

## A favourable ultrasound-assisted method for the combinatorial synthesis of 2,3-dihydroquinazolin-4(1H)-ones via $\text{CoAl}_2\text{O}_4$ spinel nanocrystal as an efficient catalyst

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### ABSTRACT

Mesoporous  $\text{CoAl}_2\text{O}_4$  spinel nanocrystals ( nano- $\text{CoAl}_2\text{O}_4$  ) were synthesized and fully characterized by X- ray diffraction patterns (XRD), energy-dispersive X-ray spectroscopy (EDS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), DLS (dynamic light scattering) and FT-IR. The nanocrystals promoted the preparation of quinazolinones via the one-pot, three component condensation reaction of benzaldehydes, isatoic anhydride, primary aromatic amine or ammonium acetate at  $45^\circ\text{C}$  under ultrasound irradiation. Experimental simplicity, great yields in concise times, the retrievability of the nanocrystals and performing the sonochemical methodology as an effective way in synthetic chemistry for the preparation of medicinally privileged heterocyclic molecules are some of the substantial features of this method. The present catalytic process is applicable to an extensive diversity of substrates for the preparation of a variety-oriented library of dihydroquinazolinones. The feasibility of doing one-pot synthesis under ultrasonic irradiation with a heterogeneous nanocrystal could improve the reaction rates and shorten the reaction times.

**Keywords:** Dihydroquinazolin; ultrasonic;  $\text{CoAl}_2\text{O}_4$  spinel nanocrystals; one-pot

### 1. Introduction

Throughout the last decades, sonochemistry was chiefly applied in the extraction operations and cleaning but this instrument has now gradually gained striking attention in the compound synthesis [1–3]. The ultrasound can be employed for reactions including enzyme-promoted reactions, phase transfer promoted reactions and ion exchange resin promoted reactions [4–8]. The usage of ultrasound in organic synthesis has been developing due to its substantial features containing great yields in concise times in comparison with the classical ways [9, 10]. The ultrasound effects are created from the cavitation collapse which generate intense conditions locally and hence compel the production of chemical components which are not facilely achieved under conventional conditions [11].

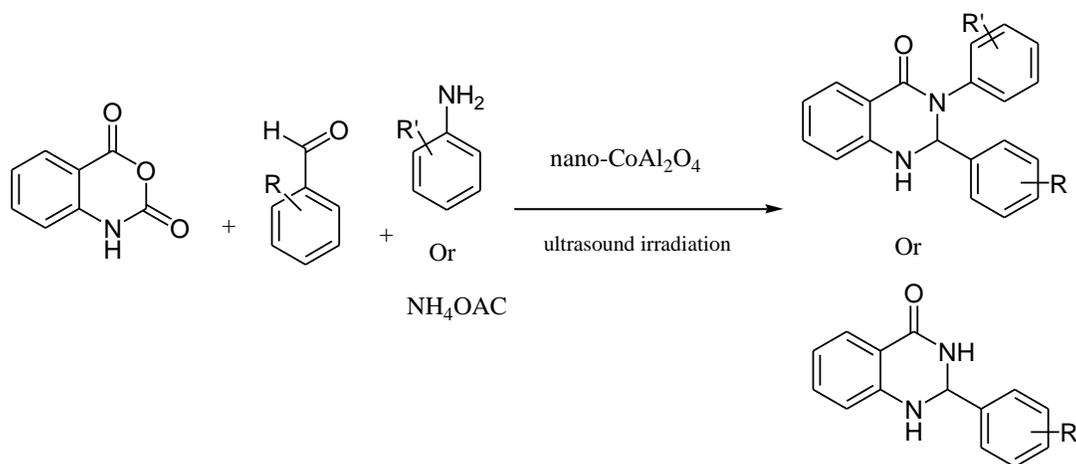
Nitrogen containing fused-heterocycles display many biological attributes [12, 13]. Hence, among a large diversity of N-containing heterocyclic compounds, quinazolinones (DHQZ-1) have received lots of attention

-on owing to their pharmacological activities: anti-inflammatory, anti-tumor, anti-bacterial, and anti-convulsant [14–17].

There are many paths for quinazolinone preparation containing high temperature, microwave or refluxing procedure [18–20]. In addition, diverse catalysts were used including, alum [18], silica sulfuric acid [20], aluminum methanesulfonate [21], nano zinc oxide [22], and  $\text{Al}(\text{H}_2\text{PO}_4)_3$  [23]. Whereas these methods have substantial negative aspects including high times, low efficiency, unwanted reaction status, costly and non-green catalysts applications. Cobalt aluminate ( $\text{CoAl}_2\text{O}_4$ ) is a ternary oxide containing  $\text{AB}_2\text{O}_4$  spinel structure which is notable owing to its great surface area, excellent mechanical resistance, and great thermal as well as chemical stabilities [24, 25]. Mesoporous metal aluminate (MMA) nanoparticles have been extensively investigated as catalyst materials for diverse chemical reactions [26, 27]. Consequently, a prompt and favorable ultrasound-assisted procedure for the synthesis of quinazolinones was performed by reaction of benzaldehydes, isatoic anhydride, primary amine or ammonium acetate by nano- $\text{CoAl}_2\text{O}_4$  (**Scheme 1**).

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**Scheme 1:** Preparation of quinazolinones under ultrasound irradiation

## 2. Experimental

### 2.1. Chemicals and apparatus

The NMR was received on a Bruker spectrometer.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were obtained at 400 and 100 MHz respectively in  $\text{DMSO}-d_6$  as solvent. CHN tests were achieved from a Carlo ERBA 1108. XRD of nano- $\text{CoAl}_2\text{O}_4$  was determined with Philips diffractometer from X'pert Corporation. SEM was taken by TESCAN: MIRA 3. EDX of the nanocrystals was determined with Sigma ZEISS, Oxford.

### 2.2. Synthesis of nano- $\text{CoAl}_2\text{O}_4$

Nanocrystals of  $\text{CoAl}_2\text{O}_4$  were synthesized using sol-gel technique by citric acid. At first, a determined amount of  $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  and  $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  was solved in deionized water. Afterward, an appropriate amount of citric acid was added (molar ratio of citric acid to metal ions was 2 to 1). Subsequently, the solution was stirred for 60 minute and heated at  $80^\circ\text{C}$  until a gel was created. The gel was dried in an oven at  $110^\circ\text{C}$  and fired at  $500^\circ\text{C}$  for 5 h.

