

Communication

Structural Modification of Epigallocatechin-3-gallate to (2R,3R)-5,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl L-valinate in Four Steps

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Abstract: Tea is a daily drink for most people, and one of its major ingredients, epigallocatechin-3-gallate (EGCG), has been widely recognized as a potent antioxidant with diverse biological activities. However, its low stability and bioavailability hinder its further clinical applications. In this study, we designed and synthesized a novel EGCG-valine derivative **4** by replacing the gallic acid with a valine moiety in four steps. The structural elucidation of derivative **4** was performed using NMR, IR, mass, and UV spectroscopies. Additionally, the physicochemical properties of **4** were predicted by SwissADME, showing improved drug-like parameters and intestinal absorption compared to the parent compound EGCG.

Keywords: EGCG; structural modification; valine



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1. Introduction

Epigallocatechin-3-gallate (EGCG) is a naturally occurring hydrophilic polyphenol, which is an active, abundant component found in tea. EGCG is a kind of catechin belonging to flavonoids and is predominant in green tea. Unlike green tea, black tea involves a fermentation process in its preparation, during which these phenolic compounds are oxidized to form new compounds, such as theobromine and theaflavin, thereby diminishing the EGCG content in black tea. EGCG exhibits a broad spectrum of biological activities, including hypoglycemic [1], antibacterial [2], antiviral [3], antioxidant [4], anti-atherosclerotic [5], anti-tumor [6] and anti-inflammatory [7] effects. Therefore, tea and its extract have been widely commercialized, commonly in the pharmaceutical, healthcare, and food industries [8–10]. However, its limitations, such as low bioavailability and low chemical and thermal stability, hinder its further clinical application [11,12].

From a structural perspective, EGCG is a polyphenolic compound consisting of a typical flavonoid moiety (two phenyl rings, A and B, and one dihydropyran ring, C) with a gallic acid group connected by an ester linkage at the C3 position (Figure 1). In addition, multiple hydroxyl groups at various positions on EGCG not only increase its water solubility but also make it versatile for chemical transformation. However, these hydroxyl groups also pose difficulties in selectively modifying EGCG's structure. Typically, a protection-deprotection strategy is employed to avoid unnecessary side reactions.

Apart from synthetic challenges, the structural modification of EGCG is still considered an effective way to improve its stability. One study reported that the incorporation of D-glucose into EGCG yields glucosylated EGCG derivatives in low yields (<30%), demonstrating higher stability and water solubility but reduced antioxidant properties [13]. Moreover, lipophilic EGCG derivatives were synthesized with improved lipid solubility and

antioxidant properties [14]. A major C3 modification of EGCG has also been reported via a five-step synthesis with a protection–deprotection strategy to afford promising derivatives with enhanced antioxidant effects [15].

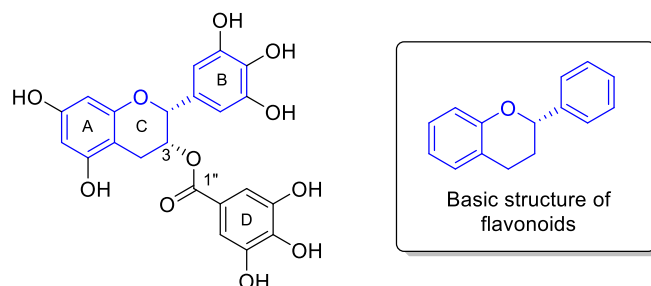
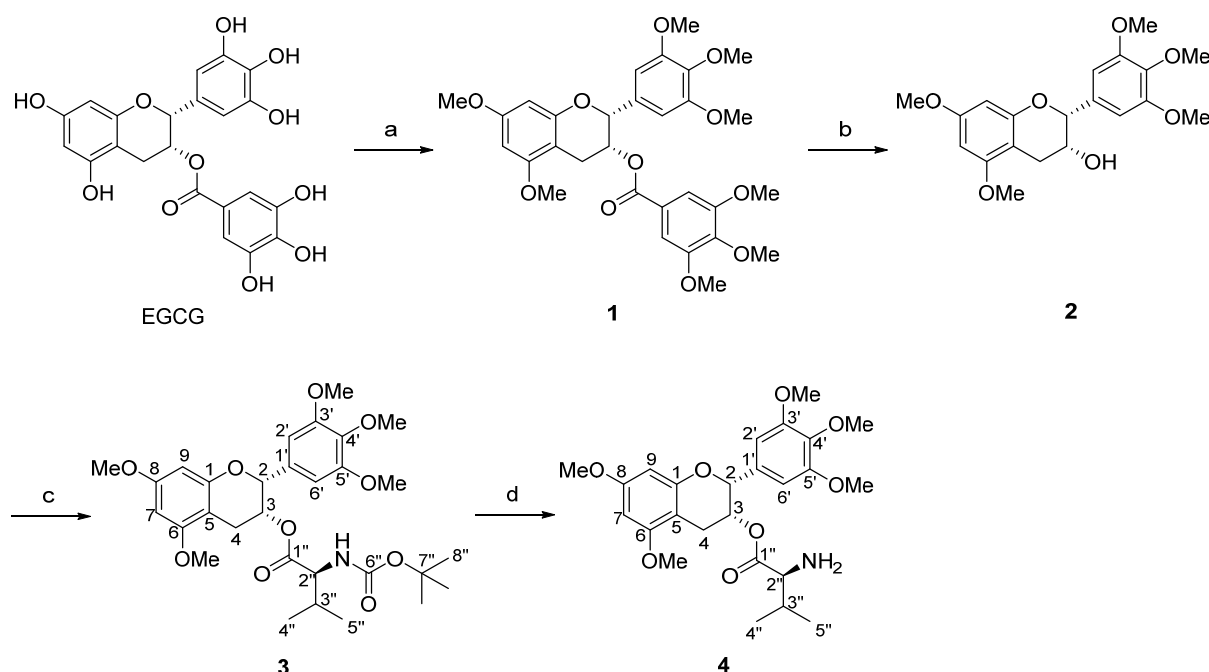


