ENDOPARASITE CONTROL AGENT

An object of the present invention is to provide a novel endoparasite control agent as a parasiticide, an antiprotozoal or the like. Provided is an endoparasite control agent comprising a carboxamide derivative represented by the general formula (I):

\[(X)_m \text{Het} E\text{N}^+\text{A}^-\text{B\text{O}}\]

(wherein Het represents a 5- or 6-membered heterocyclic group), or a salt thereof as an active ingredient.
TECHNICAL FIELD

[0001] The present invention relates an endoparasite control agent comprising a carboxamide derivative or a salt thereof as an active ingredient, and a method for controlling endoparasites, comprising orally or parenterally administering the endoparasite control agent.

BACKGROUND ART

[0002] Generally, parasitosis is caused by infestation of host animals with parasites such as unicellular protists (protozoa), multicellular helminths and arthropods. It is reported that the incidence of parasitosis in advanced countries has been remarkably decreased by improvement of environmental hygiene, but on a global scale, particularly in developing countries, parasitosis still widely prevails and causes tremendous damage.

[0003] In recent years, even in advanced countries, there has been an increasing trend in the incidence of parasitosis. This is partly because of introduction of infection sources via long- or short-term overseas travelers, and partly because of parasitic infection due to ingestion of food imports, frozen foods, raw meat, fish meat, etc. or via domestic animals and pets. Another problem is that immunodeficiency caused by mass administration of immunosuppressants, anticancer drugs, etc. or by AIDS etc. allows usually non-pathogenic or low-pathogenic parasites to express their pathogenicity and to cause opportunistic infection in hosts.

[0004] Further, parasitosis in domestic animals, such as pigs, horses, cattle, sheep, dogs, cats and domestic fowls, is a universal and serious economic problem. That is, parasitic infection of domestic animals causes anemia, malnutrition, debility, weight loss, and serious damage of intestinal tract walls, tissues and organs, and may result in decline in feed efficiency and productivity, leading to a great economic loss. Therefore, novel endoparasite control agents as a parasiticide, an antiprotozoal or the like have always been desired.

[0005] Certain kinds of carboxamide derivatives have been known to have microbicidal activity (see Patent Literature 1 to 13). Further, it is known that certain kinds of carboxamide derivative are effective against nematodes that may damage agricultural products (see Patent Literature 4 or 5). However, Patent Literature 1 to 13 has neither description nor suggestion that the disclosed compounds are effective against endoparasites in animals such as mammals and birds.

[0006] Furthermore, it has been reported that compounds that inhibit succinate-ubiquinone reductase (mitochondrial complex II), which is one of the respiratory enzymes of endoparasites, can serve as an endoparasite control agent (see Non Patent Literature 1), but it has been unknown whether carboxamide derivatives have inhibitory effect on succinate-ubiquinone reductase (mitochondrial complex II). Further, Patent Literature 1 to 13 has neither description nor suggestion on any inhibitory activity of the disclosed carboxamide derivatives on succinate-ubiquinone reductase (mitochondrial complex II).

CITATION LIST

Patent Literature

[0007]

Patent Literature 1: JP-A 01-151546
Patent Literature 7: WO 2008/101975
Patent Literature 8: WO 2008/101976
SUMMARY OF INVENTION

TECHNICAL PROBLEM

In view of the above-described circumstances, an object of the present invention is to provide a novel endoparasite control agent as a parasiticide, an antiprotozoal or the like.

SOLUTION TO PROBLEM

The present inventors conducted extensive research to solve the above-described problems. As a result, the present inventors found that a carboxamide derivative represented by the general formula (I), and a salt thereof have a high control effect against endoparasites. The present inventors further conducted a great deal of examination and then completed the present invention.

That is, the present invention relates to the following.

[1] An endoparasite control agent comprising a carboxamide derivative represented by the general formula (I):

\[(X)_m \quad \text{Het} \quad \text{E} \quad \text{N} \quad \text{A} \quad \text{B} \quad \text{(I)}\]

(wherein Het represents a 5- or 6-membered heterocyclic group,

each X may be the same or different, and represents a halogen atom; a cyano group; an amino group; a (C<sub>1</sub>-C<sub>6</sub>) alkyl group; a halo (C<sub>1</sub>-C<sub>6</sub>) alkyl group; a (C<sub>1</sub>-C<sub>6</sub>) haloalkyl group; a halo (C<sub>1</sub>-C<sub>6</sub>) alkoxy group; a halo (C<sub>1</sub>-C<sub>6</sub>) alkylthio group; a halo (C<sub>1</sub>-C<sub>6</sub>) alkylsulfinyl group; a halo (C<sub>1</sub>-C<sub>6</sub>) alkylsulfonyl group; or a halo (C<sub>1</sub>-C<sub>6</sub>) alkylsulfonyl group,

m represents an integer of 0 to 5,

A represents a (C<sub>1</sub>-C<sub>8</sub>) alkylene group; or a substituted (C<sub>1</sub>-C<sub>8</sub>) alkylene group having one or more substituents selected from a halogen atom, a (C<sub>1</sub>-C<sub>6</sub>) alkyl group and a (C<sub>3</sub>-C<sub>6</sub>) cycloalkyl group, with the proviso that the (C<sub>1</sub>-C<sub>8</sub>) alkylene group and the substituted (C<sub>1</sub>-C<sub>8</sub>) alkylene group may be modified by incorporation, into the carbon chain, of at least one group selected from -O-, -S-, -SO-, -SO<sub>2</sub>- and -N(R)- (wherein R represents a hydrogen atom, a (C<sub>1</sub>-C<sub>6</sub>) alkyl group, a (C<sub>3</sub>-C<sub>6</sub>) cycloalkyl group, a (C<sub>1</sub>-C<sub>6</sub>) alkylcarbonyl group or a (C<sub>1</sub>-C<sub>6</sub>) alkoxycarbonyl group), and with the proviso that when the alkylene group or the substituted alkylene group having one or more substituents is a (C<sub>3</sub>-C<sub>8</sub>) alkylene group or a (C<sub>2</sub>-C<sub>8</sub>) alkylene group modified by incorporation, into the carbon chain, of at least one group selected from -O-, -S-, -SO-, -SO<sub>2</sub>- and -N(R)- (wherein R is as defined above), A may form a cyclic structure,

E represents a hydrogen atom; a (C<sub>1</sub>-C<sub>6</sub>) alkyl group; a (C<sub>3</sub>-C<sub>8</sub>) cycloalkyl group; a (C<sub>1</sub>-C<sub>6</sub>) alkoxy (C<sub>1</sub>-C<sub>6</sub>) alkyl group; a (C<sub>1</sub>-C<sub>6</sub>) alkylcarbonyl group; or a (C<sub>1</sub>-C<sub>6</sub>) alkoxyalkyl group, and

B represents any of the moieties represented by the following B1 to B8:

B1

\[\text{Y}_n\]

B2

\[\text{Y}_n\]

B3

\[\text{Y}_n\]

