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Article

Synthesis and antibacterial activity of a series novel 5,7-diisoprenyloxyflavone derivatives

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In the present study, a series of novel 5,7-diisoprenyloxyflavone derivatives were designed, synthesized, and evaluated for their antibacterial activity. Most of these compounds displayed significant antibacterial effects against Gram-positive bacteria, especially against strains of multidrug-resistant clinical isolates. Compounds **4c**, **4g**, **4i**, **4j**, **4k**, **4l**, **4n**, **4q** and **4t** showed high levels of antimicrobial activity against *Staphylococcus aureus* RN4220 with minimum inhibitory concentrations of 4.0-20 μM. Compound **4k** showed the most potent activity among these compounds against all multidrug-resistant clinical isolates tested. Unfortunately, none of the compounds were active against Gram-negative bacteria at the doses of 24-164 μM.

Keywords: Flavonoids. Synthesis. Isoprenyloxyflavones. Antibacterial activity.

INTRODUCTION

According to the World Health Organization (WHO), infectious diseases are responsible for a significant proportion of deaths worldwide, with antimicrobial agents considered "miracle drugs" that are the leading weapons in the treatment of infectious diseases. However, owing to the development of antimicrobial resistance and the appearance of drug-resistant strains among community-acquired infections, there is evidence of the rapid global spread of resistant clinical isolates, with many current clinically efficacious antimicrobial agents becoming less effective. Therefore, the treatment of bacterial infections remains an important and challenging therapeutic problem (Chen *et al*., 2010). Ongoing drug discovery is necessary for identifying effective, safe, and affordable cures for an expanding spectrum of human ailments. As the treatment of these diseases has serious safety and efficacy issues, the exploration of new antibacterial agents is highly desirable.

Malaria caused by protozoan parasites of the genus plasmodium is a major cause of mortality and morbidity, especially in tropical countries. More than three billion people worldwide have been affected by this deadly disease (Verlinden, Louw, Birkholtz, 2016). The increasing resistance of malarial parasites to available drugs is a major reason for these large statistics, despite many reports on the antimalarial efficacy of flavonoids (Friedman, 2007; Kozyra *et al*., 2015). The development of novel antimicrobial drugs is still in demand owing to increasing incidence of infection caused by the rapid development of microbial resistance to most known antibiotics.

Flavonoids are natural products found throughout nature that have broad physiological activities, low toxicity, and few side effects (Harborne, Williams, 2000). Flavonoids are a diverse class of polyphenolic phytochemicals found in various vegetables and fruits, and provide color, aroma, flavor, and nutritional and health benefits (Karakaya, Sedef, 1999). Many flavonoids extracted from plants have been reported to show various biological effects, including anticancer, antioxidant, antibacterial, anti-inflammatory, and antidepressant effects (Ahmed, Khan, Saeed, 2015; Xie *et al*., 2014; Kulbacka *et al*., 2016; Yao *et al*., 2014; Keshari *et al*., 2016). Apigenin (5,7,4′-trihydroxyflavonoid; Figure 1), a bioflavonoid widely found in citrus fruits, has been found to exert a variety of pharmacological effects,

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including antibacterial, anticancer, and antiproliferative effects (Banerjee *et al*., 2015; Liu *et al*., 2013; Eumkeb, Chukrathok, 2013; Choi *et al*., 2010; Turktekin *et al*., 2011; Ruivo *et al*., 2015). The prenyl moiety is widely found in many drugs and natural products (Zhao *et al*., 2011; Winans *et al*., 1999). Prenylation has been reported to produce flavonoids with enhanced antibacterial, antioxidant, anti-inflammatory, larvicidal, cytotoxicity, and estrogenic activities (Rao *et al*., 2009; Vogel *et al*., 2008; Vogel *et al*., 2010). It has been proposed that prenyl moieties can make a compound more lipophilic, leading to a high affinity with cell membranes (Chen *et al*., 2014; Marín, Máñez, 2013; Coelho *et al*., 1992).

To obtain new compounds with better antibacterial effects, and as part of our ongoing research on structure-based design using apigenin as the lead compound, the introduction of a prenyloxy group on the A-ring of apigenin was used to prepare a series of 20 novel 5,7-diisoprenyloxyflavone derivatives (**4a**–**4t**; Scheme-1). These compounds were synthesized, characterized, and screened for their antibacterial activities. The synthesized of 5,7-diisoprenyloxyflavone derivatives (**4a**–**4t**) and antibacterial effects are not reported and is the originality compounds.

MATERIAL AND METHODS

Chemistry

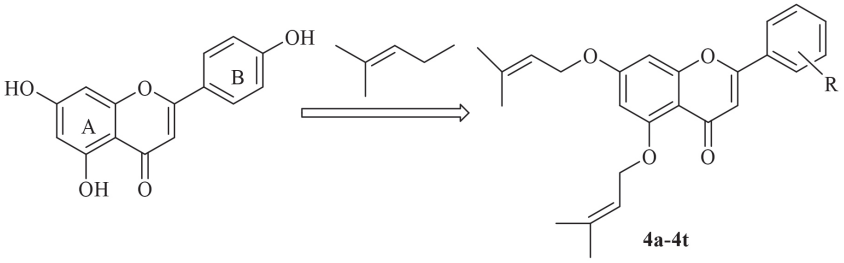
Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded on a FT-IR1730 (Bruker, Switzerland) using KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra were measured on an AV-300 spectrometer (Bruker, Switzerland), with all chemical shifts given in ppm relative to tetramethylsilane standard. High-resolution mass spectrometry (HRMS) was performed on an MALDI–TOF/TOF mass spectrometer (Bruker Daltonik, Bremen, Germany). Major chemicals were purchased from Aldrich Chemical Corporation (Shanghai, China), and all chemicals were of analytical grade. Compounds 1a–1t, 2a–2t and 3a-3t were synthesized to refer to previously published literature (Guan *et al*., 2013; Xie *et al*., 2014.).

