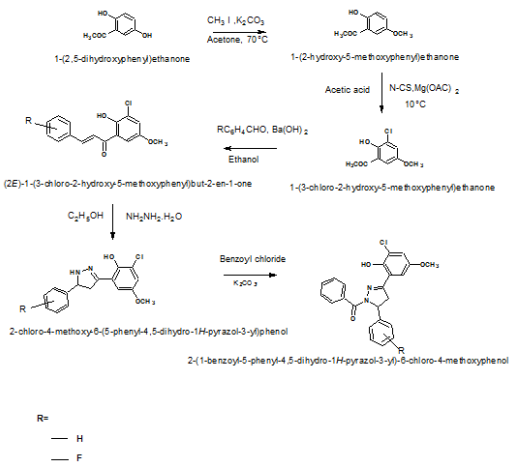
Keywords: Synthesis, Pyrazoline derivatives, Substituted pyrazoline.

INTRODUCTION

Heterocyclic compounds are acquiring more importance in recent years because of their immense biological and pharmacological potency. Various biologically active synthetic compounds have five membered nitrogen containing heterocyclic ring in their structures. Pyrazoline is a dihydro form of pyrazole which is 5-membered ring containing adjacent nitrogen atoms[1]. Pyrazoline is a new, upcoming molecule in the market, which possess anti-inflammatory, analgesic and antibacterial activity. Drugs which contain all three activities are not common. The purpose of the present study was to examine whether molecular modification might result in detection of new potential antirheumatic drugs having antimicrobial activities. Several pyrazoline derivatives reported to possesses anti-inflammatory[2] anti-fertility[3] anti-implantation[4] and insecticidal[5] activities. Pyrazolines were also found as effective chemical bleaching agents, luminescent and fluorescent agents[6, 7].

Literature survey reveals several synthetic protocols for the synthesis of these compounds and the presence of this core in any molecule plays a key role in enhancing the activity. In view of these observations and in continuation of our research programme on the synthesis of five membered hetero cyclic compounds, we report here in the synthesis of some new pyrazoline derivatives, which have been found to possess an interesting profile of anti-inflammatory, analgesic, anti bacterial activity, with significant reduction in their ulcerogenic potential[8] Literature survey revealed that many pyrazoline derivatives show higher antibacterial activity only with sulfa substitutions.[9-12] In the present work, molecular modification has been done by substituting electron withdrawing group instead of electron releasing group. In the present study we decided to substitute the pyrazoline ring with electron withdrawing moieties. The procedure adopted for the synthesis of the compounds is shown in scheme-1.

Scheme I Synthetic Route for the Compounds



MATERIALS AND METHODS

Instrumentation

HPLC

Agilent 1200 series HPLC system (Agilent Technologies, California, US) comprising of a dual piston reciprocating pump, DAD detector, an auto injector, and in-line degasser was employed. This separation was achieved using Eclipse XBD-C18 (Agilent Technologies, California, US). The data was acquired using ChemStation software (Agilent Technologies, California, US).

GC-MS

Column used was DB- MS, Detector Flame Ionization Detector- 280 °C, Injector 5.0 µL into the split port

maintained at 210 °C using Constant Pressure, Head Pressure 13 psi, Split Flow 20 mL/min. Carrier Gas Helium, Injection Port Liner 4mm i.e., deactivated open glass tube packed with fused silica wool Oven Temperature 75 °C for 2 min, increase at 15 °C/ minutes to 280 °C for 4 minutes, and hold for 4 min. Solvent Methanol Sample Preparation 5.0 mg /mL with solvent, Blank was injected followed by sample solution.

NMR

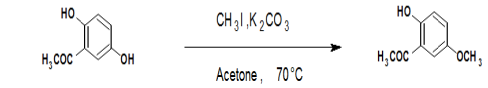
Bucker Superconducting FT-NMR Spectrometer Advance 400, Model-DPX-300, AV-400, AV3-400. Operational frequency: 400 MHz, Test-1H, Number of scans-8, Spectral width 16 ppm, Solvent: DMSO-d_6 & CDCl3.

