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Trifluoromethylation of flavonoids and anti-tumor activity of the trifluoromethylated flavonoid derivatives

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Abstract—3-Trifluoromethylflavonoid derivatives were prepared for the first time by trifluoromethylation of 3-iodoflavonoid derivatives. Other C ring and B ring trifluoromethylated flavonoid derivatives were also prepared. All the compounds were tested for their effect on the U2OS cell cycle in vitro. Bistrifluoromethylated apigenin derivative **13** showed the strongest activity against the cell growth.

Cancer is one of the most serious threats against human health in the world. In recent years, there has been growing interest in the search for anti-cancer substances with high efficacy, low toxicity, and minimum side effects.[1] Flavonoids possess a broad range of pharmacological properties including anti-tumor effects. However, flavonoids generally exhibited low activity against tumor cells. It is known that the introduction of the CF_3 group into organic molecules often changes their physiological, physical, and chemical properties without the introduction of extra steric hindrance.[2] Recent studies carried out in our laboratory have revealed that A-ring[3a] and B-ring[3b] trifluoromethylated flavonoids exhibited enhanced anti-tumor activity. These results have encouraged us to study other fluorinated flavonoids. Herein, we describe the synthesis and anti-tumor activities of C-ring and B-ring trifluoromethylated flavonoids.

The nucleophilic trifluoromethylation reaction of a carbonyl group with trifluoromethyltrimethylsilane (Me_3SiCF_3) is rapidly becoming the method for introduction of a trifluoromethyl group into organic compounds.[4] Recently, Sosnovskikh and co-workers reported a regioselective nucleophilic 1,4-trifluoromethylation of 2-polyfluoroalkylchromones with Me_3SiCF_3.[5] We were interested in extending Sosnovskikh's reaction conditions to the synthesis of C-ring trifluoromethylated flavonoids. Accordingly, methylation of chrysin **1** and genistein **2** with CH_3I in the presence of K_2CO_3 afforded compounds **3** and **4**, respectively (Scheme 1). Treatment of **3** with Me_3SiCF_3 in the presence of a catalytic amount of anhydrous Me_4NF at 0 °C for 24 h, followed by acid hydrolysis, gave the 1,2-nucleophilic addition product **5**, whereas under the same reaction conditions the reaction of compound **4** with Me_3SiCF_3 proceeded as a 1,4-nucleophilic addition to give compound **6**. The different performance of **3** and **4** in the nucleophilic trifluoromethylation could be ascribed to the interplay of steric hindrance.

As the first step to prepare 3-trifluoromethylated flavonoids, treatment of **3** with LDA, followed by addition of I_2, produced 3-iodoflavonoid **7** (Scheme 2).[6] Trifluoromethylation of **7** with $FSO_2CF_2CO_2Me$/CuI afforded 3-trifluoromethyl-5,7-dimethoxychrysin **8**.[7] It was interesting to note that the reaction of compound **9** with LDA, followed by iodination, gave compounds **10** and **11**, which were separated by column chromatography. Trifluoromethylation of **10** and **11** gave products **12** and **13**, respectively.

The trifluoromethylated flavonoids **5**, **6**, **8**, **12**, and **13**[8] were tested for their inhibitory effects on the cell cycle of U2OS cells in vitro by the FCM Assay. U2OS cells, obtained from American Type Culture Collection (Manassas, VA), were seeded 3×10^5 cells/well in a