General procedure for the preparation of compounds (4a-4t)

To a stirred solution of compounds **3a**–**3t** (0.4 mmol) in DMSO (30 mL) in a 100-mL round-bottomed flask was added I_2 (0.4 mmol). The mixture was then stirred at 100–130 °C for 3–5 h to achieve reaction completion (as monitored by TLC) (Kim *et al*., 2007). The reaction mixture was then poured into ice-water to produce a yellow precipitate, which was collected and recrystallized from ethanol to afford corresponding products **4a**–**4t**. The yields and IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectral data for each compound are provided below.

*5,7-Diisoprenyloxyflavone (**4a**)*

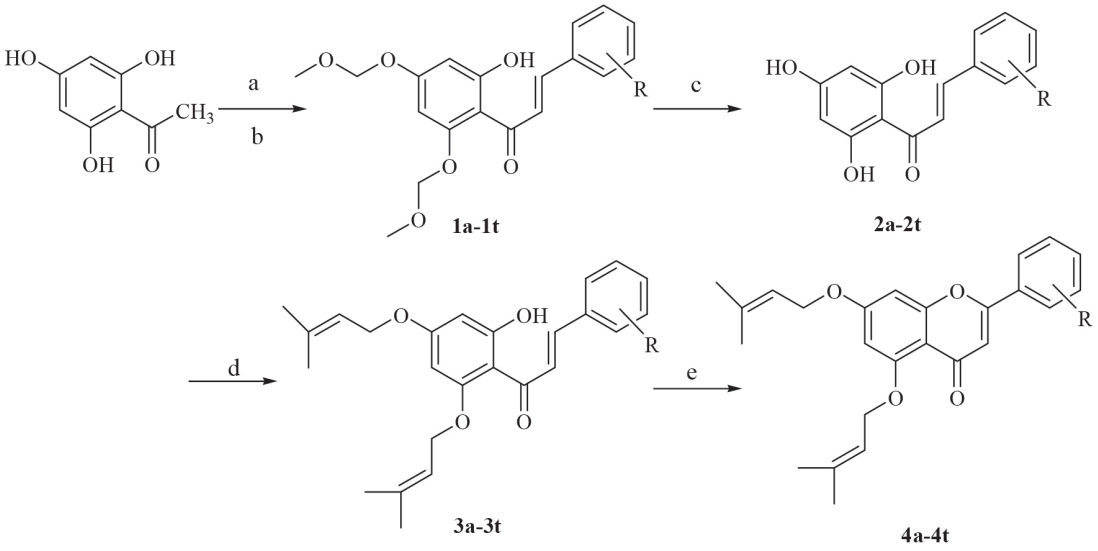
Yield: 79.3%; mp 74–76 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.63 (s, 3H, -CH_3), 1.66 (s, 3H, -CH_3), 1.72 (s, 3H, -CH_3), 1.76 (s, 3H, -CH_3), 4.42 (d, 2H, -CH_2), 4.57 (d, 2H, -CH_2), 5.38 (t, 1H, =CH), 5.49 (t, 1H, =CH), 6.09-6.12 (m, 2H, -C_6H_2), 6.81 (s, 1H, =CH), 7.16-7.38 (m, 5H, -C_6H_5); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.7, 20.1, 25.7, 26.0, 45.7, 45.9, 98.1, 99.7, 104.0, 105.3, 123.7, 124.0, 126.7, 127.0, 128.3, 128.9, 129.3, 130.7, 132.5, 132.8, 160.4, 163.3, 164.2, 168.7, 182.8; IR (KBr) cm^{-1}:



R:

4a = H	**4b** = 2-F	**4c** = 3-F	**4d** = 4-F	**4e** = 2-Cl
4f = 3-Cl	**4g** = 4-Cl	**4h** = 2-Br	**4i** = 3-Br	**4j** = 4-Br
4k = 2-Cl-4-Cl	**4l** = 4-NO_2	**4m** = 2-CH_3	**4n** = 3-CH_3	**4o** = 4-CH_3
4p = 2-OCH_3	**4q**= 3-OCH_3	**4r** = 4-OCH_3	**4s** = 4-$N(CH_3)_2$	**4t** = 3-OCH_3-4-OH

FIGURE 1 - The structure of apigenin and general structure of compounds **4a-4t.**



R:

4a = H	**4b** = 2-F	**4c** = 3-F	**4d** = 4-F	**4e** = 2-Cl
4f = 3-Cl	**4g** = 4-Cl	**4h** = 2-Br	**4i** = 3-Br	**4j** = 4-Br
4k = 2-Cl-4-Cl	**4l** = 4-NO_2	**4m** = 2-CH_3	**4n** = 3-CH_3	**4o** = 4-CH_3
4p = 2-OCH_3	**4q** = 3-OCH_3	**4r** = 4-OCH_3	**4s** = 4-$N(CH_3)_2$	**4t** = 3-OCH_3-4-OH

Reagents and conditions:

(a) $ClCH_2OCH_3$, K_2CO_3; (b) aromatic aldehyde, KOH; (c) 3 M HCl; (d) prenyl bromide, anhydrous K_2CO_3; (e) I_2, DMSO.

