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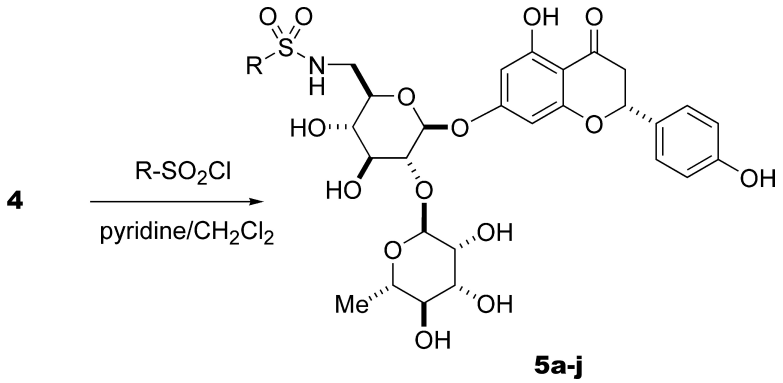

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Natural Products as Scaffolds for Chemical Diversification: Solution-Phase Parallel Synthesis of a Series of Naringin Analogues

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The flavanone glycoside naringin hydrate is widely abundant in various citrus plants. As an ongoing effort toward the exploitation of natural products as scaffolds for chemical diversification at readily accessible positions, we have prepared a series of analogues of naringin in which the 6-hydroxyl group of the β-D-glucopyranosyl subunit was converted to sulfonamides, amides, urethanes, and secondary and tertiary amines via the corresponding 6-amino derivative using a solution-phase parallel array protocol.

Introduction

The plant world is a rich reservoir of bioactive molecules. In fact, several established pharmaceuticals are obtained from plants and formulated as drugs for a variety of human disease conditions.[1] Flavonoids are widely distributed among various citrus plants and are frequent components of the human diet.[2] They exhibit a variety of properties, such as enzyme inhibitor,[3] free radical scavenger,[4] antitumor agent,[5] antibacterial,[6] and antiinflammatory and antioxidant.[7] A remarkable characteristic of citrus fruits is their high content of flavanone glycosides, such as naringin, poncirin, neohesperidin, and hesperidin. Naringin hydrate (**1**) was first isolated from *Eucalyptus globulus*. The structure was established as "naringenin-7-rhamnoglucoside"[8] by degradative studies. The configuration at C-2 of the aglycon (naringenin) was proposed to be *S* by ORD techniques.[9] Unfortunately, there is no reported X-ray crystal structure of naringin. However, the X-ray studies of a dihydrochalcone derivative has been recently disclosed.[10] The antidiarrheal effect of naringenin has been known for some time.[11] Recently, the effects of naringenin and it synthetic derivative, naringenin 7-*O*-cetyl ether, on the cholesterol-regulating enzyme activity and the excretion of sterol were reported.[12] Naringenin 7-*O*-oleic ester and naringenin 7-*O*-cetyl ether were also evaluated for antiatherogenic activity.[13] A way to increase the hydrophobic nature of naringin consists of the esterification of the hydroxyl function by fatty acids. Thus, the 6-*O*-palmitate ester of naringin was synthesized by enzymatic methods.[14]

Natural products have served as useful scaffolds for chemical diversification in the context of drug discovery.[15] As part of ongoing efforts toward the exploitation of readily available flavonoids as scaffolds for chemical diversification, we considered naringin as a versatile starting material. We chose to modify the 6-position in the D-glucopyranose ring to generate a series of 6-amino analogues which could be transformed into sulfonamides, amides, urethanes, and secondary and tertiary amines using a solution-phase parallel array protocol.

Results

Synthesis of Analogues. Selective protection of the primary hydroxyl in the β-D-glucopyranosyl moiety with methanesulfonyl chloride was achieved in pyridine/dichloromethane mixture to obtain 6-*O*-methanesulfonyl naringin (**2**). This was treated with NaN_3 in DMF at 140 °C to obtain the 6-azido-6-deoxynaringin (**3**) in 78% yield. Catalytic reduction with 10% Pd-on-carbon under hydrogen atmosphere in methanol gave the 6-amino-6-deoxynaringin (**4**) in good overall yield (Scheme 1).

The intended analogues were secured by solution-phase parallel synthesis using a 12-vessel carousel. Treatment with commercially available sulfonyl chlorides gave the corresponding sulfonamides (**5a**−**j**) (Scheme 2). On treatment with appropriate acid chlorides, the corresponding amide derivatives (**6a**−**g**) were obtained in good yields (Scheme 3). Upon treatment with various isocyanates and benzoyl, thioisocyanate ureas (**7a**−**d**) and thiourea (**7e**) were obtained (Scheme 4).

Finally, reductive amination with appropriate aldehydes using $NaCNBH_3$ and acetic acid in methanol gave the corresponding substituted secondary (**8a**−**d**) and tertiary (**9e**−**g**) amines (Scheme 5).

In all, we prepared 28 6-amino-6-deoxynaringin analogues in chromatographically and analytically pure form. These analogues encompass a large cross section of aromatic and heterocyclic *N*-appendages that may find application in biological screens searching for new activities associated with flavonoids.

Expermental Section

Flash chromatography was carried out using 230−400 mesh silica gel. Mixtures of methanol and ethyl acetate were used as the eluents unless otherwise specified. Analytical thin-layer chromatography (TLC) was performed on glass plates coated with a 0.02-mm layer of silica gel 60 F-254.

