Synthesis and Antidiabetic Activity of 5,7-Dihydroxyflavonoids and Analogs

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In a study to evaluate the structural elements essential for the antidiabetic activity of flavonoids, we synthesized two series of flavonoids, 5,7-dihydroxyflavanones and 5,7-dihydroxyflavones. In a screening for potential antidiabetic activity, most of the flavonoids showed a remarkable *in vitro* activity, and compounds **1f**, **2d**, and **3c** were significantly more effective than the positive control, metformin. The biological activity was mainly affected by structural modification at the ring *B* moiety of the flavonoid skeleton. The results suggest that 5,7-dihydroxyflavonoids can be considered as promising candidates in the development of new antidiabetic lead compounds.

Introduction. – *Diabetes mellitus* is a metabolic alteration characterized by hyperglycemia resulting from defects in insulin secretion, action, or both, currently affecting *ca.* 3% of the world population [1]. Noninsulin-dependent diabetes mellitus (type II diabetes, T2D) is a heterogeneous disease characterized by hyperglycemia, which is caused by a disorder of insulin secretion, insulin resistance (IR) in target tissues, and activation of the hepatic glucose production pathway in the liver [2][3]. The key treatment strategy is keeping patient blood glucose within normal levels. So far, several drugs have been developed to control T2D. They can be divided into the hypoglycemic (sulfonylureas) and anti-hyperglycemic ones (biguanides, α-glucosidase inhibitors, and thiazolidine-diones). Because the mechanism of *diabetes mellitus* is quite complex, many currently available synthetic chemical antidiabetic agents have low rates of response and remission, and even severe adverse-effects. Accordingly, it is necessary to search for and develop more effective hypoglycemic agents with lower adverse-effect [4].

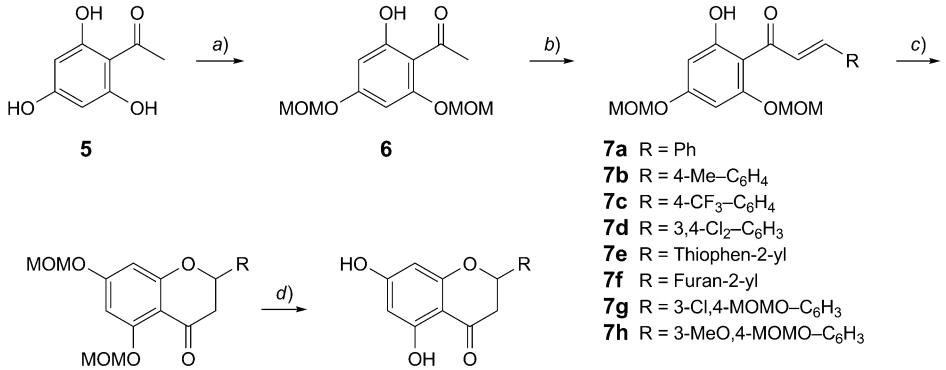
In recent years, herbal products have started to gain importance as a source of antidiabetic medicines. Several antidiabetic flavonoids, such as hesperidin and naringin [5], myricetin [6], quercetin [7], and kaempferol 3,7-dirhamnoside (= kaempferitrin) [8], have been reported. In this article, we describe the synthesis of 5,7-dihydroxyflavanone and 5,7-dihydroxyflavone derivatives, as well as their potential antidiabetic activities.

Results and Discussion. – 1. *Synthesis.* In an effort to define the structural elements essential to the antidiabetic activity, we prepared two series of flavonoids, *i.e.*, eight 5,7-dihydroxyflavanones, **1a**–**1h**, and nine 5,7-dihydroxyflavones, **2a**–**2d**, **3a**–**3c**, **4a**, and

4b. In these series, the substitution pattern at ring *B* of the flavonoids was modified to investigate structure–bioactivity relationships.

