G. H LLMANN RESTREPO
ABOGADOS LTDA.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. 00091998
Solicitud de patente.
Solicitante: Aventis CropScience GmbH.

Yo, GUSTAVO HOLLMANN RESTREPO, vecino de Bogotá, D.C., portador de la tarjeta profesional No. 5903, digo a usted que acompaño al presente memorial copia certificada de la solicitud de patente Estadunidense No. 60/168,658 presentada en Estados Unidos el 2 de diciembre de 1999, con la correspondiente traducción al castellano hasta del capítulo reivindicatorio, para que sea agregada al expediente de la referencia.

Señor Superintendente,

GUSTAVO HOLLMANN RESTREPO
C.C. No. 2.878.023 de Bogotá
T.P. No. 5903

mm.

CARRERA 11A No. 94-76 OF. 308 - TELS: 616 1425 - 616 1948 - 616 1935 - 616 1961 FAX: 616 3976 A. AEREO 3830
CABLES HOLLMANN - BOGOTA

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A TODOS CUANTOS LAS PRESENTES VIEREN:

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Diciembre 18 del 2000

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NUMERO DE SOLICITUD: 60/168,658

FECHA DE PRESENTACION: Diciembre 2 de 1999

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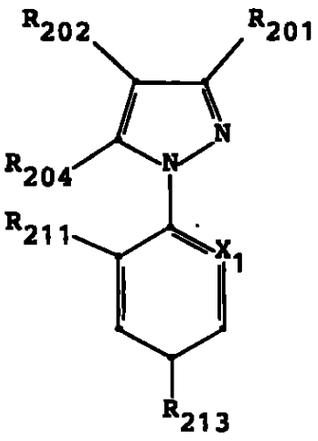
Reivindicaciones de patente:

1. Esta invención proporciona un método para controlar los parásitos presentes en un animal, método el cual comprende administrar oralmente al animal una cantidad parasiticidamente efectiva y substancialmente no-emética de un 1-arilpirazol de la fórmula I:



(I)

(XX)

en donde

R_{201} es ciano, C(O)alquilo, $C(S)NH_2$, alquilo, $C(=NOH)NH_2$ o $C(=NNH_2)NH_2$;

R_{202} es $S(O)_hR_{203}$, C_1-C_3-alquenilo, C_1-C_3-haloalquenilo, cicloalquilo, halocicloalquilo o C_1-C_3-alquinilo;

R_{203} es alquilo o haloalquilo;

R_{204} es -OH, $R_{205}O$-, HC(O)O-, $R_{205}C(O)O$-, $R_{205}OC(O)O$-, $NH_2C(O)O$-, $R_{205}NHC(O)O$-, $R_{205}R_{206}NC(O)O$-, $R_{205}S(O)_nC(O)O$;

R_{205} es alquilo, haloalquilo, cicloalquilo, halocicloalquilo, alcoxialquilo, haloalcoxialquilo, aminoalquilo, alquilaminoalquilo, dialquilaminoalquilo, haloalquilaminoalquilo, di(haloalquil)aminoalquilo;

R_{206} es alquilo, haloalquilo, cicloalquilo, halocicloalquilo, alcoxialquilo, haloalcoxialquilo;

o bien R_{205} y R_{206} pueden formar conjuntamente con el nitrógeno al cual están enlazados un anillo de 3 a 7 miembros que adicionalmente puede contener uno o varios heteroátomos seleccionados entre nitrógeno, oxígeno y azufre;

X_1 se selecciona entre nitrógeno y C-R_{212};

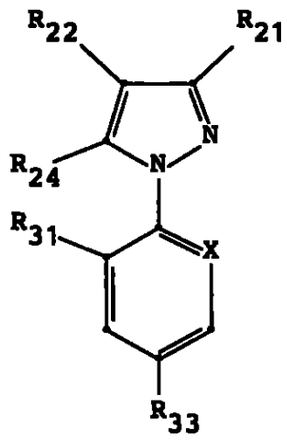
R_{211} y R_{212} son seleccionados independientemente entre halógeno hidrógeno, CN y NO_2;

R_{213} se selecciona entre halógeno, haloalquilo, -$S(O)_kCF_3$ y -SF_5; y

h, k y n son seleccionados independientemente entre 0, 1 y 2;

y sus sales veterinariamente aceptables.