SCHEME1 - Synthesis routes of target compounds **4a–4t.**

2931, 1678, 1221, 970; ESI-HRMS calcd. for $C_{25}H_{26}O_4^+$ ($[M+H]^+$): 391.183, found: 391.1820.

*2′-Fluoro-5,7-diisoprenyloxyflavone (**4b**)*

Yield: 61.2%; mp 92–94 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.62 (s, 3H, -CH_3), 1.65 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 1.74 (s, 3H, -CH_3), 4.47 (d, 2H, -CH_2), 4.61 (d, 2H, -CH_2), 5.40 (t, 1H, =CH), 5.47 (t, 1H, =CH), 6.05–6.11 (m, 2H, -C_6H_2), 6.67 (s, 1H, =CH), 6.98–7.32 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.9, 20.3, 25.5, 25.9, 45.5, 45.8, 97.8, 98.9, 103.7, 104.8, 116.4, 121.8, 123.6, 123.8, 124.7, 128.7, 129.6, 132.6, 132.7, 158.9, 162.7, 163.8, 168.5, 182.6; IR (KBr) cm^{-1}: 2934, 1676, 1220, 972; ESI-HRMS calcd. for $C_{25}H_{25}FO_4^+$ ($[M+H]^+$): 408.1737, found: 408.1742.

*3′-Fluoro-5,7-diisoprenyloxyflavone (**4c**)*

Yield: 59%; mp 98–100 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.66 (s, 3H, -CH_3), 1.69 (s, 3H, -CH_3), 1.71 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 4.44 (d, 2H, -CH_2), 4.69 (d, 2H, -CH_2), 5.47 (t, 1H, =CH), 5.65 (t, 1H, =CH), 6.06–6.14 (m, 2H, -C_6H_2), 6.67 (s, 1H, =CH), 6.82–7.28 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.2, 19.7, 25.1, 25.5, 65.8, 66.0, 99.1, 100.1, 103.9, 105.3, 111.8, 115.1, 122.8, 123.4, 123.7, 130.4, 132.4, 132.8, 133.0, 159.6, 162.3, 162.7, 163.6, 168.4, 183.1; IR (KBr) cm^{-1}: 2932, 1676, 1222, 970; ESI-HRMS calcd. for $C_{25}H_{25}FO_4^+$ ($[M+H]^+$): 408.1737, found: 408.1730.

*4′-Fluoro-5,7-diisoprenyloxyflavone (**4d**)*

Yield: 73.3%; mp 97–99 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.66 (s, 3H, -CH_3), 1.69 (s, 3H, -CH_3), 1.70 (s, 3H, -CH_3), 1.72 (s, 3H, -CH_3), 4.63 (d, 2H, -CH_2), 4.66 (d, 2H, -CH_2), 5.43 (t, 1H, =CH), 5.45 (t, 1H, =CH), 6.03–6.12 (m, 2H, -C_6H_2), 6.73 (s, 1H, =CH), 6.90–7.29 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): 19.2, 19.4, 25.2, 25.4, 45.1, 45.3, 96.8, 97.9, 103.5, 104.7, 115.2, 115.7, 123.3, 123.5, 126.5, 128.3, 128.5, 159.4, 162.2,

162.5, 163.5, 168.4, 182.4; IR (KBr) cm^{-1}: 2932, 1672, 1221, 971; ESI-HRMS calcd. for $C_{25}H_{25}FO_4^+$ ($[M+H]^+$): 408.1737, found: 408.1746.

*2′-Chloro-5,7-diisoprenyloxyflavone (**4e**)*

Yield: 74.1%, mp 105–107 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.67 (s, 3H, -CH_3), 1.70 (s, 3H, -CH_3), 1.71 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 4.58 (d, 2H, -CH_2), 4.61 (d, 2H, -CH_2), 5.42 (t, 1H, =CH), 5.47 (t, 1H, =CH), 6.03–6.10 (m, 2H, -C_6H_2), 6.65 (s, 1H, =CH), 7.06–7.28 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.3, 19.6, 25.3, 25.6, 45.3, 45.5, 97.5, 98.6, 103.6, 104.5, 123.5, 123.8, 126.6, 127.4, 128.7, 129.5, 131.2, 131.9, 132.4, 132.6, 159.2, 162.6, 163.7, 168.5, 182.5; IR (KBr) cm^{-1}: 2943, 1676, 1220, 973; ESI-HRMS calcd. for $C_{25}H_{25}ClO_4^+$ ($[M+H]^+$): 425.1441, found: 425.1430.

*3′-Chloro-5,7-diisoprenyloxyflavone (**4f**)*

Yield: 77%; mp 119–121 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.69 (s, 3H, -CH_3), 1.71 (s, 3H, -CH_3), 1.74 (s, 3H, -CH_3), 1.75 (s, 3H, -CH_3), 4.50 (d, 2H, -CH_2), 4.54 (d, 2H, -CH_2), 5.40 (t, 1H, =CH), 5.44 (t, 1H, =CH), 6.02–6.11 (m, 2H, -C_6H_2), 6.68 (s, 1H, =CH), 7.14–7.34 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.6, 19.9, 25.4, 25.8, 65.5, 65.8, 98.9, 99.4, 103.3, 104.8, 123.7, 123.9, 124.5, 126.7, 128.3, 130.7, 131.6, 132.5, 132.8, 134.5, 160.2, 162.4, 163.6, 169.1, 182.9; IR (KBr) cm^{-1}: 2940, 1677, 1222, 970; ESI-HRMS calcd. for $C_{25}H_{25}ClO_4^+$ ($[M+H]^+$): 425.1441, found: 425.1451.

