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An expedient synthesis of 6-amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(aryl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinedione derivatives using Fe_3O_4@TiO_2 nanocomposite as an efficient, magnetically separable, and reusable catalyst

https://doi.org/10.1515/znb-2018-0030
Received February 8, 2018; accepted April 22, 2018

Abstract: An efficient methodology dealing with the Fe_3O_4@TiO_2 nanocomposite-catalyzed direct condensation reaction of 4-hydroxycoumarin, aromatic aldehydes, and 6-amino-1,3-dimethyluracil in aqueous media at room temperature is reported. This new process has been successfully applied to the synthesis of 6-amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(aryl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinediones in high to excellent yields within 2–3 h.

Keywords: aqueous media; aromatic aldehydes; eco-friendly protocol; Fe_3O_4@TiO_2 nanocomposite; 4-hydroxycoumarin; magnetically reusable catalyst; pyrimidinediones.

1 Introduction

Pyrimidinones are well-known heterocycles in the field of synthetic organic chemistry as well as the pharmaceutical chemistry [1]. Pyrimidinones show important biological properties, such as antiviral, antibacterial, antihypertensive, antitumor, and calcium blocker effects [2]. The pyrimidinone is also a structural motif found in some natural marine products such as batzelladine and carambine alkaloids, which have been examined as potential HIV-gp-120CD4 activity inhibitors [3].

Chromene and its derivatives are important core units that display a wide range of pharmaceutical properties such as antioxidant [4, 5], anticancer [6–9], antimicrobial [10–13], hypotensive [14], and local anesthetic activity [15]. Moreover, some substances containing the chromene moiety have been reported to show cognitive enhancing activity [16, 17].

In the last few years, the application of metal oxide nanoparticle (NP) catalysts in organic synthesis has been preferably developed due to their special features such as a high surface area with low coordination sites [18–21]. Among them, titanium dioxide nanoparticles (TiO_2 NPs) can be used in several organic and inorganic transformations because of its superior properties such as high catalytic activity, nontoxicity, ease of availability, moisture stability, and reusability [22–31]. Currently, the magnetic nanoparticles (MNPs) doping to increase the utilization of heterogeneous solid catalysts have especially attracted great attention in organic and inorganic transformations [32]. MNPs have been reported to show an enormous range of various usages such as cancer treatment [33], drug delivery [34], and simplicity of catalyst separation. In particular, the core-shell structure of Fe_3O_4@TiO_2 NPs with their unique characteristics such as electronic properties, large specific surface area, and easy magnetic separability can be used to advantage as an efficient, easily separable heterogeneous catalyst [35–37].

There have been a few methods for the three-component coupling reaction of 4-hydroxycoumarin, aromatic aldehydes, and 6-amino-1,3-dimethyluracil in the literature in which the reaction was performed under solvent-free heating catalyzed by $Zr(HSO_4)_4$ [38] or, in another manner, the reaction occurred under water or ethanol refluxing using organocatalysts [39, 40]. However, these methods have some disadvantages such as thermal reaction conditions, longer reaction times, lower yields, and effluent pollution. Therefore, it is clearly considered that developing new and flexible procedures could be desirable.

The purpose of this study is to investigate modified TiO_2 NPs doped with Fe_3O_4 NPs as an efficient heterogeneous solid catalyst for the synthesis of 6-amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(aryl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinediones (**4**) through a condensation reaction of 4-hydroxycoumarin (**1**), aromatic aldehydes (**2**), and 6-amino-1,3-dimethyluracil (**3**) in aqueous media at room temperature (Scheme 1).

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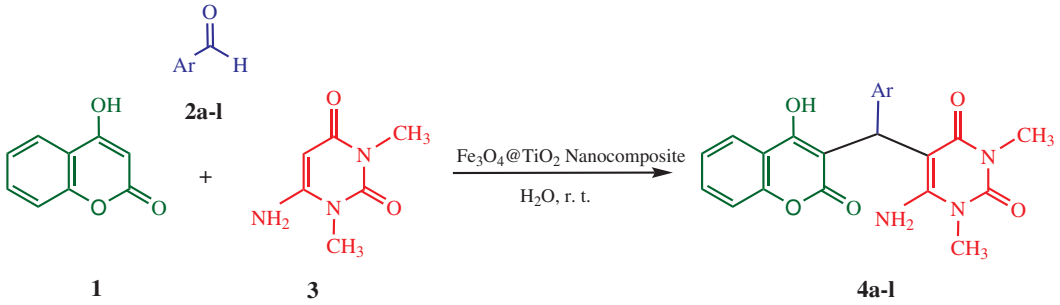


1a, 4a Ar = C_6H_5, **1b, 4b** Ar = 4-Br-C_6H_4, **1c, 4c** Ar = 4-Cl-C_6H_4, **1d, 4d** Ar = 2,4-Cl_2-C_6H_3, **1e, 4e** Ar = 4-NC-C_6H_4, **1f, 4f** Ar = 3-HO-C_6H_4, **1g, 4g** Ar = 4-CH_3O-C_6H_4, **1h, 4h** Ar = 4-CH_3-C_6H_4, **1i, 4i** Ar = 3-O_2N-C_6H_4, **1j, 4j** Ar = Furan-2-yl, **1k, 4k** Ar = Pyridin-4-yl, **1l, 4l** Ar = Thiophen-3-yl

Scheme 1: Synthesis of 6-amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(aryl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinedione derivatives using Fe_3O_4@TiO_2 NPs.