LC-MS

Column-ATLANTIS C18, Mass- Agilent Ion Trap, Ionization type- ES+APCI. Injection Volume 2.0 µl, Wavelength Maximum Chromatogram (190-400nm), Flow rate 1.0 mL/min. Column Temp Ambient, Mobile Phase A 0.1% Formic acid Mobile Phase B Methanol.

Preparation and Synthesis of Benzaldehyde Substituted Pyrazoline

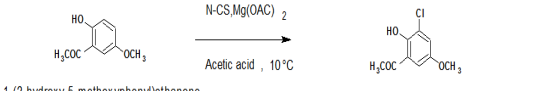
Preparation and Synthesis of 1-(2-Hydroxy-5-methoxyphenyl) ethanone



1-(2,5-dihydroxyphenyl)ethanone 1-(2-hydroxy-5-methoxyphenyl)ethanone

In a 1-1 L round bottomed flask fitted with a reflux condenser and a calcium chloride guard tube are placed 25.0 g (0.1639 mol) of quinacetophenone and 300 mL of acetone. The mixture was warmed on to dissolve the quinacetophenone. The resulting greenish solution was cooled to room temperature and 23.1 g (0.1671 mol) of anhydrous potassium carbonate was added followed by 27.90 g (0.1966 mol) of methyl iodide. The mixture was allowed to reflux at 60-70 °C for 24 hours. The completion of reaction was confirmed by TLC and HPLC. After the conformation of the absence of starting material, the reaction mass was diluted with ethyl acetate (2 x 100 mL) and washed with water (2 x 50 mL) followed by brine (50 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography with silica gel (60-120 mesh) as the stationary phase using ethyl acetate / pet ether mixture as the eluents to yield a green solid. Yield: 20g

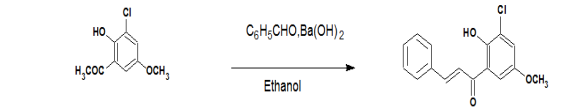
Preparation and Synthesis of 1-(3-chloro-2-hydroxy-5-methoxyphenyl) ethanone



1-(2-hydroxy-5-methoxyphenyl)ethanone 1-(3-chloro-2-hydroxy-5-methoxyphenyl)ethanone

3-Chloro-2-hydroxy-5-methoxyacetophenone was prepared by selective chlorination of 2- hydroxyl-5-methoxyacetophenone with N-Chlorosuccinamide (NCS) in acetic acid containing Mg (OAc). In a 1-1 round bottomed flask, 10.0 g (0.0600 mol) of 2-hydroxy-5-methoxyacetophenone and 100mL of acetic acid was taken under nitrogen atmosphere. The mixture was heated to 40 °C to dissolve the 2-Hydroxy-5-methoxyacetophenone completely and then cooled to RT. Then 8.78 g (0.0659 mole) of Mg (OAc) $_2$ was added to the reaction mixture at room temperature 20-30 °C. In an another 250 mL round bottomed flask 12.86 g (0.0599 mole) of NCS was dissolved in 100 mL acetic acid at 70 °C and added to the reaction mixture at 0 °C. The reaction mixture was stirred for 24 hrs at 10 °C. The reaction completion was confirmed by TLC and HPLC. The resulting solid was filtered and washed twice with water (2 x 100 mL). Yield: 5g

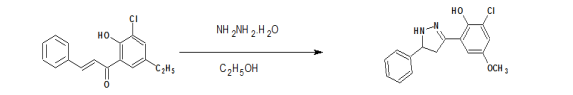
Preparation and Synthesis of (2E)-1-(3-chloro-2-hydroxy-5-methoxyphenyl) but-2-en-1-one



1-(3-chloro-2-hydroxy-5-methoxyphenyl)ethanone (2*E*)-1-(3-chloro-2-hydroxy-5-methoxyphenyl) -3-phenylprop-2-en-1-one