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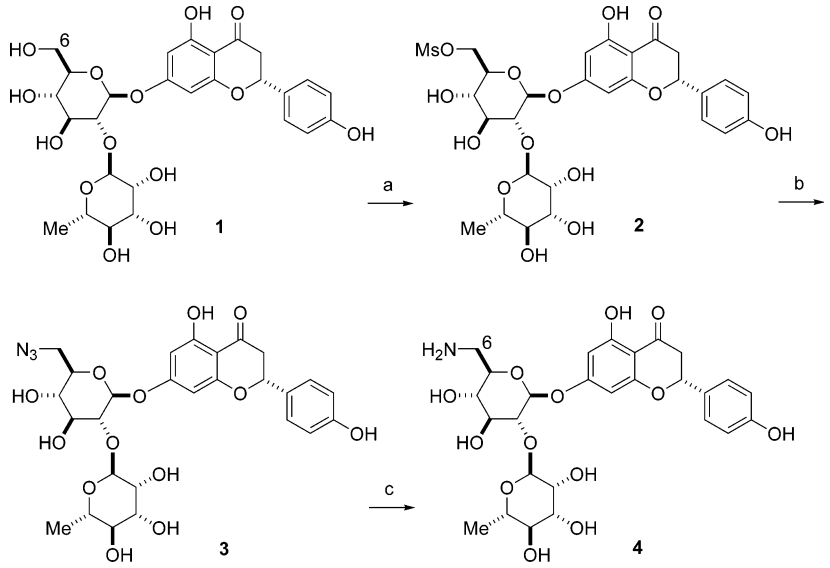
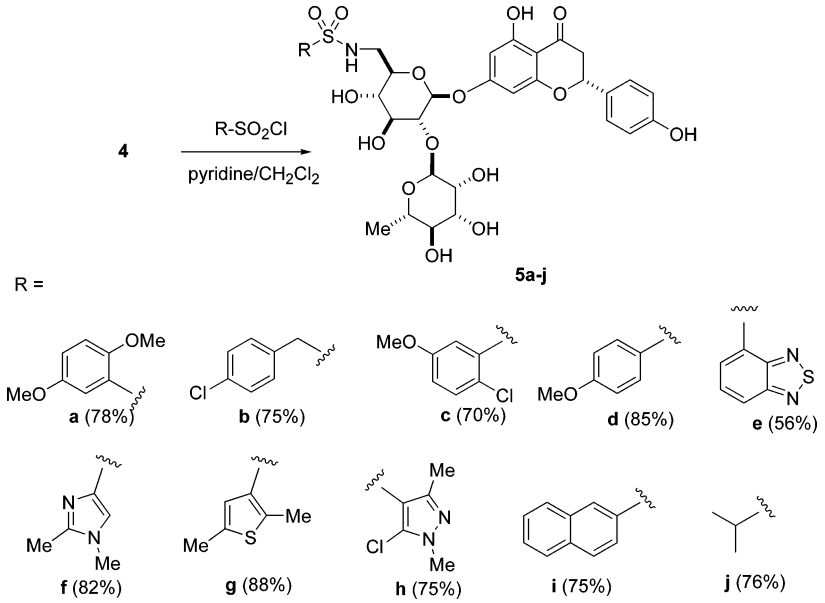
Scheme 1. Synthesis of 6-Amino-6-deoxynaringin[a]



[a] Reagents and conditions: (a) MsCl, pyridine/CH_2Cl_2, room temperature, 12 h, 50%; (b) NaN_3, DMF, 140 °C, 12 h, 78%; (c) H_2, Pd/C, MeOH, 5 h, 63%.

Scheme 2. Synthesis of Sufonamide Analogues

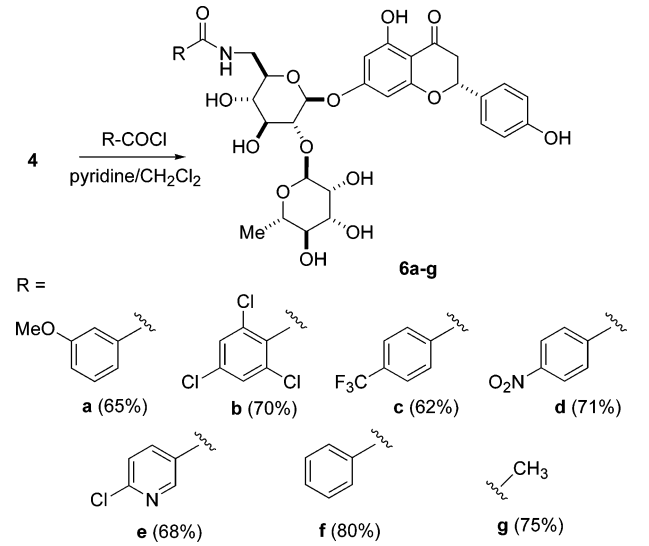


Melting points were uncorrected. IR spectra were recorded as films. ^1H and ^{13}C NMR spectra were recorded at 300 and 400 MHz, respectively, and the chemical shifts are reported in parts per million on the δ scale, with CD_3OD as reference unless otherwise specified. High-resolution and low-resolution MS spectra were recorded using an electron ionization technique. Optical rotations were measured in MeOH at 23 °C. All reactions were carried out under nitrogen or argon unless otherwise specified. Yields are reported for isolated and purified compounds.

