Synthesis of 4-(2-hydroxymethylaryl)coumarins

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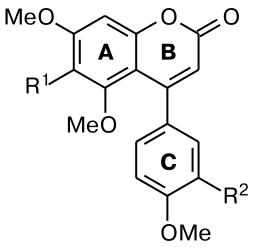
New 4-(2-hydroxymethylaryl)coumarins were prepared using the Suzuki—Miyaura cross-coupling at the key step. According to X-ray diffraction data, the compounds obtained are structural analogs of the natural stilbene combretastatin A-4, which exhibits potent antitumor activity.

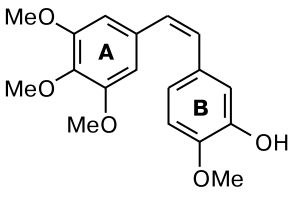
Key words: 4-trifluoromethylsulfonyloxycoumarins, arylboronic acids, 4-(2-hydroxymethylaryl)coumarins, the Suzuki—Miyaura cross-coupling, antitumor activity.

4-Arylcoumarins **1** are natural compounds isolated from the plants of the families *Guttiferae*, *Rubiaceae*, *Leguminosae*, *Passifloraceae*, and *Compositae*.[1] The presence of two non-coplanar *syn*-aryl fragments **A** and **C** linked by a rigid C—C bond makes these compounds structurally similar to combretastatin A-4 (*cis*-stilbene isolated from the African plant *Combretum cafrum* that exhibits potent antimitotic activity[2]). Indeed, neoflavonoid **1a** recently isolated from *Streptomyces aureofaciens* is highly active against tumor growth.[3] Its synthetic analogs **1b** and **1c** containing a similar set of substituents in the aromatic rings **A** and **C** can also efficiently prevent the formation of the mitotic spindle in a tumor cell by inhibiting the polymerization of the protein tubulin.[4] The higher antitumor activity of combretastatin A-4 compared to compounds **1b** and **1c** is due to the fact that hydrogen bonding between

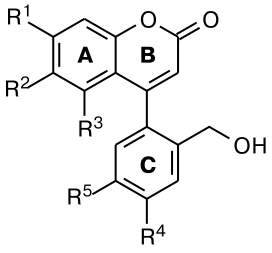


1a—c

	R^1	R^2
1		
a	H	H
b	H	OH
c	OMe	OH



Combretastatin A-4



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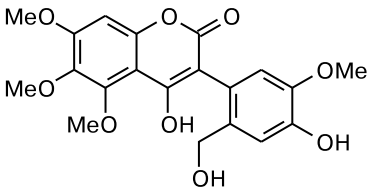

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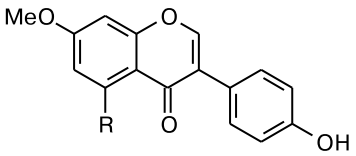

Genistein (R = OH),
Daidzein (R = H)

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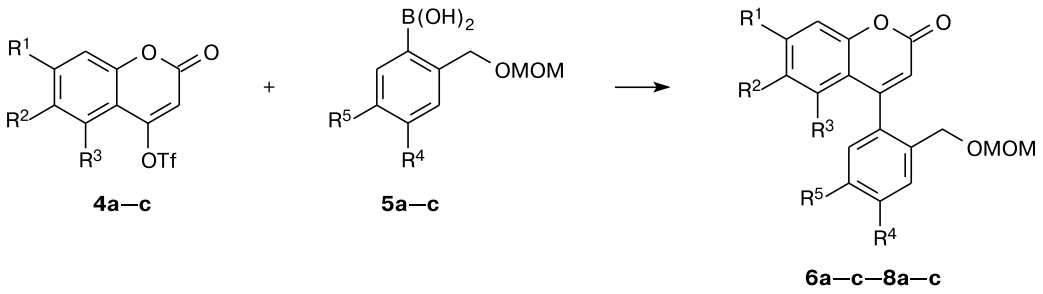
Scheme 1



4a—c **5a—c** **6a—c—8a—c**

MOM = CH_2OMe

Reagents and conditions: $Pd(dppf)Cl_2$ (5 mol.%) K_3PO_4 (3 equiv.), Bu_4NBr (0.1 equiv.), MeCN, 3 h, 80 °C.

Compound	R^1	R^2	R^3	R^4	R^5	Yield (%)
6a	H	H	H	OMe	OMe	91
6b	OMe	H	OMe	OMe	OMe	97
6c	OMe	OMe	OMe	OMe	OMe	91
7a	H	H	H	OMOM	OMe	93
7b	OMe	H	OMe	OMOM	OMe	98
7c	OMe	OMe	OMe	OMOM	OMe	97
8a	H	H	H	OMe	OMOM	91
8b	OMe	H	OMe	OMe	OMOM	95
8c	OMe	OMe	OMe	OMe	OMOM	97

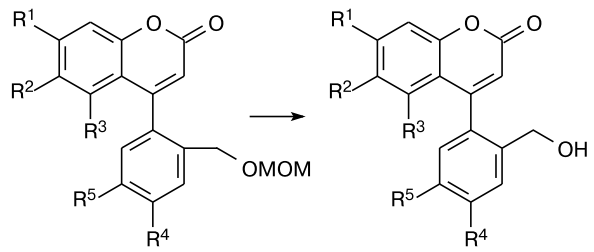
the fragment of the peptide chain of the protein tubulin Thr179 and the ring **B** of combretastatin A-4 is thermodynamically more favorable than hydrogen bonding between the same protein fragment and ring **C** of compounds **1b** and **1c** (see Ref. 5).