### 2.3. Synthesis of quinazolinones

A mixture of isatoic anhydride (1 mmol), primary aromatic amine (1.1 mmol) or ammonium acetate (1.2 mmol), benzaldehyde (1.0 mmol) and nano- $\text{CoAl}_2\text{O}_4$  in ethanol (10 mL) was sonicated at 40 W power at  $45^\circ\text{C}$ . The reaction was investigated by TLC. Then the nano- $\text{CoAl}_2\text{O}_4$  was filtered. Ice-water (10 mL) was added. The precipitate was filtered and recrystallized from EtOH.

### 2.4. Spectral information of products

#### 2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (4a):

M.p.  $219\text{--}221^\circ\text{C}$ .  $^1\text{H}$  NMR:  $\delta(\text{ppm})$ : 8.24 (1H, br s), 7.56 (1H, d,  $J = 7.8$  Hz), 7.45 (2H, d,  $J = 7.2$  Hz), 7.38–

7.32 (3H, m), 7.21 (1H, t,  $J = 7.8$  Hz), 7.08 (1H, br s), 6.72 (1H, d,  $J = 7.8$  Hz), 6.64 (1H, t,  $J = 7.8$  Hz), 5.72 (1H, s).  $^{13}\text{C}$  NMR:  $\delta(\text{ppm})$ : 162.4, 145.8, 140.3, 132.2, 127.3, 127.8 (2C), 126.4, 124.6 (2C), 116.4, 113.6, 112.8, 65.2. – FT-IR: 3308, 3185, 1662, 1603, 1512,  $1484\text{ cm}^{-1}$ .

#### 2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (4b):

M.p.  $214\text{--}215^\circ\text{C}$ .  $^1\text{H}$  NMR:  $\delta(\text{ppm})$ : 8.53 (1H, br s), 8.28 (2H, d,  $J = 8.7$  Hz), 7.76 (2H, d,  $J = 8.7$  Hz), 7.56 (1H, dd,  $J = 7.9$  Hz,  $J = 1.6$  Hz), 7.32 (1H, br s), 7.26 (1H, t), 6.77 (1H, d,  $J = 7.9$  Hz), 6.67 (1H, t), 5.88 (1H, s).  $^{13}\text{C}$  NMR:  $\delta(\text{ppm})$ : 161.5, 148.2, 146.5, 147.4, 131.5, 127.2, 126.3, 122.7, 116.7, 112.4, 112.1, 63.8. FT-IR: 3432, 3282, 1645, 1610, 1523, 1485,  $1344\text{ cm}^{-1}$ .

#### 2-(p-Tolyl)-2,3-dihydroquinazolin-4(1H)-one (4d):

M.p.  $233\text{--}235^\circ\text{C}$ .  $^1\text{H}$  NMR:  $\delta(\text{ppm})$ : 8.32 (1H, br s), 7.63 (1H, d,  $J = 7.8$  Hz), 7.29 (2H, d,  $J = 7.8$  Hz), 7.18–7.26 (3H, m), 7.14 (1H, s), 6.58 (1H, d,  $J = 8.0$  Hz), 6.52 (1H, t,  $J = 7.8$  Hz), 5.38 (1H, s), 2.25 (3H, s).  $^{13}\text{C}$  NMR:  $\delta(\text{ppm})$ : 164.5, 147.3, 137.5, 136.3, 132.5, 128.6, 126.6, 126.5, 115.2, 114.7, 113.8, 67.5, 21.4. FT-IR: 3314, 3185, 1662, 1601, 1504,  $1462\text{ cm}^{-1}$ .

#### 2-(2-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (4e):

M.p.  $192\text{--}193^\circ\text{C}$ .  $^1\text{H}$  NMR:  $\delta(\text{ppm})$ : 8.85 (1H, br s), 8.16 (1H, d,  $J = 8.4$  Hz), 7.92–7.78 (4H, m), 7.55 (2H, t,  $J = 8.0$  Hz), 7.37 (1H, t,  $J = 7.2$ ), 7.19 (1H, d,  $J = 7.6$  Hz), 6.32 (1H, br s).  $^{13}\text{C}$  NMR:  $\delta(\text{ppm})$ : 164.2, 148.4, 146.9, 145.5, 133.6, 133.4, 132.9, 128.1, 126.9, 122.8, 118.3, 114.7, 114.7, 65.5. FT-IR: 3304, 3189, 1646, 1614,  $1525, 1470\text{ cm}^{-1}$ .

#### 2-(2-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (4f):

M.p. 202-204 °C. <sup>1</sup>H NMR:  $\delta$ (ppm): 8.18 (1H, s), 7.60 (2H, d,  $J=6.0$  Hz), 7.52–7.47 (1H, m), 7.43–7.39 (2H, m), 7.26 (1H, t,  $J=8.4$  Hz), 7.12 (1H, br s), 6.55 (1H, d,  $J=8.0$  Hz), 6.68 (1H, t,  $J=7.2$  Hz), 6.12 (1H, s), <sup>13</sup>C NMR:  $\delta$ (ppm): 162.2, 145.8, 138.7, 134.1, 130.3, 129.7, 129.2, 127.3, 126.5, 125.6, 118.2, 115.3, 114.2, 64.5. FT-IR: 3363, 3181, 1652, 1506, 1395, 753 cm<sup>-1</sup>.

*2-(3-Methylphenyl)-2,3-dihydroquinazolin-4(1H)-one (4g):*

M.p. 225-226 °C. <sup>1</sup>H NMR:  $\delta$ (ppm): 8.28 (1H, br s), 7.58 (1H, d,  $J=7.4$  Hz), 7.27-7.32 (1H, m), 7.26-7.22 (1H, m), 7.14 (1H, br s), 7.05 (2H, s), 6.91-6.88 (1H, m), 6.75-6.75 (1H, m), 6.64-6.65 (1H, m), 5.73 (1H, s), 3.34 (3H, s). <sup>13</sup>C NMR:  $\delta$ (ppm): 163.4, 147.7, 137.1, 135.2, 132.5, 131.0, 127.8, 126.7, 124.3, 117.6, 115.4, 114.2, 62.8, 47.3, 19.2. FT-IR: 3303, 3187, 1655, 1608, 1508, 1484 cm<sup>-1</sup>.

