JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

ARTICLE

pubs.acs.org/JAFC

Design, Synthesis, and Biological Activities of Milbemycin Analogues

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ABSTRACT: Milbemycins have received considerable interest in agricultural chemistry due to a special action mode, extremely high activity against arachnoide pests, low toxicity to mammals, and environmentally benign characteristics. Two series of novel milbemycin analogues (**4Ia**−**6IIc**) containing alkyl and aryl groups at the 4′- and 13-positions were designed and synthesized by five schemes. These analogues were identified by ^{1}H NMR, ^{13}C NMR, and elemental analysis (or HRMS). Their insecticidal activities against carmine spider mite, oriental armyworm, and black bean aphid were evaluated. The results showed that all of the title compounds had low acaricidal activity against carmine spider mite. However, most of them exhibited good insecticidal activities against oriental armyworm and black bean aphid at a concentration of 200 mg L^{-1}. The most potent substituents of 2,2-dimethylbutanoyl (**4Ib**), phenylacetyl (**4IIm**), and (*Z*)-1-(methoxyimino)-1-phenylacetyl (**4IIn**) exhibited the highest larvicidal activities, and its insecticidal LC_{50} values against oriental armyworm were 0.250, 0.204, and 0.350 mg L^{-1}, while its insecticidal LC_{50} values against black bean aphid were 0.150, 0.070, and 0.120 mg L^{-1}, respectively. These substituents provided some hints for further investigation on structure modification.

KEYWORDS: Milbemycin analogues, alkyl and aryl groups, insecticidal activities

INTRODUCTION

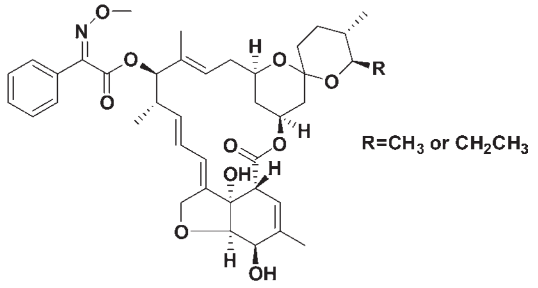
Milbemycins have become one of the most important classes of insecticides, acaricide and anthelmintic.[1−3] The milbemycins are a group of macrolides chemically related to the ivermectins and were first isolated in 1972 from *Streptomyces hygroscopicus* by researchers of Sankyo.[4,5] In contrast to traditional pesticides,[6−8] milbemycin and its derivatives have a special mechanism of opening glutamate-sensitive chloride channels in neurons and myocytes of invertebrates, leading to hyperpolarization of these cells and blocking signal transfer.[9,10] Their broad acaricidal and insecticidal spectra, together with good systemic properties and low toxicity to nontarget organisms such as mammals, vegetables, and fruit trees, make the milbemycins the most rapidly expanding insecticidal class since milbemycin A3/A4 was first introduced in the market.[11] At present, another new structural analogue, 13-(α-methoxyiminophenylacetoxy)milbemycin (lepimectin, Figure 1), excellent in acaricidal, insecticidal, and anthelmintic activities against acarids, insect pests of plants and parasities in animals, has already been brought to the market.[12]

On the other hand, there are no milbemycin analogues that can be used as acaricides and insecticides in the Chinese market at present because of the expensive raw material of milbemycin, which is supplied mainly by Sankyo Co. Ltd. Many methods of using biological fermentation and organic synthesis were carried out to solve this problem. Although the total synthesis of milbemycin was reported,[13] the high cost made it difficult to develop on an industrial scale. The milbemycin analogues exhibit excellent insecticidal activities as insecticides, acaricides, and parasiticides, while ivermectins are valuable as acaricides and insecticides.[14] Importantly, 4′- and 13-substituted milbemycin derivatives[15−19] are valuable as agricultural and horticultural anthelmintics, acaricidal and insecticidal agents, and the protection or derivatization of avermectin at the 5-position has an important effect on the insecticidal activity.[20,21] Inspired by these reports, we noted that the skeleton of the aglycone of ivermectin, the hydrogenation product of avermectin B1a and B1b,[22] was very similar with milbemycins (Figure 2). Also, the cost of ivermectin provided by many pesticide companies in China is low. In a search for novel insecticides with different activity spectra and lower costs, we designed and synthesized two series of novel milbemycin analogues (**4Ia**−**6IIc**) based on ivermectin as the starting material. The insecticidal activities of the target compounds against carmine spider mite, oriental armyworm, and black bean aphid were evaluated, some of them (compounds **4Ib**, **4IIm**, and **4IIn**) exhibited high insecticidal activities against oriental armyworm and black bean aphid, and the median lethal concentrations (LC_{50}) were calculated. The structure−activity relationships (SARs) of some substituents[23−26] are, for the first time, reported in this work.

MATERIALS AND METHODS

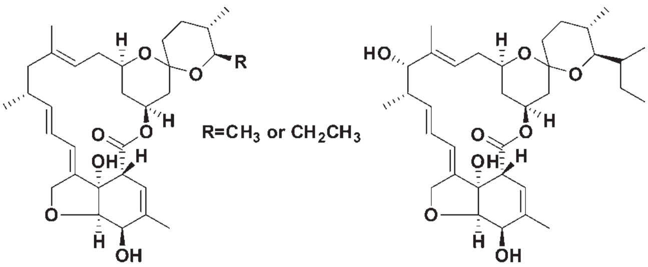
Instruments. ^{1}H NMR (500 MHz) and ^{13}C NMR (100 MHz) spectra were obtained using a Bruker AVANCE III in $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) were given in parts per million (ppm). Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. HRMS data were obtained on a FTICR-MS instrument (Ion-spec7.0T). Measurements of optical rotation at 589 nm and at 20 °C were made using a SEPA-300 spectropolarimeter (Horiba, Ltd., Kyoto, Japan) equipped with a cell with a 10 cm optical path length. Samples were made up in methanol at concentrations of 10−30 mg mL^{-1}. Specific rotations were calculated as $[\alpha]_D = [\alpha]_m/(c \times l)$ where $[\alpha]_m$ is the optical rotation measured, *c* is the concentration in mg mL^{-1}, and *l* is the length of the cell in decimeters (unit, 10^{-1} deg cm^2 g^{-1}). The melting

Received: January 14, 2011
Accepted: March 31, 2011
Revised: March 30, 2011
Published: April 01, 2011



Lipemectin

Figure 1. Chemical structure of lipemectin.



Milbemycin Ivermectin Aglycone

Figure 2. Chemical structures of milbemycin and ivermectin aglycone.

points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. Yields were not optimized. Column chromatographic purification was carried out using silica gel.

General Synthesis. The reagents were all analytically or chemically pure. All anhydrous solvents were dried and purified by standard techniques prior to use. All acyl chlorides were prepared according to the method in the literature.[27]

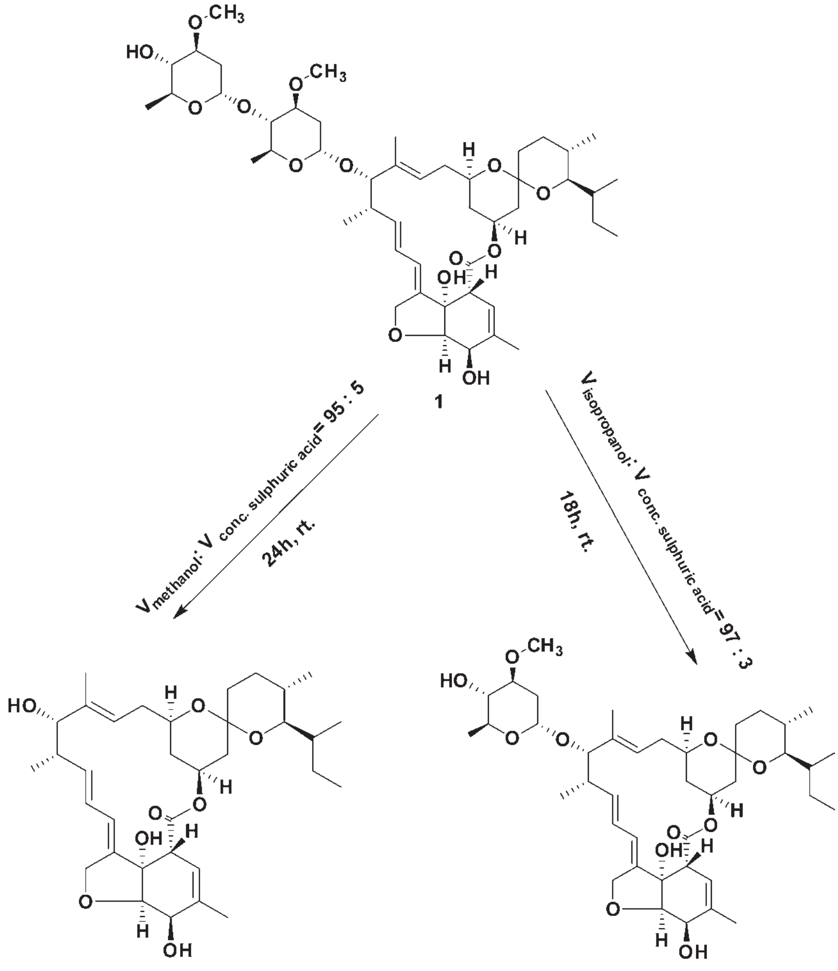
General Synthetic Procedure for 2I and 2II (Scheme 1). Compound **2I** (milbemycin aglycone) was synthesized according to published procedures.[28−31] Ivermectin (30.00 g, 33.70 mmol) was added to a solution of 30 mL of concentrated sulfuric acid in 570 mL of 2-propanol and stirred in an ice bath for 18 h. Then, 750 mL of ethyl ether was added, and the solution was washed with 5% aqueous sodium bicarbonate and water, dried, and concentrated in vacuum to 20.10 g of yellow foam. This was further purified by flash column chromatography on silica gel using a mixture of petroleum ether (60−90 °C), ethyl acetate, and formic acid (100:30:1 by volume) as the eluent to give 18.90 g (62.5%) of **2I** as a faint yellow amorphous solid; mp, 124−125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (m, 1H, H9), 5.69−5.78 (m, 2H, H10, H11), 5.69 (s, 1H, H3), 5.27−5.35 (m, 2H, H15, H19), 4.62 (m, 2H, H8a), 4.26 (m, 1H, H5), 4.10 (s, 1H, 7-OH), 3.99 (s, 1H, H13), 3.93 (d, 1H, J = 6.5 Hz, H6), 3.65 (m, 1H, H17), 3.24 (dd, 1H, J = 2.5 Hz, J = 4.5 Hz, H2), 3.19 (d, 1H, J = 8.0 Hz, H25), 2.50−2.56 (m, 2H, H12, H24), 2.24 (m, 2H, H16), 1.86−2.04 (m, 5H, H4a, H18), 1.24−1.86 (m, 12H, H14a, H20, H26, H27, H22, H23), 1.16 (m, 3H, H12a), 0.79−0.97 (m, 9H, H28, H26a, H24a). HRMS (ESI) m/z calcd for $C_{34}H_{50}O_8$: $(M + Na)^+$, 609.3404; found, 609.3402.

Compound **2II** (milbemycin monosaccharide) was synthesized according to published procedures.[28−31] Ivermectin (30.00 g, 33.70 mmol) was added to a solution of 18 mL of concentrated sulfuric acid in 582 mL of 2-propanol and stirred in an ice bath for 18 h. Then, 750 mL of ethyl ether was added, and the solution was washed with 5% aqueous sodium bicarbonate and water, dried, and concentrated in vacuo to 28.70 g of yellow foam. This was further purified by flash column chromatography on silica gel using a mixture of petroleum ether (60−90 °C), ethyl acetate, and formic acid (100:50:1 by volume) as the eluent to give 25.70 g (85.6%) of **2II** as a white amorphous solid; mp, 158−159 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (m, 1H, H9), 5.72−5.75 (m, 2H, H10, H11), 5.43 (m, 1H, H3), 5.36 (m, 1H, H19), 4.97 (m, 1H, H15), 4.82 (d, 1H, J = 3.5 Hz, H1′), 4.68 (m, 2H, H8a), 4.30 (m, 1H, H5), 3.96−3.97 (m, 3H, H6, H13, 7-OH), 3.86 (m, 1H, H5′), 3.58 (s, 1H, 4′−OH), 3.57−3.72 (m, 2H, H17, H3′), 3.49 (s, 3H, 3′-OCH_3), 3.29 (dd, 1H, J = 2.0 Hz, J = 4.5 Hz, H2), 3.21 (d, 1H, J = 8.0 Hz, H25), 3.15 (t, 1H, J = 9.0 Hz, H4′), 2.50 (m, 1H, H12), 2.18−2.33 (m, 5H, H24, H26, H2′), 1.76−2.00 (m, 5H, H4a, H18), 1.33−1.67 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.15−1.28 (m, 6H, H5′a, H12a), 0.79−0.95 (m, 9H, H28, H26a, H24a). HRMS (ESI) m/z calcd for $C_{41}H_{62}O_{11}$: $(M + Na)^+$, 753.4190; found, 753.4187.