2. Un método para controlar los parásitos presentes en un animal administrándole al animal un 1-arilpirazol de la fórmula II:



(II)

en donde

R_{21} es ciano, $C(=S)NH_2$, $C(=NOH)NH_2$ o $C(=NNH_2)NH_2$;

R_{22} es $S(O)_mR_{23}$;

R_{23} es alquilo o haloalquilo;

R_{24} es OH, HC(O)O-, $R_{25}C(O)O$-, $R_{25}OC(O)O$- o $R_{205}S(O)_nC(O)O$-;

R_{25} es alquilo, haloalquilo, cicloalquilo, halocicloalquilo, alcoxialquilo, haloalcoxialquilo;

X se selecciona entre nitrógeno y C-R_{32};

R_{31} y R_{32} son seleccionados independientemente entre halógeno, hidrógeno, CN y NO_2;

R_{33} se selecciona entre halógeno, haloalquilo, haloalcoxi, -$S(O)_r$-CF_3 y -SF_5;

m es 0, 1 o 2;

r se selecciona entre 0, 1 y 2;

y sus sales veterinariamente aceptables.

3. Un compuesto de la fórmula II o una sal de éste tal como se describió en la reivindicación 2 con la condición de que el compuesto no sea 1-(2,6-dicloro-4-trifluorometilfenil)-3-ciano-4-trifluorometiltio-5-hidropirazol.

4. Un compuesto de acuerdo con la reivindicación 3, en el que R_{21} es ciano; R_{22} es $S(O)_mR_{23}$; R_{23} es haloalquilo, preferentemente CF_3; R_{24} es OH; X se selecciona entre nitrógeno y $C\text{-}R_{32}$; R_{31} y R_{32} son seleccionados independientemente entre halógeno; R_{33} se selecciona entre halógeno, haloalquilo, haloalcoxi, $-S(O)_rCF_3$ y $-SF_5$; m y r son seleccionados independientemente entre 0, 1 y 2.

5. El compuesto de lafórmula I tal como se definió en la reivindicación 1 o el compuesto de la fórmula II tal como se definió en cualquiera de las reivindicaciones 2, 3 o 4 que es 1-(2,6-dicloro-4-trifluorometilfenil)-3-ciano-4-trifluorometilsulfinil-5-hidroxipirazol.

6. El compuesto de la fórmula I tal como se definió en la reivindicación 1 o el compuesto de la fórmula II tal como se definió en cualquiera de las reivindicaciones 2, 3 o 4 que es 1-(2,6-dicloro-4-trifluorometilfenil)-3-ciano-4-trifluorometilsulfonilo-5-hidroxipirazol.

7. Una composición que comprende una cantidad parasiticidamente efectiva y substancialmente no-emética de un compuesto de la fórmula I o de la fórmula II o una sal de éstos tal como se definió en cualquiera de las anteriores reivindicaciones y un vehículo aceptable.

8. Una composición que comprende una cantidad parasiticidamente efectiva de un compuesto de la fórmula II o una sal de éste y un vehículo aceptable tal como se definió en cualquiera de las reivindicaciones 2, 3, 4, 5 o 6.

9. El método de acuerdo con cualquiera de las reivindicaciones 1 o 2, en el cual el animal es un animal doméstico, preferentemente un perro o un gato.

10. El método de acuerdo con la reivindicación 1, en el cual el 1-arilpirazol se administra oralmente en una dosis al animal en un margen de dosis generalmente de 0,1 hasta 500 mg/kg.

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THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

December 18, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/168,658***
FILING DATE: ***December 02, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. Lawrence

T. LAWRENCE
Certifying Officer

PTO/SB/16 (11-95)
Approved for use through 01/31/98. OMB 0651-0037
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Docket Number	022650-610	Type a plus sign (+) inside this box → +

INVENTOR(s)/APPLICANT(s)

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TITLE OF THE INVENTION (280 characters max)

Control of Arthropods in Animals

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ENCLOSED APPLICATION PARTS *(check all that apply)*

- [X] Specification — *Number of Pages* 17
- [ ] Drawing(s) — *Number of Sheets* _____
- [ ] Small Entity Statement
- [X] Other (specify) — Claims & Abstract 5pgs.

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

[ ] A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT(S)	$150.00
[X] The Commissioner is hereby authorized to charge any deficiency in filing fees or credit any overpayment to Deposit Account Number 02-4800. This paper is submitted in triplicate.		

21839

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE Allen R. Baum Date December 2, 1999

TYPED or PRINTED NAME Allen R. Baum Registration No. 36,086 *(if appropriate)*

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21839

Control of Arthropods in Animals

The present invention relates to a method of control of parasites in animals, compositions comprising a compound effective for the said control and new compounds effective against parasites.

It is generally a goal of agronomists and veterinarians to possess sufficient means to control pests, particularly arthropods, when they attempt to invade or attack mammals, particularly domestic animals and/or livestock. A classical method of controlling such pests has been the use of topical and/or systemic pesticides on or in the domestic animal which is being attacked. Generally effective treatments include the oral administration of insect growth regulators, such as lufenuron, or anthelminth compounds such as an ivermectin or an avermectin, or the topical application of the insecticide fipronil. It is advantageous to apply pesticides to animals in oral form so as to prevent the possible contamination of humans or the surrounding environment.