*4′-Chloro-5,7-diisoprenyloxyflavone (**4g**)*

Yield: 81%; mp 117–119 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.65 (s, 3H, -CH_3), 1.67 (s, 3H, -CH_3), 1.72 (s, 3H, -CH_3), 1.74 (s, 3H, -CH_3), 4.62 (d, 2H, -CH_2), 4.64 (d, 2H, -CH_2), 5.40 (t, 1H, =CH), 5.43 (t, 1H, =CH), 6.05–6.12 (m, 2H, -C_6H_2), 6.81 (s, 1H, =CH), 7.21–7.26 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 20.1, 20.3, 25.4, 25.7, 65.6, 65.8, 99.2, 100.1, 103.8, 104.7, 123.7, 124.0, 127.3, 127.8, 128.2, 128.5, 129.2, 132.2, 132.5, 133.7, 159.6, 162.4, 163.5, 168.7, 182.9; IR (KBr) cm^{-1}: 2943, 1676, 1220, 973; ESI-HRMS calcd. for $C_{25}H_{25}ClO_4^+$ ($[M+H]^+$): 425.1441, found: 425.1449.

*2′-Bromo-5,7-diisoprenyloxyflavone (**4h**)*

Yield: 69%; mp 120-122 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.68 (s, 3H, -CH_3), 1.70 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 1.75 (s, 3H, -CH_3), 4.48 (d, 2H, -CH_2), 4.50 (d, 2H, -CH_2), 5.42 (t, 1H, =CH), 5.47 (t, 1H, =CH), 6.05–6.13 (m, 2H, -C_6H_2), 6.77 (s, 1H, =CH), 7.06–7.41 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.2, 19.7, 25.4, 25.6, 65.3, 65.5, 98.4, 99.2, 103.1, 104.4, 118.3, 123.6, 123.9, 127.1, 128.6, 130.4, 131.6, 132.3, 132.5, 138.4, 159.4, 162.7, 164.1, 168.5, 182.6; IR (KBr) cm^{-1}: 2936, 1674, 1220, 968; ESI-HRMS calcd. for $C_{25}H_{25}BrO_4^+$ ($[M+H]^+$): 469.0936, found: 469.0915.

*3′-Bromo-5,7-diisoprenyloxyflavone (**4i**)*

Yield: 70%; mp 114-117 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.67 (s, 3H, -CH_3), 1.69 (s, 3H, -CH_3), 1.70 (s, 3H, -CH_3), 1.72 (s, 3H, -CH_3), 4.56 (d, 2H, -CH_2), 4.59 (d, 2H, -CH_2), 5.40 (t, 1H, =CH), 5.43 (t, 1H, =CH), 6.03–6.11 (m, 2H, -C_6H_2), 6.79 (s, 1H, =CH), 7.12–7.50 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.3, 19.5, 25.5, 25.7, 64.8, 65.0, 96.4, 97.7, 103.3, 104.5, 122.8, 123.8, 124.0, 125.7, 129.1, 130.2, 130.5, 131.9, 132.3, 132.5, 162.4, 163.3, 163.9, 168.5, 182.6; IR (KBr) cm^{-1}: 2941, 1677, 1222, 972; ESI-HRMS calcd. for $C_{25}H_{26}O_4^+$ ($[M+H]^+$): 469.0936, found: 469.0943.

*4′-Bromo-5,7-diisoprenyloxyflavone (**4j**)*

Yield: 78.5%, mp 122–124 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.65 (s, 3H, -CH_3), 1.68 (s, 3H, -CH_3), 1.71 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 4.62 (d, 2H, -CH_2), 4.65 (d, 2H, -CH_2), 5.39 (t, 1H, =CH), 5.42 (t, 1H, =CH), 6.04–6.13 (m, 2H, -C_6H_2), 6.76 (s, 1H, =CH), 7.21–7.42 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.6, 19.8, 25.4, 25.7, 66.1, 66.5, 96.8, 97.9, 103.7, 104.6, 122.4, 123.4, 123.7, 128.1, 128.4, 129.9, 131.3, 131.4, 132.3, 132.5, 160.0, 162.7, 163.8, 168.6, 182.5; IR (KBr) cm^{-1}: 2941, 1678, 1222, 972; ESI-HRMS calcd. for $C_{25}H_{26}O_4^+$ ($[M+H]^+$): 469.0936, found: 469.0921.

*2′,4′-Dichloro-5,7-diisoprenyloxyflavone (**4k**)*

Yield: 78.4%, mp 107–108 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.67 (s, 3H, -CH_3), 1.69 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 1.75 (s, 3H, -CH_3), 4.48 (d, 2H, -CH_2), 4.50 (d, 2H, -CH_2), 5.42 (t, 1H, =CH), 5.45 (t, 1H, =CH), 6.05–6.11 (m, 2H, -C_6H_2), 6.78 (s, 1H, =CH), 7.10–7.28 (m, 3H, -C_6H_3); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.6, 19.8, 25.5, 25.8, 65.5, 65.7, 96.4, 97.8, 103.7, 104.5, 123.5, 123.8, 127.1, 129.3, 129.6, 130.4, 132.4, 132.7, 132.9, 159.7, 162.3, 163.8, 168.5, 182.5; IR (KBr) cm^{-1}: 2941, 1676, 1221, 968; ESI-HRMS calcd. for $C_{25}H_{24}Cl_2O_4^+$ ($[M+H]^+$): 459.1052, found: 459.1041.

