FULL PAPER

Design, Synthesis, and Bioassay of Novel Compounds of Isolongifolenone Oxime Derivatives

by **Wu Zhang**[a]), **Aiqun Wu**[a]), **Haitang Xu**[a]), **Yuxing Mo**[b]), **Jie Chen**[b]), and **Liqun Shen***[a])[c])

[a]) College of Chemistry and Chemical Engineering, Guangxi University for Nationalities, Nanning, Guangxi, P. R. China (phone: +86-771-3267019; e-mail: shenliqun@gxun.edu.cn)

[b]) Development of Biological Test, Guangxi Tianyuan Biochemistry Co., Ltd., Nanning, Guangxi, P. R. China (phone: +86-13978852256, e-mail: zhigao326@126.com)

[c]) Key Laboratory of Development and Application of Forest Chemical of Guangxi, Nanning, Guangxi, P. R. China

A succession of new isolongifolenone oxime derivatives have been designed and synthesized. The structures of these compounds were identified by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra, and elemental analysis. The bioassays of antibacterial, antifungal, and insecticidal activity were carried out. The *in vitro* antibacterial and antifungal activities were evaluated by the disk diffusion method, and the minimum inhibitory concentration was determined by the microdilution method, while the insecticidal activity was tested by the spraying method or the straw impregnation method. The results of bioassays showed that compound **3f** was more active in resisting all the tested bacterial and fungal organisms when compared to the standard drug amoxicillin at the lowest concentration of 31.3 μg/ml. Compound **4**, synthesized by *Beckmann* rearrangement reaction of isolongifone oxime, exerted moderate insecticidal activity against soybean aphid. Furthermore, compound **3m** exhibited more activity in killing armyworms than the standard drug flucycloxuron at the concentration of 0.5 mg/l.

Keywords: Synthesis, Isolongifolenone oxime, Oxime ether, Biological activities.

Introduction

Based on the natural products to synthesize novel compounds for application in medicine or agriculture, this study has been carried out as a result of biological and pharmacological properties of these compounds. Oxime ether derivatives, known as important precursors and intermediates for natural products and various drugs [1][2], have been the hot topic for research workers due to their bioactivity against antibacterial [3][4], antifungal [5][6], larvicidal [7][8], antiretroviral [9], antineoplastic [10][11], BK channel-opening [12], and acaricidal activities. In addition, oxime ether derivatives have also been reported as potent anti-inflammatory agents and inhibitors of monocyte-to-macrophage transformation [13], β-adrenergic blocking [14 – 16], anticancer agents [17], sugar surfactants [18], and ethylene inhibitor [19]. Recently, isolongifolenone, obtained through the oxidation of isolongifolene which was isomerized by natural product of longifolene [20], has been found to exert potent against tyrosinase [21] and breast cancer [22]. Besides, isolongifolenone was superior to DEET in repelling ticks [23] and deterring feeding mosquitoes [24]. However, up to date, isolongifolenone oxime ethers or esters derivatives have not been reported.

Synthesizes of novel molecules which were similar to known bioactive molecules with key structural skeleton is accorded with the search for new leads in drug designing program. Herein, we planned to synthesize isolongifolenone oxime derivatives and evaluate their potential bioactive value in medicine or agriculture. The synthesis pathway of these compounds was shown in the *Scheme*.

Results and Discussion

As outlined in the *Scheme*, reaction yields were not optimized. Our investigation was started by the preparation of isolongifolenone **1**. Usually, it was obtained by allylic oxidation of alkenes [25]. The yield was low when the preparation was carried out based on the similar methods in the literature. Isolongifolenone **1** was prepared through allylic oxidation in the presence of NaClO/^{t}BuOOH for 10 h at 2 – 5 °C to give compound **1** in good yield (82.6%). It should be noted that compound **2** was easily prepared by the reaction of $NH_2OH \cdot HCl$ and isolongifolene **1** in refluxing EtOH/H_2O for 3 h. Treatment of compound **2** with alkyl halide or acid halide resulted in the formation of the desired compounds **3a** – **3m**. Compound **2** could be converted to compound **4** *via Beckmann* rearrangement reaction. The structures of the target compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra, and elemental analysis. The IR spectra of the compound **1** showed characteristic absorption bands at 1662 cm^{-1}, which indicated the presence of C=O. The stretching frequency at 1468 cm^{-1} was assigned