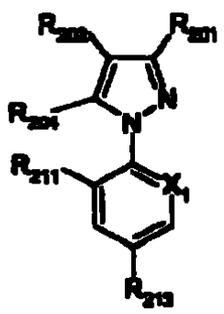
It is an object of the present invention to provide new pesticides which may be used in domestic animals.

Another object of the invention is to provide safer pesticides for domestic animals.

Another object of the invention is to provide new pesticides for domestic animals that may be used in lower doses than existing pesticides.

These objects are met in whole or in part by the present invention.

The present invention provides a method of controlling parasites in or on an animal comprising administering orally to the animal a parasiticidally effective, substantially non-emetic amount of a 1-arylpyrazole of formula (I):



(XX)

wherein:

R_{201} is cyano, C(O)alkyl, $C(S)NH_2$, alkyl, $C(=NOH)NH_2$ or $C(=NNH_2)NH_2$;

R_{202} is $S(O)_nR_{203}$, C_1-C_3 alkenyl, C_1-C_3 haloalkenyl, cycloalkyl, halocycloalkyl or C_1-C_3 alkynyl;

R_{203} is alkyl or haloalkyl;

R_{204} is -OH, $R_{205}O$-, HC(O)O-, $R_{205}C(O)O$-, $R_{205}OC(O)O$-, $NH_2C(O)O$-, $R_{205}NHC(O)O$-, $R_{205}R_{206}NC(O)O$-, $R_{205}S(O)_nC(O)O$-;

R_{205} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkylaminoalkyl, di(haloalkyl)aminoalkyl;

R_{206} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl;

or R_{205} and R_{206} may form together with the nitrogen to which they are attached a 3 to 7 membered ring which additionally may contain one or more heteroatoms selected from nitrogen, oxygen and sulfur;

X_1 is selected from nitrogen and C-R_{212};

R_{211} and R_{212} are independently selected from halogen, hydrogen, CN and NO_2;

R_{213} is selected from halogen, haloalkyl, haloalkoxy, $-S(O)_kCF_3$, and $-SF_5$; and

h, k and n are independently selected from 0, 1, and 2;

and veterinarily acceptable salts thereof.

By the term "veterinarily acceptable salts" is meant salts the anions of which are known and accepted in the art for the formation of salts for veterinary use. Suitable acid addition salts, e.g. formed by compounds of formula (I) containing a basic nitrogen atom, e.g. an amino group, include salts with inorganic acids, for example hydrochlorides, sulphates, phosphates and nitrates and salts with organic acids for example acetic acid.

Unless otherwise specified, alkyl and alkoxy groups are generally lower alkyl and alkoxy groups, that is having from one to six carbon atoms, preferably from one to four carbon atoms. Generally, the haloalkyl, haloalkoxy and haloalkylamino groups have from one to four carbon atoms. The haloalkyl and haloalkoxy and haloalkylamino groups can bear one or more halogen atoms; preferred groups of this type include $-CF_3$ and $-OCF_3$. Cycloalkyl groups generally have from 3 to 6 carbon atoms, preferably from 3 to 5 carbon atoms and may be substituted by one or more halogen atoms. Preferably in compounds of formula (I), alkyl groups are generally substituted by from one to five halogen atoms, preferably from one to three halogen atoms. Chlorine and fluorine atoms are preferred.

In compounds of formula (I) the following examples of radicals are provided:

An example of cycloalkylalkyl is cyclopropylmethyl;

an example of cycloalkoxy is cyclopropyloxy;and

an example of alkoxyalkyl is CH_3OCH_2-.

Generally, in dialkylamino or di(haloalkyl)amino radicals, the alkyl and haloalkyl groups on nitrogen may be chosen independently of one another.

It is also to be understood that enantiomeric and diastereomeric forms of the compounds of formulae (I) and salts thereof are embraced by the present invention.

By the term non-emetic is meant a compound that does not generally elicit emesis from the animal when a protective, preventative or cleaning dose is administered to the animal. By the term emesis is meant vomiting. Generally an emetic substance elicits the said emesis in less than 24 hours after administration, preferably less than 8 hours, more preferably less than 2 hours. Generally when the compounds of the invention are administered to a population of animals, more than 70% of the animals are free of emesis, preferably more than 80%, most preferably more than 90%.

Compounds of formula (I) which are preferred according to the present invention are those wherein:

wherein:

R_{201} is cyano;

R_{202} is $S(O)_hR_{203}$;

R_{203} is alkyl or haloalkyl;

R_{204} is OH or $R_{205}O$,

X_1 is selected from nitrogen and C-R_{212};

R_{211} and R_{212} are independently selected from halogen, hydrogen, CN and NO_2;

R_{213} is selected from halogen, haloalkyl, haloalkoxy, $-S(O)_kCF_3$, and $-SF_5$; and

h and k are independently selected from 0, 1, and 2.

