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Use of arylpyrroles for the control of resistant insect populations

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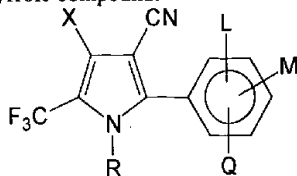
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Use of Arylpyrroles for the Control of Resistant Insect Populations

Abstract

There is provided a method for the control of pyrethroid-resistant insects and the protection of animals therefrom which comprises contacting said insects with a toxic
5 amount of a formula I arylpyrrole compound.



(I)

wherein R is hydrogen or C₁-C₄alkoxymethyl; X is Cl or Br, and L, M, and Q are each independently hydrogen, Cl, Br, I, F or C₁-C₄haloalkyl.

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COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

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Invention Title: Use of Arylpyrroles for the Control of Resistant Insect
Populations

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

Use of Arylpyrroles for the Control of Resistant Insect Populations

Background of the Invention

Virtually all commercial and most companion animals are affected by parasites. The outcome associated with parasitism in said animals is generally clinical disease and subclinical conditions that decrease performance. Insects, such as *Diptera* (flies) and *Phthiraptera* (lice), are among the most economically important parasites in animal production. Insects, such as *Siphonaptera* (fleas) are highly pestiferous to companion animals. Many insects, such as *Haematobia irritans* (*Diptera: Muscidae*), require only 1-4 weeks to complete a life cycle during periods of warm temperatures. In Southern climates, as many as 20 generations of insects may develop annually. This rapidity of regeneration enables insect populations to develop resistance to environmental toxins such as insecticides.

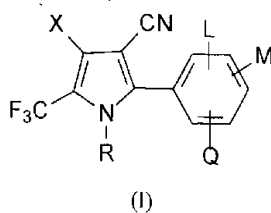
Although, numerous insecticides may control insects effectively, most require frequent application. As a result, the efficacy of the insecticides may be severely compromised by the development of resistant populations such as pyrethroid-resistant insects. Thus, a new group of insecticides with selective toxicity against pyrethroid-resistant insects would be most advantageous.

Therefore, it is an object of this invention to provide in preferred embodiments a unique and highly effective group of arylpyrrole compounds useful for the control of pyrethroid-resistant insect populations.

It is another object of this invention in preferred embodiments to provide a method to enhance the protection of animals from the infestation of pyrethroid-resistant insects.

Summary of the invention

The present invention provides a method of controlling pyrethroid-resistant insects in animals which comprises contacting said insects, their habitat, breeding area or food supply with a toxic amount of an arylpyrrole compound of formula I



wherein R is hydrogen or C₁-C₄alkoxymethyl;

X is Cl or Br, and

L, M, and Q are each independently hydrogen, Cl, Br, I, F or C₁-C₄haloalkyl.



Also provided is a method of enhancing protection of animals from the infestation of pyrethroid-resistant insects which comprises administering or applying to the animals an effective amount of a formula I arylpyrrole compound.

Detailed Description of the Invention

Resistance is a widespread phenomenon and resistant populations of nearly all economically important pests can now be found. Insects highly resistant to pyrethroid insecticides pose a serious problem to animals health worldwide. Animal production and animal performance is

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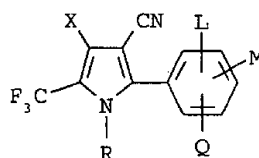


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greatly compromised by pyrethroid-resistant strains of insects, particularly of the orders *Diptera* (flies) and *Phthiraptera* (lice). Further, pyrethroid-resistant strains of *Siphonaptera* (fleas) can be a source of persistent annoyance to companion animals, as well as vectors of disease or intermediate hosts of certain tapeworms.

Resistance is herein defined as: a heritable reduction in the sensitivity of an insect population to the action of a pesticide, the reduction being expressed as a decrease in the frequency of individual insects affected by exposure to the pesticide (in comparison to the frequency observed in the same population upon initial or prior exposure).

