*molbank*

MDPI

*Short Note*

# (*E*)-6-Hydroxy-2-oxo-2*H*-chromen-7-yl 3-(4-hydroxy-3-methoxyphenyl)acrylate

**Yang-Heon Song**

Department of Chemistry, Mokwon University, Daejeon 35349, Republic of Korea; yhsong@mokwon.ac.kr; Tel.: +82-42-829-7562

**Abstract:** A hybrid compound **5**: (*E*)-6-hydroxy-2-oxo-2*H*-chromen-7-yl 3-(4-hydroxy-3-methoxyphenyl) acrylate composed of (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylic acid (ferulic acid) **1** and 6,7-hydroxycoumarin (esculetin) **3** was prepared in a 61% yield by the esterification reaction of protected ferulic acid **2a** with esculetin **3** in the presence of triethylamine in dichloromethane for 3 h, followed by deprotection using 3M HCl. The structure of compound **5** was confirmed by $^{1}$H, $^{13}$C NMR spectroscopy, mass-spectrometry and elemental analysis.

**Keywords:** coumarin; esculetin; ferulic acid; esterification; antioxidant

## 1. Introduction

Many coumarin-based derivatives are important structural scaffolds for the synthesis of potential biologically active compounds with different pharmacological applications [1]. They continue to be designed and synthesized [2] because of their remarkable biological properties, including anticancer [3], anticonvulsant [4], antimicrobial [5], and antiviral [6] activities. Coumarins with an intramolecular charge transfer character have also been investigated for fluorescence sensors [7,8]. Among them, 6,7-dihydroxycoumarin (esculetin) **3** (Figure 1) displayed various biological activities such as anticancer [9,10], free radical scavenging [11], anti-inflammatory [12], anti-arthritic [13], and hepatoprotective [14]. On the other hand, (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylic acid (ferulic acid) **1** (Figure 1), a phenolic acid widely present in seeds, vegetables, and fruits, has many pharmacological effects, including antioxidant [15], anticancer [16], neuroprotective [17], and anti-metabolic syndrome [18]. It has been widely used in the food, pharmaceutical, and cosmetic industries. However, there have been no reports on the synthesis of the hybrid compounds composed of **1** and **3**. We report herein the synthesis of a new hybrid compound **5** that is of potential biological interest, (*E*)-6-hydroxy-2-oxo-2*H*-chromen-7-yl 3-(4-hydroxy-3-methoxyphenyl)acrylate.


**Figure 1.** Two biologically active compounds, ferulic acid **1** and esculetin **3**.

## 2. Results

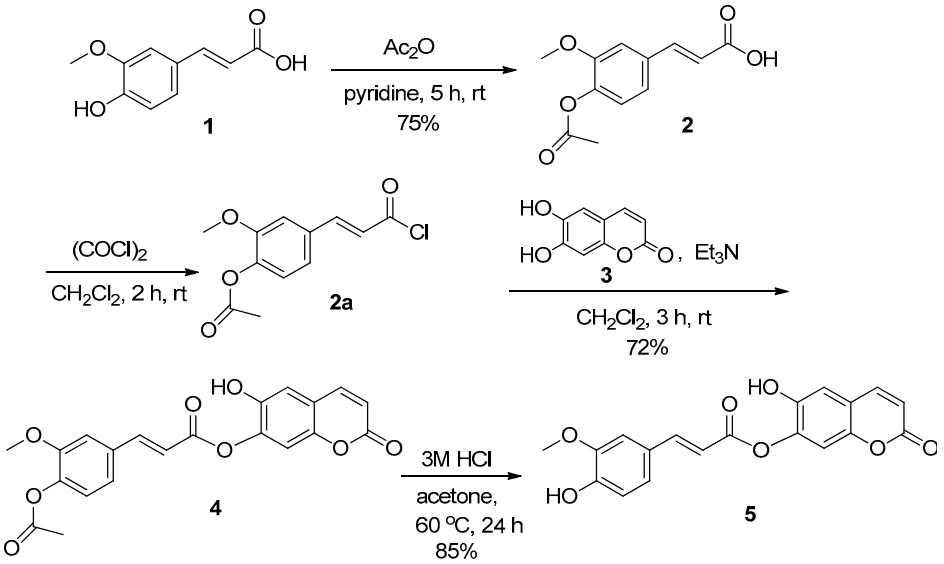
The new compound **5** was prepared as shown in Scheme 1. The hydroxy group of the starting material **1** was first protected with acetic anhydride and pyridine according to the previously reported procedure [19] to give **2**, (*E*)-3-(4-acetoxy-3-methoxyphenyl)-acrylic acid. After **2** was activated with oxalyl chloride, including DMF, the resultant **2a** was allowed to react with **3** in dichloromethane at room temperature for 3 h in the presence of triethylamine to afford an esterified product **4**, (*E*)-6-hydroxy-2-oxo-2*H*-chromen-7-yl