*4′-Nitro-5,7-diisoprenyloxyflavone (**4l**)*

Yield: 60%, mp 91–93 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.69 (s, 3H, -CH_3), 1.70 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 1.76 (s, 3H, -CH_3), 4.62 (d, 2H, -CH_2), 4.67 (d, 2H, -CH_2), 5.39 (t, 1H, =CH), 5.43 (t, 1H, =CH), 6.05–6.11 (m, 2H, -C_6H_2), 7.02 (s, 1H, =CH), 7.76–8.43 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.5, 19.7, 25.5, 25.7,

65.5, 65.8, 98.7, 99.9, 103.8, 104.3, 121.3, 121.5, 123.5, 123.7, 127.6, 127.9, 132.4, 132.7, 136.5, 148.8, 160.2, 162.5, 163.7, 168.4, 182.5; IR (KBr) cm^{-1}: 2941, 1676, 1221, 972; ESI-HRMS calcd. for $C_{25}H_{25}NO_6^+$ ([M+H]$^+$): 436.1682, found: 436.1669.

*2′-Methyl-5,7-diisoprenyloxyflavone (**4m**)*

Yield: 74.4%, mp 96–98 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.69 (s, 3H, -CH_3), 1.70 (s, 3H, -CH_3), 1.71 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 2.40 (s, 3H, -CH_3), 4.45 (d, 2H, -CH_2), 4.47 (d, 2H, -CH_2), 5.41 (t, 1H, =CH), 5.43 (t, 1H, =CH), 6.03–6.12 (m, 2H, -C_6H_2), 6.56 (s, 1H, =CH), 7.03–7.21 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 18.4, 19.5, 19.7, 25.3, 25.6, 65.5, 65.7, 97.5, 98.7, 103.5, 104.6, 123.3, 123.5, 125.7, 126.5, 127.3, 128.7, 129.3, 132.2, 132.5, 159.8, 162.7, 163.8, 168.5, 182.6; IR (KBr) cm^{-1}: 2939, 1676, 1221, 971; ESI-HRMS calcd. for $C_{26}H_{28}O_4^+$ ([M+H]$^+$): 405.1988, found: 405.1968.

*3′-Methyl-5,7-diisoprenyloxyflavone (**4n**)*

Yield: 76%, mp 101–104 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.69 (s, 3H, -CH_3), 1.71 (s, 3H, -CH_3), 1.72 (s, 3H, -CH_3), 1.75 (s, 3H, -CH_3), 2.39 (s, 3H, -CH_3), 4.42 (d, 2H, -CH_2), 4.44 (d, 2H, -CH_2), 5.40 (t, 1H, =CH), 5.42 (t, 1H, =CH), 6.03–6.12 (m, 2H, -C_6H_2), 6.73 (s, 1H, =CH), 6.95–7.13 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.8, 20.1, 24.3, 25.5, 25.8, 65.6, 65.9, 98.9, 100.2, 103.3, 104.5, 123.3, 123.7, 123.9, 126.2, 128.3, 128.8, 130.3, 132.5, 132.7, 138.7, 159.7, 162.5, 163.6, 168.8, 182.4; IR (KBr) cm^{-1}: 2942, 1677, 1222, 970; ESI-HRMS calcd. for $C_{26}H_{28}O_4^+$ ([M+H]$^+$): 405.1988, found: 405.1971.

*4′-Methyl-5,7-diisoprenyloxyflavone (**4o**)*

Yield: 85.6%, mp 113–115 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.67 (s, 3H, -CH_3), 1.71 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 1.74 (s, 3H, -CH_3), 2.38 (s, 3H, -CH_3), 4.51 (d, 2H, -CH_2), 4.53 (d, 2H, -CH_2), 5.40 (t, 1H, =CH), 5.42 (t, 1H, =CH), 6.05–6.13 (m, 2H, -C_6H_2), 6.75 (s, 1H, =CH), 7.01–7.19 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.7, 19.9, 24.1, 25.5, 25.8, 65.6, 65.9, 98.8, 99.6, 103.4, 104.5, 123.6, 123.8, 126.2, 126.4, 127.5, 129.2, 129.3, 132.4, 132.7, 137.6, 159.9, 162.8, 163.5, 168.6, 182.4; IR (KBr) cm^{-1}: 2941, 1676, 1220, 970; ESI-HRMS calcd. for $C_{26}H_{28}O_4^+$ ([M+H]$^+$): 405.1988, found: 405.1990.

*2′-Methoxy-5,7-diisoprenyloxyflavone (**4p**)*

Yield: 68.4%, mp 80–83 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.68 (s, 3H, -CH_3), 1.70 (s, 3H, -CH_3), 1.72 (s, 3H, -CH_3), 1.74 (s, 3H, -CH_3), 3.74 (s, 3H, -O CH_3), 4.63 (d, 2H, -CH_2), 4.65 (d, 2H, -CH_2), 5.41 (t, 1H, =CH), 5.44 (t, 1H, =CH), 6.04–6.11 (m, 2H, -C_6H_2), 6.73 (s, 1H, =CH), 6.73–7.20 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.7, 20.0, 25.6, 25.8, 56.5, 65.1, 65.4, 96.7, 98.9, 103.3, 104.6, 110.7, 114.4, 121.3, 123.4, 123.6, 127.2, 129.6, 132.6, 132.7, 159.7, 162.0, 163.4, 168.4, 182.6; IR (KBr) cm^{-1}: 2943, 1678, 1221, 970; ESI-HRMS calcd. for $C_{26}H_{28}O_5^+$ ([M+H]$^+$): 421.1937, found: 421.1921.

