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Synthesis of a library of glycosylated flavonols

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ABSTRACT

Flavonols are an important class of natural products isolated from plants. Some glycosylated flavonols showed very interesting biological activities. A library of flavonols has been made through Algar–Flynn–Oyamada reaction from 2′-hydroxyacetophenones and benzaldehydes. Glycosylation of these flavonols with various glycosyl donors affords a library of glycosylated flavonols. These compounds are potentially useful pharmacologically active compounds and will be studied for biological activities.

Flavonoids are a family of natural products widely found in plants. The family members include flavones, flavanes, flavonols, anthocyanins, and catechins. Flavonols are an important class of flavonoids with many interesting biological activities.[1–3] For example, quercetin-3-β-*O*-glucoside (Fig. 1a) has been reported to have ameliorative effects on a host of disorders including cancer, renal, and cardiovascular diseases and have inhibitory activity toward SARS-CoV 3CL or viral replication.[4–9] Kaempferol 3-*O*-(3″,4″-di-*O*-acetyl-α-L-rhamnopyranoside) (Fig. 1b) has been reported to inhibit the proliferation of human breast cancer cell line, MCF-7.[10] Polymethoxyflavones have been reported to inhibit HL-60 cell lines.[11]

Many flavonol natural products are glycosylated, like compounds in Figure 1. The sugar part can be almost any common sugars, such as glucose, galactose, rhamnose, fucose, xylose or arabinose. The sugar part can also be disaccharides or oligosaccharides, with or without acyl groups. The aglycon part differs in the number and position of substitution groups, including hydroxy group and methoxy group. The high structural diversity makes flavonols an interesting class of molecules for medicinal chemistry study, since the structural units have a profound effect on the biological activity. In a structure-activity relationship study of kaempferol 3-*O*-(3″,4″-di-*O*-acetyl-α-L-rhamnopyranoside) (Fig. 1b), conducted by Smith et al. indicated that, the hydroxyl groups on the aglycon are critical for the activity.[12] Replacing the hydroxyl groups with methoxy groups or acetoxy groups will cause complete loss of the activity. They also noticed that the glycosylated compound is 50 times more active than the aglycon. A broader and more complete understanding of the structural-activity relationship of glycosylated flavonols would greatly benefit their further pharmaceutical applications. However, only a small number of these compounds are available for biological studies due to the difficulty in isolating them from natural sources. Therefore, a general synthetic method and combinatorial synthesis of a library of these molecules would be very desirable.

Herein, we report our preliminary studies in the combinatorial synthesis of 3-*O*-glycosylated flavonols. Scheme 1 shows the retrosynthetic analysis of the target molecules. Our target molecules are a library of flavonols with various substitution pattern on the aglycon with different sugars at 3-position. The aglycon will be synthesized from substituted 2′-hydroxyacetophenones and substituted benzaldehydes. Glycosylation of the flavonol followed by deprotection will afford the target molecules. Changing the structure of the three building blocks (2′-hydroxyacetophenone, benzaldehyde,

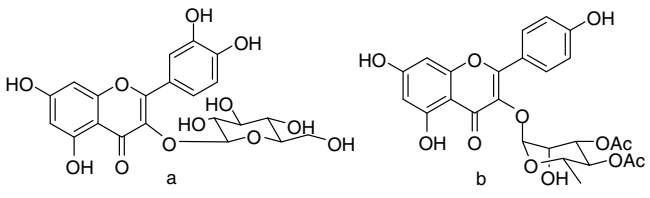
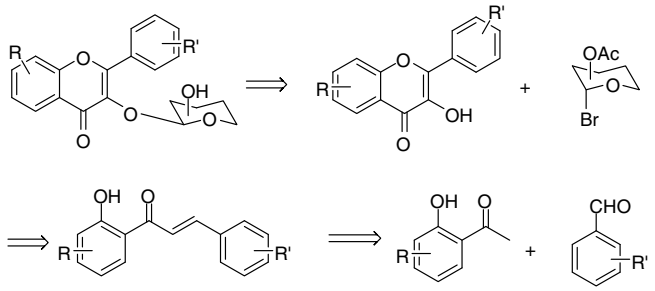


Figure 1. Some natural glycosylated flavonols.



Scheme 1.

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and glycosyl donor) will generate a library of glycosylated flavonols.

