Total Synthesis and Anti-Inflammatory Activity of Velutone F

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Abstract

Velutone F (1), a natural bioactive chalcone isolated from Millettia velutina Dunn, possesses significant anti-inflammatory activity. In this study, we have accomplished the total synthesis of velutone F (1), along with its analogues 2 and 3, from a common starting material cyclohexandione in 5 to 7 steps. The anti-inflammatory activities of compounds 1 to 3 were determined against nitric oxide (NO) production in lipopolysaccharide (LPS)-stimulated RAW264.7 cells and all of them exhibited different levels of anti-inflammatory activity.

Keywords

velutone F, anti-inflammatory activity, total synthesis, flavonoids

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Introduction

Chalcones (1,3-diphenyl-2-propen-1-one) consist of a three-carbon α, β-unsaturated carbonyl system, and are known to exhibit a variety of pharmacological activities such as anti-inflammatory, antitumor, antibacterial, antifungal, and antimalarial. Velutone F (2,5-dimethoxyfurano[4¢,5¢:3,4]chalcone, compound 1), a natural chalcone isolated from Millettia velutina in 2020, was reported to exhibit significant anti-inflammatory activity against nigericin-induced IL-1β release in THP-1 cells (IC₅₀ 1.3 μM). The initial mechanism of action study by Chen and her co-workers revealed that velutone F (1) suppressed NLRP3 inflammasome activation via blocking ASC oligomerization without affecting the priming step, which subsequently inhibited caspase-1 activation and IL-1β secretion (Figure 1).

Detailed pharmacological study of velutone F (1) so far has been minimal due to limited supply from a natural resource (0.000113% from M velutina). Such insufficient quantities to optimally explore the interesting biological properties of velutone F prompted efforts by Wu and co-workers to develop a semi-synthesis route toward the natural product. They synthesized velutone F (1) in 7 steps from a commercial natural compound khellin (4). Although the transformation of one natural product to another is of great importance, isolating a large amount of khellin (4) from plant sources needs complicated extraction, purification, and chromatography, which are disadvantageous factors for achieving the large-scale synthesis of velutone F (1).

Thus, we herein present the total synthesis of velutone F (1) from a common chemical intermediate cyclohexandione (5) as the starting material. Furthermore, as some studies indicated that changing the electron cloud density of the A-ring of chalcone would considerably affect its anti-inflammatory activity, derivatives 2 and 3 have been designed and synthesized. Anti-inflammatory activities of compounds 1 to 3 were evaluated for their inhibition of lipopolysaccharide (LPS)-induced NO production in mouse RAW264.7 cells.

Results and Discussion

As shown in Scheme 1, our synthesis for natural product 1 started from a common chemical intermediate cyclohexandione (5). Compound 6 was prepared by an aldol reaction using 5 and chloroacetaldehyde as the reagents. Transformation of 6 into its sodium enolate with an excess of NaH in refluxing tetrahydrofuran (THF) was followed by treatment with ethyl formate into drofuran (THF) was followed by treatment with ethyl formate to form 7, which was a mixture of enol and keto forms in

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88% yield. The 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-mediated dehydrogenation of compound 7 in refluxing toluene gave the aromatized compound 8 (76%). Etherification of the phenol of 8 using MeI afforded compound 9 in 99% yield. Bromination of 9 in the DMSO/HBr system afforded brominated product 10 in high yield without affecting the furan group. 5-Bromobenzofuraldehyde 10 was subjected to Claisen–Schmidt condensation with acetoephone to give bromochalcone 11 in 69% yield. To complete the total synthesis of velutone F (1), we tried methoxilation of 11 using the Ullman reaction in the presence of MeONa and CuBr initially. However, the ketone carbonyl group could be reduced by residual metallic sodium in MeONa/MeOH solution, which made the reaction system complicated and the isolated yield of 1 was only 10%. The reaction conditions were
strategy, we decided to prepare commercially available 5-bromo benzofuran through a known reaction was adopted to convert intermediate 9 to 2 in 77% yield. Despite that compound 3 could be synthesized from commercially available 5-bromo benzofuran through a known strategy,3 we decided to prepare 3 by employing 8 as a raw material, given it could be obtained from inexpensive compound 5 on a relatively large scale. The phenol of 8 was activated as the trflate with triflic anhydride (Tf₂O) to give 12. Then, the reduction of 12 in the presence of Pd[PPh₃]₄Cl₂, 1,3-bis(diphenylphosphino) propane (DPPP), Et₃N, and HCOOH gave compound 13,12 which was converted to the chalcone 3 via Claisen–Schmidt condensation with acetophenone.