B4

\[\text{Y}_n\]
(wherein each Y may be the same or different, and represents a halogen atom; a cyano group; a nitro group; a hydroxy group; a (C1-C6) alkyl group; a halo (C1-C6) alkyl group; a (C2-C6) alkenyl group; a halo (C2-C6) alkenyl group; a halo (C2-C6) alkynyl group; a halo (C2-C6) alkynyl group; a halo (C2-C6) alkoxy group; a halo (C2-C6) alkoxy group; a halo (C2-C6) alkynyl group; a halo (C2-C6) alkynyl group; a halo (C2-C6) alkythio group; a halo (C2-C6) alkythio group; a halo (C2-C6) alkylsulfinyl group; a halo (C2-C6) alkylsulfinyl group; a halo (C2-C6) alkylsulfonyl group; a halo (C2-C6) alkylsulfonyl group; a halo (C2-C6) alkoxyimino (C1-C3) alkyl group; a (C3-C30) trialkylsilyl group; a mono (C1-C6) alkysulfonylamino group; a mono halo (C1-C6) alkysulfonylamino group; a phenyl group; a substituted phenyl group having one or more substituents selected from group Z substituents on the ring; a phenoxy group; a substituted phenoxy group having one or more substituents selected from group Z substituents on the ring; a heterocyclic group; a substituted heterocyclic group having one or more substituents selected from group Z substituents on the ring; a heterocycloxy group; or a substituted heterocycloxy group having one or more substituents selected from group Z substituents on the ring,

the group Z substituents are a halogen atom; a cyano group; a nitro group; a (C1-C6) alkyl group; a halo (C1-C6) alkyl group; a (C2-C6) alkenyl group; a halo (C2-C6) alkenyl group; a (C2-C6) alkynyl group; a halo (C2-C6) alkynyl group; a (C1-C6) alkoxy group; a halo (C1-C6) alkoxy group; a (C2-C6) alkenyloxy group; a halo (C2-C6) alkenyloxy group; a (C2-C6) alkynyloxy group; a halo (C2-C6) alkynyloxy group; a (C1-C6) alkylthio group; a halo (C1-C6) alkylthio group; a (C1-C6) alkylsulfinyl group; a halo (C1-C6) alkylsulfinyl group; a (C1-C6) alkylsulfonyl group; a halo (C1-C6) alkylsulfonyl group; a (C1-C6) alkoxyimino (C1-C3) alkyl group, a (C3-C30) trialkylsilyl group; a mono (C1-C6) alkysulfonylamino group; a mono halo (C1-C6) alkysulfonylamino group; a phenyl group; a substituted phenyl group having one or more substituents selected from group Z substituents on the ring; a phenoxy group; a substituted phenoxy group having one or more substituents selected from group Z substituents on the ring; a heterocyclic group; a substituted heterocyclic group having one or more substituents selected from group Z substituents on the ring; a heterocycloxy group; or a substituted heterocycloxy group having one or more substituents selected from group Z substituents on the ring,

the numbers on each ring represent positions where the ring can be substituted by Y and the free bond extending from each ring is a bond between A and B), or

a salt thereof as an active ingredient.

[2] The endoparasite control agent according to the above [1], wherein Het is any moiety selected from the following Het1 to Het17:
(wherein each X may be the same or different, and represents a halogen atom; a cyano group; a nitro group; an amino group; a (C1-C6) alkyl group; a halo (C1-C6) alkyl group; a (C1-C6) alkoxy group; a halo (C1-C6) alkoxy group; a (C1-C6) alkythio group; a halo (C1-C6) alkythio group; a (C1-C6) alkylsulfanyl group; a halo (C1-C6) alkylsulfanyl group; a (C1-C6) alkylsulfinyl group; a halo (C1-C6) alkylsulfinyl group; a (C1-C6) alkylsulfonyl group; or a halo (C1-C6) alkylsulfonyl group,

X1 represents a (C1-C6) alkyl group; or a halo (C1-C6) alkyl group,
m represents an integer of 0 to 5, and
the numbers on each ring represent positions where the ring can be substituted by X and the free bond extending from each ring is a bond between Het and the carbonyl group in the general formula (I)).

[3] The endoparasite control agent according to the above [2], wherein Het is Het1, Het2, Het4, Het14 or Het15.

[4] The endoparasite control agent according to any one of the above [1] to [3], wherein A is a (C1-C8) alkylene group; or a substituted (C1-C8) alkylene group having one or more substituents selected from a halogen atom, a (C1-C6) alkyl group and a (C3-C6) cycloalkyl group.

[5] The endoparasite control agent according to any one of the above [1] to [4], wherein B is B1, B2 or B5.

[6] The endoparasite control agent according to the above [2], wherein Het is Het1, Het2, Het4, Het14 or Het15,
each X may be the same or different, and is a halogen atom; a (C1-C6) alkyl group; or a halo (C1-C6) alkyl group, m is 1 or 2,
A is a (C1-C6) alkylene group; or a (C1-C6) alkylene group substituted by a (C1-C6) alkyl group, E is a hydrogen atom,
B is B1, B2 or B5,
each Y may be the same or different, and is a halogen atom; a (C1-C6) alkyl group; a halo (C1-C6) alkyl group; a phenyl group; a substituted phenyl group having one or more substituents selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group on the ring; a phenoxy group; a substituted phenoxy group having one or more substituents selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group on the ring; a pyridyl group; a substituted pyridyl group having one or more substituents selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group on the ring; a pyridyloxy group; or a substituted pyridyloxy group having one or more or substituents selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group on the ring, and
n is an integer of 1 to 3.

[7] The endoparasite control agent according to the above [2], wherein Het is Het1, Het2, Het4, Het14 or Het15,
each X may be the same or different, and is a halogen atom; a (C1-C6) alkyl group; or a halo (C1-C6) alkyl group, m is 1 or 2,
A is a (C1-C6) alkylene group; or a (C1-C6) alkylene group substituted by a (C1-C6) alkyl group, E is a hydrogen atom,
B is B1,
each Y may be the same or different, and is a halogen atom; a (C1-C6) alkyl group; a halo (C1-C6) alkyl group; a phenyl group; a substituted phenyl group having one or more substituents selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group on the ring; a phenoxy group; a substituted phenoxy group having one or more substituents selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group on the ring; a pyridyl group; a substituted pyridyl group having one or more substituents selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group on the ring; a pyridyloxy group; or a substituted pyridyloxy group having one or more or substituents selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group on the ring, and
n is an integer of 1 to 3.
A method for controlling endoparasites, comprising orally or parenterally administering an effective amount of the endoparasite control agent according to any one of the above [1] to [7] to a non-human mammal or a bird.


[10] The method according to the above [9], wherein the non-human mammal is a domestic animal.

ADVANTAGEOUS EFFECTS OF INVENTION

[0012] The present invention provides a compound useful as an endoparasite control agent which excels in performance as compared with the conventional art.

DESCRIPTION OF EMBODIMENTS

[0013] The definitions in the carboxamide derivative represented by the general formula (I) are described below.

[0014] The "(C1-C6) alkoxy group" refers to a straight alkoxy group of 1 to 6 carbon atoms, for example, a methoxy group, an ethoxy group, a n-propoxy group, an isopropoxy group, a n-butoxy group, a sec-butoxy group, a tert-butoxy group, a n-pentyloxy group, an isopentyloxy group, a neopentyloxy group, a n-hexyloxy group or the like. The "halo (C1-C6) alkoxy group" refers to a straight alkoxy group of 3 to 5 carbon atoms, for example, a chloromethoxy group, a bromomethoxy group or a 2,3-dichloropropoxy group.

[0015] The "halogen atom" refers to a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

[0016] The "(C1-C6) alkyl group" refers to a straight or branched alkyl group of 1 to 6 carbon atoms, for example, a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a n-pentyl group, a neopentyl group, a n-hexyl group or the like. The "halo (C1-C6) alkyl group" refers to a straight or branched alkyl group of 3 to 6 carbon atoms substituted by one or more halogen atoms which may be the same or different from each other, for example, a trifluoromethyl group, a difluoromethyl group, a perfluoromethyl group, a perfluoroethyl group, a hexafluoropropyl group, a perfluoroisopropyl group, a chloromethyl group, a bromomethyl group, a 1-bromoethoxy group, a 2,3-dibromopropoxy group.

