Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 21 (2010) 1391–1394
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Synthesis analogues of milbemycin and their bioactivity evaluation

Jin Hao Zhao [a], Ming Hua Ji [a,b], Xu Hui Xu [a], Jing Li Cheng [a], Guo Nian Zhu [a,*]

[a] *College of Agriculture and Biotechnology, Zhejiang University, Hangzhou 310029, China*
[b] *Zhejiang NHU Ltd., Shaoxing 312500, China*

Received 12 April 2010

Abstract

Eight new 13-*O*-aminocarbonylivermectin aglycones and 4′-*O*-aminocarbonylivermectin monosaccharide were synthesized from ivermectin aglycone and ivermectin monosaccharide by the selective protection of C_5-OH group. Their bioactivities were evaluated against spider mites (*Tetranychus cinnabarinus*), aphid (*Aphis fabae*) and orlental armyworm (*Mythimma sepatara*). Their structures were confirmed by ^{1}H NMR, MS.

Keywords: 13-*O*-Aminocarbonylivermectin aglycone; 4′-*O*-Aminocarbonylivermectin monosaccharide; Synthesis; Insecticidal and acaricidal activities

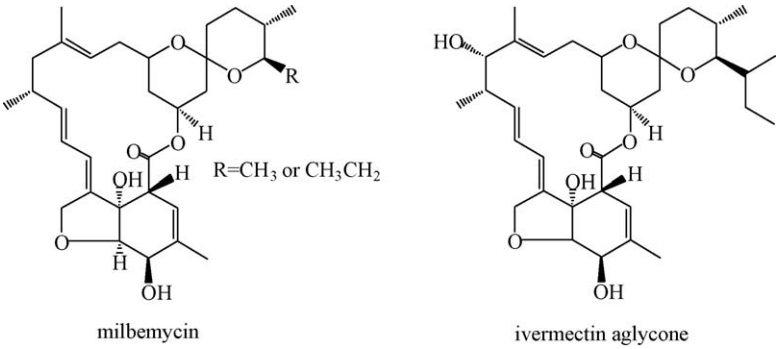
Recently, macrocyclic lactones play a great role in the pharmaceutical and pesticides [1,2]. Milbemycin, a 16-membered macrocyclic lactone produced by *Streptomyces hygroscopius*, are potent miticidal, insecticidal and anthelmintic compounds [3]. Milbemycin were both environmentally friendly and having efficient and wide biological activity features. The high intrinsic potency, remarkable biological activity and unique molecular architecture have attracted the attention of research groups concerning with chemical modification. Generally modification of milbemycin C_{13}-position group includes: alkylation, acylation, amination and sulfonylation, etc. [4–8]. However, there have been no reports on *N*-substituted-13-*O*-aminocarbonylmilbemycin. Worth noting that, milbemycin and acylivermectin aglycone have similar structure (Scheme 1). In order to explore this void field, eight novel analogues of milbemycin have been synthesized (Scheme 2) from 5-*O*-TBDMS-ivermectin aglycone and 5-*O*-TBDMS-ivermectin monosaccharide. Their bioactivity data against spider mites (*Tetranychus cinnabarinus*), aphid (*Aphis fabae*) and orlental armyworm (*Mythimma sepatara*) were obtained herein for the first time.

As shown in Scheme 2, the key intermediates **2** and **2′** were formed by selective protective reaction of C_5-OH group with *tert*-butyl dimethyl chlorosilane in 82.3% and 83.6% yields, respectively [9,10]. Compounds **1** and **1′** were obtained in the literature method [11,12].

The typical process of synthesis of novel analogues of milbemycin **4a**–**4d′** was shown as following: the key intermediate (**2**, 0.351 g, 0.5 mmol) and triethylamine (0.051 g, 0.5 mmol) were dissolved in dry dichloromethane (20 mL). And substituted isocyanate (R-NCO) (0.8 mmol) was added dropwise to the mixture at 0–5 °C. The mixture was stirred at 20–25 °C for 8 h, and quenched with 1% aqueous HCl. The organic layer was washed to neutral with

* Corresponding author.
E-mail address: zhugn@zju.edu.cn (G.N. Zhu).

