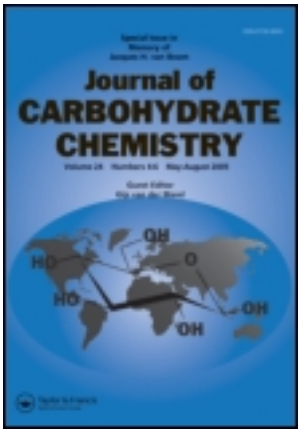

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Studies on the Synthesis and Antiproliferative Activities of 13-*cis*-Retinoyl Sugar Derivatives

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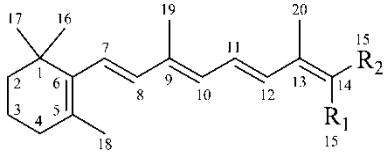
New retinoyl sugar derivatives of 13-*cis*-retinoic acid were synthesized in three ways in this paper in order to enhance pharmacal effects, especially antiproliferative activities of 13-*cis*-retinoic acid. Their structures were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectra and their antiproliferative activities were determined in vitro using human cancer lines. Results showed that some compounds possessed potential antitumor activities.

Keywords 13-*cis*-Retinoic acid, Retinoylation, Retinoyl sugar derivatives, Synthesis, Antiproliferative activities

INTRODUCTION

Retinoids include active metabolites of vitamin A (retinol, **1**) as well as a diverse spectrum of natural or synthetic derivatives. They play an essential role in vertebrate growth and development, supporting cell differentiation, embryonic development, the immune response, and reproduction.[1–3] *All-trans*-retinoic acid (**2**, ATRA), 13-*cis*-retinoic acid (**3**, 13-*cis*-RA), and other retinoids are currently used for treatment of dermatological disorders and chemotherapeutic agent against various endothelial cancers, breast cancer, and endometrial cancer.[4–7] The actions of retinoids are mediated through binding and activation of the retinoic acid receptors (RARs) or retinoid X receptors (RXRs), which function as ligand-dependent transcription factors.[8] However, retinoids, including retinoic acids, have been found to be too toxic at high dosage levels to be of practical value for cancer prevention in higher mammals. Side effects such as teratogenicity, hepatotoxicity, and headaches have been observed as a result when the most of these compounds were used.[9] Researchers have been pursuing the discovery and synthesis of novel retinoic acid analog in order to increase their therapeutic efficiency and/or reduced toxicity (Sch. 1).[10]

It is known that carbohydrates and their derivatives have a significant biological role and occur widely in all living matter and participate in many biological functions.[11] Nishikawa et al.[12] have prepared a series of saturated fatty acyl derivatives of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**4**). These agents to be tested were administrated to mice by intraperitoneal injection and with high antitumor activity.



1, $R_1 = H$; $R_2 = CH_2OH$ retinol
2, $R_1 = H$; $R_2 = COOH$ *all-trans*-retinoic acid
3, $R_1 = COOH$; $R_2 = H$ 13-*cis*-retinoic acid

Scheme 1: Structures of retinol, *all-trans*-RA, and 13-*cis*-RA.

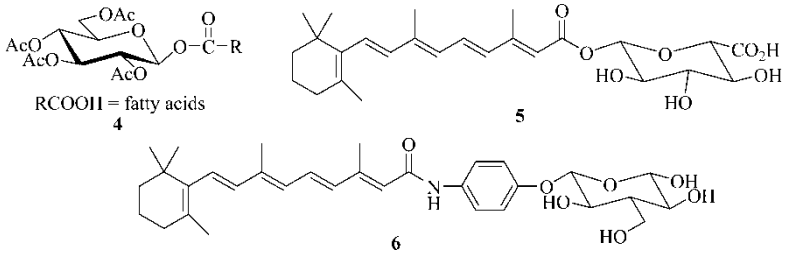
In the literatures [4] and [13–14], all-trans-retinoyl glucuronide (ARAG, **5**), which readily formed from ATRA (**2**) in several tissues, play important roles in cellular differentiation, proliferation, and other cellular events. Additionally, numerous reports have indicated that the biological activity of **5** is similar to that of **2**, otherwise without the toxic side effects of **2**,[15] and can function as a nontoxic substitute in a variety of clinic settings.[16] On the other hand, Winum et al.[17] have reported that three glycosyl conjugates of 4-hydroxyphenylretinamide (**6**) have been synthesized and tested on a broad variety of tumor cells (Sch. 2).

These retinoids with potential antiproliferative properties have led us to investigate the influence of a glycosyl moiety on the activity and the toxicity of retinoids. The carbohydrate moiety can be expected to play the role of drug carrier and improve the activity and selectivity of compounds for cancerous cell lines. There have reports that *O*-Aryl glycosides have good biological activities. For example, gastrodin is the bioactive component of *Gastrodia elata* blume and is widely used for the treatment of rheumatism, headache, and vertigo.[18] Therefore, sugar derivatives with structures of the glycosyl moiety both directly and indirectly linked with 13-*cis*-RA were designed in our study, and 10 sugar conjugates (**8a–8d**, **9**, **11a**, **17a**, **17b**, **18**, and **19**) of 13-*cis*-RA were synthesized in three ways. Their structures were characterized and bioactivities were evaluated by MTT method.

RESULTS AND DISCUSSION

Synthesis of Compound 7a–7d

The synthesis of compounds 2,3,4,6-tetra-*O*-acetyl-σ-D-glucopyranosyl bromide (**7a**), 2,3,4-tri-*O*-acetyl-σ-D-xylopyranosyl bromide (**7b**), 2,3,6,2′,3′,4′, 6′-hepta-*O*-acetyl-σ-lactosyl bromide (**7c**), and 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-σ-maltobiosyl bromide (**7d**) were performed as shown in Scheme 3. Bromo-derivatives of glucose, xylose, lactose, and maltobiose have been prepared in two steps as described in the literature[19] in high yield. Crystallization of the crude products from anhydrous ether afforded pure products. The purity and identity of these compounds were confirmed by HPLC/MS and ^{1}H NMR. They were used in the next synthetic sequence as soon as possible.



Scheme 2: Structures of **4**, **5** (ARAG), and **6**.

