Synthesis, Characterization, Antibacterial and Antifungal Evaluation of Novel Monosaccharide Esters

Yi Shen 1,2, Yufeng Sun 2, Zhipei Sang 3, Chengjun Sun 1, Ya Dai 2, and Yong Deng 3,*

1 West China School of Public Health, Sichuan University, Chengdu 610041, China
2 Harmful Components and Tar Reduction in Cigarette, Sichuan Key Laboratory. No. 56, Section 1, Chenglong Road, Chengdu 610066, China
3 Key Laboratory of Drug Targeting and Drug Delivery System of the Education Ministry, Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, China

* Authors to whom correspondence should be addressed; E-Mails: dycy@263.net (Y.D.); dengyong@scu.edu.cn (Y.D.); Tel./Fax: +86-28-8600-5092 (Y.D.); Tel./Fax: +86-28-8550-3790 (Y.D.).

Received: 13 April 2012; in revised form: 5 July 2012 / Accepted: 16 July 2012 / Published: 23 July 2012

Abstract: A novel series of 3-(2-furyl)acrylate monosaccharide esters Ia–f and menthylxoycarbonyl monosaccharide esters IIa–f were designed and synthesized. The chemical structures of the target compounds were confirmed by IR, 1H- and 13C-NMR and ESI-MS, and the target compounds were investigated for their in vitro antibacterial and antifungal activities. The antibacterial screening results showed that the 3-(2-furyl)acrylate monosaccharide ester derivatives Ia–f were either inactive or only weakly active against the three Gram-positive bacterial strains tested, whereas the menthylxoycarbonyl monosaccharide ester derivatives IIa–f exhibited higher levels of activity, with compound IIe being especially potent. The results of the antifungal screening revealed that compounds Ib, Ie, IIb and IIc displayed potent in vitro activities, whereas If and IIf showed promising activities against all of the microorganisms tested, with If exhibiting levels of activity deserving of further investigation.

Keywords: carbohydrate-acetonides; 3-(2-furyl)acrylate monosaccharide esters; menthylxoycarbonyl monosaccharide esters; antibacterial activities; antifungal activities
1. Introduction

Microbial food contamination problems have been the cause of much public concern over the last few decades because of an increase in the number of infections and diseases originating from the consumption of spoiled food [1]. Antibacterial and antifungal agents are necessary for food preservation, especially for food processors, because bacterial and fungal growth are important causes of food spoilage. For this reason, many investigators have focused their research efforts on finding new efficient, low toxicity and environmentally friendly antibacterial and antifungal agents.

Sugar esters have been widely used as cosmetic and pharmaceutical industries for many years because they are considered biocompatible, biodegradable, and nontoxic and can be synthesized from renewable resources [2–7]. Furthermore, sugar esters have attracted considerable research interest in recent years because they have exhibited a variety of biological activities, including insecticidal [8], antitumor [9–13], antimicrobial and antifungal properties [14–18]. These results prompted us to design and synthesize a novel series of sugar esters in the hope that we might find some promising antimicrobial or antifungal agents. From a review of the literature, there have been many reports concerning propyl 3-(2-furanyl)acrylate ester and (−)-menthol and their applications in the food, beverage and cosmetics industries. Furthermore, 3-(2-furyl)acrylic acid and its ester derivatives and (−)-menthol have also been reported as antimicrobial agents [19–23]. But these compounds have poor solubility in water and thus result in low bioactivity. Inspired by these observations, we planned to couple 3-(2-furyl) acrylic acid or (−)-menthol with monosaccharides to obtain the corresponding water-soluble monosaccharide esters, as it was envisaged that these novel compounds would combine the favorable properties of sugars with either the 3-(2-furyl)acrylic acid esters or (−)-menthol and will be more bioavailable.

Based upon the aforementioned considerations, herein we describe the synthesis of two novel series, including a series of 3-(2-furyl) acrylate monosaccharide esters Ia–f and a series of menthyl oxycarbonyl monosaccharide esters IIa–f (Scheme 1).

Scheme 1. Synthesis of compounds Ia–f and IIa–f.
Scheme 1. Cont.

Reagents and conditions: (i) morpholine, AcOH, reflux 5 h (85%); (ii) SOCl₂, cat. DMF, CH₂Cl₂, r.t. 5 h (99.0%); (iii) Carbohydrate-acetonides (5a–f = R₁OH), Et₃N, CH₂Cl₂, r.t., 12–15 h; (iv) 50% CF₃COOH-H₂O, r.t., 3–5 h (42.2–65.5% for 2 steps); (v) triphosgene, toluene, pyridine, r.t. 15 h (quantitative yield); (vi) Carbohydrate-acetonides (5a–f = R₁OH), Et₃N, CH₂Cl₂, r.t., 12–15 h; (vii) 50% TFA-H₂O, r.t., 3–5 h (31.5–65.0% over the 2 steps).

Furthermore, their in vitro antibacterial activities against *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli* and *Pseudomonas aeruginosa*, and antifungal activities against *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus fumigatus* and *Geotrichum candidum* were investigated.