A serious drawback of combretastatin A-4 is its high tendency toward *Z—E* isomerization, which substantially deteriorates its antitumor activity on storage and application of combretastatin-based drugs.[2,6] In a search for novel neoflavonoid analogs of combretastatin A-4 with high antitumor activity, we synthesized new 4-arylcoumarins **2** containing the 2-hydroxymethyl substituent in the aryl fragment. Earlier,[7] antitumor activity have been found in isoflavonoid **3** containing a substituted aryl fragment in position 3. Compound **3** can be regarded as a structural analog of the soybean isoflavones genistein and daidzein.[8]

The key step in the synthesis of 4-arylcoumarins **2** is the Suzuki—Miyaura cross-coupling[9] between polymethoxycoumarin triflates **4a—c** (see Refs 4, 10) and appropriate arylboronic acids **5a—c** (see Ref. 7) containing a methoxymethyl-protected OH group (Scheme 1). The preparation of compounds **6—8** was complicated by a synthetic problem to be solved, namely, introduction of electron-rich aromatic fragments into the coumarin substrate already containing the electron-donating methoxy groups. The problem arises from hindered oxidative addition stage in the catalytic cycle.[9] However, the use of the catalytic system $Pd(dppf)Cl_2$ (5 mol.%)—K_3PO_4 (3 equiv.)—Bu_4NBr (0.1 equiv.)[11] allowed the synthesis of the target products in 91—98% yields, regardless of the number of methoxy groups in the coumarin moiety and the structure of an arylboronic acid (Scheme 1).

The protecting methoxymethyl groups in compounds **6—8** were removed under the action of HCl in acetone (Scheme 2). The yields of derivatives **9—11** were 53—88%.

Scheme 2



6a—c—8a—c **9a—c—11a—c**

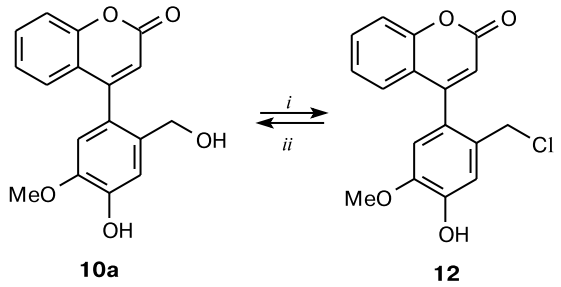
Compound	R^1	R^2	R^3	R^4	R^5	Yield (%)
9a	H	H	H	OMe	OMe	65
9b	OMe	H	OMe	OMe	OMe	67
9c	OMe	OMe	OMe	OMe	OMe	62
10a	H	H	H	OMOM	OMe	60
10b	OMe	H	OMe	OMOM	OMe	86
10c	OMe	OMe	OMe	OMOM	OMe	82
11a	H	H	H	OMe	OMOM	62
11b	OMe	H	OMe	OMe	OMOM	88
11c	OMe	OMe	OMe	OMe	OMOM	53

Reagents and conditions: HCl, acetone, 40 °C.

It should be noted that this reaction yields the corresponding 4-(2-chloromethylaryl)coumarins as by-products. For instance, removal of the methoxymethyl protection from compound **7a** resulted in the formation of benzylic chloride **12** in 25% yield, obviously, through an interac-

tion of HCl with the hydroxy group of benzylic alcohol **10a** (Scheme 3). When heated to 50 °C in water—acetone (1 : 2), chloride **12** is easily transformed into alcohol **10a**.

Scheme 3



10a **12**

Conditions: *i*. HCl, acetone, 40 °C; *ii*. H_2O, acetone, 50 °C.

Analysis of structure—antitumor activity correlations for combretastatin A-4 and its analogs showed that the activity is exhibited only by those derivatives in which the distance between rings **A** and **B** is in fine balance with their relative spatial orientations.[12] The structure of compound **9c** was ultimately determined by X-ray diffraction (Fig. 1, Table 1). The aromatic rings in this derivative are not coplanar. The dihedral angle between the planes of the aromatic fragments **A** and **C** in compound **9c** is 63.7°, which is larger than that between rings **A** and **B** in combretastatin A-4 (53.0°) (see Refs 11, 13).

The distance between the center of ring **A** in compound **9c** and the methyl C atom in substituent R^4 (C(20) atom) is 8.52 Å, while an analogous distance in combretastatin is 8.59 Å (see Ref. 13). The distance between the centers of rings **A** and **C** in neoflavonoid **9c** and between the centers of the aromatic fragments **A** and **B** in combretastatin A-4 are also nearly equal (5.21 and 5.24 Å, respectively).