Synthesis of Compounds 8a–8d and 9

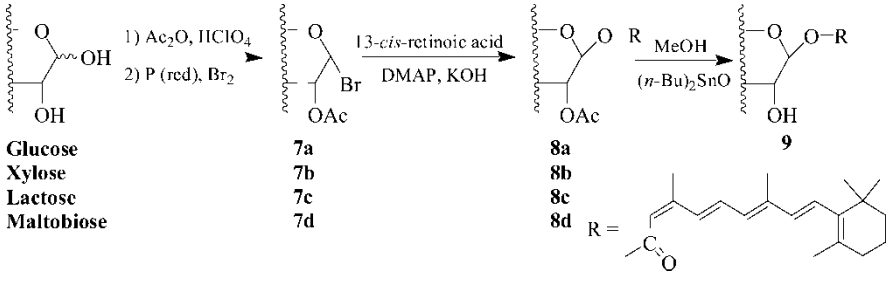
1-*O*-retinoyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**8a**), 1-*O*-retinoyl-2,3,4-tri-*O*-acetyl-β-D-xylopyranose (**8b**), 1-*O*-retinoyl-2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-lactose (**8c**), and 1-*O*-retinoyl-2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-maltose (**8d**) were synthesized by the reaction of **7a**–**7d** with 13-*cis*-RA in the presence of potassium hydroxide and 4-dimethylaminopyridine (DMAP) as a catalyst in 53% to 65% yields. 1-*O*-retinoyl-β-D-glucopyranose (**9**) was obtained by refluxing **8a** in methanol using dibutyltin oxide as a catalyst in 50% yield.[20]

Synthesis of Compound 10a and 11a

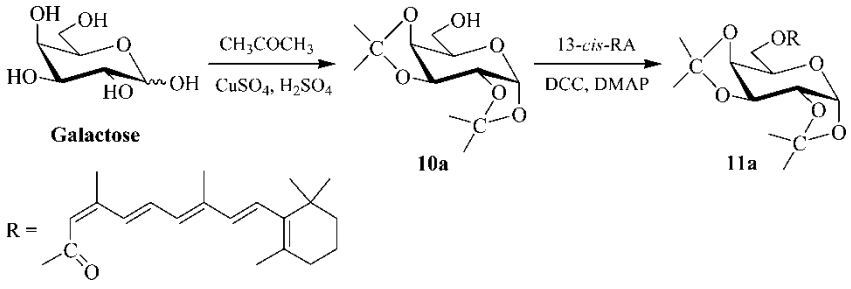
1,2:3,4-diisopropylidenegalactose (**10a**) was prepared[19] first by condensation of acetone with galactose in the presence of anhydrous cupric sulfate and concentrated sulfuric acid. Then 6-*O*-13-*cis*-retinoyl-1,2:3,4-diisopropenegalactose (**11a**) was obtained from the reaction of 13-*cis*-RA with **10a** when *N,N*-dicyclohexylcarbodiimide (DCC) was used as dehydrator and DMAP as catalyst in 73% yield (Sch. 4).

Synthesis of Compound 17a, 17b, 18, and 19

2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**12**) was prepared according to the similar procedure for **7a**. Glycosyl bromides were reacted



Scheme 3: The synthetic route to glycosyl retinoates **8a**–**9**.

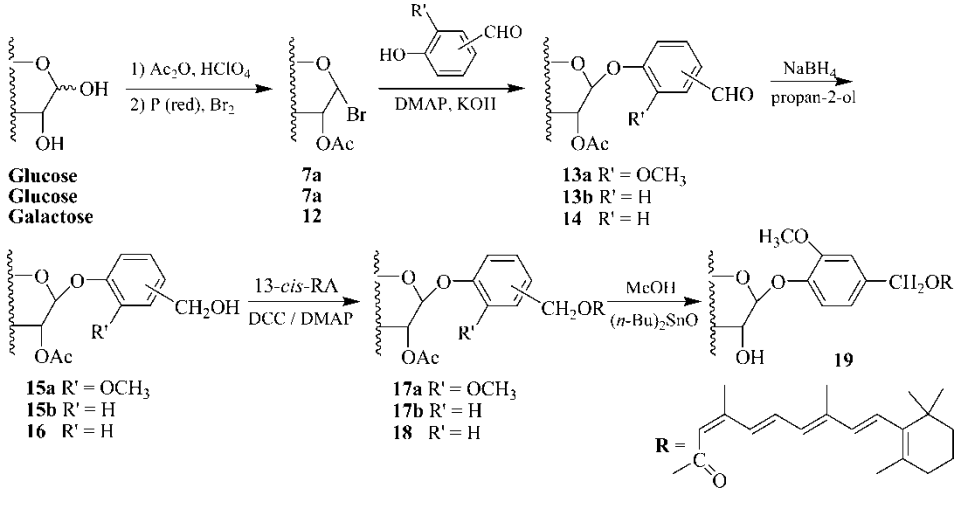


Scheme 4: The two-step synthetic route to glycosyl retinoate **11a**.

respectively with the vanillin (or *p*-hydroxylbenzaldehyde, or *o*-hydroxylbenzaldehyde) to give glycoside **13a** (**13b**, or **14**) in good yields. The reduction of the carbonyl group was facile with sodium borohydride to give **15a** (**15b**, or **16**). Then the target compounds **17a** (**17b**, or **18**) were synthesized by esterification of **15a** (**15b**, or **16**) with 13-*cis*-RA in mild reaction conditions by use of DCC as reagent under catalysis of DMAP. The **17a** was deprotected to yield **19** by the same method as **9**.

Confirming the Configuration for 8a–8d and 9

In the IR spectra of compounds **8a**–**8d**, there are two wide and strong shoulder peaks of sugar ring at 1000 to 1100 cm^{-1} and 1200 to 1300 cm^{-1}. Also, the strong carbonyl (C=O) absorption peak takes place at 1720 cm^{-1}.[21] In the NMR spectra, identical data were in all respects to the previously made



Scheme 5: The synthetic route of glycoside derivatives of 13-*cis*-RA.

materials. The mass spectra of (**8a**–**8d**, **9**) indicate their $[M + Na]^+$ peaks. All of these data identify the basic structure of the sugar ester.

Compounds **8a**–**8d** and **9** were confirmed to be β-anomeric pyranosyl derivatives by IR and ^{1}H NMR spectra, which are presented in Table 1. For example, for **8a**, there was a medium intensity absorption peak at 909 cm^{-1} in IR spectrum, which was the shear vibration characteristic absorption of β-anomeric pyranosyl derivatives. At the same time, the ^{1}H NMR spectrum notably exhibited a large coupling constant ($^3J_{1-2} = 8.4$ Hz) for the C_1–H signal of sugar ring in **8a**, indicating this compound was β-configuration. The literature[21] indicates that the coupling constant value of C_1–H and C_2–H of sugar ring are $^3J_{1-2} = 7$ to 10 Hz in β-anomer while $^3J_{1-2} = 2.5$ to 3.5 Hz in α-anomer.