5,7-Dihydroxyflavanones **1a**–**1h**, including the new compound **1g**, were synthesized as racemic compounds in four steps following the procedure described in [9], starting from 2,4,6-trihydroxyacetophenone (=1-(2,4,6-trihydroxyphenyl)ethanone; **5**), in 21–46% yield (*Scheme 1*).

Scheme 1. *Synthesis of 5,7-Dihydroxyflavanones* **1a**–**1h**



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7a R = Ph
7b R = 4-Me–C_6H_4
7c R = 4-CF_3–C_6H_4
7d R = 3,4-Cl_2–C_6H_3
7e R = Thiophen-2-yl
7f R = Furan-2-yl
7g R = 3-Cl,4-MOMO–C_6H_3
7h R = 3-MeO,4-MOMO–C_6H_3

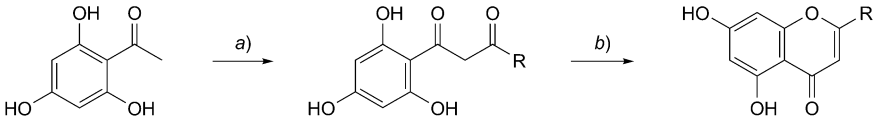
8a R = Ph
8b R = 4-Me–C_6H_4
8c R = 4-CF_3–C_6H_4
8d R = 3,4-Cl_2–C_6H_3
8e R = Thiophen-2-yl
8f R = Furan-2-yl
8g R = 3-Cl,4-MOMO–C_6H_3
8h R = 3-MeO,4-MOMO–C_6H_3

1a R = Ph
1b R = 4-Me–C_6H_4
1c R = 4-CF_3–C_6H_4
1d R = 3,4-Cl_2–C_6H_3
1e R = Thiophen-2-yl
1f R = Furan-2-yl
1g R = 3-Cl,4-HO–C_6H_3
1h R = 3-MeO,4-HO–C_6H_3

a) $ClCH_2OMe$, K_2CO_3, acetone, reflux. *b*) R^1–CHO, MeOH, NaOH (60% aq.). *c*) AcONa, EtOH, H_2O, reflux. *d*) MeOH, 3M HCl, reflux.

5,7-Dihydroxyflavones **2a**–**2d**, including the new compound **2d**, were synthesized according to [10] in two steps, starting from **5**, in 23–52% yield (*Scheme 2*).

Scheme 2. *Synthesis of 5,7-Dihydroxyflavones* **2a**–**2d**



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9a R = Ph
9b R = 4-CF_3–C_6H_4
9c R = Thiophen-2-yl
9d R = 4-CN–C_6H_4

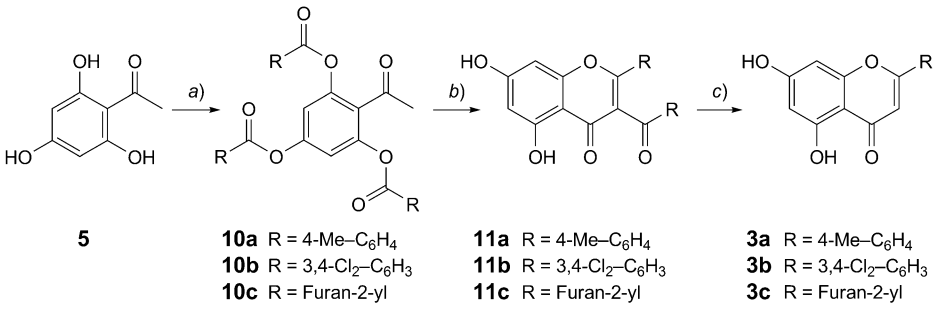
2a R = Ph
2b R = 4-CF_3–C_6H_4
2c R = Thiophen-2-yl
2d R = 4-CN–C_6H_4

a) RCOCl, K_2CO_3 (aq.), triethylbenzylammonium chloride (TEBA), benzene, 60°. *b*) K_2CO_3 (5% aq.), reflux.