check for updates

**Citation:** Song, Y.-H. (*E*)-6-Hydroxy-2-oxo-2*H*-chromen-7-yl 3-(4-hydroxy-3-methoxyphenyl)acrylate. *Molbank* **2023**, *2023*, M1656. https://doi.org/10.3390/M1656

Received: 29 April 2023
Revised: 26 May 2023
Accepted: 31 May 2023
Published: 2 June 2023

3-(4-acetoxy-3-methoxyphenyl)acrylate at a 72% yield. The deprotection of the acetyl group of **4** was achieved through the use of a 3M HCl solution in acetone at room temperature for 24 h to give a conjugate compound **5** in an 85% yield.




**Scheme 1.** Synthesis of the target compound **5**.

The $^{1}$H NMR spectrum of **4** showed an expected pattern with two sharp singlets at δ 3.82 and 2.24 ppm, which were attributed to methoxy and acetyl protons, respectively, and two doublets at δ 7.81 and 6.93 ppm (*J* = 16.0 Hz) due to *trans* vinyl protons in the ferulic acid moiety. It also showed two doublets at δ 7.89 and 6.24 ppm (*J* = 9.5 Hz) due to the *cis* vinyl protons of esculetin moiety, and the aromatic protons were shown as two singlets at δ 7.48, 6.86 and three doublets at δ 7.59 (d, *J* = 1.7 Hz), 7.36 (dd, *J* = 8.2, 1.7 Hz) and 7.13 ppm (d, *J* = 8.2 Hz). A sharp singlet at δ 10.93 of the low field was shown for a hydroxy proton of esculetin moiety (Supplementary Materials). In the $^{13}$C NMR spectrum, compound **4** displayed three peaks δ 168.8, 165.0, 160.7 ppm for the two carbonyls and newly formed ester carbon, including sixteen peaks for aromatic and vinyl carbons at δ 153.6, 153.2, 151.7, 146.4, 144.5, 141.9, 136.1, 133.3, 123.8, 122.5 (2C), 117.7, 112.9, 112.8, 111.4, 104.0 ppm, and two peaks for two methyl carbons at δ 56.6, 20.9 ppm. The mass spectrum showed $m/z$ = 395 ($M^+ - 1$) corresponding to the molecular formula, $C_{21}H_{16}O_8$, and elemental analysis also provided satisfactory results.

Compound **5** was confirmed by signals δ 10.88 (s, OH, 1H), 9.64 (s, OH, 1H), 7.88 (d, *cis* vinyl proton, *J* = 9.5 Hz, 1H), 7.71 (d, *trans* vinyl proton, *J* = 15.9 Hz, 1H), 7.45 (s, 1H), 7.39 (d, Ar, *J* = 1.6 Hz, 1H), 7.18 (dd, Ar, *J* = 8.2, 1.7 Hz, 1H), 6.85 (s, Ar, 1H), 6.79 (d, Ar, *J* = 8.2 Hz, 1H), 6.69 (d, *trans* vinyl proton, *J* = 15.9 Hz, 1H), 6.24 (d, *cis* vinyl proton, *J* = 9.5 Hz, 1H), 3.80 (s, OMe, 3H) in the $^{1}$H NMR, and signals δ 165.3, 160.7, 153.7, 153.1, 150.3, 148.5, 147.6, 144.5, 136.3, 125.9, 124.1, 122.5, 116.1, 113.6, 112.8, 112.1, 111.3, 104.0, 56.6 in the $^{13}$C NMR spectrum. It showed the absence of signals such as acetyl protons at δ 2.24 ppm in the $^{1}$H NMR and carbonyl carbon of acetyl at δ 168.8 ppm in the $^{13}$C NMR spectrum, compared to the spectra of compound **4**. Two singlets due to two hydroxy groups, including deprotection, were shown at δ 10.88 and 9.64 ppm in the $^{1}$H NMR spectrum. The mass spectrum provided $m/z$ = 353 ($M^+$-1) corresponding to the molecular formula, $C_{19}H_{14}O_7$, and elemental analysis gave satisfactory results. The preliminary biological test of DPPH's free radical scavenging activity [20,21] for **4** and **5** as an antioxidant exhibited $SC_{50}$ values of 40.4 and 2.36 μg/mL, respectively, compared to **1** (2.58 μg/mL) and **3** (0.82 μg/mL) with ascorbic acid (1.65 μg/mL) as the positive control.

