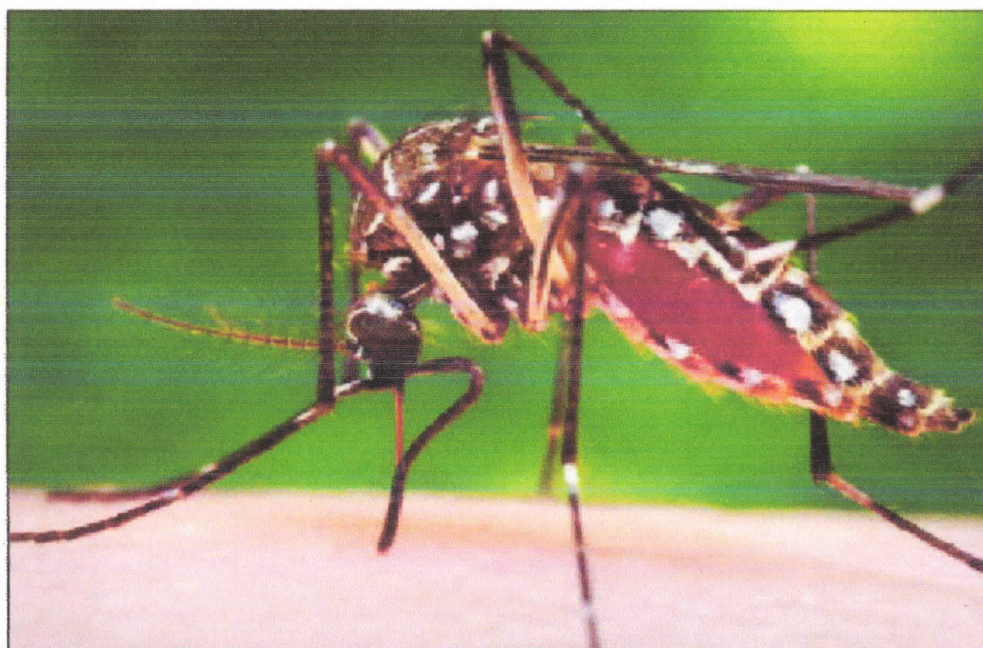


New β -triketone insecticides offer novel mode of action to control resistant insects

Peter May*



Aedes aegypti is among the insects targeted in a series of knockdown and contact activity tests in comparison to permethrin as an industry standard. The results clearly demonstrate high levels of efficacy as an adulticide.

Bio-Gene has a history in essential oils and natural products which has included the screening of compounds from Australian flora, resulting in the discovery of the β -triketone insecticides. The company has recently significantly increased its investment in development of this new class of insecticides. Qcide® is based on tasmanone and is being produced as a natural plant extract from a rare cultivar of *Eucalyptus cloeziana*. Flavocide® is based on flavesone, another β -triketone compound, that also occurs in a number of plant species, but that the company has successfully synthesised in order to make the product more readily available for commercial use.

Patents cover the use of naturally derived or synthesised active

ingredients comprising one or more β -diones, particularly β -diketones and β -triketones, for control of a range of pest groups including insects, arachnids, helminths, molluscs, protozoa and viruses. However, the company has focused developments on the β -triketones, tasmanone and flavesone, due to their demonstrated activity against a range of major pest species in public and animal health, as well as in agricultural crops.

The widespread issue of insecticide resistance in many of these applications, presents significant opportunities for products with novel modes of action to act as "resistance breakers" in integrated pest management (IPM) programs. The β -triketone group of insecticides are

being positioned to target these situations.

CEO & Director Robert Klupacs joined the company in 2015 and has been leading programs with collaborators to fully evaluate the two compounds as control agents against a number of key pests including mosquitoes, animal ectoparasites and selected agricultural pests. "We are committed to working with scientific centres of expertise and major industry participants, in rigorously testing these novel products" said

Mr Klupacs "to demonstrate activity against key target pests as well as confirm market competitiveness against industry standard products."

