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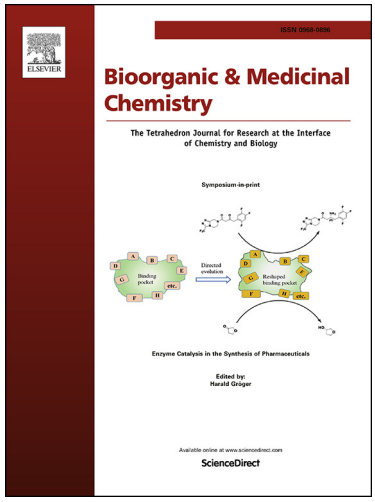

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PII: S0968-0896(18)32040-6
DOI: https://doi.org/10.1016/j.bmc.2018.12.040
Reference: BMC 14689

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 4 December 2018
Revised Date: 24 December 2018
Accepted Date: 30 December 2018

Please cite this article as: Zhang, Q., Bai, P., Zheng, C., Cheng, Y., Wang, T., Lu, X., Design, Synthesis, Insecticidal Activity and Molecular Docking of Doramectin Derivatives, *Bioorganic & Medicinal Chemistry* (2018), doi: https://doi.org/10.1016/j.bmc.2018.12.040

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Design, Synthesis, Insecticidal Activity and Molecular Docking of Doramectin Derivatives

Qi Zhang[a,c], Ping Bai[a,c], Cheng Zheng[a,c], Yao Cheng[a,c], Tao Wang[a,c], and Xiaoxia Lu[a,b*]

[a] *Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, People's Republic of China.*
[b] *Key Laboratory of Tropical Medicinal Plant Chemistry of Ministry of Education, Hainan Normal University, Hainan, 571127, People's Republic of China.*
[c] *University of Chinese Academy of Sciences, Beijing 100049, People's Republic of China.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
doramectin derivatives
insecticidal activities
molecular docking
oriental armyworm
diamondback moth
corn borer

ABSTRACT

A series of new doramectin derivatives containing carbamate, ester and sulfonate were synthesized, and their structures were characterized by ^{1}H and ^{13}C nuclear magnetic resonance (NMR) and high-resolution mass spectrum (HRMS). Their insecticidal activities against oriental armyworm, diamondback moth, and corn borer were evaluated and compared with the parent doramectin and commercial avermectins, metolcarb, fenpropathrin. Among all compounds, three compounds (**3a**, **3g** and **3h**) showed excellent insecticidal effect. In particular, compound **3g** containing cyclopropyl carbamate against oriental armyworm, diamondback moth, and corn borer, exhibited the most promising insecticidal activity with the final mortality rate of 66.67%, 36.67%, 40.00% at the concentration of 12.5 mg/L, respectively. The LC_{50} values of **3g** were 5.8859, 22.3214, and 22.0205 mg/L, showing 6.74, 2.23, 2.21-fold higher potency than parent doramectin (LC_{50} values of 39.6907, 49.7736, and 48.6129 mg/L) and 6.83, 1.93, 3.36-fold higher potency than commercial avermectins (LC_{50} values of 40.2489, 42.9922, and 73.9508 mg/L). Additionally, molecular docking simulations revealed that **3g** displayed stronger hydrogen-bonding action in binding with the GABA receptor than parent doramectin, which were crucial for keeping high insecticidal activity. The present work demonstrated that these compounds containing alkyl carbamate group could be considered as potential candidates for the development of novel pesticides in the future.

1. Introduction

Agricultural production losses caused by pest insects (oriental armyworm, diamondback moth, corn borer, *etc*.) occupy a significant proportion of the total losses.[1] By resisting of pest insects, many chemical pesticides, such as benzoylureas,[2,3] phenylpyrazoles,[4,5] and insect-growth regulators (IGRs)[6-8] play an important role in the enhancement of crop production, however, simultaneously increase pest resistance. The fermentation-derived, large, complex macrocyclic lactones (**Figure 1**), such as avermectins,[9,10] milbemycins,[11] ivermectins[12] have attracted significant attention over the years due to their occurrence as naturally bioactive products which display high efficiency, no cross-resistance, and unique mode of action (MoA). In particular, the mechanism of action of avermectins (AVMs, **Figure 1a**) is by binding to glutamate-gated chloride channels expressed on nematode neurons and pharyngeal muscle cells and disrupting normal physiological and developmental processes to exert its biological activities.[13] Benefiting from their unique mode of action, AVMs have no cross-resistance with other commercial insecticidal agents and have aroused considerable research interest in exploiting insecticidal agents of this class.[14] However, the unrestricted usage of AVMs insecticides over several decades has resulted in the development of resistance in insecticide.[15]

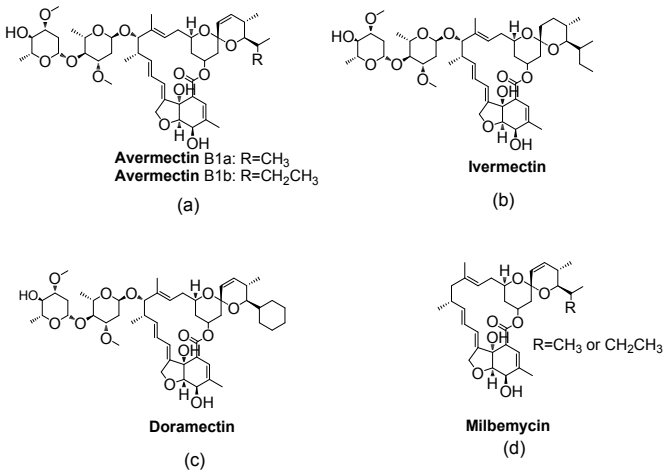


Figure 1 Chemical structures of microbial metabolites.

Due to better lipophilicity, doramectin (**Figure 1c**) as a third-generation of AVMs family with a cyclohexyl group at C-25 position in lieu of sec-butyl or isopropyl of AVMs, has better biological activity and less resistance than AVMs, which is used to treat endoparasitic nematodes and ectoparasitic insects in animals.[16,17] It has been reported that GABA receptor is the target of this macrolide. Thus, we performed docking studies with