Because of a considerable structural similarity between flavonoid **9c** and combretastatin A-4, one can expect that some of compounds **9**—**11** will show antitumor activity. Compounds **9**—**11** are being tested *in vitro* for cytotoxic activity.

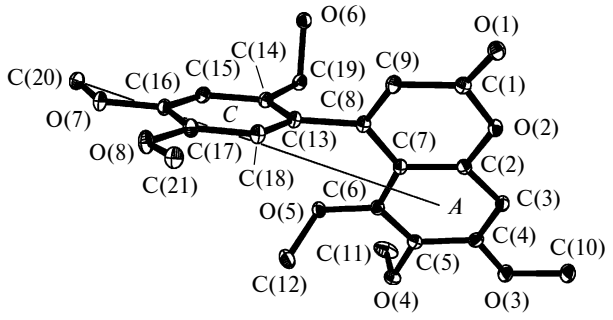


Fig. 1. Molecular structure **9c**.

Table 1. Selected crystallographic parameters and the data collection and refinement statistics for compound **9c**

Parameter	**9c**
Molecular formula	$C_{21}H_{22}O_8$
Molecular mass	402.39
Space group	*P*1
a/Å	8.6726(3)
b/Å	10.0670(3)
c/Å	12.4691(4)
α/deg	113.000(1)
β/deg	101.746(1)
γ/deg	93.022(1)
V/Å^3	970.49(5)
Z	2
d_{calc}/g cm^{-3}	1.377
μ/mm^{-1}	0.106
F(000)	424
$2\theta_{max}$/deg	56
Number of independent reflections (R_{int})	4664 (0.0137)
R_1 (on *F* for reflections with $I > 2\sigma(I)$)	0.0383
wR_2 (on F^2 for all reflections)	0.1117
Residual electron density peaks, max/min, e/Å^3	0.379/−0.268

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 400 spectrometer (300.13 and 75.54 MHz, respectively) in $CDCl_3$. Chemical shifts (δ) are referenced to Me_4Si. Elemental analysis was carried out on a Perkin-Elmer Series II CHN/O Analysis 2400 instrument. Commercial reagents (AlfaAesar, Aldrich) Pd(dppf)Cl_2, Bu_4NBr, AcCl, a dispersion of NaH in mineral oil, chloro(methoxy)methane, $NaBH_4$, BuLi, and $(Pr^iO)_3B$ were used as purchased. Solvents were purified according to standard procedures. Light petroleum with b.p. 40—70 °C was employed. Arylboronic acids **5a**—**c** and coumarin trifluoromethanesulfonates **4a**—**c** were prepared as described earlier.[4,7]

X-ray diffraction was carried out on a Smart APEX automatic diffractometer (graphite monochromator, Mo-Kα, φ-ω scan mode) at 100 K. The structure was solved by the direct methods and refined by the least-squares method on F^2_{hkl} in the anisotropic approximation for all non-hydrogen atoms with the SHELXTL program.[14] The H atoms in compound **9c** were located from difference electron-density maps and refined isotropically. Selected crystallographic parameters and the data collection and refinement statistics are given in Table 1.

Synthesis of compounds 6—8 (general procedure). 4-Trifluoromethylsulfonyloxycoumarin (1 equiv., 0.3 mmol), an arylboronic acid (1.3 equiv.), K_3PO_4 (3 equiv.), Bu_4NBr (0.1 equiv.), and Pd(dppf)Cl_2 (0.05 equiv.) were placed in freshly distilled MeCN (3 mL) under argon. The reaction mixture was stirred at 80 °C for 3 h. The solvent was removed under reduced pressure and the product was isolated by column chromatography on silica gel.

4-[4,5-Dimethoxy-2-(methoxymethoxymethyl)phenyl]chromen-2-one (6a) was obtained from 4-trifluoromethylsulfonyl-

oxycoumarin (**4a**) and arylboronic acid **5a**. The eluent for column chromatography was AcOEt—light petroleum (2 : 3). Yield 91%, beige needle-like crystals, m.p. 129—130 °C. Found (%): C, 67.20; H, 5.64. $C_{20}H_{20}O_6$. Calculated (%): C, 67.41; H, 5.66. ^{1}H NMR ($CDCl_3$), δ: 3.23 (s, 3 H, $CH_2O\underline{Me}$); 3.86 and 3.97 (both s, 3 H each, OMe); 4.33 (s, 2 H, $ArCH_2$); 4.50 (s, 2 H, OCH_2O); 6.39, 6.71, and 7.10 (all s, 1 H each, HC(3), HC(3′), HC(6′)); 7.17 (m, 2 H, HC(6), HC(8)); 7.39 (d, 1 H, HC(5), J = 8.1 Hz); 7.53 (m, 1 H, HC(7)). ^{13}C NMR ($CDCl_3$), δ: 55.3; 56.0; 56.1; 66.8; 96.0; 111.5; 112.3; 116.3; 117.1; 119.9; 124.3; 126.4; 127.0; 128.1; 132.0; 148.5; 149.6; 153.7; 154.6; 160.5.

