molbank

MDPI

Short Note

2,9-Dimethyl-4*H*-oxazolo[5′,4′:4,5]pyrano[3,2-*f*]quinolin-4-one

Evangelia-Eirini N. Vlachou [1], Thomas D. Balalas [1], Dimitra J. Hadjipavlou-Litina [2], Konstantinos E. Litinas [1,*] and Matina Douka [1]

[1] Laboratory of Organic Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece
[2] Department of Pharmaceutical Chemistry, School of Pharmacy, Faculty of Health Sciences, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece
* Correspondence: klitinas@chem.auth.gr; Tel.: +30-2310-997864

Abstract: The new 2,9-dimethyl-4*H*-oxazolo[5′,4′:4,5]pyrano[3,2-*f*]quinolin-4-one was successfully prepared through the three-component iodine-catalyzed reaction of *n*-butyl vinyl ether with the new 8-amino-2-methyl-4*H*-chromeno[3,4-*d*]oxazol-4-one. The latter was prepared by the reduction of 2-methyl-8-nitro-4*H*-chromeno[3,4-*d*]oxazol-4-one with Pd/C in a hydrogen atmosphere. The above nitro compound was synthesized by the condensation of *N*-(4-hydroxy-6-nitro-2-oxo-2*H*-chromen-3-yl)acetamide with P_2O_5 under microwave irradiation. The above acetamide derivative was prepared during the nitration of 2-methyl-4*H*-chromeno[3,4-*d*]oxazol-4-one with H_2SO_4 and KNO_3. The structure of the newly synthesized compounds was confirmed by FT-IR, LC-MS, ^{1}H-NMR, and ^{13}C-NMR analyses. Preliminary biological tests show significant anti-lipid peroxidation activity for the title compound and the other synthesized new intermediates, as well as interesting soybean lipoxygenase inhibition for acetamide **2** (IC_{50} 55 μM) and nitro-compound **3** (IC_{50} 27 μM).

Keywords: I_2-catalysis; fused pyridocoumarin; fused oxazolocoumarin; amino-substituted fused oxazolocoumarin; microwave irradiation

Citation: Vlachou, E.-E.N.; Balalas, T.D.; Hadjipavlou-Litina, D.J.; Litinas, K.E.; Douka, M. 2,9-Dimethyl-4*H*-oxazolo[5′,4′:4,5]pyrano[3,2-*f*]quinolin-4-one. *Molbank* **2023**, *2023*, M1591. https://doi.org/10.3390/M1591

Academic Editor: R. Alan Aitken

Received: 26 January 2023
Revised: 13 February 2023
Accepted: 14 February 2023
Published: 17 February 2023

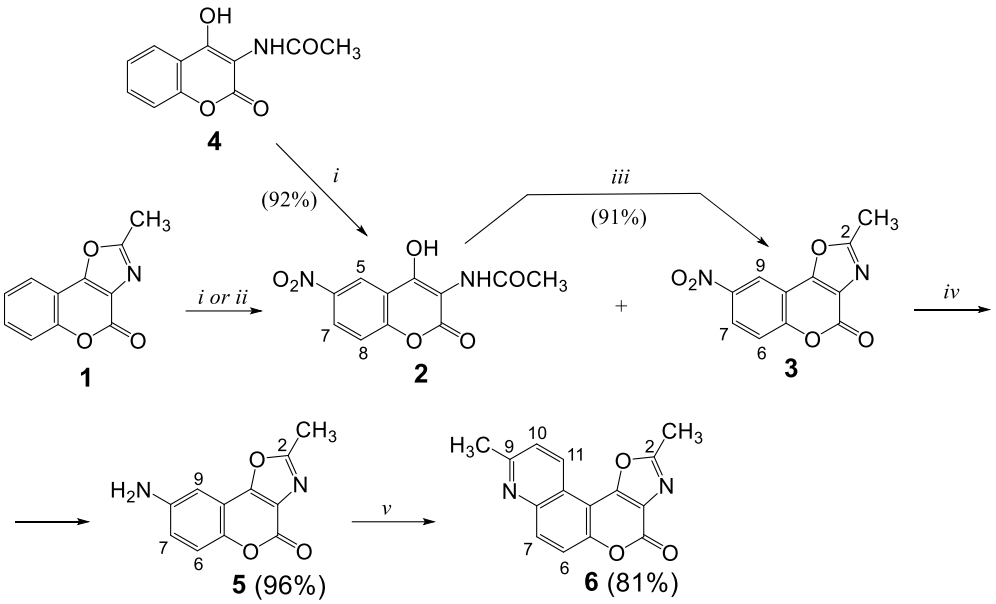
1. Introduction

Coumarin derivatives are widely distributed in nature or synthetically prepared. They act on neurodegenerative diseases and present important biological properties, such as anti-HIV, anticoagulant, anti-inflammatory, anticancer, antioxidant, and antidiabetic [1–7]. Fused coumarins, as well as fused oxazolocoumarins, exhibit antioxidant, antimicrobial, anti-inflammatory, or photoreleasing aminolevulinic acid activities [8–11]. Pyridocoumarins are also biologically active [12] with anticancer, antifungal, antibacterial, antimalarial, anti-inflammatory, antioxidant, and wound-healing properties [12–17].

