

# One-pot synthesis of 5*H*-chromeno[3,4-*b*]pyrazin-5-one derivatives from 4amino-3-nitrocoumarin and α-dicarbonyl compounds

Matina D. Douka and Konstantinos E. Litinas<sup>\*</sup>

Laboratory of Organic Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece Email: <u>klitinas@chem.auth.gr</u>

- • • •		-		~~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~		
Received 11	1-27-2020	Accer	oted	03-17-2021	Published on line	()4-11-2(
ILCCCIVCA II	1 27 2020			05 17 2021		07 11 2

#### Abstract

2,3-Disubstituted [3,4]-fused pyrazinocoumarins have been synthesized in very good yields by the one-pot reaction of 4-amino-3-nitrocoumarin with  $\alpha$ -dicarbonyl compounds in the presence of PPh<sub>3</sub> in *n*-pentanol under microwave irradiation. The reactions of 3,4-diaminocoumarin with  $\alpha$ -dicarbonyl compounds in *o*-xylene under microwaves led also to the title compounds in excellent total yields.



**Keywords**: Pyrazino[2,3-*c*]coumarins, 3,4-diaminocoumarin, 4-amino-3-nitrocoumarin, microwave irradiation, Cadogan reaction.

#### Introduction

Coumarins are compounds widely distributed in nature displaying a variety of biological activities, such as anticoagulant, antibiotic, anti-inflammatory, anti-HIV, antidiabetic, and anticancer properties.<sup>1-8</sup> Coumarins fused with aza-heterocycles are also biologically active. Especially, santiagonamine (I) is a natural product with wound-healing properties;<sup>9</sup> pyridocoumarin II present weak mutagenic activity;<sup>10</sup> lamellarin D (III) is a potent inhibitor of DNA topoisomerase I;<sup>11</sup> 1-phenyl-2-propylchromeno[3,4-*d*]imidazol-4(1*H*)-one (IV) present anti-inflammatory activity.<sup>12</sup> The pyrazinopsoralen (V) has been synthesized as a monofunctional psoralen expected to induce less photogenotoxicity than the bifunctional psoralen.<sup>13-15</sup>

There is just one synthesis of the fused pyrazinocoumarins, like **V**, known in the literature. The Suzuki coupling of (2-methoxyphenyl)boronic acid with methyl 3-iodopyrazin-2-carboxylate followed by hydrolysis and cyclization of the initially formed methyl 3-(2-methoxyphenyl)pyrazin-2-carboxylate led to the formation of 5*H*-chromeno[3,4-*b*]pyrazin-5-ones.<sup>14</sup> An *N*-analogue, the 2,3-dimethylpyrazino[2,3-c]quinoline-5(6*H*)-one, has been prepared by the condensation of 3,4-diaminoquinolin-2(1*H*)-one with diacetyl.<sup>16</sup>



Figure 1. Biologically active coumarins fused with aza-herecocycles.

Generally, the synthesis of pyrazines has been achieved through self-condensation of  $\alpha$ -aminoketones<sup>17</sup> or through intramolecular hydroamination/isomerization/ aromatization sequence of *N*-Boc-protected 2- (propargylamin)acetaldehyde oximes in the presence of catalytic amount of p-toluenesulfonic acid under microwave irradiation<sup>18</sup> or by the reactions of propargylamine with aldehydes in the presence of (Ph<sub>3</sub>P)AuNTf<sub>2</sub> as a catalyst.<sup>19</sup> The synthesis of fused benzopyrazine has been performed by the condensation of glyoxal with *o*-phenylenediamine under reflux,<sup>20</sup> while substituted benzopyrazines have been received through condensation of benzil derivatives with *o*-phenylenediamines in the presence of 2-iodoxybenzoic acid (IBX).<sup>21</sup>

Triphenylphosphine (PPh<sub>3</sub>) is a useful reagent for the reduction of nitrogen containing compounds like azides<sup>22</sup> (Staudinger reaction), nitroso compounds<sup>23</sup> and *N*-oxides.<sup>24</sup> In the Cadogan-type reaction the reduction of nitro compounds followed by reductive cyclization led also to indoles, carbazoles, benzimidazoles and benzopyrazoles.<sup>25-27</sup> Recently, we performed the one-pot synthesis of fused oxazolocoumarins and imidazolocoumarins from *o*-hydroxynitrocoumarin or *o*-aminonitrocoumarin, respectively, using the PPh<sub>3</sub> as reducing agent in the presence of carboxylic acids.<sup>28,29</sup> We envisioned that this reaction could also work for the one-pot synthesis of pyrazolocoumarins from 4-amino-3-nitrocoumarin and  $\alpha$ -dicarbonyl compounds. Herein, we present our investigations towards this goal.

#### **Results and Discussion**

The studied reactions and the products obtained are depicted in Scheme 1. The starting 4-amino-3nitrocoumarin (1) was prepared from 4-chloro-3-nitrocoumarin,<sup>30</sup> according to our recent modification,<sup>29</sup> by the treatment with 7M methanolic solution of NH<sub>3</sub>. We select glyoxal (2a) as a model substrate to test the suitable conditions for the application of the one-pot tandem reaction of 1 with  $\alpha$ -dicarbonyl compounds. The reaction of 1 with 2a in the presence of PPh<sub>3</sub> (3), using *o*-xylene as solvent under microwave irradiation at 130 °C for 15 h resulted to 5*H*-chromeno[3,4-*b*]pyrazin-5-one (4a) in low yield (Table 1, entry 1). Changing the solvent to *n*-butanol, a protic solvent, at 140 °C for 10 h the yield of the reaction increased to 34%, with 60% of the starting compound to remain unchanged (Table 1, entry 2). The use of *n*-pentanol (Method A) at higher temperature (170°C) under microwave irradiation for 8 h led to 4a in 66% yield (Table 1, entry 3). In consequence, we applied this method for the one-pot synthesis of [3,4]-fused pyrazinocoumarins 4 and 5 from 4-amino-3-nitrocoumarin (1) and  $\alpha$ -dicarbonyl compounds 2a-h.

