
(12) PATENT ABRIDGMENT (11) Document No AU-B-76581/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 606349

(54) Title
PREVENTION OF FLEA REINFESTATION OF DOGS AND CATS USING A TRIAZINE

International Patent Classification(s)
(51)⁴ **A61K 031/53 A01N 043/68**

(21) Application No. : **76581/87** (22) Application Date : **05.08.87**

(30) Priority Data

(31) Number (32) Date (33) Country
893763 06.08.86 US UNITED STATES OF AMERICA

(43) Publication Date : **11.02.88**

(44) Publication Date of Accepted Application : **07.02.91**

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(56) Prior Art Documents
AU 36082/84
AU 28041/77
AU 28042/77

(57) Claim

1. A method of systemically preventing the reinfestation of dogs and cats by fleas, which method comprises administering to said host animals orally, parenterally or by implant a larvicidally effective amount of a flea growth inhibiting substance selected from one of the classes consisting of

- a) a juvenile insect hormone or a chemical analogue thereof,
or
- b) a flea growth inhibiting benzoylurea derivative,
or
- c) a flea growth inhibiting triazine derivative.

14. Dog food or cat food for preventing the reinfestation of dogs and cats by fleas comprising a larvicidally or ovicidally effective amount of a flea growth inhibiting substance selected from one of the classes consisting of

- a) a juvenile insect hormone or a chemical analogue thereof,
or
- b) a flea growth inhibiting benzoylurea derivative,
or
- c) a flea growth inhibiting triazine derivative.

606349

S & F Ref: 32450

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

This document contains the
amendments made under
Section 49 and is correct for
printing.

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Complete Specification for the invention entitled:

Method of preventing the reinfestation of dogs and cats by
fleas

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

5845/6

5-16038/+ /CGC 1217

Method of preventing the reinfestation of dogs and cats by fleas

The present invention relates to a method of treating dogs and cats having topically disposed fleas. More particularly, the invention relates to such a method of treatment wherein the dog or cat is dosed with a larvicidally or ovicidally effective amount of flea growth inhibiting substance capable of reacting the flea via the hosts blood.

Blood sucking parasitic infestation on animals, especially the infestation of pets by fleas, has been a continued problem in the art. On account of the complexity of the life cycle of the flea, none of the methods known to the prior art of controlling said parasite is entirely satisfactory, especially since said known methods are principally directed to the control of adult fleas in the coat of the host animal and do not take into account the different juvenile stages of the fleas existing in the animals coats as well as on the floor, on carpets, in bedding, on chairs, in the garden and in all other places with which the infested animal usually comes into contact. Adult cat and dog fleas (*Ctenocephalides felis* and *C. canis*) live naturally in the coat of the cat or dog host. They feed on host blood and the females lay eggs in the coat. Since the eggs are non-sticky they quickly fall off and can be found for example on the floor, on carpets, in the animals' beddings, on chairs used by the pets, in the garden, in the backyard etc.

Thus, the total environment of the pet animal is infested with flea eggs, which in about two days hatch to larvae. There are three larval stages each lasting about three days. In the last stage the larvae spin cocoons and transform to pupae. Under optimum conditions, i.e. 33°C and 65 % relative humidity, the eggs transform to pupae in about 8 to 10 days. After a further period of approximately 8 days, the pupae develop to young adult fleas in the cocoon still lying on the floor, the carpets, the beddings, the chairs, etc. The young adult fleas wait until they sense the presence of an acceptable host animal and then emerge and attempt to jump onto it. Thus, it takes at least three weeks for eggs to develop to young adults able to reinfest the host. However, the young adults can remain for months, possibly as long as one year, in the cocoon, and in addition, under suboptimum conditions it can take 4 to 5 months for the eggs to develop into young adults. Fleas must have a blood meal in order to become sexually mature and therefore be able to reproduce. The blood must come from the correct type of host.

This long life cycle, taking place off the host, has important implications for flea treatment applied to host animals.

Even if the fleas in the coat of the host can be controlled successfully, i.e. if all adult fleas are killed by an active ingredient, the cat or dog is nevertheless exposed for weeks or even months to the risk of reinfestation by the newly emerged adults present in the host's environment.

Infestation of dogs and cats with fleas has several undesirable effects for the treated animals or the owner. Such undesirable effects may manifest themselves in the form of local irritation or annoying itching, often leading to scratching. Quite a high number of animals become allergic to flea saliva, resulting in very itchy and crusty lumps on the animal's body at the site of the bites.

Normally these lumps reach a diameter of 3 mm or more and cause the animal to bite and scratch, leading subsequent hair loss here and there. These infested animals create a nervous impression and become more and more unattractive and irritable.

Furthermore, animals which are infested by fleas are permanently exposed to the danger of being infected by Dipylidium, a tape worm, which is transmitted by the fleas.

10 Flea infestation is not only extremely annoying for the infested animal, but is also unpleasant for the owner. It is, after all, worrying for an animal owner when he sees from the unusual behaviour of his pet that it is ill and is suffering and needs help.

Furthermore, there may be unpleasant consequences for the owner if he gives away his infested animal or if it dies or is temporarily taken away from its accustomed surroundings; i.e. in the prolonged absence of a suitable host animal, the newly hatched fleas which are located on the floor are compelled to attack humans although they are not capable of reproduction if human blood is their sole source of nutrition. Even in the presence of the dog or cat, the owner may be bitten by the fleas.

20 Moreover, some humans may suffer from allergic skin diseases as a result of dog and cat fleas or their excreta. In certain cases this will mean that the pet has to be given away. It has, therefore, always been desirable to find an effective method of controlling fleas that infest dogs and cats.

30 A number of methods of control are known, but these have various drawbacks. When using flea combs for example, the animal owner has no choice than to comb the animal intensively and frequently. Depending on the size of the animal, this may take from several minutes to an hour. Not every animal will always patiently put up with being combed, nor is every owner prepared to sacrifice his time for this. The use of corresponding anti-flea shampoos is in many cases impossible since most cats and a large number of dogs simply

refuse to be given a bath or they can only be given a bath when the owner resorts to using force, in which case water and shampoo will be splashed about and the bathroom has to be cleaned up. Furthermore, the effect of such bath treatment doesn't last more than about a week and the laborious procedure has to be gone through all over again. The same or quite similar problems are encountered when using dips or rinses. Even the use of dusting powders is as a rule not tolerated by the animal without resistance since it takes several minutes to treat the entire surface of the coat uniformly and some dust is bound to get into the mouth, nose and eyes of the animal. Even in the case of careful application, it is impossible to prevent the powder from being inhaled by the animal or its owner. There is virtually no way for the owner to avoid a more or less intensive contact with the active ingredient.

When using sprays, many an owner may experience an unpleasant surprise since most animals, particularly cats, take flight or react aggressively the very moment they hear the noise of the spray. Moreover, sprays have all the drawbacks mentioned above for powders and, in addition, they disperse even more finely in the atmosphere, which means that animals and their owners simply can not help inhaling them. Fleas are frequently also controlled with flea collars which are temporarily very effective. One particular weakness of this method of treatment is that it is normally effective in a very limited region of the animal's body. In general, 100 % kill is achieved in the region of the neck and thorax; however, more remote parts of the body are hardly affected. Besides, many of these collars look unattractive and may also irritate the animal. Today medallions are available which can be attached to the collar and which are said to be active. These medallions are appealing to the eye, but their effectiveness is unsatisfactory since they do not come into sufficient contact with the animal's coat. Several anti-flea organophosphorus compounds are available in the form of spot-on formulations. These are applied to a limited spot on the coat. In general, they exhibit good short-term activity

against adult fleas, but the compositions applied often have problematic toxic values. Some organophosphorus compounds are administered orally. However, narrow safety limits are set for their use and they must never be applied simultaneously with other organophosphorus compounds.

10 On the whole it can be said that it has always been the objective of previous methods to kill the adult flea. Some of these methods can be applied quite successfully for controlling adult fleas for a short period. A fact which has so far not been acknowledged is that, owing to the particular life cycle of fleas, dogs and cats will be repeatedly reinfested because, on the one hand, the animal can not avoid coming into contact with the flea eggs, flea larvae and juvenile and adult fleas on the floor or in its immediate vicinity and, on the other hand, many pets again and again come into contact with infested members of the same species. Constantly recurring reinfestation is not prevented by using conventional pesticides.

20 Surprisingly, it has been found that by specific modes of application and by using active ingredients which block the development of juvenile flea stages, the vicious circle of constantly recurring reinfestation, described above in detail, can be brought to an end in simple manner, thereby preventing the fleas from reproducing and, in addition, keeping the habitat of dogs and cats permanently free from fleas.