The synthesis of fused oxazolocoumarins is achieved by the condensation of *o*-aminohydroxycoumarins with aldehydes [9,18–20], acids [19], or anhydrides [18,20]. The condensation of *o*-amidohydroxycoumarins with anhydrides [21], $POCl_3$ [22], or P_2O_5 [23] has also led to oxazolocoumarins. The reduction of 4-hydroxy-3-nitrosocoumarin in acetic anhydride in the presence of Pd/C [24] or 4-hydroxy-3-nitrocoumarins in liquid carboxylic acids in the presence of Pd/C or PPh_3 and P_2O_5 [11] leads to fused oxazolocoumarins. Recently, we have prepared fused oxazolocoumarins by the one-pot tandem reaction of *o*-hydroxynitrocoumarins with benzyl alcohols in toluene under gold nanoparticle catalysis supported on TiO_2 [25,26], with $FeCl_3$ [26], or with silver nanoparticles supported on TiO_2 [26].

The preparation of pyridocoumarins [12] succeeded under Skraup synthesis from nitrocoumarin and glycerol [27] via the one-pot Povarov reaction of aminocoumarins with aromatic aldehydes and cyclic enol ethers [28], the reaction of aminocoumarins with vinyl ketones [29], or the three-component reaction of aminocoumarins with phenylacetylene and benzaldehydes catalyzed by I_2 [30], by other Lewis acids [17,31], or by

o-vinylaminocoumarins under Vilsmeier conditions [32]. Earlier, we synthesized fused pyridocoumarins through the three-component reaction of aminocoumarins with *n*-butyl vinyl ether and I_2 catalysis [33]. The cycloisomerization of propargylaminocoumarins, catalyzed by $AgSbF_6$ [34] or $BF_3.Et_2O$ [35] or Au/nanoparticles [36], followed by oxidation, also resulted in the synthesis of pyridocoumarins. Due to our interest in the synthesis and biological evaluation of fused oxazolocoumarins [11,25,26] and pyridocoumarins [12,17,31,33,35,36], we combined in one new framework pyridine, oxazole, and coumarin moieties, and studied the biological impact of the new compounds. The reactions studied, and the synthesized products are depicted in Scheme 1.



Scheme 1. Reagents and Conditions: (i) H_2SO_4 (98%) (80 equiv.), HNO_3 (65%) (1.5 equiv.), 0 °C, 15 min then r.t. 1 h [**2** (61%), **3** (22%)]; (ii) H_2SO_4 (98%) (75 equiv.), KNO_3 (1.5 equiv.), 0 °C, 15 min, then r.t. 1 h [**2** (91%)]; (iii) P_2O_5 (3 equiv.), toluene, MW, 150 °C, 3 h; (iv) Pd/C (10%), ethanol, H_2, r.t., 1 h; (v) n-butyl vinyl ether (3 equiv.), I_2 (0.1 equiv.), acetonitrile, reflux, overnight.

2. Results and Discussion

2.1. Synthesis

The starting material for the synthesis of the title compound was the new compound 2-methyl-8-nitro-4*H*-chromeno[3,4-*d*]oxazol-4-one (**3**), which was prepared in 91% yield in one-pot cyclization-dehydration of *N*-(4-hydroxy-6-nitro-2-oxo-2*H*-chromen-3-yl)acetamide (**2**) in the presence of P_2O_5 under microwave irradiation (Scheme 1). In the ^{1}H-NMR spectrum of **3,** there are downfield shifts for aromatic protons at 8.72 (d, *J* = 2.6 Hz, 1H) for 5-H, 8.43 (dd, *J* = 2.7, 9.1 Hz, 1H) for 7-H and at 7.62 (d, *J* = 9.2 Hz, 1H) for 8-H.