The cytotoxicities of velutone F (I) and its derivatives 2 and 3 were evaluated by methyl thiazolyl tetrazolium (MTT) assay. As shown in Table 2, compounds 2 and 3 displayed no obvious cytotoxicity to RAW264.7 cells at concentration of 50 μM (entry 2, 3, Supplemental Figures S28 and S30). Velutone F (I) has shown cytotoxicity at 50 μM, but did not affect cell viability at a concentration of 25 μM (entry 1 and Supplemental Figure S26). Thus, the anti-inflammatory activities of each compound were evaluated at concentrations that show no cytotoxicity, and IC₅₀ values were calculated accordingly. The result revealed that velutone F (I) treatment in LPS-stimulated RAW 264.7 cells had a powerful inhibitory effect on NO release (IC₅₀ = 3.6 μM, entry 1 and Supplemental Figure S27). Compared with velutone F (I), the inhibitory effect on NO production by derivatives 2 and 3 (compounds 2, IC₅₀ = 15.5 μM, entry 2 and Supplemental Figure S29; 3, IC₅₀ = 18.5 μM, entry 3 and Supplemental Figure S31) had declined to some extent. This result suggested that the electron-donating substituents (-OCH₃) of the A-ring of 1 are significant for maintaining its nitric oxide inhibitory activity.

In conclusion, we have developed an efficient synthetic methodology for the synthesis of natural anti-inflammatory compound velutone F (I), as well as its derivatives 2 and 3. Compounds 1 to 3 were tested for inhibitory activity against NO production in the LPS-stimulated mouse macrophage cell model. Velutone F (I) inhibited NO production with an IC₅₀ value of 3.6 μM, which was comparable to that of the positive control, celecoxib (IC₅₀ = 2.3 μM). The electron-donating substituents (-OCH₃) of the A-ring of 1 are significant for maintaining its nitric oxide inhibitory activity. We believe that these results will provide ideas for the research of new anti-inflammatory agents and more profound structure modification and mechanistic studies are ongoing in our laboratory.

**Experimental**

**General Experimental Procedures**

Melting points were measured on an X-4 digital display microscopic melting point apparatus (Tianjin Xintian Optical Analytical Instruments Co., Ltd) and are uncorrected. ₁H NMR and ¹³C NMR spectra were recorded on either Bruker Avance 400 (Bruker Co.) or JEOL Eclips-600 (JEOL Co., Ltd) spectrometers. HRMS were obtained on a Bruker Apex II mass spectrometer (Bruker Co.). Column chromatography was performed on silica gel (100-200 mesh). The solvents were analytical grade and newly distilled before usage.

**General Procedures for the Synthetic Compounds**

_Synthesis of 6,7-dihydrobenzofuran-4(5H)-one (6)._ To a mechanically stirred ice-cooled suspension of 1,3-cyclohexandione (10 g, 89.2 mmol) in water (60 mL) was added a solution of potassium hydroxide (20%, 35 mL) at a rate such that the temperature of the reaction mixture did not exceed 12°C. Upon completion of

