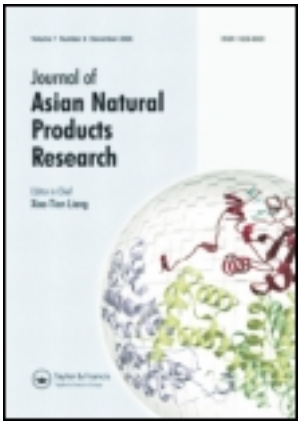

Journal of Asian Natural Products Research

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ganp20

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Available online: 25 May 2011

To cite this article: Aamer Saeed (2011): Synthesis of 5-chloro-8-hydroxy-6-methoxy-3-pentylisocoumarin, Journal of Asian Natural Products Research, 13:06, 505-511

To link to this article: http://dx.doi.org/10.1080/10286020.2011.572552

Journal of Asian Natural Products Research
Vol. 13, No. 6, June 2011, 505–511

Synthesis of 5-chloro-8-hydroxy-6-methoxy-3-pentylisocoumarin

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(*Received 13 December 2010; final version received 13 March 2011*)

The synthesis of title isocoumarin, the 5-chloro analog of naturally occurring 7-chloro-8-hydroxy-6-methoxy-3-pentylisocoumarin, isolated from *Tessmannia densiflora* is described. Chlorination of ethyl 2-(2-ethoxy-2-oxoethyl)-4,6-dimethoxybenzoate (**2**) afforded 3-chloro ester (**3**) followed by hydrolysis to furnish the 2-(carboxymethyl)-3-chloro-4,6-dimethoxybenzoic acid (**4**) that was converted to corresponding anhydride (**5**). Condensation of the latter with hexanoyl chloride in the presence of tetramethylguanidine and triethyl amine afforded 5-chloro-6,8-dimethoxy-3-pentylisocoumarin (**6**) which upon regioselective demethylation yielded the title isocoumarin (**1**).

Keywords: chlorinated isocoumarins; *Tessmannia densiflora*; 2-chloro-3,5-dimethoxy homophthalic acid

1. Introduction

Almost 300 isocoumarins and dihydroisocoumarins that have been isolated from various natural sources [1–3]; however, only a few chlorine-substituted isocoumarins are found in nature. These include 5-chloro-8-hydroxy-6-methoxy-3-methylisocoumarin [4] and its dihydroisocoumarin [5], 7-chloro-8-hydroxy-6-methoxy-3-methylisocoumarin and its dihydroisocoumarin and 5,7-dichloro-8-hydroxy-6-methoxy-3-methylisocoumarin isolated from *Periconia macrospinosa, Swartzia laevicarpa, Tovimita brasiliensis*, and *Sporormia affinis* [6], ochratoxins A–C [7] and its methyl ester [8] from *Aspergillus ochraceus*, 4-hydroxyochratoxin A from *Penicillium virdicatin* [9], 5-chloro-8-hydroxy-4-hydroxymethy-3-methylisocoumarin from *Heterobasidion annosum* [10], 4-chloro-8-hydroxy-6-methoxy-3,5-dimethyl-3,4-dihydroisocoumarin derivatives from *Lachnum papyraceum* [11], diachlorodiaportin and related isocoumarins from lichen *Graphis sp.* [12], chaetochiversins A and B from *Chaetomium chiversii* [13], avicennin A (5-chloro-6,8-dihydroxy-3-methylisocoumarin) from mangrove endophytic fungus in south China sea [14], TMC-264, a novel tricyclic heptaketide from *Phoma sp.* [15], graphislactone G, a chlorinated resorcylic lactone from *Graphis scripta* [16], and 5-chloro-4,6-dihydroxymellin from *Cephalosporium acremonium* [17]. Recently, Nkunya and coworkers (2009) during investigations for botanical insecticides for the control of malaria-transmitting *Anopheles gambiae* mosquitoes isolated among other compounds 8-hydroxy-6-methoxy-3-pentylisocoumarin and 7-chloro-8-hydroxy-6-methoxy-3-pentylisocoumarin from the stem and root bark extracts of *Tessmannia densiflora* Harms (family Caesalpiniaceae) that showed mosquito larvicidal activity [18].