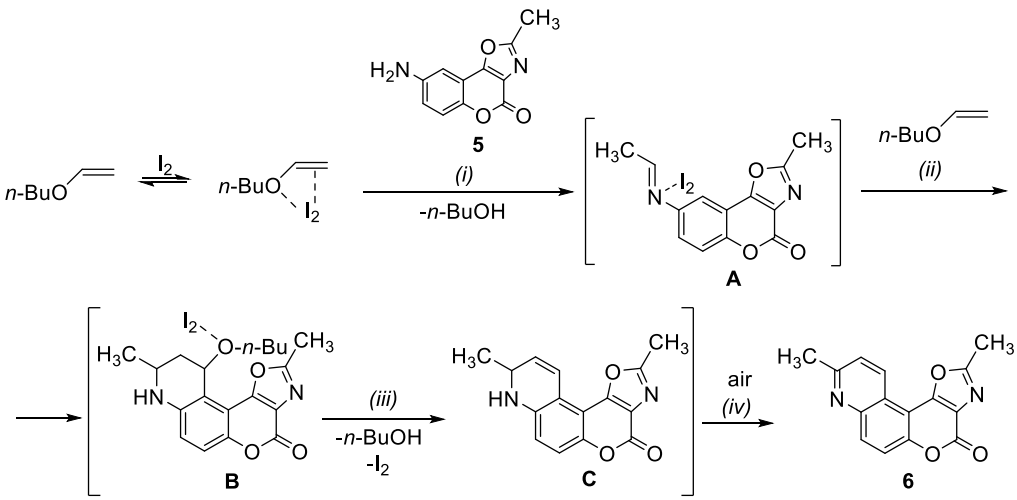
At first, we tried to synthesize nitro-compound **3** through nitration of 2-methyl-4*H*-chromeno[3,4-*d*]oxazol-4-one (**1**) [11]. The nitration in the presence of concentrated H_2SO_4 and HNO_3 resulted in nitration product **3** (22%) and the hydrolyzed nitro compound **2** (61%). When the nitration was performed in the presence of concentrated H_2SO_4 and KNO_3, acetamide **2** was the sole product with a 91% yield. Nitro-compound **2** was prepared, also, by nitration of *N*-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)acetamide (**4**) [11] in the presence of concentrated H_2SO_4 and HNO_3. In the ^{1}H-NMR (DMSO-$_{d6}$) spectrum of **2,** there is one doublet at 8.60 (d, *J* = 2.7 Hz, 1H) for 5-H, one doublet at 8.44 (dd, *J* = 2.8, 9.1 Hz, 1H) for 7-H, and one doublet at 7.65 (d, *J* = 9.1 Hz, 1H) for 8-H, revealing the 7-position for NO_2 group. The peaks for the OH and NH protons are at 12.71 and 9.56 ppm. The same protons in the ^{1}H-NMR ($CDCl_3$) are at 13.79 and 8.10 ppm, respectively.

The reduction of 2-methyl-8-nitro-4*H*-chromeno[3,4-*d*]oxazol-4-one (**3**) with Pd/C under H_2 atmosphere resulted to the preparation of 8-amino-2-methyl-4*H*-chromeno[3,4-

d]oxazol-4-one (**5**) in 96% yield. In this new compound, there is an upfield shift of aromatic protons ^{1}H-NMR spectrum at 6.92–6.88 (m, 2H) for 5-H and 7-H and at 7.27 (d, *J* = 8.8 Hz, 1H) for 8-H, while the NH_2 group appeared at 5.50 (brs, 2H). In the FT-IR, there are absorptions at 3417 and 3244 cm^{-1} for the NH_2 group.

For the formation of pyridine moiety in the fused coumarin skeleton, we applied the Povarov-type reaction as we previously used it through the three-component reaction of aminocoumarin with n-butyl vinyl ether under iodine catalysis [33]. The reaction of amine **5** with 3 equivalents of n-butyl vinyl ether in the presence of I_2 (10%) in CH_3CN under reflux overnight led to 2,9-dimethyl-4*H*-oxazolo[5′,4′:4,5]pyrano[3,2-*f*]quinolin-4-one (**6**) in 81% yield. This product was isolated from the column chromatography separation of the complicated reaction mixture. In the ^{1}H-NMR spectrum, there are four doublets for the pyridine and benzene protons at 7.53 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 8.18 (d, *J* = 9.3 Hz, 1H), 8.95 (d, *J* = 8.6 Hz, 1H), revealing the angular regioselective formation of pyridine moiety. The NOE experiment verifies the position (9-CH_3) of pyridine-methyl, as there are correlations of 11-H at 8.95 ppm with the proton at 7.53 ppm (2.75%) and the methyl-protons at 2.81 (2.67%) and 2.80 ppm (2.36%). There are also two methyls at 2.80 (s, 3H), 2.81 ppm (s, 3H), with the corresponding shifts in ^{13}C-NMR at 14.6 (methyl carbon of oxazole ring) and 25.3 ppm (methyl carbon of pyridine ring), as shown by HSQC, see Supplementary Materials. The latter is quite similar to the 2-methyl carbon (25.4 ppm) of 2-methylquinoline [37] and not the 4-methyl carbon (18.6 ppm) of 4-methylquinoline [38].