[0017] The "(C3-C6) cycloalkyl group" refers to a cycloalkyl group of 3 to 6 carbon atoms, for example, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group or the like.

[0018] The "(C2-C6) alkynyl group" refers to a straight or branched alkynyl group of 2 to 6 carbon atoms, for example, an ethynyl group, a propynyl group, a butynyl group or the like. The "halo (C2-C6) alkynyl group" refers to a straight or branched alkynyl group of 2 to 6 carbon atoms substituted by one or more halogen atoms which may be the same or different from each other, for example, a chloroethynyl group, a fluoroethyl group, a 2,3-dichloroalkynyl group.

[0019] The "(C1-C6) alkoxy group" refers to a straight or branched alkoxy group of 1 to 6 carbon atoms, for example, a methoxy group, an ethoxy group, a n-propoxy group, an isopropoxy group, a n-butoxy group, a sec-butoxy group, a tert-butoxy group, a n-pentyloxy group, an isopentyloxy group, a neopentyloxy group, a n-hexyloxy group or the like. The "halo (C1-C6) alkoxy group" refers to a straight or branched alkoxy group of 1 to 6 carbon atoms substituted by one or more halogen atoms which may be the same or different from each other, for example, a fluorovinyl group, a difluorovinyl group, a perfluorovinyl group, a chlorovinyl group, a bromovinyl group, a hexafluoropropyl group.
The \((C_1-C_6)\) alkoxy \((C_1-C_6)\) alkoxy group refers to a straight or branched alkoxy group of 1 to 6 carbon atoms having a straight or branched alkoxy group of 1 to 6 carbon atoms as a substituent at a substitutable position, for example, a methoxymethoxy group, an ethoxymethoxy group, a 1-methoxyethoxy group, a 2-methoxyethoxy group, a 1-ethoxyethoxy group, a 2-ethoxyethoxy group or the like.

The \((C_1-C_6)\) alkyl group refers to a straight or branched alkyl group of 1 to 6 carbon atoms having a straight or branched alkyl group of 1 to 6 carbon atoms as a substituent at a substitutable position, for example, a methoxymethyl group, an ethoxymethyl group, a 1-methoxyethyl group, a 2-methoxyethyl group, a 1-ethoxyethyl group, a 2-ethoxyethyl group or the like.

The \((C_2-C_6)\) alkenyloxy group refers to a straight or branched alkenyloxy group of 2 to 6 carbon atoms, for example, a propenylene group, a butenylene group, a pentenylene group or the like.

The halo \((C_1-C_6)\) alkyl group refers to a straight or branched haloalkyl group of 1 to 6 carbon atoms substituted by one or more halogen atoms which may be the same or different from each other, for example, a chloromethyl group, a bromomethyl group, a 1-bromomethyl group, a 2,3-dibromopropyl group or the like.

The \((C_1-C_6)\) alkylsulfonyl group refers to a straight or branched alkylsulfonyl group of 1 to 6 carbon atoms, for example, a methylsulfonyl group, an ethylsulfonyl group, a n-propylsulfonyl group, an isopropylsulfonyl group, a n-butylsulfonyl group, a sec-butylsulfonyl group, a tert-butylsulfonyl group, a n-pentylsulfonyl group, an isopentylsulfonyl group, a n-hexylsulfonyl group or the like.

The \((C_1-C_6)\) alkylthio group refers to a straight or branched alkylthio group of 1 to 6 carbon atoms, for example, a methylthio group, an ethylthio group, a n-propylthio group, an isopropylthio group, a n-butylthio group, a sec-butylthio group, a tert-butylthio group, a n-pentylthio group, an isopentylthio group, a n-hexylthio group or the like.

The \((C_1-C_6)\) alkoxy (C1-C6) alkoxy group refers to a straight or branched alkoxy group of 1 to 6 carbon atoms having a straight or branched alkoxy group of 1 to 6 carbon atoms as a substituent at a substitutable position, for example, a trimethoxyethoxy group, an ethoxymethoxyethoxy group, an ethoxyethoxyethoxy group or the like.

The \((C_1-C_6)\) alkoxy (C1-C6) alkyl group refers to a straight or branched alkoxy group of 1 to 6 carbon atoms having a straight or branched alkyl group of 1 to 6 carbon atoms as a substituent at a substitutable position, for example, a methoxymethoxyethyl group, an ethoxymethoxyethyl group, a 1-methoxyethoxyethyl group, a 2-methoxyethoxyethyl group, a 1-ethoxyethoxyethyl group, a 2-ethoxyethoxyethyl group or the like.

The \((C_1-C_6)\) alkoxy (C1-C6) alkyl group refers to a straight or branched alkoxy group of 1 to 6 carbon atoms having a straight or branched alkyl group of 1 to 6 carbon atoms as a substituent at a substitutable position, for example, a chloromethylthioethyl group, a bromomethylthioethyl group, a 1-bromomethylthioethyl group, a 2,3-dibromopropylthio group or the like.

The \((C_1-C_6)\) alkoxy (C1-C6) alkyl group refers to a straight or branched alkoxy group of 1 to 6 carbon atoms having a straight or branched alkyl group of 1 to 6 carbon atoms as a substituent at a substitutable position, for example, a methoxymethylthio group, an ethoxymethylthio group, an isopropylthioethyl group, a n-butylthioethyl group, a 1-bromomethylthioethyl group, a 2,3-dibromopropylthio group or the like.

The \((C_2-C_6)\) alkenyloxy group refers to a straight or branched alkenyloxy group of 2 to 6 carbon atoms, for example, a propenylene group, a butenylene group, a pentenylene group or the like.

The \((C_1-C_6)\) alkenyloxy group refers to a straight or branched alkenyloxy group of 2 to 6 carbon atoms, for example, a propenylene group, a butenylene group, a pentenylene group or the like.

The \((C_1-C_6)\) alkoxy (C1-C6) alkoxy group refers to a straight or branched alkoxy group of 1 to 6 carbon atoms having a straight or branched alkoxy group of 1 to 6 carbon atoms as a substituent at a substitutable position, for example, a trimethoxyethoxy group, an ethoxymethoxyethoxy group, an ethoxyethoxyethoxy group or the like.

The \((C_1-C_6)\) alkoxy (C1-C6) alkyl group refers to a straight or branched alkoxy group of 1 to 6 carbon atoms having a straight or branched alkyl group of 1 to 6 carbon atoms as a substituent at a substitutable position, for example, a chloromethylthioethyl group, a bromomethylthioethyl group, a 1-bromomethylthioethyl group, a 2,3-dibromopropylthio group or the like.

The \((C_1-C_6)\) alkoxy (C1-C6) alkyl group refers to a straight or branched alkoxy group of 1 to 6 carbon atoms having a straight or branched alkyl group of 1 to 6 carbon atoms as a substituent at a substitutable position, for example, a methoxymethylthio group, an ethoxymethylthio group, an isopropylthioethyl group, a n-butylthioethyl group, a 1-bromomethylthioethyl group, a 2,3-dibromopropylthio group or the like.
 Examples of the "alkyleneoxy group" include -CH₂-CH₂-O-, -CH₂-O-(CH₃)₂-O-, -CH₂-CH₂-CH₂-O- and -CH₂-CH₂-CH₂-CH₂-O-.