The two key steps in the synthesis of glycosylated flavonols are the synthesis of the aglycon and the glycosylation reaction. Many reported syntheses use natural flavonols as starting material.[6,13] Chemical synthesis of flavonol aglycons has been achieved through epoxidation of corresponding flavone compounds.[11,14] Another method is through Baker–Venkataraman type sequential cyclization–dehydration reaction from *ortho*-*O*-benzoyl acetophenone compounds.[15,16] Algar–Flynn–Oyamada reaction has also been widely used to make flavonols.[17–20]

Algar–Flynn–Oyamada reaction was chosen as our primary method to synthesize flavonols, because it is a modular synthetic method using commercially available starting materials, which makes it an ideal method for combinatorial synthesis.[21] So aldol condensation between 2′-hydroxyacetophenones **1** and benzaldehydes **2** gives chalcone products **3** (Scheme 2). Chalcones were converted to flavonols **4** by treating with hydrogen peroxide and base in ethanol. Fourteen flavonols (**4a**–**o**) have been made through this method and the results are listed in Table 1. The overall yield of the synthesis is acceptable, with an average yield at about 60% for the first step and 70% for the second step. All 14 flavonols have been reported in literature, but not all syntheses are reported.[19,20,22,23] It is noteworthy that the reaction protocol is a little different when benzyoxyl was used at protecting group, in compounds **4i**, **4j**, and **4o**. 1,4-Dioxane must be used as co-solvent for optimal yield.[24] The reason is the poor solubility of those corresponding chalcones if ethanol is the only solvent in the reaction.

The glycosylation reaction was carried out using biphase conditions with phase-transfer catalyst.[25] So 1 equiv of flavonol was treated with 1.5 equiv of peracetylglycosyl bromide (**5**), 3 equiv of TBAB (tetrabutylammonium bromide), and 3 equiv of potassium carbonate in 1:1 (chloroform/water) at 50 °C for 4 h. This method can give glycosylated product **6** at around 50% yield, however, the product is often difficult to be separated from a side product of the reaction, the lactols formed from hydrolysis of glycosyl bromides through flash chromatography. To solve this problem, the crude product was further treated with acetic anhydride and triethylamine at room temperature. The lactol side product was converted to a fully acetylated sugar which is less polar than the product and can be easily removed through chromatography (see Scheme 3).

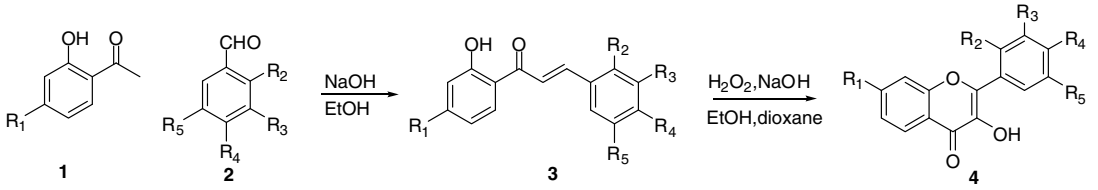
Table 1
Synthesis of flavonol

	Acetophenone (**1**)	Benzaldehyde (**2**)				Chalcone (**3**)	Flavonol (**4**)
	R1	R2	R3	R4	R5	Yield (%)	Yield (%)
a	H	H	OMe	OMe	H	50	70
b	H	H	H	OMe	H	60	73
c	H	OMe	H	H	H	46	74
e	H	H	OMe	H	H	53	69
f	H	H	OMe	OMe	OMe	35	38
g	H	OMe	H	H	OMe	38	45
h	H	OMe	H	OMe	H	65	55
i	H	H	H	OBn	H	72	71[a]
j	H	H	OMe	OBn	H	75	80[a]
k	OMe	H	OMe	OMe	H	30	69
l	OMe	H	H	OMe	H	56	69
m	OMe	H	OMe	H	H	20	59
n	OMe	OMe	OMe	H	H	72	62
o	OBn	H	H	OMe	H	54	76[a]

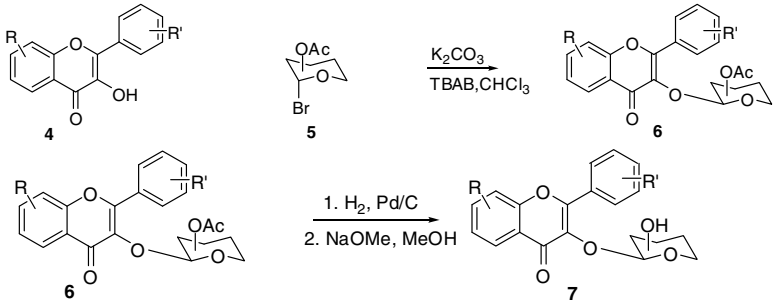
[a] Dioxane/ethanol mixture was used as solvent.

