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Palmarumycin B_6 类似物的合成及杀蚊活性

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摘要 为了提高天然产物 Palmarumycin B_6 的生物活性, 通过取代四氢萘酮烯醇醚和 1,8-二羟基萘的缩酮化反应以及吡啶重铬酸盐和过氧叔丁醇参与的苄位氧化反应作为关键步骤完成了多个 Palmarumycin B_6 A 环含氯和含氟类似物的合成, 它们的结构经过 ^{1}H NMR, ^{13}C NMR 和 HR-ESI-MS 的表征. 对它们的杀蚊活性进行了评价, 结果表明 6-氯-5-羟基-2,3-二氢-4*H*-螺[萘-1,2'-萘[1,8-*de*][1,3]-二噁烷]-4-酮(**4m**)和 6-氟-5-羟基-2,3-二氢-4*H*-螺[萘-1,2'-萘[1,8-*de*][1,3]-二噁烷]-4-酮(**4i**)是活性最好的化合物，对白纹伊蚊的 LC_{50} 值为 11.51 和 23.25 μg/mL，它们可以作为先导结构进行进一步结构优化. 在 6 位的卤素原子、5-羟基和 4-羰基对该类 Palmarumycin B_6 类似物的杀蚊活性起到了关键作用.

关键词 螺二萘; Palmarumycin B_6; 缩酮化反应; 苄位氧化反应; 杀蚊活性

Synthesis and Larvicidal Activity of Palmarumycin B_6 Analogues

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Abstract In order to improve the biological activity of naturally occurring Palmarumycin B_6, the synthesis of Palmarumycin B_6 chlorine- and fluorine-containing analogues at A ring has been achieved via ketalization of substituted 1-tetralone enol ether with 1,8-dihydroxynaphthalene and the benzyl oxidation involving pyridinium dichromate and *t*-BuOOH as the key steps. Their structures were fully characterized by ^{1}H NMR, ^{13}C NMR, and HR-ESI-MS data. Their larvicidal activities were evaluated and showed that 6-chloro-5-hydroxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*]-[1,3]dioxin]-4-one (**4m**) and 6-fluoro-5-hydroxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-*de*][1,3]dioxin]-4-one (**4i**) were the most active compounds with the LC_{50} values of 11.51 and 23.25 μg/mL against *Aedes albopictus*, and they would be the potential lead structure to be optimized. The halogen atoms at C-6, 5-hydroxy and 4-carbonyl play a critical role for the larvicidal activities of this type of Palmarumycin B_6 analogues.

Keywords spirobisnaphthalene; Palmarumycin B6; ketalization; benzyl oxidation; larvicidal activity

1 Introduction

The natural products of the spirobisnaphthalene family are widely distributed in the endophytic fungus and plants, which showed broad bioactivities such as antifungal, antimicrobial, antitumour, anticancer, antiparasitic, anti-inflammatory, and cytotoxic activity.[1-4] The attention was paid to the total synthesis, structure modification and activity evaluation of the spirobisnaphthalene natural products in recent years.[5-15] Palmarumycins B_6 and C_8 were first isolated from the endophytic fungus *Berkleasmium sp.*, which was purified from the medicinal plant *Dioscorea zingiberensis* C. H. Wright, and found that they exhibited excellent larvicidal activity against the Asian mosquito, *Aedes albopictus* in our group.[16,17] The outbreak of the Zika fever epidemic in Brazil in 2015 has raised concerns that the mosquitoes of the Genus *Aedes* (such as *A. aegypti* and *A. albopictus*) might be the vectors of the Zika virus. This issue has stimulated a renewed interest to develop sustainable vector control systems.[18-19] The resistance of the mosquitoes to traditional insecticides has developed quickly in recent years,[20-21] therefore a search for novel drugs, especially those derived from natural products, to overcome this serious problem is important. Several spirobisnaphthalene natural products such as Palmarumycins CP_{17}, B_6, BG1-6 and Guignardin E were synthesized (Figure 1), and the structure of Palmarumycin B_6 was revised based on the X-ray diffraction analysis in our laborato-

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ry.[22-24] We found that the larvicidal activity of Palmarumycin B_6 against *A. albopictus* was seven times higher than that of the A ring regioisomer of Palmarumycin B_6, and it indicated that the location of the chlorine atom played a crucial role for the larvicidal activity against *A. albopictus*.[23] It was reported that the naphthoquinone derivatives exhibited good larvicidal and antifeedant activities, and the halogenated naphthoquinones were found to be more active against *A. aegypti* than the non-halogenated congeners.[25-28] In order to gain insights into the structure-activity relationship of this kind of compounds, the Palmarumycin B_6 chlorine- and fluorine-containing analogues (**4**) were designed and synthesized (Schemes 1, 2), and their larvicidal activities against *A. albopictus* were evaluated in this article.

