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Synthesis and Antifungal Activities of Carabrol Ester Derivatives

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ABSTRACT: Thirty-eight new ester derivatives of carabrol were designed, synthesized, and characterized by ^{1}H and ^{13}C NMR and HR-ESI-MS. Their antifungal activities against the fungal pathogen *Colletotrichum lagenarium* were evaluated using a spore germination assay. Of these 38 ester derivatives, 16 showed higher antifungal activity than that of carabrol and 7 showed higher antifungal activity than that of carabrone. It was found that the C-4 position of carabrol was a key position involving its antifungal activity, which showed the variation of 50% inhibition concentration (IC_{50}) from 2.70 to 52.33 μg/mL. When substituted by the phenyl ring, the ester derivatives with electron-attracting groups showed higher activity than those with electron-donating ones. Two ester derivatives, carabryl 4-cynaobenzoate (**II-17**, IC_{50} 2.70 μg/mL) and carabryl 4-isopropylbenzoate (**II-27**, IC_{50} 2.82 μg/mL), showed only slightly lower antifungal activity than that of the positive control chlorothalonil (IC_{50} 0.87 μg/mL) and have been identified as promising leads for development of new environmentally friendly fungicides.

KEYWORDS: *carabrol, structural modification, synthesis, antifungal activity*

INTRODUCTION

Anthracnose, which is mainly caused by the fungal pathogen *Colletotrichum lagenarium*, is one of the most common and serious diseases on leaf and fruit of cucurbit crops, resulting in severe yield losses and reduction in the quality of the fruits.[1] Protection of crops against *C. lagenarium* requires the multiple applications of fungicides during the whole period of growth. However, with the extensive use of synthetic fungicides, *C. lagenarium* has developed resistance to many commercialized products.[2]

Carabrol (Figure 1) and its ketone analogue carabrone, two known sesquiterpene lactones, were first isolated from fruits of

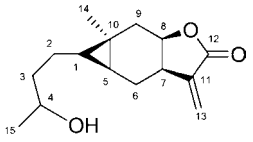

Figure 1. The structure of carabrol.

Carpesium macrocephalum and subsequently reported to be present in feverfew and other plant species,[3−11] and they exhibited significant antibactieral[12,13] and antitumor activities.[14,15]

Our previous investigation on the structure−activity relationships of carabrol and carabrone indicated that certain modifications to the C-4 substituent could improve their antifungal activity against *C. lagenarium*.[16−18] For example, carabrol showed antifungal activity against *C. lagenarium* with a 50% inhibition concentration (IC_{50}) of 20.14 μg/mL, whereas the carabrol vinyl and isopropyl esters had a IC_{50} of only 10.78 and 6.39 μg/mL, respectively.

Thus, carabrol has great potential as a template for developing more effective fungicides that may be environmentally friendly. To improve its antifungal activity, 38 new ester derivatives of carabrol were synthesized by structural modification of the hydroxyl on the C-4 position. In addition, their antifungal activities against *C. lagenarium* were evaluated using the method of spore germination.[19]

MATERIALS AND METHODS

Instruments. The melting points of these ester derivatives of carabrol were determined on an X-4 apparatus (uncorrected), which was bought from Beijing Tech. Instrument Co. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker Avance 500 MHz spectrometer in $CDCl_3$ solution with TMS as an internal standard. HR-MS (ESI) spectra were carried out with a Bruker Apex-Ultra 7.0 T spectrometer.

Carabrol was isolated from *C. macrocephalum*, which was collected in Gansu province, China.[10] Carboxylic acid reagents were purchased from J&K China Chemical Ltd. All organic solvents were commercial products and were purified when needed. Silica gel for TLC and CC was obtained from Qingdao Haiyang Chemical Co. Ltd.

Synthesis of Carabrol Esters. Carabrol (**I**, 100 mg, 0.4 mmol), DCC (103 mg, 0.5 mmol), and DMAP (13 mg, 0.1 mmol) were added to a solution of carboxylic acid (0.5 mmol) in dichloromethane (10 mL), and the mixture stirred for 0.5 h at 0 °C. The mixture was then reacted at room temperature. When the reaction was completed according to TLC analysis, saturated $NaHCO_3$ solution (20 mL) was added to the reaction mixture, which was extracted with dichloromethane (3 × 15 mL). Subsequently, the combined organic phase was washed by water and brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by silica gel column (petroleum ether/ethyl acetate, 2/1) to get the target compounds. The structures of all ester derivatives were characterized by ^{1}H NMR, ^{13}C NMR, and HR-ESI-MS, and the data are listed below.

*Carabryl Acetate (**II-1**).* Yield: 72% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.24 (d, J = 2.9 Hz, 1H, H-13), 5.56 (d, J = 2.4 Hz, 1H, H-13), 4.91−4.95 (m, 1H, H-4), 4.76−4.81 (m, 1H, H-8), 3.14−3.17 (m, 1H, H-7), 2.30−2.38 (m, 2H, H-9), 2.03 (s, 3H, H-2′), 1.40 (m, 1H, H-5), 1.35−1.44 (m, 2H, H-3), 1.22 (d, J = 6.0 Hz,

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3H, H-15), 1.07 (s, 3H, H-14), 0.90−0.99 (m, 2H, H-2), 0.40−0.43 (m, 1H, H-5), 0.31−0.34 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.8 (C-1′), 170.5 (C-12), 139.1 (C-11), 122.5 (C-13), 75.7 (C-8), 70.5 (C-4), 37.8 (C-7), 37.4 (C-9), 36.0 (C-3), 34.6 (C-1), 30.8 (C-6), 25.00 (C-2), 23.1 (C-5), 21.4 (C-2′), 20.1 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{17}H_{24}O_4Na$ ($[M + Na]^+$) 315.1567, found 315.1568.

*Carabryl Chloroacetate (**II-2**).* Yield: 49% as a yellow oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.24 (d, J = 2.8 Hz, 1H, H-13), 5.56 (d, J = 2.4 Hz, 1H, H-13), 5.01−5.05 (m, 1H, H-4), 4.76−4.81 (m, 1H, H-8), 4.03 (s, 3H, H-2′), 3.13−3.19 (m, 1H, H-7), 2.30−2.38 (m, 2H, H-9), 1.38−1.45 (m, 2H, H-3), 1.27 (d, J = 6.2 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.94−0.99 (m, 2H, H-2), 0.40−0.44 (m, 1H, H-5), 0.31−0.35 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 167.0 (C-1′), 139.0 (C-11), 122.6 (C-13), 75.7 (C-8), 73.0 (C-4), 41.2 (C-2′), 37.7 (C-7), 37.3 (C-9), 35.8 (C-3), 34.4 (C-1), 30.7 (C-6), 24.8 (C-2), 23.1 (C-5), 20.0 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{17}H_{24}ClO_4$ ($[M + H]^+$) 327.1358, found 327.1356.

*Carabryl Propanoate (**II-3**).* Yield: 68% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.24 (d, J = 2.8 Hz, 1H, H-13), 5.56 (d, J = 2.4 Hz, 1H, H-13), 4.90−4.96 (m, 1H, H-4), 4.75−4.82 (m, 1H, H-8), 3.13−3.19 (m, 1H, H-7), 2.30−2.38 (m, 2H, H-9), 1.38−1.45 (m, 2H, H-3), 1.20 (d, J = 6.2 Hz, 3H, H-15), 1.14 (m, 5H, H-2′, H-3′), 1.07 (s, 3H, H-14), 0.92−0.99 (m, 2H, H-2), 0.40−0.44 (m, 1H, H-5), 0.30−0.34 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.1 (C-1′), 170.5 (C-12), 139.1 (C-11), 122.5 (C-13), 75.7 (C-8), 70.0 (C-4), 37.8 (C-7), 37.4 (C-9), 36.0 (C-3), 34.6 (C-1), 34.2 (C-2′), 30.8 (C-6), 24.9 (C-2), 23.1 (C-5), 20.2 (C-15), 18.9 (C-3′), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{18}H_{27}O_4$ ($[M + H]^+$) 307.1904, found 307.1905.

*Carabryl n-Butyrate (**II-4**).* Yield: 71% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.24 (d, J = 2.8 Hz, 1H, H-13), 5.56 (d, J = 2.4 Hz, 1H, H-13), 4.90−4.96 (m, 1H, H-4), 4.75−4.82 (m, 1H, H-8), 3.13−3.19 (m, 1H, H-7), 2.30−2.38 (m, 2H, H-9), 1.54−1.62 (m, 2H, H-3′), 1.38−1.45 (m, 2H, H-3), 1.24 (t, J = 6.4, 3.3 Hz, 2H, H-2′), 1.21 (d, J = 6.3 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.93−0.96 (m, 5H, H-2, H-4′), 0.40−0.44 (m, 1H, H-5), 0.30−0.34 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.4 (C-1′), 170.5 (C-12), 139.1 (C-11), 122.5 (C-13), 75.7 (C-8), 70.2 (C-4), 37.8 (C-7), 37.4 (C-9), 36.6 (C-2′), 36.0 (C-3), 34.6 (C-1), 30.8 (C-6), 25.0 (C-2), 23.1 (C-5), 20.2 (C-15), 18.6 (C-14), 18.3 (C-3′), 16.9 (C-10), 13.7 (C-4′). HR-MS (ESI): m/z calcd for $C_{19}H_{28}O_4Na$ ($[M + Na]^+$) 343.1880, found 343.1873.

