

Proceeding Paper

# Synthesis and Characterization of Hybrid Structures Based on Furan-2(3*H*)-ones and Chromen-4(4*H*)-ones – Potential Antibacterial Activity †

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**Abstract:** One of the modern trends in medicinal chemistry is the design of multifunctional drugs with a wide spectrum of action. The main approaches to the creation of such drugs are the construction of new biologically active substances containing two or more pharmacophore groups in their structure or the introduction of an additional pharmacophore group into the molecule of a known drug. This work describes the synthesis of hybrid structures based on furan-2(3*H*)-ones and chromen-4(4*H*)-ones under the conditions of the Knoevenagel reaction. Various reaction conditions were screened. (E)-3-((2-oxo-5-arylfuran-3(2*H*))-ylidene)methyl)-4*H*-chromen-4-ones were obtained, and its structure was confirmed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy data. Based on NMR spectroscopy data, it was shown that the resulting compounds exist in the form of E-isomers.

**Keywords:** synthesis; hybrid structures; furan-2(3*H*)-ones; chromen-4(4*H*)-ones; spectroscopy; physicochemical methods; reactor Monowave 50

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## 1. Introduction

Currently, in the development of new biologically active compounds, a trend is developing towards the concept of molecular hybridization, which consists in combining two or more pharmacophoric fragments in one molecule [1–5]. As a result, this combination makes it possible to create new hybrid compounds with high biological activity, an altered selectivity profile, and can also reduce undesirable side effects [6].

Of great importance for the design of complex hybrid heterocyclic systems with several building blocks is the choice of available substrates with great preparative capabilities. From this point of view, chromen-4-ones and furan-2-ones are promising starting compounds. An important factor influencing the development of the chemistry of the mentioned substances is their closeness in structure to natural substrates that exhibit a wide range of biological effects [7–13]. Thus, the chromen-4-one framework is an integral part of flavonoids [7–10], and furan-2-ones are part of butenolides [11–13].

The focus of this study is on the synthesis of hybrid molecules based on based on furan-2(3*H*)-ones and 4-oxo-4*H*-chromene-3-carbaldehyde. Furan-2(3*H*)-one derivatives are found among a large number of compounds that have antinociceptive, anti-inflammatory, antiviral and antitumor effects [14–17]. It is important to note nitrofurans derivatives, which have pronounced antibacterial activity [18–22]. The 4*H*-chromen-4-one cycle is included in the structure of compounds that have anticancer, antibacterial, antiviral and other types of activity [23–25].

Thus, this work is devoted to searching for optimal synthesis conditions and establishing the structure of hybrid structures—chromenyl-2(3*H*)-furanones, potential antibacterial drugs.

## 2. Materials and Methods

### 2.1. Physical Measurements

<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra were measured for solutions in DMSO-*d*<sub>6</sub> on a Varian (Agilent) 400 spectrometer. Elemental analysis was done on an Elementar Vario MICRO cube CHNS analyzer. The progress of the reaction and the purity of the synthesized compounds were monitored by TLC on ALUGRAM® SIL G UV254 plates, with hexane–ethyl acetate–acetone (3:1:1) as the eluent.

### 2.2. Synthesis and Characterization of Compounds 3a–d

#### 2.2.1. Under Conventional Heating Conditions (Method A)

A mixture of 3 mmol of the corresponding 5-arylfuran-2(3*H*)-one 1a–d, 3 mmol of 4-oxo-4*H*-chromene-3-carboxaldehyde (2) was refluxed in 7 mL of glacial acetic acid. The precipitated crystals were filtered, washed with glacial acetic acid, recrystallized from benzene, and dried.

#### 2.2.2. Under Microwave Irradiation (Method B)

A mixture of 1 mmol of the corresponding 5-arylfuran-2(3*H*)-one 1a–d, 1 mmol of 4-oxo-4*H*-chromene-3-carboxaldehyde (2) and 3.5 mL of glacial acetic acid are placed in a borosilicate glass vial, equipped with a magnetic stirrer. The vial is hermetically sealed with a silicone stopper and placed in a Monovave 50 (Anton Paar) reactor. The reaction is carried out at a temperature of 135 °C with the stirring of 600 min<sup>−1</sup>. The precipitated crystals were filtered, washed with glacial acetic acid, recrystallized from benzene, and dried.