In continuation of our ongoing research in developing nanocatalysts for the environmentally synthetic methods, we have designed a new approach for direct condensation reaction of 4-hydroxycoumarin, aromatic aldehydes, and 6-amino-1,3-dimethyluracil in the presence of the synthesized Fe_3O_4@TiO_2 nanocomposite as a highly active and recyclable catalyst.

Initially, we prepared Fe_3O_4@TiO_2 nanocatalyst using a simple solvothermal method reported in the literature [41]. The X-ray powder diffraction (XRD) pattern of the synthesized nanocomposite reveals relatively weak and broad diffraction peaks of Fe_3O_4 and TiO_2 structure, confirming the lower crystallinity of the TiO_2 phase in the structure of the NPs (Fig. 1) [42].

The morphology and the average particle size of the Fe_3O_4@TiO_2 nanocomposite were also determined by transmission electron microcopy (TEM) images (Fig. 2). They reveal the Fe_3O_4@TiO_2 NPs to have an average diameter of 20 nm and a typical core-shell structure. The thickness of the black Fe_3O_4 core and the light-colored TiO_2 shell is approximately 12 and 9 nm, respectively.

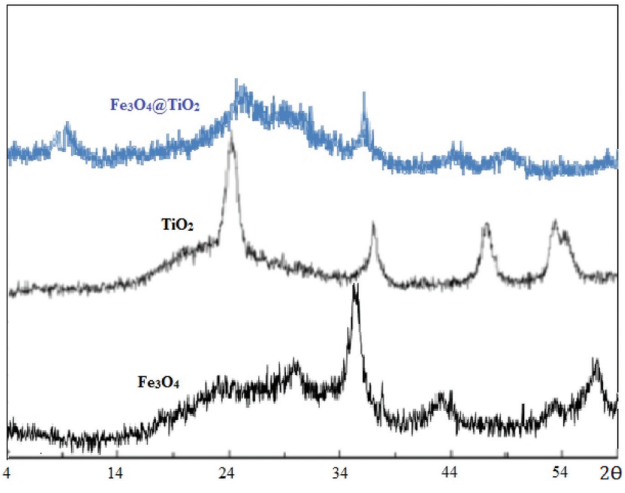


Fig. 1: XRD pattern of the synthesized Fe_3O_4 NPs, TiO_2 NPs, and the Fe_3O_4@TiO_2 NPs.

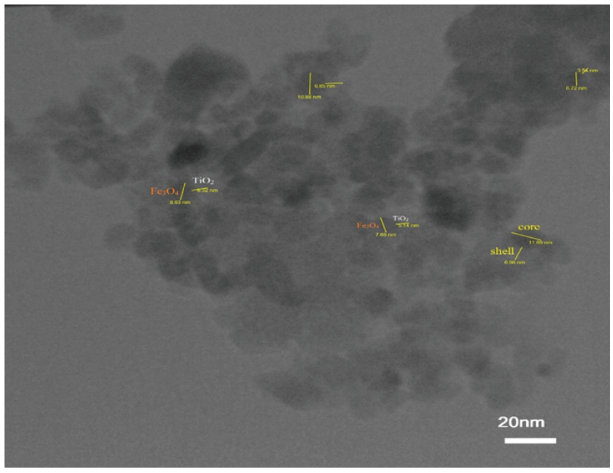


Fig. 2: TEM image of the synthesized Fe_3O_4@TiO_2 NPs.

The elemental composition of the catalyst was determined using energy-dispersive spectroscopy (EDS). The results showed the presence of Fe, Ti, C, and Cu in the composites, with contents of 3.45%, 19.38%, 50.24%, 20.71%, and 6.22%, respectively (Fig. 3). According to the results, the weight ratio of the synthesized nanocomposite is 30:70 referred to Fe_3O_4 and TiO_2, respectively.

The reaction optimization was next undertaken in our experiments, which was achieved by using 4-chlorobenzaldehyde **2c** as a model substrate for the reaction with 4-hydroxycoumarin **1**, and 6-amino-1,3-dimethyluracil **3** (Table 1).

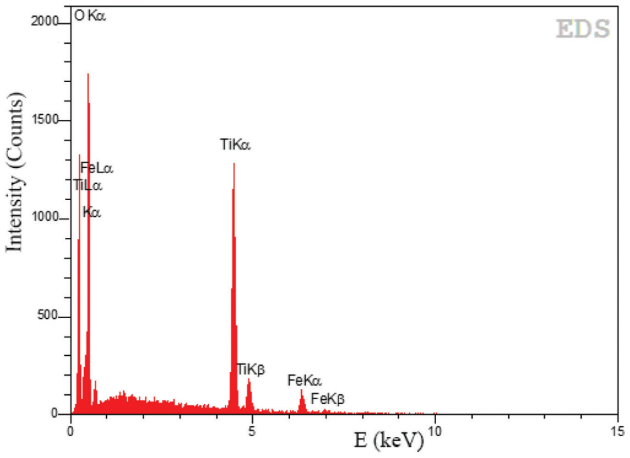


Fig. 3: EDS analysis of the synthesized Fe_3O_4@TiO_2 NPs.