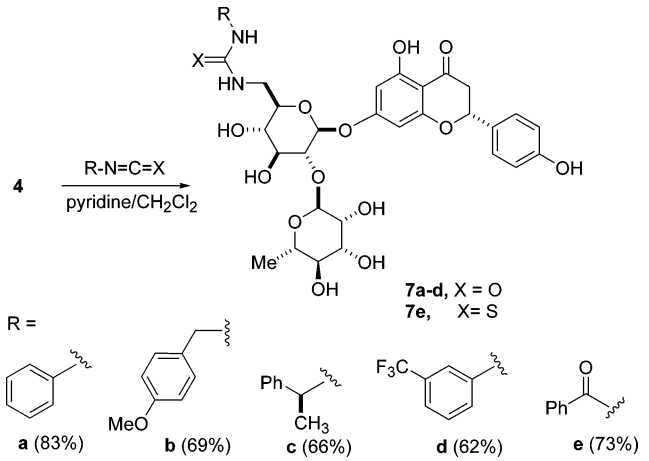
6-*O*-Methanesulfonylnaringin (2). To a solution of naringin **1** (4.0 g, 6.89 mmol) in pyridine (25 mL) and CH_2Cl_2 (100 mL) was added methanesulfonyl chloride (0.59 mL, 7.58 mmol) at 0 °C under argon atmosphere, and stirring was continued at room temperature for 12 h. The mixture was quenched with ice, extracted with EtOAc (300 mL), washed with brine, dried over Na_2SO_4, and then concentrated under vacuum. The residue was purified by column chromatography (MeOH/EtOAc, 3:97) to afford compound **2** as a pale yellow solid (2.3 g, 50%); mp 153 °C; $[\alpha]_D$ −70° (*c* 1, MeOH). IR (KBr) 3399, 1642 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.23 (d, 3H, J = 7.9 Hz), 2.74−2.78 (m, 1H), 2.95 (s, 3H), 3.15−3.18 (m, 1H), 3.38−3.40 (m, 2H), 3.59−3.63 (m, 3H), 3.74−3.76 (m, 1H), 3.86−4.11 (m, 2H), 4.31−4.35 (m, 1H), 4.54−4.58 (m, 1H), 5.16−5.18 (m, 1H), 5.24−5.25 (brs, 1H), 5.38−5.39 (m, 1H), 6.16−6.19 (m, 2H), 6.83 (d, 2H, J = 11.2 Hz), 7.31 (d, 2H, J = 11.2 Hz). ^{13}C NMR (400 MHz, CD_3OD): δ 17.36, 36.67, 60.70, 69.88, 71.12, 72.91, 74.23, 77.65, 79.59, 95.81, 97.05, 98.16, 104.05, 115.49, 128.33, 128.41, 129.63, 129.73, 158.05, 163.63, 163.78, 163.84, 165.08, 165.15, 172.23, 197.63. HRMS calcd for $C_{28}H_{34}O_{16}S$ (M^+) 658.2, found 659.3.

6-Azido-6-deoxynaringin (3). A mixture of compound **2** (1.4 g, 2.13 mmol) and NaN_3 (0.69 g, 10.64 mmol) was heated in dry DMF (10 mL) at 140 °C for 12 h. The mixture was concentrated, taken up in *n*-BuOH (50 mL), washed with

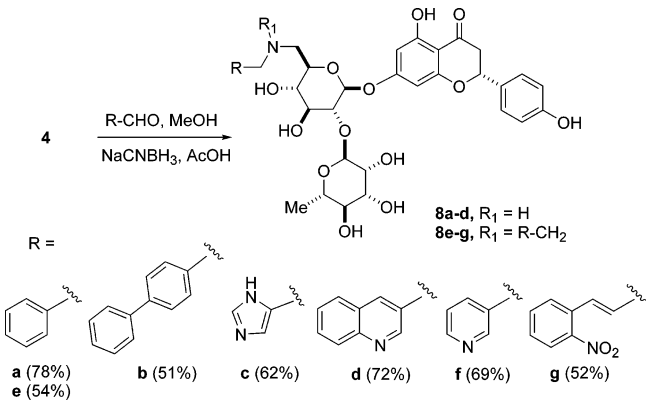
Scheme 3. Synthesis of Amide Analogues



Scheme 4. Synthesis of Urea and Thiourea Analogues



Scheme 5. Synthesis of Amine Analogues



water (10 mL) then with brine, dried over Na_2SO_4, and then concentrated under vacuum. The residue was purified by column chromatography (MeOH/EtOAc, 2:98) to afford compound **3** as a yellow solid (1.0 g, 78%); mp 217 °C; $[\alpha]_D$ −129° (*c* 0.5, MeOH). IR (KBr): 3371, 2104, 1652 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 1.29 (d, 3H, J = 7.9 Hz), 2.79−2.83 (m, 1H), 2.85−2.89 (dd, 1H, J = 1.9, 14.2 Hz), 3.21−3.29 (m, 1H), 3.37−3.41 (m, 2H), 3.49−3.69 (m, 5H), 3.82−3.95 (m, 2H), 5.17−5.19 (m, 1H), 5.25 (brs, 1H), 5.40−5.41 (m, 1H), 6.15−6.18 (m, 2H), 6.79−6.83 (d, 2H, J = 11.2 Hz), 7.37 (d, 2H, J = 11.2 Hz). ^{13}C NMR (300 MHz, CD_3OD): δ 15.68, 59.01, 67.43, 69.55, 71.30, 76.02, 76.35, 78.14, 94.17, 95.21, 96.43, 99.95, 102.36, 113.78, 126.56, 126.60, 128.16, 128.24, 156.49, 162.05, 162.36, 163.62, 195.99. MS calcd for $C_{27}H_{31}N_3O_{13}$ (M^+) 605.2, found 606.2.