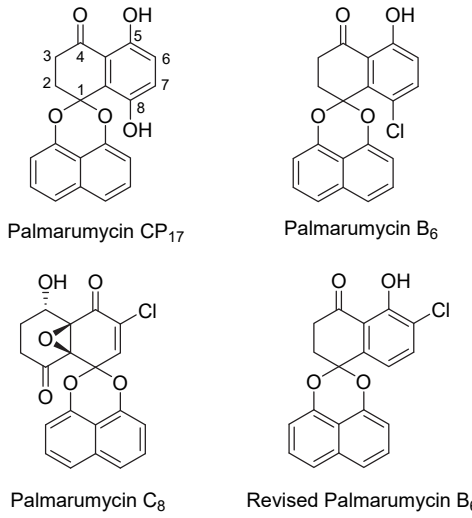
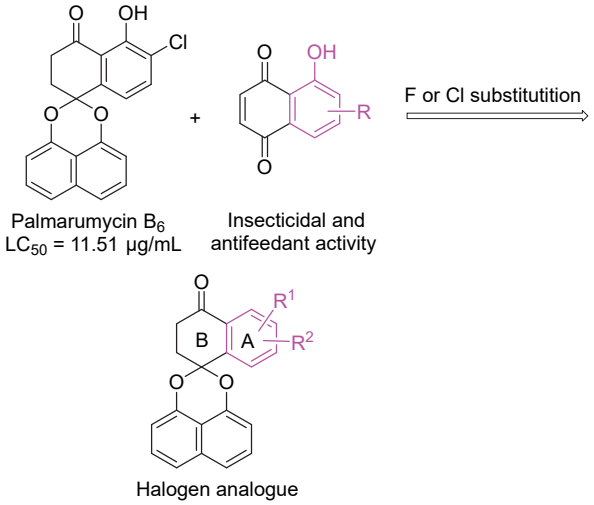


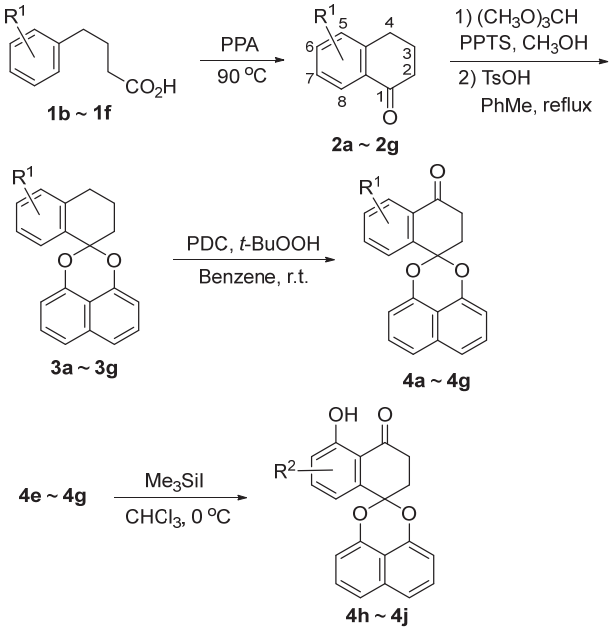
Figure 1 Representing naturally occurring spirobisnaphthalene synthesized in our laboratory[22-24]



Scheme 1 Design strategy of Palmarumycin B_6 chlorine- and fluorine-containing analogues

2 Results and discussion

The halogen bond is an important mode of action, and fluorine-containing compounds are hot topic in the drug design and discovery in recent years.[29-32] The larvicidal activity of Palmarumycin B_6 against *A. albopictus* was seven times higher than that of the regioisomer of Pal marumycin B_6, which indicated that the location of the



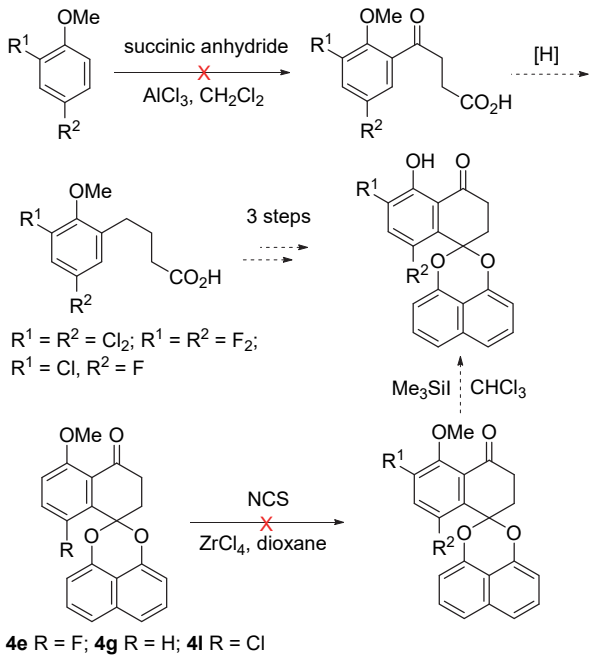
2a ~ 4a R^1 = 7-Cl; **1b ~ 4b** R^1 = 6-Cl, 7-OMe; **1c ~ 4c** R^1= 5-Cl, 7-OMe; **1d ~ 4d** R^1 = 6-F, 7-OMe; **1e ~ 4e** R^1 = 8-F, 5-OMe; **1f ~ 4f** R^1 = 6-F, 5-OMe; **2g ~ 4g** R^1 = 5-OMe; **4h** R^2 = 8-F; **4i** R^2 = 6-F; **4j** R^2 = H

Scheme 2 Synthesis of Palmarumycin B_6 chlorine- and fluorine-containing analogues