### Table 1. Comparison of the ¹³C and ¹H NMR Spectroscopic Data of Synthesized 1 with Literature data

| Position | δ_H (J in Hz) | δ_C | Synthetic velutone Fb |
|----------|---------------|-----|----------------------|
| 1        | 120.9         | 120.9 |
| 2        | 148.2         | 148.3 |
| 3        | 121.6         | 121.6 |
| 4        | 147.5         | 147.6 |
| 5        | 142.1         | 142.1 |
| 6        | 7.05, s       | 7.04, s | 105.1 |
| β        | 8.22, d (15.8)| 8.22, d (15.8) | 140.5 |
| α        | 7.51, d (15.8)| 7.52, d (15.8) | 121.8 |
| α'       | 191.2         | 191.2 |
| 1'       | 138.7         | 138.8 |
| 2'       | 8.08, d (7.5) | 8.05 to 8.00, m | 128.7 |
| 3'       | 7.52, d (7.5) | 7.51 to 7.47, m | 128.7 |
| 4'       | 7.58, d (7.3) | 7.56, d (7.3)  | 132.7 |
| 5'       | 7.52, d (7.5) | 7.51 to 7.47, m | 128.7 |
| 6'       | 8.03, d (7.5) | 8.05 to 8.00, m | 128.7 |
| 2''      | 7.62, d (1.5) | 7.60, d (2.1)  | 145.2 |
| 3''      | 6.94, d (1.5) | 6.93, d (2.2)  | 105.6 |
| CH₃O-2  | 4.04, s       | 61.7  |
| CH₃O-3  | 4.05, s       | 56.7  |

aData are obtained from Ref. 4 recorded in CDCl₃ at 400 MHz for ¹H NMR and 100 MHz for ¹³C NMR.
bData are recorded in CDCl₃ at 400 MHz for ¹H NMR and 100 MHz for ¹³C NMR.
the addition, potassium iodide (2.9 g, 17.4 mmol) was added to the resulting clear amber solution followed by the dropwise addition of 50% aqueous chloroacetaldehyde (80 mL) for 25 min. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the dropwise addition of 2 M HCl, and then CH₂Cl₂ (100 mL × 3) was added. After filtering to clarify the emulsion, the organic layer was separated and the aqueous layer was extracted with 2 additional portions of CH₂Cl₂ (75 mL) and the combined organic layers were washed with brine, and dried over Na₂SO₄. The solvent was evaporated under vacuum to give compound 6 (10 g, 82%) as a colorless oil. 

1H NMR (600 MHz, CDCl₃): δ: 7.22 (d, J = 1.9 Hz, 1H, H-2′′), 6.55 [d, J = 2.0 Hz, 1H, H-3′′], 2.77 [t, J = 6.3 Hz, 2H, H-5], 2.38 [t, J = 6.3, 2H, H-6], 2.09 to 2.05 [m, 2H, H-1]; 13C NMR [150 MHz, CDCl₃]: 194.5 [C-2], 167.2 [C-4], 144.6 [C-3′′], 121.0 [C-3], 106.4 [C-3′′], 37.6 [C-1], 23.3 [C-5], 22.6 [C-6]. The spectroscopic data were in agreement with the literature.

**Synthesis of 4-oxo-4,5,6,7-tetrahydrobenzofuran-5-carbaldehyde (7).** To a suspension of NaH (4.4 g, 183.4 mmol) in dry THF (30 mL) was added a solution of compound 6 (3.2 g, 22 mmol) and DMSO (5.76 ml, 50 mmol) in dry THF (120 mL) was added dropwise. Then the mixture was heated at 65 °C for 3 h. After the reaction was completed (detected by TLC), the mixture was cooled to room temperature and poured into ice water. Then the mixture was neutralized with 1M HCl, the aqueous layer was extracted with EtOAc (110 mmol) in dry THF (120 mL) was added dropwise. Then the mixture was heated at 65 °C for 3 h. After the reaction was completed (detected by TLC), the mixture was cooled to room temperature, and solids were removed by filtration. The residue was purified by chromatography on silica gel (eluent of EtOAc/light petroleum, 1:30) to give compound 7 (3.2 g, 88%) as a colorless oil. Compound 7 was a mixture of enol and keto forms.