*2-(4-nitrophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (4l):*

M.p. 193-195 °C. <sup>1</sup>H NMR:  $\delta$ (ppm): 8.02 (2H, d,  $J=8.8$  Hz), 7.89(1H, dd,  $J=7.9, 1.4$  Hz), 7.46(2H, d,  $J=8.7$  Hz), 7.22 (3H, t,  $J=7.5$  Hz), 7.15 (3H, dd,  $J=7.5, 6.2$  Hz), 6.85-6.78 (1H, m), 6.67 (1H, d,  $J=8.0$  Hz), 6.15 (1H, s), 4.55 (1H, s). <sup>13</sup>C NMR:  $\delta$  (ppm): = 157.5, 132.8, 131.6, 129.4, 128.8, 128.4, 127.2, 126.3, 125.6, 125.2, 122.3(2C), 120.8, 116.6, 114.5, 68.7. FT-IR: 3272, 1633, 1524, 1346, 752 cm<sup>-1</sup>.

*2-(4-chlorophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (4m):*

M.p. 217-219 °C. <sup>1</sup>H NMR:  $\delta$ (ppm): 8.23 (1H, d,  $J=7.9$  Hz), 7.32–7.40 (2H, m), 7.20–7.27 (5H, m), 7.14–7.19 (3H, m), 6.74–6.77 (1H, m), 6.54 (1H, d,  $J=8.1$  Hz), 6.02 (1H, br s), 4.56 (1H, s). <sup>13</sup>C NMR:  $\delta$ (ppm): 161.3, 144.6, 132.8, 130.3, 126.6, 125.6, 124.4(2C), 123.8, 120.6, 120.1(2C), 119.8, 113.2, 112.4, 65.4, FT-IR: 3308, 1651, 1642, 1611, 1504, 1432 cm<sup>-1</sup>.

*3-phenyl-2-(p-tolyl)-2,3-dihydroquinazolin-4(1H)-one (4n):*

M.p. 213-214 °C. <sup>1</sup>H NMR:  $\delta$ (ppm): 8.17 (1H, d,  $J=7.6$  Hz), 7.51–7.49 (2H, m), 7.47–7.33 (6H, m), 7.09-7.06 (1H, m), 6.84 (1H, d,  $J=8.0$  Hz), 6.62 (2H, d,  $J=8.4$  Hz), 6.08 (1H, s), 4.68 (1H, s), 2.14 (3H, s). <sup>13</sup>C NMR:  $\delta$ (ppm): 164.7, 149.3, 134.2, 127.4, 126.7, 125.5(2C), 124.6, 123.8, 122.3, 120.5, 117.6, 116.4, 113.5, 109.3, 72.9, 19.8. FT-IR: 3305, 3177, 1654, 1601, 1512, 1462 cm<sup>-1</sup>.

*2-(3-nitrophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (4o):*

M.p. 184-185 °C. <sup>1</sup>H NMR:  $\delta$ (ppm): 8.46 (1H, d,  $J=7.9$  Hz), 7.72–7.70 (2H, m), 7.56–7.48 (2H, m), 7.37–7.30 (6H, m), 6.61–6.52 (1H, m), 6.47 (1H, d,  $J=7.9$  Hz), 6.12 (1H, s), 4.40 (1H, s). <sup>13</sup>C NMR:  $\delta$ (ppm): 160.3, 147.2, 131.8, 126.2 (2C), 123.9(2C), 121.6, 120.5, 115.4, 113.5, 112.7, 70.2, 33.4, 17.4, 14.3. FT-IR (KBr): 3276, 1626, 1524, 1333, 752 cm<sup>-1</sup>.

*2-(4-bromophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (4p):*

M.p. 217-218 °C. <sup>1</sup>H NMR:  $\delta$ (ppm): 7.73-7.63 (2H, m), 7.56-7.47 (2H, m), 7.32-7.10 (8H, m), 6.82-6.75 (2H, m), 6.25 (1H, d,  $J=4.8$  Hz); <sup>13</sup>C NMR:  $\delta$ (ppm): 161.6, 145.2, 140.8, 139.9, 133.3, 131.2, 128.5, 127.8, 127.4, 125.8, 122.2, 120.9, 117.2, 115.6, 114.7, 73.2. FT-IR: 3347, 1660, 1607, 1517, 1454 cm<sup>-1</sup>.

*2-(4-nitrophenyl)-3-(p-tolyl)-2,3-dihydroquinazolin-4(1H)-one (4q):*

M.p. 212-213 °C. <sup>1</sup>H NMR:  $\delta$ (ppm): 10.23 (1H, s), 8.75 (1H, s), 8.35 (2H, d,  $J=8.6$  Hz), 8.18 (2H, d,  $J=8.6$  Hz), 7.75 (1H, dd,  $J=1.0, 6.4$  Hz), 7.61–7.55 (3H, m), 7.39 (1H, t,  $J=7.6$  Hz), 7.28 (1H, d,  $J=7.8$  Hz), 7.16 (2H, d,  $J=8.2$  Hz), 2.49 (3H, s). <sup>13</sup>C NMR:  $\delta$ (ppm): 161.4, 148.7, 147.5, 140.6, 135.3, 133.4, 132.4, 130.3, 128.8, 129.2, 128.7, 125.9, 123.5, 118.5, 118.4, 73.1, 21.3. FT-IR: 3654, 3032, 2361, 1663, 1594, 1512, 1456, 764 cm<sup>-1</sup>.

*3-benzyl-2-phenyl-2,3-dihydroquinazolin-4(1H)-one (4t):*

M.p. 156-157 °C. <sup>1</sup>H NMR:  $\delta$ (ppm): 7.92 (1H, dd,  $J=1.4, 6.4$  Hz), 7.34–7.18 (12H, m), 6.55–6.47 (2H, m), 5.49 (1H, d,  $J=2.6$  Hz), 5.56 (1H, d,  $J=15.4$  Hz), 3.32 (1H, d,  $J=15.4$  Hz). <sup>13</sup>C NMR:  $\delta$ (ppm): 164.1, 142.7, 140.1, 135.9, 133.8, 129.6, 127.6, 126.7, 125.1(2C), 124.2, 122.7, 118.0, 115.5, 113.1, 70.1, 49.3. FT-IR: 3412, 3015, 2358, 1635, 1580, 1511, 1432, 756 cm<sup>-1</sup>.

### 3. Result and Discussion

FT-IR of nano-CoAl<sub>2</sub>O<sub>4</sub> is displayed in **Fig. 1**. Two peaks are seen at around, 666 and 559 cm<sup>-1</sup>, respectively, indicating formation of metal oxide. The absorption peak at 3436 cm<sup>-1</sup> corresponds to the vibration modes of metal tethered hydroxyl groups. The peak at 1629 cm<sup>-1</sup> displays the stretching vibrations of carboxyl groups (COO<sup>-</sup>) of citrate ions. The spectrum proves that the nano-CoAl<sub>2</sub>O<sub>4</sub> were synthesized.