In a 250 mL round bottomed flask 3-Chloro-2-hydroxy-5-methoxyacetophenone 5.0 g (0.0249 mol) and benzaldehyde 3.17 g (0.0299 mol) were mixed with 100 mL absolute ethanol under nitrogen atmosphere. Barium hydroxide 6.40g (0.0373 mol) was added, and refluxed at 70-80 °C for 4 hours. The reaction completion was confirmed by TLC and HPLC. After the absence of starting material aqueous HCl (10 mL, 1.5M) was added to the solid. The reaction mass was diluted with MTBE (2 x 50 mL) and washed twice with water (2 x 30 mL), dried over anhydrous sodium sulphate. The organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography with silica gel (60:120 mesh) as the stationary phase, using ethylacetate / pet ether mixture as the eluents. Yield: 5g

Preparation and Synthesis of 2-chloro-4-methoxy-6-(5-phenyl-4, 5-dihydro-1H-pyrazol-3-yl) phenol



(2E)-1-(3-chloro-5-ethyl-2-hydroxyphenyl)-3-phenylprop-2-en-1-one

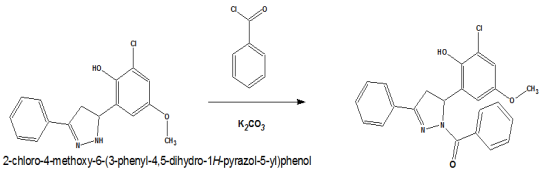
2-chloro-4-methoxy-6-(5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)phenol

A mixture of 3-Chloro-2-hydroxy-5-methoxyacetophenone chalcone 2.0g (0.0099 mol) and 99% hydrazine hydride 1.5 mL (0.0149 mol) in ethanol (50 mL) was refluxed at 70-80 °C for 4 hours under nitrogen atmosphere.

The reaction completion was confirmed by TLC and HPLC. After the absence of starting material, the mixture was concentrated and allowed to cool.

The resulting solid was washed with ethanol and crystallized from ethanol to obtain pyrazoline. Yield: 2.2g.

Preparation and Synthesis of 2-(1-benzoyl-3-[(1E)-1-methylbuta-1,3-dienyl]-4,5-dihydro-1Hpyrazol-5-yl)-6-chloro-4-methoxyphenol



2-chloro-4-methoxy-6-(3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)phenol

2-[1-benzoyl-3-[(1*E*)-1-methylbuta-1,3-dienyl]-4,5-dihydro-1*H*-pyrazol-5-yl]-6-chloro-4-methoxyphenol

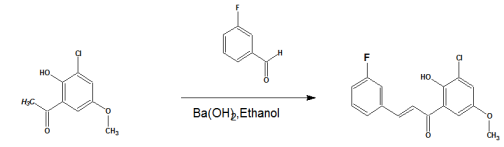
1-H-3-[2'-hydroxy-3'-chloro-5'-ethyl phen-1'-yl]-5-aryl-2-pyrazolines 1.5 g (0.004966 mol) was dissolved in 10 mL of dichloro methane (MDC) and 0.82 g (0.005959 mol) of potassium carbonate was added to the mixture under nitrogen atmosphere. The reaction mass was stirred for 30 minutes to generate the anion. Benzoyl chloride 0.69 mL (0.004966 mol) was added to the mixture slowly drop wise at 0 °C. The reaction was carried out at room temperature 20-30 °C for an hour. The reaction completion was confirmed by TLC and HPLC.

After the absence of starting material the dichloro methane layer was concentrated and the resulting solid was diluted with ethyl acetate (2 x 15 mL) and washed with sodium bicarbonate (15 mL). Again the organic layer was washed with water (2 x 30 mL), followed by brine solution (20 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The resulting solid has 80 % purity by HPLC, which was further purified by continuous stirring in diethyl ether for 2 hours.

