# Promoting ZnO Nanoparticles for Synthesis of Chromene Derivatives Using Natural Starting Reagent

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***Abstract:*** *Three-component reactions of 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone, aldehydes and malononitrile or ethyl cyanoacetate in the presence of nanoparticles of ZnO as catalyst are explained as effective and green synthetic method for generating 9H-furo[2,3-f]chromenes in good yield.*

***Keywords:*** *Chromene; Malononitrile, Ethyl cyanoacetate, Aldehyde, Petasites hybridus, 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone, Three-component reactions.*

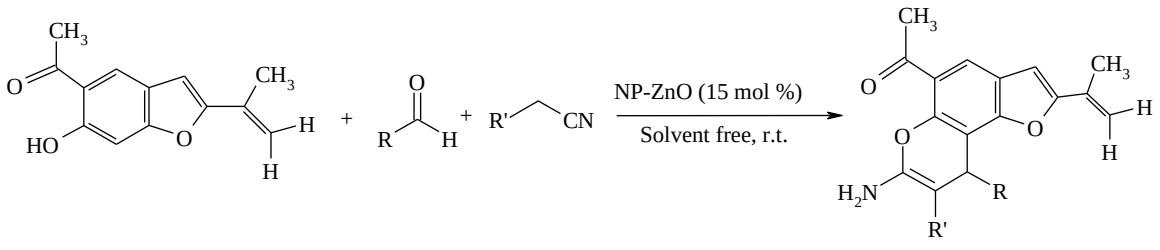
## 1. Introduction

Chromenes are an important group of compounds that are present in natural compounds because of chemical properties and biological activity [1-3]. The bicyclic ring system of chromenes has been produced by a number of different synthetic methods [4-5]. Many natural and synthetic chromone derivatives have the same biological and pharmacological activities, including anti-vira [6], anti-allergic [7] and neuroleptic activities [8]. Benzofuran derivatives exist in some natural products. For example, 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone **1** that was extracted from Rhizomes of *Petasites hybridus* and the structure of **1** was confirmed [9]. This extracted benzofuran derivative is soluble in water. It is noteworthy to mention that these classes of compounds have potent biological and medicinal properties and are used in the treatment of severe migraine and MS diseases. The nano catalyst exhibit better catalytic activity compared to their bulk sized counterparts [10, 11]. Herein, we display an effective synthesis of 9*H*-furo[2,3-f]chromenes *via* the reaction of 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone **1**, aldehydes **2** and malononitrile or ethyl cyanoacetate **3** in the presence of ZnO nanoparticles under solvent-free conditions at room temperature (Scheme 1).

## 2. Result and discussion

As showed in Scheme1, 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone **1**, with aldehydes **2** and malononitrile or ethyl cyanoacetate **3** undergo a 1:1:1 addition reaction under solvent-free conditions (the aldehydes **2**, malononitrile or ethyl cyanoacetate **3** and ZnO nanoparticles are combined first and then 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone **1** is added) to produce 9*H*-furo[2,3-f]chromene derivatives **4** in 68-87 % yields (Scheme 1).

**Scheme 1**. Condensation reactions of aldehydes, malononitrile or ethyl cyanoacetate and 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone.




**1** **2** **3** **4**

| **2, 3, 4** | R | R' | Yield (%) of **4** |
|---|---|---|---|
| **a** | $C_6H_5$ | CN | 85 |
| **b** | 4-Me-$C_6H_4$ | CN | 87 |
| **c** | 4-MeO-$C_6H_4$ | CN | 87 |
| **d** | Furan | CN | 85 |
| **e** | $(CH_3)_3C$ | CN | 75 |
| **f** | 4-Br-$C_6H_4$ | $CO_2Et$ | 80 |

Structures of compounds **4a–4f** were assumed from their IR, mass, $^1$H NMR and $^{13}$C NMR spectra. The $^1$H NMR spectrum of **4e** displayed six singlet for the *tert*-butyl (□□1.32 ppm), methyl (2.162 and 2.42), and methine (□ 3.25, 6.25, and 7.95 ppm) protons along with one singlet for $NH_2$ proton at□□ 7.12 ppm. The $^{13}$C NMR spectrum of **4e** illustrates 21 separate resonances in conformity the recommended structure. Three single resonances at δ = 197.4 pm are viewed in the $^{13}$C NMR spectrum of **4e**, which are attributed to the carbonyl group. The starting point for our experiments was to optimize the reaction conditions. At first**,** compound **1**, benzaldehyde and malononitrile were chosen as the model reaction (scheme 1) and commercial zinc oxide (CM-ZnO) was employed as the catalyst. It was establish to give 56% yield of product at room temperature under solvent free condition (Table 1, entry 2). Confident by this outcome, further optimization studies were carried out by nano particle of ZnO (NP-ZnO) as catalyst.