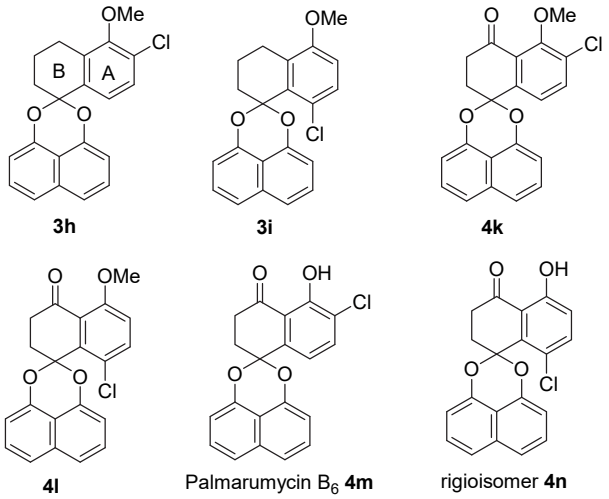
chlorine atom played a crucial role for the larvicidal activity against *A. albopictus* in our previous report.[23] Ribeiro reported that the halogenated naphthoquinones were found to be more active against *A. aegypti* than the non-halogenated congeners,[26] Palmarumycin B_6 actually was a ketal derivative of naphthoquinone with 1,8-dihydroxynaphthalene. So Palmarumycin B_6 chlorine- and fluorine-containing analogues (Scheme 2, **4a**～**4f**, **4h** and **4i**) were designed, **4g** and **4j** were also prepared following the procedures in the literatures[33-34] for the larvicidal active comparison. The starting materials **2a** and **2g** were commercially available, 4-substituted phenyl butanoic acids **1b**～**1f** were subjected to an intramolecular cyclization catalyzed by polyphosphoric acid (PPA) at 90 ℃ to afford compounds **2b**～**2f** according to the protocol in the literatures.[35-38] The yields of **3a**～**3g** were too low by the direct ketalization synthesis using **2a**～**2g** and 1,8-dihydroxynaphthalene as the raw material and *p*-toluene sulfonic acid as catalyst. Then enol ethers of 1-tetralones **2a**～**2g** were formed with trimethyl orthoformate in methanol under the pyridinium 4-toluenesulfonate (PPTS) as the catalyst, and the reactions of enol ethers with 1,8-dihydroxynaphthalene were successfully carried out in the toluene solution to provide **3a**～**3g** in an overall yields of 22%～60% over the two steps. Then compounds **3a**～**3g** were oxidized with pyridinium di-

chromate (PDC) and *t*-BuOOH as the oxidizing reagents to provide substituted 2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtha[1,8-de]-[1,3]dioxin]-4-ones **4a**～**4g** in 59%～83% yields. Finally compounds **4e**, **4f** and **4g** were demethylated with Me_3SiI to afford **4h**, **4i** and **4j** in 58%～74% yields, but the demethylation of **4b**, **4c** and **4d** with Me_3SiI at room temperature resulted in ring aromatization and acetal cleavage to produce the complex mixture of binaphthyl ether as before.[22]

Actually, the novel compounds having two chlorine or fluorine atoms or one chlorine and fluorine atoms at the C-6 and C-8 positions of A ring were also designed for observing the impact of one more halogen atoms at A ring on the larvicidal activity against *A. albopictus*. However, 4-(3,5-dichloro-2-methoxyphenyl)butanoic acid, 4-(3,5-difluoro-2-methoxyphenyl)butanoic acid and 4-(3-chloro-5-fluoro-2-methoxyphenyl)butanoic acid were not commercially available, our endeavor to synthesize them by Friedel-Crafts acylation through 2,4-dichloro-1-methoxybenzene, 2,4-difluoro-1-methoxybenzene and 2-chloro-4-fluoro-1-methoxybenzene with succinic anhydride and anhydrous $AlCl_3$ in dichloromethane were unsuccessful due to their low electrophilic substitution reactivity (Scheme 3). In the other side, Koerner reported the regioselective chlorination of complex phenol derivatives with *N*-chlorosuccinimide (NCS) and zirconium chloride ($ZrCl_4$).[39] We tried the chlorination of **4e**, **4g**, **4l**, **4m** and **4n** following Koerner's procedure, but did not obtain the chlorination products (Scheme 3). Then the synthesis of the 6,8-dichloro, 6,8-difluoro and 6-chloro-8-fluoro analogues of Palmarumycin B_6 was abandoned. The structures of Palmarumycin B_6 (**4m**), its regioisomer (**4n**) and their synthetic intermediates **3h**, **3i**, **4k** and **4l** in Scheme 4 and their larvicidal activities were also provided in Table 1.



Scheme 3 Synthesis exploration of Palmarumycins B_6 6,8-dihalogen analogues



Scheme 4 Structures of Palmarumycins B_6, its regioisomer and their synthetic intermediates[23]

Table 1 LC_{50} (μg/mL) values for larvicidal activity against *A. albopictus* of the title compounds **3** and **4**

Compd.	LC_{50}	Compd.	LC_{50}	Compd.	LC_{50}
3a	>200	**4a**	>200	**4j**	97.08
3b	>200	**4b**	187.24	**4k**	67.36
3c	>200	**4c**	>200	**4l**	130.27
3d	>200	**4d**	>200	**4m**	11.51[23]
3e	>200	**4e**	155.49	**4n**	80.11[23]
3f	143.28	**4f**	127.61	Rotenone	3.75
3g	>200	**4g**	170.53	Juglone	6.19
3h	122.17	**4h**	82.31		
3i	>200	**4i**	23.25		