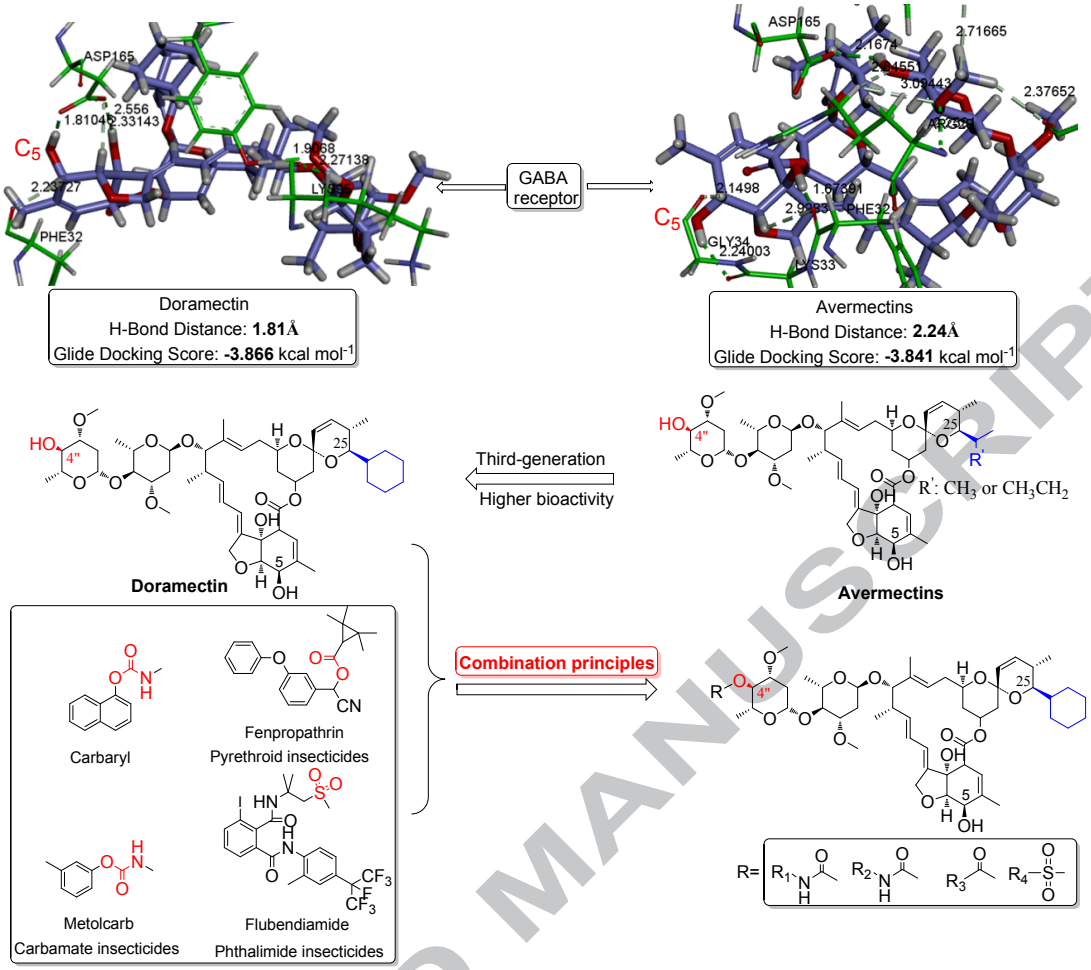


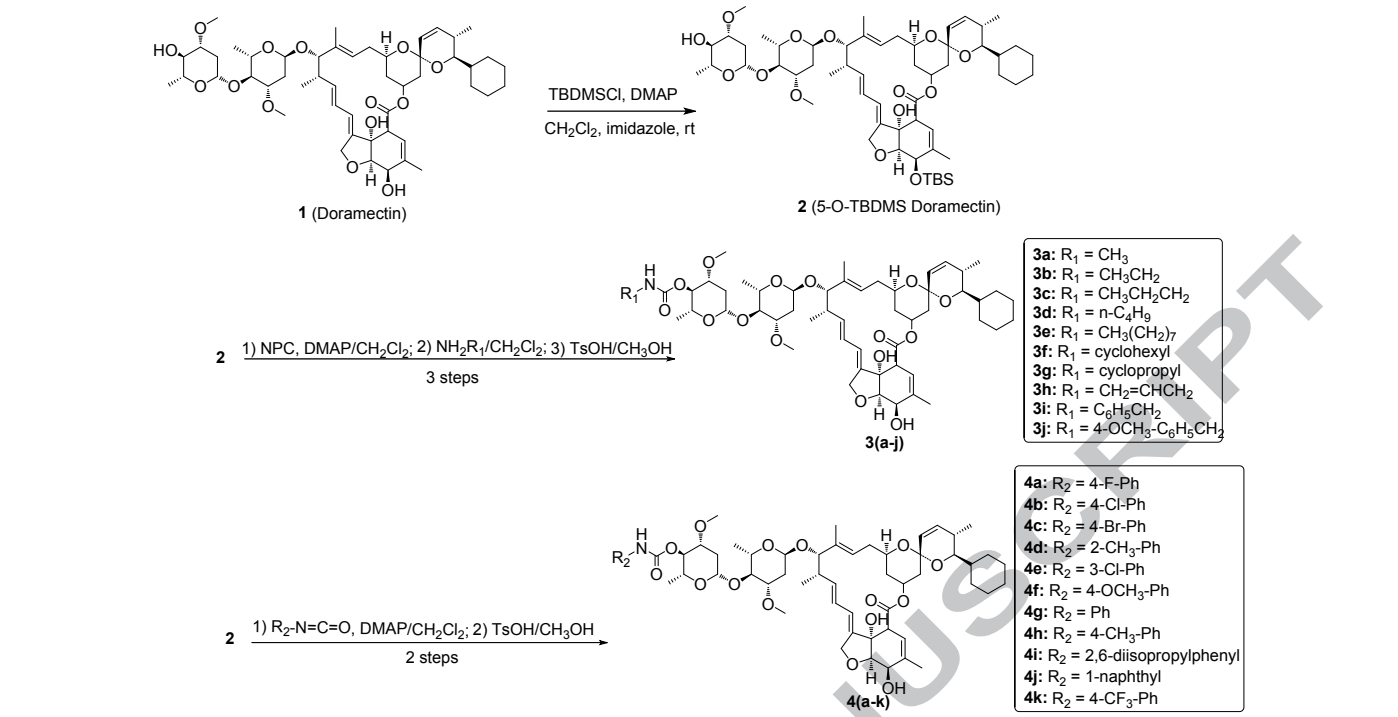
Figure 2 Design of the target compounds.

Schrodinger-Glide and investigate the binding pose of AVMs and doramectin in the active site of target protein (*Plutella xylostella* GABA receptor) by homology modeling based on Human Glycine Receptor alpha-3 retrieved from the Protein Data Bank (PDB ID 5TIN). By comparing the docking poses of AVMs and doramectin, the binding free energy (The glide score is an empirical scoring function that is an approximation of the ligand binding free energy) of doramectin (-3.866 kcal mol^{-1}) was lower than that of AVMs (-3.841 kcal mol^{-1}), and the H-bonding distance of doramectin (1.81 Å) at the C5-OH was much shorter than that of AVMs (2.24 Å) (**Figure 2**). Therefore, we speculate that doramectin as the lead compound has excellent insecticidal activity, due to the docking posture bind to GABA receptor better than AVMs.

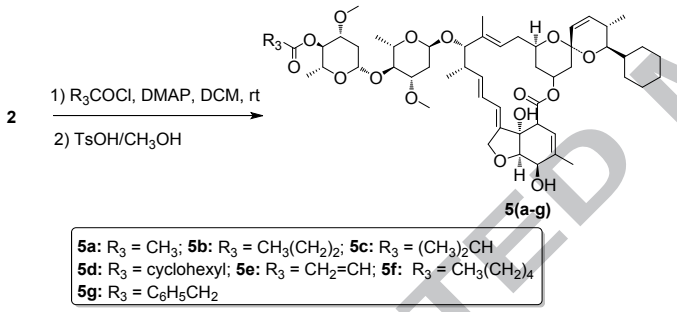
The introduction of new active groups in lead compounds is an important tool for drug discovery. It is well known that carbamate, ester, and sulfonate esters which can form H-bonds are the active groups in common pesticides because of their respective advantages. The carbamate insecticides (metolcarb, carbaryl, *etc*.) can inhibit acetylcholinesterase (AChE) in insects nervous system by covalently carbamylating the serine residue within the active site for insecticidal effects.[18] Many ester insecticides, such as pyrethroid insecticide fenpropathrin, bind to voltage-sensitive sodium channels and modify their gating kinetics, thereby disrupting nerve function.[19] Most sulfone compounds possess excellent biological activities, such as insecticidal,[20] antifungal,[21] and antitumor,[22] especially in the field of pesticides.[23]

Avermectins (AVMs) has been widely used as the lead molecule for chemical modifications to discover more potent insecticidal agents due to their remarkable biological activities on insecticidal and anthelmintic activities. AVMs analogs mainly modified at C-5,[24,25] C-13,[26,27] C22～C23,[28,29] and C4" position[30, 31] have been reported. From the structure-activity relationship (SAR) study on AVMs analogues, we noted that different hydroxyls (C5 and C4") have different biological activities and selectivities. A slight modification at the C5-OH group may resulted in loss of activity, which indicates free OH group at the C5 is crucial to activity.[25] Whereas, small changes at the C4"-OH group in the chemical structure of the AVMs often lead to pronounced differences in physical and biological properties.[32,33] Up to present, the modification of C4"-OH is being continually investigated.

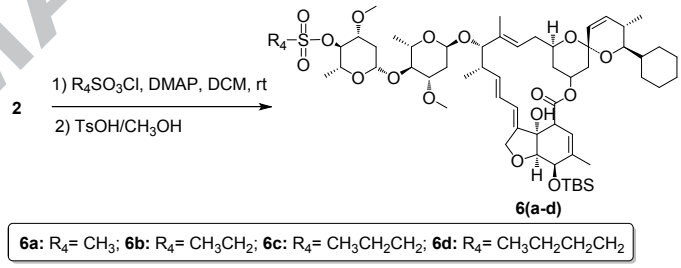
Inspired by these reports, herein, we aim at developing novel macrolide pesticides by combining principles, introducing active groups (carbamate, ester, and sulfonate groups) replace the hydroxyl group at C4"-position (**Figure 2**). A series of novel carbamate, ester, and sulfonate based doramectin derivatives are rationally designed, synthesized, and characterized. The insecticidal activities of these target compounds against oriental armyworm, diamondback moth, and corn borer are evaluated. Furthermore, docking analysis and structure-activity relationship (SAR) studies are extensively performed on the derivatives to identify key structural features responsible for their insecticidal potency.



