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 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 antihelminth 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.

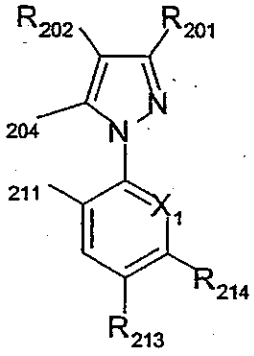
Another object of the invention is to provide safer pesticides for domestic animals.

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.

US 5,079,370, EP-A 0,846,686, WO 98/24769 and WO 97/28126 disclose the use of arylpyrazoles as parasiticidal agents. However, these references are completely silent on the problem that anti parasitical agents often elicit emesis in the animal to be protected or cured from the parasites.

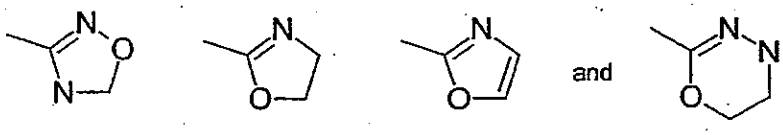
In one aspect, the present invention provides a use of a parasiticidally effective, substantially non-emetic amount of a 1-arylpyrazole of formula (I):



(I)

wherein:

R_{201} is cyano, C(O)alkyl, $C(S)NH_2$, $C(NH)OR_{203}$, $C(NH)SR_{203}$, alkyl, $C(=NOH)NH_2$, $C(=NNH_2)NH_2$, $C(O)NH_2$, $C(O)NHR_{205}$, $C(O)NR_{205}R_{206}$, haloalkyl or heterocyclyl from the group:



optionally substituted by R_{203};

R_{202} is $S(O)_nR_{203}$, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, cycloalkyl, halocycloalkyl, cycloalkyl-alkyl , C_2-C_6 alkynyl, nitro or imidazol-2-yl optionally substituted by alkyl, alkoxy, haloalkyl, halogen, cyano and/or nitro;

R_{203} is alkyl or haloalkyl;

R_{204} is -OH, $R_{205}O$-, HC(O)O-, $R_{205}C(O)O$-, $R_{205}OC(O)O$-, $NH_2C(O)O$-, $R_{205}NHC(O)O$-, $R_{205}R_{206}NC(O)O$-, $R_{205}S(O)_nC(O)O$-, $R_{206}SO_2O$-, aryl-SO_2O-, (C_4-C_7)-oxacycloalkyloxy, $R_{205}R_{206}N$-$C(NR_{205})$-O-, $R_{205}R_{206}N$-C(NH)-O- , $R_{205}NH$-$C(NR_{205})$-O-, $R_{205}NH$-C(NH)-O-, $R_{205}N$=CH-O-, $R_{205}N=C(R_{206})$-O-, $R_{205}NH$-C(S)-O-, $R_{205}R_{206}N$-C(S)-O- ;

R_{205} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl, adamantyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkylaminoalkyl, di(haloalkyl)aminoalkyl, aryl optionally substituted, hetaryl optionally substituted,

arylalkyl optionally substituted, hetarylalkyl optionally substituted, C_2-C_6 alkenyl, C_2-C_6 alkinyl;

R_{206} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl optionally substituted, hetaryl optionally substituted, arylalkyl optionally substituted, hetarylalkyl optionally substituted;

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}, R_{212} are independently selected from halogen, hydrogen, CN, C_1-C_3 alkyl and NO_2;

R_{213} is selected from halogen, haloalkyl, haloalkoxy, -$S(O)_kCF_3$, and $-SF_5$ or forms a ring with R_{214};

R_{214} is hydrogen or may constitute together with R_{213} a group of OCF_2O, CF_2OCF_2, CF_2OCF_2O and CF_2CF_2O, which forms together with the carbons they are attached to a five to six membered ring;

and

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

and veterinarily acceptable salts thereof for the manufacture of a medicament for controlling parasites in or on an animal.

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.

When R_{204} is OH the pyrazole structure can also be exhibited by its tautomeric form as pyrazolon structure.

Unless otherwise specified, alkyl and alkoxy groups are straight chain or branched and 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. Halogen means F, Cl, Br, and I, preferably F and Cl. 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.

Generally, the term "aryl" means a carbocyclic aromatic radical having preferably 6 to 14, in particular 6 to 12, carbon atoms, for example phenyl, naphthyl or biphenylyl, preferably phenyl;

the term "heterocyclyl" preferably a hetaryl or heteroaliphatic ring system, "hetaryl" preferably being understood as meaning an aryl radical in which at least one CH group is replaced by N and/or at least two adjacent CH groups are replaced by S, NH or O, for example a radical of thiophene, furan, pyrrole, thiazole, oxazole, imidazole, isothiazole, isoxazole, pyrazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3,4-triazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,2,4-triazole, 1,2,3-triazole, 1,2,3,4-tetrazole, benzo[b]thiophene, benzo[b]furan, indole, benzo[c]thiophene, benzo[c]furan, isoindole, benzoxazole, benzothiazole, benzimidazole, benzisoxazole, benzisothiazole, benzopyrazole, benzothiadiazole, benzotriazole, dibenzofuran, dibenzothiophene, carbazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,3,5-triazine, 1,2,4-triazine, 1,2,4,5-triazine, quinoline, isoquinoline, quinoxaline, quinazoline, cinnoline, 1,8-naphthyridine, 1,5-naphthyridine, 1,6-naphthyridine, 1,7-naphthyridine, phthalazine, pyridopyrimidine, purine, pteridine or 4H-quinolizine;

and the term "heteroaliphatic ring system" preferably a (C_3-C_8)cycloalkyl radical in which at least one carbon unit is replaced by O, S or a group NR' and R' is hydrogen, (C_1-C_4)alkyl, (C_1-C_4)alkanoyl, (C_1-C_4)alkoxycarbonyl, (C_1-C_4)alkylsulfonyl, (C_1-C_4)alkoxy or aryl;

