PYRETHROID INSECTICIDES[1]

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Introduction

Pyrethroid insecticides are synthetic analogues of the naturally occurring insecticidal pyrethrins (Figure 1) found in the pyrethrum daisy, *Tanacetum cinerariaefolium* (Asteraceae). The insecticidal activity of these plant compounds has been known for centuries but their use in the field is limited by rapid breakdown in sunlight. Investigation of the active ingredients and ways to improve photostability date back to the early part of the 1900s. Breakthroughs in the 1970s eventually led to the commercialisation of photostable synthetic pyrethroids for use in the field. Most agrochemical companies ceased research and development (R&D) activity in the late 1980s, but some have continued development, particularly of products enriched in active isomers.

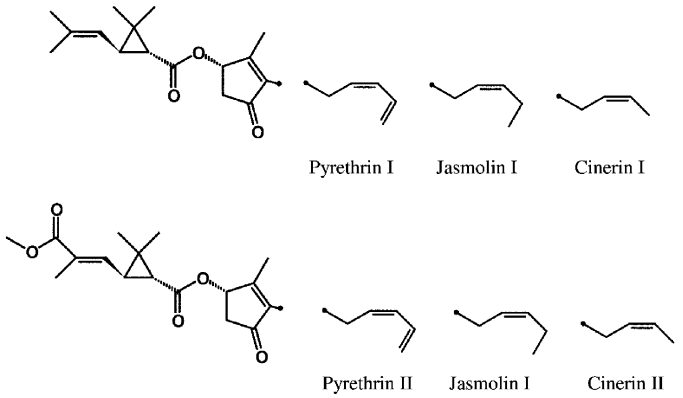


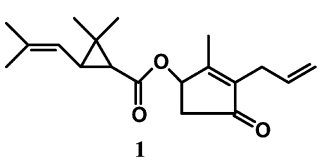
Figure 1

Currently pyrethroids account for about a fifth of the total insecticide market; their major use is in the control of lepidopterous pests of cotton, but are also used in a wide variety of applications including other field crops (*e.g.* maize), horticulture and animal health. The main challenges to the continued use of pyrethroids, especially in cotton, have arisen from the development of resistance and the introduction of plants genetically modified to express the toxin from *Bacillus thuringiensis*. This trend has, to a limited extent, been compensated by newly emerging niche markets including control of headlice, sealice and mosquitoes (using impregnated bednets). However the outstanding properties of pyrethroids, including the occurrence of negative cross-resistance between them and certain other classes of insecticides, indicate potential for their continued exploitation.

Discovery of synthetic pyrethroids

Several comprehensive and authoritative publications (Leahey, 1985; Naumann, 1990; Briggs, 1994; Henrick, 1995; Elliott, 1996; Matsuo and Miyamoto, 1997; Chamberlain *et al*., 1998; Katsuda, 1999) are available that provide a comprehensive review of the discovery and development of pyrethroids. The present survey will emphasise the importance of systematic investigations, foresight, persistence and serendipity in this discovery process

In my view, the first significant study was that reported by Staudinger and Ruzicka in the 1920s. They elucidated the structure of the acid and alcohol (in part) moieties of the pyrethrins and esterified each component to produce 82 esters from the acid and 32 from the alcohol. These were tested by dusting cockroaches caught in the laboratory (perhaps the world's first R&D laboratory for pesticide discovery) with the compounds impregnated onto flour. However all the compounds tested were significantly less active than the natural products with the only exception (later to be exploited by Elliott) that the simple benzylic esters of the component acids exhibited some activity. The next major investigation was by Schechter in 1949. He synthesised allethrin (**1**), the first non-natural pyrethroid to be commercialised. This compound was structurally simpler than pyrethrin I (Figure 1) but was more effective against houseflies than the pyrethrins. In 1953, Schechter also demonstrated the importance of the (1*R*)-*trans* stereochemistry in the acid moiety that led to the synthesis of *S*-bioallethrin, the (1*R*)-*trans*, α*S* isomer of allethrin. Although allethrin was commercialised (1954) by Sumitomo fairly soon after its discovery, production of the single isomer, *S*-bioallethrin took over a decade to develop.



