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# Green synthesis, characterization, structure, biological activity, theoretical calculations and drug-likeness analysis of coumarins



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## ABSTRACT

Condensation of salicylaldehydes and 2-hydroxynaphthaldehyde with various  $\beta$ -dicarbonyl derivatives **2a-c**, in the presence of  $\text{KF-Al}_2\text{O}_3$ , leads to the synthesis of a series of coumarins **3-8** and benzo[*f*]coumarins **10** respectively by a solvent free reaction under microwave irradiation. The catalyst is recovered by a simple filtration and reused in subsequent reactions. The structure of all synthesized compounds has been established by using analytical techniques such as IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic spectra and elemental analysis. Most of the coumarins exhibited significant antibacterial activity against *S. aureus* Gram-positive bacteria compared to Cefotaxime as positive control. The compounds **4a** and **7a** demonstrated moderate antimicrobial activity against compound **8a** is extremely sensitive. In addition, the compounds showed moderate to good antiradical (DPPH) activity. Theoretical calculations let us to confirm the reaction mechanism. Parameters drug-likeness and physicochemical properties including pharmacokinetic analysis of the synthesized compounds was performed using DruliTo program.

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## Specifications table

Subject area	Organic Chemistry
Compounds	Coumarins
Data category	Spectral, synthesized, computational simulations
Data acquisition format	NMR, IR, Mass spectra, Elemental analysis
Data type	analyzed, simulated
Procedure	Brief description of procedure (e.g., transformation, simulation, etc.)
Data accessibility	A series of coumarins was synthesized in the presence of KF-Al <sub>2</sub> O <sub>3</sub> and characterized by spectroscopic analysis. Compounds were evaluated for their biological activities.

## 1. Rationale

In the last years, organic chemists have focused their attention towards the development of novel methodologies for the synthesis of heterocyclic compounds. Amongst them, coumarin derivatives have become popular due to their large pharmacological properties, such as antioxidant, anti-HIV, anticancer, and vasorelaxant activities and enzymatic inhibitors [1]. 3-Substituted coumarins (warfarin, coumachlor, dicoumarol and acenocoumarol) are clinically used as blood anticoagulants as well as rodenticides [2]. The application of their fluorescence properties is also widely known [3].

Coumarins are used as food additives and cosmetics [4] and dispersed fluorescent and laser dyes [5]. It is very important that the synthesis of coumarins should be achieved by a simple and effective method. There are several methods for the synthesis of coumarins, such as the Claisen rearrangement, Perkin and Pechmann reactions as well as the Knoevenagel condensation [6].

The use of microwaves in organic synthesis has increased dramatically in the last years, receiving widespread acceptance and becoming an indispensable tool. Recently it was shown that the Knoevenagel reaction could be quickly achieved using microwave irradiation [7]. Since the solvent free synthesis under microwave irradiation is the main topic of our laboratory [7–9], we are describing our results on the microwave assisted Knoevenagel condensation to synthesize coumarins.

Following our interest on the synthesis of coumarins [10,11] herein we describe a simple and efficient strategy for the synthesis of a series of substituent coumarins **3–8** and benzof[*h*]coumarins **10**, under mild conditions. These compounds have been obtained by using salicylaldehydes and 2-hydroxynaphthaldehyde as key synthons, using KF supported on alumina (KF-Al<sub>2</sub>O<sub>3</sub>) as a reusable solid support catalyst (Scheme 1) in a solvent free reaction under microwave irradiation. IR, NMR, UV–visible spectroscopic and biological evaluations have been studied for all the prepared compounds. Theoretical calculations let us to confirm the reaction mechanism. Drug-likeness and physicochemical properties, including pharmacokinetic analysis of the synthesized compounds was performed using DruliTo program.

## 2. Experimental

### 2.1. Materials

The chemicals reagents and solvents (Fluka products) used were of analytical grade and were used without further purification. Melting points were determined on a Stuart scientific SPM3 apparatus fitted with a microscope and are uncorrected. The IR spectra were recorded in the region 4000–400 cm<sup>-1</sup> on a Bruker Tensor 27 IR spectrophotometer without KBr. UV–visible spectra were measured on a Jenway 6800 ultraviolet-visible spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in DMSO-d<sub>6</sub>/CDCl<sub>3</sub> solutions in a Bruker Avance 300 (300.13 MHz for <sup>1</sup>H and 75.47 MHz for <sup>13</sup>C) spectrometer. Chemical shifts are reported in parts per million ( $\delta$  ppm) using TMS as internal reference. Screening of the compounds for antimicrobial activity was done at the Pharmaceutic laboratory. The microwave assisted synthesis is a multimode microwave reactor (a modified microwave oven candy mga20 m) used a single magnetron (2450 MHz) with a maximum delivered power of 800 W. Experiments were carried out in a pyrex reactor fitted with a condenser).

### 2.2. Procedure

#### 2.2.1. Synthesis of catalyst

To a solution of KF salt in water (30 g of salt in 100 mL of solvent), Al<sub>2</sub>O<sub>3</sub> (100 g) was added. The mixture was poured into an evaporation flask, until the weight of the evaporation flask was stable.