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ISSN 1028-6020 print/ISSN 1477-2213 online

DOI: 10.1080/10286020.2011.572552
http://www.informaworld.com

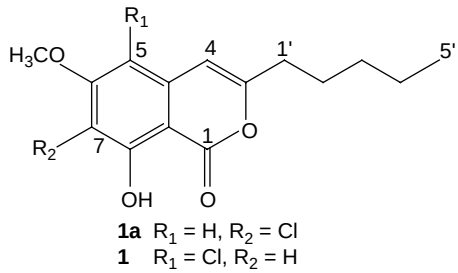
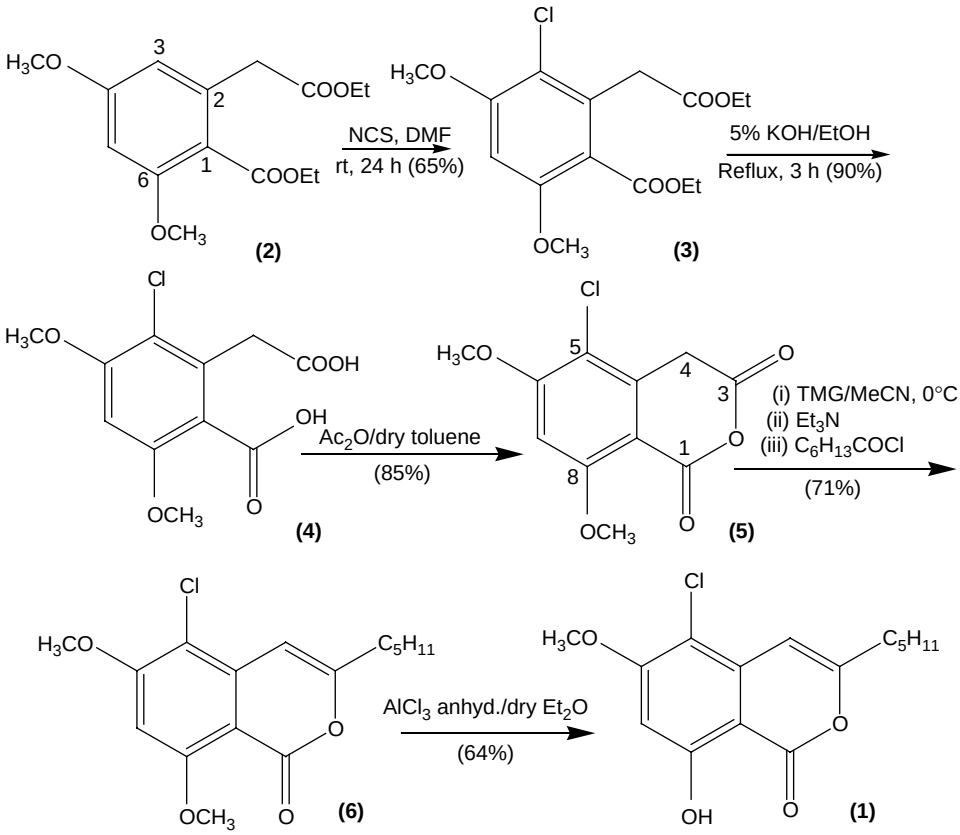


Figure 1. Structures of compounds **1a** and **1**.

As a continuance of our endeavors in the synthesis, characterization, crystal structure, and bioevaluation of this important class of natural lactones [19–21], a synthesis of the title compound was undertaken as the 5-chloro analog (**1**) of the natural 7-chloro-8-hydroxy-6-methoxy-3-pentylisocoumarin (**1a**) for comprehensive bioevaluation and comparison (Figure 1).

2. Results and discussion

The synthetic pathway employed to prepare the target compound is outlined in Scheme 1. Ethyl 2-(2-ethoxy-2-oxoethyl)-4,6-dimethoxybenzoate (**2**) obtained by the esterification of 2-(3,5-dimethoxyphenyl)acetic acid was converted into ethyl 3-chloro-2-(2-ethoxy-2-oxoethyl)-4,6-dimethoxybenzoate (**3**) by reaction with N-chlorosuccinimide (NCS) in dry DMF. The structure was ascertained on the basis of IR, NMR, and mass spectral characteristics and elemental analysis. IR spectrum showed peaks at 2978 (C—H), 1722 (C═O), 1591 (C═C), 1077 (C—O) cm^{-1} and a characteristic peak at



Scheme 1. Synthesis of 5-chloro-8-hydroxy-6-methoxy-3-pentylisocoumarin.