Confirming the Structure of Compound 11

^{1}H NMR spectrum of compound **10a** matched data reported in the literature[22] and its structure was confirmed to be a six-ring structure (**10a**) and not a five-ring structure (**10b**) (shown as Sch. 6) because the chemical shift value of H-1 peak of the galactose sugar ring appears in $\delta = 5.57$ ppm higher field, not in $\delta = 5.80$ ppm lower field. Compound **11a** should be a six-ring structure and not a five-ring structure (**11b**) since esterification reaction of **10a** does not involve conversion of the sugar ring configuration.

Confirming the Configurations for Compounds 17a, 17b, 18, and 19

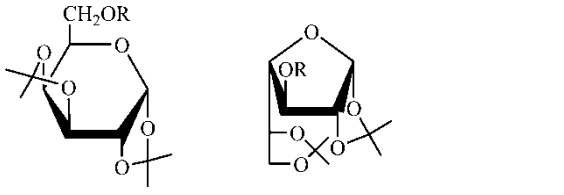
Compounds **17a**, **17b**, and **18** were confirmed to be β-configuration by IR and ^{1}H NMR spectra data, which are presented in Table 2. Take **17a** as an example, There was a medium intensity absorption peak in 908 cm^{-1} in IR spectra, which was the shear vibration characteristic absorption of β-anomeric pyranosyl derivatives. Besides, C_1–H signal of sugar ring in **17a** in ^{1}H NMR spectrum had a chemical shift value smaller than 5.32 ppm and exhibited a large coupling constant ($^3J_{1-2} = 8.0$ Hz) for indicating this compound was β-configuration.[20] The ^{13}C NMR spectra were also in accordance with their expected structures.

Optimal Reaction Conditions

The reported reaction of 13-*cis*-RA to react with thionyl chloride (PCl_5/PCl_3 or other carbonyl chlorides) to form retinoyl chloride, which in turn is reacted with alcohols to produce retinoates, failed in our laboratory because hydrogen chloride in solution of retinoyl chloride isomerizes the polyene chain.[23,24] Our method was established by use of DCC as the dehydrator and DMAP as the catalyst. It presents the advantages of mild conditions, high yield, and ease of operation.

Table 1: The characteristic ^{1}H NMR, IR, and MS data of compound **8a**–**8d** and **9**.

	^{1}H NMR (C_1–H)		IR			
Compounds	**δ (ppm)**	**$^{3}J_{1-2}$ (Hz)**	**Shoulder peak of sugar ring (cm^{-1})**	**C_1–H (cm^{-1})**	**MS $(M + Na)^+$**	**Configuration**
8a	5.77	8.4	1044–1082, 1232	909	653	β
8b	5.75	6.8	1044–1081, 1229	903	581	β
8c	5.74	8.0	1068, 1230	910	941	β
8d	5.77	8.4	—	—	941	β
9	Overlapped		1026, 999	827	485	β



Scheme 6: The possible configurations for compound **10** and **11**.

Sugar esters were mostly conveniently prepared using the Koenigs-Knorr reaction,[25] phase-transfer catalysis,[26] carbonyl halide method,[27] and enzy me-catalyzed method.[28] Recently, phase transfer catalysis has proven to be a very useful method on various synthetic transformations. This methodology allows synthetic modifications under mild conditions that were heretofore reserved for very drastic reagents and reaction media.[29] In the present paper, four glycosyl esters (**8a**–**8d**) were synthesized by reaction of sugar bromide (**7a**–**7d**) with 13-*cis*-RA in the presence of potassium hydroxide and DMAP as phase-transfer catalyst. This method has advantages of mild reaction conditions and easy separation of products.

Glucovanillin was extracted from green pods, which have sedative and anticonvulsant actions, retrieval, and antioxidant. It belongs to *O*-glucoside, in which the phenolic hydroxyl group is linked to the glucose.[30] Therefore, the vanillyl alcohol, and *p*-hydroxybenzyl alcohol, and *o*-hydroxybenzyl alcohol were used as spaces to link the glycosyl and retinoic acid, respectively. Four glucoside derivatives (**17a**, **17b, 18**, and **19**) of 13-*cis*-RA were synthesized by a series of synthetic steps such as acetylation, glycosidation, esterification, and deprotection. The synthetic procedure of glycosidation was modified with DMAP as phase-transfer catalyst and simpler workup procedure than the methods[5] reported and give higher yields.

The reaction condition of deacetylation was crucial in our synthetic route (Sch. 3 and Sch. 5) because there were two kinds of ester functions both in **8a** and **17a**. The deacetylation must be carried out without breaking of retinoyl. According to the literature[20] retinoates **8a** and **17a** suffered selectively deacetylation by using dibutyltin oxide as catalyst in methanol and the target compounds **9** and **19** were prepared successfully with good yield.

Biological Assays

8a was tested for antiproliferative activities toward three different cancer cell lines: human lung cancer cell line (A549), human liver cancer cell line (BEL7404), and human tongue cancer cell line (Tca). The antiproliferative activities were summarized in terms of the IC_{50} values in Table 3. It was

Table 2: The characteristic ^{1}H NMR, IR, and MS data of compound **17a**, **17b**, **18**, and **19**.

	^{1}H NMR (C_1–H)		IR		MS		
Compounds	**δ (ppm)**	**$^{3}J_{1-2}$ (Hz)**	**Shoulder peak of sugar ring (cm^{-1})**	**C_1-H (cm^{-1})**	**$(M + Na)^+$**	**$(M + H)^+$**	**Configuration**
17a	4.96	8.0	1044–1070, 1231	908	789.5	—	β
17b	5.08	7.6	1045, 1230	908	759.4	737.1	β
18	Overlapped	—	—	—	759.3	737.0	β
19	Overlapped	—	1026, 1003	825	622.0	600.0	β

Table 3: Antiproliferative activity of **8a**.[a]

Human cell lines	A549	BEL7404	Tca
IC_{50} (μM)	32.4	>100	71.1

[a] IC_{50}: The concentration of drug required for 50% inhibition.

found that **8a** possessed selective antiproliferative activity toward A549. Therefore, the material retinoic acid **3** and compounds **8b**–**8d, 11a,** and **17a**–**19** were also tested for antiproliferative activity against A549. The antiproliferative activities are summarized in terms of their IC_{50} values in Table 4.

Based on the data in Table 4, the glycosyl esters **8b**–**8d** showed lower antiproliferative activity than **3**. Antiproliferative activity of **8a** and **3** were similar. **8a** was hydrolyzed to yield the 1-*O*-retinoyl-β-D-glucopyranose (**9**), which exhibited interesting antiproliferative activities and was stronger than **3**. The result was in accordance with what we expected. The compound **9** showed higher antiproliferative activity than **8a**, with perhaps the former presenting better water soluability.