A broad spectrum of arylpyrrole compounds are known to be useful for the control of endo- and ectoparasites on warm-blooded mammals (U.S. Patent 5,455,263). However, it has now been found that the specific subset of arylpyrroles of formula I



(I)

wherein R is hydrogen or C₁-C₄alkoxymethyl;

X is Cl or Br, and

L, M, and Q are each independently hydrogen, Cl, Br,

I, F or C₁-C₄haloalkyl

is highly efficacious against pyrethroid-resistant insects. Surprisingly, the formula I arylpyrroles are about 700%-1,100% more effective against pyrethroid-

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resistant insects than they are against pyrethroid-susceptible insects.

Important agronomic and companion animals such as cattle, sheep, horses, pigs, goats, water buffalo, deer, cats, dogs, rabbits, and the like are prone to attack and infestation by biting and sucking insects such as *Diptera*, *Phthiraptera* and *Siphonaptera*. In particular, *Diptera*: *Muscidae* such as *Musca autumnalis* (face flies), *Haematobia irritans* (horn flies), *Stomoxys calcitrans* (stable flies), heel flies, tsetse flies and the like are breeders of filth and vectors of disease and are serious pests of animals such as cattle, horses and sheep. Further, *Diptera*: *Hippoboscidae* (louse flies) such as *Melophagus ovinus* (sheep ked), which is a serious parasite of sheep are problematic in animal production.

Among the *Phthiraptera* families known to be parasites of animals are: *Trichodectidae* such as *Bovicola bovis* (important cattle-biting louse) or *B. equi* (horse-biting louse); *Haematopinidae* such as *Haematopinus suis* (hog louse), or *H. asini* (horse sucking louse); *Linognathidae* such as *Linognathus stenopsis* (goat sucking louse) or *L. vitali* (long-nosed cattle louse); and the like.

One of the *Siphonaptera* families known to infest companion animals is *Pulicinae* such as *Archaeopsyllinae* (cat and dog fleas), *Spilopsyllinae* (rabbit fleas), and the like.

Resistant insect populations may be detected and monitored readily by traditional methods such as bioassays or biochemical assays or by molecular techniques. Traditional bioassays, such as those described by Shepard and Hinkle in *J. Agric. Entomol.* 4(1): 87-89 (1987), are able to detect the overall level of resistance present in a population in a single test.

Pyrethroid-resistant insects, particularly of the orders of *Diptera*, *Phthiraptera*, or *Siphonaptera*, more particularly of the families mentioned hereinabove, and most particularly of the species mentioned hereinabove
5 may be effectively controlled by contacting said insects, their habitat, breeding area or food supply with a toxic amount of a formula I arylpyrrole compound. Preferred arylpyrrole compounds are those wherein X is Br and L, M and Q are each independently hydrogen or Cl. More preferred compounds are those wherein L and Q are hydrogen
10 and M is 4-Chloro.

Among the formula I arylpyrrole compounds particularly useful in the method of the invention are:

- 4-bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-
15 (trifluoromethyl)pyrrole-3-carbonitrile;
4-chloro-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-
(trifluoromethyl)pyrrole-3-carbonitrile;
4-bromo-2-(3,5-dichlorophenyl)-1-(ethoxymethyl)-5-
(trifluoromethyl)pyrrole-3-carbonitrile;
20 4-bromo-2-(p-chlorophenyl)-5-(trifluoromethyl)-
pyrrole-3-carbonitrile;
4-chloro-2-(p-chlorophenyl)-5-(trifluoromethyl)-
pyrrole-3-carbonitrile;
4-bromo-2-(3,5-dichlorophenyl)-5-(trifluoromethyl)-
25 pyrrole-3-carbonitrile; and the like.

Protection of animals from the infestation of pyrethroid-resistant insects, particularly of the orders *Diptera*, *Phthiraptera* and *Siphonaptera*, may be enhanced by the application or administration of an effective amount
30 of an arylpyrrole compound of formula I. In actual practice, the formula I compound may be applied to the animal as a dip, spray, pour-on, backrubber, oiler, dustbag, powder, lotion or the like; or as an ear-tag or collar; or as an oral drench, bolus, pill, implant, capsule, feed

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or drinking water additive or the like; or as a parenteral injection; or the like.