General Synthetic Procedure for 3I and 3II (Schemes 2 and 3). *Synthesis of **3I** [5-O-(tert-Butyldimethylsilyl)milbemycin Aglycone]*[32]. Imidazole (6.80 g, 100 mmol), *N,N*-dimethylpyridin-4-amine (DMAP, 0.12 g, 1.0 mmol), and *tert*-butyldimethylsilyl chloride (TBDMS-Cl, 3.31 g, 22.0 mmol) were added to a solution of aglycone **2I** (5.86 g, 10.0 mmol) in 100 mL of dry dichloromethane. The resulting yellow solution was stirred at room temperature for 6 h and then partitioned between water (100 mL) and dichloromethane (100 mL). The aqueous layer was extracted with dichloromethane (3 × 80 mL), and the combined organic layers were washed with saturated sodium chloride solution (3 × 80 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to a yellow solid. The crude product was purified by flash chromatography on silica gel using a mixture of petroleum ether (60−90 °C), ethyl acetate, and formic acid (100:10:1 by volume) as the eluent to afford 5.70 g (83.60%) of **3I** as a white foamy solid; mp, 134−136 °C; $[\alpha]_D^{20}$ +55.9365 10^{-1} deg cm^2 g^{-1} (c 21 mg mL^{-1}, methanol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.64 (m, 1H, H9), 5.54−5.61 (m, 2H, H10, H11), 5.09−5.23 (m, 3H, H3, H15, H19), 4.41 (m, 2H, H8a), 4.29 (m, 1H, H5), 4.04 (s, 1H, 7-OH), 3.84 (s, 1H, H13), 3.66 (d, 1H, J = 6.5 Hz, H6), 3.51 (m, 1H, H17), 3.20 (dd, 1H, J = 2.0 Hz, J = 4.5 Hz, H2), 3.06 (d, 1H, J = 8.0 Hz, H25), 2.11−2.39 (m, 4H, H12, H16, H24), 1.61−1.90 (m, 5H, H4a, H18), 1.12−1.53 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.02 (m, 3H, H12a), 0.79−0.97 (m, 18H, H28, H26a, H24a, $C(CH_3)_3$), 0.11 (s, 6H, Si(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): 173.76 (C1), 140.27, 138.69, 137.27, 136.47 (C8, C11, C14, C4), 124.79 (C10), 119.29 (C9), 117.32, 117.06 (C3 or C15), 97.41 (C21), 80.03, 77.32, 77.00, 76.69 (C25, C13, C7, C6), 69.39, 68.62, 67.91, 67.19 (C8a, C19, C17, C5), 45.68 (C2), 41.29, 39.90, 36.78 (C12, C20, C18), 35.67, 34.28, 34.08, 33.82 (C2′, C26, C16, C22), 31.15 ($SiC(CH_3)_3$), 28.03, 27.22 (C23, C24), 25.84 ($SiC(CH_3)_3$), 20.27, 20.03, 18.38, 17.78, 17.42, 15.16, 12.42, 12.06 (C27, C4a, C5′a, C12a, C24a, C14a, C26a, C28), −2.00 (2C−$Si(CH_3)_2$).

*Synthesis of **3II** [5-O-(tert-Butyldimethylsilyl)milbemycin Monosaccharide].* Compound **3II** was prepared by the same procedure as **3I** to afford a white solid (6.97 g, 82.30%); mp, 161−162 °C; $[\alpha]_D^{20}$ −12.9167 10^{-1} deg cm^2 g^{-1} (c 20 mg mL^{-1}, methanol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (m, 1H, H9), 5.71−5.73 (m, 2H, H10, H11), 5.30−5.33 (m, 2H, H3, 19H), 4.98 (m, 1H, H15), 4.82 (d, 1H, J = 3.5 Hz, H1′), 4.56 (m, 2H, H8a), 4.43 (m, 1H, H5), 3.97 (m, 1H, H13), 3.82 (m, 1H, H5′), 3.81 (d, 1H, H6), 3.52−3.71 (m, 3H, H17, H3′, 4′-OH), 3.48 (s, 3H, 3′-OCH_3), 3.38 (dd, 1H, J = 2.0 Hz, J = 4.5 Hz, H2), 3.20 (d, 1H, J = 8.0 Hz, H25), 3.15 (t, 1H, J = 9.0 Hz, H4′), 2.50 (m, 1H, H12), 2.17−2.33 (m, 5H, H16, H24, H2′), 1.79−2.05 (m, 5H, H4a, H18), 1.51−1.79 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.14−1.28 (m, 6H, H5′a, H12a), 0.94 (s, 9H, C(CH_3)$_3$), 0.85−0.94 (m, 9H, H28, H26a, H24a), 0.13 (s, 6H, Si(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): 174.04 (C1), 140.08, 137.50, 135.00 (C8, C11, C14, C4), 124.70 (C10), 119.35 (C9), 118.19, 117.19 (C3 or C15), 97.46 (C21), 94.84 (C1′), 81.69, 80.15, 78.27, 77.32, 76.69, 76.23, 76.00 (C3′, C13, C25, C7, C6, C4′, C5′), 69.40, 68.66, 67.97, 67.26 (C8a, C19, C17, C5), 56.42 (3C3′-OCH_3), 45.69 (C2), 41.12, 39.55, 36.78 (C12, C20, C18), 35.75, 35.46, 34.21 (C26, C16, C22), 31.21 ($SiC(CH_3)_3$), 28.04, 27.45 (C23, C24),

Scheme 1. General Synthetic Routes for Milbemycin Aglycone (2I) and Milbemycin Monosaccharide (2II)



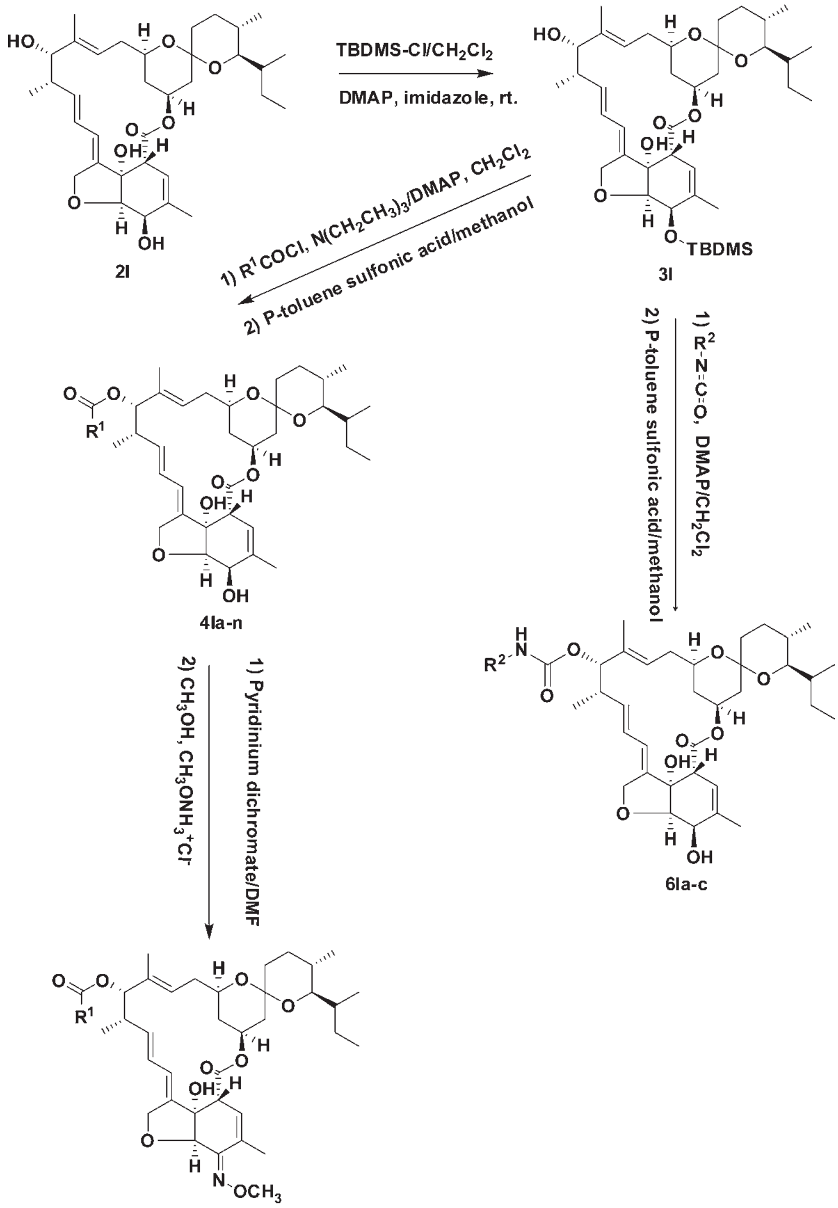
25.85 ($SiC(CH_3)_3$), 20.02, 19.22, 18.40, 17.44, 14.64, 12.54, 11.71 (C27, C4a, C12a, C24a, C14a, C26a, C28), −2.10 ($2C-Si(CH_3)_2$).

General Synthetic Procedure for 4Ia−n, 4Ia−n, 6Ia−c, and 6IIa−c (Schemes 2 and 3). *Synthesis of* ***4IIa*** *(4′-O-Benzoylmilbemycin Monosaccharide).* A solution of benzoyl chloride (0.50 mmol) in dried dichloromethane (5 mL) at 0 °C was added dropwise to a solution of **3II** (0.21 g, 0.25 mmol), triethylamine (0.05 g, 0.50 mmol), and DMAP (0.001 g, 0.01 mmol) in dichloromethane (8 mL). The mixture was stirred at room temperature for 8 h. The reaction mixture was poured into water and extracted with dichloromethane (3 × 10 mL). The organic layer was washed with 5% dilute hydrochloric acid (3 × 10 mL), 5% aqueous sodium bicarbonate (3 × 10 mL), and saturated sodium chloride solution (3 × 10 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to a yellow solid (0.23 g). Then, a deprotection reagent solution of 15 mL of *p*-toluenesulfonic acid−methanol complex ($0.02\ g\ mL^{-1}$) was added dropwise to a solution of the yellow foamy solid (0.23 g) in methanol (10 mL). The mixture was stirred at room temperature for 30 min and then partitioned between ethyl acetate (30 mL) and 5% aqueous sodium bicarbonate (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were washed with saturated sodium chloride solution (3 × 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate (3:1 by volume) as the eluent to afford 0.17 g (80.20%) of **4IIa** as a white solid; mp, 130−133 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (m, 2H, Ar−H), 7.58 (m, 1H, Ar−H), 7.46 (m, 2H, Ar−H), 5.88 (m, 1H, H9), 5.72−5.83 (m, 2H, H10, H11), 5.43 (s, 1H, H3), 5.35 (m, 1H, H19), 5.02 (d, 1H, H15), 4.93 (t, 1H, *J* = 9.5 Hz, 4′H), 4.87 (d, 1H, *J* = 3.5 Hz, H1′), 4.66 (m, 2H, H8a), 4.23 (m, 1H, H5), 4.17 (s, 1H, 7-OH), 4.07 (m,1H, H5′), 3.98−3.99 (m, 2H, H6, H13), 3.80 (m, 1H, H17), 3.67 (m, 1H, H3′), 3.42 (s, 3H, 3′-OCH_3), 3.22−3.30 (m, 2H, H2, H25), 2.54 (m, 1H, H12), 2.17−2.40 (m, 5H, H16, H2′, H24), 1.84−2.00 (m, 5H, H4a, H18), 1.34−1.79 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.18−1.27 (m, 6H, H5′a, H12a), 0.79−1.00 (m, 9H, H28, H26a, H24a). Anal. calcd (%) for $C_{48}H_{66}O_{12}$: C, 69.04; H, 7.97. Found (%): C, 69.23; H, 8.20.

The target compounds **4Ia−n**, **4IIb−n**, **6Ia−c**, and **6IIa−c** were prepared by following the same procedure as for **4IIa**, respectively. The properties and elemental analyses (or HRMS) of compounds **4Ia−n**, **4IIb−n**, **6Ia−c**, and **6IIa−c** are listed in Tables 1 and 2, and their ^{1}H and ^{13}C NMR data are listed in Table 3.

General Synthetic Procedure for 5Ia-e and 5IIa-e (Schemes 2 and 3). *Synthesis of* ***5IIa*** *(5-Methoxyimino-4′-O-(4-chlorobenzoyl)-milbemycin Monosaccharide)*[33]. A solution of **4IIh** [4′-*O*-(4-chlorobenzoyl)milbemycin monosaccharide] (0.22 g, 0.25 mmol) in dried *N*,*N*-dimethylformamide (DMF, 15 mL) was added dropwise to a solution of pyridinium dichromate (PDC, 0.19 g, 0.50 mmol) in dried DMF (15 mL), and the mixture was then stirred at room temperature for 40 min, after which it was concentrated by evaporation under reduced pressure to one-half of its

