Synthesis of Coumarin-Isatin Conjugates

Winda Seviani, Arif Fadlan a), Landaeta Yolga Pratama, Heni Masitoh and Herdayanto Sulistyo Putro

Department of Chemistry, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh Nopember

Kampus ITS Sukolilo, Surabaya 60111, East Java, Indonesia

a) Corresponding author: afadlan@its.ac.id

**Abstract.** Coumarins show various biological activities including antibacterial, anti-inflammatory, antifungal, antioxidant, anticoagulant, anticancer, and anti-HIV. Herein we report the synthesis of coumarin-isatin conjugates **9a,b**. The *O*-alkylation of coumarin **3** using ethyl chloroacetate **4** followed by a reaction with hydrazine hydrate **6** afforded the acetohydrazide **7**, which further reaction with isatin **8a** and 5,7-dibromoisatin **8b** produced the conjugates **9a,b**. The products were successfully synthesized in good yields and their structures were elucidated by 1H & 13CNMR, FTIR, and MS.

# INTRODUCTION

Coumarin or 2*H*-chromen-2-one composed of a benzene ring fused with a benzopyrone ring is a heterocyclic compound generally found naturally in the seeds, roots, and leaves of many plants [1-2]. Xanthotoxin, xanthyletin, and aeternaryiol are coumarins classified as furanocoumarin, pyranocoumarin, and 3,4-disubstituted benzocoumarin [2]. Neopeucedalactone and novobiocin are natural products with coumarin skeleton isolated *Peucedanum praeruptorum* root and *Streptomyces niveus* (**FIGURE 1**) [3,4]. Coumarin and its derivatives show a wide variety of biological activities such as antimicrobial, antibacterial, antifungal, antiviral, anti-inflammatory, anti-leishmanial, anticoagulant, anti-HIV, antidiabetic, and anticancer [2–4].



**FIGURE 1.** Structure of (a) coumarin, (b) xanthotoxin, (c) xanthyletin, (d) aeternaryiol, (e) neopeucedalactone, and (f) novobiocin

7-Hydroxy-4-methyl-2*H*-chromen-2-one with a methyl group on C4 and a hydroxy group on C7 in its coumarin structure has also been widely used as an antiviral agent for hepatitis B, hepatitis C virus infections, and HIV as well as for treating Alzheimer's disease by inhibiting acetylcholine production [9-11]. Modification through alkylation and hydroxylation of 7-hydroxy-4-methyl-2*H*-chromen-2-one could produce derivatives and potential agents with improved bioactivities. Structure modification is also could be performed by molecular hybridization which combines heterocyclic ring systems and provides hybrid molecules. This is an important strategy to seek new biologically active compounds [4,13]. Reddy et al. (2014) reported the synthesis of hybrid molecule 7-((5-(4-methoxy/bromophenylamino)-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (**FIGURE 2a**) with a zone of inhibition of 12 and 6 mm at a concentration of 1000 μg/mL against *Aspergillus niger* [10]. The synthesis and antiproliferation evaluation of *N*’-(1-(4-chlorophenyl)ethylidene)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy) acetohydrazide (**FIGURE 2b**) were also communicated by Duangdee et al. (2020). The hybrid molecule of coumarin and carbonyl compounds exhibited activity against HepG2 (IC50 2,84 μg/mL) and SKBR-3 (IC50 2,34 μg/mL) cell lines [11]. 7-((8-(4-Benzylpiperidin-1-yl)octyl)oxy)-4-methyl-2H-chromen-2-one (**FIGURE 2c**) has also been synthesized and shows DPPH radical-scavenging activity [12].



**FIGURE 2.** Structure of hybrid molecules with coumarin skeleton

Considering the potential of isatin in the area of medicinal chemistry [15,16] and to continue our works on the exploration of biologically active molecules [17-21], herein we report the synthesis of coumarin-isatin conjugates **9a,b** by hybridization of 7-hydroxy-4-methylcoumarin **3** with isatin framework. The reaction included the alkylation of coumarin **3**, substitution of the formed ester **5** to give the acetohydrazide **7** and coupling of this hydrazide with isatins.