The compounds of formula (I) of the present invention preferably have one or more of the following features:

R_{201} is cyano;

R_{203} is haloalkyl, preferably CF_3;

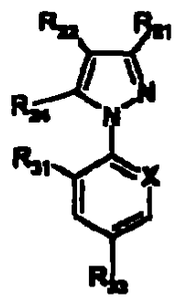
R_{211} and R_{212} are independently halogen;

X_1 is C-R_{212};

R_{213} is haloalkyl, haloalkoxy or -SF_5; or

h is 0 or 1, or 2.

In another aspect of the present invention there is provided a method of controlling parasites in or on an animal by administering to the animal an 1-arylpyrazole of formula (II):



(II)

wherein:

R_{21} is cyano, C(=S)NH_2, C(=NOH)NH_2 or C(=NNH_2)NH_2;

R_{22} is $S(O)_{m}R_{23}$;

R_{23} is alkyl or haloalkyl;

R_{24} is OH, HC(O)O-, R_{25}C(O)O-, R_{25}OC(O)O-, or R_{205}S(O)$_2$C(O)O-

R_{25} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl;

X is selected from nitrogen and C-R_{32};

R_{31} and R_{32} are independently selected from halogen, hydrogen, CN and NO_2;

R_{33} is selected from halogen, haloalkyl, haloalkoxy, $-S(O)_rCF_3$, and $-SF_5$;

m is 0, 1 or 2;

r is selected from 0, 1, and 2;

and veterinarily acceptable salts thereof.

In another aspect of the present invention there is provided a compound of formula (II) or salt there of as hereinbefore described with the proviso that the compound is not 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylthio-5-hydroxypyrazole.

A further class of novel compounds of formula (II) are those wherein:

R_{21} is cyano;

R_{22} is $S(O)_mR_{23}$;

R_{23} is haloalkyl, preferably CF_3;

R_{24} is OH;

X is selected from nitrogen and C-R_{32};

R_{31} and R_{32} are independently selected from halogen,

R_{33} is selected from halogen, haloalkyl, haloalkoxy, $-S(O)_rCF_3$, and $-SF_5$;

m and r are independently selected from 0, 1, and 2

with the proviso that the compound is not 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylthio-5-hydroxypyrazole.

The compounds 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfinyl-5-hydroxypyrazole and 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfinyl-5-hydroxypyrazole are highly preferred compounds according to the invention.

The following compounds of formula (I) are preferred according to the present invention as listed in Tables 1 to 3. The Compound Numbers are for identification purposes only. The following symbols are hereby defined: Me means methyl; Et means ethyl; n-Pr means n-propyl; i-Pr means isopropyl; and n-Bu means n-Butyl.

Table 1

Compounds of formula (I) wherein R_{201} is cyano; R_{202} is SCF_3; R_{211} is Cl, X_1 is C-Cl, and R_{213} is CF_3 or SF_5.

Compound Number (R_{213}= CF_3)	Compound Number (R_{213}=SF_5)	R_{204}
1-1	1-2	OH
2-1	2-2	OMe
3-1	3-2	OEt
4-1	4-2	OPr
5-1	5-2	O-i-Pr
6-1	6-2	O-n-Bu
7-1	7-2	OCH_2OMe
8-1	8-2	OCH_2CH_2OMe
9-1	9-2	OCH_2OEt
10-1	10-2	OCH_2CH_2OEt
11-1	11-2	OC(O)Me
12-1	12-2	OC(O)Et
13-1	13-2	OC(O)n-Pr
14-1	14-2	OC(O)H
15-1	15-2	$OC(O)NH_2$
16-1	16-2	OC(O)NHMe
17-1	17-2	OC(O)NHEt
18-1	18-2	OC(O)NHnPr
19-1	19-2	$OC(O)NMe_2$

Table 2

Compounds of formula (I) wherein R_{201} is cyano; R_{202} is $SOCF_3$; R_{211} is Cl, X_1 is C-Cl, and R_{213} is CF_3 or SF_5.

Compound Number (R_{213}= CF_3)	Compound Number (R_{213}=SF_5)	R_{204}
1-3	1-4	OH
2-3	2-4	OMe
3-3	3-4	OEt
4-3	4-4	OPr
5-3	5-4	O-i-Pr
6-3	6-4	O-n-Bu
7-3	7-4	OCH_2OMe
8-3	8-4	OCH_2CH_2OMe
9-3	9-4	OCH_2OEt
10-3	10-4	OCH_2CH_2OEt
11-3	11-4	OC(O)Me
12-3	12-4	OC(O)Et
13-3	13-4	OC(O)n-Pr
14-3	14-4	OC(O)H
15-3	15-4	$OC(O)NH_2$
16-3	16-4	OC(O)NHMe
17-3	17-4	OC(O)NHEt
18-3	18-4	OC(O)NHnPr
19-3	19-4	$OC(O)NMe_2$

Table 3

Compounds of formula (I) wherein R_{201} is cyano; R_{202} is SO_2CF_3; R_{211} is Cl, X_1 is C-Cl, and R_{213} is CF_3 or SF_5.