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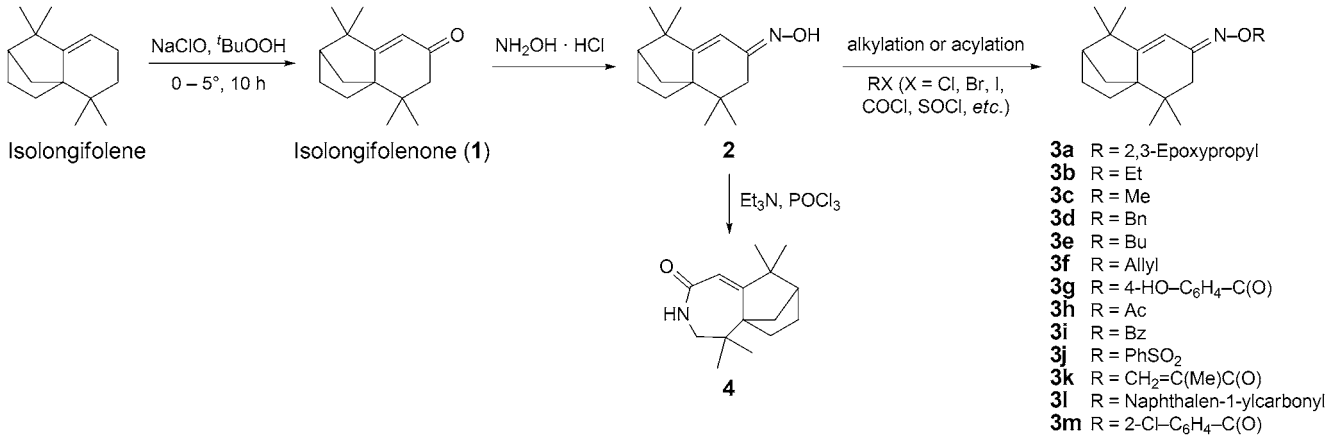
Scheme. The synthesis pathway of compounds **1** – **4**.



to C=C vibrations. The main characteristic of the ^{1}H-NMR spectra for the isolongifolenone oxime derivatives was at δ(H) 0.89 – 1.16 for Me. The functional group –C=CH showed a *singlet* at 5.70 – 6.46 ppm.

Antibacterial and Antifungal Activities

The target compounds **1** – **4** were screened for both antibacterial and antifungal activities. The *in vitro* antimicrobial activity was carried out by the disk diffusion method. Amoxicillin was used as a positive control for bacteria and amphotericin B for antifungal activity.

The screened compounds were further checked by a serial dilution assay to find the minimum inhibitory concentrations (*MIC*s) values. The results of antibacterial activity were summarized in *Tables 1* and *2*. Compounds **1** and **3k** exhibited potent *in vitro* antibacterial activity against *Pseudomonas aeruginosa* and *Escherichia coli*. Compound **1** at

Table 1. Antibacterial activity of target compounds, measured by the inhibition zones test [mm]

Compound	Inhibition zones of *Gram* bacteria [mm]				
	Pneumobacillus	*Pseudomonas aeruginosa*	*Proteus vulgaris*	*Escherichia coli*	*Staphylococcus aureus*
1	10.5 ± 0.3	18.0 ± 0.5	17.5 ± 0.3	18.7 ± 0.3	15.8 ± 0.3
3a	10.1 ± 0.3	10.5 ± 0.4	15.7 ± 0.4	18.2 ± 0.5	17.2 ± 0.4
3b	15.4 ± 0.4	14.7 ± 0.3	10.2 ± 0.5	14.5 ± 0.4	11.0 ± 0.4
3c	10.3 ± 0.3	16.5 ± 0.3	10.7 ± 0.4	14.5 ± 0.3	15.7 ± 0.5
3e	10.6 ± 0.3	16.7 ± 0.4	15.8 ± 0.5	10.7 ± 0.4	13.7 ± 0.4
3f	17.3 ± 0.4	18.4 ± 0.3	17.5 ± 0.3	19.2 ± 0.3	17.3 ± 0.5
3j	14.0 ± 0.3	18.3 ± 0.4	15.0 ± 0.3	17.2 ± 0.3	17.5 ± 0.3
3k	10.7 ± 0.3	18.1 ± 0.4	14.8 ± 0.5	19.0 ± 0.4	13.7 ± 0.3
3m	14.1 ± 0.3	14.5 ± 0.3	14.7 ± 0.3	17.3 ± 0.3	13.5 ± 0.3
Amoxicillin	17.2 ± 0.5	18.2 ± 0.4	17.2 ± 0.8	19.0 ± 0.2	17.2 ± 0.4
DMSO	–	–	–	–	–

Table 2. The minimum inhibitory concentration (*MIC*) of test compounds, positive control: amoxicillin [μg/ml]

Compound	*MIC* [μg/ml]				
	Pneumobacillus	*Pseudomonas aeruginosa*	*Proteus vulgaris*	*Escherichia coli*	*Staphylococcus aureus*
1	250	31.3	31.3	31.3	62.5
3a	250	250	62.5	31.3	31.3
3b	62.5	125	250	125	250
3c	250	62.5	250	125	62.5
3e	250	62.5	62.5	250	125
3f	31.3	31.3	31.3	31.3	31.3
3j	125	31.3	125	62.5	31.3
3k	250	31.3	125	31.3	125
3m	125	125	125	62.5	125
Amoxicillin	31.3	31.3	31.3	31.3	31.3

the concentration of 31.3 μg/ml was effective in killing *Proteus vulgaris*. Compound **3a** proved to be potent against *E. coli* and *Staphylococcus aureus*. Besides, compound **3j** was found to be active against *P. aeruginosa* and *S. aureus*. As for antifungal activity, it can be clearly seen from *Tables 3* and *4* that both compounds **3b** and **3i** showed very good antifungal activity against *Aspergillus niger*, *Colletotrichum musae*, and corn sheath blight at the concentration of 31.3 μg/ml. Compounds **2** and **3g** were as effective as amphotericin in *Exserohilum turcicum* and *Alternaria musae*, respectively. Compound **3f** showed excellent activity against all the tested bacterial and fungus when compared with the standard drug at the concentration of 31.3 μg/ml. From the obtained antibacterial and antifungal activity data, we can conclude that compounds with R (R = allyl, 4-hydroxybenzoyl, or hydrogen) have high activity against microorganism.