XRD of nano-CoAl<sub>2</sub>O<sub>4</sub> is presented in **Fig. 2**. This shape displays excellent phase purity of nano-CoAl<sub>2</sub>O<sub>4</sub> that has a complete agreement with the recorded XRD for nano-CoAl<sub>2</sub>O<sub>4</sub>. Average crystalline size of the nano-

CoAl<sub>2</sub>O<sub>4</sub> using Scherrer's formula was computed to be 15–25 nm.

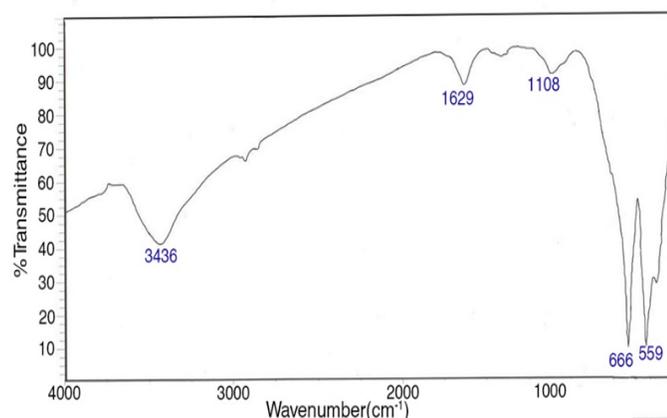


Fig. 1. FT-IR of CoAl<sub>2</sub>O<sub>4</sub> spinel nanocrystal

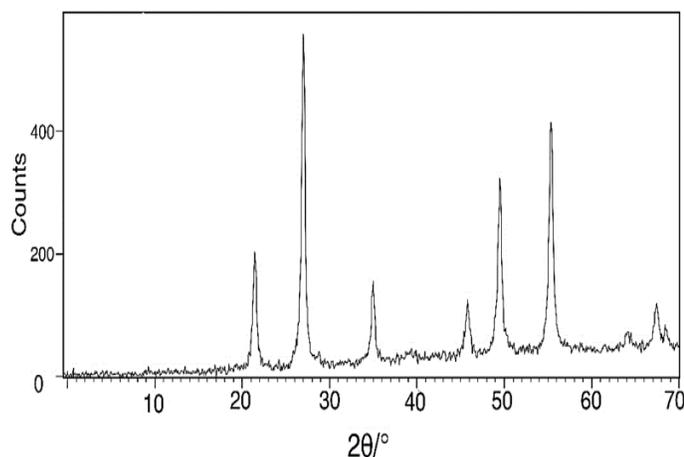


Fig. 2. XRD of CoAl<sub>2</sub>O<sub>4</sub> spinel nanocrystal

The size and morphology of nano-CoAl<sub>2</sub>O<sub>4</sub> was considered using SEM and TEM images (Fig. 3). The results display particles with diameters in the size of nanometers. The size distribution of nano CoAl<sub>2</sub>O<sub>4</sub> was determined using DLS measurements, (Fig. 4) that is centered at a value of 37.5 nm. The elemental composition of nano-CoAl<sub>2</sub>O<sub>4</sub> was investigated by EDS (Fig. 5) that showed the cobalt, aluminium and oxygen amount of the nano-CoAl<sub>2</sub>O<sub>4</sub> was 48.58, 15.13, 36.32 (wt %). First, the reaction of benzaldehyde, isatoic anhydride, and aniline were selected as a model reaction. The effect of solvent, catalyst and amount of catalyst were investigated in Table 1.

KAl(SO<sub>4</sub>)<sub>2</sub>·12H<sub>2</sub>O, silica sulfuric acid, Al(H<sub>2</sub>PO<sub>4</sub>)<sub>3</sub> and nano CoAl<sub>2</sub>O<sub>4</sub> as catalyst in diverse solvents containing acetonitrile, water, methanol, acetone and ethanol were checked. The best results were acquired with nano-CoAl<sub>2</sub>O<sub>4</sub> (8 mol%) in EtOH under ultrasound irradiation (40 W power) (Table 2).

