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(54) Title: (S)-ENANTIOMER ENRICHED FIPRONIL COMPOSITION			
(57) Abstract A composition comprising (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and (R)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole wherein the composition is enantiomerically enriched in the S-enantiomer.			

(S)-ENANTIOMER ENRICHED FIPRONIL COMPOSITION

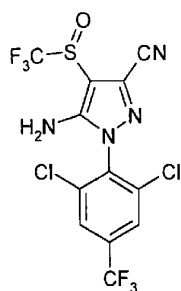
The present invention relates to a new composition comprising pesticidal
5 compounds having a chiral center, which chiral center cooperates with an adjacent
amino group.

Although chirality usually arises from the presence of a carbon atom to
which four different atoms or groups are attached other atoms, including sulphur,
can also give rise to chiral centres.

10 It is known from *inter alia*, European Patent Application EP-A-0 295 117 that
certain N-phenylpyrazole compounds are useful to control arthropod, plant nematode,
helminth and protozoan pests. These compounds include N-phenylpyrazoles having
an optionally substituted amino group attached to the 5-position. Such substituted
amino groups include amino substituted by one or two groups selected from alkyl and
15 alkanoyl. Compounds of interest include those having a cyano group attached to the
3-position and a group R-S(O)_n attached to the 4-position, R being selected from alkyl
and haloalkyl. When the group RS(O)_n represents a sulfoxide, RS(O), the resulting
compounds are generally chiral compounds which exist as a mixture of two
enantiomers (also known as enantiomeric isomers).

20 Among the compounds in the publication is listed 5-amino-3-cyano-1-(2,6-
dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole which is
depicted as formula (A).

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(A)

This compound is presently used commercially to control pests in, for
5 example, agriculture, public health and animal health.

The compound of formula (A), although it does not contain any chiral carbon atoms is a mixture of enantiomers by virtue of the -S(O)CF₃ group. The existence of the enantiomers has not been previously disclosed. The compound causes emesis in animals to which it is administered orally.

10 It is desirable in the control of arthropod pests on animals for compounds to be orally administered. Investigation of the class of N-phenylpyrazoles having an optionally substituted amino group attached to the 5-position of the pyrazole ring has now shown that the level of emetic effect of such oral administration is influenced by a combination of parameters: the presence or absence of substitution on the 5-
15 position; the nature of the substitution; and the chirality of the sulfoxide group on the 4-position.

3

Placement of an acetyl group on the 5-amino group in formula (A) causes a dramatic increase in toxicity and emesis. At a dose of 10mg/kg in dogs both enantiomers cause emesis in about two thirds of the animals. However, the (S) enantiomer caused 100% mortality whereas the (R) enantiomer caused 33% mortality.

Although monosubstitution by acetyl causes an increase in emetic activity and mortality it has been discovered that addition of a methyl substituent on the amino group and replacement of acetyl by ethoxyacetyl or tetrahydrofur-2-oyl can reduce both emetic activity and mortality.

Such chemical modification of the 5-amino group can, however, be avoided by separation of compound A into its component (R) and (S) enantiomers. In contrast to the 5-acetylamino enantiomers (where the (S) enantiomer caused 100% mortality) it is the (S) enantiomer of the 5-amino compound which is the better of the two enantiomers having lower emetic activity. The (S) enantiomer of the 5-amino compound also possesses a second advantageous property. Improved long term control of ticks can be obtained by its use. For example at a dose of 10 mg/Kg administered orally to dogs, the (S) enantiomer gave 85% compared with only 71 % by the (R) enantiomer (this corresponds to only 15% of ticks remaining instead of 29%).

The present invention may provide a composition comprising 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole which is substantially enriched as an enantiomer.

The invention may also provide a composition which is generally safer to use in veterinary medicine or agriculture or public health.

The invention may also provide a composition which when administered orally to animals is substantially non-emetic, most preferably when about 70% or more of the animals so treated are free of emesis.

The present invention relates to a composition comprising (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and (R)-5-amino-3-cyano-1-(2,6-dichloro-4-

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trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole wherein the composition is enriched in the (S) enantiomer. By the term "enriched" is meant wherein the S/R weight:weight ratio is at least approximately 1.05 or higher.

Preferably the composition of the invention is substantially enriched in the S enantiomer. By the term substantially enriched is meant wherein the S/R weight:weight ratio is at least approximately 1.5 or higher.

10

In a related aspect of the invention, the S/R weight-weight ratio is at least approximately 2 or greater, preferably is at least approximately 5 or greater, most preferably is at least approximately 10 or greater.

15

According to one aspect of the invention there is provided a composition comprising (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and (R)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole wherein the composition is enriched in the (S) enantiomer.

20

According to another aspect of the invention there is provided a method of controlling pests at a locus which method comprises applying the composition according to the invention in a pesticidally effective amount at the locus.

