

## A Facile Solvent-Free Route for One-Pot Multicomponent Synthesis of Benzylpyrazolyl Coumarins Derivatives in Presence of Effective Synergetic Catalytic System

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analysis of all the synthesized compounds

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A combinatorial library of benzylpyrazolyl coumarin derivatives have been synthesized by a green one-pot four-component reaction between aryl hydrazine/hydrazine hydrate (1), ethyl acetoacetate (2), aromatic aldehydes (3) and 4-hydroxycoumarin (4) catalyzed by niobium pentachloride with silver salt under solvent-free conditions has been developed. Experimental simplicity, simple work-up procedure and solvent-free reaction condition at room temperature are important features of the present protocol.

**Keywords:** Niobium pentachloride, Silver salt, Benzylpyrazolyl coumarin.

### INTRODUCTION

Recently, green chemistry has received more attention due to its great applications and approaches that aim to prevent pollution and reduce the use of the waste materials that affect the human health and environment. Therefore, a number of chemists focused on designing of methodologies to create chemical protects without toxicity to human health. In this sense, a green chemistry focuses mainly on chemical syntheses using novel synthetic methods that provide affordable protects and services to the human and society [1-5]. To enhance chemical processes and environment friendly protects, the chemists working in green chemistry carry out multicomponent reactions that offer great advantages in the green chemistry, in which various flow one-pot transformations occur in the same step to offer the product without a need to segregate or isolate any compounds produced in the intermediate steps [6-8].

The important synthesized compounds by multicomponent reactions were these derivatives containing coumarins and pyrazolone nucleus. 3-Substituted 4-hydroxycoumarin, especially 3-benzyl substituted 4-hydroxycoumarin derivatives that are of extreme significance because they exist abundantly in natural products and exhibit a wide range of biological activities as they are used in medicinal scaffolds, namely warfarin,

phenprocoumon, coumatetralyl, carbochromen, bromadiolone, offering antibacterial, anti-HIV [9], antiviral [10], anticoagulant [11], antioxidant [12] and anticancer activities [13]. Moreover, pyrazolones are regarded as important structural nuclei in many drugs such as convenient antipyretic and analgesic drugs [14], whereas edaravone (MCI-186) has been useful for curing brain [15,16] and myocardial ischemia [17]. In addition, pyrazolones have kinase inhibitory effects, particularly in the case of enzymes which catalyze both phosphorylation of serine and threonine in proteins. They are also used for treating diseases related to these enzymes, such as rheumatoid arthritis, psoriasis, bone loss, cancer and other proliferative diseases including antifungal [18], antimycobacterial [19,20], antibacterial [21], anti-inflammatory [22], antitumor [23], gastric secretion stimulatory [24], antidepressant [25], antifilarial activities [26] and antitubercular activities [27].

In the present work, a novel route was used for the synthesis of benzylpyrazolyl coumarins (5) with high yields by one pot four component condensation reaction of hydrazine (1), ethyl acetoacetate (2), aromatic aldehyde (3) and 4-hydroxycoumarin (4) reacted in the presence of a mixture of NbCl<sub>5</sub> and AgClO<sub>4</sub> as Lewis acid and a combined catalyst under room temperature and stirring conditions, in short reaction time and environmentally benign.

## EXPERIMENTAL

**General procedures for the synthesis of benzylpyrazolyl coumarin derivatives:** In a mixture of 5 mol of ethanol and 5 mL of water, phenyl hydrazine (1 mmol), ethyl acetoacetate (1 mmol), aromatic aldehyde (1 mmol) and 4-hydroxycoumarin (1 mmol), 1 mol % of NbCl<sub>5</sub> and 3 mol % of AgClO<sub>4</sub> were dissolved and stirred at room temperature. After completing the reaction monitor by thin-layer chromatography, the reaction mixture was left to be cooled at room temperature. Then, the reaction mixture was poured into cold water and the crystalline product was filtered. After that, the product was washed by water for 2-3 times and, then, dried at the room temperature and recrystallized from hot ethanol to afford the corresponding benzylpyrazolyl coumarin derivatives. To recover the catalyst from the filtrate, the aqueous layer was evaporated under reduced pressure to yield the final product. All the products were characterized by IR, <sup>1</sup>H NMR and mass spectra.