Figure 1. Structure of EGCG.

Given the importance of EGCG in our daily products and its potential therapeutic use, we herein report the synthesis and characterization of (2*R*,3*R*)-5,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl L-valinate. This EGCG–valine hybrid compound may offer a potential direction for the modification of EGCG's properties.

2. Results and Discussion

To improve the physicochemical properties of EGCG, we attempted to modify the gallic acid group to a valine (Val) moiety, where valine is a biocompatible scaffold with the ability to enhance bioavailability [16]. By modifying a similar synthetic strategy reported in the literature [15], we designed the synthesis of EGCG derivative **4** with the use of the *O*-methyl group due to its reaction tolerance as well as its enhancement in metabolic stability [17,18]. As depicted in Scheme 1, derivative **4** was prepared in four steps involving *O*-methylation, hydrolysis, esterification, and *N*-deprotection.



Scheme 1. Synthetic routes of (2*R*,3*R*)-5,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl L-valinate from EGCG. (a) K_2CO_3 , dimethyl sulfate, acetone, reflux; (b) K_2CO_3 , methanol, reflux, 64% yield over 2 steps; (c) DCC, DMAP, Boc-Val-OH, CH_2Cl_2 , r.t., 98% yield; and (d) TFA, CH_2Cl_2 , r.t., 84% yield.

Briefly, all hydroxyl groups of EGCG were first protected upon treatment with dimethyl sulfate, resulting in the formation of intermediate **1**. Its formation is recognized by the intense peaks of methoxy groups ranging from 3.71 to 3.86 ppm in the ^1H NMR of a crude product (Supplementary Materials, Figure S1). Subsequently, under alkaline conditions, hydrolysis of intermediate **1** yielded intermediate **2**, which illustrated the loss of the gallic acid group by the absence of an aromatic ring signal at 7.17 ppm and the corresponding three methoxy signals in ^1H NMR spectrum (Supplementary Materials, Figure S3). Following that, the typical Steglich esterification of **2** and the subsequent *N*-Boc deprotection afforded the EGCG–Val hybrid compound a high yield. Finally, the desired compound **4** was subjected to characterization using NMR, IR, MS, and UV spectroscopies.

The structure of **4** was determined by ^1H and ^{13}C NMR spectra (Supplementary Materials, Figures S10 and S11). The ^1H -NMR spectrum showed two doublets at 0.69 and 0.75 ppm corresponding to $-\text{CH}_3$ protons on the isopropyl group and a doublet of the quintet at 1.80 ppm corresponding to the $-\text{CH}-$ proton on the isopropyl group of valine residue (Supplementary Materials, Figure S10). These characteristic peaks indicate the incorporation of valine moiety into derivative **4**.

For the ^{13}C NMR signals, the appearance of the characteristic peak of quaternary carbon of the ester group at 174.7 ppm and the aliphatic carbon peaks at 17.0, 18.8, and 32.0 ppm proposed relevant characteristics to recognize the valine moiety in EGCG derivative (Supplementary Materials, Figure S11).