5,7-Dihydroxyflavones **3a**–**3c** were synthesized from **5**, as outlined in *Scheme 3*. After the peracylation of **5**, **10a**–**10c** were treated with KOH in pyridine at 50° to afford

11a–**11c**, which then were treated with 5% aq. K_2CO_3 at reflux to yield **3a**–**3c** in 12–20% yield. In the literature, compounds **11a**–**11c** were synthesized using K_2CO_3 in pyridine [11], which failed in our cases.

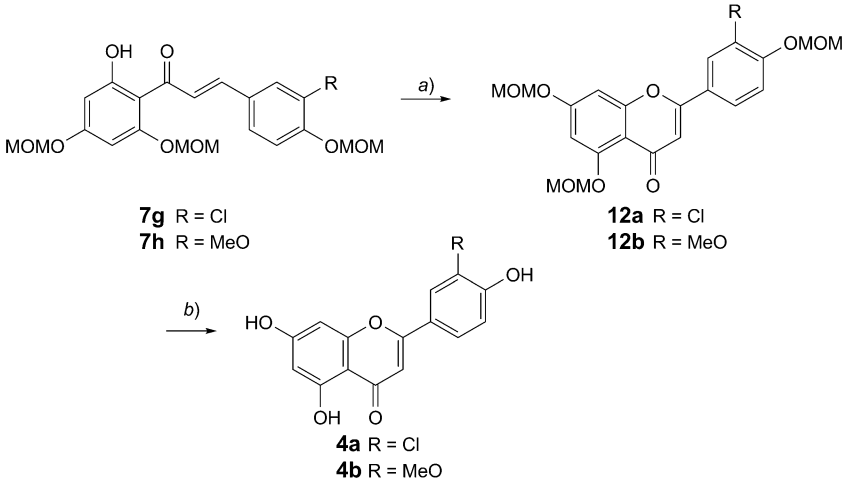
Scheme 3. *Synthesis of 5,7-Dihydroxyflavones* **3a**–**3c**



a) RCOCl, pyridine, r.t. *b*) KOH, pyridine, 50°. *c*) K_2CO_3 (5% aq.), reflux.

A new 5,7-dihydroxyflavone **4a** and a know compound **4b** were synthesized in two steps [12] starting from chalcone derivatives **7g** and **7h** in 4 and 12% yield, respectively (*Scheme 4*).

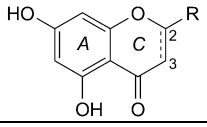
Scheme 4. *Synthesis of 5,7-Dihydroxyflavones* **4a** *and* **4b**



a) I_2, pyridine, reflux. *b*) MeOH, 3M HCl, reflux.

2. *Biological Activities.* We tested the *in vitro* activities of the compounds in insulin-resistant (IR) HepG2 cells according to a well-established procedure [13][14]. Most of the compounds showed a remarkable potential antidiabetic activity *in vitro* [15], and compounds **1f**, **2d**, and **3c** appeared significantly more effective than the positive control, metformin (*Table*).

Table. EC_{50} *Data for the Synthesized Flavonoids Compared with the Positive Control Metformin*



R (ring *B*)	Flavanones (C(2)–C(3))		Flavones (C(2)=C(3))	
	Compound	EC_{50} [μM]	Compound	EC_{50} [μM]
Ph	**1a**	0.880 ± 0.045	**2a**	1.566 ± 0.102
4-Me–C_6H_4	**1b**	0.340 ± 0.032	**3a**	1.250 ± 0.062
4-CF_3–C_6H_4	**1c**	1.280 ± 0.079	**2b**	> 10
3,4-Cl_2–C_6H_3	**1d**	0.540 ± 0.038	**3b**	0.320 ± 0.023
Thiophen-2-yl	**1e**	0.340 ± 0.022	**2c**	2.310 ± 0.175
Furan-2-yl	**1f**	0.034 ± 0.004	**3c**	0.083 ± 0.007
3-Cl,4-HO–C_6H_3	**1g**	0.290 ± 0.021	**4a**	0.430 ± 0.037
4-HO,3-MeO–C_6H_3	**1h**	0.480 ± 0.031	**4b**	0.590 ± 0.052
4-NC–C_6H_4			**2d**	0.170 ± 0.011
Metformin[a])		0.270 ± 0.018		

[a]) Positive control.