It should be noted that four glucoside derivatives—**17a**, **17b**, **18**, and **19**—exhibited interesting antiproliferative activities and were stronger than **3**. There have reports that gastrodin and glucovanillin are natural compounds with biological activities.[18,30] **15a** and **15b** were the derivatives of gastrodin and glucovanillin, respectively, and were obtained after the glucose was linked to 4-hydroxylbenzylalcohol and 2-methoxyl-4-hydroxylbenzylalcohol, respectively (see Sch. 5). **17a** and **17b** were achieved by the reaction of **15a** and **15b** with 13-*cis*-RA. On the other hand, the novel structure of **17a** and **17b** presented the characteristics for antiproliferative activity, and among them the bifunctional group compounds such as 4-hydroxylbenzylalcohol were used as space to link glycosyl and 13-*cis*-RA, just like the structure of **6**. Unfortunately, the unobvious difference means that antiproliferative activity presented small differentiation between the glycosyl molecules and acetylated glycosyl molecules with linking space, for example, **17a** and **19**. Perhaps both the bioactive component group and the structure improved the bioactivity of 13-*cis*-RA.

Table 4: The antiproliferative activity of compound **8b**–**8d**, **9**, **11a**, and **17a**–**19** against A549.

Compound	3	8b	8c	8d	9	11a	17a	17b	18	19
IC_{50} (μM)	33.3	35.8	42.0	32.8	23.6	21.4	13.0	13.6	21.7	10.2

Further investigations of structure–activity relationships of these kinds of compounds are currently underway in our group.

EXPERIMENTAL SECTION

13-*cis*-RA was purchased from Sigma Chemical Co. DCC and DMAP were purchased from Alfa Aesar. The sugars and all other reagents were of the highest commercially available quality. All retinoids were stored at $-20^{\circ}C$ under dry nitrogen atmosphere. All operations involved in the preparation, isolation, purification, and transfer of retinoids were carried out under an atmosphere of dry nitrogen. All operations were also performed in dim light or photographic darkroom light with containers wrapped with aluminum foil or black cloths. All reactions were monitored by TLC.

Melting points were measured with a XRC-1 melting point apparatus and are uncorrected. FT infrared (IR) spectra were recorded in KBr disks using FD-5DX spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian INOVA-400 Spectrometer, using $CDCl_3$ as a solvent; TMS (δ 0.00 ppm) was used as an internal standard. All NMR chemical shifts are reported as δ values in parts per million (ppm) and coupling constants (J) are given in hertz (Hz). The splitting pattern abbreviations are as follows: s, singlet; d, doublet; br, broad peak; and m, multiplet. Mass spectra were carried out on a ZAB-HS mass spectrometer.

A General Procedure for Compound 8a–8d

13-*cis*-RA (1.200 g, 4.0 mmol) and DMAP (0.489 g, 4.0 mmol) were suspended in a mixture of 40 mL dichloromethane and 4% aqueous KOH (5 mL, about 4.0 mmol). The suspension was slowly heated to completely dissolve, the reactant vigorously stirred, and a solution of **7** (4.0 mmol) in dichloromethane (10 mL) added dropwise. The reaction solution was heated to reflux and stirred for 6 h under nitrogen atmosphere. The solution was washed with 4% aqueous NaOH (15 mL) and distilled water (20 mL × 3). The organic layer was dried over with anhydrous Na_2SO_4 and filtrated, and the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by column chromatography (silica gel 60, mesh size 200–300, ethyl acetate/petroleum ether, v/v).

1-O-retinoyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (**8a**) was synthesized via the procedure described. The crude product was purified by column chromatography (eluent: ethyl acetate: petroleum ether = 1:3, $R_f = 0.38$) to give **8a** as yellow solid, the yield: 61.4%, m.p. 122–124°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (s, 6H, 2 × CH_3); 1.46–1.49 (m, 2H, H on C_2); 1.59–1.65 (m, 2H, H on C_3); 1.72 (s, 3H, CH_3 on C_5); 1.97–2.09 (m, 20H, 4 × $COCH_3$ and 2 × CH_3 and CH_2); 3.84–3.88 (m, 1H, glycosyl-ring-H); 4.11–4.31 (m, 2H, glycosyl-ring-H);

5.13–5.30 (m, 3H, glycosyl-ring-H); 5.62 (s, 1H, H14); 5.77 (d, 1H, $J = 8.4$ Hz, glycosyl-ring-H_1); 6.16 (d, 1H, $J = 16.0$ Hz, H_8); 6.25 (d, 1H, $J = 11.6$ Hz, H_{10}); 6.31 (d, 1H, $J = 16.0$ Hz, H_7); 7.06 (dd, 1H, $J = 11.6$ Hz, $J = 11.6$ Hz, H_{11}); 7.71 (d, 1H, $J = 15.2$ Hz, H_{12}). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.9, 19.2, 20.2, 20.6, 21.1, 21.7, 28.9, 33.1, 34.3, 61.0, 66.9, 67.8, 67.9, 71.0, 71.6, 88.1, 91.7, 114.16, 128.8, 129.2, 130.1, 130.3, 133.7, 137.3, 137.6, 141.0, 154.9, 163.7, 169.5, 170.0, 170.2,170.3. MS: $m/z = 653$ ($[M + Na]^+$), 581, 493, 372, 353, 331, 270, 211. IR (KBr), ν/cm^{-1}: 3437 (broad), 2930 (CH_3), 1749 (C=O), 1606–1579, 1440–1378, 1044–1082, 1232 (shoulder peak of sugar ring), 977, 909.

1-O-retinoyl-2,3,4-tri-O-acetyl-β-D-xylopyranose (**8b**) was prepared, following the same procedure, and the reaction time was prolonged to 9 h. After purification by column chromatography (eluent: ethyl acetate: petroleum ether = 1:3, $R_f = 0.52$), **8b** was obtained as a pale yellow solid, the yield: 65.0%, m.p. 93–94°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (s, 6H, 2 × CH_3); 1.46–1.49 (m, 2H, H on C_2); 1.59–1.65 (m, 2H, H on C_3); 1.72 (s, 3H, CH_3 on C_5); 2.00–2.10 (m, 17H, 3 × $COCH_3$ and 2 × CH_3 and CH_2); 3.54 (dd, 1H, $J = 12.0$ Hz, $J = 12.0$ Hz, glycosyl-ring-H); 4.16 (dd, 1H, $J = 12.0$ Hz, $J = 12.0$ Hz, glycosyl-ring-H); 5.00 (tt, 1H, $J = 8.4$ Hz, $J = 8.8$ Hz, glycosyl-ring-H); 5.09 (t, 1H, $J = 7.6$ Hz, glycosyl-ring-H); 5.24 (t, 1H, $J = 8.4$ Hz, glycosyl-ring-H); 5.61 (s, 1H, H_{14}); 5.75 (d, 1H, $J = 6.8$ Hz, glycosyl-ring-H_1); 6.15 (d, 1H, $J = 16.4$ Hz, H_8); 6.24 (d, 1H, $J = 11.6$ Hz, H_{10}); 6.30 (d, 1H, $J = 15.6$ Hz, H_7); 7.05 (dd, 1H, $J = 12.0$ Hz, $J = 11.2$ Hz, H_{11}); 7.73 (d, 1H, $J = 14.8$ Hz, H_{12}). MS: $m/z = 581$ ($[M + Na]^+$), 523, 465, 299, 281. IR (KBr), ν/cm^{-1}: 3437 (broad), 2939 (CH_3), 1749 (C=O), 1608–1580, 1440–1377, 1229, 1044–1081 (shoulder peak of sugar ring), 975, 903.

