The potency of cyclopropane pyrethroid ethers against susceptible and resistant strains of the house fly *Musca domestica*[1]

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Summary. A new class of pyrethroids (cyclopropane ethers) is highly effective against susceptible house flies. Its activity is comparable to that of commercial pyrethroids like fenvalerate. On a fly strain with high multi-resistance to organophosphorus and pyrethroid insecticides, and on a *super-kdr* strain, these pyrethroids are not very effective; therefore they are unable to break metabolic or target site resistance against ester pyrethroids and DDT.
Key words. Flies; pyrethroids; ethers; resistance; kdr.

A large number of natural pyrethrins and synthetic pyrethroids have proved to be highly toxic to house flies and other insects[2-4]. A handful of these compounds have been developed into commercial insecticides which are currently used against important pests all over the world; this has made the pyrethroids a major class of insecticides[5].

All the commercially-used, and virtually all of the originally-synthesized active pyrethroids are characterized by being esters[2,3]. However, molecules possessing an oxime ether linkage instead of an ester function are also known to be active insecticides[6,7]. Recently the important discovery was made that structures with an ether linkage instead of the traditional ester bond form a series of very active pyrethroid molecules[8,9]. The compound MTI-500 (**XIII**) from this series is currently being commercially developed under the trade name 'Trebon'. This new type of pyrethroid has been further improved by the introduction of a cyclopropane ring in the molecule to give several highly active insecticides[10-14].

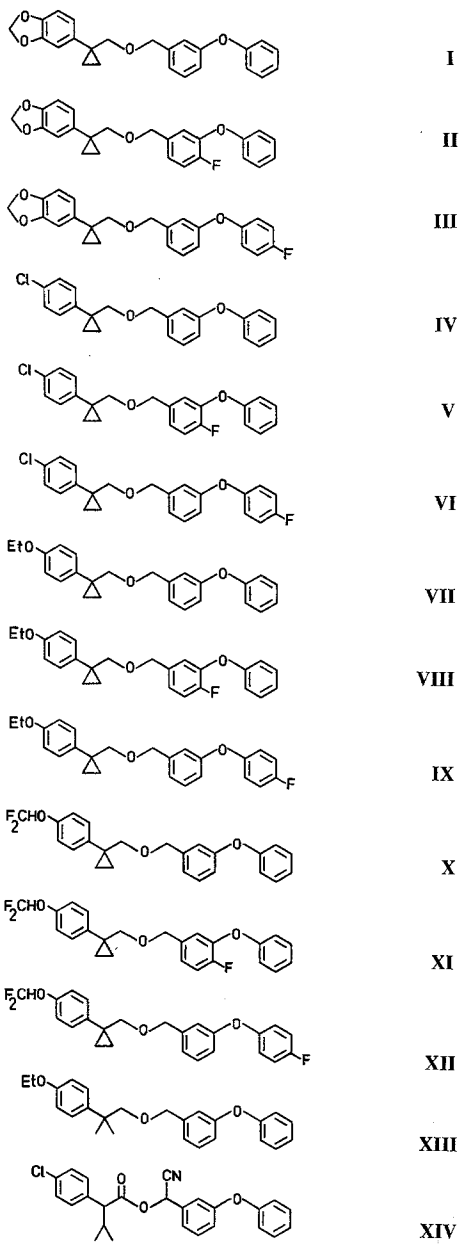
It has been shown recently that an exchange of the ether oxygen with a carbonyl group in some of the ether pyrethroids leads to molecules that are only slightly less active than MTI-500[15], and a substitution of the ether oxygen by an alkylene bond gives extremely promising insecticidal structures[9]. The structural diversity amongst the pyrethroids has increased significantly with these discoveries, which means that the scope for developing new insecticides of pyrethroid nature has been widened considerably. The classical pyrethroids are performing excellently, but owing to previous insecticide exposure, and pyrethroid selection pressure, resistance has developed in several field populations of insect pests[16,17]. The number of pyrethroid-resistant insect species in 1980 was 22, and this figure seems to be growing[18]. In house flies one of the resistance-factors common to DDT and pyrethroids is the *kdr* (knock-down resistance) or *super-kdr* which renders the insect nervous system insensitive to DDT or pyrethroid regardless of which of the two types has been used for selection[19,20]. Cross-resistance is also found between the different pyrethroids so that resistance caused by selection with one pyrethroid will also render other pyrethroids less effective[21]. Because of the growing resistance and cross-resistance problems, it is very important to develop new compounds with high toxicity against the insensitive strains of pest.