The substituents with which the various aliphatic, cycloaliphatic, aromatic and heterocyclic ring systems can be provided are, for example, halogen, nitro, cyano, di-(C_1-C_4)alkylamino, (C_1-C_4)alkyl, (C_3-C_8)cycloalkyl, (C_1-C_4)trialkylsilyl, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy-(C_1-C_4)alkyl, (C_1-C_2)alkoxy-$[CH_2CH_2O]_{0,1,2}$-ethoxy, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl, (C_1-C_4)alkylsulfonyl, phenyl, benzyl, phenoxy, halophenoxy, (C_1-C_4)alkylphenoxy, (C_1-C_4)alkoxyphenoxy, phenylthio, heterocyclyl, heterocyclylthio or heterocyclyloxy, it being possible for one or more, in the case of fluorine also up to the maximum number of, hydrogen atoms in the alkyl radicals and the radicals derived therefrom to be replaced by halogen, preferably chlorine or fluorine, where, in the event that these substituents are (C_1-C_4)alkyl, they may also be linked cyclically and where one or two aliphatic carbon units in these fused ring systems, such as, for example, the indane, di-, tetra- or decahydronaphthyl or benzocycloheptane system, may be replaced by heteroatom units such as oxygen or sulfur and where one or more, in the case of fluorine also up to the maximum number of, hydrogen atoms on the aliphatic carbon atom units can be replaced by halogen or (C_1-C_4)alkyl.

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%.

Preferred compounds of the formula (I) are those 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 $S(O)_hR_{203}$, C_2-C_3 alkenyl, C_2-C_3 haloalkenyl, cycloalkyl, halocycloalkyl, cycloalkyl-alkyl , C_2-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}, 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 $-SF_5$
R_{214} is hydrogen;
and
h, k and n are independently selected from 0, 1, and 2.

Further compounds of formula (I) which are preferred according to the present invention are those 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 halomethyl, preferably CF_3;

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

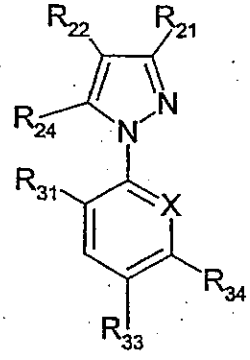
X_1 is C-R_{212};

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

h is 0 or 1, or 2.

A further embodiment of the invention includes compounds of the formula (I), with the proviso that if R_{201} is CN and R_{202} is $S(O)_hR_{203}$ then R_{204} is not $R_{205}O$ or $R_{205}R_{206}N$-C(O)-O-.

In another aspect of the present invention there is provided a use according to the first aspect wherein the medicament comprises a 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;

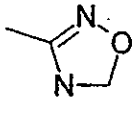
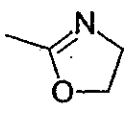
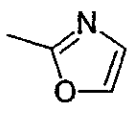
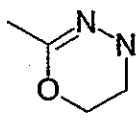
R_{24} is OH, HC(O)O-, $R_{25}C(O)O$-, $R_{25}OC(O)O$-, $R_{25}R_{25}$-N-C(O)-O- or $R_{25}S(O)_nC(O)O$-;
R_{25} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl, adamantyl, adamantyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkylaminoalkyl, di(haloalkyl)aminoalkyl, aryl optionally substituted, hetaryl optionally substituted, arylalkyl optionally substituted, hetarylalkyl optionally substituted, C_2-C_6 alkenyl, C_2-C_6 alkinyl;
or two groups R_{25} 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 is selected from nitrogen and C-R_{32};
R_{31} and R_{32} are independently selected from halogen, hydrogen, CN, C_1-C_3 alkyl and NO_2;
R_{33} is selected from halogen, haloalkyl, haloalkoxy, -S(O)$_r$$CF_3$, and –$SF_5$ or forms a ring together with R_{34} ;
R_{34} is hydrogen or may constitute together with R_{213} a group of OCF_2O, CF_2OCF_2, CF_2OCF_2O and CF_2CF_2O, which forms together with the carbons they are attached to a five to six membered ring;
m is 0, 1 or 2;
r is selected from 0, 1, and 2;
and veterinarily acceptable salts thereof;
provided that if R_{21} is cyano then R_{24} is not $R_{25}R_{25}$-N-C(O)-O-.
Preferred are compounds of formula (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 $R_{25}S(O)_nC(O)O$-;
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, C_1-C_3 alkyl and NO_2;

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

In another aspect of the present invention there is provided a compound of formula (II) or salt thereof 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 preferred class of 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 $C\text{-}R_{32}$;
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.

In a further aspect of the invention the following groups of compounds are provided:
Compounds of the formula (I), wherein
R_{201} is $C(O)NH_2$, $C(O)NHR_{205}$, $C(O)NR_{205}R_{206}$, $C(O)N{=}S(R_{203})_2$, haloalkyl or heterocyclyl from the group:




and


optionally substituted by R_{203}.

Compounds of the formula (I), wherein

R_{202} is nitro or imidazol-2-yl optionally substituted by alkyl, alkoxy, haloalkyl, halogen, cyano, nitro.

Compounds of the formula (I), wherein
R_{204} is $R_{206}SO_2O$-, aryl-SO_2O-, (C_4-C_7)-oxacycloalkyloxy, $R_{205}R_{206}N$-$C(NR_{205})$-O-, $R_{205}R_{206}N$-C(NH)-O- , $R_{205}NH$-$C(NR_{205})$-O-, $R_{205}NH$-C(NH)-O-, $R_{205}N$=CH-O-, $R_{205}N$=$C(R_{206})$-O-, $R_{205}NH$-C(S)-O-, $R_{205}R_{206}N$-C(S)-O-.

Compounds of the formula (I), wherein
R_{214} constitute together with R_{213} a group of OCF_2O, CF_2OCF_2, CF_2OCF_2O and CF_2CF_2O, which forms together with the carbons they are attached to a five to six membered ring.

The compounds 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluromethylsulfinyl-5-hydroxypyrazole and 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluromethylsulfonyl-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; n-Bu means n-Butyl; and Ph means Phenyl.