The "halo (C₁-C₆) alkylsulfonyl group" refers to an alkylene sulfonate group of 1 to 3 carbon atoms, for example, -O-CH₂-O-, -O-CH₂-CH₂-O-, -O-CH₂-CH₂-CH₂-O- or the like. The "halo (C₁-C₆) alkylsulfonyl group" refers to an alkylene sulfonate group of 1 to 3 carbon atoms substituted by one or more halogen atoms which may be the same or different from each other, for example, -O-CF₂-O-, -O-CF₂-CF₂-O-, -O-CCl₂-O- or the like.

The "heterocyclic group" refers to a 5- or 6-membered monocyclic aromatic or 3- or 6-membered monocyclic non-aromatic heterocyclic group containing, as ring atoms, a carbon atom(s) and 1 to 4 heteroatoms selected from a nitrogen atom, an oxygen atom, a sulfur atom, a halogen atom or a (C₁-C₆) alkyl group. A is preferably a (C₁-C₈) alkylene group; or a substituted (C₁-C₈) alkylene group having a substituent(s) which may be the same or different from each other and is/are selected from a halogen atom, a (C₁-C₆) alkyl group and a (C₃-C₆) cycloalkyl group. It is also preferred that the (C₁-C₈) alkylene group and the substituted (C₁-C₈) alkylene group having a substituent(s) which may be the same or different from each other and is are selected from a halogen atom, a (C₁-C₈) alkylene group and a (C₃-C₆) cycloalkyl group. It is also preferred that the (C₁-C₈) alkylene group and the substituted (C₁-C₈) alkylene group having a substituent(s) which may be the same or different from each other and is are selected from a halogen atom, a (C₁-C₈) alkylene group and a (C₃-C₆) cycloalkyl group. It is also preferred that the (C₁-C₈) alkylene group and the substituted (C₁-C₈) alkylene group having a substituent(s) which may be the same or different from each other and is are selected from a halogen atom, a (C₁-C₈) alkylene group and a (C₃-C₆) cycloalkyl group. It is also preferred that the (C₁-C₈) alkylene group and the substituted (C₁-C₈) alkylene group having a substituent(s) which may be the same or different from each other and is are selected from a halogen atom, a (C₁-C₈) alkylene group and a (C₃-C₆) cycloalkyl group. It is also preferred that the (C₁-C₈) alkylene group and the substituted (C₁-C₈) alkylene group having a substituent(s) which may be the same or different from each other and is are selected from a halogen atom, a (C₁-C₈) alkylene group and a (C₃-C₆) cycloalkyl group.
phenyl group having, on the ring, a substituent (s) which may be the same or different from each other and is/are selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group; a phenoxy group; a substituted phenoxy group having, on the ring, a substituent(s) which may be the same or different from each other and is/are selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group; a pyridyl group; a substituted pyridyl group having, on the ring, a substituent(s) which may be the same or different from each other and is/are selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group; a pyridyloxy group; or a substituted pyridyloxy group having, on the ring, a substituent (s) which may be the same or different from each other and is/are selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group. Y is particularly preferably a halogen atom; a halo (C1-C6) alkyl group; or a substituted phenyl group having, on the ring, a substituent(s) which may be the same or different from each other and is/are selected from a halogen atom, a (C1-C6) alkyl group, a halo (C1-C6) alkyl group, a (C1-C6) alkoxy group and a halo (C1-C6) alkoxy group. Y1 is preferably a (C1-C6) alkyl group. n is preferably an integer of 1 to 3.

The carboxamide derivative represented by the general formula (I) can have one or more chiral centers or double bonds in the structural formula, and can exist as two or more kinds of optical isomers, diastereomers and geometric isomers. All mixtures of these isomers at any ratio are also included in the present invention.


Production Method 1

(In the formula, Het, X, A, E, B and m are as defined above, and hal represents a halogen atom.)

The carboxamide derivative represented by the general formula (I) can be produced by allowing an acid halide represented by the general formula (II) to react with an amine represented by the general formula (III) in the presence of a base in an inert solvent.

The reaction temperature in this reaction is usually from -20 to 120°C, and the reaction time is usually from 0.2 to 24 hours. The amine represented by the general formula (III) is usually used in a 0.8- to 5-fold molar amount relative to the acid halide represented by the general formula (II).

Examples of the base that can be used in the reaction include inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and potassium hydrogen carbonate; acetates such as sodium acetate and potassium acetate; alkali metal alkoxides such as potassium t-butoxide, sodium methoxide and sodium ethoxide; tertiary amines such as triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene; and nitrogen-containing aromatic compounds such as pyridine and dimethyl aminopyridine. The base is usually used in a 0.5- to 10-fold molar amount relative to the acid halide represented by the general formula (II).

The reaction may be performed with or without a solvent. As the solvent, any solvent can be used unless it markedly inhibits the reaction, and the examples include alcohols such as methanol, ethanol, propanol, butanol and 2-propanol; straight-chain or cyclic ethers such as diethyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as methylene chloride, chloroform and carbon tetrachloride; halogenated aromatic hydrocarbons such as chlorobenzene and dichlorobenzene; nitriles such as acetonitrile; esters such as ethyl acetate and butyl acetate; and polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, 1,3-dimethyl-2-imidazolidinone, water and acetic acid. These inert solvents may be used alone or as a mixture of two or more kinds.

After the reaction is completed, the compound of interest is isolated from the post-reaction mixture according
to a usual method. As needed, the compound of interest can be purified by recrystallization, column chromatography, etc.

The acid halide represented by the general formula (II) used for the reaction can be produced by the method described in known literature (for example, WO 05/115994, WO 01/42223, WO 03/066609, WO 03/066610, WO 03/099803, WO 03/099804, WO 03/080628 or the like) or a modified method thereof. The amine represented by the general formula (III) can be produced by the method described in WO 2007/108483 etc., or a modified method thereof.

Production Method 2

**[0054]**

![Diagram](https://via.placeholder.com/150)

(In the formula, Het, X, A, E, B and m are as defined above.)

The carboxamide derivative represented by the general formula (I) can be produced by allowing a carboxylic acid represented by the general formula (II') to react with an amine represented by the general formula (III) in the presence of a condensing agent and a base in an inert solvent.

Examples of the condensing agent used in this reaction include diethyl phosphorocyanidate (DEPC), carbon- yldimidazole (CDI), 1,3-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, chlorocarbonic esters and 2-chloro-1-methylpyridinium iodide. The condensing agent is usually used in a 0.5- to 3-fold molar amount relative to the carboxylic acid represented by the general formula (II').

The reaction temperature, the reaction time, the base, the solvent, the isolation method and the like are in accordance with those of Production Method 1.

Representative examples of the carboxamide derivative of the general formula (I) which have been produced by Production Method 1, 2 or the like are shown in Table 1, but the present invention is not limited thereto. In Table 1, "Ph" represents a phenyl group, "Py" represents a pyridyl group, and "Ac" represents an acetyl group. "Het1" to "Het16" and "B1" to "B8" are as defined above, and "A1" to "A7" represent the moieties shown below. The physical property refers to a melting point (°C) or a refractive index nD.