The experiments reported here were carried out on house flies because this pest is commonly used for testing pyrethroids; insecticide resistance has been studied extensively in this species,

Results from tests on three strains of *Musca domestica*

Compound No.	Susceptible Cheminova strain	*Super-kdr*-resistant A_2b, Oppenoorth		Multiresistant 381 zb, Keiding	
	LD_{50}	LD_{50}	R/S	LD_{50}	R/S
I	0.041 ± 0.008	1.3 ± 0.1	32	8.4 ± 0.9	205
II	0.024 ± 0.006	1.7 ± 0.5	71	3.2 ± 0.2	133
III	0.16 ± 0.03	0.97 ± 0.23	6	5.4 ± 1.3	34
IV	0.049 ± 0.007	36.0 ± 7.2	735	> 50	> 1020
V	0.030 ± 0.007	7.2 ± 2.5	240	8.9 ± 2.2	297
VI	0.16 ± 0.05	7.4 ± 2.1	46	41.0 ± 7.5	256
VII	0.044 ± 0.009	19.7 ± 5.1	448	~ 50.0	1136
VIII	0.012 ± 0.003	3.2 ± 0.6	267	14.0 ± 2.8	1167
IX	0.057 ± 0.011	9.7 ± 1.9	170	> 50	> 877
X	0.033 ± 0.007	23.0 ± 5.6	697	23.0 ± 6.1	697
XI	0.035 ± 0.005	12.7 ± 3.7	363	15.5 ± 2.6	443
XII	0.10 ± 0.03	9.0 ± 2.1	90	35.0 ± 7.0	350
XIII	0.023 ± 0.011	17.7 ± 4.3	770	13.0 ± 2.4	556
XIV	0.014 ± 0.003	5.0 ± 1.3	357	4.2 ± 1.2	300

The LD_{50} values are expressed in µg/fly ± 95% confidence limit. R/S is the resistance ratio, i.e. the ratio between the LD_{50} of the resistant strain and the LD_{50} of the susceptible strain.



and several strains with an isolated and well described type of resistance are obtainable[2,21,22,24]. The present communication describes the potency of a series of cyclopropane pyrethroid ethers against two resistant and one susceptible strain of *Musca domestica*. The results are discussed in relation to the ester compound fenvalerate (**XIV**) and the ether compound MTI-500 (**XIII**).

Materials and methods. The insecticide application (topical, acetone solution) was carried out as previously described[24]. The house flies used were 1) the standard Cheminova susceptible strain, 2) the *super-kdr* strain, A_2b, originating from Dr Oppenoorth, Holland. This strain contains the *super-kdr* gene on chromosome 3 from strain 381z but has other chromosomes from a susceptible strain[25]. And 3) the multiresistant strain 381 zb originating from flies collected on a Danish farm in 1978. This strain is resistant to pyrethroids and organophosphorus compounds.

Pupae of the two resistant strains were supplied by the Danish Pest Infestation Laboratory, where they are kept in continuous culture[23]. The resistance of strain 381 zb is maintained by selecting it with permethrin and dimethoate a few times a year.

The pyrethroids were synthesized according to methods described in the literature[10-14].

Results and discussion. The results from tests with the three strains of *Musca domestica* appear in the table, which also includes the results obtained with MTI-500 (**XIII**) and fenvalerate (**XIV**).

Generally, the cyclopropane ether pyrethroids are highly active against the susceptible flies, and it appears that compound **VIII** is the most toxic of the series; it shows an activity comparable to that of fenvalerate and better than that of MTI-500. All the fluorinated compounds **II**, **V**, **VIII**, and **XI** are very active regardless of the substitution pattern in the monoaromatic part of the molecule. This is an accordance with the finding that this F-substitution also improves the activity of conventional ester pyrethroids[26].

Another general observation is that none of the compounds **I–XIV** are highly effective against either of the resistant house fly strains as evidenced bvy the high R/S factors presented in the table.

The R/S is relatively low for the analogues **III**, **VI**, and **XII**, which show a weak activity against susceptible flies.

Most of the cyclopropane ether pyrethroids show an R/S ratio on the *super-kdr*-strain that is less than that of the reference compounds, especially MTI-500. This means that these new compounds, to some extent, can overcome the *kdr*-resistance. The absolute toxicity against *super-kdr*-flies is however not impressive.

On the multi-resistant strain it is observed that the R/S ratio for compound **I–III**, **V–VI**, is less than that of the reference compounds. The multifactorial resistance of this strain is thus relatively better bypassed by these compounds than by the reference pyrethroids. None of the compounds **I–XII** has a higher toxicity against this strain against the *super-kdr*-strain.

The difference in toxicity found when most of the cyclopropane ethers were applied to the resistant strains is clearly greater than that obtained for the two reference compounds. This may mean that MTI-500 and fenvalerate either penetrate better or are less subject to metabolic degradation than the cyclopropane ethers. Compounds **V**, **X** and **XI** resemble the reference compounds closely in this respect.

The synergist-like property (the methylene dioxo substituent) of compounds **I–III** only has a weak effect, as evidenced by the relatively low activity of these compounds on the multiresistant strain.

In conclusion it appears that although some interesting differences are observed when testing the two resistant strains, the overall evidence is that none of the compounds, including the reference pyrethroids, are able to overcome the types of resistance present in these experiments.

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