# EXPERIMENTAL

## General

The uncorrected melting points were determined using a Fischer John apparatus (Cole Parmer, Illinois, USA). FTIR spectra were recorded on a Shimadzu 8400S spectrophotometer (Kyoto, Japan) in the range 4000-400 cm-1 using KBr pellets. The measurement of NMR spectra was performed in DMSO-d6 on a Bruker Avance Neo-Ascend 500 (Karlsruhe, Germany) (1H, 500 MHz; 13C, 125 MHz) using TMS as internal standard. The chemical shifts are expressed in ppm, multiplicities are singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and coupling constant (*J*) in Hz. Mass spectra were recorded on a ESI Xevo G2-S QTof (Waters, USA). Pre-coated silica gel plates (0.20 mm, 60 F54) (Merck, Germany) were used for TLC analysis and detection of the spots under UV light or iodine chamber.

## Synthesis 7-hydroxy-4-methylcoumarin 3

Concentrated sulfuric acid (50 mL) was placed in a round bottom flask in an ice bath (5ºC). Resorcinol **1** (3.7481 g, 34 mmol) in ethyl acetoacetate **2** (4.5 mL, 34 mmol) was added dropwise and the reaction mixture was stirred for 60 minutes [15]. The mixture was poured into crushed ice and filtered to obtain precipitate which was then dried and redissolved in 1M aqueous NaOH solution. Concentrated H2SO4 was added and the formed solid was filtered, washed with cold distilled water, and recrystallized from ethanol to give the product **1** as pink solid (3.8228 g, 64%). mp 222‒224ºC. FTIR (KBr) *ν* cm-1: 3501, 3119, 2953, 1670, 1606, 1276. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 10.52 (s, 1H, OH), 7.58 (d, *J* = 8.5 Hz, 1H, ArH), 6.70‒6.81 (m, 2H, ArH), 6.12 (d, *J* = 1.5 Hz, 1H, ArH), 2.36 (d, *J* = 1 Hz, 3H, CH3). 13C-NMR (DMSO-*d6*, 125 MHz): *δ* 161.6 (C=O); 160.8, 155.3, 154.0, 127.1, 113.3, 112.5, 110.7, 102.6 (ArC); 18.6 (CH3). HRESIMS [Found: *m*/*z* 177.0567 (M+H)+, calcd for C10H9O3: (M+H)+, 177.0552].

## Synthesis ethyl 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetate 5

7-Hydroxy-4-methylcoumarin **3** (1.0572 g, 6 mmol) was dissolved in DMF (25 mL) and stirred at 0ºC for 15 minutes. Next, K2CO3 (0.9684 g, 7 mmol) was added, and the mixture was further stirred for 30 minutes. Ethyl chloroacetate **4** (1.1 mL, 10 mmol) was added and the mixture was stirred again at 0ºC for 1 hour followed by stirring at room temperature for 3 hours (TLC monitor) [16]. The reaction mixture was poured into crushed ice and the obtained precipitate was filtered, dried, and purified by recrystallization from ethanol to give the title compound **5** a white solid (0.9033 g, 57%). mp 118‒120ºC. FTIR (KBr) *ν* cm-1: 3001, 2918, 1764, 1728, 1616, 1227, 1198. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 7.70 (d, *J* = 9.5 Hz, 1H, ArH), 6.99‒7.00 (m, 2H, ArH), 6.23 (d, *J* = 1 Hz, 1H, ArH), 4.93 (s, 2H, CH2), 4,19 (q, *J* = 7.0; 7.5 Hz, 2H, CH2), 2.40 (d, *J* = 1 Hz, 3H, CH3), 1.23 (t, *J* = 7; 7 Hz, 3H, CH3).13C-NMR (DMSO-*d6*, 125 MHz): *δ* 168.7, 160.5 (C=O); 161.1, 155.0, 153.8, 127.0, 114.2, 112.8, 112.0, 102.0 (ArC); 65.4, 61.3 (CH2); 18.6, 14.5 (CH3). HRESIMS [Found: *m*/*z* 263.0911 (M+H)+, calcd for C14H15O5: (M+H)+, 263.0919].

