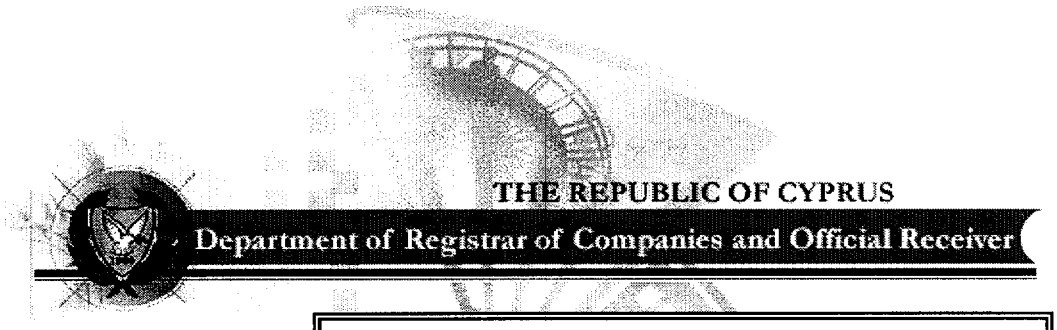

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

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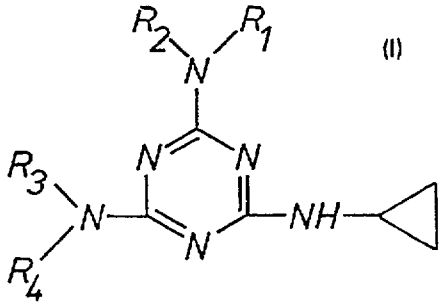
(54) **Compounds and compositions containing them for use in the treatment of mammals for controlling parasitic Diptera larvae**

(57) The present invention relates to insecticidal substances of the general formula I



(I)

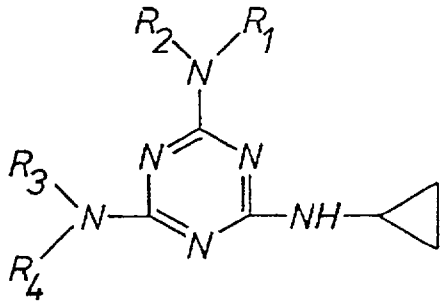
in which R_1 is hydrogen, methyl, ethyl or cyclopropyl, R_2 is hydrogen or methyl, R_3 is hydrogen, methyl or cyclopropyl and R_4 is hydrogen or methyl, or of acid addition salts thereof which are non-toxic to mammals. These compounds are used in the treatment of domestic animals and productive livestock belonging to the class of Mammalia for the systemic control of parasitic larvae of the order Diptera which feed on tissue. The active substances and compositions containing them are administered perorally.

GB 2 014 449 A

SPECIFICATION

Compounds and compositions containing them for use in the treatment of mammals for controlling parasitic Diptera larvae.

The present invention relates to compounds and compositions containing them for use in the treatment of domestic animals and productive livestock belonging to the class of Mammalia (mammals) for systemically controlling parasitic insect larvae of the order of Diptera which feed on tissue. The compounds are active substances of the formula I



(I)

wherein R_1 is hydrogen, methyl, ethyl or cycloproply, R_2 is hydrogen or methyl, R_3 is hydrogen, methyl or cyclopropyl and R_4 is hydrogen or methyl, or of an acid addition salt thereof which is nonltoxic to mammals. The active substances or compositions containing them are administered perorally.

The term acid addition salts of compounds of the formula I is to be understood as meaning salts with pharmaceutically acceptable acids, for example with strong mineral acids, such as hydrochloric acid or sulfuric acid, or with organic acids, such as acetic acid, tartaric acid or citric acid.

On account of its outstanding action, the most preferred compound of the formula I for controlling parasitic insect larvae of the order Diptera is 2, 4-diamino-6-cyclopropylamino-s-triazine.

The control of Diptera larvae, which live as parasites in the tissues of their host animals, is of extreme importance, especially in view of the considerable damage which can be caused by the parasites in livestock husbandry and most particularly in the husbandry of grazing animals.