To demonstrate the effectiveness of the Fe_3O_4@TiO_2 NPs as a catalyst, the model reaction was performed in the absence of the catalyst. After 6 h, only 54% of product (**4c**) was obtained at reflux in H_2O (Table 1, entry 1). In contrast, the product (**4c**) was obtained in a high yield (96%) by treating the reaction using a catalytic amount (0.02 g) of Fe_3O_4@TiO_2 NPs in H_2O at room temperature. There was an improvement in the product yield when the catalyst loading was increased from 0.01 to 0.02 g, but no significant change was observed when the catalyst loading was further increased to 0.03 g (Table 1, entries 2–4).

To investigate the influence of the reaction temperature, the model reaction was also examined under reflux. It does not affect the product yield but it does increase the reaction rate (Table 1, entries 3 and 5).

In the next step, the model reaction was carried out in various solvents including H_2O, EtOH, CH_3CN, CH_2Cl_2, and dimethylformamide (DMF). It was found that the best results were obtained in water (Table 1, entries 3 and 6–9).

The scope and limitation of this new protocol was extensively evaluated for various differently substituted aromatic aldehydes with 4-hydroxycoumarin and 6-amino-1,3-dimethyluracil by applying the optimized conditions (Table 2). The isolated compounds (**4a–l)** were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data and also by elemental analyses.

A plausible mechanism for this reaction is proposed in Scheme 2. It is supposed that TiO_2 NPs accelerate the formation of alkene **7**, which forms through a Knoevenagel condensation between aromatic aldehydes **2** and 6-amino-1,3-dimethyluracil **3** through intermediates **5** and **6**. TiO_2 NPs are also used in the subsequent Michael-type addition of 4-hydroxycoumarin **1** to alkenes **7**. Finally, product **4** is obtained and the catalyst is released for further reactions.

To confirm the recyclability of the catalyst, after completion of the model reaction, the catalyst was successfully separated magnetically from the reaction mixtures as explained in the general procedure. The recovered catalyst was used in four subsequent runs for the same reaction, with only a slight decrease in activity (Fig. 4).

The structures of the compounds were confirmed by their satisfactory elemental analyses, IR, ^{1}H, and ^{13}C NMR spectroscopy. Selected spectroscopic data are given in the Experimental Section. The synthesized catalyst was fully characterized by XRD, TEM, and EDS.

2 Conclusion

An efficient and magnetically reusable Fe_3O_4@TiO_2 nanocatalyst was prepared through a simple solvothermal method. Using this catalyst, a simple, economical, and environmentally benign route for the synthesis of 2-amino-6-aryl-5,6-dihydro-4(3*H*)-pyrimidinones was developed. In general, the present approach offers several advantages such as simplicity of operation; use of a nontoxic, cost-effective, and magnetically recyclable catalyst; high product yields; short reaction times; and the use of water as a green reaction medium.

Table 1: Optimization of the reaction conditions in the synthesis of **4c**.

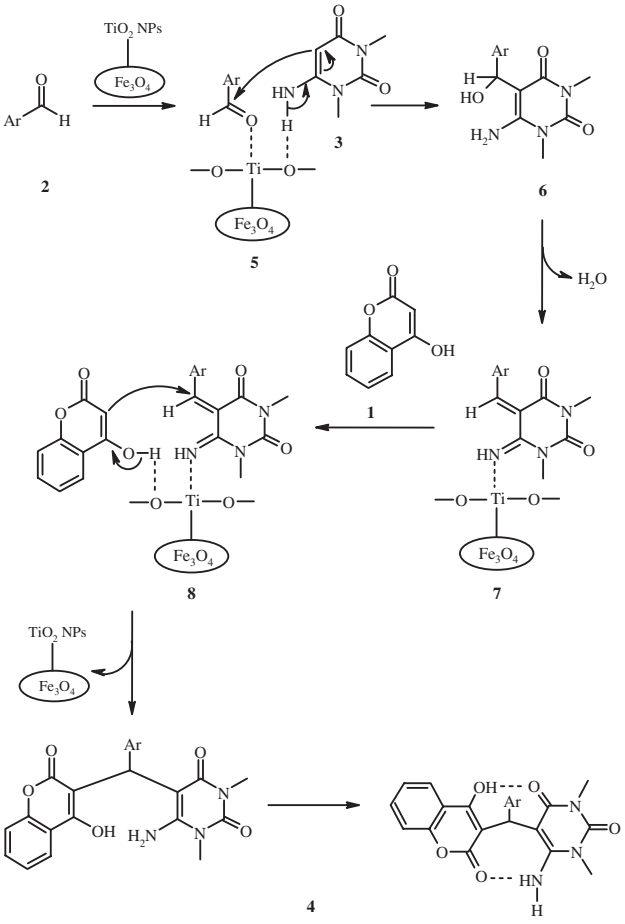
Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	None	H_2O	Reflux	6	54
2	Fe_3O_4@TiO_2 (0.01 g)	H_2O	r. t.	2	75
3	Fe_3O_4@TiO_2 (0.02 g)	H_2O	r. t.	2	96
4	Fe_3O_4@TiO_2 (0.03 g)	H_2O	r. t.	2	96
5	Fe_3O_4@TiO_2 (0.02 g)	H_2O	Reflux	1	96
6	Fe_3O_4@TiO_2 (0.02 g)	EtOH	r. t.	2.5	70
7	Fe_3O_4@TiO_2 (0.02 g)	CH_3CN	r. t.	3	62
8	Fe_3O_4@TiO_2 (0.02 g)	CH_2Cl_2	r. t.	3	43
9	Fe_3O_4@TiO_2 (0.02 g)	DMF	r. t.	2	79

[a]Isolated yield.