Heteronuclear single quantum coherence spectroscopy (HSQC), heteronuclear multiple bond correlation (HMBC), and ^1H - ^1H correlated spectroscopy (COSY) were also used to assign ^1H and ^{13}C signals of compound **4**, as shown in Table S1 (see Supplementary Materials for 2D spectra, Figures S12–S14).

The IR spectrum of compound **4** showed the following characteristic peaks: N–H stretching (weak) at 3387 cm^{-1} , C–H stretching at 2954 and 2924 cm^{-1} , C=O stretching of ester group at 1728 cm^{-1} and C=C stretching of aromatic rings at 1597 cm^{-1} (Supplementary Materials, Figure S15). Other vibrational peaks at 1458 cm^{-1} were attributed to the O–C bending in the methoxy groups. Moreover, strong absorption bands found at 1149 and 1100 cm^{-1} could be assigned to the characteristic C–O stretching vibrations of methoxy groups.

The UV spectrum of derivative **4** was also recorded for further characterization, showing an absorption peak at 209 nm and another lower absorption peak at 229 nm (Supplementary Materials, Figure S16).

Moreover, HRMS analysis was performed for **4**, showing a good agreement with the theoretical mass (mass error <1 ppm). Therefore, these findings further support the proposed structure determined by NMR spectra (Supplementary Materials, Figure S18).

In addition, the physicochemical properties and oral bioavailability of derivatives **1** and **4** were predicted using the SwissADME website [19]. From the calculated physicochemical properties (Supplementary Materials, Table S2), compound **4** showed a greater improvement in its predicted physicochemical properties compared to parent compound EGCG and analog **1**. Notably, O-methylation of the hydroxy groups increased *i*LogP significantly, which is a parameter representing the lipophilicity of the compound. Replacing gallic acid with valine moiety in **4** showed a decrease in *i*LogP, probably due to the incorporation of amine. In addition, these two derivatives exhibited no significant difference in TPSA. Overall, derivative **4** did not violate any of Lipinski's rules, unlike its parent compound EGCG and analog **1** [20]. This indicates that the structural modification of EGCG into **4** improved the physicochemical properties greatly with regard to the drug-like characters.

Meanwhile, the BOILED-Egg model was also employed to evaluate the properties of **4**, with the results showing a high probability of its absorption in the human intestine [21] (Supplementary Materials, Figure S20). Compound **4** was predicted to be orally bioavailable and absorbed in the human intestine by SwissADME [19].

3. Materials and Methods

3.1. General

All chemicals were purchased from Macklin Biochemical Technology Co., Ltd. (Shanghai, China). Silica gel (particle size 230–400 mesh) was used for purification in column chromatography. Thin-layer chromatography was carried out using E. Merck precoated silica gel 60 F₂₅₄ plates and visualized under a UV lamp.

¹H-NMR, ¹³C-NMR, and 2D NMR spectra were acquired in CDCl₃ at 25 °C on a Bruker Ascend[®]-600 NMR spectrometer (600 MHz for ¹H and 150 MHz for ¹³C). All chemical shifts were reported in the standard δ notation of parts per million using TMS as an internal reference (δ_{H} 0 ppm; δ_{C} 0 ppm).

High-resolution mass spectroscopy (HRMS) analysis was conducted by an Agilent 1290 infinity system equipped with an Agilent 6230 electrospray ionization (ESI) time-of-flight (TOF) mass spectrometer using the UPLC column (Waters ACQUITY UPLC BEH C18, 100 mm $\times$ 2.1 mm, 1.7 μ m). The measurements were conducted in a positive ion mode (interface capillary voltage 4500 V); the mass ratio was from m/z 50 to 3000 Da. The chromatographic conditions were as follows: mobile phase (acetonitrile/water with 0.1% formic acid), gradient elution, 20% acetonitrile/water for 2 min, 40% acetonitrile/water for 2 min, 60% acetonitrile/water for 2 min, 80% acetonitrile/water for 2 min, 100% acetonitrile/water for 3 min; flow rate 0.3 mL/min; and the injection volume was 1 μ L. The purity of the compound was assessed by UPLC-UV analysis using an Agilent 1290 infinity system equipped with a 1290 DAD detector under the same chromatographic conditions.

UV analysis was performed by a Shimadzu UV—2600 with a 1 cm quartz cell and a slit width of 2.0 nm. The analysis was carried out using wavelength in the range of 200–400 nm.