In conclusion, a new hybrid compound **5** was effectively prepared at a 61% yield by the esterification reaction of a protected ferulic acid **2a** with esculetin **3** in the presence of triethylamine in dichloromethane for 3 h, followed by the deprotection of the acetyl group

using 3M of HCl in acetone. This compound could be useful as a potential material with various biological activities.

## 3. Materials and Methods

### *3.1. General Information*

Ferulic acid, esculetin, oxalic chloride, acetic anhydride, triethylamine, 1,1-diphenyl-2-picryhydrazyl (DPPH), ascorbic acid, and the dry organic solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA) and TCI (Tokyo, Japan). The melting point was determined on the Kofler apparatus. Thin-layer chromatography (TLC) was used to monitor reactions and was performed using aluminum sheets precoated with silica gel 60 ($HF_{254}$, Merck, Waltham, MA, USA) and visualized with UV radiation (Fisher Scientific, Waltham, MA, USA). The $^{1}H$ and $^{13}C$ NMR spectrum was recorded in deuterated DMSO with TMS as the standard on a JEOL JNM-ECZ600R 500 FT-NMR (Tokyo, Japan). The mass spectrum was obtained with AGILENT1100 LCMS (Santa Clara, CA, USA) under electrospray ionization (ESI) conditions. The absorbance for the compounds was measured using a SpectraMax Paradigm multi-mode microplate reader (San Jose, CA, USA).

### *3.2. Synthesis of (E)-6-hydroxy-2-oxo-2H-chromen-7-yl 3-(4-acetoxy-3-methoxyphenyl)acrylate* (**4**)

To a stirred solution of **2** (1.0 g, 4.23 mmol) in dry dichloromethane (20 mL), a few drops of DMF was added in the form of oxalyl chloride (1.07 g, 8.45 mmol) and stirred at room temperature for 2 h. After the evaporation of the solution, the mixture was diluted with dichloromethane (20 mL) and was added with **3** (0.75 g, 4.23 mmol) and triethylamine (1.19 mL, 8.50 mmol). The resulting solution was stirred at room temperature for 3 h with monitoring. When the reaction was complete, the mixture was washed with a 0.1M HCl solution (10 mL) and water (10 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product was purified by column chromatography (eluent: ethyl acetate/*n*-hexane = 1/1, *v*/*v*) and recrystallized from ethanol to give a white solid of **4** at a 72% yield (1.20 g). Mp 212–213 °C; TLC *R*f = 0.48 (dichloromethane/MeOH = 90/10). $^{1}H$ NMR (500 MHz, DMSO-$d_6$) (ppm) δ 10.93 (s, 1H), 7.89 (d, *J* = 9.5 Hz, 1H), 7.81 (d, *J* = 16.0 Hz, 1H), 7.59 (d, *J* = 1.7 Hz, 1H), 7.48 (s, 1H), 7.36 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 16.0 Hz, 1H), 6.86 (s, 1H), 6.24 (d, *J* = 9.5 Hz, 1H), 3.81 (s, 3H), 2.24 (s, 3H). $^{13}C$ NMR (126 MHz, DMSO-$d_6$) (ppm) δ 168.8, 165.0, 160.7, 153.6, 153.2, 151.7, 146.4, 144.5, 141.9, 136.1, 133.3, 123.8, 122.5 (2C), 116.1, 113.6, 112.8, 112.1, 111.3, 104.0, 56.3. MS (ESI) *m*/*z* = 395 ($M^+ - 1$). Anal. calcd. for $C21H16O_8$, %: C, 63.64; H, 4.07. Found, %: C, 63.88; H, 4.20.