The reactions of **1** with methylglyoxal (**2b**) or phenylglyoxal (**2c**) at 170 °C for 6 or 7 h led to the fused pyrazinocoumarins **4b** and **5b** or **4c** and **5c**, respectively (Table 3, entries 4 or 5). The higher yields of the products **4b** and **4c**, in comparison to their isomers **5b** and **5c**, reveals the increased reactivity of formyl group to acetyl or benzoyl group.<sup>31</sup> As the 4-amino group of coumarin of the intermediate 3,4-diaminocoumarin has less nucleophilic character due to the conjugation with the carbonyl of coumarin,<sup>32,33</sup> the 3-amino group reacted first with the formyl group followed by the condensation of 4-amino group with the acetyl or benzoyl group. HMBC experiments for the above products confirmed the proposed structures of those isomers, as pyrazine protons H-3 of **4b** and **4c** show interaction with the C-3 (C-4a) of the coumarin ring (Supplementary Information, S6, S13).

The similar reaction of **1** with diacetyl (**2d**) for 5 h gave the 2,3-dimethyl-5*H*-chromeno[3,4-*b*]pyrazin-5-one (**4d**) in 84% yield (Table 1, entry 6), while the reaction of **1** with benzil (**2e**) led to the 2,3-diphenyl-5*H*-chromeno[3,4-*b*]pyrazin-5-one (**4f**) and 2-methyl-3-phenyl-5*H*-chromeno[3,4-*b*]pyrazin-5-one (**5f**) were isolated (48% and 27% yields, respectively) from the reaction of **1** with 1-phenylpropane-1,2-dione (**2f**) (Table 1, entry 8). The above regioselectivity follows the reactivity of **2f**, which upon treatment with hydroxylamine hydrochloride in the presence of sodium carbonate gave 2-(hydroxyimino)-1-phenylpropan-1-one.<sup>34</sup> HMBC experiments for **4f** and **5f** revealed the proposed structures, as there are interactions between the protons of 3-methyl (C-3-methyl) with the C-3 carbon (C-4a) of the coumarin ring and the protons of 2-methyl (C-2-methyl) with the C-4 carbon (C-10b) of coumarin ring, respectively (Supplementary Information, S22, S25). The analogous reaction of **1** with **2g** for 10 h at 170 °C led to a tar material containing a small amount of expected **4g** and **5g**. There was a little increase in the yields of the products, when this reaction performed at 150 °C for 20 h (Table 1, entries 9,10). The use of *n*-butanol at 140 °C gave better results for those products (Table 1, entry 11). The reaction of **1** with 1*H*-indene-1,2(3*H*)-dione (**2h**) in the presence of triphenylphosphine (**3**) resulted to a tar material. The expected products **4h** and **5h** were not detected in the above mixture (Table 1, entry 12).



Scheme 1. *Reagents and conditions*: (*i*) Method A: 2a-h (1.1 equiv.), PPh<sub>3</sub> (3) (3.5 equiv.), *n*-pentanol, MW irradiation, 170 °C (8 h for 4a, 6 h for 4b, 5b, 7 h for 4c, 5c, 5 h for 4d, 4f, 5f, 5.5 h for 4e, 20 h at 150 °C for 4g, 5g); (*ii*) 5% Pd/C, H<sub>2</sub>, 1 atm, MeOH, r.t., 45 min; (*iii*) Method B: 2a-h (1.1 equiv.), *o*-xylene, MW, 120 °C, 10-20 min (2 h, 150°C for 4e).

In parallel, we examined also the transformations of 3,4-diaminocoumarin (6) (prepared in 95% yield by the treatment of 1 with Pd/C in methanol under H<sub>2</sub> atmosphere at room temperature for 45 min)<sup>29</sup> to the [3,4]-fused pyrazinocoumarins 4 and 5 by the treatment of 6 with the  $\alpha$ -dicarbonyl compounds 2 in o-xylene under microwave irradiation (Method B) (Scheme 1). The reaction of 6 with glyoxal (2a) at 120 °C for 10 min resulted to 4a in 77% yield (Table 1, entry 13). The reactions of 6 with 2b or 2c at 120 °C for 15 or 10 min led to the products 4b and 5b or 4c and 5c, respectively (Table 3, entries 14 or 15). The isomers 4b and 4c were formed in higher yields, in comparison to Method A. The reaction of 6 with diacetyl (2d) for 15 min gave 4d (71% yield) (Table 1, entry 16), while the similar reaction with benzil (2e) for 2 h at 150°C led to 4e (76% yield) (Table 1, entry 17). The reactions of 6 with 1-phenylpropan-1,2-dione (2f) or 1-(4-nitrophenyl)propan-1,2-dione (2g) for 15 or 20 min resulted to the regioisomers 4f and 5f or 4g and 5g, respectively in excellent total yields (Table 1, entries 18, 19). HMBC experiments for 4g and 5g supported the proposed structures, as there are interactions between the protons of 3-methyl (C-3-methyl) with the C-3 carbon (C-4a) of the coumarin ring and the protons of 2-methyl (C-2-methyl) with the C-4 carbon (C-10b) of coumarin ring, respectively (Supplementary Information, S28, S31). The regioisomers **4h** and **5h** were obtained also by the reaction of **6** with indene-1,2dione (2h) (Table 1, entry 20). The regioselectivity of the above reaction seems to follow the regioselectivities of compounds 2f and 2g. HMBC experiments for 4h and 5h supported the proposed structure, as there are interactions between the protons (H-8) of methylene group with the C-3 carbon (C-6a) of coumarin ring and the protons (H-12) of methylene group with the C-2 carbon (C-13a) of coumarin ring, respectively (Supplementary Information, S34, S37).

