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Avermectins and Flea Control: Structure–Activity Relationships and the Selection of Selamectin for Development as an Endectocide for Companion Animals

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Abstract—Evaluation of a wide range of avermectin derivatives for flea activity in an in vitro feeding screen using the cat flea, *Ctenocephalides felis,* revealed a narrow structure–activity relationship (SAR) with activity surprisingly associated with monosaccharides and especially their C-5-oximes. We discovered commercially exploitable flea activity in a single compound, selamectin **33**, which also possessed the necessary antiparasitic spectrum and margin of safety for development as a broad-spectrum companion animal endectocide.

Introduction

Commercial products containing avermectins (e.g. Dectomax® and Ivomec®) or milbemycins (e.g. Cydectin®) are well established for the treatment of a wide range of both *endo*- and ecto-parasite infections of livestock and hence are referred to as endectocides. Although safe for use as an endectocide in livestock, ivermectin **2** produces idiosyncratic toxicity in collie dogs and crossbred collies at doses required to give effective control of gastrointestinal nematodes. Its use in dogs (as Heartgard™), at the very low dose required for safety in all dog breeds, provides only prophylactic control of heartworm. Milbemycin oxime **20** has also been commercialised (as Interceptor®). The compound's greater safety permits doses that provide additional control of gastrointestinal nematodes but it is ineffective against fleas, the major ectoparasite of commercial importance of cats and dogs. We set ourselves the objective of finding a safe, broad-spectrum endectocide for companion animals from this class of macrolides. Most importantly we wished to identify a compound which had systemic in vivo activity against fleas. Prior to the inception of our work, significant flea activity was not associated with the structural class.

Avermectins and milbemycins have been the subjects of extensive research and are known to bind to chloride channels in a wide range of invertebrates and vertebrates.[1] However, their antiparasitic potencies are also known to be dramatically altered by (sometimes minor) structural modification.[2] We therefore screened a wide range of compounds in an in vitro feeding screen using the cat flea, *Ctenocephalides felis*. Close analogues of the flea active structures discovered were then prepared and the optimum compound, selamectin **33**, was identified. Extensive evaluation demonstrated that the compound satisfied all our antiparasitic spectrum and safety criteria (including safety in collies) and it was developed as a safe, broad-spectrum endectocide for cats and dogs.[3]

Results

The majority of the compounds evaluated have been previously reported and are referenced in the Tables. Syntheses of novel avermectin derivatives, which generally follow reported strategies,[4] are shown in Schemes 1 and 2. C-5-oximes and related compounds were obtained by selective oxidation employing manganese dioxide followed by treatment of the crude ketone so obtained with the appropriate nitrogen nucleophile (Scheme 1).

C-4′-deoxygenation of the sugar was achieved via selective protection of the C-5-alcohol as its *tert*-butyldimethylsilyl ether and thiocarbonylation of the C-4′-

