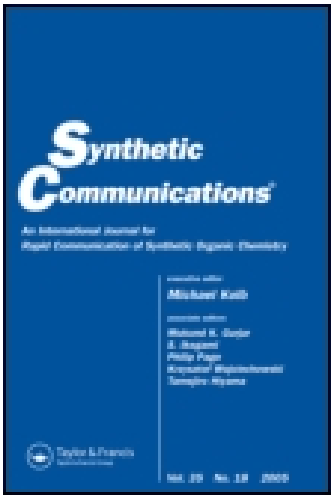

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SEMISYNTHESIS OF FLUORO-SUBSTITUTED BENZOATES OF *EPI*-GALLOCATECHIN

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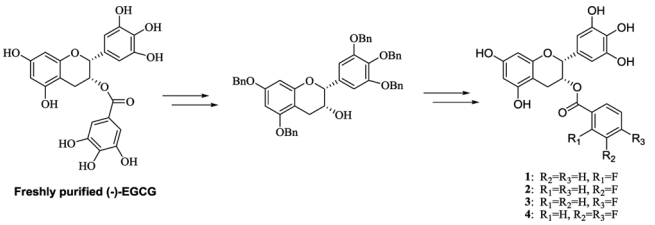
GRAPHICAL ABSTRACT



Abstract *In the present study, four fluoro-substituted benzoates of* epi-*gallocatechin (EGC) were prepared through a semisynthetic strategy, and the yield of benzylation of* epi-*gallocatechin gallate (−)-EGCG was improved by using freshly purified (−)-EGCG as starting material and a mild base of K_2CO_3. All structures of new compounds were characterized by ^1H NMR, ^{13}C NMR, high-resolution mass spectrometry, and optical rotation.*

Keywords (−)-EGCG; fluoro-substituted benzoates of *epi*-gallocatechin; proteasome inhibitor; semi-synthesis

INTRODUCTION

Epi-gallocatechin gallate [(−)-EGCG, shown in Fig. 1] has displayed the greatest potency against the growth of four selected human tumor cell lines.[1] In addition, a series of O-acyl derivatives of (−)-EGCG have also been semisynthesized and

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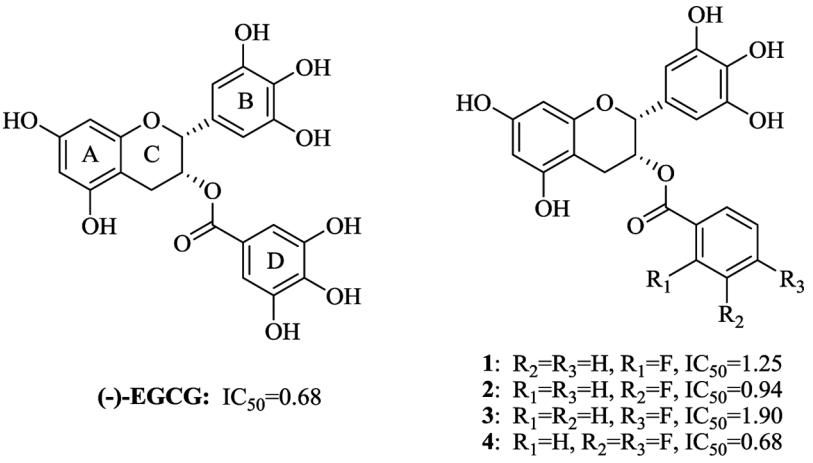


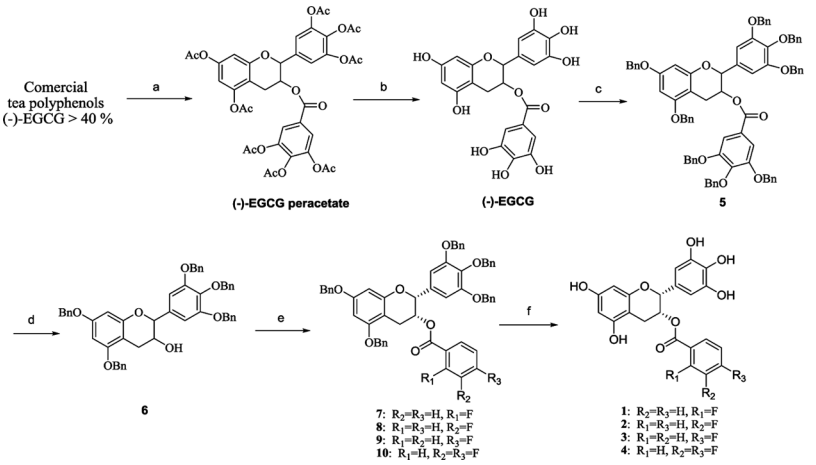
Figure 1. (−)-EGCG and fluoro-substituted benzoates of EGC.