3. *Discussion.* Insulin resistance in liver cells principally causes impaired glycogen synthesis and fails to suppress glucose production, which is the major contribution to hyperglycemia [16]. HepG2 Cells are hepatocellular carcinoma cells and have been proven to be valuable in investigating liver-derived functions. They maintain most functions of liver and are steady through many passages [17][18]. A number of research groups have used HepG2 cells to investigate T2D *via* an insulin-resistant model [19–21].

So far, many anti-diabetic flavonoids have been reported [5][22–24], such as myricetin with insulinomimetic effects [6], quercetin with antidiabetic effects in streptozotocin-induced diabetic rats [7], and kaempferol 3,7-dirhamnoside with hypoglycemic and antioxidant effects [8][25]. However, the above-mentioned flavonoids had weak activity, as high doses were necessary to observe the desired effects, in comparison with market drugs. We synthesized two series of flavonoid derivatives, which revealed for the first time significant anti-diabetic activities compared with the market drug metformin. Furthermore, by considering the action of flavonoid analogs in the AMPK (= 5′-AMP-activated protein kinase) signal transduction pathway [26], we expect that 5,7-dihydroxyflavonoid derivatives could activate AMPK activity, reduce acetyl-CoA carboxylase activity, and enhance glucose consumption in insulin resistance HepG2 cells. The results suggest that flavonoid derivatives can be considered as promising candidates in the development of a new antidiabetic lead compound.

Conclusions. – Alteration of the 5,7-dihydroxyflavone skeleton at ring *B*, leads to a smaller activity when OH substitutents are lacking, but to a rise in activity, when ring *B* is replaced by a heterocycle, especially by a furan group. With the identical ring *B* alteration, flavanone analogs have better antidiabetic activity than the flavone analogs,

which could be possibly attributed to the stereochemical difference between the saturated ring *C* of the flavanones and the unsaturated one of the flavones. However, naturally occurring flavanones are enantiomerically pure compounds, racemic compounds **1a**–**1h** should be further investigated concerning the relationship of the stereogenic center C(2) with its activity.

The results suggest that 5,7-dihydroxyflavonoids can be considered as promising candidates in the development of new antidiabetic lead compounds.

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Experimental Part

General. All reagents and solvents were obtained from commercial suppliers. The reagents were used as received. Solvents were routinely distilled prior to use. Isolation and purification of the compounds were performed by flash column chromatography (FC) on silica gel *60* (SiO_2; 200–300 mesh). IR Spectra: *Bio-Rad Excalibur FTS3000* spectrometer (4000–400 cm^{-1}) in KBr. ^{1}H- and ^{13}C-NMR spectra: *Bruker AV-400* instrument in (D_6)DMSO; chemical shifts in ppm with TMS as the internal standard. LR-MS: *Agilent 6310* Ion Trap.

General Procedure for the Preparation of **1a**–**1h**. See [9].

*(±)-2,3-Dihydro-5,7-dihydroxy-2-phenyl-4*H*-1-benzopyran-4-one* (**1a**) [9]. FC (petroleum ether (PE)/AcOEt 10:1). Yield: 38%.

*(±)-2,3-Dihydro-5,7-dihydroxy-2-(4-methylphenyl)-4*H*-1-benzopyran-4-one* (**1b**) [9]. FC (PE/AcOEt 8:1). Yield: 36%.

*(±)-2,3-Dihydro-5,7-dihydroxy-2-[4-(trifluoromethyl)phenyl]-4*H*-1-benzopyran-4-one* (**1c**) [9]. FC (PE/AcOEt 8:1). Yield: 46%.