6-Amino-6-deoxynaringin (4). A mixture of compound **3** (1 g, 1.65 mmol) and 10% Pd-on-carbon (50 mg) in MeOH (5 mL) was stirred under hydrogen atmosphere for 5 h. The suspension was filtered, washed with MeOH (15 mL), then concentrated to yield **4** as a yellow solid (600 mg, 63%); mp 261 °C; $[\alpha]_D$ −62.4° (*c* 0.5, MeOH). IR (KBr): 3361, 1619 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.28 (d, 3H, J = 7.7 Hz), 2.73−2.78 (m, 1H), 2.86−2.89 (dd, 1H, J = 1.9, 13.9 Hz), 3.16−3.20 (m, 1H), 3.35−3.38 (m, 2H), 3.51−3.71 (m, 5H), 3.79−3.82 (m, 2H), 5.14−5.17 (m, 1H), 5.24−5.25 (m, 1H), 5.41−5.43 (m, 1H), 6.16−6.19 (m, 2H), 6.82 (d, 2H, J = 11.2 Hz), 7.34 (d, 2H, J = 11.2 Hz). ^{13}C NMR (400 MHz, CD_3OD): δ 19.05, 34.83, 61.67, 69.09, 71.19, 72.92, 78.03, 79.72, 96.76, 101.61, 115.35, 128.21, 128.26, 128.97, 129.63, 129.73, 156.49, 158.12, 158.27, 163.67, 164.01, 197.52. MS calcd for $C_{27}H_{33}NO_{13}$ (M^+) 579.2, found 580.4.

General Procedure for the Preparation of *N*-Sulfonamides (5a−j). To a solution of compound **4** (20 mg, 0.035 mmol) in pyridine (2 mL)/CH_2Cl_2 (1 mL) was added the appropriate sulfonyl chloride (0.035 mmol), and the reaction was stirred overnight at room temperature. The mixture was quenched with ice, then concentrated under vacuum. The residue was washed sequentially with CH_2Cl_2 and CH_2Cl_2/MeOH (9:1) to remove impurities, then it was dissolved in MeOH, filtered, and concentrated to give the *N*-sulfonamides (**5a**−**j**).

6-(2,5-Dimethoxybenzenesulfonamido)-6-deoxynaringin (5a). Yield 78%; mp 212 °C; $[\alpha]_D$ −24° (*c* 0.25, MeOH). IR (KBr): 3360, 1616, 1570 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.22 (d, 3H, J = 7.7 Hz), 2.78−2.81 (m, 1H), 3.15−3.19 (m, 1H), 3.35−3.39 (m, 3H), 3.53−3.87 (m, 9H), 3.97−3.40 (m, 4H), 5.19−5.42 (m, 3H), 6.16−6.19 (m, 1H), 6.67 (m, 1H), 6.83−6.89 (m, 3H), 7.42 (m, 4H). ^{13}C NMR (400 MHz, CD_3OD): δ 17.86, 42.93, 56.01, 71.31, 71.73, 72.99, 73.41, 77.45, 77.93, 78.28, 80.29, 98.56, 102.59, 103.73, 105.13, 115.35, 119.38, 123.91, 128.86, 130.13, 130.96, 133.64, 135.37, 140.09, 142.71, 154.10, 156.41, 162.58, 164.32, 166.16, 167.41, 198.61. HRMS calcd for $C_{35}H_{41}NO_{17}S$ (M^+) 779.2, found 780.2.

6-(4-Chlorophenylmethanesulfonamido)-6-deoxynaringin (5b). Yield 75%; mp 202 °C; $[\alpha]_D$ −22° (*c* 0.5, MeOH). IR (KBr): 3362, 1616, 1565, 1519 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.25 (d, 3H, J = 7.4 Hz), 2.75−2.79 (m, 1H), 3.16−3.21 (m, 1H), 3.34−3.38 (m, 2H), 3.55−3.78 (m, 5H), 3.99−4.07 (m, 3H), 5.27 (m, 3H), 5.36−5.39 (m, 1H), 5.53−5.55 (m, 1H), 6.16−6.18 (m, 1H), 6.67−6.81 (m, 1H), 6.83 (m, 4H), 7.35−7.39 (m, 4H). MS calcd for $C_{34}H_{38}ClNO_{15}S$ (M^+) 767.2, found 768.4.

6-(2-Chloro-5-methoxybenzenesulfonamido)-6-deoxynaringin (5c). Yield 70%; mp 215 °C; $[\alpha]_D$ −32.4° (*c* 0.25, MeOH). IR (KBr): 3352, 1617, 1575, 1519 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.23 (d, 3H, J = 7.4 Hz), 2.81−

2.83 (m, 1H), 3.18−3.21 (m, 1H), 3.36−3.39 (m, 2H), 3.62−3.64 (m, 5H), 3.79−4.07 (m, 6H), 5.23−5.26 (m, 3H), 6.18 (m, 1H), 6.66−6.69 (m, 1H), 6.78−6.87 (m, 3H), 7.23−7.32 (m, 4H). HRMS calcd for $C_{34}H_{38}ClNO_{16}S$ (M^+) 783.2, found 784.2.

6-(4-Methoxybenzenesulfonamido)-6-deoxynaringin (5d). Yield 85%; mp 197 °C; $[\alpha]_D$ −26.3° (*c* 0.4, MeOH). IR (KBr): 3402, 1618, 1556, 1519 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.29 (d, 3H, J = 7.4 Hz), 2.79−2.83 (m, 1H), 3.18−3.22 (m, 1H), 3.41−3.45 (m, 2H), 3.61−3.64 (m, 5H), 3.78−4.01 (m, 6H), 5.20−5.23 (m, 3H), 6.19 (m, 1H), 6.63−6.66 (m, 1H), 6.81−6.84 (d, 2H, J = 8.1 Hz), 6.96 (d, 2H, J = 8.7 Hz), 7.32 (d, 2H, J = 8.1 Hz), 7.78 (d, 2H, J = 8.7 Hz). MS calcd for $C_{34}H_{39}NO_{16}S$ (M^+) 749.2, found 750.4.