*Carabryl n-Pentanoate (**II-5**).* Yield: 61% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.24 (d, J = 2.9 Hz, 1H, H-13), 5.56 (d, J = 2.5 Hz, 1H, H-13), 4.90−4.96 (m, 1H, H-4), 4.75−4.82 (m, 1H, H-8), 3.13−3.19 (m, 1H, H-7), 2.30−2.38 (m, 2H, H-9), 1.54−1.62 (m, 2H, H-4′), 1.38−1.45 (m, 4H, H-3, H-3′), 1.24 (t, J = 6.4, 3.3 Hz, 2H, H-2′), 1.21 (d, J = 6.3 Hz, 3H, H-15), 1.08 (s, 3H, H-14), 0.91−0.95 (m, 5H, H-2, H-5′), 0.40−0.44 (m, 1H, H-5), 0.30−0.34 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.5 (C-1′), 170.5 (C-12), 139.1 (C-11), 122.5 (C-13), 75.7 (C-8), 70.2 (C-4), 37.8 (C-7), 37.4 (C-9), 36.0 (C-3), 34.7 (C-1), 34.5 (C-2′), 30.8 (C-6), 27.2 (C-3′), 25.0 (C-2), 23.1 (C-5), 22.3 (C-4′), 20.2 (C-15), 18.3 (C-14), 16.9 (C-10), 13.7 (C-5′). HR-MS (ESI): m/z calcd for $C_{20}H_{30}O_4Na$ ($[M + Na]^+$) 357.2036, found 357.2042.

*Carabryl 2,4-Hexadienoate (**II-6**).* Yield: 66% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25−7.28 (m, 1H, H-3′), 6.24 (d, J = 2.8 Hz, 1H, H-13), 6.14−6.17 (m, 1H, H-4′), 6.08−6.13 (m, 1H, H-5′), 5.74 (d, J = 5.40 Hz, 1H, H-2′), 5.56 (d, J = 2.3 Hz, 1H, H-13), 4.97−5.04 (m, 1H, H-4), 4.74−4.80 (m, 1H, H-8), 3.13−3.18 (m, 1H, H-7), 2.30−2.38 (m, 2H, H-9), 1.85 (d, J = 5.6 Hz, 3H, H-6′), 1.38−1.45 (m, 2H, H-3), 1.24 (d, J = 6.3 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.89−0.98 (m, 2H, H-2), 0.40−0.44 (m, 1H, H-5), 0.30−0.34 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6 (C-12), 167.0 (C-1′), 144.8 (C-3′), 139.1 (C-11), 130.0 (C-4′), 122.5 (C-13), 120.3 (C-2′), 119.4 (C-5′), 75.7 (C-8), 70.2 (C-4), 37.8 (C-7), 37.4 (C-9), 36.1 (C-3), 34.7 (C-1), 30.9 (C-6), 25.0 (C-2), 23.1 (C-5), 20.2 (C-15), 18.7 (C-6′), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{21}H_{28}O_4Na$ ($[M + Na]^+$) 367.1880, found 367.1882.

*Carabryl Laurate (**II-7**).* Yield: 48% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.24 (d, J = 2.8 Hz, 1H, H-13), 5.56 (d, J = 2.4 Hz, 1H, H-13), 4.88−4.91 (m, 1H, H-4), 4.72−4.75 (m, 1H, H-8), 3.11−3.14 (m, 1H, H-7), 2.30−2.38 (m, 2H, H-9), 1.57−1.70 (m, 2H), 0.41−0.84 (m, 23H, $CH_3(CH_2)_9CH_2-$), 0.40−0.44 (m, 1H, H-5), 0.30−0.34 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.5 (C-1′), 170.5 (C-12), 139.1 (C-11), 122.5 (C-13), 75.7 (C-8), 70.2 (C-4), 37.8 (C-7), 37.4 (C-9), 36.0 (C-3), 34.7 (C-2′), 34.6 (C-1), 31.9 (C), 30.8 (C-6), 29.6 (C-6′, C-7′, C-8′), 25.1 (C-2), 22.7 (C-5), 20.2 (C-15), 18.3 (C-14), 16.9 (C-10), 14.1(C-12′). HR-MS (ESI): m/z calcd for $C_{27}H_{45}O_4$ ($[M + H]^+$) 433.3312, found 433.3297.

*Carabryl 3-Fluorobenzoate (**II-8**).* Yield: 45% as a colorless solid. Mp: 57−59 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83 (d, J = 7.4 Hz, 1H, Ar−H), 7.71 (d, J = 9.0 Hz, 1H, Ar−H), 7.34−7.45 (m, 1H, Ar−H), 6.25 (d, J = 2.7 Hz, 1H, H-13), 5.57 (d, J = 2.2 Hz, 1H, H-13), 5.15−5.25 (m, 1H, H-4), 4.74−4.82 (m, 1H, H-8), 3.12−3.20 (m, 1H, H-7), 2.30−2.39 (m, 2H, H-9), 1.41−1.53 (m, 2H, H-3), 1.37 (d, J = 6.3 Hz, 3H, H-15), 1.09 (s, 3H, H-14), 0.91−0.95 (m, 2H, H-2), 0.41−0.49 (m, 1H, H-5), 0.31−0.37 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 165.0 (C-1′), 163.6 (C-4′), 139.1 (C-11), 133.0 (C-2′), 130.0 (C-6′), 125.2 (C-7′), 122.5 (C-13), 119.9 (C-5′), 116.5 (C-3′), 75.7 (C-8), 71.8 (C-4), 37.8 (C-7), 37.4 (C-9), 36.1 (C-3), 34.6 (C-1), 30.8 (C-6), 25.0 (C-2), 23.1 (C-5), 20.2 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{44}H_{50}F_2O_8Na$ ($[2M + Na]^+$) 767.3366, found 767.3345.

*Carabryl 4-Fluorobenzoate (**II-9**).* Yield: 44% as a colorless solid. Mp: 61−63 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05−8.07 (m, 2H, Ar−H), 7.08−7.16 (m, 2H, Ar−H), 6.24 (d, J = 2.7 Hz, 1H, H-13), 5.56 (d, J = 2.1 Hz, 1H, H-13), 5.17−5.20 (m, 1H, H-4), 4.75−4.81 (m, 1H, H-8), 3.13−1.17 (m, 1H, H-7), 2.30−2.39 (m, 2H, H-9), 1.41−1.53 (m, 2H, H-3), 1.36 (d, J = 6.2 Hz, 3H, H-15), 1.08 (s, 3H, H-14), 0.89−1.00 (m, 2H, H-2), 0.41−0.49 (m, 1H, H-5), 0.31−0.37 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 170.0 (C-5′), 165.2 (C-1′), 139.1 (C-11), 132.0 (C-3′, C-7′), 129.3 (C-2′), 122.5 (C-13), 115.7 (C-4′, C-6′), 75.7 (C-8), 71.4 (C-4), 37.8 (C-7), 37.4 (C-9), 36.2 (C-3), 34.6 (C-1), 30.8 (C-6), 26.2 (C-2), 23.1 (C-5), 20.3 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{44}H_{50}F_2O_8Na$ ($[2M + Na]^+$) 767.3366, found 767.3366.

*Carabryl 3-Chlorobenzoate (**II-10**).* Yield: 75% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.00 (s, 1H, Ar−H), 7.96 (d, J = 6.2 Hz, 1H, Ar−H), 7.52 (d, J = 6.9 Hz, 1H, Ar−H), 7.31−7.44 (m, 1H, Ar−H), 6.24 (d, J = 2.7 Hz, 1H, H-13), 5.56 (d, J = 2.3 Hz, 1H, H-13), 5.16−5.23 (m, 1H, H-4), 4.75−4.80 (m, 1H, H-8), 3.10−3.19 (m, 1H, H-7), 2.30−2.38 (m, 2H, H-9), 1.41−1.53 (m, 2H, H-3), 1.35 (d, J = 6.3 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.91−0.95 (m, 2H, H-2), 0.40−0.48 (m, 1H, H-5), 0.30−0.34 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 164.9 (C-1′), 139.1 (C-11), 134.5 (C-2′, 4′), 132.8 (C-5′), 129.7 (C-6′), 129.6 (C-3′), 127.6 (C-7′), 122.5 (C-13), 75.7 (C-8), 71.8 (C-4), 37.8 (C-7), 37.4 (C-3), 36.1 (C-9), 34.6 (C-1), 30.8 (C-6), 25.1 (C-2), 23.1 (C-5), 20.2 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{44}H_{50}Cl_2O_8Na$ ($[2M + Na]^+$) 799.2775, found 799.2766.