**Synthesis of Compound 4-hydroxybenzofuran-5-carbaldehyde (8).** A mixture of 7 (3.2 g, 19.5 mmol) and DDQ (4.98 g, 21.9 mmol) in dry toluene (50 mL) was heated under reflux for 3 h. After the reaction was completed (detected by TLC), the resulting mixture was cooled in an ice bath and solids were removed by filtration through Celite. The filtrate was evaporated under reduced pressure and purified by flash column chromatography on silica gel (eluent of EtOAc/light petroleum, 1:30) to give 8 (2.4 g, 76%) as a white solid, MP 60.2 to 60.8°C. 

1H NMR (600 MHz, CDCl₃): 11.97 (s, 1H, -OH), 9.89 (s, 1H, -CHO), 7.59 (d, J = 2.2 Hz, 1H, H-2′′), 7.43 [d, J = 8.6 Hz, 1H, H-5], 7.13 [dd, J = 8.6, 0.9 Hz, 1H, H-6], 6.98 [dd, J = 2.2, 0.9 Hz, 1H, H-3′′]; 13C NMR [150 MHz, CDCl₃]: 196.1 [C-CHO], 160.5 [C-4], 158.0 [C-2], 145.0 [C-2′′], 129.8 [C-6], 117.3 [C-1], 115.54 [C-3], 104.9 [C-3′′], 104.8 [C-6]. The spectroscopic data were in agreement with the literature.

**Synthesis of 7-bromo-4-methoxybenzofuran-5-carbaldehyde (9).** Under a N₂ atmosphere, a solution of 8 (3.8 g, 23.4 mmol), K₂CO₃ (16.8 g, 121.7 mmol) in acetone (240 mL) was added CH₃I (14.5 ml, 234 mmol). The resulting mixture was refluxed for 3 h. After the reaction was completed (detected by TLC), the mixture was cooled to room temperature and the precipitated inorganic material was removed by filtration. The filtrate was concentrated and the residue was diluted with ether to precipitate the remaining inorganic impurities, which were removed by a second filtration. The filtrate thus obtained was concentrated and purified by flash column chromatography on silica gel (eluent of EtOAc/light petroleum, 1:20) to give compound 9 (4.1 g, 99%) as a white solid, MP 118.2 to 118.5°C; 1H NMR (600 MHz, CDCl₃): 7.79 (d, J = 8.6 Hz, 1H, H-5), 7.61 [d, J = 2.3 Hz, 1H, H-2′′], 7.20 [d, J = 8.6 Hz, 1H, H-6], 7.05 [d, J = 2.3 Hz, 1H, H-3′′], 4.23 [s, 3H, -OCH₃]; 13C NMR [150 MHz, CDCl₃]: 189.3 [C-CHO], 160.8 [C-4], 158.0 [C-2], 144.8 [C-2′′], 124.7 [C-6], 121.6 [C-3], 117.3 [C-1], 106.6 [C-3′′], 105.9 [C-5], 60.6 [-OCH₃]. The spectroscopic data were in agreement with the literature.

**Synthesis of 7-methoxybenzofuran-6-carbaldehyde (10).** Compound 9 (1.41 g, 8 mmol) and DMSO (5.76 ml, 80 mmol) were dissolved in EtOAc (40 mL). Aqueous hydrobromic acid (48%, 80 mmol) was added to the solution at 60°C and the mixture was stirred for 8 h in the dark at that temperature. After cooling to room temperature, the solution was diluted with EtOAc, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by chromatography on silica gel (eluent of EtOAc/light petroleum, 1:20) to give compound 10 (1.16 g, 57%) as a white solid. 1H NMR (600 MHz, CDCl₃): 10.39 (s, 1H, -CHO), 7.95 (s, 1H, H-6), 7.70 (s, 1H, H-2′′), 7.13 [s, 1H, H-3′′], 4.24 [s, 3H, -OCH₃]; 13C NMR [150 MHz, CDCl₃]: 188.0 [-CHO], 157.3 [-C-4], 145.6 [-C-2], 127.1 [-C-2′′], 122.9 [-C-6], 118.6 [-C-3], 118.6 [-C-1], 106.8 [-C-3′′], 98.7 [-C-5], 60.8 [-OCH₃]; HRMS[E] cale for C₉H₆BrO₃ [M + H]⁺: 254.9651, found 254.9658.