It has been found that by administering to dogs or cats orally or parenterally or by implant a larvicidally or ovicidally effective amount of a flea growth inhibiting substance, the reinfestation of dogs and cats by fleas can be drastically reduced or completely prevented.

30 It has further been found that in particular the following three classes of active ingredients are suitable for such use:

- insect hormone or a chemical analogue thereof, or.
- a) ~~a juvenile hormone or juvenile hormone-like chemical,~~
 - b) a flea growth inhibiting benzoylurea derivative,
- or
- c) a flea growth inhibiting triazine derivative.

10 It is known that some representatives of the substance classes (a), (b) and (c) inhibit or completely suppress the further development of juvenile stages; however, this activity has always been observed when the active ingredient is applied direct to the parasites. In connection with the present invention, it is surprising, however, that the full activity is still achieved even when the active ingredient is administered to the host animal in relatively low concentrations and it reaches, in an indirect way, the adult flea via the blood ingested and, additionally, the flea larvae (the actual target) when they feed upon the faeces excreted by the adults. By killing merely the adult fleas, which has so far been the objective of methods of control, the host animal is freed from fleas for a short time only. It has been found that fleas can only be effectively controlled if the development of new flea populations from the flea eggs is successfully prevented.

20 Target pests may be exposed to compounds in two ways. Chemicals are ingested in the blood meal by adult insects and pass from adults to the egg where they are effective. Death may occur at the egg, larval or pupal stage. Research on fleas indicates reduced egg production, high larval mortality and inability of adults to eclose from the pupal case. In addition to transmission to the egg, larval fleas are exposed when they feed upon faeces excreted by adult fleas. Flea faeces contain large amounts of undigested blood taken from the host and serve as a protein source for the developing flea.

30 Accordingly, the present invention embraces two aspects; namely the above-described method of preventing dogs and cats from being reinfested by fleas, and, at the same time, the suppression of the propagation of fleas, or to put it more precisely:



A method of preventing the propagation of fleas, comprising the step of providing the fleas with nutrient blood which contain an effective amount of at least one of the active ingredients as identified above. This method also includes the aspect that the nutrient blood is provided to the fleas by feeding an effective amount of one of said active ingredients to a host dog or a host cat and letting the fleas feed thereon.

10 All three substance classes (a), (b) und (c) and the preparation thereof are described in the literature. Juvenile hormones or ~~chemical analogues thereof~~ ~~juvenile hormone-like chemicals~~ [class (a)] are described in the following publications: Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel (The Chemistry of Plant Protectants and Pesticides), R. Wegler, Springer-Verlag Berlin, Heidelberg, New York 1981, Vol. 6, pp. 185 to 214.

20 Insecticide Mode of Action, Joel R. Coats, Academic Press (1982) pp. 315 to 402.

US-PS-4,172,146; US-PS-3,987,102; US-PS-3,987,108; US-PS-3,988,477; US-PS-4,007,280; US-PS-4,100,296; US-PS-4,097,581; US-PS-4,060,629; US-PS-4,080,470; EP-4,334; UK-2,084,574; EP-169,169; EP-72,475; US-PS-4,092,365; US-PS-4,057,587; US-PS-4,017,549; DE-OS-2,528,345; EP-37,092; US-PS-4,061,683; DE-OS-2,925,113; Chem.Abstr., Vol. 102, p 668, 113025e; Chem.Abstr., Vol. 102, p. 222, 57842e; Chem.Abstr., Vol. 102, p. 569, 61919c; UK-2,102,425, and Agric.Biol.Chem., Vol. 49, pp. 3197 to 3202 (1985).

Representative examples of particularly preferred substances of class (a) are the following compounds:



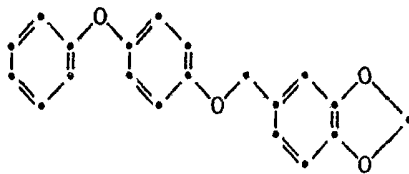
Table 1: Juvenile hormone-like chemicals

Compound No.	Structure
1.1	
1.2	
1.3	
1.4	
1.5	
1.6	
1.7	
1.8	
1.9	

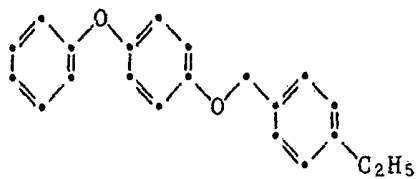
Compound No.

Structure

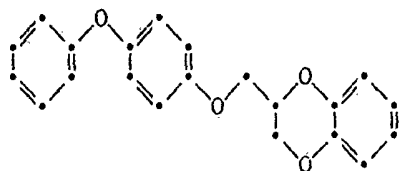
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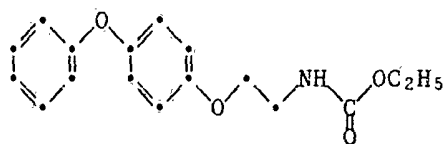
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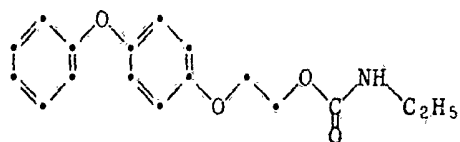
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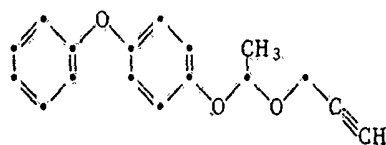
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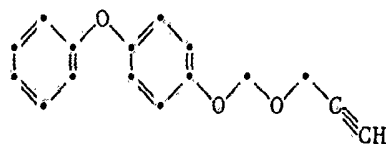
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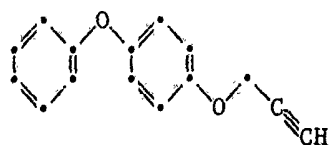
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1.16



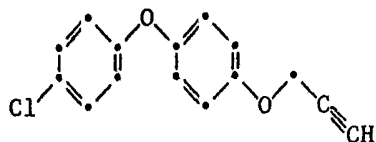
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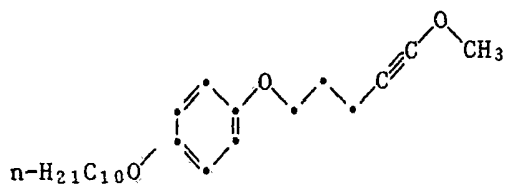
Compound No.

Structure

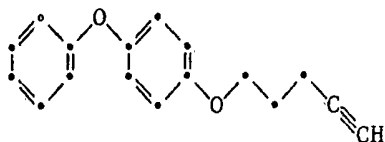
1.18



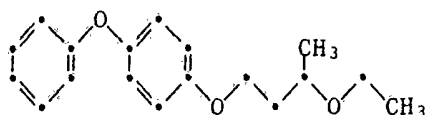
1.19



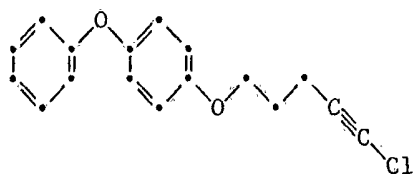
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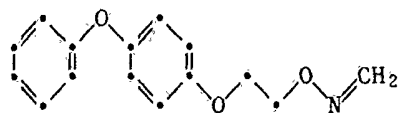
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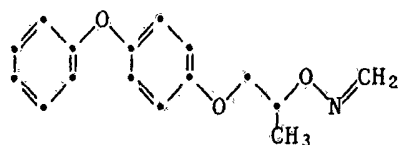
1.22



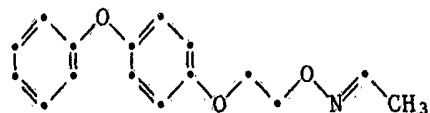
1.23



1.24



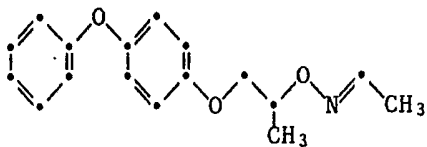
1.25



Compound No.

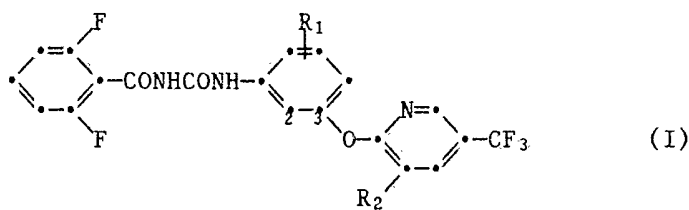
Structure

1.26



Class (b): Flea growth inhibiting benzoylurea derivatives, which are also known to the skilled person under the name of "dimiloids", are described e.g. in DE-OS-2,123,236; DE-OS-2,601,780; DE-OS-3,240,975; EP-72,438, EP-42,533 and especially EP-79,311.