4-[4,5-Dimethoxy-2-(methoxymethoxymethyl)phenyl]-5,7-dimethoxychromen-2-one (6b) was obtained from 5,7-dimethoxy-4-trifluoromethylsulfonyloxycoumarin (**4b**) and arylboronic acid **5a**. The eluent for column chromatography was AcOEt—light petroleum (1 : 1). Yield 97%, colorless crystals, m.p. 94—96 °C. Found (%): C, 63.28; H, 5.77. $C_{22}H_{24}O_8$. Calculated (%): C, 63.45; H, 5.81. ^{1}H NMR ($CDCl_3$), δ: 3.26 (s, 3 H, $CH_2O\underline{Me}$); 3.39, 3.84, 3.86, and 3.95 (all s, 3 H each, OMe); 4.32 (s, 2 H, $ArCH_2$); 4.54 (s, 2 H, OCH_2O); 5.99 (s, 1 H, HC(3)); 6.19 (d, 1 H, HC(6), J = 2.0 Hz); 6.51 (d, 1 H, HC(8), J = 2.0 Hz); 6.62 and 6.99 (both s, 1 H each, HC(3′), HC(6′)). ^{13}C NMR ($CDCl_3$), δ: 55.2; 55.71; 55.74; 55.9; 56.0; 66.8; 93.5; 95.6; 95.7; 104.1; 110.6; 111.0; 113.0; 126.7; 131.4; 147.7; 148.4; 154.0; 156.9; 158.2; 160.7; 163.4.

4-[4,5-Dimethoxy-2-(methoxymethoxymethyl)phenyl]-5,6,7-trimethoxychromen-2-one (6c) was obtained from 5,6,7-trimethoxy-4-trifluoromethylsulfonyloxycoumarin (**4c**) and arylboronic acid **5a**. The eluent for column chromatography was AcOEt—light petroleum (2 : 3). Yield 91%, beige crystals, m.p. 108—109 °C. Found (%): C, 62.99; H, 5.90. $C_{23}H_{26}O_9$. Calculated (%): C, 62.88; H, 5.87. ^{1}H NMR ($CDCl_3$), δ: 3.25 (s, 3 H, $CH_2O\underline{Me}$); 3.27, 3.75, 3.86, 3.91, and 3.94 (all s, 3 H each, OMe); 4.35 (s, 2 H, $ArCH_2$); 4.56 (s, 2 H, OCH_2O); 6.07, 6.68, 6.71, and 7.03 (all s, 1 H each, HC(3), HC(8), HC(3′), HC(6′)). ^{13}C NMR ($CDCl_3$), δ: 55.3; 56.0; 56.1; 56.2; 60.9; 61.0; 67.0; 95.9; 96.2; 107.8; 110.8; 111.2; 114.4; 127.1; 130.6; 139.4; 147.6; 148.5; 151.0; 151.4; 153.7; 156.9; 160.5.

4-[5-Methoxy-4-methoxymethoxy-2-(methoxymethoxymethyl)phenyl]chromen-2-one (7a) was obtained from 4-trifluoromethylsulfonyloxycoumarin (**4a**) and arylboronic acid **5b**. The eluent for column chromatography was AcOEt—light petroleum (1 : 2). Yield 93%, colorless crystals, m.p. 72—73 °C. Found (%): C, 65.44; H, 5.75. $C_{21}H_{22}O_7$. Calculated (%): C, 65.28; H, 5.74. ^{1}H NMR ($CDCl_3$), δ: 3.21 and 3.57 (both s, 3 H each, $CH_2O\underline{Me}$); 3.86 (s, 3 H, OMe); 4.30 (s, 2 H, $ArCH_2$); 4.51 (s, 2 H, $CH_2OC\underline{H}_2O$); 5.32 (s, 2 H, OCH_2O); 6.38 and 7.03 (both s, 1 H each, HC(3), HC(3′)); 7.17 (m, 3 H, HC(6′), HC(6), HC(8)); 7.39 (d, 1 H, HC(5), J = 11.7 Hz); 7.53 (m, 1 H, HC(7)). ^{13}C NMR ($CDCl_3$), δ: 55.3; 56.1; 56.4; 66.8; 95.4; 96.0; 112.1; 116.3; 117.0; 117.4; 119.8; 124.2; 127.1; 128.1; 128.2; 132.0; 147.2; 149.3; 153.7; 154.5; 160.5.

