

## One-pot synthesis of 2-substituted chromeno[3,4-*d*]imidazol-4(3*H*)-ones from 4-amino-3-nitrocoumarin and acids

Thomas D. Balalas,<sup>a</sup> Michael G. Kallitsakis,<sup>a</sup> Ioannis Fotopoulos,<sup>b</sup> Dimitra J. Hadjipavlou-Litina,<sup>b</sup> and Konstantinos E. Litinas<sup>\*a</sup>

<sup>a</sup>Laboratory of Organic Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

<sup>b</sup>Department of Pharmaceutical Chemistry, School of Pharmacy, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece  
Email: [klitinas@chem.auth.gr](mailto:klitinas@chem.auth.gr)

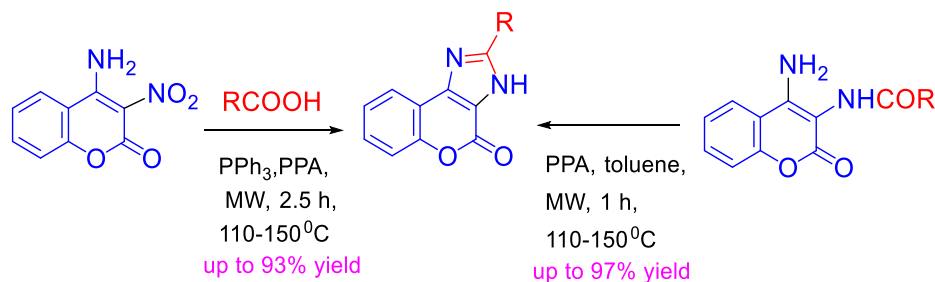
Received 11-01-2018

Accepted 03-09-2019

Published on line 05-13-2019

### Abstract

2-Substituted chromeno[3,4-*d*]imidazol-4(3*H*)-ones have been synthesized in excellent yields by the one-pot reaction of 4-amino-3-nitrocoumarin with aliphatic acids in the presence of PPh<sub>3</sub> and PPA under microwave irradiation. The reactions of 4-amino-3-carboxamidocoumarins (prepared from 3,4-diaminocoumarin, or in situ from 4-amino-3-nitrocoumarin and PPh<sub>3</sub>, and acids) with PPA in toluene under microwaves led also to the aforementioned compounds. Furthermore, the latter has been synthesized by the one pot reaction of 3,4-diaminocoumarin with acids in the presence of PPA under MW irradiation. Preliminary biological tests indicated inhibition of soybean lipoxygenase for some of the new compounds.



**Keywords:** Chromeno[3,4-*d*]imidazol-4(3*H*)-ones, 4-amino-3-nitrocoumarin, PPh<sub>3</sub>, PPA, one-pot reaction, microwave irradiation

## Introduction

Coumarin derivatives occur in a variety of natural products and biologically active compounds,<sup>1-5</sup> while they are utilized also in various practical applications.<sup>6,7</sup> Particularly derivatives combining coumarin and imidazole moieties present interesting properties. Chromeno[3,4-*d*]imidazol-4(3*H*)-ones appear to have biological actions as phosphodiesterase (PDE) VII inhibitors,<sup>8,9</sup> for the treatment of inflammatory disorders, autoimmune diseases,<sup>8</sup> and movement disorders.<sup>9</sup> They can behave as antagonists of toll-like receptor (TLR) 7,<sup>10</sup> CNS depressants,<sup>11,12</sup> and growth inhibitors for mammalian cancer.<sup>13</sup> They have also been studied as benzodiazepine receptors,<sup>14</sup> being isosters to oxazolo[4,5-*c*]quinolin-4-ones.<sup>15</sup> Chromeno[3,4-*d*]imidazol-4(3*H*)-one in conjugates can further act as aromatase inhibitors,<sup>16</sup> cytochrome P450 enzymes inhibitors,<sup>17</sup> antifungals,<sup>18</sup> anticancers,<sup>19</sup> antibacterials,<sup>20</sup> fluorescence agents,<sup>21</sup> against hepatitis C virus.<sup>22</sup>

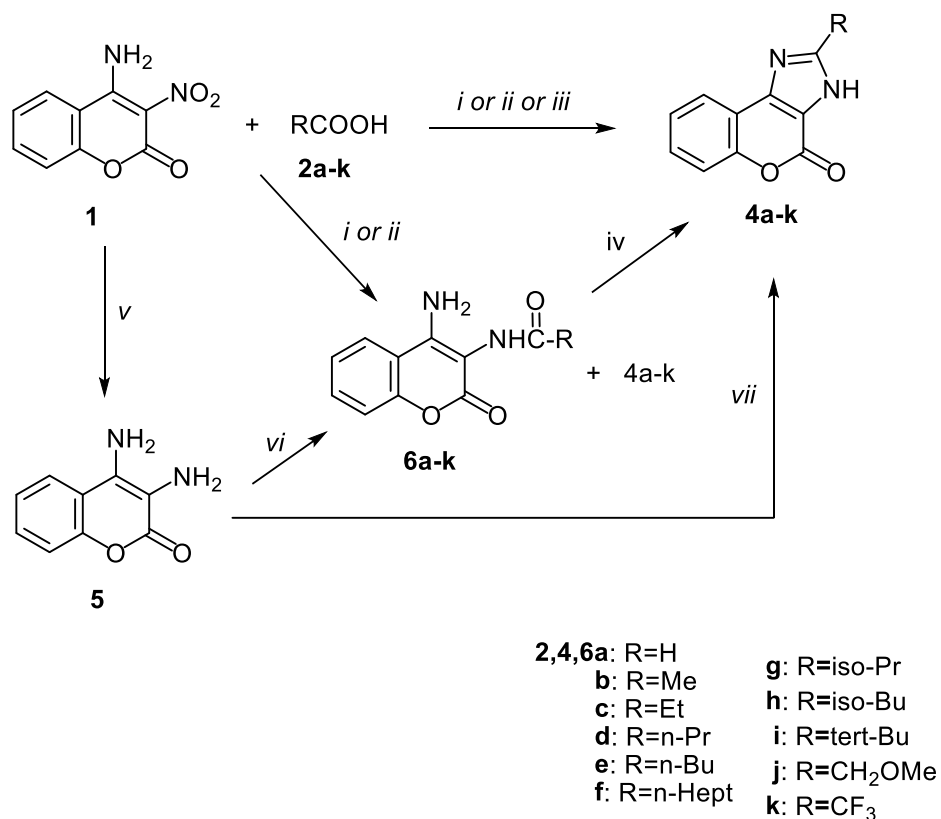
A few approaches for the synthesis of fused imidazolocoumarin derivatives have been developed: (a) Formation of the pyranone ring, for the *N*-substituted chromeno[3,4-*d*]imidazol-4(1*H*)-ones, by cyclization of alkyl 5-(2-hydroxyphenyl)-1*H*-imidazole-4-carboxylates under heating in acid<sup>10</sup> or MW irradiation in the presence of base.<sup>23</sup> (b) Imidazole ring formation in the benzene moiety of coumarin by the reactions of *o*-diaminocoumarins with acids or aldehydes under heating.<sup>24</sup> These synthetic processes are analogous to the preparation of benzimidazole derivatives.<sup>25</sup> *N*-substituted chromeno[3,4-*d*]imidazol-4(1*H*)-ones were prepared by the reaction of 4-alkylamino-3-aminocoumarin in boiling formic acid.<sup>11,12</sup> The parent chromeno[3,4-*d*]imidazol-4(1*H*)-one was derived from the reaction of 3-amino-4-*tert*-butylaminocoumarin with formic acid,<sup>11,12</sup> or from 3,4-diaminocoumarin by refluxing a formic acid solution,<sup>26,27</sup> or by heating a polyphosphoric acid (PPA) dispersion containing formic acid at 140°C.<sup>20</sup> The 2-phenylchromeno[3,4-*d*]imidazol-4(1*H*)-ones was obtained from the corresponding 3-benzoylamino-4-aminocoumarins by heating at 310-320°C or the corresponding 4-amino-3-iminocoumarin by oxidation with Pb(OCOCH<sub>3</sub>)<sub>4</sub>.<sup>14</sup> The 2-propyl-, isopropyl-, benzyl-, 2'-phenylethyl-substituted compounds was formed in moderate yields from the corresponding 4-amidino-3-nitrocoumarins under treating with NaBH<sub>4</sub> and 10% Pd/C.<sup>13</sup> The starting 3,4-diaminocoumarin was prepared from the corresponding 4-amino-3-nitrocoumarins by electrochemical reduction<sup>26,27</sup> or reduction with hydrogen<sup>11,12,28</sup> in Pd/BaSO<sub>4</sub> or Pd/C or with Zn in HCl<sup>20</sup>.

Triphenylphosphine (PPh<sub>3</sub>) is a versatile reagent for the reduction of different compounds including azides<sup>29</sup> (Staudinger reaction), disulfides,<sup>30</sup> sulfonyl chloride,<sup>31</sup> peroxides,<sup>32</sup> ozonides,<sup>33</sup> nitroso compounds,<sup>34</sup> *N*-oxides.<sup>35</sup> Through the reduction of nitro compounds in the Cadogan-type reductive cyclization indoles, carbazoles, benzimidazoles and benzopyrazoles have been prepared.<sup>36-38</sup> PPA is a powerful dehydrating agent with low nucleophilicity and moderate activity useful for the synthesis of nitrogen heterocycles.<sup>39,40</sup> In our recent work in the synthesis of coumarin derivatives fused with a 5-membered heterocyclic ring,<sup>41-43</sup> we have used the PPh<sub>3</sub> for the one-pot synthesis of of 4*H*-chromeno[3,4-*d*]oxazol-4-ones from 4-hydroxy-3-nitrocoumarin in the presence of acids and phosphorus pentoxide.<sup>41</sup> Building on the latter, we would like to present, herein, the one-pot synthesis of chromeno[3,4-*d*]imidazol-4(1*H*)-ones from 4-amino-3-nitrocoumarin in the presence of acids, PPh<sub>3</sub> and PPA.

## Results and Discussion

The reactions studied and the products obtained are depicted in Scheme 1. At first, the starting 4-amino-3-nitrocoumarin<sup>44,45</sup> (**1**) is obtained from 4-chloro-3-nitrocoumarin<sup>46,47</sup> by treatment with 7M methanolic solution of NH<sub>3</sub>. The suitable conditions for the one-pot tandem transformation of **1** to the fused

imidazolocoumarins **4** were investigated by us by performing the reactions of **1** with formic acid (**2a**) and acetic acid (**2b**) in the presence of tin(II) chloride under microwave irradiation (*Method A*). These reactions were expected to lead to the derivatives **4a** and **4b** in analogy to the synthesis of benzimidazoles from o-nitroanilines.<sup>48</sup> Indeed the imidazolocoumarin **4a** was obtained in 48% yield (Table 1, entry 1), but the reaction of **1** with acetic acid (**2a**) gave only the intermediate acetamide **6b** in 59% yield (Table 1, entry 2). Next PPh<sub>3</sub> was used as reducing agent under microwaves (*Method B*) and at 110°C the chromeno[3,4-*d*]imidazol-4(1*H*)-one (**4a**) was isolated in high yield (80%) along with the new compound, formamide **6a** (7%), while at 130°C the derivative **4b** formed in low yield (15%) with the amide **6b**<sup>28</sup> being the main product (68% yield) (Table 1, entries 3,4). When the latter reaction took place at 120°C only the amide **6b** was prepared in 92% yield (Table 2, entry 2). NOE experiment for **6b** shows 0.2% interaction of CH<sub>3</sub> protons with NH<sub>2</sub> protons and 4% interaction of 5-*H* with NH<sub>2</sub> protons. This confirms, that the acetyl-amino-substituent of compound **6b** is in the 3-position, in accordance with the less nucleophilic, amide, character of 4-NH<sub>2</sub> group.<sup>28</sup> It was then selected to carry out the above reactions in the presence of PPA as a condensation agent (*Method C*). The reactions of **1** with formic acid (**2a**) at 110°C and acetic acid (**2b**) at 130°C led to the fused coumarins **4a** and **4b** respectively in excellent yields (93% and 91%) (Table 1, entries 5,6). Subsequently, *Method C* was utilized for the one-pot tandem synthesis of chromeno[3,4-*d*]imidazol-4(1*H*)-ones **4** from 4-amino-3-nitrocoumarin (**1**) and acids **2**.