Compound Number (R_{213}= CF_3)	Compound Number (R_{213}=SF_5)	R_{204}
1-5	1-6	OH
2-5	2-6	OMe
3-5	3-6	OEt
4-5	4-6	OPr
5-5	5-6	O-i-Pr
6-5	6-6	O-n-Bu
7-5	7-6	OCH_2OMe
8-5	8-6	OCH_2CH_2OMe
9-5	9-6	OCH_2OEt

10-5	10-6	OCH_2CH_2OEt
11-5	11-6	OC(O)Me
12-5	12-6	OC(O)Et
13-5	13-6	OC(O)n-Pr
14-5	14-6	OC(O)H
15-5	15-6	$OC(O)NH_2$
16-5	16-6	OC(O)NHMe
17-5	17-6	OC(O)NHEt
18-5	18-6	OC(O)NHnPr
19-5	19-6	$OC(O)NMe_2$

The present invention also relates to a composition comprising a parasiticidally effective, substantially non-emetic amount of a compound of formula (I) or a salt thereof and an acceptable carrier. Acceptable carriers for the use of the compounds are generally known to the skilled addressee concerned with pest control in animals, particularly domestic animals, most preferably dogs or cats.

The compositions which can be used in the invention can comprise generally from about 0.001 to 95% of the compound of formula (I) or a salt thereof. The remainder of the composition up to 100% comprises a carrier as well as generally various additives. In this specification and the accompanying claims, percentages are by weight.

The diluted liquid formulations generally comprise from about 0.001 to about 3% of compound of formula (I) or a salt thereof, preferably from about 0.1 to about 0.5%.

Solid formulations generally comprise from about 0.1 to about 8% of compound of formula (I) or a salt thereof, preferably from about 0.5 to about 1.5%.

Compositions for oral administration comprise one or more of the compounds of general formula (I) or salts thereof in association with veterinarily acceptable carriers or coatings and include, for example, tablets, pills, capsules, gels, drenches, medicated feeds, medicated drinking water, medicated dietary supplements, slow-release boluses or other slow-release devices intended to be retained within the gastro-

intestinal tract. Any of these may incorporate the active ingredients contained within micro-capsules or coated with acid-labile or alkali-labile or other pharmaceutically acceptable enteric coatings. Feed premixes or concentrates containing compounds of the present invention for use in preparation of medicated diets, drinking water or other materials for consumption by animals may also be used. In a highly preferred embodiment, the compositions are administered postprandially, preferably from just after a meal to 2 hours after the meal.

In a highly preferred embodiment, there is provided a product which is readily chewed by the animal and which product does generally not allow human contamination when the product is provided to the animal by hand.

The compounds of general formula (I) or salts thereof may be administered before, during or after meals The compounds of general formula (I) or salts thereof may be mixed with a carrier and/or a foodstuff.

According to the present invention the compound of formula (I) or a salt thereof is administered orally in a dose to the animal in a dose range generally from 0.1 to 500 mg/kg of the compound of formula (I) or a salt thereof per kilogram of animal body weight (mg/kg), preferably from 1 to 100 mg/kg, more preferably from 1 to 50 mg/kg, even more preferably from 2 to 25 mg/kg, most preferably from 3 to 15 mg/kg

According to the present invention, the frequency of treatment of the animal, preferably the domestic animal to be treated by the compound of formula (I) or a salt thereof is generally from about once per week to about once per year, preferably from about once every two weeks to about once every six months, more preferably from about once every two weeks to once every three months, and most preferably from about once every two weeks to about once every six weeks.

Generally the animal to be treated is a domestic animal, preferably a domestic companion animal. More preferably the animal to be treated is a dog and/or a cat.

The present invention also relates to a composition comprising a parasiticidally effective amount of a compound of formula (II) or a salt thereof and an acceptable carrier. Acceptable carriers for the use of the compounds are generally known to the skilled addressee concerned with pest control in animals, particularly domestic animals, most preferably dogs or cats.

In another aspect of the present invention, the compounds of formula (II) or salts thereof may be used in the field of veterinary medicine or livestock husbandry or in the maintenance of public health against arthropods, helminths or protozoa which are parasitic internally or externally upon vertebrates, particularly warm-blooded vertebrates, for example domestic animals, e.g. cattle, sheep, goats, equines, swine, poultry, dogs or cats.