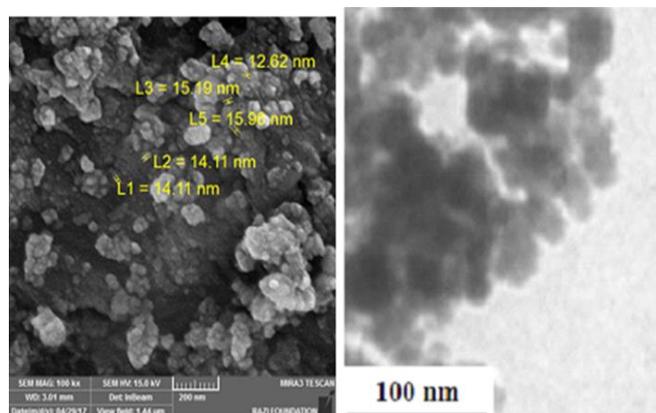


Fig. 3. SEM and TEM of CoAl<sub>2</sub>O<sub>4</sub> spinel nanocrystal

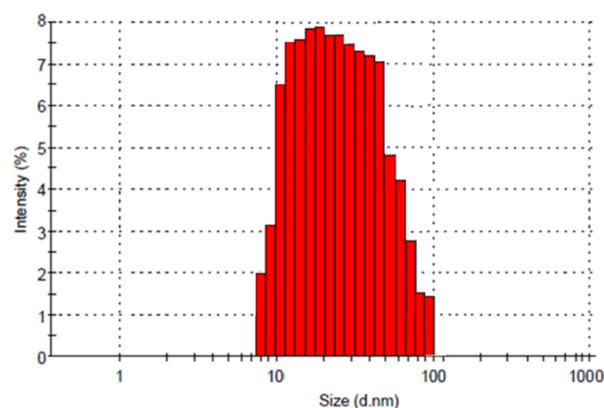


Fig. 4. DLS of CoAl<sub>2</sub>O<sub>4</sub> spinel nanocrystal

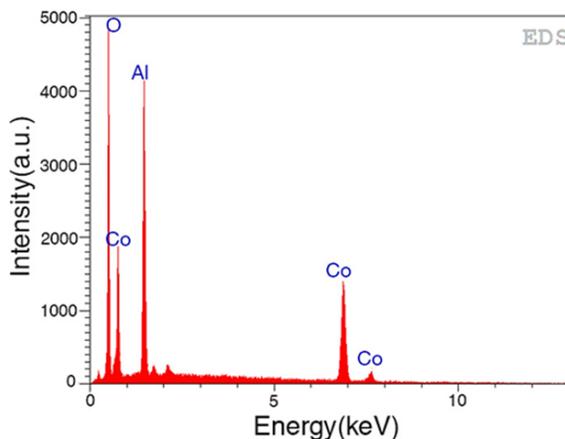


Fig. 5. EDX of CoAl<sub>2</sub>O<sub>4</sub> spinel nanocrystal

Variously mono and disubstituted quinazolinones were prepared using nano-CoAl<sub>2</sub>O<sub>4</sub> under heating and sonication conditions (Table 3, 4). When the dihydroquinazolinones were produced under heating, they were created in higher times, however performing these reactions under sonication created great yields of dihydroquinazolinones at shorter times. The ultrasound technique gives several benefits, including generation of purer products in great yields and raised reaction rates [28-31].

To evaluate the efficiency of nano-CoAl<sub>2</sub>O<sub>4</sub> as a catalyst with the introduced catalysts for the preparation of quinazolinones, we have compared the outcomes in **Table 5**. This table displays, that nano-CoAl<sub>2</sub>O<sub>4</sub> is

premiere with respect to the introduced catalysts in terms of reaction yield and time. **Table 5**. Comparison of catalytic performance of nano-CoAl<sub>2</sub>O<sub>4</sub> with other introduced catalysts for the preparation **4k**

**Table 1.** Optimization of reaction conditions <sup>a</sup>

Entry	Solvent	Temp. (°C)		Catalytic system (mol%)	Time (min)		Isolated Yield <sup>b</sup> (%)	
		US <sup>c</sup>	Δ		US <sup>c</sup>	Δ	US <sup>c</sup>	Δ
1	Solvent-free	45	100	Nano CoAl <sub>2</sub> O <sub>4</sub> (8%)	20	120	50	40
2	Water	45	100	Nano CoAl <sub>2</sub> O <sub>4</sub> (8%)	25	180	55	45
3	DCM	45	39	Nano CoAl <sub>2</sub> O <sub>4</sub> (8%)	20	180	35	trace
4	Acetone	45	56	Nano CoAl <sub>2</sub> O <sub>4</sub> (8%)	20	180	40	25
5	Acetonitrile	45	82	Nano CoAl <sub>2</sub> O <sub>4</sub> (8%)	20	180	45	30
6	Methanol	45	64	Nano CoAl <sub>2</sub> O <sub>4</sub> (8%)	15	150	80	60
7	Ethanol	45	78	Nano CoAl <sub>2</sub> O <sub>4</sub> (8%)	15	120	94	75
8	Ethanol	45	–	Nano CoAl <sub>2</sub> O <sub>4</sub> (12%)	15	–	93	–
9	Ethanol	–	78	KAl(SO <sub>4</sub> ) <sub>2</sub> .12H <sub>2</sub> O (4 %)	–	240	–	88
10	Solvent-free	–	80	Silica sulfuric acid (20%)	–	300	–	80
11	Solvent-free	–	100	Al(H <sub>2</sub> PO <sub>4</sub> ) <sub>3</sub> (16%)	–	35	–	80
12	Solvent-free	–	70	Nano ZnO(20%)	–	180	–	88

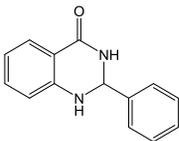
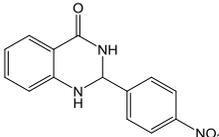
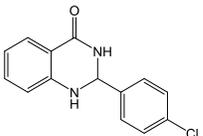
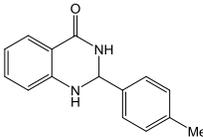
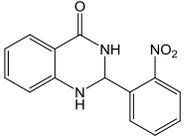
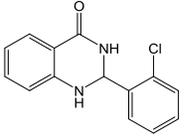
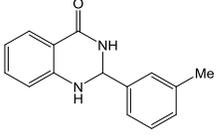
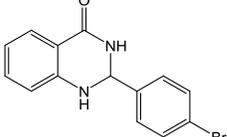
a) Reactions conditions: isatoic anhydride (1 mmol), aniline (1.2 mmol) and benzaldehyde (1.0 mmol); b) Isolated yield.

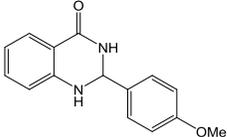
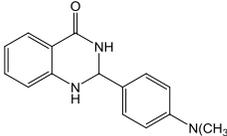
**Table 2:** Comparison of the power of ultrasonic irradiation for the synthesis of quinazolinone <sup>a</sup>

Entry	Power (W)	Time (min)	Yield <sup>b</sup> (%)
1	30	20	84
2	35	20	89
3	40	15	94
4	45	15	94

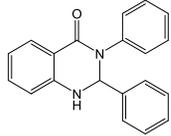
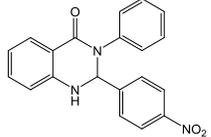
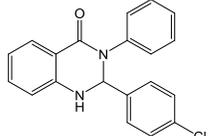
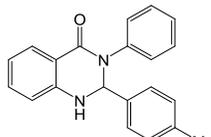
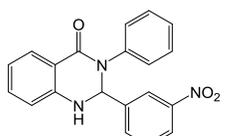
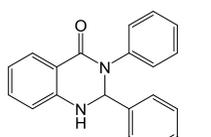
a) Reactions conditions: isatoic anhydride (1 mmol), aniline (1.2 mmol) and benzaldehyde (1.0 mmol), nano-CoAl<sub>2</sub>O<sub>4</sub> (8%); b) Isolated yields

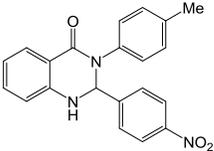
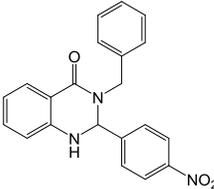
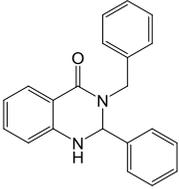
**Table 3:** Preparation of monosubstituted quinazolineones with nano-CoAl<sub>2</sub>O<sub>4</sub><sup>a</sup>