Scheme 1 General procedure for the synthesis of carbamate derivatives of doramectin (**3a-3j**) and (**4a-4k**).



Scheme 2 General procedure for the synthesis of ester derivatives of doramectin (**5a-5g**).



Scheme 3 General procedure for the synthesis of sulfonate derivatives of doramectin (**6a-6d**).

2. Results and discussion

2.1. Chemistry synthesis

Three series of novel carbamate, ester and sulfonate derivatives of doramectin (**3a−3j**, **4a−4k**, **5a−5g** and **6a−6d**) modified at position C4″-OH were prepared as shown in **Scheme 1-3**. Since structure-activity relationship studies had demonstrated that the presence of free 5-OH in doramectin played an important role in insecticidal activity, commercially available doramectin was first selective protection of hydroxyl group at the 5-position by using *tert*-butylchlorodimethylsilane (TBDMS-Cl) as a protective agent in the presence of trimethylamine and DMAP to provide 5-*O*-TBDMS doramectin **2** as described previously.[35] For the synthesis of *N*-aliphatic substituted carbamate derivatives of doramectin **3a−3j**, protective intermediate **2** was first reacted with bis(4-nitrophenyl) carbonate (NPC) to produce 4-nitrophenyl intermediate, which was further nucleophilic substituted with different alkylamine, and the *t*-butyldimethylsilyl was deprotected using *p*-toluenesulfonic acid-methanol complex according to published procedures.[35] The initial attempt to obtain the *N*-aromatic substituted carbamate derivatives of doramectin **4a-4k** using similar method like **3a−3j** was not so successful because of the low activities of corresponding aromatic amines. Notably, compound **2** were reacted with newly prepared aromatic isocyanates using triphosgene and aromatic amines in the solution of dichloromethane and saturated sodium bicarbonate without further purified to afford the target compounds **4a-4k**. Finally, ester and sulfonate derivatives of doramectin **5a-5g** and **6a-6d** were obtained by reaction of **2** with different acyl chlorides or sulfonyl chlorides in the presence of Et_3N.

2.2. Insecticidal activities

All compounds prepared were evaluated for insecticidal efficacy against oriental armyworm and diamondback moth, and a few representative compounds **3a**, **3g** and **3h** were further evaluated for insecticidal efficacy against corn borer, and the results were listed in **Figure 3-4** and **Table 1**. The LC_{50} values for **3a**, **3g** and **3h** were calculated through five different concentrations and were listed in **Table 2**. Doramectin, avermectins, metolcarb and fenpropathrin were used as a positive control, and leaves treated with acetone alone were used as a blank control group.

As shown in **Figure 3**, compared with doramectin and avermectins, most of the alkyl carbamate derivatives of doramectin except **3e** and **3f** displayed desirable insecticidal

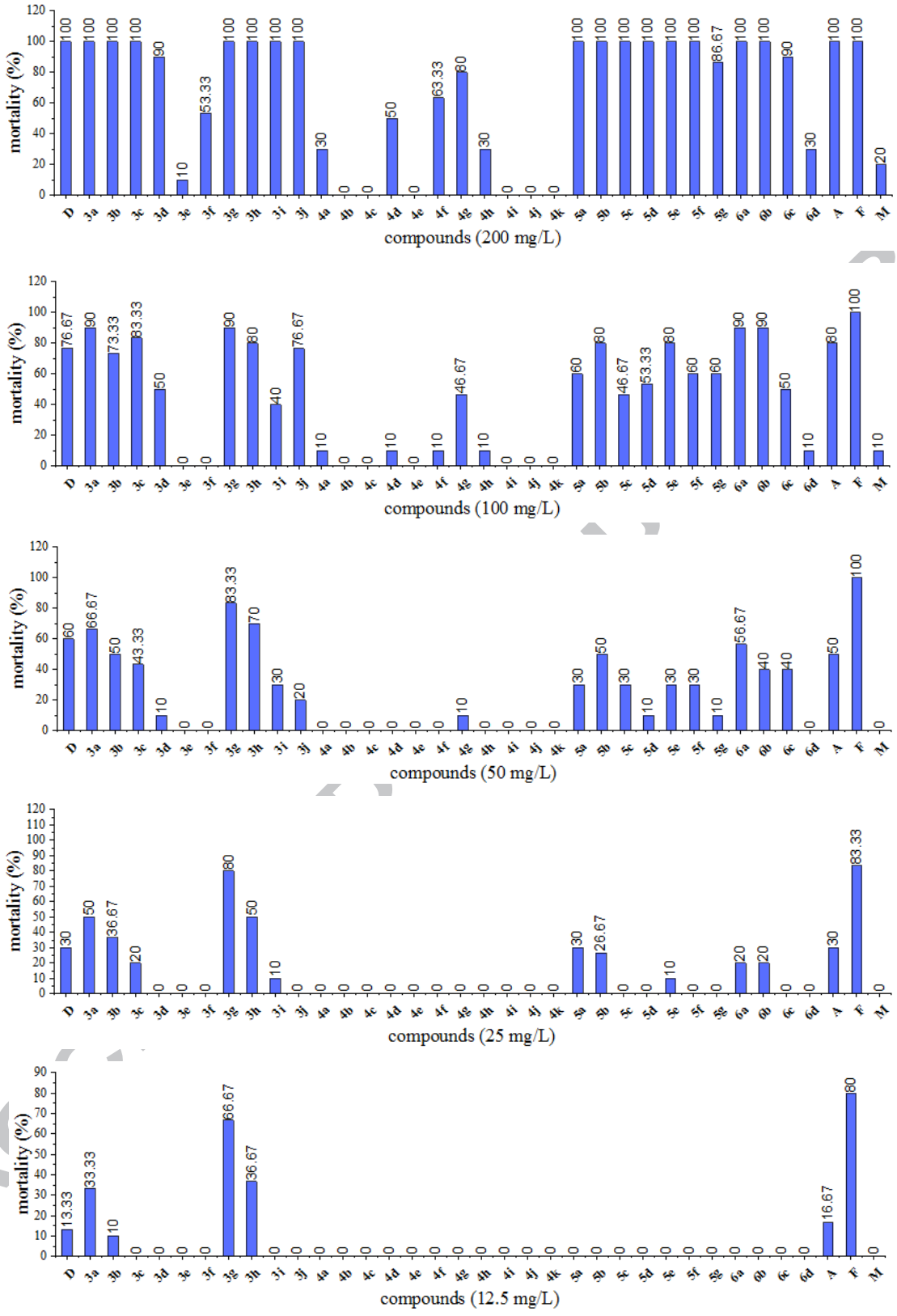


Figure 3 Insecticidal activities of target compounds against oriental armyworm.

(D: Doramectin; A: Avermectins; F: Fenpropathrin; M: Metolcarb)

activities against oriental armyworm, whereas phenyl carbamate derivatives tended to be less active. The ester and sulfonate derivatives of doramectin, **5a-5g** and **6a-6d**, were less active than the doramectin and avermectins. Among these derivatives, **3a**, **3g** and **3h** afforded the best insecticidal activities and had 33.33%, 66.67% and 36.67% mortality at 12.5 mg/L, whereas doramectin and avermectins had only 13.33% and 16.67% under the same conditions. **3a**, **3g** and **3h** had LC_{50} (mg/L) values of 23.8730, 5.8859, and 23.1370, respectively, particularly, the LC_{50} value of **3g** was 6.83-fold as that of avermectins (LC_{50}= 40.2389 mg/L). The insecticidal activities against oriental armyworm of compound **3g** was far superior to that of metolcarb and inferior to the insecticidal activity of fenpropathrin.