Insecticidal Activity

The insecticidal activity of the test compounds against armyworm, *Ostrinia nubilalis*, *Prodenia litura*, aphids, and rice planthoppers was carried out. Initially, screened out bioactive compounds were evaluated by a serial dilution assay to find the optimal concentration when compared with the standard drug of flucycloxuron. The results of *Table 5* indicate that compounds **3i** and **3l** have excellent insecticidal activities against armyworm. Besides, compound **3m** was found to be more effective than flucycloxuron in killing armyworm at a lower concentration of 1 mg/l. For insecticidal activity against soybean aphid, compound **4** showed moderate insecticidal activity (*Table 6*). Of all the tested compounds, compounds **3f** and **3k**, which were inferior to flucycloxuron, provided us with excellent guides to find better pesticides against rice planthoppers.

Conclusions

In summary, a series of novel isolongifolenone oxime derivatives were designed and synthesized. The biological assay results indicated that compound **3f** exhibited good activities against all the tested bacteria and fungi when compared with the respective drug. Compound **3m** exhibited much better larvicidal activities against armyworms than flucycloxuron. These outcomes provide a useful reference in the search for novel isolongifolenone derivatives.

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Table 3. Antifungal activity of test compounds, measured by the inhibition zones test [mm]

Compound	Inhibition zones of fungi [mm]				
	Aspergillus niger	*Colletotrichum musae*	*Exserohilum turcicum*	Corn sheath blight	*Alternaria musae*
2	9.3 ± 0.3	9.7 ± 0.4	11.3 ± 0.3	9.2 ± 0.3	12.3 ± 0.3
3b	11.2 ± 0.3	13.1 ± 0.5	9.5 ± 0.3	14.1 ± 0.3	11.0 ± 0.3
3e	10.5 ± 0.3	8.2 ± 0.4	9.4 ± 0.5	11.7 ± 0.4	10.7 ± 0.4
3f	11.7 ± 0.3	13.4 ± 0.5	11.5 ± 0.3	14.2 ± 0.3	13.5 ± 0.3
3g	9.5 ± 0.3	11.7 ± 0.3	10.6 ± 0.3	11.3 ± 0.3	13.3 ± 0.3
3i	11.5 ± 0.5	13.0 ± 0.5	10.5 ± 0.4	14.0 ± 0.4	12.1 ± 0.5
3m	10.3 ± 0.3	11.5 ± 0.5	9.7 ± 0.4	10.9 ± 0.5	8.5 ± 0.3
Amphotericin	11.2 ± 0.5	13.2 ± 0.4	11.2 ± 0.8	14.0 ± 0.2	13.2 ± 0.4
DMSO	–	–	–	–	–

Table 4. *In vitro* antifungal activity of compounds of minimum inhibitory concentration (MIC) [μg/ml], positive control: amphotericin

Compound	*MIC* [μg/ml]				
	Aspergillus niger	*Colletotrichum musae*	*Exserohilum turcicum*	Corn sheath blight	*Alternaria musae*
2	125	125	31.3	250	62.5
3b	31.3	31.3	125	31.3	125
3e	62.5	250	125	62.5	125
3f	31.3	31.3	31.3	31.3	31.3
3g	125	62.5	62.5	125	31.3
3i	31.3	31.3	62.5	31.3	62.5
3m	62.5	62.5	125	125	250
Amphotericin	31.3	31.3	31.3	31.3	31.3

Table 5. Insecticidal activity against armyworms

Compound	Toxicities activity against armyworms	
	Concentration [mg/l]	Insecticidal activity [%]
3i	50	100
	25	100
	10	100
	5	71
	2.5	35
	1	0
3l	50	100
	25	100
	10	100
	5	71.4
	2.5	43
	1	0
3m	50	100
	25	100
	10	100
	5	100
	2.5	73.3
	1	48
	0.5	0
Flucycloxuron	10	100
	5	90
	2.5	45
	1	0

Table 6. Insecticidal activity against aphid

Compound	Toxicities activity against soybean aphids	
	Concentration [mg/l]	Reduced rate [%]
3d	200	65
	100	22
	50	0
3f	200	43
	100	17.46
	50	0
4	100	100
	50	100
	25	61
	10	17
	5	0
Flucycloxuron	50	100
	25	60
	10	11
	5	0

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Experimental Part

General

All reagents in the experiment were of anal. grade except isolongifolenone, which were used without further disposal, if not mentioned. TLC: SiO_2 *60* F_{254} (SiO_2). M.p.: *WRS-1B* apparatus; uncorrected. IR Spectra: *MAGNA-1R550* FT-IR spectrophotometer with KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker AV600* (600 and 125 MHz, resp.) spectrometer; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-MS: *TSQ Quantum Access MAX* spectrometer; in *m*/*z*. Elemental analysis: *Cary60* elemental analyzer; CHNS mode; in %. O.D.: *UVmini-1240* spectrophotometer.