(*E*)-3-((2-oxo-5-phenylfuran-3(2*H*)-ylidene)methyl)-4*H*-chromen-4-one (3a).

Yellow crystals (benzene), yield 0.66 g (70%) (method A), yield 0.25 g (80%) (method B), mp 219–220 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.09 (s, 1H, C-H<sub>Chromone</sub>), 8.15 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.90–7.80 (m, 3H, Ar-H), 7.75 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.59 (s, 1H, C-H<sub>Furanone</sub>), 7.57–7.46 (m, 4H, Ar-H), 7.38 (s, 1H, =CH-); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.06 (C=O), 168.74 (O-C=O), 159.43 (C-H<sub>Chromone</sub>), 156.19, 155.92, 155.86, 135.40, 131.18, 129.57, 128.12, 126.79, 126.09, 125.69, 125.37, 125.28, 125.27 (=CH-), 123.46, 119.79, 119.15, 102.35 (C-H<sub>Furanone</sub>). Anal. Calcd. for C<sub>20</sub>H<sub>12</sub>O<sub>4</sub>: C: 75.94%; H: 3.82%; Found: C: 75.45%; H: 3.87%.

(*E*)-3-((2-oxo-5-(*p*-tolyl)furan-3(2*H*)-ylidene)methyl)-4*H*-chromen-4-one (3b).

Yellow crystals (benzene), yield 0.52 g (52%) (method A), yield 0.22 g (66%) (method B), mp 243–245 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.09 (s, 1H, C-H<sub>Chromone</sub>), 8.15 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.88 (t, *J* = 8.7 Hz, 1H, Ar-H), 7.79–7.69 (m, 3H, Ar-H), 7.69–7.51 (m, 2H, Ar-H and C-H<sub>Furanone</sub>), 7.35–7.30 (m, 3H, 2H Ar-H and =CH-), 2.36 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.09 (C=O), 168.86 (O-C=O), 159.24 (C-H<sub>Chromone</sub>), 156.45, 155.92, 141.32, 135.40, 130.50, 130.19, 126.78, 126.09, 125.70, 125.39, 125.33, 124.57 (=CH-), 123.44, 123.41, 119.83, 119.16, 101.50 (C-H<sub>Furanone</sub>), 21.58 (CH<sub>3</sub>). Anal. Calcd. for C<sub>21</sub>H<sub>14</sub>O<sub>4</sub>: C: 76.35%; H: 4.27%; Found: C: 76.80%; H: 4.41%.

(*E*)-3-((5-(4-chlorophenyl)-2-oxofuran-3(2*H*)-ylidene)methyl)-4*H*-chromen-4-one (3c).

Yellow crystals (benzene), yield 0.58 g (55%) (method A), yield 0.22 g (63%) (method B), mp 284–285 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.09 (s, 1H, C-H<sub>Chromone</sub>), 8.15 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.92–7.81 (m, 3H, Ar-H), 7.76 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.65 (s, 1H, C-H<sub>Furanone</sub>), 7.63–7.54 (m, 3H, Ar-H), 7.41 (s, 1H, =CH-); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.25 (C=O), 168.75 (O-C=O), 159.04 (C-H<sub>Chromone</sub>), 157.30, 156.29, 155.10, 154.97, 135.52, 129.74, 127.50, 127.42, 126.10, 126.01 (=CH-), 126.78, 125.98, 125.09, 123.36, 119.22, 119.18,

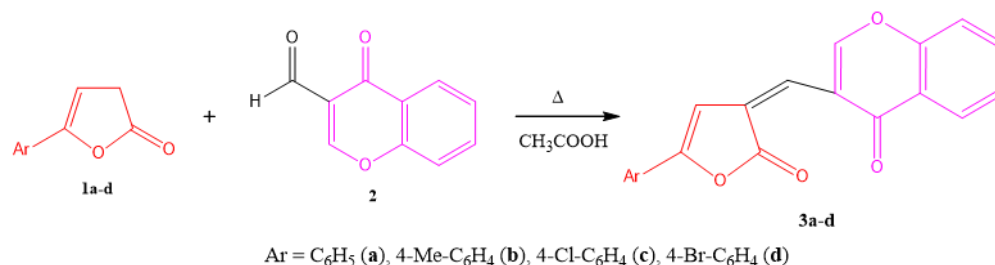
103.13 (C-H<sub>Furanone</sub>). Anal. Calcd. for C<sub>20</sub>H<sub>11</sub>ClO<sub>4</sub>: C: 68.49%; H: 3.16%; Cl: 10.11%; Found: C: 68.54%; H: 3.35%; Cl: 10.04%.