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Key breakthroughs in the development of synthetic pyrethroids were made primarily by Elliott's team at Rothamsted and later by researchers at Sumitomo in Japan. Elliott started work on pyrethroids at Rothamsted in 1948. In 1962, he reconstituted pyrethrin I, the major component in pyrethrum extract, showed it to be the most insecticidal, and upon which he based his structure-activity studies. He also showed that the second most abundant component in the natural extract, pyrethrin II (Figure 1), had superior knockdown activity to pyrethrin I.

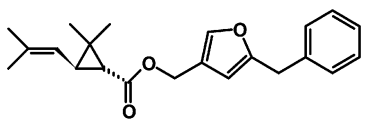
Using specifically designed bioassays, especially against houseflies (*Musca domestica*) and mustard beetles (*Phaedon cochleariae*), he embarked on a detailed and systematic investigation of structure-activity relationships. Very early on he showed that allethrin was superior to pyrethrin I only against houseflies. Against a range of other insects, pyrethrin I was superior. This led him to consider the use of a phenyl group as a more suitable replacement for the diene side-chain. Combining this with a 3,5-disubstituted furan ring (replacement for the cyclopentenone moiety) led to the discovery in 1967 of resmethrin and its 1*R* isomer, bioresmethrin (**2**). This compound was over 50-fold more effective then pyrethrin I against houseflies and a range of other species. However it too lacked sufficient photostability for use in agriculture. Rapid progress was then made when a combination of several ideas, i.e. a benzyl group (as noted by Staudinger) to replace the cyclopentenone, oxygen as a bridging group instead of CH_2 and dichlorovinyl to replace dimethylvinyl in the acid moiety, led to improved stability (both to metabolism and photodegradation) for compounds such as permethrin (**3**). Interestingly the alcohol moiety (3-phenoxybenzyl) was independently discovered by researchers at Sumitomo. The circumstances surrounding the subsequent discovery of cypermethrin (**4**) and deltamethrin (**5**) by Elliott were a result of diligence in monitoring developments in pyrethroid chemistry combined with serendipity.

Table 1. Relative toxicity of synthetic pyrethroids to insects and mammals

Compounds	Activity relative to pyrethrin I	
	Houseflies	Mammals
Bioresmethrin (**2**)	× 50	× 0.0024
Permethrin (**3**)	× 35	× 0.015
Cypermethrin (**4**)	× 130	× 0.017
Deltamethrin (**5**)	× 1400	< × 0.013

Elliott saw the patent application by Sumitomo for fenvalerate (**6**) during his regular visits to the patent office in London in 1976 just before announcing the discovery of permethrin (and related analogues). This patent highlighted the enhancement of insecticidal activity by the introduction of an α-cyano group in the 3-phenoxybenzyl moiety. Elliott was thus able to realise the optimum combination of this alcohol with the dihaloacids leading to the discovery of deltamethrin and cypermethrin analogues that were not only more active than the natural pyrethrins but had lower mammalian toxicity (Table 1). Interestingly the introduction of an α-cyano group does not enhance activity for the 5-benzyl-3-furyl moiety (as in bioresmethrin) or chrysanthemic acid analogues. These discoveries prompted much R and D activity in agrochemical companies and led to the discovery of many pyrethroids with an extended range of properties.

Other examples of commercially successful pyrethroids with variations in the acid moiety include tralomethrin (**7**), a proinsecticide derived from deltamethrin by the addition of bromine. Flumethrin (**8**), incorporating a phenyl group in the acid moiety, is a particularly effective tickicide. Kadethrin (**9**), with a thiolactone group, exhibits high knockdown activity against flying insects. Acrinathrin (**10**),



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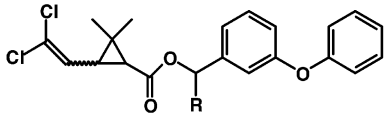

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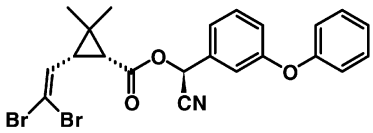
4 R = CN



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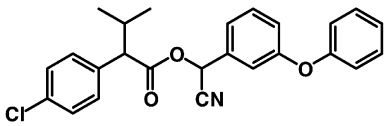