5,7-Dimethoxy-4-[5-methoxy-4-methoxymethoxy-2-(methoxymethoxymethyl)phenyl]chromen-2-one (7b) was obtained from 5,7-dimethoxy-4-trifluoromethylsulfonyloxycoumarin (**4b**) and arylboronic acid **5b**. The eluent for column chromatography was AcOEt—light petroleum (1 : 1). Yield 98%, pink powdery solid, m.p. 99 °C. Found (%): C, 61.73; H, 5.87. $C_{23}H_{26}O_9$. Calculated (%): C, 61.88; H, 5.87. ^{1}H NMR ($CDCl_3$), δ: 3.24 (s, 3 H, $CH_2O\underline{Me}$); 3.39 (s, 3 H, OMe); 3.55 (s, 3 H, $CH_2OC\underline{H}_3$); 3.83 and 3.86 (both s, 3 H each, OMe); 4.29 (s, 2 H, $ArCH_2$); 4.51 (s, 2 H, $CH_2OC\underline{H}_2O$); 5.26 and 5.29 (both d, 1 H each, $OC\underline{H}_AH_BO$, $OCH_A\underline{H}_BO$, J = 5.1 Hz); 6.01 (s, 1 H, HC(3)); 6.19 (d, 1 H, HC(6), J = 1.8 Hz); 6.51 (d, 1 H, HC(8), J = 1.8 Hz); 6.65 and 7.24 (both s, 1 H each, HC(3′), HC(6′)). ^{13}C NMR ($CDCl_3$), δ: 55.2; 55.72; 55.75; 56.1; 56.3; 66.8; 93.5; 95.6 (intense peak); 95.8; 104.0; 111.1; 112.8; 116.4; 127.0; 133.2; 145.8; 148.6; 153.9; 156.8; 158.2; 160.7; 163.4.

5,6,7-Trimethoxy-4-[5-methoxy-4-methoxymethoxy-2-(methoxymethoxymethyl)phenyl]chromen-2-one (7c) was obtained from 5,6,7-trimethoxy-4-trifluoromethylsulfonyloxycoumarin (**4c**) and arylboronic acid **5b**. The eluent for column chromatography was AcOEt—light petroleum (1 : 1). Yield 97%, white needle-like crystals, m.p. 104—105 °C. Found (%): C, 60.39; H, 5.87. $C_{24}H_{28}O_{10}$. Calculated (%): C, 60.50; H, 5.92. ^{1}H NMR ($CDCl_3$), δ: 3.24 (s, 3 H, $CH_2O\underline{Me}$); 3.28 (s, 3 H, OMe); 3.55 (s, 3 H, $CH_2O\underline{Me}$); 3.75, 3.86, and 3.93 (all s, 3 H each, OMe); 4.31 and 4.35 (both d, 1 H each, $ArC\underline{H}_AH_B$, $ArCH_A\underline{H}_B$, J = 5.1 Hz); 4.52 and 4.55 (both d, 1 H each, $CH_2OC\underline{H}_AH_BO$, $CH_2OCH_A\underline{H}_BO$, J = 5.1 Hz); 5.27 and 5.30 (both d, 1 H each, $OC\underline{H}_AH_BO$, $OCH_A\underline{H}_BO$, J = 5.1 Hz); 6.08 (s, 1 H, HC(3)); 6.70, 6.72, and 7.28 (all s, 1 H each, HC(8), HC(3′), HC(6′)). ^{13}C NMR ($CDCl_3$), δ: 55.2; 56.1; 56.2; 56.3 (intense peak); 60.9; 61.0; 66.0; 95.6; 95.9; 96.2; 107.7; 111.2; 114.3; 116.4; 127.3; 132.4; 139.3; 146.0; 148.4; 151.0; 153.6; 156.9; 160.5.

4-[4-Methoxy-5-methoxymethoxy-2-(methoxymethoxymethyl)phenyl]chromen-2-one (8a) was obtained from 4-trifluoromethylsulfonyloxycoumarin (**4a**) and arylboronic acid **5c**. The eluent for column chromatography was AcOEt—light petroleum (2 : 3). Yield 91%, yellow crystals, m.p. 80—81 °C. Found (%): C, 65.39; H, 5.77. $C_{21}H_{22}O_7$. Calculated (%): C, 65.28; H, 5.74. ^{1}H NMR ($CDCl_3$), δ: 3.23 and 3.49 (both s, 3 H each, $CH_2O\underline{Me}$); 3.98 (s, 3 H, OMe); 4.33 (s, 2 H, $ArCH_2$); 4.54 (s, 2 H, $CH_2OC\underline{H}_2O$); 5.22 (s, 2 H, OCH_2O); 6.37 and 7.03 (both s, 1 H each, HC(3), HC(3′)); 7.16 (m, 3 H, HC(6′), HC(6), HC(8)); 7.38 (d, 1 H, HC(5), J = 11.7 Hz); 7.53 (m, 1 H, HC(7)). ^{13}C NMR ($CDCl_3$), δ: 55.4; 56.0; 56.3; 66.8; 95.6; 96.0; 112.7; 116.4; 116.8; 117.1; 119.8; 124.2; 126.4; 127.0; 129.8; 131.9; 146.0; 150.4; 153.7; 154.2; 160.5.