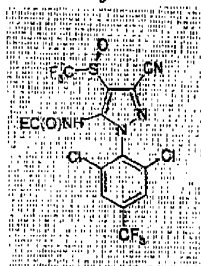
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According to another aspect of the invention there is provided the isolated compound (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole.

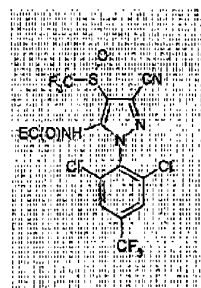
According to another aspect of the invention there is provided a compound of the formula

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(III-A)

5 or
5

(III-B)

10

wherein E is an organic radical which is enantiomerically enriched.

According to another aspect of the invention there is provided a composition comprising (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and (R)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole wherein the composition is enriched in the (R) enantiomer.

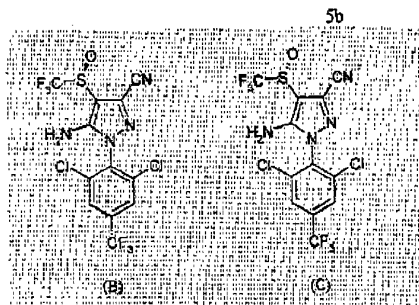
5a

According to another aspect of the invention there is provided a composition comprising (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and (R)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole wherein the composition is substantially enriched in the (R) enantiomer so as to have a R/S weight-weight ratio of at least approximately 2 or greater.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

For greater clarity, the structures of (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and (R)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole are depicted as formulas (B) and (C) respectively. The optical configurations of formulas (B) and (C) are assigned by the use of the Cahn-Ingold-Prelog system as generally described in Advanced Organic Chemistry, J. March, 3rd edition pp. 96-97, Wiley Interscience, NY, 1985. Such depictions are generally understood by those skilled in the art.



The composition of the invention may further comprise a carrier for use in
 5 veterinary medicine, animal health, agriculture, or public health. Such compositions are
 generally described in EP-A-0 295 117.

The present invention also relates to a method of controlling pests at a locus
 which method comprises applying the composition according to the invention in a
 10 pesticidally effective amount at the locus.

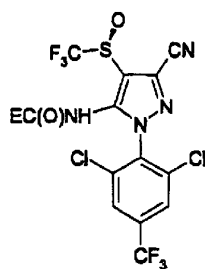
Compound A may be prepared according to the methods described in EP-A-0
 295 117.

15 In another aspect of the invention, the composition may be prepared by
 separating the enantiomers in whole or in part by, for example, use of column
 chromatography or reverse-phase column chromatography using a substantially
 optically active (or "chiral") stationary phase as known to those skilled in the art.

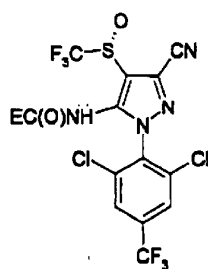
20 In another aspect of the invention, the enantiomers may be separated by a
 process which comprises:

(a) reacting compound (A) with a compound (BG) wherein:

E is an organic radical which is enantiomerically enriched, for example, substantially enantiomerically pure, and G is a group reactive with amino, for example a carboxylic acid, carboxylic acid anhydride, carboxylic acid halide or a carboxylic acid derivative suitable for use in the reaction as known to the skilled addressee; to provide the compounds of formula (III-A) and formula (III-B) (which are novel and therefore constitute a feature of the invention);



(III-A)



(III-B)

- (b) separating the compounds of formula (III-A) and (III-B); and
- (c) removing the groups EC(O) of compounds of formula (III-A) and/or (III-B) to separately provide (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and/or (R)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole respectively.
- The products of step (a), that is the compounds of formula (III-A) and (III-B), are two diastereomers which may be separated by use of, for example, column chromatography or reverse-phase column chromatography as known to those skilled in the art.

When the radical E comprises a primary amine, secondary amine or tertiary amine, the products of step (a), that is the compounds of formula (III-A) and (III-B),
5 are two diastereomers which may be converted to the corresponding acid addition salts, and then separated by, for example, use of fractional crystallization as known to those skilled in the art.

When the radical E comprises a carboxylic acid, sulfonic acid or other such
10 acidic moiety, the products of step (a), that is the compounds of formula (III-A) and (III-B), are two diastereomers which may be converted to the corresponding salts which may be separated by, for example, use of fractional crystallization as known to those skilled in the art.

15 In step (c) the removal of the amide generally comprises a chemical hydrolysis as known to those skilled in the art.

The present invention relates to the isolated compound
(S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-
20 trifluoromethylsulfinylpyrazole.