5 The effective amount of the formula I arylpyrrole compound to be used in the method of invention will vary according to the specific compound used, the mode of application used, the identity of the pyrethroid-resistant insect to be controlled, the degree of
10 infestation, the extent of the pyrethroid-resistant insect population, the nature of the target host, the weather conditions and the like. Effective dosages may range from about 0.1 mg/kg to 100 mg/kg, preferably about 1.0 mg/kg to 30 mg/kg. Naturally, quantities of
15 greater than effective amounts of the arylpyrrole compound may be administered, but are not required for protection of the target animal from the pyrethroid-resistant insects.

 The formula I arylpyrrole compounds can be
20 prepared by the methods disclosed in U. S. Patent No. 5,455,263.

 In order to present a more clear understanding of the invention, the following specific examples are set forth below. These examples are merely illustrative
25 and are not to be understood as limiting the scope and underlying principles of the invention in any way. Indeed, various modifications of the invention, in addition to those illustrated and described herein, will become apparent to persons skilled in the art from
30 the following examples and the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

EXAMPLE 1Evaluation Of The Effect Of Test Compounds vs.
Cypermethrin On Susceptible And Resistant Strains Of Horn
Flies (*Haematobia irritans*).

5 In this bioassay, highly pyrethroid-resistant wild
flies and flies of a pyrethroid-susceptible lab strain
are used. All flies are held in plastic petri dishes and
exposed to sequential rates of test compound residue on
10 filter paper¹. A 1.25 inch hole is cut in the bottom half
of the 100 mL petri dish and covered with fiberglass win-
dow screen. The bottom is used as the top in this bioas-
say, in order that the flies may be blood fed through the
screened opening with a muslin pad saturated with cit-
15 rated cattle blood.

The experiments are conducted in triplicate to de-
termine 24 hour LC₅₀ data for the test compound and cyper-
methrin on susceptible and pyrethroid-resistant horn
flies. The experiments are conducted on site so that
20 freshly captured pyrethroid-resistant horn flies can be
used. On the exemplified site, very high levels of pyre-
throid resistance had been selected through several years
of pyrethroid cattle ear tag use². Wild pyrethroid-
resistant horn flies are tested within 1 hour of capture
25 to minimize check mortality. The resistance factor (RF)
is determined by the following equation:

$$RF = \text{Resistant } LC_{50} \div \text{Susceptible } LC_{50}$$

30 The LC₅₀ is the concentration in µg/cm² of test com-
pound required to kill 50% of the fly population tested.
The LC₅₀ values are determined from the mortality data us-
ing standard log probit analysis techniques³, and are
within 95% confidence limits¹. The data obtained is shown

in Table I. The references listed below are incorporated herein by reference thereto.

5

Table I

Exp. ⁴	Test Compound	Susceptible	Resistant	RF
		LC ₅₀ (µg/cm ²)	LC ₅₀ (µg/cm ²)	
1	A	1.2	0.356	0.30
	B	0.122	79.02	640
2	A	2.15	0.294	0.14
	B	0.057	65.20	1144
3	A	1.25	0.287	0.23
	B	0.013	47.27	3636
10	Compound A =	4-Bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile		
	Compound B =	Cypermethrin		

15 ¹ Sheppard, D.C. and Hinkle, N.C., Journal Agricultural Entomology, 4, p. 87-89 (1987)

² Sheppard, D.C. and Joyce, J.A., Journal Economic Entomology, 85, p. 1587-1593 (1992)

20 ³ Daum, R.J., Bulletin of the Entomology Society of America, 16 (1): 10-12 (1970)

⁴ Experiment

EXAMPLE 2**Evaluation Of Test Compounds vs. Permethrin On Susceptible And Resistant Strains Of Horn Flies (*Haematobia irritans*).**

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Using essentially the standard treated filterpaper-tarsal contact 24 hour bioassay described in Example 1, the following test compounds and pyrethroid insecticide are evaluated:

- 10 Compound A = 4-Bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile
- Compound C = 4-Bromo-2-(p-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile
- 15 Compound D = 4-Chloro-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile
- 20 Compound E = Permethrin

The results are shown in Table II.