screened for their tumor inhibitory potential against 7,12-dimethylbenz[a]anthracene (DMBA)/12-O-tetradecanoyl phorbol 13-acetate (TPA)-induced skin carcinogenesis in Swiss albino mice.[2] Further more, the (−)-EGCG analogs of 3-O-octanoyl- or 3-O-(2-methyloctanoyl)-(−)-*epi*-gallo-catechins have been found to inhibit papilloma formation 1.3 to 1.6-fold more strongly than (−)-EGCG.[3] One mechanism research study has found that ester bond–containing green tea polyphenols, such as EGCG, gallocatechin gallate (GCG), and *epi*-gallocatechin (ECG), possess the ability to inhibit proteasome activity in vitro and in vivo.[1] The 26S proteasome is a multicatalytic protease complex responsible for the degradation of most cellular proteins.[4,5] Because the ubiquitin/proteasome-dependent degradation pathway plays an important role in the up-regulation of cell proliferation and down-regulation of cell death in human cancer cells, proteasome inhibitors have been considered as potential anticancer drugs.[6] To study the structure–activity relationship of EGCG on the proteasome inhibition, a number of (−)-EGCG analogs with various hydroxy or methoxy substituents at B- or D-rings have been prepared and evaluated,[7] showing that (−)-EGCG demonstrates superior proteasome-inhibitory activity among the natural green tea polyphenols and the synthetic analogs.

In our previous study, four novel fluoro-substituted benzoates of -(EGC [**1, 2, 3**, and **4** (Fig. 1)] were found to inhibit the proteasomal chymotrypsin-like activity with potency similar to (−)-EGCG,[8] and the biological results have been reported. In this article, we report the semisynthetic strategy and physical data of the four compounds.

RESULTS AND DISCUSSION

A semisynthetic strategy was developed in the preparation of the four fluoro-substituted benzoates of EGC, shown in Scheme 1. First of all, freshly purified (−)-EGCG obtained through chemical modification and purification of tea polyphenols was used as starting material to replace commercial pure (−)-EGCG. In the purification experiment, commercial tea polyphenols containing 40% (−)-EGCG



Scheme 1. Synthetic route of fluoro-substituted benzoates of EGC 1, 2, 3 and 4 (a): Ac_2O/Py, 0 °C-rt; (b): saturated methanolic hydrogen chloride, rt; (c): $BnBr/K_2CO_3$/DMF, rt; (d): K_2CO_3/DME/MeOH, rt; (e): 2-fluorobenzoyl chloride, 3-fluorobenzoyl chloride, 4-fluorobenzoyl chloride, or 3,4-difluorobenzoyl chloride/DMAP/CH_2Cl_2, rt; and (f): H_2/Pd/C/MeOH, rt.

were treated with acetic anhydride in pyridine at room temperature for 24 h, and a mixture of acetylated tea polyphenols were obtained and then purified by column chromatography on silica gel to afford pure (−)-EGCG peracetate with 81% yield based on (−)-EGCG. Deprotection of (−)-EGCG peracetate in saturated HCl/methanol provided quantitatively pure (−)-EGCG, with the same ^{1}H NMR and ^{13}C NMR spectra and optical rotation as natural (−)-EGCG. Subsequent benzylation of freshly obtained (−)-EGCG by benzyl bromide and K_2CO_3 in dry dimethylformamide (DMF) at room temperature afforded key intermediate perbenzylated (−)-EGCG **5.** The yield of perbenzylated (−)-EGCG **5** from (−)-EGCG peracetate was 45%, greater than the 25% yield of enantioselective synthesis,[9] 18% yield of semisynthesis from commercial pure (−)-EGCG with NaH as a base, and 27% yield of semisynthesis from (−)-EGCG peracetate with NaH as a base.[10] Then hydrolysis of **5** in K_2CO_3/DME/MeOH gave pentabenzylated epigallocatechin **6** with an 87% yield. The compounds **5** and **6** have the same configurations as reported in total and semisynthesis.[9,10] Esterification of **6** with various fluoro-substituted benzoyl chlorides afforded compounds **7, 8, 9**, and **10**. Subsequent hydrogenolysis of **7, 8, 9**, and **10** provided provided the four fluoro-substituted benzoates of EGC **1, 2, 3**, and **4,** respectively, with the total yields of 28–32% based on freshly obtained (−)-EGCG. All structures of new compounds were characterized by ^{1}H NMR, ^{13}C NMR, high-resolution mass spectrometry (HRMS), and optical rotation.