### *3.3. Synthesis of (E)-6-hydroxy-2-oxo-2H-chromen-7-yl 3-(4-hydroxy-3-methoxyphenyl)acrylate* (**5**)

A solution of **4** (1.0 g, 2.82 mmol) in acetone (15 mL) containing 3M HCl (1 mL) was heated at 60 °C while stirring for 24 h. After the reaction was complete, the mixture was added to saturated aqueous sodium bicarbonate (10 mL) and was extracted with ethyl acetate (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/MeOH = 95/5, *v*/*v*) and recrystallized from ethanol to give a white solid of **5** at an 85% yield (0.84 g). Mp 232–233 °C; TLC *R*f = 0.38 (dichloromethane/MeOH = 90/10). $^{1}H$ NMR (500 MHz, DMSO-$d_6$) (ppm) δ 10.88 (s, 1H), 9.64 (s, 1H), 7.88 (d, *J* = 9.5 Hz, 1H), 7.71 (d, *J* = 15.9 Hz, 1H), 7.45 (s, 1H), 7.39 (d, *J* = 1.6 Hz, 1H), 7.18 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.85 (s, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 15.9 Hz, 1H), 6.24 (d, *J* = 9.5 Hz, 1H), 3.80 (s, 3H). $^{13}C$ NMR (126 MHz, DMSO-$d_6$) (ppm) δ 165.3, 160.7, 153.7, 153.1, 150.3, 148.5, 147.6, 144.5, 136.3, 125.9, 124.1, 122.5, 116.1, 113.6, 112.8, 112.1, 111.3, 104.0, 56.6. MS (ESI) *m*/*z* = 353 ($M^+ - 1$). Anal. calcd. for $C19H14O_7$, %: C, 64.41; H, 3.98. Found, %: C, 64.30; H, 4.09.

### *3.4. DPPH Radical Scavenging Assay for the Compounds*

Each sample was dissolved in methanol at various concentrations ranging from 0 to 100 μg/mL. Then, 50 μL of the sample solution was mixed with 450 μL of a DPPH solution (400 μM) and incubated for 30 min at 4 °C. The absorbance was measured at 517 nm using a microplate reader (SpectraMax Paradigm). The $SC_{50}$, which is the minimum concentration (μg/mL) required scavenging at 50% of the DPPH radicals, was calculated based on the measured absorbance. Ascorbic acid was used as a positive control.

**Supplementary Materials:** The following supporting information can be downloaded online. Figures S1–S6: $^{1}$H NMR, $^{13}$C NMR, and Mass spectra of compound **4** and **5**.

**Funding:** This research received no external funding.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** This work was supported by Mokwon University.