**Synthesis of (E)-3-(7-bromo-4-methoxybenzofuran-5-yl)-1-phenylprop-2-en-1-one (11).** To a solution of 10 (0.37 g, 1.45 mmol) and acetophenone (202 μL, 1.74 mmol) in methanol (22 mL), was added a solution of NaOH (3M, 4.5 mL). The reaction mixture was stirred for 24 h at room temperature. After the reaction was completed (detected by TLC), 10% HCl was used to adjust the pH to 7. The solution was extracted with EtOAc (70 mL × 3). The organic phases were combined, washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by chromatography on silica gel (eluent of EtOAc/light petroleum, 1:30) to give compound 11 (0.36 g, 69%) as a yellow solid, MP 123.3 to 123.7°C; 1H NMR (600 MHz, CDCl₃): 8.18 (d, J = 15.8 Hz, 1H, H-β), 8.05 to 8.01 (m, 3H, H-2′′, 6′′), 7.77 [s, 1H, H-6], 7.65 [d, J = 2.2 Hz, 1H, H-2′′], 7.60 to 7.56 [m, 1H, H-4′′], 7.55 to 7.48 [m, 3H, H-α, 3′, 5′], 7.05 [d, J = 2.3 Hz, 1H, H-3′′], 4.14 [s, 3H, -OCH₃]; 13C NMR [150 MHz, CDCl₃]: 190.2 [-C-α′′],...
154.6 [C-4], 152.7 [C-2], 144.9 [C-2′], 138.6 [C-β], 138.1 [C-1′], 132.5 [C-4′], 128.4 [C-3′, 5′], 128.3 [C-2′, 6′], 126.3 [C-6], 121.8 [C-α], 121.7 [C-3], 119.4 [C-1], 106.0 [C-3′], 97.9 [C-5], 60.6 [-OCH3]; HRMS [ESI] calecd for C10H11BrO3 [M + H]^+ 357.0121, found 357.0114.

*Synthesis of Veluteone F (I).* Under a N2 atmosphere, to a solution of 111 (400 mg, 1.12 mmol), Cs2CO3 (547 mg, 1.68 mmol), [(allylPdCl2)]2 (8 mg, 1.0 mol %), Bu3P (24 mg, 2.5 mol %) in toluene (10 mL) was added methanol (131 μL, 5.6 mmol). The mixture was heated at 90°C for 15 min. After the reaction was completed (detected by TLC), the mixture was cooled to room temperature. The solution was diluted with EtOAc (30 mL × 3), washed with brine, dried over anhydrous Na2SO4, and concentrated. The residue was purified by chromatography on silica gel (eluent of EtOAc/light petroleum, 1:30) to give compound 1 (0.22 g, 63%) as a yellow oil. ^1H NMR (400 MHz, CDCl3) δ: 8.22 (d, J = 15.8 Hz, 1H, H-β), 8.05 (s, 2H, H-2, 6′), 7.60 (d, J = 2.1 Hz, 1H, H-2′), 7.56 [d, J = 7.3 Hz, 1H, H-4], 7.52 [d, J = 15.8 Hz, 1H, H-β], 7.51 to 7.47 [m, 2H, H-5, 3′], 7.04 [s, 1H, H-6], 6.93 [d, J = 2.2 Hz, 1H, H-3′], 4.03 [s, 6H, -OCH3]; ^13C NMR [100 MHz, CDCl3] δ: 191.2 [C-α′], 148.3 [C-2], 147.6 [C-4], 145.2 [C-2′], 142.1 [C-5], 140.5 [C-β], 138.8 [C-1′], 132.7 [C-4′], 128.7 [C-3′, 5′], 128.7 [C-2′, 6′], 121.8 [C-3], 121.6 [C-α], 120.9 [C-1], 105.6 [C-3′], 105.1 [C-6], 61.7 [-OCH3 to 2], 56.7 [-OCH3 to 5]; HRMS[ESI] calecd for C19H17O4 [M + H]^+ 309.1121, found 309.1123.