5,7-Dimethoxy-4-[4-methoxy-5-methoxymethoxy-2-(methoxymethoxymethyl)phenyl]chromen-2-one (8b) was obtained from 5,7-dimethoxy-4-trifluoromethylsulfonyloxycoumarin (**4b**) and arylboronic acid **5c**. The eluent for column chromatography was AcOEt—light petroleum (1 : 1). Yield 95%, colorless powdery solid, m.p. 133 °C. Found (%): C, 61.96; H, 5.88. $C_{23}H_{28}O_9$. Calculated (%): C, 61.88; H, 5.87. ^{1}H NMR ($CDCl_3$), δ: 3.27 (s, 3 H, $CH_2O\underline{Me}$); 3.40 (s, 3 H, OMe); 3.49 (s, 3 H, $CH_2O\underline{Me}$); 3.86 and 3.94 (both s, 3 H each, OMe); 4,33 (s, 2 H, $ArCH_2$); 4.54 (s, 2 H, $CH_2OC\underline{H}_2O$); 5.19 (s, 2 H, OCH_2O); 5.99 (s, 1 H, HC(3)); 6.18 and 6.51 (both d, 1 H each, HC(6), HC(8), J = 1.8 Hz); 6.91 and 7.02 (both s, 1 H each, HC(3′), HC(6′)). ^{13}C NMR ($CDCl_3$), δ: 55.3; 55.7; 55.75; 56.0; 56.2; 66.8; 93.6; 95.7 (intense peak); 95.8; 104.1; 111.4; 113.0; 115.9; 128.6; 131.5; 145.2; 149.2; 153.6; 156.9; 158.3; 160.7; 163.4.

5,6,7-Trimethoxy-4-[4-methoxy-5-methoxymethoxy-2-(methoxymethoxymethyl)phenyl]chromen-2-one (8c) was obtained from 5,6,7-trimethoxy-4-trifluoromethylsulfonyloxycoumarin (**4c**) and arylboronic acid **5c**. The eluent for column chromatography was AcOEt—light petroleum (1 : 1). Yield 97%, colorless crystals, m.p. 72—73 °C. Found (%): C, 60.39; H, 5.90. $C_{24}H_{28}O_{10}$. Calculated (%): C, 60.50; H, 5.92. ^{1}H NMR ($CDCl_3$), δ: 3.26 (s, 3 H, $CH_2O\underline{Me}$); 3.28 (s, 3 H, OMe); 3.47 (s, 3 H, $CH_2O\underline{Me}$);

3.75, 3.93, and 3.95 (all s, 3 H each, OMe); 4.37 (s, 2 H, $ArCH_2$); 4.57 (s, 2 H, OCH_2O); 5.19 and 5.22 (both d, 1 H each, $OC\underline{H}_AH_BO$, $OCH_A\underline{H}_BO$, J = 5.1 Hz); 6.06, 6.70, 6.97, and 7.06 (all s, 1 H each, HC(3), HC(8), HC(3′), HC(6′)). ^{13}C NMR ($CDCl_3$), δ: 55.3; 56.0; 56.1; 56.3; 60.9; 61.0; 67.0; 95.6; 95.9; 96.2; 107.8; 111.5; 114.4; 115.8; 129.0; 130.6; 139.4; 144.9; 149.3; 151.0; 151.4; 153.4; 156.9; 160.5.

Synthesis of compounds 9—11 (general procedure). The starting substrate (~100 mg) was dissolved in distilled acetone (2 mL). Five to six drops of 15% HCl were added and the mixture was stirred at 40 °C for 1 h. Then 3—4 drops of conc. HCl were added and stirring was continued at 40 °C until the starting compound was completely consumed (TLC). The reaction mixture was diluted with water until the solution became slightly turbid (~1 mL) and stirred at 50 °C for ~30 min until the by-product benzylic chloride disappeared (TLC). The solvent was removed under reduced pressure. The residue was diluted with ethyl acetate (30 mL) and washed with a saturated solution of $NaHCO_3$ (3×7 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The product was isolated by column chromatography on silica gel.

4-(2-Hydroxymethyl-4,5-dimethoxyphenyl)chromen-2-one (9a) was obtained from compound **6a**. The eluent for column chromatography was AcOEt—light petroleum (1 : 1). Yield 65%, colorless polycrystalline powder, m.p. 177—178 °C. Found (%): C, 69.29; H, 5.17. $C_{18}H_{16}O_5$. Calculated (%): C, 69.22; H, 5.16. ^1H NMR ($CDCl_3$), δ: 3.87 and 3.98 (both s, 3 H each, OMe); 4.46 (s, 2 H, CH_2); 6.36 (s, 1 H, HC(3)); 6.71 (s, 1 H, HC(3′)); 7.18 (m, 3 H, HC(6′), HC(6), HC(8)); 7.39 (d, 1 H, HC(5), J = 8.0 Hz); 7.54 (m, 1 H, HC(7)). ^{13}C NMR ($CDCl_3$), δ: 56.0; 56.1; 62.3; 111.4; 111.6; 116.3; 117.2; 119.9; 124.4; 125.5; 126.9; 130.9; 132.1; 148.4; 149.8; 153.7; 154.7; 160.6.

4-(2-Hydroxymethyl-4,5-dimethoxyphenyl)-5,7-dimethoxychromen-2-one (9b) was obtained from compound **6b**. The eluent for column chromatography was AcOEt—light petroleum (7 : 3). Yield 67%, colorless powder, m.p. 173—174 °C. Found (%): C, 64.43; H, 5.43. $C_{20}H_{20}O_7$. Calculated (%): C, 64.51; H, 5.41. ^1H NMR ($CDCl_3$), δ: 3.41, 3.83, 3.86, and 3.95 (all s, 3 H each, OMe); 4.42 (s, 2 H, CH_2); 5.97 (s, 1 H, HC(3)); 6.22 and 6.52 (both d, 1 H each, HC(6), HC(8), J = 2.4 Hz); 6.60 and 7.05 (both s, 1 H each, HC(3′), HC(6′)). ^{13}C NMR ($CDCl_3$), δ: 55.8; 55.97; 56.0 (intense peak); 62.8; 93.9; 96.2; 104.3; 110.5; 110.7; 113.0; 129.6; 130.8; 147.8; 148.6; 154.0; 156.8; 158.0; 160.6; 163.5.