Preferred compounds of class (b) for being employed in the method of the present invention are the following compounds of the formula I



wherein

R₁ is hydrogen, halogen or methyl; and

R₂ is hydrogen or halogen.

A preferred subgroup within the compounds of the formula I consists of those representatives, wherein

R₁ is hydrogen, fluorine, chlorine or bromine; and

R₂ is hydrogen, fluorine, chlorine or bromine.

Most preferred are those representatives of the formula I, wherein

R₁ is 4-fluorine, 4-chlorine, 4-bromine or 4-methyl; and

R₂ is chlorine.

20

Representative examples of particularly preferred individual compounds of class (b) are:

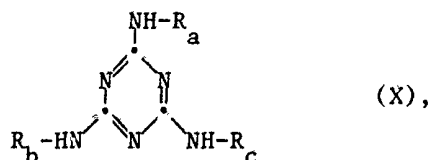
Table 2: Flea growth inhibiting benzoylureas of the formula I

Compound No.	R ₁	R ₂	m.p. [°C]
2.1	4-CH ₃	Cl	178-179
2.2	4-Br	Cl	190-194
2.3	4-CH ₃	H	188-189
2.4	4-F	Cl	174-177
2.5	4-Cl	Cl	185-189
2.6	4-F	H	185-188
2.7	4-Cl	H	185-188
2.8	H	Cl	172-173
2.9	H	H	186-188
2.10	4-Br	Cl	198-200
2.11	H	Br	
2.12	H	J	
2.13	4-Br	Cl	
2.14	4-CH ₃	F	
2.15	5-CH ₃	H	
2.16	5-CH ₃	Cl	
2.17	5-CH ₃	F	
2.18	6-CH ₃	Cl	
2.19	6-F	Cl	
2.20	6-Cl	Cl	
2.21	6-Cl	F	
2.22	6-Cl	H	
2.23	H	F	

Class (c): Flea growth inhibiting triazine derivatives which can be employed in the method of this invention are described e.g. in US-PS-4,225,598; US-PS-4,160,831; US-PS-4,160,832; US-PS-4,187,304; US-PS-4,187,305 and DE-OS-3,030,646.

The following group of compounds of this class (c) is to be singled out as being particularly suitable:

compounds of formula X



wherein



R_a is cyclopropyl or isopropyl;

R_b is hydrogen, halogen, C_1 - C_{12} alkylcarbonyl, cyclopropylcarbonyl, C_1 - C_{12} alkylcarbamoyl, C_1 - C_{12} alkylthiocarbamoyl or C_2 - C_6 alkenylcarbamoyl; and

R_c is hydrogen, C_1 - C_{12} alkyl, cyclopropyl, C_2 - C_6 alkenyl, C_1 - C_{12} alkylcarbonyl, cyclopropylcarbonyl, C_1 - C_{12} alkylcarbamoyl, C_1 - C_{12} alkylthiocarbamoyl or C_2 - C_6 alkenylcarbamoyl, and the acid addition salts thereof which are non-toxic for warm-blooded animals.

10 The following Table 3 shows typical representatives of compound of formula X.

Table 3: Flea growth inhibiting triazine derivatives

Compound No.	R _a	R _b	R _c	m.p. [°C]
3.1	cyclopropyl	H	H	219-222
3.2	cyclopropyl	H	CH ₃	228-231
3.3	cyclopropyl	H	C ₂ H ₅	228-230
3.4	cyclopropyl	H	C ₃ H ₇ -n	211-213
3.5	cyclopropyl	H	C ₄ H ₉ -n	206-207
3.6	cyclopropyl	H	C ₅ H ₁₁ -n	202-205
3.7	cyclopropyl	H	C ₆ H ₁₃ -n	204-205
3.8	cyclopropyl	H	C ₇ H ₁₅ -n	168-170
3.9	cyclopropyl	H	C ₈ H ₁₇ -n	203-204
3.10	cyclopropyl	H	C ₁₂ H ₂₅ -n	201-204
3.11	cyclopropyl	H	CH ₂ -C ₄ H ₉ -t	191-193
3.12	cyclopropyl	H	CH ₂ CH(CH ₃)C ₂ H ₅	181-184
3.13	cyclopropyl	H	CH ₂ CH=CH ₂	100-105
3.14	cyclopropyl	Cl	C ₂ H ₅	200-201
3.15	cyclopropyl	Cl	C ₄ H ₉ -n	152-153
3.16	cyclopropyl	Cl	C ₆ H ₁₃ -n	138-140
3.17	cyclopropyl	Cl	C ₈ H ₁₇ -n	127-128
3.18	cyclopropyl	Cl	C ₁₂ H ₂₅ -n	119-120
3.19	cyclopropyl	H	Cyclopropyl	137-140
3.20	cyclopropyl	H	COCH ₃	190-195
3.21	cyclopropyl	H	COCH ₃ •HCl	245-247
3.22	cyclopropyl	H	COC ₂ H ₅ •HCl	226-229
3.23	cyclopropyl	H	COC ₂ H ₅	210-212
3.24	cyclopropyl	H	COC ₃ H ₇ -n	216-218
3.25	cyclopropyl	H	COC ₃ H ₇ -i	232-236
3.26	cyclopropyl	H	COC ₄ H ₉ -t•HCl	80-85
3.27	cyclopropyl	H	COC ₄ H ₉ -n	182-183

Table 3 (continuation)

Compound No.	R _a	R _b	R _c	m.p. [°C]
3.28	cyclopropyl	H	COC ₆ H ₁₃ -n	195-197
3.29	cyclopropyl	H	COC ₁₁ H ₂₃ -n	175-177
3.30	cyclopropyl	COCH ₃	COC ₂ H ₅	259-262
3.31	cyclopropyl	COC ₃ H ₇ -n	COC ₆ H ₁₃ -n	180-182
3.32	cyclopropyl	COCH ₃	COC ₃ H ₇ -n	232-233
3.33	cyclopropyl	COC ₂ H ₅	COC ₃ H ₇ -n	242-244
3.34	cyclopropyl	H	COcyclopropyl	232-234
3.35	cyclopropyl	COcyclopropyl	COcyclopropyl	273-276
3.36	cyclopropyl	COCH ₃	COCH ₃	75-80
3.37	isopropyl	H	H	225-228
3.38	isopropyl	H	COCH ₃	202-204
3.39	isopropyl	H	COC ₃ H ₇ -n	194-198
3.40	cyclopropyl	H	CONHCH ₃	303 decomp.
3.41	cyclopropyl	H	CONHC ₃ H ₇ -i	290 decomp.
3.42	cyclopropyl	CONHCH ₃	CONHCH ₃	304 decomp.
3.43	cyclopropyl	H	CSNHCH ₃	210-212
3.44	cyclopropyl	H	CONHCH ₂ CH=CH ₂	270 decomp.
3.45	cyclopropyl	CONHCH ₂ CH=CH ₂	CONHCH ₂ CH=CH ₂	297 decomp.
3.46	cyclopropyl	CSNHCH ₃	CSNHCH ₃	285 decomp.

Compound 3.1, cyromazine is particularly preferred.

It is an essential feature of the present invention that the active ingredient selected from the above-mentioned substance classes (a), (b) and (c) is administered in such a manner that it can be ingested by the adult sucking flea with the blood of the host animal and can then exhibit activity against the juvenile flea stages. In accordance with the present invention, this is achieved with several forms of application, e.g. by administering a formulated active ingredient orally. In this case, the term "formulated" means e.g. in the form of a powder, a tablet, a granulate, a capsule, an emulsion, a foam etc. The preparation does not necessarily have to be admini-

10 stered to the animal direct; it may be convenient to mix it with the animal's feed. In addition to containing adjuvants conventionally employed in the art of formulation, the compositions to be administered orally may of course contain further additives which stimulate voluntary ingestion by the animal, e.g. suitable scents or flavourings. Owing to its simplicity, oral application is one of the preferred objects of the present invention. A further mode of application is parenteral application, e.g. by subcutaneous, intravenous or intramuscular injection or by means of a sustained action preparation in the form of an implant or other depot formulation.

Methods of oral application include but are not limited to compounds premixed in dog and cat food, fed in biscuits or treats, chewable tablets, water-dissolvable capsules or tablets, water-soluble compounds applied with a dropper into water or materials applied in any form onto dog food. Implants include any device applied into the animal for release of compounds to control fleas.

20 Percutaneous administration is conveniently accomplished by subcutaneous, dermal, intramuscular and even intravenous application of the injectable formulation. Conventional needle-type injection devices as well as needle-less air-blast injection devices and pour-on and spot-on formulations may be useful.