6-(2,1,3-Benzothiazolesulfonamido)-6-deoxynaringin (5e). Yield 56%; mp 201 °C; $[\alpha]_D$ −40.8° (*c* 0.4, MeOH). IR (KBr): 3351, 1616, 1565, 1519 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.29 (d, 3H, J = 7.4 Hz), 2.81−2.83 (m, 1H), 3.17−3.22 (m, 1H), 3.37−3.41 (m, 2H), 3.63−3.67 (m, 5H), 3.80−3.83 (m, 2H), 3.92−3.94 (m, 1H), 5.23 (m, 3H), 6.16−6.19 (m, 1H), 6.67 (m, 1H), 6.81−6.83 (d, 2H, J = 8.1 Hz), 7.31 (d, 2H, J = 8.1 Hz), 7.67−7.69 (m, 1H), 8.10−8.12 (m, 2H). HRMS calcd for $C_{33}H_{35}N_3O_{15}S_2$ (M^+) 777.2, found 778.4.

6-(1,2-Dimethyl-1*H*-imidazole-4-sulfonamido)-6-deoxynaringin (5f). Yield 82%; mp 185 °C; $[\alpha]_D$ −49.4° (*c* 0.35, MeOH). IR (KBr): 3361, 1617, 1573, 1521 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.22 (d, 3H, J = 7.4 Hz), 2.22−2.27 (m, 3H), 2.40−2.42 (m, 3H), 2.79−2.81 (m, 1H), 3.18−3.21 (m, 1H), 3.40−3.42 (m, 2H), 3.56−3.68 (m, 5H), 3.81−3.83 (m, 1H), 3.93−3.95 (m, 2H), 5.20−5.22 (m, 3H), 6.16−6.19 (m, 1H), 6.66−6.68 (m, 1H), 6.82 (d, 2H, J = 8.1 Hz), 6.93−6.97 (m, 1H), 7.32 (d, 2H, J = 8.1 Hz). MS calcd for $C_{32}H_{39}N_3O_{15}S$ (M^+) 737.2, found 738.4.

6-(2,5-Dimethylthiophene-3-sulfonamido)-6-deoxynaringin (5g). Yield 88%; mp 213 °C; $[\alpha]_D$ −62.5° (*c* 0.2, MeOH). IR (KBr): 3369, 1617, 1563, 1519 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.21 (d, 3H, J = 7.4 Hz), 2.35−2.37 (s, 3H), 2.56−2.58 (s, 3H), 2.76−2.78 (m, 1H), 3.16−3.18 (m, 1H), 3.35−3.39 (m, 2H), 3.62−3.65 (m, 5H), 3.78−3.81 (m, 1H), 3.92−3.94 (m, 2H), 5.23−5.24 (m, 2H), 5.46−5.48 (m, 1H), 6.19 (m, 1H), 6.68−6.74 (m, 1H), 6.84 (d, 2H, J = 8.1 Hz), 6.91 (m, 1H), 7.36 (d, 2H, J = 8.1 Hz). MS calcd for $C_{33}H_{39}NO_{15}S_2$ (M^+) 753.2, found 754.4.

6-(5-Chloro-1,3-dimethyl-pyrazole-4-sulfonamido)-6-deoxynaringin (5h). Yield 75%; mp 191 °C; $[\alpha]_D$ −60.6° (*c* 0.3, MeOH). IR (KBr): 3352, 1617, 1564, 1520 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.24 (d, 3H, J = 7.4 Hz), 2.20−2.24 (m, 3H), 2.75−2.78 (m, 1H), 3.22−3.24 (m, 1H), 3.36−3.39 (m, 2H), 3.51−3.87 (m, 9H), 3.89−3.92 (m, 2H), 5.22−5.24 (m, 2H), 5.38−5.41 (m, 1H), 6.18 (m, 1H), 6.68−6.78 (m, 1H), 6.81 (d, 2H, J = 8.1 Hz), 7.38 (d, 2H, J = 8.1 Hz). MS calcd for $C_{33}H_{38}ClN_3O_{15}S$ (M^+) 771.2, found 770.3.

6-(2-Naphthalenesulfonamido)-6-deoxynaringin (5i). Yield 75%; mp 219 °C; $[\alpha]_D$ −43.4° (*c* 0.3, MeOH). IR (KBr): 3357, 1617, 1575, 1517 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.22 (d, 3H, J = 7.4 Hz), 3.17−3.19 (m, 2H), 3.37−3.38 (m, 2H), 3.44−3.66 (m, 5H), 3.78−4.07 (m, 3H), 5.21−5.24 (m, 3H), 6.78−6.81 (m, 4H), 7.37 (m, 2H), 7.42−7.66 (m, 3H), 7.78−7.81 (m, 1H), 7.96−7.98 (m, 1H), 8.14−8.16 (m 1H), 8.29 (m, 1H). MS calcd for $C_{37}H_{39}NO_{15}S$ (M^+) 769.2, found 770.3.

6-(Isopropylsulfonamido)-6-deoxynaringin (5j). Yield 76%; mp 221 °C; $[\alpha]_D$ −33.8° (*c* 0.4, MeOH). IR (KBr): 3370, 1617, 1566, 1519 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.26 (brs, 9H), 2.79 (m, 1H), 2.97−3.06 (m, 1H), 3.17−3.21 (m, 1H), 3.41−4.44 (m, 2H), 3.60−3.64 (m, 5H), 3.95−3.98 (m, 3H), 5.18−5.46 (m, 3H), 6.19 (m, 1H), 6.69−6.77 (m, 1H), 6.81 (d, 2H, J = 7.9 Hz), 7.33 (d, 2H, J = 7.9 Hz). MS calcd for $C_{30}H_{39}NO_{15}S$ (M^+) 685.2, found 686.4.