*3′-Methoxy-5,7-diisoprenyloxyflavone (**4q**)*

Yield: 65.2 %, mp. 77-79 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.66 (s, 3H, -CH_3), 1.67 (s, 3H, -CH_3), 1.71 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 3.71 (s, 3H, -O CH_3), 4.45 (d, 2H, -CH_2), 4.48 (d, 2H, -CH_2), 5.39 (t, 1H, =CH), 5.43 (t, 1H, =CH), 6.06–6.12 (m, 2H, -C_6H_2), 6.59 (s, 1H, =CH), 6.71–7.19 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.8, 20.1, 25.6, 25.8, 56.0, 64.9, 65.4, 98.8, 100.1, 103.2, 104.3, 110.3 113.5, 118.5, 123.5, 123.6, 129.8, 131.4, 132.5, 132.8, 159.8, 162.5, 163.8, 168.3, 182.6; IR (KBr) cm^{-1}: 2942, 1677, 1220, 971; ESI-HRMS calcd. for $C_{26}H_{28}O_5^+$ ([M+H]$^+$): 421.1937, found: 421.1921.

*4′-Methoxy-5,7-diisoprenyloxyflavone (**4r**)*

Yield: 81.1%, mp 88–90 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.69 (s, 3H, -CH_3), 1.70 (s, 3H, -CH_3), 1.71 (s, 3H, -CH_3), 1.72 (s, 3H, -CH_3), 3.71 (s, 3H, -O CH_3), 4.50 (d, 2H, -CH_2), 4.52 (d, 2H, -CH_2), 5.39 (t, 1H, =CH), 5.42 (t, 1H, =CH), 6.02–6.10 (m, 2H, -C_6H_2), 6.69 (s, 1H, =CH), 6.67–7.13 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.4, 20.3, 25.4, 25.6, 55.9, 65.8, 60.2, 97.8, 99.9, 103.4, 104.5, 114.7, 114.9, 122.7, 123.3, 123.5, 127.4, 127.6, 132.4, 132.7, 160.1, 162.3, 163.6, 168.5, 182.4; IR (KBr) cm^{-1}: 2941, 1675, 1221, 969; ESI-HRMS calcd. for $C_{26}H_{28}O_5^+$ ([M+H]$^+$): 421.1937, found: 421.1942.

*4′-Dimethylamine-5,7-diisoprenyloxyflavone (**4s**)*

Yield: 63%, mp 83–85 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.68 (s, 3H, -CH_3), 1.69 (s, 3H, -CH_3), 1.70 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 2.80, 2.89 (s, 6H, -N(CH_3)$_2$), 4.61 (d, 2H, -CH_2), 4.63 (d, 2H, -CH_2), 5.40 (t, 1H, =CH), 5.42 (t, 1H, =CH), 6.03–6.11 (m, 2H, -C_6H_2), 6.76 (s, 1H, =CH), 6.60–7.16 (m, 4H, -C_6H_4); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.8, 20.2, 25.4, 25.7, 40.5, 40.8, 65.4, 65.6, 97.8, 99.6, 103.4, 104.5, 114.3, 114.5, 119.3, 123.3, 123.4, 127.1, 127.4, 132.4, 132.5, 148.4, 160.0, 162.5, 163.4, 168.4, 182.5; IR (KBr) cm^{-1}: 2940, 1676, 1220, 970; ESI-HRMS calcd. for $C_{27}H_{31}NO_4^+$ ([M+H]$^+$): 434.2253, found: 434.2243.

*3-Methoxy-4′-hydroxy-5,7-diisoprenyloxyflavone (**4t**)*

Yield: 73.4%; obtained as an oil; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.67 (s, 3H, -CH_3), 1.69 (s, 3H, -CH_3), 1.71 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 3.75 (s, 3H,

-OCH_3), 4.60 (d, 2H, -CH_2), 4.63 (d, 2H, -CH_2), 5.41 (t, 1H, =CH), 5.44 (t, 1H, =CH), 6.03–6.12 (m, 2H, -C_6H_2), 6.73 (s, 1H, =CH), 6.53–6.79 (m, 3H, -C_6H_3), 9.12 (s, 1H, -OH); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 19.7, 19.9, 25.7, 25.9, 56.8, 65.6, 65.8, 98.9, 99.9, 103.6, 104.3, 113.4, 115.4, 120.3, 123.4, 123.7, 124.6, 132.5, 132.7, 145.7, 150.1, 159.7, 162.2, 163.5, 168.5, 182.3; IR (KBr) cm^{-1}: 3250, 2942, 1678, 1221, 970; ESI-HRMS calcd. for $C_{26}H_{28}O_6^+$ ([M+H]$^+$): 437.1886, found: 437.1864.

Evaluation of the antibacterial activity *in vitro*

The microorganisms used in the present study were *S. aureus* (*S. aureus* KCTC 503, *S. aureus* RN4220, and *S. aureus* KCTC 209), *S. mutans* (*S. mutans* KCTC 3289 and *S. mutans* KCTC 3065), and *Escherichia coli* (*E. coli* 1924 and *E. coli* 1356). The strains of multidrug-resistant clinical isolates used were multidrug-resistant *S. aureus* (MRSA CCARM 3167 and MRSA CCARM 3506) and quinolone-resistant *S. aureus* (QRSA CCARM 3505 and QRSA CCARM 3519). Clinical isolates were collected from various patients hospitalized in several clinics (Hosseinkhani *et al*., 2016; Fan, Reichling, Wink, 2013; Sharma *et al*., 2011).