The larvicidal activities of synthesized Palmarumycin B_6 chlorine- and fluorine-containing analogues were evaluated using the the protocol in reference,[17,23] rotenone and juglone were used as positive control. The LC_{50} values were determined from the mortalities of five different concentrations of the compounds, which were given in Table 1. The data showed that most of the Palmarumycin B_6 analogues had significant larvicidal activities against *A. albopictus* with LC_{50} values of 11.51～187.24 μg/mL, but weaker than the positive controls of rotenone and juglone. From these data, it was found that compounds **3a**～**3e** and **3g** without 4-carbonyl were no active except **3f** and **3h**, but compounds **4b**, **4e**～**4g**, **4k** and **4l** with 4-carbonyl were active. These results indicated that 4-carbonyl was a key factor for the larvicidal activities. In the other aspect, compounds **4h**～**4j**, **4m** and **4n** having 5-hydroxy exhibited much better activities than those compounds without 5-hydroxy such as **3a**～**3d** and **4a**～**4d**. Comparison these data of **4e**, **4f**, **4k**, **4l**, **4h**, **4i**, **4m** and **4n** with that of **4g** and **4j**, the chlorine and fluorine atoms at C-6 and C-8 positions improved the larvicidal activities, especially the chlorine and fluorine atoms at C-6 position. These results indicated that the halogen atoms were also an important factor for the larvicidal activities.[17,23] For those compounds having 4-carbonyl, 5-hydroxy and 6-halogen atoms, compounds **4i**

and **4m** exhibited the best larvicidal activities against *A. albopictus*. These results confirmed that the halogen atoms at C-6, 5-hydroxy and 4-carbonyl played a crucial role for the larvicidal activities of this type of compounds.[17,23] Among these compounds, the LC_{50} values of compounds **4i** and **4m** were 23.25 and 11.51 μg/mL, respectively, which showed that they were the most active compounds and could be used as the potential lead structures to improve the activity further. The B ring optimization of Palmarumycin B_6 was initiated based on the above results in our laboratory.

3 Conclusion

In conclusion, the synthesis of Palmarumycin B_6 chlorine- and fluorine-containing analogues at A ring were carried out through ketalization of substituted 1-tetralone enol ether with 1,8-dihydroxynaphthalene, and benzyl oxidation of with pyridinium dichromate and *t*-BuOOH as the key steps. Their structures were characterized by the ^{1}H NMR, ^{13}C NMR and HR-ESI-MS spectra. Their larvicidal activities were evaluated, and the results showed that the LC_{50} values of compounds **4i** and **4m** were 23.25 and 11.51 μg/mL against *A. albopictus*, respectively. These results indicated that they were the most active compounds and could be used as the potential lead structures.

4 Experimental section

4.1 General information

All reactions were performed with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Organic solutions were concentrated under reduced pressure using a rotary evaporator or oil pump. Flash column chromatography was performed using Qingdao Haiyang silica gel (200～300 mesh). Melting points were measured on a Yanagimoto apparatus (Yanagimoto MFG Co., Kyoto, Japan) and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker DPX 300 spectrometer (Bruker Biospin Co., Stuttgart, Germany) with $CDCl_3$ as a solvent and TMS as an internal standard. HR-ESI-MS spectra were analyzed on a Bruker Apex II mass spectrometer (Bruker Co., Bremen, Germany). The solvents were analytical grade and distilled before usage.

4.2 Synthesis of substituted 3,4-dihydronaphthalen-1(2*H*)-one **2b**～**2f**

General procedure[22-24] for compounds **2**: Compound **1b** (0.96 g, 4.5 mmol) was added to polyphosphoric acid (30 mL) in a 100 mL round-bottom flask at 90 ℃. The mixture was stirred for 2 h, quenched with iced water, and extracted with EtOAc (20 mL×3). The organic phase was combined, washed with saturated $NaHCO_3$ solution (20 mL×3), and dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was recrystallized from dichloromethane (DCM) to provide compound **2b** (879 mg, 65%) as a yellow solid. In a similar way, compounds **2c**～**2f** were also prepared. The m.p., ^{1}H NMR and MS data of **2b**～**2f** were identical with the published data.[35-38]

6-Chloro-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**2b**): Yellow solid, yield 65%. m.p. 104～105 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 (s, 1H), 7.29 (s, 1H), 3.94 (s, 3H), 2.88 (t, J=6.1 Hz, 2H), 2.64 (t, J=6.1 Hz, 2H), 2.17～2.08 (m, 2H). HR-ESI-MS cacld for for $C_{11}H_{12}ClO_2$ $[M+H]^+$ 211.0520, found 211.0516.

5-Chloro-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**2c**): Yellow solid, yield 50%. m.p. 67～69 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.06 (s, 1H), 6.85 (s, 1H), 3.80 (s, 3H), 2.65 (t, J=7.2 Hz, 2H), 2.46 (t, J=7.2 Hz, 2H), 2.00～1.85 (m, 2H). HR-ESI-MS cacld for for $C_{11}H_{12}ClO_2$ $[M+H]^+$ 211.0520, found 211.0521.

6-Fluoro-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**2d**): White solid, yield 58%. m.p. 94～95 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (d, J=9.0 Hz, 1H), 6.95 (d, J=11.0 Hz, 1H), 3.92 (s, 3H), 2.89 (t, J=6.0 Hz, 2H), 2.63 (t, J=6.0 Hz, 2H), 2.18～2.08 (m, 2H). HR-ESI-MS cacld for $C_{11}H_{12}FO_2$ $[M+H]^+$ 195.0816, found 195.0818.

8-Fluoro-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**2e**): White solid, yield 55%. m.p. 86～87 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.98～6.91 (m, 2H), 3.83 (s, 3H), 2.88 (t, J=6.0 Hz, 2H), 2.62 (t, J=6.0 Hz, 2H), 2.15～2.06 (m, 2H). HR-ESI-MS cacld for $C_{11}H_{12}FO_2$ $[M+H]^+$ 195.0816, found 195.0812.