It is possible to delay or sustain the permeation of the active ingredient through the animal's living tissues by proper formulation. For example, a very insoluble compound may be used. In this case, the slight solubility of the compound causes sustained action because the body fluids of the animal can dissolve only a small amount of the compound at any one time.

30 Sustained action of the active ingredient can also be obtained by formulating the compound in a matrix which will physically inhibit dissolution. The formulated matrix is injected into the body where it remains as a depot from which the compound slowly dissolves.

Matrix formulations, now known in the art, are formulated in waxy semisolids such as vegetable waxes and high molecular weight polyethylene glycols.

10 Very effective sustained action is obtained by introducing into the animal an implant containing one of the active ingredients. Such implants are now well known in veterinary art and are usually made of a silicone-containing rubber. The active ingredient is dispersed through a solid rubber implant or is contained inside a hollow implant. Care must be taken to choose an active ingredient which is soluble in the rubber from which the implant is made, since it is dispersed by first dissolving in the rubber and then leaching out of the rubber into the body fluids of the treated animal.

The rate at which active ingredient is released from an implant, and hence the length of time during which the implant remains effective, is controlled with good accuracy by the proper adjustment of the concentration of the compound in the implant, the external area of the implant, and the formulation of the polymer from which the implant is made.

20 Administration of the active ingredient by means of an implant is a further particularly preferred embodiment. Such administration is highly economical and efficacious because a properly designed implant maintains a constant concentration of the compound in the tissues of the host animal. An implant can be designed to supply compound for several months and is easily inserted in the animal. No further handling of the animal or concern over the dosage is necessary after the insertion of the implant.

30 The formulation of veterinary additives in animal feed is an extremely well-known art. It is usual to formulate the compound first as a premix in which the active ingredient is dispersed in a liquid or particulate solid carrier. The premix may conveniently contain from about 1 to 800 g of compound per kilogram, depending on the desired concentration in the feed. As is known in the art, many

active ingredients can be hydrolysed or degraded by constituents of animal feed. Such compounds are routinely formulated in protective matrices such as gelatin before addition to the premix.

Therefore, the present invention is directed to a method of
5 systemically preventing the reinfestation of dogs and cats by fleas, which method comprises administering to said host animals orally, parenterally or by implant a larvicidally effective amount of a flea growth inhibiting substance selected from one of the classes consisting of:

a) a juvenile insect hormone or a chemical analogue thereof;

10 or

b) a flea growth inhibiting benzoylurea derivative;

or

c) a flea growth inhibiting triazine derivative.

The present invention also relates to a method of preventing the
15 propagation of fleas, comprising the administration of a larvicidally effective amount of a flea growth inhibiting substance selected from one of the classes consisting of

a) a juvenile insect hormone or a chemical analogue thereof,
or

20 b) a flea growth inhibiting benzoylurea derivative,
or

c) a flea growth inhibiting triazine derivative to a dog or a cat and letting fleas feed thereon.

The present invention further relates to dog food or cat food for
25 preventing the reinfestation of dogs and cats by fleas comprising a larvicidally or ovicidally effective amount of a flea growth inhibiting substance selected from one of the classes consisting of

a) a juvenile insect hormone or a chemical analogue thereof,
or

30 b) a flea growth inhibiting benzoylurea derivative,
or

c) a flea growth inhibiting triazine derivative.

Within the scope of this invention, a juvenile hormone-like chemical will be understood as meaning a chemical which acts like a juvenile hormone.



The active ingredient selected from one of the classes (a), (b) or (c) is conveniently applied in a dose of 0.01 to 800, preferably 0.5 to 200, most preferably 1 to 30, mg/kg body weight, based on the host animal, with oral administration being preferred.

A good dose for regular administration is in general in the range from 1 to 100 mg/kg body weight of the host animal. Doses are usefully regularly repeated at daily to weekly intervals.

10 The total dose of a particular active ingredient may vary from one genus of animal to the other and may even vary within the same genus since said dose depends, inter alia, on the weight and constitution of the animal.

In the method of the present invention, the active ingredient is not normally applied in pure form, but preferably in the form of a composition which, in addition to containing the active ingredient, contains application promoters which are tolerated by the host animal. Naturally, in addition to the method of controlling juvenile development stages in accordance with the present invention, the adult fleas may also be controlled by conventional methods. However, these additional measures are not absolutely necessary.

20 The composition to be applied in the method of this invention usually contain 0.1 to 99 % by weight, preferably 0.1 to 95 % by weight, of active ingredient selected from one of the classes (a), (b) or (c), and 99.9 to 1 % by weight, preferably 0.1 to 25 % by weight, of a solid or liquid non-toxic adjuvant, including 0 to 25 % by weight, preferably 0.1 to 25 % by weight, of a non-toxic surfactant.

Whereas commercial products are preferably formulated as concentrates, the end user will normally employ dilute formulations.

The compositions may also contain further ingredients, such as stabilisers, antifoams, viscosity regulators, binders, tackifiers as well as other active ingredients for obtaining special effects. Materials known from veterinary practice as being suitable for being administered orally, parenterally or by implant may be employed as formulation assistants. A number of examples are cited below.

10 Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatine, tragacanth, methylcellulose and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxy-methyl starch, cross-linked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Adjuncts are especially flow-regulating agents and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragée cores can be provided with suitable coatings that may be resistant to gastric juices, e.g. 20 concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or lacquer in suitable organic solvents or solvent mixtures or, for the production of coatings that are resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings, flavourings or pigments can be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

30 Further orally administrable preparations are dry-filled capsules consisting of gelatine and also soft, sealed capsules consisting of gelatine and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magne-

sium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also to add stabilisers. Preferred are, inter alia, capsules that
5 can be easily bitten through or swallowed without being chewed.

Especially suitable for parenteral administration are aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, also suspensions of the active ingredient, such as corresponding oily injection suspensions, e.g. suitable lipophilic solvents
10 or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate, or triglycerides, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, optionally, also stabilisers.

15 The preparations of the present invention can be manufactured in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical preparations for oral administration can be obtained by combining the active ingredient with solid carriers, optionally
20 granulating a resultant mixture, and processing the mixture or granulate, if desired or necessary after the addition of suitable adjuncts, to form tablets or dragée cores.

The following Examples illustrate the invention described hereinbefore, but do not limit its scope in any way.

25 Example 1: Tablets containing 25 mg of active ingredient, 2-cyclopropylamino-4,6-bis(dimethylamino)-s-triazine or N-(2,6-difluorobenzoyl)-N'-[4-chloro-3-(3-chloro-5-trifluoromethylpyridyl-2-yloxy)phenyl]-urea can be manufactured as follows:

Constituents (for 1000 tablets)

30	active ingredient	25.0 g
	lactose	100.7 g
	wheat starch	7.5 g
	polyethylene glycol (mol.wt. 6000)	5.0 g
	talc	5.0 g
35	magnesium stearate	1.8 g
	demineralised water	q.s.



Manufacture

All the solid ingredients are first forced through a sieve having a mesh width of 0.6 mm. Then the active ingredient, the lactose, the talc, the magnesium stearate and half of the starch are mixed. The other half of the starch is suspended in 40 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 ml of water. The resulting starch paste is added to the main batch and the mixture, if necessary with the addition of water, is granulated. The granulate is dried overnight at 35°C, forced through a sieve having a mesh width of 1.2 mm and pressed to form tablets having a diameter of approximately 6 mm that are concave on both sides.

Example 2: Tablets containing 0.02 g of active ingredient, 2-cyclopropylamino-4,6-bis(dimethylamino)-s-triazine or N-(2,6-difluorobenzoyl)-N'-[4-chloro-3-(3-chloro-5-trifluoromethylpyridyl-2-yloxy)phenyl]-urea, are manufactured as follows:

Composition

active ingredient	200.00 g
lactose	290.80 g
potato starch	274.70 g
stearic acid	10.00 g
talc	200.00 g
magnesium stearate	2.50 g
colloidal silica	32.00 g
ethanol	q.s.

A mixture of the active ingredient, the lactose and 194.70 g of the potato starch is moistened with an ethanolic solution of the stearic acid and granulated through a sieve. After drying, the remainder of the potato starch, the talc, the magnesium stearate and the colloidal silica are admixed and the mixture is pressed to form 0.1 g tablets which, if desired, can be provided with breaking grooves for finer adjustment of the dosage.

Example 3: Capsules containing 0.025 g of the active ingredient, 2-cyclopropylamino-4,6-bis(dimethylamino)-s-triazine or N-(2,6-difluorobenzoyl)-N'-[4-chloro-3-(3-chloro-5-trifluoromethylpyridyl-2-yloxy)phenyl]-urea, can be manufactured as follows:

Composition (for 1000 capsules)

active ingredient	25.00 g
lactose	249.00 g



KXW:1009y

gelatine	2.00 g
corn starch	10.00 g
talc	15.00 g
water	q.s.