*Carabryl 4-Chlorobenzoate (**II-11**).* Yield: 78% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (d, J = 8.0 Hz, 2H, Ar−H), 7.41 (d, J = 8.0 Hz, 2H, Ar−H), 6.24 (d, J = 2.8 Hz, 1H, H-13), 5.56 (d, J = 2.2 Hz, 1H, H-13), 5.15−5.21 (m, 1H, H-4), 4.70−4.81 (m, 1H, H-8), 3.08−3.16 (m, 1H, H-7), 2.26−2.41 (m, 2H, H-9), 1.40−1.63 (m, 2H, H-3), 1.34 (d, J = 6.1 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.88−1.01 (m, 2H, H-2), 0.38−0.48 (m, 1H, H-5), 0.28−0.34 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7 (C-12), 165.3 (C-1′), 139.3 (C-5′), 139.1 (C-11), 130.9 (C-3′, C-7′), 128.7 (C-4′, C-6′), 122.5 (C-13), 75.7 (C-8), 71.6 (C-4), 37.8 (C-7), 37.4 (C-3), 36.2 (C-9), 34.6 (C-1), 30.8 (C-6), 25.1 (C-2), 23.1 (C-5), 20.1 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{22}H_{26}ClO_4$ ($[M + H]^+$) 389.1514, found 389.1503.

*Carabryl 2-Bromobenzoate (**II-12**).* Yield: 57% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.73 (d, J = 7.5 Hz, 1H, Ar−H), 7.65 (d, J = 8.1 Hz, 1H, Ar−H), 7.29−7.38 (m, 2H, Ar−H), 6.24 (d, J = 2.8 Hz, 1H, H-13), 5.56 (d, J = 2.3 Hz, 1H, H-13), 5.22−5.26 (m, 1H, H-4), 4.71−4.80 (m, 1H, H-8), 3.12−3.19 (m, 1H, H-7), 2.29−2.41 (m, 2H, H-9), 1.44−1.57 (m, 2H, H-3), 1.38 (d, J = 6.2 Hz,

3H, H-15), 1.07 (s, 3H, H-14), 0.92−0.99 (m, 2H, H-2), 0.42−0.46 (m, 1H, H-5), 0.34−0.38 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 166.0 (C-1′), 139.1 (C-11), 134.2 (C-5′), 133.0 (C −4′), 132.3 (C-2′), 131.0 (C-6′), 127.2 (C-7′), 122.5 (C-13), 121.3 (C-3′), 75.7 (C-8), 72.3 (C-4), 37.7 (C-7), 37.4 (C-9), 36.0 (C-3), 34.6 (C-1), 30.8 (C-6), 25.0 (C-2), 23.1 (C-5), 20.2 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{22}H_{25}BrO_4Na$ ($[M + Na]^+$) 455.0828, found 455.0830.

*Carabryl 3-Bromobenzoate (**II-13**).* Yield: 71% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.16 (s, 1H, Ar−H), 7.96 (d, J = 8.8 Hz, 1H, Ar−H), 7.68 (d, J = 7.8 Hz, 1H, Ar−H), 7.29−7.34 (m, 1H, Ar−H), 6.24 (d, J = 2.7 Hz, 1H, H-13), 5.56 (d, J = 2.2 Hz, 1H, H-13), 5.15−5.22 (m, 1H, H-4), 4.71−4.80 (m, 1H, H-8), 3.12−3.19 (m, 1H, H-7), 2.29−2.41 (m, 2H, H-9), 1.43−1.64 (m, 2H, H-3), 1.37 (d, J = 6.3 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.92−0.99 (m, 2H, H-2), 0.42−0.46 (m, 1H, H-5), 0.34−0.38 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 164.8 (C-1′), 139.1 (C-11), 135.7 (C-5′), 132.7 (C-2′), 132.5 (C-3′), 130.0 (C-7′), 128.1 (C-6′), 122.5 (C-4′), 122.4 (C-13), 75.7 (C-8), 71.8 (C-4), 37.7 (C-7), 37.4 (C-9), 36.1 (C-3), 34.5 (C-1), 30.8 (C-6), 25.1 (C-2), 23.1 (C-5), 20.3 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{22}H_{26}BrO_4$ ($[M + H]^+$) 433.1009, found 433.0991.

*Carabryl 4-Bromobenzoate (**II-14**).* Yield: 73% as a white needlelike crystal. Mp: 68−70 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (d, J = 8.0 Hz, 2H, Ar−H), 7.55 (d, J = 9.6 Hz, 2H, Ar−H), 6.23 (d, J = 2.7 Hz, 1H, H-13), 5.54 (d, J = 2.3 Hz, 1H, H-13), 5.12−5.22 (m, 1H, H-4), 4.71−4.80 (m, 1H, H-8), 3.08−3.16 (m, 1H, H-7), 2.26−2.41 (m, 2H, H-9), 1.40−1.63 (m, 2H, H-3), 1.33 (d, J = 6.2 Hz, 3H, H-15), 1.05 (s, 3H, H-14), 0.92−0.99 (m, 2H, H-2), 0.42−0.46 (m, 1H, H-5), 0.34−0.38 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 165.4 (C-1′), 139.1 (C-11), 131.7 (C-3′, 7′), 131.1 (C-4′, 6′), 129.7 (C-2′), 128.6 (C-5′), 122.5 (C-13), 75.6 (C-8), 71.6 (C-4), 37.7 (C-7), 37.6 (C-9), 36.1 (C-3), 34.5 (C-1), 30.7 (C-6), 25.0 (C-2), 23.1 (C-5), 20.3 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{44}H_{50}Br_2O_8Na$ ($[2M + Na]^+$) 887.1765, found 887.1757.

*Carabryl 2-Iodobenzoate (**II-15**).* Yield: 59% as a milk-white oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.98 (d, J = 8.2 Hz, 1H, Ar−H), 7.76 (d, J = 7.7 Hz, 1H, Ar−H), 7.39 (t, J = 7.7, 7.6 Hz, 1H, Ar−H), 7.14 (t, d=7.7, 7.6 Hz, 1H, Ar−H), 6.23 (d, J = 2.9 Hz, 1H, H-13), 5.56 (d, J = 2.2 Hz, 1H, H-13), 5.19−5.27 (m, 1H, H-4), 4.71−4.80 (m, 1H, H-8), 3.12−3.19 (m, 1H, H-7), 2.27−2.42 (m, 2H, H-9), 1.42−1.57 (m, 2H, H-3), 1.39 (d, J = 6.2 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.92−0.99 (m, 2H, H-2), 0.40−0.49 (m, 1H, H-5), 0.25−0.39 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 166.2 (C-1′), 141.2 (C-4′), 139.1 (C-11), 135.9 (C-2′), 132.4 (C-5′), 130.6 (C-7′), 127.9 (C-6′), 122.5 (C-13), 93.8 (C-3′), 75.7 (C-8), 72.3 (C-4), 37.7 (C-7), 37.4 (C-9), 36.0 (C-3), 34.6 (C-1), 30.8 (C-6), 25.0 (C-2), 23.1 (C-5), 20.2 (C-15), 18.4 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{22}H_{25}O_4INa$ ($[M + Na]^+$) 503.0690, found 503.0708.

*Carabryl 4-Iodobenzoate (**II-16**).* Yield: 70% as a light yellow solid. Mp: 60−61 °C. ^{1}H NMR(500 MHz, $CDCl_3$) δ: 7.79 (d, J = 7.1 Hz, 2H, Ar−H), 7.74 (d, J = 8.2 Hz, 2H, Ar−H), 6.22 (d, J = 2.8 Hz, 1H, H-13), 5.54 (d, J = 2.2 Hz, 1H, H-13), 5.13−5.21 (m, 1H, H-4), 4.70−4.79 (m, 1H, H-8), 3.10−1.18 (m, 1H, H-7), 2.27−2.43 (m, 2H, H-9), 1.39−1.50 (m, 2H, H-3), 1.34 (d, J = 6.3 Hz, 3H, H-15), 1.06 (s, 3H, H-14), 0.90−0.99 (m, 2H, H-2), 0.39−0.47 (m, 1H, H-5), 0.21−0.33 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.4 (C-12), 165.6 (C-1′), 139.1 (C-11), 137.7 (C-4′), 137.6 (C-6′), 131.0 (C-3′), 130.2 (C-7′), 128.5 (C-2′), 122.5 (C-13), 100.5 (C-5′), 75.6 (C-8), 71.6 (C-4), 37.7 (C-7), 37.4 (C-9), 36.1 (C-3), 34.5 (C-1), 30.7 (C-6), 25.1 (C-2), 23.1 (C-5), 20.3 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{22}H_{25}O_4INa$ ($[M + Na]^+$) 503.0690, found 503.0678.