![Chemical Structures](https://via.placeholder.com/150)

**Table 1**

<table>
<thead>
<tr>
<th>No.</th>
<th>(X)m</th>
<th>X1</th>
<th>Het</th>
<th>E</th>
<th>A</th>
<th>B</th>
<th>(Y)m</th>
<th>Y1</th>
<th>Physical property</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-Cl</td>
<td>Het2</td>
<td>H</td>
<td>A1</td>
<td>B2</td>
<td>3-Cl</td>
<td>5-CF3</td>
<td>105-106</td>
<td></td>
</tr>
</tbody>
</table>
### Table: Physical Properties of Compounds

<table>
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<tr>
<th>No.</th>
<th>(X)ₘ X¹</th>
<th>Het</th>
<th>E</th>
<th>A</th>
<th>B</th>
<th>(Y)ₙ Y¹</th>
<th>Physical property</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2-NH₂-4-CF₃</td>
<td>Het14</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,4-Cl₂</td>
<td>173.5-174.8</td>
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<tr>
<td>3</td>
<td>3-CF₃</td>
<td>Het4</td>
<td>H</td>
<td>A1</td>
<td>B2</td>
<td>3-Cl-5-CF₃</td>
<td>130-131</td>
</tr>
<tr>
<td>4</td>
<td>3-CF₃</td>
<td>Het4</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2-Cl-4-(4-OCF₃-Ph)</td>
<td>124-125</td>
</tr>
<tr>
<td>5</td>
<td>3-CH₃</td>
<td>Het4</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>4-(4-OCF₃-Ph)</td>
<td>122-123</td>
</tr>
<tr>
<td>6</td>
<td>2-CF₃</td>
<td>Het2</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,4-Cl₂</td>
<td>133-139</td>
</tr>
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<td>A1</td>
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<td>2,4-Cl₂</td>
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<td>Het2</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,4-Cl₂</td>
<td>133-139</td>
</tr>
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<td>H</td>
<td>A1</td>
<td>B1</td>
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<td>H</td>
<td>A2</td>
<td>B1</td>
<td>2,4-Cl₂</td>
<td>164-166</td>
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<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2-Cl-4-F</td>
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<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2-F-4-(4-OCF₃-Ph)</td>
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</tr>
<tr>
<td>13</td>
<td>3-Cl</td>
<td>Het4</td>
<td>H</td>
<td>A5</td>
<td>B1</td>
<td>2,4-Cl₂</td>
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<td>B1</td>
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<td>A2</td>
<td>B1</td>
<td>2,4-Cl₂</td>
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<td>H</td>
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<td>2,4-Cl₂</td>
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<td>H</td>
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<td>B1</td>
<td>2-F-4-(4-OCF₃-Ph)</td>
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<tr>
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<td>H</td>
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<td>B1</td>
<td>2,4-Cl₂</td>
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<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2-Cl-4-Cl₂</td>
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<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2-F-4-Cl</td>
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<tr>
<td>21</td>
<td>3-CF₃</td>
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<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2-Cl-4-O(3-Cl-5-CF₂-Py-2-yl)</td>
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<tr>
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<td>3-CF₃</td>
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<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2-Cl-4-O(3-Cl-5-CF₂-Py-2-yl)</td>
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<tr>
<td>23</td>
<td>3-Cl</td>
<td>Het2</td>
<td>H</td>
<td>A2</td>
<td>B1</td>
<td>2-F-4-Cl</td>
<td>143.2-145.8</td>
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<tr>
<td>24</td>
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<td>Het4</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,5-F₂-4-Cl</td>
<td>110.3-112.9</td>
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<tr>
<td>25</td>
<td>2-Cl</td>
<td>Het2</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,5-F₂-4-Cl</td>
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<td>A2</td>
<td>B1</td>
<td>2-Cl-4,5-F₂</td>
<td>161.4-162.5</td>
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<tr>
<td>27</td>
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<td>Het4</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2-Cl-4,5-F₂</td>
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<td>28</td>
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<td>A1</td>
<td>B1</td>
<td>2,4-Cl₂-5-F</td>
<td>123.3-125.5</td>
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<td>29</td>
<td>2-Cl</td>
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<td>B1</td>
<td>2,4-Cl₂-5-F</td>
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<tr>
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<td>Het1</td>
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<td>A1</td>
<td>B1</td>
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<td>31</td>
<td>4-CF₃</td>
<td>Het2</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,4-Cl₂</td>
<td>116-117</td>
</tr>
<tr>
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<td>4-CF₃</td>
<td>Het7</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,4-Cl₂</td>
<td>145.7-146.5</td>
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<td>3-CF₃</td>
<td>Het8</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,4-Cl₂</td>
<td>139</td>
</tr>
<tr>
<td>34</td>
<td>1,3,5-(CH₃)₃</td>
<td>Het10</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,4-Cl₂</td>
<td>145-150</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>(X)ₘ X¹</th>
<th>Het</th>
<th>E</th>
<th>A</th>
<th>B</th>
<th>(Y)ₙ Y¹</th>
<th>Physical property</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>1,5-(CH₃)₂-3-CF₃</td>
<td>Het10</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,4-Cl₂</td>
<td>129</td>
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<td>1-Ac-3,5-(CH₃)₂</td>
<td>Het10</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,4-Cl₂</td>
<td>128-129</td>
</tr>
<tr>
<td>37</td>
<td>2,4-(CH₃)₂</td>
<td>Het14</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,4-Cl₂</td>
<td>95-97</td>
</tr>
<tr>
<td>38</td>
<td>2-CH₃-4-CF₃</td>
<td>Het14</td>
<td>H</td>
<td>A1</td>
<td>B1</td>
<td>2,4-Cl₂</td>
<td>136</td>
</tr>
</tbody>
</table>
The endoparasite control agent of the present invention has excellent anti-endoparasite effect, and exerts appropriate control effect against endoparasites. The animal for which the endoparasite control agent of the present invention can be used is a human, an animal of non-human mammalian or avian species, and a fish. Exemplary members of the non-human mammalian species include domestic animals, such as pigs, horses, cattle, sheep, goats, rabbits, camels, water buffalos, deer, mink and chinchillas; pet animals, such as dogs, cats and monkeys; and experimental animals, such as rats, mice, golden hamsters and guinea pigs. Exemplary members of the avian species include domestic fowls, such as chickens, ducks, aigamo ducks (crossbreeds of wild and domestic ducks), quails, domestic ducks, geese and turkeys. Exemplary members of the fish include marine farmed fish such as yellowtail, greater amberjack, red seabream, Japanese sea bass, olive flounder, striped jack, yellowtail amberjack, spotted knifejaw, cobia and Pacific bluefin tuna; and freshwater farmed fish such as sweetfish, seema, char, carp, crucian carp and rainbow trout.

Human endoparasites against which the endoparasite control agent of the present invention is effective are roughly classified into protozoa and helminths. Examples of the protozoa include, but are not limited thereto, Rhizopoda, such as Entamoeba histolytica; Mastigophora, such as Leishmania, Trypanosoma and Trichomonas; Sporozoea, such as Plasmodium and Toxoplasma; and Ciliophora, such as Balantidium coli. Examples of the helminths include, but are not limited thereto, Nematoda, such as Ascaris lumbricoides, Anisakis, Toxocara canis, Trichostrongylus spp., Enterobius vermicularis, hookworms (for example, Ancylostoma duodenale, Necator americanus, Ancylostoma braziliense, etc.), Angiostrongylus spp., Gnathostoma spp., filarial worms (filaria, Wuchereria bancrofti, Brugia malayi, etc.), Onchocerca volvulus, Dracunculus medinensis, Trichinella spiralis and Strongyloides stercoralis; Acanthocephala, such as Macracanthorhynchus hirudinaceus; Gordioidea, such as Gordioidea; Hirudinea, such as Hirudo nipponia; Trematoda, such as Schistosoma japonicum, Schistosoma mansoni, Schistosoma haematobium, Clonorchis sinensis, Heterophyes heterophyes, Fasciola spp. and Paragonimus spp.; and Cestoda, such as Diphyllolothrium latum, Sparganum mansoni, Sparganum proliferum, Diplogonoporus grandis, Taeniidae (for example, Taenia echinocola, Taenia solium, Echinococcus, etc.), Hymenolepis spp., Dipylidium caninum, Mesocestoides lineatus, Bertiella spp. and Nylbelinia surmencula.