Figure 4 showed that all compounds prepared displayed different insecticidal activities against diamondback moth. In general, the insecticidal activities of alkyl carbamate derivatives (**3a-3d** and **3g-3j**) were much better than that of phenyl carbamate derivatives (**4a-4e**, **4g** and **4i-4k**), which displayed no insecticidal activities against diamondback moth at 100 mg/L. In addition, the insecticidal activities of alkyl carbamate derivatives (**3a-3j**) showed almost the same level of activity as the ester derivatives (**5a-5g**) and sulfonate derivatives (**6a-6c**) at 100 mg/L. In particular, compounds (**3a**, **3g**, **3h**) exhibited good

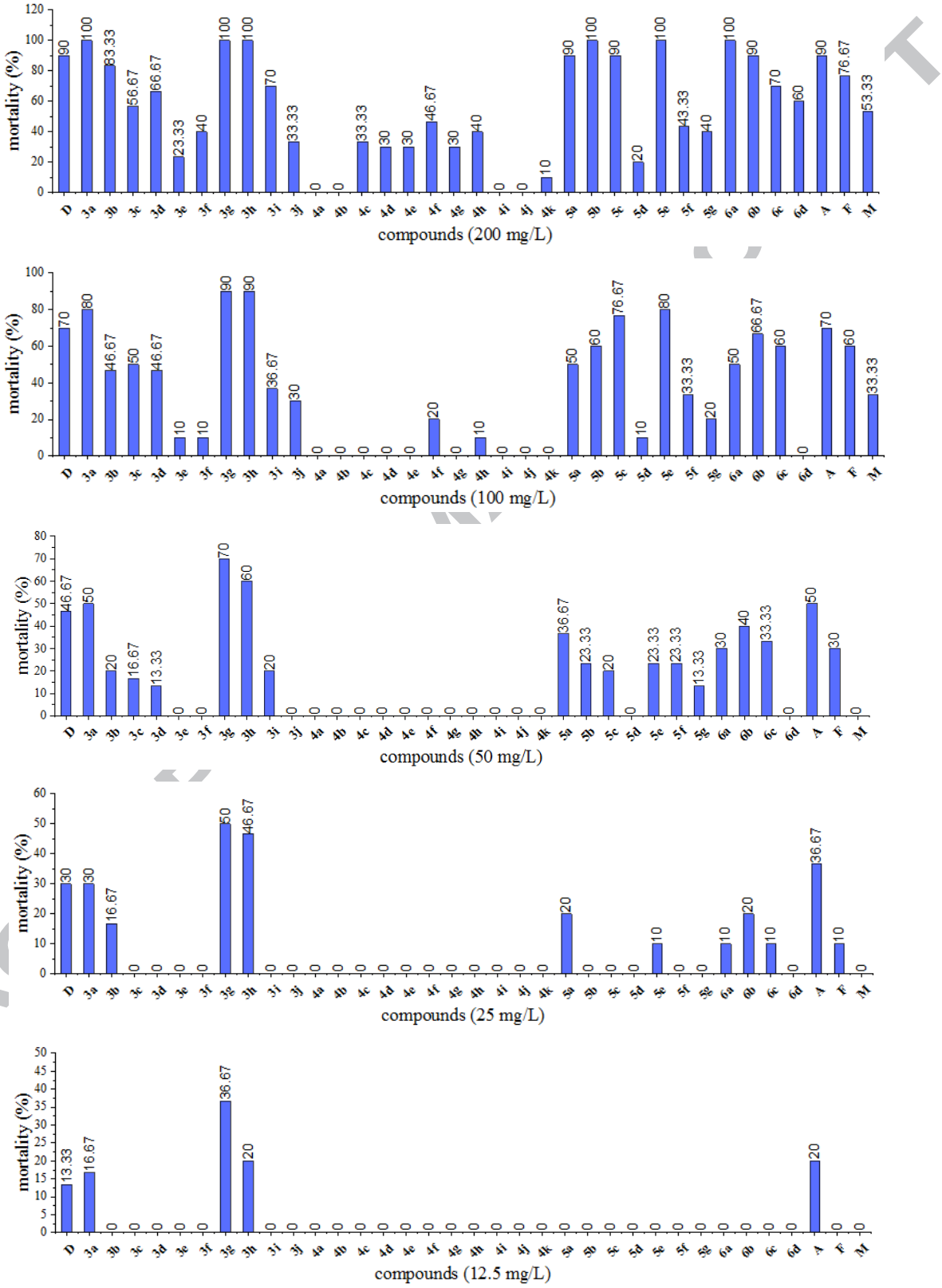


Figure 4 Insecticidal activities of target compounds against diamondback moth.

(D: Doramectin; A: Avermectins; F: Fenpropathrin; M: Metolcarb)

insecticidal activities against diamondback moth with mortality 16.67%, 36.67% and 20.00% at 12.5 mg/L, which was superior or parallel to that of doramectin (13.33%) and avermectins (20.00%) under the same concentration. The LC_{50} values of compounds **3a**, **3g**, **3h**, doramectin and avermectins against diamondback moth were 40.2389, 22.3214, 29.9907, 49.7736, and 42.9922 mg/L, respectively. The compound **3g** exhibited better insecticidal activities than fenpropathrin and metolcarb against diamondback moth.

Since compounds **3a**, **3g**, and **3h** exhibited best insecticidal activities against oriental armyworm and diamondback moth among all compounds prepared, the three compounds were further evaluated for insecticidal efficacy against corn borer in **Table 1**. From **Table 1**, we found that compounds **3a**, **3g**, and **3h** exhibited better insecticidal activities against corn borer than the contrast doramectin and avermectins. At the concentration of 12.5 mg/L, compound **3g** exhibited high insecticidal activities against corn borer was 40.00%, while insecticidal activities of compounds **3a** and **3h** were equal or superior to the contrast doramectin (13.33%) and avermectins (10.00%). The LC_{50} values in **Table 2** showed that the activity of **3g** was 3.36-fold as high as avermectins. The compound **3g** also exhibited better insecticidal activities than fenpropathrin against corn borer.

2.3. Structure-activity relationship (SAR).

Comparison of the insecticidal activities in **Figure 3**, **Figure 4**, and **Table 1** showed that substitution patterns of C4" in doramectin have significant effects on the activity. The contrasting trends are as follow: (1) the insecticidal activities: carbamate > ester ≈ sulfonate groups, (2) the activities of short alkyl groups of compounds were superior to the long alkyl-substituted compounds, such as, **3a** >> **3e**, **5a** > **5f**, **6a** > **6d**, (3) aromatic-substituted compounds (**4a-4k**) exhibited much lower insecticidal activities than alkyl-substituted compounds (**3a-3d**, **3g-3j**), (4) straight-substituted compound (**5b**) better than the branched compound (**5c**), cyclopropyl-substituted compound (**3g**) better than the cyclohexyl-substituted compound (**3f**), (5) The insecticidal activity of compound **3g** was superior to that of doramectin and avermectins at the same concentration.

2.4. Docking analysis

As described above, **3g** was identified as the most promising pesticide against oriental armyworm, diamondback moth, and corn borer. To better understand structure-activity relationship of doramectin derivatives, we carried out a molecular docking study of three compounds (**3g**, **5a** and **6a**) on *Plutella xylostella* GABA receptor using Schrodinger-Glide. As shown in **Figure 5**, compound **3g**, **5a** and **6a** had a different docking mode. Considering their molecular structures, the main difference was in the C4" position, indicating that this position might have a significant effect on the binding between the ligand and GABA receptor. To explain this finding, we conducted binding free energy calculations and compared the binding conformations among the different compounds. The results (**Table 3**) revealed that compound **3g** showed the best binding affinity with GABA receptor. The binding free energy of **3g** (-3.964kcal mol^{-1}) was much lower than that of **5a** (-2.467 kcal mol^{-1}) and **6a** (-2.791 kcal mol^{-1}). Additionally, the presence of hydrogen bonds might also explain the structure-activity relationship. The H-bonding strengths of compounds **3g** (1.66 Å, 3.01 Å) was better than that of **5a** (2.06 Å) and **6a** (2.14 Å) at C5-OH. Simultaneously, nitrogen atom on carbamate in compound **3g** could form the N−H···O H-bond (2.12 Å), and no H-bond formed on the ester group in compound **5a**. Although the H-bond (2.49 Å) was formed on the sulfonate in compound **6a**, the binding affinity was also weaker than that of **3g**. The docking results of compounds **3g**, **5a**, **6a**, doramectin and avermectins were in good agreement with our insecticidal assays, for which the activity of the carbamate was better than that of the ester, and the ester was similar to the sulfonate. Therefore, the binding between the compound **3g** and the target protein was the best one among these compounds in the docking simulation.