In another aspect of the invention the composition of the invention may be prepared by a selective oxidation of 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole to preferentially provide the
25 (S) enantiomer. Such oxidation methods are known to those skilled in the art of organic synthesis. It is also possible to utilize such separation methods as for example hereinbefore described to recover the R-enantiomer of fipronil and convert it by a reduction/oxidation scheme to produce the S-enantiomer.

It has been unexpectedly found that (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole provides a substantial advantage in the control of certain arthropods at an animal locus. Another unexpected substantial advantage is that the (S) enantiomer provides a substantial reduction in
5 emesis when administered to an animal by oral application. 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.

The present invention also relates to a use of the composition as hereinbefore
10 defined for the manufacture of a veterinary composition for the control of arthropod 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 the composition as hereinbefore defined.

15 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
20 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.

The present invention also provides the use of a composition as described *supra* as an active veterinary substance.

The compositions which may be used according to the invention generally comprise from about 0.001 to 99% of active ingredient. 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 20% of active ingredient, preferably from about 0.1 to about 3%. Solid formulations generally comprise from about 10% to 99% active ingredient, preferably from about 40% to 70%.

Compositions for oral administration comprise the active ingredient in association with pharmaceutically 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 microcapsules 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.

According to the present invention the active ingredient (ai) is administered orally in a dose to the animal in a dose range generally from 0.1 to 500 mg/kg of ai

per kilogram of animal body weight (mg/kg), more preferably from 1 to 100 mg/kg, even more preferably from 1 to 50 mg/kg, most preferably from 1 to 20 mg/kg.

Examples of the pests that may be controlled by the active ingredient are generally described in European Patent Application EP-A-0 295 117. Illustrative of specific parasites of various host animals which may be controlled by the present invention include arthropods such as mites (e.g., mesostigmatids, itch, mange, scabies, chiggers), ticks (e.g., soft-bodied and hard-bodied), lice (e.g., sucking, biting), fleas (e.g., dog flea, cat flea, oriental rat flea, human flea), true bugs (e.g., bed bugs, Triatomid bugs), bloodsucking adult flies (e.g., horn fly, horse fly, stable fly, black fly, deer fly, louse fly, tsetse fly, mosquitoes), and parasitic fly maggots (e.g., bot fly, blow fly, screwworm, cattle grub, fleece worm); helminths such as nematodes (e.g., threadworm, lungworm, hookworm, whipworm, nodular worm, stomach worm, round worm, pinworm, heartworm), cestodes (e.g., tapeworms) and trematodes (e.g., liver fluke, blood fluke); protozoa such as coccidia, trypanosomes, trichomonads, amoebas and plasmodia; acanthocephalans such as thorny-headed worms (e.g., lingulatulida); and pentastomids such as tongue worms. Arthropod pests that are particularly well controlled by the present invention are fleas and ticks.

It will be understood that by the term animals is meant mammals, preferably domestic animals, e.g. pets, or commercial animals to produce a commercial product such as leather or wool. e.g., cows and horses; and mammals in captivity such as zebras, lions or bears. It will be understood that by the term pets is meant for example dogs or cats.

Another aspect of the present invention is the use of the compound R-Fipronil as an emetic substance in the field of pest control where an emetic effect is desired, for example to act as a protection mean in order to increase the safety of the use.

Generally the use of R-Fipronil is at the same rates as those indicated here above for the S-Fipronil and the compositions containing this R-Fipronil are having the same forms, ratios and components as those described here above for S-Fipronil; it is also possible to adjust the use rates and forms to maximize the emetic effect.

The following examples provide non-limiting methods to work the invention.

10 EXAMPLE 1

About 120 mg of a 1:1 mixture by weight of S-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and R-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole are separated by HPLC (high-pressure liquid chromatography) using a stationary phase which was a Chiralcel® OD 21mm x 250mm column, particle size about 20 microns (micrometers) and a mobile phase of isooctane: isopropanol 96:6 v/v ratio to provide 60 mg each of each enantiomer. The elution rate was about 6mL per minute. Compound C came off the column after about 20 minutes and Compound B came off the column after about 40 minutes.

20 Solvent is removed from both samples and white powders are obtained.

The melting point of Compound B was about 204°C and the melting point of the Compound C was about 201°C.

The absolute configurations of the enantiomers as shown in formulae B and C were determined by recrystallisations of both substances from isopropanol and subsequent analysis by single crystal X-ray diffraction.

EXAMPLE 2

5 The Compounds B and C of Example 1 were formulated as a capsule in gelatin and orally administered to 10 mixed breed dogs at a rate of 20 mg of the compound per kg of body weight of the animal treated.

All animals were infested with cat fleas (*Ctenocephalides felis*) and brown dog ticks (*Rhipicephalus sanguineus*) 1 day prior to administration of the compounds.

10 Counts of arthropods were made 1 day after treatment (DAT). Immediately after the determination of efficacy all arthropods were removed from the dogs. The animals were re-infested with arthropods at 8, 15, 22, and 30 days after treatment and efficacy determinations were made at 9, 16, 23, and 31 days after treatment.