## Synthesis 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetohydrazide 7

Ethyl 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetate **5** (0.6554 g, 2.5 mmol) and hydrazine hydrate **6** (0.4 mL, 7.5 mmol) in a round bottom flask were dissolved in ethanol (12.5 mL). The reaction mixture was stirred and refluxed for 5 hours (TLC monitor) [22]. The obtained solid was filtered, dried, and purified by recrystallization from ethanol to yield 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetohydrazide **7** as white solid (0.5887 g, 95%). mp 246‒248ºC. FTIR (KBr) *ν* cm-1: 3331, 3269, 3082, 2958, 1726, 1610, 1284, 1074. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 9.42 (s, 1H, NH2), 7.70 (d, *J* = 8.5 Hz, 1H, ArH), 6,97‒7,02 (m, 2H, ArH), 6.23 (s, 1H, ArH), 4.62 (s, 2H, CH2), 4.36 (d, *J* = 3.5 Hz, 2H, NH2), 2.40 (s, 3H, CH3). 13C-NMR (DMSO-*d6*, 125 MHz): *δ* 166.5, 160.6 (C=O); 161.2, 155.0, 153.9, 126.9, 114.0, 113.0, 111.9, 102.0 (ArC), 67.0 (CH2), 18.6 (CH3). HRESIMS [Found: *m*/*z* 249.0878 (M+H)+, calcd for C12H13N2O4: (M+H)+, 249.0875].

## Synthesis 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)-*N*’-(2-oxoindolin-3-ylidene)acetohydrazide 9a

2-((4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetohydrazide **7** (0.1248 g, 0.5 mmol) and isatin **8a** (0.0740 g, 0.5 mmol) were dissolved in ethanol (5 mL). Glacial acetic acid (0.06 mL) was added and the reaction mixture was refluxed for 5 hours (TLC monitor) [23]. The solid was filtered and dried to produce product **9a** as a yellow solid (0.1659 g, 88%). mp >344ºC. FTIR (KBr) *ν* cm-1: 3220, 1715, 1610, 1513, 1267. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 11.27 (s, 1H, NH), 10.83 (s, 1H, NH), 7.71 (d, *J* = 8.5 Hz, 1H, ArH), 7.58 (s, 1H, ArH), 7.38‒7.42 (m, 1H, ArH), 6.91‒7.12 (m, 4H, ArH), 6.23 (s, 1H, ArH), 5.02 (s, 2H, CH2), 2.41 (s, 3H, CH3). HRESIMS [Found: *m*/*z* 378.1092 (M+H)+, calcd for C20H16N3O5: (M+H)+, 378.1090].

## Synthesis *N*’-(5,7-dibromo-2-oxoindolin-3-ylidene-2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetohydrazide 9b

*N*’-(5,7-Dibromo-2-oxoindolin-3-ylidene-2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetohydrazide **9b** was synthesized according to the procedure applied to **9a** by using compound **7** (0.1250 g, 0.5 mmol) and 5,7-dibromoisatin **8b** (0.1536 g, 0.5 mmol) [23]. The product **9b** was obtained as a yellow solid (0.2543 g, 95%). mp >344ºC. FTIR (KBr) *ν* cm-1: 3406, 3056, 1692, 1610, 1513, 1274. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 11.73 (s, 1H, NH), 11.27 (s, 1H, NH), 7.85 (d, *J* = 7.5 Hz, 1H, ArH), 7.71 (d, *J* = 9 Hz, 1H, ArH), 7.01‒7.10 (m, 3H, ArH), 6.23 (s, 1H, ArH), 5.32 (s, 2H, CH2), 2.41 (s, 3H, CH3). HRESIMS [Found: *m*/*z* 533.9300 (M+H)+, calcd for C20H14N3O5Br2: (M+H)+, 533.9300].

# RESULTs AND DISCUSSION

Coumarins and their derivatives can be synthesized through several reactions such as Pechmann condensation, Knoevenagel, Perkin, Wittig, and Reformatsky reactions [5,24]. However, Pechmann condensation between phenol and β-keto ester is considered the general and easiest method to prepare coumarins [6,7]. This reaction is executed in water, ethanol, ethyl acetate, dichloromethane, acetonitrile, or toluene in the presence of acid catalysts i.e. sulphuric acid, hydrochloric acid, phosphoric acid, lewis acids such as trifluoroacetic acid, phosphorous pentaoxide, ZrCl4, and TiCl4 [7,25,26]. Various methods have been developed to prepare coumarin including solvent-free using solid acids as heterogeneous catalysts, grinding technique, microwave irradiation, and sonication [25,27–29]. In the present study, the classical Pechmann condensation employing sulphuric acid as a catalyst has been selected.