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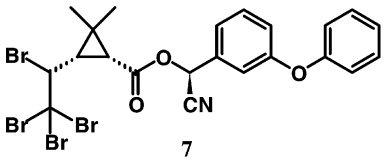

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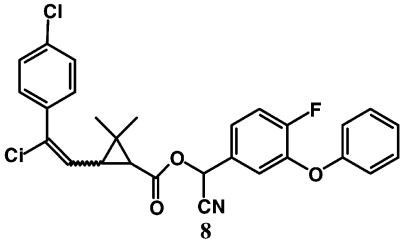

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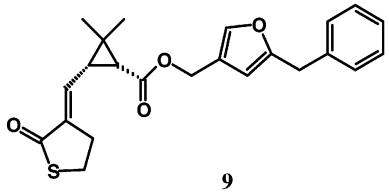

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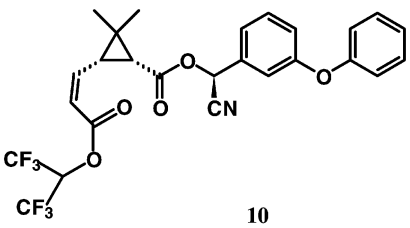

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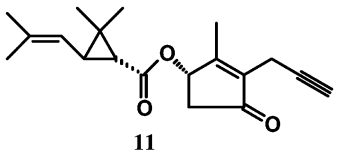
based on pyrethric acid, is a powerful acaricide. An even larger number of variations have been identified in the alcohol moiety. Prallethrin (**11**) is a simple variation of allethrin. Bifenthrin (**12**) incorporating a biphenyl moiety has a broad spectrum of activity including some acrine species. Introduction of a fluorine atom at the 4 position, as in cyfluthrin (**13**), generally leads to increased activity against some pests. Increased volatility in pyrethroids to control flying insects has been achieved either by using low molecular weight (*e.g.* empenthrin (**14**)) or polyfluorinated alcohol groups (*e.g.* transfluthrin (**15**)). High volatility also confers activity in soil for which tefluthrin (**16**) is the only pyrethroid commercialised so far.

Another breakthrough came in the 1980s. The discovery of pyrethroids lacking the ester group (the absence of which should lead to enhanced metabolic stability) had been a major objective for many researchers. Replacement with isosteric groups had always led to a substantial loss of activity, until the announcement of etofenprox (**17**) in 1981 by Mitsui Toatsu prompted a major resurgence of interest in this area. It became clear that activity in non-ester pyrethroids was largely dependent on the spatial positioning of the gem-dimethyl group. Although some useful compounds have been discovered (*e.g.* NRDC 199 (**18**), NRDC 207 (**19**), silafluofen (**20**) and ZX8901 (**21**), on the whole success has been limited as judged by the number of compounds commercialised. Despite this, some companies have retained an interest as illustrated by the announcement of novel non-ester pyrethroids *e.g.* protriefenbute (**22**) in 1994 by FMC. These highly lipophilic compounds are mainly used in the control of rice pests, because, in contrast to the ester pyrethroids, they exhibit remarkably low levels of fish toxicity.

NRDC 207 (**19**), also discovered at Rothamsted, provides an illustration of the significance of physical properties on the application/bioactivity of pyrethroids. It is a simple mono-fluorinated analogue of NRDC 199 (**18**). In contrast to NRDC 199, it exhibited significant activity against the cotton rootworm, *Diabrotica balteata*, in our soil assays. However, it soon became apparent that the level of soil activity varied appreciably with conditions in the soil (*e.g.* organic matter and water content) used in the bioassay. The dominating factor for soil activity is vapour pressure (target range 1–100 mPa). For tefluthrin, it is 8 mPa. However for NRDC 207 the calculated value is approximately 0.6–1.0 mPa. This is considered to be borderline for soil activity and thus its performance is influenced by the bioassay conditions; for example increasing organic content of the soil leads to decreased activity due to increased sorption.