#### 2.2.2. General procedure for synthesis of coumarins

A mixture of a salicylaldehyde derivative **1** (1 mmol),  $\beta$ -dicarbonyl **2** (1 mmol) and the catalyst amount was irradiated under microwave by the time indicated in Table 3. After cooling the reaction mixture the crude product was recovered by filtration. The catalyst is separated from the product by addition of acetone and recovered by a simple filtration and subjected to a second run of the reaction process.

After evaporation of acetone, the obtained products were recrystallized from ethanol to afford coumarins **3–8** and **10**. All the products are known in the literature and the corresponding references are mentioned in Table 3. The structure of all synthesized compounds has been established by using analytical techniques such as IR, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic

spectra and elemental analysis. Also the identity of these compounds was established by comparison of their melting point with those of reported samples (Table 3). However, the spectral data of all the products are given.

### **3-acetyl-2H-chromen-2-one (3a)**

Fine pale yellow needles, Yield 71 %; mp 113–115 °C; IR (cm<sup>-1</sup>): 2930 (C-H aliphatic), 1742 (C=O), 1677 (O-C=O); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm: 2.55 (s, 3H, CH<sub>3</sub>), 7.38–7.40 (m, 2H, Ar-H), 7.70–7.89 (m, 2H, Ar-H), 8.58 (s, 1H, H-pyrone ring); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ ppm: 30.1 (C-12), 116.1 (C-8), 118.2 (C-10), 124.4 (C-3), 124.9 (C-6), 130.8 (C-5), 134.5 (C-7), 147.1 (C-4), 154.6 (C-9), 158.5 (C-2), 195.1 (C-11). Anal. calcd. for C<sub>11</sub>H<sub>8</sub>O<sub>3</sub>: C 70.21, H 4.25; Found: C 70.14, H 4.38.

### **Ethyl 2-oxo-2H-chromene-3-carboxylate (3b)**

Solid; Yield 75 %; mp 88–93 °C; IR (cm<sup>-1</sup>): 3053-(C-H aromatic and olefinic), 2928–2853 (C-H aliphatic), 1772 (C=O ester), 1689 (C=O coumarin), 1632 (C=O), 1581(C-O); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ ppm: 1.37 (t, J = 7.2 Hz, 3H, CH<sub>3</sub>), 4.36 (q, J = 7.2 Hz, 2H, OCH<sub>2</sub>), 7.29–7.34 (m, 2H, Ar-H), 7.60–7.66 (m, 2H, ArH), 8.51 (s, 1H, H-pyrone ring); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ ppm: 14.2, 61.9, 116.7, 117.8, 118.3, 124.8, 129.5, 134.3, 148.5, 155.1, 156.6, 163.0; Anal. calcd. for C<sub>12</sub>H<sub>10</sub>O<sub>4</sub>: C 66.05, H 4.58; Found C 66.17, H 4.49.

### **Methyl 2-oxo-2H-chromene-3-carboxylate (3c)**

Colourless crystals, Yield 76%; mp 104–107 °C; IR (cm<sup>-1</sup>): 1710 (C=O coumarin), 1670 (C=O), 1750 (C=O ester), 1200 (C-O); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm: 3.83 (s, 3H, OCH<sub>3</sub>), 7.35–7.86 (m, 4H, Ar-H), 8.72 (s, 1H, H-pyrone ring); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ ppm: 52.3, 116.1, 117.3, 117.7, 124.7, 130.2, 134.5, 148.9, 154.5, 155.8, 163.0; Anal. calcd. for C<sub>11</sub>H<sub>8</sub>O<sub>4</sub> C 64.71; H 3.95; Found: C 64.42; H 3.640.

### **3-acetyl-6-hydroxy-2H-chromen-2-one (4a)**

Yellow powder, Yield 73 %; mp 242–244 °C; IR (cm<sup>-1</sup>): 3178 (OH), 2928 (C-H aliphatic), 1742(C=O), 1645 (O-C=O); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ ppm: 2.57 (s, 3H, CH<sub>3</sub>), 7.13 (t, J = 4.38 Hz, 1H, Ar-H), 7.23 (s, 1H, Ar-H), 7.30 (d, J = 8.87 Hz, 1H, Ar-H), 8.53 (s, 1H, H-pyrone ring), 9.90 (br s, 1H, OH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ ppm: 29.9, 114.1, 115.1, 116.9, 118.6, 122.7, 124.3, 146.9, 147.9, 153.9, 159.6, 195.2.

### **Ethyl 6-hydroxy-2-oxo-2H-chromene-3-carboxylate (4b)**

This compound obtained as brown solid, Yield 78 %; mp 190–194 °C; IR (cm<sup>-1</sup>): 3471 (OH), 1728 (C=O ester), 1621 (C=O coumarin); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm: 1.27 (t, J = 6.3 Hz, 3H, CH<sub>3</sub>), 4.24 (q, J = 6.9 Hz, 2H, OCH<sub>2</sub>), 6.99–7.28 (m, 3H, Ar-H), 8.63 (s, 1H, H-pyrone ring), 9.88 (br s, 1H, OH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ ppm: 14.0, 61.1, 113.7, 117.0, 117.7, 118.2, 122.6, 147.8, 148.4, 153.9, 156.23, 162.7.