The morphologies of the products were examined by SEM. Fig. 1 shows the typical SEM image of the samples obtained by the reflux method.

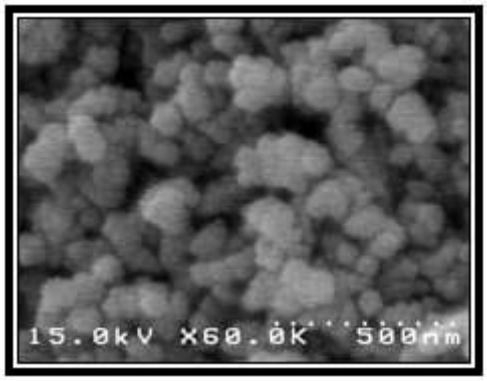



Fig. 1: SEM image of NP-ZnO

In XRD image, all the main peaks in the model corresponded to the wurtzite structure of ZnO, which can be indexed on the basis of JCPDS file No. 36-1451. No other characteristic peaks of the impurities are detected, showing the high purity of the catalysis.

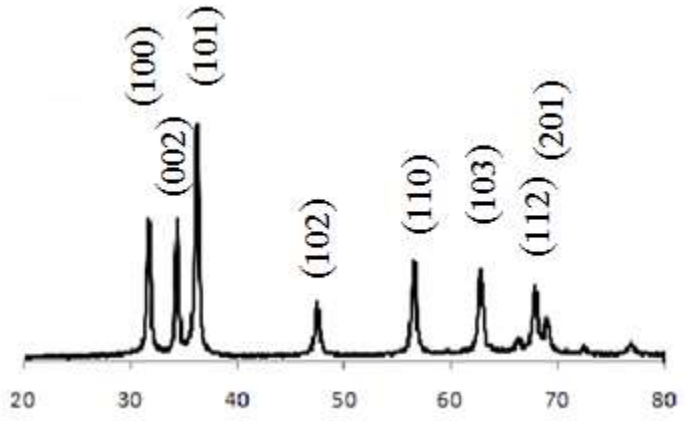
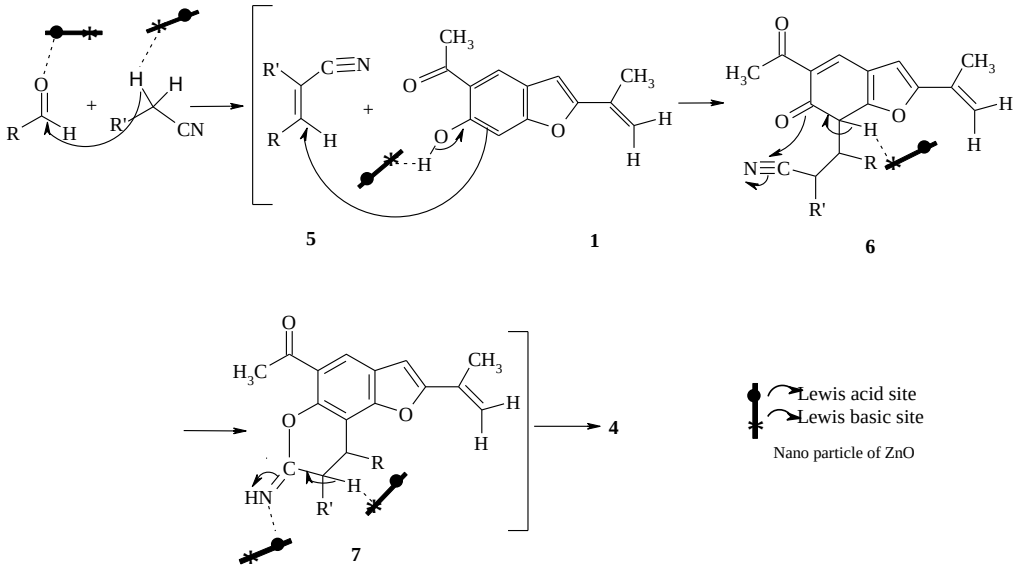



Fig. 2: XRD spectra of NP-ZnO.