2. Results and Discussion

2.1. Chemical Synthesis

The target compounds Ia–f and IIa–f were synthesized according to conventional procedures as outlined in Scheme 1. Compound 3 [24] was prepared by a modified procedure which provided the product more conveniently and in higher yield, and was subsequently reacted with thionyl chloride to afford α-furanacryloyl chloride 4. Compounds 6a–f were obtained via the esterification of intermediate 4 with the corresponding one anomer of O-isopropylidene-protected monosaccharides 5a–f in dry dichloromethane in the presence of Et₃N at room temperature. Subsequent deprotection of the O-isopropylidene with a 50% TFA-H₂O solution at room temperature gave the desired 3-(2-furyl)acrylate monosaccharide esters Ia–f as a mixture of anomers for Ia, Ib, Ie and If due to mutarotation [25]. The menthylxoycarbonyl monosaccharide esters IIa–f were synthesized from the readily available alcohol (−)-menthol (7), which was reacted with triphosgene and pyridine in toluene to give menthyl chloroformate 8 in quantitative yield [26]. Chloroformate 8 was taken into the next step without purification and reacted with the one anomer of O-isopropylidene protected monosaccharides 5a–f in dry dichloromethane in the presence of Et₃N at room temperature to afford the corresponding menthol carbonates 9a–f in high yields. Subsequent deprotection of the O-isopropylidenes with a 50% TFA-H₂O solution at room temperature gave the desired anomeric mixture of menthylxoycarbonyl
monosaccharide esters IIa–f. Among them, IIa, IIb, Ile and IIf were obtained as a mixture of anomers due to mutarotation. All of the target compounds were purified by silica gel flash column chromatography, and their chemical structures were confirmed by IR, $^1$H- and $^{13}$C-NMR and ESI-MS. To the best of our knowledge, none of these monosaccharide esters have been reported in the literature, and therefore represent novel compounds.

2.2. Antibacterial and Antifungal Activities

2.2.1. Antibacterial Activities

The in vitro antibacterial activities of the monosaccharide esters Ia–f and IIa–f were tested against five bacterial strains, including the three Gram-positive organisms, *B. subtilis*, *S. aureus*, and *S. epidermidis*, and the two Gram-negative organisms *E. coli* and *P. aeruginosa*. The antibacterial assays were conducted according to the NCCLS (National Committee for Clinical Laboratory Standards) document M100-S12 method [27]. Standard antibacterial agents, including penicillin and streptomycin, were also screened under identical conditions for the sake of comparison. The minimum inhibitory concentrations (MIC) values of the tested compounds are shown in Table 1.

| Compound | MIC (µg/mL) |
|----------|-------------|
|          | Gram-positive | Gram-negative |
|          | *B. subtilis* | *S. aureus* | *S. epidermidis* | *E. coli* | *P. aeruginosa* |
| Ia       | 32 | 32 | 32 | >64 | >64 |
| Ib       | 32 | 32 | 32 | >64 | >64 |
| Ic       | >64 | 32 | >64 | >64 | >64 |
| Id       | >64 | 32 | >64 | >64 | >64 |
| Ie       | 32 | 32 | >64 | >64 | >64 |
| If       | 32 | >64 | >64 | >64 | >64 |
| IIa      | 32 | 16 | 32 | >64 | >64 |
| IIb      | 8  | 32 | 32 | >64 | >64 |
| IIc      | 32 | 32 | 16 | >64 | >64 |
| IIId     | 32 | 32 | 32 | >64 | >64 |
| IIe      | 2  | 2  | 8  | >64 | >64 |
| IIIf     | 8  | 16 | 16 | >64 | >64 |
| 3        | 8  | 32 | 16 | >64 | >64 |
| (−)-Menthol | 8  | 16 | 8  | 8  | 4  |
| Penicillin | 1  | 1  | 4  | 32 | 16 |
| Streptomycin | 8  | 8  | 16 | 4  | 2  |

Negative control 5% DMSO---no activity.

The compounds tested clearly exhibited varying degrees of antibacterial activity. The 3-(2-furyl)acrylate monosaccharide ester derivatives Ia–f were either inactive or only weakly active against the three Gram-positive bacterial strains tested, whereas the menthyloxycarbonyl monosaccharide ester derivatives IIa–f showed greater levels of activity, with compound IIe exhibiting remarkably high
levels of antibacterial activities against all three bacterial strains. It was also shown that all of the target compounds were inactive against the gram-negative bacterial strains tested.

2.2.2. Antifungal Activities

The *in vitro* antifungal activities of the monosaccharide esters Ia–f and IIa–f were determined against four fungal strains, including *A. flavus*, *A. niger*, *A. fumigatus*, and *G. candidum*, using clotrimazole as a reference standard. The antifungal activity assays were conducted according to the NCCLS standard M27-A method [28]. The MIC data of the tested compounds are presented in Table 2.

| Compound | MIC (µg/mL) |
|----------|-------------|
|          | *A. flavus* | *A. niger* | *A. fumigatus* | *G. candidum* |
| Ia       | 32          | 32         | 32             | 32           |
| Ib       | 16          | 16         | 8              | 32           |
| Ic       | 32          | >64        | >64            | >64          |
| Id       | >64         | >64        | 32             | >64          |
| Ie       | 16          | 16         | 8              | 32           |
| If       | 2           | 2          | 2              | 4            |
| IIa      | >64         | >64        | >64            | >64          |
| IIb      | 16          | 16         | 8              | 32           |
| IIc      | 16          | 32         | 8              | 16           |
| IIe      | >64         | >64        | >64            | >64          |
| IIf      | 4           | 4          | 4              | 8            |
| 3        | 32          | >64        | >64            | >64          |
| (-)-Menthol | 32      | 32         | 32             | >64          |
| Clotrimazole | 8       | 8          | 4              | 16           |

Negative control 5% DMSO---no activity.

The *in vitro* antifungal activity results showed that compounds If and IIf exhibited potent activities against all of the microorganisms tested. Furthermore, both of these compounds, especially If, exhibited activities comparable to those of the standard fungicide, clotrimazole, indicating that these compounds are worthy of further investigation. It was also found that compounds Ib, Ie, IIb and IIc showed potent *in vitro* antifungal activities, and that their activities were superior to those of the corresponding 3-(2-furyl)acrylic acid (3) and (-)-menthol. The other monosaccharide esters Ia, Ic, Id, IIa, IIId and IIe showed no activity against the antifungal strains tested.