Entry	Starting	α-Dicarbonyl	<b>Conditions</b> <sup>a</sup>	Time	T (°C) / <i>P</i> (W)	Yields (%)
	coumarin	compounds <b>2a-h</b>				
1	1	<b>2a</b> (R <sup>1</sup> =R <sup>2</sup> =H)	<i>o</i> -xylene, PPh₃	15 h	130/100	<b>4a</b> (18) <i>,</i> <b>1</b> (75)
2	1	2a	<i>n</i> -butanol, PPh₃	10 h	140/80	<b>4a</b> (34) <i>,</i> <b>1</b> (60)
3	1	2a	Method A	8 h	170/150	<b>4a</b> (66) <i>,</i>
4	1	<b>2b</b> (R <sup>1</sup> =Me, R <sup>2</sup> =H)	Method A	6 h	170/150	<b>4b</b> (62) <i>,</i> <b>5b</b> (8)
5	1	<b>2c</b> (R <sup>1</sup> =Ph, R <sup>2</sup> =H)	Method A	7 h	170/150	<b>4c</b> (70), <b>5c</b> (15)
6	1	<b>2d</b> (R <sup>1</sup> =R <sup>2</sup> =Me)	Method A	5 h	170/150	<b>4d</b> (84)
7	1	<b>2e</b> (R <sup>1</sup> =R <sup>2</sup> =Ph)	Method A	5.5 h	170/150	<b>4e</b> (57)
8	1	<b>2f</b> (R <sup>1</sup> =Ph, R <sup>2</sup> =Me)	Method A	5 h	170/150	<b>4f</b> (48) <i>,</i> <b>5f</b> (27)
9	1	<b>2g</b> (R <sup>1</sup> = <i>p</i> -NO <sub>2</sub> -	Method A	10 h	170/150	<b>4g</b> (8), <b>5g</b> (3)
		C <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> =Me)				
10	1	2g	Method A	20 h	150/140	<b>4g</b> (15), <b>5g</b> (5)
11	1	2g	<i>n</i> -butanol, PPh₃	6h	140/80	<b>4g</b> (24), <b>5g</b> (22)
12	1	<b>2h</b> (R <sup>1</sup> -R <sup>2</sup> = <i>o</i> -C <sub>6</sub> H <sub>4</sub> -	Method A	15 h	150 <sup>b</sup> /140	-
		CH2-)				
13	6	2a	Method B	10 min	120/70	<b>4a</b> (77)
14	6	2b	Method B	15 min	120/70	<b>4b</b> (79) <i>,</i> <b>5b</b> (8)
15	6	2c	Method B	10 min	120/70	<b>4c</b> (88), <b>5c</b> (2)
16	6	2d	Method B	15 min	120/70	<b>4d</b> (71)
17	6	2e	Method B	2 h	150/90	<b>4e</b> (76)
18	6	2f	Method B	15 min	120/70	<b>4f</b> (65) <i>,</i> <b>5f</b> (32)
19	6	2g	Method B	20 min	120/70	<b>4g</b> (74), <b>5g</b> (18)
20	6	2h	Method B	20 min	120/70	<b>4h</b> (54) <i>,</i> <b>5h</b> (32)

**Table 1.** Synthesis of pyrazino[2,3-*c*]coumarins **4a-h**, **5b,c,g,f,h** from  $\alpha$ -dicarbonyl compounds **2** and 4-amino-3-nitrocoumarin (**1**) or 3,4-diaminocoumarin (**6**)

<sup>a</sup> Method A: 1 (1 equiv.), 2a-h (1.1 equiv.), PPh<sub>3</sub> (3.5 equiv.), *n*-pentanol, MW irradiation;

Method B: 1 (1 equiv.), 2a-h (1.1 equiv.), o-xylene, MW.

<sup>b</sup> 8 h at 170 °C gave, also, no results.

As we observed above, **Method B** is better than **Method A**. Generally (except for the case of **4d**), the synthesis of fused pyrazinocoumarin derivatives by the condensation of 3,4-diaminocoumarin (**6**) (prepared before from **1**) with  $\alpha$ -dicarbonyl compounds **2a-h** (**Method B**) was achieved in very good to excellent total yields in less reaction time. The one-pot synthesis of those derivatives (**Method A**) led to the products in moderate to good yields by spending enough time for the completion of the reactions. In order to explain the one-pot synthesis of the products, we could assume that PPh<sub>3</sub> (**3**), as a modification of Cadogan reaction, was added to the nitro-group of 4-amino-3-nitrocoumarin (**1**) and by abstraction of Ph<sub>3</sub>PO gave as intermediate the 4-amino-3-nitrosocoumarin (**A**) (Scheme 2), in analogy to the reductive cyclization of 2-nitrobiphenyls to carbazoles in the presence of **3**.<sup>35</sup> New addition of **3** to the nitroso-group of **A** resulted possibly, to the nitrene **B**, after removing of Ph<sub>3</sub>PO. Hydrogenation of **B** by the acidic proton of the present alcohol led to the 3,4-diaminocoumarin (**6**), as it has been checked by the TLC of a blanc experiment, without the presence of glyoxal (**2a**). Pyrazinocoumarin **4a** was synthesized by the condensation of **6** with the **2a**.



Scheme 2. Proposed mechanism for the one-pot reaction of 1 with 2a in the presence of PPh<sub>3</sub>.

## Conclusions

In conclusion, 2- or/and 3-substituted [3,4]-fused pyrazinocoumarins were synthesized in very good to excellent yields by the reactions of 3,4-diaminocoumarin with  $\alpha$ -dicarbonyl compounds under microwave irradiation for a short time. The one-pot reaction of 4-amino-3-nitrocoumarin with  $\alpha$ -dicarbonyl compounds in the presence of PPh<sub>3</sub> under microwaves in *n*-pentanol led also to the title compounds in moderate to very good yields, but under longer reaction time and higher temperature. Most of the synthesized derivatives are 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 a Agilent 500/54 (DD2) (500 MHz and 125 MHz for <sup>1</sup>H and <sup>13</sup>C respectively) or on a Agilent AM600 (600 MHz and 150 MHz for <sup>1</sup>H and <sup>13</sup>C respectively) using CDCl<sub>3</sub> 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 Agilent Q-TOF Mass Spectrometer, G6540B model with Dual AJS