Non-human mammalian or avian endoparasites against which the endoparasite control agent of the present invention is effective are roughly classified into protozoa and helminths. Examples of the protozoa include, but are not limited thereto, Apicomplexa, such as Coccidia (for example, Eimeria, Isospora, Toxoplasma, Neospora, Sarcocystis, Besnoitia, Hammondia, Cryptosporidium, Caryospirula, etc.), Haemosporina (for example, Leucocytozoon, Plasmodium, etc.), Tremaidae (for example, Theileria, Anaplasmata, Eperythrozoon, Haemobartonella, Ehrlichia, etc.), and others (for example, Hepatozoon, Haemogregarina, etc.); Microspora, such as Encephalitozoon and Nosema; Mastigophora, such as Trypanosomatina (for example, Trypanosoma, Leishmania, etc.), Trichomonadida (for example, Chilomastix, Trichomonas, Monocercomonas, Histomonas, etc.), and Diplomonadida (for example, Hexamita, Giardia, etc.); Sarcocystis, such as Homobosida (for example, Entamoeba histolytica (Entamoeba) etc.); and Ciliophora, such as Balanitida (Balanitida), Buxtonella and Entodinium.

Examples of the helminths include, but are not limited thereto, Nematoda, such as Ascaris (for example,
guatulida, such as Marshallagia multiceps (Multiiceps), Echinococcus granulosus (Spirometra), Paramphistomatidae (for example, etc.); Trematoda, such as Fasciolata (for example, Mesocestoides), Taenia pisiformis mamillana (Paranoplocephala), Moniezia benedeni (Moniezia), Dipylidium caninum (Dipylidium), Mesocestoides lineatus chobilharzia Acanthocephala (for example, lurostrongylus ovatus (Prosthogonimus) etc.), Opisthorchiida (for example, cordatum pancreaticum (Eurytrema), Dicrocoelium dendriticum (Dicrocoelium), equorum (Parascaris), Ascaridia galli (Ascaridia), Heterakis gallinarum etc.); Trematoda including subclasses, such as Monogenea (for example, Elaphostrongylus spp., etc.), Spirurida (for example, Fasciolopsis Gigantoctyle Parafilaria), Oxyurida (for example, Elaphostrongylus spp., etc.), Ascaridia (for example, Macracanthorhynchus hirudinaceus, etc.), and Schistosomatidae (for example, Metagonimus yokogawai, etc.), Echinostomata (for example, Heterophyes, Metagonimus yokogawai (Metagonimus), etc.), Strongylida (for example, Prosthogonimus ovatus (Prosthogonimus) etc.), and Schistosomatidae (for example, Schistosoma japonicum (Schistosoma) etc.); Cestoda, such as Pseudophyllidea (for example, Diphyllobothrium nihonkaiense (Diphyllobothrium), Spirometra erinacei (Spirometra), etc.), and Cyclophyllidea (for example, Anoplocephala perfoliata (Anoplocephala), Paranoplocephala mamillana (Paranoplocephala), Moniezia benedeni (Moniezia), Dipylidium caninum (Dipylidium), Mesocostoides lineatus (Mesocostoides), Taenia pisiformis and Taenia hydatigena (Taenia), Hydatigera taeniaeformis (Hydatigera), Multipect multiceps (Multipect), Echinococcus granulosus (Echinococcus), Echinococcus multilocularis (Echinococcus), Taenia solium (Taenia), Taeniarhynchus saginatus (Taeniarhynchus), Hymenolepis diminuta (Hymenolepis), Vampiroplepis nana (Vampiroplepis), Raillietina tetragona (Raillietina), Amoebotaenia sphenoidea (Amoebotaenia), etc.); Acanthocephala, such as Macracanthorhynchus hirudinaceus and Moniliformis moniliformis (Moniliformis); Linguatulida, such as Linguatula serrata (Linguatula); and other various parasites.

In different designations, examples of the helminths include, but are not limited to, Nematoda, such as Enoploida (for example, Trichuris spp., Capillaria spp., Trichomosoides spp., Trichinella spp., etc.), and Schistosomatidae (for example, Schistosoma japonicum (Schistosoma) etc.); Cestoda, such as Pseudophyllidea (for example, Diphyllobothrium nihonkaiense (Diphyllobothrium), Spirometra erinacei (Spirometra), etc.), and Cyclophyllidea (for example, Anoplocephala perfoliata (Anoplocephala), Paranoplocephala mamillana (Paranoplocephala), Moniezia benedeni (Moniezia), Dipylidium caninum (Dipylidium), Mesocostoides lineatus (Mesocostoides), Taenia pisiformis and Taenia hydatigena (Taenia), Hydatigera taeniaeformis (Hydatigera), Multipect multiceps (Multipect), Echinococcus granulosus (Echinococcus), Echinococcus multilocularis (Echinococcus), Taenia solium (Taenia), Taeniarhynchus saginatus (Taeniarhynchus), Hymenolepis diminuta (Hymenolepis), Vampiroplepis nana (Vampiroplepis), Raillietina tetragona (Raillietina), Amoebotaenia sphenoidea (Amoebotaenia), etc.); Acanthocephala, such as Macracanthorhynchus hirudinaceus and Moniliformis moniliformis (Moniliformis); Linguatulida, such as Linguatula serrata (Linguatula); and other various parasites.

Examples of fish parasites include skin parasites, such as *Neobenedenia girellos*, *Benedenia serialae*, *Benedenia seki*, *Benedenia hoshinai*, *Benedenia epinepheli*, *Benedenia girellos*, *Anoplodiscus* spp., *Nanopplectus* spp., *Cirriformella* spp., *Uronema* spp., *Echinoderiella* spp., *Echinolepis* spp., *Pseudocaligus fugu*; and gill parasites, such as *Heteraxine heterocerca*, *Zeuxapta japonica*, *Bivagina tai*, *Heterobothrium okamotoi*, *Heterobothrium tetrodonis*, *Neoheterobothrium hirame* and *Caligus spinosus*. Also included are *Dactylogyrus*, *Pseudodactylogyrus*, *Tetraonchus*, *Gyrodactylus*, *Benedenia*, *Neobenedenia* and *Anoplodiscus*; *Polyopisthocotylea*, such as *Microcotyle*, *Bivagina*, *Heteraxine*, *Heterobothrium*, *Neoheterobothrium* and *Eudiplozoon*; *Trematoda*, such as *Diplostomum*, *Galactosomum* and *Paradeontactylus*; and *Cestoda*, such as *Bothriocephalus* and *Proteocephalus*.