The structure-activity relationships in pyrethroids are clearly complex and at times difficult to resolve. For example, the stereochemistries at position 1 in the acid moiety in flufenprox (**23**) and the α position in empenthrin (**14**) are opposite to the corresponding positions in *S*-fenvalerate yet correct stereochemistry at these positions is considered to be critical for activity in pyrethroids. Compound (**24**) (Bushell and Salmon, 1994) is an example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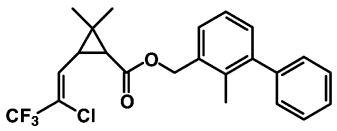
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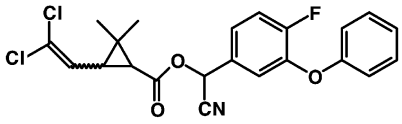
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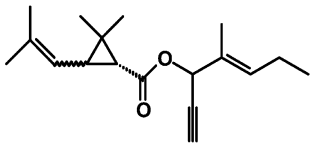
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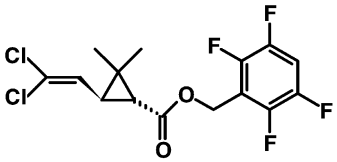
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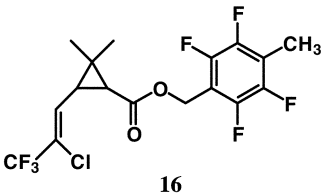
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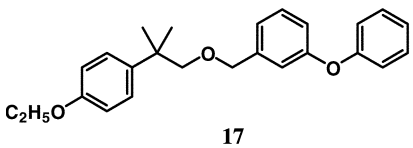
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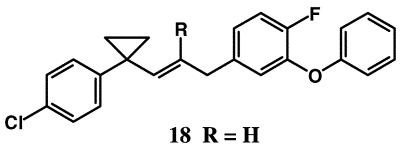
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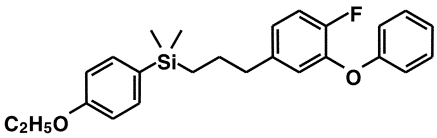
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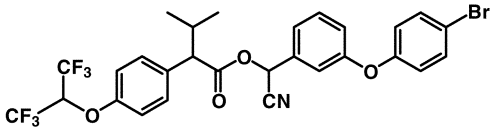
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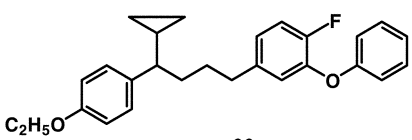
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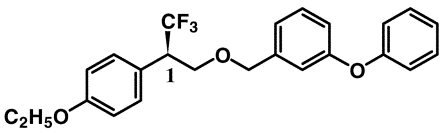
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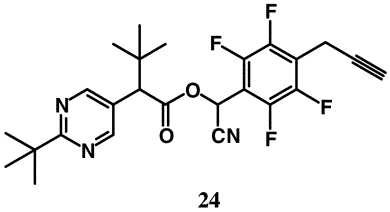
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Factors which influence the effectiveness of pyrethroids, and selectivity between insect species

- Overall shape.
- Key structural features (e.g. ester or non-ester, specific chirality and *cis* or *trans* stereochemistry across the cyclpropane ring)
- Physical properties (e.g. volatile compounds good against flying insects)
- Chemical properties (e.g. polar compound better for knockdown, high lipophilicity results in decreased fish toxicity and fluorinated compounds often have high miticidal activity).

of how extremes in the spectrum of activity can be achieved; it exhibits high miticidal activity but very poor insecticidal activity.

The ester pyrethroids typically have three chiral centres and thus a possibility of eight isomers of which only two (1*R* cis and trans, with α*S* configuration) are active. Thus commercial processes aimed at producing single or enriched isomers have been sought ever since the commercialisation of synthetic pyrethroids. The commercial process for the production of deltamethrin, one of eight possible isomers, announced by Roussel Uclaf in 1984 is a tribute to their process chemists. Thereafter, developments in this regard have appeared regularly (Table 2), the most recent being "super cyhalothrin" (a collaborative commercial venture between Cheminova and Dow in 2001).