3. Conclusions

In summary, 32 doramectin derivatives containing carbamate, ester, sulfonate groups were synthesized, and their structures were characterized by ^{1}H NMR, ^{13}C NMR, and high resolution mass spectrum (HRMS). The insecticidal activities against oriental armyworm, diamondback moth and corn borer were evaluated. The results of bioassays indicated that compounds **3a**, **3g** and **3h** exhibited excellent insecticidal activities, especially the insecticidal activities of compound **3g**, which was superior to the doramectin and commercial avermectins at concentration 12.5 mg/L. Furthermore, the LC_{50} values of the insecticidal activities of **3g** against oriental armyworm, diamondback moth and corn borer were 6.83, 1.93, 3.36-fold as high as that of commercial avermectins, respectively. Molecular docking also showed that compound **3g** could bind well to the target protein receptor, it may lead to a new insecticide in the future. Future detailed study of structure activity relationships is in progress at our group.

4. Materials and methods

4.1. Instruments

Reaction progress was monitored by thin-layer chromatography (TLC) on silica gel GF254 with ultraviolet (UV) detection. The melting points were determined on an X-6 precision micro-melting point apparatus (Beijing Fukui Technology Development Co., Ltd) and were uncorrected. ^{1}H NMR (400 MHZ) and ^{13}C NMR (100 MHZ) spectra were obtained using a Bruker 400 spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical shifts (δ values) and coupling constants (J values) were given in parts per million and hertz, respectively. Data for ^{1}H NMR (400 Hz) were reported as follows: chemical shift (δ: ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant (Hz), integration and assignment (H). Data for ^{13}C NMR (100 Hz) were reported in terms of chemical shift (δ: ppm), with (C) standing for quaternary carbon, (CH) standing for tertiary carbon, (CH_2) standing for secondary carbon, and (CH_3) standing for primary carbon. High resolution mass spectra （HRMS） data were recorded under on a Micro Q-TOF II mass spectrometer (the HR-ESI-MS, Bruker, Germany) in the negative ion detection mode.

Table 1 Insecticidal activities of target compounds against corn borer

Compound	200mg/L	100mg/L	50mg/L	25mg/L	12.5mg/L
Doramectin	86.67%	66.67%	50.00%	36.67%	13.33%
3a	90.00%	80.00%	50.00%	33.33%	20.00%
3g	100.00%	90.00%	70.00%	46.67%	40.00%
3h	90.00%	70.00%	50.00%	33.33%	13.33%
Avermectins	83.33%	50.00%	40.00%	20.00%	10.00%
Fenpropathrin	100%	80%	50%	36.67%	23.33%
Metolcarb	60%	40%	16.67%	0	0

Table 2 LC_{50}(mg/L) values of **3a**, **3g**, **3h**, doramectin, and avermectins against oriental armyworm, diamondback moth and corn borer

	Oriental armyworm		Diamondback moth		Corn borer	
	LC_{50}	toxic ratio	LC_{50}	toxic ratio	LC_{50}	toxic ratio
3a	23.8730	1.69	40.2389	1.07	40.9950	1.80
3g	5.8859	6.83	22.3214	1.93	22.0205	3.36
3h	23.1370	1.74	29.9907	1.43	47.2510	1.57
Doramectin	39.6907	1.01	49.7736	0.86	48.6129	1.52
Avermectins	40.2389	1.00	42.9922	1.00	73.9508	1.00

Table 3 Glide docking score of **3g**, **5a**, **6a**, doramectin, and avermectins

Compound	Glide Docking Score (kcal mol^{-1})
Doramectin	-3.866
Avermectins	-3.841
3g	**-3.964**
5a	-2.467
6a	-2.791

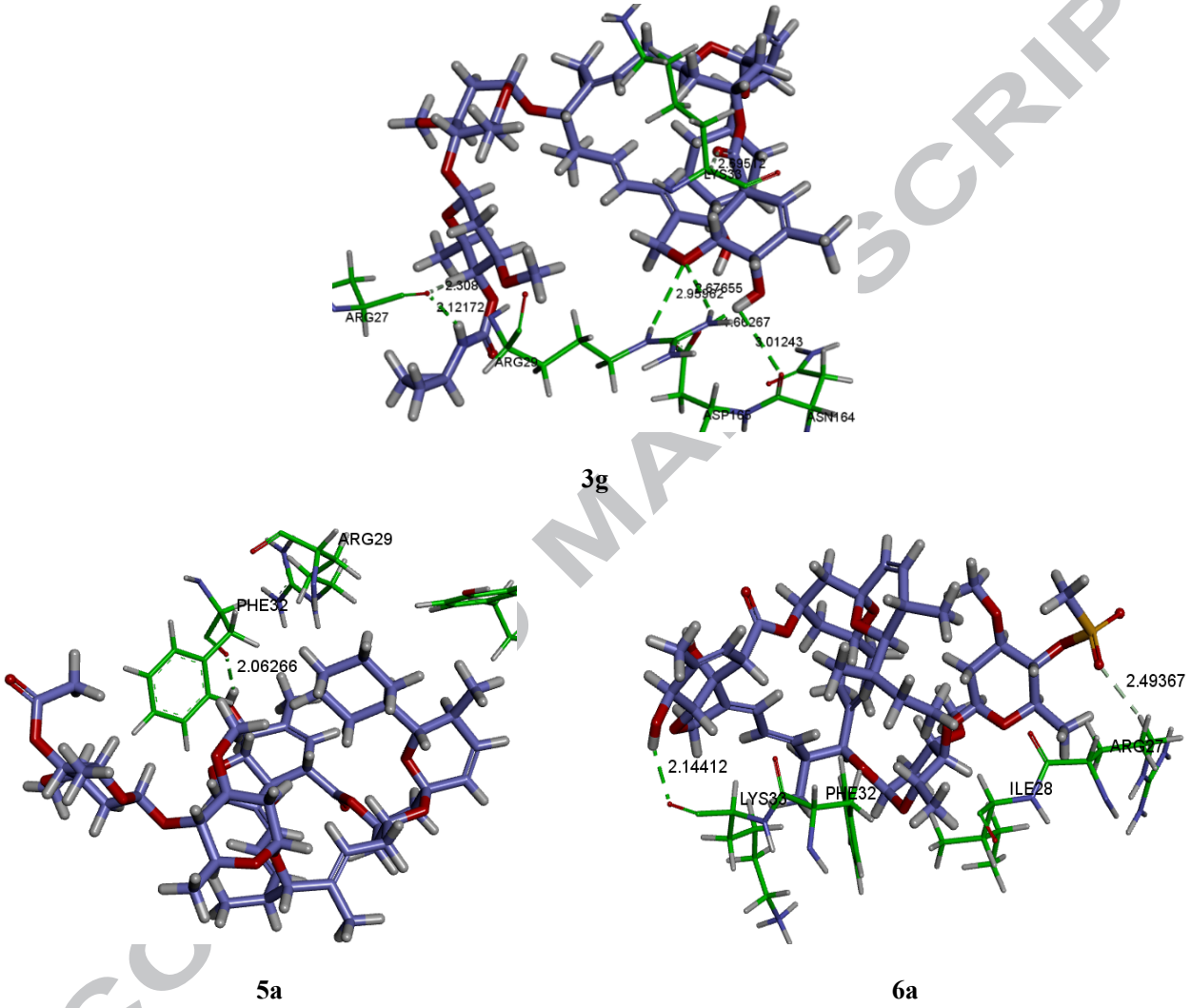


Figure 5 Molecular docking of compounds **3g**, **5a**, and **6a**. The H-bonding distances are shown as follows: **3g** (1.66 Å, 2.12 Å, 3.01 Å); **5a** (2.06 Å); **6a** (2.14 Å, 2.49 Å)

4.2. General synthesis.

The general synthetic methods for doramectin derivatives containing alkyl carbamate (**3a-3j**), phenyl carbamate (**4a-4k**), ester (**5a-5g**), and sulfonate (**6a-6d**) groups were shown in **Schemes 1**, **2**, and **3**, and their structures were listed in Supporting Information. The silica gel chromatography was performed with a column of 254 mm × 26 mm i.d. (Synthware glass Co. Ltd., Beijing, China) using 100−140 mesh silica gel (Sinopharm Chemical reagent Co.Ltd., Shanghai, China). Aromatic isocyanates were prepared according to the literature methods.[34]