### **Methyl 6-hydroxy-2-oxo-2H-chromene-3-carboxylate (4c)**

Light brown solid, Yield 80 %; mp 207–210 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm: 3.82 (s, 3H, OCH<sub>3</sub>), 7.14–7.29 (m, 3H, Ar-H), 8.68 (s, 1H, H-pyrone ring), 9.89 (br s, 1H, OH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ ppm: 52.3, 113.8, 118.0, 117.1, 117.4, 118.2, 122.7, 147.9, 148.8, 153.9, 156.2, 163.3; Anal. Calcd for C<sub>11</sub>H<sub>8</sub>O<sub>5</sub>: C 60.00, H 3.66. Found: C 59.87, H 3.71.

### **3-acetyl-8-hydroxy-2H-chromen-2-one (5a)**

Light yellow, Yield 74 %; mp 258–260 °C; IR (cm<sup>-1</sup>): 3227 (OH) -1742 (C=O), 1697 (O-C=O); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ ppm: 2.58 (s, 3H, CH<sub>3</sub>), 7.08–7.21 (m, 2H, Ar-H), 7.28–7.39(m, 1H, Ar-H), 8.57 (s, 1H, H-pyrone ring), 10.38 (br s, 1H, OH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ ppm: 30.0, 119.0, 120.5, 120.6, 124.2, 124.8, 143.2, 144.4, 147.4, 158.3, 195.1.

### **Methyl 8-hydroxy-2-oxo-2H-chromene-3-carboxylate (5b)**

Light yellow solid, Yield 50 %; mp 208–210 °C; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm: 3.83 (s, 3H, OCH<sub>3</sub>), 7.17–7.21 (m, 2H, Ar-H), 7.30–7.34 (m, 1H, Ar-H), 8.72 (s, 1H, H-pyrone ring), 10.38 (br s, 1H, OH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ ppm: 52.4, 117.2, 118.7, 120.1, 120.6, 124.8, 143.2, 144.4, 149.4, 156.0, 163.2.

### **3-acetyl-6-iodo-2H-chromen-2-one (6a)**

Yellowish brown crystals, Yield 71 %; mp 206–208 °C; IR (cm<sup>-1</sup>): 3057–3039 (C-H aromatic and olefinic), 2997–2918 (C-H aliphatic), 1728–1725 (C=O), 1604 (C=C aromatic), 557 (C-I); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 2.74 (s, 3H, CH<sub>3</sub>), 7.14 (d, J = 8.7 Hz, 1H, Ar-H), 7.90 (dd, J = 8.7, 2.0 Hz, 1H, Ar-H), 8.30 (d, J = 2.0 Hz, 1H, Ar-H), 8.40 (s, 1H, H-pyrone ring); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ ppm: 30.5, 87.6, 118.6, 138.3, 142.7, 145.9, 150.76, 154.9, 160.0, 193.2; Anal. Calcd for C<sub>11</sub>H<sub>7</sub>IO<sub>3</sub>: C 42.07; H 2.25. Found: C 42.03; H 2.24.

### **3-acetyl-7-hydroxy-2H-chromen-2-one (7a)**

Beige solid, Yield 74 % mp 240–243 °C; IR (cm<sup>-1</sup>): 3214 (-OH), 3067–3046 (C-H aromatic and olefinic), 2921 (C-H aliphatic), 1723 (C=O), 1705 (C=O), 1680, 1648 (C=C olefinic), 1606 and 1505 (C=C Ar); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm: 2.55 (s, 3H, CH<sub>3</sub>), 6.76 (d, J = 2.2 Hz, 1H, Ar-H), 6.86 (dd, J = 8.6, 2.2 Hz, 1H, Ar-H), 7.79 (d, J = 8.6 Hz, 1H, Ar-H), 8.60 (s, 1H, H-pyrone ring), 11.12 (br s, 1H, OH). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ ppm: 35.3, 106.9, 115.9, 114.8, 119.4, 133.2, 148.4, 157.8, 159.6, 165.0, 195.1.

### **3-acetyl-6-nitro-2H-chromen-2-one (8a)**

Pale yellow solid, Yield 70 %; mp 192–195 °C; IR (cm<sup>-1</sup>): 3101 (C-H olefinic), 2927 (C-H aliphatic), 1751 (C=O), 1721 (C=O), 1679–1648 (C=C olefinic), 1605–1496 (C=C Aromatic), 1535–1345 (-NO<sub>2</sub> symmetric and asymmetric str.), 1238, 1212, 1200, 1129, 1112 (C-O); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 2.76 (s, 3H, CH<sub>3</sub>), 7.53 (d, J = 9.0 Hz, 1H, Ar-H), 8.50 (dd, J = 9.1, 2.6 Hz, 1H, Ar-H), 8.56 (s, 1H, H-pyrone ring), 8.60 (d, J = 2.4 Hz, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ ppm: 30.4, 118.0, 125.8, 128.6, 145.9, 154.9, 160.0, 193.2.