*(±)-2-(3,4-Dichlorophenyl)-2,3-dihydro-5,7-dihydroxy-4*H*-1-benzopyran-4-one* (**1d**) [9]. FC (PE/AcOEt 8:1). Yield: 44%. IR: 3148, 3057, 2895, 2763, 2621, 1637, 1597, 1493, 1472, 1402, 1343, 1309, 1089, 821, 763, 530. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.81 (*d*, *J* = 16.5, 1 H of CH_2(3)); 3.24 (*dd*, *J* = 16.5, 12.0, 1 H of CH_2(3)); 5.61 (*d*, *J* = 12.0, H–C(2)); 5.90 (*s*, H–C(6)); 5.94 (*s*, H–C(8)); 7.51 (*d*, *J* = 7.5, H–C(6′)); 7.69 (*d*, *J* = 7.5, H–C(5′)); 7.79 (*s*, H–C(2′)); 10.86 (*s*, HO–C(7)); 12.07 (*s*, HO–C(5)). ^{13}C-NMR (100 MHz, (D_6)DMSO): 42.3 (C(3)); 77.5 (C(2)); 95.6 (C(8)); 96.6 (C(6)); 102.2 (C(4a)); 127.4 (C(6′)); 129.2 (C(2′)); 131.3 (C(5′)); 131.6 (C(4′)); 131.8 (C(3′)); 140.2 (C(1′)); 162.8 (C(8a)); 163.9 (C(5)); 167.3 (C(7)); 195.9 (C(4)). ESI-MS: 323 ($[M-H]^-$).

*(±)-2,3-Dihydro-5,7-dihydroxy-2-(thiophen-2-yl)-4*H*-1-benzopyran-4-one* (**1e**) [9]. FC (PE/AcOEt 6:1). Yield: 22%.

*(±)-2-(Furan-2-yl)-2,3-dihydro-5,7-dihydroxy-4*H*-1-benzopyran-4-one* (**1f**) [9]. FC (PE/AcOEt 6:1). Yield: 25%.

*(±)-2-(3-Chloro-4-hydroxyphenyl)-2,3-dihydro-5,7-dihydroxy-4*H*-1-benzopyran-4-one* (**1g**) [9]. FC (PE/AcOEt 4:1). Yield: 24%. IR: 3440, 3144, 1647, 1516, 1461, 1428, 1400, 1347, 1291, 1227, 1163, 1089, 1061, 979, 824. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.71 (*dd*, *J* = 17.2, 2.8, 1 H of CH_2(3)); 3.31 (*dd*, *J* = 17.2, 13.2, 1 H of CH_2(3)); 5.47 (*dd*, *J* = 13.2, 2.8, H–C(2)); 5.90 (*s*, H–C(6)); 5.91 (*s*, H–C(8)); 7.01 (*d*, *J* = 8.4, H–C(6′)); 7.29 (*d*, *J* = 8.4, H–C(5′)); 7.51 (*s*, H–C(2′)); 10.38 (*s*, HO–C(4′)); 10.82 (*s*, HO–C(7)); 12.13 (*s*, HO–C(5)). ^{13}C-NMR (100 MHz, (D_6)DMSO): 42.3 (C(3)); 78.2 (C(2)); 95.5 (C(8)); 96.4 (C(6)); 102.2 (C(4a)); 117.0 (C(5′)); 120.0 (C(3′)); 127.2 (C(1′)); 129.0 (C(6′)); 130.8 (C(2′)); 153.8 (C(4′)); 163.2 (C(8a)); 164.0 (C(5)); 167.1 (C(7)); 196.6 (C(4)). ESI-MS: 305 ($[M-H]^-$).

*(±)-2,3-Dihydro-5,7-dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-4*H*-1-benzopyran-4-one* (**1h**) [27]. FC (PE/AcOEt 4:1). Yield: 21%.