3. Experimental

3.1. Materials and Reagents

Melting points were determined in open glass capillaries using a paraffin bath and are uncorrected. $^1$H- and $^{13}$C-NMR spectra were measured on a Varian INOVA-400 instrument at 400 and 100 MHz, respectively, using TMS as an internal standard in CDCl$_3$ or D$_2$O solvents. IR spectra were obtained on
a Thermo Nicolet AVATAR 370 FT-IR instrument using KBr plates. Mass spectra were recorded on a Waters Q-TOF Premier mass spectrometer. Optical rotation data were collected after mutarotation equilibration in about 10 min on a Perkin-Elmer 341 Polarimeter using HPLC grade anhydrous MeOH. All commercially available reagents and anhydrous solvents were purchased at the highest commercial quality and were used without further purification. The bacterial and fungal strains were obtained from Sichuan Industrial Institute of Antibiotics, Sinopharm Group Co. Ltd., (SINOPHARM-SIIA, Chengdu, China).

3.2. Chemical Synthesis

3.2.1. Preparation of 3-(2-furyl)acrylic acid (3)

Furfural (28.8 g, 0.30 mol) was dissolved in AcOH (120 mL) and morpholine (26.1 g, 0.30 mol) was slowly added to the stirred mixture at 25 °C over a period of 10 min. Malonic acid (31.2 g, 0.30 mol) was then added to the reaction mixture and the resulting mixture was heated at reflux for 5.0 h. The mixture was then cooled to 25 °C and poured into cold water (400 mL). The resulting precipitate was collected by filtration, washed with water, and dried under vacuum at 40 °C in a vacuum oven to give the desired product. Yield: 35.2 g (85%), mp 140–141 °C (lit. m.p. 140–141 °C [24]).

3.2.2. Preparation of 3-(2-furyl)acryloyl chloride (4)

Thionyl chloride (17.85 g, 0.15 mol) was added to a stirred solution of 3-(2-furyl)acrylic acid (3, 13.8 g, 0.1 mol) in CH₂Cl₂ (70 mL) at room temperature and the resulting mixture was heated at reflux for 3 h. The mixture was then cooled and concentrated in vacuo to afford 3-(2-furyl)acryloyl chloride quantitatively, which was used directly without further purification in the following reaction.

3.2.3. A general procedure for the synthesis of compounds Ia–f

A solution of 3-(2-furyl)acryloyl chloride (4, 0.024 mol or 0.048 mol in the synthesis of 6f) in dry CH₂Cl₂ (15 mL) was added in a dropwise manner to a solution of carbohydrate-acetonide 5a–f (only one anomer was used, 0.02 mol) and Et₃N (0.05 mol) in dry CH₂Cl₂ (60 mL) at 0 °C in an ice bath. The resulting solution was allowed to warm to room temperature and stirred for 12–15 h. The reaction mixture was then diluted with CH₂Cl₂ (40 mL) and washed sequentially with H₂O (2 × 25 mL), saturated aqueous sodium bicarbonate (25 mL) and saturated aqueous sodium chloride (25 mL) and dried (Na₂SO₄). The solvent was then removed in vacuo and to give the crude products 6a–f (only one anomer was obtained), which were used directly in the next steps without further purification. A 50% TFA-H₂O solution (30 mL) was added to each of the compounds 6a–f and the mixture was continuously stirred at room temperature for 3–5 h. Upon completion of the reaction (TLC, developing solvent: CHCl₃/CH₃OH = 15:1), the solvents were removed in vacuo and residue was purified by silica gel flash column chromatography (elucent: CHCl₃/CH₃OH = 10:1) to give the compounds Ia–f as light yellow foams.

3-O-[3-(2-Furyl)acryloyl]-α/β-D-glucopyranose (Ia): yield 48.5%, (α:β isomer = 2:3 based on ¹H-NMR); [α]D²⁰ = +30.1 (c = 0.5, CH₃OH); IR (KBr, cm⁻¹): 3405.65, 2936.51, 1688.63, 1635.15,
6-O-[3-(2-Furyl)acryloyl]-α/β-D-galactopyranose (Ib): yield 65.5%, (α:β isomer = 1:3 based on ¹H-NMR); [α]₂⁰ = +33.2 (c = 0.5, CH₃OH); IR (KBr, cm⁻¹): 3421.48, 2921.46, 1689.56, 1646.43, 1484.23, 1311.05, 1287.52, 1267.55, 1219.03, 1178.91, 1068.70, 1028.97, 766.04; ¹H-NMR (D₂O): δ 7.70 (s, 1H, Ar-H), 7.60 (d, J = 16 Hz, 1H, =CH), 6.90 (s, 1H, Ar-H), 6.65 (s, 1H, Ar-H), 6.42 (d, J = 16 Hz, 1H, =CH), 5.33 (d, J = 4.0 Hz, 0.33H, 1'-Hₐ), 4.65 (d, J = 8.0 Hz, 0.67H, 1'-H₉); ¹3C-NMR (D₂O): δ 171.05, 152.68, 148.31, 143.49, 130.33, 114.13, 111.38, 110.27, 93.36, 89.59, 74.93, 73.26, 72.85, 70.03, 69.97, 68.74, 67.43, 65.47, 58.07, 57.90; ESI-MS (m/z): 623.5 [M+Na]⁺, 339.05 [M+K]⁺, 323.10 [M+Na]⁺.