3.2. Synthesis of (2R,3R)-5,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 3,4,5-trimethoxybenzoate (**1**)

To a solution of EGCG (1.0211 g, 2.23 mmol) in acetone (11 mL), dimethyl sulfate (2.0 mL, 21.1 mmol) and K₂CO₃ (3.62 g, 26.2 mmol) were added. The reaction mixture was refluxed for 3 h. The reaction was diluted with acetone, filtered through celite, and concentrated in vacuo. The crude product of **1** was used directly in the next step without further purification. δ_{H} (600 MHz, CDCl₃) 7.17 (s, 2H), 6.71 (s, 1H), 6.25 (d, J = 2.2 Hz, 1H), 6.13 (d, J = 2.2 Hz, 1H), 5.67 (t, J = 2.9 Hz, 1H), 5.09 (s, 1H), 3.86 (s, 2H), 3.81 (s, 3H), 3.80 (d, J = 2.1 Hz, 2H), 3.80 (s, 1H), 3.79 (s, 1H), 3.72 (s, 3H), 3.05 (d, J = 3.3 Hz, 1H) ppm; δ_{C} (150 MHz, CDCl₃) 165.24, 159.85, 158.99, 155.59, 153.25, 152.97, 142.61, 137.98, 133.50, 125.20, 107.28, 103.99, 100.25, 93.35, 91.99, 77.89, 68.78, 61.00, 60.89, 56.36, 56.10, 55.52, 55.50, 26.04 ppm. These special characteristics are consistent with those reported in the literature [22].

3.3. Synthesis of (2R,3R)-5,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-ol (**2**)

To a solution of crude product **1** in methanol (22 mL) K₂CO₃ (362 mg, 2.62 mmol) was added. The reaction mixture was refluxed for 1.5 h. The reaction was diluted with CH₂Cl₂, filtered through celite, and concentrated in vacuo. The crude product was purified by silica column chromatography (eluent: 1–2% MeOH/CH₂Cl₂) to afford title compound **2** as a white solid (537.2 mg, 64% over 2 steps). δ_{H} (600 MHz, CDCl₃) 6.75 (s, 2H), 6.21 (d, J = 2.3 Hz, 1H), 6.13 (d, J = 2.3 Hz, 1H), 4.94 (s, 1H), 4.29 (s, 1H), 3.90 (s, 6H), 3.86 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 2.98–2.94 (m, 1H), 2.89 (dd, J = 17.2, 4.4 Hz, 1H), 1.82 (d, J = 5.4 Hz, 1H) ppm; δ_{C} (150 MHz, CDCl₃) 159.71, 159.28, 155.05, 153.48, 137.70, 133.97, 103.30, 100.26, 93.37, 92.28, 78.67, 66.49, 60.84, 56.22, 55.49, 55.40, 28.08 ppm. These special characteristics are consistent with those reported in the literature [23].

3.4. Synthesis of (2R,3R)-5,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl (tert-butoxycarbonyl)-L-valinate (**3**)

To a solution of intermediate **2** (50.3 mg, 0.134 mmol) in CH₂Cl₂ (8.9 mL), DCC (81.9 mg, 0.397 mmol), DMAP (19.5 mg, 0.160 mmol) and Boc-Val-OH (88.2 mg, 0.406 mmol) were

added. The reaction mixture was stirred at room temperature overnight. The reaction was filtered through a short pad of silica gel, washed with CH_2Cl_2 , and concentrated in vacuo. The crude product was purified by silica column chromatography (eluent: 25% EtOAc/Hex) to afford title compound **3** as a colorless oil (75.6 mg, 98%). R_f (30% EtOAc/Hex) 0.56; δ_H (600 MHz, CDCl_3) 6.69 (s, 2H, H-2'/6'), 6.21 (d, $J = 2.2$ Hz, 1H, H-9), 6.10 (d, $J = 2.2$ Hz, 1H, H-7), 5.46 (s, 1H, H-3), 5.03 (s, 1H, H-2), 4.88 (d, $J = 8.8$ Hz, 1H, N-H), 4.09 (dd, $J = 8.7, 4.6$ Hz, 1H, H-2''), 3.88 (s, 6H, 3'/5'-OMe), 3.84 (s, 3H, 4'-OMe), 3.79 (s, 3H, 8-OMe), 3.77 (s, 3H, 6-OMe), 2.95 (s, 2H, H-4), 1.91 (td, $J = 12.9, 6.5$ Hz, 1H, H-3''), 1.36 (s, 9H, H-8''), 0.72 (d, $J = 6.8$ Hz, 3H, H-4'' or -5''), 0.64 (d, $J = 6.9$ Hz, 3H, H-4'' or -5'') ppm; δ_C (150 MHz, CDCl_3) 171.45 (1''), 159.75 (8), 158.81 (6), 155.36 (6''), 155.20 (1), 153.27 (2C, 3'/5'), 137.83 (4'), 133.13 (1'), 103.55 (2C, 2'/6'), 99.68 (5), 93.27 (9), 92.04 (7), 79.65 (7''), 77.38 (2), 68.96 (3), 60.83 (4'-OMe), 58.60 (2''), 56.21 (2C, 3'/5'-OMe), 55.44 (6- or 8-OMe), 55.38 (6- or 8-OMe), 31.43 (3''), 28.21 (3C, 8''), 25.68 (4), 18.37 (4'' or 5''), 17.24 (4'' or 5'') ppm; HRMS-ESI m/z 598.2626 $[\text{M} + \text{Na}]^+$ (calcd. for $\text{C}_{30}\text{H}_{41}\text{NO}_{10}$, m/z 598.2623).