### **3-acetyl-2H-benzof[*f*]chromen-2-one (10a)**

Dark red solid, Yield 70 %; mp 180–183 °C; IR (cm<sup>-1</sup>): 3066, 2976(C-H olefinic), 2930 (C-H aliphatic), 1723 (C=O), 1705 (C=O), 1674, 1650 (C=C olefinic), 1596 and 1500 (C=C Ar), 1214, 1187, 1135, 1094, 1075, 966, 950 (C-O); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ

ppm: 2.82 (s, 3H, CH<sub>3</sub>), 7.41 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.57 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H, Ar-H), 7.70 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H, Ar-H), 7.89 (d, *J* = 8.1 Hz, 1H, Ar-H), 8.05 (d, *J* = 9.0 Hz, 1H, Ar-H), 8.29 (d, *J* = 8.3 Hz, 1H, Ar-H), 9.22 (s, 1H, H-pyrone ring). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ ppm: 30.7, 112.7, 116.5, 121.6, 122.4, 126.6, 129.2, 129.8, 130.1, 136.2, 143.1, 156.1, 159.4, 195.5;

#### **Ethyl 3-oxo-3H-benzof[chromene-2-carboxylate (10b)**

This compound obtained as light yellow solid; Yield 60 %; mp 113–116 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.48 (t, 3H, CH<sub>3</sub>), 4.5 (q, 2H, OCH<sub>2</sub>), 7.49 (d, *J* = 9.2 Hz, 1H, ArH), 7.62 (m, 1H, ArH), 7.76 (m, 1H, ArH), 7.95 (d, *J* = 8.0 Hz, 1H, ArH), 8.12 (d, *J* = 9.2 Hz, 1H, ArH), 8.35 (d, *J* = 8.0 Hz, 1H, ArH), 9.35 (s, 1H, H-pyrone ring); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ ppm: 14.3, 62.1, 112.3, 116.5, 116.7, 121.5, 126.6, 129.1, 129.3, 129.4, 130.2, 136.2, 144.6, 156.0, 156.9, 163.6.

### 2.3. Biological evaluation

#### 2.3.1. Screening for Antibacterial Activity

The antimicrobial activity of compounds **3a**, **4a**, **5a**, **6a**, **7a**, **8a**, and **10a** were evaluated against *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853) and *Staphylococcus aureus* (ATCC 25923) bacterial strains by the agar diffusion method [12]. A sterile physiological water solution containing a bacterial colony was prepared at room temperature, with an optical density of 0.08–0.10 corresponding to a concentration of 10<sup>6</sup> cells/mL. The bacterial solution was inoculated in the Muller-Hinton agar medium by swabbing using Petri dishes at room temperature. The tested compounds were dissolved in dimethyl sulfoxide (DMSO) with a concentration of 10<sup>-1</sup> M. 25 μL of the tested sample were poured onto filter paper discs with 6 mm in diameter, which were then delicately placed on the surface of the agar plates. These were later maintained at 37 °C for 24 h. Activities were determined by measuring the diameter of the inhibition zone (mm).

#### 2.3.2. Antiradical activity

The antiradical activity of the synthesized compounds was evaluated by the first time using the DPPH• scavenging assay [13,14]. DPPH• solution was prepared in ethanol to give a concentration of 4 mg/100 mL. The solutions of the tested compounds were prepared in DMSO at 10<sup>-1</sup> M and then diluted to get final concentrations of 0.05, 0.025 and 0.0125 mol/L. The standards were further diluted to give additional concentration solutions of 0.00625, 0.003125 and 0.0015625 mol/L. Each tested concentration of each compound (40 μL) was added to each well separately in duplicate and then the DPPH• solution (2 mL) was added. Each negative control well were loaded with 40 μL of DMSO and 2 mL of DPPH• solution. After vortexing, the mixtures were incubated at room temperature for 1 h in darkness at 25 °C, and then the absorbance of these compounds at different concentrations was recorded at 517 nm. Ascorbic acid (AA) was used as standard for the antiradical activity screening. A blank solution containing only ethanol with DMSO was used as the control. Each measurement was performed in triplicate. The reduction of the DPPH• was measured by monitoring continuously the decrease of absorption at 517 nm. DPPH scavenging effect was calculated as percentage of DPPH discoloration using Eq. (1):

$$\text{RSA}(\%) = [(Ac - As)/Ac] \times 100 \quad (1)$$

where Ac is the absorbance of the control (absorbance of DPPH• ethanol solution without sample), and As is the absorbance of the tested compound after 60 min incubation.

### 2.4. DFT analysis and drug-likeness analysis

The structures of synthesized compounds were optimized with density functional theory (DFT) using Becke's three-parameter hybrid model, Lee–Yang–Parr (B3LYP) [15,16] and 6–31 G\*\* basis set using ORCA software [17,18]. Frequency analysis was performed at the same level of theory. The UV-Vis absorption spectra were calculated using the Time-Dependent Density Functional Theory (TD-DFT) calculations. To discuss the observed activity values at the molecular level, the optimized geometries of compounds **3a**, **4a**, **5a**, **7a** and **8a** were used for calculations of DFT based global reactivity descriptors, namely Highest Occupied Molecular Orbital (HOMO), Lowest Unoccupied Molecular Orbital energy (LUMO) and energy gap (ΔE), ionization potential (I), electron affinity (A), electronic chemical potential (μ) [19] and absolute hardness (η) [20–23]. The calculation of these descriptors was performed using equations below:

$$\Delta E = E_{\text{HOMO}} - E_{\text{LUMO}} \quad (2)$$

$$\mu = -\frac{1}{2}(I + A) = -X \quad (3)$$

$$\eta = \frac{1}{2}(I - A) \quad (4)$$

Drug-likeness analysis was performed to determine if synthesized compounds are similar to known drugs. In the present study, we used as molecular properties rule the well-known Lipinski [24], Veber [25], BBB likeness and quantitative estimate of drug-likeness (QED) [26], implemented in DruLiTo software [27]. It is worth noting that, in general, an orally active drug has no more than one violation of the number of hydrogen bond donors out of 5, number of hydrogen bond acceptors less than 10, a molecular weight less than 500 Daltons and an octanol-water partition coefficient (log P) smaller than 5.