Although we have not confirmed the mechanism of the reaction between the aldehydes, malononitrile or ethyl cyanoacetate and 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone in the presence of NP-ZnO, a possible description is recommended in Scheme 2. NP-ZnO has Lewis acid sites ($Zn^{2+}$) and Lewis basic sites ($O^{2-}$). It is equitable to suppose that the compound **5** generates from an initial addition of the aldehydes to malononitrile or ethyl cyanoacetate in the presence of NP-ZnO. After 30 min 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone **1** was added to the mixture of reaction that intermediate **6** generate. Intermediate **6** undergoes cyclization to produce intermediate **7** that finally produce compound **4** by hydrogen shift (Scheme 2).

**Scheme 2**. Proposed mechanism for the synthesis of **4**.




## 3. Conclusion

In conclusion, we have expanded a suitable and one-pot method for preparing stabilized 9*H*-furo[2,3-f]chromene. The current method conveys the advantage that, not only is the reaction carry out under neutral conditions, but also the substrates can be reacted without any previous activation or modification. The ease of the present method makes it an attractive alternative to complex multistep approaches. Also one precursor for reaction is natural compound and reaction was performed without solvent.

## 4. Acknowledgments

We gratefully acknowledge financial and spiritual support from Islamic Azad University of Qaemshahr, Gonbad Kavous University and Islamic Azad University of Firoozkooh.


## 5. Experimental

1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone was extracted from rhizomes of *Petasites hybridus* in northern Iran area [9]. All chemicals were gained from Fluka or Merck and were utilized without further purification. Sample of nanoparticle ZnO were synthesized in the labratory. The morphology of nanostructure ZnO was find out by employing scanning electron microscopy (SEM) of a Holland Philips XL30 microscope. X-ray diffraction (XRD) analysis was performed at room temperature with a Holland Philips Xpert X-ray powder diffractometer with Cu Ka radiation (λ=0.15406 nm), over the 2θ collection range of 20–80°. Average crystallite sizes of products were calculated using Scherrer's formula: D= 0.9λ/β cos θ [20], where D is the diameter of the nanoparticles, λ (Cu Kα) =1.5406 Å and $\beta$ is the full-width at half-maximum of the diffraction lines. $^{1}$H NMR and $^{13}$C NMR spectra were obtained with a Bruker FT-500 spectrometer in chloroform-d1, and tetramethylsilane (TMS) was used as an internal standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicollet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated values.

### General Procedure for the Preparation of nanoparticle ZnO (NP-ZnO).

Sodium hydroxid (0.44 g) was disolved in distilled water (75 mL) at room temprature, zinc acetate dihydrate (0.6 g) was added to the mixture and the solution was refluxed for 1.5 h at 80 °C. The solution was then cooled at room temperature, the precipitate was assembled by filtration and washed with distilled water and ethanol (96%) several times. NP-ZnO was dried in the air at room temprature during 24 h.

### General procedure for the preparation of chromenes 4

To a stirred mixture of aldehydes (2 mmol) and malononitrile or ethyl cyanoacetate (2 mmol) was added NP-ZnO (15% mol). After 10 min 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone (2 mmol) was added at room temperature. The mixture was stirred for about 2 h (TLC monitoring). The viscous residue was purified by column chromatography on silica gel (Merck 230-400 mesh) using n-hexane-EtOAc (5:1) as eluent.

*5-acetyl-7-amino-2-isopropenyl-9-phenyl-9H-furo[2,3-f]chromene-8-yl cyanide* **(4a)**

White powder, mp 147-149°C, yield: 0.63 g (85%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1715, 1694, 1587, 1242 cm$^{-1}$. $^{1}$H NMR (500 MHz, $CDCl_3$): □ = 2.14 (3 H, s, Me), 2.56 (3 H, s, Me), 4.67 (1 H, s, CH), 4.79 (1 H, d, $^{2}J$ = 3.4 Hz, CH), 5.37 (1 H, s, CH), 5.75 (1 H, d, $^{2}J$ = 3.4 Hz, CH), 6.78 (2 H, s, $NH_2$), 7.26 (1 H, t, $^{3}J$ = 7.5 Hz, CH), 7.52 (2 H, t, $^{3}J$ = 7.5 Hz, 2 CH), 7.76 (2 H, d, $^{3}J$ = 7.5 Hz, 2 CH), 7.85 (1 H, s, CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 18.7 (Me), 27.4 (Me), 38.7 (CH), 78.6 (C), 110.4 (CH), 112.4 ($CH_2$), 114.2 (CN), 116.8 (C), 118.5 (C), 121.4 (C), 122.8 (CH), 125.7 (2 CH), 127.6 (CH), 129.4 (2 CH), 131.8 (C), 137.5 (C), 141.5 (C), 148.7 (C), 150.4 (C), 155.3 (C), 198.3 (C=O) ppm. MS: *m*/*z* (%) = 370 ($M^+$, 15), 327 (68), 293 (88), 77 (100), 43 (98). Anal. Calc. for $C_{23}H_{18}N_2O_3$ (370.41): C, 74.58; H, 4.90; N, 7.56 found: C, 74.62; H, 5.02; N, 7.63%.