Coumarin **3** was synthesized according to the previously reported method [23]. To obtain the coumarin-isatin conjugates, the key intermediate was 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetohydrazide **7**. This compound could be accomplished by *O*-alkylation of 7-hydroxy-4-methylcoumarin **3** using ethyl chloroacetate **4** [30], followed by substitution of the ester **5** with hydrazine hydrate **6** [31]. The coumarin-isatin conjugates **9a-b** were then produced by the reaction of intermediate **7** with isatin **8a** or 5,7-dibromoisatin **8b** [32].



**FIGURE 1.** Synthesis of coumarin-isatin conjugates **9a-b**. Reagents/conditions: (a) ethyl acetoacetate **2**, ice bath, 1M aq NaOH, H2SO4 c, 64%; (b) ethyl chloroacetate **4**, K2CO3, DMF, 0°C to rt, 57%; (c) hydrazine hydrate **6**, ethanol, reflux 5 h, 95%; (d) isatin **8a** or 5,7-dibromoisatin **8b**, glacial acetic acid (cat.), reflux 5 h, 88% **9a**, 95% **9b**.

The synthesis of coumarin-isatin conjugates **9a-b** is described in **FIGURE 1**. It started with the formation of 7-hydroxy-4-methylcoumarin **3** (64% yield) from the reaction of resorcinol **1** and ethyl acetoacetate **2** with concentrated sulfuric acid as a catalyst through Pechmann condensation involving transesterification, intramolecular hydroxy alkylation, and dehydration [33]. The reaction was performed in an ice bath with a dropwise addition of resorcinol **1** in ethyl acetoacetate **2**. The precipitate was redissolved in sodium hydroxide and precipitated again with the addition of concentrated sulfuric acid. Next, the *O*-alkylation of coumarin **3** was done by using ethyl chloroacetate **4** which involves the nucleophilic substitution of the chlorine atom of ester **4** by the hydroxyl group of coumarin **3**, in the presence of potassium carbonate in DMF [34]. The reaction was carried out at 0ºC to room temperature to give the ethyl 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetate **5** (57% yield). The key intermediate **7** (95% yield) was then obtained from the reaction of the ester **5** with hydrazine hydrate **6** in ethanol. It is associated with acyl-substitution involving nucleophilic addition of hydrazine hydrate **6** to the ester **5** and elimination of alcohol as leaving group [29]. Finally, the coupling reaction of 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetohydrazide **7** with isatin **8a** and 5,7-dibromoisatin **8b** in ethanol with the addition of glacial acetic acid yielded coumarin-isatin conjugates **9a-b** in 88 and 95% yields. This reaction follows the acid-catalyzed nucleophilic addition of amine to the carbonyl group of ketone [29]. All the synthesized compounds were characterized by 1H and 13C NMR, FTIR, and HRMS spectroscopies and the spectra showed the predicted signals.

The chemical structure of 7-hydroxy-4-methylcoumarin **3** was elucidated based on analytical data. The IR spectrum displayed absorption peaks at 3501 and 1670 cm-1 due to the presence of hydroxyl and carbonyl groups. The 1H NMR spectrum of **3** showed a singlet signal at *δ* 10.52 ppm attributed to hydroxyl proton and its 13C NMR spectrum indicated signals at *δ* 18.6 and 161.6 ppm for methyl and carbonyl carbons, respectively. The HRESIMS spectrum of coumarin **3** exhibited a molecular ion peak at *m/z* 177.0567 [M + H]+ corresponding to its relative mass (*m/z* 177.0552). The formation of ethyl 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetate **5** was confirmed by spectral data of IR, 1H NMR, 13C NMR, and MS. For example, the hydroxyl peak present in IR spectrum of the precursor **3** disappeared in the IR spectrum of **5** and revealed the presence of ester C-O absorption bands in the region of 1227-1198 cm−1. The 1H NMR spectrum of **5** exhibited a quartet signal at *δ* 4.19 ppm (*J* = 7.0; 7.5 Hz, 2H) correlates to methylene protons and the 13C NMR showed signals at *δ* 61.3, 65.4 ppm for methylene carbon and at *δ* 160.5, 168.7 ppm for carbonyl carbons. The mass spectrum demonstrated the molecular ion peak at *m/z* 263.0911 [M + H]+ fit with the relative mass of **5** (*m/z* 263.0919). Next, the analytical data of 1H NMR, 13C NMR, IR, and HRMS were used for identifying the structure of 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetohydrazide **7**. Its IR spectrum displayed peaks at 3269 and 3331 cm-1 assigned to NH groups. The 1H NMR spectrum showed singlet signals at *δ* 4.36 and 9.42 ppm for =NH-NH2 protons. The methylene and carbonyl carbons existed at *δ* 67.0, 160.6, and 166.5 ppm in the 13C NMR spectrum. The HRESIMS spectrum exhibited the molecular ion peak at *m/z* 249.0878 [M + H]+ and coincided with the relative mass of **7** (*m/z* 249.0875). Further, the amine and carbonyl groups of **9a** and **9b** appeared in their IR spectrum at 3220, 3406, 1715, and 1692 cm-1, respectively. Their 1H NMR spectra appeared singlets at *δ* 10.83 and 11.27 ppm for **9a** and at *δ* 11.27 and 11.73 ppm for **9b** assignable to the protons of amine groups. In the HRESIMS spectra, the molecular ion peaks of **9a** and **9b** were at *m/z* 378.1092 and *m/z* 533.9300 appropriate for the relative mass of **9a** (*m/z* 378.1090) and **9b** (*m/z* 533.9300). **TABLE 1** and **TABLE 2** display the analytical data.