Synthesis of Isolongifolenone (**1**). To a mixture of isolongifolene (1 mmol) and 70 wt-% aq. ^{t}BuOOH (6 mmol) in AcOEt (4 ml), NaClO (2 mmol) was added slowly using a minipulse pump, stirred at 2 – 5 °C for 10 h. After completion of the reaction (monitored by GC), sat. aq. $Na_2S_2O_3$ soln. (10 ml) was added to remove any redundant ^{t}BuOOH. The product was isolated by extraction with AcOEt and the combined org. layers were washed with sat. NaCl soln. and H_2O for three times and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was purified by SiO_2 column chromatography (petroleum ether/AcOEt 20:1). The product was analyzed by IR, ^1H-NMR, GC, and GC/MS.

Synthesis of Isolongifolenone Oxime (**2**). The product was prepared following the procedure [26]. A mixture of **1** (1.0 g, 4.6 mmol), anh. Na_2CO_3 (1.4 g, 12.8 mmol), and $NH_2OH \cdot HCl$ (1 g, 9.2 mmol) was dissolved in EtOH (3.8 ml) and H_2O (4.6 ml). The soln. was refluxed for 3 h (TLC control). The product was isolated by extraction with AcOEt and the combined org. layers were washed with sat. NaCl soln. and H_2O for three times and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 (petroleum ether/AcOEt) to yield the title compound **2**.

Synthesis of Isolongifolenone Oxime Ether Derivatives (**3a** – **3f**). The product **3a** was synthesized following the report [27]. To a stirred soln. of **2** (0.5 g, 2.14 mmol) in H_2O/DMSO 1:9 (20 ml) was added epichlorohydrin (0.792 g, 8.56 mmol) and KOH (0.12 g, 2.14 mmol). The mixture was stirred for 10 h at r.t. The product was isolated by extraction with $CHCl_3$ and the combined org. layers were washed with sat. NaCl soln. and H_2O for three times and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 to yield the compound **3a**. Isolongifolenone oxime ether derivatives were prepared by the reported experimental method [8]. To a soln. of **2** (0.5 g, 2.14 mmol) in CH_2Cl_2 (10 ml) was added RX (X = Cl, Br or I, 1.5 equiv.), benzyl(triethyl) ammonium bromide (TEBA, 0.5 g), NaOH (1.80 g, 45 mmol), and H_2O (3 ml), resp. The mixture was refluxed for 1 – 1.5 h. The product was isolated by extraction with CH_2Cl_2 and the combined org. layers were washed with sat. NaCl soln. and H_2O for three times and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 to yield the target compound.

Synthesis of Isolongifolenone Oxime Ester Derivatives (**3g** – **3m**). To a stirred soln. of **2** (0.5 g, 2.14 mmol) in CH_2Cl_2 (10 ml) was added RCOX or RSO_2X (X = Cl or Br, 1.5 equiv.), Et_3N (1 ml), DMAP (52 mg). The mixture was stirred for 10 h at r.t. and monitored by TLC. When completed, the suspension was filtered and the filtrate was extracted with CH_2Cl_2 (3 × 15 ml), and the combined org. layers were washed with sat. NaCl soln. (3 × 10 ml) and H_2O (3 × 10 ml) and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 to yield the target compound.

Synthesis of **4,5,6,7,8,9-Hexahydro-5,5,9,9-tetramethyl-5a,8-methano-3-benzazepin-2(3*H*)-one** (**4**). **2** (0.5 g) was dissolved in THF (15 ml), and Et_3N (5 ml) and anh. Et_2O (2 ml) was added resp. under Ar atmosphere, then $POCl_3$ (2 ml) was added slowly using a minipulse pump at −5 °C, and finally, the mixture was stirred for 30 min at 0 °C. The product was isolated by extraction with CH_2Cl_2 and the combined org. layers were washed with sat. NaCl soln. and H_2O for three times and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 to yield the compound **4**.

Isolongifolenone (= **1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one**; **1**). Yield: 82.6%. White solid. M.p. 31 – 32 °C. IR: 2968, 2880, 1662, 1468, 1384. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.99 (*s*, Me); 1.05 (*s*, Me); 1.08 (*s*, Me); 1.13 (*s*, Me); 1.28 – 1.32 (*m*, 1 H); 1.40 (*m*, 1 H); 1.57 – 1.63 (*m*, 1 H); 1.67 – 1.69 (*m*, 1 H); 1.73 – 1.78 (*m*, 1 H); 1.92 – 1.98 (*m*, 2 H); 2.07 (*d*, *J* = 16.2, 1 H); 2.38 (*d*, *J* = 16.2, 1 H); 5.70 (*s*, C=CH).