*Carabryl 4-Cyanobenzoate (**II-17**).* Yield: 71% as a white solid. Mp: 121−123 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.14 (d, J = 7.9 Hz, 2H, Ar−H), 7.76 (d, J = 8.5 Hz, 2H, Ar−H), 6.24 (d, J = 2.8 Hz, 1H, H-13), 5.54 (d, J = 2.2 Hz, 1H, H-13), 5.19−5.27 (m, 1H, H-4), 4.70−4.84 (m, 1H, H-8), 3.10−3.22 (m, 1H, H-7), 2.27−2.43 (m, 2H, H-9), 1.42−1.55 (m, 2H, H-3), 1.38 (d, J = 6.3 Hz, 3H, H-15), 1.08 (s, 3H, H-14), 0.90−0.99 (m, 2H, H-2), 0.42−0.50 (m, 1H, H-5), 0.23−0.37 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.4 (C-12), 164.5 (C-1′), 139.1 (C-11), 134.6 (C-2′), 132.2 (C-4′, C-6′), 130.0 (C-3′, C-7′), 122.6 (C-13), 118.0 (C-8′), 116.3 (C-5′), 75.6 (C-8), 72.4 (C-4), 37.7 (C-7), 37.3 (C-9), 36.1 (C-3), 34.5 (C-1), 30.7 (C-6), 25.1 (C-2), 23.1 (C-5), 20.2 (C-15), 18.3 (C-14), 17.0 (C-10). HR-MS (ESI): m/z calcd for $C_{23}H_{26}NO_4$ ($[M + H]^+$) 380.1856, found 380.1854.

*Carabryl 2-Methylbenzoate (**II-18**).* Yield: 31% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.87 (d, J = 8.3 Hz, 1H, Ar−H), 7.39 (t, J = 4.8, 7.7 Hz, 1H, Ar−H), 7.22−7.27 (m, 2H, Ar−H), 6.24 (d, J = 2.7 Hz, 1H, H-13), 5.56 (d, J = 2.2 Hz, 1H, H-13), 5.15−5.22 (m, 1H, H-4), 4.71−4.80 (m, 1H, H-8), 3.11−3.18 (m, 1H, H-7), 2.60 (s, 3H, H-6′), 2.29−2.41 (m, 2H, H-9), 1.44−1.55 (m, 2H, H-3), 1.35 (d, J = 6.2 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.92−0.99 (m, 2H, H-2), 0.42−0.48 (m, 1H, H-5), 0.31−0.37 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 167.3 (C-1′), 139.9 (C-3′), 139.1 (C-11), 131.8 (C-6′), 131.7 (C-5′), 130.3 (C-2′), 125.7 (C-7′), 122.5 (C-13), 75.7 (C-8), 71.0 (C-4), 37.8 (C-7), 37.4 (C-9), 36.2 (C-3), 34.7 (C-1), 30.8 (C-6), 25.1 (C-2), 23.1 (C-5), 21.8 (C-8′), 20.3 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{46}H_{56}BrO_8Na$ ($[2M + Na]^+$) 759.3867, found 759.3866.

*Carabryl 2-Methoxybenzoate (**II-19**).* Yield: 43% as a colorless solid. Mp: 74−76 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.77 (d, J = 8.0 Hz, 1H, Ar−H), 7.45−7.50 (m, 1H, Ar−H), 6.98−7.01 (m, 2H, Ar−H), 6.25 (d, J = 2.9 Hz, 1H, H-13), 5.56 (d, J = 2.2 Hz, 1H, H-13), 5.17−5.27 (m, 1H, H-4), 4.73−4.84 (m, 1H, H-8), 3.92 (s, 3H, Ar−O−CH_3), 3.12−3.21 (m, 1H, H-7), 2.28−2.51 (m, 2H, H-9), 1.43−1.67 (m, 2H, H-3), 1.36 (d, J = 6.3 Hz, 3H, H-15), 1.10 (s, 3H, H-14), 0.91−1.02 (m, 2H, H-2), 0.41−0.50 (m, 1H, H-5), 0.26−0.41 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 165.9 (C-1′), 159.1 (C-3′), 139.1 (C-11), 133.2 (C-5′), 131.3 (C-7′), 122.5 (C-13), 120.1 (C-2′), 112.1 (C-4′), 75.7 (C-8), 70.9 (C-4), 55.9 (C-8′), 37.8 (C-7), 37.5 (C-9), 36.2 (C-3), 34.7 (C-1), 30.8 (C-6), 25.0 (C-2), 23.1 (C-5), 20.3 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{46}H_{56}O_8Na$ ($[2M + Na]^+$) 759.3867, found 759.3866.

*Carabryl 3-Methoxybenzoate (**II-20**).* Yield: 76% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.62 (d, J = 7.8 Hz, 1H, Ar−H), 7.56 (s, 1H, Ar−H), 7.32−7.37 (m, 1H, Ar−H), 7.09−7.10 (m, 1H, Ar−H), 6.24 (d, J = 2.6 Hz, 1H, H-13), 5.56 (d, J = 2.3 Hz, 1H, H-13), 5.15−5.23 (m, 1H, H-4), 4.72−4.81 (m, 1H, H-8), 3.85 (s, 3H, Ar−O−CH_3), 3.12−3.21 (m, 1H, H-7), 2.28−2.51 (m, 2H, H-9), 1.43−1.67 (m, 2H, H-3), 1.36 (d, J = 6.4 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.91−0.99 (m, 2H, H-2), 0.40−0.49 (m, 1H, H-5), 0.22−0.36 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 166.0 (C-1′), 159.6 (C-4′), 139.1 (C-11), 132.1 (C-2′), 129.4 (C-6′), 122.5 (C-7′), 121.9 (C-13), 119.1 (C-5′), 114.2 (C-3′), 75.7 (C-8), 71.3 (C-4), 55.4 (C-8′), 37.8 (C-7), 37.4 (C-9), 36.2 (C-3), 34.6 (C-1), 30.8 (C-6), 25.1 (C-2), 23.1 (C-5), 20.3 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{46}H_{56}O_8Na$ ($[2M + Na]^+$) 759.3843, found 759.3847.

*Carabryl 4-Methoxybenzoate (**II-21**).* Yield: 28% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.98 (d, J = 8.9 Hz, 2H, Ar−H), 7.55 (d, J = 7.2 Hz, 2H, Ar−H), 6.24 (d, J = 2.7 Hz, 1H, H-13), 5.56 (d, J = 2.2 Hz, 1H, H-13), 5.12−5.20 (m, 1H, H-4), 4.72−4.81 (m, 1H, H-8), 3.86 (s, 3H, Ar−O−CH_3), 3.12−3.21 (m, 1H, H-7), 2.28−2.41 (m, 2H, H-9), 1.43−1.67 (m, 2H, H-3), 1.33 (d, J = 6.4 Hz, 3H, H-15), 1.06 (s, 3H, H-14), 0.91−0.99 (m, 2H, H-2), 0.40−0.49 (m, 1H, H-5), 0.22−0.36 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.2 (C-12), 166.0 (C-1′), 163.3 (C-5′), 139.1 (C-11), 131.5 (C-3′, C-7′), 129.1 (C-2′), 122.5 (C-13), 113.8 (C-4′), 113.6 (C-6′), 75.7 (C-8), 70.8 (C-4), 55.4 (C-8′), 37.8 (C-7), 37.4 (C-9), 36.3 (C-3), 34.7 (C-1), 30.9 (C-6), 24.5 (C-2), 23.1 (C-5), 20.4 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{23}H_{28}O_4Na$ ($[M + Na]^+$) 391.1880, found 391.1871.

*Carabryl 2,3-Dimethoxybenzoate (**II-22**).* Yield: 77% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28 (d, J = 7.3 Hz, 1H, Ar−H), 7.04−7.12 (m, 2H, Ar−H), 6.24 (d, J = 2.7 Hz, 1H, H-13), 5.56 (d, J = 2.3 Hz, 1H, H-13), 5.18−5.27 (m, 1H, H-4), 4.73−4.81 (m, 1H, H-8), 3.89 (s, 6H, Ar−O−CH_3), 3.12−3.19 (m, 1H, H-7), 2.28−2.40 (m, 2H, H-9), 1.50−1.60 (m, 2H, H-3), 1.37 (d, J = 6.3 Hz, 3H, H-15), 1.08 (s, 3H, H-14), 0.91−0.99 (m, 2H, H-2), 0.39−0.49 (m, 1H, H-5), 0.25−0.39 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 166.1 (C-1′), 153.5 (C-4′), 148.8 (C-3′), 139.1

(C-11), 127.1 (C-7′), 123.8 (C-6′), 122.5 (C-13), 121.9 (C-5′), 115.5 (C-2′), 75.7 (C-8), 71.2 (C-4), 61.5 (C-8′), 56.1 (C-9′), 37.8 (C-7), 37.4 (C-9), 36.1 (C-3), 34.6 (C-1), 30.8 (C-6), 24.9 (C-2), 23.1 (C-5), 20.3 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{24}H_{31}O_6$ ($[M + H]^+$) 415.2115, found 415.2114.