1-O-[3-(2-Furyl)acryloyl]-β-D-fructopyranose (Ic): yield 51.5%; [α]₂⁰ = −16.8 (c = 0.5, CH₃OH); IR (KBr, cm⁻¹): 3425.36, 2919.49, 1689.56, 1633.87, 1392.49, 1309.13, 1280.21, 1268.82, 1212.08, 1165.22, 1079.39, 751.26; ¹H-NMR (D₂O): δ 7.69 (s, 1H, Ar-H), 7.62 (d, J = 16 Hz, 1H, =CH), 6.90 (s, 1H, Ar-H), 6.64 (s, 1H, Ar-H), 6.43 (d, J = 16 Hz, 1H, =CH), 4.35 (d, J = 11.6 Hz, 1H, 1'-H), 4.33 (d, J = 11.6 Hz, 1H, 1'-H), 4.12–4.06 (m, 2H, 4'-H+3'-H), 3.99–3.96 (m, 1H, 5'-H), 3.88–3.86 (m, 1H, 6'-H), 3.77–3.74 (m, 1H, 6'-H); ¹3C-NMR (D₂O): δ 170.93, 152.77, 148.44, 135.40, 119.14, 115.94, 115.20, 99.62, 71.83, 71.46, 70.51, 68.19, 66.10; ESI-MS (m/z): 623.58 [M+Na]⁺, 339.28 [M+K]⁺, 323.34 [M+Na]⁺.

3-O-[3-(2-Furyl)acryloyl]-β-D-fructopyranose (Id): yield 42.2%; [α]₂⁰ = −15.0 (c = 0.5, CH₃OH); IR (KBr, cm⁻¹): 3423.50, 2919.06, 1690.32, 1639.41, 1390.12, 1311.75, 1285.37, 1267.76, 1216.13, 1175.78, 1075.620, 1048.93, 750.55; ¹H-NMR (D₂O): δ 7.71 (s, 1H, Ar-H), 7.66 (d, J = 16 Hz, 1H, =CH), 6.92 (s, 1H, Ar-H), 6.65 (s, 1H, Ar-H), 6.42 (d, J = 16 Hz, 1H, =CH), 5.34 (d, J = 10.0 Hz, 1H, 3'-H), 4.18 (d, J = 10.8 Hz, 2H, 6'-H), 4.13 (s, 2H, 1'-H), 3.91–3.78 (m, 1H, 4'-H), 3.65–3.49 (m, 1H, 3'-H); ¹3C-NMR (D₂O): δ 170.93, 152.77, 148.52, 135.64, 119.29, 115.79, 115.22, 99.64, 72.23, 71.69, 70.63, 66.43, 65.99; ESI-MS (m/z): 339.28 [M+K]⁺, 323.34 [M+Na]⁺.

5-O-[3-(2-Furyl)acryloyl]-α/β-D-xylofuranose (Ie): yield 54.8%, (α:β isomer = 3:1 based on ¹H-NMR); [α]₂⁰ = +15.6 (c = 0.5, CH₃OH); IR (KBr, cm⁻¹): 3418.32, 2921.25, 1695.67, 1482.55, 1348.08, 1304.12, 1266.78, 1209.46, 1068.42, 1033.91, 752.10; ¹H-NMR (D₂O): δ 7.69 (s, 1H, Ar-H), 7.63 (d, J = 16 Hz, 1H, =CH), 6.89 (s, 1H, Ar-H), 6.64 (s, 1H, Ar-H), 6.43 (d, J = 16 Hz, 1H, =CH), 5.29 (d, J = 2.8 Hz, 0.75H, 1'-Hₐ), 5.26–5.03 (m, 1H, 4'-H), 4.74 (d, J = 8.0 Hz, 0.25H, 1'-H₉), 4.06–3.86 (m, 2H, 5'-H), 3.84–3.80 (m, 1H, 3'-H), 3.53–3.45 (m, 1H, 2'-H); ¹3C-NMR (D₂O): δ 171.05, 152.68, 148.31, 143.49, 130.33, 114.13, 111.38, 110.27, 93.36, 89.59, 74.93, 73.26, 72.85, 70.03, 69.97, 68.74, 67.43, 65.47, 58.07, 57.90; ESI-MS (m/z): 623.5 [2M+Na]⁺, 339.05 [M+K]⁺, 323.10 [M+Na]⁺.
Molecules 2012, 17, 8668

169.35, 151.66, 147.22, 132.54, 116.26, 114.84, 112.45, 99.72, 96.68, 77.66, 77.05, 76.12, 75.39, 73.96, 73.80, 65.55, 63.23; ESI-MS (m/z): 563.48 [2M+Na]+, 309.30 [M+K]+, 293.28 [M+Na]+.

3,5-Bi-O-[3-(2-furyl)acryloyl]-α/β-D-xylofuranose (II): yield 63.6%, (α:β isomer = 6:1 based on 1H-NMR); [α]D20 = -15.4 (c = 0.5, CH3OH); IR (KBr, cm⁻¹): 3417.95, 2921.02, 1703.85, 1638.68, 1479.26, 1479.26, 1351.47, 1308.86, 1264.24, 1210.32, 1168.12, 1077.95, 1045.66, 748.99; 1H-NMR (CDCl3): δ 7.50 (d, J = 2.0 Hz, 1H, Ar-H), 7.47 (d, J = 1.6 Hz, 1H, Ar-H), 7.44 (d, J = 16.0 Hz, 1H, =CH), 7.43 (d, J = 16.0 Hz, 1H, =CH), 6.65 (d, J = 3.2 Hz, 1H, Ar-H), 6.61 (d, J = 3.2 Hz, 1H, Ar-H), 6.48 (dd, J = 3.2, 1.6 Hz, 1H, Ar-H), 6.46 (dd, J = 3.2, 2.0 Hz, 1H, Ar-H), 6.32 (d, J = 16.0 Hz, 1H, =CH), 6.30 (d, J = 16.0 Hz, 1H, =CH), 5.57 (d, J = 4.4 Hz, 0.85H, 1'-Hα), 5.37 (d, J = 8.4 Hz, 0.15H, 1'-Hβ), 5.35–5.28 (m, 1H, 2'-H), 4.76–4.70 (m, 1H, 4'-H), 4.40–4.35 (m, 2H, 5'-H), 4.34–4.29 (m, 1H, 3'-H); 13C-NMR (CDCl3): δ 166.84, 166.75, 150.66, 150.44, 145.27, 144.92, 132.69, 132.61, 131.88, 131.78, 115.98, 115.30, 115.24, 114.86, 113.97, 112.45, 112.29, 102.98, 96.08, 78.66, 77.35, 77.03, 76.72, 75.39, 74.98, 63.80, 62.47; ESI-MS (m/z): 803.25 [2M+Na]+, 429.12 [M+K]+, 413.14 [M+Na]+.