6-Fluoro-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**2f**): White solid, yield 62%. m.p. 82～84 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (dd, J=8.4, 5.1 Hz, 1H), 7.02 (dd, J=8.4, 11.0 Hz, 1H), 3.93 (s, 3H), 2.95 (t, J=6.0 Hz, 2H), 2.61 (t, J=6.0 Hz, 2H), 2.16～2.05 (m, 2H). HR-ESI-MS cacld for $C_{11}H_{12}FO_2$ $[M+H]^+$ 195.0816, found 195.0815.

4.3 Synthesis of substituted 3,4-dihydro-2*H*-spiro-[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxine] **3a**～**3g**

General procedure[22,23] for compounds **3**: Compound **2e** (4.20 g, 20 mmol) and pyridinium 4-toluenesulfonate (PPTS) (1.03 g, 5 mmol) were added into MeOH (100 mL) solution of trimethyl orthoformate (60 mL) in a 250 mL round-bottom flask at room temperature. The mixture was heated at reflux for 12 h, then Et_3N (1.1 mL) was added, and the solvent was removed under reduced pressure. The residue was diluted with EtOAc (50 mL), the solution was washed with brine, and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed, and the crude product was purified by flash column chromatography on neutral Al_2O_3 (petroleum ether/EtOAc, V∶V=20∶1) to afford enol ether as a colorless liquid. Then the enol ether, 1,8-dihydroxynaphthalene (3.84 g, 24 mmol), *p*-toluenesulfonic acid (569 mg, 3 mmol), and toluene (120 mL) were added into a 250 mL round-bottom flask, the mixture was stirred and heated at reflux under a N_2 atmosphere for 3 d. After completion of the reaction, Et_3N (1.0 mL) was added, the solution was diluted with EtOAc (100 mL), washed with brine, and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed and the crude product

was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, V∶V=20∶1) to give compound **3e** (3.05 g, 48% for two steps) as yellow solid. In a similar way, compounds **3b**～**3g** were prepared.

7-Chloro-3,4-dihydro-2*H*-spiro[naphthalene-1,2'-naphtho-[1,8-de][1,3]dioxine] (**3a**): Yellow solid, yield 22%. m.p. 166～168 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87 (d, J=2.3 Hz, 1H), 7.52 (dd, J=8.3, 1.0 Hz, 2H), 7.45 (t, J=8.3 Hz, 2H), 7.34 (dd, J=8.3, 2.3 Hz, 1H), 7.16 (d, J=8.3 Hz, 1H), 6.94 (dd, J=8.3, 1.0 Hz, 2H), 2.89 (t, J=6.4 Hz, 2H), 2.16～2.10 (m, 2H), 1.96～1.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.1, 137.0, 136.6, 134.3, 132.5, 130.2, 129.7, 127.9, 127.5, 120.6, 113.7, 109.5, 100.2, 30.8, 28.9, 19.6. HR-ESI-MS cacld for $C_{20}H_{16}ClO_2$ [M + H]$^+$ 323.0833, found 323.0838.

6-Chloro-7-methoxy-3,4-dihydro-2*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxine] (**3b**): White solid, yield 35%. m.p. 162～164 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 (dd, J=8.4, 1.1 Hz, 2H), 7.44 (t, J=7.3 Hz, 2H), 7.38 (s, 1H), 7.25 (s, 1H), 6.94 (dd, J=8.4, 1.1 Hz, 2H), 3.91 (s, 3H), 2.83 (t, J=6.3 Hz, 2H), 2.16～2.11 (m, 2H), 1.95～1.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.9, 148.2, 134.7, 134.3, 131.3, 130.2, 127.6, 124.2, 120.6, 113.8, 110.7, 109.6, 100.5, 77.6, 77.2, 76.7, 56.4, 30.9, 28.5, 19.8. HR-ESI-MS cacld for $C_{21}H_{18}ClO_3$ [M + H]$^+$ 353.0939, found 353.0936.

5-Chloro-7-methoxy-3,4-dihydro-2*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxine] (**3c**): Yellow solid, yield 60%. m.p. 144～146 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55～7.40 (m, 5H), 6.92 (dd, J=7.2, 1.0 Hz, 2H), 6.89 (d, J=2.0 Hz, 1H), 3.87 (3H, s), 2.75 (t, J=6.3 Hz, 2H), 2.13 (t, J=6.0 Hz, 2H), 1.93-1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.6, 148.0, 137.5, 134.3, 132.7, 130.8, 127.5, 126.3, 120.6, 119.4, 113.7, 111.3, 109.5, 100.2, 55.9, 30.4, 22.9, 18.7. HR-ESI-MS cacld for $C_{21}H_{18}ClO_3$ [M+H]$^+$ 353.0939, found 353.0934.

6-Fluoro-7-methoxy-3,4-dihydro-2*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxine] (**3d**): Colorless crystal, yield 34%. m.p. 143～145 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 (dd, J=8.3, 1.0 Hz, 2H), 7.49～7.38 (m, 3H), 6.94 (dd, J=7.4, 1.0 Hz, 2H), 6.91 (d, J=11.7 Hz, 1H), 3.88 (s, 3H), 2.81 (t, J=6.3 Hz, 2H), 2.16～2.10 (m, 2H), 1.95～1.86 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.1 (d, $^1J_{FC}$=247.7 Hz), 148.2, 146.7 (d, $^2J_{FC}$=11.0 Hz), 134.3, 131.5 (d, $^3J_{FC}$=6.8 Hz), 131.2 (d, $^3J_{FC}$=3.5 Hz), 127.5, 120.6, 115.7 (d, $^2J_{FC}$=18.0 Hz), 113.8, 112.3, 109.5, 100.5, 56.4, 30.9, 28.7, 19.8. HR-ESI-MS cacld for $C_{21}H_{18}FO_3$ [M+H]$^+$ 337.1234, found 337.1235.