**TABLE 1.** The 1H NMR data of compounds **3**, **5**, **7**, **9a**, and **9b**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Proton** | **Chemical Shifts (δ) (ppm)** | | | | |
| **3** | **5** | **7** | **9a** | **9b** |
| -CH3 | 2.36 (d, *J* = 1 Hz, 3H) | 1.23 (t, *J* = 7; 7 Hz, 3H)  2.40 (d, *J* = 1 Hz, 3H) | 2.40 (s, 3H) | 2.41 (s, 3H) | 2.41 (s, 3H) |
| -CH2 |  | 4.19 (q, *J* = 7.0; 7.5 Hz, 2H)  4.93 (s, 2H) | 4.62 (s, 2H) | 5.02 (s, 2H) | 5.32 (s, 2H) |
| ArH | 6.12 (d, *J* = 1.5 Hz, 1H)  6.70‒6.81 (m, 2H)  7.58 (d, *J* = 8.5 Hz, 1H) | 6.23 (d, *J* = 1 Hz, 1H)  6.99‒7.00 (m, 2H)  7.70 (d, *J* = 9.5 Hz, 1H) | 6.23 (s, 1H)  6,97‒7,02 (m, 2H)  7.70 (d, *J* = 8.5 Hz, 1H) | 6.23 (s, 1H)  6.91‒7.12 (m, 4H)  7.71 (d, *J* = 8.5 Hz, 1H)  7.38‒7.42 (m, 1H)  7.58 (s, 1H) | 6.23 (s, 1H)  7.01‒7.10 (m, 3H)  7.71 (d, *J* = 9 Hz, 1H)  7.85 (d, *J* = 7.5 Hz, 1H) |
| -NH |  |  | 9.42 (s, 1H) | 10.83 (s, 1H)  11.27 (s, 1H) | 11.27 (s, 1H)  11.73 (s, 1H) |
| -NH2 |  |  | 4.36 (d, *J* = 3.5 Hz, 2H) |  |  |
| -OH | 10.52 (s, 1H) |  |  |  |  |

**TABLE 2.** The 13C NMR data of compounds **3**, **5**, and **7**

|  |  |  |  |
| --- | --- | --- | --- |
| **Carbon** | **Chemical Shifts (δ) (ppm)** | | |
| **3** | **5** | **7** |
| -CH3 | 18.6 | 14.5  18.6 | 18.6 |
| -CH2 |  | 61.3  65.4 | 67.0 |
| ArC | 102.6  110.7  112.5  113.3  127.1  154.0  155.3  160.8 | 102.0  112.0  112.8  114.2  127.0  153.8  155.0  161.1 | 102.0  111.9  113.0  114.0  126.9  153.9  155.0  161.2 |
| C=O | 161.6 | 160.5  168.7 | 160.6  166.5 |

# CONCLUSION

Coumarin-isatin conjugates **9a-b** were successfully synthesized in 88 and 95% yields. The structure of the products **9a-b** was established by spectroscopic techniques (1H & 13CNMR, FTIR, HRMS).

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