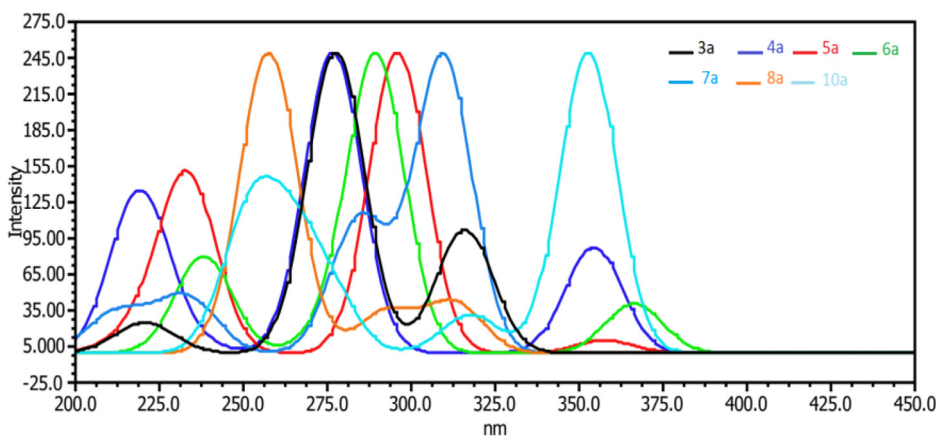


Fig.1. Calculated UV-Vis absorption of 3-acetylcoumarins in DMSO using the B3LYP method with with 6-31G\*\* basis set.

### 3. Data, value and validation

#### 3.1. Chemistry

The object of this work is to study the microwave assisted Knoevenagel condensation, under solvent free conditions, to prepare a number of 3-substituted coumarins **3-8** and 3-substituent benzocoumarins **10** using a recyclable catalyst (Scheme 1).

In our first attempt, we tested the reaction of salicylaldehyde **1a** with ethyl acetoacetate **2a** in equimolar amounts (1/1), in different solvents and under solvent free conditions in the presence of three mineral basic catalysts  $\text{Na}_2\text{CO}_3$ ,  $\text{Ba}(\text{OH})_2$  and  $\text{KF-Al}_2\text{O}_3$ . This resulted in 3-acetylcoumarin **3a** as the only product and optimized yield of 45% was obtained in the presence of KF supported on alumina in free of solvent (Table 1). The structure of **3a** is further confirmed by NMR spectroscopy of  $^1\text{H}$  and  $^{13}\text{C}$  and IR spectroscopy.

For economic and ecological reasons, the reaction was performed using  $\text{KF-Al}_2\text{O}_3$  as catalyst, under microwave irradiation and in solvent free conditions. The advantage of this method is the shorter reaction time in comparison to conventional synthesis methods (Table 2). The yield of **3a** increases from 45% to 60% for the same amount of the tested catalyst by the conventional method (10% weight). Three different amounts of catalysts are tested and 15% weight offers a better yield of 71%.

Subsequently, the optimized conditions ( $\text{KF-Al}_2\text{O}_3$  15%Weight, solvent free conditions) were applied also for the conversion of various salicylaldehydes **1a-f** and 2-hydroxynaphthaldehyde **1g** with various  $\beta$ -dicarbonyl derivatives **2a-c** into the corresponding coumarins analogs **3a-c**, **4a-c**, **5a-b**, **6a**, **7a**, **8a** and **10a-b** respectively (Table 3).

#### 3.2. Recyclability and reusability of $\text{KF-Al}_2\text{O}_3$ in the Knoevenagel condensation

We have also investigated the reusability and recycling of KF-alumina catalyst. At the end of the reaction, the catalyst was recovered by filtration, washed with acetone and subjected to other runs of the reaction process. In Table 4, the comparison of efficiency of KF-alumina in synthesis of **3a** after four runs is reported. The first reaction (first run) afforded a good yield. In the second, third and fourth runs, the yield were gradually decreased, which may be due to the loss of some catalyst during the recovering process.

#### 3.3. Effect of the substituent on the UV-visible spectrum

Absorption bands were observed at 262–284 nm and 315–396 nm which are due to  $\pi \rightarrow \pi^*$  transitions (Table 5). The longer wavelength band show significant variation due to the presence of substituent in the benzo-ring. All the studied coumarin derivatives showed more than one absorption band due to  $\pi \rightarrow \pi^*$  transitions.

The calculated UV-vis absorption in DMSO of 3-acetylcoumarins using the B3LYP method with 6-31G\*\* basis set is in agreement with the experimental results. For example, the calculated absorption spectrum of the compound **4a** (Fig. 1) shows in the ultraviolet domain three bands transitions  $\pi \rightarrow \pi^*$ .