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, R_{214} is H and $R_{213}$is CF_3 or SF_5.

Phys. data: melting point (°C) or NMR (^1H, ^{19}F-NMR, ppm)

Compound Number (R_{213}= CF_3)	Compound Number (R_{213}=SF_5)	R_{204}	Phys. data
1-1	1-2	OH	19F: -44.9 -63.8 ppm
2-1	2-2	OMe	mp. 83
3-1	3-2	OEt	mp. 105
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	$OC(O)NMe_2$	mp. 126

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, R_{214} is H and R_{213} is CF_3 or SF_5.

Phys. data: melting point (°C) or NMR (^1H, ^{19}F-NMR, ppm)

Compound Number (R_{213}= CF_3)	Compound Number (R_{213}=SF_5)	R_{204}	Phys. data
1-3	1-4	OH	mp. 185
2-3	2-4	OMe	mp. 136
3-3	3-4	OEt	mp. 157
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	ONa	19F: -60.9 -72.6
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, R_{214} is H and R_{213} is CF_3 or SF_5.

Phys. data: melting point (°C) or NMR (^1H, ^{19}F-NMR, ppm)

Compound Number (R_{213}= CF_3)	Compound Number (R_{213}=SF_5)	R_{204}	Phys. data
1-5	1-6	OH	19F: -63.8 -79.9 ppm
2-5	2-6	OMe	mp. 151
3-5	3-6	OEt	mp. 132
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	$OC(O)NMe_2$	

Table 4

Compounds of formula (I) wherein R_{201} is alkyl or haloalkyl; R_{202} is SO_hR_{203}; R_{211} is Cl, X_1 is C-Cl, R_{214} is H and R_{213} is CF_3 ;

Phys. data: melting point (°C) or NMR (^1H, ^{19}F-NMR, ppm)

Compound No	R_{201}	R_{202}	R_{204}	Phys.Data
1-7	CH_3	SCF_3	OH	19F: -45.9 -63.5 ppm
2-7	CH_3	$SOCF_3$	OH	
3-7	CH_3	SO_2CF_3	OH	
4-7	CH_3	$SCClF_2$	OH	19F: -30.4 -63.7 ppm
5-7	CH_3	$SOCClF_2$	OH	
6-7	CH_3	SO_2CClF_2	OH	
7-7	CH_3	$SCCl_2F$	OH	
8-7	CH_3	$SOCCl_2F$	OH	
9-7	CH_3	SC_2F_5	OH	
10-7	CH_3	SC_2H_5	OH	
11-7	CH_3	SCF_3	OMe	
12-7	CH_3	SCF_3	OEt	
13-7	CH_3	SMe	OH	
14-7	C_2H_5	SCF_3	OH	
15-7	CF_3	SCF_3	OH	
16-7	CHF_2	SCF_3	OH	
17-7	CF_3	$SOCF_3$	OH	
18-7	CF_3	SO_2CF_3	OH	
19-7	CF_3	$SCClF_2$	OH	
20-7	CF_3	$SCCl_2F$	OH	

Table 5

Compounds of formula (I) wherein R_{202} is SO_hR_{203}; R_{211} is Cl, X_1 is C-Cl, R_{214} is H and R_{213} is CF_3 ;

Phys. data: melting point (°C) or NMR (^1H, ^{19}F-NMR, ppm)

Compound No	R_{201}	R_{202}	R_{204}	Phys. data
1-8	$CONH_2$	SCF_3	OH	mp. 197
2-8	$CONH_2$	$SOCF_3$	OH	
3-8	$CONH_2$	SO_2CF_3	OH	
4-8	$CSNH_2$	SCF_3	OH	mp. 150
5-8	$CSNH_2$	$SOCF_3$	OH	
6-8	$CSNH_2$	SO_2CF_3	OH	
7-8	$CONMe_2$	SCF_3	OH	
8-8	$C(NOH)NH_2$	$SCClF_2$	OH	mp. 156
9-8	$C(NOH)NH_2$	SCF_3	OH	mp. 184
10-8	$COCH_3$	SCF_3	OH	19F: -44.5 -61.7
11-8	$COCH_3$	$SCClF_2$	OH	19F: -29.4 -61.0
12-8	$CONH_2$	SCF_3	OEt	
13-8	$CONH_2$	$SCClF_2$	OEt	
14-8	Oxadiazolin-3-yl	SCF_3	OH	
15-8	Oxazolin-2-yl	SCF_3	OH	
16-8	$CON=S(iPr_2)$	SCF_3	OH	
17-8	$CON=S(iPr)_2$	$SOCF_3$	OH	
18-8	$CON=S(iPr)_2$	$SO2CF_3$	OH	
19-8	$CONH_2$	SCF_3	OMe	mp. 148-151
20-8				

Table 6

Compounds of formula (I) wherein R_{201} is CN; R_{202} is SO_hR_{203}; R_{211} is Cl, X_1 is C-Cl, R_{214} is H and R_{213} is CF_3 ;

Phys. data: melting point (°C) or NMR (^1H, ^{19}F-NMR, ppm)

Compound No	R_{202}	R_{204}	Phys. data
1-9	$SCClF_2$	OH	19F: -30.7 -63.7
2-9	$SOCClF_2$	OH	
3-9	SO_2CClF_2	OH	
4-9	$SCCl_2F$	OH	
5-9	$SOCCl_2F$	OH	
6-9	SO_2CCl_2F	OH	
7-9	SC_2F_5	OH	
8-9	SCH_2CF_3	OH	
9-9	$SCCl_2CF_3$	OH	
10-9	$SCCl_2CH_3$	OH	
11-9	SC_2H_5	OH	1H: 1.25,3H; 2.71,3H; 7.72,2H;
12-9	$SCHF_2$	OH	
13-9	$SCClF_2$	OEt	mp. 91
14-9	$SOCClF_2$	OEt	mp. 161
15-9	$SCClF_2$	$OCONMe_2$	
16-9	$SCClF_2$	OCOtBu	
17-9	SCH_3	OH	mp. 66
18-9	SCH_3	$OCONMe_2$	1H: 2.43,3H; 2.96,6H;7.75,2H;
19-9	$SCBrF_2$	OH	
20-9	$SCCl_3$	OH	
21-9	$SCCl_2F$	OMe	mp. 154
22-9	$SOCCl_2F$	OMe	mp. 136
23-9	SO_2CCl_2F	OMe	mp. 189
24-9	SO_2CClF_2	OEt	mp. 130
25-9	$SCClF_2$	OMe	mp. 87
26-9	$SOCClF^2$	OMe	mp. 139
27-9	SO^2CClF^2	OMe	mp. 166