ESI-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-2*H*-chromen-2-one (**1**) and 3,4-diamino-2*H*-chromen-2-one (**6**) were prepared according to our recent publication.<sup>29</sup>

## 5*H*-Chromeno[3,4-*b*]pyrazin-5-one (4a); Typical Procedures

**Method A.** 4-Amino-3-nitrocoumarin (1) (40 mg, 0.19 mmol), triphenylphosphine (3) (0.174 g, 0.66 mmol), glyoxal (2a) (12.5 mg, 0.21 mmol, from 0.025 mL 40% solution in petroleum spirit) and *n*-pentanol (1.5 mL) were mixed in a flask for MW oven. The mixture was irradiated at 170 °C for 8 h. After cooling, the resulted mixture was evaporated and separated by column chromatography [silica gel, hexane/ethyl acetate (6:1) to ethyl acetate/MeOH (7:1)] to give compound **4a** (25 mg, 66%). Beige solid, mp 180-182 °C (methanol/ethyl ether), lit.<sup>14</sup> 174-175 °C. IR (KBr): 3071, 1756, 1612, 1538 cm<sup>-1</sup>. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  9.01 (d, *J* 1.4 Hz, 1H, H-2), 8.92 (d, *J* 1.5 Hz, 1H, H-3), 8.56 (d, *J* 7,4 Hz, 1H, H-10), 7.67 (dd, *J*<sub>1</sub> 7.4 Hz, *J*<sub>2</sub> 8.3 Hz, 1H, H-8), 7.46 (t, *J* 7,5 Hz, 1H, H-9), 7.45 (d, *J* 8.3 Hz, 1H, H-7).<sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  159.0 (C-5), 152.4 (C-6a), 149.8 (C-2), 148.4 (C-10b), 146.1 (C-3), 134.0 (C-4a), 133.3 (C-8), 125.3 (C-9), 125.1 (C-10), 118.2 (C-10a), 117.5 (C-7) ppm. MS (ESI): *m/z* 199 [M+H]<sup>+</sup>, 221 [M+Na]<sup>+</sup>. HRMS: Calcd for C<sub>11</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>, [M+H]<sup>+</sup>: 199.0507. Found: 199.0511, [M+Na]<sup>+</sup>: 221.0327. Found: 221.0326.

*o*-Xylene as solvent. 4-Amino-3-nitrocoumarin (1) (40 mg, 0.19 mmol), triphenylphosphine (3) (0.174 g, 0.66 mmol), glyoxal (2a) (12.5 mg, 0.21 mmol, from 0.025 ml 40% solution in petroleum spirit) and *o*-xylene (1.5 mL) were mixed in a flask for MW oven. The mixture was irradiated at 130 °C for 15 h (no more changes as checked by TLC). After cooling, the resulted mixture was separated as above to give unreacted material 1 (30 mg, 75%) and compound 4a (7 mg, 18%).

*n*-Butanol as solvent. 4-Amino-3-nitrocoumarin (1) (40 mg, 0.19 mmol), triphenylphosphine (3) (0.174 g, 0.66 mmol), glyoxal (2a) (12.5 mg, 0.21 mmol, from 0.025 mL 40% solution in petroleum spirit) and *n*-butanol (1.5 mL) were mixed in a flask for MW oven. The mixture was irradiated at 140 °C for 10 h (no more changes as checked by TLC). After cooling, the resulted mixture was separated as above to give unreacted material 1 (24 mg, 60%) and compound 4a (13 mg, 34%).

**Method B**. In a flask for MW oven were placed 3,4-diaminocoumarin (6) (88 mg, 0.5 mmol), glyoxal (2a) (32 mg, 0.55 mmol, from 0.063 mL 40% solution in petroleum spirit) and *o*-xylene (1.5 mL) and irradiated at 120 °C for 10 min. After cooling, a solid was precipitated, filtered and washed by petroleum spirit (2 x 2 mL) and dried under vacuum to give **4a** (76 mg, 77%).

The separation of regioisomers, following Method B, was achieved in the special cases of **4b**, **5b**, 4c, **5c**, **4f**, **5f**, **4g**, **5g**, **4h**, **5h** by column chromatography [silica gel, hexane/ethyl acetate (6:1) to ethyl acetate/MeOH (7:1)], where the isomers **4** were received first followed by isomers **5**.

**2-Methyl-5***H***-chromeno[3,4-***b***]pyrazin-5-one (4b).** 25 mg, 62% (Method A), 84 mg, 79% (Method B), pearl-white solid, mp 246-248 °C (methanol/ethyl ether). IR (KBr): 3070, 2890, 1752, 1611, 1543 cm<sup>-1</sup>. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.73 (s, 1H, H, H-3), 8.51 (dd, *J*<sub>1</sub> 1.3 Hz, *J*<sub>2</sub> 8.1 Hz, 1H, H-10), 7.62 (dd, *J*<sub>1</sub> 1.3 Hz, *J*<sub>2</sub> 8.1 Hz, 1H, H-8), 7.40 (dd, *J*<sub>1</sub> 1.3 Hz, *J*<sub>2</sub> 8.1 Hz, 1H, H-9), 7.39 (d, *J* 8.1 Hz, 1H, H-7), 2.79 (s, 3H). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 160.5 (C-2), 159.3 (C-5), 152.4 (C-6a), 147.2 (C-3), 146.4 (C-10b), 132.9 (C-8), 131.2 (C-4a), 125.0 (C-9), 124.9 (C-10), 118.2 (C-10a), 117.3 (C-7), 22.7 ppm. MS (ESI): *m/z* 213 [M+H]<sup>+</sup>. HRMS: Calcd for C<sub>12</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>, [M+H]<sup>+</sup>: 213.0664. Found: 213.0664, [M+Na]<sup>+</sup>: 235.0484. Found: 235.0485.