3.2.4. Preparation of Menthyl Chloroformate 8

A solution of pyridine (21.9 mL, 0.27 mmol) in toluene (150 mL) was added in a dropwise manner to a stirred solution of triphosgene (21.96 g, 0.074 mol) in toluene (260 mL) at 0 °C under an argon atmosphere. Stirring was continued for 15 min at 0 °C and a solution of (−)-menthol (7, 28.12 g, 0.18 mol) in toluene (100 mL) was then slowly added through a dropping funnel. The reaction mixture was allowed to warm to ambient temperature and stirred for 15 h. The reaction mixture was then diluted with water (300 mL) and extracted with toluene (2 × 200 mL). The combined organics were washed sequentially with water (200 mL) and brine (200 mL) and dried (Na2SO4). The solvent was removed in vacuo to give the title compound 8 as colorless oil (39.3 g, quant.), which was used directly in the next step without further purification.

3.2.5. A General Procedure for the Synthesis of Compounds IIa–f

A solution of menthyl chloroformate 8 (0.024 mol or 0.05 mol for the synthesis of 9f) in dry CH2Cl2 (15 mL) was added in a drop-wise manner to a solution of carbohydrate-acetonide 5a–f (only one anomer was used, 0.02 mol) and Et3N (0.05 mol) in dry CH2Cl2 (60 mL) at 0 °C in an ice bath. The resulting solution was allowed to warm to room temperature and stirred for 12–15 h. The reaction mixture was then diluted with CH2Cl2 (40 mL) and washed sequentially with H2O (2 × 25 mL), saturated aqueous sodium bicarbonate (25 mL) and saturated aqueous sodium chloride (25 mL) before being dried (Na2SO4). The solvent was removed in vacuo to give a crude product from 9a–f (only one anomer was obtained), which was used directly in the next step without further purification. A 50% TFA-H2O solution (30 mL) was added to one of the compounds 9a–f and the resulting mixture continuously stirred at room temperature for 3–5 h. Upon completion of the reaction (TLC, developing solvent: CHCl3/CH3OH = 20:1), the solvents were removed in vacuo and the crude residue was purified by silica gel flash column chromatography (eluent: CHCl3/CH3OH = 30:1) to give the compounds IIa–f as a colorless foam.
3-O-Menthylcarboxylic acid/β-D-glucopyranose (IIa): yield 60.0%, (α:β isomer = 1:1 based on 1H-NMR); [α]20D = +5.6 (c = 1.0, CH3OH); 1H-NMR (CDCl3): δ 5.36–5.30 (m, 0.5H, 1'-Hβ), 5.00–4.90 (m, 0.5H, 1'-Hα), 4.82–4.72 (m, 1H, 3'-H), 4.58–4.48 (m, 1H, 5'-H), 4.05–3.92 (m, 2H, 4'-H+CHO), 3.83–3.72 (m, 1H, 6'-H), 3.70–3.44 (m, 2H, 6'-H+2'-H), 2.10–2.02 (m, 1H, CH), 2.01–1.92 (m, 1H, CH), 1.72–1.62 (m, 2H, CH2), 1.54–1.38 (m, 2H, CH2+CH2), 1.12–0.99 (m, 2H, CH2), 0.91 (d, J = 6.4 Hz, 3H, CH3), 0.88 (d, J = 6.4 Hz, 3H, CH3), 0.88–0.84 (m, 1H, CH2), 0.76 (d, J = 4.4 Hz, 3H, CH3); 13C-NMR (CDCl3): δ 156.10, 92.30, 88.45, 79.52, 73.55, 73.08, 72.80, 71.05, 70.66, 69.25, 68.82, 62.02, 58.40, 57.96, 47.02, 40.48, 34.02, 31.35, 25.94, 23.24, 22.00, 20.68, 16.21; ESI-MS (m/z): 401.28 [M+K]+, 385.30 [M+Na]+.

6-O-Menthylcarboxylic acid/β-D-galactopyranose (IIb): yield 65.0%, (α:β isomer = 1:4 based on 1H-NMR); [α]20D = −9.9 (c = 1.0, CH3OH); 1H-NMR (CDCl3): δ 5.38 (d, J = 3.6 Hz, 0.2H, 1'-Hα), 4.64 (d, J = 8.4 Hz, 0.8H, 1'-Hβ), 4.63–4.47 (m, 1H, 6'-H), 4.38–4.06 (m, 2H, 2'-H+6'-H), 4.05–3.95 (m, 2H, 3'-H+CHO), 3.82–3.75 (m, 1H, 5'-H), 3.73–3.62 (m, 1H, 4'-H), 2.07–2.04 (m, 1H, CH), 2.01–1.92 (m, 1H, CH), 1.72–1.63 (m, 2H, CH2), 1.52–1.34 (m, 2H, CH2+CH2), 1.10–0.99 (m, 2H, CH2), 0.91 (d, J = 6.0 Hz, 3H, CH3), 0.88 (d, J = 6.8 Hz, 3H, CH3), 0.86–0.84 (m, 1H, CH2), 0.76 (d, J = 6.8 Hz, 3H, CH3); 13C-NMR (CDCl3): δ 154.89, 96.88, 92.52, 78.97, 73.10, 72.74, 72.28, 69.60, 69.06, 68.78, 67.30, 66.90, 66.23, 66.02, 46.90, 40.60, 34.02, 31.34, 25.84, 23.14, 21.97, 20.76, 16.16; ESI-MS (m/z): 401.31 [M+K]+, 385.29 [M+Na]+.

