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Research paper

Synthesis, biological activities and structure–activity relationships for new avermectin analogues

Jian Zhang [a, 1], Xiang Nan [a, 1], Hai-Tao Yu [c], Pi-Le Cheng [a], Yan Zhang [a], Ying-Qian Liu [a, *], Shao-Yong Zhang [b], Guan-Fang Hu [c], Huanxiang Liu [a, **], An-Liang Chen [b]

[a] School of Pharmacy, Lanzhou University, Lanzhou, 730000, China
[b] Provincial Engineering Laboratory of Biopesticide Preparation, Zhejiang A&F University, Lin'an, 311300, Zhejiang Province, China
[c] Institute of Plant Protection, Gansu Academy of Agricultural Sciences, Lanzhou, 730070, China

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ABSTRACT

In an effort to discover new molecules with good insecticidal activities, more than 40 new avermectin derivatives were synthesized and evaluated for their biological activities against three species of arachnids, insects and nematodes, namely, *Tetranychus Cinnabarinus*, *Aphis craccivora* and *Bursaphelenchus xylophilus*. All the tested compounds showed potent inhibitory activities against three insect species. Notably, the majority of compounds exhibited high selectivity against *T. cinnabarinus*, some of which were much better in comparison with avermectin. Especially compounds **9j** (LC_{50}: 0.005 μM) and **16d** (LC_{50}: 0.002 μM) were 2.5- and 4.7-fold more active than avermectin (LC_{50}: 0.013 μM), respectively, against *T. cinnabarinus*. Moreover, compounds **9b**, **9d–f**, **9h**, **9j**, **9l**, **9n**, **9p**, **9r**, **9v** and **17d** showed superior activities with LC_{50} values of 2.959–5.013 μM compared to that of **1** (LC_{50}: 6.746 μM) against *B. xylophilus*. Meanwhile, the insecticidal activities of compounds **9f, 9g, 9h,** and **9m** against *A. craccivora* were 7–8 times better than that of avermectin, with LC_{50} values of 7.744, 5.634, 6.809, 7.939 and 52.234 μM, respectively. Furthermore, QSAR analysis showed that the molecular shape, size, connectivity degree and electronic distribution of avermectin analogues had substantial effects on insecticidal potency. These preliminary results provided useful insight in guiding further modifications of avermectin in the development of potential new insecticides.

1. Introduction

Avermectins are a family of 16-membered ring macrocyclic lactones isolated from the fermentation broth of *Streptomyces avermitilis*, which are known to possess exceptionally potent anthelmintic, acaricidal, and insecticidal activities [1,2]. A major fermentation product, avermectin B1a (**1**, Fig. 1), is the most effective avermectin against insects and mites, and has widely been commercialized for agricultural use in China now [3]. Its semi-synthetic derivative with the generic name ivermectin, the 22,23-dihydroavermectin B1a (**2**), has been introduced as a broad spectrum antiparasitic agent for veterinary uses [4,5]. These compounds selectively act on the γ-aminobutyric acid (GABA)-related chloride ion channels unique to nematodes, insects, ticks, and arachnids, with relatively low or no mammalian toxicity [6–8]. Their remarkable biological activities and intriguing mechanism of action have stimulated considerable interest in the scientific community. In this vein, a number of publications and patents in an attempt to obtain compounds with higher potency and broader spectra of activities have appeared describing intensive modification of avermectin at different positions [9–22].

Among the many reports on SAR investigation, the compounds which were modified at the 4″-position appeared to be the most efficient approach to increase the insecticidal potency, as a result of which most structural modifications of avermectins have focused on position 4″. In particular, various substituents, such as alkylamino, oxyiminoalkyl, alkylsilyl, and alkylthio, *etc* were introduced at the 4″-position of **1** to afford highly potent analogs [23–32]. Following these efforts, some 4″-substituted analogs, particularly 4″-*N*-linked congeners were found to exhibit improved activities and pharmacokinetic profiles compared to **1** [33–37]. Among them,

* Corresponding author.
** Corresponding author.
E-mail address: yqliu@lzu.edu.cn (Y.-Q. Liu).
[1] These authors contributed equally to this work.