*5-acetyl-7-amino-2-isopropenyl-9-(4-methylphenyl)-9H-furo[2,3-f]chromene-8-yl cyanide* **( 4b)**

Pale yellow powder, mp 152-154°C, yield: 0.67 g (87%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1717, 1687, 1567, 1264 cm$^{-1}$. $^{1}$H NMR (500 MHz, $CDCl_3$): □ = 2.17 (3 H, s, Me), 2.24 (3 H, s, Me), 2.54 (3 H, s, Me), 4.62 (1 H, s, CH), 4.75 (1 H, d, $^{2}J$ = 3.7 Hz, CH), 5.42 (1 H, s, CH), 5.68 (1 H, d, $^{2}J$ = 3.7 Hz, CH), 6.82 (2 H, s, $NH_2$), 7.38 (2 H, d, $^{3}J$ = 7.8 Hz, 2 CH), 7.76 (2 H, d, $^{3}J$ = 7.8 Hz, 2 CH), 7.87 (1 H, s, CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 18.5 (Me), 21.8 (Me), 27.6 (Me), 40.2 (CH), 79.5 (C), 110.8 (CH), 112.6 ($CH_2$), 114.7 (CN), 117.0 (C), 119.4 (C), 122.1 (C), 123.5 (CH), 127.9 (2 CH), 128.2 (C), 129.5 (2 CH), 137.8 (2 C), 142.4 (C), 149.2 (C), 151.3 (C), 154.8 (C), 197.6 (C=O) ppm. MS: *m*/*z* (%) = 384 ($M^+$, 20), 341 (88), 293 (86), 91 (100), 43 (68). Anal. Calc. for $C_{24}H_{20}N_2O_3$ (384.43): C, 74.98; H, 5.24; N, 7.29 found: C, 74.87; H, 5.18; N, 7.17%.

*5-acetyl-7-amino-2-isopropenyl-9-(4-methoxyphenyl)-9H-furo[2,3-f]chromene-8-yl cyanide* **( 4c)**

Yellow powder, mp 158-160˚C, yield: 0.69 g (87%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1720, 1694, 1574, 1287 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): □ = 2.13 (3 H, s, Me), 2.55 (3 H, s, Me), 3.78 (3 H, s, MeO), 4.65 (1 H, s, CH), 4.74 (1 H, d, $^2J$ = 4.2 Hz, CH), 5.47 (1 H, s, CH), 5.70 (1 H, d, $^2J$ = 4.2 Hz, CH), 6.85 (2 H, s, $NH_2$), 7.23 (2 H, d, $^3J$ = 7.6 Hz, 2 CH), 7.78 (2 H, d, $^3J$ = 7.6 Hz, 2 CH), 7.92 (1 H, s, CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 18.7 (Me), 28.2 (Me), 40.5 (CH), 54.8 (MeO), 80.2 (C), 112.4 (CH), 113.4 ($CH_2$), 114.8 (2 CH), 115.2 (CN), 116.7 (C), 118.5 (C), 121.6 (C), 124.7 (CH), 126.8 (C), 132.6 (2 CH), 139.4 (C), 143.4 (C), 148.3 (C), 153.7 (2 C), 159.4 (C), 198.2 (C=O) ppm. MS: *m*/*z* (%) = 400 ($M^+$, 10), 397 (64), 293 (88), 107 (100), 43 (52). Anal. Calc. for $C_{24}H_{20}N_2O_4$ (400.43): C, 71.99; H, 5.03; N, 7.00 found: C, 72.08; H, 5.12; N, 7.14%.