The mechanism of this reaction is similar to that proposed by us [33], with the initial formation of an *N*-iminocoumarin **A**, which was at first catalyzed by iodine acting as a mild Lewis acid (Scheme 2). An Aza-Diels–Alder reaction of the imine **A** with a second molecule of *n*-butyl vinyl ether, also catalyzed by iodine, gave, after tautomerization, the intermediate **B**. The elimination of *n*-BuOH resulted in intermediate **C**, which by air oxidation, led to the final product **6**.



Scheme 2. (i) Lewis acid catalyzed imine formation. (ii) Aza-Diels–Alder reaction catalyzed by the Lewis acid, followed by tautomerization. (iii) Lewis acid catalyzed *n*-butanol elimination. (iv) Oxidation.

2.2. Biology

Preliminary biological experiments were performed in vitro. The new compounds **2**, **3**, **5**, and **6** were tested as possible antioxidant agents and inhibitors of soybean lipoxygenase according to our previous published assays [11,17]. The anti-lipid peroxidation activity was very high at 100 μM (74.4%, 93.1%, 98.1%, and 91.7% for compounds **2**, **3**, **5**, and **6**, respectively), as tested by the 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH) protocol. The inhibition of soybean lipoxygenase was low at 100 μM for the title compound

6 (28%) and the intermediate amine **5** (41%), while the intermediates **2** and **3** were more potent with IC_{50} 55 μM and 27 μM, respectively.

3. Materials and Methods

3.1. Materials

All the chemicals were purchased from either Sigma–Aldrich Co. or Merck & Co., Inc. Melting points were determined with a Kofler hotstage apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer Spectrum BX spectrophotometer as KBr pellets. NMR spectra were recorded with an Agilent 500/54 (DD2) (500 MHz and 125 MHz for ^{1}H and ^{13}C, respectively) using TMS as an internal standard. *J* values are reported in Hz. Mass spectra were determined with an LCMS-2010 EV Instrument (Shimadzu) under electrospray ionization (ESI) conditions. HRMS (ESI-MS) were recorded with a ThermoFisher Scientific (168 Third Avenue, Waltham, MA USA 02451) model LTQ Orbitrap Discovery MS. Silica gel No. 60, Merck KGAA (Frankfurter Strasse 250, Darmstadt, 64293, Germany) was used for column chromatography.

*3.2. Nitration of 2-Methyl-4H-chromeno[3,4-d]oxazol-4-one (**1**) Synthesis of N-(4-hydroxy-6-nitro-2-oxo-2H-chromen-3-yl)acetamide (**2**) and 2-methyl-8-nitro-4H-chromeno[3,4-d]oxazol-4-one (**3**)*

A. H_2SO_4 98% (2 mL, 37.5 mmol) and compound **1** (101 mg, 0.5 mmol) were placed in a round-bottom flask in an ice bath. A mixture of H_2SO_4 98% 1.12 mL, 2.25 mmol) and HNO_3 65% (0.052 mL, 0.75 mmol) was then added dropwise for 15 min. The resulting mixture was stirred at room temperature for 1 h, and then it was poured into a 20 mL mixture of water and crushed ice. The mixture was filtered under vacuum, and the precipitate was washed with 2 × 20 mL cooled water, dried under vacuum, and separated by column chromatography [silica gel, hexane/ethyl acetate (2:1)] to give compound **3** (27 mg, 22% yield) followed by compound **2** (81 mg, 61% yield).

B. H_2SO_4 98% (2 mL, 37.5 mmol) and compound **1** (101 mg, 0.5 mmol) were added in a round-bottom flask in an ice bath, followed by the addition of KNO_3 (76 mg, 0.75 mmol) for 15 min. The mixture was then stirred at room temperature for 1 h, poured into a 20 mL mixture of water and crushed ice, and filtered under a vacuum. The precipitate was washed with 2 × 20 mL cooled water and dried under vacuum to give compound **2** (120 mg, 91% yield).

N-(4-hydroxy-6-nitro-2-oxo-2*H*-chromen-3-yl)acetamide (**2**): Light beige solid, m.p. 231–232 °C ($CHCl_3$). IR (KBr): 3412, 3311, 3070, 2924, 2857, 1698, 1684, 1634, 1614 cm^{-1}. ^{1}H-NMR (500 MHz, $DMSO_{-d6}$) δ: 2.11 (s, 3H), 7.65 (d, *J* = 9.1 Hz, 1H), 8.44 (dd, *J* = 2.8, 9.1 Hz, 1H), 8.60 (d, *J* = 2.7 Hz, 1H), 9.56 (s, 1H), 12.71 (brs, 1H). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 7.46 (d, *J* = 9.1 Hz, 1H), 8.10 (brs, 1H), 8.40 (dd, *J* = 2.5, 9.1 Hz, 1H), 8.89 (d, *J* = 2.4 Hz, 1H), 13.79 (s, 1H). ^{13}C- NMR (125 MHz, $CDCl_3$) δ: 22.7, 104.6, 117.2, 117.9, 119.5, 126.7, 143.6, 154.7, 156.1, 159.3, 171.0. LC-MS (ESI): 297 $[M + H + MeOH]^+$.