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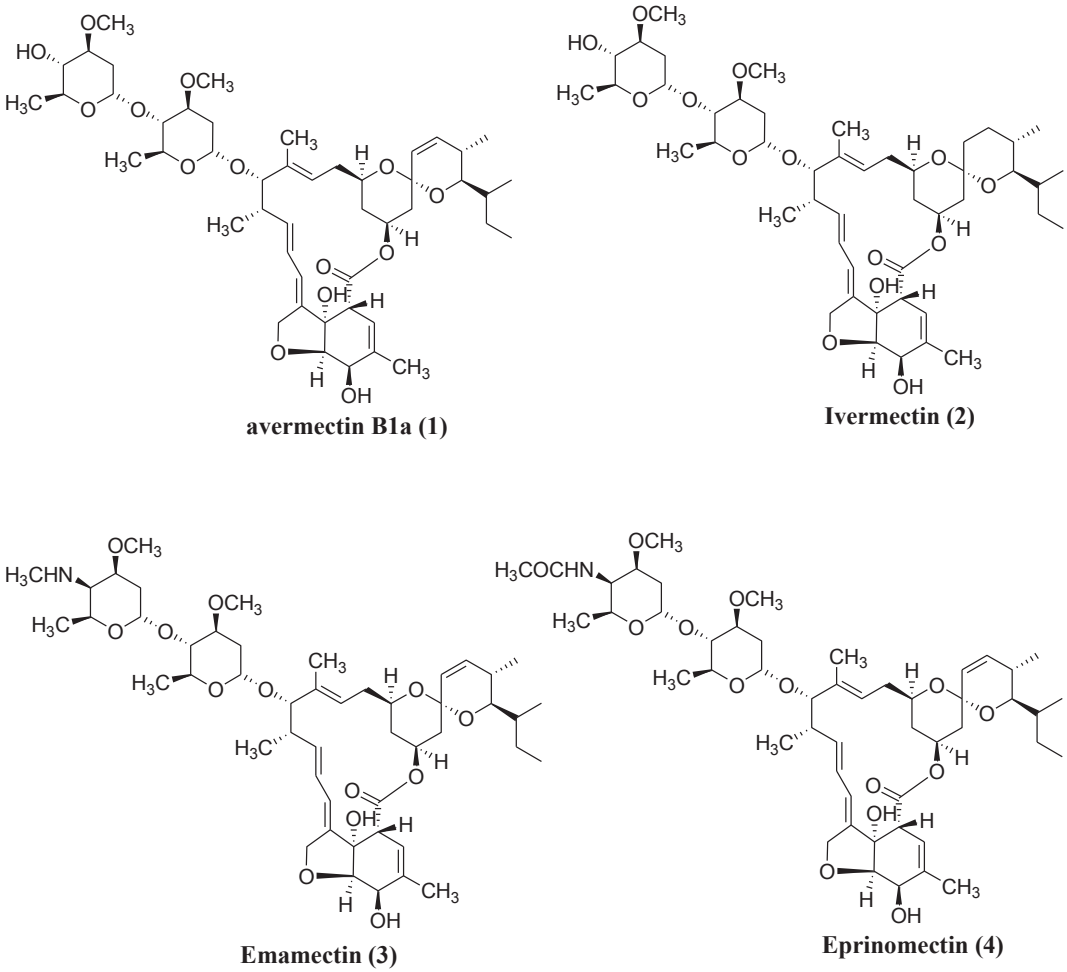

Fig. 1. Chemical structures of avermectin B1a (**1**), ivermectin (**2**), emamectin (**3**) and eprinomectin (**4**).

a major breakthrough came from the discovery of 4″-amino-avermectins. For instance, emamectin (**3**) having a methylamino group in epi-orientation at the 4″-position was one of the most effective compounds reported, with a 1500-fold increase in potency vs avermectin B1 in insecticidal activity, which has achieved commercial success. Eprinomectin (**4**) in which the 4″-hydroxyl group was replaced by an *epi* acetylamino group exhibited potent endectocidal activity with minimal residues in milk, and is used for treatment of lactating dairy cattle against parasites. Overall, these variants displayed preferable characteristics in their solubility, distribution, chemical stability as well as activity spectra, suggesting the possibility of further optimizing avermectins through rational C-4″ modifications.

Based on these critical clues, in continuation of our program aimed at the discovery and development of natural-product-based pesticidal agents, more than 40 new avermectin derivatives were synthesized. Three types of sulfonyl groups (i.e. sulfonylamidine, sulfonylurea and sulfonylamine) were chosen based on the facts that these groups are commonly found in various drugs and introduction of a sulfonyl group could usually potentiate the biochemical or pharmacological properties of the original molecule [38,39]. In addition, to the best of our knowledge, there is no report on the synthesis of avermectin analogs with *N*-sulfonylamidino group at the C-4″ position of **1** using the copper-catalyzed three-component coupling reaction as the key reaction. For further insight into SAR investigation, the synthesis of the *N*-sulfonylamidino derivatives of avermectin monosaccharide and avermectin aglycone was described, respectively. The activities of all target compounds against *Tetranychus cinnabarinus*, *Aphis craccivora* and *Bursaphelenchus xylophilus* were evaluated accordingly. Furthermore, the structure-activity relationship (SAR) of these analogs is also discussed. Quantitative structure-activity relationships (QSARs) models were built to understand the relationship between the biological activity and molecular structure of avermectin analogues.

2. Chemistry

The synthesis of intermediate and target compounds were performed as illustrated in Schemes1–3. Initially, the 5-hydroxyl group of avermectin B1 (**1**) was selectively protected with *tert*-butyldimethylsilyl chloride (TBDMSCl) in acetonitrile to give 5-*O*-*tert*-butyldimethylsilylavermectin B1 (**5**) in 82% yield. Subsequent oxidation of **5** using $PhOPOCl_2/Et_3N$ reagent system in dried DMSO afforded 4″-oxo-5-*O*-*tert*-butyl dimethysilyl avermectin B1 (**6**) in 60% yield. Reductive amination of **6** using ammonium acetate/$NaBH_3CN$ to give 4″-*epi*-NH_2-5-O-TBDMS-4″-deoxyavermectin B1 (**7**) in 40% yield. Subsequent removal of the *t*-butyldimethylsilyl protecting group of **7** with *p*-toluenesulfonic acid in methanol (1:1) formed the key intermediate 4″-*epi*-Amino-4″-deoxyavermectinB1 (**8**) [33,36], which was successfully employed as an efficient reacting partner in the Cu-catalyzed three-component reaction