In summary, a modified semisynthetic strategy was developed for the preparation of the four fluoro-substituted benzoates of EGC. The yield of benzylation of EGCG was improved by using freshly purified (−)-EGCG as starting material and a mild base of K_2CO_3. This strategy may be helpful to synthesize more (−)-EGCG analogs.

EXPERIMENTAL

The starting materials and reagents, purchased from commercial suppliers, were used without further purification. Anhydrous methylene chloride and DMF were distilled under nitrogen from CaH_2. Reaction flasks were flamedried under a stream of N_2. All moisture-sensitive reactions were conducted under a nitrogen atmosphere. Flash chromatography was carried out using silicagel 60 (70–230 mesh). The melting points were uncorrected. ^{1}HNMR and ^{13}C NMR spectra were measured with tetramethylsilane (TMS) as an internal standard when $CDCl_3$ and dimethylsulfoxide (DMSO-d_6) were used as a solvent. HRMS (ESI) spectra were recorded using a QTOF-2 micromass spectrometer.

(2 R,3 R)-5,7-*Bis*(acetoxy)-2-[3′,4′,5′-*tris*(acetoxy)phenyl]chroman-3-yl 3,4,5-*tris*(acetoxy)benzoate [(−)-EGCG Peracetate]

Crude tea polyphenol (5 g) containing 40% (−)-EGCG was dissolved in a solution of acetic anhydride (20 mL) and pyridine (18 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then was stirred at rt overnight until thin-layer chromatography (TLC) showed the reaction had been completed. The solution was poured into a stirred mixture of ice water (300 mL), and a solid was formed. The mixture was filtered, and the solid was thoroughly washed by water. The solid was then dissolved in ethyl acetate (120 mL) and washed by 2 M HCl (3 × 30 mL) and distilled water (3 × 30 mL) respectively. The organic phase was dried by Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography on silica gel to afford (−)-EGCG peracetate (2.79 g, 81% yield based on (−)-EGCG). The spectroscopic data of the title compound were identical to those reported in the literature.[11] Mp 110–111 °C; $[\alpha]^{20}_D$ −44.6 (lit.[10] −42) (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.62 (s, 2H), 7.24 (s, 2H), 6.74 (d, J = 2.3 Hz, Hz, 1H), 6.61 (d, J = 2.3 Hz, 1H), 5.63 (m, 1H), 5.18 (bs, 1H), 3.06 (A of ABq, J = 17.9 Hz, 4.6 Hz, 1H), 3.00 (B of ABq, J = 17.9 Hz, 2.3 Hz, 1H), 2.29 (m, 24H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 168.8, 168.3, 167.9, 167.4, 166.2, 163.5, 154.9, 149.7, 143.3, 142.0, 141.9, 138.9, 135.3, 127.4, 124.3, 123.5, 122.2, 121.8, 109.4, 108.9, 108.0, 68.1, 25.9, 21.0, 20.7, 20.5, 20.1; HRMS (ESI) calcd for $(C_{38}H_{34}O_{19}+H)^+$ 795.1773; found 795.1786.