**3-Methyl-5***H***-chromeno[3,4-***b***]pyrazin-5-one (5b).** 3 mg, 8% (Method A, the yield counted from <sup>1</sup>H-NMR spectrum), 8.5 mg, 8% (Method B, the yield counted from <sup>1</sup>H-NMR spectrum), beige solid, mp 178-181°C (hexane/ethyl acetate), lit.<sup>36</sup> 182-184 °C (chloroform). IR (KBr): 3034,2923, 2852, 1752, 1612 cm<sup>-1</sup>. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.87 (s, 1H, H-2), 8.52 (d, *J* 8.1 Hz, 1H, H-10), 7.60 (t, *J* 8.1 Hz, 1H, H-8), 7.37 (t, *J* 8.1 Hz, 1H,

H-9), 7.36 (d, *J* 8.1 Hz, 1H, H-7), 2.82 (s, 3H). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 159.5 (C-5), 156.2 (C-3), 151.9 (C-6a), 150.4 (C-2), 146.4 (C-10b), 132.7 (C-8), 130.9 (C-4a), 125.3 (C-9), 124.7 (C-10), 118.4(C-10a), 117.4 (C-7), 22.1 ppm. MS (ESI): *m/z* 213 [M+H]<sup>+</sup>. HRMS: Calcd for C<sub>12</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>, [M+Na]<sup>+</sup>: 235.0484. Found: 235.0485.

**2-Phenyl-5***H***-chromeno[3,4-***b***]pyrazin-5-one (4c).** 36 mg, 70% (Method A), 0.121 g, 88% (Method B), white solid, mp 268-270 °C (dec.) (hexane/ethyl acetate). IR (KBr): 3056, 1747, 1613, 1530 cm<sup>-1</sup>. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  9.34 (s, 1H, H-3), 8.70 (dd,  $J_1$  1.5 Hz,  $J_2$  7.8 Hz, 1H, H-10), 8.30-8.28 (m, 2H), 7.67 (dt,  $J_1$  1.5 Hz,  $J_2$  7.8 Hz, 1H, H-8), 7.64-7.60 (m, 3H), 7.47 (t, *J* 7.8 Hz, 1H, H-9), 7.45 (d, *J* 7.8 Hz, 1H, H-7). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  159.2 (C-5), 156.7 (C-2), 152.7 (C-6a), 147.5 (C-10b), 143.4 (C-3), 135.0 (C-4a), 133.2 (C-8), 132.0 (C-2'), 131.8 (C-1'), 129.5 (C-4'), 128.1 (C-3'), 125.2 (C-9), 125.1 (C-10), 118.5 (C-10a), 117.5 (C-7) ppm. MS (ESI): *m/z* 275 [M+H]<sup>+</sup>, 297 [M+Na]<sup>+</sup>. HRMS: Calcd for C<sub>17</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>, [M+H]<sup>+</sup>: 275.0820. Found: 275.0820, [M+Na]<sup>+</sup>: 297.0640. Found: 297.0642.

**3-Phenyl-5***H***-chromeno[3,4-***b***]pyrazin-5-one (5c).** 8 mg, 15% (Method A), 3 mg, 2% (Method B), light yellow solid, mp 183-185 °C (hexane/ethyl acetate). IR (KBr): 3022, 1750, 1608 cm<sup>-1</sup>. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ 9.44 (s, 1H, H-2), 8.56 (d, *J* 8.4 Hz, 1H, H-10), 8.22 (d, *J* 6,5 Hz, 2H, H-2'), 7.64 (t, *J* 7.6 Hz, 1H, H-8), 7.57-7.54 (m, 3H), 7.47-7.44 (m, 2H, H-7, H-9). <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): δ δ 159.4 (C-5), 153.8 (C-3), 152.2 (C-6a), 147.3, 146.2, 134.9, 133.0, 132.9, 131.1, 129.3, 127.5, 125.3 (C-9), 124.9 (C-10), 118.3 (C-10a), 117.4 (C-7) ppm. MS (ESI): *m/z* 275 [M+H]<sup>+</sup>. HRMS: Calcd for C<sub>17</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>, [M+Na]<sup>+</sup>: 297.0640. Found: 297.0642.

**2,3-Dimethyl-5***H***-chromeno[3,4-***b***]pyrazin-5-one (4d).** 36 mg, % (Method A), 80 mg, 71% (Method B), white solid, mp 239-241 °C (hexane/dichloromethane). IR (KBr): 3065, 2949, 2914, 1742, 1610, 1549 cm<sup>-1</sup>. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.50 (d, *J* 8.3 Hz, 1H, H-10), 7.58 (t, *J* 8.3 Hz, 1H, H-8), 7.39 (t, *J* 8.3 Hz, 1H, H-9), 7.37 (d, *J* 8.3 Hz, 1H, H-7), 2.77 (s, 3H, H-3'), 2.76 (s, 3H, H-2'). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 159.9 (C-2), 159.8 (C-5), 155.3 (C-3), 152.1 (C-6a), 145.3 (C-10b), 132.3 (C-8), 130.7 (C-4a), 124.9 (C-9), 124.6 (C-10), 118.5 (C-10a), 117.2 (C-7), 23.3 (C-1''), 22.6 (C-1') ppm. MS (ESI): *m/z* 227 [M+H]<sup>+</sup>. HRMS: Calcd for C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>, [M+H]<sup>+</sup>: 227.0820. Found: 227.0818, [M+Na]<sup>+</sup>: 249.0640. Found: 249.0638.

**2,3-Diphenyl-5***H***-chromeno[3,4-***b***]pyrazin-5-one (4e).** 38 mg, 57% (Method A), 0.133 g, 76% (Method B), light yellow solid, mp 203-205 °C (dichloromethane/hexane). IR (KBr): 3056, 1746, 1607, 1541, 1525 cm<sup>-1</sup>. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.64 (dd, *J*<sub>1</sub> 1.3 Hz, *J*<sub>2</sub> 8.1 Hz, 1H, H-10), 7.67-7.63 (m, 3H), 7.59 (d, *J* 7.4 Hz, 2H), 7.48-7.42 (m, 3H), 7.41-7.36 (m, 3H), 7.36-7.29 (m, 2H, H-7, H-8). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 159.2 (C-5), 157.8, 154.6, 152.5 (C-6a), 145.3 (C-10b), 137.6, 137.4, 132.8, 130.9, 130.2, 130.1, 139.9, 129.5, 128.5 (2C), 125.1 (C-9), 125.0 (C-10), 118.3 (C-10a), 117.3 (C-7) ppm. MS (ESI): *m/z* 351 [M+H]<sup>+</sup>. HRMS: Calcd for C<sub>23</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>, [M+H]<sup>+</sup>: 351.1133. Found: 351.1128, [M+Na]<sup>+</sup>: 373.0953. Found: 373.0948.