General Procedure for the Preparation of Amides (6a−g). To a solution of compound **4** (20 mg, 0.035 mmol) in pyridine (2 mL)/CH_2Cl_2 (1 mL) was added the appropriate acid chloride (0.035 mmol), and the mixture was stirred overnight at room temperature. The mixture was quenched with ice, then concentrated under vacuum. The residue was washed sequentially with CH_2Cl_2 and CH_2Cl_2/MeOH (9:1) to remove impurities, then dissolved in MeOH, filtered, and concentrated to obtain the amides (**6a−g**).

6-(3-Methoxybenzoylamido)-6-deoxynaringin (6a). Yield 65%; mp 200 °C; $[\alpha]_D$ −35° (*c* 0.4, MeOH). IR (KBr): 3352, 1733, 1615 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.22 (brs, 3H), 2.75−2.81 (m, 1H), 3.17−3.21 (m, 1H), 3.37−3.39 (m, 2H), 3.55−3.78 (m, 5H), 3.79−4.04 (m, 6H), 5.07−5.42 (m, 3H), 6.19 (m, 1H), 6.79−6.82 (m, 2H), 6.97−7.04 (m, 1H), 7.36−7.39 (m, 6H). MS calcd for $C_{35}H_{39}NO_{15}$ (M^+) 713.2, found 714.4.

6-(2,4,6-Trichlorobenzoylamido)-6-deoxynaringin (6b). Yield 70%; mp 215 °C; $[\alpha]_D$ −36.6° (*c* 0.3, MeOH). IR (KBr): 3344, 1762, 1615 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.23 (brs, 3H), 2.67−2.79 (m, 1H), 3.15−3.21 (m, 1H), 3.34−3.38 (m, 2H), 3.49−3.76 (m, 5H), 3.81−3.84 (m, 1H), 3.91−3.94 (m, 2H), 5.12−5.44 (m, 3H), 6.16−6.18 (m, 1H), 6.79−6.82 (m, 2H), 7.32−7.38 (m, 2H), 7.59−7.67 (m, 3H). HRMS calcd for $C_{34}H_{34}Cl_3NO_{14}$ (M^+) 785.1, found 786.1.

6-(4-Trifluoromethylbenzoylamido)-6-deoxynaringin (6c). Yield 62%; mp 219 °C; $[\alpha]_D$ −47.3° (*c* 0.3, MeOH). IR (KBr): 3369, 1742, 1616 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.25 (brs, 3H), 2.73−2.78 (m, 1H), 3.15−3.17 (m, 1H), 3.36−3.39 (m, 2H), 3.46−3.71 (m, 5H), 3.84−3.87 (m, 3H), 5.07−5.41 (m, 3H), 6.18 (m, 1H), 6.81−6.82 (m, 3H), 7.31−7.33 (m, 3H), 7.81−7.94 (m, 3H). MS calcd for $C_{35}H_{36}F_3NO_{14}$ (M^+) 751.2, found 752.7.

6-(4-Nitrobenzoylamido)-6-deoxynaringin (6d). Yield 71%; mp 223 °C; $[\alpha]_D$ −40.5° (*c* 0.4, MeOH). IR (KBr): 3352, 1745, 1615 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.24 (brs, 3H), 2.71−2.85 (m, 1H), 3.15−3.26 (m, 1H), 3.36−3.38 (m, 2H), 3.49−3.69 (m, 5H), 3.79−3.99 (m, 3H), 5.21−5.23 (m, 2H), 5.36 (m, 1H), 6.16−6.19 (m, 1H), 6.80−6.83 (m, 3H), 7.28−7.32 (m, 3H), 7.98−8.01 (m, 1H), 8.34−8.39 (m, 2H). HRMS calcd for $C_{34}H_{36}N_2O_{16}$ (M^+) 728.2, found 729.2.

6-(6-Chloronicotinoylamido)-6-deoxynaringin (6e). Yield 68%; mp 208 °C; $[\alpha]_D$ −33° (*c* 0.35, MeOH). IR (KBr): 3340, 1739, 1616 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.29 (brs, 3H), 2.79−2.86 (m, 1H), 3.15−3.19 (m, 1H), 3.35−3.39 (m, 2H), 3.53−3.79 (m, 5H), 3.89−3.92 (m, 3H),

5.05−5.42 (m, 3H), 6.19 (m, 1H), 6.79−6.82 (m, 2H), 7.24−7.32 (m, 3H), 8.02−8.06 (m, 1H), 8.34−8.36 (m, 1H), 9.52−9.53 (m, 1H). MS calcd for $C_{33}H_{35}ClN_2O_{14}$ (M^+) 718.2, found 719.4.

6-(Benzamido)-6-deoxynaringin (6f). Yield 80%; mp 211 °C; $[\alpha]_D$ −54.3° (*c* 0.3, MeOH). IR (KBr): 3369, 1747, 1614 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.25 (brs, 3H), 2.76−2.85 (m, 1H), 3.13−3.15 (m, 1H), 3.39−3.41 (m, 2H), 3.60−3.63 (m, 5H), 3.82−3.86 (m, 1H), 3.96−3.99 (m, 2H), 5.23−5.26 (m, 2H), 5.37−5.39 (m, 1H), 6.16−6.19 (m, 1H), 6.81−6.83 (m, 3H), 7.29−7.71 (m, 7H). MS calcd for $C_{34}H_{37}NO_{14}$ (M^+) 683.2, found 684.4.