680 cm^{-1} for (C—Cl) indicated the substitution of chloro group on the ring. The ^{1}H NMR spectrum showed the triplet and quartets of ethyl groups of the phenacetyl ester moiety slightly upfield as compared with the corresponding signals for benzoyl ester moiety and a singlet at 6.94 ppm for H-5 aromatic proton. In ^{13}C NMR spectrum, the carbonyl carbon of phenacetyl ester appeared at 169.5 ppm and that of benzoyl ester carbonyl at 166.7 ppm. A peak at 106.6 ppm is indicative of the carbon attached to the chloro group. The structure was finally confirmed by single crystal X-ray diffraction data, which unequivocally showed that chlorination had taken place regioselectively at the less-hindered 3- rather than the 5-position on the ring. The molecular structure of compound **3** is shown in Figure 2. It crystallizes in the monoclinic space group P2(1)/c with $Z = 4$ and unit cell dimensions: $a = 8.6616(6)$, $b = 22.3998(16)$, $c = 8.9963(7)$ Å, $\alpha = 90°$, $\beta = 114.351(2)°$, $\gamma = 90°$, and $V = 1590.2(2)$ $Å^3$ [22].

Alkaline hydrolysis of chloro diester (**3**) afforded 2-(carboxy methyl)-3-chloro-4,6-dimethoxybenzoic acid (**4**) as the key intermediate. IR spectrum showed a broad peak of OH groups of acid at 3500 cm^{-1}, indicating the hydrolysis of ester to acid functionality in addition to those at 2990 (C—H), 1722 (C═O), 1586 (C═C), 1081 (C—O), and 652 (C—Cl) cm^{-1}. The ^{1}H NMR spectrum of chlorinated homophthalic acid showed broad peaks at 11.2 and 11.0 ppm for two OH of carboxylic acid groups, whereas the peaks in the alkyl region were absent. In ^{13}C NMR spectrum, the carbonyl carbons of phenacetyl appeared at 173.3 ppm and those of benzoyl ester carbonyl group at 169.4 ppm.

Diacid (**4**) was smoothly converted into 5-chloro-6,8-dimethoxyiso chroman-1,3-dione (**5**) by refluxing with acetic anhydride in dry toluene. In IR spectrum of the anhydride, the peaks for OH group of acid were absent whereas peaks at 1797 and 1749 cm^{-1} indicated the anhydride functionality. H-7 appeared at δ 6.56, CH_2

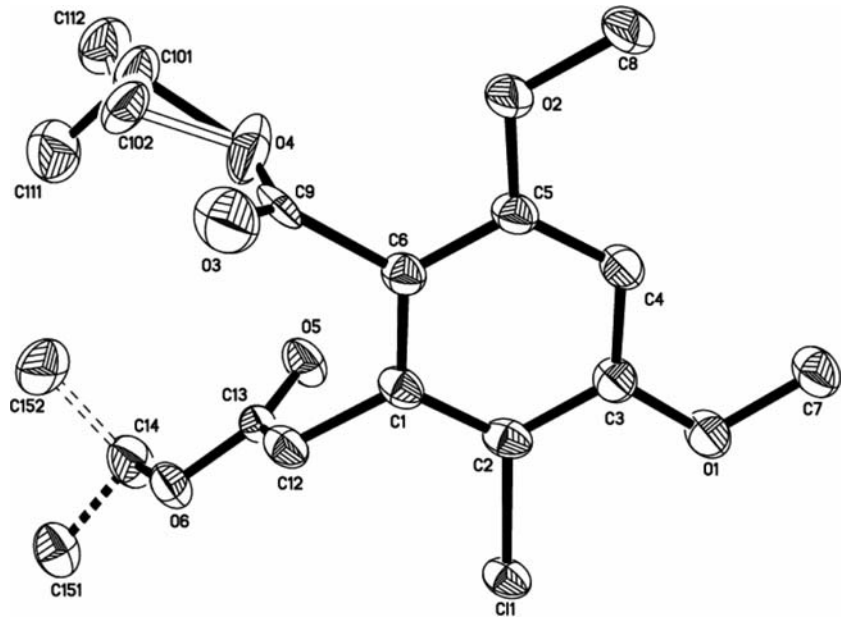


Figure 2. X-ray crystal structure of compound **3**.

at δ 3.94, and MeO at δ 4.05 ppm. In ^{13}C NMR spectrum, the carbonyls appeared at δ 168.0 and 162.7, CH_2 at δ 38.4, and MeO at δ 57.3.