Mosquitoes have been very much in the news lately, in particular the *Aedes* vectors of Dengue and Zika arboviruses, that are contributing to the rapid spread of these and other diseases around the globe. Recent testing programs with flavesone were undertaken by the University of Technology in Sydney. *Aedes aegypti* and *Culex quinquefasciatus* were targeted in a series of tests to assess knockdown and contact activity of when compared to permethrin as an industry standard. The results clearly demonstrated high levels of efficacy as an adulticide that would greatly assist control of pyrethroid-resistant strains of *Aedes aegypti* that are prevalent in many Dengue and Zika virus infected areas.

Flavesone has also been successfully tested against in animal health

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Robert Klupacs, CEO & Director of Bio-Gene states the company is committed to working with scientific centres of expertise and major industry participants, in rigorously testing these novel products.

applications, most notably against ectoparasites such as ticks and buffalo fly and including pyrethroid- and organophosphate-resistant strains. When compared to the pyrethroid cypermethrin, the new compound gave superior control of a commonly occurring pyrethroid-resistant strain of larval stage of the cattle tick *Rhipicephalus microplus* with an LC₉₉ ten times lower than that of cypermethrin.

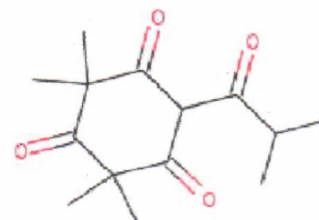
Several agricultural crop and crop-related applications have been investigated as potential markets for the two β -triketones. A recent program has been initiated to test flavesone against grain storage pests, in particular those resistant to pyrethroids and organophosphates, which are commonly used as grain protectants. Lesser grain borer (*Rhyzopertha dominica*) is a common pest of stored grain and is being targeted in bioassay testing to first establish an effective dose rate against non-resistant susceptible strains of the pest and then

to use this rate in comparative studies with industry standards including synergised deltamethrin, chlorpyrifos and spinosad, against SP and OP resistant strains of the pest.

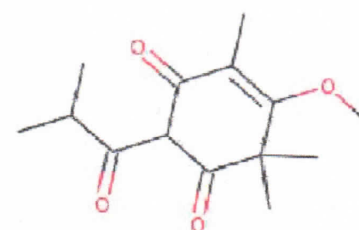
The task of demonstrating a novel mode of action is not easy. Showing activity against resistant insect populations is only part of the story and needs to be supported by studies aimed at identifying the specific mechanisms of toxicity against the target pest. The company is working with research organisations in a series of tests to demonstrate the differences in modes of action of flavesone and tasmanone compared to other commonly used insecticides, and also to more clearly understand the nature of the insecticidal mode of action of β -triketones.

Another area being targeted by the Australian company is the control of ectoparasites such as head lice (*Pediculus humanus capitis*) and the scabies mite (*Sarcoptes scabiei*) in human health. There is a heavy reliance on pyrethroids, in particular permethrin, in this sector with repeated applications leading inevitably to the development of insecticide resistance, in particular by head lice. Tasmanone has been tested with considerable success and is being developed as a natural control solution for these problem pests.

Apart from mode of action the strategy is to determine the scope of pest activity of this new class of insecticides, confirm competitiveness



Flavesone, a β -triketone compound that occurs in a number of plant species, but which has been successfully synthesised in order to make the product more readily available for commercial use.



Tasmanone, a natural plant extract from a rare cultivar of *Eucalyptus cloeziana*

against industry standard products and to position these products in markets where either a natural or synthetic product is preferred. The company is also seeking commercial partners already present in the market, and with an interest in expanding or complementing their portfolios with new and novel produce, in particular based on a novel chemistry group.

- β -triketone insecticide compounds have shown promising activity against a range of insects known to cause damage to agricultural crops such as aphids and mirids, animal ectoparasites such as fleas, ticks and buffalo fly and against insects causing major public health issues such as *Aedes* mosquitoes which are carriers of Zika and Dengue viruses.
- Studies have shown that β -triketone insecticides appear to act effectively on pyrethrin resistant insect populations indicating that they may have a unique mode of action.
- New research by Australian company Bio-Gene Technology is aimed at demonstrating a novel mode of action for the company's β -triketone insecticides Qcide® and Flavocide®.