Also included are *Anguillicoloides*, *Philometra* and *Philometroides*; *Acantoecephalus*; *Ancephalota* and *Longicolum*; *Bivalvia* (a class of the phylum *Mollusca*), such as *Margartifera*; *Hirudinea* (a class of the phylum Annelida), such as *Limnorchelobdella*; and *Crustacea* (a subphylum of the phylum *Arthropoda*), such as *Ergasilus*, *Lemna*, *Caligus*, *Bromolochus*, *Chondrochaenus*, *Lepeophetheirus* (for example, *L. salmonis* etc.), *Elythrophora*, *Dicheleistum*, *Lamprotoglenz*, *Hatschekia*, *Legosphiilus*, *Spymphodus*, *Ceudroalus*, *Pseudoscyymnus*, *Lernaecorea*, *Pennaella*, *Achthales*, *Basanistes*, *Salmincola*, *Brachiella*, *Epibrachiella* and *Pseudotrichelasties*. Further included are *Ergasilidae*, *Bromolochidae*, *Chondracanthidae*, *Caligidae*, *Phylichthyidae*, *Pseudocycentidae*, *Lernaeidae*, *Lernaeopodidae*, *Sphyriidae*, *Cercopidae*, *Copepoda* (for example, *Cyclops*, *fish-lice*, etc.), *Branchiura* (carp lice), which includes the family *Argulidae*, *Moniezia* spp., *Diplostomum*, *Galactosomum* and *Paradeontactylus*; and *Cestoda*, such as *Bothriocephalus* and *Proteocephalus*.

The endoparasite control agent of the present invention is effective against not only parasites that live in the body of an intermediate or final host, but also parasites that live in the body of a reservoir host. The carbamoxime derivative represented by the general formula (I) is effective at every developmental stage of parasites. For example, in the case of protozoa, the compound is effective against their cysts, precystic forms and trophozoites; schizonts and amoeboid forms at the asexual stage; gametocytes, gametes and zygotes at the sexual stage; sporozoites; etc. In the case of nematodes, the compound is effective against their eggs, larvae, and adults. The compound of the present invention is capable of not only combating parasites in the living body, but also even preventing parasitic infection by application to the environment as a route of infection. For example, soil-borne infection, i.e., infection from soil of crop fields and parks; percutaneous infection from water in rivers, lakes, marshes, paddy fields, etc.; oral infection from feces of animals such as dogs and cats; oral infection from saltwater fish, freshwater fish, crustaceans, shellfish, raw meat of domestic animals, etc.; infection from mosquitoes, gadflies, flies, cockroaches, mites, fleas, lice, assassin bugs, trombiculid mites, etc.; and the like can be prevented from occurring.

The endoparasite control agent of the present invention can be administered as a pharmaceutical for treatment or prevention of parasitosis in humans, animals of non-human mammalian or avian species and fish. The mode of administration may be oral or parenteral administration. In the case of oral administration, the endoparasite control agent of the present invention can be administered, for example, as a capsule, a tablet, a pill, a powder, a granule, a fine granule, a powder, a syrup, an enteric-coated preparation, a suspension or a paste, or after blended in a liquid drink or feed for animals. In the case of parenteral administration, the endoparasite control agent of the present invention can be administered in a dosage form which allows sustained mucosal or percutaneous absorption, for example, as an injection, an infusion, a suppository, an emulsion, a suspension, a drop, an ointment, a cream, a solution, a lotion, a spray, an aerosol, a cataplasm or a tape.

In the case where the endoparasite control agent of the present invention is used as a pharmaceutical for humans, animals of non-human mammalian or avian species and fish, the optimum amount (effective amount) of the active ingredient varies with the purpose (treatment or prevention), the kind of infectious parasite, the type and severity of infection, the dosage form, etc., but in general, the oral daily dose is in the range of about 0.001 to 10000 mg/kg body weight and the parenteral daily dose is in the range of about 0.001 to 10000 mg/kg body weight, and such a dose may be administered as a single dose or multiple doses.

The concentration of the active ingredient in the endoparasite control agent of the present invention is generally about 0.001 to 100% by mass, preferably about 0.001 to 99% by mass, and more preferably about 0.005 to 20% by mass.
mass. The endoparasite control agent of the present invention may be a composition that can be directly administered, or a highly concentrated composition that is used for administration after diluted to a suitable concentration. [0073] For the purpose of reinforcing or complementing the effect of the endoparasite control agent of the present invention, a combined use with any existing endoparasite control agent is possible. In such a combined use, two or more active ingredients may be mixed and formulated into a preparation before administration, or two or more different preparations may be administered separately.

EXAMPLES

[0074] Next, the present invention will be illustrated in detail by formulation examples and test examples of the endoparasite control agent of the present invention, but the scope of the present invention is not limited by the following formulation examples and test examples.

[0075] In the Examples, the "part(s)" refers to a part(s) by weight.

Formulation Example 1 (emulsion)

[0076] Ten parts of the carboxamide derivative represented by the general formula (I), 6 parts of Sorpol 355S (surfactant, manufactured by Toho Chemical Industry), and 84 parts of Solvesso 150 (manufactured by Exxon) are uniformly mixed with stirring to give an emulsion.

Formulation Example 2 (ointment)

[0077] One part of the carboxamide derivative represented by the general formula (I), 50 parts of white beeswax, and 49 parts of white petrolatum are well mixed to give an ointment.

Formulation Example 3 (tablet)

[0078] Two parts of the carboxamide derivative represented by the general formula (I), 10 parts of vegetable oil (olive oil), 3 parts of crystalline cellulose, 20 parts of white carbon, and 65 parts of kaolin are well mixed and compressed into a tablet.

Formulation Example 4 (injection)

[0079] Ten parts of the carboxamide derivative represented by the general formula (I), 10 parts of propylene glycol for use as a food additive, and 80 parts of vegetable oil (corn oil) are mixed to give an injection.

Formulation Example 5 (solution)

[0080] Five parts of the carboxamide derivative represented by the general formula (I), 20 parts of surfactant, and 75 parts of ion exchanged water are well mixed to give a solution.

Test Example 1 (in vitro measurement of inhibitory activity on Ascaris suum succinate-ubiquinone reductase (mitochondrial complex II))

[0081] To a solution containing 50 mM potassium phosphate (pH 7.4) and 0.1% (w/v) sucrose monolaurate, an electron acceptor ubiquinone-2 (UQ2) was added at a final concentration of 60 μM, and the mixture was allowed to stand at 25°C for 20 minutes. To this, potassium cyanide (final concentration: 2 mM) and mitochondria prepared from adult Ascaris suum muscle were added, and thorough mixing was done. To aliquots of the mixture, an inhibitor to be tested was added at various concentrations, and the mixtures were allowed to stand at 25°C for 3 minutes. The enzymatic reaction was initiated by addition of potassium succinate (final concentration: 10 mM). The enzymatic activity was calculated based on the measurement of change in the absorbance at 278 nm of UQ2 (ε = 1.5 × 10^4 M^-1 cm^-1), and IC50 was determined from the plot of the inhibition percentage against the inhibitor concentration. The results are shown in Table 2.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Ascaris suum IC50 value (A)</th>
<th>Compound No.</th>
<th>Ascaris suum IC50 value (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47 nM</td>
<td>23</td>
<td>10 nM</td>
</tr>
</tbody>
</table>
As is clear from the results in Table 2, the carboxamide derivatives represented by the general formula (I) and salts thereof showed a strong inhibitory activity on the parasitic succinate-ubiquinone reductase (mitochondrial complex II) (IC$_{50}$ values: 1.1 to 57 nM). Therefore, the carboxamide derivatives and salts thereof are highly active in parasite control.