Isolongifolenone Oxime (= **1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one Oxime**; **2**). Yield: 68.2%. White solid. M.p. 124.8 – 131.4 °C. IR: 3233, 2956, 1647, 1461, 1383. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.89 (*s*, Me); 1.0 (*s*, Me); 1.10 (*s*, Me); 1.14 (*s*, Me); 1.18 – 1.27 (*m*, 3 H); 1.33 (*m*, 1 H); 1.49 – 1.67 (*m*, 1 H); 1.69 – 1.76 (*m*, 1 H); 1.78 – 1.85 (*m*, 1 H); 1.91 (*s*, 1 H); 1.95 (*d*, *J* = 18, 1 H); 2.31 (*d*, *J* = 12, 1 H); 6.46 (*s*, C=CH). ^{13}C-NMR ($CDCl_3$, 150 MHz): 153.7; 103.2; 58.5; 46.4; 43.3; 40.2; 36.5; 32.9; 29.4; 27.8; 27.6; 25.5; 24.8; 24.5; 24.3. Anal. calc. for $C_{15}H_{23}NO$: C 77.21, H 9.93, N 6.00; found: C 77.19, H 10.01, N 6.13.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one *O*-(Oxiran-2-ylmethyl)oxime (**3a**). Yield: 63.5%. Yellow oil. ^{1}H-NMR: ($CDCl_3$, 600 MHz): 0.92 (*s*, Me); 1.06 (*s*, 2 Me); 1.13 (*s*, Me); 1.16 – 1.29 (*m*, 1 H); 1.31 – 1.37 (*m*, 1 H); 1.50 – 1.59 (*m*, 1 H); 1.62 (*m*, 1 H); 1.69 – 1.83 (*m*, 2 H); 1.91 (*s*, 1 H); 1.95 – 2.05 (*m*, 1 H); 2.61 – 2.70 (*m*, 1 H); 2.79 – 2.90 (*m*, 2 H); 3.29 (*s*, 1 H); 3.94 – 4.07 (*m*, 1 H); 4.23 – 4.34 (*m*, 1 H); 5.76 (*s*, C=CH). MS: 290 ([*M* + H]$^+$). Anal. calc. for $C_{18}H_{27}NO_2$: C 74.70, H 9.40, N 4.84; found: C 74.68, H 9.41, N 4.85.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one *O*-Ethyloxime (**3b**). Yield: 43.8%. yellow solid. IR: 2934, 2893, 2865, 1636, 1459, 1381, 1054. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.89 (*s*, Me); 1.02 (*s*, Me); 1.06 (*s*, Me); 1.13 (*s*, Me); 1.16 – 1.23 (*m*, 1 H); 1.23 – 1.34 (*m*, 4 H); 1.50 – 1.58 (*m*, 2 H); 1.69 – 1.75 (*m*, 1 H); 1.76 – 1.84 (*m*, 1 H); 1.89 (*s*, 1 H); 1.97 (*d*, *J* = 15, 1 H); 2.30 (*d*, *J* = 15, 1 H); 4.04 – 4.13 (*m*, 2 H); 6.38 (*s*, C=CH). MS: 262 ([*M* + H]$^+$). Anal. calc. for $C_{17}H_{27}NO$: C 78.11, H 10.41, N 5.36; found: C 78.15, H 10.40, N 5.37.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one *O*-Methyloxime (**3c**). Yield: 47.9%. Yellow oil. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.90 (*s*, Me); 1.04 (*s*, 2 Me); 1.10 (*s*, Me); 1.23 – 1.33 (*m*, 2 H); 1.48 – 1.55 (*m*, 1 H); 1.57 – 1.62 (*m*, 1 H); 1.66 – 1.80 (*m*, 2 H); 1.91 (*s*, 1 H); 1.98 (*d*, *J* = 16.8, 1 H); 2.78 (*d*, *J* = 16.8, 1 H); 3.88 (*s*, Me); 5.74 (*s*, C=CH). ^{13}C-NMR ($CDCl_3$, 150 MHz): 167.1; 156.9; 110.4; 61.6; 57.8; 46.9; 43.5; 37.0; 35.2; 32.1; 28.3; 27.7; 26.0; 25.9; 25.2; 24.6. MS: 248 ([*M* + H]$^+$). Anal. calc. for $C_{16}H_{25}NO$: C 77.68, H 10.19, N 5.66; found: C 77.70, H 10.18, N 5.67.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one *O*-Benzyloxime (**3d**). Yield: 53.7%. White solid. IR: 2964, 2934, 2893, 2865, 1636, 1593, 1497, 1459. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.89 (*s*, Me); 1.02 (*s*, Me); 1.05 (*s*, Me); 1.11 (*s*, Me); 1.16 – 1.27 (*m*, 1 H); 1.29 – 1.33 (*m*, 2 H); 1.49 – 1.62 (*m*, 1 H); 1.70 – 1.75 (*m*, 1 H); 1.76 – 1.94 (*m*, 1 H); 1.89 (*s*, 1 H); 1.98 (*d*, *J* = 15, 1 H); 2.30 (*d*, *J* = 15, 1 H); 5.08 – 5.11 (*m*, CH_2); 6.44 (*s*, C=CH); 7.29 – 7.43 (*m*, 5 arom. H). MS: 324 ([*M* + H]$^+$). Anal. calc. for $C_{22}H_{29}NO$: C 81.69, H 9.04, N 4.33; found: C 81.70, H 9.03, N 4.32.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one *O*-Butyloxime (**3e**). Yield: 47.9%. White solid. IR: 2964, 2893, 2865, 1638, 1453. ^{1}H-NMR: ($CDCl_3$, 600 MHz): 0.89 (*s*, Me); 0.91 – 0.97 (*m*, CH_2Me); 1.02 (*s*, Me); 1.06 (*s*, Me); 1.13 (*s*, Me); 1.25 (*s*, 1 H); 1.27 – 1.34 (*m*, 2 H); 1.35 – 1.45 (*m*, 2 H); 1.50 – 1.59 (*m*, 1 H); 1.60 – 1.68 (*m*, 2 H); 1.68 – 1.76 (*m*, 1 H); 1.76 – 1.84 (*m*, 1 H); 1.89 (*s*, 1 H); 1.97 (*d*, *J* = 15, 1 H); 2.30 (*d*, *J* = 14.4, 1 H); 3.99 – 4.04 (*m*, CH_2); 6.37 (*s*, C=CH). MS: 290 ([*M* + H]$^+$). Anal. calc. for $C_{19}H_{31}NO$: C 78.84, H 10.79, N 4.84; found: C 78.79, H 10.81, N 4.87.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one *O*-Prop-2-en-1-yloxime (**3f**). Yield: 55.3%. White oil. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.92 (*s*, Me); 1.06 (*s*, Me); 1.09 (*s*, Me); 1.16 (*s*, Me); 1.23 – 1.38 (*m*, 1 H); 1.38 – 1.47 (*m*, 1 H); 1.62 – 1.63 (*m*, 2 H); 1.71 – 1.79 (*m*, 1 H); 1.80 – 1.88 (*m*, 1 H); 1.93 (*m*, 1 H); 2.02 (*d*, *J* = 15, 1 H); 2.33 (*d*, *J* = 15, 1 H); 4.52 – 4.65 (*m*, CH_2); 5.23 (*d*, *J* = 10.2, 1 H, CH_2=C); 5.34 (*d*, *J* = 17.4, 1 H, CH_2=C); 6.00 – 6.04 (*m*, =CH); 6.39 (*s*, 1 H, C=CH). MS: 274 ([*M* + H]$^+$). Anal. calc. for $C_{18}H_{27}NO$: C 79.07, H 9.95, N 5.12; found: C 79.06, H 9.04, N 4.33.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one *O*-(4-Hydroxybenzoyl)oxime (**3g**). Yield: 57.8%. White solid. IR: 3332, 2961, 1716, 1649, 1606, 1515, 1438. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.96 (*s*, Me); 1.05 (*s*, Me); 1.12 (*s*, 2 Me); 1.36 (*m*, 1 H); 1.51 – 1.60 (*m*, 1 H); 1.61 – 1.78 (*m*, 3 H); 1.78 – 1.87 (*m*,