Table 7

Compounds of formula (I) wherein R_{201} is CN; R_{202} is SO_nR_{203}; R_{211} is Cl, X_1 is C-Cl, R_{214} is H and R_{213} is CF_3 ;

Phys. data: melting point (°C) or NMR (^1H, ^{19}F-NMR, ppm)

Compound No	R_{202}	R_{204}		Phys. data
1-10	SCF_3	OCH_2-CCH		19F: -44.6 -63.8
2-10	SCF_3	OCH_2COOEt		mp. 71
3-10	SCF_3	OCOtBu		mp. 82
4-10	SCF_3	OCO-Ph-4-OMe		19F: -43.5 -63.9
5-10	SCF_3	OSO_2Me		mp. 110
6-10	SCF_3	OCO-Pyrrolidin		mp. 101
7-10	SCF_3	OCO-Morpholin		19F: -43.5 -63.8
8-10	SCF_3	OCO-$N(i\text{-}Pr)_2$		mp. 120
9-10	SCF_3	OCO-NPh_2		mp. 142
10-10	SCF_3	OCO-N(Me)Ph		19F: -43.6 -63.7
11-10	SCF_3	OCO-Carbazol		mp. 148
12-10	SCF_3	OCO-Adamantyl		mp. 142
13-10	SCF3	OCO-Mesityl		mp. 103
14-10	SCF3	OCH_2Ph		mp. 73
15-10	SCF3	OSO_2-4-Tolyl		
16-10	SCF3	O-C(NMe)Nme_2		
17-10	SCF3	O-CH=NC_2H_4OEt		
18-10	SCF3	OCH_2CONH_2		mp. 156
19-10	SCF3	O-C(N(i-Pr))NHiPr		
20-10	SCF3	O-C(S)-NHEt		

Table 8

Compounds of formula (I) wherein R_{211} is Cl, X_1 is C-Cl, R_{214} is H and R_{213} is CF_3 ; Phys. data: melting point (°C) or NMR (^1H, ^{19}F-NMR, ppm)

Compound No	R_{201}	R_{202}	R_{204}	Phys. data
1-11	CN	4,5-Dicyano-imidazol-2-yl	OH	
2-11	CN	4,5-Dicyano-imidazol-2-yl	OEt	
3-11	CH_3	4,5-Dicyano-imidazol-2-yl	OH	
4-11	CH_3	4,5-Dicyano-imidazol-2-yl	OEt	1H: 1.28, 3H; 2.55, 3H; 4.08, 2H; 7.77, 2H;
5-11	CN	$-CH=CCl_2$	OEt	
6-11	CN	$-CH_2CH=CH_2$	OAllyl	mp. 62-66
7-11	CN	$-CH=CBr_2$	OEt	
8-11	CN	Cyclopropyl	OEt	
9-11	CN	$c\text{-}C_6H_{11}$	OEt	
10-11	CN	NO_2	OH	mp. 107
11-11	CN	NO_2	OEt	
12-11	CN	-CC-Me	OEt	
13-11	CN	$-CC\text{-}SiMe_3$	OEt	

Table 9

Compounds of formula (I) wherein R_{201} is CN; R_{202} is SO_hR_{203}; R_{211} is Cl, R_{214} and R_{213} form the unit CF_2OCF_2;

Phys. data: melting point (°C) or NMR (^1H, ^{19}F-NMR, ppm)

Compound No	R_{202}	R_{204}	$X=CR_{212}$	Phys. data
1-12	SCF_3	OH	CH	
2-12	SCF_3	OH	C-Cl	
3-12	SCF_3	OEt	C-Cl	
4-12	$SOCF_3$	OH	CH	
5-12	$SOCF_3$	OH	C-Cl	
6-12	SO_2CF_3	OH	CH	
7-12	SO_2CF_3	OH	C-Cl	
8-12	$SCClF_2$	OH	C-Cl	
9-12	$SCCl_2F$	OH	C-Cl	
10-12	SC_2H_5	OH	C-Cl	

Table 10

Compounds of formula (I) wherein R_{201} is CN; R_{202} is SO_hR_{203}; R_{211} is Cl, X_1 is C-Cl, R_{214} is H and R_{213} is OCF_3 ;

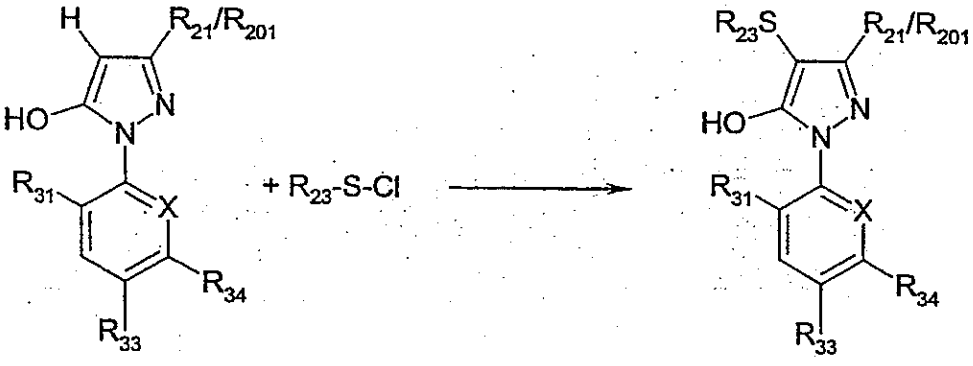
Phys. data: melting point (°C) or NMR (^1H, ^{19}F-NMR, ppm)