2-Methyl-8-nitro-4*H*-chromeno[3,4-d]oxazol-4-one (**3**): Beige solid, m.p. 171–172 °C (ethyl acetate/hexane). IR (KBr): 3017, 2924, 2857, 1751, 1636, 1618 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.76 (s, 3H), 7.62 (d, *J* = 9.2 Hz, 1H), 8.43 (dd, *J* = 2.7, 9.1 Hz, 1H), 8.72 (d, *J* = 2.6 Hz, 1H). ^{13}C- NMR (125 MHz, $CDCl_3$) δ: 14.5, 112.1, 117.7, 118.9, 126.2, 126.25, 144.3, 154.3 (2C), 155.9, 165.2. LC-MS (ESI): 269 $[M + Na]^+$.

*3.3. Nitration of N-(4-Hydroxy-2-oxo-2H-chromen-3-yl)acetamide (**4**) Synthesis of N-(4-hydroxy-6-nitro-2-oxo-2H-chromen-3-yl)acetamide (**2**)*

According to method 3.2.A., from 4 (110 mg, 0.5 mmol) compound **2** (121 mg, 92% yield) was obtained after drying.

*3.4. Condensation of N-(4-Hydroxy-6-nitro-2-oxo-2H-chromen-3-yl)acetamide (**2**) Synthesis of 2-Methyl-8-nitro-4H-chromeno[3,4-d]oxazol-4-one (**3**)*

The compound **2** (132 mg, 0.5 mmol), toluene (5 mL), and P_2O_5 (0.213 g, 1.5 mmol) were added in a vial suitable for a microwave oven and irradiated at 150 °C for 3 h. After

cooling, the mixture was transferred to a separatory funnel containing H_2O (20 mL) and ethyl acetate (10 mL). After separation, the organic layer was washed with a saturated solution of $NaHCO_3$ (3 × 10 mL) and then, with H_2O (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to give compound **3** (112 mg, 91% yield).

*3.5. Synthesis of 8-Amino-2-methyl-4H-chromeno[3,4-d]oxazol-4-one (**5**)*

Compound **3** (123 mg, 0.5 mmol) was added to ethanol (20 mL) in a round bottom flask. After removing of air, Pd/C 10 % (27 mg, 0.025 mmol) was added to the solution under argon, and the mixture was stirred under an H_2 atmosphere for 1 h. Filtration through the celite layer was followed, the celite was washed with ethanol (30 mL), and the filtrate was evaporated to afford 8-amino-2-methyl-4*H*-chromeno[3,4-*d*]oxazol-4-one (**5**) (104 mg, 96% yield), light beige solid, m.p. 295–297 °C (dec.) (ethyl acetate/hexane). IR (KBr): 3417, 3244, 3017, 2924, 2857, 1731, 1634, 1611 cm^{-1}. ^{1}H-NMR (500 MHz, $DMSO_{-d6}$) δ: 2.64 (s, 3H), 5.50 (brs, 2H), 6.92–6.88 (m, 2H), 7.27 (d, *J* = 8.8 Hz, 1H). ^{13}C- NMR (125 MHz, $CDCl_3$) δ: 13.9, 102.4, 111.3, 117.7, 118.4, 123.9, 144.0, 146.2, 155.4, 155.7, 163.33. LC-MS (ESI): 239 $[M + Na]^+$.

*3.6. Synthesis of 2,9-Dimethyl-4H-oxazolo[5′,4′:4,5]pyrano[3,2-f]quinolin-4-one (**6**)*

8-Amino-2-methyl-4*H*-chromeno[3,4-*d*]oxazol-4-one (**5**) (30 mg, 0.139 mmol) was added to CH_3CN (2 mL) in a round bottom flask followed by the addition of *n*-butylvinyl ether (0.053 mL, 0.416 mmol) and I_2 (3.5 mg, 0.014 mmol). The mixture was refluxed overnight and, after cooling, poured in ethyl acetate (20 mL) and washed with saturated $Na_2S_2O_4$ (25 mL), brine (25 mL), and H_2O (25 mL). The complicated reaction mixture, after drying over anhydrous Na_2SO_4, filtration, and evaporation, was separated by column chromatography [silica gel, hexane/ethyl acetate (2:1)] and gave 2,9-dimethyl-4*H*-oxazolo[5′,4′:4,5]pyrano[3,2-*f*]quinolin-4-one (**6**) (30 mg, 81% yield), light yellow solid, m.p. 231–233 °C (ethyl acetate/hexane). IR (KBr): 3016, 2924, 2857, 1748, 1636, 1614 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.80 (s, 3H), 2.81 (s, 3H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 8.18 (d, *J* = 9.3 Hz, 1H), 8.95 (d, *J* = 8.6 Hz, 1H). ^{13}C- NMR (125 MHz, $CDCl_3$) δ: 14.6, 25.3, 106.2, 120.2, 120.8, 124.1, 125.4, 133.0, 133.2, 145.0, 151.8, 155.8, 156.3, 159.7, 163.9. LC-MS (ESI): 267 $[M + H]^+$, 289 $[M + Na]^+$. HR-MS (ESI), (M.W.: 266): *m*/*z* $[M + Na]^+$ calcdfor $C_{15}H_{10}NaN_2O_3$: 289.0589, found: 289.0594.