1 H); 1.93 (*s*, 1 H); 2.26 (*m*, 1 H); 2.86 – 2.95 (*m*, 1 H); 6.00 (*s*, C=CH); 6.40 (*s*, OH); 6.93 (*d*, *J* = 8.4, 2 arom. H); 7.99 (*d*, *J* = 8.4, 2 arom. H). MS: 354 ([*M* + H]$^+$). Anal. calc. for $C_{22}H_{27}NO_3$: C 74.76, H 7.70, N 3.96; found: C 74.56, H 7.68, N 4.01.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one *O*-Acetyloxime (**3h**). Yield: 61.7%. White oil. IR: 2959, 1765, 1637, 1464, 1054. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.91 (*s*, Me); 1.06 (*s*, Me); 1.09 (*s*, Me); 1.15 (*s*, Me); 1.23 – 1.29 (*m*, 1 H); 1.36 (*m*, 1 H); 1.52 – 1.65 (*m*, 2 H); 1.69 – 1.77 (*m*, 1 H); 1.82 – 1.89 (*m*, 1 H); 1.95 (*s*, 1 H); 2.20 (*s*, 3 H); 2.23 (*d*, *J* = 15, 1 H); 2.38 (*d*, *J* = 9.6, 1 H); 6.32 (*s*, C=CH). ^{13}C-NMR ($CDCl_3$, 150 MHz): 176.1; 168.8; 160.3; 104.0; 58.8; 46.4; 39.8; 36.5; 33.1; 27.6; 27.4; 25.5; 24.7; 24.4; 24.1; 19.6. MS: 276 ([*M* + H]$^+$). Anal. calc. for $C_{17}H_{25}NO_2$: C 74.14, H 9.15, N 5.09; found: C 73.89, H 9.26, N 5.14.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one *O*-Benzoyloxime (**3i**). Yield: 37.5%. Yellow solid. IR: 3064, 2959, 1738, 1695, 1632, 1600, 1489, 1453. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.99 (*s*, Me); 1.11 (*s*, Me); 1.14 (*s*, Me); 1.17 (*s*, Me); 1.25 – 1.33 (*m*, 2 H); 1.35 – 1.44 (*m*, 1 H); 1.68 (*m*, 1 H); 1.73 – 1.82 (*m*, 1 H); 1.82 – 1.91 (*m*, 1 H); 1.97 (*s*, 1 H); 2.31 (*d*, *J* = 16.8, 1 H); 2.97 (*d*, *J* = 16.8, 1 H); 6.09 (*s*, C=CH); 7.47 – 7.55 (*m*, 2 arom. H); 7.58 – 7.69 (*m*, 1 arom. H); 8.06 – 8.18 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 150 MHz): 172.7; 164.2; 133.8; 133.2; 130.3; 129.7; 129.6; 128.6; 109.9; 58.0; 46.7; 44.1; 37.1; 36.7; 32.6; 28.2; 27.5; 26.0; 25.9; 25.0; 24.6. MS: 338 ([*M* + H]$^+$). Anal. calc. for $C_{22}H_{27}NO_2$: C 78.30, H 8.06, N 4.15; found: C 78.23, H 8.11, N 4.20.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one *O*-(Phenylsulfonyl)oxime (**3j**). Yield: 76.3%. Yellow solid. IR: 3068, 2962, 1648, 1589, 1518, 1448, 1371. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.85 (*s*, Me); 1.03 (*s*, Me); 1.06 (*s*, Me); 1.09 (*s*, Me); 1.31 – 1.37 (*m*, 1 H); 1.51 – 1.63 (*m*, 2 H); 1.65 (*s*, 1 H); 1.68 – 1.74 (*m*, 1 H); 1.76 – 1.84 (*m*, 1 H); 1.93 (*s*, 1 H); 2.09 (*d*, *J* = 16.8, 1 H); 2.86 (*d*, *J* = 16.8, 1 H); 5.74 (*s*, C=CH); 7.54 – 7.61 (*m*, 2 arom. H); 7.64 – 7.69 (*m*, 1 arom. H); 8.02 (*d*, *J* = 8.4, 2 arom. H). MS: 373 ([*M* + H]$^+$). Anal. calc. for $C_{21}H_{27}NO_3S$: C 67.53, H 7.29, N 3.75, S, 8.58; found: C 67.51, H 7.33, N 3.75; S, 8.60.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one 7-[*O*-(2-Methyl-1-oxoprop-2-en-1-yl)oxime] (**3k**). Yield: 46.5%. White oil. ^{1}H-NMR: ($CDCl_3$, 600 MHz): 0.94 (*s*, Me); 1.06 (*s*, Me); 1.07 (*s*, Me); 1.16 (*s*, Me); 1.22 – 1.32 (*m*, 2 H); 1.34 – 1.42 (*m*, 2 H); 1.54 – 1.65 (*m*, 2 H); 1.70 – 1.79 (*m*, 1 H); 1.84 – 1.92 (*m*, 1 H); 1.97 (*s*, 1 H); 2.06 (*s*, Me); 2.31 (*d*, *J* = 15, 1 H); 2.43 (*d*, *J* = 15.6, 1 H); 5.64 (*s*, C=CH); 6.19 (*s*, 1 H, C=CH$_2$); 6.33 (*s*, 1 H, C=CH$_2$). MS: 316 ([*M* + H]$^+$). Anal. calc. for $C_{20}H_{29}NO_2$: C 76.15, H 9.27, N 4.44; found: C 75.07, H 9.33, N 4.47.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one *O*-(Naphthalene-1-ylcarbonyl)oxime (**3l**). Yield: 57.8%. White solid. IR: 3061, 2957, 2871, 1733, 1647, 1575, 1508, 1459. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.97 (*s*, Me); 1.06 (*s*, Me); 1.08 (*s*, Me); 1.16 (*s*, Me); 1.37 (*m*, 1 H); 1.53 – 1.68 (*m*, 3 H); 1.71 – 1.79 (*m*, 1 H); 1.79 – 1.85 (*m*, 1 H); 1.95 (*s*, 1 H); 2.26 (*d*, *J* = 16.8, 1 H); 2.92 (*d*, *J* = 16.8, 1 H); 6.10 (*s*, C=CH); 7.49 – 7.58 (*m*, 2 arom. H); 7.59 – 7.66 (*m*, 1 arom. H); 7.9 (*d*, *J* = 7.8, 1 arom. H); 8.05 (*d*, *J* = 8.4, 1 arom. H); 8.13 (*d*, *J* = 7.2, 1 arom. H); 8.82 (*d*, *J* = 8.4, 1 arom. H). MS: 388 ([*M* + H]$^+$). Anal. calc. for $C_{26}H_{29}NO_2$: C 80.59, H 7.54, N 3.61; found: C 80.51, H 7.57, N 3.73.