1-O-retinoyl-2,3,6,2′,3′,4′,6′-hepta-O-acetyl-β-lactose (**8c**) was synthesized via the same procedure used for **8b**. The crude product was purified by column chromatography (eluent: ethyl acetate: petroleum ether = 1:1, $R_f = 0.56$), **8c** as yellow solid, the yield: 55.6%, m.p. 130–132°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (s, 6H, 2 × CH3); 1.46–1.49 (m, 2H, H on C_2); 1.59–1.65 (m, 2H, H on C_3); 1.72 (s, 3H, CH_3 on C_5); 1.97–2.16 (m, 29H, 7 × $COCH_3$ and 2 × CH_3 and CH_2); 3.77–3.90 (m, 3H, glycosyl-ring-H); 4.06–4.92 (m, 5H, glycosyl-ring-H); 4.93–5.36 (m, 5H, glycosyl-ring-H); 5.59 (s, 1H, H_{14}); 5.74 (d, 1H, $J = 8.0$ Hz, glycosyl-ring-H_1); 6.16 (d, 1H, $J = 16.0$ Hz, H_8); 6.25 (d, 1H, $J = 11.2$ Hz, H_{10}); 6.31 (d, 1H, $J = 16.0$ Hz, H_7); 7.05 (dd, 1H, $J = 11.6$ Hz, $J = 11.2$ Hz, H_{11}); 7.71 (d, 1H, $J = 15.2$ Hz, H_{12}). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.9, 19.2, 20.5, 20.7, 20.8, 20.9, 21.1, 21.8, 29.0, 33.1, 34.3, 39.6, 60.9, 61.9, 66.6, 69.0, 70.6, 70.7, 71.0, 72.8, 73.4, 75.8, 91.1, 101.0, 114.2, 128.8, 129.2, 130.1, 130.3, 133.7, 137.3, 137.6, 141.0, 154.8, 163.6, 169.1, 169.7, 170.1, 170.2, 170.4. MS: $m/z = 941$ ($[M + Na]^+$), 659, 641, 619, 331. IR (KBr), ν/cm^{-1}: 3455 (broad), 2950 (CH_3), 1753 (C=O), 1609–1583, 1443–1376, 1230, 1068 (shoulder peak of sugar ring), 977, 910.

1-O-retinoyl-2,3,6,2′,3′,4′,6′-hepta-O-acetyl-β-maltose (**8d**) was prepared according to the procedure described for the synthesis of **8c**. After purification by column chromatography (eluent: ethyl acetate: petroleum ether = 1:1, $R_f = 0.68$), **8d** was obtained as viscous syrup, the yield: 53.1%, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.00 (s, 6H, $2 \times CH_3$); 1.43–1.46 (m, 2H, H on C_2); 1.56–1.62 (m, 2H, H on C_3); 1.69 (s, 3H, CH_3 on C_5); 1.94–2.14 (m, 29H, $7 \times COCH_3$ and $2 \times CH_3$ and CH_2); 3.83–4.08 (m, 4H, glycosyl-ring-H); 4.20–4.23 (m, 2H, glycosyl-ring-H); 4.42 (d, 1H, $J = 12.8$ Hz, glycosyl-ring-H); 4.87 (dd, 1H, $J = 10.4$ Hz, $J = 4.0$ Hz, glycosyl-ring-H); 4.98–5.43 (m, 4H, glycosyl-ring-H); 5.57 (s, 1H, H_{14}); 5.77 (d, 1H, $J = 8.4$ Hz, glycosyl-ring-H_1); 6.13 (d, 1H, $J = 16.0$ Hz, H_8); 6.23 (d, 1H, $J = 11.6$ Hz, H_{10}); 6.28 (d, 1H, $J = 16.4$ Hz, H_7); 7.04 (dd, 1H, $J = 11.6$ Hz, $J = 15.6$ Hz, H_{11}); 7.69 (d, 1H, $J = 15.2$ Hz, H_{12}). MS: $m/z = 941$ ($[M + Na]^+$), 919 ($[M + H]^+$), 619, 331.

Synthesis of the Compound *1-O-retinoyl-β-D-glucopyranose* (9)

8a (1.890 g, 3.0 mmol) was dissolved in methanol (50 mL), and then a catalytic amount of dibutyltin oxide was added. The reaction mixture was stirred and refluxed for 16 h under nitrogen atmosphere. The reaction solution was filtered. The solvent was removed from the filtrate. The residue was purified by column chromatography (eluent: methanol: chloroform = 1:8) to give the title compound **9** (0.711 g, 51.5%) as a yellow syrup. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.01 (s, 6H, $2 \times CH_3$); 1.44–1.45 (m, 2H, H on C_2); 1.56–1.59 (m, 2H, H on C_3); 1.69 (s, 3H, CH_3 on C_5); 1.97–1.99 (m, 6H, CH_3 on C_{19} and CH_3 on C_{20}); 2.09–2.11 (m, 2H, H on C_4); 3.67–3.69 (m, 1H, glycosyl-ring-H); 4.52 (d, 1H, $J = 4.0$ Hz, glycosyl-ring-H); 4.65 (d, 1H, $J = 4.8$ Hz, glycosyl-ring-H); 4.87 (d, 1H, $J = 7.2$ Hz, glycosyl-ring-H); 5.09 (d, 1H, $J = 4.0$ Hz, glycosyl-ring-H); 5.33–5.35 (m, 2H, glycosyl-ring-H); 5.70 (s, 1H, H_{14}); 6.11 (d, 1H, $J = 16.0$ Hz, H_8); 6.22 (d, 1H, $J = 11.6$ Hz, H_{10}); 6.30 (d, 1H, $J = 16.0$ Hz, H_7); 7.08 (dd, 1H, $J = 11.6$ Hz, $J = 12.0$ Hz, H_{11}); 7.65 (d, 1H, $J = 15.2$ Hz, H_{12}). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 12.7, 18.7, 20.6, 21.6, 28.8, 32.6, 33.9, 38.9, 40.1, 60.2, 68.0, 69.5, 73.3, 76.2, 94.4, 115.6, 128.4, 128.8, 129.5, 129.7, 130.2, 130.4, 133.3, 137.0, 137.2, 140.5, 152.9, 164.2. MS: $m/z = 485.0$ ($[M + Na]^+$). IR (KBr), ν/cm^{-1}: 3427(broad), 2935, 1649(C═O), 1454, 1375, 1236, 1157, 1026 (shoulder peak of sugar ring), 999, 827, 766.