Entry	Cpd. numbers	Product <sup>b</sup>	Time (min)		Yield (%)		Mp (°C) [ref]
			US <sup>c</sup>	Δ	US <sup>c</sup>	Δ	
1	4a		10	100	96	78	219–221 [18]
2	4b		10	100	97	78	214–215 [23]
3	4c		12	110	97	78	199–201 [18]
4	4d		15	120	95	77	233–235 [18]
5	4e		12	110	95	77	192–193 [33]
6	4f		12	110	94	76	203–204 [21]
7	4g		15	120	93	76	225–226 [35]
8	4h		12	110	96	78	203–204 [23]

9	4i		15	120	92	75	177–179 [18]
10	4j		15	120	89	72	209–211 [35]

**Table 4:** Preparation of disubstituted quinazolineones with nano-CoAl<sub>2</sub>O<sub>4</sub><sup>a</sup>

Entry	Cpd. numbers	Product <sup>b</sup>	Time (min)		Yield (%) <sup>d</sup>		Mp (°C) <sup>e</sup> [ref]
			US <sup>c</sup>	Δ	US <sup>c</sup>	Δ	
1	4k		15	120	94	73	205–207 [18]
2	4l		15	120	96	70	193–195 [18]
3	4m		15	120	95	73	217–219 [18]
4	4n		17	150	93	70	212–214 [34]
5	4o		17	150	92	70	184–185 [21]
6	4p		15	120	95	73	216–218 [23]

7	4q		17	150	92	70	211–213 [35]
8	4r		20	170	90	68	237–239
9	4s		15	120	94	72	211–213
10	4t		15	120	95	78	156–157 [21]

a) Reactions conditions: isatoic anhydride (1 mmol), primary amine (1.2 mmol) and aldehyde (1.0 mmol), nano-CoAl<sub>2</sub>O<sub>4</sub> (8%), *T* = 45 °C; b) all products were characterized by their IR, <sup>1</sup>H and <sup>13</sup>CNMR data; c) ultrasonic irradiation (40 W); d) isolated yields.

**Table 5.** Comparison of catalytic performance of nano-CoAl<sub>2</sub>O<sub>4</sub> with other introduced catalysts for the preparation **4k**

Entry	Catalyst (condition)	Time (min)	Yield, <sup>a</sup> %	[Ref]
1	Alum (10 mol%, EtOH, reflux)	240	83	[18]
2	Silica sulfuric acid (15 mol%, H <sub>2</sub> O, 80 °C)	180	84	[20]
3	Aluminum methanesulfonate (5 mol%, EtOH/H <sub>2</sub> O)	60	91	[21]
4	Nano-ZnO (20 mol%, 70°C)	180	88	[22]
5	Al(H <sub>2</sub> PO <sub>4</sub> ) <sub>3</sub> (16 mol%, 100 °C)	60	85	[23]
6	nano-CoAl <sub>2</sub> O <sub>4</sub> (8 mol%, EtOH, Ultrasonic irradiation, 40 W)	15	94	This work

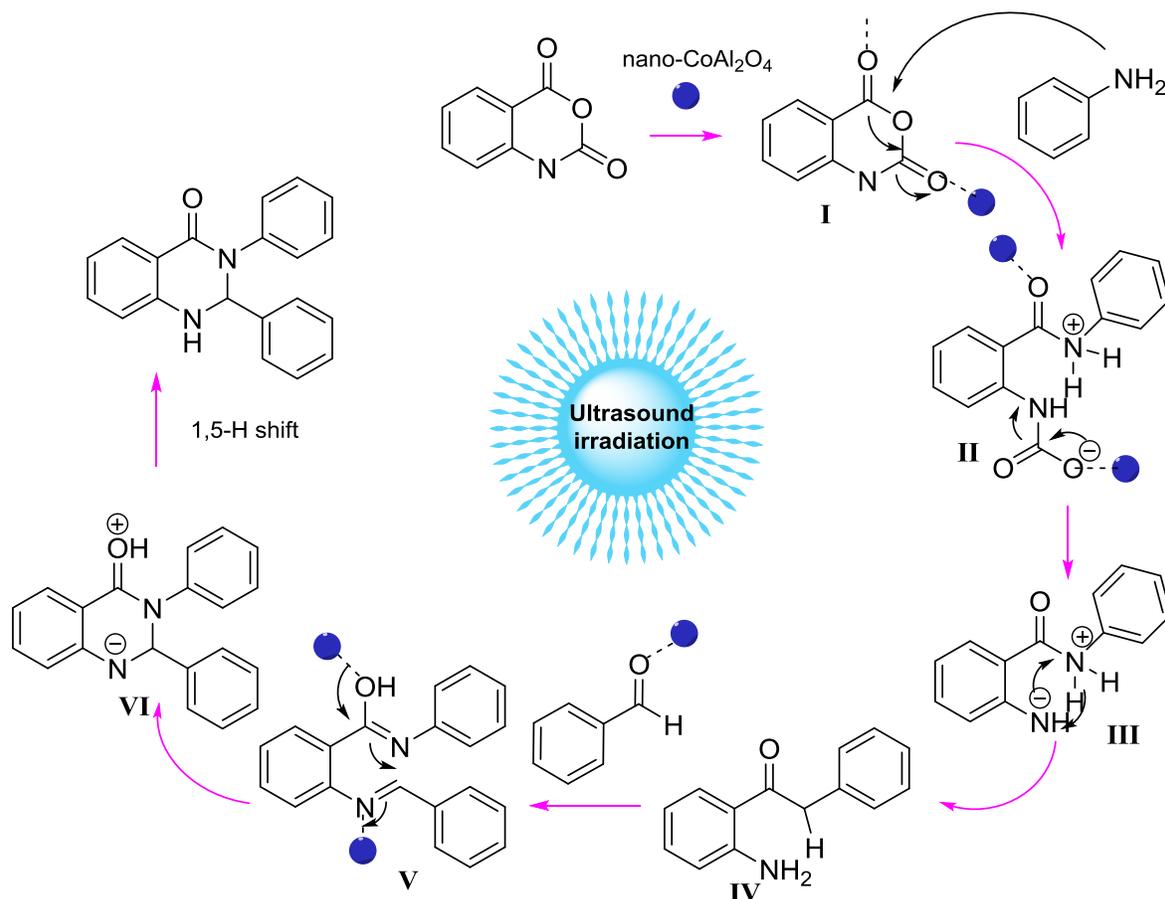
a) Isolated yield

The mechanism of synthesis of quinazolinones is proposed in **Scheme 2**. The interaction of nano-CoAl<sub>2</sub>O<sub>4</sub> and isatoic anhydride to produce intermediate (**I**). Then,

the *N*-nucleophilic amine assaults on the carbonyl unit of **I** to generate intermediate **II**, which in turn gives **III** through decarboxylation. The proton transfer of **III**