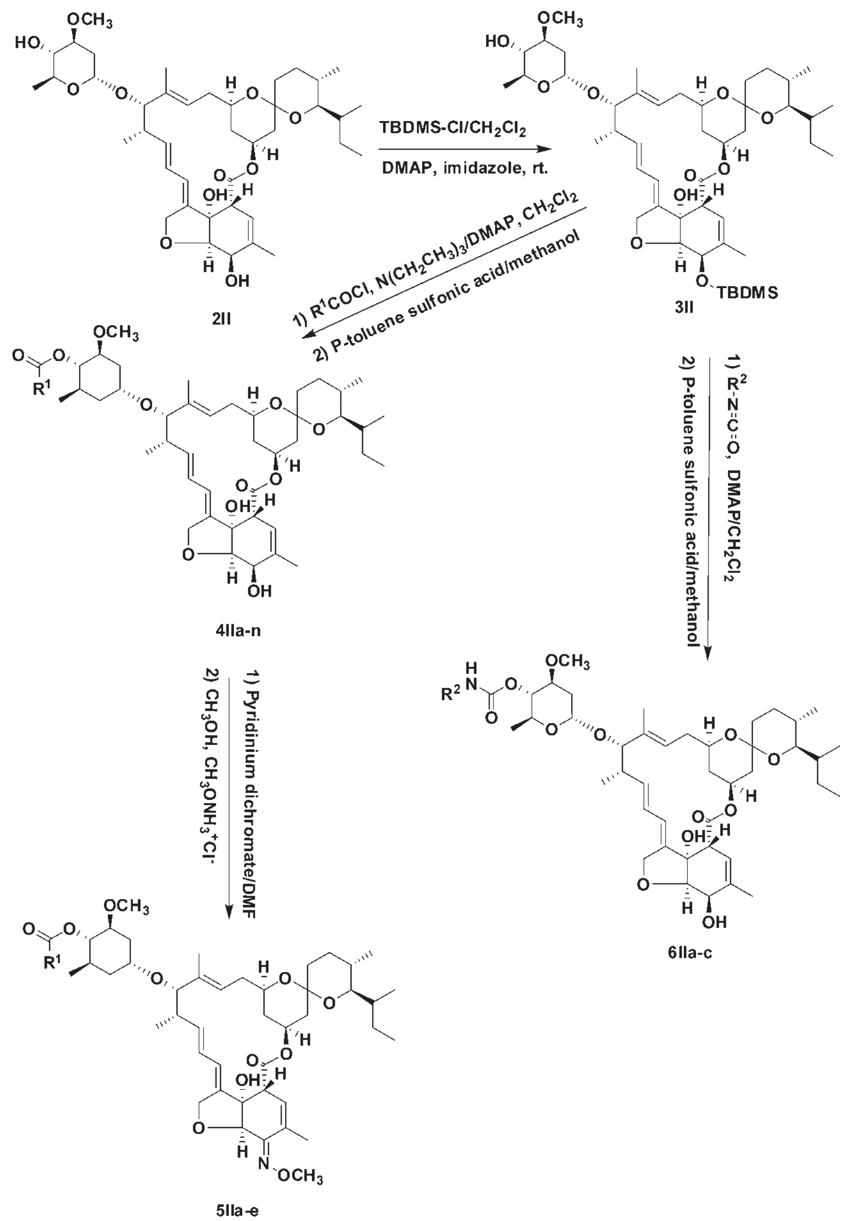
Scheme 2. General Synthetic Routes for the Target Compounds 4Ia−n, 5Ia−e, and 6Ia−c



original volume. This concentrate was diluted with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The extract was washed with diluted hydrochloric acid (5%, 3 × 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate (5:1 by volume) as the eluent to afford 0.19 g (85.60%) of the intermediate of 5-didehydromibemycin **4IIh** as a white foamy oil. Then, a solution of 5-didehydromibemycin **4IIh** (0.22 g, 0.25 mmol) in 10 mL of methanol was added dropwise to a solution of *O*-methylhydroxylammonium chloride (0.04 g, 0.25 mmol) in 10 mL of methanol. The mixture was stirred at room temperature for 1 h, and the reaction mixture was poured into water (30 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with 5% dilute hydrochloric acid (3 × 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography through silica gel eluted with a 5:1 by volume mixture of petroleum ether (60−90 °C) and ethyl acetate, to give 0.18 g (79.1%) of **5IIa** as a yellow solid; mp, 98−100 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.02 (m, 2H, Ar−H), 7.43 (m, 2H, Ar−H), 5.94 (d, 1H, H9), 5.74−5.80 (m, 3H, H3, H10, H11), 5.38 (m, 1H, H19), 5.02 (d, 1H, H15), 4.91 (t, 1H, *J* = 9.5 Hz, H4′), 4.88 (m, 1H, H1′), 4.67 (m, 2H, H8a), 4.58 (s, 1H, 7-OH), 4.08 (m, 1H, H5′), 4.00 (s, 3H, N−OC*H*$_3$), 3.99−4.00 (m, 2H, H6, H13), 3.68−3.84 (m, 2H, H17, H3′), 3.40 (s, 3H, 3′-OC*H*$_3$), 3.41 (t, 1H, *J* = 2.5 Hz, H2), 3.23 (m, 1H, H25), 2.56 (m, 1H, H12), 2.02−2.37 (m, 5H, H16, H2′, H24), 1.76−1.90 (m, 5H, H4a, H18), 1.40−1.69 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.18−1.22 (m, 6H, H5′a, H12a), 0.79−0.97 (m, 9H, H28, H26a, H24a). Anal. calcd (%) for $C_{49}H_{66}ClNO_{12}$: C, 65.65; H, 7.42; N, 1.56. Found (%): C, 65.54; H, 7.42; N, 1.58.

The target compounds **5Ia−e** and **5IIb−e** were prepared by following the same procedure as for **5IIa**, respectively. The properties and elemental analyses (or HRMS) of compounds **5Ia−e** and **5IIb−e** are listed in Table 1, and their ^{1}H NMR data are listed in Table 3.

Scheme 3. General Synthetic Routes for the Target Compounds 4IIa−n, 5IIa−e, and 6IIa−c



Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula.[34] Evaluations are based on a percentage scale of 0−100, in which 0 = no activity and 100 = total kill. The deviation of values was ±5%.

Larvicidal Activity against Carmine Spider Mite (Tetranychus cinnabarinus). The larvicidal activities of compounds **4Ia**−**6IIc** against carmine spider mite were tested according to the reported procedure.[35,36] Each test sample was prepared in acetone at a concentration of 500 mg L^{-1} and diluted to the required concentration with distilled water containing TW-80. Ten fourth-instar mite larvaes were dipped in the diluted solutions of related chemicals for 5 s, and the superfluous liquid was removed, and larvae were kept in a conditioned room. The mortality was evaluated 48 h after treatment. Controls were performed under the same conditions. Each test was performed in triplicate. For comparative purposes, ivermectin was tested under the same condition.

Larvicidal Activity against Oriental Armyworm (Mythimna sepatara). The larvicidal activities of compounds **4Ia**−**6IIc** against oriental armyworm were evaluated by foliar application using the reported procedure.[37] For the foliar armyworm tests, individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution (the test compound was resolved in acetone) and allowed to dry. The dishes were infested with 10 fourth-instar oriental armyworm larvaes. Percentage mortalities were evaluated 2 days after treatment. Each treatment was performed three times. Ivermectin was tested under the same condition.

Larvicidal Activity against Black Bean Aphid (Aphis fabae). The larvicidal activities of compounds **4Ia**−**6IIc** against bean aphid were evaluated according to the reported procedure.[38,39] Bean aphids were dipped according into a slightly modified FAO dip test. The tender shoots of soybean with 10 healthy apterous adult aphids were dipped in

Table 1. Physical Properties and Elemental Analyses of Compounds 4Ia−5IIe

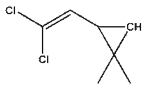
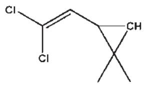
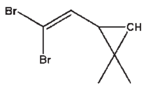
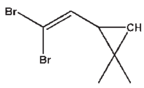
compd.	R^1	yield	m.p.(°C)	Elemental analyses (%, calc.) C	H	N
4Ia	C_6H_5	85.6%	yellow oil	71.38 (71.28)	7.95 (7.88)	/
4Ib	$CH_3CH_2C(CH_3)_2$	81.3%	pale yellow oil	70.36 (70.15)	8.97 (8.83)	/
4IIb	$CH_3CH_2C(CH_3)_2$	67.9%	white solid 144-146	68.31 (68.09)	8.80 (8.75)	/
4Ic	$CH_3C(CH_3)_2CH_2$	83.1%	yellow solid 146-149	70.26 (70.15)	8.75 (8.83)	/
4IIc	$CH_3C(CH_3)_2CH_2$	68.3%	white solid 134-136	68.33 (68.09)	8.93 (8.75)	/
4Id		84.9%	yellow oil	63.86 (63.83)	7.53 (7.65)	/
4IId		68.3%	white solid 134-136	64.81 (64.86)	7.58 (7.52)	/
4Ie		80.1%	pale yellow oil		889.2323 (889.2325)	
4IIe		69.5%	pale yellow solid 137-139	58.43 (58.22)	7.01 (6.98)	/
4If	2,6-dichloro-5-fluoropyridin-3-yl	82.9%	pale yellow solid 138-141	61.70 (61.69)	6.50 (6.47)	1.81 (1.80)
4IIf	2,6-dichloro-5-fluoropyridin-3-yl	78.6%	yellow solid 127-129	61.21 (61.17)	6.83 (6.77)	1.51 (1.52)
4Ig	$CH_3CH{=}CH$	88.6%	pale yellow oil		677.3664 (677.3666)	
4IIg	$CH_3CH{=}CH$	81.1%	pale yellow solid 105-108	67.51 (67.64)	8.40 (8.33)	/
4Ih	4-Cl-C_6H_4	76.6%	pale yellow solid 198-200	67.85 (67.89)	7.54 (7.37)	/
4IIh	4-Cl-C_6H_4	82.6%	white solid 157-159	66.39 (66.31)	7.63 (7.54)	/
4Ii	4-F-C_6H_4	81.6%	yellow solid 159-162	69.70 (69.47)	7.74 (7.54)	/
4IIi	4-F-C_6H_4	76.2%	yellow oil		875.4360 (875.4358)	
4Ij	4-OCH_3-C_6H_4	78.8%	yellow oil	69.97 (69.98)	8.05 (7.83)	/
4IIj	4-OCH_3-C_6H_4	78.1%	pale yellow oil	68.27 (68.03)	7.81 (7.92)	/
4Ik	2-OCH_3-C_6H_4	79.4%	yellow oil		743.3770 (743.3771)	
4IIk	2-OCH_3-C_6H_4	75.3%	yellow oil		887.4556 (887.4558)	
4Il	4-CH_3-C_6H_4	81.5%	pale yellow solid 148-151	71.55 (71.56)	8.09 (8.01)	/
4IIl	4-CH_3-C_6H_4	81.1%	yellow oil		871.4611 (871.4609)	
4Im	$C_6H_5CH_2$	83.2%	pale yellow solid 172-175	71.57 (71.56)	8.04 (8.01)	/
			pale yellow			

Table 1. Continued

compd.	R^1	yield	m.p.(°C)	Elemental analyses (%, calc.)		
				C	H	N
4IIm	$C_6H_5CH_2$	80.3%	solid 161-163	69.59 (69.32)	8.21 (8.07)	/
4In	$C_6H_5C{=}NOCH_3$	79.6%	yellow oil	69.08 (69.05)	7.65 (7.68)	1.85 (1.87)
4IIn	$C_6H_5C{=}NOCH_3$	76.3%	pale yellow solid 120-123	67.33 (67.32)	7.91 (7.80)	1.57 (1.57)
5Ia	4-Cl-C_6H_4	45.6%	yellow oil	67.14 (67.05)	7.19 (7.23)	1.87 (1.86)
5Ib	4-OCH_3-C_6H_4	42.5%	yellow oil	69.30 (69.05)	7.80 (7.68)	1.86 (1.87)
5IIb	4-OCH_3-C_6H_4	77.1%	pale yellow oil		914.4665 (914.4667)	
5Ic	C_6H_5	39.6%	pale yellow oil	70.38 (70.27)	7.95 (7.72)	1.95 (1.95)
5IIc	C_6H_5	77.1%	white solid 116-118	68.28 (68.27)	8.02 (7.83)	1.60 (1.62)
5Id	4-F-C_6H_4	46.1%	yellow oil	68.63 (68.55)	7.51 (7.40)	1.91 (1.90)
5IId	4-F-C_6H_4	77.1%	pale yellow oil		902.4465 (902.4467)	
5Ie	$C_6H_5C{=}NOCH_3$	35.9%	yellow oil		797.3988 (797.3989)	
5IIe	$C_6H_5C{=}NOCH_3$	77.1%	yellow oil	66.69 (66.65)	7.50 (7.68)	3.06 (3.05)

Table 2. Physical Properties and Elemental Analyses of Compounds 6Ia−6IIc

compd	R^2	yield (%)	mp (°C)	elemental analyses (%, calcd)		
				C	H	N
6Ia	C_6H_5	47.8	pale yellow oil		728.3773 (728.3775)	
6IIa	C_6H_5	62.3	pale yellow solid 135−137	67.80. (67.82)	8.05 (7.94)	1.64 (1.65)
6Ib	3-CH_3−C_6H_4	45.3	pale yellow oil		742.3930 (742.3931)	
6IIb	3-CH_3−C_6H_4	55.4	pale yellow oil		886.4720 (886.4718)	
6Ic	4−Cl-C_6H_4	45.6	pale yellow oil	66.61 (66.52)	7.50 (7.35)	1.90 (1.89)
6IIc	4−Cl-C_6H_4	67.1	pale yellow solid 175−178	65.33 (65.18)	7.54 (7.52)	1.60 (1.58)

the diluted solutions of the compounds for 5 s, and the superfluous fluid was removed, and the plants placed in a conditioned room. Mortality was calculated 48 h after treatment. Each treatment was performed three times. Ivermectin was tested under the same condition. The insecticidal activity is summarized in Table 4.

RESULTS AND DISCUSSION

Synthesis. The intermediate **2I** (milbemycin aglycone) and **2II** (milbemycin monosaccharide) were synthesized from ivermectin as shown in Scheme 1. Ivermectin was desugared by 3% concentrated sulfuric acid in isopropanol as solvent to afford compound **2II**, and the yield was 85.6%, which is higher than previously reported.[29] Compound **2I** was prepared by a reaction between ivermectin and 5% concentrated sulfuric acid in methanol as solvent using the same method. Also, it was found that the yields of intermediate **2I** and **2II** were low if the concentration of concentrated sulfuric acid exceeded 10%, and the reaction temperature had an important effect on the yields of intermediate **2I** and **2II** because significant byproducts were produced without in an ice bath. The subsequent reaction protecting the hydroxyl at the 5-position yielded compounds **3I** and **3II** by using *tert*-butylchlorodimethylsilane (TBDMS-Cl) as a protective agent.