**3-Methyl-2-phenyl-5***H***-chromeno[3,4-***b***]pyrazin-5-one (4f).** 26 mg, 48% (Method A), 94 mg, 65% (Method B), light yellow solid, mp 200-202 °C (hexane/ethyl acetate). IR (KBr): 3050, 2946, 2915, 1745, 1612, 1595, 1531 cm<sup>-1</sup>. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.59 (d, *J* 8.4 Hz, 1H, H-10), 7.70 (d, *J* 6.4 Hz, 2H, H-2'), 7.63 (t, *J* 8.4 Hz, 1H, H-8), 7.55-7.48 (m, 3H, H-3', H-4'), 7.44 (t, *J* 8.4 Hz, 1H, H-9), 7.43 (d, *J* 8.4 Hz, 1H, H-7), 2.87 (s, 3H, H-1''). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 159.5 (C-5), 158.9 (C-3), 156.0 (C-2), 152.5 (C-6a), 145.5 (C-10b), 137.3 (C-1'), 132.7 (C-8), 131.0 (C-4a), 129.6 (C-4'), 129.3 (C-3'), 128.6 (C-2'), 125.1 (C-9), 124.9 (C-10), 118.3 (C-10a), 117.4 (C-7), 24.6 (C-1'') ppm. MS (ESI): *m/z* 343 [M+Na + CH<sub>3</sub>OH]<sup>+</sup>. HRMS: Calcd for C<sub>18</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>, [M+H]<sup>+</sup>: 289.0977. Found: 289.0978, [M+Na]<sup>+</sup>: 311.0797. Found: 311.0793.

**2-Methyl-3-phenyl-5***H***-chromeno[3,4-***b***]pyrazin-5-one (5f).** 15 mg, 27% (Method A), 46 mg, 32% (Method B), light yellow, mp 214-217 °C (hexane/ethyl acetate). IR (KBr): 3053, 2923, 2847, 1761, 1608, 1537 cm<sup>-1</sup>. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.56 (d, *J* 7.8 Hz, 1H, H-10), 7,77 (dd, *J*<sub>1</sub> 2.9 Hz, *J*<sub>2</sub> 6.5 Hz, 2H, H-2'), 7.61 (t, *J* 7.8 Hz, 1H, H-8), 7.59-7.55 (m, 3H, H-3', H-4'), 7.42 (d, *J* 7.8 Hz, 1H, H-7), 7.41 (t, *J* 7.8 Hz, 1H, H-9), 2.87 (s, 3H, H-1''). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 159.6 (C-2), 159.3 (C-5), 154.3 (C-3), 152.3 (C-6a), 145.3 (C-10b), 137.5 (C-1'), 132.6

(C-8), 131.0 (C-4a), 130.2 (C-4'), 129.4 (C-2'), 128.7 (C-3'), 125.1 (C-9), 124.9 (C-10), 118.5 (C-10a), 117.3 (C-7), 24.0 (C-1'') ppm. MS (ESI): *m/z* 311 [M+Na]<sup>+</sup>. HRMS: Calcd for C<sub>18</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>, [M+H]<sup>+</sup>: 289.0977. Found: 289.0973, [M+Na]<sup>+</sup>: 311.0797. Found: 311.0792.

**3-Methyl-2-(4-nitrophenyl)-5***H***-chromeno[3,4-***b***]pyrazin-5-one (4g). 5 mg, 8% (Method A, 170 °C), 9.5 mg, 15% (Method A, 150 °C), 15 mg, 24% (n-butanol), 0.123 g, 74% (Method B), white solid, mp 260-261 °C (hexane/ethyl acetate). IR (KBr): 3068, 2918, 2849, 1757, 1605, 1519 cm<sup>-1</sup>. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.60 (dd, J\_1 1.6 Hz, J\_2 7.9 Hz, 1H, H-10), 8.39 (d, J 8.7 Hz, 2H, H-2'), 7.91 (d, J 8.7 Hz, 2H, H-3'), 7,67 (dt, J\_1 1.6 Hz, J\_2 7.9 Hz, 1H, H-8), 7.47 (t, J 7.9 Hz, 1H, H-9), 7.45 (d, J 7.9 Hz, 1H, H-7), 2.88 (s, 3H, H-1"). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 159.0 (C-3), 158.5 (C-5), 153.4 (C-2), 152.7 (C-6a), 148.5 (C-3'), 146.5 (C-10b), 143.3 (C-4'), 133.4 (C-8), 131.1 (C-4a), 130.5 (C-2'), 125.3 (C-10), 125.2 (C-9), 123.9 (C-1'), 118.0 (C-7), 117.5 (C-10a), 24.4 (C-3) ppm. MS (ESI): m/z 372 [M+K]<sup>+</sup>. HRMS: Calcd for C<sub>18</sub>H<sub>11</sub>N<sub>3</sub>O<sub>4</sub>, [M+H]<sup>+</sup>: 334.0828. Found: 334.0829, [M+Na]<sup>+</sup>: 356.0648. Found: 356.0648.** 