(E)-3-((5-(4-bromophenyl)-2-oxofuran-3(2H)-ylidene)methyl)-4H-chromen-4-one (**3d**).

Yellow crystals (benzene), yield 0.97 g (82%) (method A), yield 0.36 g (90%) (method B), mp 271–272 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.09 (s, 1H, C-H<sub>Chromone</sub>), 8.16 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.88 (t, 1H, Ar-H), 7.79–7.74 (m, 5H, Ar-H), 7.66 (s, 1H, C-H<sub>Furanone</sub>), 7.57 (t, *J* = 8.1 Hz, 1H, Ar-H), 7.42 (s, 1H, =CH-); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 175.24 (C=O), 168.42 (O-C=O), 157.06 (C-H<sub>Chromone</sub>), 156.31, 155.94, 155.26, 154.47, 133.66, 130.12, 127.61, 127.54, 126.74, 125.98 (=CH-), 125.15, 124.54, 124.08, 123.44, 119.71, 119.18, 103.23 (C-H<sub>Furanone</sub>). Anal. Calcd. for C<sub>20</sub>H<sub>11</sub>BrO<sub>4</sub>: C: 60.78%; H: 2.81%; Br: 20.22%; Found: C: 60.57%; H: 2.92%; Br: 20.15%.

### 3. Results and Discussion

As a result of the search for optimal conditions for the synthesis of (het)arylmethylene-3H-furan-2-ones, we have obtained a number and developed new methods for the preparation of (E)-3-((2-oxo-5-arylfuran-3(2H)-ylidene)methyl)-4H-chromene-4-ones **3a–d**, based on the reaction of equimolar amounts of 5-arylfuran-2(3H)-ones **1a–d**, obtained according to the method [26], with 4-oxo-4H-chromene-3-carboxaldehyde (**2**) in glacial acetic acid without the use of a catalyst, with thermal and microwave activation of the reaction mixture with various yields (Table 1). Considering the presence of three electrophilic centers in 4-oxo-4H-chromene-3-carboxaldehyde (**2**), several reaction directions can be expected. Taking into account the structure of (E)-3-((2-oxo-5-arylfuran-3(2H)-ylidene)methyl)-4H-chromene-4-ones **3a–d**, it is assumed that the initial enolization of the furanone ring in acetic acid occurs with subsequent formation of a new C=C bond due to the involvement of the aldehyde group of substrate **2** in the reaction (Scheme 1).



**Scheme 1.** Synthesis of hybrid structures—(E)-3-((2-oxo-5-arylfuran-3(2H)-ylidene)methyl)-4H-chromene-4-ones.

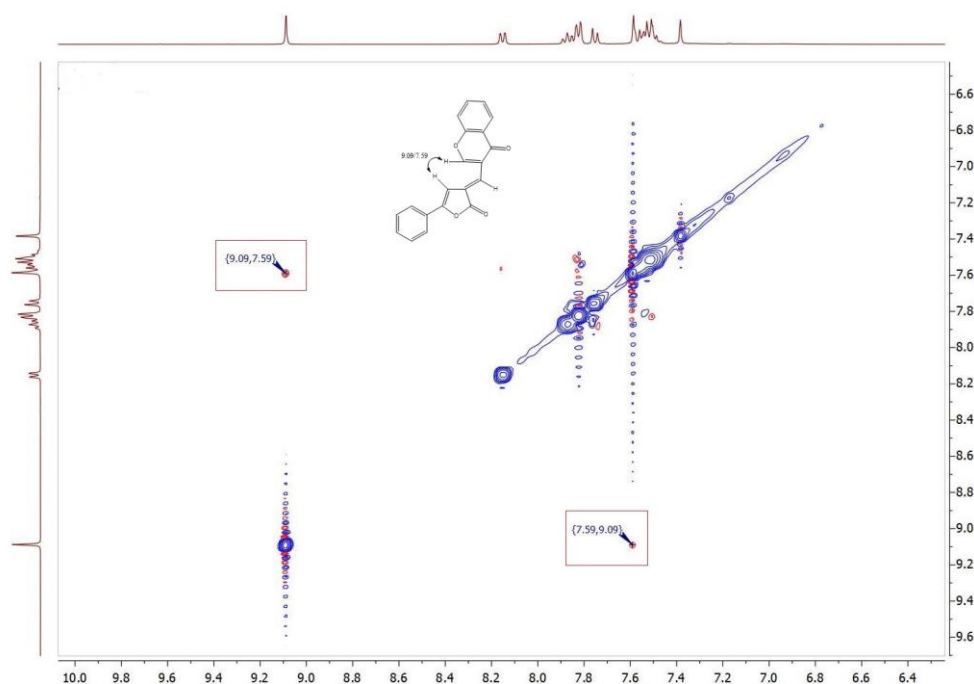
A comparison of two methods of interaction was carried out—the classical method under normal pressure conditions and in a closed vessel system, a Monowave 50 reactor (Anton Paar) at elevated pressure. Using a reactor of sealed vessels, one can expect an increase in the efficiency of the process due to an increase in the temperature and pressure of the reaction, which will significantly reduce its time, unattainable under normal conditions of classical heating at atmospheric pressure and the boiling point of the solvent. The parameters of the two modes are presented in Table 1.