To obtain the target compounds **4Ia**−**n** and **4IIa**−**n**, compounds **3I** and **3II** were reacted with newly prepared acyl chlorides using triethylamine and DMAP as acid acceptor and catalyst, and the *t*-butyldimethylsilyl was deprotected using *p*-toluenesulfonic acid−methanol complex to form the target compounds **4Ia**−**n** and **4IIa**−**n**. Then, subsequent oxidation of 5-hydroxymilbymecin analogues **4Ia**−**n** and **4IIa**−**n** using pyridinium dichromate as an oxidant in dried DMF afforded intermediates 5-didehydroxymilbymecin analogues **4Ia**−**n** and **4IIa**−**n**, further oximization with *O*-methylhydroxylammonium chloride yielded compounds **5Ia**−**e** and **5IIa**−**e** as shown in Schemes 2 and 3.

The target compounds **6Ia**−**c** and **6IIa**−**c** were synthesized from **3I** and **3II** as shown in Schemes 2 and 3. Compounds **3I** and **3II** were reacted with aromatic isocyanates using DMAP as a catalyst in dried dichloromethane, and then, subsequent deprotection provided compounds **6Ia**−**c** and **6IIa**−**c**, which were

Table 3. ^{1}H and ^{13}C NMR Data of Compounds 4Ia−6IIc

compd	^{1}H and ^{13}C NMR δ (ppm)
4Ia	^{1}H NMR (500 MHz, $CDCl_3$): 8.12 (m, 2H, Ar−H), 7.61 (m, 1H, Ar−H), 7.50 (m, 2H, Ar−H), 5.92 (m, 1H, H9), 5.84−5.86 (m, 2H, H10, H11), 5.44 (s, 1H, H3), 5.43 (s, 1H, H13), 5.32 (m, 1H, H19), 5.10 (m, 1H, H15), 4.67 (m, 2H, H8a), 4.30 (m, 1H, H5), 4.12 (s, 1H, 7-OH), 3.98 (d, 1H, J = 6.5 Hz, H6), 3.58 (m, 1H, H17), 3.30 (dd, 1H, J = 2.0 Hz, J = 4.5 Hz, H2), 3.11 (d, 1H, J = 8.0 Hz, H25), 2.77 (m, 1H, H12), 2.47 (d, 1H, J = 8.5 Hz, H24), 2.24 (m, 2H, H16), 1.77−2.04 (m, 5H, H4a, H18), 1.26−1.65 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.11 (m, 3H, H12a), 0.73−0.89 (m, 9H, H28, H26a, H24a).
4Ib	^{1}H NMR (500 MHz, $CDCl_3$): 5.84 (m, 1H, H9), 5.67−5.80 (m, 2H, H10, H11), 5.42 (s, 1H, H3), 5.30 (m, 1H, H19), 5.14 (s, 1H, H13), 5.01 (m, 1H, H15), 4.64 (m, 2H, H8a), 4.28 (m, 1H, H5), 4.11 (s, 1H, 7-OH), 3.95 (d, 1H, J = 6.5 Hz, H6), 3.62 (m, 1H, H17), 3.27 (dd, 1H, J = 2.0 Hz, J = 4.5 Hz, H2), 3.18 (d, 1H, J = 8.0 Hz, H25), 2.62 (m, 1H, H12), 2.46 (d, 1H, J = 8.5 Hz, H24), 2.32 (m, 2H, H16), 1.74−2.00 (m, 5H, H4a, H18), 1.30−1.67 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.13 (m, 12H, O=C-$(CH_3)_2CH_2CH_3$, H12a), 0.79−0.96 (m, 9H, H28, H26a, H24a).
4IIb	^{1}H NMR (500 MHz, $CDCl_3$): 5.87 (m, 1H, H9), 5.74−5.77 (m, 2H, H10, H11), 5.43 (s, 1H, H3), 5.34 (m, 1H, H19), 5.01 (m, 1H, H15), 4.83 (m, 1H, H1′), 4.68−4.69 (m, 3H, H8a, H4′), 4.29 (m, 1H, H5), 4.18 (s, 1H, 7-OH), 3.96−3.97 (m, 3H,, H6, H5′, H13), 3.62−3.68 (m, 2H, H17, H3′), 3.39 (s, 3H, 3′-OCH_3), 3.21−3.39 (m, 2H, H2, H25), 2.26−2.55 (m, 6H, H16, H2′, H12, H24), 1.75−2.01 (m, 5H, H4a, H18), 1.33−1.65 (m, 14H, H4a, H20, H26, H27, H22, H23, CH_2CH_3), 1.12−1.20 (m, 15H, O=C$(CH_3)_2$, CH_2CH_3, H5′a, H12a), 0.79−0.94 (m, 9H, H28, H26a, H24a).
4Ic	$[\alpha]_D^{20}$ +133.8551 10^{-1} deg cm^2 g^{-1} (c 34 mg mL^{-1}, methanol). ^{1}H NMR (500 MHz, $CDCl_3$): 5.85 (m, 1H, H9), 5.74−5.81 (m, 2H, H10, H11), 5.42 (s, 1H, H3), 5.31 (m, 1H, H19), 5.30 (s, 1H, H13), 5.08 (m, 1H, H15), 4.64 (m, 2H, H8a), 4.29 (m, 1H, H5), 4.12 (s, 1H, 7-OH), 3.96 (d, 1H, J = 6.5 Hz, H6), 3.63 (m, 1H, H17), 3.27 (dd, 1H, J = 2.0 Hz, J = 4.5 Hz, H2), 3.18 (d, 1H, J = 8.0 Hz, H25), 2.62 (m, 1H, H12), 2.43 (d, 1H, J = 8.5 Hz, H24), 2.23 (m, 2H, H16), 1.74−2.00 (m, 7H, O=CCH_2, H4a, H18), 1.30−1.67 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.13 (m, 3H, H12a), 1.06 (s, 9H, C$(CH_3)_3$), 0.79−0.96 (m, 9H, H28, H26a, H24a).
4IIc	^{1}H NMR (500 MHz, $CDCl_3$): 5.86 (m, 1H, H9), 5.73−5.76 (m, 2H, H10, H11), 5.43 (s, 1H, H3), 5.36 (m, 1H, H19), 5.00 (m, 1H, H15), 4.83 (m, 1H, H1′), 4.67−4.71 (m, 3H, H8a, H4′), 4.30 (m, 1H, H5), 4.17 (s, 1H, 7-OH), 3.93−3.97 (m, 3H, H6, H5′, H13), 3.64−3.67 (m, 2H, H17, H3′), 3.39 (s, 3H, 3′-OCH_3), 3.21−3.29 (m, 2H, H2, H25), 2.23−2.53 (m, 8H, H16, H2′, O=CCH_2, H12, H24), 1.76−1.94 (m, 5H, H4a, H18), 1.33−1.65 (m, 12H, H4a, H20, H26, H27, H22, H23, Ph−CH_2), 1.19−1.22 (m, 6H, H5′a, H12a), 1.07 (s, 9H, C$(CH_3)_3$), 0.78−0.95 (m, 9H, H28, H26a, H24a). ^{13}C NMR (100 MHz, $CDCl_3$): 171.66 (C1), 168.40 (O-C=O), 145.18, 138.76, 138.30, 134.56 (C8, C11, C14, C4), 126.00 (C10), 124.40 (C9), 120.19, 118.25 (C3 or C15), 97.39 (C21), 94.83 (C1′), 82.02, 81.08, 79.38, 77.32, 76.69, 75.79, 75.34 (C25, C13, C3′, C4′ C5′, C7, C6), 69.24, 67.31, 67.16, 66.42 (C8a, C19, C17, C5), 56.74 (C3′-OCH_3), 48.02, 47.31 (C2, CCH_2C=O), 40.39, 39.61, 36.75, 35.75, 35.39 (C12, C2′, C20, C18), 31.21, 30.99, 30.84 (C26, C16, C22), 29.54 ($(CH_3)_3C-CH_2$), 29.22 ($(CH_3)_3C-CH_2$), 28.00, 27.25 (C23, C24), 20.11, 17.56, 17.40, 15.27, 15.15, 12.42, 11.97 (C27, C4a, C12a, C24a, C5′a, C14a, C26a, C28).
4Id	^{1}H NMR (500 MHz, $CDCl_3$): 6.28 (m, 1H, H−C=CCl_2), 5.81 (m, 1H, H9), 5.74−5.78 (m, 2H, H10, H11), 5.42 (s, 1H, H3), 5.31 (m, 1H, H19), 5.29 (s, 1H, H13), 4.95 (m, 1H, H15), 4.64 (m, 2H, H8a), 4.29 (m, 1H, H5), 4.14 (s, 1H, 7-OH), 3.96 (d, 1H, J = 6.5 Hz, H6), 3.65 (m, 1H, H17), 3.27 (dd, 1H, J = 2.0 Hz, J = 4.5 Hz, H2), 3.19 (d, 1H, J = 8.0 Hz, H25), 2.65 (m, 1H, H12), 2.45 (d, 1H, J = 8.5 Hz, H24), 2.23−2.28 (m, 4H, H16, O=C−$CHCH$), 1.74−2.00 (m, 5H, H4a, H18), 1.21−2.06 (m, 18H, H4a, H20, H26, H27, H22, H23, C$(CH_3)_2$), 1.03 (m, 3H, H12a), 0.79−0.97 (m, 9H, H28, H26a, H24a). ^{13}C NMR (100 MHz, $CDCl_3$): 168.59 (C1), 165.31 (O-C=O), 135.24, 132.76, 132.01, 129.74, 129.39, (C8, C11, C=C-CH, C14, C4), 121.73 (C10), 115.21 (C9), 113.08, 112.92 (C3 or C15), 99.14 (C21), 92.50 ($(CH_3)_2C$=CH), 75.29, 74.15, 74.10, 71.88 (C25, C13, C7, C6), 63.65, 63.39, 62.68, 62.13 (C8a, C19, C17, C5), 40.65, 36.25, 33.87, 31.72 (C2, C12, C20, C18), 27.56, 27.49 (C26, C16, C22), 29.11, 26.75, 26.23 (CHCOO, $(CH_3)_2C$=CHCHC, C24), 24.67, 23.94 (C23, CH$C(CH_3)_2$ CH), 23.36, 23.03 ($2(CH_3)_2C(CH)_2$), 17.60, 15.22, 14.90, 12.95, 12.42, 10.31, 9.57 (C27, C4a, C12a, C24a, C14a, C26a, C28).
4IId	^{1}H NMR (500 MHz, $CDCl_3$): 6.27 (m, 1H, H−C=CCl_2), 5.86 (m, 1H, H9), 5.74−5.81 (m, 2H, H10, H11), 5.42 (s, 1H, H3), 5.35 (m, 1H, H19), 4.98 (m, 1H, H15), 4.83 (m, 1H, H1′), 4.65−4.72 (m, 3H, H8a, H4′), 4.29 (m, 1H, H5), 4.20 (s, 1H, 7-OH), 3.96−3.97 (m, 3H,, H6, H5′, H13), 3.67−3.69 (m, 2H, H17, H3′), 3.43 (s, 3H, 3′-OCH3), 3.21−3.28 (m, 2H, H2, H25), 2.24−2.52 (m, 8H, H12, H16, H2′, H24, O=C−$CHCH$), 1.88−1.92 (m, 5H, H4a, H18), 1.34−1.67 (m, 18H, H4a, H20, H26, H27, H22, H23, C$(CH_3)_2$), 1.13−1.17 (m, 6H, H5′a, H12a), 0.78−0.96 (m, 9H, H28, H26a, H24a).
4Ie	^{1}H NMR (500 MHz, $CDCl_3$): 6.70 (m, 1H, H−C=CBr_2), 5.86 (m, 1H, H9), 5.73−5.81 (m, 2H, H10, H11), 5.41 (s, 1H, H3), 5.29 (m, 1H, H19), 5.13 (s, 1H, H13), 4.95 (m, 1H, H15), 4.63 (m, 2H, H8a), 4.29 (m, 1H, H5), 4.18 (s, 1H, 7-OH), 3.96 (d, 1H, J = 6.5 Hz, H6), 3.65 (m, 1H, H17), 3.26 (dd, 1H, J = 2.0 Hz, J = 4.5 Hz, H2), 3.20 (d, 1H, J = 8.0 Hz, H25), 2.65 (m, 1H, H12), 2.58 (d, 1H, J = 8.5 Hz, H24), 2.23−2.28 (m, 4H, H16, O=C−$CHCH$), 1.74−2.00 (m, 5H, H4a, H18), 1.21−2.04 (m, 18H, H4a, H20, H26, H27, H22, H23, C$(CH_3)_2$), 1.04 (m, 3H, H12a), 0.79−0.97 (m, 9H, H28, H26a, H24a); ^{13}C NMR (100 MHz, $CDCl_3$): 173.62 (C1), 169.64 (O-C=O), 140.35, 137.74, 136.88, 134.33, 133.43 (C8, C11, C=C−CH, C14, C4), 125.15 (C10), 120.10 (C9), 118.02, 117.93 (C3 or C15), 97.40 (C21), 89.38 ($(CH_3)_2C$=CH), 80.23, 79.08, 78.71, 77.00 (C25, C13, C7, C6), 68.62, 68.36, 67.65, 67.08 (C8a, C19, C17, C5), 45.62, 41.21, 38.84, 36.75 (C2,, C12, C20, C18), 35.71, 35.55, 35.49 (C26, C16, C22), 34.18, 31.73, 31.19 (CHCOO, $(CH_3)_2C$=CHCHC, C24), 28.37, 27.89 (C23, CH$C(CH_3)_2$ CH), 27.45, 27.36 ($2(CH_3)_2C(CH)_2$), 19.86, 18.70, 17.40, 15.22, 14.55, 12.65, 11.63 (C27, C4a, C12a, C24a, C14a, C26a, C28).
4IIe	^{1}H NMR (500 MHz, $CDCl_3$): 6.32 (m, 1H, H−C=CBr_2), 5.86 (m, 1H, H9), 5.73−5.76 (m, 2H, H10, H11), 5.43 (s, 1H, H3), 5.36 (m, 1H, H19), 4.98 (m, 1H, H15), 4.83−4.85 (m, 2H, H1′, H4′), 4.68 (m, 2H, H8a), 4.30 (m, 1H, H5), 4.17 (s, 1H, 7-OH), 3.95−3.98 (m, 3H,, H6, H5′′, H13), 3.67−3.68 (m, 2H, H17, H3′), 3.41 (s, 3H, 3′-OCH_3), 3.21−3.29 (m, 2H, H2, H25), 2.20−2.65 (m, 8H, H12, H16, H2′, H24, O=C−$CHCH$), 1.88−2.00 (m, 5H, H4a, H18), 1.34−1.67 (m, 18H, H4a, H20, H26, H27, H22, H23, C$(CH_3)_2$), 1.13−1.16 (m, 6H, H5′a, H12a), 0.78−0.95 (m, 9H, H28, H26a, H24a).
4If	$[\alpha]_D^{20}$ +25.4524 10^{-1} deg cm^2 g^{-1} (c 28 mg mL^{-1}, methanol). ^{1}H NMR (500 MHz, $CDCl_3$): 8.04 (s, 1H, Py-H), 5.70−5.87 (m, 3H, H9, H10, H11), 5.42 (s, 2H, H3, H13), 5.30 (m, 1H, H19), 5.07 (m, 1H, H15), 4.65 (m, 2H, H8a), 4.28 (m, 1H, H5), 4.07 (s, 1H, 7-OH), 3.96 (d, 1H, J = 6.5 Hz, H6), 3.60 (m, 1H, H17), 3.27 (dd, 1H, J = 2.0 Hz, J = 4.5 Hz, H2), 3.14 (d, 1H, J = 8.0 Hz, H25), 2.76 (m, 1H, H12), 2.44 (d, 1H, J = 8.5 Hz, H24), 2.26 (m, 2H, H16), 1.71−2.04 (m, 5H, H4a, H18), 1.26−1.66 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.14 (m, 3H, H12a), 0.76−0.88 (m, 9H, H28, H26a, H24a).
4IIf	$[\alpha]_D^{20}$ +31.5882 10^{-1} deg cm^2 g^{-1} (c 17 mg mL^{-1}, methanol). ^{1}H NMR (500 MHz, $CDCl_3$): 7.99 (d, J = 2.5 Hz, 1H, Py-H), 5.87 (m, 1H, H9), 5.74−5.76 (m, 2H, H10, H11), 5.43 (s, 1H, H3), 5.36 (m, 1H, H19), 5.01 (m, 1H, H15), 4.91 (t, 1H, J = 9.5 Hz, H4′), 4.89 (m, 1H, H′), 4.68 (m, 2H, H8a), 4.29 (m, 1H, H5), 4.08 (m,1H, H5′), 3.96- 3.97 (m, 2H,, H6, H13), 3.83 (m, 1H, H17), 3.69 (m, 1H, H3′), 3.42 (s, 3H, 3′-OCH_3), 3.22−3.29 (m, 2H, H2, H25), 2.56 (m, 1H, H12), 2.31−2.37 (m, 5H, H16, H2′, H24), 1.87−2.02 (m, 5H, H4a, H18), 1.42−2.01 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.18−1.24 (m, 6H, H5′a, H12a), 0.79−0.96 (m, 9H, H28, H26a, H24a).