1-O-Menthylcarboxylic acid/β-D-fructopyranose (IIc): yield 60.0%; [α]20D = −44.8 (c = 1.0, CH3OH); 1H-NMR (CDCl3): δ 4.54 (d, J = 11.2 Hz, 1H, 1'-H), 4.52 (d, J = 11.6 Hz, 1H, 1'-H), 4.34–4.25 (m, 2H, 4'-H+3'-H), 4.14–4.06 (m, 1H, 5'-H), 4.05–4.00 (m, 1H, CHO), 3.92–3.82 (m, 1H, 6'-H), 3.80–3.73 (m, 1H, 6'-H), 2.07–2.03 (m, 1H, CH), 2.00–1.90 (m, 1H, CH), 1.72–1.64 (m, 2H, CH2), 1.52–1.36 (m, 2H, CH2+CH2), 1.10–0.99 (m, 2H, CH2), 0.91 (d, J = 7.2 Hz, 3H, CH3), 0.88 (d, J = 7.2 Hz, 3H, CH3), 0.86–0.84 (m, 1H, CH2), 0.76 (d, J = 7.2 Hz, 3H, CH3); 13C-NMR (CDCl3): δ 155.03, 96.81, 79.32, 73.39, 70.31, 69.25, 67.51, 63.57, 46.92, 40.54, 33.99, 31.34, 25.84, 23.13, 21.96, 20.73, 16.13; ESI-MS (m/z): 401.29 [M+K]+, 385.29 [M+Na]+.

3-O-Methylcarboxylic acid/β-D-fructopyranose (IId): yield 53.4%; [α]20D = −61.3 (c = 1.0, CH3OH); 1H-NMR (CDCl3): δ 4.89 (d, J = 9.6 Hz, 1H, 3'-H), 4.59–4.51 (m, 1H, 6'-H), 4.15–4.10 (m, 1H, 6'-H), 4.06 (s, 2H, 1'-H), 3.88–3.82 (m, 1H, CHO), 3.67–3.63 (m, 1H, 4'-H), 3.52–3.45 (m, 1H, 3'-H), 2.10–2.03 (m, 1H, CH), 1.98–1.88 (m, 1H, CH), 1.70–1.67 (m, 2H, CH2), 1.54–1.36 (m, 2H, CH2+CH2), 1.14–0.99 (m, 2H, CH2), 0.91 (d, J = 7.2 Hz, 3H, CH3), 0.88 (d, J = 7.2 Hz, 3H, CH3), 0.87–0.85 (m, 1H, CH2), 0.76 (d, J = 7.8 Hz, 3H, CH3); 13C-NMR (CDCl3): δ 155.67, 97.06, 79.59, 73.90, 69.79, 68.67, 64.74, 63.16, 46.90, 40.46, 33.97, 31.35, 26.12, 23.23, 21.95, 20.66, 16.18; ESI-MS (m/z): 401.30 [M+K]+, 385.31 [M+Na]+.

5-O-Methylcarboxylic acid/α/β-D-xylofuranose (IIE): yield 42.0%, (α:β isomer = 4:1 based on 1H-NMR); [α]20D = −29.7 (c = 1.0, CH3OH); 1H-NMR (CDCl3): δ 5.53 (d, J = 2.0 Hz, 0.8H, 1'-Hα), 4.58–4.48 (m, 1.2H, 1'-Hβ+4'-H), 4.46–4.38 (m, 2H, 3'-H+5'-H), 4.36–4.24 (m, 2H, 2'-H+5'-H), 4.20–4.13 (m, 1H, CHO), 2.10–2.03 (m, 1H, CH), 1.98–1.90 (m, 1H, CH), 1.72–1.64 (m, 2H, CH2), 1.53–1.36
(m, 2H, CH+CH₂), 1.10–0.99 (m, 2H, CH₂), 0.92 (d, J = 7.2 Hz, 3H, CH₃), 0.89 (d, J = 6.8 Hz, 3H, CH₃), 0.87–0.85 (m, 1H, CH₂), 0.77 (d, J = 6.8 Hz, 3H, CH₃); ¹³C-NMR (CDCl₃): δ 155.21, 155.06, 102.80, 96.09, 80.15, 79.83, 79.19, 79.10, 76.36, 75.70, 75.47, 69.85, 67.40, 66.45, 65.96, 46.83, 40.54, 33.94, 31.31, 25.86, 23.12, 21.92, 20.68, 16.13; ESI-MS (m/z): 371.27 [M+K]+, 355.31 [M+Na]+.