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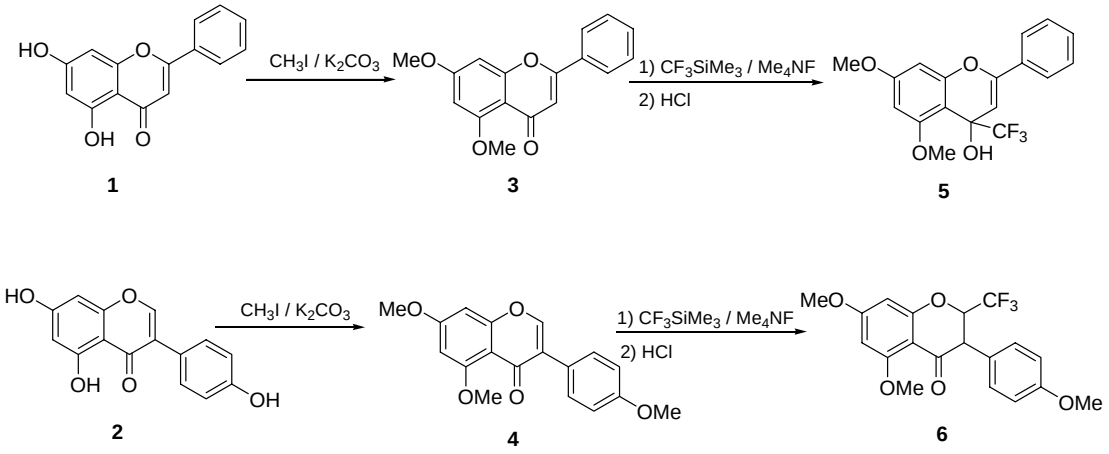
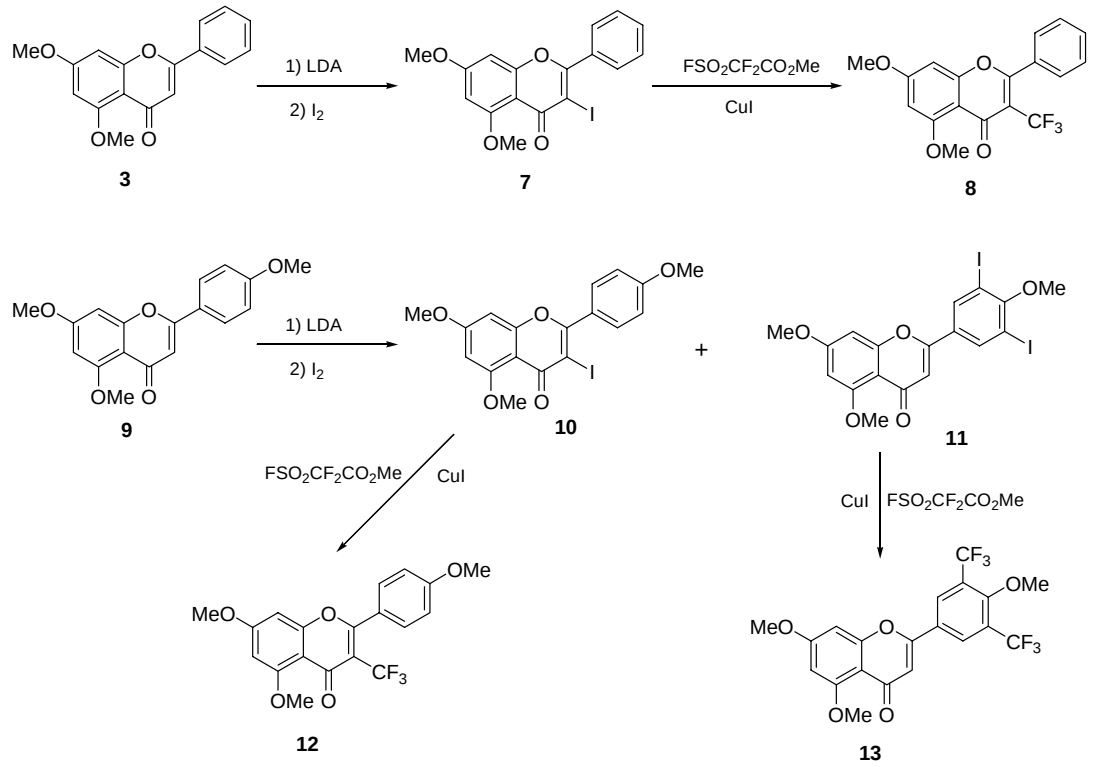


Scheme 1.



Scheme 2.

96-well plate. When the density of cells cultured at 37 °C reaches 40–50%, each compound was added, respectively, to maintain the concentration of each compound at 500 nM. The suspensions were incubated for 24 h. The cell cycle distribution was evaluated with a BD Biosciences FACScan flow cytometer and CellQuest software. Cells were maintained at 37 °C with 5% CO_2 in DMEM supplemented with 10% fetal bovine serum (FBS). The pharmacological activity of all compounds against the U2OS cell cycle is shown in Table 1. Compound **13**, the bistrifluoromethylated apigenin derivative, showed the strongest inhibitory effect on U2OS cells in the G_2/M phase. Compound **5** had so strong a cytotoxicity that

Table 1. Effect of the trifluoromethylated flavonoids on the cell cycle of U2OS

Compound	Content of cell cycle (%)		
	G_1	S	G_2/M
Control[a]	48.21	41.90	9.89
5[b]	—	—	—
6	46.69	48.02	5.29
8	53.06	31.95	14.99
12	44.09	49.24	6.67
13	55.08	44.92	0.00

[a] Negative control added 1%DMSO.
[b] In the concentration, all the cell died.

all the cells were killed at the test concentration. Compounds **6** and **12** showed some activities and compound **8** had the lowest activity in the series. From the above results, it seems reasonable to conclude that: (1) B-ring trifluoromethylated flavonoids showed stronger inhibitory effects on U2OS cells than C-ring trifluoromethylated flavonoids and (2) the strong cytotoxicity of compound **5** is attributed, at least partly, to the existence of the 4-hydroxy group.