#### 3.4. Biological activity

##### 3.4.1. Antiradical Activity

The antiradical activity of compounds **3a**, **4a**, **5a**, **7a** and **8a** was expressed as  $\text{IC}_{50}$  with a low  $\text{IC}_{50}$  value indicating the compounds act as an effective DPPH $^\bullet$  scavenger (Fig. 2).  $\text{IC}_{50}$  values were between 0.0175 and 1.707 mol/dm $^3$  for compounds

**Table 1**  
Effect of the catalyst and solvent in the synthesis of 3-acetylcoumarin **3a**.

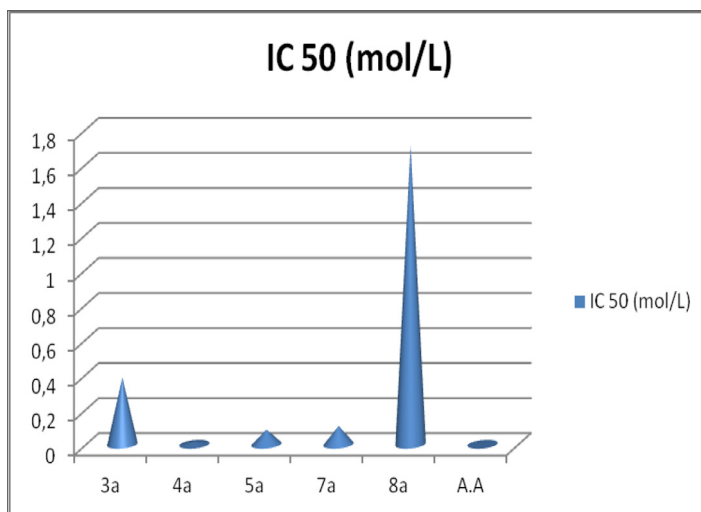
Compound	Catalyst	Time (min) / (Temperature °C)					Yields (%)				
		Solvents					Free	EtOH	DMF	ACN	Toluene
		Free	EtOH	DMF	ACN	Toluene					
<b>3a</b>	–	240 / (100)	240 / (100)	240 / (100)	240 / (100)	240 / (100)	–	–	–	–	–
	Na <sub>2</sub> CO <sub>3</sub> (5 mol %)	240 / (100)	90 / (reflux)	90 / (reflux)	90 / (reflux)	90 / (reflux)	36	34	26	34	25
	Ba(OH) <sub>2</sub> ·8H <sub>2</sub> O (5 mol%)	240 / (100)	90 / (reflux)	90 / (reflux)	90 / (reflux)	90 / (reflux)	38	28	30	36	28
	KF-Al <sub>2</sub> O <sub>3</sub> 10 % Weight	240 / (100)	300 / (reflux)	240 / (reflux)	240 / (reflux)	240 / (reflux)	<b>45</b>	37	31	39	28

Reaction condition: Salicylaldehyde **1a** (1 equiv), ethyl acetoacetate **2a** (1 equiv), catalyst, solvent or solvent free.

**Table 2**

Synthesis of 3-acetylcoumarin **3a** under microwave irradiation in the presence of KF-Al<sub>2</sub>O<sub>3</sub> (% Weight) and without solvent.

Entry	Amount of KF-Al <sub>2</sub> O <sub>3</sub> (%Weight)	Time (min)	Yield (%)
1	10	15	60
2	15	15	71
3	20	15	57



**Fig.2.** IC50 values of the antioxidant compounds tested (3a, 4a, 5a, 7a and 8a)

**3a, 4a, 5a, 7a and 8a**, while 0.0013 mol/dm<sup>3</sup> for ascorbic acid (positive control). No activity was observed for compounds **6a** and **10a**. Compounds **4a, 5a** and **7a** display significant antiradical capacity, due to the presence and position of -OH groups in the benzene ring [33]. Compound **4a** with a *para*-OH group exhibited a promising antiradical activity following by **5a** (*ortho*-position) and then **7a** (*meta*-position) respectively.

### 3.4.2. Antibacterial activity

The result of the antimicrobial activity indicated that all compounds were both inactive to the Gram-negative bacteria and they only demonstrated antimicrobial action against *S. aureus* Gram-positive bacteria (Table 6). The reason for this is not quite evident. This therefore serves as an indication that activity does not depend solely on the ease of movement of an antimicrobial agent through the cell wall of the microbes, but rather a synergistic effects of many factors [34–36]. Table 6 shows that the compounds **4a** and **7a** demonstrated moderate antimicrobial activity against compound **8a** is extremely sensitive against *S. aureus* Gram-positive bacteria.

### 3.5. DFT based global reactivity descriptors

Table 7 and Fig. 3 reports calculated descriptors results and location of frontier molecular orbitals, HOMO and LUMO, for compounds **3a, 4a, 5a, 7a** and **8a**. According to calculated energy gap ( $\Delta E$ ) and hardness ( $\eta$ ), the most potent compound was **4a** followed by **5a** and **7a**. Note that, large energy gap or when hardness increases the reactivity should decrease and small  $\Delta E$  or when hardness decreases the reactivity should increase. Chemical potential results revealed that compound **4a** has the highest value followed by **7a** and **5a** indicating that these three compounds were the most potent. It is worth to note that chemical potential ( $\mu$ ), is defined as the average values of the HOMO and LUMO energies and negative of the chemical potential was known as the electronegativity ( $\chi = -\mu$ ). The electronegativity represents the power of molecules to attract electrons.