3.7. Biological Experiments: In Vitro Assays

The compounds were dissolved in DMSO.

- Antilipid peroxidation. The AAPH protocol was performed [17].
- Lipoxygenase inhibition. The soybean lipoxygenase/linoleic sodium protocol was used [17].

4. Conclusions

We have demonstrated the regioselective formation of 2,9-dimethyl-4*H*-oxazolo[5′,4′:4,5] pyrano[3,2-*f*]quinolin-4-one (**6**) via the three-component iodine-catalyzed reaction of 8-amino-2-methyl-4*H*-chromeno[3,4-*d*]oxazol-4-one (**5**) with *n*-butyl vinyl ether. The preliminary biological assays pointed out that compound **6** presents significant anti-lipid peroxidation activity and low inhibition activity on soybean lipoxygenase, while the intermediates *N*-(4-hydroxy-6-nitro-2-oxo-2*H*-chromen-3-yl)acetamide (**2**) and 2-methyl-8-nitro-4*H*-chromeno[3,4-*d*]oxazol-4-one (**3**) possess interesting soybean lipoxygenase inhibition.

Supplementary Materials: ^{1}H-NMR and ^{13}C- NMR spectra of compounds **2**, **3**, **5**, **6**.

Author Contributions: Conceptualization, writing—original draft preparation, supervision, K.E.L.; biological tests, review, and editing the manuscript, D.J.H.-L.; the experiments, E.-E.N.V.; the experiments, editing, in part, the manuscript, T.D.B.; the experiments, data curation, M.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research is co-financed by Greece and the European Union (European Social Fund—ESF) through the Operational Programme «Human Resources Development, Education and Lifelong Learning 2014–2020» in the context of the project "Synthesis of Fused Pyranoquinolinone Derivatives with possible Biological Interest" (MIS 5066801). (For K.E.L., D.J.H.-L., E.-E.N.V., and T.D.B.).

Institutional Review Board Statement: Not applicable.