The compounds to animals infested by or exposed to infestation by arthropods, helminths or protozoa, by parenteral, oral or topical application of compositions in which the active ingredient exhibits an immediate and/or prolonged action over a period of time against the arthropods, helminths or protozoa, for example by incorporation in feed or suitable orally-ingestible pharmaceutical formulations, edible baits, salt licks, dietary supplements, pour-on formulations, sprays, baths, dips, showers, jets, dusts, greases, shampoos, creams, wax smears or livestock self-treatment systems.

Solid or liquid compositions for application topically to animals, timber, stored products or household goods usually contain from about 0.00005% to about 90%, more particularly from about 0.001% to about 10%, by weight of one or more compounds of formula (II) or veterinarily acceptable salts thereof. For administration to animals

orally or parenterally, including percutaneously solid or liquid compositions, these normally contain from about 0.1% to about 90% by weight of one or more compounds of formula (II) or veterinarily acceptable salts thereof. Medicated feedstuffs normally contain from about 0.001% to about 3% by weight of one or more compounds of formula (II) or veterinarily acceptable salts thereof. Concentrates or supplements for mixing with feedstuffs normally contain from about 5% to about 90%, preferably from about 5% to about 50%, by weight of one or more compounds of formula (II) or veterinarily acceptable salts thereof. Mineral salt licks normally contain from about 0.1% to about 10% by weight of one or more compounds of formula (II) or veterinarily acceptable salts thereof.

Dusts or liquid compositions for application to livestock, goods, premises or outdoor areas may contain from about 0.0001% to about 15%, more especially from about 0.005% to about 2.0%, by weight, of one or more compounds of formula (II) or veterinarily acceptable salts thereof. Suitable concentrations in treated waters are between about 0.0001 ppm and about 20 ppm, more particularly about 0.001 ppm to about 5.0 ppm. of one or more compounds of formula (II), or veterinarily acceptable salts thereof, and may be used therapeutically in fish farming with appropriate exposure times. Edible baits may contain from about 0.01% to about 5%, preferably from about 0.01% to about 1.0%, by weight, of one or more compounds of formula (II) or veterinarily acceptable salts thereof.

When administered to vertebrates parenterally, orally or by percutaneous or other means, the dosage of compounds of formula (II), or veterinarily acceptable salts thereof, will depend upon the species, age, or health of the vertebrate and upon the nature and degree of its actual or potential infestation by arthropod, helminth or protozoan pests. A single dose of about 0.1 to about 500, preferably from 0.1 to about 100 mg, preferably about 2.0 to about 20.0 mg, per kg body weight of

the animal or doses of about 0.01 to about 20.0 mg, preferably about 0.1 to about 5.0 mg, per kg body weight of the animal per day, for sustained medication, are generally suitable by oral or parenteral administration. By use of sustained release formulations or devices, the daily doses required over a period of months may be combined and administered to animals on a single occasion.

The compounds of the invention may be administered most advantageously with another parasiticidally effective material, such as an endoparasiticide, and/or an ectoparasiticide, and/or an endectoparasiticide. For example, such compounds include macrocyclic lactones such as avermectins or milbemycins e.g., ivermectin, pyrantel (generally administered as pyrantel pamoate) or an insect growth regulator such as lufenuron or methoprene.

By the term "parasites" as used in the specification and claims is meant endoparasites and ectoparasites of warm-blooded animals, particularly ectoparasites. Preferably, fleas and/or ticks are controlled by the method of the present invention.

Illustrative of specific parasites of various host animals which may be controlled by the methods of this invention include arthropods such as:

Mites: Mesostigmata spp. e.g. mesostigmatids such as the chicken mite, Dermanyssus gallinae; itch or mob mites such as Sarcoptidae spp. for example Sarcoptes scabiei; mange mites such as Psoroptidae spp. including Chorioptes bovis and Psoroptes ovis; chiggers e.g. Trombiculidae spp. for example the north american chigger, Trombicula alfreddugesi;

Ticks: e.g., soft-bodied ticks including Argasidae spp. for example Argas spp. and Ornithodoros spp ; hard-bodied ticks including Ixodidae spp., for example Rhipicephalus sanguineus, and Boophilus spp.;

Lice: sucking lice, e.g., Menopon spp. and Bovicola spp.; biting lice, e.g., Haematopinus spp., Linognathus spp. and Solenopotes spp.;

Fleas: e.g., Ctenocephalides spp., such as dog flea (Ctenocephalides canis) and cat flea (Ctenocephalides felis); Xenopsylla spp. such as oriental rat flea [Xenopsylla cheopis]; and Pulex spp. such as human flea [Pulex irritans];

True bugs: e.g., Cimicidae or including the common bed bug (Cimex lectularius);. Triatominae spp. including triatomid bugs also known as kissing bugs; for example Rhodnius prolixus and Triatoma spp.;

bloodsucking adult flies: (e.g., horn fly [Haematobia irritans], horse fly [Tabanus spp.], stable fly [Stomoxys calcitrans], black fly [Simulium spp.], deer fly [Chrysops spp.], louse fly [Melophagus ovinus], tsetse fly [Glossina spp.], mosquitoes [Culex spp., Anopheles spp., and Aedes spp.); and

parasitic fly maggots: (e.g., bot fly [Oestrus ovis and Cuterebra spp.], blow fly [Phaenicia spp.], screwworm [Cochliomyia hominivorax], cattle grub [Hypoderma spp.], fleeceworm.