The ether layer was decanted and the resulting solid was 96 % pure by HPLC. Yield: 1.3g

Preparation and Synthesis of 3-Fluoro-Benzaldehyde Substituted Pyrazoline

Preparation and Synthesis of (2E)-1-(3-chloro-2-hydroxy-5-methoxyphenyl)-3-(3-fluorophenyl) prop-2-en-1-one



1-(3-chloro-2-hydroxy-5-methoxyphenyl)ethanone

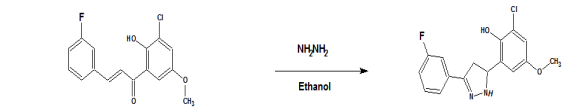
(2*E*)-1-(3-chloro-2-hydroxy-5-methoxyphenyl)-3-(3-fluorophenyl)prop-2-en-1-one

In a 250 mL three necked round bottomed flask fitted with refluxed condenser 1-(3-chloro-2-hydroxy-5-methoxyphenyl) ethanone 1.0 g (0.004984 mol) and 3-fluoro-benzaldehyde 3.17 g (0.00498mole) were mixed with 100 mL absolute ethanol under nitrogen atmosphere. Barium hydroxide 6.40 g (0.00747 mol) was added, and refluxed at 70-80 °C for 4 hours.

The reaction completion was confirmed by TLC and HPLC. After the absence of starting material, aqueous HCl (10 mL, 1.5 M) was added to the reaction mass.

The reaction mass was diluted with MTBE (2 x 50 mL) and washed with water (2 x 30 mL), dried over anhydrous sodium sulphate and. concentrated under reduced pressure. The crude product was purified by column chromatography with silica gel (60:120 mesh) as the stationary phase, using ethylacetate / pet ether mixture as the eluents. Yield: 0.8g

Preparation and Synthesis of 2-chloro-6-[3-(-3-fluorophenyl)-4, 5-dihydro-1-H-pyrazol-5-yl]-4 methoxyphenol

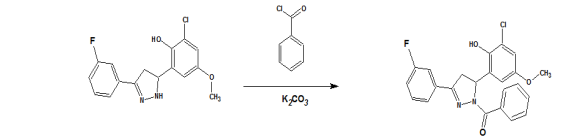


(2*E*)-1-(3-chloro-2-hydroxy-5-methoxyphenyl)-3-(3-fluorophenyl)prop-2-en-1-one

2-chloro-6-[3-(3-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl]-4-methoxyphenol

A mixture of (2E)-1-(3-chloro-2-hydroxy-5-methoxyphenyl)-3-(3-fluorophenyl)prop-2-en-1-one 2.0 g (0.00651 mole) and 99 % hydrazine hydride 0.48 mL (0.0097 mol) in ethanol (50 mL) was refluxed at 70-80 °C for 4 hours under nitrogen atmosphere. The reaction completion was confirmed by TLC and HPLC. After the absence of starting material, the mixture was concentrated and allowed to cool. The resulting solid was washed with ethanol and crystallized from ethanol to obtain pyrazoline. Yield: 1.2g

Preparation and Synthesis of 2-[1-benzoyl-3-(3-fluorophenyl)-4, 5-dihydro-1H-pyrazol-5-yl]-6-chloro-4-methoxyphenol



2-chloro-6-[3-(3-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl]-4-methoxyphenol

2-[1-benzoyl-3-(3-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl]-6-chloro-4-methoxyphenol

2-chloro-6-[3-(3-fluorophenyl)-4, 5-dihydro-1H-pyrazol-5-yl]-4-methoxyphenol 1.0 g (0.00311 mol) was dissolved in 10 mL of dichloro methane under nitrogen atmosphere. 0.51 g (0.00371 mol) of potassium carbonate was added to the reaction mixture.

The reaction mass was stirred at RT for 30 minutes to generate the anion. Benzoyl chloride 0.69 mL (0.00311 mol) was added to the reaction mixture slowly drop wise at 0 °C. Warm the reaction mass to RT and stirred for an hour. The reaction completion was confirmed by TLC and HPLC. After the absence of starting material the dichloro methane layer was concentrated and the resulting solid diluted with ethyl acetate (2 x 15 mL) and washed with sodium bicarbonate (15 mL).

Again the organic layer was washed with water (2 x 30mL), followed by brine solution (20 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure.