Table 2: Synthesis of 6-amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(aryl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinediones **4a–l** in the presence of 0.02 g Fe_3O_4@TiO_2.

Product	Ar	Time (h)	Yield (%)[a,b]	M. p. (°C)	
				Obsd.	Lit.
4a	C_6H_5	3	95	190–192	192–193 [38]
4b	4-Br-C_6H_4	2.5	97	234–236	233–234 [38]
4c	4-Cl-C_6H_4	2	96	191–192	193–194 [38]
4d	2,4-Cl_2-C_6H_3	3	94	290–291	–
4e	4-NC-C_6H_4	2	97	204–205	204–206 [38]
4f	3-HO-C_6H_4	2.5	96	230–232	234–236 [38]
4g	4-CH_3O-C_6H_4	2.5	95	206–208	205–207 [38]
4h	4-CH_3-C_6H_4	3	98	202–204	203–205 [38]
4i	3-O_2N-C_6H_4	2	98	259–261	257–259 [38]
4j	Furan-2-yl	2	96	218–220	–
4k	Pyridin-4-yl	3	94	227–229	–
4l	Thiophen-3-yl	3	97	214–216	–

[a]Yields refer to pure isolated products characterized by IR, ^{1}H, and ^{13}C NMR spectral data and by elemental analyses. [b]In all cases, the reactions were done at room temperature in H_2O (2 mL) for 2–3 h under stirring.



Scheme 2: A plausible mechanism for the reaction of 4-hydroxycoumarine, aromatic aldehydes, and 6-amino-1,3-dimethyluracil catalyzed by Fe_3O_4@TiO_2 NPs.

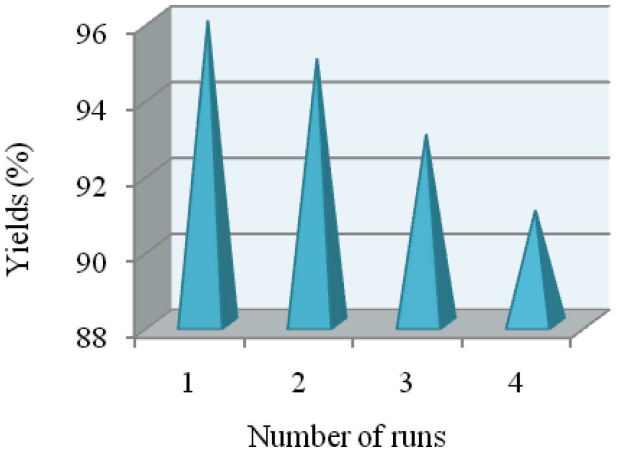


Fig. 4: Recyclability of the Fe_3O_4@TiO_2 nanocatalyst for the synthesis of **4c**.

3 Experimental section

3.1 Materials and methods

All chemicals used in this work were purchased from Merck and Fluka in high purity. Melting points were determined with Electrothermal 9100 apparatus. IR spectra were obtained using a Bruker, Equinox 55, Golden Gate Micro-ATR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 AVANCE spectrometer at 500 and 125 MHz, respectively, using TMS as internal standard and [D_6]DMSO as a solvent. Elemental analyses were carried out using a Foss-Heraeus CHN-O-Rapid analyzer. The microscopic morphology of the catalyst was extracted using a TEM technique on a Philips CM300 operating at 100 kV electron beam accelerating voltage. Powder X-ray diffraction data were determined on a Philips XPERT PW1800 diffractometer using CuKα radiation ($\lambda = 1.5406$ Å). The composition of the catalyst was determined using EDS analysis.

3.2 General procedure for the preparation of Fe_3O_4@TiO_2 nanocomposite

To a magnetically stirred mixture of Fe_3O_4 (3 g) in 30 mL of absolute ethanol, polyvinylpyrolidine (0.1 g) and tetrabuthylorthotitanat (3.1 mL) were added and the resulting mixture was continuously stirred at 87°C for approximately 15 h. During this process, an aqueous solution of 0.15 M urea (10 mL) was added dropwise to this mixture. In order to achieve maximum adsorption of $Ti(OH)_4$ on the surface of the Fe_3O_4 NPs, the suspension was kept

for 24 h at ambient temperature without any movement. Afterward, the prepared magnetic nanocomposite was separated magnetically, rinsed with distilled water and absolute ethanol for three times, respectively, and then dried at 60°C for approximately 6 h. The obtained nanocomposite was dispersed in 30 mL of ethylene glycol, stirred for 30 min, and treated with ultrasonic vibration for 20 min. Then, the mixture was again vigorously stirred with a magnetic stirrer until a homogeneous mixture was obtained. The mixture was then transferred to a Teflon-sealed autoclave and heated at 200°C for 7 h to produce a dark-brown magnetic nanocomposite. The produced core-shell Fe_3O_4@TiO_2 NPs were finally separated using an external magnet, rinsed with absolute ethanol three times, and then dried at 80°C for 3 h in a vacuum oven.