5 The active ingredient is mixed with the lactose and the mixture is moistened uniformly with an aqueous solution of the gelatine and granulated through a sieve having a mesh width of 1.2-1.5 mm. The granulate is mixed with the dried corn starch and the talc and introduced in portions of 300 mg into hard gelatine capsules (size 1).

10 Example 4: Premix (feed additive)

0.25 parts by weight of active ingredient (2-cyclopropylamino-4,6-bis(dimethylamino)-s-triazine or N-(2,6-difluorobenzoyl)-N'-[4-chloro-3-(3-chloro-5-trifluoromethylpyridyl-2-yloxy)phenyl]urea) and
4.75 parts of secondary calcium phosphate, or China clay, aerosil or carbonate or lime are homogeneously mixed with
95 parts of an animal feed.

Example 5: Injection solution

8 parts by weight active ingredient 2-cyclopropylamino-4,6-bis(dimethylamino)-s-triazine or N-(2,6-difluorobenzoyl)-N'-[4-chloro-3-(3-chloro-5-trifluoromethylpyridyl-2-yloxy)-phenyl]urea,
3.6 parts of acetic acid
88.4 parts of water for injection

25 The acetic acid and the water are added to the active ingredient and the mixture is stirred until everything has dissolved. The solution is then filtered and sterilised by a suitable method. pH of the solution: 5.0.

Example 6: Emulsifiable concentrate

20 parts of active ingredient 2-cyclopropylamino-4,6-bis(dimethylamino)-s-triazine or N-(2,6-difluorobenzoyl)-N'-[4-chloro-3-(3-chloro-5-trifluoromethylpyridyl-2-yloxy)-phenyl]urea are mixed with
20 parts of emulsifier, e.g. a mixture of alkylaryl polyglycol ether with alkylarylsulphonates, and
35 60 parts of solvent until the solution is completely homogeneous. By diluting this concentrate with water it is possible to obtain an emulsion of the desired concentration.



Example 7: Solutions (for dilution with drinking water)

15% active ingredient in 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane

10% active ingredient in diethylene glycol monoethyl ether

10% active ingredient in polyethylene glycol (mol.wt. 300)

5 5% active ingredient in glycerol

where the active ingredient is 2-cyclopropylamino-4,6-bis(dimethylamino)-s-triazine or N-(2,6-difluorobenzoyl)- N'-[4-chloro-3-(3-chloro-5-trifluoromethylpyridyl-2-yloxy)-phenyl]urea.

Example 8: Soluble powder

10 25 parts of active ingredient 2-cyclopropylamino-4,6-bis(dimethylamino)-s-triazine or N-(2,6-difluorobenzoyl)-N'-[4-chloro-3-(3-chloro-5-trifluoromethylpyridyl-2-yloxy)-phenyl]urea.

1 part of sodium lauryl sulfate

15 3 parts of colloidal silica

71 parts of urea

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



Other biocidal active ingredients or agents which are inert towards the active ingredients and acceptable to the animals to be treated, or mineral salts or vitamins can be admixed to the compositions described.

In a manner analogous to that described in the formulation Examples 1 to 8, it is possible to manufacture corresponding preparations containing a compound of the classes (a), (b) or (c) as defined above.

Example 9: Flea control through the oral administration of an active ingredient

Dogs with a proven ability to maintain flea infestations were infested with 100 cat fleas (*Ctenocephalides felis* (Bouche)). Animals were then divided into 3 groups of two (See Table A). The dogs from two groups were then treated orally with the active ingredient for 10 consecutive days at a dose rate of either 3 or 5 mg/kg body weight/day (Table A). The active ingredient was administered (via a syringe) as suspension formulation dissolved in water. The third group of two animals served as non-treated controls.

3, 8 and 10 days after the start of treatment flea eggs were collected on paper placed under boxes in which the dogs were kept overnight. The eggs were counted, placed on a larval rearing medium and incubated. The number of pupae and adult fleas which hatched was determined (Table B).

The data show that by 3 days after the start of treatment with 5 mg active ingredient kg/day no adult fleas developed from the eggs of fleas which fed on these treated dogs.

These findings show that when adult female fleas take a blood meal from dogs dosed with 5 mg/kg/day, all eggs which are laid by these fleas fail to develop into adult fleas. In this manner the life cycle of the flea is broken and flea control is achieved.

Table A: Breed, sex, weight and treatment regime of animals used in trial

Active ingredient: 2-cyclopropylamino-4,6-bis(dimethylamino)-s-triazine

Animal No.	Dose (mg/kg/day)	Breed	Sex	Weight (kg)	Daily dose (mg a.i. in 5 ml H ₂ O)
IP4	0 (control)	kelpie	female	15	0
IP7	0 (control)	bull terrier cross	female	24	0
IP3	3	labrador cross	male	15	45
IP5	3	labrador cross	female	14	42
IP2	5	kelpie cross	female	17	85
IP11	5	not recognisable	female	16	80

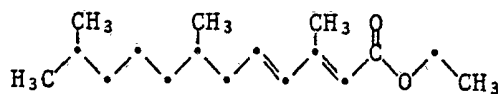
Table B Efficacy of 2-cyclopropylamino-4,6-bis(dimethylamino)-s-triazine in controlling fleas when administered orally to dogs

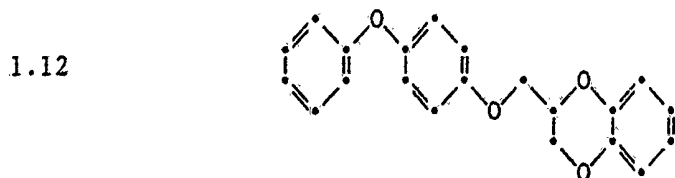
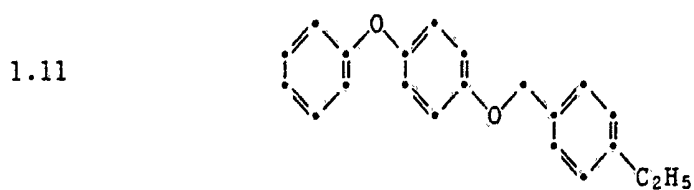
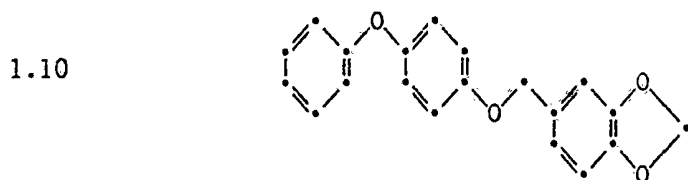
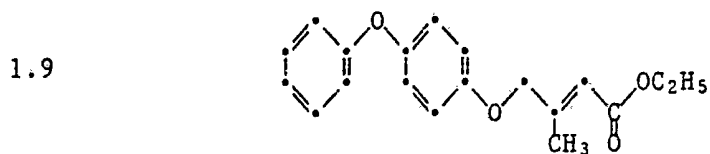
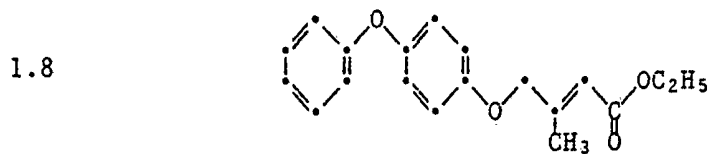
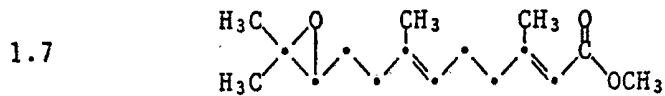
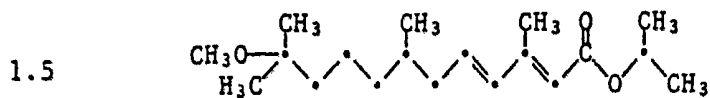
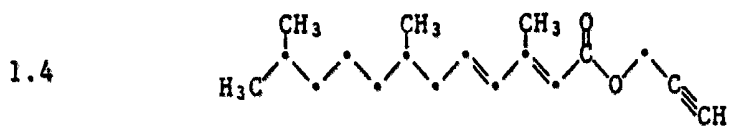
Animal No.	Dose (mg/kg/day)		Days post-treatment		
			+3	+8	+10
IP4	0 (control)	eggs	532	367	143
		pupae	358	288	127
		fleas hatched	313	244	127
IP7	0 (control)	eggs	1070	542	306
		pupae	553	451	246
		fleas hatched	368	403	221
IP3	3	eggs	118	75	34
		pupae	35	14	12
		fleas hatched	35	9	10
IP5	3	eggs	446	278	157
		pupae	221	179	126
		fleas hatched	220	164	120
IP2	5	eggs	315	120	66
		pupae	0	0	1
		fleas hatched	0	0	0
IP11	5	eggs	190	13	11
		pupae	0	0	2
		fleas hatched	0	0	0

Identical results were found, when the compound No. 2.5 was used as active ingredient.