Table 3. Continued

compd	^{1}H and ^{13}C NMR δ (ppm)
4Ig	^{1}H NMR (500 MHz, CDCl$_3$): 7.02 (qd, 1H, *J* = 16.5 Hz, *J* = 9.0 Hz, O═C−CH═C*H*CH$_3$), 5.88−5.93 (m, 2H, O═C−C*H*=CHCH$_3$, H9), 5.69−5.78 (m, 2H, H10, H11), 5.69 (s, 1H, H3), 5.27−5.35 (m, 2H, H15, H19), 4.62 (m, 2H, H8a), 4.26 (m, 1H, H5), 4.10 (s, 1H, 7-OH), 3.99 (s, 1H, H13), 3.93 (d, 1H, *J* = 6.5 Hz, H6), 3.65 (m, 1H, H17), 3.24 (dd, 1H, *J* = 2.5 Hz, *J* = 4.5 Hz, H2), 3.19 (d, 1H, *J* = 8.0 Hz, H25), 2.50−2.56 (m, 2H, H12, H24), 2.24 (m, 2H, H16), 1.86−2.04 (m, 5H, H4a, H18), 1.24−1.86 (m, 15H, H4a, O═C−CH═CHC*H*$_3$, H20, H26, H27, H22, H23), 1.16 (m, 3H, H12a), 0.79−0.97 (m, 9H, H28, H26a, H24a).
4IIg	^{1}H NMR (500 MHz, CDCl$_3$): 7.03 (qd, 1H, *J* = 16.5 Hz, *J* = 9.0 Hz, O═C−CH═C*H*CH$_3$), 5.87−5.93 (m, H, O═C−C*H*═CHCH$_3$, H9), 5.73−5.77 (m, 2H, H10, H11), 5.43 (s, 1H, H3), 5.36 (m, 1H, H19), 4.98 (m, 1H, H15), 4.83 (m, 1H, H1′), 4.75 (t, 1H, *J* = 9.5 Hz, H4′), 4.68 (m, 2H, H8a), 4.30 (m, 1H, H5), 4.18 (s, 1H, 7-OH), 3.94−3.98 (m, 3H,, H6, H5′, H13), 3.67−3.71 (m, 2H, H17, H3′), 3.41 (s, 3H, 3′-OC*H*$_3$), 3.23−3.30 (m, 2H, H2, H25), 2.56 (m, 1H, H12), 1.72−1.92 (m, 8H, H4a, H18, O═C−CH═CHC*H*$_3$), 1.36−1.67 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.13−1.17 (m, 6H, H5′a, H12a), 0.78−0.95 (m, 9H, H28, H26a, H24a).
4Ih	^{1}H NMR (500 MHz, CDCl$_3$): 8.04 (m, 2H, Ar−H), 7.47 (m, 2H, Ar−H), 5.92 (m, 1H, H9), 5.78−5.88 (m, 2H, H10, H11), 5.44 (m, 1H, H3), 5.40 (s, 1H, H13), 5.32 (m, 1H, H19), 5.04 (m, 1H, H15), 4.67 (m, 2H, H8a), 4.30 (m, 1H, H5), 4.13 (s, 1H, 7-OH), 3.98 (d, 1H, *J* = 6.5 Hz, H6), 3.57 (m, 1H, H17), 3.29 (dd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, H2), 3.11 (d, 1H, *J* = 8.0 Hz, H25), 2.75 (m, 1H, H12), 2.45 (d, 1H, *J* = 8.5 Hz, H24), 2.24 (m, 2H, 1H6), 1.86−2.04 (m, 5H, H4a, H18), 1.24−1.86 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.16 (m, 3H, H12a), 0.74−0.91 (m, 9H, H28, H26a, H24a). ^{13}C NMR (100 MHz, CDCl$_3$): 172.33 (C1), 165.06 (O−*C*═O), 139.59, 138.77, 137.95, 136.79, 134.92 (C8, C11, C-4-Ar, C14, C4), 131.15, 128.75, 128.35 (2C-2,6-Ar, 2C-3,5-Ar, C-1-Ar), 124.78 (C10), 121.77 (C9), 118.37 (C3 or C15), 97.47 (C21), 81.84, 80.69, 77.00, 75.89 (C25, C13, C7, C6), 69.84, 69.30, 67.15, 66.52 (C8a, C19, C17, C5), 46.53 (C2), 41.12, 39.76, 36.85 (C12, C20, C18), 35.67, 35.38, 34.89 (C26, C16, C22), 31.17, 27.28 (C23, C24), 20.13, 17.47, 17.40, 15.48, 15.15, 12.44, 12.03 (C27, C4a, C12a, C24a, C14a, C26a, C28).
4IIh	^{1}H NMR (500 MHz, CDCl$_3$): 8.02 (m, 2H, Ar−H), 7.29 (m, 2H, Ar−H), 5.89 (m, 1H, H9), 5.76 (m, 2H, H10, H11), 5.44 (s, 1H, H3), 5.36 (m, 1H, H19), 5.02 (d, 1H, H15), 4.91 (t, 1H, *J* = 9.5 Hz, H4′), 4.88 (d, 1H, *J* = 3.5 Hz, H1′), 4.68 (m, 2H, H8a), 4.30 (m, 1H, H5), 4.07 (m, 1H, H5′), 3.97−3.99 (m, 2H, H6, H13), 3.81 (m, 1H, H17), 3.69 (m, 1H, H3′), 3.40 (s, 3H, 3′-OC*H*$_3$), 3.22−3.30 (m, 2H, H2, H25), 2.56 (m, 1H, H12), 2.17−2.35 (m, 5H, H16, H2′, H24), 1.73−1.87 (m, 5H, H4a, H18), 1.34−1.68 (m, 12H, H4a, H20, H26, H27, H22, H23), 0.93−1.00 (m, 6H, H5′a, H12a), 0.79−0.93 (m, 9H, H28, H26a, H24a).
4Ii	^{1}H NMR (500 MHz, CDCl$_3$): 8.13 (m, 2H, Ar−H), 7.17 (m, 2H, Ar−H), 5.92 (m, 1H, H9), 5.82−5.89 (m, 2H, H10, H11), 5.44 (m, 1H, H3), 5.40 (s, 1H, H13), 5.34 (m, 1H, H19), 5.08 (m, 1H, H15), 4.70 (m, 2H, H8a), 4.31 (m, 1H, H5), 4.13 (s, 1H, 7-OH), 3.98 (d, 1H, *J* = 6.5 Hz, H6), 3.51 (m, 1H, H17), 3.30 (dd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, H2), 3.12 (d, 1H, *J* = 8.0 Hz, H25), 2.75 (m, 1H, H12), 2.47 (d, 1H, *J* = 8.5 Hz, H24), 2.24 (m, 2H, H16), 1.88−2.04 (m, 5H, H4a, H18), 1.24−1.83 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.12 (m, 3H, H12a), 0.74−0.97 (m, 9H, H28, H26a, H24a). ^{13}C NMR (100 MHz, CDCl$_3$): 172.40 (C1), 164.94 (O−*C*═O), 138.82, 137.95, 136.84, 134.93, 132.38 (C8, C11, C-4-Ar, C14, C4), 131.87, 127.51, 127.21 (2C-2,6-Ar, 2C-3,5-Ar, C-1-Ar), 126.14 (C10), 124.77 (C9), 115.68, 115.47 (C3 or C15), 97.47 (C21), 81.81, 80.67, 77.32, 75.92 (C25, C13, C7, C6), 69.87, 69.32, 67.15, 66.56 (C8a, C19, C17, C5), 46.54 (C2), 41.12, 39.76, 36.88 (C12, C20, C18), 35.69, 35.39, 34.90 (C26, C16, C22), 31.18, 27.29 (C23, C24), 20.14, 17.50, 17.42, 15.51, 15.18, 12.46, 12.05 (C27, C4a, C12a, C24a, C14a, C26a, C28).
4IIi	^{1}H NMR (500 MHz, CDCl$_3$): 8.10 (m, 2H, Ar−H), 7.13 (m, 2H, Ar−H), 5.89 (m, 1H, H9), 5.75−5.79 (m, 2H, H10, H11), 5.44 (s, 1H, H3), 5.31 (m, 1H, H19), 5.02 (d, 1H, H15), 4.91 (t, 1H, *J* = 9.5 Hz, H4′), 4.87 (m, 1H, H1′), 4.69 (m, 2H, H8a), 4.29 (m, 1H, H5), 4.20 (s, 1H, 7-OH), 4.07 (m,1H, H5′), 3.98- 3.99 (m, 2H,, H6, H13), 3.81 (m, 1H, H17), 3.68 (m, 1H, H3′), 3.40 (s, 3H, 3′-OC*H*$_3$), 2.56 (m, 1H, H12), 3.22−3.31 (m, 2H, H2, H25), 2.29−2.43 (m, 5H, H16, H2′, H24), 1.88−2.00 (m, 5H, H4a, H18), 1.35−1.65 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.18−1.26 (m, 6H, H5′a, H12a), 0.79−0.95 (m, 9H, H28, H26a, H24a).
4Ij	^{1}H NMR (500 MHz, CDCl$_3$): 8.07 (m, 2H, Ar−H), 6.98 (m, 2H, Ar−H), 5.91 (m, 1H, H9), 5.83−5.85 (m, 2H, H10, H11), 5.44 (s, 1H, H3), 5.48 (s, 1H, H13), 5.32 (m, 1H, H19), 5.09 (m, 1H, H15), 4.67 (m, 2H, H8a), 4.29 (m, 1H, H5), 4.10 (s, 1H, 7-OH), 3.98 (d, 1H, *J* = 6.5 Hz, H6), 3.89 (s, 3H, Ar-OC*H*$_3$), 3.58 (m, 1H, H17), 3.29 (dd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, H2), 3.12 (d, 1H, *J* = 8.0 Hz, H25), 2.76 (m, 1H, H12), 2.52 (d, 1H, *J* = 8.5 Hz, H24), 2.24 (m, 2H, H16), 1.77−2.04 (m, 5H, H4a, H18), 1.26−1.64 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.10 (m, 3H, H12a), 0.74−0.97 (m, 9H, H28, H26a, H24a).
4IIj	^{1}H NMR (500 MHz, CDCl$_3$): 8.04 (dd, 2H, *J* = 2.0 Hz, *J* = 6.0 Hz, Ar−H), 6.94 (dd, 2H, *J* = 2.0 Hz, *J* = 6.0 Hz, Ar−H), 5.89 (m, 1H, H9), 5.76−5.80 (m, 2H, H10, H11), 5.44 (s, 1H, H3), 5.36 (m, 1H, H19), 5.01 (m, 1H, H15), 4.90 (t, *J* = 9.5 Hz, 1H, H4′), 4.87 (m, 1H, H1′), 4.69 (m, 2H, H8a), 4.31 (m, 1H, H5), 4.21 (s, 1H, 7-OH), 4.06 (m, 1H, 5′-H), 3.97- 3.98 (m, 2H, H6, H13), 3.87 (s, 3H, Ar-OC*H*$_3$), 3.83 (m, 1H, H17), 3.67 (m, 1H, H3′), 3.44 (s, 3H, 3′-OC*H*$_3$), 3.22−3.30 (m, 2H, H2, H25), 2.56 (m, 1H, H12), 2.28−2.59 (m, 5H, H16, H2′, H24), 1.75−2.17 (m, 5H, H4a, H18), 1.43−2.05 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.18−1.26 (m, 6H, H5′a, H12a), 0.79−0.96 (m, 9H, H28, H26a, H24a).
4Ik	^{1}H NMR (500 MHz, CDCl$_3$): 7.86 (m, 2H, Ar−H), 7.45 (m, 2H, Ar−H), 5.86 (m, 1H, H9), 5.80−5.85 (m, 2H, H10, H11), 5.61 (s, 1H, H13), 5.38 (s, 1H, H3), 5.30 (m, 1H, H19), 5.16 (m, 1H, H15), 4.58 (m, 2H, H8a), 4.29 (m, 1H, H5), 4.22 (d, 1H, *J* = 6.5 Hz, H6), 4.08 (s, 1H, 7-OH), 3.89 (s, 3H, Ar-OC*H*$_3$), 3.60 (m, 1H, H17), 3.47 (dd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, H2), 3.13 (d, 1H, *J* = 8.0 Hz, H25), 2.71 (m, 1H, H12), 2.52 (d, 1H, *J* = 8.5 Hz, H24), 2.26 (m, 2H, H16), 1.78−2.04 (m, 5H, H4a, H18), 1.26−1.66 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.13 (m, 3H, H12a), 0.75−0.87 (m, 9H, H28, H26a, H24a).
4IIk	^{1}H NMR (500 MHz, CDCl$_3$): 7.78 (d, 1H, Ar−H), 7.47 (d, 2H, Ar−H), 6.98 (d, 2H, Ar−H), 5.87 (m, 1H, H9), 5.71−5.81 (m, 2H, H10, H11), 5.43 (s, 1H, H3), 5.34 (m, 1H, H19), 5.01 (m, 1H, H15), 4.92 (t, 1H, *J* = 9.5 Hz, H4′), 4.87 (m, 1H, H1′), 4.64 (m, 2H, H8a), 4.29 (m, 1H, H5), 4.11 (s, 1H, 7-OH), 4.08 (m, 1H, H5′), 3.96−3.98 (m, 2H, H6, H13), 3.90 (s, 3H, Ar-OC*H*$_3$), 3.69−3.83 (m, 2H, H17, H3′), 3.45 (s, 3H, 3′-OC*H*$_3$), 3.22−3.30 (m, 2H, H2, H25), 2.56 (m, 1H, H12), 2.17−2.35 (m, 5H, H16, H2′, H24), 1.73−1.87 (m, 5H, H4a, H18), 1.34−1.68 (m, 12H, H4a, H20, H26, H27, H22, H23), 0.93−0.96 (m, 6H, H5′a, H12a), 0.79−0.93 (m, 9H, H28, H26a, H24a).
4Il	^{1}H NMR (500 MHz, CDCl$_3$): 8.01 (m, 2H, Ar−H), 7.28 (m, 2H, Ar−H), 5.92 (m, 1H, H9), 5.84−5.86 (m, 2H, H10, H11), 5.44 (s, 1H, H3), 5.40 (s, 1H, H13), 5.33 (m, 1H, H19), 5.11 (m, 1H, H15), 4.67 (m, 2H, H8a), 4.31 (m, 1H, H5), 4.12 (s, 1H, 7-OH), 3.98 (d, 1H, *J* = 6.5 Hz, H6), 3.56 (m, 1H, H17), 3.30 (dd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, H2), 3.11 (d, 1H, *J* = 8.0 Hz, H25), 2.74 (m, 1H, H12), 2.51 (d, 1H, *J* = 8.5 Hz, H24), 2.45 (s, 3H, Ar−C*H*$_3$), 2.23 (m, 2H, H16), 1.77−2.04 (m, 5H, H4a, H18), 1.31−1.64 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.11 (m, 3H, H12a), 0.74−0.89 (m, 9H, H28, H26a, H24a).
4IIl	^{1}H NMR (500 MHz, CDCl$_3$): 7.98 (m, 2H, Ar−H), 7.26 (m, 2H, Ar−H), 5.90 (m, 1H, H9), 5.72−5.89 (m, 2H, H10, H11), 5.44 (s, 1H, H3), 5.36 (m, 1H, H19), 5.02 (m, 1H, H15), 4.92 (t, 1H, *J* = 9.5 Hz, H4′), 4.87 (d, 1H, *J* = 3.5 Hz, H1′), 4.69 (m, 2H, H8a), 4.29 (m, 1H, H5), 4.29 (s, 1H, 7-OH), 4.07 (m, 1H, 5′-H), 3.98−3.99 (m, 2H, H6, H13), 3.69−3.83 (m, 2H, H17, H3′), 3.41 (s, 3H, 3′-OC*H*$_3$), 3.23−3.30 (m, 2H, H2, H25), 2.56 (m, 1H, H12), 2.43 (s, 3H, Ar−C*H*$_3$), 2.28−2.44 (m, 5H, H16, H2′, H24), 1.76−1.88 (m, 5H, H4a, H18), 1.37−1.55 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.18−1.21 (m, 6H, H5′a, H12a), 0.79−0.96 (m, 9H, H28, H26a, H24a).