(2 R,3 R)-5,7-*Bis* (benzyloxy)-2-[3′,4′,5′- *tris*(benzyloxy)phenyl]chroman-3-yl 3,4,5-*tris*(benzyloxy)benzoate (5)

(−)-EGCG peracetate (2.00 g, 2.5 mmol) was dissolved in saturated methanolic hydrogen chloride (50 mL) under an ice bath. After stirring at rt for 4 h, TLC showed the reaction had been completed. Evaporation of solvent and hydrogen chloride yielded a pale yellow solid (1.15 g, 99.6% yield). The spectroscopic data of the pale yellow solid were identical to those of the synthetic (−)-EGCG reported in the literature.[9] The freshly obtained (−)-EGCG (1.15 g, 2.5 mmol) was dissolved in dry DMF (50 mL). Potassium carbonate (7.5 g, 54.3 mmol) and benzyl bromide (6 mL, 50.4 mmol) were added successively. The mixture was stirred at rt for 48 h and then was poured into ice water (200 mL). The mixture was extracted with EtOAc. The

organic layers were combined, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatograph on silica gel and then recrystallized in petroleum ether–EtOAc to afford 1.33 g (45% yield) of the title compound **5** as a white solid. The spectroscopic data of compound **5** were identical to those reported in the literature.[9] Mp 117–118 °C; $[\alpha]^{20}_D$ −44.6 (c = 1.0, $CHCl_3$) (lit.[9] −45); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.41 (m, 42H), 6.72 (bs, 2H), 6.39 (d, J = 2.3 Hz, 1H), 6.34 (d, J = 2.3 Hz, 1H), 5.67 (m, 1H), 5.05 (m, 17H), 3.12 (A of ABq, J = 17.9 Hz, 4.6 Hz, 1H), 3.06 (B of ABq, J = 17.9 Hz, 2.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 158.8, 158.3, 155.1, 153.0, 138.3, 137.8, 136.9, 133.7, 128.6, 127.2, 106.1, 100.9, 94.6, 94.1, 78.5, 75.2, 71.3, 70.1, 69.9, 66.4, 28.1; HRMS (ESI) calcd. for $(C_{78}H_{66}O_{11} + H)^+$ 1179.4683; found 1179.4671.

(2R,3R)-5,7-*Bis* (Benzyloxy)-2-[3′,4′,5′-*tris* (benzyloxy)phenyl]chroman-3-ol (6)

Compound **5** (0.5 g, 0.4 mmol) was dissolved in a solution of methanol (10 mL) and ethylene glycol dimethyl ether (10 mL), and then potassium carbonate (0.2 g, 1.4 mmol) was added successively. The resulting mixture was stirred at rt for 1 h until TLC showed the reaction had been completed. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel to afford the desired compound **6** (0.28 g, 87% yield). The spectroscopic data of compound **6** were identical to those reported in the literature.[9] Mp 131–132 °C; $[\alpha]^{20}_D = -9.60$ (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.43 (m, 25H), 6.78 (s, 2H), 6.28 (s, 2H), 5.13 (m, 10H), 4.89 (bs, 1H), 4.21 (bs, 1H), 3.01 (A of ABq, J = 17.5 Hz, 1.9 Hz, 1H), 2.93 (B of ABq, J = 17.5 Hz, 4.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 158.8, 158.3, 155.1, 153.0, 138.3, 137.8, 136.9, 133.7, 128.6, 127.2, 106.1, 100.9, 94.6, 94.1, 78.5, 75.2, 71.3, 70.1, 69.9, 66.4, 28.1. HRMS (ESI) calcd. for $(C_{50}H_{44}O_7+H)^+$ 757.3165:found 757.3177.

(2R,3R)-5,7-*Bis*(benzyloxy)-2-[3′,4′,5′-*tris*(benzyloxy)phenyl]chroman-3-yl 2-Fluorobenzoate (7)

Oxalyl chloride (5 mL) was added, to a solution of 2-fluorobenzoic acid (1.4 g, 10.0 mmol) in dry CH_2Cl_2(50 mL), and then one drop of DMF was added. The mixture was refluxed for 5 h. After evaporation of oxalyl chloride, the resulting oil was dried completely under a reduced pressure for 2 h. The desired solid was dissolved in dry CH_2Cl_2(10 mL) and then added dropwise into a solution of compound **6** and dimethylaminopgridine (DMAP) (0.40 g) in CH_2Cl_2(20 mL) at 0 °C. The mixture was stirred at rt overnight, the solvent was evaporated, and the resulting mixture was purified by flash chromatography on silica gel to give the desired compound **7** (0.90 g, 89% yield). Mp 113–115 °C; $[\alpha]^{20}_D$ −56.8 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.84 (m, 1H), 7.45 (m, 2H), 7.41 (m, 21H), 7.22 (m, 3H), 7.12 (m, 1H), 7.06 (m, 1H), 6.85 (bs, 2H), 6.34 (d, J = 2.3 Hz, 1H), 6.29 (d, J = 2.3 Hz, 1H), 5.67 (m, 1H), 5.06 (m, 11H), 3.13 (d, J = 3.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.2, 161.2, 158.8, 157.9, 155.5, 152.8, 138.2, 137.8, 137.0, 136.8, 136.8, 134.7, 134.7, 133.2, 132.3, 128.4, 128.1, 127.2, 123.9, 118.4, 117.0, 106.5, 100.7, 94.7, 93.9, 77.6, 75.1,