Compound No	R_{202}	R_{204}	Phys data
1-13	SCF_3	OH	
2-13	$SOCF_3$	OH	
3-13	SO_2CF_3	OH	
4-13	SCF_3	OMe	mp. 101
5-13	$SOCF_3$	OMe	mp. 104
6-13	SO_2CF_3	OMe	mp. 117
7-13	$SCCl_2F$	OMe	mp. 123
8-13	SCF_3	OEt	
9-13	$SOCF_3$	OEt	
10-13	SO_2CF_3	OEt	

Methods of Synthesis

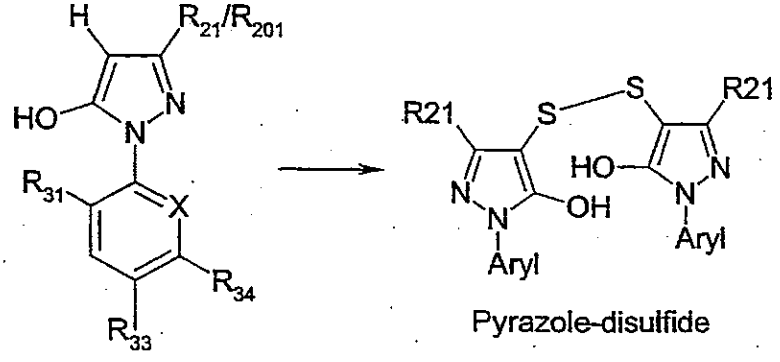
Method 1

The compounds of formula (I) and (II) with R_{204}/R_{24} = OH and R_{22}= SR_{23} can be synthesized by reacting 5-hydroxypyrazoles with sulfenylchlorides with or without bases in organic solvents (see e.g. EP-A-295 117):

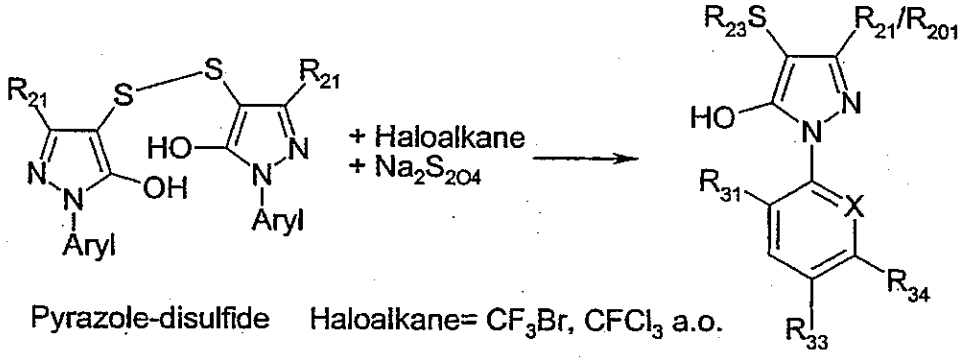


Method 2

The compounds of formula (I) and (II) with R_{204}/R_{24} = OH and R_{22}= SR_{23} can be synthesized by reacting 5-hydroxypyrazoles with disulfurdichloride. The resulting pyrazoledisulfides can be alkylated to yield 4-pyrazolsulfides (see e.g. EP-A-374 061, EP295117, C. Wakselman, J. Chem. Soc. Perkin Trans 1, 1992 3371-3375) :



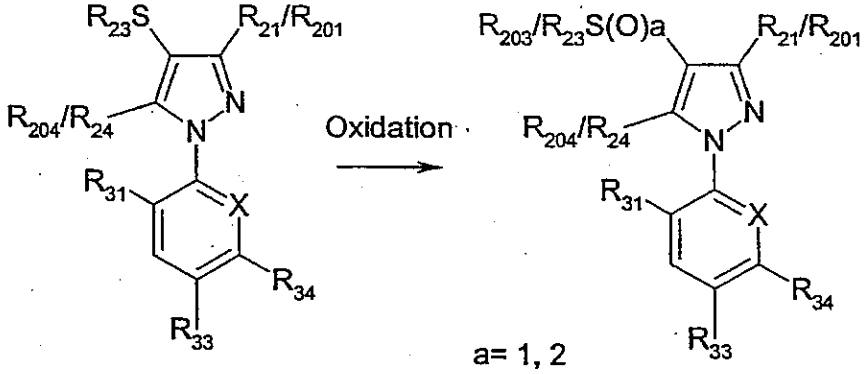
Pyrazole-disulfide



Pyrazole-disulfide Haloalkane= CF_3Br, $CFCl_3$ a.o.

Method 3

The compounds of formula (I) and (II) with R_{204}/R_{24} = OH and R_{22}= $S(O)_aR_{23}$ (a=1,2) can be synthesized by reacting pyrazolsulfides R_{22}= SR_{23} with oxidizing agents like peroxy compounds (hydrogenperoxide, organic peroxides as peroxyaceticacid), halogenderivatives (like periodate salts) and others to obtain sulfoxides R_{22}= SOR_{23} and sulfones R_{22}=SO_2R_{23} (see e.g. EP-A-295 117).



a= 1, 2

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 formulae (III), (IV), (V), and (VI) respectively wherein X_2 is a leaving group such as a halogen atom or an acetyl group:

$HC(O)X_2$ $R_{25}C(O)X_2$ $R_{25}OC(O)X_2$ $R_{25}S(O)_nC(O)X_2$

(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 385809, and United States Patent 5232940, 5047550 or other methods known to the person skilled in the art.

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.

Accordingly, in a preferred embodiment there is provided a method of controlling parasites in or on a cat comprising administering orally to the cat a parasitically effective, substantially non emetic amount of a 1-arylpyrazole of formula (I).

In a further preferred embodiment there is provided a method of controlling parasites in or on a dog comprising administering orally to the dog a parasitically effective, substantially non emetic amount of a 1-arylpyrazole of formula (I).