Data Availability Statement: Data is contained within the article or supplementary material.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Yu, D.L.; Suzuki, M.; Xie, L.; Morris-Natsche, S.L.; Lee, K.H. Recent progress in the development of coumarin derivatives as potent anti-HIV agents. *Med. Res. Rev.* **2003**, *23*, 322–345. [CrossRef] [PubMed]
2. Fylaktakidou, K.; Hadjipavlou-Litina, D.; Litinas, K.; Nicolaides, D. Natural and Synthetic Coumarin Derivatives with Anti-Inflammatory/Antioxidant Activities. *Curr. Pharm. Des.* **2004**, *10*, 3813–3833. [CrossRef] [PubMed]
3. Lacy, A.; O'Kennedy, R. Studies on Coumarins and Coumarin-Related Compounds to Determine their Therapeutic Role in the Treatment of Cancer. *Curr. Pharm. Des.* **2004**, *10*, 3797–3811. [CrossRef] [PubMed]
4. Medina, F.G.; Marrero, J.G.; Macías-Alonso, M.; González, M.C.; Córdova-Guerrero, I.; García, A.G.T.; Osegueda-Robles, S. Coumarin heterocyclic derivatives: Chemical synthesis and biological activity. *Nat. Prod. Rep.* **2015**, *32*, 1472–1507. [CrossRef] [PubMed]
5. Stefanachi, A.; Leonetti, F.; Pisani, L.; Catto, M.; Carotti, A. Coumarin: A Natural, Privileged and Versatile Scaffold for Bioactive Compounds. *Molecules* **2018**, *23*, 250. [CrossRef] [PubMed]
6. Li, H.; Yao, Y.; Li, L. Coumarins as potential antidiabetic agents. *J. Pharm. Pharmacol.* **2017**, *69*, 1253–1264. [CrossRef] [PubMed]
7. Salehian, F.; Nadri, H.; Jalili-Baleh, L.; Youseftabar-Miri, L.; Bukhari, S.N.A.; Foroumadi, A.; Küçükkilinç, T.T.; Sharifzadeh, M.; Khoobi, M. A review: Biologically active 3,4-heterocycle-fused coumarins. *Eur. J. Med. Chem.* **2020**, *212*, 113034. [CrossRef]
8. Kontogiorgis, C.; Hadjipavlou-Litina, D. Biological Evaluation of Several Coumarin Derivatives Designed as Possible Anti-inflammatory/Antioxidant Agents. *J. Enzym. Inhib. Med. Chem.* **2003**, *18*, 63–69. [CrossRef]
9. Prasanna, B.; Sandeep, A.; Revathi, T. Green approach to synthesis of novel substituted *8H*-pyrano[2,3-e]benzoxazole-8-ones. *World J. Pharm. Pharm. Sci.* **2014**, *3*, 404–411.
10. Soares, A.M.S.; Hungerford, G.; Gonçalves, M.S.T.; Costa, S.P.G. Light triggering of 5-aminolevulinic acid from fused coumarin ester cages. *New J. Chem.* **2017**, *41*, 2997–3005. [CrossRef]
11. Balalas, T.D.; Stratidis, G.; Papatheodorou, D.; Vlachou, E.-E.; Gabriel, C.; Hadjipavlou-Litina, D.J.; Litinas, K.E. One-pot Synthesis of 2-Substituted 4H-Chromeno[3,4-d]oxazol-4-ones from 4-Hydroxy-3-nitrocoumarin and Acids in the Presence of Triphenylphosphine and Phosphorus Pentoxide under Microwave Irradiation. *Synopen* **2018**, *2*, 105–113. [CrossRef]
12. Douka, M.D.; Litinas, K.E. An Overview on the Synthesis of Fused Pyridocoumarins with Biological Interest. *Molecules* **2022**, *27*, 7256. [CrossRef] [PubMed]
13. Khan, I.A.; Kulkarni, M.V.; Gopal, M.; Shahabuddin, M.; Sun, C.-M. Synthesis and biological evaluation of novel angularly fused polycyclic coumarins. *Bioorganic Med. Chem. Lett.* **2005**, *15*, 3584–3587. [CrossRef] [PubMed]
14. Markey, M.D.; Fu, Y.; Kelly, T.R. Synthesis of Santiagonamine. *Org. Lett.* **2007**, *9*, 3255–3257. [CrossRef] [PubMed]
15. El-Saghier, A.M.M.; Naili, M.B.; Rammash, B.K.; Saleh, N.A.; Kreddan, K.M. Synthesis and antibacterial activity of some new fused chromenes. *Arkivoc* **2007**, *16*, 83–91. [CrossRef]
16. Levrier, C.; Balastrier, M.; Beattie, K.; Carroll, A.; Martin, F.; Choomuenwai, V.; Davis, R.A. Pyridocoumarin, aristolactam and aporphine alkaloids from the Australian rainforest plant *Goniothalamus australis*. *Phytochemistry* **2013**, *86*, 121–126. [CrossRef]
17. Symeonidis, T.S.; Hadjipavlou-Litina, D.J.; Litinas, K.E. Synthesis Through Three-Component Reactions Catalyzed by $FeCl_3$ of Fused Pyridocoumarins as Inhibitors of Lipid Peroxidation. *J. Heterocycl. Chem.* **2014**, *51*, 642–647. [CrossRef]
18. Sahoo, S.S.; Shukla, S.; Nandy, S.; Sahoo, H. Synthesis of novel coumarin derivatives and its biological evaluations. *Eur. J. Exp. Biol.* **2012**, *2*, 899–908.
19. Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Giusti, L.; Lucacchini, A. Tricyclic heteroaromatic systems. Synthesis and benzodiazepine receptor affinity of 2-substituted-1-benzopyrano[3,4-d]oxazol-4-ones, -thiazol-4-ones, and -imidazol-4-ones. *Il Farm.* **1998**, *53*, 375–381. [CrossRef]
20. Nofal, Z.M.; El-Zahar, M.I.; El-Karim, A. Novel Coumarin Derivatives with Expected Biological Activity. *Molecules* **2000**, *5*, 99–113. [CrossRef]
21. Dallacker, F.; Kratzer, P.; Lipp, M. Derivate des 2.4-Pyronons und 4-Hydroxy-cumarins. *Eur. J. Org. Chem.* **1961**, *643*, 97–109. [CrossRef]
22. Gammon, D.W.; Hunter, R.; Wilson, S.A. An efficient synthesis of 7-hydroxy-2,6-dimethylchromeno[3,4-d]oxazol-4-one—A protected fragment of novenamine. *Tetrahedron* **2005**, *61*, 10683–10688. [CrossRef]
23. Saikachi, H.; Ichikawa, M. Studies on synthesis of coumarin derivatives. XV. On the preparation of ethyl pyranobenzoxazole-carboxylates. *Chem. Pharm. Bull.* **1966**, *14*, 1162–1167. [CrossRef] [PubMed]