Reaction of anhydride **5** with hexanoyl chloride in the presence of 1,1,3,3-tetramethylguanidine (TMG) and triethyl amine [23] furnished 5-chloro-6,8-dimethoxy-3-pentylisocoumarin (**6**) in 71% yield. IR spectrum showed absorption bands of 2998 (C—H), 1713 (C═O), 1585 (C═C), 1086 (C—O), and 646 (C—Cl) cm^{-1}. Isocoumarin **6** exhibited the characteristic singlet for H-4 olefinic proton at δ 6.50, the triplet for H-1′ at δ 2.47 ($J = 7.1$ Hz), and the carbon signals at δ 103.4 (C-4), 159.6 (C-3), and 163.2 (C═O).

6,8-Dimethoxy isocoumarin **6** was regioselectively demethylated at C-8 methoxyl using anhydrous aluminum chloride in dry ether [24], due to chelation of the resulting hydroxyl with periplanar lactonic carbonyl to yield 5-chloro-8-hydroxy-6-methoxy-3-pentylisocoumarin (**1**). Besides the disappearance of C-8 methoxyl, the downfield shift of singlet for H-4 was detected. A similar shift for C-4 and C-3 (δ 103.1 and 159.7), respectively, was also noted in ^{13}C NMR spectrum. The lactonic carbonyl absorption was also lowered to 1681 cm^{-1} due to chelation with C-8 hydroxyl that appeared at 11.2 ppm.

A comparison of the spectral data of **1** with those of the naturally occurring C-7 analog **1a** indicates that in compound **1**, H-5 and C-5 rather than H-7 and C-7 appeared downfield in addition to other slight changes.

3. Experimental

3.1 General experimental procedures

Melting points were recorded using a digital Gallenkamp (SANYO, Leicester, UK) model MPD BM 3.5 apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ or acetone-d_6 solutions at 300 and 75.4 MHz, respectively, using Bruker AM-300 spectrophotometer. FT-IR spectra were recorded using an FTS 3000 MX spectrophotometer; Mass spectra (EI, 70 eV) with a GC-MS instrument and elemental analyses with a LECO-183 CHNS analyzer. All compounds were purified by thin layer chromatography using silica gel from Merck (Darmstadt, Germany).

Crystallographic data were collected on a Bruker-AXS SMART APEX CCD diffractometer. The crystal structure was solved by direct methods. H-atoms were located from difference Fourier maps and then refined at idealized positions with a riding model. CCDC 804525 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK.

3.2 Ethyl 3-chloro-2-(2-ethoxy-2-oxoethyl)-4,6-dimethoxybenzoate (3)

To a stirred solution of ethyl 2-(2-ethoxy-2-oxoethyl)-4,6-dimethoxybenzoate (**2**) (1.00 g, 3.38 mmol) in dry DMF (10 ml) was added NCS (0.45 g, 3.4 mmol) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was poured into ice cold water (100 ml) and extracted with ethyl acetate (3 × 50 ml). The combined organic phase was separated, dried ($MgSO_4$), and concentrated to yield a solid. This was recrystallized from ethanol to leave **3** as colorless crystals (0.72 g, 2.2 mmol, 65.0%), R_f: 0.7 (petroleum ether: ethyl acetate; 4:1), m.p. 95–97°C; IR (KBr): ν 2978 (C—H), 1722 (C═O), 1591 (C═C), 1077 (C—O), 680 (C—Cl) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): δ 6.94 (1H, s, H-5), 4.35 (2H, q, $J = 7.2$ Hz, $\underline{CH_2}CH_3$), 4.16 (2H, q,