The Diptera larvae can invade the tissues of their host animals in many different ways. Thus, after the Diptera females have laid their eggs, which they can do in or on various parts of the body of the host animals, the larvae hatched from the eggs can be ingested by the host animals by licking and they then bore into the pharynx, or the larvae can bore into the skin of the host animals. However, the eggs can also first be deposited on mosquitoes or flies. The larvae develop in the eggs and hatch as soon as the carrier insect seeks out a suitable host animal. In the case of the viviparous Diptera species the larvae can be deposited direct by the Diptera females into the nose or the eyes of the host animals.

After the larvae have invaded the host animals, they can migrate to those parts of the body which they prefer. The larvae can locate, for example, in or under the skin, in the gastro-intestinal tract or in the nasal cavities, the cavity of the pharynx or the frontal sinus of their hosts.

The various types of parasitism by Diptera larvae in animals are termed myiases.

Myiases can occur in numerous species of animals, for example in cattle, horses, donkeys, mules, reindeer, sheep, pigs, dogs and cats,

In the host animals, the infestation by parasitic Diptera larvae can, in addition to other adverse effects, result in a reduction in the milk yield, loss of wool, loss of weight or even in death. If the host animals are infested by skin parasites which cause swellings to form in the skin, the consequence can also be a depreciation in the value of the skins on account of perforation, because the swellings have a small orifice which is enlarged by the larvae before they leave the host for pupation.

As the larvae can infest very different, and in some cases very inaccessible parts of the body of the host animals, their control is highly problematical.

Surprisingly, it has now been found that compounds of the formula I and compositions which contain these compounds as active ingredients, are outstandingly suitable for the control of parasitic Diptera larvae. The substances develop a systemic action which means that, on peroral application to the host animal, an action against the parasitic Diptera larvea also takes place in parts of the body which have not been treated. The use of the compounds of the formula I thus enables parasitic Diptera larvae to be effectively controlled even in those parts of the body in which direct application is extremely difficult or virtually impossible.

The compounds of the formula I and their acid addition salts which are non-toxic to mammals are advantageously used in a concentration in the range of 1 to 20 mg/kg of body weight.

A particularly advantageous method of controlling the parasites consists in providing the animals to be treated with the active substance as a constituent of licking blocks or administering to them a formulation which effects release of the active substance in the rumen.

The use of licking blocks which contain the active substance proves particularly advantageous in the

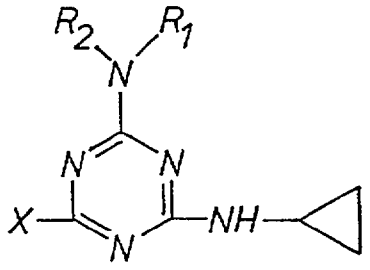
treatment of large herds living outdoors, where the individual treatment of the animals is laborious and timeconsuming.

The advantage of a formulation which effects release of the active substance in the rumen is that the active substance is released slowly and thus develops its action over a prolonged period of time.

Furthermore, the application of the active substance by spraying a liquid formulation into the oesophagus of the animals to be treated, using a suitable applicator (drench gun), is also very advantageous.

The compounds of the formula I have, in particular, a good action against myiasis-inducing larvae of insects of the order Diptera, which belong to the families Calliphoridae, Oestridae, CUTEREBRIDAE, Gasterophilidae, Sarcophagidae and Hypodermatididae, for example against larvae of Lucilia spec., Cochlyomyia hominivorax, Chrysomyia bezziana, Hypoderma lineata, Hypoderma bovis, Dermatobia hominis, Oedemagena tarandi, Gasterophilus spec., Oestrus ovis, Rhinoestrus purpureus, Wohlfahrtia vigil and Cuterebra spec.