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; pyratel (generally adminsitered 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 scab 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 provides for the 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 provides for the 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.

In a further embodiment of the invention there is provided the use of a compound of formula (I) or salt thereof for controlling parasites in or on an animal without causing emesis of the animal.

Preferred is the use for orally administering the compound to the animal, which is preferably a domestic animal, highly preferred a cat or a dog.

In a further embodiment of the invention there is provided the use of a compound of formula (I) or salt thereof for the manufacture of a substantially non emetic composition, for controlling parasites in or on an animal, preferably for oral administering.

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.

The compounds of the invention also have utility in the control of arthropod or nematode pests of plants. The active compound is generally applied to the locus in which arthropod or nematode infestation is to be controlled at a rate of about 0.005 kg to about 25 kg of active compound per hectare of locus treated, preferably 0.02 to 2 kg/ha. Under ideal conditions, depending on the pest to be controlled, the lower rate may offer adequate protection. On the other hand, adverse weather conditions, resistance of the pest and other factors may require that the active ingredient be used in higher proportions. For foliar application, a rate of 0.01 to 1 kg/ha may be used.

When the pest is soil-borne, the formulation containing the active compound is distributed evenly over the area to be treated in any convenient manner. Application may be made, if desired, to the field or crop-growing area generally or in close proximity to the seed or plant to be protected from attack. The active component can be washed into the soil by spraying with water over the area or can be left to the natural action of rainfall. During or after application, the formulation can, if desired, be distributed mechanically in the soil, for example by ploughing or disking.

Application can be prior to planting, at planting, after planting but before sprouting has taken place or after sprouting.

The compounds of the invention may be applied in solid or liquid compositions to the soil principally to control those nematodes dwelling therein but also to the foliage principally to control those nematodes attacking the aerial parts of the plants (e.g. aphelenchoides spp. and ditylenchus spp. listed above).

The compounds of the invention are of value in controlling pests which feed on parts of the plant remote from the point of application, e.g. leaf feeding insects are killed by the subject compounds applied to roots. In addition the compounds may reduce attacks on the plant by means of antifeeding or repellent effects.

The compounds of the invention are of particular value in the protection of field, forage, plantation, glasshouse, orchard and vineyard crops, or ornamentals and of plantation and forest trees, for example, cereals (such as maize, wheat, rice, sorghum), cotton, tobacco, vegetables and salads (such as beans, cole crops, curcurbits, lettuce, onions, tomatoes and peppers), field crops (such as potato, sugar beet, ground nuts, soyabean, oil seed rape), sugar cane, grassland and forage (such as maize, sorghum, lucerne), plantations (such as of tea, coffee, cocoa, banana, oil palm, coconut, rubber, spices), orchards and groves (such as of stone and pip fruit, citrus, kiwifruit, avocado, mango, olives, and walnuts), vineyards, ornamental plants, flowers and shrubs under glass and in gardens and parks, forest trees (both deciduous and evergreen) in forests, plantations and nurseries.

They are also valuable in the protection of timber (standing, felled, converted, stored or structural) from attack by sawflies (e.g. urocerus) or beetles (e.g. scolytids, platypodids, lyctids, bostrychids, cerambycids, anobiids), or termites, for example, reticulitermes spp., heterotermes spp., coptotermes.

They have applications in the protection of stored products such as grains, fruits, nuts, spices and tobacco, whether whole, milled or compounded into products, from moth, beetle and mite attack. Also protected are stored animal products such as skins, hair, wool and feathers in natural or converted form (e.g. as carpets or textiles) from moth and beetle attack; also stored meat and fish from beetle, mite and fly attack.

The disclosure in US provisional application No. 60/168658 from which this application claims priority is incorporated herein by reference.

The invention is further illustrated by the following examples, without limiting it thereto.

Examples and Preparations

Example 1

Preparation of 1-(2,6-Dichloro-4-trifluoromethylphenyl)- 3-cyano-4-trifluoromethylsulfinyl-5-hydroxypyrazole. To a solution of 15 g (35.5 mmol) of 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfenyl-5-hydroxypyrazole in 125 ml of dichloromethane at room temperature was added a solution of m-chloroperbenzoic acid (8.76 g, 70 %, 35.5 mmol) in 375 ml of dichloromehane. The resulting solution was stirred at room temperature for 17 hr. It was then concentrated and triturated with ethyl acetate and heptane(1:2). Upon filtration a solid was obtained. This solid was dissolved in ethyl acetate and stirred with saturated sodium bicarbonate solution. Ther layers were separated and the aqueous layer was extracted with three times of ethyl acetate. The combined organic layer was dried (magnesium sulfate) and concentrated. Upon chromatographic purification via silica gel column, a solid (5.7 g, 13.01 mol, 37 %) was obtained as the desired product, mp 185-187d.

Example 2

Preparation of 1-(2,6-Dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfonyl-5-hydroxypyrazole. To the solution of 2 g (4.74 mmol) of 1-(2,6-dichloro-4trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfenyl-5-

hydroxypyrazole in 1,2-dichloroethane was added 1.83 ml (9.52 mmol, 35 % in acetic acid) of peracetic acid at room temperature. The resulting solution was heated up to 60 C for 9 hr. It was then cooled and concentrated to give 2.05 g of residue. Upon chromatographic purification via silica gel column eluting with gradient solvent mixture (heptance/ethyl acetate), an oil (1.08 g, 2.38 mmol, 50.2 % yield) was obtained as the desired product with 98 % HPLC puriety; F-NMR, -60.999 ppm (AR-CF3), -79.893 ppm (SO2CF3). H-NMR, 8.18 ppm (s, 2 H).

Example 3

Preparation of 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-amido-4-trifluoromethylsulfenyl-5-hydroxypyrazole. To the mixture of 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfenyl-5-hydroxypyrazole (3.0 g, 7.13 mmol) and concentrated sulfuric acid (3 ml) was heated at 100 C for 3 hr. The reaction mixture was cooled and poured into ice-water. A solid was collected via filtration and was washed with water. It was then vacuum dried to obtain a solid (2.88 g, 6.56 mmol, 92 % yield) with 98 % HPLC puriety, m. p. 197-198 C.