General Procedure for the Preparation of **2a**–**2d**. See [10].

Chrysin (=*5,7-Dihydroxy-2-phenyl-4*H*-1-benzopyran-4-one*; **2a**) [28]. FC (PE/AcOEt 4:1). Yield: 48%.

*5,7-Dihydroxy-2-[4-(trifluoromethyl)phenyl]-4*H*-1-benzopyran-4-one* (**2b**). FC (PE/AcOEt 4:1). Yield: 52%. IR: 3393, 3087, 2953, 1746, 1653, 1615, 1581, 1500, 1428, 1326, 1270, 1168, 1023, 907, 844.

^{1}H-NMR (400 MHz, (D_6)DMSO): 6.21 (*d*, *J* = 2.0, H–C(6)); 6.51 (*d*, *J* = 2.0, H–C(8)); 7.08 (*s*, H–C(3)); 7.89 (*d*, *J* = 9.0, H–C(2′), H–C(6′)); 8.25 (*d*, *J* = 8.5, H–C(3′), H–C(5′)); 11.00 (*s*, HO–C(7)); 12.68 (*s*, HO–C(5)). ^{13}C-NMR (100 MHz, (D_6)DMSO): 94.7 (C(8)); 99.6 (C(6)); 104.6 (C(3)); 107.2 (C(4a)); 126.4 (C(3′), C(5′)); 126.6 (CF_3(4′)); 127.7 (C(2′), C(6′)); 131.9 (C(4′)); 135.1 (C(1′)); 157.9 (C(8a)); 161.8 (C(5)); 161.9 (C(2)); 165.1 (C(7)); 182.2 (C(4)). ESI-MS: 321 ([*M* – H]$^-$).

*5,7-Dihydroxy-2-(thiophen-2-yl)-4*H*-1-benzopyran-4-one* (**2c**). FC (PE/AcOEt 6:1). Yield: 41%. IR: 3437, 3100, 1655, 1624, 1582, 1515, 1470, 1421, 1391, 1358, 1305, 1278, 1165, 1116, 1028, 956, 823. ^{1}H-NMR (400 MHz, (D_6)DMSO): 6.19 (*d*, *J* = 2.0, H–C(6)); 6.41 (*d*, *J* = 2.0, H–C(8)); 6.84 (*s*, H–C(3)); 7.28 (*m*, H–C(4′)); 7.98 (*m*, H–C(5′)); 8.03 (*m*, H–C(3′)); 10.89 (*s*, HO–C(7)); 12.82 (*s*, HO–C(5)). ^{13}C-NMR (100 MHz, (D_6)DMSO): 94.9 (C(8)); 100.0 (C(6)); 104.4 (C(3)); 104.8 (C(4a)); 130.0 (C(3′)); 130.9 (C(5′)); 133.1 (C(4′); 134.7 (C(1′)); 158.0 (C(8a)); 160.1 (C(5)); 162.5 (C(2)); 165.3 (C(7)); 182.3 (C(4)). ESI-MS: 259 ([*M* – H]$^-$).

*4-(5,7-Dihydroxy-4-oxo-4*H*-1-benzopyran-2-yl)benzonitrile* (**2d**). FC (PE/AcOEt 6:1). Yield: 23%. IR: 3409, 3078, 2238, 1662, 1631, 1590, 1512, 1455, 1424, 1367, 1279, 1161, 1118, 1027, 907, 844. ^{1}H-NMR (400 MHz, (D_6)DMSO): 6.22 (*d*, *J* = 1.5, H–C(6)); 6.54 (*s*, H–C(8)); 7.15 (*s*, H–C(3)); 8.04 (*d*, *J* = 8.5, H–C(2′), H–C(6′)); 8.24 (*d*, *J* = 8.5, H–C(3′), H–C(5′)); 11.00 (*s*, HO–C(7)); 12.68 (*s*, HO–C(5)). ^{13}C-NMR (100 MHz, (D_6)DMSO): 94.7 (C(8)); 99.7 (C(6)); 104.6 (C(3)); 107.5 (C(4a)); 114.4 (C(4′)); 118.7 (CN(4′)); 127.5 (C(2′), C(6′)); 133.4 (C(3′), C(5′)); 135.3 (C(1′)); 157.9 (C(8a)); 161.4 (C(5)); 161.9 (C(2)); 165.1 (C(7)); 182.1 (C(4)). ESI-MS: 278 ([*M* – H]$^-$).