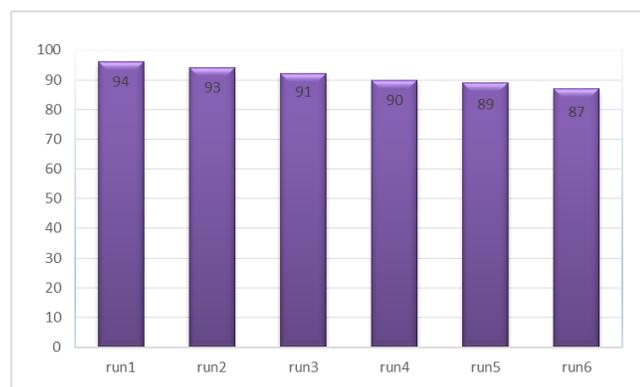
obtains intermediate **IV**. Further, the reaction of benzaldehyde with intermediate **IV** proceed to create the intermediate **V**. Accordingly, intermediate **VI** could be

obtained by an intermolecular attack of the amide nitrogen on activated imine carbon, followed by a 1,5-proton transfer to give product.



**Scheme 2.** The offered mechanism of preparation of quinazolinones using nano-CoAl<sub>2</sub>O<sub>4</sub>

The nano-CoAl<sub>2</sub>O<sub>4</sub> was reused for the synthesis of **4k** under similar reaction conditions up to six cycles and it was found that product yield lessened to a certain extent after each reuse (**Fig. 6**). For recycling of nano-CoAl<sub>2</sub>O<sub>4</sub>, the solution was filtered and the nanocrystal was recovered. The recovered nano-CoAl<sub>2</sub>O<sub>4</sub> was rinsed four times with ethyl acetate and dried at 80 °C for 4 h.



**Fig. 6.** Recovery of CoAl<sub>2</sub>O<sub>4</sub> spinel nanocrystal

#### 4. Conclusions

We have reported an efficient way for the synthesis of quinazolinones using benzaldehydes, isatoic anhydride and primary amines or ammonium acetate with nano-CoAl<sub>2</sub>O<sub>4</sub> at 45°C under ultrasound irradiation. The salient features of this protocol are: great yields in concise times, retrievability of the nanocatalyst and little nanocatalyst loading.

#### Acknowledgements

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#### References

- [1] F. Mojtabazade, B. Mirtamizdoust, A. Morsali, P. Talemi, Ultrasonic-assisted synthesis and the structural characterization of novel the zigzag Cd(II) metal-organic polymer and their nanostructures, *Ultrason. Sonochem.* 42 (2018) 134-140.
- [2] S. Sadjadi, Graphene-ZnO@SiO<sub>2</sub> hybrid: An efficient and solid acid catalyst for synthesis of azlactones under ultrasound irradiation, *Iran. J. Catal.* 8(3), (2018) 189-194.