**Scheme 1.** Reagents and conditions: (i) *Method A*: **2a-k** (1 M), SnCl<sub>2</sub>·2H<sub>2</sub>O (3 equiv.), MW irradiation, 100°C (for **4a**), 130°C (for **6b**), 2 h; (ii) *Method B*: **2a-k** (1 M), PPh<sub>3</sub> (**3**) (2.5 equiv.), MW, 120°C, 110°C (for **4a** and **6a**), 130°C (for **4b** and **6b**), 2.5 h; (iii) *Method C*: **2a-k** (1 M), **3** (2.5 equiv.), PPA (5 equiv.), MW, 110-150°C, 2.5 h (a complicated mixture for **2j**); (iv) *Method D*: PPA (3 equiv.), toluene, MW, 110-150°C, 1 h; (v) 5% Pd/C, H<sub>2</sub>, 1 atm, MeOH, r.t., 45 min; (vi) *Method E*: **2a-k** (1 M), MW, 0.5-2 h, 70-150°C; (vii) *Method F*: **2a-k** (1 M), PPA (5 equiv.), MW, 1.5 h, 150°C (130°C for **4a**, 140°C for **4b**, multicomponent mixture for **2j**).

The reaction of **1** with propionic acid (**2c**) at 140°C resulted to 2-ethyl-substituted imidazolocoumarin **4c** with 92% yield (Table 1, entry 7). The 2-propyl- and 2-butyylimidazolocoumarins **4d** and **4e** was obtained at 150°C from the reactions of **1** with butanoic acid (**2d**) and pentanoic acid (**2e**) respectively in excellent yields (Table 1, entries 8,9). The one-pot tandem reactions of **1** with the acids **2f-i** led also to the 2-substituted chromeno[3,4-*d*]imidazol-4(1*H*)-ones **4f-i** in 85-87% yield (Table 1, entries 10-13). The methoxyacetic acid (**2j**) at lower temperature (130°C) resulted to a complicated mixture (Table 1, entry 14). Lower temperature (110°C) is necessary for trifluoroacetic acid (**2k**) (Table 1, entry 15). As we observed above, bulkier acids need higher temperature for this transformation.

The fused coumarins **4** were also quantitatively prepared by the treatment of amides like the **6a,b** with PPA under microwave irradiation (*Method D*). The reaction of amide **6a** with PPA in toluene under microwaves at 100°C for 1 h resulted quantitatively to unsubstituted compound **4a** (Table 1, entry 16). Recently **4a** was prepared in 67% yield by heating a PPA suspension of 3,4-diaminocoumarin (**5**) and formic acid (**2a**) for 45 min at 140°C.<sup>26,27</sup> The reactions of amides **6b,c** gave the fused coumarins **4b,c** by irradiation at 130°C or 140°C respectively (Table 1, entries 17,18). The amides **6d-i** at 150°C led also quantitatively to the compounds **4d-i** (Table 1, entries 19-24), while amides **6j,k** at 130°C or 100°C respectively resulted to **4j,k** (Table 1, entries 25,26). An effort to increase the temperature for **6j** to 140°C resulted in rapid increase of pressure and the mixture carbonized.

**Table 1.** Synthesis of chromeno[3,4-*d*]imidazol-4(1*H*)-ones **4a-k** from 4-amino-3-nitrocoumarin (**1**) and acids **2** by one-pot tandem procedure or through the 3-acylamino-4-aminocoumarins **6a-k**.

Entry	Acids <b>2a-k</b> or 3-alkylamino-4-aminocoumarins <b>6a-k</b>	Method <sup>a</sup>	Time, h	Temperature °C	Product (Yield %)
1	<b>2a</b> (R=H)	<b>A</b>	2	100	<b>4a</b> (48)
2	<b>2b</b> (R=Me)	<b>A</b>	2	130	<b>6b</b> (59)
3	<b>2a</b>	<b>B</b>	2.5	110	<b>4a</b> (80), <b>6a</b> (7)
4	<b>2b</b>	<b>B</b>	2.5	130	<b>4b</b> (15), <b>6b</b> (68)
5	<b>2a</b>	<b>C</b>	2.5	110	<b>4a</b> (93)
6	<b>2b</b>	<b>C</b>	2.5	130	<b>4b</b> (91)
7	<b>2c</b> (R=Et)	<b>C</b>	2.5	140	<b>4c</b> (92)
8	<b>2d</b> (R=n-Pr)	<b>C</b>	2.5	150	<b>4d</b> (89)
9	<b>2e</b> (R=n-Bu)	<b>C</b>	2.5	150	<b>4e</b> (90)
10	<b>2f</b> (R=n-hept)	<b>C</b>	2.5	150	<b>4f</b> (85)
11	<b>2g</b> (R= <i>iso</i> -Pr)	<b>C</b>	2.5	150	<b>4g</b> (87)
12	<b>2h</b> (R= <i>iso</i> -Bu)	<b>C</b>	2.5	150	<b>4h</b> (87)
13	<b>2i</b> (R= <i>tert</i> -Bu)	<b>C</b>	2.5	150	<b>4i</b> (86)
14	<b>2j</b> (R=CH <sub>2</sub> OMe)	<b>C</b>	2.5	130	-
15	<b>2k</b> (R=CF <sub>3</sub> )	<b>C</b>	2.5	110	<b>4k</b> (86)
16	<b>6a</b>	<b>D</b>	1	100	<b>4a</b> (97)
17	<b>6b</b>	<b>D</b>	1	130	<b>4b</b> (96)
18	<b>6c</b>	<b>D</b>	1	140	<b>4c</b> (96)
19	<b>6d</b>	<b>D</b>	1	150	<b>4d</b> (95)
20	<b>6e</b>	<b>D</b>	1	150	<b>4e</b> (96)
21	<b>6f</b>	<b>D</b>	1	150	<b>4f</b> (96)

22	<b>6g</b>	<b>D</b>	1	150	<b>4g</b> (95)
23	<b>6h</b>	<b>D</b>	1	150	<b>4h</b> (95)
24	<b>6i</b>	<b>D</b>	1	150	<b>4i</b> (95)
25	<b>6j</b>	<b>D</b>	1.5	130	<b>4j</b> (45), <b>6j</b> (55)
26	<b>6k</b>	<b>D</b>	1	100	<b>4k</b> (96)

<sup>a</sup> *Method A*: **2a-k** (1 M), SnCl<sub>2</sub>·2H<sub>2</sub>O (3 equiv.), MW irradiation; *Method B*: **2a-k** (1 M), PPh<sub>3</sub> (**3**) (2.5 equiv.), MW; *Method C*: **2a-k** (1 M), **3** (2.5 equiv.), PPA (5 equiv.), MW (a multicomponent mixture was obtained with **2j**); *Method D*: PPA (3 equiv.), toluene, MW.

The aforementioned treatment of 4-amino-3-nitrocoumarin (**1**) with formic acid (**2a**) in the presence of PPh<sub>3</sub> (**3**) under microwaves (*Method B*) at 110°C resulted mainly in fused coumarin **4a** (Table 1, entry 3), while the similar reaction with acetic acid (**2b**) at 130°C gave mainly the acetamide **6b** (Table 1, entry 4). The latter reaction at 120°C led only to **6b** in 92% yield (Table 2, entry 2). The analogous treatment of **1** with **2a** at 80°C for 2.5 h left unchanged the starting materials (Table 2, entry 1). The new compounds, amides **6c-j**, were synthesized in high yields (77-95%) from the reactions with other acids **2c-j** following *Method B* at 120°C (Table 2, entries 3-10). For the synthesis of the bulky amide **6i** longer time (4 h) was necessary, while the amide **6j** was obtained by MW irradiation at 100°C. When trifluoroacetic acid (**2k**) was used at 100°C, the reaction led to the isolation of both imidazole **4k** and amide **6k** (Table 2, entry 11).

**Table 2.** Synthesis of amides **6a-k** by an one-pot tandem procedure from 4-amino-3-nitrocoumarin (**1**) and acids **2** or through acylation of 3,4-diaminocoumarin (**5**) with the acids **2**.

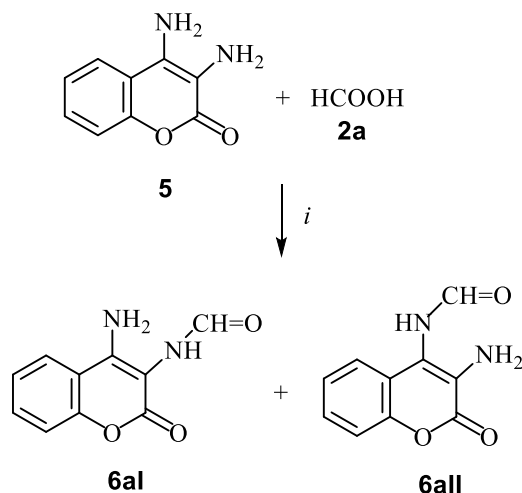
Entry	Starting materials	Method <sup>a</sup>	Time	Temperature °C	Products (Yield %)
1	<b>1, 2a</b>	<b>B</b>	2,5 h	80	-
2	<b>1, 2b</b>	<b>B</b>	2,5 h	120	<b>6b</b> (92)
3	<b>1, 2c</b>	<b>B</b>	2,5 h	120	<b>6c</b> (88)
4	<b>1, 2d</b>	<b>B</b>	2,5 h	120	<b>6d</b> (89)
5	<b>1, 2e</b>	<b>B</b>	2,5 h	120	<b>6e</b> (89)
6	<b>1, 2f</b>	<b>B</b>	2,5 h	120	<b>6f</b> (80)
7	<b>1, 2g</b>	<b>B</b>	2,5 h	120	<b>6g</b> (86)
8	<b>1, 2h</b>	<b>B</b>	2,5 h	120	<b>6h</b> (85)
9	<b>1, 2i</b>	<b>B</b>	4 h	120	<b>6i</b> (77)
10	<b>1, 2j</b>	<b>B</b>	2,5 h	100	<b>6j</b> (95)
11	<b>1, 2k</b>	<b>B</b>	2,5 h	100	<b>4k</b> (44), <b>6k</b> (44)
12	<b>5, 2a</b>	<b>E</b>	30 min	70	<b>6a</b> (93)
13	<b>5, 2b</b>	<b>E</b>	2 h	120	<b>6b</b> (91)
14	<b>5, 2c</b>	<b>E</b>	2 h	120	<b>6c</b> (90)
15	<b>5, 2d</b>	<b>E</b>	2 h	120	<b>6d</b> (89)
16	<b>5, 2e</b>	<b>E</b>	2 h	120	<b>6e</b> (86)
17	<b>5, 2f</b>	<b>E</b>	2 h	120	<b>6f</b> (80)
18	<b>5, 2g</b>	<b>E</b>	2 h	120	<b>6g</b> (85)
19	<b>5, 2h</b>	<b>E</b>	2 h	120	<b>6h</b> (80)
20	<b>5, 2i</b>	<b>E</b>	4 h	120	<b>6i</b> (85)
21	<b>5, 2j</b>	<b>E</b>	2 h	100	<b>6j</b> (95)
22	<b>5, 2k</b>	<b>E</b>	1 h	100	<b>4k</b> (47), <b>6k</b> (23)

<sup>a</sup> Conditions: *Method B*: **2a-k** (1 M), PPh<sub>3</sub> (**3**) (2.5 equiv.), MW; *Method E*: MW.