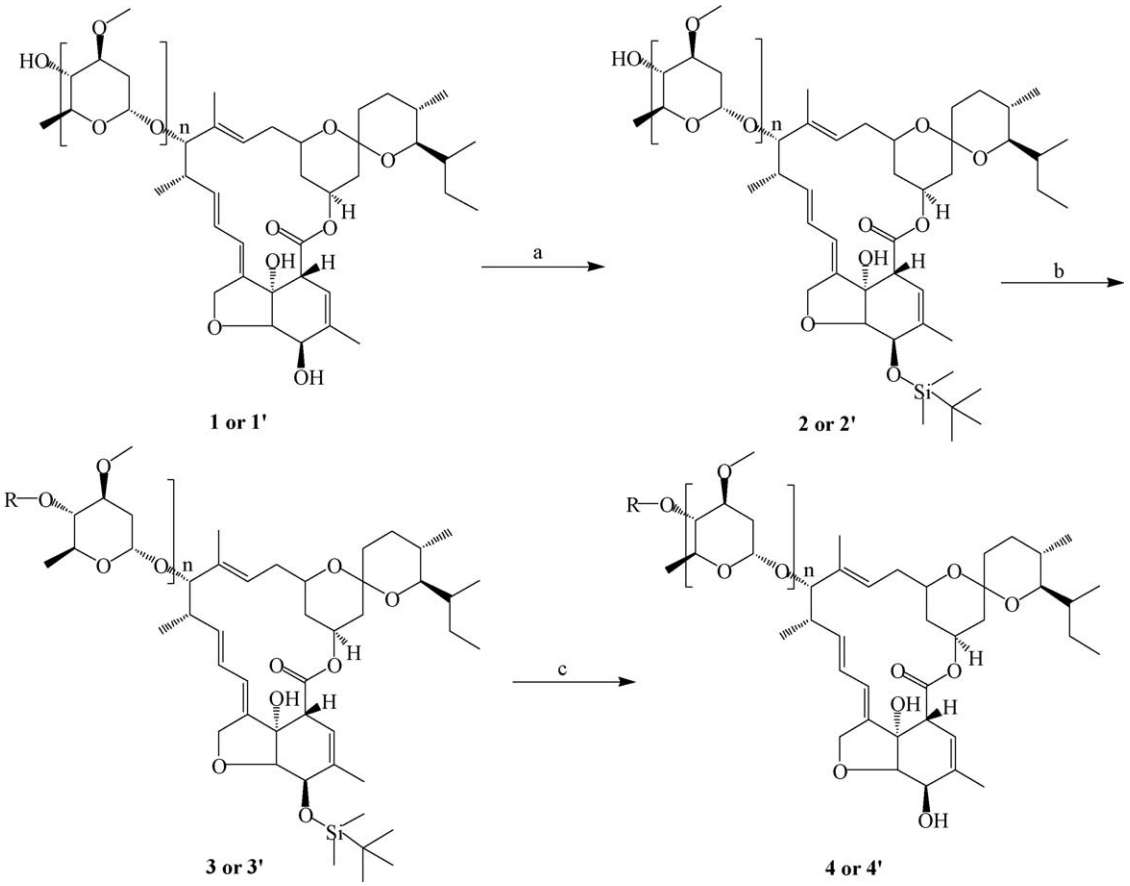
1001-8417/$ – see front matter
doi:10.1016/j.cclet.2010.06.035



Scheme 1. Structures of milbemycin and ivermectin aglycone.

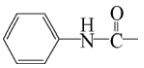
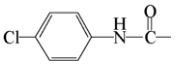
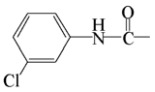
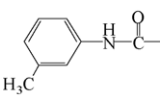
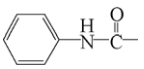
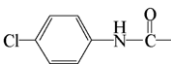
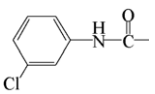
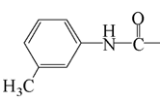
water and dried over Na_2SO_4. After filtration and concentration, the organic residue was purified by silica gel column-chromatography (ethyl acetate/petroleum ether, 1:2.5, v/v) to give gum (in 70–80% yield). Their structures were shown in Table 1 ($n = 0$, compounds: **4a**, **4b**, **4c**, **4d**; $n = 1$, compounds: **4′a**, **4′b**, **4′c**, **4′d**).