**1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(3-nitrophenyl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-3-one:** Yield: 90 %, Yellow crystalline solid, m.p.: 200-202 °C, IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 2918, 1764, 1681, 1521, 1458, 1173, 1043, 756, <sup>1</sup>H NMR (400 MHz, DMSO) δ = 2.20 (s, 3H), 5.79 (s, 1H), 7.05-7.07 (m, 4H), 7.11-7.20 (m, 2H), 7.24-7.31 (m, 2H), 7.41-7.49 (m, 2H), 7.82-7.89 (m, 2H) ppm, LC-MS (ESI) *m/z* [M<sup>+</sup> + H] = 434.1.

**1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-3-one:** Yield: 80 %, White crystalline solid, m.p.: 230-232 °C, IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3062, 2803, 1764, 1720, 1668, 1450, 1174, 1028, 750, <sup>1</sup>H NMR (400 MHz, DMSO) δ = 1.75 (s, 1H), 2.21 (s, 3H), 5.74 (s, 1H), 7.73-7.80 (m, 4H), 7.18-7.35 (m, 5H), 5.74-7.69 (m, 5H) ppm, LC-MS (ESI) *m/z* [M<sup>+</sup> + H] = 388.1.

**4-((4-Chlorophenyl)(4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-3-one:** Yield: 93 %, White crystalline solid m.p.: 225-227 °C, IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3064, 1651, 1602, 1492, 1177, 1095, 752, <sup>1</sup>H NMR (400 MHz, DMSO) δ = 2.44 (s, 3H), 5.72 (s, 1H), 7.17-7.24 (m, 8H), 7.34-7.50 (m, 3H), 7.58-7.91 (m, 3H) ppm, LC-MS (ESI) *m/z* [M<sup>+</sup> + H] = 461.1.

**1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(4-Methoxyphenyl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-3-one:** Yield: 85 %, Yellow crystalline solid, m.p.: 199-202 °C, IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 2989, 1693, 1614, 1566, 1512, 1450, 1151, 1021, 756, <sup>1</sup>H NMR (400 MHz, DMSO) δ = 2.38 (s, 3H), 3.99 (s, 3H), 4.22 (s, 1H), 6.57-6.59 (m, 3H), 7.14-7.19 (m, 5H), 7.31-7.43 (m, 3H), 7.51-7.55 (d, *J* = 8.1 Hz, 2H), 7.78-7.80 (d, *J* = 7.8 Hz, 1H) ppm, LC-MS (ESI) *m/z* [M<sup>+</sup> + H] = 419.1.

**1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(4-nitrophenyl)methyl)-5-methyl-2-phenylpyrazol-3-one:** Yield: 92 %, Pale yellow crystalline solid, m.p.: 248-250 °C, IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3073, 1649, 1608, 1560, 1525, 1178, 1039, 748, <sup>1</sup>H NMR (400 MHz, DMSO) δ = 2.65 (s, 3H), 6.12 (s, 1H), 7.46-7.78 (m, 9H), 7.94-8.97 (m, 5H) ppm, LC-MS (ESI) *m/z* [M<sup>+</sup> + H] = 469.

**1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(*p*-tolyl)methyl)-5-methyl-2-phenylpyrazol-3-one:** Yield: 92 %, White crystalline solid, m.p.: 222-224 °C, IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3081, 1649, 1610, 1494, 1184, 1031, 752, <sup>1</sup>H NMR (400 MHz, DMSO) δ = 2.18 (s, 3H), 2.34 (s, 3H), 5.68 (s, 1H), 6.92-7.19 (m, 7H), 7.31-7.41 (m, 4H), 7.58-7.61 (d, *J* = 7.8 Hz, 2H), 7.75-7.78 (m, 1H) ppm, LC-MS (ESI) *m/z* [M<sup>+</sup> + H] = 438.1.

**4-((4-Fluorophenyl)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-1,2-dihydro-5-methyl-2-phenylpyrazol-3-one:** Yield: 93 %, White crystalline solid, m.p.: 240-242 °C, IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3081, 1656, 1607, 1566, 1499, 1187, 1040, 754, <sup>1</sup>H NMR (400 MHz, DMSO) δ = 2.36 (s, 3H), 5.70 (s, 1H), 6.80-6.86 (m, 2H), 7.09-7.19 (m, 5H), 7.31-7.42 (m, 3H), 7.57-7.60 (d, *J* = 8.1 Hz, 2H), 7.76-7.79 (m, 1H), 12.03 (bs, 1H) ppm, LC-MS (ESI) *m/z* [M<sup>+</sup> + H] = 442.1.