The amides **6a-k** were also prepared by the acylation of 3,4-diaminocoumarin (**5**). This compound was obtained by the treatment of **1** with Pd/C in methanol under H<sub>2</sub> atmosphere at room temperature for 45 min. The reactions of **5** with carboxylic acids **2a-k** under microwaves (*Method E*) resulted in very high to excellent yields (80-95%) of the amides **6a-k**. The temperature was the same, 120°C, for most of the amides (Table 2, entries 13-19). The tert-butyl substituted amide **6i** was obtained after prolonged irradiation for 4 h (Table 2, entry 20). The methoxyacetamide **6j** and the trifluoroacetamide **6k** were also prepared by irradiation at 100°C (Table 2, entries 21,22). The latter received together with fused coumarin **4k**. These amides are the same as the ones synthesized by *Method B*.

In the case of formic acid (**2a**) the temperature was kept at 70°C for the synthesis of amide **6a** to avoid the cyclization/condensation to the imidazole **4a** (Table 2, entry 12). This reaction led to an inseparable mixture of 3-formamide **6aI** and 4-formamide **6aII** (Scheme 2) in a ratio 10:4, as indicated by the <sup>1</sup>H-NMR spectrum. There are distinct protons for these two formamides: **6aI** [9.02 (brs, 1H, 3-N-H, disappeared with D<sub>2</sub>O), 8.16 (s, 1H, 3-NH-CH=O), 8.07 (d, *J* = 7.9 Hz, 1H, 5-H), 7.18 (brs, 2H, 4-NH<sub>2</sub>, disappeared with D<sub>2</sub>O)]; **6aII** [8.45 (d, *J* = 11.4 Hz, 1H, 4-N-H, disappeared with D<sub>2</sub>O), 8.10 (d, *J* = 8.4 Hz, 1H, 5-H), 7.94 (d, *J* = 11.5 Hz, 1H, 4-NH-CH=O), 7.46 (brs, 2H, 3-NH<sub>2</sub>, disappeared with D<sub>2</sub>O)]. NOE experiments show interactions of 4-NHCH=O proton (8.45) with 5-H proton (8.10) (0.6%) and 3-NH<sub>2</sub> protons (7.46) (1%), while 3-NHCH=O proton (8.16)

interact (0.06%) only with 4-NH<sub>2</sub> protons (7.18). Carbon atoms also are different in the <sup>13</sup>C-NMR spectrum: **6al** (160.9, 159.3, 151.84, 149.8, 131.9, 123.6, 123.5, 116.7, 114.4, 94.0); **6all** (166.4, 160.7, 151.83, 150.9, 132.2, 123.8, 123.7, 116.8, 114.3, 94.8). It must be mentioned that in the case of *Method B* only the **6al** isomer was isolated along with imidazole **4a** (Table 1, entry 3).



**Scheme 2.** Reagents and conditions: (i) **Method E**: MW.

With the 3,4-diaminocoumarin (**5**) as starting material, we also performed the one-pot synthesis of fused coumarins **4** by irradiation under microwaves in the presence of acids **2** in higher temperature than before (*Method E*) (Table 3). The irradiation with formic acid (**2a**) for 1 h at 100°C resulted to the chromeno[3,4-*d*]imidazol-4(1*H*)-one **4a** in excellent yield (92%) (Table 3, entry 1). The reactions with acetic acid (**2b**) or propionic acid (**2c**) for 2 h at 130°C or 140°C respectively gave both compounds **4b,c** and the amides **6b,c** in almost equal yields (Table 3, entries 2,3). The outcome of the reactions of acids **2d-i** at 150°C was similar giving both fused coumarins **4d-i** and amides **6d-i** (Table 3, entries 4-9). The methoxyacetic acid (**2j**) reacted at 130°C (Table 3, entry 10). The analogous reaction with trifluoroacetic acid (**2k**) at 70°C for 30 min led only to the amide **6k** in excellent yield (93%) (Table 3, entry 11). It can be seen that, the same *Method E*, at lower temperature gave only amides **6a-k** (Table 2, entries 12-22), while at higher temperature led to compounds **4b-j** and amides **6a-k** (Table 3, entries 1-11).

When the reactions with the acids **2b-i,k** were performed in the presence of PPA under microwaves (**Method F**), only the chromeno[3,4-*d*]imidazol-4(1*H*)-ones **4b-i,k** were isolated in excellent yields (83-92%). The acetic acid (**2b**) reacted at 130°C (Table 3, entries 12), while the propionic acid (**2c**) at 140°C (Table 3, entry 13). The reactions of the other acids **2d-i** at 150°C led to **4d-i** respectively (Table 3, entries 14-19). The trifluoroacetic acid (**2k**) reacted at 110°C to give **4k** (Table 3, entry 21). In the case of methoxyacetic acid (**2j**) a multicomponent mixture was isolated (Table 3, entry 20).

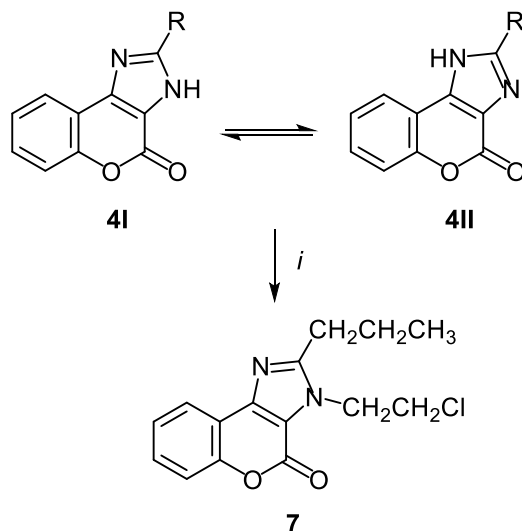
**Table 3.** One-pot synthesis of fused chromeno[3,4-*d*]imidazol-4(1*H*)-one **4** from 3,4-diaminocoumarin (**5**) and acids **2**.

Entry	Acid	Method, <sup>a</sup>	Time (h), Temperature	Compound (Yield %)
1	<b>2a</b>		E, 1, 100°C	<b>4a</b> (92)
2	<b>2b</b>		E, 2, 130°C	<b>4b</b> (48), <b>6b</b> (46)
3	<b>2c</b>		E, 2, 140°C	<b>4c</b> (49), <b>6c</b> (48)
4	<b>2d</b>		E, 2, 150°C	<b>4d</b> (47), <b>6d</b> (47)
5	<b>2e</b>		E, 2, 150°C	<b>4e</b> (45), <b>6e</b> (45)
6	<b>2f</b>		E, 2, 150°C	<b>4f</b> (45), <b>6f</b> (46)
7	<b>2g</b>		E, 2, 150°C	<b>4g</b> (48), <b>6g</b> (47)
8	<b>2h</b>		E, 2, 150°C	<b>4h</b> (47), <b>6h</b> (46)
9	<b>2i</b>		E, 2, 150°C	<b>4i</b> (45), <b>6i</b> (45)
10	<b>2j</b>		E, 2, 130°C	<b>4j</b> (66), <b>6j</b> (33)
11	<b>2k</b>		E, 0.5, 70°C	<b>6k</b> (93)
12	<b>2b</b>	F	1.5, 130°C	<b>4b</b> (92)
13	<b>2c</b>	F	1.5, 140°C	<b>4c</b> (90)
14	<b>2d</b>	F	1.5, 150°C	<b>4d</b> (88)
15	<b>2e</b>	F	1.5, 150°C	<b>4e</b> (89)
16	<b>2f</b>	F	1.5, 150°C	<b>4f</b> (83)
17	<b>2g</b>	F	1.5, 150°C	<b>4g</b> (89)
18	<b>2h</b>	F	1.5, 150°C	<b>4h</b> (86)
19	<b>2i</b>	F	1.5, 150°C	<b>4i</b> (84)
20	<b>2j</b>	F	1.5, 130°C	-
21	<b>2k</b>	F	1.5, 110°C	<b>4k</b> (92)

<sup>a</sup>Conditions: *Method E*: MW; *Method F*: PPA (5 equiv.), MW (multicomponent mixture for **2j**).

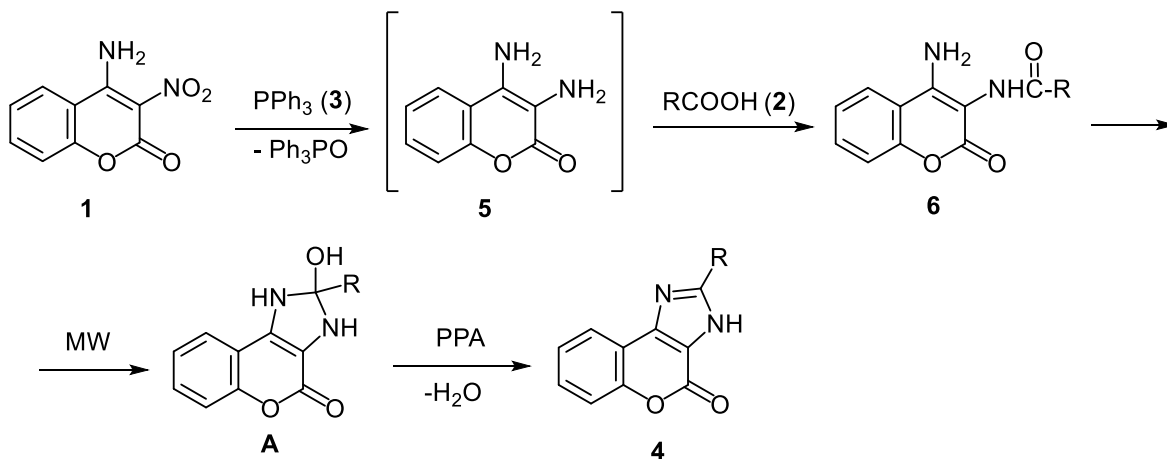
Compounds **4** have the possibility to exist in two tautomeric forms **4I** and **4II** (Scheme 3). The former **4I** is the form suggested in the literature.<sup>13,14</sup> Mixtures of the two tautomers obtained in the case of compounds **4b** [13.61 (brs, 0,6H), 13.53 (brs, 0,4H), 7.99 (d, *J* = 6.7 Hz, 0,6H), 7.90 (d, *J* = 5.9 Hz, 0,4H)], **4g** [13.55 (brs, 0,6H), 13.33 (brs, 0,4H)], **4h** [7.99 (s, *J* = 7.6 Hz, 0,3H), 7.96 (d, *J* = 7.6 Hz, 0,7H)] as indicated from the <sup>1</sup>H-NMR spectra and the <sup>13</sup>C-NMR spectra (**4g** and **4h**).