General Procedure for the Preparation of **3a**–**3c**. Substituted acyl chloride (9.0 mmol) was added to **5** (505.0 mg, 3.0 mmol) in anh. pyridine, and the mixture was stirred at r.t. for 75 min. After addition of ice-water (5 ml), a precipitate was formed and filtered. Then, the filtrate was washed with H_2O, and evaporated to give **10a**–**10c**, which was treated with KOH (1.008 g, 18.0 mmol) in anh. pyridine at 50° for 1 h. The soln. was adjusted to pH 6 with 2M HCl, then extracted with AcOEt. The org. layer was washed with H_2O, dried ($MgSO_4$), and evaporated to give **11a**–**11c**, which were heated in 5% aq. K_2CO_3 soln. (20 ml) at reflux overnight. The soln. was adjusted to pH 6 with 2M HCl, then extracted with AcOEt. The org. layer was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was purified by FC to give **3a**–**3c** as yellow solids.

*5,7-Dihydroxy-2-(4-methylphenyl)-4*H*-1-benzopyran-4-one* (**3a**) [29]. FC (PE/AcOEt 8:1). Yield: 12%.

*2-(3,4-Dichlorophenyl)-5,7-dihydroxy-4*H*-1-benzopyran-4-one* (**3b**). FC (PE/AcOEt 8:1). Yield: 20%. IR: 3428, 3076, 1655, 1624, 1582, 1515, 1470, 1421, 1391, 1358, 1305, 1278, 1165, 1116, 1028, 956, 920, 823. ^{1}H-NMR (400 MHz, (D_6)DMSO): 6.22 (*d*, *J* = 2.0, H–C(6)); 6.57 (*d*, *J* = 2.0, H–C(8)); 7.12 (*s*, H–C(3)); 7.84 (*d*, *J* = 8.5, H–C(6′)); 8.07 (*d*, *J* = 8.5, H–C(5′)); 8.37 (*s*, H–C(2′)); 10.98 (*s*, HO–C(7)); 12.71 (*s*, HO–C(5)). ^{13}C-NMR (100 MHz, (D_6)DMSO): 94.8 (C(8)); 99.6 (C(6)); 100.0 (C(3)); 106.8 (C(4a)); 127.0 (C(6′)); 128.7 (C(2′)); 131.8 (C(1′)); 131.9 (C(4′)); 132.7 (C(2′)); 135.1 (C(1′)); 157.9 (C(8a)); 161.1 (C(5)); 161.9 (C(2)); 165.1 (C(7)); 182.3 (C(4)). ESI-MS: 321 ([*M* – H]$^-$).

*2-(Furan-2-yl)-5,7-dihydroxy-4*H*-1-benzopyran-4-one* (**3c**). FC (PE/AcOEt 6:1). Yield: 14%. IR: 3423, 3127, 1653, 1626, 1598, 1513, 1470, 1430, 1360, 1278, 1251, 1166, 1110, 1016. ^{1}H-NMR (400 MHz, (D_6)DMSO): 6.19 (*s*, H–C(6)); 6.41 (*s*, H–C(8)); 6.57 (*s*, H–C(4′)); 6.80 (*s*, H–C(3)); 7.44 (*d*, *J* = 1.5, H–C(5′)); 8.05 (*s*, H–C(3′)); 10.93 (*s*, HO–C(7)); 12.79 (*s*, HO–C(5)). ^{13}C-NMR (100 MHz, (D_6)DMSO): 94.5 (C(8)); 99.6 (C(6)); 103.2 (C(3)); 104.4 (C(4a)); 113.6 (C(4′)); 115.1 (C(5′)); 145.5 (C(3′)); 147.9 (C(1′)); 155.5 (C(8a)); 157.4 (C(5)); 162.0 (C(2)); 164.9 (C(7)); 181.6 (C(4)). ESI-MS: 243 ([*M* – H]$^-$).