8-Fluoro-5-methoxy-3,4-dihydro-2*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxine] (**3e**): Yellow solid, yield 48%. m.p. 149～151 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (dd, J=8.4, 1.0 Hz, 2H), 7.43 (t, J=8.4 Hz, 2H), 7.00 (1H, dd, J=10.5, 9.0 Hz), 6.93 (dd, J=7.2, 1.0 Hz, 2H), 6.86 (dd, J=9.0, 4.0 Hz, 1H), 3.85 (s, 3H), 2.79 (t, J=6.3 Hz, 2H), 2.21～2.16 (m, 2H), 1.91～1.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.3 (d, $^1J_{FC}$=246.9 Hz), 152.7 (d, $^4J_{FC}$=2.2 Hz), 147.9, 134.4, 129.9, 127.5, 123.7 (d, $^2J_{FC}$=11.0 Hz), 120.3, 114.2 (d, $^2J_{FC}$=23.4 Hz), 113.4, 111.5 (d, $^3J_{FC}$=8.9 Hz), 109.3, 105.5, 56.1, 32.2, 23.9, 19.1. HR-ESI-MS cacld for $C_{21}H_{18}FO_3$ [M + H]$^+$ 337.1234, found 337.1238.

6-Fluoro-5-methoxy-3,4-dihydro-2*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxine] (**3f**): Pale yellow solid, yield 25%. m.p. 166～168 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 (dd, J=8.8, 5.0 Hz, 1H), 7.50 (dd, J=8.4, 1.0 Hz, 2H), 7.44 (t, J=7.2 Hz, 2H), 7.11 (dd, J=11.2, 8.8 Hz, 1H), 6.92 (dd, J=7.2, 1.1 Hz, 2H), 3.97 (s, 3H), 2.88 (t, J=6.3 Hz, 2H), 2.15～2.11 (m, 2H), 1.97～1.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.8 (d, $^1J_{FC}$=246.9 Hz), 148.2, 144.4 (d, $^2J_{FC}$=10.3 Hz), 134.3, 133.9 (d, $^4J_{FC}$=2.7 Hz), 132.2 (d, $^3J_{FC}$=3.4 Hz), 127.5, 123.3 (d, $^3J_{FC}$=8.2 Hz), 120.5, 115.3 (d, $^2J_{FC}$=19.9 Hz), 113.7, 109.5, 100.4, 61.0, 30.6, 23.7 (d, $^4J_{FC}$=2.2 Hz), 19.1. HR-ESI-MS cacld for $C_{21}H_{18}FO_3$ [M+H]$^+$ 337.1234, found 337.1232.

5-Methoxy-3,4-dihydro-2*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxine] (**3g**): Pale yellow solid, yield 51%. m.p. 150～151 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54 (dd, J=8.0, 1.0 Hz, 1H), 7.51 (dd, J=8.4, 1.0 Hz, 2H), 7.44 (t, J=7.2 Hz, 2H), 7.36 (t, J=8.0 Hz, 1H), 6.95 (dd, J=7.2, 1.1 Hz, 2H), 6.94 (d, J=8.0 Hz, 1H), 3.89 (s, 3H), 2.83 (t, J=6.3 Hz, 2H), 2.18～2.13 (m, 2H), 1.97～1.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.8, 148.4, 136.4, 134.3, 127.6, 127.5, 127.2, 120.3, 119.3, 113.8, 110.5, 109.4, 100.7, 55.7, 30.5, 23.2, 18.9. HR-ESI-MS cacld for $C_{21}H_{19}O_3$ [M+H]$^+$ 319.1329, found 319.1326. These data were identical with the published data.[33,34]

4.4 Synthesis of substituted 2,3-dihydro-4*H*-spiro-[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one **4a**～**4g**

General procedure[22-24] for compounds **4**: Compound **3g** (1.18 g, 3.7 mmol) and pyridinium dichromate (PDC, 4.12 g, 11 mmol, 3 eq.) were added to a 250 mL round-bottom flask containing Celite (2.80 g) and benzene (100 mL) in an iced water bath. The mixture was stirred, and 5～6 mol/L *t*-BuOOH (12 mL) was injected into the mixture with a syringe over 15 min. The iced water bath was removed, and the mixture was stirred at room temperature for 24 h. The mixture was diluted with EtOAc (50 mL), and the solids were filtered off. The organic phase was washed with 0.2 mol/L HCl (50 mL×2) solution and brine, and dried over anhydrous Na_2SO_4. The organic phase was concentrated under reduced pressure, and the residue was purified by a flash column chromatography on silica gel (petroleum ether/EtOAc, V∶V=10∶1) to afford compound **4g** (970 mg, 79%) as white solid. In a similar way, compounds **4a**～**4f** were prepared.

7-Chloro-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho-[1,8-de][1,3]dioxin]-4-one (**4a**): Yellow solid, yield 59%. m.p. 206～208 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.07 (d, J=8.4 Hz, 1H), 7.99 (d, J=2.0 Hz, 1H), 7.58～7.52 (m, 3H), 7.46 (dd, J=8.4, 7.4 Hz, 2H), 6.98 (dd, J=7.5, 1.0 Hz, 2H), 2.79 (t, J=6.2 Hz, 2H), 2.51 (t, J=6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 195.2, 147.3, 142.0, 141.0,

134.3, 130.7, 130.1, 128.9, 127.7, 126.8, 121.2, 113.4, 109.7, 98.3, 34.2, 29.7. HR-ESI-MS cacld for $C_{20}H_{14}ClO_3$ $[M+H]^+$ 337.0626, found 337.0629.