24. Chantegrel, B.; Nadi, A.I.; Gelin, S. Synthesis of [1]benzopyrano[3,4-d]isoxazol-4-ones from 2-substituted chromone-3-carboxylic esters. A reinvestigation of the reaction of 3-acyl-4-hydroxycoumarins with hydroxylamine. Synthesis of 4-(2-hydroxybenzoyl)isoxazol-5-ones. *J. Org. Chem.* **1984**, *49*, 4419–4424. [CrossRef]
25. Vlachou, E.-E.; Balalas, T.; Hadjipavlou-Litina, D.; Litinas, K. 4-Amino-2-(*p*-tolyl)-7*H*-chromeno[5,6-*d*]oxazol-7-one. *Molbank* **2021**, *2021*, M1237. [CrossRef]
26. Vlachou, E.-E.N.; Armatas, G.S.; Litinas, K.E. Synthesis of Fused Oxazolocoumarins from o -Hydroxynitrocoumarins and Benzyl Alcohol Under Gold Nanoparticles or $FeCl_3$ Catalysis. *J. Heterocycl. Chem.* **2017**, *54*, 2447–2453. [CrossRef]
27. Liska, K.J.; Fentiman, A.F., Jr.; Foltz, R.L. Use of tris-(dipivalomethanato)europium as a shift reagent in the identification of 3-H-pyrano[3,2-f]quinolin-3-one. *Tetrahedron Lett.* **1970**, *11*, 4657–4660. [CrossRef]
28. Kudale, A.A.; Kendall, J.; Miller, D.O.; Collins, J.L.; Bodwell, G.J. Povarov Reactions Involving 3-Aminocoumarins: Synthesis of 1,2,3,4-Tetrahydropyrido[2,3-*c*]coumarins and Pyrido[2,3-*c*]coumarins. *J. Org. Chem.* **2008**, *73*, 8437–8447. [CrossRef]
29. Heber, D.; Berghaus, T. Synthesis of 5*H*-[1]benzopyrano[4,3-*b*]pyridin-5-ones containing an azacannabinoidal structure. *J. Heterocycl. Chem.* **1994**, *31*, 1353–1359. [CrossRef]
30. Khan, A.T.; Das, D.K.; Islam, K.; Das, P. A simple and expedient synthesis of functionalized pyrido[2,3-c] coumarin derivatives using molecular iodine catalyzed three-component reaction. *Tetrahedron Lett.* **2012**, *53*, 6418–6422. [CrossRef]
31. Majumdar, K.C.; Ponra, S.; Ghosh, D.; Taher, A. Multicomponent Aza-Diels–Alder Synthesis of Phenanthrolines and Pyranoquinolines. *Synlett* **2011**, *2011*, 104–110. [CrossRef]
32. Heber, D.; Ivanov, I.C.; Karagiosov, S.K. The Vilmeier reaction in the synthesis of 3-subtituted 5*H*-[1]benzopyrano[4,3-b]pyridine-5-ones. An unusual pyridine ring closure. *J. Heterocycl. Chem.* **1995**, *32*, 505–509. [CrossRef]
33. Symeonidis, T.S.; Litinas, K.E. Synthesis of methyl substituted [5,6]- and [7,8]-fused pyridocoumarins via the iodine-catalyzed reaction of aminocoumarins with n-butyl vinyl ether. *Tetrahedron Lett.* **2013**, *54*, 6517–6519. [CrossRef]
34. Ahn, S.; Yoon, J.A.; Han, Y.T. Total Synthesis of the Natural Pyridocoumarins Goniothaline A and B. *Synthesis* **2018**, *51*, 552–556. [CrossRef]
35. Symeonidis, T.S.; Kallitsakis, M.G.; Litinas, K.E. Synthesis of [5,6]-fused pyridocoumarins through aza-Claisen rearrangement of 6-propargylaminocoumarins. *Tetrahedron Lett.* **2011**, *52*, 5452–5455. [CrossRef]
36. Symeonidis, T.S.; Lykakis, I.N.; Litinas, K.E. Synthesis of quinolines and fused pyridocoumarins from N-propargylanilines or propargylaminocoumarins by catalysis with gold nanoparticles supported on TiO_2. *Tetrahedron* **2013**, *69*, 4612–4616. [CrossRef]
37. Hao, Z.; Zhou, X.; Ma, Z.; Zhang, C.; Han, Z.; Lin, J.; Lu, G.-L. Dehydrogenative Synthesis of Quinolines and Quinazolines via Ligand-Free Cobalt-Catalyzed Cyclization of 2-Aminoaryl Alcohols with Ketones or Nitriles. *J. Org. Chem.* **2022**, *87*, 12596–12607. [CrossRef] [PubMed]
38. Jiang, B.-J.; Zhang, S.-L. Synthesis of Quinolines and 2-Functionalized Quinolines by Difluorocarbene Incorporation. *Adv. Synth. Catal.* **2022**, *364*, 2157–2162. [CrossRef]