General Procedure for the Preparation of **4a** *and* **4b**. I_2 (0.69 mmol) was added to a mixture of **7g** or **7h** (0.69 mmol) in anh. pyridine (6 ml) and heated at reflux for 24 h. Then, the mixture was cooled to r.t. and partitioned between AcOEt (40 ml) and sat. brine (40 ml). The org. layer was dried ($MgSO_4$), and then evaporated to afford **12a** or **12b**, resp., which was then treaded with 3M HCl (2 ml) in MeOH (6 ml) at reflux for 1.5 h. H_2O (20 ml) was added, and the soln. was extracted with AcOEt. The org. layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The residue was purified by FC to give **4a** or **4b**, resp., each as a yellow solid.

*2-(3-Chloro-4-hydroxyphenyl)-5,7-dihydroxy-4*H*-1-benzopyran-4-one* (**4a**). FC (PE/AcOEt 4:1). Yield: 4%. IR: 3321, 3092, 2929, 2753, 2707, 2629, 1727, 1649, 1613, 1507, 1403, 1353, 1251, 1159, 1032, 839,

814, 735. ^{1}H-NMR (400 MHz, (D_6)DMSO): 6.21 (*d*, *J* = 2.0, H–C(6)); 6.53 (*d*, *J* = 2.0, H–C(8)); 6.89 (*s*, H–C(3)); 7.11 (*d*, *J* = 8.6, H–C(5′)); 7.90 (*dd*, *J* = 2.2, 8.6, H–C(6′)); 8.10 (*d*, *J* = 2.2, H–C(2′)); 10.88 (*s*, HO–C(7)); 11.17 (*s*, HO–C(4′)); 12.90 (*s*, HO–C(5)). ^{13}C-NMR (100 MHz, (D_6)DMSO): 94.6 (C(8)); 99.4 (C(6)); 104.2 (C(3)); 117.4 (C(4a)); 121.1 (C(5′)); 122.9 (C(3′)); 127.3 (C(1′)); 128.7 (C(6′)); 129.1 (C(2′)); 157.0 (C(4′)); 157.8 (C(8a)); 161.9 (C(5)); 162.7 (C(2)); 164.7 (C(7)); 182.2 (C(4)). ESI-MS: 303 ($[M-H]^-$).

*5,7-Dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-4*H*-1-benzopyran-4-one* (**4b**) [30]. FC (PE/AcOEt 8:1). Yield: 12%.

General Procedure for the Bioassay. HepG2 Cells were cultured in high-glucose *Dulbecco*'s modified eagle serum (DMEM) supplemented with 10% fetal bovine serum (FBS). After confluence, cells were cultured in 96-well cluster plates in high-glucose DMEM supplemented with 10% FBS for 24 h, and then the cells were treated with 10^{-7} M insulin for 36 h in serum-free and phenol red-free high-glucose DMEM. After 36 h high concentration insulin stimulated, the cells were washed with pH = 4 high-glucose DMEM for four times and phosphate buffered saline for two times, then added in serum-free and phenol red-free high-glucose DMEM with the test compounds in different concentrations and incubated for 24 h. Then, the glucose content in the culture medium was measured by a glucose assay kit to study the effect of insulin resistance HepG2 on glucose consumption. The enhancement ratio of glucose consumption (*GC*) was calculated as follows: *GC* [%] = (drug group of *GC* – model group of *GC*)/model group of *GC* × 100. The potencies of the products, expressed as median effective concentration (EC_{50}) values, are collected.

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