Synthesis of the Compound *6-O-13-cis-retinoyl-1,2:3,4-diisopropylidenegalactose* (11a)

13-*cis*-RA (1.801 g, 4.2 mmol), 1,2:3,4-diisopropylidenegalactose (1.040 g, 4.0 mmol), and a catalytic amount of DMAP were dissolved in anhydrous

dichloromethane (50 mL) at 0°C. A solution of DCC (0.911 g, 4.4 mmol) in anhydrous dichloromethane (15 mL) was added dropwise to the above mixture. The reaction solution was slowly warmed to room temperature and stirred for 10 h. The reaction mixtures were diluted with dichloromethane (30 mL) and cooled at 0°C overnight, and the mixture was filtered to remove the by product urine. Reaction mixture concentrated in vacuo. The residue was purified by column chromatography (elute: ethyl acetate: petroleum ether = 1 : 12, $R_f = 0.45$) to give title compound 1.590 g (yield 73.2%) of the orange yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (s, 6H, 2 × CH_3); 1.25–1.30 (m, 2H, H on C_2); 1.33 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 1.45–1.48 (m, 2H); 1.46 (s, 3H, CH_3); 1.52 (s, 3H, CH_3); 1.61 (s, 3H, CH_3); 1.71 (s, 3H, CH_3 on C_5); 1.99 (s, 3H, CH_3); 2.00–2.05 (m, 2H); 2.07 (s, 3H, CH_3); 4.06 (m, 1H); 4.21–4.36 (m, 4H, glycosyl-ring-H); 4.63 (dd, 1H, $J = 7.6$ Hz, $J = 2.8$ Hz); 5.56 (d, 1H, $J = 5.2$ Hz); 5.70 (s, 1H); 6.14 (d, 1H, H_8, $J = 15.6$ Hz); 6.25 (d, 1H, $J = 5.6$ Hz); 6.29 (s, 1H); 6.98 (dd, 1H, H_{11}, $J = 15.2$ Hz, $J = 11.6$ Hz); 7.76 (d, 1H, H_{12}, $J = 15.2$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.8, 19.2, 20.8, 21.7, 24.7, 25.3, 25.5, 26.4, 28.9, 29.0, 30.7, 30.8, 32.7, 32.8, 33.1, 34.2, 39.5, 49.4, 57.7, 119.8, 128.3, 129.4, 130.0, 130.1, 131.3, 137.4, 137.6, 139.3, 147.1, 154.2. MS: $m/z = 543$ ($[M + H]^+$).

A General Synthetic Method for Compound 13a, 13b, and 14

3-Hydroxy-4-methoxylbenzaldehyde (2.990 g, 22 mmol) was dissolved in dichloromethane (75 mL), and then 4% KOH solution (30 mL, about 24 mmol) and DMAP (1.223 g, 10 mmol) were added. The reaction was slowly heated to reflux with stirring. A solution of **7a** (8.220 g, 20 mmol) in dichloromethane (40 mL) was added dropwise with magnetic stirring. The solution was stirred for an additional 5 h. The solution was slowly cooled to 0°C and the organic layer was separated. The organic layer was washed with 4% NaOH solution (30 mL × 2) and distilled water (40 mL × 3). Then the organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was recrystallized in anhydrous ethanol. The product **13a** was obtained as white solid, the yield: 68.4%, m.p. 144–146°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.05–2.09 (m, 12H, 4 × $COCH_3$); 3.84–3.88 (m, 1H, H-5′); 3.90 (s, 3H, OCH_3); 4.20 (dd, 1H, $J = 12.0$ Hz, $J = 2.4$ Hz, H-6′); 4.28 (dd, 1H, $J = 12.4$ Hz, $J = 5.2$ Hz, H-6′); 5.11 (d, 1H, $J = 7.2$ Hz, H-1′); 5.16–5.21 (m, 1H, H-4′); 5.29–5.36 (m, 2H, H-2′, H-3′); 7.22 (d, 1H, $J = 8.0$ Hz, Ar-H); 7.42–7.44 (m, 2H, Ar-H); 9.90 (s, 1H, CHO).

Compound **13b** was synthesized with the same procedure used for **13a**. 4-Hydroxybenzaldehyde was used as starting material. **13b** is obtained as white solid, the yield: 61.2% m.p. 117–118°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.06 (s, 3H, $COCH_3$); 2.07 (s, 6H, 2 × $COCH_3$); 2.08 (s, 3H, $COCH_3$); 3.92–3.96

(m, 1H); 4.19 (dd, 1H, $J = 12.4$ Hz, $J = 2.0$ Hz); 4.30 (dd, 1H, $J = 12.0$ Hz, $J = 5.2$ Hz); 5.17–5.20 (m, 1H,); 5.23 (m, 1H); 5.30–5.36 (m, 2H); 7.11 (d, 2H, $J = 8.0$ Hz, Ar-H); 7.86 (d, 2H, $J = 8.0$ Hz, Ar-H); 9.93 (s, 1H, CHO).

Compound **14** was prepared according to the procedure described for the synthesis of **13a** except that 2-hydroxybenzaldehyde and compound **12** were used as starting materials to afford **14** as white solid, the yield: 64.3%, m.p. 87–90°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.01 (s, 3H, $COCH_3$); 2.05 (s, 6H, $2 \times COCH_3$); 2.18 (s, 3H, $COCH_3$); 4.09–4.24 (m, 3H); 5.13 (dd, 2H, $J = 9.6$ Hz, $J = 4.0$ Hz); 5.47 (d, 1H, $J = 3.2$ Hz); 5.58 (dd, 1H, $J = 10.4$ Hz, $J = 8.0$ Hz); 7.11 (d, 1H, $J = 8.0$ Hz); 7.16 (t, 1H, $J = 7.6$ Hz); 7.55 (t, 1H, $J = 8.4$ Hz); 7.84 (d, 1H, $J = 7.6$ Hz); 10.34 (s, 1H, CHO).