1,2,3,4,5,6-Hexahydro-1,1,5,5-tetramethyl-7*H*-2,4a-methanonaphthalen-7-one *O*-(2-Chlorobenzoyl)oxime (**3m**). Yield: 37.9%. Yellow solid. IR: 3064, 2960, 1757, 1639, 1596, 1512, 1463. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.94 (*s*, Me); 1.07 (*s*, Me); 1.08 (*s*, Me); 1.14 (*s*, Me); 1.17 – 1.27 (*m*, 1 H); 1.36 (*m*, 1 H); 1.61 – 1.67 (*m*, 2 H); 1.71 – 1.77 (*m*, 1 H); 1.78 – 1.85 (*m*, 1 H); 1.93 (*s*, 1 H); 2.21 (*d*, *J* = 16.8, 1 H); 2.94 (*d*, *J* = 16.8, 1 H); 6.04 (*s*, C=CH); 7.33 – 7.39 (*m*, 1 arom. H); 7.41 – 7.50 (*m*, 2 arom. H); 7.83 (*d*, *J* = 7.8, 1 arom. H). MS: 372 ([*M* + H]$^+$). Anal. calc. for $C_{22}H_{26}ClNO_2$: C 71.05, H 7.05, Cl 9.53, N 3.77; found: C 70.88, H 7.13, Cl 9.51, N 3.76.