*Carabryl 3,4-Dimethoxybenzoate (**II-23**).* Yield: 53% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.67 (d, J = 7.7 Hz, 1H, Ar−H), 7.55 (s, 1H, Ar−H), 6.89 (d, J = 7.8 Hz, 1H, Ar−H), 6.24 (d, J = 2.9 Hz, 1H, H-13), 5.56 (d, J = 2.3 Hz, 1H, H-13), 5.12−5.23 (m, 1H, H-4), 4.73−4.81 (m, 1H, H-8), 3.94 (s, 6H, Ar−O−CH_3), 3.12−3.19 (m, 1H, H-7), 2.28−2.51 (m, 2H, H-9), 1.43−1.67 (m, 2H, H-3), 1.36 (d, J = 6.3 Hz, 3H, H-15), 1.08 (s, 3H, H-14), 0.91−0.99 (m, 2H, H-2), 0.49−0.52 (m, 1H, H-5), 0.23−0.39 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 166.0 (C-1′), 152.9 (C-5′), 148.6 (C-4′), 139.1 (C-11), 123.4 (C-2′), 123.3 (C-7′), 122.5 (C-13), 112.0 (C-3′), 110.3 (C-6′), 75.7 (C-8), 71.0 (C-4), 56.1 (C-8′), 56.0 (C-9′), 37.7 (C-7), 37.4 (C-9), 36.3 (C-3), 34.6 (C-1), 30.8 (C-6), 25.1 (C-2), 23.1 (C-5), 20.4 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{24}H_{31}O_6$ ($[M + H]^+$) 415.2115, found 415.2113.

*Carabryl 2-Ethoxybenzoate (**II-24**).* Yield: 75% as a colorless solid. Mp: 77−79 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71 (d, J = 6.5 Hz, 1H, Ar−H), 7.41 (d, J = 7.6 Hz, 1H, Ar−H), 6.94−6.97 (m, 2H, Ar−H), 6.23 (d, J = 2.7 Hz, 1H, H-13), 5.56 (d, J = 2.2 Hz, 1H, H-13), 5.19−5.22 (m, 1H, H-4), 4.74−4.80 (m, 1H, H-8), 4.08−4.12 (m, 2H, Ar−O−CH_2), 3.13−3.15 (m, 1H, H-7), 2.28−2.40 (m, 2H, H-9), 1.42−1.57 (m, 5H, H-3, Ar−O−CH_2CH_3), 1.34 (d, J = 6.1 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.92−0.99 (m, 2H, H-2), 0.40−0.49 (m, 1H, H-5), 0.25−0.39 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 166.4 (C-1′), 158.2 (C-3′), 139.1 (C-11), 133.0 (C-5′), 131.2 (C-7′), 122.5 (C-13), 120.1 (C-2′), 113.2 (C-4′), 75.7 (C-8), 70.9 (C-4), 64.5 (C-8′), 37.8 (C-7), 37.4 (C-9), 36.2 (C-3), 34.8 (C-1), 30.8 (C-6), 25.0 (C-2), 23.1 (C-5), 20.3 (C-15), 18.3 (C-14), 16.9 (C-10), 14.8 (C-9′). HR-MS (ESI): m/z calcd for $C_{24}H_{31}O_5$ ($[M + H]^+$) 399.2166, found 399.2154.

*Carabryl 4-Bromophenylacetate (**II-25**).* Yield: 67% as a white solid. Mp: 48−49 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44 (d, J = 7.1 Hz, 2H, Ar−H), 7.16 (d, J = 8.3 Hz, 2H, Ar−H), 6.23 (d, J = 2.8 Hz, 1H, H-13), 5.54 (d, J = 2.4 Hz, 1H, H-13), 4.88−4.96 (m, 1H, H-4), 4.70−4.79 (m, 1H, H-8), 3.53 (s, 2H, H-2′), 3.08−3.16 (m, 1H, H-7), 2.26−2.41 (m, 2H, H-9), 1.51−1.70 (m, 2H, H-3), 1.21 (d, J = 6.3 Hz, 3H, H-15), 0.98 (s, 3H, H-14), 0.84−0.97 (m, 2H, H-2), 0.27−0.35 (m, 1H, H-5), 0.10−0.16 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6 (C-1′), 170.5 (C-12), 139.1 (C-11), 133.4 (C-3′), 131.6 (C-5′, C-7′), 131.0 (C-4′, C-8′), 122.5 (C-13), 121.0 (C-6′), 75.7 (C-8), 71.2 (C-4), 41.3 (C-2′), 37.7 (C-7), 37.3 (C-9), 35.9 (C-3), 34.4 (C-1), 30.7 (C-6), 24.8 (C-2), 23.0 (C-5), 20.1 (C-15), 18.2 (C-14), 16.8 (C-10). HR-MS (ESI): m/z calcd for $C_{23}H_{28}BrO_4$ ($[M + H]^+$) 447.1166, found 447.1165.

*Carabryl 3-Phenylpropanoate (**II-26**).* Yield: 64% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.19−7.31 (m, 5H, Ar−H), 6.24 (d, J = 2.6 Hz, 1H, H-13), 5.56 (d, J = 2.2 Hz, 1H, H-13), 4.93−4.97 (m, 1H, H-4), 4.74−4.81 (m, 1H, H-8), 3.10−3.18 (m, 1H, H-7), 2.92−2.95 (m, J = 7.8, 7.8 Hz, 2H, H-2′), 2.59−2.62 (m, J = 7.8, 7.6 Hz, 2H, H-3′), 2.26−2.42 (m, 2H, H-9), 1.51−1.70 (m, 2H, H-3), 1.18 (d, J = 6.2 Hz, 3H, H-15), 1.03 (s, 3H, H-14), 0.86−0.98 (m, 2H, H-2), 0.31−0.41 (m, 1H, H-5), 0.16−0.28 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.5 (C-1′), 170.5 (C-12), 140.5 (C-4′), 139.1 (C-11), 128.5 (C-6′, C-8′), 128.3 (C-5′, C-9′), 126.2 (C-7′), 122.5 (C-13), 75.7 (C-8), 70.5 (C-4), 37.8 (C-7), 37.4 (C-9), 36.1 (C-2′), 36.0 (C-3), 34.6 (C-1), 31.0 (C-3′), 30.8 (C-6), 24.9 (C-2), 23.1 (C-5), 20.2 (C-15), 18.3 (C-14), 16.8 (C-10). HR-MS (ESI): m/z calcd for $C_{24}H_{30}O_4Na$ ($[M + Na]^+$) 405.2036, found 405.2035.

*Carabryl 4-Isopropylbenzoate (**II-27**).* Yield: 82% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.98 (d, J = 8.0 Hz, 2H, Ar−H), 7.31 (d, J = 6.9 Hz, 2H, Ar−H), 6.25 (d, J = 2.6 Hz, 1H, H-13), 5.56 (d, J = 2.3 Hz, 1H, H-13), 5.16−5.24 (m, 1H, H-4), 4.73−4.82 (m, 1H, H-8), 3.10−3.19 (m, 1H, H-7), 2.29−2.46 (m, 2H, H-9), 1.96−2.09 (m, 1H, H-6′), 1.46−1.58 (m, 2H, H-3), 1.36 (d, J = 6.2 Hz, 3H, H-15), 1.29 (d, J = 5.9 Hz, 6H, H-9′, H-10′), 1.08 (s, 3H, H-14), 0.92−0.99 (m, 2H, H-2), 0.42−0.51 (m, 1H, H-5), 0.32−0.37 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 166.2 (C-1′), 154.2 (C-5′), 139.1 (C-11), 129.7 (C-3′, C-7′), 126.6 (C-2′), 126.4 (C-4′, C-6′), 122.5 (C-13), 75.7 (C-8), 70.9 (C-4), 37.8 (C-7), 37.4 (C-9), 36.2 (C-3), 34.7 (C-1), 34.2 (C-8′), 30.8 (C-6), 25.1 (C-2), 23.7 (C-9′, C-10′), 23.1 (C-5), 20.4 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{50}H_{64}O_8Na$ ($[2M + Na]^+$) 815.4493, found 815.4450.