6-(Acetamido)-6-deoxynaringin (6g). Yield 75%; mp 215 °C; $[\alpha]_D$ −30.8° (*c* 0.5, MeOH). IR (KBr): 3374, 1747, 1638 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.28 (brs, 3H), 2.19 (s, 3H), 2.79−2.86 (m, 1H), 3.16−3.24 (m, 1H), 3.38−3.43 (m, 2H), 3.64−3.66 (m, 5H), 3.82−3.83 (m, 1H), 3.98 (m, 2H), 5.14−5.44 (m, 3H), 6.17−6.19 (m, 1H), 6.69 (m, 1H), 6.81−6.83 (m, 2H), 7.32−7.35 (m, 2H). HRMS calcd for $C_{29}H_{35}NO_{14}$ (M^+) 621.2, found 622.3.

General Procedure for the Preparation of Ureas (7a−e). To a solution of compound **4** (20 mg, 0.035 mmol) in pyridine (2 mL)/CH_2Cl_2 (1 mL) was added the appropriate isocyanate (0.035 mmol), and the mixture was stirred overnight at room temperature. The mixture was quenched with ice and then concentrated under vacuum. The residue was washed sequentially with CH_2Cl_2 and CH_2Cl_2/MeOH (9:1) to remove impurities, then dissolved in MeOH, filtered, and concentrated to obtain the ureas (**7a**−**e**).

6-(Phenylureido)-6-deoxynaringin (7a). Yield 83%; mp 240 °C; $[\alpha]_D$ −35° (*c* 0.3, MeOH). IR (KBr): 3354, 1733, 1616 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 1.24 (brs, 3H), 2.65−2.68 (m, 1H), 3.15−3.19 (m, 1H), 3.36−3.39 (m, 2H), 3.61−3.63 (m, 5H), 3.93−3.95 (m, 3H), 5.13−5.37 (m, 3H), 6.16 (m, 1H), 6.78−6.84 (m, 3H), 7.07−7.59 (m, 7H). MS calcd for $C_{34}H_{38}N_2O_{14}$ (M^+) 698.2, found 699.5.

6-(4-Methoxybenzylureido)-6-deoxynaringin (7b). Yield 69%; mp 215 °C; $[\alpha]_D$ −46° (*c* 0.2, MeOH). IR (KBr): 3401, 1728, 1616 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 1.26 (brs, 3H), 2.71−2.92 (m, 1H), 3.17−3.24 (m, 1H), 3.41−3.44 (m, 2H), 3.54−3.74 (m, 8H), 3.91−3.93 (m, 4H), 4.21−4.25 (m, 1H), 5.08−5.31 (m, 3H), 6.14 (m, 1H), 6.85−6.89 (m, 5H), 7.17−7.20 (m, 2H), 7.30−7.32 (m, 2H). MS calcd for $C_{36}H_{42}N_2O_{15}$ (M^+) 743.3, found 743.5.

6-((*S*)-α-Methylbenzylureido)-6-deoxynaringin (7c). Yield 66%; mp 230 °C; $[\alpha]_D$ −35° (*c* 0.3, MeOH). IR (KBr): 3368, 1723, 1616 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 1.25 (m, 6H), 2.71−2.89 (m, 1H), 3.22−3.24 (m, 1H), 3.39−3.42 (m, 2H), 3.61−3.64 (m, 5H), 3.89−3.93 (m, 4H), 5.14−5.29 (m, 3H), 6.18 (m, 1H), 6.77−6.79 (m, 3H), 7.15−7.39 (m, 7H). MS calcd for $C_{36}H_{42}N_2O_{14}$ (M^+) 726.3, found 727.5.

6-(3-Trifluoromethylphenylureido)-6-deoxynaringin (7d). Yield 62%; mp 232 °C; $[\alpha]_D$ −32° (*c* 0.25, MeOH). IR (KBr): 3394, 1713, 1610 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 1.23 (brs, 3H), 2.69−2.79 (m, 1H), 3.19−3.23 (m, 1H), 3.38−3.40 (m, 2H), 3.57−3.61 (m, 5H), 3.90−3.93 (m, 3H), 5.04−5.22 (m, 3H), 6.17−6.19 (m, 1H), 6.76−6.81 (m, 3H), 7.15−7.39 (m, 6H). MS calcd for $C_{35}H_{37}F_3N_2O_{14}$ (M^+) 766.2, found 767.7.

6-(Benzoylthioureido)-6-deoxynaringin (7e). Yield 73%; mp 243 °C; $[\alpha]_D$ −109° (*c* 0.2, MeOH). IR (KBr): 3366, 1733, 1616 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.29 (brs, 3H), 2.69−2.73 (m, 1H), 3.19−3.21 (m, 1H), 3.39−3.42 (m, 2H), 3.57−3.61 (m, 5H), 3.89−3.91 (m, 3H), 5.15−5.31 (m, 3H), 6.16−6.19 (m, 1H), 6.77−6.82 (m, 3H), 7.14−7.69 (m, 7H). MS calcd for $C_{35}H_{38}N_2O_{14}S$ (M^+) 742.2, found 743.4.

General Procedure for Reductive Amination. To a mixture of compound **4** (20 mg, 0.035 mmol), an appropriate aldehyde (0.035 mmol) in MeOH (2 mL) was added AcOH (8 μL), then the mixture was stirred for 1 h. $NaCNBH_3$ (5 mg, 0.08 mmol) was then added, and the mixture was stirred for 10 h at room temperature. The mixture was quenched with ice and then concentrated under vacuum. The residue was washed sequentially with CH_2Cl_2 and CH_2Cl_2/MeOH (9:1) to remove impurities. The residue was then dissolved in MeOH, filtered, and concentrated to obtain compounds **8a**−**d**. For compounds **8e**−**g**: aldehyde (0.07 mmol), AcOH (16 μL), and $NaCNBH_3$ (0.14 mmol) were used.