3.3 General procedure for the synthesis of compounds 4a–l

A mixture of 4-hydroxycoumarine **1** (162 mg, 1 mmol), the aromatic aldehydes **2a–l** (1 mmol; 106, 185, 141, 175, 131, 122, 136, 120, 151, 96, 107, and 112 mg, respectively), 6-amino-1,3-dimethyluracil **3** (155 mg, 1 mmol), and Fe_3O_4@TiO_2 NPs (0.02 g), in H_2O (2 mL) were stirred at ambient temperature for 2–3 h (see Table 2). After completion of the reaction as indicated by thin layer chromatography (eluent/ethyl acetate-petrol = 3:1), the reaction mixture was diluted with DMF (1 mL) and the catalyst was recovered from the reaction mixture by simply using an external magnet. For reuse, the catalyst was washed with EtOH and dried in air at ambient temperature for several hours. The remaining solution was diluted with H_2O (1 mL), to yield the pure products by recrystallization from this solution.

3.4 Selected spectroscopic data

3.4.1 6-Amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(phenyl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinedione (4a)

White solid, yield: 0.385 g (95%), m. p. 190°C–192°C (lit.: 192°C–193°C [38]). – IR (KBr): ν_{max} = 3430, 3336 (NH_2), 3244 (OH), 1689, 1668, 1619 (3CO), 1570, 1510 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 3.17 (s, 3 H, CH_3), 3.40 (s, 3 H, CH_3), 5.65 (s, 1 H, H-7), 7.17 (d, $^3J_{HH}$ = 6.3 Hz, 3 H, H-Ar), 7.25 (t, $^3J_{HH}$ = 7.0 Hz, 2 H, H-Ar), 7.34 (brs, 2 H, NH_2), 7.39 (t, $^3J_{HH}$ = 8.2 Hz, 1 H, H-Ar), 7.45 (d, $^3J_{HH}$ = 8.2 Hz, 1 H, H-Ar), 7.67 (t, $^3J_{HH}$ = 7.6 Hz, 1 H, H-Ar), 7.86 (d, $^3J_{HH}$ = 7.6 Hz, 1 H, H-Ar), 14.00 (s, 1 H, OH) ppm. – ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 29.1 (NCH_3), 31.4 (NCH_3), 36.9 (C-5), 63.7 (*C*=C–NH_2), 87.7 (*C*=C–OH), 105.5 (CH), 117.0, 117.8, 124.6, 125.2, 126.6, 127.2, 129.0, 133.3, 135.2, 139.2, 150.9, 152.8, 156.0, 164.7, 165.0, 166.7 ppm. – Analysis calcd. for $C_{22}H_{19}N_3O_5$ (405.41): C 65.18, H 4.72, N 10.36; found C 65.22, H 4.78, N 10.27.

3.4.2 6-Amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(2,4-dichlorophenyl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinedione (4d)

White solid, yield: 0.446 g (94%), m. p. 290°C–291°C. – IR (KBr): ν_{max} = 3438, 3359 (NH_2), 3240 (OH), 1702, 1684, 1621 (3CO), 1566, 1505 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 3.15 (s, 3 H, CH_3), 3.40 (s, 3 H, CH_3), 5.63 (s, 1 H, H-7), 7.36 (brs, 2 H, NH_2), 7.40 (m, 2 H, H-Ar), 7.43 (d, $^3J_{HH}$ = 7.9 Hz, 1 H, H-Ar), 7.60 (t, $^3J_{HH}$ = 8.0 Hz, 1 H, H-Ar), 7.76 (t, $^3J_{HH}$ = 7.8 Hz, 1 H, H-Ar), 7.80 (d, $^3J_{HH}$ = 7.0 Hz, 1 H, H-Ar), 7.84 (d, $^3J_{HH}$ = 7.2 Hz, 1 H, H-Ar), 13.99 (s, 1 H, OH) ppm. – ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 29.1, 31.2, 36.6, 62.8, 89.1, 105.2, 117.3, 118.1, 122.2, 124.4, 130.5, 132.4, 133.4, 135.6, 136.7, 140.1, 150.9, 151.1, 156.1, 164.8, 165.0, 165.4 ppm. – Analysis calcd. for $C_{22}H_{17}Cl_2N_3O_5$ (474.30): C 55.71, H 3.61, N 8.86; found C 55.86, H 3.49, N 8.77.