The compounds of the formula I can be prepared methods which are known per se by, for example, a) reacting a 2-cyclopropylamino-4-amino-6-halogeno-s-triazine of the formula II, in which R_1 and R_2 are as defined for formula I and X is halogen, preferably chlorine, with ammonia or a primary and/or secondary amine of the formula V, in which R_3 and R_4 are as defined for formula I:



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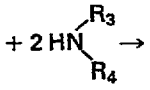

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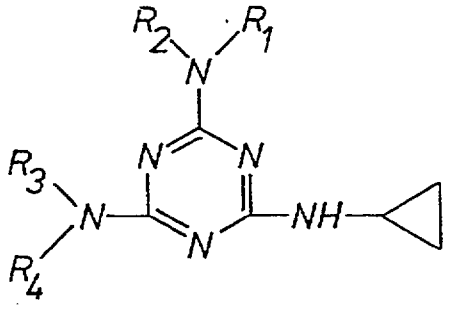
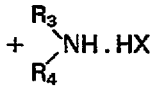
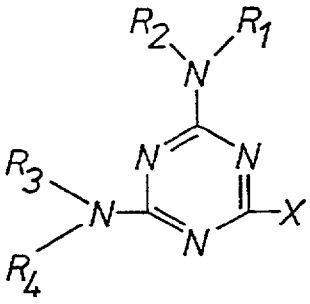


I



or b) reacting a 2,4-diamino-6-halogeno-s-triazine of the formula III, in which R_1, R_2, R_3 and R_4 are as defined for formula I and X is halogen. preferably chlorine, with cyclopropylamine (formula VI):



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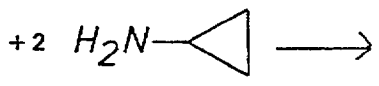
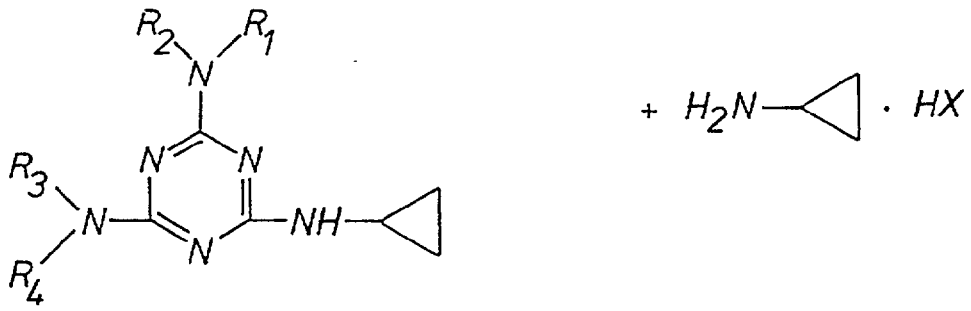
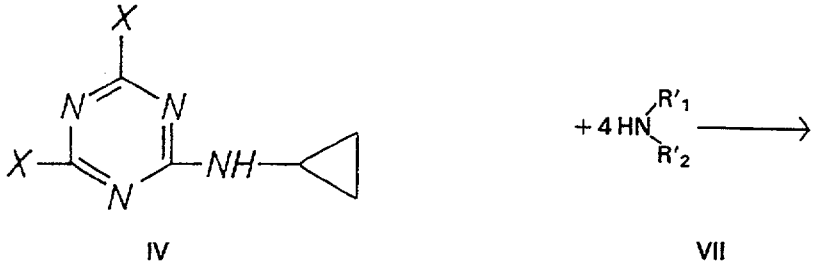


VI

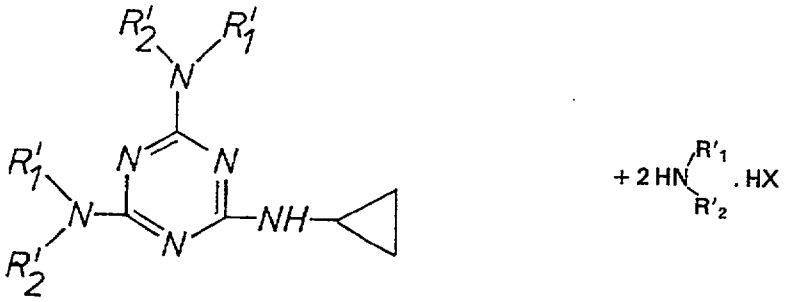


I

or c) if, in the compounds of the formula I, R_1 has the same meaning as R_3 and R_2 has the same meaning as R_4, reacting a 2-cyclopropylamino-4,6-dihalogeno-s-triazine of the formula IV, in which X is halogen, preferably chlorine, with ammonia or a primary and/or secondary amine of the formula VII, in which R'_1 has the meaning defined for $R_1 = R_3$, as indicated for formula I, and R'_2 has the meaning defined for $R_2 = R_4$, as indicated for formula I:



IV VII



Ia

The replacement of the halogen atoms by ammonia or primary and/or secondary amines of the formulae V, VI and VIII takes place by dissolving the starting materials of the formulae II, III and IV in inert solvent, for example acetone, acetone/water mixtures, methyl ethyl ketone, dioxan or dioxan/water mixtures, and reacting these mixtures under normal or, if desired, elevated pressure and at temperatures of 20 - 150°C and preferably 50 - 140°C with ammonia or primary and/or secondary amines.

The starting materials of the formulae II, III and IV are known in most cases or can be prepared analogously to known processes.

Example 1

a) *2-Cyclopropylamino-4,6-diamino-s-triazine*

A mixture of 100 g of 2-cyclopropylamino-4-amino-6-chloro-s-triazine, 51 g of ammonia and 500 ml of dioxan is heated to 140°C in an autoclave for 24 hours. After cooling, the dioxan is removed by filtering with suction in vacuo and the crystalline residue is washed with water and dried. The crude product is recrystallised from methanol; melting point 219-222°C.

b) *2-Cyclopropylamino-4,6-diamino-s-triazine, salt with 2 mols of hydrochloric acid*

25 g of 2-cyclopropylamino-4,6-diamino-s-triazine are dissolved in 2,000 ml of hot absolute ethanol. This solution is cooled to 15°C and cooled further with ice and hydrogen cloride gas is then introduced until the solution is saturated, whereupon white crystals precipitate. These crystals are collected by filtration and the crude salt is washed copiously with ether; melting point 195°C (decomposition).

Example 2

a) *2 -Cyclopropylamino-4-methylamino-6-amino-s-triazine*

A mixture of 12.7 g of 2-cyclopropylamino-4-methyl-amino-6-chloro-s-triazine, 17.4 g of 28% aqueous ammonia solution and 30 ml of dioxan is heated to 140°C in an autoclave for 4 hours. After cooling, the reaction mixture is poured into 350 ml of a solution, which has been cooled to 0°C, of potassium carbonate in water and extracted with 1:1 benzene/ether. After drying over sodium sulfate, the solvents are removed in vacuo and the residue is recrystallised from isopropanol/hexane; melting point 159-162°C.

b) *2-Cyclopropylamino-4-methylamino-6-amino-s-triazine, salt with 2 mols of hydrochloric acid*

38 g of 2-cyclopropylamino-4-methylamino-6-amino-s-triazine are dissolved in 280 ml of chloroform. This solution is cooled with ice to 0 - 5°C and hydrogen chloride gas is introduced until the solution is saturated, whereupon white crystals precipitate. 280 ml of ether are added to bring precipitation to completion. The crude hydrochloride is filtered off and recrystallised from methanol; melting point 197 - 199°C.

Example 3

2,4,6-Tris-cyclopropylamino-s-triazine

A mixture of 20 g of 2-chloro-4,6-bis-cyclopropyl-amino-s-triazine, 10.1 g of cyclopropylamine and 80 ml of dioxan is heated to 140°C in an autoclave for 22 hours. The reaction mixture is concentrated in vacuo to half its volume and 300 ml of water are added. The mixture is extracted with ethyl acetate, the product phase is dried over sodium sulfate and the solvents are removed in vacuo. The residue is recrystallised from dioxan/petroleum ether; melting point 75-77°C.

The following compounds of the formula I can, for example, also be prepared in a manner analogous to that in Examples 1 to 3:

No.	Compound	Melting point in °C
1	2-cyclopropylamino-4-amino-6-dimethyl-amino-s-triazine	182-184
2	2,4-bis-(cyclopropylamino)-6-amino-s-triazine	137-140
3	2-cyclopropylamino-4-methylamino-6-dimethylamino-s-triazine dihydrochloride	164-165
4	2-cyclopropylamino-4,6-bis-(dimethyl-amino)-s-triazine	140-142
5	2-cyclopropylamino-4-amino-6-ethylamino-s-triazine	141-145
6	2-cyclopropylamino-4-amino-6-ethylamino-s-triazine dihydrochloride	199-200
7	2,4-bis-(cyclopropylamino)-6-dimethyl-amino-s-triazine	136-137

The compounds of the formula I or their acid addition salts which are non-toxic to mammals can be used as pure active substance or together with suitable carriers and/or adjuvants. Suitable carriers and adjuvants can be solid or liquid and are the substances conventionally employed in the art of formulation, for example natural or regenerated substances, solvents and/or dispersants.