4,5,6,7,8,9-Hexahydro-5,5,9,9-tetramethyl-5a,8-methano-3-benzazepin-2(3*H*)-one (**4**). Yield: 67.4%. Yellow solid. IR: 3175, 3035, 2963, 1665, 1624, 1485. ^{1}H-NMR ($CDCl_3$, 600 MHz): 1.03 (*s*, Me); 1.04 (*s*, Me); 1.06 (*s*, Me); 1.11 (*s*, Me); 1.19 – 1.31 (*m*, 1 H); 1.36 (*d*, *J* = 9.6, 1 H); 1.47 – 1.58 (*m*, 1 H); 1.59 – 1.88 (*m*, 3 H); 1.92 (*s*, 1 H); 2.71 (*d*, *J* = 12, 1 H); 3.34 (*d*, *J* = 12, 1 H); 5.60 (*s*, C=CH); 6.00 (*s*, NH). MS: 234 ([*M* + H]$^+$). Anal. calc. for $C_{15}H_{23}NO$: C 77.21, H 9.93, N 6.00; found: C 77.19, H 10.01, N 6.05.

Biological Evaluation

In Vitro *Screening for Antibacterial Activity*. The antibacterial activities of compounds **1** – **4** were screened in beef-protein medium by the disk diffusion method [3]. Five test organisms, one *Gram*-positive strain *S. aureus*, and four *Gram*-negative bacteria, *E. coli*, *Pneumobacillus*, *P. aeruginosa*, and *P. vulgaris*, were subcultured in a *HPS-250* biochemical incubator and inoculated for 18 h at 37 °C. The colony-forming units (cfu) were adjusted in the range of 10^4 – 10^5 cfu/ml by determining the OD_{600} in 0.08 – 0.1 range using a spectrophotometer. Seven paper disks (6.0 mm diameter) were fixed onto a nutrient agar plate. The stock soln. was prepared into 100 μg/ml by dissolving a test compound in DMSO. The test compounds were diluted to different concentrations of 250, 125, 62.5, 31.3, 15.6, and 7.8 μg/ml with dist. H_2O (containing 0.1% *Tween 80*). Amoxicillin and DMSO were used as positive and negative controls, resp. After 18 h of incubation at 37 °C, the growth inhibitory zone around the paper disk was determined [28]. The inhibition zones (mm) of each compound including the controls

were displayed in *Table 1* and the *MIC*s were measured by the microdilution method *Table 2*.

Antifungal Activity. The *in vitro* fungicidal activities of target compounds **1** – **4** were screened in potato dextrose agar medium by the disk diffusion method. *MIC* was determined and compared with standard drug amphotericin for antifungal [29]. Previously, dissolved 5 mg of each tested compound in 5 ml of DMSO as stock soln., resp. Dist. H_2O (containing 0.1% *Tween 80*) was added to the soln. in order to dilute to the tested concentration.

First, hot potato glucose agar medium was poured at a third position of the *Petri* dish. After cooling to r.t., the disks of different concentration were placed on it, including amphotericin B used as standard drug (positive control) and DMSO was poured on disk as a negative control, and the appropriate quantity of mycelium was placed in the center of the *Petri* dish. Finally, the solidified plates were incubated at 28 °C for 96 h. Sterile H_2O was used as a blank. Three replications were performed in antifungal activity assays. The result of the *in vitro* fungicidal activities of target compounds against five fungal species *A. niger*, *C. musae*, corn sheath blight, *E. turcicum*, and *A. musae* were shown in *Tables 3* and *4*.

Insecticidal Activity. The insecticidal experiments were performed on representative test organisms cultivated in the laboratory. The experiments were repeated at 25 °C according to statistical requirements and assessed by a dead/alive method. Mortality rates were corrected according to the *Abbott*'s formula [30]. The percent of mortality rates which 0 = no activity and 100 = total kill. Insecticidal activity of the target compounds against armyworm, *O. nubilalis*, *P. litura*, soybean aphid, and rice planthopper were evaluated by the spraying method, except for rice planthopper which adopted the straw impregnation method. The target compounds dissolving in DMSO were prepared at concentrations of 200 mg/l. Percentage mortalities were evaluated 3 d after treatment.

For armyworm tests, individual fresh corn leaves were placed in clean and dry *Petri* dishes. The leaves were then sprayed with the test soln. and allowed to dry. The dishes were infested with 20 armyworms. Different concentration of 1.0 ml of liquids was sprayed under 80 – 90 kpa pressure in a spray tower and kept still for 20 s to make droplets sedimentation completely. After dried, *Petri* dishes were taken to indoor incubator at 25 °C to cultivate. Percentage mortalities were assessed 72 h after treatment. Each treatment was repeated four times and flucycloxuron was used as standard drug.

For rice planthopper test, the insecticidal activity was determined by the straw impregnation method. The experimental procedure was as follows. Initially, fresh root rice stalks were impregnated into the solns. of different concentrations (200, 100, 50, 25, 10, and 5 mg/l) of test compounds for 10 s. Then, 50 rice planthoppers were reared into it using the predried rice stalks under suitable conditions and each treatment was done in quadruplicate. The results of preliminary screening assay for *O. nubilalis* showed that the target compounds **1** – **4** had little insecticidal activity under 200 mg/l as well as against *P. litura*.

Table 7. Insecticidal activity against rice planthoppers

Compound	Toxicities activity against rice planthoppers	
	Concentration [mg/l]	Insects reduced rate [%]
3f	200	47
	100	11
	50	0
3k	200	100
	100	85
	50	45
	10	0
Flucycloxuron	100	100
	50	100
	25	61
	10	17
	5	0

According to the preliminary screening, the active compound was selected to further study with different concentrations, aiming to find the lowest concentration of insecticidal activity. The results are represented in *Tables 5 – 7*.

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