The reaction of **4d** (R=*n*-propyl) with 1,2-dichloroethane, as a control experiment for the differentiation of **4I** or **4II** tautomers, resulted in the synthesis of *N*-3-substituted derivative **7** (Scheme 3). NOE experiments show only interactions between 9-*H* (8.14) with 8-*H* (7.36) (2%) and hydrogen of N-CH<sub>2</sub> (4.67) with C-CH<sub>2</sub> hydrogen (2.93) (2%). In the NOESY 2D experiment there are only interactions between N-CH<sub>2</sub> (4.67) with C-CH<sub>2</sub> hydrogen (2.93) and C-CH<sub>2</sub>CH<sub>2</sub> hydrogen (1.90-1.97, m). In the same experiment, vicinal proton's interaction appeared at 8.14 and 7.36 due to the COSY parallel procedure (Supplemental Material). This implies predominance of **4I** tautomer in solution.



**Scheme 3.** Tautomeric forms of compounds **4**. Reagents and conditions: (i) (R=*n*-propyl) 1,2-Dichloroethane, Et<sub>3</sub>N, reflux, Ar atmosphere, 24 h.

A possible pathway for the one-pot transformation of **1** to **4** in the presence of PPh<sub>3</sub> and PPA is outlined in Scheme 4. Reduction at first with PPh<sub>3</sub> of **1** gave the 3,4-diaminocoumarin (**5**), not isolated. Acylation then of more nucleophilic 3-amino position to the amide **6**, followed by cyclisation during the microwave irradiation formed the hydroxy-intermediate **A**. Finally, water elimination in the presence of PPA led to the chromeno[3,4-*d*]imidazol-4(1*H*)-one **4**.



**Scheme 4.** Possible pathway for the one-pot synthesis of chromeno[3,4-*d*]imidazol-4(1*H*)-ones **4** from 4-amino-3-nitrocoumarin (**1**) in the presence of PPh<sub>3</sub> and PPA.

The reported compounds have been tested as antioxidants. In our studies AAPH<sup>42</sup> was used as a free radical initiator to follow oxidative changes of linoleic acid to conjugated diene hydroperoxide. Lipoxygenase LO is the key enzyme in leukotrienes biosynthesis,<sup>49</sup> an important inflammatory mediator. LOs play a role in membrane lipid peroxidation by forming hydroperoxides in the lipid bilayer. Inhibitors of LOX have attracted attention initially as potential agents for the treatment of inflammatory diseases. Most of the LO inhibitors are antioxidants or free radical scavengers, since lipoxygenation occurs via a carbon-centered radical. Among the

tested compounds the most interesting representatives are **4a**, **4b**, **6d**, **6h**, for which we were able to determine their IC<sub>50</sub> values under our experimental conditions. The rest do not present significant biological activity under the reported experimental conditions.

**Table 4.** % Inhibition of Lipid Peroxidation (LP %); *In vitro* inhibition of soybean lipoxygenase (%LOX) / (IC<sub>50</sub> μM)<sup>a</sup>.

Entry	Compound	LP%	% LOX/IC <sub>50</sub> μM) <sup>a</sup>
1	4-Aminocoumarin	6	23%
2	<b>4a</b>	19	98
3	<b>4b</b>	No	98
4	<b>4f</b>	85	No
5	<b>4g</b>	21	No
6	<b>4i</b>	No	30%
7	<b>4j</b>	31	No
8	<b>4k</b>	35	No
9	<b>5</b>	31	19%
10	<b>6c</b>	24	No
11	<b>6d</b>	32	87.5
12	<b>6g</b>	23	No
13	<b>6h</b>	No	90
14	<b>6k</b>	38	No
15	NDGA		93% (0.5)
16	Trolox	95	

<sup>a</sup>Values are means ± SD of three or four different determinations. No; no activity under the reported experimental conditions.

## Conclusions

In conclusion, 2-substituted chromeno[3,4-*d*]imidazol-4(1*H*)-ones were synthesized in excellent yields by the one-pot reaction of 4-amino-3-nitrocoumarin with aliphatic acids in the presence of PPh<sub>3</sub> and PPA under microwave irradiation. Most of them are new compounds. The title compounds were also obtained under microwaves by the cyclisation and dehydration of 4-amino-3-carboxamidocoumarins in the presence of PPA or by the one pot reaction of 3,4-diaminocoumarin with acids in the presence of PPA. The new 4-amino-3-carboxamidocoumarins were prepared in excellent yield from 3,4-diaminocoumarin and acids in lower temperature under microwaves, while higher temperature led to mixtures of these compounds and the title compounds. Preliminary biological tests indicated inhibition of soybean lipoxygenase for some of the new compounds.

## Experimental Section

**General.** All the chemicals were procured from either Sigma- Aldrich Co. or Merck & Co., Inc. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained with a

Perkin- Elmer 1310 spectrophotometer as KBr pellets. NMR spectra were recorded on an Agilent 500/54 (DD2) (500 MHz, 125 and 188 MHz for  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  respectively) using  $\text{DMSO-}d_6$  or  $\text{CDCl}_3$  as solvent and TMS as an internal standard.  $J$  values are reported in Hz. Mass spectra were determined on a LCMS-2010 EV Instrument (Shimadzu) under Electrospray Ionization (ESI) conditions. HRMS (ESI-MS) were received on ThermoFisher Scientific model LTQ Orbitrap Discovery MS. Silica gel N° 60, Merck A.G. was used for column chromatography. The MW experiment was performed in a scientific focused microwave reactor (Biotage Initiator 2.0).

**4-Amino-3-nitro-2H-chromen-2-one (1)** (Modification of literature method.<sup>45</sup>). A solution of 7M  $\text{NH}_3$  in MeOH (10 ml, 70 mmol) was placed in a flask containing MeOH (5 ml) in an ice-bath. Then, 4-chloro-3-nitrocoumarin (7.9 g, 35 mmol) was added gradually during 15 min, the ice-bath was then removed and the stirring continued for 30 min at r.t. Cooled water (50 ml) was added to the mixture and the precipitate was filtered, washed with cooled water (3 x 10 ml) and ether (3 x 10 ml) and dried under vacuum to give compound **1** (6.8 g, 94% yield), m.p. 274-276°C (ethanol) (lit.<sup>45</sup> 272-274°C).

**3,4-Diamino-2H-chromen-2-one (5)** (Modification of literature method.<sup>6,7,28</sup>). In a solution of **1** (1.44 g, 7 mmol) in MeOH (20 ml) 10% Pd/C (0.373 g, 0.35 mmol) was added and the mixture stirred under  $\text{H}_2$  atmosphere for 45 min (consumption of starting material checked by tlc). The mixture was filtered and the precipitate washed by hot MeOH (3 x 20 ml). The filtrate was evaporated to give compound **5**, m.p. 212-214°C (ethanol), lit.<sup>12</sup> 201-205°C (dec).

#### Chromeno[3,4-d]imidazol-4(3H)-one (4a). typical procedures

**Method A.** 4-Amino-3-nitrocoumarin (**1**) (0.103 g, 0.5 mmol), formic acid (**2a**) (0.5 ml, 0.61 g, 13.3 mmol) and  $\text{SnCl}_2 \cdot \text{H}_2\text{O}$  (0.338 g, 1.5 mmol) were added to a flask for MW oven. The mixture was irradiated at 100°C for 2 h. After cooling, the resulted solution was filtered through celite and washed by hot MeOH (3 x 10 ml). The filtrate was evaporated under vacuum and the remaining solid partitioned between  $\text{H}_2\text{O}$  (20 ml) and ethyl acetate (20 ml). The organic layer was washed with  $\text{H}_2\text{O}$  (20 ml), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated to give compound **4a** (45 mg, 48%). White solid, m.p. 305-307°C (ethanol), lit.<sup>26</sup> 299-301°C. IR (KBr): 3134, 3098, 3023, 1745, 1637, 1578, 1534  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR ( $\text{DMSO-}d_6$ ):  $\delta$  8.31 (s, 1H), 8.01 (d,  $J$  7.4 Hz, 1H), 7.52 (t,  $J$  7.3 Hz, 1H), 7.47 (d,  $J$  7.9 Hz, 1H), 7.40 (t,  $J$  7.1 Hz, 1H).  $^{13}\text{C}$ -NMR ( $\text{DMSO-}d_6$ ):  $\delta$  155.6, 151.7, 143.1, 140.7, 129.3, 124.4, 122.1, 121.5, 116.9, 114.9. MS (ESI):  $m/z$  187[M+H]<sup>+</sup>, 209[M+Na]<sup>+</sup>, 225[M+K]<sup>+</sup>.

**Method B.** In a flask for MW oven 4-amino-3-nitrocoumarin (**1**) (0.103 g, 0.5 mmol), formic acid (**2a**) (0.5 ml, 0.61 g, 13.3 mmol) and  $\text{PPh}_3$  (0.328 g, 1.25 mmol) were placed and irradiated at 110°C for 2.5 h. After cooling, the resulted mixture was poured in ethyl acetate (30 ml) and extracted with an aqueous solution of 5%  $\text{NaHCO}_3$  (3 x 20 ml). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated. The resulted solid was separated by column chromatography [silica gel, hexane/ethyl acetate (1:1) to ethyl acetate/MeOH (9:1)] to give a non-separable mixture of **4a** (74 mg, 80%) and **6a** (7 mg, 7%) (the yield counted from  $^1\text{H}$ -NMR spectrum).

**Method C.** 4-Amino-3-nitrocoumarin (**1**) (0.103 g, 0.5 mmol), formic acid (**2a**) (0.5 ml, 0.61 g, 13.3 mmol),  $\text{PPh}_3$  (0.328 g, 1.25 mmol) and PPA (0.245 g, 2.5 mmol) were added to a flask for MW oven. (**Caution!** PPA must be covered by the mixture, otherwise the glass might melt and explosion in the MW oven is likely to happen). The mixture was irradiated at 110°C for 2.5 h. After cooling, the resulting product was treated with ethyl acetate (30 ml) and water (30 ml). The organic layer was washed with a 5% aqueous solution of  $\text{NaHCO}_3$  (3 x 20 ml), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , evaporated and separated by column chromatography [silica gel, hexane/ethyl acetate (1:1) to ethyl acetate/MeOH (9:1)] to give compound **4a** (87 mg, 93%).

**Method D.** In a flask for MW oven were placed 4-amino-3-formamidocoumarin (**6a**) (51 mg, 0.25 mmol), toluene (1 ml) and PPA (74 mg, 0.75 mmol) and irradiated at 100°C for 1 h. After cooling, the resulted mixture

was treated with ethyl acetate (20 ml) and water (20 ml). The organic layer was washed with a 5% aqueous solution of  $\text{NaHCO}_3$  (3 x 15 ml), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated to give compound **4a** (45 mg, 97%).

**Method E.** 3,4-Diaminocoumarin (**5**) (88 g, 0.5 mmol) and formic acid (**2a**) (0.5 ml, 0.61 g, 13.3 mmol) were added to a flask for MW oven and irradiated at 100°C for 1 h. After cooling ethyl acetate (1 ml) was added and the mixture filtered under vacuum. The precipitate was washed with ethyl acetate (2 x 0.5 ml) and hexane (0.5 ml) to give compound **4a** (86 mg, 92%).