*Synthesis of (E)-3-(4-methoxybenzofuran-5-yl)-1-phenylprop-2-en-1-one (3).* To a solution of 13 (200 mg, 1.37 mmol) and acetophenone (191 μL, 1.64 mmol) in methanol (20 mL), was added a solution of NaOH (3M, 4 mL). The reaction mixture was stirred for 24 h at room temperature. After the reaction was completed (detected by TLC), 10% HCl was used to adjust the pH to 7, and then 30 mL water was added. The precipitate was filtered and recrystallized from ethanol (10 mL) to give compound 3 (0.25 g, 74%) as a yellow oil, MP 94.5 to 94.8°C; ^1H NMR (400 MHz, CDCl3) δ: 8.04 (d, J = 7.7 Hz, 2H, H-2, 6′), 7.96 to 7.86 [m, 2H, H-3′, 5′], 7.67 to 7.47 [m, 7H, H-2, 6, 3′, 2′, 5, 6, α, β], 6.84 to 6.78 [m, 1H, H-2′], ^13C NMR [100 MHz, CDCl3] δ: 189.5 [C-α′], 153.2 [C-4′], 145.1 [C-2′], 144.4 [C-β], 137.3 [C-1′], 131.7 [C-4′], 129.0 [C-1], 127.6 [C-3′, 5′], 127.4 [C-2′, 6′], 127.1 [C-3], 126.3 [C-6], 121.2 [C-2], 120.0 [C-α], 111.0 [C-5], 105.8 [C-3′], 105.8 [C-6]; HRMS[ESI] calecd for C17H17O3 [M + H]^+ 249.0910, found 249.0914.

*Nitric Oxide Production in RAW264.7 Cells*

RAW264.7 cells (Solarbio SCC-211800) were cultured in DMEM medium (Invitrogen, 12100-046) supplemented with 10% fetal bovine serum (Invitrogen, 10099-141) and 1% penicillin/streptomycin (Betoyime C0222) at 37°C under 5% CO2 in a saturated humidified incubator. These cells were seeded in 96-well plates (Corning Costar 3599) (2 × 10^5 cells/well) and treated with various concentration of compounds 1 to 3 for 2 h. After a 2-hour preincubation, the cells were stimulated with LPS (Sigma-Aldrich L2880) (1 μg/mL) for 18 h. NO production in the supernatant was assessed by the Griess reagent.
The absorbance at 550 nm was measured using a Varioskan® Flash (Thermo Scientific). Statistical analyses were performed with GraphPad Prism 5.0 software (GraphPad). Celecoxib was used as a positive control. The viability of RAW264.7 cells was evaluated by MTT assay (Beyotime C0009S) simultaneously to exclude the interference of the cytotoxicity of the test compounds. The absorbance was read at 570 nm using a Varioskan® Flash (Thermo Scientific).

**Declaration of Conflicting Interests**
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**Statement of Human and Animal Rights**
This article does not contain any studies with human or animal subjects.

**Ethical Approval**
Not applicable, because this article does not contain any studies with human or animal subjects.

**Informed Consent**
Not applicable, because this article does not contain any studies with human or animal subjects.

**Trial Registration**
Not applicable, because this article does not contain any clinical trials.

**Supplemental Material**
Supplemental material for this article is available online.

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