4.2.1. General procedure for the synthesis of alkyl carbamate derivatives of doramectin (3a-3j) (Scheme 1).[35]

4.2.1.1. Synthesis of 2[5-*O*-(*tert*-butyldimethylsilyl)doramectin].

Imidazole (7.55 g, 111.00 mmol), *N, N*-dimethypyridin-4-amine (DMAP, 0.13 g, 1.11 mmol), and *tert*-butyldimethylsiyl chloride (TBDMS-Cl, 5.86 g, 38.85 mmol) were added to a solution of doramectin (10.00 g, 11.12 mmol) in 100 mL of dry dichloromethane. The mixture was stirred for 10 h at room temperature and then added water (100 mL) and dichloromethane (100 mL). The aqueous layer was extracted with dichloromethane (3 × 50 mL), the combined organic layers were washed with saturated sodium chloride solution (3 × 50 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo

to give a white solid. The crude product was purified by column chromatography on a silica gel using mixture of petroleum ether/ethyl acetate (2:1 by volume) as the eluent to afford 9.12 g (80.9%) of compound **2** as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87–5.80 (m, 1H, H9), 5.79–5.66 (m, 3H, H10, H11, H23), 5.53 (dd, *J* = 9.9, 2.6 Hz, 1H, H22), 5.41–5.31 (m, 3H, H3, H19, H1"), 5.04–4.97 (m, 1H, H15), 4.78 (dd, *J* = 4.0, 1.3 Hz, 1H, H1'), 4.68 (dd, J = 14.5, 2.4 Hz, 1H, H8a-a), 4.58 (dd, *J* = 14.5, 2.3 Hz, 1H, H8a-b), 4.46–4.39 (m, 1H, H4"), 4.12 (d, *J* = 13.1 Hz, 1H, H13), 3.93 (s, 1H, H7-OH), 3.90–3.72 (m, 4H, H17, H5', H5", H5), 3.61(ddd, *J* = 11.0, 8.4, 4.6 Hz, 1H, H3'), 3.51–3.44 (m, 1H, H3"), 3.41 (d, *J* = 2.9 Hz, 6H, H3'-OMe, H3"-OMe), 3.39 (d, *J* = 2.4 Hz, 1H, H6), 3.33–3.11 (m, 3H, H2, H25, H4'), 2,58 (s, 1H, H4"-OH), 2.55–2.47 (m, 1H, H12), 2.37–2.19 (m, 5H, H16, H18a, H2'a, H2"a), 2.04–1.96 (m, 1H, H20a), 1.83–1.75 (m, 6H, H4a-CH_3, H27a, H30a, H31a), 1.73–1.55 (m, 5H, H24, H28a, H26, H29), 1.52–1.44 (m, 4H, H14a-CH_3, H20b), 1.32–1.10 (m, 15H, H2"b, H27b, H28b, H30b, H31b, H2'b, H5'-Me, H5"-Me, H12a-CH_3), 0.98–0.79 (m, 13H, H24a-CH_3, H18b, H-C$(CH_3)_3$), 0.13 (s, 6H, H-Si$(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 140.1, 137.6, 137.5, 136.1, 135.1, 127.7, 124.7, 119.4, 118.2, 117.2, 98.4, 95.7, 94.8, 81.8, 80.4, 80.2, 80.1, 79.3, 78.2, 77.2, 76.1, 69.5, 68.3, 68.2, 68.1, 67.9, 67.2, 56.5, 56.4, 45.7, 40.3, 39.6, 38.7, 36.6, 34.6, 34.4, 34.1, 31.4, 30.0, 27.0, 26.9, 26.6, 26.5, 25.8(3-C), 25.5, 20.3, 20.0, 18.4, 17.6, 16.6, 15.2, -4.5, -4.8.

4.2.1.2. Synthesis of [4"-*O*-(4-nitrophenyl)carbonate-5-*O*-(tert-butyldimethylsilyl)doramectin].[36]

Bis(4-nitrophenyl) carbonate (NPC, 1.80 g, 5.91 mmol), DMAP (59.86 mg, 0.49 mmol) were added to a solution of compound **2** (5.00 g, 4.93 mmol) in 50 mL of dry dichloromethane. The mixture was stirred at room temperature until TLC indicated the reaction was completed. Water (50 mL) was added, the aqueous layer was extracted with dichloromethane (3 × 20 mL), the combined organic layers were washed with saturated sodium chloride solution (3 × 20 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a yellow solid (4.92 g, 84.7%), and was not purified for use in the next step.

4.2.1.3. Synthesis of (4"-*O*-methylcarbonate doramectin) (3a).[35, 37]

Methylamine (17.11 mg, 0.55 mmol) and 4"-*O*-(4-nitrophenyl) carbonate-5-*O*-(*tert*-butyldimethylsilyl) doramectin (500.00 mg, 0.42 mmol) were added in 30 mL of dry dichloromethane. The mixture was stirred 2 h at room temperature. Water (30 mL) was added, the aqueous layer was extracted with dichloromethane (3 × 10 mL), the combined organic layers were washed with saturated sodium chloride solution (3 × 10 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a white solid (310.00 mg, 68.3%). Then, a deprotection reagent solution of 10 mL of *p*-toluenesulfonic acid-methanol complex (0.02 g/mL) was added dropwise to a solution of white solid (310.00 mg) in methanol (10 mL). The mixture was stirred 1h at room temperature, until TLC indicated the reaction was completed. Saturated sodium bicarbonate (15 mL) and dichloromethane (15 mL) were added, the aqueous layer was extracted with dichloromethane (3 × 10 mL), the combined organic layers were washed with saturated sodium chloride solution (3 × 10 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a white solid. The crude product was purified by column chromatography on a silica gel using mixture of petroleum ether/ethyl acetate (2.5:1 by volume) as the eluent to afford 161.43 mg (58.3%) of compound **3a** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (d, *J* = 10.1 Hz, 1H, H9), 5.80–5.68 (m, 3H, H10, H11, H23), 5.53 (dd, *J* = 9.8, 2.5 Hz, 1H, H22), 5.47–5.32 (m, 3H, H3, H19, H1″), 5.04–4.96 (m, 1H, H15), 4.78 (d, *J* = 3.8 Hz, 1H, H1′), 4.68 (t, *J* = 3.3 Hz, 2H, H8a), 4.63 (s, 1H, NHCOO), 4.53 (t, *J* = 9.4 Hz, 1H, H4″), 4.29 (d, *J* = 6.2 Hz, 1H, H5), 4.06 (s, 1H, H7-OH), 3.97 (d, *J* = 6.2 Hz, 1H, H6), 3.93 (s, 1H, H13), 3.90–3.73 (m, 3H, H17, H5′, H5″), 3.60 (qd, *J* = 14.3, 12.0, 4.9 Hz, 2H, H3′, H3″), 3.42 (s, 3H, H3′-OMe), 3.37 (s, 3H, H3″-OMe), 3.33–3.19 (m, 3H, H2, H25, H4′), 2.82 (d, *J* = 4.7 Hz, 3H, $\underline{CH_3}$NH), 2.59–2.45 (m, 1H, H12), 2.27 (ddt, *J* = 23.7, 13.0, 5.2 Hz, 6H, H5-OH, H16, H24, H2′a, H2″a), 2.00 (dd, *J* = 12.2, 4.7 Hz, 1H, H20a), 1.87 (s, 3H, H4a-CH_3), 1.79 (d, *J* = 7.9 Hz, 3H, H27a, H30a, H31a), 1.73–1.59 (m, 5H, H18a, H28a, H26, H29), 1.48 (d, *J* = 6.2 Hz, 4H, H14a-CH_3, H20b), 1.38–1.09 (m, 15H, H2″b, H27b, H28b, H30b, H31b, H2′b, H5′-Me, H5″-Me, H12a-CH_3), 0.92 (d, *J* = 7.1 Hz, 3H, H24a-CH_3), 0.85 (d, *J* = 12.1 Hz, 1H, H18b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 156.5, 139.5, 138.1, 137.9, 136.2, 135.0, 127.7, 124.7, 120.4, 118.2, 118.0, 98.2, 95.7, 94.9, 81.8, 80.5, 80.4(2-C), 79.2, 79.1, 77.2, 75.7, 68.4, 68.3, 68.2, 67.7, 67.2, 66.8, 56.8, 56.5, 45.7, 40.3, 39.7, 38.7, 36.7, 35.0, 34.6, 34.3, 31.4, 30.0, 27.7, 26.9, 26.6, 26.5, 25.5, 20.2, 19.9, 18.3, 17.3, 16.6, 15.1. HRMS (ESI) m/z calcd. for $C_{52}H_{77}O_{15}NNa$: $(M+Na)^+$, 978.5185; found 978.5231.

The target compounds (**3b-3j**) were synthesized according to a procedure similar to that used for compound **3a**. Their HRMS data, ^{1}H NMR and ^{13}C NMR date are list in Supporting Information.