6-(*N*-Benzylamino)-6-deoxynaringin (8a). Yield 64%; mp 212 °C; $[\alpha]_D$ −16.4° (*c* 0.25, MeOH). IR (KBr): 3306, 1603 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.28 (brs, 3H), 2.79−2.92 (m, 1H), 3.19−3.23 (m, 1H), 3.38−3.41 (m, 2H), 3.62−3.65 (m, 7H), 3.88−3.93 (m, 1H), 3.98−4.01 (m, 2H), 5.11−5.44 (m, 3H), 6.18−6.21 (m, 1H), 6.82−6.85 (m, 3H), 7.17−7.21 (m, 2H), 7.38−7.41 (m, 5H). MS calcd for $C_{34}H_{39}NO_{13}$ (M^+) 669.2, found 670.5.

6-(*p*-Phenylbenzylamino)-6-deoxynaringin (8b). Yield 51%; mp 204 °C; $[\alpha]_D$ −47° (*c* 0.2, MeOH). IR (KBr): 3346, 1600 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.23 (brs, 3H), 2.65−2.78 (m, 1H), 3.18−3.21 (m, 1H), 3.39−3.42 (m, 2H), 3.60−3.63 (m, 7H), 3.93−3.95 (m, 3H), 5.15−5.29 (m, 3H), 6.17−6.21 (m, 1H), 6.77−6.79 (m, 3H), 7.13−7.63 (m, 11H). MS calcd for $C_{40}H_{43}NO_{13}$ (M^+) 745.3, found 748.5.

6-(2-Imidazolomethylamino)-6-deoxynaringin (8c). Yield 62%; mp 211 °C; $[\alpha]_D$ −33.4° (*c* 0.3, MeOH). IR (KBr): 3336, 1601 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.28 (brs, 3H), 2.64−2.82 (m, 1H), 3.16−3.19 (m, 1H), 3.34−3.37 (m, 2H), 3.59−3.62 (m, 7H), 3.94−3.98 (m, 3H), 5.13−5.37 (m, 3H), 6.15−6.19 (m, 1H), 6.78−6.83 (m, 4H), 7.22−7.24 (m, 3H). MS calcd for $C_{31}H_{37}N_3O_{13}$ (M^+) 659.2, found 660.5.

6-(3-Quinolinomethylamino)-6-deoxynaringin (8d). Yield 72%; mp 244 °C; $[\alpha]_D$ −42.9° (*c* 0.45, MeOH). IR (KBr): 3266, 1602 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.26 (brs, 3H), 2.69−2.81 (m, 1H), 3.18−3.21 (m, 1H), 3.35−3.38 (m, 2H), 3.61−3.63 (m, 7H), 3.84−3.88 (m, 3H), 5.08−5.28 (m, 3H), 6.15−6.17 (m, 1H), 6.78−6.79 (m, 5H), 7.24−7.28 (m, 4H), 7.75−7.77 (m, 1H), 7.92−7.95 (m, 1H). MS calcd for $C_{37}H_{40}N_2O_{13}$ (M^+) 720.3, found 721.5.

6-(Bisbenzylamino)-6-deoxynaringin (8e). Yield 54%; mp 207 °C; $[\alpha]_D$ −22.9° (*c* 0.35, MeOH). IR (KBr): 3338, 1601 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.27 (brs, 3H), 2.62−2.79 (m, 1H), 3.13−3.16 (m, 1H), 3.40−3.43 (m, 2H), 3.57−3.62 (m, 9H), 3.90−3.93 (m, 3H), 5.07−5.41 (m, 3H), 6.21−6.24 (m, 1H), 6.78−6.84 (m, 3H), 7.13−7.17 (m, 6H), 7.29−7.34 (m, 6H). MS calcd for $C_{41}H_{45}NO_{13}$ (M^+) 759.3, found 760.6.

6-(Bis-3-pyridinomethylamino)-6-deoxynaringin (8f). Yield 69%; mp 225 °C; $[\alpha]_D$ −37° (*c* 0.3, MeOH). IR (KBr): 3338, 1602 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.26 (brs, 3H), 2.64−2.81 (m, 1H), 3.15−3.18 (m, 1H), 3.35−3.39 (m, 2H), 3.59−3.61 (m, 9H), 3.92−3.95 (m, 3H), 5.09−5.39 (m, 3H), 6.15−6.19 (m, 1H), 6.77−6.79 (m, 6H), 7.22−7.29 (m, 5H), 7.60−7.62 (m, 1H), 8.33−8.36 (m, 1H). MS calcd for $C_{39}H_{43}N_3O_{13}$ (M^+) 761.3, found 762.5.

6-(Bis-2-nitrocinnamylamino)-6-deoxynaringin (8g). Yield 52%; mp 214 °C; $[\alpha]_D$ −18.3° (*c* 0.4, MeOH). IR (KBr): 3358, 1601 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.27 (brs, 3H), 2.64−2.73(m, 1H), 3.18−3.21 (m, 1H), 3.39−3.43 (m, 2H), 3.62 (m, 9H), 3.88−3.92 (m, 3H), 5.05−5.38 (m, 3H), 6.31−6.37 (m, 1H), 6.65−6.69 (m, 6H), 7.03−7.57 (m, 7H), 7.85−7.88 (m, 4H). MS calcd for $C_{45}H_{47}N_3O_{17}$ (M^+) 901.3, found 902.6.

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