$J = 7.2$ Hz, $\underline{CH_2}CH_3$), 3.93 (6H, s, $2 \times OCH_3$), 3.81 (2H, s, Ar-CH_2), 1.34 (3H, t, $J = 7.8$ Hz, $-CH_2\underline{CH_3}$), 1.25 (3H, t, $J = 7.8$ Hz, $-\underline{CH_2}CH_3$); ^{13}C NMR ($CDCl_3$ δ ppm): δ169.5 (C=O), 166.7 (C=O), 157.7, 156.5, 134.0, 117.0, 115.6, 106.6, 61.4 ($2 \times$ C) (2C, $\underline{CH_2}CH_3$), 56.3, 39.5, 14.1 ($2 \times CH_3$); MS (70eV): *m/z* (%) 330 $[M]^+$(46), 332 $[M + 2]^+$ 193 ($2 \times$ C) (43), 165 (100), 59 (12); Elemental analysis: Found: C, 54.13%, H, 5.81%; calcd for $C_{15}H_{19}ClO_6$: C, 54.47%, H, 5.79%.

3.3 2-(Carboxymethyl)-3-chloro-4,6-dimethoxybenzoic acid (4)

Potassium hydroxide (5%, 40 ml) was added to a solution of (**3**) (1.0 g, 3.03 mmol) in ethanol (20 ml). The reaction mixture was refluxed for 3 h. The solvent was rotary evaporated, and cold water (10 ml) was added and the reaction mixture acidified using concn. hydrochloric acid. The solid was filtered and recrystallized from MeOH to give **4** (0.74 g, 2.72 mmol, 90%). m.p. 240°C (decomp). IR (KBr) ν 3500 (C—H), 2990 (Ar—C—H), 1722 (C=O), 1586 (C=C), 1081, 652 cm^{-1}; ^{1}H NMR (acetone-d_6, δ ppm): δ 11.2 (1H, br s, COOH), 11.0 (1H, br s, COOH), 6.85 (1H, s, H-5), 3.98 (2H, s, Ar-CH_2), 3.93 (6H, s, $2 \times OCH_3$); ^{13}C NMR ($CDCl_3$ δ ppm): δ 173.3 (C=O), 169.7 (C=O), 159.2 (C-3, C-5), 138.4, 119.6 (C-4), 108.2, 68.6, 102.5, 55.3 (Ar-OCH_3), 42.6 (CH_2); MS (70 eV): *m/z* (%) 274 $[M]^+$ (46), 276 $[M + 2]^+$, 193 (43), 165 (100), 59 (12); Elemental analysis: Found: C, 48.07%; H, 3.97%; calcd for $C_{11}H_{11}ClO_6$: C, 48.10%; H, 4.04%.

3.4 5-Chloro-6,8-dimethoxyisochroman-1,3-dione (5)

A solution of diacid **4** (0.6 g, 2.2 mmol) in dry toluene (10 ml) was treated with acetic anhydride (0.3 ml). The reaction mixture was refluxed for 1 h and then added to ice water. The organic layer was separated, dried ($MgSO_4$), and concentrated to yield **5** as colorless solid (0.47 g, 1.85 mmol, 85%); m.p. 190°C (decomp). IR (KBr): ν 2948 (C—H), 1797 (C=O), 1749 (C=O), 1566 (C=C), 1081, 658 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ ppm): δ 6.56 (1H, s, H-7), 4.05 (6H, s, $2 \times OCH_3$), 3.94 (2H, s, CH_2); ^{13}C NMR ($CDCl_3$, δ ppm): δ 168.0 (C3, $\underline{CO}$), 162.7 (C1, $\underline{CO}$), 160.2, 138.4, 106.2 (C8a), 109.9 (C5), 107.3, 103.1, 57.3 ($2 \times OCH_3$), 38.4 (CH_2), MS (70 eV): *m/z* (%) 256 $[M]^{+\cdot}$(46), 258 $[M + 2]^+$, 193(43), 165(100), 59(12); Elemental analysis: Found: C, 51.56; H%, 3.59%; calcd for $C_{11}H_9ClO_5$: C, 51.48%; H, 3.53%.