4.2.2. General procedure for the synthesis of phenyl carbamate derivatives of doramectin (4a-4k) (Scheme 1).[35]

4.2.2.1. Synthesis of 4-fluorophenyl isocyanate.[34]

A solution of triphosgene (980.00 mg, 3.30 mmol) in dried dichloromethane (10 mL) at 0 °C was added to a solution of *p*-fluoroaniline (1.11 g, 10.00 mmol), dichloromethane (75 mL), and saturated sodium bicarbonate (75 mL). The mixture was stirred at 0 °C for 4 h. The aqueous layer was extracted with dichloromethane (3 × 10 mL), dried over anhydrous magnesium sulfate, filtered, then add petroleum ether (10 mL), filtered, concentrated in vacuo to give a white liquid (970.03 mg, 70.7%), and was not purified for use in the next step.

4.2.2.2. Synthesis of (4"-*O*-*p*-fluorophenyl carbamate doramectin) (4a).[35]

P-fluorophenyl isocyanate (134.36 mg, 0.98mmol), compound **2** (500.00 mg, 0.49 mmol), *N*, *N*-dimethypyridin-4-amine (DMAP, 6.02 mg, 0.049 mmol) were added in dried dichloromethane (15 mL) at room temperature under N_2 atmosphere. The mixture was stirred for 6 h. Water (30 mL) was added, the aqueous layer was extracted with dichloromethane (3 × 10 mL), the combined organic layers were washed with saturated sodium chloride solution (3 × 10 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a white solid (410.40 mg, 72.8%). Then, a deprotection reagent solution of 15 mL of *p*-toluenesulfonic acid-methanol complex (0.02 g/mL) was added dropwise to a solution of white solid (410.40 mg) in methanol (10 mL). The mixture was stirred 1 h at room temperature, until TLC indicated the reaction was completed. Saturated sodium bicarbonate (15 mL) and dichloromethane (15 mL) were added, the aqueous layer was extracted with dichloromethane (3 × 10 mL), the combined organic layers were washed with saturated sodium chloride solution (3 × 10 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a white solid. The crude product was purified by column chromatography on a silica gel using mixture of petroleum ether/ethyl acetate (2:1 by

volume) as the eluent to afford 263.92 mg (71.4%) of compound **4a** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 8.8, 4.8 Hz, 2H, Ph), 7.00 (t, *J* = 8.6 Hz, 2H, Ph), 6.59 (s, 1H, NHCOO), 5.89 (d, *J* = 10.1 Hz, 1H, H9), 5.84–5.67 (m, 3H, H10,H11,H23), 5.54 (dd, *J* = 9.9, 2.5 Hz, 1H, H22), 5.48–5.30 (m, 3H, H3, H19, H1″), 5.01 (d, *J* = 10.8 Hz, 1H, H15), 4.82–4.77 (m, 1H, H1′), 4.69 (t, *J* = 3.4 Hz, 2H, H8a), 4.62 (t, *J* = 9.4 Hz, 1H, H4″), 4.30 (t, *J* = 7.2 Hz, 1H, H5), 4.07 (s, 1H, H7-OH), 3.98 (d, *J* = 6.3 Hz, 1H, H6), 3.95 (s, 1H, H13), 3.92–3.79 (m, 3H, H17, H5′, H5″), 3.64 (dt, *J* = 11.9, 9.2 Hz, 2H, H3′, H3″), 3.44 (s, 3H, H3′-OMe), 3.39 (s, 3H, H3″-OMe), 3.35–3.21 (m, 3H, H2, H25, H4′), 2.53 (t, *J* = 7.4 Hz, 1H, H12), 2.39–2.18 (m, 6H, H5-OH, H16, H24, H2′a, H2″a), 2.05–1.97 (m, 1H, H20a), 1.88 (s, 3H, H4a-CH_3), 1.80 (d, *J* = 9.2 Hz, 3H, H27a, H30a, H31a), 1.72–1.65 (m, 2H, H18a, H28a), 1.56 (d, *J* = 3.5 Hz, 3H, H26, H29), 1.49 (d, *J* = 6.3 Hz, 4H, H14a-CH_3, H20b), 1.38–1.12 (m, 15H, H2"b, H27b, H28b, H30b, H31b, H2′b, H5′-Me, H5″-Me, H12a-CH_3), 0.93 (d, *J* = 7.1 Hz, 3H, H24a-CH_3), 0.86 (d, *J* = 12.7 Hz, 1H, H18b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 157.6, 152.9, 139.6, 138.1, 137.9, 136.2, 135.0, 133.8, 127.7, 124.7, 120.4, 118.2, 118.0, 115.7(2-C_{Ar}), 115.5(2-C_{Ar}) , 98.2, 95.7, 94.9, 81.9, 80.5, 80.4(2-C), 79.2, 79.1, 77.2, 75.6, 68.4, 68.3, 68.2, 67.7, 67.1, 66.6, 56.7, 56.5, 45.7, 40.3, 39.7, 38.7, 36.7, 34.9, 34.6, 34.3, 31.4, 30.0, 27.0, 26.6, 26.5, 25.5, 20.2, 19.9, 18.4, 17.4, 16.6, 15.2. HRMS (ESI) m/z calcd. for $C_{57}H_{78}O_{15}NFNa$: $(M+Na)^+$, 1058.5248; found 1058.5294.

The target compounds (**4b-4k**) were prepared by following the same procedure as for **4a**. Their HRMS data, ^{1}H NMR and ^{13}C NMR data are list in Supporting Information.

4.2.3. General procedure for the synthesis of ester derivatives of doramectin (5a-5g) (Scheme 2).[35]

Synthesis of (4"-*O*-acetate doramectin) (5a). A solution of acetyl chloride (116.00 mg, 1.47 mmol) in dried dichloromethane (5 mL) at 0 °C was added to a solution of triethylamine (148.74 mg, 1.47 mmol), dichloromethane (15 mL), *N*, *N*-dimethypyridin-4-amine (DMAP, 6.02 mg, 0.049 mmol), and compound **2** (500.00 mg, 0.49 mmol). The mixture was stirred at 0 °C for 24 h. Water (30 mL) was added, the aqueous layer was extracted with dichloromethane (3 × 10 mL), the combined organic layers were washed with saturated sodium chloride solution (3 × 10 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a white solid (427.17 mg, 82.6%). Then, a deprotection reagent solution of 15 mL of *p*-toluenesulfonic acid-methanol complex (0.02 g/mL) was added dropwise to a solution of white solid (427.17 mg) in methanol (10 mL). The mixture was stirred 1.5 h at room temperature, until TLC indicated the reaction was completed. Saturated sodium bicarbonate (15 mL) and dichloromethane (15 mL) were added, the aqueous layer was extracted with dichloromethane (3 × 10 mL), the combined organic layers were washed with saturated sodium chloride solution (3 × 10 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a white solid. The crude product was purified by column chromatography on a silica gel using mixture of petroleum ether/ethyl acetate (3:1 by volume) as the eluent to afford 294.64 mg (77.3%) of compound **5a** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (d, *J* = 10.1 Hz, 1H, H9), 5.82–5.68 (m, 3H, H10, H11, H23), 5.54 (dd, *J* = 9.9, 2.5 Hz, 1H, H22), 5.48–5.33 (m, 3H, H3, H19, H1″), 5.01 (d, *J* = 10.7 Hz, 1H, H15), 4.79 (d, *J* = 3.8 Hz, 1H, H1′), 4.74–4.60 (m, 3H, H8a, H4″), 4.30 (t, *J* = 7.2 Hz, 1H, H5), 4.06 (s, 1H, H7-OH), 3.97 (d, *J* = 6.2 Hz, 1H, H6), 3.94 (s, 1H, H13), 3.85 (ddt, *J* = 9.6, 6.4, 3.3 Hz, 3H, H17, H5′, H5″), 3.61 (tt, *J* = 11.1, 5.3 Hz, 2H, H3′, H3″), 3.43 (s, 3H, H3′-OMe), 3.37 (s, 3H, H3″-OMe), 3.34–3.19 (m, 3H, H2, H25, H4′), 2.53 (t, *J* = 7.8 Hz, 1H, H12), 2.39–2.17 (m, 6H, H5-OH, H16, H18a, H2′a, H2″a), 2.10 (s, 3H, $\underline{CH_3}$CO), 2.00 (dd, *J* = 12.2, 4.6 Hz, 1H, H20a), 1.88 (s, 3H, H4a-CH_3), 1.80 (d, *J* = 8.2 Hz, 3H, H27a, H30a, H31a), 1.71–1.62 (m, 3H, H24, H28a, H26), 1.55 (d, *J* = 3.3 Hz, 3H, H29), 1.49 (d, *J* = 6.0 Hz, 4H, H14a-CH_3, H20b), 1.36–1.08 (m,15H, H2"b, H27b, H28b, H30b, H31b, H2′b, H5′-Me, H5″-Me, H12a-CH_3), 0.93 (d, *J* = 7.1 Hz, 3H, H24a-CH_3), 0.88–0.81 (m, 1H, H18b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 170.2, 139.5, 138.1, 137.9, 136.2, 135.0, 127.7, 124.7, 120.4, 118.2, 118.0, 98.3, 95.7, 94.8, 81.8, 80.6, 80.4, 79.2, 79.1, 77.2, 76.2, 75.6, 68.4, 68.3, 68.2, 67.7, 67.1, 66.4, 56.8, 56.5, 45.7, 40.3, 39.7, 38.7, 36.7, 35.0, 34.6, 34.3, 31.4, 30.0, 27.0, 26.6, 26.5, 25.5, 21.1, 20.2, 19.9, 18.4, 17.4, 16.6, 15.1. HRMS (ESI) m/z calcd. for $C_{58}H_{81}O_{15}NNa$: $(M+Na)^+$, 963.5076; found 963.5115.