6-Chloro-7-methoxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (**4b**): Yellow solid, yield 83%. m.p. 200～202 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15 (s, 1H), 7.55 (dd, J=8.4, 1.0 Hz, 2H), 7.47 (t, J=8.4 Hz, 2H), 7.46 (s, 1H), 6.99 (dd, J=8.4, 1.0 Hz, 2H), 4.00 (s, 3H), 2.76 (t, J=6.4 Hz, 2H), 2.50 (t, J=6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.1, 159.7, 147.5, 141.1, 134.4, 129.4, 127.7, 125.7, 125.4, 121.2, 113.5, 109.7, 108.8, 98.6, 56.8, 34.1, 29.9. HR-ESI-MS cacld for $C_{21}H_{16}ClO_4$ $[M+H]^+$ 367.0732, found 367.0728.

5-Chloro-7-methoxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (**4c**): Yellow solid, yield 83%. m.p. 203～204 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60～7.42 (m, 5H), 7.10 (d, J=1.0 Hz, 1H), 6.97 (dd, J=7.2, 1.0 Hz, 2H), 3.97 (s, 3H), 2.74 (t, J=6.6 Hz, 2H), 2.44 (t, J=6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.4, 160.6, 147.3, 144.1, 141.1, 134.3, 127.7, 121.1, 119.7, 118.5, 114.3, 113.5, 109.6, 98.5, 56.8, 35.4, 29.3. HR-ESI-MS cacld for $C_{21}H_{16}ClO_4$ $[M+H]^+$ 367.0732, found 367.0735.

6-Fluoro-7-methoxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (**4d**): Yellow solid, yield 76%. m.p. 185～186 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.81 (d, J=11.2 Hz, 1H), 7.57～7.44 (m, 5H), 6.99 (d, J=8.3 Hz, 2H), 3.99 (s, 3H), 2.77 (t, J=6.0 Hz, 2H), 2.50 (t, J=6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.4, 153.3 (d, $^1J_{FC}$=250.3 Hz), 153.0 (d, $^2J_{FC}$=11.2 Hz), 147.5, 138.3 (d, $^3J_{FC}$=3.4 Hz), 134.4, 127.7, 125.8 (d, $^3J_{FC}$=5.5 Hz), 121.1, 114.3 (d, $^2J_{FC}$=19.3 Hz), 113.5, 110.3 (d, $^4J_{FC}$=2.1 Hz), 109.7, 98.6, 56.6, 34.1, 29.9. HR-ESI-MS cacld for $C_{21}H_{16}FO_4$ $[M+H]^+$ 351.1027, found 351.1028.

8-Fluoro-5-methoxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (**4e**): Yellow solid, yield 61%. m.p. 167～168 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 (dd, J=8.4, 1.0 Hz, 2H), 7.44 (t, J=8.4 Hz, 2H), 7.36 (dd, J=10.3, 9.3 Hz, 1H), 7.10 (dd, J=9.3, 3.7 Hz, 1H), 6.96 (dd, J=8.4, 1.0 Hz, 2H), 3.94 (s, 3H), 2.79-2.73 (m, 2H), 2.56～2.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 195.0, 155.5 (d, $^4J_{FC}$=2.2 Hz), 154.7 (d, $^1J_{FC}$=250.2 Hz), 147.1, 134.4, 128.2 (d, $^2J_{FC}$=9.7 Hz), 127.6, 123.3 (d, $^2J_{FC}$=24.2 Hz), 122.1, 120.9, 115.5 (d, $^3J_{FC}$=8.3 Hz), 113.1, 109.5, 99.4, 57.0, 36.8, 30.8. HR-ESI-MS cacld for $C_{21}H_{16}FO_4$ $[M+H]^+$ 351.1027, found 351.1024.

6-Fluoro-5-methoxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (**4f**): Yellow solid, yield 74%. m.p. 101～102 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (dd, J=8.4, 4.7 Hz, 1H), 7.53 (dd, J=8.4, 1.0 Hz, 2H), 7.45 (t, J=8.4 Hz, 2H), 7.40 (dd, J=10.4, 8.7 Hz, 1H), 6.96 (dd, J=8.4, 1.0 Hz, 2H), 4.03 (s, 3H), 2.78 (t, J=6.5 Hz, 2H), 2.45 (t, J=6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.7, 157.3, 147.8, 147.5, 137.6, 134.3, 127.7, 127.3, 122.1, 121.6, 121.1, 113.5, 109.6, 98.6, 62.5, 35.5, 29.5. HR-ESI-MS cacld for $C_{21}H_{16}FO_4$ $[M+H]^+$ 351.1027, found 351.1025.