3.5 5-Chloro-6,8-dimethoxy-3-pentylisocoumarin (6)

A solution of **5** (0.4 g, 1.56 mmol) in acetonitrile (15 ml) was added slowly to a solution of TMG (0.2 g, 1.71 mmol) in acetonitrile (5 ml), while maintaining the internal temperature ≤ 0°C. Triethyl amine (0.3 ml, 3.12 mmol) was added in a single portion, followed by dropwise addition of hexanoyl chloride (0.34 g, 2.5 mmol). The reaction mixture was further stirred for 20 min, allowed to warm to ambient temperature, and then quenched by addition of 1 M HCl (15 ml). The organic layer was separated, washed with saturated brine, dried, and concentrated. The crude compound was purified by thin layer chromatography followed by recrystallization from methanol to yield isocoumarin **6** (0.37 g, 1.1 mmol, 71%) as colorless semisolid. IR (KBr): ν 2998, 2849, 1713, 1605, 1585, 1086, 860, 835, 810, 646 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, $J = 7.1$ Hz, 3H, H-5′), 1.30 (m, 2H, H-4′), 1.35 (q, $J = 3.5$ Hz, 2H, H-3′), 1.67 (q, $J = 7.1$ Hz, 2H, H-2′), 2.47 (2H, t, $J = 7.1$ Hz, H-1′), 3.85 (s, 3H, MeO), 3.95 (s, 3H, MeO), 6.50 (s, 1H, H-4), 6.71 (s, 1H, H-7); ^{13}C NMR ($CDCl_3$): δ 163.2 (C=O), 158.3 (C-6), 159.6 (C-3), 141.8

(C-9), 103.4 (C-4), 106.7 (C-5), 100.9 (C-7), 99.9 (C-10), 55.3 (MeO), 56.6 (MeO), 33.3 (C-1′), 31.1 (C-3′), 26.4 (C-2′), 22.3 (C-4′), 14.2 (C-5′); MS: *m/z* 338 (16), 340, 219 (18), 206 (52), 191 (15), 177 (27), 165 (14), 164 (98). Elemental analysis: Found: C, 63.92%; H, 6.76%; calcd for $C_{18}H_{23}ClO_4$: C, 63.81%; H, 6.84%.

3.6 5-Chloro-6-methoxy-8-hydroxy-3-pentylisocoumarin (1)

Aluminum chloride (0.3 g, 1.08 mmol) was added to a stirred solution of **6** (0.35 g, 1.26 mmol) in freshly distilled dry ether (40 ml). The reaction mixture was refluxed for 6 h, then poured into ice-water and acidified with 0.5 N HCl. The layers were separated and the organic layer was dried ($MgSO_4$) and concentrated to yield **1** as colorless solid and this was aqueous purified by thin layer chromatography (petroleum ether: ethyl acetate; 8:2) to afford pure compound **1** (0.20 g, 0.8 mmol, 64%). m.p.76–78°C, IR (KBr): ν 2945, 28421, 1681, 1605, 1585, 860, 835, 810, 645 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.90 (t, $J = 7.1$ Hz, 3H, H-5′), 1.31 (m, 2H, H-4′), 1.39 (q, $J = 3.5$ Hz, 2H, H-3′), 1.68 (q, $J = 7.6$ Hz, 2H, H-2′), 2.49 (t, $J = 7.6$ Hz, 2H, H-1′), 3.85 (s, 3H, MeO), 6.18 (s, 1H, H-4), 6.39 (d, $J = 2.2$ Hz, 1H, H-7), 11.2 (1H, br s, OH); ^{13}C NMR ($CDCl_3$): δ 164.4 (C═O), 163.7 (C-8), 163.3 (C-6), 159.7 (C-3), 142.4 (C-9), 103.1 (C-4), 102.9 (C-5), 107.1 (C-7), 98.7 (C-10), 56.3 (MeO), 33.3 (C-1′), 31.1 (C-3′), 26.4 (C-2′), 22.3 (C-4′), 13.9 (C-5′); MS: *m/z* 324 (37), 326, 206 (52), 191 (15), 177 (27), 164 (100), 149 (29); Elemental analysis: Found: C, 62.89%; H, 6.32%; calcd for $C_{17}H_{21}ClO_4$ C, 62.86%; H, 6.52%.

4. Conclusion

An efficient synthesis of the unnatural analog of a naturally occurring isocoumarin was carried out for complete bioevaluation and comparison.

Acknowledgements

The author gratefully acknowledges a research grant from the Higher Education Commission of Pakistan under Project No. 20-Miscel/R&D/00/3834.

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