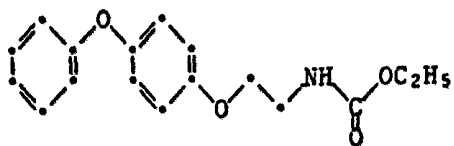
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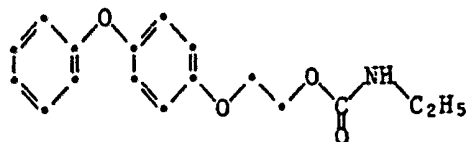




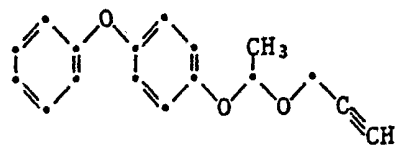
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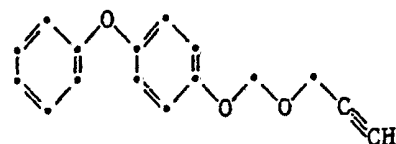
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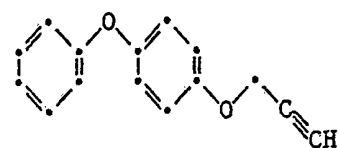
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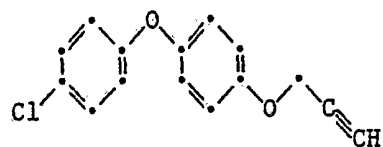
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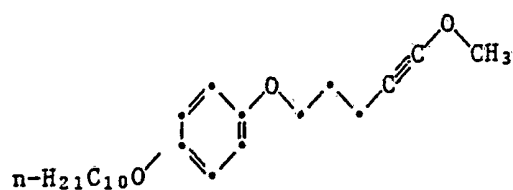
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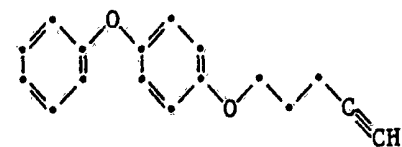
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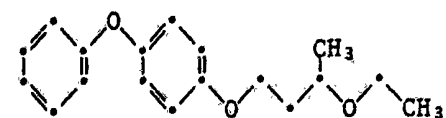
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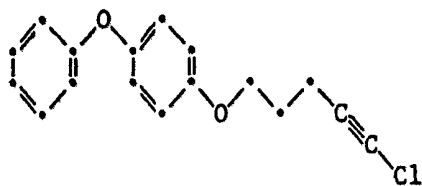
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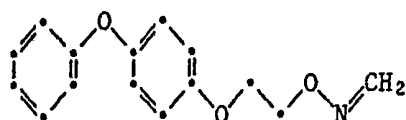
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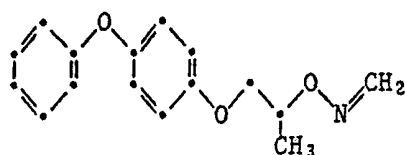
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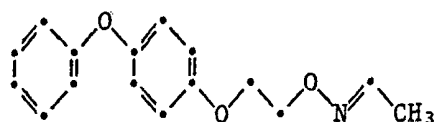
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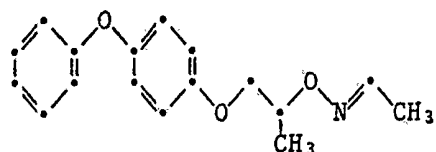


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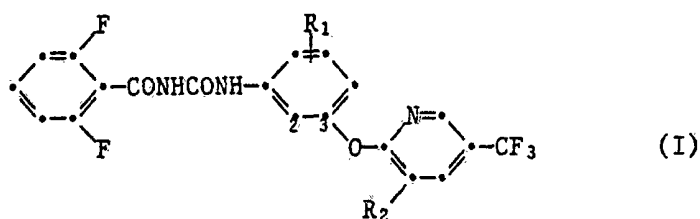


and

1.26



3. The method according to claim 1, wherein the flea growth inhibiting benzoylurea derivative is a compound of the formula I



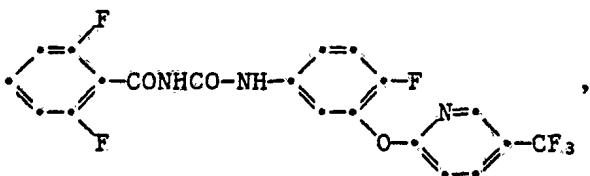
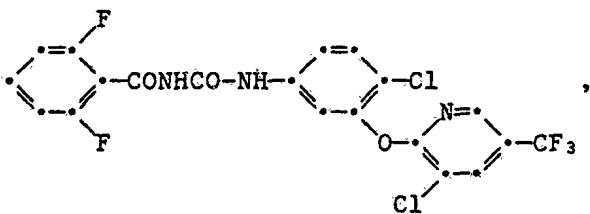
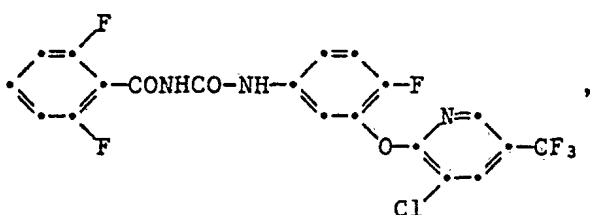
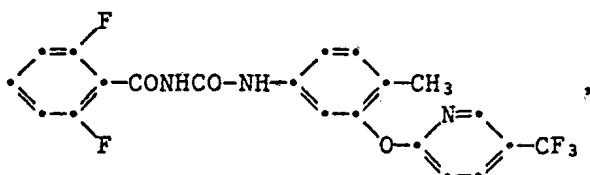
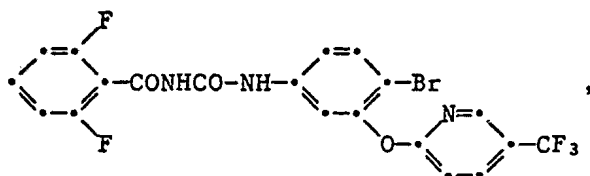
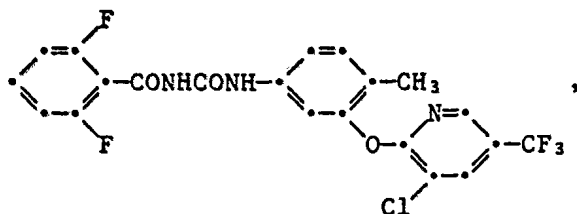
wherein

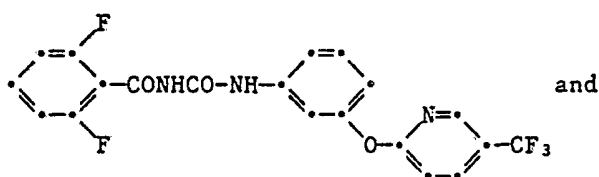
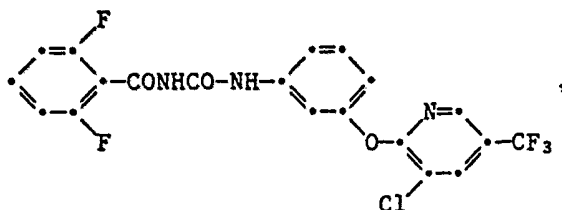
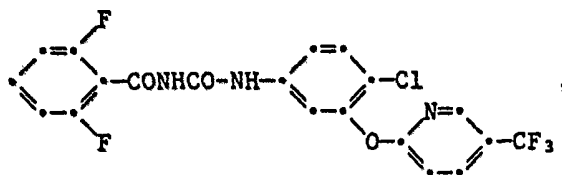
R₁ is hydrogen, halogen or methyl; and

R₂ is hydrogen or halogen.