The following efficacy results were obtained in per cent (%) mortality of the

15 arthropods test.

	Compound B	Compound B	Compound C	Compound C
DAT	Flea	Tick	Flea	Tick
1	100	99	100	97
9	96	97	86	96
16	86	87	69	85
23	88	86	67	77
31	84	92	69	81

Within 5 hours after administration of the compounds, 50% of the dogs treated with the S-enantiomer showed emesis whereas 90% of the dogs treated with the R-enantiomer showed emesis.

EXAMPLE 3:

- 5 The test of EXAMPLE 2 was repeated at the levels indicated and the following results were obtained:

Compound B						Compound C						
1mg/kg		3 mg/kg		10 mg/kg		1 mg/kg		3mg/kg		10mg/kg		
DAT	Flea	Tick	Flea	Tick	Flea	Tick	Flea	Tick	Flea	Tick	Flea	Tick
1	100	100	100	98	100	99	100	100	100	93	100	97
9	100	100	98	99	99	100	100	100	78	89	95	97
16	90	87	67	75	87	85	76	66	72	71	72	71
23	79	85	50	63	83	85	72	78	64	65	86	71

At 1 mg/kg treatment level, neither compound showed emesis in the animals

- 10 At 3 mg/kg treatment level 20% of the animals treated with Compound C showed emesis symptoms after 2 hours.

At 10 mg/kg treatment level 40% of the animals treated with Compound C showed emesis symptoms after 1 hour. After 3 hours 20% of the animals treated showed emesis symptoms.

- 15 There were substantially no symptoms of emesis in animals treated with Compound B at any rate.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A composition comprising (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and (R)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole wherein the composition is enriched in the (S) enantiomer.
2. The composition according to Claim 1 wherein the composition is substantially enriched in the (S) enantiomer.
3. The composition according to either Claim 1 or Claim 2 wherein the S/R weight-weight ratio is at least approximately 2 or greater.
4. The composition according to any one of Claims 1 to 3, wherein the S/R weight-weight ratio is at least approximately 5 or greater.
5. The composition according to any one of Claims 1 to 4, wherein the S/R weight-weight ratio is at least approximately 10 or greater.
6. The composition according to any one of the foregoing claims in association with a pesticidally acceptable carrier.
7. The composition according to any one of the foregoing claims which is acceptable for use in veterinary medicine.
8. The composition according to any one of claims 1 - 6 which is acceptable for use in agriculture.
9. The composition according to any one of claims 1 - 6 which is acceptable for use in public health.
10. A method of controlling pests at a locus which method comprises applying the composition as defined in any one of the foregoing claims in a pesticidally effective amount at the locus.
11. The method according to claim 10 wherein the locus is an animal.

12. The method according to claim 11 wherein the composition is administered to the animal orally.

5 13. The isolated compound (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole.

14. A method of controlling pests at a locus which method comprises applying the compound as defined in Claim 13 in a pesticidally effective amount at the locus.

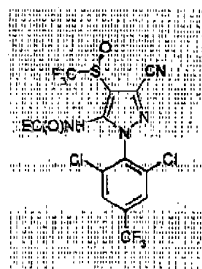
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15. The method according to claim 14 wherein the locus is an animal.

16. The method according to claim 15 wherein the compound is administered to the animal orally.

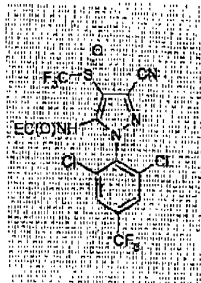
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17. A compound of the formula



(III-A)

20 or



(III-B)

wherein E is an organic radical which is enantiomerically enriched.

5

18. A composition comprising (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and (R)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole wherein the composition is enriched in the (R) enantiomer.

10

19. The isolated compound (R)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole.

15

20. A composition comprising (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and (R)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole wherein the composition is substantially enriched in the (R) enantiomer so as to have a R/S weight-weight ratio of at least approximately 2 or greater.

20

21. The composition according Claim 20 wherein the composition is substantially enriched in the (R) enantiomer so as to have a R/S weight-weight ratio of at least approximately 5 or greater.

25

22. The composition according to either Claim 20 or Claim 21 wherein the composition is substantially enriched in the (R) enantiomer so as to have a R/S weight-weight ratio of at least approximately 10 or greater.

23. A composition comprising (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and (R)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole wherein the composition is enriched in the (S) enantiomer, substantially as herein described with
5 reference to the Examples.

24. A method of controlling pests at a locus, substantially as herein described with reference to the Examples.

10 25. A composition comprising (S)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole and (R)-5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole wherein the composition is enriched in the (R) enantiomer, substantially as herein described with
15 reference to the Examples.

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