The resulting solid has 80 % purity by HPLC, which was further purified by continuous stirring in diethyl ether for

2 hours. The ether layer was decanted and the resulting solid was 96 % pure. Yield: 0.8 g

RESULTS AND DISCUSSION

Characterization and Spectral Data of Synthesized Compounds

Spectral data of Benzaldehyde Substituted Pyrazoline

Spectral data of 1-(2-Hydroxy-5-methoxyphenyl) ethanone

%YIELD-73.2%,HPLCPURITY-99.8%,NMR-^{1}HNMR(DMSOD6):Δ=2.6(S,3H,$COCH_3$),3.7(S,3H,OCH_3), 6.8(D,1H,CH),7.1(D,1H,CH),7.3(S,1H,CH),11.4(1H,OH),GC MS-CALCULATED MASS FOR $C_9H_{10}O_2$=166.17 FOUND MASS FOR $C_9H_{10}O_2$=166

Spectral data of 1-(3-chloro-2-hydroxy-5-methoxyphenyl) ethanone

%YIELD-60%,HPLCPURITY-99.1%,NMR-^{1}HNMR(DMSOd6)δ=2.6(S,3H,COCH3),3.7(S,3H,OCH_3),7.3 (S,1H,CH),7.4(S,1H,CH),12.0(1H,OH),GCMS-CALCULATED MASS=200.16 FOUND MASS=200

Spectral data of (2E)-1-(3-chloro-2-hydroxy-5-methoxyphenyl) but-2-en-1one

%YIELD:69.4%,HPLCPURITY:85%,NMR-^{1}HNMR($CDCl_3$)δ=3.8(S,3H,OCH_3),7.2(S,1H,CH),7.3(S,1H,CH),7.4-7.7(M,5H),7.96(d,1H,CH),7.99(d,1H,CH),12.9(1H,OH),LCM S-CALCULATED MASS=288.72 FOUND MASS=286.8

Spectral data of 2-chloro-4-methoxy-6-(5-phenyl-4, 5-dihydro-1H-pyrazol-3-yl) phenol

%YIELD:70.06%,HPLCPURITY:99.2%,NMR-^{1}HNMR($CDCl_3$)δ=3.1(Q,2H,CH_2),(Q,1H,CH2),3.7(S,3H,OCH_3),4.9(Q,1H,CH),6.6(S,1H,CHAromatic),6.9(S,1H,CH-Ar),7.3(M,5H),12.9(1H,OH),LCMS-CALCULATED MASS=302.755 FOUND MASS=302.8

Spectral data of 2-(1-benzoyl-3-[(1E)-1-methylbuta-1,3-dienyl]-4,5-dihydro-1Hpyrazol-5-yl)-6 chloro4methoxyphenol

%YIELD:65%,HPLCPURITY:96%,NMR-^{1}HNMR($CDCl_3$)δ=3.3(Q,1H,CH_2),3.7(S,3H,OCH_3),3.9(Q,1H,C H_2),5.7(Q,1H,CH),6.6(S,1H,CH-Ar),7.0(S,1H,CH-Ar),7.3(M,10H,CH-Ar),10.1(S,1H,OH),LCMS-CALCULATED MASS=406.86, FOUND MASS=407.2

Spectral data of 3-Fluoro-Benzaldehyde substituted pyrazoline

Spectral data of (2E)-1-(3-chloro-2-hydroxy-5-methoxyphenyl)-3-(3-fluorophenyl) prop-2-en-1-one

%YIELD:52.1%,HPLCPURITY:91%,NMR-^{1}HNMR($CDCl_3$)δ=3.8(S,3H,OCH_3),7.9(S,1H,CH),7.5(S,1H,CH),71-7(M,6H,CHAr),12.7(S,1H,OH),LCMS-CALCULATED MASS=307, FOUND MASS=308

Spectral data of 2-chloro-6-[3-(-3-fluorophenyl)-4,5-dihydro-1-H-pyrazol-5-yl]-4methoxyphenol

%YIELD:60%, HPLC PURITY:97.8%, NMR-^{1}HNMR($CDCl_3$) δ=3.3 (Q,1H,CH_2), 5.7(Q,1H,CH), 6.6(S,1H,NH), 7.8(S,1H,CH), 7-7.7(M,9H,CH), 10.0(S,1H,OH), LCMS-CALCULATED MASS=320.74 FOUND MASS=321.1