Depending on the use, the active substances can be administered in the form of solutions, emulsions, wettable powders, suspensions, granules, pellets, bolusses, tablets or capsules. The active substances or compositions containing these can, however, also be added to the feed or drink or can be contained in a premix. The active substances can, for example, be combined with adjuncts such as kaolin, lime, aluminium oxide, ground mussel shells, bolus alba, aerosil, starch or lactose, talc, bentonite, sodium chloride, calcium phosphate, cottonseed meal or liquids which are inert to the active substances, such as oils and other solvents and diluents harmless to the animals to be treated.

The active substances can also be administered, to the animals to be treated, as a constituent of licking blocks.

The use of the formulation which effects release of the active substance or of a non-toxic acid addition salt thereof in the rumen is particularly suitable for slow release of the active substance.

Formulation Examples 8 to 13

The active substances of the formula I or their non-toxic acid addition salts can be processed to the following formulations.

Granules: (Example 8)

5 parts of active substance are dissolved in a solvent such as methylene chloride and the solution is mixed

with 2 parts of polyethylene glycol ("carbowax"). 91.5 parts of calcium carbonate are impregnated with the mixture and 1.5 parts of precipitated silica are mixed in and the solvent is then evaporated.

Wettable powder: (Example 9)

50 parts of active substance are mixed with 5 parts of a dispersant, for example sodium ligninsulfonate, 5 parts of a wetting agent, for example dibutylnaphtha-lenesulfonic acid, 10 parts of silica and 30 parts of kaolin and the mixture is finely ground.

Emulsifiable concentrate: (Example 10)

20 parts of active substance are mixed with 20 parts of emulsifier, for example a mixture of alkylaryl polyglycol ether with alkylarylsulfonates, and 60 parts of solvent, until the solution is completely homogeneous. With water, this concentrate gives an emulsion of any desired concentration.

Premix: (Feed additive) (Example 11)

5 parts of active substance and 5 parts of secondary calcium phosphate, or kaolin, aerosil or carbonated lime, are mixed homogeneously with 90 parts of a feed, for example feed concentrate.

Solutions (for dilution with drinking water) (Example 12)

a) 15% active substance in "Solketal ®" (2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane)
b) 10% active substance in "Carbitol ®" (diethylene glycol monoethyl ether)
c) 10% active substance in polyethylene glycol 300
d) 5% active substance in glycerol

Soluble powder (Example 13)

25 parts of active substance
1 part of Tensopol SP-USP (sodium lauryl-sulfate USP)
3 parts of colloidal silica K320
71 parts of urea

The constituents are mixed and the mixture is ground finely in a suitable mill.

Other biocidal active substances or agents, which are inert to the active substances and tolerated by the animals to be treated, or mineral salts or vitamins can be admixed to the compositions described.

Test

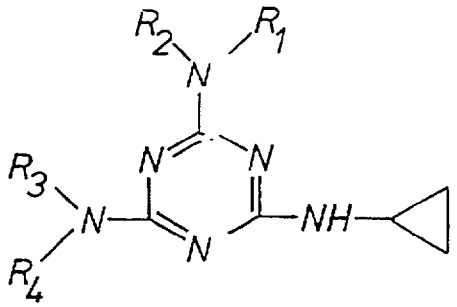
Peroral use in sheep and cattle

An active substance of the formula I is administered perorally in an amount of 5 mg/kg of body weight in a suitable formulation to sheep and cattle, using a drench gun. The animals treated are artificially infested with larvae of *Lucilia sericata*. The larvicidal action is assessed after 72 hours.

In this test, compounds of the formula I show a pronounced larvicidal action.