The present invention also relates to a use of a compound of formula (I) or a salt thereof hereinbefore described as a therapeutic agent, preferably for animals, more preferably for domestic animals.

The veterinary composition may be sterile or non-sterile. It may be a liquid (e.g. aqueous) or solid (e.g., dry) composition, in particular a freeze-dried composition, which, by addition of water or another liquid, orally effective solutions may be prepared.

The present invention also relates to a use of a compound of formula (I) or a salt thereof as hereinbefore defined for the manufacture of a veterinary composition for the control of parasites in or on an animal.

The present invention also relates to a method of cleaning animals in good health comprising the application to the animal of a compound of formula (I) or a salt thereof as hereinbefore defined to the animal.

The method of cleaning an animal is not a method of treatment by therapy of the animal body per se, because

(a) the animal is in good health and requires no substantial treatment to correct a deficiency of health;

(b) the cleaning of the animal is not intended to be done by veterinary personnel, but by persons interested in the cleaning of the animal; and

(c) the purpose of such cleaning is to avoid unpleasant conditions for humans and the environment in which humans inhabit so as to not infest the said humans with arthropods carried by the animal.

By "carrier" is meant an organic or inorganic material, which can be natural or synthetic, and which is associated with the compound and which facilitates its application to the animal. This carrier is thus generally inert and should be arthropocidally acceptable. The carrier can be solid (e.g., clay, silicates, silica, resins, wax.) or liquid (e.g., water, alcohols, ketones, oil solvents, polar aprotic solvents) An example of an oil solvent is corn oil. An example of a polar aprotic solvent is dimethyl sulfoxide.

In another aspect of the present invention, compounds of formula (II) wherein R_{24} is $HC(O)O$-, $R_{25}C(O)O$-, $R_{25}OC(O)O$-, or $R_{25}S(O)_nC(O)O$ and R_{21}, R_{22}, R_{31}, R_{33}, X and n are defined above are generally prepared by reaction of compounds of formula (II) wherein R_{24} is OH and R_{21}, R_{22}, R_{31}, R_{33}, X and n are defined above with a compounds of formulas (III), (IV), (V), and (VI) respectively wherein X_a is a leaving group such as a halogen atom or an acetyl group:

$HC(O)X_3$ $R_{25}C(O)X_3$ $R_{25}OC(O)X_3$ $R_{25}S(O)_nC(O)X_3$

(III) (IV) (V) (VI)

Compounds of general formula (II) wherein of formula (II) wherein R_{24} is OH and R_{21}, R_{22}, R_{31}, R_{33}, X and n are defined above may be prepared by methods known in the art generally or by methods described in International Patent Publications WO 94/21606, WO 97/07102, WO 98/24767, WO 98/28277, WO 98/28278 and WO 98/28279, European Patent Application 385808, and United States Patent 5232940, 5047550 or other methods known to the person skilled in the art.

Biological Example

The compounds 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylthio-5-hydroxypyrazole, 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfinyl-5-hydroxypyrazole and 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfonyl-5-hydroxypyrazole are formulated as a 30 mg/mL formulations in a 1:1 volume/volume solution of dimethyl sulfoxide and corn oil. Using this formulation, mixed breed dogs and cats are treated at a rate of 10 mg of the compound per kg (mg/kg) of body weight of the dog and 20 mg/kg of the cat treated. The animals are fasted for at least 8 hours prior to treatment, fed half of the daily ration immediately prior to treatment, then allowed access to the remainder of the daily ration immediately following treatment.

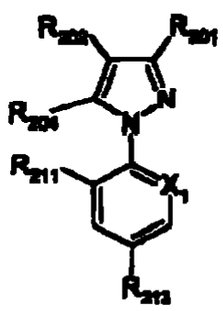
All dogs are infested with cat fleas (Ctenocephalides felis) and with ticks (Rhipicephalus sanguineus) 1 day prior to administration of the compound. Cats are only infested with fleas. The initial flea and tick

counts are performed 1 day after the administration of the compounds. At 7, 14, 21 and 28 days after treatment the dogs are re-infested with ticks and 8, 15, 22 and 29 days after treatment the dogs and cats are re-infested with fleas. At 1, 9, 16, 23 and 30 days after treatment the control of fleas and ticks in treated dogs and cats is determined versus a group of infested dogs and cats which receive a placebo consisting of a 1:1 volume/volume solution of dimethyl sulfoxide and corn oil. To determine the efficacies of the compounds, the arthropods are combed from the animals and counted.