25

Table II

Test Compound	Susceptible LC ₅₀ (µg/cm ²)	Resistant LC ₅₀ (µg/cm ²)	RF
A	1.691	0.391	0.23
C	21.237	1.877	0.088
D	8.692	1.066	0.123
E	0.102	8.16	80.0

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EXAMPLE 3Evaluation Of Test Compound Activity Against Susceptible And Resistant Sheep Body Lice

- 5 In this evaluation, test compounds are dissolved in acetone and diluted in a gradient series. One mL aliquots of the acetone dilutions are pipetted onto 6 cm cotton squares. The treated squares are dried and put into 9 cm petri dishes. Adult lice from the pyrethroid-susceptible Peak Hill strain and the pyrethroid-resistant Rowena strain are collected by suction from sheep, transferred onto each treated square and confined using a stainless steel ring (50 mm diameter x 20 mm). After 16 hours, the lice are scored as dead, moribund or alive.
- 10 In this bioassay, the test compound killed, rather than knocked-down lice. Each treatment is replicated. Standard log probit analysis techniques are used to determine the LC_{50} and LC_{99} values from the mortality data, and are within 95% confidence limits. The LC_{50} values are then
- 15 used to determine the resistance factor (RF) as shown below.

$$RF = \text{Resistant } LC_{50} \div \text{Susceptible } LC_{50}$$

- 25 The LC_{50} is the concentration in mg/L of test compound required to kill 50% of the lice population tested. The LC_{99} is the concentration in mg/L of test compound required to kill 99% of the lice population tested. The data are shown in Table III.

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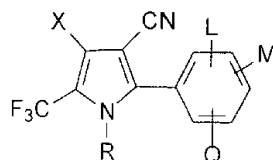
Table III

Test Compound	Susceptible LC ₅₀ (mg/L)	Resistant LC ₅₀ (mg/L)	RF
4-Bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-pyrrole-3-carbonitrile	8.30	5.85	0.7048

Test Compound	Susceptible LC ₉₉ (mg/L)	Resistant LC ₉₉ (mg/L)
4-Bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-pyrrole-3-carbonitrile	52.8	24.5

The claims defining the invention are as follows:

1. A method of controlling pyrethroid-resistant insects of animals which comprises contacting said insects, their habitat, breeding area, or food supply with a toxic amount of an arylpyrrole compound of formula I



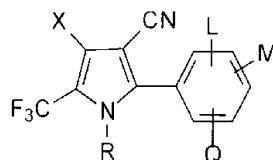
(I)

wherein R is hydrogen or C₁-C₄alkoxymethyl;

X is Cl or Br, and

L, M, and Q are each independently hydrogen, Cl, Br, I, F or C₁-C₄haloalkyl.

2. A method of enhancing the protection of animals from the infestation of pyrethroid-resistant insects which comprises administering or applying to the animals an effective amount of the arylpyrrole compound of formula I



(I)

wherein R is hydrogen or C₁-C₄alkoxymethyl;

X is Cl or Br, and

L, M, and Q are each independently hydrogen, Cl, Br, I, F or C₁-C₄haloalkyl.

3. The method according to claim 1 or 2 wherein the animals are cattle, sheep or buffalo.

4. The method according to claim 1 or 2 wherein the pyrethroid-resistant insects are *Diptera*, *Phthiraptera* or *Siphonaptera*.

5. The method according to claim 4 wherein the *Phthiraptera* is *Trichodectidae*, *Haematopinidae* or *Linognathidae*; the *Siphonaptera* is *Pulicidae*; and the *Diptera* is *Muscidae* or *Hippoboscidae*.

6. The method according to claim 1 or 2 wherein R is ethoxymethyl.

7. The method according to claim 6 wherein the arylpyrrole compound is 4-bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile or 4-chloro-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile.

8. The method according to claim 1 or 2 wherein R is hydrogen.



9. The method according to claim 8 wherein the arylpyrrole compound is 4-bromo-2-(p-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile.

10. The method according to claim 1 or 2 wherein L and Q are each hydrogen and M is 4-chloro.

11. A method of controlling pyrethroid-resistant insects of animals substantially as hereinbefore described with reference to any one of the examples but excluding the comparative examples.

12. A method of enhancing the protection of animals from the infestation of pyrethroid-resistant insects substantially as hereinbefore described with reference to any one of the examples but excluding the comparative examples.

Dated 30 May, 2001
American Cyanamid Company

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

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