Example 4

Preparation of 1-(2,6-dichloro4-trifluoromethylphenyl)-3-thioamido-4-trifluoromethylsulfenyl-5-hydroxypyrazole. To the mixture of 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-amido-4-trifluoromethylsulfenyl-5-hydroxypyrazole (1 g, 2.28 mmol) and Lawesson's reagent (0.49 g, 1.21 mmol) in toluene was heated up to reflux for 4 hr. The reaction mixture turned into a solution during this time. This solution was then cooled , concentrated, and via chromatographic purification to provide a solid (0.283 g, 0.623 mmol, 27.3 % yield) with 96 % HPLC puriety m. p. 150--151 decomp.

Example 5

Preparation of 1-(2,6-Dichloro-4-trifluoromethylphenyl)-3-oximicamido-4-trifluoromethylsulfenyl-5-hydroxypyrazole. To the solution of 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfenyl-5-hydroxypyrazole (3.0 g, 7.11 mmol) in 15 ml of methanol at room temperature was added hydroxyamine hydrochloride (0.59 g, 8.53 mmol) and triethylamine (0.94 g, 9.24 mmol). The resulting mixture was stirred at room temperature for a total of 48 hr with additional hydroxyamine hydrochloride (1.18g, 17.06 mmol) and triethylamine (1.88 g, 18.5 mmol) added portionwise. The resulting reaction mixture was concentrated and then dissolved in ethyl acetate. The organic layer was washed with saturated ammonium chloride, water,dried (sodium sulfate), concentrated to give a brown oil which solidified after standing, m. p. 184 C.

Example 6

Preparation of 1-(2,6-Dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfenyl-5-trimethylacetoxypyrazole. To the solution of 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfenyl-5-hydroxypyrazole (7.00 g, 16.6 mmol) and pyridine (4.91 g, 62.1 mmol) in 1,2-dichloroethane at room temperature was added trimethylacetyl chloride (4.37 g, 36.2 mmol) dropwise. Ice bath was used to maintain the temperature of the reaction. After 20 hr at room temperature, the orgainc layer was washed with five times of aqueous KHSO4 till the aqueous solution was at pH 1. The orgainc layer was then dried (Mg SO4) and concentrated to give a solid residue. Upon chromatographic purification via silica gel column of the solid residue, after trituration with pentane, a off white solid (2.403 g, 28.6 % yield, 97.0 % HPLC puriety) was provided as the desired product, m. p. 82-83 C.

Example 7

Preparation of 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-chlorodifluoromethylsulfenyl-5-hydroxypyrazole. To the solution of 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-5-hydroxypyrazole (12.0 g, 37.3 mmol.) and pyridine (3.25 g, 41.0 mmol) in dichloromethane at -50-- -60 C was added chlorodifluoromethanesulfenyl chloride (8.1 g, 46.6 mmol). The resulting solution was gradually warmed up to room temperature. After 20 hr, the organic layer was washed five times with water. It was then washed with brine and dried (Na2SO4) to provide an oil. Upon chromatographic purification of the oil , a total of 11.6 g (26.4 mmol., 71 % yield) of the desired product with 97 % HPLC puriety was isolated. F-NMR: -30.05 ppm (CClF2), -63.80 ppm (ArCF3).

Biological Example

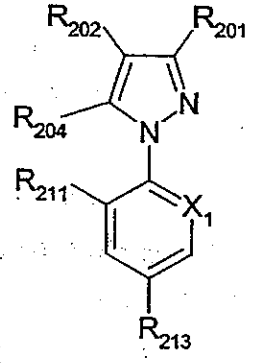
The compounds 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluromethylthio-5-hydroxypyrazole, 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluromethylsulfinyl-5-hydroxypyrazole and 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluromethylsulfonyl-5-hydroxypyrazole are formulated 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 many of the above-mentioned compounds in any of the three areas of evaluation without any significant side effect for a period ranging from eight to thirty days: control of flea on dog, control of tick on dog, and control of flea on cat. They are: 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfenyl-5-trimethylacetoxypyrazole 3-10 , 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfenyl-5-ethoxypyrazole 3-1, 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-chlorodifluoromethylsulfenyl-5-hydroxypyrazole 1-9 , 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfenyl-5-hydroxypyrazole 1-1 , 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfonyl-5-hydroxypyrazole 1-5, 1-(2,6-dichloro-4-trifluoromethylphenyl)-3-cyano-4-trifluoromethylsulfinyl-5-hydroxypyrazole 1-3 , 1-(2,6-dichloro-4-trifluormethyl(phenyl)-3-cyano-4-trifluormethylsulfonyl-5-N,N-dimethylcarbamyloxypyrazole 19-1.

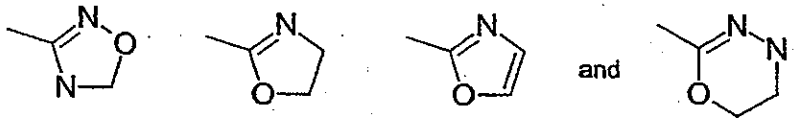
CLAIMS

1. A use of a parasiticidally effective, substantially non-emetic amount of a 1-arylpyrazole of formula (I):



wherein:

R_{201} is cyano, C(O)alkyl, $C(S)NH_2$, $C(NH)OR_{203}$, $C(NH)SR_{203}$, alkyl, $C(=NOH)NH_2$, $C(=NNH_2)NH_2$, $C(O)NH_2$, $C(O)NHR_{205}$, $C(O)NR_{205}R_{206}$, haloalkyl or heterocyclyl from the group:



optionally substituted by R_{203};

R_{202} is $S(O)_nR_{203}$, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, cycloalkyl, halocycloalkyl, cycloalkyl-alkyl , C_2-C_6 alkynyl, nitro or imidazol-2-yl optionally substituted by alkyl, alkoxy, haloalkyl, halogen, cyano and/or nitro;