5-Methoxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (**4g**): Yellow solid, yield 79%. m.p. 156～158 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (t, J=8.0 Hz, 1H), 7.56 (dd, J=8.0, 1.4 Hz, 1H), 7.51 (dd, J=7.8, 1.0 Hz, 2H), 7.43 (t, J=7.8 Hz, 2H), 7.11 (dd, J=8.0, 1.4 Hz, 1H), 6.96 (dd, J=7.8, 1.0 Hz, 2H), 3.97 (s, 3H), 2.76 (t, J=6.8 Hz, 2H), 2.47 (t, J=6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 195.4, 159.7, 147.7, 142.8, 134.9, 134.3, 127.6, 121.1, 120.9, 117.9, 113.7, 113.6, 109.5, 99.0, 56.5, 35.5, 29.6. HR-ESI-MS cacld for $C_{21}H_{17}O_4$ $[M+H]^+$ 333.1121, found 333.1126. These data were identical with the published data.[33,34]

4.5 Synthesis of 4h～4j by demethylation of 4e～4g

General procedure [22-24] for compounds **4h**～**4j**: Trimethylsilyl iodide (TMSI) (0.3 mL, 2.1 mmol) was added into $CHCl_3$ (2 mL) solution of compound **4g** (70 mg, 0.21 mmol) in a 10 mL round- bottom flask in an iced water bath. The mixture was stirred at 0 ℃ for 12 h. The solution was extracted with saturated aqueous $Na_2S_2O_3$ (20 mL×2) solution. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was subjected to flash column chromatography on silica gel and eluted with petroleum/EtOAc (V∶V=20∶1) to afford compound **4j** (55 mg, 82%) as a light yellow solid. In a similar way, compounds **4h** and **4i** were prepared.

8-Fluoro-5-hydroxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (**4h**): Green solid, yield 74%. m.p. 163～165 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.28 (s, 1H), 7.54 (dd, J=8.4, 1.0 Hz, 2H), 7.46 (t, J=8.4 Hz, 2H), 7.38 (dd, J=10.3, 9.2 Hz, 1H), 7.11 (dd, J=9.2, 3.8 Hz, 1H), 6.98 (dd, J=8.4, 1.0 Hz, 2H), 2.84～2.78 (m, 2H), 2.56～2.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 203.6 (d, $^4J_{FC}$=2.1 Hz), 152.1 (d, $^1J_{FC}$=249.4 Hz), 150.8 (d, $^2J_{FC}$=12.6 Hz), 147.4, 136.2 (d, $^3J_{FC}$=4.2 Hz), 134.4, 127.7, 122.7 (d, $^2J_{FC}$=17.2 Hz), 121.1, 117.3 (d, $^4J_{FC}$=3.4 Hz), 116.7 (d, $^3J_{FC}$=6.3 Hz), 113.4, 109.6, 98.2, 34.5, 29.7 (d, $^4J_{FC}$=2.7 Hz). HR-ESI-MS cacld for $C_{20}H_{14}FO_4$ $[M+H]^+$ 337.0871, found 337.0876.

6-Fluoro-5-hydroxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (**4i**): Yellow solid, yield 58%. m.p. 160～161 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.44 (s, 1H), 7.54 (dd, J=8.4, 1.0 Hz, 2H), 7.48～7.41 (m, 4H), 6.97 (dd, J=8.4, 1.0 Hz, 2H), 2.87 (t, J=6.3 Hz, 2H), 2.49 (t, J=6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 202.8 (d, $^4J_{FC}$=3.4 Hz), 158.68, 158.66, 153.2 (d, $^1J_{FC}$=249.0 Hz), 147.1, 134.4, 127.6, 127.2 (d, $^2J_{FC}$=24.9 Hz), 121.5 (d, $^3J_{FC}$=8.2 Hz), 121.0, 115.2, 113.1, 109.6, 99.0, 34.3, 29.9. HR-ESI-MS cacld for $C_{20}H_{14}FO_4$ $[M+H]^+$ 337.0871, found 337.0876.

5-Hydroxy-2,3-dihydro-4*H*-spiro[naphthalene-1,2'-naphtho[1,8-de][1,3]dioxin]-4-one (**4j**): Pale yellow solid, yield 82%. m.p. 148～150 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.45 (s, 1H), 7.62 (t, J=8.4 Hz, 1H), 7.54 (dd, J=8.4, 1.0 Hz, 2H), 7.46 (t, J=8.4 Hz, 2H), 7.44 (dd, J=7.5, 1.0 Hz, 1H), 7.10 (dd, J=7.5, 1.0 Hz, 1H), 6.97 (dd, J=8.4, 1.0

Hz, 2H), 2.85 (t, J=6.3 Hz, 2H), 2.49 (t, J=6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 203.4, 162.6, 147.5, 140.9, 137.3, 134.3, 127.7, 121.0, 119.7, 116.8, 115.5, 113.5, 109.5, 98.5, 34.2, 29.5. HR-ESI-MS cacld for $C_{20}H_{15}O_4$ $[M+H]^+$ 319.0965, found 319.09706. These data were consistence with the published data.[33,34]

4.6 Bioassay of larvicidal activity

The larvicidal activities of compounds **3a**～**3i** and **4a**～**4n** against *A. albopictus* were evaluated using methods in the references, and larval mortality bioassays were carried out according to the larval susceptibility test method suggested by World Health Organization (WHO).[17,23] Twenty larvae were placed in a glass beaker with 250 mL of aqueous suspension of the tested materials at different concentrations. Five replicates were run simultaneously per concentration, and with each experiment a set of controls using 0.05% dimethyl sulfoxide (DMSO) and untreated sets of larvae in tap water were also run for comparison. Rotenone and juglone (purchased from the National Centre of Pesticide Standards, Shenyang, China) were used as positive controls. The toxicities of rotenone and juglone were determined at 15.00, 10.00, 6.67, 4.44, 2.96, 1.98 and 1.32 μg/mL. The assays were placed in a growth chamber (L16:D8, 26～28 ℃, 78%～80% RH). Mortality was recorded after 24 h of exposure.

Supporting Information ^{1}H NMR and ^{13}C NMR spectra of compounds **2**, **3** and **4**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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