Interestingly, all calculated reactivity descriptors predicted the compound **8a** as the less potent, indicating that our results are in perfect agreement with the experimental one. To compare theoretical and experimental results, the correlation between calculated chemical hardness ( $\eta$ ) and experimental activities converted to pIC50 [pIC50 = -LOG(IC50)] was calculated and plotted in Fig. 4. The comparison represented the best correlation since the correlation coefficient  $R = 0.84$  was obtained.

**Table 3**  
Synthesis of coumarin derivatives catalyzed by KF (32%)-Al<sub>2</sub>O<sub>3</sub> (15 % weight) under MW (100 W).

Entry	Compound	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Time (min)	Yield (%)	mp (°C) This work	Literature
123	3a3b3c	H	COCH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> CO <sub>2</sub> CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> C <sub>2</sub> H <sub>5</sub> CH <sub>3</sub>	152020	717576	113–11588–93104–107	118–122 [28]91–92 [28]–
456	4a4b4c	6-OH	COCH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> CO <sub>2</sub> CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> C <sub>2</sub> H <sub>5</sub> CH <sub>3</sub>	404040	737880	242–244190–194207–210	247–248 [28]205–206 [28]–
78	5a5b	8-OH	COCH <sub>3</sub> CO <sub>2</sub> CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> CH <sub>3</sub>	3840	7450	258–260208–210	253–255 [28]–
9	6a	6-I	COCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	25	71	206–208	189–190 [31]
10	7a	7-OH	COCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	30	64	240–243	240–241 <sup>[32]</sup>
11	8a	6-NO <sub>2</sub>	COCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	35	70	192–195	200–203 [28]
1213	10a10b	2-hydroxynaphthaldehyde	COCH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> C <sub>2</sub> H <sub>5</sub>	1620	7060	180–183113–116	189–190 [29]116–118 [30]

**Table 4**

Studies on KF-alumina recycling in the Knoevenagel condensation of 2-hydroxybenzaldehyde with ethyl acetoacetate.<sup>a</sup>

Run	Yield (%)
1	71
2	51
3	44
4	37

<sup>a</sup> The reaction was conducted with 15 mol% KF-alumina, 1 mmol of 2-hydroxybenzaldehyde and 1 mmol ethyl acetoacetate in solvent-free conditions, under MW. <sup>b</sup>Isolated yields.

**Table 5**

Absorption bands of 3-acetylcoumarins **3a-10a** in DMSO at 10<sup>-5</sup> mol/dm<sup>3</sup>.

Compound	$\lambda_1 (\pi \rightarrow \pi^*)$	$\lambda_2 (\pi \rightarrow \pi^*)$	$\lambda_3 (\pi \rightarrow \pi^*)$
3a	284	347	–
4a	263	322	396
5a	266	324	–
6a	275	–	369
7a	262	327	375
8a	269	315	335
10a	263	329	383

**Table 6**

Diameters of inhibition zones (in mm) for the compounds **3a-10a** and the references antibiotics.

Compounds	Diameters of inhibition zones (in mm)		
	<i>E. coli</i> ATCC25922 Gram -	<i>P. aeruginosa</i> ATCC27853 Gram -	<i>S. aureus</i> ATCC25923 Gram +
3a	6–	6–	7–
5a	6–	6–	10+
7a	6–	6–	12+
4a	6–	6–	13+
8a	6–	6–	34+++
6a	6–	6–	8–
10a	6–	6–	8–
DMSO	6–	6–	5–
ATB(Cefotaxime)	30+++	32+++	37+++

**Table 7.**

DFT based global reactivity descriptors (eV) calculated for studied compounds.

	3a	4a	5a	7a	8a
HOMO	–6.64	–6.22	–6.43	–6.31	–7.27
LUMO	–2.44	–2.45	–2.51	–2.25	–2.97
$\Delta E$	4.21	3.77	3.92	4.06	4.30
I	6.64	6.22	6.43	6.31	7.27
A	2.44	2.45	2.51	2.25	2.97
$\mu$	–4.54	–4.33	–4.47	–4.28	–5.12
$\eta$	2.10	1.88	1.96	2.03	2.15

### 3.6. Drug-likeness analysis

Physicochemical properties include pharmacokinetics analysis of synthesized compounds **3a**, **4a**, **5a**, **6a**, **7a**, **8a** and **10a** was performed using Drulito program [27]. As results, all studied compounds are within the acceptable range of Lipinski's rule [24], Veber rule [25], BBB likeness and quantitative estimate of drug-likeness rule (QED) [26]. It is worth noting that, the synthesized compounds have acceptable physico-chemical properties such as hydrogen-bonding capacity, an important determinant of permeability [37], and molecular weight (MW <500), which can predict if these compounds can be easily transported. In addition, the octanol–water partition coefficient ( $-0.4 \leq \log P \leq 5.6$ ), usually quantified molecular lipophilicity, and total polar surface area (TPSA  $\leq 160$ ), a good indicator of the bioavailability of the drug molecule, are in acceptable range (see Table 8).