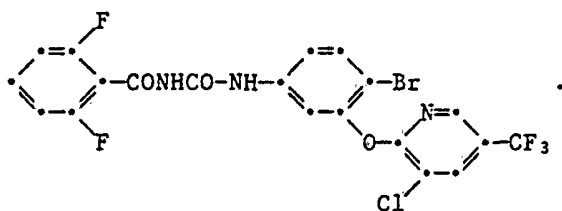


4. The method according to claim 3, wherein the flea growth inhibiting benzoylurea derivative of the formula I is a compound selected from the group consisting of

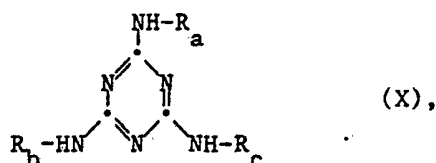




and



5. The method according to claim 1, wherein the flea growth inhibiting triazine derivative is a compound of the formula X



wherein

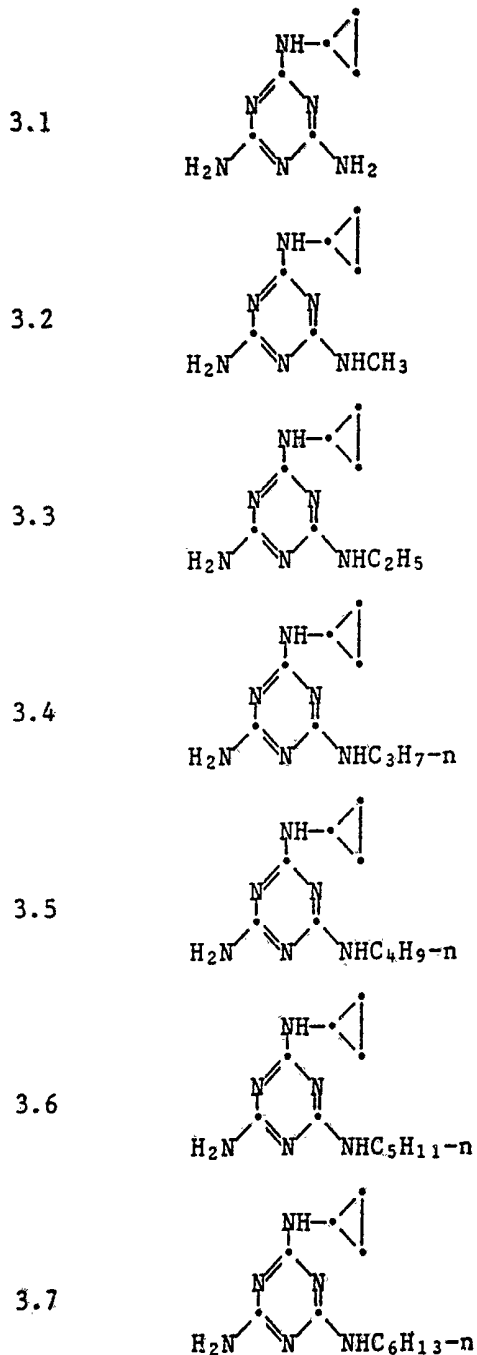
R_a is cyclopropyl or isopropyl;

R_b is hydrogen, halogen, C_1 - C_{12} alkylcarbonyl, cyclopropylcarbonyl, C_1 - C_{12} alkylcarbamoyl, C_1 - C_{12} alkylthiocarbamoyl or C_2 - C_6 alkenylcarbamoyl; and

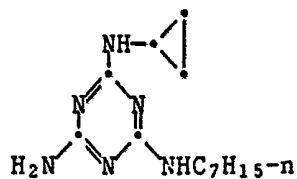
R_c is hydrogen, C_1 - C_{12} alkyl, cyclopropyl, C_2 - C_6 alkenyl, C_1 - C_{12} alkylcarbonyl, cyclopropylcarbonyl, C_1 - C_{12} alkylcarbamoyl, C_1 - C_{12} alkylthiocarbamoyl or C_2 - C_6 alkenylcarbamoyl, and the acid addition salts thereof which are non-toxic for warm-blooded animals.



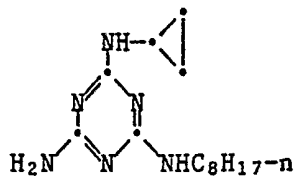
6. The method according to claim 5, wherein the flea growth inhibiting triazine derivative of the formula X is a compound selected from the group consisting of



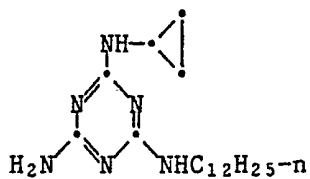
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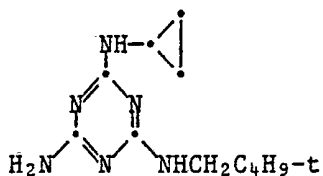
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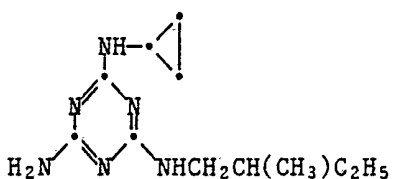
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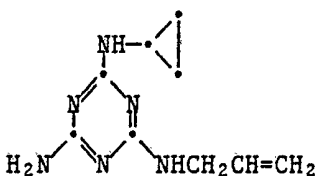
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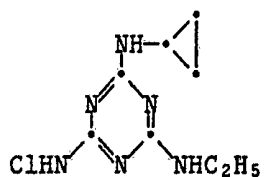
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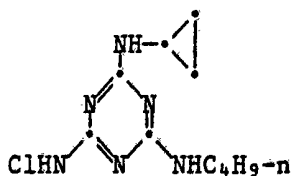
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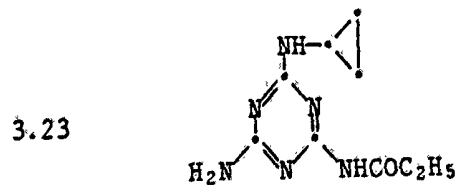
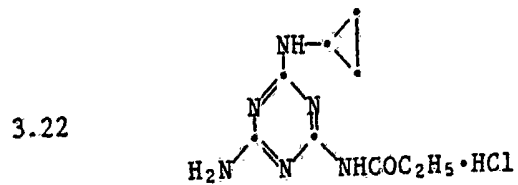
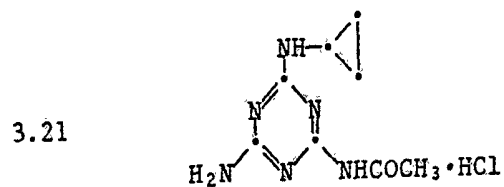
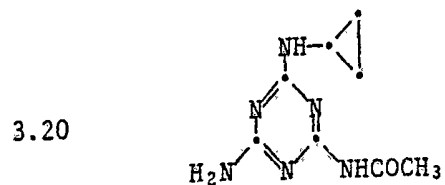
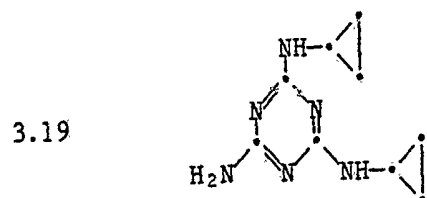
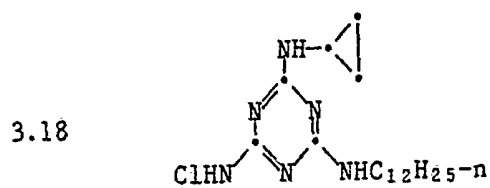
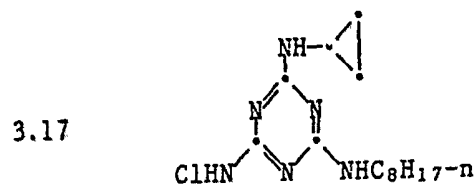
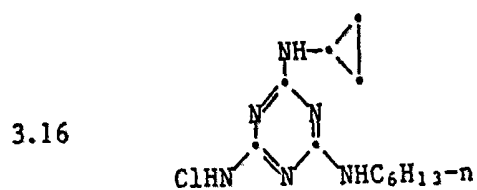