Resistance to pyrethroids

This was observed in the field soon after widespread use of the photostable synthetic pyrethroids. A major contributory factor is that pyrethroids exhibit cross-resistance to DDT, which is thought to act at the same binding site on the voltage-gated sodium channel. However despite a large number of reports on the occurrence of resistance to pyrethroids, not all have resulted in complete control failure in the field. The two main resistance mechanisms observed in the field are increased detoxification and target-site insensivity. These mechanisms can occur singly or together. For example, target-site insensitivity was thought to be the main resistance mechanism when resistance to pyrethroids was first reported in Australian *Helicoverpa armigera*, but metabolic resistance is now implicated as the major mechanism. In Indian *H. armigera*, site-insensitivity is considered to be an additional mechanism (Kranthi *et al.*, 2001)

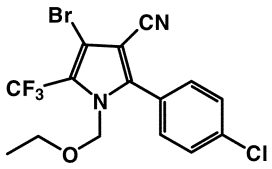
Increased metabolism

This is manifested in two main forms: overproduction of esterases (that can sequester and/or hydrolyse pyrethroids) and increased mixed-function oxidase activity. Since these are general mechanisms, it not surprising that cross-resistance to other classes (*e.g.* organophosphates and carbamates) has been observed in the field. However, metabolic degradation can be minimised in general by the use of synergists and in particular by incorporation of appropriate structural features within the pyrethroid molecule. Potential for this approach has been demonstrated in the case of *H. armigera* (Forrester *et al.* 1993). Our work at Rothamsted has also identified specific structure-activity relationships in this regard and thus the potential for developing practical resistance-defeating pyrethroids. Collaboration with companies will be the next step towards commercial exploitation of these findings.

The occurrence of negative cross-resistance for some classes of insecticides towards insects resistant to pyrethroids offers a possibility not observed frequently for the other main classes of insecticide. For example, chlorfenapyr (**25**) is a proinsecticide that is activated within insects by the action of mixed function oxidases (Brooke *et al.*, 2001). Another example is indoxacarb (**26**), likewise activated but by esterases. These insecticides, therefore, are more effective against pyrethroid-resistant insects than against the susceptible strains. The practical value of this phenomenon has been demonstrated in the control of *H. armigera* (Gunning and Devonshire, 2001).

Table 2. Examples of products based on isomer enrichment

Pyrethroid	Product	Number of isomers	Stereochemistry
Cypermethrin		8	(1*R*)-*cis*, α*S* ; (1*S*)-*cis*, α*R* (1*R*)-*cis*, α*R* ; (1*S*)-*cis*, α*S* (1*R*)-*trans*, α*S* ; (1*S*)-*trans*, α*R* (1*R*)-*trans*, α*R* ; (1*S*)-*trans*, α*S*
	Alpha	2	(1*R*)-*cis*, α*S* ; (1*S*)-*cis*, α*R*
	Beta	4	(1*R*)-*cis*, α*S* ; (1*S*)-*cis*, α*R* (1*R*)-*trans*, α*S* ; (1*S*)-*trans*, α*R*
	Theta	2	(1*R*)-*trans*, α*S* ; (1*S*)-*trans*, α*R*
	Zeta	4	(1*R*)-*cis*, α*S* ; (1*S*)-*cis*, α*S* (1*R*)-*trans*, α*S* ; (1*S*)-*trans*, α*S*
Cyhalothrin		4	(1*R*)-*cis*, α*S* ; (1*S*)-*cis*, α*R* (1*R*)-*trans*, α*S* ; (1*S*)-*trans*, α*R*
	Lambda	2	(1*R*)-*cis*, α*S* ; (1*S*)-*cis*, α*R*
	Super	1	(1*R*)-*cis*, α*S*



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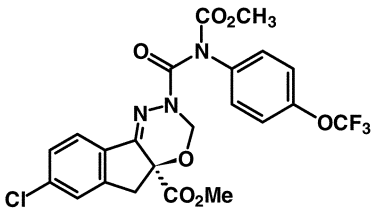