4-(2-Hydroxymethyl-4,5-dimethoxyphenyl)-5,6,7-trimethoxychromen-2-one (9c) was obtained from compound **6c**. The eluent for column chromatography was AcOEt—light petroleum (7 : 3). Yield 62%, transparent crystals, m.p. 177—178 °C. Found (%): C, 62.79; H, 5.53. $C_{21}H_{22}O_8$. Calculated (%): C, 62.68; H, 5.51. ^1H NMR ($CDCl_3$), δ: 3.26, 3.77, 3.87, 3.93, and 3.96 (all s, 3 H each, OMe); 4.38 and 4.43 (both d, 1 H each, $C\underline{H}_AH_B$, $CH_A\underline{H}_B$, J = 8.4 Hz); 6.05, 6.68, 6.73, and 7.09 (all s, 1 H each, HC(3), HC(8), HC(3′), HC(6′)). ^{13}C NMR ($CDCl_3$), δ: 56.0; 56.1; 56.3; 61.1; 61.4; 62.9; 96.9; 108.0; 110.7; 111.7; 114.9; 130.1; 130.5; 139.8; 147.8; 149.0; 150.3; 151.3; 153.7; 157.0; 160.3.

4-(4-Hydroxy-2-hydroxymethyl-5-methoxyphenyl)chromen-2-one (10a) was obtained from compound **7a**. The eluent for column chromatography was AcOEt—light petroleum (1 : 1). Yield 60%, colorless polycrystalline solid, m.p. 180—181 °C. Found (%): C, 68.51; H, 4.74. $C_{17}H_{14}O_5$. Calculated (%): C, 68.45; H, 4.73. ^1H NMR ($CDCl_3$), δ: 3.88 (s, 3 H, OMe); 4.39 and 4.42 (both d, 1 H each, $C\underline{H}_AH_B$, $CH_A\underline{H}_B$, J = 8.2 Hz); 5.91 (s, 1 H, ArOH); 6.37 and 6.70 (both s, 1 H each, HC(3), HC(3′)); 7.17 (m, 3 H, HC(6′), HC(6), HC(8)); 7.39 (d, 1 H, HC(5), J = 7.8 Hz); 7.53 (m, 1 H, HC(7)). ^{13}C NMR ($CDCl_3$), δ: 56.2; 62.2; 111.1; 115.0; 116.3; 117.2; 119.9; 124.4; 125.2; 126.9; 131.7; 132.1; 146.1; 146.6; 153.7; 154.8; 160.7.

4-(4-Hydroxy-2-hydroxymethyl-5-methoxyphenyl)-5,7-dimethoxychromen-2-one (10b) was obtained from compound **7b**. The eluent for column chromatography was AcOEt—light petroleum (7 : 3). Yield 86%, colorless polycrystalline solid, m.p. 116—117 °C. Found (%): C, 63.54; H, 5.06. $C_{19}H_{18}O_7$. Calculated (%): C, 63.68; H, 5.06. ^1H NMR ($CDCl_3$), δ: 3.43 (s, 3 H, OMe); 3.86 (s, 6 H, OMe); 4.38 (s, 2 H, $ArCH_2$); 5.98 (s, 1 H, HC(3)); 6.22 and 6.52 (both d, 1 H each, HC(6), HC(8), J = 2.2 Hz); 6.59 and 7.07 (both s, 1 H each, HC(3′), HC(6′)). ^{13}C NMR ($CDCl_3$), δ: 55.8; 56.0 (intense peak); 62.7; 93.8; 96.1; 104.3; 109.9; 113.0; 113.9; 130.4; 130.5; 145.3; 145.4; 154.1; 156.8; 158.0; 160.7; 163.4.

4-(4-Hydroxy-2-hydroxymethyl-5-methoxyphenyl)-5,6,7-trimethoxychromen-2-one (10c) was obtained from compound **7c**. The eluent for column chromatography was AcOEt—light petroleum (7 : 3). Yield 82%, colorless polycrystalline solid, m.p. 150—152 °C. Found (%): C, 61.69; H, 5.17. $C_{20}H_{20}O_8$. Calculated (%): C, 61.85; H, 5.19. ^1H NMR ($CDCl_3$), δ: 3.27, 3.77, 3.88 and 3.93 (all s, 3 H each, OMe); 4.33 and 4.40 (both d, 1 H each, $C\underline{H}_AH_B$, $CH_A\underline{H}_B$, J = 8.8 Hz); 5.72 (s, 1 H, ArOH); 6.03 (s, 1 H, HC(3)); 6.75, 7.07 and 7.25 (all s, 1 H each, HC(3′), HC(6′), HC(8)). ^{13}C NMR ($CDCl_3$), δ: 56.2; 56.4; 61.2; 61.6; 63.1; 97.0; 108.1; 111.3; 113.7; 115.0; 130.0; 131.0; 139.9; 144.6; 146.6; 150.3; 151.4; 153.6; 157.0; 160.5.