**2-Methyl-3-(4-nitrophenyl)-5***H***-chromeno[3,4-***b***]pyrazin-5-one (5g). 2 mg, 3% (Method A, 170 °C), 3 mg, 5% (Method A, 150 °C), 14 mg, 22% (n-butanol), 11 mg, 18% (Method B), white solid, mp 272-274 °C (hexane/ethyl acetate). IR (KBr): 3056, 2920, 2851, 1756, 1610, 1520 cm<sup>-1</sup>. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ 8.54 (d,** *J***=7.8 Hz, 1H, H-10), 8.45 (d,** *J***=8.6 Hz, 2H, H-2'), 7.96 (d,** *J***=8.6 Hz, 2H, H-3'), 7.65 (t,** *J***=7.8 Hz, 1H, H-8), 7.45 (d,** *J***=7.8 Hz, 1H, H-7), 7.44 (t,** *J***=7.8 Hz, 1H, H-9), 2.88 (s, 3H, H-1"). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 159.1 (C-5), 156.9 (C-3), 153.9 (C-2), 152.3 (C-6a), 148.7 (C-4'), 145.5 (C-10b), 143.4 (C-1'), 133.1 (C-8), 131.9 (C-4a), 130.5 (C-3'), 125.3 (C-10), 124.8 (C-9), 123.9 (C-2'), 118.0 (C-10a), 117.9 (C-7), 23.8 (C-1") ppm. MS (ESI):** *m/z* **372 [M+K]<sup>+</sup>. HRMS: Calcd for C<sub>18</sub>H<sub>11</sub>N<sub>3</sub>O<sub>4</sub>, [M+H]<sup>+</sup>: 334.0828. Found: 334.0829.** 

**Chromeno[3,4-***b***]indeno[1,2-e]pyrazin-6(8***H***)-one (4h). 77 mg, 54% (Method B), white solid, mp >285 °C (hexane/ethyl acetate). IR (KBr): 3090, 2924, 2852, 1748, 1613, 1553 cm<sup>-1</sup>. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ 8.75 (d,** *J* **7.6 Hz, 1H, H-1), 8.31 (d,** *J* **7.3 Hz, 1H, H-12), 7.71 (d,** *J* **7.2 Hz, 1H, H-9), 7,67-7.62 (m, 2H, H-3, H-10), 7.60 (t,** *J* **7,3 Hz, 1H, H-11), 7.48 (t,** *J* **7.6 Hz, 1H, H-2), 7.44 (d,** *J* **8.1 Hz, 1H, H-4), 4.21 (s, 2H, H-8). <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): δ 160.6 (C-7a), 160.2 (C-6), 159.4 (C-12b), 152.1 (C-4a), 147.4 (C-13a), 145.0 (C-8a), 136.9 (C-12a), 132.61 (C-3), 132.59 (C-10), 130.2 (C-6a), 128.4 (C-11), 126.0 (C-9), 125.03 (C-2), 125.00 (C-1), 123.7 (C-12), 118.9 (C-13b), 117.3 (C-4), 36.2 (C-8) ppm. MS (ESI):** *m/z* **309 [M+Na]<sup>+</sup>. HRMS: Calcd for C<sub>18</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>, [M+Na]<sup>+</sup>: 309.0640. Found: 309.0634.** 

**Chromeno[3,4-***b***]indeno[2,1-***e***]pyrazin-6(12***H***)-one (5h). 46 mg, 32% (Method B), light yellow solid, mp >285 °C (hexane/ethyl acetate). IR (KBr): 3003, 2933, 2857, 1747, 1614, 1571 cm<sup>-1</sup>. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): \delta 8.63 (d,** *J* **.8 Hz, 1H, H-1), 8.37 (d,** *J* **7.4 Hz, 1H, H-8), 7.70 (d,** *J* **7.2 Hz, 1H, H-11), 7.65-7.55 (m, 3H), 7.49-7.44 (m, 2H), 4.23 (s, 2H, H-12).<sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): \delta ): 160.4 (C-12a), 158.9 (C-6), 156.4 (C-7a), 151.9 (C-4a), 145.6 (C-7b), 142.8 (C-13a), 137.2 (C-11a), 132.6 (C-6a), 132.5 (C-3), 131.6 (C-10), 128.5 (C-9), 125.7 (C-8), 125.1 (C-2), 124.8 (C-1), 123.5 (C-11), 119.0 (C-13b), 117.3 (C-4), 36.7 (C-12) ppm. MS (ESI):** *m/z* **287 [M+H]<sup>+</sup>. HRMS: Calcd for C<sub>18</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>, [M+H]<sup>+</sup>: 287.0820. Found: 287.0810, [M+Na]<sup>+</sup>: 309.0640. Found: 309.0637.** 

## Acknowledgements

We are grateful to Dr. Catherine Gabriel," Health and Exposome Research: Assessing Contributors to Lifetime Exposure and State of health (HERACLES)", KEDEK, Aristotle University of Thessaloniki, Thessaloniki, Greece for obtaining the HRMS spectra.

#### **Supplementary Material**

<sup>1</sup>HNMR and <sup>13</sup>CNMR Spectra and some HMBC experiments for compounds **4a-h**, **5c**, **5f-h**, and a mixture of **4b** and **5b** are provided in the Supplementary Material in the online version of the text.