A General Synthetic Method for Compound 15a, 15b, and 16

Compound **15a** (3.860 g, 8.0 mmol) was suspended in propan-2-ol (200 mL) and heated to 50°C with stirring. Then the solution was cooled to 26°C. $NaBH_4$ (0.150 g, 3.95 mmol) was added with magnetic stirring. The reaction mixture was stirred for an additional hour at 25°C and then poured into ice-water (80 mL). The pH was adjusted to about 6.0 to 7.0. The mixture was extracted with chloroform (150 mL × 3). The combined organic layers were washed with distilled water (70 mL × 2), dried with $MgSO_4$, and evaporated by vacuum. The residue was crystallized in anhydrous ethanol and yielded **15a** as a white solid (**16** is yellow viscous syrup), the yield: 86.1%, m.p. 191–193°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.02–2.07 (m, 12H, $4 \times COCH_3$); 3.72–3.76 (m, 1H, H-5′); 3.81 (s, 3H, OCH_3); 4.14 (dd, 1H, $J = 12.0$ Hz, $J = 2.4$ Hz, H-6′); 4.26 (dd, 1H, $J = 12.4$ Hz, $J = 4.8$ Hz, H-6′); 4.62 (s, 2H, Ar-CH_2O); 4.91 (d, 1H, $J = 7.6$ Hz, H-1′); 5.12–5.16 (m, 1H, H-4′); 5.25–5.27 (m, 2H, H-2′, H-3′); 6.81–6.85 (m, 1H, Ar-H); 6.92 (d, 1H, $J = 1.6$ Hz, Ar-H); 7.06–7.09 (m, 1H, Ar-H).

Compound **15b** was prepared following the same procedure used for **15a**. **13b** was used as starting material and obtained as white solid, the yield: 83.4%, m.p. 170–171°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.04 (s, 3H, $COCH_3$); 2.06 (s, 3H, $COCH_3$); 2.07 (s, 3H, $COCH_3$); 2.09 (s, 3H, $COCH_3$); 3.80–3.92 (m, 1H, H-5′); 4.15–4.18 (m, 1H, H-6′); 4.27–4.30 (m, 1H, H-6′); 4.65 (s, 2H, Ar-CH_2O); 5.07 (d, 1H, $J = 7.6$ Hz, H-1′); 5.16–5.19 (m, 1H, H-4′); 5.28–5.31 (m, 2H, H-2′, H-3′); 6.99 (d, 2H, $J = 8.4$ Hz, Ar-H); 7.31 (d, 2H, $J = 8.4$ Hz, Ar-H).

A General Synthetic Method for Compound 17a, 17b, and 18

13-*cis*-RA (1.260 g, 4.2 mmol), compound **15a** (1.940 g, 4.0 mmol), and a catalytic amount of DMAP were dissolved in anhydrous dichloromethane

(50 mL) at 0°C. A solution of DCC (0.911 g, 4.4 mmol) in anhydrous dichloromethane (15 mL) was added dropwise to the above mixture. The reaction solution was slowly warmed to rt and stirred for 10 h. The reaction mixture was diluted with dichloromethane (30 mL) and cooled at 0°C overnight, and the mixture was filtered to remove the byproduct urine. The solvent was evaporated off under reduced pressure. The remaining residue was purified by column chromatography (elute: ethyl acetate: petroleum ether = 1:2) to give **17a** as yellow solid, the yield: 67.1% m.p. 154–155°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (s, 6H, 2 × CH_3); 1.46–1.49 (m, 2H, H on C_2); 1.59–1.65 (m, 2H, H on C_3); 1.72 (s, 3H, CH_3 on C_5); 2.00–2.08 (m, 20H, 4 × $COCH_3$ and 2 × CH_3 and CH_2); 3.74–3.81 (m, 1H); 3.83 (s, 3H, OCH_3); 4.15 (dd, 1H, J = 12.4 Hz, J = 2.4 Hz); 4.28 (dd, 1H, J = 12.0 Hz, J = 4.8 Hz); 4.93 (d, 1H, J = 8.0 Hz, H-1′); 5.09 (s, 2H, Ar-CH_2O); 5.14–5.18 (m, 1H, H-4′); 5.27–5.30 (m, 2H, H-2′, H-3′); 5.68 (s, 1H, H_{14}); 6.15 (d, 1H, J = 16.0 Hz, H_8); 6.24–6.30 (m, 2H, H_{10} and H_7); 6.88–6.93 (m, 2H, Ar-H); 7.01 (dd, 1H, J = 15.2 Hz, J = 7.2 Hz, H_{11}); 7.09 (d, 1H, J = 8.0 Hz, Ar-H); 7.79 (d, 1H, J = 15.2 Hz, H_{12}). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.9, 19.2, 20.6, 20.7, 20.8, 21.0, 21.7, 28.9, 33.1, 34.2, 39.5, 60.0, 65.2, 68.3, 71.1, 71.9, 72.5, 100.8, 112.6, 115.8, 120.0, 120.7, 128.7, 129.0, 130.1, 130.2, 132.6, 133.1, 137.4, 137.6, 140.1, 145.8, 150.6, 152.1, 166.0, 169.4, 170.3, 170.6. IR (KBr), ν/cm^{-1}: 3466, 2961, 1755, 1637, 1609, 1515, 1231, 1044, 1070, 1045, 908. MS: m/z = 789.5 ($[M + Na]^+$).

Compound **17b** was prepared following a similar procedure as described for **17a**. After purification by column chromatography, **17b** was obtained as yellow powder solid, the yield: 74.0%, m.p. 154–155°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (s, 6H, 2 × CH_3); 1.46–1.49 (m, 2H, H on C_2); 1.58–1.65 (m, 2H, H on C_3); 1.72 (s, 3H, CH_3 on C_5); 2.00–2.08 (m, 20H, 4 × $COCH_3$ and 2 × CH_3 and CH_2); 3.84–3.88 (m, 1H, H-5′); 4.16 (dd, 1H, J = 12.4 Hz, J = 2.4 Hz, H-6′); 4.29 (dd, 1H, J = 12.0 Hz, J = 5.2 Hz, H-6′); 5.08 (d, 1H, J = 7.6 Hz, H-1′); 5.10 (s, 2H, Ar-CH_2O); 5.17 (t, 1H, J = 9.2 Hz, H-4′); 5.25–5.33 (m, 2H, H-2′, H-3′); 5.66 (s, 1H, H_{14}); 6.15 (d, 1H, J = 16.0 Hz, H_8); 6.23–6.30 (m, 2H, H_{10} and H_7); 6.98 (d, 2H, J = 8.8 Hz, Ar-H); 6.97–7.03 (m, 1H, H_{11}); 7.32 (d, 2H, J = 8.8 Hz, Ar-H); 7.79 (d, 1H, J = 15.6 Hz, H_{12}). IR (KBr), ν/cm^{-1}: 3468, 2925, 1750, 1611, 1514, 1230, 1045, 908. MS: m/z = 759.4 ($[M + Na]^+$), 737.1 ($[M + H]^+$).