3.4.3 6-Amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(4-cyanophenyl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinedione (4e)

Yellow solid, yield: 0.418 g (97%), m. p. 204°C–205°C (lit.: 204°C–206°C [38]). – IR (KBr): ν_{max} = 3432, 3364 (NH_2), 3211 (OH), 2226 (CN), 1699, 1667, 1618 (3CO), 1571, 1507 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 3.16 (s, 3 H, CH_3), 3.40 (s, 3 H, CH_3), 5.72 (s, 1 H, H-7), 7.37 (brs, 2 H, NH_2), 7.40 (m, 3 H, H-Ar), 7.46 (d, $^3J_{HH}$ = 8.2 Hz, 1 H, H-Ar), 7.68 (t, $^3J_{HH}$ = 7.8 Hz, 1 H, H-Ar), 7.71 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, H-Ar), 7.86 (d, $^3J_{HH}$ = 7.8 Hz, 1 H, H-Ar), 13.96 (s, 1 H, OH) ppm. – ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 29.1, 31.5, 37.4, 63.7, 87.1, 105.1, 109.5, 117.0, 117.7, 119.9, 124.0, 124.6, 125.2, 128.6, 132.8, 133.4, 145.8, 150.9, 152.9, 156.2, 164.7, 165.0, 166.5 ppm. – Analysis calcd. for $C_{23}H_{18}N_4O_5$ (430.42): C 64.18, H 4.22, N 13.02; found C 64.23, H 4.28, N 13.12.

3.4.4 6-Amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(4-methylphenyl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinedione (4h)

White solid, yield: 0.411 g (98%), m. p. 202°C–204°C (lit.: 203°C–205°C [38]). – IR (KBr): ν_{max} = 3464, 3411 (NH_2),

3212 (OH), 1699, 1672, 1621 (3CO), 1570, 1508 (C=C) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 2.25$ (s, 3 H, CH_3), 3.16 (s, 3 H, CH_3), 3.40 (s, 3 H, CH_3), 5.60 (s, 1 H, H-7), 7.04 (brs, 4 H, H-Ar), 7.27 (brs, 2 H, NH_2), 7.36 (t, $^3J_{HH} = 7.8$ Hz, 1 H, H-Ar), 7.44 (d, $^3J_{HH} = 7.8$ Hz, 1 H, H-Ar), 7.66 (t, $^3J_{HH} = 7.0$ Hz, 1 H, H-Ar), 7.85 (d, $^3J_{HH} = 7.0$ Hz, 1 H, H-Ar), 13.98 (s, 1 H, OH) ppm. – ^{13}C NMR (125 MHz, [D_6]DMSO): $\delta = 21.3$, 29.1, 31.4, 36.6, 63.7, 87.9, 105.6, 117.6, 117.8, 124.6, 125.2, 127.1, 129.6, 132.2, 133.3, 135.5, 136.0, 150.9, 152.8, 156.0, 164.7, 164.9, 166.7 ppm. – Analysis calcd. for $C_{23}H_{21}N_3O_5$ (419.43): C 65.86, H 5.05, N 10.02; found C 65.93, H 5.12, N 10.09.

3.4.5 6-Amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(2-furanylphenyl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinedione (4j)

White solid, yield: 0.380 g (96%), m. p. 218°C–220°C. – IR (KBr): $\nu_{max} = 3418$, 3324 (NH_2), 3211 (OH), 1707, 1676, 1616 (3CO), 1569, 1486 (C=C) cm^{-1}. – ^1H NMR (500 MHz, [D_6] DMSO): $\delta = 3.15$ (s, 3 H, CH_3), 3.41 (s, 3 H, CH_3), 5.71 (s, 1 H, H-7), 7.17 (m, 3 H, H-Ar), 7.29 (brs, 2 H, NH_2), 7.30 (t, $^3J_{HH} = 7.6$ Hz, 1 H, H-Ar), 7.32 (d, $^3J_{HH} = 8.0$ Hz, 1 H, H-Ar), 7.49 (d, $^3J_{HH} = 8.1$ Hz, 1 H, H-Ar), 7.69 (d, $^3J_{HH} = 8.0$ Hz, 1 H, H-Ar), 14.04 (s, 1 H, OH) ppm. – ^{13}C NMR (125 MHz, [D_6] DMSO): $\delta = 29.1$, 31.3, 37.2, 62.5, 89.1, 105.2, 116.9, 117.7, 117.8, 119.0, 120.1, 133.3, 138.8, 141.9, 150.3, 151.8, 155.8, 163.9, 165.5, 166.4 ppm. – Analysis calcd. for $C_{20}H_{17}N_3O_6$ (395.37): C 60.76, H 4.33, N 10.63; found C 60.84, H 4.23, N 10.50.

3.4.6 6-Amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(4-pyridylphenyl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinedione (4k)

Yellow solid, yield: 0.382 g (94%), m. p. 227°C–229°C. – IR (KBr): $\nu_{max} = 3459$, 3402 (NH_2), 3220 (OH), 1688, 1663, 1620 (3CO), 1589, 1515 (C=C) cm^{-1}. – ^1H NMR (500 MHz, [D_6] DMSO): $\delta = 3.18$ (s, 3 H, CH_3), 3.42 (s, 3 H, CH_3), 5.74 (s, 1 H, H-7), 7.25 (d, $^3J_{HH} = 8.1$ Hz, 1 H, H-Ar), 7.29 (d, $^3J_{HH} = 8.0$ Hz, 1 H, H-Ar), 7.33 (brs, 2 H, NH_2), 7.51 (t, $^3J_{HH} = 7.9$ Hz, 1 H, H-Ar), 7.39 (d, $^3J_{HH} = 8.0$ Hz, 2 H, H-Ar), 7.80 (d, $^3J_{HH} = 7.7$ Hz, 1 H, H-Ar), 8.44 (d, $^3J_{HH} = 8.1$ Hz, 2 H, H-Ar), 13.99 (s, 1 H, OH) ppm. – ^{13}C NMR (125 MHz, [D_6]DMSO): $\delta = 29.6$, 30.9, 38.0, 63.8, 86.5, 104.5, 116.1, 119.3, 121.0, 127.6, 134.7, 148.1, 149.9, 150.7, 153.4, 156.0, 163.8, 164.6, 165.7 ppm. – Analysis calcd. for $C_{21}H_{18}N_4O_5$ (406.40): C 62.07, H 4.46, N 13.79; found C 62.19, H 4.55, N 13.94.