This protocol was used to synthesize a series of glycosylated flavonols. Flavonol **4a**, **4j**, **4l**, and **4o** (Table 1) were used to react with four different types of monosaccharide donors, including tetraacetylglucosyl bromide (**5a**), tetraacetylgalactosyl bromide (**5b**), triacetylxylosyl bromide (**5c**), and triacetylarabinosyl bromide (**5d**). Sixteen glycosylated flavonols were obtained in acceptable yield (24–85%). The glycosylation selectively affords β-products for all reactions. The xylose donor tended to give lower glycosylation yield, which is likely due to the low stability of xylosyl bromide. Xylosyl lactol was a major side product on TLC, together with unreacted flavonols starting material. Another possible reaction for the varying yield is the biphase reaction nature, which might depend on how well the biphase reactants were mixed. The glycosylated flavonols (**6**) were then deprotected under standard conditions to afford target molecules (**7**) in good yield (see Table 2).[26]

In summary, we have described a combinatorial synthesis of a library of glycosylated flavonols with 16 members. The synthetic



Scheme 2. Synthesis of flavonols.



Scheme 3. Glycosylation reactions.

Table 2
Synthesis of glycosylated flavonols

Flavonol	Donor (**5**)	Yield (%) (**6**)	Yield (%) (**7**)
4a	Glucose (**5a**)	63 **6aa**	95 **7aa**
4a	Galactose (**5b**)	69 **6ab**	85 **7ab**
4a	Xylose (**5c**)	54 **6ac**	92 **7ac**
4a	Arabinose (**5d**)	85 **6ad**	93 **7ad**
4j	Glucose (**5a**)	57 **6ja**	95 **7ja**
4j	Galactose (**5b**)	44 **6jb**	90 **7jb**
4j	Xylose (**5c**)	26 **6jc**	90 **7jc**
4j	Arabinose (**5d**)	59 **6jd**	92 **7jd**
4l	Glucose (**5a**)	77 **6la**	79 **7la**
4l	Galactose (**5b**)	56 **6lb**	94 **7lb**
4l	Xylose (**5c**)	42 **6lc**	99 **7lc**
4l	Arabinose (**5d**)	50 **6ld**	93 **7ld**
4o	Glucose (**5a**)	65 **6oa**	85 **7oa**
4o	Galactose (**5b**)	56 **6ob**	86 **7ob**
4o	Xylose (**5c**)	24 **6oc**	99 **7oc**
4o	Arabinose (**5d**)	34 **6od**	81 **7od**

protocol gave decent yield of desired products. This general procedure can be used to make more glycosylated flavonols with potential biological activities.

Acknowledgment

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26. *Spectroscopic data for respresentative library members*: Compound **6ab**: H NMR ($CDCl_3$): δ 8.16 (dd, J = 7.2, 1.4 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H), 7.69–7.62 (m, 2H), 7.48 (d, J = 7.2 Hz, 1H), 7.37 (t, J = 7.2 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 5.72 (d, J = 7.9 Hz, 1H), 5.40 (dd, J = 10.8, 7.2 Hz, 1H), 5.38 (d, J = 3.6 Hz, 1H), 5.13 (dd, J = 10.8, 3.6 Hz, 1H), 4.03 (s, 3H), 3.95 (s, 3H), 3.88–3.87 (m, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 1.97 (s, 3H), 1.86 (s, 3H). Compound **7ab**: H NMR (DMSO-d_6): δ 8.10 (dd, J = 1.7, 8.1 Hz, 1H), 8.05 (d, J = 1.7 Hz, 1H), 7.83 (dt, J = 7.7, 15.4 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.69 (dd, J = 2.1, 8.5 Hz, 1H), 7.50 (dt, J = 0.9, 7.3 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1H), 5.60 (d, J = 8.1 Hz, 1H), 5.22 (d, J = 4.2 Hz, 1H), 4.87 (d, J = 5.6 Hz, 1H), 4.52 (d, J = 3.8 Hz, 1H), 4.45 (t, J = 5.1 Hz, 1H), 3.85 (s, 6H), 3.68 (t, J = 3.4 Hz, 1H), 3.58 (m, 1H), 3.44 (m, 2H), 3.36 (d, J = 3.8 Hz, 1H), 3.17 (d, J = 5.5 Hz, 1H).