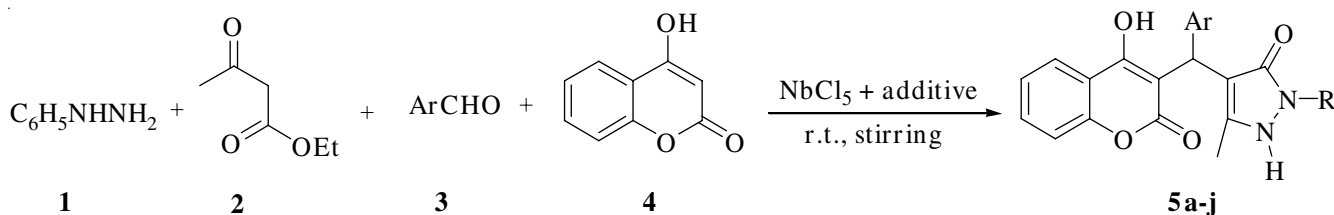
## RESULTS AND DISCUSSION

As a part of the current ongoing studies devoted to the development of practical, safe and environmentally friendly procedures for synthesizing several important biologically active organic compounds, a simple and highly efficient route was used for the synthesis of benzylpyrazolyl coumarins as shown in **Scheme-I**.

First, to recognize the optimization of the reaction conditions, phenyl hydrazine (1.0 mmol), ethyl acetoacetate (1.0 mmol), 3-nitrobenzaldehyde (1.0 mmol) and 4-hydroxycoumarin (1.0 mmol) were, carrying out the reaction without using any catalyst. Table-1 shows that the reaction completed in a long period of time (300 min) and it was very sluggish and

TABLE-1  
OPTIMIZATION OF THE AMOUNT OF NbCl<sub>5</sub> AND ADDITIVE FOR BENZYLPIRAZOLYL COUMARIN DERIVATIVES

| Entry | NbCl <sub>5</sub> (mol %) | Additive (mol %) | Time (min) | Yield (%) |
|-------|---------------------------|------------------|------------|-----------|
| 1     | No catalyst               | No catalyst      | 300        | 10        |
| 2     | 1                         | –                | 300        | 40        |
| 3     | –                         | 1                | 300        | 25        |
| 4     | 5                         | –                | 100        | 70        |
| 5     | –                         | 5                | 150        | 58        |
| 6     | 1                         | 3                | 30         | 90        |
| 7     | 3                         | 3                | 30         | 88        |
| 8     | 5                         | 5                | 30         | 88        |



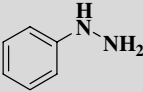
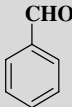
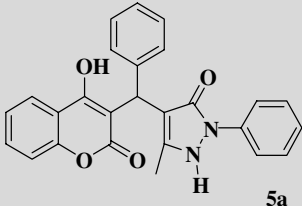
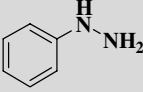
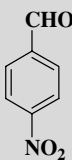
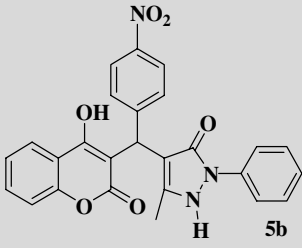
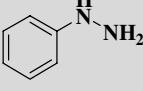
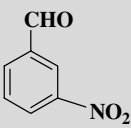
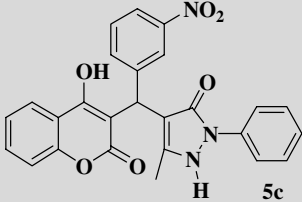
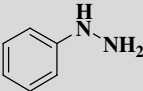
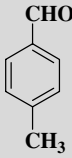
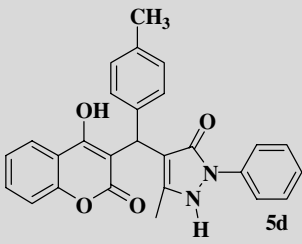
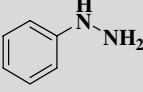
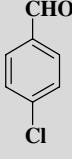
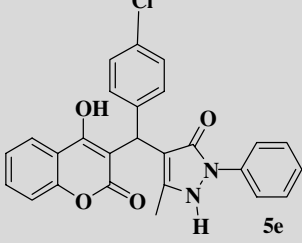
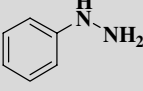
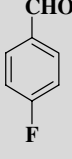
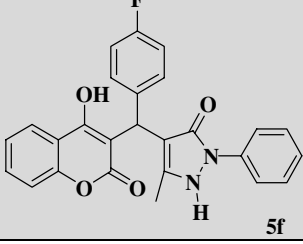
the yield of product was very low (10 %) (Table-1, entry 1). Secondly, for examining and finding out the ideal amounts of the catalysts  $\text{NbCl}_5$  and  $\text{AgClO}_4$ , added to the reaction, the reaction was carried out several times in each which specific amounts of  $\text{NbCl}_5$  and  $\text{AgClO}_4$  were added. Table-1 shows that the best amounts were 1 mol % of  $\text{NbCl}_5$  and 3 mol % of  $\text{AgClO}_4$ ; the reaction completed in the shortest period of time (30 min) and the yield of the product was excellent (90 %) (entry 6).