3.4.7 6-Amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(3-thienylphenyl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinedione (4l)

Brick-red solid, yield: 0.399 g (97%), m. p. 214°C–216°C. – IR (KBr): $\nu_{max} = 3434$, 3381 (NH_2), 3217 (OH), 1710, 1685, 1618 (3CO), 1579, 1520 (C=C) cm^{-1}. – ^1H NMR (500 MHz, [D_6] DMSO): $\delta = 3.16$ (s, 3 H, CH_3), 3.42 (s, 3 H, CH_3), 5.69 (s, 1 H, H-7), 6.87 (d, $^3J_{HH} = 4.6$ Hz, 1 H, H-Ar), 7.26 (t, $^3J_{HH} = 7.8$ Hz, 1 H, H-Ar), 7.28 (d, $^3J_{HH} = 4.3$ Hz, 1 H, H-Ar), 7.31 (d, $^3J_{HH} = 7.9$ Hz, 1 H, H-Ar), 7.35 (brs, 2 H, NH_2), 7.39 (s, 1 H, H-Ar), 7.52 (d, $^3J_{HH} = 7.6$ Hz, 1 H, H-Ar), 7.71 (d, $^3J_{HH} = 7.6$ Hz, 1 H, H-Ar), 14.11 (s, 1 H, OH) ppm. – ^{13}C NMR (125 MHz, [D_6]DMSO): $\delta = 29.6$, 31.1, 36.8, 63.0, 89.0, 104.6, 117.7, 118.6, 119.2, 124.1, 126.5, 132.4, 139.0, 140.4, 151.0, 151.7, 156.1, 163.6, 164.0, 165.8 ppm. – Analysis calcd. for $C_{20}H_{17}N_3O_5S$ (411.43): C 58.39, H 4.16, N 10.21; found C 58.25, H 4.26, N 10.04.

Acknowledgments: We thank East Tehran Branch, Islamic Azad University, for its financial support.

References

[1] C. O. Kappe, *Tetrahedron* **1993**, *49*, 6937.
[2] G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. DiMarco, J. Gougoutas, A. Hedberg, M. Malley, J. P. McCarthy, *J. Med. Chem.* **1995**, *38*, 119.
[3] A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. De Brosse, S. Mai, A. Truneh, B. Carte, *J. Org. Chem.* **1995**, *60*, 1182.
[4] L. Alvey, S. Prado, V. Huteau, B. Saint-Joanis, S. Michel, M. Koch, S. T. Cole, F. Tillequin, Y. L. Janin, *Bioorg. Med. Chem.* **2008**, *16*, 8264.
[5] T. Symeonidis, M. Chamilos, D. J. Hadjipavlou-Litina, M. Kallitsakis, K. E. Litinas, *Bioorg. Med. Chem.* **2009**, *19*, 1139.
[6] J. L. Wang, D. Liu, Z. J. Zhang, S. Shan, X. Han, S. M. Srinivasula, C. M. Croce, E. S. Alnemri, Z. Huang, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 7124.
[7] F. Cheng, A. Ishikawa, Y. Ono, T. Arrheniusa, A. Nadzana, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3647.
[8] D. Grée, S. Vorin, V. L. Manthati, F. Caijo, G. Viault, F. Manero, P. Juin, R. Grée, *Tetrahedron Lett.* **2008**, *49*, 3276.
[9] W. Kemnitzer, S. Jiang, H. Zhang, S. Kasibhatla, C. Crogan-Grundy, C. Blais, G. Attardo, R. Denis, S. Lamothe, H. Gourdeau, B. Tseng, J. Drewe, X. Cai, *Bioorg. Med. Chem.* **2008**, *18*, 5571.
[10] M. M. Khafagy, A. H. Abd el-Wahab, F. A. Eid, A. M. el-Agrody, *Farmaco* **2002**, *57*, 715.
[11] K. Mazaahir, S. Shilpi, R. Khalilur, S. T. Sharanjit, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4295.
[12] I. O. Donkor, C. L. Klein, L. Liang, N. Zhu, E. Bradley, A. M. Clark, *J. Pharm. Sci.* **1995**, *84*, 661.
[13] R. R. Kumar, S. Perumal, P. Senthilkumar, P. Yogeeswari, D. Sriram, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6459.