3.5. Synthesis of (2R,3R)-5,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl L-valinate (**4**)

To a solution of intermediate **3** (52.7 mg, 0.0915 mmol) in CH_2Cl_2 (1 mL), TFA (57 μL) was added. The reaction mixture was then stirred at room temperature overnight. The reaction was quenched with K_2CO_3 , then filtered off the solid and concentrated in vacuo. The crude product was purified by silica column chromatography (eluent: 50% EtOAc/Hex with 1% Et_3N) to afford desired product **4** as a colorless oil (36.5 mg, 84%). R_f (50% EtOAc/Hex with 1% Et_3N) 0.34; IR (ATR, $\nu_{\text{max}}/\text{cm}^{-1}$): 3387, 2954, 2924, 1728, 1597, 1458, 1149, 1100; δ_H (600 MHz, CDCl_3) 6.70 (s, 2H, H-2'/6'), 6.21 (d, $J = 2.3$ Hz, 1H, H-9), 6.11 (d, $J = 2.3$ Hz, 1H, H-7), 5.46 (t, $J = 2.7$ Hz, 1H, H-3), 5.04 (s, 1H, H-2), 3.88 (s, 6H, 3'/5'-OMe), 3.84 (s, 3H, 4'-OMe), 3.79 (s, 3H, 8-OMe), 3.78 (s, 3H, 6-OMe), 3.12 (t, $J = 5.4$ Hz, 1H, H-2''), 2.96 (d, $J = 3.2$ Hz, 2H, H-4), 1.80 (qd, $J = 12.1, 6.8$ Hz, 1H, H-3''), 0.75 (d, $J = 6.9$ Hz, 3H, H-4'' or -5''), 0.69 (d, $J = 6.9$ Hz, 3H, H-4'' or -5'') ppm; δ_C (150 MHz, CDCl_3) 174.67 (1''), 159.70 (8), 158.85 (6), 155.18 (1), 153.19 (2C, 3'/5'), 137.76 (4'), 133.36 (1'), 103.56 (2C, 2'/6'), 99.81 (5), 93.32 (9), 92.01 (7), 77.37 (2), 68.40 (3), 60.85 (4'-OMe), 59.94 (2''), 56.21 (2C, 3'/5'-OMe), 55.48 (8-OMe), 55.38 (6-OMe), 32.03 (3''), 25.72 (4), 18.81 (4'' or 5''), 16.99 (4'' or 5'') ppm; HRMS-ESI m/z 476.2282 $[\text{M} + \text{H}]^+$ (calcd. for $\text{C}_{25}\text{H}_{33}\text{NO}_8$, m/z 476.2279); $[\alpha]_D^{20} = -88.0$ (0.000136, EtOH); UV (EtOH, λ_{max}) 209 and 229 nm. The purity of **4** was assessed by UPLC-UV at 254 nm to be >95%.

4. Conclusions

A hybrid compound of EGCG and valine was synthesized in four steps. The gallic acid moiety was substituted by a valine moiety at the C3 position of EGCG via an ester linkage. This novel derivative **4** was fully characterized by NMR, IR, mass, and UV spectroscopies. An *in silico* analysis of its physicochemical properties was performed, demonstrating improved drug-like parameters and better intestinal absorption in comparison with the parent compound EGCG.

Supplementary Materials: Figures S1–S14: NMR spectra; Figure S15: IR spectrum of compound **4**; Figure S16: UV spectrum of compound **4**; Figures S17 and S18: mass spectra; Figure S19: UPLC-UV chromatogram of **4**; Figure S20: BOILED-Egg graph resuming the predicted properties for EGCG and derivative **4**; Table S1: Assignment of ^1H and ^{13}C NMR chemical shifts of **4**; Table S2: Physicochemical properties of EGCG and derivatives **1** and **4** calculated by SwissADME.

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