*5-acetyl-7-amino-2-isopropenyl-9-(2-furyl)-9H-furo[2,3-f]chromene-8-yl cyanide* **( 4d)**

Yellow powder, mp 128-130˚C, yield: 0.61 g (85%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1728, 1624, 1537, 1224 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): □ = 2.15 (3 H, s, Me), 2.52 (3 H, s, Me), 4.45 (1 H, s, CH), 4.62 (1 H, d, $^2J$ = 3.8 Hz, CH), 5.45 (1 H, s, CH), 5.73 (1 H, d, $^2J$ = 3.8 Hz, CH), 5.94 (1 H, d, $^3J$ = 6.7 Hz, CH), 6.65 (2 H, s, $NH_2$), 6.96 (1 H, d, $^3J$ = 7.3 Hz, CH), 7.07 (1 H, d, $^3J$ = 7.3 Hz, CH), 8.02 (1 H, s, CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 17.8 (Me), 29.2 (Me), 39.5 (CH), 78.5 (C), 110.4 (CH), 109.4 (C), 111.8 (CH), 112.6 (CH), 113.5 ($CH_2$), 114.2 (CN), 116.7 (C), 119.6 (C), 122.6 (CH), 134.2 (C), 136.8 (CH), 139.5 (C), 146.3 (C), 153.7 (C), 156.2 (2 C), 199.3 (C=O) ppm. MS: *m*/*z* (%) = 360 ($M^+$, 15), 293 (86), 67 (100), 43 (52). Anal. Calc. for $C_{21}H_{16}N_2O_4$ (360.36): C, 69.99; H, 4.48; N, 7.77 found: C, 69.83; H, 4.36; N, 7.62%.

*5-acetyl-7-amino-2-isopropenyl-9-(4-tert-butyl)-9H-furo[2,3-f]chromene-8-yl cyanide* **( 4e)**

White powder, mp 122-124˚C, yield: 0.72 g (75%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1720, 1654, 1542, 1368, 1234 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): □ = 1.32 (9 H, s, $Me_3$C), 2.16 (3 H, s, Me), 2.42 (3 H, s, Me), 3.25 (1 H, s, CH), 4.78 (1 H, d, $^2J$ = 3.7 Hz, CH), 5.82 (1 H, d, $^2J$ = 3.7 Hz, CH), 6.25 (1 H, s, CH), 7.12 (2 H, s, $NH_2$), 7.95 (1 H, s, CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 18.5 (Me), 29.4 ($Me_3$C), 29.4 (Me), 36.7 (CH), 39.6 ($Me_3C$), 76.5 (C), 98.4 (CH), 113.4 (C), 114.5 (CN), 115.2 ($CH_2$), 116.4 (C), 119.3 (C), 124.2 (CH), 136.2 (C), 141.7 (C), 147.5 (C), 154.2 (C), 156.4 (C), 197.4 (C=O) ppm. MS: *m*/*z* (%) = 350 ($M^+$, 20), 293 (68), 57 (100), 43 (36). Anal. Calc. for $C_{21}H_{22}N_2O_3$ (350.41): C, 71.98; H, 6.33; N, 7.99 found: C, 72.14; H, 6.42; N, 8.12%.

*Ethyl 5-acetyl-7-amino-2-isopropenyl-9-(4-bromophenyl)-9H-furo[2,3-f]chromene-8-carboxylate* **( 4f)**

Pale yellow powder, mp 178-180˚C, yield: 0.79 g (80%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1742, 1723, 1695, 1587, 1286, 1167 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): □ = 1.27 (3 H, t, $^3J$ = 7.5 Hz, $CH_3$), 2.15 (3 H, s, Me), 2.57 (3 H, s, Me), 4.18 (2 H, q, $^3J$ = 7.5 Hz, $CH_2O$), 4.87 (1 H, s, CH), 4.82 (1 H, d, $^2J$ = 4.0 Hz, CH), 5.55 (1 H, s, CH), 5.74 (1 H, d, $^2J$ = 4.0 Hz, CH), 7.12 (2 H, s, $NH_2$), 7.38 (2 H, d, $^3J$ = 7.6 Hz, 2 CH), 7.56 (2 H, d, $^3J$ = 7.6 Hz, 2 CH), 7.82 (1 H, s, CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 13.6 (Me), 18.6 (Me), 28.4 (Me), 35.7 (CH), 61.4 ($CH_2O$), 80.3 (C), 111.4 (CH), 113.7 ($CH_2$), 115.5 (C), 116.7 (C), 119.7 (C), 121.2 (C), 122.4 (CH), 129.8 (2 CH), 131.4 (2 CH), 132.4 (C), 137.55 (C), 139.8 (C), 152.3 (2 C), 158.4 (C), 165.3 (C=O), 196.5 (C=O) ppm. MS: *m*/*z* (%) = 496 ($M^+$, 10), 453 (38), 156 (100), 43 (88). Anal. Calc. for $C_{25}H_{22}BrNO_5$ (496.35): C, 60.50; H, 4.47; N, 2.82 found: C, 60.62; H, 4.53; N, 2.90%.

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