Table 3. Continued

compd	^{1}H and ^{13}C NMR δ (ppm)
4Im	^{1}H NMR (500 MHz, $CDCl_3$): 8.08 (m, 2H, Ar−H), 7.60 (m, 1H, Ar−H), 7.50 (m, 2H, Ar−H), 5.93 (m, 1H, H9), 5.84−5.86 (m, 2H, H10, H11), 5.44 (s, 1H, H3), 5.42 (s, 1H, H13), 5.32 (m, 1H, H19), 5.01 (m, 1H, H15), 4.67 (m, 2H, H8a), 4.31 (m, 1H, H5), 3.99 (d, 1H, *J* = 6.5 Hz, H6), 3.58 (m, 1H, H17), 3.30 (dd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, H2), 3.11 (d, 1H, *J* = 8.0 Hz, H25), 2.76 (m, 1H, H12), 2.51 (d, 1H, *J* = 8.5 Hz, H24), 2.23 (m, 2H, H16), 1.77−2.04 (m, 5H, H4a, H18), 1.24−1.65 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.11 (m, 3H, H12a), 0.73−0.89 (m, 9H, H28, H26a, H24a).
4IIm	^{1}H NMR (500 MHz, $CDCl_3$): 8.09 (m, 2H, Ar−H), 7.57 (m, H, Ar−H), 7.46 (m, 2H, Ar−H), 5.91 (m, 1H, H9), 5.73−5.89 (m, 2H, H10, H11), 5.43 (s, 1H, H3), 5.37 (m, 1H, H19), 5.01 (m, 1H, H15), 4.94 (t, 1H, *J* = 9.5 Hz, H4′), 4.88 (m, 1H, H1′), 4.69 (m, 2H, H8a), 4.30 (m, 1H, H5), 4.21 (s, 1H, 7-OH), 4.11 (m,1H, H5′), 3.97- 4.10 (m, 2H,, H6, H13), 3.82 (m, 1H, H17), 3.67 (m, 1H, H3′), 3.41 (s, 3H, 3′-OCH_3), 3.23−3.30 (m, 2H, H2, H25), 2.56 (m, 1H, H12), 2.30−2.51 (m, 5H, H16, H2′, H24), 1.76−1.88 (m, 5H, H4a, H18), 1.37−1.65 (m, 14H, H4a, H20, H26, H27, H22, H23, CH_2−Ar), 1.185−1.22 (m, 6H, H5′a,H12a), 0.79−0.96 (m, 9H, H28, H26a, H24a).
4In	^{1}H NMR (500 MHz, $CDCl_3$): 7.59 (m, 2H, Ar−H), 7.36 (m, 3H, Ar−H), 5.63−5.82 (m, 3H, H9, H10, H11), 5.44 (s, 1H, H3), 5.39 (s, 1H, H13), 5.23 (m, 1H, H19), 5.17 (m, 1H, H15), 4.65 (m, 2H, H8a), 4.26 (m, 1H, H5), 4.09 (s, 1H, 7-OH), 4.02 (s, 3H, N−OCH_3), 3.92 (d, 1H, *J* = 6.5 Hz, H6), 3.55 (m, 1H, H17), 3.22 (dd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, H2), 3.11 (d, 1H, *J* = 8.0 Hz, H25), 2.70 (m, 1H, H12), 2.48 (d, 1H, *J* = 8.5 Hz, H24), 2.25 (m, 2H, H16), 1.71−2.04 (m, 5H, H4a, H18), 1.26−1.66 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.11 (m, 3H, H12a), 0.76−0.88 (m, 9H, H28, H26a, H24a).
4IIn	^{1}H NMR (500 MHz, $CDCl_3$): 7.70 (m, 2H, Ar−H), 7.37 (m, 3H, Ar−H), 5.83 (m, 1H, H9), 5.67−5.75 (m, 2H, H10, H11), 5.41 (s, 1H, H3), 5.35 (m, 1H, H19), 5.01 (m, 1H, H15), 4.92 (t, 1H, *J* = 9.5 Hz, H4′), 4.87 (m, 1H, H1′), 4.60 (m, 2H, H8a), 4.25 (m, 1H, H5), 4.17 (s, 1H, 7-OH), 4.11 (s, 3H, N−OCH_3), 4.02 (m,1H, 5′-H), 3.91- 4.10 (m, 2H,, H6, H13), 3.68−3.67 (m, 2H, H17, H3′), 3.42 (s, 3H, 3′-OCH_3), 3.22−3.27 (m, 2H, H2, H25), 2.56 (m, 1H, H12), 2.30−2.54 (m, 5H, H16, H2′, H24), 1.88−2.00 (m, 5H, H4a, H18), 1.44−1.70 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.12−1.36 (m, 6H, H5′a, H12a), 0.79−0.96 (m, 9H, H28, H26a, H24a).
5Ia	^{1}H NMR (500 MHz, $CDCl_3$): 8.05 (m, 2H, Ar−H), 7.47 (m, 2H, Ar−H), 5.98 (m, 1H, H9), 5.80−5.91 (m, 3H, H3, H10, H11), 5.41 (s, 1H, H13), 5.37 (m, 1H, H19), 5.05 (m, 1H, H15), 4.69 (m, 2H, H8a), 4.59 (s, 1H, 7-OH), 4.00 (m, 4H, N−OCH_3, H6), 3.58 (m, 1H, H17), 3.34 (dd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, H2), 3.12 (d, 1H, *J* = 8.0 Hz, H25), 2.77 (m, 1H, H12), 2.24 (m, 2H, H16), 1.78−2.82 (m, 5H, H24, H4a, H18), 1.34−1.65 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.11 (m, 3H, H12a), 0.74−0.88 (m, 9H, H28, H26a, H24a).
5Ib	^{1}H NMR (500 MHz, $CDCl_3$): 8.01 (m, 2H, Ar−H), 7.00 (m, 2H, Ar−H), 5.92 (m, 1H, H9), 5.76−5.89 (m, 3H, H3, H10, H11), 5.37 (s, 1H, H13), 5.34 (m, 1H, H19), 5.10 (m, 1H, H15), 4.66 (m, 2H, H8a), 4.54 (s, 1H, 7-OH), 4.00 (s, 3H, N−OCH_3), 3.88 (s, 1H, H6), 3.58 (m, 1H, H17), 3.43 (s, 3H, Ar-OCH_3), 3.37 (dd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, H2), 3.12 (d, 1H, *J* = 8.0 Hz, H25), 2.76 (m, 1H, H12), 2.24 (m, 2H, H16), 1.76−2.27 (m, 6H, H24, H4a, H18), 1.28−1.66 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.12 (m, 3H, H12a), 0.76−0.93 (m, 9H, H28, H26a, H24a).
5IIb	^{1}H NMR (500 MHz, $CDCl_3$): 8.04 (m, 2H, Ar−H), 6.94 (m, 2H, Ar−H), 5.94 (m, 1H, H9), 5.76−5.81 (m, 3H, H3, H10, H11), 5.76 (m, 1H, H19), 5.02 (d, 1H, H15), 4.90 (t, 1H, *J* = 9.5 Hz, H4′), 4.87 (m, 1H, H1′), 4.69 (m, 2H, H8a), 4.57 (s, 1H, 7-OH), 4.08 (m, 1H, H5′), 4.00 (s, 3H, N−OCH_3), 3.93−3.99 (m, 2H, H6, H13), 3.89 (s, 3H, Ar-OCH_3), 3.69−3.84 (m, 2H, H17, H3′), 3.41 (s, 3H, 3′-OCH_3), 3.39 (t, 1H, *J* = 2.5 Hz, H2), 3.27 (m, 1H, H25), 2.54 (m, 1H, H12), 2.28−2.38 (m, 5H, H16, H2′, H24), 1.74−2.00 (m, 5H, H4a, H18), 1.39−1.68 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.18−1.22 (m, 6H, H5′a, H12a), 0.79−0.96 (m, 9H, H28, H26a, H24a).
5Ic	^{1}H NMR (500 MHz, $CDCl_3$): 8.12 (m, 2H, Ar−H), 7.60 (m, 1H, Ar−H), 7.50 (m, 2H, Ar−H), 5.98 (m, 1H, H9), 5.85−5.87 (m, 2H, H10, H11), 5.80 (m, 1H, H3), 5.42 (s, 1H, H13), 5.39 (m, 1H, H19), 5.10 (m, 1H, H15), 4.70 (m, 2H, H8a), 4.59 (s, 1H, 7-OH), 4.00 (s, 3H, N−OCH_3), 3.93 (s, 1H, H6), 3.58 (m, 1H, H17), 3.40 (dd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, H2), 3.11 (d, 1H, *J* = 8.0 Hz, H25), 2.78 (m, 1H, H12), 2.24 (m, 2H, H16), 1.79−2.26 (m, 6H, H24, H4a, H18), 1.33−1.65 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.12 (m, 3H, H12a), 0.74−0.88 (m, 9H, H28, H26a, H24a).
5IIc	^{1}H NMR (500 MHz, $CDCl_3$): 8.09 (m, 2H, Ar−H), 7.57 (m, 1H, Ar−H), 7.46 (m, 2H, Ar−H), 5.94 (m, 1H, H9), 5.76−5.80 (m, 3H, H3, H10, H11), 5.41 (m, 1H, H19), 5.02 (m, 1H, H15), 4.93 (t, 1H, *J* = 9.5 Hz, H4′), 4.87 (m, 1H, H1′), 4.67−4.76 (m, 2H, H8a), 4.57 (s, 1H, 7-OH), 4.11 (m, 1H, H5′), 4.00 (s, 3H, N−OCH_3), 3.97−3.99 (m, 2H, H6, H13), 3.67−3.85 (m, 2H, H17, H3′), 3.42 (s, 3H, 3′-OCH_3), 3.38 (t, 1H, *J* = 2.5 Hz, H2), 3.22 (m, 1H, H25), 2.54 (m, 1H, H12), 2.28−2.38 (m, 5H, H16, H2′, H24), 1.74−2.00 (m, 5H, H4a, H18), 1.39−1.68 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.18−1.22 (m, 6H, H5′a, H12a), 0.79−0.96 (m, 9H, H28, H26a, H24a).
5Id	^{1}H NMR (500 MHz, $CDCl_3$): 8.13 (m, 2H, Ar−H), 7.17 (m, 2H, Ar−H), 5.96 (m, 1H, H9), 5.79−5.90 (m, 3H, H3, H10, H11), 5.39 (m, 2H, H13, H19), 5.04 (m, 1H, H15), 4.69 (m, 2H, H8a), 4.58 (s, 1H, 7-OH), 4.00 (m, 4H, N−OCH_3), 3.93 (s, 1H, H6), 3.57 (m, 1H, H17), 3.40 (dd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, H2), 3.11 (d, 1H, *J* = 8.0 Hz, H25), 2.77 (m, 1H, H12), 2.25 (m, 2H, H16), 1.76−2.56 (m, 5H, H24, H4a, H18), 1.26−1.65 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.11 (m, 3H, H12a), 0.74−0.90 (m, 9H, H28, H26a, H24a).
5IId	^{1}H NMR (500 MHz, $CDCl_3$): 8.10 (d, 2H, Ar−H), 7.13 (d, 2H, Ar−H), 5.96 (m, 1H, H9), 5.77−5.82 (m, 3H, H3, H10, H11), 5.41 (m, 1H, H19), 5.02 (d, 1H, H15), 4.91 (t, 1H, H4′), 4.87 (m, 1H, H1′), 4.66 (m, 2H, H8a), 3.99−4.10 (m,3H, H6, H17, H13), 4.07 (s, 3H, N−OCH_3), 3.69−3.84 (m, 2H, H5′, H3′), 3.41 (s, 3H, 3′-OCH_3), 3.39 (t, 1H, H2), 3.22 (m, 1H, H25), 2.28−2.38 (m, 5H, H16, H2′, H24), 1.74−2.00 (m, 5H, H4a, H18), 1.39−1.68 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.17−1.22 (m, 6H, H5′a, H12a), 0.79−0.97 (m, 9H, H28, H26a, H24a).
5Ie	^{1}H NMR (500 MHz, $CDCl_3$): 7.60 (m, 2H, Ar−H), 7.35 (m, 3H, Ar−H), 5.85 (m, 1H, H9), 5.76−5.80 (m, 2H, H10, H11), 5.64 (m, 1H, H3), 5.45 (s, 1H, H13), 5.28 (m, 1H, H19), 5.17 (m, 1H, H15), 4.64 (m, 2H, H8a), 4.54 (s, 1H, 7-OH), 4.01 (s, 3H, N−OCH_3), 3.98 (s, 3H, N−OCH_3), 3.93 (s, 1H, H6), 3.55 (m, 1H, H17), 3.33 (dd, 1H, *J* = 2.0 Hz, *J* = 4.5 Hz, H2), 3.11 (d, 1H, *J* = 8.0 Hz, H25), 2.70 (m, 1H, H12), 2.28 (m, 2H, H16), 1.70−2.02 (m, 6H, H24, H4a, H18), 1.23−1.69 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.12 (m, 3H, H12a), 0.76−0.97 (m, 9H, H28, H26a, H24a).
5IIe	^{1}H NMR (500 MHz, $CDCl_3$): 7.70 (m, 2H, Ar−H), 7.37 (m, 3H, Ar−H), 5.92 (m, 1H, H9), 5.70−5.82 (m, 3H, H3, H10, H11), 5.42 (m, 1H, H19), 5.02 (m, 1H, H15), 4.93 (t, 1H, *J* = 9.5 Hz, H4′), 4.87 (m, 1H, H1′), 4.68 (m, 2H, H8a), 4.57 (s, 1H, 7-OH), 4.11 (m, 1H, H5′), 4.01 (s, 3H, N−OCH_3), 4.00 (s, 3H, N−OCH_3), 3.97−3.99 (m, 2H, H6, H13), 3.67−3.85 (m, 2H, H17, H3′), 3.42 (s, 3H, 3′-OCH_3), 3.38 (t, 1H, *J* = 2.5 Hz, H2), 3.22 (m, 1H, H25), 2.54 (m, 1H, H12), 2.28−2.38 (m, 5H, H16, H2′, H24), 1.74−2.00 (m, 5H, H4a, H18), 1.39−1.68 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.16−1.24 (m, 6H, H5′a, H12a), 0.78−0.97 (m, 9H, H28, H26a, H24a).