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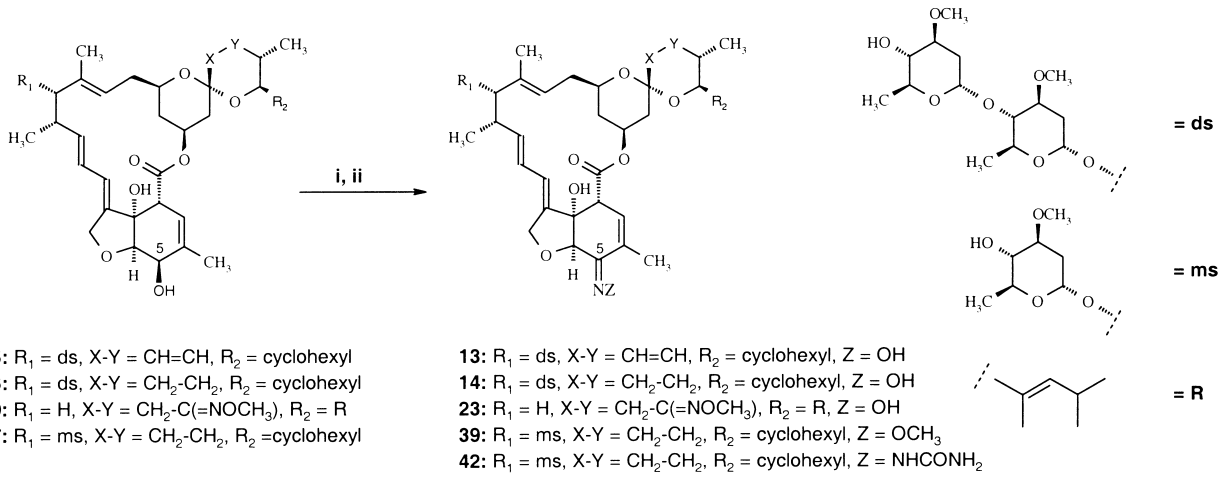
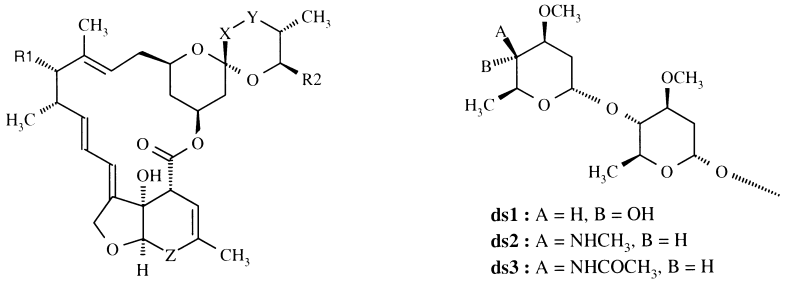


Scheme 1. Synthesis of oximes **13**, **14**, **23** and **39** and semicarbazone **42**. Reagents and conditions: i. manganese dioxide, diethyl ether, 25 °C, 3–20 h; ii. 12.2–27.6 equiv of hydroxylamine hydrochloride, 30 equiv of methoxylamine hydrochloride or 5.43 equiv of semicarbazide hydrochloride, methanol, dioxan, water, 25–50 °C, 2–48 h, 9–66% for two steps.

Table 1. Avermectins, milbemycins and C-5-oxime derivatives



Compound number	R_1	R_2	X–Y	Z
1,[5,a]	ds1	*sec*-Butyl	CH = CH	CH(◄OH)
2,[6,b]	ds1	*sec*-Butyl	CH_2-CH_2	CH(◄OH)
3,[7,c]	ds2	*sec*-Butyl	CH = CH	CH(◄OH)
4,[7,d]	ds3	*sec*-Butyl	CH = CH	CH(◄OH)
5[8,e]	ds1	Cyclohexyl	CH = CH	CH(◄OH)
6[9]	ds1	Cyclohexyl	CH_2-CH_2	CH(◄OH)
7[8]	ds1	Cyclohexyl	$CH_2CH($⋯OH)	CH(◄OH)
8[10]	ds1	Cyclohexyl	$CH_2CH($⋯OCH_3)	CH(◄OH)
9[8]	ds1	Cyclohexyl	CH = CH	CH(◄OCH_3)
10[8]	ds1	Cyclohexyl	$CH_2CH($⋯OH)	CH(◄OCH_3)
11[11]	ds1	*sec*-Butyl	CH = CH	C = NOH
12[12]	ds1	*sec*-Butyl	CH_2-CH_2	C = NOH
13	ds1	Cyclohexyl	CH = CH	C = NOH
14	ds1	Cyclohexyl	CH_2-CH_2	C = NOH
15[11]	ds1	Cyclohexyl	$CH_2CH($⋯OH)	C = NOH
16[10]	ds1	Cyclohexyl	$CH_2CH($⋯OCH_3)	C = NOH
17[13]	H	Isopropyl	CH_2-CH_2	CH(◄OH)
18[14]	H		$CH_2CH($⋯OH)	CH(◄OH)
19[15,f]	H		$CH_2C(=NOCH_3)$	CH(◄OH)
20[16,g]	H	Methyl/ethyl	CH_2-CH_2	C = NOH
21[16]	H	Isopropyl	CH_2-CH_2	C = NOH
22[17]	H		$CH_2CH($⋯OH)	C = NOH
23	H		$CH_2C(=NOCH_3)$	C = NOH

[a]Abamectin.
[b]Ivermectin.
[c]Emamectin.
[d]Eprinomectin.
[e]Doramectin.
[f]Moxidectin.
[g]Milbemycin oxime.