**Table 1.** Optimal conditions for the synthesis of hybrid structures 3a–f.**Table 1.** Optimal conditions for the synthesis of hybrid structures 3a–f

Compound	Thermal activation			Microwave activation		
	T, °C	P, Bar	Yield, %	T, °C	P, Bar	Yield, %
<b>3a</b>	118	1	70	135	4	80
<b>3b</b>	118	1	52	135	4	66
<b>3c</b>	118	1	55	135	4	63
<b>3d</b>	118	1	82	135	4	90

It was shown that the reaction of 5-arylfuran-2(3H)-ones **1a–d** with 4-oxo-4H-chromene-3-carboxaldehyde (**2**), carried out both under classical conditions and in a sealed vessel reactor, does not affect the nature of the reaction products and leads to (E)-3-((2-oxo-5-arylfuran-3(2H)-ylidene)methyl)-4H-chromen-4-ones **3a–d**. However, it should be noted that the use of a reactor in sealed vessels made it possible to increase the yield of products, as well as significantly increase the efficiency of interaction, which is reflected in a significant reduction in reaction time compared to classical conditions.

The structure of hybrid structures **3a–d** was confirmed by  $^1\text{H}$ ,  $^{13}\text{C}$  NMR spectroscopy data. The key signals of 3-((2-oxo-5-phenylfuran-3(2H)-ylidene)methyl)-4H-chromen-4-one **3a**, registered in  $\text{DMSO-}d_6$ , are the proton singlet of the furanone ring at 7.58 ppm, a proton singlet of the chromone fragment at 9.09 ppm, and a singlet of the vinyl proton of the exocyclic bond at 7.38 ppm. The  $^{13}\text{C}$  NMR spectrum of compound **3a** showed signals from the lactone carbon atom at 168.75 ppm and the carbonyl carbon atom of the chromen-4-one fragment at 175.08 ppm. Based on NMR spectroscopy, it was shown that the resulting compounds **3a–d** exist in the form of E-isomers. Proof of this is the absence of duplication of signals in the  $^1\text{H}$  NMR spectra recorded in  $\text{DMSO-}d_6$ , as well as the presence of a cross-peak at 9.09/7.59 ppm in the NOESY2D spectrum of compound **3a**. (Figure 1) both in general and with selective excitation within the NOESY1D method, which indicates the spatial proximity of the proton of the chromen-4-one fragment and the vinyl proton of the furan-2-one fragment.

**Figure 1.** NOESY2D spectrum.

(E)-3-((2-oxo-5-phenylfuran-3(2H)-ylidene)methyl)-4H-chromen-4-one (3a)

Additional confirmation is the absence in the NOESY2D spectrum of a correlation between the vinyl proton of the exocyclic bond and the vinyl proton of the furan-2-one fragment.

#### 4. Conclusions

In this work, we have expanded the range and developed new methods for obtaining hybrid structures—(E)-3-((2-oxo-5-arylfuran-3(2H)-ylidene)methyl)-4H-chromen-4-ones. By screening various reaction conditions, it was shown that the use of the Monowave 50 reactor made it possible to increase the yield of products, as well as significantly improve the efficiency of the interaction of the starting substrates. The structure of the target compounds was confirmed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy data. According to NMR spectroscopy data, it was found that the target compounds exist in the form of E-isomers.

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