Spectral data of 2-[1-benzoyl-3-(3-fluorophenyl)-4, 5-dihydro-1H-pyrazol-5-yl]-6-chloro-4-methoxyphenol

%YIELD:61.53%,HPLCPURITY:99%,NMR-^{1}HNMR($CDCl_3$)δ=3.3(Q,1H,CH_2),3.7(S,3H,OCH_3),3.9(Q,1H,C H_2),5.7(Q,1H,CH),6.6(S,1H,CH-Ar),7.0(S,1H,CH-Ar),7.3(M,10H,CH-Ar),10.1(S,1H,OH),LCMS-CALCULATED MASS=425 FOUND MASS=423.5

Figure 1 shows the IR Spectra of 2-(1-benzoyl-3-[(1E)-1-methylbuta-1,3-dienyl]-4,5-dihydro-1Hpyrazol-5-yl)-6 chloro4methoxyphenol

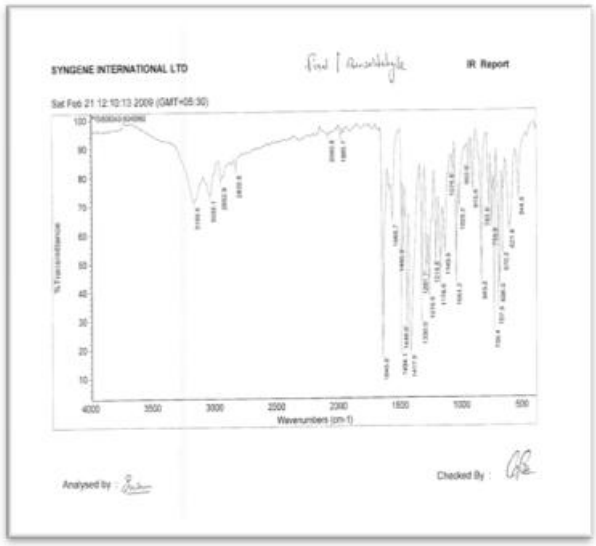


Figure 1: IR Spectra of the Final Compound

Figure 2 shows the HPLC Chromatogram of 2-(1-benzoyl-3-[(1E)-1-methylbuta-1,3-dienyl]-4,5-dihydro-1Hpyrazol-5-yl)-6 chloro4methoxyphenol

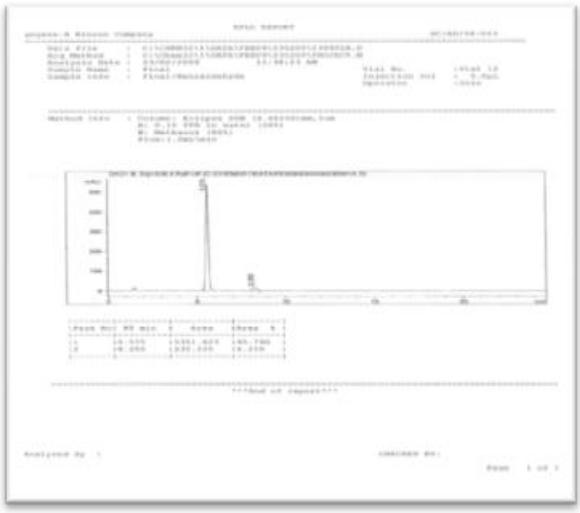


Figure 2: HPLC Chromatogram of the Final Compound

Figure 3 shows the LCMS—2 Chromatogram of 2-(1-benzoyl-3-[(1E)-1-methylbuta-1,3-dienyl]-4,5-dihydro-1Hpyrazol-5-yl)-6 chloro4methoxyphenol