In conclusion, we have synthesized a series of trifluoromethylated flavonoid derivatives. The preliminary biological activity screening tests indicated that 3′,5′-bistrifluoromethylapigenin derivative **13** was the most active compound against U2OS cells.

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8. All the new compounds were characterized by the detailed spectroscopic analysis. **5**: m.p. 100–101 °C; MS (EI, 70 eV) *m*/*z*: 352 (M^+, 16), 335 (9), 332 (13), 321 (14), 105 (100), 77 (30); IR (KBr): 3298 (OH), 2962, 2844, 1655, 1612, 1517, 1436, 1354; ^{1}H NMR (400 MHz, $CDCl_3$): 3.71 (3H, s), 3.89 (3H, s), 5.38 (1H, s), 5.66 (1H, s), 6.36 (1H, d, J = 2.32 Hz), 6.45 (1H, d, J = 2.32 Hz), 7.42–7.44 (3H, m), 7.76–7.78 (2H, m); ^{19}F NMR (376 MHz): −81.60. Anal. Calcd. for $C_{18}H_{15}O_4F_3$: C, 61.36 H, 4.26. Found: C, 61.55 H, 4.12. **6**: m.p. 127–128 °C; MS (EI, 70 eV) *m*/*z*: 382 (M^+), 181 (13), 180 (100), 152 (19), 137 (15); IR (KBr): 1674 (C═O), 1612, 1572, 1513, 1469, 1427; ^{1}H NMR (400 MHz, $CDCl_3$): 3.75 (3H, s), 3.78 (1H, d, J = 3.4 Hz), 3.83 (3H, s), 3.89 (3H, s), 4.97 (1H, q, J = 3.4 Hz), 6.18 (1H, d, J = 2.24 Hz), 6.30 (1H, d, J = 2.24 Hz), 6.77–6.80 (2H, m), 7.13–7.16 (2H, m); ^{19}F NMR (376 MHz): −73.56. Anal. Calcd. for $C_{19}H_{17}O_5F_3$: C, 59.69 H, 4.45. Found: C, 59.26 H, 4.56. **8**: m.p. 166–167 °C; MS (EI 70 eV) *m*/*z*: 350 (M^+, 14), 151 (15), 100 (23), 87 (100), 77 (11); IR (KBr): 1655 (C═O), 1635, 1611, 1474, 1449, 1425, 1355; ^{1}H NMR (300 MHz, $CDCl_3$): 3.88 (3H, s), 3.96 (3H, s), 6.39-6.42 (1H), 6.44–6.47 (1H), 7.53–7.56 (5H, m); ^{19}F NMR (282 MHz): −59.28. Anal. Calcd. for $C_{18}H_{13}O_4F_3$: C, 61.71 H, 3.71. Found: C, 61.75 H, 4.12. **12**: m.p. 186–187 °C; MS (EI 70 eV) *m*/*z*: 380 (M^+, 78), 359 (79), 334 (47), 150 (72), 137 (100); IR (KBr): 1650 (C═O), 1630, 1601, 1491, 1470, 1424, 1353; ^{1}H NMR (300 MHz, $CDCl_3$): 3.88–3.95 (9H, m), 6. 40 (1H, d, J = 14.1 Hz), 6.45 (1H, d, J = 14.1 Hz), 6.99 (1H, d, J = 8.7 Hz), 7.02 (1H, d, J = 8.7 Hz), 7.53 (1H, d, J = 8.7 Hz), 7.56 (1H, d, J = 8.7 Hz); ^{19}F NMR (282 MHz): −56.18. Anal. Calcd. for $C_{19}H_{15}O_5F_3$: C, 60.00 H, 3.95. Found: C, 59.53 H, 4.17. **13**: m.p. 159–160 °C; MS (EI 70 eV) *m*/*z*: 448 (M^+, 6); IR (KBr): 1655 (C═O), 1634, 1611, 1467, 1450, 1355; ^{1}H NMR (400 MHz, $CDCl_3$): 3.89 (3H, s), 4.02 (3H, s), 4.05 (3H, s), 6.44 (1H, s), 6.99 (1H, d, J = 2.04 Hz), 7.01 (1H, d, J = 2.04 Hz), 7.60-7.62 (2H); ^{19}F NMR (376 MHz): −54.11 (3F, s), −56.30 (3F, s). Anal. Calcd. for $C_{20}H_{14}O_5F_6$: C, 53.57 H, 3.13. Found: C, 52.99 H, 3.43.