Table 3. Continued

compd	^{1}H and ^{13}C NMR δ (ppm)
6Ia	^{1}H NMR (500 MHz, $CDCl_3$): 7.58 (s, 1H, O═C−N*H*-Ar), 7.44 (m, 1H, Ar−H), 7.32 (m, 2H, Ar−H), 7.08 (m, 2H, Ar−H), 5.67−5.85 (m, 2H, H9, H10, H11), 5.41 (s, 1H, H3), 5.30 (m, 1H, H19), 5.02 (m, 1H, H15), 4.64 (m, 2H, H8a), 4.31 (m, 1H, H5), 4.21 (s, 1H, H13), 3.96 (d, 1H, *J* = 6.5 Hz, H6), 3.65 (m, 1H, H17), 3.15−3.29 (m, 2H, H2, H25), 2.59 (m, 1H, H12), 2.16−2.31 (m, 5H, H16, H2′, H24), 1.72−1.88 (m, 5H, H4a, H18), 1.21−1.68 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.14−1.63 (m, 6H, H5′a, H12a), 0.79−0.98 (m, 9H, H28, H26a, H24a).
6IIa	$[\alpha]_D^{20}$ +8.2029 10^{-1} deg cm^2 g^{-1} (*c* 23 mg mL^{-1}, methanol). ^{1}H NMR (500 MHz, $CDCl_3$): 8.02 (s, 1H, O═C−N*H*−Ar), 7.45 (m, 1H, Ar−H), 7.31 (m, 2H, Ar−H), 7.09 (m, 2H, Ar−H), 5.78−5.84 (m, 2H, H9, H10, H11), 5.43 (s, 1H, H3), 5.30 (m, 1H, H19), 5.02 (d, 1H, H15), 4.84 (d, 1H, *J* = 3.5 Hz, H1′), 4.68 (m, 2H, H8a), 4.60 (t, 1H, *J* = 9.5 Hz, H4′), 4.31 (m, 1H, H5), 3.97−3.98 (m, 3H, 5′-H, H6, H13), 3.64−3.72 (m, 1H, H17, H3′), 3.44 (s, 3H, 3′-OCH_3), 3.21−3.30 (m, 2H, H2, H25), 2.65 (m, 1H, H12), 2.17−2.35 (m, 5H, H16, H2′, H24), 1.73−1.87 (m, 5H, H4a, H18), 1.21−1.68 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.15−1.63 (m, 6H, H5′a, H12a), 0.79−0.96 (m, 9H, H28, H26a, H24a). ^{13}C NMR (100 MHz, $CDCl_3$): 173.85 (C1), 169.54 (O−C═O), 139.69, 138.51, 137.79, 137.00, 136.84, 134.79, 130.15. (C8, C-1-Ar, C11, C4, C14, 2C-3,5-Ar, C-4-Ar), 124.78 (C10), 122.56 (C9), 120.35 (2C-2,6-Ar), 118.32, 118.00 (C3 or C15), 97.45 (C21), 81.76, 80.33, 78.98, 77.31 (C25, C13, C7, C6), 68.44, 67.67, 67.11, 66.33 (C8a, C19, C17, C5), 56.96 (3C3′−OCH_3), 45.62 (C2), 41.09, 39.64, 36.90 (C12, C20, C18), 35.69, 35.38, 34.64 (C26, C16, C22), 31.16, 27.26 (C23, C24), 20.17, 19.98, 17.40, 15.13, 15.02, 12.44, 12.01 (C27, C4a, C12a, C24a, C14a, C26a, C28).
6Ib	^{1}H NMR (500 MHz, $CDCl_3$): 7.56 (s, 1H, O═C−N*H*−Ar), 7.13 (m, 3H, Ar−H), 7.05 (m, 1H, Ar−H), 5.68−5.86 (m, 2H, H9, H10, H11), 5.41 (s, 1H, H3), 5.31 (m, 1H, H19), 5.01 (m, 1H, H15), 4.65 (m, 2H, H8a), 4.32 (m, 1H, H5), 4.21 (s, 1H, H13), 3.98 (d, 1H, *J* = 6.5 Hz, H6), 3.65 (m, 1H, H17), 3.12−3.29 (m, 2H, H2, H25), 2.58 (m, 1H, H12), 2.15−2.32 (m, 5H, H16, H2′, H24), 1.71−1.88 (m, 5H, H4a, H18), 1.21−1.68 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.15−1.61 (m, 6H, H5′a, H12a), 0.78−0.98 (m, 9H, H28, H26a, H24a).
6IIb	^{1}H NMR (500 MHz, $CDCl_3$): 7.58 (s, 1H, O═C−N*H*−Ar), 7.12 (m, 3H, Ar−H), 7.01 (m, 1H, Ar−H), 5.87 (m, 1H, H9), 5.73−5.76 (m, 2H, H9, H10, H11), 5.43 (s, 1H, H3), 5.30 (m, 1H, H19), 5.02 (m, 1H, H15), 4.83 (d, 1H, *J* = 3.5 Hz, H1′), 4.61−69 (m, 3H, H8a, H4′), 4.30 (m, 1H, H5), 4.20 (s, 1H, 7-OH), 3.97−3.98 (m, 3H, H5′, H6, H13), 3.64−3.72 (m, 1H, H17, H3′), 3.44 (s, 3H, 3′-OCH_3), 3.21−3.30 (m, 2H, H2, H25), 2.65 (m, 1H, H12), 2.17−2.35 (m, 5H, H16, H2′, H24), 1.73−1.87 (m, 5H, H4a, H18), 1.21−1.68 (m, 15H, H4a, H20, H26, H27, H22, H23, Ar−CH_3), 1.13−1.65 (m, 6H, H5′a, H12a), 0.78−0.96 (m, 9H, H28, H26a, H24a).
6Ic	^{1}H NMR (500 MHz, $CDCl_3$): 7.38 (m, 2H, Ar−H), 7.26 (m, 2H, Ar−H), 6.96 (s, 1H, O═C−N*H*−Ar), 5.65−5.82 (m, 2H, H9, H10, H11), 5.42 (s, 1H, H3), 5.30 (m, 1H, H19), 5.08 (m, 1H, H15), 4.64 (m, 2H, H8a), 4.31 (m, 1H, H5), 4.22 (s, 1H, H13), 3.97 (d, 1H, *J* = 6.5 Hz, H6), 3.65 (m, 1H, H17), 3.12−3.28 (m, 2H, H2, H25), 2.65 (m, 1H, H12), 2.17−2.35 (m, 5H, H16, H2′, H24), 1.73−1.87 (m, 5H, H4a, H18), 1.21−1.68 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.14−1.63 (m, 6H, H5′a, H12a), 0.78−0.97 (m, 9H, H28, H26a, H24a).
6IIc	$[\alpha]_D^{20}$ +6.4706 10^{-1} deg cm^2 g^{-1} (*c* 17 mg mL^{-1}, methanol). ^{1}H NMR (500 MHz, $CDCl_3$): 7.37 (m, 2H, Ar−H), 7.26 (m, 2H, Ar−H), 6.79 (s, 1H, O═C−N*H*−Ar), 5.87 (m, 1H, H9), 5.73−5.76 (m, 2H, H10, H11), 5.43 (s, 1H, H3), 5.30 (m, 1H, H19), 5.02 (d, 1H, H15), 4.84 (d, 1H, *J* = 3.5 Hz, H1′), 4.68 (m, 2H, H8a), 4.60 (t, 1H, *J* = 9.5 Hz, H4′), 4.31 (m, 1H, H5), 3.97−3.98 (m, 3H, H5′, H6, H13), 3.64−3.72 (m, 1H, H17, H3′), 3.44 (s, 3H, 3′-OCH_3), 3.21−3.30 (m, 2H, H2, H25), 2.65 (m, 1H, H12), 2.17−2.35 (m, 5H, H16, H2′, H24), 1.73−1.87 (m, 5H, H4a, H18), 1.21−1.68 (m, 12H, H4a, H20, H26, H27, H22, H23), 1.15−1.63 (m, 6H, H5′a, H12a), 0.79−0.96 (m, 9H, H28, H26a, H24a).

prepared by following the same procedure as for **4Ia−n** and **4IIa−n**, respectively.