[14] V. K. Tandon, M. Vaish, S. Jain, D. S. Bhakuni, R. C. Srimal, *Indian J. Pharm. Sci.* **1991**, *53*, 22.
[15] M. Longobardi, A. Bargagna, E. Mariani, P. Schenone, S. Vitagliano, L. Stella, A. Di Sarno, E. Marmo, *Farmaco* **1990**, *45*, 399.
[16] A. H. Bedair, N. A. El-Hady, A. El-Latif, A. H. Fakery, A. M. El-Agrody, *Farmaco* **2000**, *55*, 708.
[17] M. M. Heravi, K. Bakhtiari, V. Zadsirjan, F. F. Bamoharram, O. M. Heravi, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4262.
[18] C. Burda, X. B. Chen, R. Narayanan, M. A. El-Sayed, *Chem. Rev.* **2005**, *105*, 1025.
[19] A. Y. Kim, H. J. Lee, J. C. Park, H. Kang, H. Yang, H. Song, K. H. Park, *Molecules* **2009**, *14*, 5169.
[20] K. S. Lin, C. Y. Pan, S. Chowdhury, M. T. Tu, W. T. Hong, C. T. Yeh, *Molecules* **2011**, *16*, 348.
[21] A. Monopoli, A. Nacci, V. Caló, F. Ciminale, P. Cotugno, A. Mangone, L. C. Giannossa, P. Azzone, N. Cioffi, *Molecules* **2010**, *15*, 4511.
[22] M. L. Kantam, S. Laha, J. Yadav, B. Sreedhar, *Tetrahedron Lett.* **2006**, *47*, 6213.
[23] M. Hosseini-Sarvari, *Acta Chim. Slov.* **2007**, *54*, 354.
[24] J. L. Ropero-Vega, A. Aldana-Péreza, R. Gómez, M. E. Niño-Gómez, *Appl. Catal. A* **2010**, *379*, 24.
[25] M. Z. Kassaee, R. Mohammadi, H. Masrouri, F. Movahedi, *Chin. Chem. Lett.* **2011**, *22*, 1203.
[26] F. Shirini, M. Alipour Khoshdel, M. Abedini, S. V. Atghia, *Chin. Chem. Lett.* **2011**, *22*, 1211.
[27] F. Shirini, S. V. Atghia, M. Alipour Khoshdel, *Iran. J. Catal.* **2011**, *1*, 93.
[28] S. Abdolmohammadi, *Curr. Catal.* **2013**, *2*, 116.
[29] S. Abdolmohammadi, *Chin. Chem. Lett.* **2012**, *23*, 1003.
[30] S. Abdolmohammadi, *Chin. Chem. Lett.* **2013**, *24*, 318.
[31] S. Abdolmohammadi, M. Mohammadnejad, F. Shafaei, *Z. Naturforsch.* **2013**, *68b*, 362.
[32] J. Deng, L. P. Mo, F. Y. Zhao, L. L. Hou, L. Yang, Z. H. Zhang, *Green Chem.* **2011**, *13*, 2576.
[33] Y. M. Huh, Y. W. Jun, H. T. Song, S. Kim, J. S. Choi, J. H. Lee, S. Yoon, K. S. Kim, J. S. Shin, J. S. Suh, J. Cheon, *J. Am. Chem. Soc.* **2005**, *127*, 12387.
[34] P. Sharma, S. Rana, K. C. Barick, C. Kumar, H. G. Salunked, P. A. Hassan, *New J. Chem.* **2014**, *38*, 5500.
[35] T. A. Gad Allah, S. Kato, S. Satokawa, T. Kojima, *Solid State Sci.* **2007**, *9*, 737.
[36] M. Ahmadi Golsefidi, B. Sarkhosh, *J. Iran. Chem. Soc.* **2017**, *14*, 1089.
[37] S. Salamat, H. Younesi, N. Bahramifar, *RSC Adv.* **2017**, *7*, 19391.
[38] S. Abdolmohammadi, S. Balalaie, M. Barari, F. Rominger, *Comb. Chem. High Throughput Screen.* **2013**, *16*, 150.
[39] R. Bharti, T. Parvin, *RSC Adv.* **2015**, *5*, 66833.
[40] R. Bharti, T. Parvin, *Synth. Commun.* **2015**, *45*, 1442.
[41] H. Niu, Q. Wang, H. Liang, M. Chen, C. Mao, J. Song, S. Zhang, Y. Gao, C. Chen, *Materials* **2014**, *7*, 4034.
[42] L. Tana, X. Zhang, Q. Liua, X. Jinga, J. Liua, D. Songa, S. Hua, L. Liub, J. Wang, *Colloids Surf. A* **2015**, *469*, 279.

Graphical synopsis

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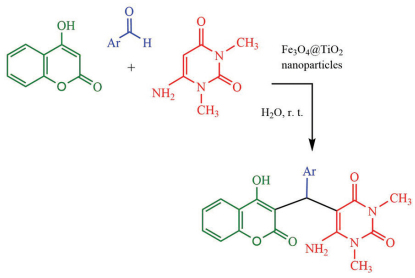
An expedient synthesis of 6-amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(aryl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinedione derivatives using Fe_3O_4@TiO_2 nanocomposite as an efficient, magnetically separable, and reusable catalyst



https://doi.org/10.1515/znb-2018-0030
Z. Naturforsch. 2018; x(x)b: xxx–xxx