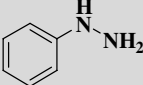
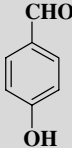
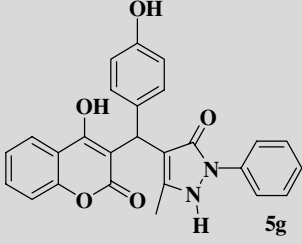
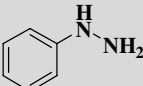
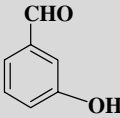
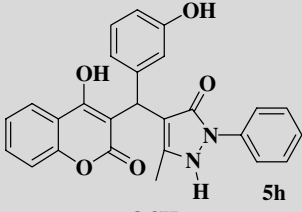
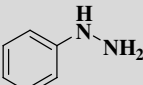
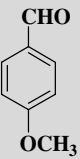
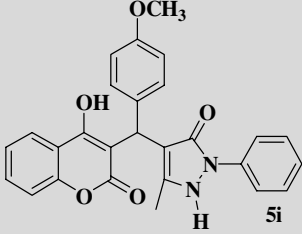
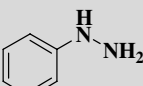
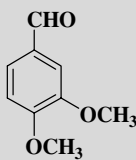
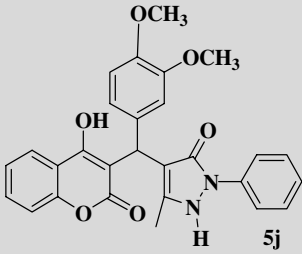
Moreover, the efficiency of current method was evaluated by utilizing an extensive variety of aromatic aldehydes

whenever electron withdrawing and electron donating groups for synthesis of the corresponding benzyl pyrazolyl coumarin derivatives. The reaction successes efficiently provided excellent yields and tolerated many electron-withdrawing and electron-donating substituted benzaldehydes (Table-2, entries 1-10).

Finally, we examined the advantage of our catalyst in synthesis of benzyl pyrazolyl coumarin derivatives used in the present work to comparison with other results reported in the literature review to show the advantages of our catalyst under room temperature condition. the reactants; phenyl hydrazine (1.0 mmol), ethyl acetoacetate (1.0 mmol), benzaldehyde

TABLE-2  
SUBSTRATES SCOPE OF BENZYLPIRAZOLYL COMPOUND

| Entry | Hydrazines  | Aldehydes   | Products   | Time (min) | Yield (%) |
|-------|---|---|--|------------|-----------|
| 1     |    |    | <br>5a   | 30         | 93        |
| 2     |    |    | <br>5b  | 35         | 92        |
| 3     |  |  | <br>5c | 40         | 90        |
| 4     |  |  | <br>5d | 45         | 88        |
| 5     |  |  | <br>5e | 35         | 93        |
| 6     |  |  | <br>5f | 40         | 90        |

|    |   |  |   |    |    |
|----|---|--|---|----|----|
| 7  |  |   |   | 50 | 88 |
| 8  |  |   |   | 60 | 85 |
| 9  |  |   |   | 45 | 88 |
| 10 |  |  |  | 50 | 85 |

(1.0 mmol) and 4-hydroxycoumarin (1.0 mmol) and 1 mol % of  $\text{NbCl}_5$  and 3 mol % of  $\text{AgClO}_4$  as catalysts using solvent free condition comparing with different catalysts as  $\text{Al}(\text{AcOH})$  [28] and  $\text{Ca}(\text{OTf})_2$  [29] under reflux conditions. After comparing the combined acid catalyst under various conditions (room temp., reflux) with these catalysts, it was found that the combined acid catalyst under neat condition was the best catalyst for synthesis 1,2-dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-5-methyl-2-phenyl 1H-pyrazol-3(2H)-one with respect to the reaction time and the product yield.

### CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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