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Site insensitivity

This form of resistance occurs as a consequence of mutations in the amino acid sequence of the voltage-gated sodium channel. Changes have been shown to occur at (or close by) positions 1014 (for *kdr*) and 918 (*super-kdr*) (Williamson *et al.*, 1996). The level of resistance due to the former (*kdr* mutation) alone is generally similar for all pyrethroid molecules (20–50 fold). In contrast, it is much higher (up to 500 fold) for the *super-kdr* mutation (methionine to threonine in houseflies). The importance of a methionine residue at position 918 for sensitivity to pyrethroids has recently been demonstrated by Vais *et al.* (2000). They observed a significant increase in the sensitivity of mammalian sodium channels to pyrethroids when the isoleucine residue at the position equivalent to 918 in houseflies was replaced with methionine. In contrast to the *kdr* mutation, the levels of resistance observed for the *super kdr* mutations are closely linked to the structure of the pyrethroid molecule (Farnham and Khambay, 1995a; Farnham and Khambay, 1995b; Beddie *et al.*, 1996). For example, there is high resistance to compounds that contain both an α-cyano group and a cyclic moiety (Figure 2) attached to position 3 of the benzylic moiety, as in deltamethrin. The lowest resistance levels are observed for compounds that do not contain either of these two features *e.g.* tefluthrin (**16**). Thus there is scope for the identification and development of pyrethroids that retain high efficacy against the pest but exhibit relatively low levels of resistance.

The *kdr* and *super kdr* mutations can occur singly or in combination. For example, in houseflies and *Plutella xylostella* (diamond-back moth), both mutations are found

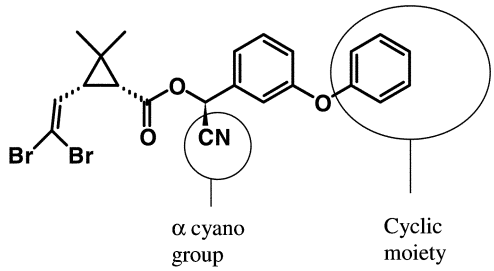


Figure 2

Table 3. Negative cross-resistance to pyrethroids

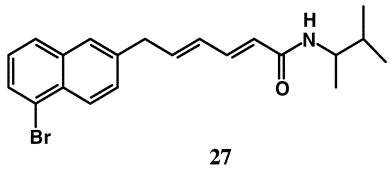
Class of compound	Resistance factors*
Pyrethroids	240 [n=12]
N-Alkylamides (*e.g.* **25**)	0.44 [n=7]
Dihydropyrazoles (*e.g.* **26**)	0.45 [n=9]

* Resistance factors = LD_{50} for *super kdr* strain of houseflies divided by LD_{50} for susceptible (Cooper) strain

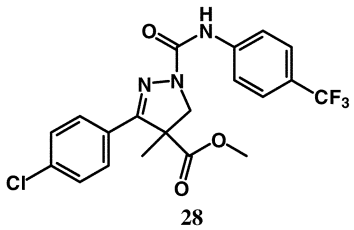
but in *Aphis gossypii* only the *super kdr* mutation is found (M. Williamson, personal communication). Recent studies have indicated different combinations of these mutations can confer variable levels of resistance (Vais *et al.*, 2001).

Negative cross-resistance involving site-insensitivity mechanisms has also been observed between pyrethroids and two other classes. These are the *N*-alkylamides (*e.g.* BTG 502 (**27**)) (Elliott *et al.*, 1986) and the dihydropyrazoles (*e.g.* RH 63421 (**28**)) (Khambay *et al.*, 2001) from which indoxacarb was developed (Table 3). Further work is being undertaken to understand the molecular basis of this effect.

Finally, both metabolic and site-insensivity mechanisms can occur simultaneously. This aspect is currently under investigation at Rothamsted, but assessment of the relative contributions of the two mechanisms is not yet possible.



27



28

Conclusions and prospects for developing resistance-defeating pyrethroids

Pyrethroids constitute a particularly versatile class of insecticides, no more likely in principle to develop resistance than any other class. The potential for developing resistance-breaking pyrethroids has already been clearly demonstrated and the selection of target compounds can be refined by taking into consideration the resistance mechanism(s) involved. The decision to pursue this strategy is clearly dependent on commercial considerations. Though patent protection of new compounds may not be possible given the very large number of generic structures in patents (now mostly expired), the process technology for manufacture of pyrethroids is well established. Furthermore new compounds could be partly based on existing intermediates (*e.g.* permethric acid; 3-phenoxybenzyl alcohol) which in

turn might result in a reduction in the amount of new data required for registration purposes.

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