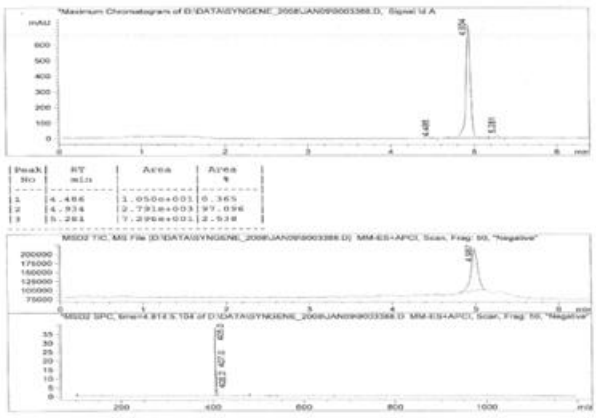


Figure 3: LCMS Chromatogram of the Final Compound

Figure 4 shows the ^{1}H-NMR Spectra of 2-(1-benzoyl-3-[(1E)-1-methylbuta-1,3-dienyl]-4,5-dihydro-1Hpyrazol-5-yl)-6 chloro4methoxyphenol

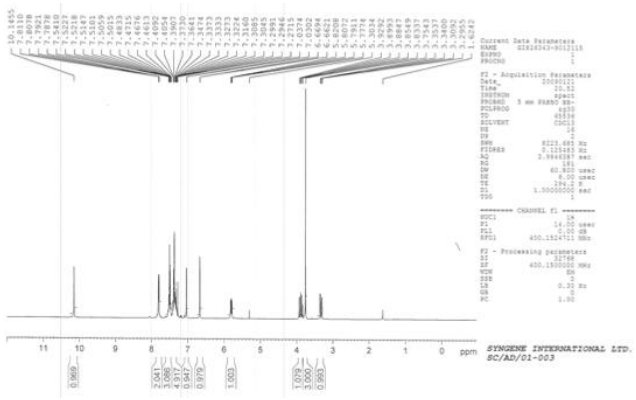


Figure 4: ^{1}H-NMR Chromatogram of the Final Compound

CONCLUSION

Pyrazoline is a new upcoming molecule in the market. According to literature survey only very few methods were developed for the pyrazoline molecule. Hence pyrazoline derivative compound was synthesized. The synthesis of the compound 2-(1-benzoyl-5-phenyl-4,5-dihydro-1h-pyrazol-3-yl)-6-chloro-4-methoxyphenol derivatives paves a way for the other pyrazoline derivatives. Further, this would lead to the synthesis of other cost effective novel lead molecules. The two synthesized compounds Benzaldehyde substituted pyrazoline, 3-Fluoro-benzaldehyde substituted pyrazoline were confirmed and characterized by ^{1}H NMR, ^{13}C-NMR, GC-MS and LC-MS. The synthesized compounds were purified by column chromatography using silica gel and appropriate solvents and the percentage purity was measured using RP-HPLC.

Figure 5 shows the ^{13}C-NMR Spectra of 2-(1-benzoyl-3-[(1E)-1-methylbuta-1,3-dienyl]-4,5-dihydro-1Hpyrazol-5-yl)-6 chloro4methoxyphenol

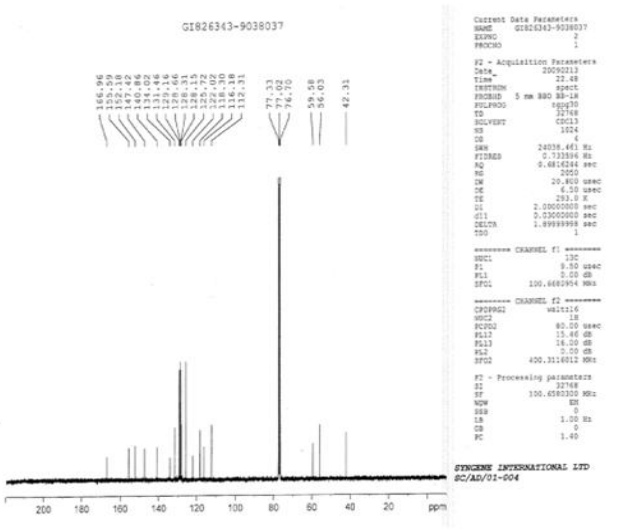


Figure 5: ^{13}C-NMR Spectra of the Final Compound

Acknowledgement: The authors would like to acknowledge our sincere thanks to Syngene International Limited, Bangalore, India and Anna University Tiruchirappalli, Tiruchirappalli, India for the technical support to complete this study successfully.

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Source of Support: Nil, **Conflict of Interest:** None.