Discovery of novel avermectins with unprecedented insecticidal activity

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Summary. A new class of insecticidal and antiparasitic agents, 4″-amino-4″-deoxy avermectins, has been developed by chemical modification of avermectin B_1. The most effective of these compounds are 1500-fold more potent than avermectin B_1 (abamectin) against the beet armyworm *Spodoptera exigua* and show similar potency against other lepidopteran larvae.
Key words. 4″-Amino-4″-deoxyavermectins; avermectin; insecticide; Lepidoptera.

The avermectins are a group of closely related macrocyclic lactones with exceedingly high activity against helminths and arthropods [1].

Ivermectin (**1**), the 22,23-dihydro derivative of avermectin B_1 (**2**), is widely used as a systemic antiparasitic agent against endo and ectoparasites of animals [2]. It has also recently been found effective for the prevention of 'river blindness' in man caused by infection with the filarial worm *Onchocerca volvulus* [3].

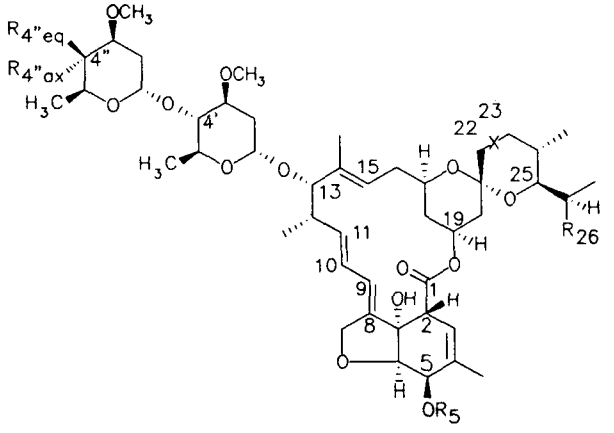
Avermectin B_1 (abamectin, **2**) is broadly effective against most important agricultural pests with LC_{90}s in the range of 0.02 ppm for mites. However, it is much less toxic to insects, especially lepidopteran larvae, where for example, a concentration of 6 ppm is required for LC_{90} level control of the southern armyworm *Spodoptera eridania* [4].

An extensive program of chemical modification has been carried out in these laboratories to discover new avermectin derivatives with increased potency and spectrum of activity against armyworm species and other commercially important lepidopteran larvae.

As part of this program a series of 4″-amino avermectins was obtained by oxidation of the 4″-hydroxy group with the Swern reagent (oxalyl chloride, DMSO, NEt_3), after protection of other reactive hydroxy groups as O-*t*-butyldimethylsilyl ethers [5].

Reductive amination of the thus obtained 5-O-*t*-butyldimethylsilyl-4″-oxoavermectin B_1 (**3**) with NH_4OAc and $NaCNBH_3$ gave a mixture which was separated by preparative silicagel chromatography into the axial (epi)-amino derivative (**4**) as the major product, the equatorial amino derivative (**5**) and a small amount of 4″-epiavermectin B_1 (**6**). Deprotection gave the desired 4″-epiamino-4″-deoxyavermectin (**7**) [6]. N-alkylated derivatives were synthesized either by reductive amination using an alkylamine or by alkylation of 4″-amino-4″-deoxyavermectins.

The two epimeric 4″-amino-4″-deoxyavermectin B_1 derivatives had similar biological properties with the 4″-epiamino compound (**7**) being a somewhat more potent insecticide. Since the 4″-epiamino derivatives were also the major products of reductive amination they were selected for further



Compound	$R_{4''eq}$	$R_{4''ax}$	R_5	R_{26}	$C_{22}-X-C_{23}$
1	HO	H	H	>80% C_2H_5 <20% CH_3	$-CH_2-CH_2-$
2	HO	H	H	>80% C_2H_5 <20% CH_3	$-CH=CH-$
3	O		$Si(CH_3)_2C(CH_3)_3$	>80% C_2H_5 <20% CH_3	$-CH=CH-$
4	H	H_2N	$Si(CH_3)_2C(CH_3)_3$	>80% C_2H_5 <20% CH_3	$-CH=CH-$
5	H_2N	H	$Si(CH_3)_2C(CH_3)_3$	>80% C_2H_5 <20% CH_3	$-CH=CH-$
6	H	HO	$Si(CH_3)_2C(CH_3)_3$	>80% C_2H_5 <20% CH_3	$-CH=CH-$
7	H	H_2N	H	>80% C_2H_5 <20% CH_3	$-CH=CH-$
8	H	H_3CHN	H	>80% C_2H_5 <20% CH_3	$-CH=CH-$

Table 1. The biological activity of 4″-amino avermectin B_1 derivatives against neonate *Spodoptera eridania* larvae on sieva beans in a foliage spray bioassay. % Mortality after 96 hours

Compound	0.1 ppm	0.02 ppm	0.004 ppm
Avermectin B_1 (abamectin) (**2**)	5	5	—
4″-epiamino (**7**)	100	100	53
4″-epimethylamino (**8**)	100	100	51

Table 2. Activity after topical application to neonate larvae of *S. eridania*

Compound 0.1 μg/g	% Mortality
4″-epiamino (**7**)	55
4″-epimethylamino (**8**)	100

study, details of which will be reported elsewhere. This report describes studies on the two most active members of the series shown in the figure.

Since the LC_{90} for avermectin B_1 is 6 ppm, this represents a 300–400-fold improvement in insecticidal activity in this assay with the 4″-amino derivatives.

The activities of these two compounds, 4″-epiamino-4″-deoxyavermectin B_1 (**7**) and 4″-epimethylamino-4″-deoxyavermectin B_1 (**8**) were then compared by topical application with observation of mortality after 72 h. As can be seen in table 2 the 4″-epimethylamino compound (**8**) was considerably more active when applied topically.

Since contact activity can be an important attribute for an insecticide, the 4″-epimethylamino analog was selected for more detailed study.

In a diet incorporation assay 4″-epimethylamino-4″-deoxyavermectin B_1 (**8**) was approximately 1500-fold more toxic to *Spodoptera exigua* larvae than avermectin B_1. The dose necessary to cause 90% mortality was 1972 ng/ml of diet for avermectin B_1 (**2**) compared to 1.067 ng/ml diet for 4″-epimethylamino-4″-deoxyavermectin B_1 (**8**)[7]. In a contact plus residue test comparing 4″-epimethylamino-4″-deoxyavermectin B_1 applied at a rate of 0.012 kg/ha with methomyl at 1.008 kg/ha against *S. exigua* larvae, the acute toxicity of both treatments was similar but only 4″-epimethylamino-4″-deoxyavermectin B_1 treatment showed significantly less leaf consumption 14 days after application[7]. These data indicate that 4″-epimethylamino-4″-deoxyavermectin B_1 is one of the most potent insecticides yet discovered particularly for those lepidopteran larvae which are primarily foliage feeders. It is presently being studied against insects of several orders[8,9].

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