4-(5-Hydroxy-2-hydroxymethyl-4-methoxyphenyl)chromen-2-one (11a) was obtained from compound **8a**. The eluent for column chromatography was AcOEt—light petroleum (1 : 1). Yield 62%, beige crystals, m.p. 143—144 °C. Found (%): C, 68.32; H, 4.72. $C_{17}H_{14}O_5$. Calculated (%): C, 68.41; H, 4.73. ^1H NMR ($CDCl_3$), δ: 4.00 (s, 3 H, OMe); 4.45 (s, 2 H, $ArCH_2$); 5.73 (s, 1 H, ArOH), 6.34 and 6.81 (both s, 1 H each, HC(3), HC(3′)); 7.18 (m, 3 H, HC(6′), HC(6), HC(8)); 7.39 (d, 1 H, HC(5), J = 8.2 Hz); 7.53 (m, 1 H, HC(7)). ^{13}C NMR ($CDCl_3$), δ: 56.1; 62.3; 110.9; 114.8; 116.2; 117.1; 119.8; 124.3; 126.3; 127.0; 130.3; 132.0; 145.1; 147.4; 153.7; 154.4; 160.6.

4-(5-Hydroxy-2-hydroxymethyl-4-methoxyphenyl)-5,7-dimethoxychromen-2-one (11b) was obtained from compound **8b**. The eluent for column chromatography was AcOEt—light petroleum (7 : 3). Yield 88%, colorless polycrystalline solid, m.p. 166 °C. Found (%): C, 63.61; H, 5.07. $C_{19}H_{18}O_7$. Calculated (%): C, 63.68; H, 5.06. ^1H NMR ($CDCl_3$), δ: 3.49, 3.91 and 3.93 (all s, 3 H each, OMe); 4.37 and 4.43 (both d, 1 H each, $C\underline{H}_AH_B$, $CH_A\underline{H}_B$, J = 7.8 Hz); 5.86 (s, 1 H, HC(3)); 6.38 and 6.57 (both d, 1 H each, HC(6), HC(8), J = 2.4 Hz); 6.65 and 7.16 (both s, 1 H each, HC(3′), HC(6′)). ^{13}C NMR ($CDCl_3$), δ: 56.2; 56.3; 56.4; 62.3; 94.4; 96.3; 111.3; 113.3; 114.9; 131.0; 131.9; 141.3; 143.3; 147.8; 155.1; 157.2; 157.7; 159.5; 164.4.

4-(5-Hydroxy-2-hydroxymethyl-4-methoxyphenyl)-5,6,7-trimethoxychromen-2-one (11c) was obtained from compound **8c**. The eluent for column chromatography was AcOEt—light petroleum (7 : 3). Yield 53%, colorless polycrystalline solid, m.p. 128—129 °C. Found (%): C, 61.99; H, 5.19. $C_{20}H_{20}O_8$. Calculated (%): C, 61.85; H, 5.19. ^1H NMR ($CDCl_3$), δ: 3.28, 3.75, 3.94, and 3.95 (all s, 3 H each, OMe); 4.37 (s, 2 H, $ArCH_2$);

6.05, 6.75, 6.97, and 7.08 (all s, 1 H each, HC(3), HC(8), HC(3´), HC(6´)). ^{13}C NMR ($CDCl_3$), δ: 56.0; 56.3; 60.9; 61.1; 65.0; 96.2; 107.8; 111.5; 114.0; 115.5; 129.8; 130.6; 139.4; 146.0; 149.7; 151.0; 151.4; 153.6; 156.9; 160.5.

4-(2-Chloromethyl-4-hydroxy-5-methoxyphenyl)chromen-2-one (12) was obtained along with product **10a**. The eluent for column chromatography was AcOEt—light petroleum (1 : 1). Yield 25%, colorless polycrystalline solid, m.p. 192—193 °C. Found (%): C, 64.26; H, 4.15. $C_{17}H_{13}ClO_4$. Calculated (%): C, 64.46; H, 4.14. ^{1}H NMR ($CDCl_3$), δ: 3.89 (s, 3 H, OMe); 4.28 and 4.38 (both d, 1 H each, $C\underline{H}_AH_B$, $CH_A\underline{H}_B$, J = 9.0 Hz); 5.91 (s, 1 H, ArOH); 6.43 and 6.69 (both s, 1 H each, HC(3), HC(3´)); 7.20 (m, 3 H, HC(6´), HC(6), HC(8)); 7.40 (d, 1 H, HC(5), J = 7.8 Hz); 7.55 (m, 1 H, HC(7)). ^{13}C NMR ($CDCl_3$), δ: 43.4; 56.2; 111.0; 116.6; 116.8; 117.2; 119.8; 124.4; 126.3; 127.0; 128.4; 132.2; 146.6; 146.8; 153.8; 153.9; 160.4.

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