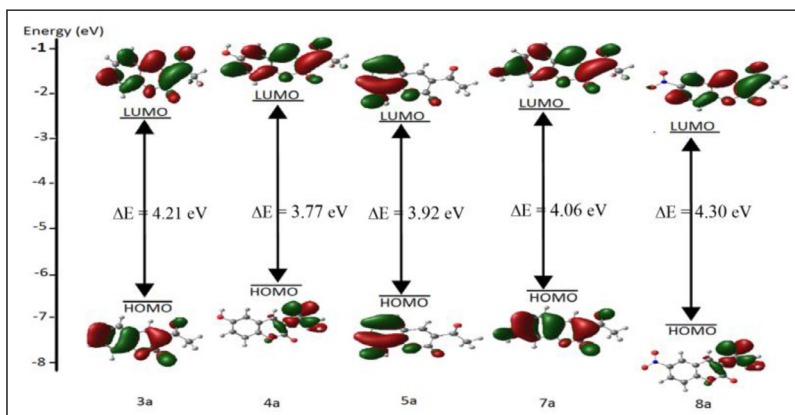


Fig.3. Calculated HOMO, LUMO and  $\Delta E$  for synthesized compounds 3a, 4a, 5a, 7a and 8a.

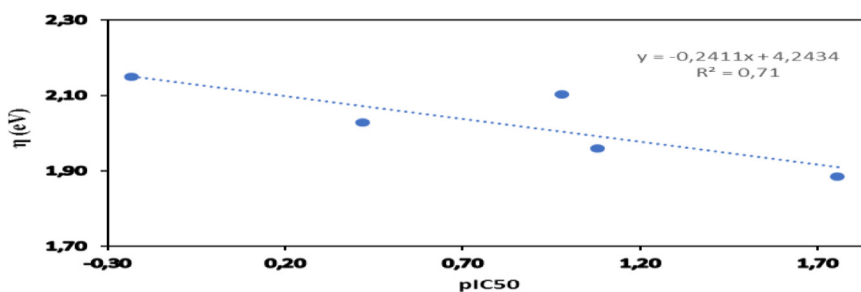
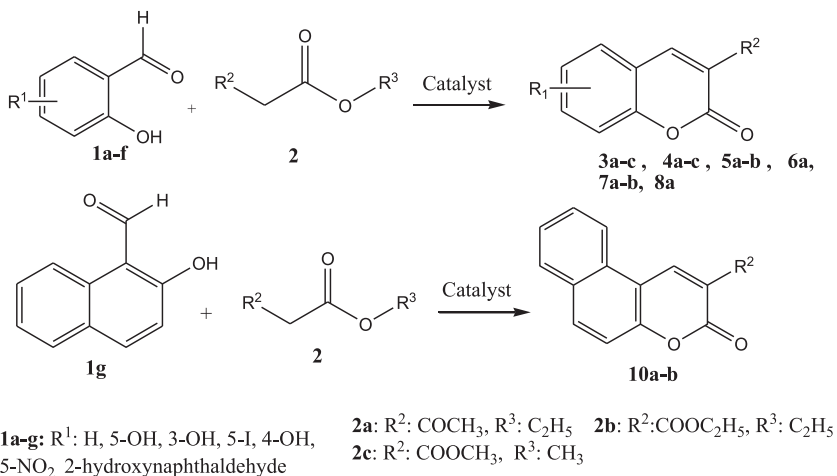


Fig.4. Plot of the experimental values (pIC50) versus the calculated chemical hardness ( $\eta$ ) of compounds 3a, 4a, 5a, 7a and 8a.



Scheme 1. Synthesis of coumarins by the Knoevenagel condensation under microwave irradiation.

Table 8

Physicochemical properties depicting the drug-likeness of synthesized compound. HBD: H Bond Donor, HBA: H Bond Acceptor, TPSA: Topological Polar Surface Area, log p: octanol-water partition coefficient and MW: Molecular Weight

Compound	MW	logP	TPSA	HBD	HBA	Lipinski	Verber	QED	BBB
3a	188.05	2.52	13.14	0	1	yes	yes	yes	yes
4a	204.04	1.34	33.37	1	1	yes	yes	yes	yes
5a	204.04	1.34	33.37	1	1	yes	yes	yes	yes
6a	313.94	2.94	13.14	0	1	yes	yes	yes	yes
7a	204.04	1.34	33.37	1	1	yes	yes	yes	yes
8a	233.03	2.19	58.96	0	1	yes	yes	yes	yes
10a	238.06	4.39	13.14	0	1	yes	yes	yes	yes

## 4. Conclusion

We have developed a simple and efficient synthesis of 3-acetylcoumarins via Knoevenagel condensations of salicylaldehydes with  $\beta$ -dicarbonyl derivatives using  $\text{KF}\cdot\text{Al}_2\text{O}_3$  as a solid catalyst. The features of this procedure short reaction time are mild reaction conditions, good to excellent yields and operational simplicity (work-up procedure is reduced to the recrystallization of the formed products). Moreover the low cost and low toxicity of the catalyst, fast reaction times, simple experimental procedure, recyclability of the catalyst and high yields of the products are the advantages. The synthesized coumarins showed a high intensity in UV-Visible absorption spectrophotometry and the wavelengths are much affected by the nature of substituents of the benzaldehyde moiety. The compounds were evaluated for antiradical (antioxidant) and antibacterial activity. The compounds with -OH groups on the benzene ring showed good antiradical activity. Excellent antibacterial activity was found for the compound **8a** while compounds **4a**, **7a** and **5a** showed moderate antibacterial activity.

Drug-Likeness analysis shows that the synthesized compounds have acceptable physico-chemical properties and a good indicator of the bioavailability of the drug molecule and are in an acceptable range.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.cdc.2020.100341](https://doi.org/10.1016/j.cdc.2020.100341).

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