Satisfactory results are obtained for the compounds used.

CLAIMS

1. The present invention provides a method of controlling parasites in or on an animal comprising administering orally to the animal a parasiticidally effective, substantially non-emetic amount of a 1-arylpyrazole of formula (I):



(XX)

wherein:

R_{201} is cyano, C(O)alkyl, $C(S)NH_2$, alkyl, $C(=NOH)NH_2$ or $C(=NNH_2)NH_2$;

R_{202} is $S(O)_tR_{203}$, C_1-C_6 alkenyl, C_1-C_3 haloalkenyl, cycloalkyl, halocycloalkyl or C_1-C_3 alkynyl;

R_{203} is alkyl or haloalkyl;

R_{204} is -OH, $R_{205}O$-, HC(O)O-, $R_{205}C(O)O$-, $R_{205}OC(O)O$-, $NH_2C(O)O$-, $R_{205}NHC(O)O$-, $R_{205}R_{206}NC(O)O$-, $R_{205}S(O)_tC(O)O$-;

R_{205} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkylaminoalkyl, di(haloalkyl)aminoalkyl;

R_{206} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl;

or R_{205} and R_{206} may form together with the nitrogen to which they are attached a 3 to 7 membered ring which additionally may contain one or more heteroatoms selected from nitrogen, oxygen and sulfur;

X_1 is selected from nitrogen and C-R_{212};

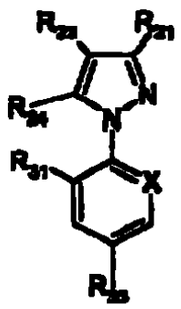
R_{211} and R_{212} are independently selected from halogen, hydrogen, CN and NO_2;

R_{213} is selected from halogen, haloalkyl, haloalkoxy, $-S(O)_kCF_3$, and $-SF_5$; and

h, k and n are independently selected from 0, 1, and 2;

and veterinarily acceptable salts thereof.

2. A method of controlling parasites in or on an animal by administering to the animal an 1-arylpyrazole of formula (II):



(II)

wherein:

R_{21} is cyano, $C(=S)NH_2$, $C(=NOH)NH_2$ or $C(=NNH_2)NH_2$;

R_{22} is $S(O)_mR_{23}$;

R_{23} is alkyl or haloalkyl;

R_{24} is OH, $HC(O)O$-, $R_{25}C(O)O$-, $R_{25}OC(O)O$-, or $R_{205}S(O)_rC(O)O$-

R_{25} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl;

X is selected from nitrogen and C-R_{32};

R_{31} and R_{32} are independently selected from halogen, hydrogen, CN and NO_2;

R_{33} is selected from halogen, haloalkyl, haloalkoxy, $-S(O)_rCF_3$, and $-SF_5$;

m is 0, 1 or 2;

r is selected from 0, 1, and 2;

and veterinarily acceptable salts thereof.

3. A compound of formula (II) or salt there of as hereinbefore described in claim 2 with the proviso that the compound is not 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylthio-5-hydroxypyrazole.

4. A compound according to Claim 3 wherein

R_{21} is cyano;

R_{22} is $S(O)_mR_{23}$;

R_{23} is haloalkyl, preferably CF_3;

R_{24} is OH;

X is selected from nitrogen and C-R_{32};

R_{31} and R_{32} are independently selected from halogen,

R_{33} is selected from halogen, haloalkyl, haloalkoxy, $-S(O)_rCF_3$, and $-SF_5$;

m and r are independently selected from 0, 1, and 2.

5. The compound of formula (I) as defined in Claim 1 or the compound of formula (II) as defined in any one of claims 2,3 or 4 which is 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluromethylsulfinyl-5-hydroxypyrazole.

6. The compound of formula (I) as defined in Claim 1 or the compound of formula (II) as defined in any one of claims 2,3 or 4 which is 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluromethylsulfonyl-5-hydroxypyrazole.

7. A composition comprising a parasiticidally effective, substantially non-emetic amount of a compound of formula (I) or (II) or a salt thereof as defined in any one of the foregoing claims and an acceptable carrier.

8. A composition comprising a parasiticidally effective, amount of a compound of formula (II) or a salt thereof and an acceptable carrier as defined in any one of claims 2, 3, 4, 5 or 6.

9. The method according to any one of Claims 1 to 2 wherein the animal is a domestic animal, preferably a dog or a cat.

10. The method according to Claim 1 wherein the 1-arylpyrazole is administered orally in a dose to the animal in a dose range generally from 0.1 to 500 mg/kg.

ABSTRACT

A method of controlling parasites in or on an animal comprising administering to the animal a parasiticidally effective, substantially non-emetic 1-arylpyrazole.