**2-Methylchromeno[3,4-*d*]imidazol-4(3*H*)-one (4b). Typical procedure. Method F.** 3,4-Diaminocoumarin (**5**) (44 g, 0.25 mmol), acetic acid (**2b**) (0.25 ml, 0.26 g, 4.3 mmol) and PPA (0.123 g, 1.25 mmol) were added to a flask for MW oven and irradiated at 130°C for 1.5 h. After cooling ethyl acetate (1 ml) was added and the mixture filtered under vacuum. The precipitate was washed with ethyl acetate (2 x 0.5 ml) and hexane (0.5 ml) to give compound **4b** (46 mg, 92%). **4b** [Method B, 130°C, 15% (from the  $^1\text{H}$ -NMR, mixture with **6b**); Method C, 130°C, 91 mg (91%); Method D, 130°C, 48 mg (96%); Method E, 2 h, 130°C, 24 mg (48%)]. White solid, m.p. 259-261°C (ethanol), lit.<sup>26</sup> 334-336°C, lit.<sup>11</sup> 278-280°C. IR (KBr): 3165, 3090, 3039, 2873, 2820, 1706, 1619, 1549, 1500, 1489  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR ( $\text{DMSO-}d_6$ ) (two tautomers):  $\delta$  13.61 (brs, 0,6H, disappeared with  $\text{D}_2\text{O}$ ), 13.53 (brs, 0,4H, disappeared with  $\text{D}_2\text{O}$ ), 7.99 (d, *J* 6.7 Hz, 0,6H), 7.90 (d, *J* 5.9 Hz, 0,4H), 7.51 (t, *J* 7.1 Hz, 1H), 7.47 (d, *J* 7.9 Hz, 1H), 7.40 (t, *J* 6.6 Hz, 1H), 2.51 (s, 3H).  $^{13}\text{C}$ -NMR ( $\text{DMSO-}d_6$ ):  $\delta$  154.8, 152.7, 151.7, 142.1, 129.3, 124.5, 121.9, 119.6, 116.9, 115.0, 14.2. MS (ESI): *m/z* 201[ $\text{M}+\text{H}$ ]<sup>+</sup>, 223[ $\text{M}+\text{Na}$ ]<sup>+</sup>, 239[ $\text{M}+\text{K}$ ]<sup>+</sup>.

**2-Ethylchromeno[3,4-*d*]imidazol-4(3*H*)-one (4c).** 98 mg, 92% (Method C, 140°C), 51 mg, 96% (Method D, 140°C), 52 mg, 49% (Method E, 2 h, 140°C), 48 mg, 90% (Method F, 140°C), white solid, m.p. 236-238°C (ethanol). IR (KBr): 3173, 3089, 2985, 2872, 2822, 1712, 1621, 1547, 1498  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR ( $\text{DMSO-}d_6$ ):  $\delta$  7.97 (d, *J* 7.7 Hz, 1H), 7.51 (t, *J* 7.7 Hz, 1H), 7.46 (d, *J* 8.3 Hz, 1H), 7.39 (t, *J* 7.4 Hz, 1H), 2.85 (q, *J* 7.6 Hz, 2H), 1.32 (t, *J* 7.6 Hz, 3H).  $^{13}\text{C}$ -NMR ( $\text{DMSO-}d_6$ ):  $\delta$  157.5, 155.0, 151.8, 141.6, 129.4, 124.6, 122.1, 119.8, 117.0, 114.1, 21.8, 12.2. MS (ESI): *m/z* 215[ $\text{M}+\text{H}$ ]<sup>+</sup>, 237[ $\text{M}+\text{Na}$ ]<sup>+</sup>, 253[ $\text{M}+\text{K}$ ]<sup>+</sup>. HRMS (ESI): Calcd for  $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_2$  ( $\text{M}+\text{H}$ )<sup>+</sup> 215.0815. Found: 215.0812. Calcd for  $\text{C}_{12}\text{H}_{10}\text{N}_2\text{NaO}_2$  ( $\text{M}+\text{Na}$ )<sup>+</sup> 237.0634. Found: 237.0632.

**2-Propylchromeno[3,4-*d*]imidazol-4(3*H*)-one (4d).** 0.102 g, 89% (Method C, 150°C), 54 mg, 95% (Method D, 150°C), 54 mg, 47% (Method E, 2 h, 150°C), 50 mg, 88% (Method F, 150°C), pale yellow solid, m.p. 231-233°C (ethanol), lit.<sup>13</sup> 202°C (dec). IR (KBr): 3175, 3063, 2963, 2867, 2813, 1692, 1619, 1544, 1493  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR ( $\text{DMSO-}d_6$ ):  $\delta$  7.93 (d, *J* 7.7 Hz, 1H), 7.48 (t, *J* 7.7 Hz, 1H), 7.43 (d, *J* 8.2 Hz, 1H), 7.36 (t, *J* 7.4 Hz, 1H), 2.78 (t, *J* 7.4 Hz, 2H), 1.81 – 1.72 (m, 2H), 0.92 (t, *J* 7.3 Hz, 3H).  $^{13}\text{C}$ -NMR ( $\text{DMSO-}d_6$ ):  $\delta$  156.4, 155.0, 151.8, 141.9, 129.3, 124.5, 122.0, 119.7, 117.0, 115.0, 30.2, 21.0, 13.6. MS (ESI): *m/z* 215[ $\text{M}+\text{H}$ ]<sup>+</sup>, 237[ $\text{M}+\text{Na}$ ]<sup>+</sup>, 253[ $\text{M}+\text{K}$ ]<sup>+</sup>.

**2-Butylchromeno[3,4-*d*]imidazol-4(3*H*)-one (4e).** 0.109 g, 90% (Method C, 150°C), 58 mg, 96% (Method D, 150°C), 54 mg, 45% (Method E, 2 h, 150°C), 54 mg, 89% (Method F, 150°C), white solid, m.p. 221-222°C (ethanol). IR (KBr): 3472, 3059, 2956, 2931, 2863, 1742, 1633, 1575, 1536, 1505  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR ( $\text{DMSO-}d_6$ ):  $\delta$  13.49 (brs, 1H), 7.93 (d, *J* 7.5 Hz, 1H), 7.48 (t, *J* 7.2 Hz, 1H), 7.43 (d, *J* 8.2 Hz, 1H), 7.36 (t, *J* 7.4 Hz, 1H), 2.80 (t, *J* 7.6 Hz, 2H), 1.79 – 1.67 (m, 2H), 1.38 – 1.27 (m, 2H), 0.89 (t, *J* 7.4 Hz, 3H).  $^{13}\text{C}$ -NMR ( $\text{DMSO-}d_6$ ):  $\delta$  156.3, 154.5, 151.5, 141.0, 128.8, 124.0, 121.6, 118.3, 116.5, 115.1, 29.3, 27.7, 21.4, 13.2. MS (ESI): *m/z* 243[ $\text{M}+\text{H}$ ]<sup>+</sup>, 265[ $\text{M}+\text{Na}$ ]<sup>+</sup>, 281[ $\text{M}+\text{K}$ ]<sup>+</sup>. HRMS (ESI): Calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_2$  ( $\text{M}+\text{H}$ )<sup>+</sup> 243.1128. Found: 243.1126.

**2-Heptylchromeno[3,4-*d*]imidazol-4(3*H*)-one (4f).** 0.121 g, 85% (Method C, 150°C), 68 mg, 96% (Method D, 150°C), 64 mg, 45% (Method E, 2 h, 150°C), 59 mg, 83% (Method F, 150°C), white solid, m.p. 141-142°C (ethanol). IR (KBr): 3189, 3086, 2951, 2915, 2850, 1723, 1626, 1545, 1497  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR ( $\text{DMSO-}d_6$ ):  $\delta$  13.53 (brs, 1H), 7.97 (d, *J* 7.1 Hz, 1H), 7.52 (t, *J* 7.7 Hz, 1H), 7.47 (d, *J* 8.1 Hz, 1H), 7.40 (t, *J* 7.4 Hz, 1H), 2.81 (t, *J* 7.5 Hz, 2H), 1.80 – 1.72 (m, 2H), 1.37 – 1.28 (m, 4H), 1.28 – 1.19 (m, 4H), 0.85 (t, *J* 6.4 Hz, 3H).  $^{13}\text{C}$ -NMR ( $\text{DMSO-}d_6$ ):  $\delta$  158.4, 154.2, 151.7, 146.4, 129.3, 124.5, 121.9, 116.9, 115.8, 113.0, 31.1, 28.5, 28.3, 28.3, 27.5, 22.1, 13.9. MS

(ESI):  $m/z$  285[M+H]<sup>+</sup>, 307[M+Na]<sup>+</sup>, 323[M+K]<sup>+</sup>. HRMS (ESI): Calcd for C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub> (M+H)<sup>+</sup> 285.1598. Found: 285.1601. Calcd for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>NaO<sub>2</sub> (M+Na)<sup>+</sup> 307.1417. Found: 307.1420.

**2-Isopropylchromeno[3,4-*d*]imidazol-4(3*H*)-one (4g).** 99 mg, 87% (Method C, 150°C), 54 mg, 95% (Method D, 150°C), 55 mg, 48% (Method E, 2 h, 150°C), 51 mg, 89% (Method F, 150°C), white solid, m.p. 243–245°C (ethanol), lit.<sup>13</sup> 230°C (dec.). IR (KBr): 3174, 3088, 2976, 2875, 1713, 1624, 1546, 1497 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) (two tautomers): 13.55 (brs, 0,6H), 13.33 (brs, 0,4H), 7.98 (d, *J* 6.1 Hz, 1H), 7.50 (t, *J* 7.6 Hz, 1H), 7.46 (d, *J* 8.0 Hz, 1H), 7.38 (t, *J* 6.9 Hz, 1H), 3.22 – 3.13 (m, 1H), 1.35 (d, *J* 6.9 Hz, 6H). <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>) (two tautomers): δ 163.0, 158.8, 156.35, 153.9, 151.9, 151.5, 145.9, 136.8, 129.4, 129.0, 124.5, 124.3, 122.0, 121.9, 116.9, 116.8, 115.8, 112.9, 28.4, 28.2, 21.2. MS (ESI):  $m/z$  229[M+H]<sup>+</sup>, 251[M+Na]<sup>+</sup>, 267[M+K]<sup>+</sup>.

**2-Isobutylchromeno[3,4-*d*]imidazol-4(3*H*)-one (4h).** 0.105 g, 87% (Method C, 150°C), 57 mg, 95% (Method D, 150°C), 57 mg, 47% (Method E, 2 h, 150°C), 52 mg, 86% (Method F, 150°C), white solid, m.p. 209–211°C (ethanol). IR (KBr): 3197, 3085, 2958, 2872, 2836, 1717, 1621, 1545, 1494 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) (two tautomers): δ 13.50 (brs, 1H), 7.99 (s, *J* 7.6 Hz, 0,3H), 7.96 (d, *J* 7.6 Hz, 0,7H), 7.49 (t, *J* 7.6 Hz, 1H), 7.45 (d, *J* 8.1 Hz, 1H), 7.38 (t, *J* 7.4 Hz, 1H), 2.69 (d, *J* 7.2 Hz, 2H), 2.21 – 2.10 (m, 1H), 0.93 (d, *J* 6.6 Hz, 6H). <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>) (two tautomers): δ 159.6, 154.5, 151.7, 143.0, 129.2, 124.4, 124.4, 122.0, 121.9, 116.9, 115.7, 112.2, 37.2, 27.7, 22.1. MS (ESI):  $m/z$  243[M+H]<sup>+</sup>, 265[M+Na]<sup>+</sup>, 281[M+K]<sup>+</sup>. HRMS (ESI): Calcd for C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub> (M+H)<sup>+</sup> 243.1128. Found: 243.1130. Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>NaO<sub>2</sub> (M+Na)<sup>+</sup> 265.0947. Found: 265.0950.