*Carabryl 3-Phenylacrylate (**II-28**).* Yield: 70% as a white solid. Mp: 105−106 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63 (d, J = 7.6 Hz, 2H, Ar−H), 7.05−7.12 (m, 3H, Ar−H), 6.88 (d, J = 8.1 Hz, 1H, H-3′), 6.31 (d, J = 15 Hz, 1H, H-2′), 6.24 (d, J = 2.9 Hz, 1H, H-13), 5.56 (d, J = 2.3 Hz, 1H, H-13), 5.05−5.12 (m, 1H, H-4), 4.72−4.81 (m, 1H, H-8), 3.09−3.17 (m, 1H, H-7), 2.29−2.37 (m, 2H, H-9), 1.39−1.52 (m, 2H, H-3), 1.30 (d, J = 6.3 Hz, 3H, H-15), 1.09 (s, 3H, H-14), 0.90−1.02 (m, 2H, H-2), 0.40−0.48 (m, 1H, H-5), 0.24−0.37 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6 (C-12), 166.6 (C-1′), 144.5 (C-3′), 139.1 (C-11), 134.8 (C-8′), 134.5 (C-6′,), 130.3 (C-4′,), 128.9 (C-9′), 128.0 (C-5′), 122.5 (C-13), 119.5 (C-7′), 118.6 (C-2′), 75.7 (C-8), 70.6 (C-4), 37.8 (C-7), 37.4 (C-9), 36.2 (C-3), 34.7 (C-1), 31.0 (C-6), 24.7 (C-2), 23.1 (C-5), 20.3 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{48}H_{56}O_8Na$ ($[2M + Na]^+$) 783.3867, found 783.3852.

*Carabryl 3-(4-Nitrophenyl)acrylate (**II-29**).* Yield: 70% as a light yellow granular solid. Mp: 122−123 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.26 (d, J = 7.3 Hz, 2H, Ar−H), 7.68 (d, J = 3.4 Hz, 2H, Ar−H), 6.55 (d, J = 15 Hz, 1H, H-2′), 6.24 (d, J = 2.7 Hz, 1H, H-13), 5.56 (d, J = 2.2 Hz, 1H, H-13), 5.03−5.15 (m, 1H, H-4), 4.71−4.82 (m, 1H, H-8), 3.09−3.17 (m, 1H, H-7), 2.29−2.37 (m, 2H, H-9), 1.39−1.52 (m, 2H, H-3), 1.30 (d, J = 6.2 Hz, 3H, H-15), 1.09 (s, 3H, H-14), 0.90−1.02 (m, 2H, H-2), 0.40−0.48 (m, 1H, H-5), 0.22−0.38 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 165.7 (C-1′), 148.5 (C-7′), 141.5 (C-3′), 140.6 (C-4′), 139.1 (C-11), 130.2 (C-2′), 128.6 (C-5′, C-9′), 124.2 (C-6′, C-8′), 122.6 (C-13), 75.7 (C-8), 71.4 (C-4), 37.7 (C-7), 37.4 (C-9), 36.1 (C-3), 34.5 (C-1), 30.8 (C-6), 25.0 (C-2), 23.1 (C-5), 20.2 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{24}H_{27}NO_6Na$ ($[M + Na]^+$) 448.1731, found 448.1733.

*Carabryl 3-(3,4-Dimethoxyphenyl)acrylate (**II-30**).* Yield: 76% as a milky white solid. Mp: 68−69 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.62 (d, J = 15 Hz, 1H, H-3′), 7.11 (d, J = 9.8 Hz, 1H, Ar−H), 7.07 (s, 1H, Ar−H), 6.88 (d, J = 8.3 Hz, 1H, Ar−H), 6.31 (d, J = 16.3 Hz, 1H, H-2′), 6.24 (d, J = 2.7 Hz, 1H, H-13), 5.56 (d, J = 2.2 Hz, 1H, H-13), 5.07−5.09 (m, 1H, H-4), 4.71−4.82 (m, 1H, H-8), 3.92 (s, 6H, Ar−O−CH_3), 3.09−3.17 (m, 1H, H-7), 2.29−2.37 (m, 2H, H-9), 1.39−1.52 (m, 2H, H-3), 1.31 (d, J = 6.2 Hz, 3H, H-15), 1.09 (s, 3H, H-14), 0.90−1.02 (m, 2H, H-2), 0.40−0.48 (m, 1H, H-5), 0.24−0.38 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 166.9 (C-1′), 151.1 (C-7′), 149.2 (C-6′), 144.4 (C-3′), 139.1 (C-11), 127.4 (C-4′), 122.6 (C-9′), 122.5 (C-13), 116.3 (C-2′), 111.1 (C-8′), 109.6 (C-5′), 75.7 (C-8), 70.4 (C-4), 56.0 (C-11′), 55.9 (C-10′), 37.8 (C-7), 37.4 (C-9), 36.2 (C-3), 34.6 (C-1), 30.8 (C-6), 25.2 (C-2), 23.1 (C-5), 20.3 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{26}H_{33}O_6$ ($[M + H]^+$) 441.2272, found 441.2255.

*Carabryl α-Naphthylcarboxylate (**II-31**).* Yield: 78% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.90 (d, J = 8.6 Hz, 1H, Ar−H), 8.14 (d, J = 6.7 Hz, 1H, Ar−H), 8.01 (d, J = 8.4 Hz, 1H, Ar−H), 7.88 (d, J = 8.5 Hz, 1H, Ar−H), 7.60 (t, J = 7.8, 7.9 Hz, 1H, Ar−H), 7.46−7.56 (m, 2H, Ar−H), 6.24 (d, J = 2.6 Hz, 1H, H-13), 5.56 (d, J = 2.3 Hz, 1H, H-13), 5.29−5.35 (m, 1H, H-4), 4.72−4.81 (m, 1H, H-8), 3.12−3.21 (m, 1H, H-7), 2.28−2.41 (m, 2H, H-9), 1.43 (d, J = 6.3 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.89−1.01 (m, 2H, H-2), 0.42−0.51 (m, 1H, H-5), 0.24−0.38 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 167.2 (C-1′), 139.1 (C-11), 133.9 (C-11′), 133.2 (C-5′), 131.4 (C-10′), 129.8 (C-3′), 128.6 (C-6′), 127.9 (C-8′), 127.7 (C-2′), 126.2 (C-7′), 125.8 (C-9′), 124.5 (C-4′), 122.5 (C-13), 75.7 (C-8), 71.3 (C-4), 37.8 (C-7), 37.4 (C-9), 36.3 (C-3), 34.7 (C-1), 30.8 (C-6), 25.2 (C-2), 23.2 (C-5), 20.4 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{52}H_{56}O_8Na$ ($[2M + Na]^+$) 831.3867, found 831.3850.

*Carabryl α-Naphthylacetate (**II-32**).* Yield: 88% as a light yellow oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29 (d, J = 7.1 Hz, 1H, Ar−H), 8.06 (d, J = 5.7 Hz, 1H, Ar−H), 7.99 (m, 1H, Ar−H), 7.67−7.77 (m, 2H, Ar−H), 7.61−7.66 (m, 2H, Ar−H), 6.42 (d, J = 2.7 Hz,

1H, H-13), 5.72 (d, J = 2.2 Hz, 1H, H-13), 5.10−5.16 (m, 1H, H-4), 4.83−4.91 (m, 1H, H-8), 3.11−3.21 (m, 1H, H-7), 2.31−2.56 (m, 2H, H-9), 1.78−1.80 (s, 2H, H-2′) 1.41 (d, J = 6.2 Hz, 3H, H-15), 0.97 (s, 3H, H-14), 0.34−0.43 (m, 1H, H-5), 0.19−0.25 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.1 (C-1′), 170.5 (C-12), 139.1 (C-11), 133.9 (C-4′), 132.2 (C-5′), 131.0 (C-12′), 128.7 (C-7′), 128.1 (C-6′), 128.0 (C-11′), 126.2 (C-9′), 125.8 (C-8′), 125.5 (C-10′), 124.1 (C-3′), 122.4 (C-13), 75.7 (C-8), 70.9 (C-4), 39.9 (C-2′), 37.7 (C-7), 37.3 (C-9), 35.9 (C-3), 34.2 (C-1), 30.6 (C-6), 24.6 (C-2), 22.9 (C-5), 20.2 (C-15), 18.0 (C-14), 16.4 (C-10). HR-MS (ESI): m/z calcd for $C_{27}H_{31}O_4$ ($[M + H]^+$) 419.2217, found 419.2202.