The bioactivity of novel compounds against spider mites (*T. cinnabarinus*), aphid (*A. fabae*) and orlental armyworm (*M. sepatara*) were evaluated according to the standard method (dipping method in insecticide general screen) [13]. The biological data were listed in Table 1. As shown in Table 1, the compounds **4′a–4′d** show better bioactivity than **4a–4d** against spider mites (*T. cinnabarinus*). Interestingly, the compounds **4a–4d** show better bioactivity than **4′a–4′d** against aphid (*A. fabae*) and orlental armyworm (*M. sepatara*). Exhilaratingly, the preliminary



Scheme 2. (a) TBDMS-Cl, imidazole, CH_2Cl_2/RT; (b) R–N═C═O, DMAP, CH_2Cl_2/RT; (c) PTSA, CH_3OH (2%)/RT.

Table 1
The structures and biological data of new compounds.

Compd.	*n*	R	Inhibitory rate (0.006 mg/L)	Inhibitory rate (200 mg/L)	
			Tetranychus cinnabarinus	*Aphis fabae*	*Mythimma sepatara*
Ivermectin	–	–	57.9	100	100
4a	0		45.2	97.6	100
4b	0		29.8	77.9	90.3
4c	0		30.6	79.1	100
4d	0		49.2	100	100
4′a	1		55.2	89.2	97.1
4′b	1		30.8	67.8	88.5
4′c	1		31.5	65.4	91.2
4′d	1		56.6	100	100
Spiromesifen	–	–	41.0	98.6	96.5
Pymetrozine	–	–	23.0	85.0	88.0

bioassay indicated that the compounds **4d** and **4′d** given an inhibition rate up to 100% against aphid (*A. fabae*) and orlental armyworm (*M. sepatara*) as same as ivermectin. Although the biological activities of these compounds are near or the same as lead compound, they are higher than pymetrozine and spiromesifen [14], which were the commercial varieties. Further toxicity evaluation of **4d**, **4′a**, **4′d**, structural optimization and insecticidal activity about all of these compounds are well under way.

Acknowledgments

This work is financially supported by National Natural Science Foundation of China (No. 30700532) and the Science and Technology Project of Zhejiang province (No. 2008C02007-3).

References

[1] P. Sarasola, D.A. Jernigan, D.K. Walker, J. Vet. Pharmacol. Therap. 25 (2002) 265.
[2] E. Rodrigue, S. Peiru, J.R. Carney, Microbiology 152 (2006) 667.
[3] G.H. Baker, S.E. Blanchflower, J.J. Roderich, J. Antibiot. 49 (1996) 272.

[4] S. Naito, T. Nanba, Y. Owatari, J. Antibiot. 47 (1994) 233.
[5] P. Ina, S. Anderew, J. Roderick, Tetrahedron Lett. 37 (1996) 4811.
[6] G.H. Baker, J.J. Roderich, N. Hussian, Tetrahedron Lett. 35 (1994) 2381.
[7] K. Sato, T. Tsukiyama, M. Suzuki, WO 9961447 1999-12-2.
[8] N.V. Derek, WO 9522552 1995-8-24.
[9] H. Mrozik, P. Eskola, M.H. Fisher, J. Med. Chem. 25 (1982) 658.
[10] T.A. Blizzard, G.M. Margiatto, H. Mrozik, J. Med. Chem. 35 (1992) 3873.
[11] J.C. Chabala, H. Mrozik, R.L. Tolman, J. Med. Chem. 23 (1980) 1134.
[12] H. Mrozik, P. Eskola, B.H. Arison, J. Org. Chem. 47 (1982) 489.
[13] J.L. Cheng, F.L. Wei, L. Zhu, Chin. J. Org. Chem. 28 (2008) 622.
[14] J.H. Zhao, M.H. Ji, X.X. Hui, et al. Chin. Chem. Lett. 20 (2009) 1307.