R_{203} is alkyl or haloalkyl;

R_{204} is -OH, $R_{205}O$-, HC(O)O-, $R_{205}C(O)O$-, $R_{205}OC(O)O$-, $NH_2C(O)O$-, $R_{205}NHC(O)O$-, $R_{205}R_{206}NC(O)O$-, $R_{205}S(O)_nC(O)O$-, $R_{206}SO_2O$-, aryl-SO_2O-, (C_4-C_7)-oxacycloalkyloxy,

$R_{205}R_{206}N$-C(NR_{205})-O-, $R_{205}R_{206}N$-C(NH)-O- , $R_{205}NH$-C(NR_{205})-O-, $R_{205}NH$-C(NH)-O-, $R_{205}N$=CH-O-, $R_{205}N$=C(R_{206})-O-, $R_{205}NH$-C(S)-O-, $R_{205}R_{206}N$-C(S)-O- ;

R_{205} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl, adamantyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkylaminoalkyl, di(haloalkyl)aminoalkyl, aryl optionally substituted, hetaryl optionally substituted, arylalkyl optionally substituted, hetarylalkyl optionally substituted, C_2-C_6 alkenyl, C_2-C_6 alkinyl;

R_{206} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl optionally substituted, hetaryl optionally substituted, arylalkyl optionally substituted, hetarylalkyl optionally substituted;

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}, R_{212} are independently selected from halogen, hydrogen, CN, C_1-C_3 alkyl and NO_2;

R_{213} is selected from halogen, haloalkyl, haloalkoxy, -$S(O)_kCF_3$, and –SF_5 or forms a ring with R_{214};

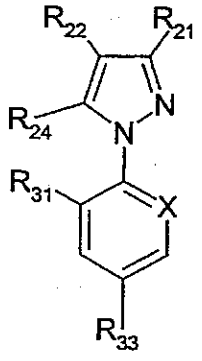
R_{214} is hydrogen or may constitute together with R_{213} a group of OCF_2O, CF_2OCF_2, CF_2OCF_2O and CF_2CF_2O, which forms together with the carbons they are attached to a five to six membered ring;

and

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

and veterinarily acceptable salts thereof for the manufacture of a medicament for controlling parasites in or on an animal.

2. The use as claimed in claim 1 wherein the medicament comprises a 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 $R_{25}S(O)_nC(O)O$-

R_{25} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl, adamantyl, adamantyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkylaminoalkyl, di(haloalkyl)aminoalkyl, aryl optionally substituted, hetaryl optionally substituted, arylalkyl optionally substituted, hetarylalkyl optionally substituted, C_2-C_6 alkenyl, C_2-C_6 alkinyl,

or two groups R_{25} 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 is selected from nitrogen and C-R_{32};

R_{31} and R_{32} are independently selected from halogen, hydrogen, CN, C_1-C_3 alkyl and NO_2;

R_{33} is selected from halogen, haloalkyl, haloalkoxy, -$S(O)_rCF_3$, and –SF_5 or forms a ring together with R_{34} ;

R_{34} is hydrogen or may constitute together with R_{213} a group of OCF_2O, CF_2OCF_2, CF_2OCF_2O and CF_2CF_2O, which forms together with the carbons they are attached to a five to six membered ring;

m is 0, 1 or 2;

r is selected from 0, 1, and 2;

and veterinarily acceptable salts thereof; provided that if R_{21} is cyano then R_{24} is not $R_{25}R_{25}$-N-C(O)-O-.

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, 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.

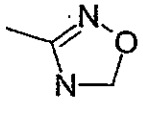
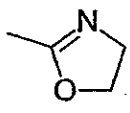
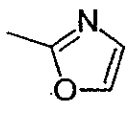
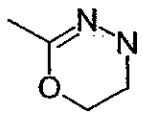
9. The use according to claim 1 wherein the animal is a domestic animal.

10. The use according to claim 1 wherein the 1-arylpyrazole is used to manufacture the medicament to be administered orally in a dose range from 0.1 to 500 mg/kg of body weight.

11. A compound of formula (I) according to claim 1

wherein

R_{201} is cyano, C(O)alkyl, $C(S)NH_2$, $C(NH)OR_{203}$, $C(NH)SR_{203}$, alkyl, $C(=NOH)NH_2$, $C(=NNH_2)NH_2$, $C(O)NH_2$, $C(O)NHR_{205}$; $C(O)NR_{205}R_{206}$, haloalkyl or heterocyclyl from the group:




and


optionally substituted by R_{203};

and/or

R_{202} is $S(O)_hR_{203}$, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, cycloalkyl, halocycloalkyl, cycloalkyl-alkyl , C_2-C_6 alkynyl, nitro or imidazol-2-yl optionally substituted by alkyl, alkoxy, haloalkyl, halogen, cyano and/or nitro;

and/or

R_{204} is -OH, $R_{205}O$-, HC(O)O-, $R_{205}C(O)O$-, $R_{205}OC(O)O$-, $NH_2C(O)O$-, $R_{205}NHC(O)O$-, $R_{205}R_{206}NC(O)O$-, $R_{205}S(O)_nC(O)O$-, $R_{205}SO_2O$-, aryl-SO_2O-, (C_4-C_7)-oxacycloalkyloxy, $R_{205}R_{206}N$-$C(NR_{205})$-O-, $R_{205}R_{206}N$-C(NH)-O- , $R_{205}NH$-$C(NR_{205})$-O-, $R_{205}NH$-C(NH)-O-, $R_{205}N$=CH-O-, $R_{205}N=C(R_{206})$-O-, $R_{205}NH$-C(S)-O-, $R_{205}R_{206}N$-C(S)-O- ;

and/or

R_{214} constitutes together with R_{213} a group of OCF_2O, CF_2OCF_2, CF_2OCF_2O and CF_2CF_2O, which forms together with the carbons they are attached to a five to six membered ring.