**2-(*tert*-Butyl)chromeno[3,4-*d*]imidazol-4(3*H*)-one (4i).** 0.105 g, 86% (Method C, 150°C), 57 mg, 95% (Method D, 150°C), 54 mg, 45% (Method E, 2 h, 150°C), 51 mg, 84% (Method F, 150°C), pale yellow solid, m.p. 267–269°C (dec.) (ethanol). IR (KBr): 3262, 3188, 3059, 2966, 2930, 2908, 2866, 1733, 1711, 1623, 1554, 1496 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 13.43 (brs, 1H), 8.06 (d, *J* 6.2 Hz, 1H), 7.51 (t, *J* 7.6 Hz, 1H), 7.46 (d, *J* 8.3 Hz, 1H), 7.40 (t, *J* 7.4 Hz, 1H), 1.41 (s, 9H). <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): δ 159.1, 155.3, 151.8, 141.3, 129.3, 124.4, 122.2, 116.9, 116.0, 111.7, 33.5, 29.1. MS (ESI):  $m/z$  243[M+H]<sup>+</sup>, 265[M+Na]<sup>+</sup>, 281[M+K]<sup>+</sup>. HRMS (ESI): Calcd for C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub> (M+H)<sup>+</sup> 243.1128. Found: 243.1127. Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>NaO<sub>2</sub> (M+Na)<sup>+</sup> 265.0947. Found: 265.0946.

**2-(Methoxymethyl)chromeno[3,4-*d*]imidazol-4(3*H*)-one (4j).** Multicomponent mixture (Method C, 130°C), 26 mg, 45% (Method D, 130°C), 76 mg, 66% (Method E, 2 h, 130°C), multicomponent mixture (Method F, 130°C), white solid, m.p. 203–205°C (ethanol). IR (KBr): 3418, 3228, 3079, 2948, 2884, 2825, 1720, 1638, 1619, 1542, 1491 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 13.94 (brs, 1H), 8.06 (d, *J* 7.7 Hz, 1H), 7.54 (t, *J* 7.7 Hz, 1H), 7.49 (d, *J* 8.0 Hz, 1H), 7.42 (t, *J* 7.4 Hz, 1H), 4.63 (s, 2H), 3.38 (s, 3H). <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): δ 155.5, 154.0, 151.7, 142.6, 129.6, 124.5, 122.2, 117.0, 115.6, 114.2, 66.9, 58.1. MS (ESI):  $m/z$  231 [M+H]<sup>+</sup>, 253[M+Na]<sup>+</sup>, 269 [M+K]<sup>+</sup>. HRMS (ESI): Calcd for C<sub>12</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub> (M+H)<sup>+</sup> 231.0764. Found: 231.0764. Calcd for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>NaO<sub>3</sub> (M+Na)<sup>+</sup> 253.0584. Found: 253.0584.

**2-(Trifluoromethyl)chromeno[3,4-*d*]imidazol-4(3*H*)-one (4k).** 28 mg, 44% (Method B, 100°C), 0.109 g, 86% (Method C, 110°C), 61 mg, 96% (Method D, 100°C), 60 mg, 47% (Method E, 100°C), 59 mg, 93% (Method F, 1 h, 100°C), white solid, m.p. 289–290°C (ethanol). IR (KBr): 3303, 3078, 2965, 2898, 2835, 1712, 1636, 1583, 1542, 1508, 1482 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 7.95 (d, *J* 7.7 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.31 (t, *J* 7.0 Hz, 1H). <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): δ 157.3, 151.8, 147.6 (q, *J* 36.7 Hz), 145.0, 127.9, 125.6, 123.9, 121.8, 120.9 (q, *J* = 270.0 Hz), 117.7, 116.6. <sup>19</sup>F-NMR (DMSO-*d*<sub>6</sub>): -61.87. MS (ESI):  $m/z$  255[M+H]<sup>+</sup>. HRMS (ESI): Calcd for C<sub>11</sub>H<sub>6</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> (M+H)<sup>+</sup> 255.0376. Found: 255.0374. Calcd for C<sub>11</sub>H<sub>5</sub>F<sub>3</sub>N<sub>2</sub>NaO<sub>2</sub> (M+Na)<sup>+</sup> 277.0195. Found: 277.0194.

#### ***N*-(4-Amino-2-oxo-2*H*-chromen-3-yl)acetamide (6b); Typical procedures**

**Method B.** At 120°C for 2.5 h, 0.1 g, 92%; at 130°C, 68% (from the <sup>1</sup>H-NMR, mixture with **4b**).

**Method E.** At 120°C for 2 h, 99 mg, 91%; at 130°C for 2 h, 50 mg, 46%.

**6b.** 64 mg, 59% (Method A, 130°C for 2 h), white solid, m.p. 234–235°C (ethanol), lit.<sup>28</sup> 264–265.5°C (methanol). IR (KBr): 3426, 3347, 3228, 3075, 3029, 2870, 2814, 1682, 1646, 1607, 1561, 1504, 1441 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-

$\delta$  8.91 (bs, 1H), 8.07 (d,  $J$  7.7 Hz, 1H), 7.59 (t,  $J$  7.5 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.16 (bs, 2H), 1.99 (s, 3H).  $^{13}\text{C}$ -NMR (DMSO- $d_6$ ):  $\delta$  169.3, 159.5, 151.9, 150.2, 131.7, 123.5 (2C), 116.6, 114.66, 95.6, 40.2, 22.9. MS (ESI):  $m/z$  241  $[\text{M}+\text{Na}]^+$ , 257  $[\text{M}+\text{K}]^+$ .

***N*-(4-Amino-2-oxo-2H-chromen-3-yl)formamide (6al) / *N*-(3-amino-2-oxo-2H-chromen-4-yl)formamide (6all).**

**6al**, 7 mg, 7% (Method B, the yield counted from  $^1\text{H}$ -NMR spectrum), **6al/6all** (10/4), 95 mg, 93% (Method E, 30 min, 70°C), white solid, m.p. 264–268°C and 307–308°C (subl.) (ethanol). IR (KBr): 3401, 3350, 3228, 3071, 3013, 2896, 2760, 1690, 1650, 1606, 1558, 1510  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR (DMSO- $d_6$ ) (two isomers):  $\delta$  9.02 (brs, 1H, disappeared with  $\text{D}_2\text{O}$ ), 8.45 (d,  $J$  11.4 Hz, 0.4H), 8.16 (s, 1H), 8.10 (d,  $J$  8.4 Hz, 0.4H), 8.07 (d,  $J$  7.9 Hz, 1H), 7.94 (d,  $J$  11.5 Hz, 0.4H), 7.58–7.64 (m, 1.4H), 7.46 (brs, 0.8H, disappeared with  $\text{D}_2\text{O}$ ), 7.37 – 7.30 (m, 2.8H), 7.18 (brs, 2H, disappeared with  $\text{D}_2\text{O}$ ).  $^{13}\text{C}$ -NMR (DMSO- $d_6$ ) (two isomers):  $\delta$  166.4, 160.9, 160.7, 159.3, 151.84, 151.83, 149.8, 132.2, 131.9, 123.8, 123.6, 123.5, 116.8, 116.7, 114.3, 114.4, 94.8, 94.0. MS (ESI):  $m/z$  205  $[\text{M}+\text{H}]^+$ , 227  $[\text{M}+\text{Na}]^+$ , 243  $[\text{M}+\text{K}]^+$ . HRMS (ESI): Calcd for  $\text{C}_{10}\text{H}_8\text{N}_2\text{NaO}_3$  ( $\text{M}+\text{Na}$ ) $^+$  227.0427. Found: 227.0419.

***N*-(4-Amino-2-oxo-2H-chromen-3-yl)propionamide (6c).** 0.102 g, 88% (Method B), 0.105 g, 90% (Method E), white solid, m.p. 267–268°C (ethanol). IR (KBr): 3393, 3328, 3231, 3068, 3031, 2971, 2936, 2876, 1683, 1654, 1638, 1607, 1564, 1510  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR (DMSO- $d_6$ ):  $\delta$  8.63 (bs, 1H), 8.07 (d,  $J$  7.9 Hz, 1H), 7.59 (t,  $J$  7.7 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.04 (bs, 2H), 2.32 (q,  $J$  7.5 Hz, 2H), 1.06 (t,  $J$  7.5 Hz, 3H).  $^{13}\text{C}$ -NMR (DMSO- $d_6$ ):  $\delta$  173.0, 159.6, 151.9, 150.2, 131.7, 123.5, 123.5, 116.6, 114.6, 95.7, 28.3, 9.5. MS (ESI):  $m/z$  233  $[\text{M}+\text{H}]^+$ , 255  $[\text{M}+\text{Na}]^+$ , 271  $[\text{M}+\text{K}]^+$ . HRMS (ESI): Calcd for  $\text{C}_{12}\text{H}_{12}\text{N}_2\text{NaO}_3$  ( $\text{M}+\text{Na}$ ) $^+$  255.0740. Found: 255.0737.

***N*-(4-Amino-2-oxo-2H-chromen-3-yl)butyramide (6d).** 0.110 g, 89% (Method B), 0.110 g, 89% (Method E), white solid, m.p. 264–266°C (ethanol). IR (KBr): 3399, 3329, 3232, 3071, 3031, 2961, 2871, 1682, 1652, 1640, 1606, 1563, 1509  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR (DMSO- $d_6$ ):  $\delta$  8.65 (bs, 1H), 8.06 (d,  $J$  7.9 Hz, 1H), 7.59 (t,  $J$  7.8 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.02 (bs, 2H), 2.28 (t,  $J$  7.4 Hz, 2H), 1.64 – 1.55 (m, 2H), 0.94 (t,  $J$  7.3 Hz, 3H).  $^{13}\text{C}$ -NMR (DMSO- $d_6$ ):  $\delta$  172.3, 159.5, 151.9, 150.1, 131.7, 123.5, 123.5, 116.6, 114.6, 95.8, 37.3, 18.4, 13.8. MS (ESI):  $m/z$  247  $[\text{M}+\text{H}]^+$ , 269  $[\text{M}+\text{Na}]^+$ , 285  $[\text{M}+\text{K}]^+$ . HRMS (ESI): Calcd for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{NaO}_3$  ( $\text{M}+\text{Na}$ ) $^+$  269.0897. Found: 269.0892.

***N*-(4-Amino-2-oxo-2H-chromen-3-yl)pentanamide (6e).** 0.112 g, 86% (Method B), 0.116 g, 89% (Method E), white solid, m.p. 253–255°C (ethanol). IR (KBr): 3410, 3294, 3199, 3079, 3030, 2962, 2928, 2869, 1687, 1651, 1607, 1564, 1509  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR (DMSO- $d_6$ ):  $\delta$  8.65 (bs, 1H), 8.06 (d,  $J$  7.9 Hz, 1H), 7.59 (t,  $J$  7.8 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.01 (bs, 2H), 2.30 (t,  $J$  7.5 Hz, 2H), 1.60 – 1.52 (m, 2H), 1.39 – 1.31 (m, 2H), 0.90 (t,  $J$  7.3 Hz, 3H).  $^{13}\text{C}$ -NMR (DMSO- $d_6$ ):  $\delta$  172.3, 159.5, 151.9, 150.1, 131.7, 123.5, 123.5, 116.6, 114.6, 95.8, 35.0, 27.1, 21.9, 13.9. MS (ESI):  $m/z$  261  $[\text{M}+\text{H}]^+$ , 283  $[\text{M}+\text{Na}]^+$ , 299  $[\text{M}+\text{K}]^+$ . HRMS (ESI): Calcd for  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{NaO}_3$  ( $\text{M}+\text{Na}$ ) $^+$  283.1053. Found: 283.1053.