CLAIMS

1. Compound of the general formula I



(I)

in which R_1 is hydrogen , methyl, ethyl or cyclopropyl, R_2 is hydrogen or methyl, R_3 is hydrogen, methyl or cyclopropyl and R_4 is hydrogen or methyl, or an acid addition salt thereof which is non-toxic to mammals for peroral administration to mammalian domestic animals and livestock to systemically control parasitic insects of the order Diptera.

2. Compound as claimed in claim 1 in which R_1, R_2, R_3 and R_4 are hydrogen.

3. Compound as used in claim 1 or 2 whereby said compound is administered in a form which allows its release in the rumen.

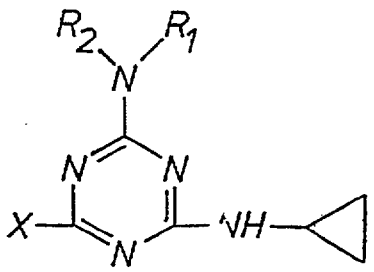
4. Compound as used in claim 1 or 2 whereby said compound is formulated as a licking block prior to administration.

5. Compound as used in claim 1 or 2 whereby administration is carried out by spraying into the oesophagus of the animal to be treated.

6. Compound of formula I substantially as described with reference to any of Examples 1 to 7.

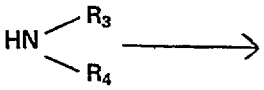
7. A process of producing a compound of formula I, as defined in claim 1, comprising:

(a) reacting a 2-cyclopropylamino-4-amino-6-halogeno-s-triazine of formula:-



II

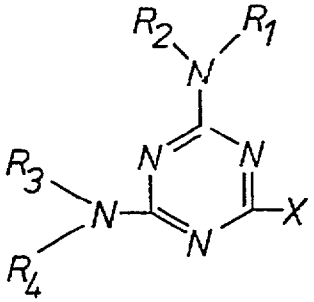
in which R_1 and R_2 are as defined in claim 1 and X is halogen, with ammonia or a primary and/or secondary amine of formula:-



V

In which R_3 and R_4 are as defined in claim 1; or

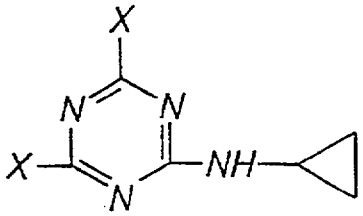
(b) reacting a 2,4-diamino-6-halogeno-s-triazine of formula:-



III

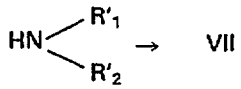
in which R_1, R_2, R_3 and R_4 are as defined in claim 1 and X is halogen, with cyclopropylamine; or

(c) when in the compounds of formula I, R_1 has the same meaning as R_3 and R_2 has the same meaning as R_4, reacting a 2-cyclopropylamino-4,6-dihalogeno-S-triazine of the formula:-



IV

in which X is halogen, with ammonia or a primary and/or secondary amine of the formula:-



VII

in which R_1' has the meaning defined in claim 1 for R_1 and $R_1 = R_3$ and R_2' has the meaning defined in claim 1 for R_2 and $R_2 = R_4$.

8. A process as claimed in claim 7 in which X is chlorine.

9. A process of producing a compound of formula I substantially as described with reference to any of Examples 1 to 7.

10. A compound of formula I when produced by a process claimed in any of claims 7 to 9.

11. A composition comprising a compound of formula I as defined in claim 1 or an acid addition salt thereof which is non-toxic to mammals, for peroral administration to mammalian domestic animals and livestock, to systemically control tissue parasitic insects of the order Diptera.

12. Composition as claimed in claim 6, containing a compound of formula I in which R_1, R_2, R_3 and R_4 are

hydrogen.

13. Composition as used in claim 6 whereby said composition is administered in a form which allows its release in the rumen.

14. Composition as used in claim 6 whereby said composition is formulated as a licking block prior to administration.

15. Composition as used in claim 6 whereby administration is carried out by spraying into the oesophagus of the animal to be treated.

16. A composition as claimed in claim 11 substantially as described with reference to and of Examples 8 to 13.

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