71.2, 70.1, 69.9, 68.9, 58.5, 26.0, HRMS (ESI) calcd. for $(C_{57}H_{47}FO_8+H)^+$ 879.3333; found 879.3345.

(2 R,3 R)-5,7-*Bis*(benzyloxy)-2-[3′,4′,5′-*tris*(benzyloxy) phenyl]chroman-3-yl 3-Fluorobenzoate (8)

Following the procedure used for the preparation of compound **7**, but with 3-fluorobenzoic acid as starting material, the title compound **8** was obtained (91% yield) as a white solid. Mp 113–115 °C; $[\alpha]^{20}_D$ −72.9 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.76 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.45 (m, 2H), 7.41 (m, 25H), 6.79 (bs, 2H), 6.34 (d, J = 2.3 Hz, 1H), 6.30 (d, J = 2.3 Hz, 1H), 5.65 (m, 1H), 5.08 (m, 11H), 3.14 (A of ABq, J = 17.9 Hz, 4.6 Hz, 1H), 3.09 (B of ABq, J = 17.9 Hz, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.2, 163.2, 158.8, 157.8, 155.3, 152.8, 138.1, 137.6, 136.8, 136.7, 136.7, 133.0, 132.1, 130.0, 128.5, 128.0, 127.3, 127.1, 125.5, 120.1, 116.5, 106.3, 100.6, 94.7, 94.0, 75.0, 71.1, 70.0, 69.9,68.9, 25.9, HRMS (ESI) calcd. for $(C_{57}H_{47}FO8+H)^+$ 879.3333; found 879.3339.

(2 R,3 R)-5,7-*Bis*(benzyloxy)-2-[3′,4′,5′-*tris*(benzyloxy) phenyl]chroman-3-yl 4-Fluorobenzoate (9)

Following the procedure used for the preparation of **7**, but with 4-fluorobenzoic acid as starting material, the title compound **9** was obtained (90% yield) as a white solid. Mp 102–104 °C: $[\alpha]^{20}_D$ −61.1 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.97 (m, 2H), 7.45 (m, 2H), 7.41 (m, 23H), 7.05 (m, 2H), 6.79 (bs, 2H), 6.34 (d, J = 2.3 Hz, 1H), 6.30 (d, J = 2.3 Hz, 1H), 5.67 (m, 1H), 5.08 (m, 11H), 3.13 (A of ABq, J = 17.9 Hz, 4.6 Hz, 1H), 3.08 (B of ABq, J = 17.9 Hz, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 166.6, 164.9, 164.4, 158.8, 158.0, 155.4, 152.8, 138.2, 137.7, 136.9, 136.8, 136.7, 133.2, 132.3, 132.2, 128.6, 127.2, 126.2, 115.6, 115.4,106.5, 100.8, 94.7, 93.9, 77.6, 75.1, 71.2, 70.1, 69.9, 68.5, 26.1, HRMS (ESI) calcd. for $(C_{57}H_{47}FO_8+H)^+$ 879.3333; found 879.3325.