***N*-(4-Amino-2-oxo-2H-chromen-3-yl)octanamide (6f).** 0.121 g, 80% (Method B), 0.121 g, 80% (Method E), white solid, m.p. 240–242°C (ethanol). IR (KBr): 3390, 3341, 3231, 3074, 3030, 2956, 2925, 2855, 1747, 1684, 1651, 1605, 1562, 1506  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR (DMSO- $d_6$ ):  $\delta$  8.65 (bs, 1H), 8.07 (d,  $J$  7.9 Hz, 1H), 7.59 (t,  $J$  7.8 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.00 (bs, 2H), 2.30 (t,  $J$  7.5 Hz, 2H), 1.59 – 1.54 (m, 2H), 1.33 – 1.24 (m, 8H), 0.87 (t,  $J$  6.4 Hz, 3H).  $^{13}\text{C}$ -NMR (DMSO- $d_6$ ):  $\delta$  172.3, 159.5, 151.9, 150.1, 131.7, 123.5, 123.5, 116.6, 114.6, 95.8, 35.3, 31.2, 28.8, 28.6, 25.0, 22.01, 14.0. MS (ESI):  $m/z$  303  $[\text{M}+\text{H}]^+$ , 325  $[\text{M}+\text{Na}]^+$ , 341  $[\text{M}+\text{K}]^+$ . HRMS (ESI): Calcd for  $\text{C}_{17}\text{H}_{22}\text{N}_2\text{NaO}_3$  ( $\text{M}+\text{Na}$ ) $^+$  325.1523. Found: 325.1523.

***N*-(4-Amino-2-oxo-2H-chromen-3-yl)isobutyramide (6g).** 0.106 g, 86% (Method B), 0.109 g, 89% (Method E), white solid, m.p. 302–303°C (ethanol). IR (KBr): 3399, 3322, 3233, 3071, 3028, 2968, 2871, 1747, 1683, 1654, 1607, 1563, 1504  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR (DMSO- $d_6$ ):  $\delta$  8.61 (bs, 1H), 8.08 (d,  $J$  7.8 Hz, 1H), 7.59 (t,  $J$  7.7 Hz, 1H), 7.36 – 7.31 (m, 2H), 6.94 (bs, 2H), 2.66 – 2.58 (m, 1H), 1.11 (d,  $J$  6.8 Hz, 6H).  $^{13}\text{C}$ -NMR (DMSO- $d_6$ ):  $\delta$  176.4, 159.4,

151.8, 150.1, 131.7, 123.5, 123.5, 116.6, 114.6, 95.9, 34.0, 19.5. MS (ESI):  $m/z$  247 [M+H]<sup>+</sup>, 269 [M+Na]<sup>+</sup>, 285 [M+K]<sup>+</sup>. HRMS (ESI): Calcd for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>NaO<sub>3</sub> (M+Na)<sup>+</sup> 269.0897. Found: 269.0891.

**N-(4-Amino-2-oxo-2H-chromen-3-yl)-3-methylbutanamide (6h).** 0.110 g, 85% (Method B), 0.110 g, 85% (Method E), white solid, m.p. 266-268°C (ethanol). IR (KBr): 3407, 3303, 3232, 3071, 3031, 2958, 2868, 1747, 1689, 1653, 1607, 1563, 1509 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 8.65 (bs, 1H), 8.06 (d, *J* 7.7 Hz, 1H), 7.59 (t, *J* 7.7 Hz, 1H), 7.35 – 7.31 (m, 2H), 6.98 (bs, 2H), 2.18 (d, *J* 7.1 Hz, 2H), 2.10 – 2.01 (m, 1H), 0.96 (d, *J* 6.6 Hz, 6H).

<sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ 171.8, 159.4, 151.9, 150.0, 131.7, 123.5, 123.4, 116.6, 114.6, 95.9, 44.7, 25.5, 22.5. MS (ESI):  $m/z$  261 [M+H]<sup>+</sup>, 283 [M+Na]<sup>+</sup>, 299 [M+K]<sup>+</sup>. HRMS (ESI): Calcd for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>NaO<sub>3</sub> (M+Na)<sup>+</sup> 283.1053. Found: 283.1052.

**N-(4-Amino-2-oxo-2H-chromen-3-yl)pivalamide (6i).** 0.102 g, 77% (Method B), 0.110 g, 85% (Method E), yellow solid, m.p. >315°C (ethanol). IR (KBr): 3381, 3295, 3220, 3068, 2961, 2927, 2862, 1748, 1684, 1646, 1612, 1557, 1511 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 8.25 (brs, 1H), 8.10 (d, *J* 7.9 Hz, 1H), 7.60 (t, *J* 7.6 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.19 (brs, 1H), 6.82 (brs, 1H), 1.23 (s, 9H). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ 177.90, 159.30, 151.88, 150.14, 131.69, 123.52, 123.50, 116.61, 114.61, 96.39, 38.56, 27.43. MS (ESI):  $m/z$  261 [M+H]<sup>+</sup>, 283 [M+Na]<sup>+</sup>, 299 [M+K]<sup>+</sup>. HRMS (ESI): Calcd for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>NaO<sub>3</sub> (M+Na)<sup>+</sup> 283.1053. Found: 283.1048.

**N-(4-Amino-2-oxo-2H-chromen-3-yl)-2-methoxyacetamide (6j).** 0.117 g, 95% (Method B), 0.117 g, 95% (Method E), 41 mg, 33% (Method E, 130°C), white solid, m.p. 241-243°C (ethanol). IR (KBr): 3388, 3357, 3217, 3079, 3063, 3006, 2955, 2906, 2832, 1655, 1644, 1604, 1559, 1508 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 8.58 (brs, 1H), 8.07 (d, *J* 7.9 Hz, 1H), 7.61 (t, *J* 7.7 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.13 (brs, 2H), 3.99 (s, 2H), 3.40 (s, 3H). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ 169.3, 159.4, 151.9, 150.2, 131.9, 123.6, 123.5, 116.7, 114.6, 94.7, 71.6, 58.7. MS (ESI):  $m/z$  249 [M+H]<sup>+</sup>, 271 [M+Na]<sup>+</sup>, 287 [M+K]<sup>+</sup>. HRMS (ESI): Calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>NaO<sub>4</sub> (M+Na)<sup>+</sup> 271.0695. Found: 271.0689.

**N-(4-Amino-2-oxo-2H-chromen-3-yl)-2,2,2-trifluoroacetamide (6k).** 60 mg, 44% (Method B), 0.126 g, 93% (Method E), white solid, m.p. 271-273°C (ethanol). IR (KBr): 3322, 3240, 3202, 3077, 3035, 2949, 2883, 1711, 1651, 1607, 1564, 1520, 1505 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 10.17 (brs, 1H), 8.11 (d, *J* 7.9 Hz, 1H), 7.65 (t, *J* 7.8 Hz, 1H), 7.53 (brs, 2H), 7.41 – 7.35 (m, 2H). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ 158.5, 156.5 (q, *J* = 36.1 Hz), 152.0, 151.0, 132.5, 123.8, 123.6, 116.9, 116.0 (q, *J* 288.4 Hz), 114.1, 92.3. MS (ESI):  $m/z$  295 [M+Na]<sup>+</sup>, 311 [M+K]<sup>+</sup>. HRMS (ESI): Calcd for C<sub>11</sub>H<sub>7</sub>F<sub>3</sub>N<sub>2</sub>NaO<sub>3</sub> (M+Na)<sup>+</sup> 295.0301. Found: 295.0302.

**3-(2-Chloroethyl)-2-propylchromeno[3,4-d]imidazole-4(3H)-one (7).** Et<sub>3</sub>N (0.14 ml, 0.101 g, 1 mmol) was added to a mixture of 2-propylchromeno[3,4-d]imidazol-4(3H)-one (**4d**) (0.114 g, 0.5 mmol) in 1,2-dichloroethane (5 ml). The resulting solution was refluxed under Argon atmosphere for 24 h. After cooling the mixture was partitioned between ethyl acetate (20 ml) and water (20 ml). The organic layer was washed with water (2 x 20 ml), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and separated by column chromatography [silica gel, hexane/ethyl acetate (2:1)] to give from the faster moving band compound **7** (65 mg, 45% yield) [followed from the unchanged **4d** (57 mg, 50%)]. White solid, m.p. 155-157°C (ethanol). IR (KBr): 3028, 2953, 2925, 2871, 2854, 1721, 1624, 1590, 1515, cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 8.14 (d, *J* 7.7 Hz, 1H), 7.47 (t, *J* 7.6 Hz, 1H), 7.42 (d, *J* 8.1 Hz, 1H), 7.36 (t, *J* 7.4 Hz, 1H), 4.67 (t, *J* 5.7 Hz, 2H), 3.98 (t, *J* 5.7 Hz, 2H), 2.93 (t, *J* 7.8 Hz, 2H), 1.97 – 1.90 (m, 2H), 1.09 (t, *J* 7.4 Hz, 3H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 159.0, 155.1, 152.6, 147.5, 129.6, 124.75, 122.7, 117.2, 117.0, 115.8, 46.8, 43.6, 29.5, 21.6, 14.1. MS (ESI):  $m/z$  291/293[M+H]<sup>+</sup>, 345/347 [M+MeOH+Na]<sup>+</sup>. HRMS (ESI): Calcd for C<sub>15</sub>H<sub>15</sub>ClN<sub>2</sub>NaO<sub>2</sub> (M+Na)<sup>+</sup> 313.0714/315.0685. Found: 313.0717/315.0688.

**Inhibition of linoleic acid lipid peroxidation.**<sup>42</sup> Production of conjugated diene hydroperoxide by oxidation of linoleic acid sodium salt in an aqueous solution was monitored at 234 nm. 2,2'-Azobis(2-amidinopropane) dihydrochloride (AAPH) was used as a free radical initiator. 16 mM linoleic acid sodium salt solution and 0.05 M phosphate buffer, pH 7.4 prethermostated at 37 °C. The oxidation reaction was initiated at 37°C under air

by the addition of 40 mM AAPH solution in the presence of the examined compounds (diluted in DMSO). (Table 4). Trolox was used as a standard.

**Soybean lipoxygenase inhibition study in vitro.**<sup>42</sup> *In vitro* study was evaluated as reported previously. The tested compounds dissolved in DMSO were incubated at room temperature with sodium linoleate (0.1 mM) and 0.2 ml of enzyme solution ( $1/9 \times 10^{-4}$  w/v in saline). The conversion of sodium linoleate to 13-hydroperoxy-linoleic acid at 234 nm was recorded and compared with the appropriate standard inhibitor NDGA ( $IC_{50}$  0.5  $\mu$ M) (Table 4).

## Acknowledgements

We are grateful to Dr. Catherine Gabriel, Center for Research of the Structure of Matter, Magnetic Resonance Laboratory, Department of Chemical Engineering, Aristotle University of Thessaloniki, Thessaloniki, Greece for her help in the arrangement of obtaining HRMS spectra.