*Carabryl Nicotinate (**II-33**).* Yield: 67% as a yellow oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.21 (s, 1H, Ar−H), 8.78 (d, J = 4.6 Hz, 1H, Ar−H), 7.29 (d, J = 6.9 Hz, 1H, Ar−H), 7.38−7.42 (m, 1H, Ar−H), 6.24 (d, J = 2.7 Hz, 1H, H-13), 5.56 (d, J = 2.2 Hz, 1H, H-13), 5.17−5.28 (m, 1H, H-4), 4.72−4.81 (m, 1H, H-8), 3.12−3.19 (m, 1H, H-7), 2.28−2.41 (m, 2H, H-9), 1.37 (d, J = 6.3 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.89−1.01 (m, 2H, H-2), 0.40−0.49 (m, 1H, H-5), 0.23−0.36 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 164.9 (C-1′), 153.3 (C-4′), 150.8 (C-3′), 139.1 (C-11), 137.0 (C-6′), 126.6 (C-2′), 123.3 (C-5′), 122.6 (C-13), 75.6 (C-8), 72.0 (C-4), 37.7 (C-7), 37.4 (C-3), 36.1 (C-9), 34.5 (C-1), 30.7 (C-6), 25.0 (C-2), 23.1 (C-5), 20.2 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{21}H_{26}NO_4$ ($[M + H]^+$) 356.1856, found 356.1842.

*Carabryl Isonicotinate (**II-34**).* Yield: 53% as a yellow oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.78 (d, J = 4.7 Hz, 2H, Ar−H), 7.84 (d, J = 5.3 Hz, 2H, Ar−H), 6.24 (d, J = 2.6 Hz, 1H, H-13), 5.56 (d, J = 2.3 Hz, 1H, H-13), 5.17−5.28 (m, 1H, H-4), 4.72−4.81 (m, 1H, H-8), 3.12−3.19 (m, 1H, H-7), 2.28−2.41 (m, 2H, H-9), 1.38 (d, J = 6.2 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.89−1.01 (m, 2H, H-2), 0.40−0.49 (m, 1H, H-5), 0.22−0.36 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 164.9 (C-1′), 150.6 (C-4′, C-5′), 139.0 (C-11), 137.9 (C-2′), 122.8 (C-3′, C-6′), 122.6 (C-13), 75.6 (C-8), 72.5 (C-4), 37.7 (C-7), 37.3 (C-3), 36.1 (C-9), 34.5 (C-1), 30.7 (C-6), 25.0 (C-2), 23.1 (C-5), 20.2 (C-15), 18.3 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{21}H_{26}NO_4$ ($[M + H]^+$) 356.1856, found 356.1842.

*Carabryl 2-Chloronicotinate (**II-35**).* Yield: 69% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.51 (d, J = 3.8 Hz, 1H, Ar−H), 8.11 (d, J = 3.8 Hz, 1H, Ar−H), 7.30−7.36 (m, 1H, Ar−H), 6.24 (d, J = 2.8 Hz, 1H, H-13), 5.56 (d, J = 2.4 Hz, 1H, H-13), 5.19−5.30 (m, 1H, H-4), 4.72−4.82 (m, 1H, H-8), 3.12−3.20 (m, 1H, H-7), 2.28−2.52 (m, 2H, H-9), 1.39 (d, J = 6.3 Hz, 3H, H-15), 1.08 (s, 3H, H-14), 0.88−1.03 (m, 2H, H-2), 0.39−0.49 (m, 1H, H-5), 0.24−0.38 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 164.4 (C-1′), 151.7 (C-5′), 149.7 (C-3′), 140.0 (C-6′), 139.1 (C-11), 127.7 (C-2′), 122.5 (C-7′), 122.1 (C-13), 75.6 (C-8), 73.0 (C-4), 37.7 (C-7), 37.4 (C-9), 36.0 (C-3), 34.5 (C-1), 30.7 (C-6), 25.0 (C-2), 23.1 (C-5), 20.0 (C-15), 18.3 (C-14), 17.0 (C-10). HR-MS (ESI): m/z calcd for $C_{21}H_{25}O_4NCl$ ($[M + H]^+$) 390.1467, found 390.1467.

*Carabryl 5-Methyl-2-pyrazinoate (**II-36**).* Yield: 34% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.16 (s, 1H, Ar−H), 8.61 (s, 1H, Ar−H), 6.24 (s, 1H, H-13), 5.56 (s, 1H, H-13), 5.28−5.37 (m, 1H, H-4), 4.72−4.83 (m, 1H, H-8), 3.12−3.21 (m, 1H, H-7), 2.69 (s, 3H, H-5′), 2.25−2.45 (m, 2H, H-9), 1.43 (d, J = 6.3 Hz, 3H, H-15), 1.08 (s, 3H, H-14), 0.91−1.01 (m, 2H, H-2), 0.43−0.53 (m, 1H, H-5), 0.24−0.39 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.3 (C-12), 163.7 (C-1′), 157.6 (C-4′), 145.1 (C-3′), 144.3 (C-5′), 140.8 (C-2′), 139.0 (C-11), 122.3 (C-13), 75.5 (C-8), 72.5 (C-4), 37.6 (C-7), 37.2 (C-9), 35.8 (C-3), 34.3 (C-1), 30.6 (C-6), 24.9 (C-2), 23.0 (C-5), 21.8 (C-6′), 20.1 (C-15), 18.2 (C-14), 16.8 (C-10). HR-MS (ESI): m/z calcd for $C_{21}H_{27}N_2O_4$ ($[M + H]^+$) 371.1965, found 371.1955.

*Carabryl 2-Thiophenecarboxylate (**II-37**).* Yield: 42% as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.79 (s, 1H, Ar−H), 7.53 (d, J = 4.7 Hz, 1H, Ar−H), 7.10 (s, 1H, Ar−H), 6.24 (s, 1H, H-13), 5.56 (s, 1H, H-13), 5.07−5.18 (m, 1H, H-4), 4.72−4.83 (m, 1H, H-8), 3.10−3.19 (m, 1H, H-7), 2.28−2.52 (m, 2H, H-9), 1.14 (d, J = 6.3 Hz, 3H, H-15), 1.07 (s, 3H, H-14), 0.88−1.01 (m, 2H, H-2), 0.37−0.49 (m, 1H, H-5), 0.21−0.38 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (C-12), 161.9 (C-1′), 139.1 (C-11), 134.5 (C-2′), 133.1 (C-3′), 132.1 (C-5′), 127.7 (C-4′), 122.5 (C-13), 75.7 (C-8), 71.6 (C-4), 37.8 (C-7), 37.4 (C-9), 36.1 (C-3), 34.6 (C-1), 30.8 (C-6), 25.0 (C-2), 23.1 (C-5), 20.3 (C-15), 18.2 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{20}H_{24}SO_4Na$ ($[M + Na]^+$) 383.1288, found 383.1278.

*Carabryl 3-Indolepropionate (**II-38**).* Yield: 63% as a light yellow oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.31 (s, 1H, Ar−N*H*), 7.59 (d, J = 8.4 Hz, 1H, Ar−H), 7.31 (d, J = 8.4 Hz, 1H, Ar−H), 7.16 (t, J = 6.7, 8.4 Hz, 1H, Ar−H), 7.09 (t, J = 7.3, 7.9 Hz, 1H, Ar−H), 6.98 (s, 1H, Ar−H), 6.22 (d, J = 2.6 Hz, 1H, H-13), 5.52 (d, J = 2.3 Hz, 1H, H-13), 4.92−4.95 (m, 1H, H-4), 4.70−4.75 (m, 1H, H-8), 3.12−3.21 (m, 1H, H-7), 3.09 (t, J = 7.4, 8.0 Hz, 2H, H-3′), 2.69 (t, J = 7.7, 7.6 Hz, 2H, H-2′), 2.22−2.43 (m, 2H, H-9), 1.19 (d, J = 6.3 Hz, 3H, H-15), 0.97 (s, 3H, H-14), 0.81−0.94 (m, 2H, H-2), 0.27−0.35 (m, 1H, H-5), 0.08−0.20 (m, 1H, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.1 (C-1′), 170.8 (C-12), 139.2 (C-11), 136.4 (C-6′), 127.2 (C-11′), 122.6 (C-5′), 122.1 (C-9′), 121.9 (C-8′), 119.2 (C-13), 118.7 (C-10′), 114.8 (C-4′), 111.3 (C-7′), 75.8 (C-8), 70.5 (C-4), 37.7 (C-7), 37.4 (C-9), 36.0 (C-3), 35.3 (C-2′), 34.5 (C-1), 30.7 (C-6), 24.9 (C-2), 23.0 (C-5), 20.8 (C-3′), 20.2 (C-15), 18.2 (C-14), 16.9 (C-10). HR-MS (ESI): m/z calcd for $C_{26}H_{32}O_4N$ ($[M + H]^+$) 422.2326, found 422.2320.