- [3] D. Chen, D.-y. Li, Z.-t. Kang, Preparation of magnesium ferrite nanoparticles by ultrasonic wave-assisted aqueous solution ball milling, *Ultrason. Sonochem.* 20 (2013) 1337-1340.
- [4] N.Z. Gheorghiuță, A.M.V. Zbancioc, D. Mantu, A. Miron, C. TĂNASE, I.I. Mangalagiu, Ultrasounds-assisted synthesis of highly functionalized acetophenone derivatives in heterogeneous catalysis, *Rev. Roum. Chim.* 55 (2010) 983-987.
- [5] V. Rajendran, K. Harikumar, Ultrasound assisted synthesis of diethyl-2, 2'-thiodiacetate with 2-bromoethylacetate under a new polymer-supported phase-transfer catalyst in solid-liquid condition, *Chem. Sci. J.* 6 (2015) 1-9.
- [6] C. Leonelli, T.J. Mason, Microwave and ultrasonic processing: now a realistic option for industry, *Chem. Eng. Process.* 49 (2010) 885-900.
- [7] J. Luo, Z. Fang, R.L. Smith, Ultrasound-enhanced conversion of biomass to biofuels, *Prog. Energy Combust. Sci.* 41 (2014) 56-93.
- [8] M. Amereh, M. Haghghi, P. Estifae, The potential use of HNO<sub>3</sub>-treated clinoptilolite in the preparation of Pt/CeO<sub>2</sub>-Clinoptilolite nanostructured catalyst used in toluene abatement from waste gas stream at low temperature, *Arabian J. Chem.* 11 (2018) 81-90.
- [9] H. Shahbazi-Alavi, J. Safaei-Ghomi, R. Talebi, PbWO<sub>4</sub> nanoparticles: A robust and reusable heterogeneous catalyst for the synthesis of benzopyranopyridines under ultrasonic irradiation, *Iran. J. Catal.* 7(2), (2017) 103-109.
- [10] J.S. Ghomi, S. Zahedi, Novel ionic liquid supported on Fe<sub>3</sub>O<sub>4</sub> nanoparticles and its application as a catalyst in Mannich reaction under ultrasonic irradiation, *Ultrason. Sonochem.* 34 (2017) 916-923.
- [11] R. Cella, H.A. Stefani, Ultrasound in heterocycles chemistry, *Tetrahedron*, 65 (2009) 2619-2641.
- [12] Z. Xu, Y. Zhang, H. Fu, H. Zhong, K. Hong, W. Zhu, Antifungal quinazolinones from marine-derived *Bacillus cereus* and their preparation, *Bioorg. Med. Chem. Lett.* 21 (2011) 4005-4007.
- [13] M.-J. Hour, L.-J. Huang, S.-C. Kuo, Y. Xia, K. Bastow, Y. Nakanishi, E. Hamel, K.-H. Lee, 6-Alkylamino- and 2, 3-Dihydro-3'-methoxy-2-phenyl-4-quinazolinones and related compounds: Their synthesis, cytotoxicity, and inhibition of tubulin polymerization, *J. Med. Chem.* 43 (2000) 4479-4487.
- [14] Y. Hu, E. Ehli, J. Hudziak, G. Davies, Berberine and evodiamine influence serotonin transporter (5-HTT) expression via the 5-HTT-linked polymorphic region, *Pharmacogenomics J.* 12 (2012) 372-378.
- [15] O. Cruz-Lopez, A. Conejo-García, M. C Nunez, M. Kimatrai, M. E Garcia-Rubino, F. Morales, V. Gomez-Perez, J. M Campos, Novel substituted quinazolines for potent EGFR tyrosine kinase inhibitors, *Curr. Med. Chem.* 18 (2011) 943-963.
- [16] R. Noel, N. Gupta, V.r. Pons, A.I. Goudet, M.D. Garcia-Castillo, A.I. Michau, J. Martinez, D.-A. Buisson, L. Johannes, D. Gillet, N-methyl-dihydroquinazolinone derivatives of Retro-2 with enhanced efficacy against Shiga toxin, *J. Med. Chem.* 56 (2013) 3404-3413.
- [17] R. Williams, C.M. Niswender, Q. Luo, U. Le, P.J. Conn, C.W. Lindsley, Positive allosteric modulators of the metabotropic glutamate receptor subtype 4 (mGluR4). Part II: Challenges in hit-to-lead, *Bioorg. Med. Chem. Lett.* 19 (2009) 962-966.
- [18] M. Dabiri, P. Salehi, S. Otokesh, M. Baghbanzadeh, G. Kozehgary, A.A. Mohammadi, Efficient synthesis of mono- and disubstituted 2, 3-dihydroquinazolin-4 (1H)-ones using KAl(SO<sub>4</sub>)<sub>2</sub>·12H<sub>2</sub>O as a reusable catalyst in water and ethanol, *Tetrahedron Lett.* 46 (2005) 6123-6126.
- [19] M. Bakavoli, O. Sabzevari, M. Rahimizadeh, Microwave activated synthesis of 2-aryl-quinazolin-4 (3H) ones, *Chin. Chem. Lett.* 18 (2007) 1466-1468.
- [20] M. Dabiri, P. Salehi, M. Baghbanzadeh, M.A. Zolfigol, M. Agheb, S. Heydari, Silica sulfuric acid: An efficient reusable heterogeneous catalyst for the synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones in water and under solvent-free conditions, *Catal. Comm.* 9 (2008) 785-788.
- [21] Z. Song, L. Liu, Y. Wang, X. Sun, Efficient synthesis of mono- and disubstituted 2, 3-dihydroquinazolin-4 (1H)-ones using aluminum methanesulfonate as a reusable catalyst, *Res. Chem. Intermed.* 38 (2012) 1091-1099.
- [22] I. Yavari, S. Beheshti, ZnO nanoparticles catalyzed efficient one-pot three-component synthesis of 2, 3-disubstituted quinalolin-4 (1H)-ones under solvent-free conditions, *J. Iran. Chem. Soc.* 8 (2011) 1030-1035.
- [23] H.R. Shaterian, A.R. Oveisi, M. Honarmand, Synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones, *Synth. Commun.* 40 (2010) 1231-1242.
- [24] I. Gul, A. Maqsood, M. Naem, M.N. Ashiq, Optical, magnetic and electrical investigation of cobalt ferrite nanoparticles synthesized by co-precipitation route, *J. Alloys Compd.* 507 (2010) 201-206.
- [25] N. Ballarini, F. Cavani, S. Passeri, L. Pesaresi, A.F. Lee, K. Wilson, Phenol methylation over nanoparticulate CoFe<sub>2</sub>O<sub>4</sub> inverse spinel catalysts: the effect of morphology on catalytic performance, *Appl. Catal., A* 366 (2009) 184-192.
- [26] C. Ragupathi, J.J. Vijaya, P. Surendhar, L.J. Kennedy, Comparative investigation of nickel aluminate (NiAl<sub>2</sub>O<sub>4</sub>) nano and microstructures for the structural, optical and catalytic properties, *Polyhedron*, 72 (2014) 1-7.
- [27] S. Farhadi, S. Panahandehjoo, Spinel-type zinc aluminate (ZnAl<sub>2</sub>O<sub>4</sub>) nanoparticles prepared by the co-precipitation method: a novel, green and recyclable heterogeneous catalyst for the acetylation of amines, alcohols and phenols under solvent-free conditions, *Appl. Catal., A* 382 (2010) 293-302.
- [28] J. Safaei-Ghomi, M. Navvab, H. Shahbazi-Alavi, One-pot sonochemical synthesis of 1, 3-thiazolidin-4-ones using nano-CdZr<sub>4</sub>(PO<sub>4</sub>)<sub>6</sub> as a robust heterogeneous catalyst, *Ultrason. Sonochem.* 31 (2016) 102-106.
- [29] J. Safaei-Ghomi, Z. Akbarzadeh, Sonochemically synthesis of arylethynyl linked triaryl amines catalyzed by CuI nanoparticles: A rapid and green procedure for Sonogashira coupling, *Ultrason. Sonochem.* 22 (2015) 365-370.
- [30] X. Wang, Y. Wei, J. Wang, W. Guo, C. Wang, The kinetics and mechanism of ultrasonic degradation of p-nitrophenol in aqueous solution with CCl<sub>4</sub> enhancement, *Ultrason. Sonochem.* 19 (2012) 32-37.

- [31] A. Javidan, A. Ziarati, J. Safaei-Ghomi, Simultaneous sonication assistance for the synthesis of tetrahydropyridines and its efficient catalyst  $ZrP_2O_7$  nanoparticles, *Ultrason. Sonochem.* 21 (2014) 1150-1154.
- [32] P. Gunasekaran, S. Perumal, P. Yogeewari, D. Sriram, A facile four-component sequential protocol in the expedient synthesis of novel 2-aryl-5-methyl-2, 3-dihydro-1H-3-pyrazolones in water and their antitubercular evaluation, *Eur. J. Med. Chem.* 46 (2011) 4530-4536.
- [33] J. Chen, D. Wu, F. He, M. Liu, H. Wu, J. Ding, W. Su, Gallium (III) triflate-catalyzed one-pot selective synthesis of 2, 3-dihydroquinazolin-4 (*1H*)-ones and quinazolin-4 (*3H*)-ones, *Tetrahedron Lett.* 49 (2008) 3814-3818.
- [34] S. Santra, M. Rahman, A. Roy, A. Majee, A. Hajra, Nano-indium oxide: An efficient catalyst for one-pot synthesis of 2, 3-dihydroquinazolin-4 (*1H*)-ones with a greener prospect, *Catal. Commun.* 49 (2014) 52-57.
- [35] M. Wang, T.T. Zhang, Y. Liang, J.J. Gao, Efficient synthesis of mono-and disubstituted 2,3-dihydroquinazolin-4 (*1H*)-ones using copper benzenesulfonate as a reusable catalyst in aqueous solution, *Monatsh. Chem.* 143 (2012) 835-839.