According to the procedure described for the synthesis of **17a**. After column chromatography, compound **18** was obtained as yellow viscous syrup, the yield: 55.4%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (s, 6H, 2 × CH_3); 1.45–1.48 (m, 2H, H on C_2); 1.59–1.64 (m, 2H, H on C_3); 1.72 (s, 3H, CH_3 on C_5); 2.00–2.19 (m, 20H, 4 × $COCH_3$ and 2 × CH_3 and CH_2); 4.08–4.27 (m, 3H); 5.07–5.16 (m, 3H); 5.23 (d, 1H, J = 13.6 Hz); 5.47 (d, 1H, J = 3.2 Hz); 5.56 (dd, 1H, J = 10.4 Hz, J = 8.0 Hz); 5.70 (s, 1H, H_{14}); 6.15 (d, 1H, J = 16.4 Hz, H_8); 6.24–6.30 (m, 2H, H_{10} and H_7); 7.00 (dd, 1H, J = 15.2 Hz, J = 11.2 Hz, H_{11});

7.08–7.12 (m, 2H, Ar-H); 7.26 (t, 1H, $J = 8.4$ Hz, Ar-H); 7.36 (d, 1H, $J = 7.2$ Hz, Ar-H); 7.81 (d, 1H, $J = 15.6$ Hz, H_{12}). MS: $m/z = 759.3$ ($[M + Na]^+$), 737.0 ($[M + H]^+$).

Synthesis of the Compound 19

Compound **19** was synthesized with the same procedure used for **9**. **17a** was used as starting material. **19** was obtained as yellow viscous syrup, the yield: 61.2%. ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 1.02 (s, 6H, 2 × CH_3); 1.44–1.46 (m, 2H, H on C_2); 1.56–1.58 (m, 2H, H on C_3); 1.68 (s, 3H, CH_3 on C_5); 1.99–2.01 (m, 6H, CH_3 on C_{19} and CH_3 on C_{20}); 2.05–2.07 (m, 2H, H on C_4); 3.19 (d, 1H, $J = 8.4$ Hz, glycosyl-ring-H); 3.27–3.32 (m, 2H, glycosyl-ring-H); 3.44–3.48 (m, 3H, glycosyl-ring-H); 3.67 (d, 1H, $J = 11.2$ Hz, glycosyl-ring-H); 3.77 (s, 3H, OCH_3); 5.03 (s, 2H, Ar-CH_2O); 5.73 (s, 1H, H_{14}); 6.21 (d, 1H, $J = 16.0$ Hz, H_8); 6.28–6.32 (m, 2H, H_{10} and H_7); 6.89 (d, 1H, $J = 8.0$ Hz, Ar-H); 7.02–7.11 (m, 3H, Ar-H and H_{11}); 7.72 (d, 1H, $J = 15.2$ Hz, H_{12}). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 12.6, 18.7, 20.5, 21.5, 28.8, 32.6, 33.8, 40.4, 55.7, 60.6, 64.9, 69.6, 73.2, 76.9, 77.0, 100.0, 112.8, 115.2, 115.8, 120.8, 128.2, 128.9, 129.7, 129.9, 130.2, 132.8, 136.9, 137.2, 140.1, 146.3, 148.8, 151.8, 165.3. IR (KBr), ν/cm^{-1}: 3426, 2956, 1653, 1514, 1454, 1381, 1271, 1151, 1026 (shoulder peak of sugar ring), 1003, 825, 764. MS: $m/z = 622.0$ ($[M + Na]^+$), 600.0 ($[M + H]^+$).

Antiproliferative Activities Assays

The antiproliferative activities of **3**, **8a–8d**, **11a**, and **17a–19** were assessed by use of the MTT assay. The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazol-ium bromide) assay is a simple nonradioactive colorimetric assay to measure cell cytotoxicity, proliferation, or viability. MTT is a yellow, water-soluble, tetrazolium salt. Metabolically active cells are able to convert this dye into a water-insoluble dark blue formazan by reductive cleavage of the tetrazolium ring. Formazan crystals then can be dissolved and quantified by measuring the absorbance of the solution at 570 nm, and the resultant value is related to the number of living cells.

The effect of **8a** on the cells' proliferation efficiency was determined after 24 h incubation with cells. To determine cell proliferation, the A549 cell lines, BEL7404 cell lines, and Tca cell lines were individually plated at a density of 1×10^4 cells/well in 96 well plates at 37°C in 5% CO_2 atmosphere. After 24 h of culture, the medium in the wells was replaced with the fresh medium containing **8a** of varying concentrations respectively. The **8a** concentration given upon is the final concentration in the well. Every concentration added five wells as parallel control. After 24, 10 μL of MTT dye solution (5 mg/mL in phosphate buffer pH 7.4) was added to each well and incubated

for 4 h at 37°C and 5% CO_2 for exponentially growing cells and 10 min for steady-state confluent cells. The formazan crystals were solubilized with 100 μL of DMSO and the solution was vigorously mixed to dissolve the reacted dye. The absorbance of each well was read on a microplate reader (DYNATECH MR7000 instruments) at 570 nm. The spectrophotometer was calibrated to zero using culture medium without cells. We selected inhibitory effect to evaluate side effects of the silica-coated fluorescent **8a** to cells proliferation. The inhibitory effect of **8a** was calculated as percentage inhibition in comparison to the value obtained in untreated well to which no **8a** was added. All the other compounds were determined by the same method except that the cancer cell line is only A549.

CONCLUSION

Ten 13-*cis*-RA analog were synthesized in three ways by structural modifications with glycosyl groups in order to decrease toxicities of 13-*cis*-RA and enhance its antiproliferative activities. Secondly, a new retinoylation method using of DCC as reagent under catalysis DMAP was developed after evaluated various reaction conditions. The *O*-glycosylation method was investigated using DMAP as phase-transfer catalyst. Furthermore, deacetylation of glycosyl retinoates was studied using catalytic amount of dibutyltin oxide as catalyst in methanol. Finally, **8a** was tested by MTT assay on growth of three different tumor cell lines. Among the tested cell lines, **8a** possessed selective antiproliferative activity toward A549. Therefore, the antiproliferative activities of compounds **8b**–**8d**, **11a**, and **17a**–**19** against A549 cell line were evaluated. The results show that **9**, **17a**, **17b**, and **19** demonstrated stronger potential antitumor activities.

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