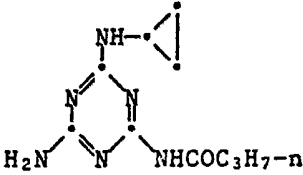
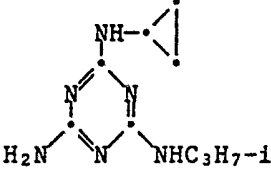
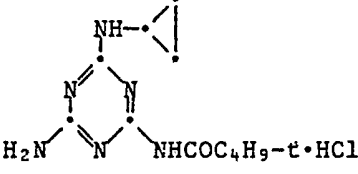
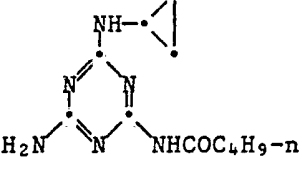
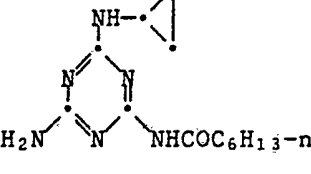
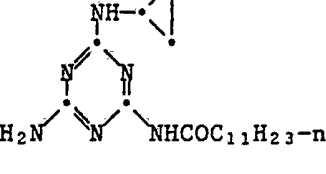
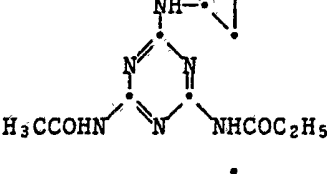
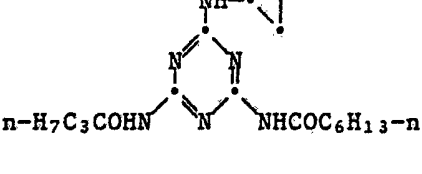
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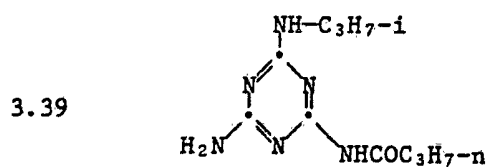
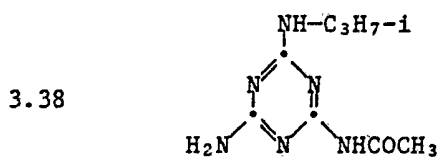
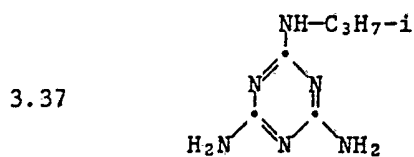
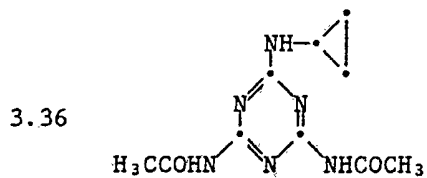
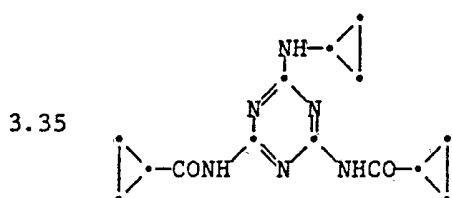
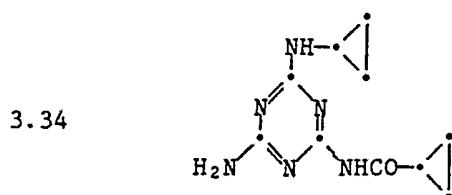
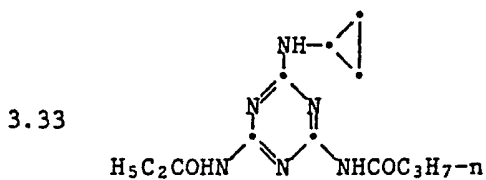
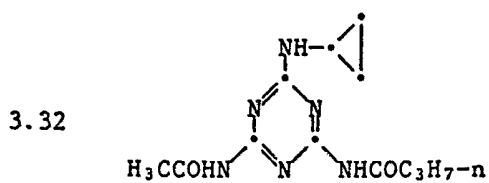
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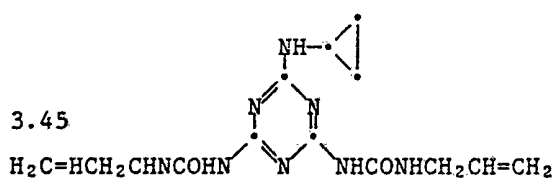
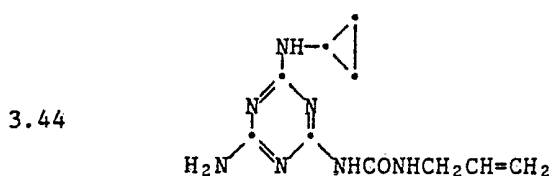
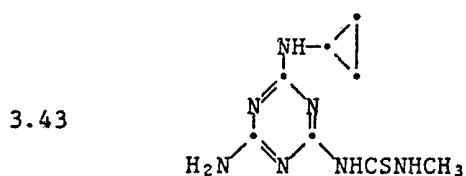
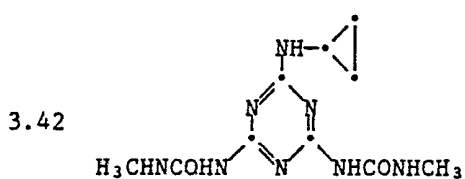
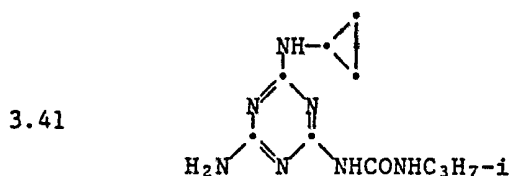
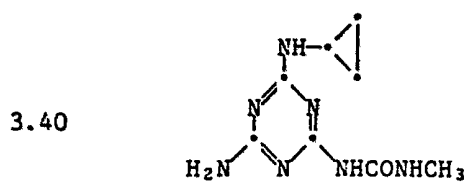




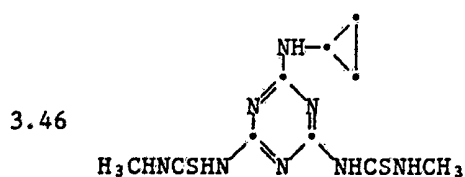
- 3.24 
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- 3.25 
Nc1nc(NC(=O)CC)c2nc3[nH]cnc3n21
- 3.26 
Nc1nc(NC(=O)C(C)(C)C)c2nc3[nH]cnc3n21.Cl
- 3.27 
Nc1nc(NC(=O)CCC)c2nc3[nH]cnc3n21
- 3.28 
Nc1nc(NC(=O)CCCCC)c2nc3[nH]cnc3n21
- 3.29 
Nc1nc(NC(=O)CCCCCCCCC)c2nc3[nH]cnc3n21
- 3.30 
CC(=O)Nc1nc(NC(=O)CC)c2nc3[nH]cnc3n21
- 3.31 
CCCCCNC(=O)c1nc(NC(=O)CC)c2nc3[nH]cnc3n21







and



7. The method according to claim 6, wherein the triazine derivative is N-cyclopropyl-1,3,5-triazine-2,4,6-triamine.



8. The method according to claim 1, wherein the active ingredient is administered to the host animal at a dose level of from 0,01 mg/kg of animal body weight to 800 mg/kg of animal body weight.

9. The method according to claim 8, wherein the active ingredient is administered to the host animal at a dose level of from 0,5 mg/kg of animal body weight to 200 mg/kg of animal body weight.

10. The method according to claim 8, wherein the active ingredient is administered to the host animal at a dose level of from 1 mg/kg of animal body weight to 30 mg/kg of animal body weight.

11. The method according to claim 8, wherein the active ingredient is administered orally.

12. The method according to claim 8, wherein a regularly repeated dose is administered to the host animal at a dosage level of from 0.01 mg/kg of animal body weight to 100 mg/kg of animal body weight

13. A method of preventing the propagation of fleas, comprising the administration of a larvicidally effective amount of a flea growth inhibiting substance selected from one of the classes consisting of

a) a juvenile insect hormone or a chemical analogue thereof,
or

b) a flea growth inhibiting benzoylurea derivative,
or

c) a flea growth inhibiting triazine derivative
to a dog or a cat and letting fleas feed thereon.

14. Dog food or cat food for preventing the reinfestation of dogs and cats by fleas comprising a larvicidally or ovidically effective amount of a flea growth inhibiting substance selected from one of the classes consisting of

a) a juvenile insect hormone or a chemical analogue thereof,
or

b) a flea growth inhibiting benzoylurea derivative,
or

c) a flea growth inhibiting triazine derivative.

15. The food according to claim 14, wherein the active ingredient is N-cyclopropyl-1,3,5-triazine-2,4,6-triamine.



16. A method of systematically preventing the reinfestation of dogs and cats by fleas, substantially as hereinbefore described with reference to Example 9.

17. A method of preventing the propagation of fleas, substantially as hereinbefore described with reference to Example 9.

18. A method of systematically preventing the reinfestation of dogs and cats by fleas, which method comprises administering to said host animals orally, parenterally or by implant a larvicidally effective amount of a composition according to any one of Examples 1 to 8.

19. A method of preventing the propagation of fleas, comprising the administration of a larvicidally effective amount of a flea growth inhibiting composition according to any one of Examples 1 to 8 to a dog or a cat and letting fleas feed thereon.

DATED this TWELFTH day of OCTOBER 1990
Ciba-Geigy AG

Patent Attorneys for the Applicant
SPRUSON & FERGUSON



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