A twofold serial dilution technique (Song *et al*., 2013) was used to determine the minimum inhibitory concentrations (MICs) of the compounds against susceptible microorganisms in the preliminary test (Gram-positive and Gram-negative bacteria) and against strains of clinical isolates of multidrug-resistant Gram-positive bacteria. The compounds dissolved in DMSO and two-fold diluted at concentrations from 200 μg/mL to 0.1 μg/mL, and they were added to culture media (Brain heart infusion for *S. mutans* and Mueller–Hinton agar for other bacteria) to obtain final concentrations of 0.5–64 μg/mL. The final amount of bacteria applied was 105 CFU/mL. MIC values were determined after incubation at 37 °C for 20 h. The lowest concentration of the test substance that completely inhibited microorganism growth was recorded as the MIC (expressed in μM). Norfloxacin was used as the drug standard. All experiments were conducted in triplicate.

RESULTS AND DISCUSSION

Chemistry

The target compounds were obtained as outlined in Scheme 1. Compounds **1a**–**1t** were synthesized from the Claisen–Schmidt condensation of commercially available 2,4,6-trihydroxyacetophenone (protected as methoxymethyl ethers) with different substituted aromatic aldehydes in aqueous ethanolic sodium hydroxide (Zhen *et al*., 2016). Intermediates **1a**–**1t** were then treated with 3 M HCl in methanol to yield 2,4,6-trihydroxychalcones derivatives **2a**–**2t** (Xie *et al*., 2014). Subsequent substitution with prenyl bromide in acetone under reflux in the presence of anhydrous K_2CO_3 afforded compounds **3a**–**3t** (Wang *et al*., 2015). 5,7-Diisoprenyloxyflavone derivatives **4a**–**4t** were obtained in good yields by treating **3a**–**3t** with I_2 in DMSO. The chemical structures of the target compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and high-resolution mass spectroscopy. The IR spectra of the newly synthesized 5,7-diisoprenyloxyflavone derivatives **4a**–**4t** showed absorption stretching bands at 2931–2943 cm^{-1} and 1672–1678 cm^{-1} stretching (1220–1222 cm^{-1}) corresponding to (-CH_3), (C=O) and (C–O–C) group, respectively. IR spectrum of compound **4t** showed absorption bands at 3250 cm^{-1} corresponding to stretching absorption of -OH group. The characteristic feature in the ^{1}H-NMR spectrum of compound **2t** is the appearance of two triplet peaks at 5.41 and 5.44 ppm which represented the prenyl protons in (CH=C-) group. Furthermore, two singlet peaks at 6.73 ppm and 9.12 ppm related to flavone ring 3-C protons in (CH=) group and at phenyl ring 4′-C protons in (-OH) group were observed. ^{1}H-NMR spectra showed the =CH protons of the group at 6.56–7.02 ppm, The characteristic feature in the ^{13}C-NMR spectrum of compound **2t** displayed four signals peakes in (-CH_3) group (19.7 ppm, 19.9 ppm, 25.7 ppm, 25.9 ppm), while showed C=O signals at 182.3 ppm. The structure of **2t** was further verified by mass spectroscopy that showed a molecular ion peak [M+H]$^+$ at ESI-HRMS 437.1864 (55.4%) in accordance with the molecular formula $C_{26}H_{28}O_6$.

Antibacterial activity

In this study, antibacterial activity was determined from the MIC with different strains *in vitro*, including multidrug-resistant clinical isolates. Norfloxacin was used as a positive control for bacteria. As shown in Table I, compounds **4a**–**4t** did not exhibit antibacterial activity against Gram-negative strains at a dose of 24-164 μM *in vitro*, but some compounds displayed potent antibacterial activity against Gram-positive strains. Nine compounds gave MIC values of 4.4-19 μM. Compounds **4c**, **4g**, **4i**, **4j**, **4k**, **4l**, **4n**, **4q** and **4t** were highly active against *S. aureus* (*S. aureus* RN4220, *S. aureus* KCTC 503, and *S. aureus* KCTC 209) and *Streptococcus mutans* KCTC (*S. mutans* KCTC 3065 and *S. mutans* KCTC 3289) strains, with MIC values of 4.4-19 μM, but were less active than

standard drug norfloxacin. The synthesized derivatives showed significant antibacterial effects against *S. aureus*, with 2,4-Cl_2 substituted compound **4k** giving a MIC value of 4.4 μM, which was similarly active to standard drug norfloxacin.

By analyzing the activities of synthesized compounds **4a-4t**, the following structure activity relationships were observed. Eight electron-donor compounds including *o*-CH_3, *m*-CH_3, *p*-CH_3, *o*-OCH_3, *m*-OCH_3, *p*-OCH_3, *p*-$N(CH_3)_2$, and 3-OCH_3-4-OH on the substituent of phenyl ring, were designed and synthesized. Pharmacological test results showed that their activities were lower than those of halogen-substituted derivatives of phenyl ring, with activities in the order 3-OCH_3-4-OH > *m*-OCH_3 > *m*-CH_3 > H > *o*-CH_3, *p*-CH_3 > *o*-OCH_3, *p*-OCH_3, *p*-$N(CH_3)_2$. For different position methyl and methoxy groups on the substituent of phenyl ring influenced the antibacterial effects with activities in the order *m*-CH_3 > *o*-CH_3, *p*-CH_3, and *m*-OCH_3 > *o*-OCH_3, *p*-OCH_3. Furthermore, the position of electron-withdrawing (F, Cl, and Br) groups on the B ring (of phenyl ring) significantly influenced the antibacterial activity, with activities in the order *m*-F > *p*-F > *o*-F for fluoro-substituted compounds of phenyl ring, and *p*-Br > *m*-Br > *o*-Br for bromo-substituted compounds of phenyl ring. In comparison, the chloro-substituted derivatives of phenyl ring showed activities in the order 2,4-dichloro > *p*-Cl > *m*-Cl > *o*-Cl. Therefore, compounds **4c**, **4g**, and **4j** bearing *m*-F, *p*-Cl, and *p*-Br substituents of phenyl ring, respectively, showed better activities, while those bearing *o*-F, *o*-Cl, and *o*-Br substituents of phenyl ring (**4b**, **4e**, and **4f**, respectively) were inactive for all microorganisms, even at doses of 24-151 μM. Compound **4k** (MIC = 4.4 μM) was 30-fold more potent than apigenin (MIC = 118.5 μM). It has been proposed that the prenyl moiety on A ring