### References

- 1. Preliminary communication presented at 6th EFMC Young Medicinal Chemist Symposium, September 1-3, 2019, Athens, Greece, P021, Book of Abstracts p.64.
- Yu, D. L.; Suzuki, M.; Xie, L.; Morris-Natsche, S. L.; Lee, K. H. Med. Res. Rev. 2003, 23, 322. https://doi.org/10.1002/med.10034
- 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. Lacy, A.; O'Kennedy, R. *Curr. Pharm. Design.* **2004**, *10*, 3797. https://doi.org/10.2174/1381612043382693
- Medina, F. G.; Marrero, J. G.; Alonso, M. M.; González, M. C.; Córdova-Guerrero, I.; García, A. G. T.; Osegueda-Robles, S. *Nat. Prod. Rep.* 2015, *32*, 1472. <u>https://doi.org/10.1039/C4NP00162A</u>
- Kubrak, T.; Podgorski, R.; Stompor, M. Eur. J. Clin. Exp. Med. 2017, 15, 169. https://doi.org/10.15584/ejcem.2017.2.12
- 7. Stefanachi, A.; Leonetti, F.; Pisani, L.; Catto M.; Carotti, A. *Molecules* **2018**, *23*, 250. https://doi.org/10.3390/molecules23020250
- Li, H.; Yao, Y.; Li, L. J. Pharm. Pharmacol. 2017, 69, 1253. https://doi.org/10.1111/jphp.12774
- Salehian, F.; Nadri, H.; Jalili-Baleh, L.; Youseftabar-Miri, L.; Abbas Bukhari, S. N.; Foroumadi, A.; Küçükkilinç, T. T.; Sharifzadeh, M.; Khoobi, M. Eur. J. Med. Chem. 2021, 113034, in press https://doi.org/10.1016/j.ejmech.2020.113034
- 10. Markey, M. D.; Fu, Y.; Kelly. T. R. *Org. Lett.* **2007**, *9*, 3255. <u>https://doi.org/10.1021/ol0711974</u>
- 11. Quinto, I.; Averbeck, D.; Moustacchi. E.; Hrisoho, Z.; Moron, J. *Mutation Res.* **1984**, *136*, 49. <u>https://doi.org/10.1016/0165-1218(84)90133-2</u>
- 12. Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264. <u>https://doi.org/10.1021/cr078199m</u>
- Balalas, T. D.; Theologis, A. K.; Mazaraki, K.; Gabriel, C.; Pontiki, E.; Hadjipavlou-Litina, D. J.; Litinas, K. E. *Arkivoc* 2020, vi, 126. <u>https://doi.org/10.24820/ark.5550190.p011.180</u>
- 14. Han, G. S.; Shim, S. C. *Photochem. Photobiol.* **1998**, *67*, 84. https://doi.org/10.1111/j.1751-1097.1998.tb05168.x
- 15. Shim, S. C.; Han, G. S. *Photochem. Photobiol.* **1997**, *66*, 156. https://doi.org/10.1111/j.1751-1097.1997.tb08637.x
- 16. Han, G. S.; Yoo, D. J.; Kim, S. K.; Shim, S. C.; Kang, H. K. *Photochem. Photobiol.* **1996**, *64*, 525. <u>https://doi.org/10.1111/j.1751-1097.1996.tb03100.x</u>

Arkivoc **2021**, viii, 0-0

- 17. Gewald, K.; Shafer, H.; Bellman, P.; Muller, H. *Chem. Ber.* **1991**, *124*, 1237. <u>https://doi.org/10.1002/cber.19911240542</u>
- Gutknecht, H. Chem. Ber. 1879, 12, 2290. https://doi.org/10.1002/cber.187901202284
- 19. Rizk, T.; Bilodeau, E. J. F.; Beauchemin, A. M. Angew. Chem. Int. Ed. **2009**, 48, 8325. https://doi.org/10.1002/anie.200903922
- Alcaide, B.; Almendros, P.; Alonso, J. M.; Fernandez, I.; Gomez-Campillos, G.; Torres, M. R. Chem. Commun. 2014, 50, 4567. https://doi.org/10.1039/C4CC01485E
- 21. Billman, J. H.; Rendall, J. L. *J. Am. Chem. Soc.* **1944**, *66*, 540. <u>https://doi.org/10.1021/ja01232a011</u>
- 22. Heravi, M. M.; Bakhtiari, K.; Tehrani, M. H.; Javadi, N. M.; Oskooie, H. A. Arkivoc **2006**, xvi, 16. https://doi.org/10.3998/ark.5550190.0007.g02
- 23. Pal, B.; Jaisankar, P.; Giri, V. S. *Synth. Commun.* **2004**, *34*, 1317. <u>https://doi.org/10.1081/SCC-120030322</u>
- 24. Odum, R. A.; Brenner, M. *J. Am. Chem. Soc.* **1966**, *88*, 2074. <u>https://doi.org/10.1021/ja00961a058</u>
- 25. Kaneko, C.; Yamamori, M.; Yamamoto, A.; Hayashi, R. *Tetrahedron Lett.* **1978**, *31*, 2799. <u>https://doi.org/10.1016/S0040-4039(01)94866-X</u>
- 26. Mustafa, A. H.; Malakar, C. C.; Ajaar, N.; Merisor, E.; Conrad, J.; Beifuss, U. *Synlett* **2013**, *24*, 1573. <u>https://doi.org/10.1055/s-00032269</u>
- 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
- 28. 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
- Balalas, T. D.; Stratidis, G.; Papatheodorou, D.; Vlachou, E.-E.; Gabriel, C.; Hadjipavlou-Litina, D. J.; Litinas, K. E. SynOpen 2018, 2, 105. <u>https://doi.org/10.1055/s-0036-1591977</u>
- 30. Balalas, T. D.; Kallitsakis, M. G.; Fotopoulos, I.; Hadjipavlou-Litina, D. J.; Litinas, K. E. *Arkivoc* **2019**, *v*, 237. https://doi.org/10.24820/ark.5550190.p010.803
- 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
- 32. Nicolaides, D. N.; Litinas, K. E. Chimika Chronika, New Series, 1982, 11, 137.
- 33. Savel'ev, V. L.; Artamonova, O. S.; Zagorevskii, V. A. Khim. Farm. Zh. 1976. 316; Engl. Transl. 1976. 268.
- 34. Stamboliyska, B.; Janevska, V.; Shivachev, B.; Nikolova, R. P.; Stojkovic, G.; Mikhova, B.; Popovski, E. *Arkivoc* **201**, *x*, 62.

https://doi.org/10.3998/ark.5550190.0011.a06

- 35. Kolb, A. *Liebigs Ann*. **1896**, *291*, 253. https://doi.org/10.1002/jlac.18962910302
- 36. Freeman, A. W.; Urvoy, M.; Criswell, M. E. *J. Org. Chem.* **2005**, *70*, 5014. <u>https://doi.org/10.1021/jo0503299</u>

37. Emre Hoplamaz, E.; Keskin, S.; Balci, M. *Eur. J. Org. Chem.* **2017**, *11*, 1489. <u>https://doi.org/10.1002/ejoc.201601661</u>

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (<u>http://creativecommons.org/licenses/by/4.0/</u>)