(2 R,3 R)-5,7-*Bis*(benzyloxy)-2-[3′,4′,5′-*tris*(benzyloxy)phenyl] chroman-3-yl 3,4-Difluorobenzoate (10)

Following the procedure used for the preparation of **7**, but with 3,4-difluorobenzoic acid as starting material, the title compound **10** was obtained (88% yield). Mp 121–122 °C; $[\alpha]^{20}_D$ −60.4 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.67 (m, 1H), 7.64 (m, 1H), 7.43 (m, 25H), 7.27 (m, 1H), 6.74 (s, 2H), 6.30 (d, J = 2.3 Hz, 1H), 6.29 (d, J = 2.3 Hz, 1H), 5.49 (m, 1H), 5.15 (d, J = 11.8 Hz, 1H), 5.10 (d, J = 11.8 Hz, 1H), 5.07 (s, 2H), 5.02 (d, J = 1.8 Hz, 1H), 5.01 (d, J = 1.8 Hz, 1H), 3.03–3.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.2, 163.2, 160.0, 158.9, 157.9, 155.1, 152.7, 138.2, 137.7, 137.0, 136.7, 136.7, 132.8, 128.6, 128.5, 128.4, 128.1-127.2, 106.2, 100.2, 94.6, 94.1, 77.2, 77.0, 75.1, 71.1, 70.1, 69.9, 67.4, 26.1, HRMS (ESI) calcd. for $(C_{57}H_{46}F_2O_8+H)^+$ 897.3239; found 897.3227.

(2 R,3 R)-5,7-*Bis*(hydroxyl)-2-[3′,4′,5′-*tris*(hydroxy)phenyl] chroman-3-yl 2-Fluorobenzoate (1)

Under a hydrogen atmosphere, 10% Pd/C (50 mg) was added to a solution of compound **7** (0.50 g, 0.57 mmol) in methanol (20 mL) and ethyl acetate (20 mL). The resulting mixture was stirred at room temperature for 5 h until TLC showed that the reaction had been completed. Then the mixture was filtered to remove the catalyst. The filtrate was evaporated in vacuum to afford the desired compound **1** (0.22 g, 91% yield). Mp 157–159 °C; $[\alpha]^{20}_{D}$ −74.3 (c = 1.0, CH_3OH); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.29 (s, 1H), 8.08 (s, 1H), 7.79 (s, 2H), 7.76 (m, 1H), 7.57 (m, 1 H), 7.29 (bs, 1H), 7.20 (m, 1H), 7.15 (m, 1H), 6.63 (bs, 2H), 6.04 (d, J = 2.3 Hz, 1H), 6.00 (d, J = 2.3 Hz, 1H), 5.64 (m, 1H), 5.11 (s, 1H), 3.08 (A of ABq, J = 17.9 Hz, 4.6 Hz, 1H), 2.90 (B of ABq, J = 17.9 Hz, 2.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 164.7, 162.2, 157.7, 157.6, 157.0, 146.7, 135.8, 133.7, 132.8, 130.6, 125.1, 119.6, 117.8, 106.6, 99.1, 96.5, 95.8, 78.2, 70.9, 26.6. HRMS (ESI) calcd. for $(C_{22}H_{17}FO8 + H)^+$ 429.0986; found 429.0997.

(2 R,3 R)-5,7-*Bis*(hydroxyl)-2-[3′,4′,5′-*tris*(hydroxy)phenyl] chroman-3-yl 3-Fluorobenzoate (2)

Following the procedure used for the preparation of **1**, but with compound **8** as starting material, compound **2** was obtained (89% yield). Mp 131–133 °C; $[\alpha]^{20}_{D}$ − 78.7 (c = 1.0, CH_3OH); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.68 (m, 1H), 7.51 (m, 1H), 7.41 (m, 1H), 7.26 (m, 1H), 6.49 (bs, 2H), 5.97 (d, J = 2.3 Hz, 1H), 5.95 (d, J = 2.3 Hz, 1H), 5.56 (m, 1H), 5.00 (m, 1H), 3.01 (A of ABq, J = 17.9 Hz, 4.6 Hz, 1H), 2.97 (B of ABq, J = 17.9 Hz, 2.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 166.0, 164.5, 157.8, 157.7, 157.0, 146.7, 133.6, 133.5, 131.4, 130.6, 126.4, 121.0, 117.0, 107.0, 99.1, 96.5, 95.8, 78.2, 71.1, 26.5, HRMS (ESI) calcd for $(C_{22}H_{17}FO_8+H)^+$ 429.0986; found 429.0995.