TABLE I - Inhibitory activity of compounds **4a-4t** expressed as MIC (μM)

Compounds	*S. aureus*			*S. mutans*		*E. coli*	
	4220	**503**	**209**	**3065**	**3289**	**1924**	**1356**
apigenin	118.5	118.5	118.5	118.5	118.5	>237	>237
4a	82	82	82	164	164	>164	>164
4b	>24	>24	>24	>24	>24	>24	>24
4c	9.8	9.8	9.8	9.8	9.8	>24	>24
4d	24	24	24	24	24	>24	>24
4e	>151	>151	>151	>151	>151	>151	>151
4f	151	151	151	151	151	>151	>151
4g	9.4	9.4	9.4	9.4	9.4	>151	>151
4h	>136.8	>136.8	>136.8	>136.8	>136.8	>136.8	>136.8
4i	17	17	17	17	17	>136.8	>136.8
4j	8.5	8.5	8.5	8.5	8.5	>136.8	>136.8
4k	4.4	4.4	4.4	4.4	4.4	>139.7	>139.7
4l	9.2	9.2	9.2	18.4	18.4	>147	>147
4m	158	158	158	158	158	>158	>158
4n	19.8	19.8	19.8	19.8	19.8	>158	>158
4o	158	158	158	158	158	>158	>158
4p	>152	>152	>152	>152	>152	>152	>>152
4q	19	19	19	19	19	>152	>>152
4r	>152	>152	>152	>152	>152	>152	>>152
4s	>147.8	>147.8	>147.8	>147.8	>147.8	>147.8	>147.8
4t	9	9	9	9	9	>146.8	>146.8
Norfloxacin	6	6	12	3	3	50	50

S. aureus RN4220, *Staphylococcus aureus* RN4220; *S. aureus* 503, *Staphylococcus aureus* 503; *S. aureus* 209, *Staphylococcus aureus* 209; *S. mutans* 3065, *Streptococus mutans* 3065; *S. mutans* 3289, *Streptococus mutans* 3289; *E. coli* 1924, *Escherichia coli* CCARM 1924; *E. coli* 1356, *Escherichia coli* CCARM 1356.

makes compounds more lipophilic, which leads to a higher affinity with cell membranes, with prenylation shown to afford flavonoids with enhanced antibacterial activities (Ei-Bassuony, Abouzid, 2010; Yu *et al*., 2015).

Activity against clinical isolates of multidrug-resistant Gram-positive bacteria

The most active compounds, **4c**, **4g**, **4i**, **4j**, **4k**, **4l**, **4n**, **4q** and **4t**, were also evaluated for antibacterial effects against clinical isolates of multidrug-resistant Gram-positive bacteria (Table II). These derivatives were found to be highly active against these clinical isolates, giving MIC values of 4.0-20 μM. Compound **4k** was more potent than norfloxacin against most microorganisms tested, giving an MIC value of 4.0 μM. This suggested that the introduction of two halogen atoms of phenyl ring and a prenyl moiety on A ring into the hybrid compound played an important role in improving the antibacterial properties (Chen *et al*., 2014; Marín, Máñez, 2013). Therefore, compound **4k** should be used as the lead compound for further design and investigations.

TABLE II - MIC values (in μM) against clinical isolates of multidrug-resistant Gram-positive bacterial strains

Compounds	MRSA		QRSA	
	3167	3506	3505	3519
4c	10	10	10	10
4g	9.0	9.0	9.0	9.0
4i	17	17	17	17
4j	8.5	8.5	8.5	8.5
4k	4.0	4.0	4.0	4.0
4l	9.2	9.2	9.2	9.2
4n	20	20	20	20
4q	19	19	19	19
4t	9.1	9.1	9.1	9.1
Norfloxacin	25	13	>200	>200

MRSA 3167, methicillin-resistant *S. aureus* CCARM 3167; MRSA 3506, methicillinresistant, *S. aureus* CCARM 3506; QRSA 3505, quinolone-resistant *S. aureus* CCARM 3505; QRSA 3519, quinolone-resistant *S. aureus* CCARM 3519

CONCLUSION

We synthesized a series of novel 5,7-diisoprenyl-oxyflavone derivatives and evaluated their antibacterial effects against Gram-positive and Gram-negative bacteria.

Compounds **4c**, **4g**, **4i**, **4j**, **4k**, **4l**, **4n**, **4q** and **4t** were highly active against *S. aureus* and *S. mutans* KCTC, giving MIC values of 4.0-20 μM, and also showed high activities against clinical isolates of multidrug-resistant Gram-positive bacteria, with MIC values of 4.0-20 μM. In particular, compound **4k** was more potent than norfloxacin against most microorganisms tested, giving a better MIC value of 4.0 μM. This indicated that hybrid compounds possessing flavone and prenyl moieties might possess improved antibacterial properties. These results indicate that the further design and development of such compounds will be of interest in future research.

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