## Supplementary Material

Supplementary material is provided.

## References

1. Murray, D. H.; Mendez, J.; Brown, S. A. *"The Natural Coumarins: Occurrence, Chemistry and Biochemistry"*, J. Wiley & Sons: N. York, 1982.
2. O'Kennedy, R.; Thornes, R. D. *"Coumarins: Biology, Applications and Mode of Action"*, J. Wiley & Sons: Chichester, 1997.
3. Fylaktakidou, K. C.; Hadjipavlou-Litina, D. J.; Litinas, K. E.; Nicolaides, D. N. *Curr. Pharm. Design* **2004**, *10*, 3813.  
<https://doi.org/10.2174/1381612043382710>
4. Santana, L.; Uriarte, E.; Roleira, F.; Milhazes, N.; Borges, F. *Curr. Med. Chem.* **2004**, *1*, 3239.  
<https://doi.org/10.2174/0929867043363721>
5. Zhang, X.-S.; Li, Z.-W.; Shi, Z.-J. *Org. Chem. Front.* **2014**, *1*, 44.  
<https://doi.org/10.1039/C3QO00010A>
6. Shiraishi, Y.; Sumiya, S.; Hirai, T. *Org. Biomol. Chem.* **2010**, *8*, 1310.  
<https://doi.org/10.1039/B924015B>
7. Tsukamoto, K.; Shinohara, Y.; Iwasaki, S.; Maeda, H. *Chem. Commun.* **2011**, *47*, 5073.  
<https://doi.org/10.1039/C1CC10933B>
8. Eggenweiler, H. M.; Jonas, R.; Wolf, M.; Gassen, M.; Poschke, O. U.S. Patent 7 491 742, 2009.
9. Bergmann, J. E.; Cutshall, N. S.; Demopoulos, G. A.; Florio, V. A.; Gaitanaris, G. A.; Gray, P.; Hohmann, J.; Ourust, R.; Zeng, H. U.S. Patent 9 119 822, 2014.
10. Svajger, U.; Horvat, Z.; Knez, D.; Rozman, P.; Turk, S.; Gobec, S. *Med. Chem. Res.* **2015**, *24*, 362.  
<https://doi.org/10.1007/s00044-014-1127-5>

11. Savel'ev, V. L.; Pryanishnikova, N. T.; Zagorevskii, V. A.; Chernyakova, I. V.; Artamonova, O. S.; Shavyrina, V. V.; Malysheva, L. I. *Khim. Farm. Zh.* **1983**, *17*, 697; Engl. Transl. **1983**, *17*, 423.
12. Savel'ev, V. L.; Artamonova, O. S.; Zagorevskii, V. A. *Khim. Geterotsikl. Soedin.* **1972**, 1147. Engl. Transl. **1972**, 1038.
13. Beccalli, E. M.; Contini, A.; Trimarco, P. *Eur. J. Org. Chem.* **2003**, 3976.  
<https://doi.org/10.1002/ejoc.200300109>
14. Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Giusti, L.; Lucacchini, A. *Il Farmaco* **1998**, *53*, 375.  
[https://doi.org/10.1016/S0014-827X\(98\)00028-7](https://doi.org/10.1016/S0014-827X(98)00028-7)
15. Albaugh, P. U.S. Patent 5 182 290, 1993.
16. Stefanachi, A.; Favia, A. D.; Nicolotti, O.; Leonetti, F.; Pisani, L.; Catto, M.; Zimmer, C.; Hartmann, R. W.; Carotti, A. *J. Med. Chem.* **2011**, *54*, 1613.  
<https://doi.org/10.1021/jm101120u>
17. Zhang, L.; Peng, X.-M.; Damu, G. L. V.; Geng, R.-X.; Zhou, C.-H. *Med. Res. Rev.* **2014**, *34*, 340.  
<https://doi.org/10.1002/med.21290>
18. Parameshwar, R.; Sri Ranganath, Y.; Harinadha Babu V.; Sandeep, G. *Res. J. Pharm. Biol. Chem. Sci.* **2011**, *2*, 514.
19. Pangal, A. A.; Shaikh, J. A.; Khan, E. M. *In. J. Pharm. Sci. Rev. Res.* **2017**, *42*, 161.
20. Ombrato, R.; Garofalo, B.; Mangano, G.; Capezzone de Joannon, A.; Corso, G.; Cavarischia, C.; Furlotti, G.; Iacoangeli, T. U.S. Patent Appl. 0 369 450A1, 2017.
21. Medina, F. G.; Marrero, J. G.; Alonso, M. M.; González, M. C.; Córdova-Guerrero, I.; Teissier García, A. G.; Osegueda-Robles, S. *Nat. Prod. Rep.* **2015**, *32*, 1472.  
<https://doi.org/10.1039/C4NP00162A>
22. Tsay, S.-C.; Lin, S.-Y.; Huang, W.-C.; Hsu, M.-H.; Hwang, K. C.; Lin, C.-C.; Horng, J.-C.; Chen, I.-C.; Hwu, J. R.; Shieh, F.-K.; Leyssen, P.; Neyts, J. *Molecules* **2016**, *21*, 228.  
<https://doi.org/10.3390/molecules21020228>
23. Meng, T.; Zou, Y.; Khorev, O.; Jin, Y.; Zhou, H.; Zhang, Y.; Hu, D.; Ma, L.; Wang, X.; Shen, J. *Adv. Synth. Catal.* **2011**, 353, 918.  
<https://doi.org/10.1002/adsc.201000895>
24. Reddy, T. S.; Reddy, A. R. *Dyes Pigments*. **2013**, *96*, 525. DOI: 10.1016/j.dyepig.2012.08.021  
<https://doi.org/10.1016/j.dyepig.2012.08.021>
25. Alaqeel, S. A. *J. Saudi Chem. Soc.* **2017**, *21*, 229. DOI: 10.1016/j.jscs.2016.08.001  
<https://doi.org/10.1016/j.jscs.2016.08.001>
26. Trkovnik, M.; Kalaj, V.; Kitan, D. *Org. Prep. Proc. Int.* **1987**, *19*, 450.  
<https://doi.org/10.1080/00304948709356209>
27. Tabakovic, K.; Tabakovic, I. *Croat. Chem. Acta* **1981**, *54*, 451.
28. Savel'ev, V. L.; Artamonova, O. S.; Zagorevskii, V. A. *Khim. Farm. Zh.* **1976**, 316; Engl. Transl. **1976**, 268.
29. Pal, B.; Jaisankar, P.; Giri, V. S. *Synth. Commun.* **2004**, *34*, 1317.  
<https://doi.org/10.1081/SCC-120030322>
30. Humphrey, R. E.; McGrary, A. L.; Webb, R. M. *Talanta* **1965**, *12*, 727.  
[https://doi.org/10.1016/0039-9140\(65\)80108-4](https://doi.org/10.1016/0039-9140(65)80108-4)
31. EBellale, E. V.; Chaudhari, M. K.; Akamanchi, K. G. *Synthesis*, **2009**, 3211.  
<https://doi.org/10.1055/s-0029-1216955>
32. Erden, I.; Gartner, C.; Azimi, M. S. *Org. Lett.* **2009**, *11*, 3986.

- <https://doi.org/10.1021/ol901652u>
33. Carles, J.; Fliszar, S. *Can. J. Chem.* **1969**, 47, 1113.  
<https://doi.org/10.1139/v69-180>
34. Odum, R. A.; Brenner, M. *J. Am. Chem. Soc.* **1966**, 88, 2074.  
<https://doi.org/10.1021/ja00961a058>
35. Kaneko, C.; Yamamori, M.; Yamamoto, A.; Hayashi, R. *Tetrahedron Lett.* **1978**, 31, 2799.  
[https://doi.org/10.1016/S0040-4039\(01\)94866-X](https://doi.org/10.1016/S0040-4039(01)94866-X)
36. Mustafa, A. H.; Malakar, C. C.; Ajaar, N.; Merisor, E.; Conrad, J.; Beifuss, U. *Synlett* **2013**, 24, 1573.  
<https://doi.org/10.1055/s-0033-1339195>
37. Creencia, E. C.; Kosaka, M.; Muramatsu, T.; Kobayashi, M.; Oizuka, T.; Horaguchi, T. *J. Heterocyclic Chem.*, **2009**, 46, 1309.  
<https://doi.org/10.1002/jhet.267>
38. Sanz, R.; Escribano, J.; Pedrosa, M. R.; Aguado, R.; Arnaiz, F. J. *Adv. Synth. Catal.* **2007**, 349, 713.  
<https://doi.org/10.1002/adsc.200600384>
39. Dodd, J. H. "Polyphosphoric Acid", "Encyclopedia of Reagents for Organic Synthesis", John Wiley: New York, 2001.  
<https://doi.org/10.1002/047084289X.rp186>
40. Aksenov, A. V.; Amirnov, A. N.; Aksenov, N. A.; Bijieva, A. S.; Aksenova, I. V.; Rubin, M. *Org. Biomol. Chem.* **2015**, 13, 4289.  
<https://doi.org/10.1039/C5OB00131E>
41. Balalas, T. D. ; Stratidis, G. ; Papatheodorou, D. ; Vlachou, E.-E. ; Gabriel, C. ; Hadjipavlou-Litina, D. J. ; Litinas, K. E. *SynOpen* **2018**, 2, 105. DOI: 10.1055/s-0036-1591977  
<https://doi.org/10.1055/s-0036-1591977>
42. Balalas, T. ; Abdul-Sada, A. ; Hadjipavlou-Litina, D. J. ; Litinas, K. E. *Synthesis* **2017**, 2575.  
<https://doi.org/10.1055/s-0036-1588955>
43. Vronteli, A.; Hadjipavlou-Litina, D. J.; Konstantinidou, M.; Litinas, K. E. *Arkivoc* **2015**, (iii), 111.  
<https://doi.org/10.3998/ark.5550190.p009.004>
44. Goriya, Y.; Ramana, C. V. *Tetrahedron* **2010**, 66, 7642.  
<https://doi.org/10.1016/j.tet.2010.07.032>
45. Savel'ev, V. L.; Samsonova, O. L.; Troitskaya, V. S.; Vinokurov, V. G.; Lezina, V. P.; Smirnov, L. D. *Khim. Geterotsikl. Soedin.* **1988**, 977. Engl. Transl. **1989**, 805.
46. Radulovic, N. S.; Stojanovic-Radic, Z.; Stojanovic, P.; Stojanovic, N.; Dekic, V.; Dekic, B. *J. Serb. Chem. Soc.* **2015**, 80, 315.  
<https://doi.org/10.2298/JSC140619085R>
47. Iarosenko, V. O.; Mkrtchyan, S.; Gevorkyan, A.; Vilches-Herrera, M.; Sevenard, D. V.; Villinger, A.; Ghochikyan, T. V.; Saghiyan, A.; Sosnovskikh, V. Y.; Langer, P. *Tetrahedron* **2012**, 68, 253  
<https://doi.org/10.1016/j.tet.2011.06.101>
48. VanVliet, D. S.; Gillespie, P.; Scicinski, J. J. *Tetrahedron Lett.* **2005**, 46, 6741. DOI: 10.1016/j.tetlet.2005.07.130  
<https://doi.org/10.1016/j.tetlet.2005.07.130>
49. Brash, A. R. *J. Biol. Chem.* **1999**, 274, 23679. DOI: 10.1074/jbc.274.34.23679  
<https://doi.org/10.1074/jbc.274.34.23679>