The target compounds (**5b-5g**, **6a-6d**) were prepared by following the same procedure as for **5a**. Their HRMS data, ^{1}H NMR and ^{13}C NMR data are list in Supporting Information.

5. Biological assay

All bioassays were performed on representative test organisms reared in the laboratory. The bioassays were repeated in triplicate at 25 ± 1 °C. The error of the experiments was 5%. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott′s formula.[38] Evaluations were based on a percentage scale of 0-100, where 0 is no activity, 100 is total kill.

5.1. Insecticidal activity against oriental armyworm (*Mythimna sepatara*). The insecticidal activities of targets compounds **3a-3j**, **4a-4j**, **5a-5g**, **6a-6d** against oriental armyworm were evaluated by foliar application using the reported procedure.[39,40] Individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed dry. The dishes were infested with 10 third-instar oriental armyworm larvae. Percentage mortalities were evaluated 2 days after treatment. Each treatment was performed 3 times. For comparative purposes, doramectin, commercial avermectins, fenpropathrin and metolcarb were tested under the same condition.

5.2. Insecticidal activity against diamondback moth (*Plutella xylostella*). The insecticidal activities of targets compounds **3a-3j**, **4a-4k**, **5a-5g**, **6a-6d** against diamondback moth were evaluated using the reported procedure.[40] Targets compounds were prepared in acetone at a concentration of 1 mg/mL and added distilled water containing TW-80 to dilute the different concentrations. Leaf disks (3 × 3 cm) were cut from fresh cabbage leaves and then were dipped into the test solution for 10 s. After air drying, the treated leaf disks were placed in a Petri dish lined with a filter paper, and then, 10 third-instar diamondback moth larvae were transferred to the Petri dish. Percentage mortalities were evaluated 2 days after treatment. Each treatment was performed 3 times. For comparative purposes, doramectin commercial avermectins, fenpropathrin, and metolcarb were tested under the same condition.

5.3. Insecticidal activity against corn borer (*Ostrinia nubilalis*). The insecticidal activities of targets compounds **3a**, **3g**, **3h** against corn borer were evaluated by the leaf-dip method using the reported procedure.[41] Leaf disk (4 × 4 cm) were cut from fresh corn leaves and dipped into the test solution for 10 s. After air-drying, the treated leaf disks were placed in a Petri dish, and then, 10 third-instar corn borers were transferred to the Petri dish. Percentage mortalities were evaluated 2 days after treatment. Each treatment was performed 3 times. For comparative purposes, doramectin, commercial avermectins, fenpropathrin and metolcarb were tested under the same condition.

6. Homology modeling and molecular docking

The target sequences of *Plutella xylostella* Rdl-1(NCBI ID 105389786) subunits was retrieved from the NCBI database(**https://www.ncbi.nlm.nih.gov/gene/105389786**). The sequences were subjected to template search using the BLAST program of the NCBI (**https://www.ncbi.nlm.nih.gov/**). Finally, the crystal structure of Human Glycine Receptor alpha-3 (PDB ID 5TIN) was chosen as the template to build the 3D structure of *Plutella xylostella* GABA receptor. We selected the sequence of *Plutella xylostella* Rdl-1 for homology modeling to investigate the binding mode between compounds and target protein using Schrodinger-Glide. The crystal structure of Human Glycine Receptor alpha-3 (PDB ID 5TIN) was derived from the RCSB Protein Data Bank. The 3D structures of compounds were drawn by Chem Bio Draw Ultra 12.0 and ChemBio3D Ultra 12.0 software packages (Cambridge Soft, Cambridge, MA, USA). For Glide docking, the default parameters were used if it was not mentioned. The best-scoring pose judged by the Glide docking score was chosen and analyzed using Schrodinger software.

Acknowledgements

This work was partly supported by Technology Service Network Initiative of Chinese Academy of Sciences (No. KFJ-SW-STS-143-1), Key Laboratory of Tropical Medicinal Plant Chemistry of Ministry of Education Hainan Normal University, and National Science Foundation of China (No. 21272229).

Supporting Information

Supplementary data associated with this article can be found in Supporting Information. ^{1}H NMR and ^{13}C NMR data and spectrums of compounds **3a-3j**, **4a-4j**, **5a-5g**, **6a-6d** were available free of charge via the Supporting Information.

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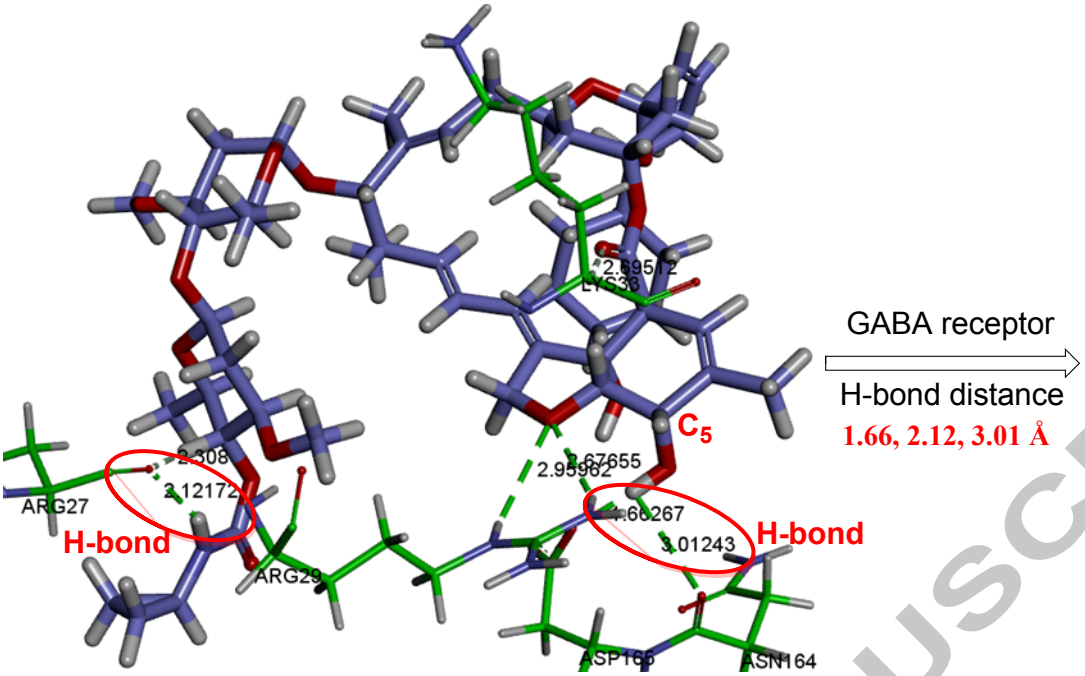

42.

Highlights

1. 32 doramectin derivatives were synthesized and characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.
2. The insecticidal activities, structure-activity relationship and molecular docking analysis were discussed.
3. Compound **3g** exhibited the most promising insecticidal activity.
4. Compound **3g** has stronger hydrogen-bonding action and lower binding free energy.

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