**Conflicts of Interest:** The author declares no conflict of interest.

## References

1. Flores-Morales, V.; Villasana-Ruíz, A.P.; Garza-Veloz, I.; González-Delgado, S.; Martinez-Fierro, M.L. Therapeutic effects of coumarins with different substitution patterns. *Molecules* **2023**, *28*, 2413. [CrossRef] [PubMed]
2. Lončarić, M.; Gašo-Sokač, D.; Jokič, S.; Molnar, M. Recent advances in the synthesis of coumarin derivatives from different starting materials. *Biomolecules* **2020**, *10*, 151. [CrossRef] [PubMed]
3. Bhattarai, N.; Kumbhar, A.A.; Pokharel, Y.R.; Yadav, P.N. Anticancer potentials of coumarin and its derivatives. *Mini Rev. Med. Chem.* **2021**, *21*, 2996–3029. [CrossRef] [PubMed]
4. Keri, R.S.; Budagumpi, S.; Balappa Somappa, S. Synthetic and natural coumarins as potent anticonvulsant agents: A review with structure-activity relationship. *J. Clin. Pharm. Ther.* **2022**, *47*, 915–931. [CrossRef]
5. Cheke, R.S.; Patel, H.M.; Ansari, I.A.; Ambhore, J.P.; Shinde, S.D.; Kadri, A.; Snoussi, M.; Adnan, M.; Kharkar, P.S.; Pasupuleti, V.R.; et al. Molecular insights into coumarin analogues as antimicrobial agents: Recent developments in drug discovery. *Antibiotics* **2022**, *11*, 566. [CrossRef]
6. Li, Z.; Kong, D.; Liu, Y.; Li, M. Pharmacological perspectives and molecular mechanisms of coumarin derivatives against virus disease. *Genes Dis.* **2021**, *9*, 80–94. [CrossRef]
7. Zhang, H.; Yu, T.Z.; Zhao, Y.L.; Fan, D.W.; Xia, Y.J.; Zhang, P. Synthesis, crystal structure, photo- and electro-luminescence of 3-(4-(anthracen-10-yl)phenyl)-7-(N,N′-diethylamino)coumarin. *Synth. Met.* **2010**, *160*, 1642–1647. [CrossRef]
8. Voutsadaki, S.; Tsikalas, G.K.; Klontzas, E.; Froudakis, G.E.; Katerinopoulos, H.E. A "turn-on" coumarin-based fluorescent sensor with high selectivity for mercury ions in aqueous media. *Chem. Commun.* **2010**, *46*, 3292–3294. [CrossRef]
9. Arora, R.; Sawney, S.; Saini, V.; Steffi, C.; Tiwari, M.; Saluja, D. Esculetin induces antiproliferative and apoptotic response in pancreatic cancer cells by directly binding to KEAP1. *Mol. Cancer* **2016**, *15*, 64. [CrossRef]
10. Wang, G.; Lu, M.; Yao, Y.; Wang, J.; Li, J. Esculetin exerts antitumor effect on human gastric cancer cells through IGF-1/PI3K/Akt signaling pathway. *Eur. J. Pharmacol.* **2017**, *814*, 207–215. [CrossRef]
11. Kim, S.H.; Kang, K.A.; Zhang, R.; Piao, M.J.; Ko, D.O.; Wang, Z.H.; Chae, S.W.; Kang, S.S.; Lee, K.H.; Kang, H.K.; et al. Protective effect of esculetin against oxidative stress-induced cell damage via scavenging reactive oxygen species. *Acta Pharmacol. Sin.* **2008**, *29*, 1319–1326. [CrossRef] [PubMed]
12. Jayakumar, T.; Huang, C.J.; Yen, T.L.; Hsia, C.W.; Sheu, J.R.; Bhavan, P.S.; Huang, W.C.; Hsieh, C.Y.; Hsia, C.H. Activation of Nrf2 by esculetin mitigates inflammatory responses through suppression of NF-κB signaling cascade in RAW 264.7 Cells. *Molecules* **2022**, *27*, 5143. [CrossRef] [PubMed]
13. Rzodkiewicz, P.; Gasińska, E.; Gajewski, M.; Bujalska-Zadrożny, M.; Szukiewicz, D.; Maśliński, S. Esculetin reduces leukotriene B4 level in plasma of rats with adjuvant induced arthritis. *Reumatologia* **2016**, *54*, 161–164. [CrossRef] [PubMed]
14. Choi, R.Y.; Ham, J.R.; Lee, M.K. Esculetin prevents non-alcoholic fatty liver in diabetic mice fed high-fat diet. *Chem. Biol. Interact.* **2016**, *260*, 13–21. [CrossRef]
15. Srinivasan, M.; Sudheer, A.R.; Menon, V.P. Ferulic acid: Therapeutic potential through its antioxidant property. *J. Clini. Biochem. Nutr.* **2007**, *40*, 92–100. [CrossRef]
16. Singh Tuli, H.; Kumar, A.; Ramniwas, S.; Coudhary, R.; Aggarwal, D.; Kumar, M.; Sharma, U.; Chaturvedi Parashar, N.; Haque, S.; Sak, K. Ferulic Acid: A Natural Phenol That Inhibits Neoplastic Events through Modulation of Oncogenic Signaling. *Molecules* **2022**, *27*, 7653. [CrossRef]
17. Di Giacomo, S.; Percaccio, E.; Gullì, M.; Romano, A.; Vitalone, A.; Mazzanti, G.; Gaetani, S.; Di Sotto, A. Recent advances in the neuroprotective properties of ferulic acid in Alzheimer's disease: A narrative review. *Nutrients* **2022**, *14*, 3709. [CrossRef]

18. Li, Y.; Sair, A.T.; Zhao, W.; Li, T.; Liu, R.H. Ferulic acid mediates metabolic syndrome via the regulation of hepatic glucose and lipid metabolisms and the insulin/IGF-1 receptor/PI3K/AKT pathway in palmitiate-treated HepG2 cells. *Agric. Food Chem.* **2022**, *70*, 14706–14717. [CrossRef]
19. Shirai, A.; Kajiura, M.; Omasa, T. Synergistic photobactericidal activity based on ultraviolet-A irradiation and ferulic acid derivatives. *Photochem. Photobiol.* **2015**, *91*, 1422–1428. [CrossRef]
20. Um, J.N.; Mim, J.W.; Joo, K.S.; Kang, H.C. Antioxidant, anti-wrinkle activity and whitening effect of fermented mixture extracts of *Angelica gigas*, *Paeonia lactiflora*, *Rehmannia chinensis* and *Cnidium officinale*. *Korean J. Med. Crop Sci.* **2017**, *25*, 152–159. [CrossRef]
21. Blois, M.S. Antioxidant determinations of by the use of a stable free radical. *Nature* **1958**, *181*, 1199–1200. [CrossRef]