SAR. *Larvicidal Activity against Carmine Spider Mite (T. cinnabarinus).* Table 4 shows the larvicidal activities of compounds **4Ia−6IIc** and ivermectin against carmine spider mite. Table 4 shows that most compounds had no or poor larvicidal activities, and few compounds exhibited similar larvicidal activities as the corresponding parent compound, ivermectin. For example, Table 4 shows that the larvicidal activities of compounds **4Ib** (2,2-dimethyl butanoylmilbemycin aglycone), **6Ia** (*N*-phenylformacylamidemilbemycin aglycone), and **6Ib** (*N*-*m*-tolylformacylamidemilbemycin aglycone) against carmine spider mite at 0.006 mg L^{-1} were 60.7, 55.2, and 56.6%, respectively, as compared with 57.9% mortality of ivermectin at the same concentration. However, other compounds such as **4Ia**, **4If**, **4IIm**, and **4IIn** showed no or poor larvicidal activities against carmine spider mite, which suggested that the 2,2-dimethylbutanoyl, *N*-phenylformoxyl, and *N*-*p*-tolylformoxyl groups at 13-position would have great influence on the activities. It was reported that the ether groups at 5-position of avermectin monosaccharide analogues had 100% effectiveness in killing larva after 2 days at 0.8 ppm,[40] but the **5II** analogues with methoxyimino-substituted at 5-position had poor insecticidal activities against carmine spider mite at 0.006 ppm after 2 days, that maybe 0.006 ppm of the test concentration was not high and suitable or the difference of the substituents at 5-position has a primary effect in the insecticidal activity.

Larvicidal Activity against Oriental Armyworm (M. sepatara). Table 4 shows that the target compounds **4Ia−6IIc** displayed different larvicidal activities against oriental armyworm. On the whole, the larvicidal activities of substituents at 4′- and 13- positions (**4Ia−4IIn** and **6Ia−6IIc**) against oriental armyworm and black bean aphid were much better than that of methoxylamine at 5-position (**5Ia−5IIe**), which displayed no larvicidal activity against oriental armyworm. The results in Table 4 indicated that compounds **4Ib** (2,2-dimethylbutanoylmilbemycin aglycone), **4IIm** (phenylacetylmilbemycin monosaccharide), and **4IIn** [(*Z*)-1-(methoxyimino)-1- phenylacetylmilbemycin monosaccharide] displayed the larvicidal activities against oriental armyworm 10−100 times better than that of other target compounds but was similar to ivermectin, as the larvicidal LC_{50} values of compounds **4Ib**, **4IIm**, **4IIn**, and ivermectin against oriental armyworm were 0.250, 0.204, 0.350, and 0.190 mg L^{-1}, respectively. The results in Table 4 showed that there exist steric and electric effects on the larvicidal activities. The activity was higher with the insertion of a methylene between the phenyl and the formoxyl; for example, compounds **4IIm** and **4IIn** exhibited higher larvicidal activities against oriental armyworm than compounds **4Ia**, **4IIa**, and **4Ih−4IIl**. The larvicidal activities of compounds **4Ia**, **4Ie**, **4Ig**, **4Ih**, **6Ib**, and **4IIn** against oriental armyworm increased subsequently with the electron density as the carbon atom connecting the oxygen atom

Table 4. Larvicidal Activities against Carmine Spider Mite, Oriental Armyworm, and Black Bean Aphid of Compounds 4Ia−6IIc and Ivermectin

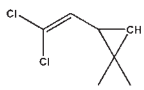
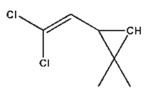
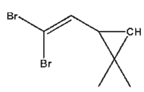
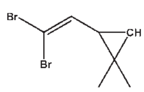
Compd.	R^1 or R^2	Toxicities against Carmine Spider Mite		Toxicities against Oriental Armyworm		Toxicities against Black Bean Aphid	
		concentration (mg L^{-1})	larvicidal activity (%)	concentration (mg L^{-1})	larvicidal activity (%)	concentration (mg L^{-1})	larvicidal activity (%)
4Ia	C_6H_5	0.006	31.1	200	88.6	200	76.5
4IIa	C_6H_5	0.006	24.8	10	100	10	100
				2.5	100	2.5	100
				0.625	38.8	0.625	86.3
4Ib	$CH_3CH_2C(CH_3)_2$	0.006	60.7	1	96.9	2	92.9
				0.5	75.2	1	85.4
				0.25	60.0	0.5	68.2
				0.125	16.7	0.25	57.6
				0.0625	0	0.125	45.5
				0.03125	0	0.0625	38.0
				10	100	10	100
4IIb	$CH_3CH_2C(CH_3)_2$	0.006	39.6	2.5	83.6	2.5	100
				0.625	0	0.625	89.1
4Ic	$CH_3C(CH_3)_2CH_2$	0.006	35.5	200	88.9	200	76.5
4IIc	$CH_3C(CH_3)_2CH_2$	0.006	34.2	10	88.6	10	80.2
				2.5	51.2	2.5	30.2
				0.625	0	0.625	0
4Id		0.006	31.7	10	6.7	200	87.9
				2.5	6.4		
				0.625	3.3		
4IId		0.006	11.8	200	87.2	200	92.3
4Ie		0.006	32.1	200	100	200	72.9
4IIe		0.006	13.4	200	83.3	200	100
4If	2,6-dichloro-5-fluoropyridin-3-yl	0.006	7.7	200	50.9	10	66.9
						2.5	38.2
						0.625	8.3
4IIf	2,6-dichloro-5-fluoropyridin-3-yl	0.006	16.5	200	0	200	88.2
4Ig	$CH_3CH{=}CH$	0.006	40.9	200	76.8	200	73.5
4IIg	$CH_3CH{=}CH$	0.006	25.1	200	88.9	200	100
4Ih	4-Cl-C_6H_4	0.006	26.9	10	100	200	87.9
				2.5	24.9		
				0.625	0		
4IIh	4-Cl-C_6H_4	0.006	32.3	10	93.9	200	100
				2.5	16.7		
				0.625	0		
4Ii	4-F-C_6H_4	0.006	47.4	200	83.3	200	56.8
4IIi	4-F-C_6H_4	0.006	9.9	10	55.8	10	100

Table 4. Continued

Compd.	R^1 or R^2	Toxicities against Carmine Spider Mite		Toxicities against Oriental Armyworm		Toxicities against Black Bean Aphid	
		concentration (mg L^{-1})	larvicidal activity (%)	concentration (mg L^{-1})	larvicidal activity (%)	concentration (mg L^{-1})	larvicidal activity (%)
				2.5	16.7	2.5	100
				0.625	0	0.625	97.1
4Ij	4-OCH_3-C_6H_4	0.006	34.8	200	100	200	75.2
4IIj	4-OCH_3-C_6H_4	0.006	9.7	200	100	200	92.3
4Ik	2-OCH_3-C_6H_4	0.006	19.5	10	97.0	200	68.6
				2.5	77.3		
				0.625	19.7		
4IIk	2-OCH_3-C_6H_4	0.006	16.4	200	98.2	200	100
4Il	4-CH_3-C_6H_4	0.006	27.1	200	87.6	200	56.4
4IIl	4-CH_3-C_6H_4	0.006	4.5	200	89.7	200	92.5
4Im	$C_6H_5CH_2$	0.006	44.9	200	89.9	200	62.7
4IIm	$C_6H_5CH_2$	0.006	14.3	1	100	1	100
				0.5	90.2	0.5	86.7
				0.25	60.3	0.25	65.8
				0.125	20.5	0.125	31.2
				0.0625	10.1	0.0625	3.3
				0.03125	0	0.03125	0
4In	$C_6H_5C{=}NOCH_3$	0.006	41.5	200	75.5	200	86.3
4IIn	$C_6H_5C{=}NOCH_3$	0.006	38.7	1	100	1	100
				0.5	80.0	0.5	70.0
				0.25	30.2	0.25	34.2
				0.125	6.3	0.125	3.3
				0.0625	0	0.0625	0
				0.03125	0	0.03125	0
5Ia	4-Cl-C_6H_4	0.006	10.2	200	0	200	0
5IIa	4-Cl-C_6H_4	0.006	6.2	200	0	200	8.7
5Ib	4-OCH_3-C_6H_4	0.006	5.9	200	0	200	6.3
5IIb	4-OCH_3-C_6H_4	0.006	6.8	200	0	200	9.3
5Ic	C_6H_5	0.006	9.2	200	0	200	7.2
5IIc	C_6H_5	0.006	8.6	200	0	200	5.9
5Id	4-F-C_6H_4	0.006	19.8	200	0	200	0
5IId	4-F-C_6H_4	0.006	11.1	200	0	200	11.2
5Ie	$C_6H_5C{=}NOCH_3$	0.006	49.0	200	0	200	6.5
5IIe	$C_6H_5C{=}NOCH_3$	0.006	36.6	200	0	200	15.9
6Ia	C_6H_5	0.006	55.2	200	100	200	96.8
6IIa	C_6H_5	0.006	45.2	200	100	200	97.6
6Ib	3-CH_3-C_6H_4	0.006	56.6	10	98.6	10	100
				2.5	76.7	2.5	98.9
				0.625	43.2	0.625	86.1
6IIb	3-CH_3-C_6H_4	0.006	49.2	10	100	10	100
				2.5	98.6	2.5	100
				0.625	56.3	0.625	88.5
6Ic	4-Cl-C_6H_4	0.006	30.8	200	88.5	200	67.8
6IIc	4-Cl-C_6H_4	0.006	29.8	200	77.9	200	90.3
Ivermectin		0.006	57.9	1	100	2	100
				0.5	90.9	1	93.5
				0.25	66.7	0.5	89.1
				0.125	29.1	0.25	74.1
				0.0625	6.4	0.125	66.3
				0.03125	0	0.0625	53.6

in the ester chain decreased. Although the electron density as the carbon atom connecting to the oxygen atom in the ester chain of compound **4Ib** (2,2-dimethylbutanoylmilbemycin aglycone) was higher than that of compound **4Ic** (3,3-dimethylbutanoylmilbemycin aglycone), and compound **4Ib** displayed better larvicidal activities against oriental armyworm than compound **4Ic**. Compound **4IIm** (phenylacetylmilbemycin monosaccharide) displayed excellent larvicidal activity against oriental armyworm, whereas compound **6Ia** exhibited poor larvicidal activity against oriental armyworm when the carbon atom connecting to the oxygen atom in the ester chain was replaced by a nitrogen atom. However, compounds **4If** and **4IIf** showed lower larvicidal activities against oriental armyworm than lepimectin, due to the difference of the alkyl group at the 26-position. Interestingly, most of the milbemycin monosaccharide analogues displayed comparable or higher larvicidal activities against oriental armyworm than milbemycin aglycone analogues.

Larvicidal Activity against Black Bean Aphid (A. fabae). As shown in Table 4 that compounds **4Ia**−**6IIc** displayed similar SAR against black bean aphid. In particular, the larvicidal activities of compounds **4Ib**, **4IIi**, **4IIm**, **4IIn**, **6Ib**, and **6IIb** against black bean aphid were 10−100 times better than that of other compounds. The LC_{50} values of compounds **4Ib**, **4IIm**, **4IIn**, and ivermectin against black bean aphid were 0.150, 0.070, 0.120, and 0.06 mg L^{-1}, respectively. Compound **4IIm** (phenylacetylmilbemycin monosaccharide) exhibited the best larvicidal activity against black bean aphid, and its insecticidal LC_{90} value at 48 h was 0.742 mg L^{-1}, which was similar to ivermectin (LC_{90} value at 48 h was 0.646 mg L^{-1}). The larvicidal activity of commercial Emamectin against black bean aphid was tested under the same condition, and the LC_{90} value at 96 h was 19.9 mg L^{-1};[41] thus, compound **4IIm** exhibited much better larvicidal activity against black bean aphid than emamectin.

In summary, two series of novel milbemycin analogues (**4Ia**−**6IIc**) containing alkyl and aryl groups at the 4′- and 13-positions were designed and synthesized, and their structures were identified by ^{1}H NMR, ^{13}C NMR, and elemental analysis (or HRMS). The larvicidal activities against carmine spider mite, oriental armyworm, and black bean aphid were evaluated. The results showed that all of the title compounds had low acaricidal activity against carmine spider mite. However, most of them exhibited good insecticidal activities against oriental armyworm and black bean aphid. The SAR indicated that larger substituents increased larvicidal activities. In particular, the most potent substituents of 2,2-dimethylbutanoyl (**4Ib**), phenylacetyl (**4IIm**), and (*Z*)-1-(methoxyimino)-1-phenylacetyl (**4IIn**) exhibited high larvicidal activities. Compound **4IIm** exhibited the best larvicidal activity against black bean aphid (LC_{50} = 0.070 mg L^{-1}), and most of the milbemycin monosaccharide analogues displayed comparable or higher larvicidal activities against oriental armyworm and black bean aphid than the milbemycin aglycone analogues.

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Funding Sources

We acknowledge the support of Important Technology Special Topic Project of Zhejiang Province (2008C02007-3).

ACKNOWLEDGMENT

We thank the National Engineering Research Center for Agrochemicals for the test of biological activity.

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