(2 R,3 R)-5,7-*Bis*(hydroxyl)-2-[3′,4′,5′-*tris*(hydroxy)phenyl] chroman-3-yl 4-Fluorobenzoate (3)

Following the procedure used for the preparation of **1**, but with compound **9** as starting material, compound **3** was obtained (80% yield). Mp 134–136 °C; $[\alpha]^{20}_{D}$ − 71.4 (c = 1.0, CH_3OH); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.95 (m, 2H), 7.18 (m, 2H), 6.62 (bs, 2H), 6.04 (d, J = 2.3 Hz, 1H), 6.03 (d, J = 2.3 Hz, 1H), 5.59 (m, 1H), 5.10 (s, 1H), 3.08 (A of ABq, J = 17.9 Hz, 4.6 Hz, 1H), 2.95 (B of ABq, J = 17.9 Hz, Hz, 2.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 118.0, 116.3, 157.9, 157.1, 146.8, 133.7, 133.4, 133.3, 130.7, 127.8, 116.5, 116.3, 106.6, 99.1, 96.5, 95.8, 78.4, 70.9, 26.6, HRMS (ESI) calcd. for $(C_{22}H_{17}FO_8+H)^+$ 429.0986; found 429.0976.

(2 R,3 R)-5,7-*Bis*(hydroxyl)-2-[3′,4′,5′-*tris* (hydroxy)phenyl] chroman-3-yl 3,4-Difluoro-benzoate (4)

Following the procedure used for the preparation of **1**, but with compound **10** as starting material, compound **4** was obtained (88% yield). Mp 136–138 °C; $[\alpha]^{20}_{D}$ −72.3

(c = 1.0, CH_3OH); ^1H NMR (DMSO-d_6, 600 MHz): δ 8.35 (s, 1H), 8.15 (s, 1H), 7.74 (s, 1H), 7.73 (m, 2H), 7.43 (m, 2H), 7.29 (bs, 1H), 6.69 (bs, 2H), 6.05 (d, $J = 2.3$ Hz, 1H), 6.03 (d, $J = 2.3$, 1H), 5.61 (m, 1H), 5.11 (s, 1H), 3.03 (m, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 165.2, 158.0, 157.8, 157.1, 153.9, 150.4, 146.8, 133.7, 130.6, 128.8, 128.0, 119.0, 106.5, 99.0, 96.6, 95.8, 78.3, 71.3, 26.6, HRMS (ESI) calcd for $(C_{22}H_{16}F_2O_8+H)^+$ 447.0891; found 447.0882.

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REFERENCES

1. Nam, S.; Smith, D. M.; Dou, Q. P. *J. Biol. Chem.* **2001**, *276*, 13322–13330.
2. Kumagai, A.; Nagaoka, Y.; Obayashi, T.; Terashima, Y.; Tokuda, H.; Hara, Y.; Mukainaka, T.; Nishino, H.; Kuwajima, H.; Uesato, S. *Bioorg. Med. Chem.* **2003**, *11*, 5143–5148.
3. Vyas, S.; Sharma, M.; Singh, T. V. *J. Agric. Food Chem.* **2007**, *15*, 6319–6324.
4. Goldberg, A. L. *Science* **1995**, *268*, 522–523.
5. Groll, M.; Ditzel, L.; Lowe, J.; Stock, D.; Bochtler, M.; Bartunik, H. D.; Huber, R. *Nature* **1997**, *386*, 463–471.
6. Seemuller, E.; Lupas, A.; Stock, D.; Lowe, J.; Huber, R.; Baumeister, W. *Science* **1995**, *268*, 579–582.
7. Huo, C.; Wan, S. B.; Lam, W. H.; Li, L.; Wang, Z.; Landis-Piwowar, K. R.; Chen, D.; Dou, Q. P.; Chan, T. H. *Inflammopharmacol.* **2008**, *16*, 248–252.
8. Yu, Z.; Qin, X. L.; Gu, Y. Y.; Chen, D.; Cui, Q. C.; Jiang, T.; Wan, S. B.; Dou, Q. P. *Int. J. Mol. Sci.* **2008**, *9*, 951–961.
9. Li, L. H.; Chan, T. H. *Org. Lett.* **2001**, *3*, 739–741.
10. Osanai, K.; Huo, C.; Landis-Piwowar, K. R.; Dou, Q. P.; Chan, T. H. *Tetrahedron* **2007**, *63*, 7565–7570.
11. Huo, C.; Shi, G.; Lam, Wai, H.; Chen, D.; Cui, Q. C.; Dou, Q. P.; Chan, T. H. *Can. J. Chem.* **2008**, *86*, 495–502.