Microorganism and Preparation of Spore Suspension. The fungal pathogen *C. lagenarium* (Accession No. 36199) was provided by Agricultural Culture Collection of China. This isolate was cultured for 2 weeks at 25 ± 1 °C on potato dextrose agar (PDA) after being retrieved from the storage tube. Plates were then flooded with sterile distilled water, and then conidia were scraped with a glass rod. Mycelial debris was removed by filtration through double-layer cheesecloth. The spores were harvested and suspended in sterile distilled water containing 0.1% (v/v) Tween 20. Concentration of the spore suspension was adjusted to 1.0×10^6 spore/mL by diluting with sterilized distilled water using a SUPERIOR hemocytometer (Berlin, Germany).[21]

Spore Germination Assay. The tested samples (10 mg) dissolved in methanol (0.1 mL) were diluted with sterile distilled water to prepare 10 mL of stock solution, which was further diluted to prepare test solutions in which the final concentration of methanol was <1% (v/v). A series of concentrations of tested samples and one control (1% methanol with sterile distilled water) were separately tested for spore germination of *C. lagenarium*. The samples were mixed with spore suspension of *C. lagenarium* containing 1.0×10^6 spores/mL. Aliquots of 10 μL of prepared spore suspension were placed on separate glass slides in triplicate. Slides containing the spores were incubated in a moisture chamber at 24 ± 1 °C for 8 h. Each slide was then observed under the microscope for spore germination. The spore generated germ tubes were enumerated, and the percentage of spore germination was calculated. Spores were considered to have germinated if the length of the germ tube was at least half the length of the spore. The numbers of generated spores were counted, and the percentage of germinated spores was calculated. Chlorothalonil, purchased from Xiangtan Huayuan Fine-Chem Co., Ltd., used as the positive control and tested along with carabrol and carabrone.

Statistical Analysis. The experimental data on the antifungal activity of ester derivatives of carabrol against *C. lagenarium* were analyzed using SPSS 16.0 for Windows.

RESULTS AND DISCUSSION

Synthesis. As shown in Scheme 1, 38 new ester derivatives (**II**) of carabrol were synthesized by the reaction of carabrol with various carboxylic acids, in the presence of DCC as coupling reagent and DMAP as catalyst.[20]

Scheme 1. Synthetic Route of Carabrol Ester Derivatives

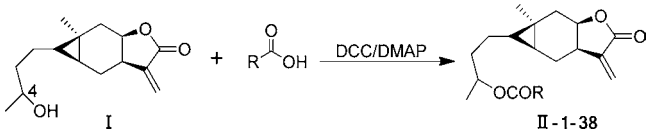

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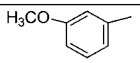
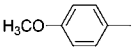
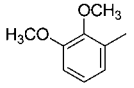
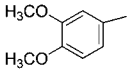
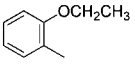
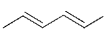
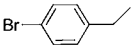
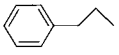
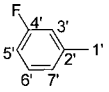
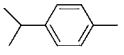
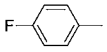
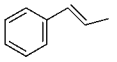
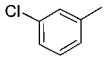
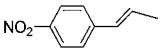
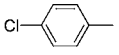
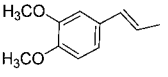
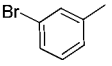
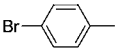
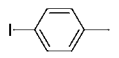
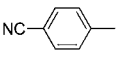
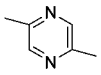
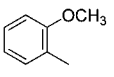
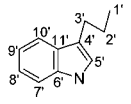
Table 1. The 50% Inhibition Concentration (IC_{50}) of 38 Ester Derivatives of Carabrol against Spore Germination of *C. lagenarium*

No.	R [a]	IC_{50} [b] (μg/mL)	No.	R [a]	IC_{50} [b] (μg/mL)
Ⅱ-1	CH_3—	10.77±0.09	Ⅱ-20		49.45±0.8
Ⅱ-2	CH_2Cl—	4.51±0.06	Ⅱ-21		47.47±0.37
Ⅱ-3	CH_3CH_2—	23.28±0.57	Ⅱ-22		35.79±0.64
Ⅱ-4	$CH_3CH_2CH_2$—	20.84±0.41	Ⅱ-23		32.97±1.66
Ⅱ-5	$CH_3(CH_2)_2CH_2$—	31.19±0.59	Ⅱ-24		41.64±1.64
Ⅱ-6		8.41±0.53	Ⅱ-25		44.43±1.04
Ⅱ-7	$CH_3(CH_2)_9CH_2$—	33.6±1.96	Ⅱ-26		13.24±0.26
Ⅱ-8		30.43±0.82	Ⅱ-27		2.82±0.12
Ⅱ-9		21.24±0.11	Ⅱ-28		33.2±1.29
Ⅱ-10		26.7±0.87	Ⅱ-29		22.85±0.22
Ⅱ-11		31.82±0.24	Ⅱ-30		25.06±0.79
Ⅱ-12		29.18±1.12	Ⅱ-31		23.29±0.29
Ⅱ-13		36.71±0.9	Ⅱ-32		30.27±0.21
Ⅱ-14		31.29±0.28	Ⅱ-33		8.26±0.25
Ⅱ-15		39.05±0.68	Ⅱ-34		4.31±0.09
Ⅱ-16		33.48±0.85	Ⅱ-35		4.62±0.04
Ⅱ-17		2.70±0.13	Ⅱ-36		20.49±1.16
Ⅱ-18		52.33±1.84	Ⅱ-37		30.82±0.44
Ⅱ-19		46.11±1.5	Ⅱ-38		12.82±0.63
	Carabrol	24.81±0.34		Carabrone	9.98±0.18
	Chlorothalonil [c]	0.87±0.11			

[a] Substituent group on the C-4 position of carabrol. [b] All values are presented as means ± SD (n = 3). [c] Chlorothalonil was used as the positive control.

Antifungal Activity. It was found that the substituent group on the C-4 position had an important effect on the activity of carabrol and its derivatives. The changes of size, conformation, and chemical property of carabrol and its ester derivatives had significant influence on its antifungal activity, with IC_{50} values ranging from 2.70 to 52.33 μg/mL (Table 1).

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With the increase in length of the carbon chain to aliphatic acids series, the antifungal activity of the corresponding derivatives gradually reduced, apart from compounds **II-2** and **II-6**, which had a chlorine atom and two double bonds, respectively. It was observed that when chlorine atom was introduced to the methyl group of **II-1**, affording **II-2**, the antifungal activity was increased, with the IC_{50} going from 10.77 to 4.51 μg/mL. Whereas upon the introduction of a double bond at the side chain of **II-26**, generating **II-28**, the antifungal activity was reduced, with the IC_{50} going from 13.24 to 33.20 μg/mL.

Variation of the substituent on the phenyl ring also resulted in different antifungal activity of derivatives with IC_{50} values ranging from 2.70 to 52.33 μg/mL, while most of these derivatives ranged from 21 to 52 μg/mL. The derivatives with electron-attracting groups in the phenyl ring showed higher activity than those with electron-donating ones. This trend was observed irrespective of whether the substituent was in an ortho, meta, and para position, which was shown by comparison of IC_{50}s of the bromo-substituted compounds **II-12** (29.18 μg/mL), **II-13** (36.71 μg/mL), and **II-14** (31.29 μg/mL) with the corresponding methoxy-substituted compounds **II-19** (46.11 μg/mL), **II-20** (49.45 μg/mL), and **II-21** (47.47 μg/mL). When a cyano or isopropyl group was introduced in the phenyl ring, as in **II-17** (4-cyanophenyl) and **II-27** (4-isopropyl), high antifungal activity was observed with an IC_{50} of 2.70 and 2.82 μg/mL, respectively. Introduction of a pyridyl group in place of a phenyl group resulted in higher antifungal activity, as shown by **II-33** with an IC_{50} of 8.26 μg/mL and **II-34** with an IC_{50} of 4.31 μg/mL. Introduction of a chlorine atom to the pyridyl compound **II-33**, resulting in **II-35**, increased the antifunfal activity, with the IC_{50} going from 8.26 to 4.62 μg/mL.

Of these 38 ester derivatives, 16 showed higher antifungal activity than that of carabrol and 7 showed higher antifungal activity than that of carabrone. Antifungal activity increased, with the IC_{50} of 24.81 μg/mL for carabrol improving to 2.70 μg/mL for **II-17**, which showed only slightly lower antifungal activity than that of the commercial fungicide chlorothalonil (IC_{50} 0.87 μg/mL).

In conclusion, to improve the antifungal activity of carabrol, 38 new ester derivatives were designed and synthesized, and their antifungal activity against *C. lagenarium* was evaluated. Ester derivatives **II-17** and **II-27** have been identified as promising leads toward to the development of new environmentally friendly fungicides for sustainable agricultural production.

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Notes

The authors declare no competing financial interest.

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