3,5-Di-O-menthoxycarbonyl-α/β-D-xylofuranose (II): yield 31.5%, (α:β isomer = 3:1 based on ¹H-NMR); [α]²⁰D = −40.2 (c = 1.0, CH₃OH); ¹H-NMR (CDCl₃): δ 5.21 (d, J = 3.6 Hz, 0.75H, 1'-Hα), 5.02 (d, J = 8.4 Hz, 0.25H, 1'-Hβ), 4.61–4.47 (m, 3H, 4'-H+5'-H+3'-H), 4.38–4.29 (m, 1H, 2'-H), 4.29–4.14 (m, 2H, 5'-H+CHO), 4.14–3.96 (m, 1H, CHO), 2.09–2.03 (m, 2H, 2CH), 1.98–1.91 (m, 2H, 2CH), 1.72–1.57 (m, 4H, 2CH₂), 1.53–1.36 (m, 4H, 2CH₂+2CH₃), 1.16–0.99 (m, 4H, 2CH₂), 0.96–0.85 (m, 16H, 4CH₃), 0.84–0.75 (m, 6H, 2CH₃); ¹³C-NMR (CDCl₃): δ 155.66, 155.62, 101.45, 96.35, 79.75, 79.60, 79.12, 78.03, 77.16, 76.58, 75.30, 73.67, 63.72, 63.25, 46.85, 40.58, 33.92, 31.38, 26.32, 23.20, 21.95, 20.67, 16.20; ESI-MS (m/z): 553.21 [M+K]+, 537.44 [M+Na]+, 493.49 [M-CO₂+Na]+.

3.3. Antibacterial and Antifungal Activity Assays

For each tested compound, 1.28 mg sample was put in a 25 mL flask and dissolved in 10 mL 5% DMSO. The drug was filtered into autoclaving centrifuge tubes in super clean bench. Penicillin, streptomycin and clotrimazole solutions were prepared to the same concentration as the positive control drug. After all bacteria and fungi were recovered, each single colony was picked and inoculated in 3 mL of either a sterilized Mueller-Hinton (MH) broth cultured at 37 °C for 18–24 h (for bacteria) or a Sabouraud Dextrose (SD) broth cultured at 28 °C for 48 h (for fungi). The microorganism solution was corrected to 0.5 McFarland standard turbidity using either the MH or SD broths, and subsequently diluted by 1:100 (amount of microorganism approximately 10⁶ colony forming units/mL) with either the MH or SD broth and inoculated immediately. Blank broth (100 µL) was added into all the wells of rows 2–12 of a 96-well plate. Broth (180 µL) and dispensed drug liquor (20 µL) where added to the first row of the 96-well plate and the mixture was well mixed. A sample of the resulting mixture (100 µL) was inhaled and added into the corresponding wells of the second row. The same mixing and transferring operations were repeated until the wells in the 12th row were filled. The concentrations of drug in the wells of rows 1–12 were 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.0625 µg/mL, respectively. The seventh and eighth rows of the 96-well plate were used for the positive and negative controls, respectively. A diluted microorganism solution (100 µL) was added to each well of the 96-well plate and the plate was shaken on a shaker instrument and subsequently stored in an incubator for 24–48 h at 37 °C (for bacteria) and at 28 °C (for fungi). Each experiment was performed in triplicate.

4. Conclusions

In summary, the design and synthesis of two novel series of 3-(2-furyl) acrylate monosaccharide esters Ia–f and menthoxycarbonyl monosaccharide esters IIa–f from simple starting materials and under mild reaction conditions has been reported. The antibacterial and antifungal properties of these novel compounds were evaluated. The results revealed that the 3-(2-furyl)acrylate monosaccharide ester derivatives Ia–f were either inactive or only weakly active against the three Gram-positive bacterial strains tested (B. subtilis, S. aureus, S. epidermidis), whereas the menthoxycarbonyl carbonyl monosaccharide
ester derivatives IIa–f exhibited greater degrees of activity, with compound IIe showing remarkably high antibacterial activity. Compound Ib, Ie, IIb and IIc displayed potent in vitro antifungal activities, whereas If and IIff showed promising antifungal activities against all of the microorganisms tested, with compound If exhibiting significantly high activities, which are worthy of further investigation.

Acknowledgments

This work was financially supported by the National Science and Technology Major Project on “Key New Drug Creation and Manufacturing Program” (2009ZX09103-037), the Chinese National Natural Science Foundation (20872099), the Research Program of Sichuan Science and Technology Agency (2008JY0142), and the related Post-Doctoral Research Program.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Wilson, C.L. Microbial Food Contamination, 2nd ed.; CRC Press, Taylor & Francis Group, LLC: Boca Raton, FL, USA, 2007.
2. Louis, B.B.C. A Sugar Ester Process and Its Applications in Calf Feeding and Human Food Additives. In Sucrochemistry; Hickson, J., Ed.; American Chemical Society: Washington, DC, USA, 1977; Chapter 8, pp. 115–120.
3. Garti, N.; Aaerin, A.; Fanun, M. Non-ionic sucrose esters microemulsions for food applications. Colloids Surf. A Physicochem. Eng. Asp. 2000, 164, 27–38.
4. Ahsan, F.; Arnold, J.; Meezan, E.; Pillion, D. Sucrose cocoate, a component of cosmetic preparations, enhances nasal and ocular peptide absorption. Int. J. Pharm. 2003, 251, 195–203.
5. Cázares-Delgadillo, J.; Naik, A.; Kalia, Y.N.; Quintanar-Guerrero, D.; Ganem-Quintanar, A. Skin permeation enhancement by sucrose esters: A pH-dependent phenomenon. Int. J. Pharm. 2005, 297, 204–212.
6. Csóka, G.; Marton, S.; Zelko, R.; Otomo, N.; Antal, I. Application of sucrose fatty acid esters in transdermal therapeutic systems. Eur. J. Pharm. Biopharm. 2007, 65, 233–237.
7. Szűts, A.; Pallagi, E.; Regdon, G., Jr.; Aigner, Z.; Szabó-Révész, P. Study of thermal behaviour of sugar esters. Int. J. Pharm. 2007, 336, 199–207.
8. Chortyk, O.T.; Pomonis, J.G.; Johnson, A.W. Syntheses and characterizations of insecticidal sucrose esters. J. Agric. Food Chem. 1996, 44, 1551–1557.
9. Pouillart, P.; Cerutti, I.; Ronco, G.; Villa, P.; Chany, C. Butyric monosaccharide ester-induced cell differentiation and anti-tumor activity in mice. Importance of their prolonged biological effect for clinical applications in cancer therapy. Int. J. Cancer 1991, 49, 89–95.
10. Calabresse, C.; Venturini, L.; Ronco, G.; Villa, P.; Chomienne, C.; Belpomme, D. Butyric acid and its monosaccharide ester induce apoptosis in the HL-60 cell line. Biochem. Biophys. Res. Commun. 1993, 195, 31–38.
11. Pouillarta, P.; Douilleta, O.; Scappini, B.; Gozzinia, A.; Santinib, V.; Grossi, A.; Pagliai, G.; Strippoli, P.; Rigaccia, L.; Ronco, G.; et al. Regioselective synthesis and biological profiling of butyric and phenylalkylcarboxylic esters derivated from D-mannose and xylitol: influence of alkyl chain length on acute toxicity. *Eur. J. Pharm. Sci.* 1998, 7, 93–106.

12. Santini, V.; Gozzinni, A.; Scappinib, B.; Caporale, R.; Zoccolante, A.; Rigacci, L.; Gelardi, E.; Grossi, A.; Alterinia, R.; Ferrini, P.R. Induction of apoptosis by monosaccharide butyrate stable derivatives in chronic lymphocytic leukemia cells. *Haematologica* 1999, 84, 897–904.

13. Wang, C.J.; Wang, Y.X.; Song, J.Y.; Zhao, J. Study on the synthesis and biological activity of diacid solanesyl galactosyl diesters (in Chinese). *Chin. Chem. Bull.* 2004, 67, 1–4.

14. Ferrer, M.; Soliveri, J.; Plou, F.J.; López-Cortés, N.; Reyes-Duarte, D.; Christensen, M.; Copa-Patiño, J.L.; Ballesteros, A. Synthesis of sugar esters in solvent mixtures by lipases from *Thermomyces lanuginosus* and *Candida antarctica* B, and their antimicrobial properties. *Enzym. Microb. Technol.* 2005, 36, 391–398.

15. Zhou, R.J.; Huang, Y.X.; Zeng, X.; Huang, M.; Zhang, Q.; Lin, P.X.; Zhong, G.J.; Qi, K.Q. Synthesis and antimicrobial activity of Sucrose Methyl Fumarate (in Chinese). *Food Sci. Technol.* 2007, 32, 193–197.

16. Habulin, M.; Šabeder, S.; Knez, Ž. Enzymatic synthesis of sugar fatty acid esters in organic solvent and in supercritical carbon dioxide and their antimicrobial activity. *J. Supercrit. Fluids* 2008, 45, 338–345.

17. Huang, D.; Zhong, K.G.; Zhu, W.F.; Gao, W.D. Ultrasonic synthesis, characteristic and application of sucrose octanoate. *Chin. J. Org. Chem.* 2009, 29, 1951–1955.

18. Řiháková, Z.; Plocková, M.; Filip, V.; Šmidrkal, J. Antifungal activity of lauric acid derivatives against *Aspergillus niger*. *Eur. Food Res. Technol.* 2001, 213, 488–490.

19. Yu, H.; Ning, Z.X. Synthesis and antibacterial activity of α-furan acrylate (in Chinese). *Sci. Technol. Food Ind.* 2005, 26, 145–147.

20. Zhang, Q.; Teng, J.J.; Qiao, Y.H.; Huang, Z.X.; Chen, X.D. Study on synthesis of sucrose α-furylacrylate and its inhibiting activity (in Chinese). *Food Sci. Technol.* 2009, 34, 222–224.

21. Kalemba, D.; Kunicka, A. Antibacterial and antifungal properties of essential oils. *Curr. Med. Chem.* 2003, 10, 813–829.

22. Soković, M.D.; Vukojević, J.; Marin, P.D.; Brkić, D.D.; Vajs, V.; van Griensven, L.J.L.D. Chemical composition of essential oils of *Thymus* and *Mentha* species and their antifungal activities. *Molecules* 2009, 14, 238–249.

23. Soković, M.; Glamočlija, J.; Marin, P.D.; Brkić, D.; van Griensven, L.J.L.D. Antibacterial effects of the essential oils of commonly consumed medicinal Herbs using an *In Vitro* model. *Molecules* 2010, 15, 7532–7546.

24. Rajagopalan, S.; Raman, P.V.A. Furylacrylic Acid. In *Organic Syntheses*; John Wiley & Sons. Inc.: New York, NY, USA, 1963; Volume 3, pp. 425–427.

25. Da Fde Silva, C.; de Souza, M.C.B.V.; Frugulhetti, I.I.P.; Castro, H.C.; de O. Souza, S.L.; de Souza, T.M.L.; Rodrigues, D.Q.; Souza, A.M.T.; Abreu, P.A.; Passamani, F.; et al. Synthesis, HIV-RT inhibitory activity and SAR of 1-benzyl-1H-1,2,3-triazole derivatives of carbohydrates. *Eur. J. Med. Chem.* 2009, 44, 373–383.
26. Li, Z.A.; Liang, X.M.; Wu, F.; Wan, B.S. A convenient resolution method for 1,1'-bi-2-naphthol and 4,4'-dibromo-1,1'-spirobiindane-7,7'-diol with menthyl chloroformate in the presence of TBAB. *Tetrahedron Asymmetry* **2004**, *15*, 665–669.

27. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing*. Document M100-S12; National Committee for Clinical Laboratory Standards: Wayne, PA, USA, 2002.

28. National Committee for Clinical Laboratory Standards. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts*. Approved standard M27-A; National Committee for Clinical Laboratory Standards: Wayne, PA, USA, 1997.

*Sample Availability*: Samples of the compounds Ia–f and IIa–f are available from the authors.

© 2012 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).