Test Example 2 (in vivo activity test on *Haemonchus* nematode)

In a 96-well plate, twenty LI-stage larvae (*Haemonchus contortus*) per well were maintained so that they could freely move, and solutions of compounds of the present invention dissolved at predetermined concentrations in DMSO (the final concentration of DMSO was 0.78% (v/v)) were added at 0.5 μl/well each. The plate was kept under the conditions of 27°C/95%RH for 4 days. The motor ability of the larvae was examined and the concentration required for 50% inhibition of the motor ability (EC$_{50}$) was determined. Based on the EC$_{50}$ value, the activity against the *Haemonchus* nematode was graded according to the criterion shown below. The results are shown in Table 3.

Grading criterion

A: The EC$_{50}$ value is lower than 0.5 ppm.
B: The EC$_{50}$ value is 0.5 ppm or higher but lower than 5 ppm.
C: The EC$_{50}$ value is 5 ppm or higher.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Ascaris suum IC$_{50}$ value (A)</th>
<th>Compound No.</th>
<th>Ascaris suum IC$_{50}$ value (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>57 nM</td>
<td>24</td>
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<tr>
<td>3</td>
<td>9.4 nM</td>
<td>25</td>
<td>18 nM</td>
</tr>
<tr>
<td>4</td>
<td>1.3 nM</td>
<td>26</td>
<td>2.9 nM</td>
</tr>
<tr>
<td>5</td>
<td>26 nM</td>
<td>27</td>
<td>2.2 nM</td>
</tr>
<tr>
<td>6</td>
<td>4.4 nM</td>
<td>28</td>
<td>1.3 nM</td>
</tr>
<tr>
<td>7</td>
<td>1.1 nM</td>
<td>29</td>
<td>6.7 nM</td>
</tr>
<tr>
<td>11</td>
<td>3.4 nM</td>
<td>30</td>
<td>6.0 nM</td>
</tr>
<tr>
<td>13</td>
<td>2.7 nM</td>
<td>31</td>
<td>42 nM</td>
</tr>
<tr>
<td>14</td>
<td>3.3 nM</td>
<td>33</td>
<td>7.3 nM</td>
</tr>
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<td>42 nM</td>
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<tr>
<td>17</td>
<td>2.0 nM</td>
<td>42</td>
<td>13 nM</td>
</tr>
<tr>
<td>18</td>
<td>3.1 nM</td>
<td>43</td>
<td>9.9 nM</td>
</tr>
<tr>
<td>19</td>
<td>1.3 nM</td>
<td>44</td>
<td>20 nM</td>
</tr>
<tr>
<td>20</td>
<td>4.9 nM</td>
<td>45</td>
<td>4.5 nM</td>
</tr>
<tr>
<td>21</td>
<td>1.3 nM</td>
<td>47</td>
<td>2.3 nM</td>
</tr>
<tr>
<td>22</td>
<td>1.7 nM</td>
<td>50</td>
<td>1.6 nM</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Grade</th>
<th>Compound No.</th>
<th>Grade</th>
</tr>
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<tr>
<td>1</td>
<td>A</td>
<td>22</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>23</td>
<td>A</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>24</td>
<td>A</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>25</td>
<td>A</td>
</tr>
</tbody>
</table>
As is clear from the results in Table 3, the carboxamide derivatives represented by the general formula (I) and salts thereof were graded as B or higher in the in vivo test using the *Haemonchus* nematode. Therefore, the carboxamide derivatives and salts thereof also have a strong and high in vivo activity in parasite control.

### Claims

1. An endoparasite control agent comprising a carboxamide derivative represented by the general formula (I):

![Chemical Structure](image)

\[
\text{wherein } \text{Het represents a 5- or 6-membered heterocyclic group,}
\]

\(X\) may be the same or different, and represents a halogen atom; a cyano group; a nitro group; an amino group; a (C\(_1\)–C\(_6\)) alkyl group; a halo (C\(_1\)–C\(_6\)) alkyl group; a (C\(_1\)–C\(_8\)) alkoxy group; a halo (C\(_1\)–C\(_8\)) alkoxy group; a (C\(_1\)–C\(_6\)) alkylthio group; a halo (C\(_1\)–C\(_6\)) alkylthio group; a (C\(_1\)–C\(_6\)) alkylsulfinyl group; a halo (C\(_1\)–C\(_6\)) alkylsulfinyl group; a (C\(_1\)–C\(_6\)) alkylsulfonyl group; or a halo (C\(_1\)–C\(_6\)) alkylsulfonyl group,

\(m\) represents an integer of 0 to 5,

\(A\) represents a (C\(_1\)–C\(_6\)) alkylene group; or a substituted (C\(_1\)–C\(_6\)) alkylene group having one or more substituents selected from a halogen atom, a (C\(_1\)–C\(_6\)) alkyl group and a (C\(_3\)–C\(_6\)) cycloalkyl group, with the proviso that the (C\(_1\)–C\(_6\)) alkylene group and the substituted (C\(_1\)–C\(_6\)) alkylene group may be modified by incorporation, into the carbon chain, of at least one group selected from \(-\text{O}, \text{-SO}_{2}, \text{-SO}_{3}\text{-}, \text{-N(R)_{2}}\); (wherein \(R\) represents a hydrogen atom, a (C\(_1\)–C\(_6\)) alkyl group, a (C\(_3\)–C\(_6\)) cycloalkyl group, a (C\(_1\)–C\(_6\)) alkoxy (C\(_1\)–C\(_6\)) alkyl group or a (C\(_1\)–C\(_6\)) alkoxy (C\(_1\)–C\(_6\)) alkoxycarbonyl group), and with the proviso that when the alkylene group or the substituted alkylene group having one or more substituents is a (C\(_3\)–C\(_6\)) or (C\(_3\)–C\(_8\)) alkylene group, or a (C\(_2\)–C\(_6\)) or (C\(_2\)–C\(_8\)) alkylene group modified by incorporation, into the carbon chain, of at least one group selected from \(-\text{O}, \text{-SO}_{2}, \text{-SO}_{3}\text{-}, \text{-N(R)_{2}}\); \(E\) represents a hydrogen atom; a (C\(_1\)–C\(_6\)) alkyl group; a (C\(_3\)–C\(_6\)) cycloalkyl group; a (C\(_1\)–C\(_6\)) alkoxy (C\(_1\)–C\(_6\)) alkyl group; a (C\(_1\)–C\(_6\)) alkoxy (C\(_1\)–C\(_6\)) alkoxycarbonyl group; and \(B\) represents any of the moieties represented by the following B1 to B8:
wherein each Y may be the same or different, and represents a halogen atom; a cyano group; a nitro group; a hydroxy group; a (C₁-C₆) alkyl group; a halo (C₁-C₆) alkyl group; a (C₂-C₆) alkenyl group; a halo (C₂-C₆) alkenyl group; a (C₂-C₆) alkynyl group; a halo (C₂-C₆) alkynyl group; a (C₁-C₆) alkoxy group; a halo (C₁-C₆) alkoxy group; a (C₂-C₆) haloalkoxy group; a halo (C₂-C₆) haloalkoxy group; a (C₃-C₆) haloalkoxy group; a (C₂-C₆) haloalkynoxy group; a halo (C₂-C₆) haloalkynoxy group; a (C₁-C₆) alkylthio group; a halo (C₁-C₆) alkylthio group; a (C₁-C₆) alkylsulfinyl group; a halo (C₁-C₆) alkylsulfinyl group; a (C₁-C₆) alkylsulfonyl group; a halo (C₁-C₆) alkylsulfonyl group; a (C₁-C₆) alkoxycarbonyl group; a (C₁-C₆) alkoxyimino (C₁-C₃) alkyl group; a (C₃₋₂₀) trialkylsilyl group; a mono (C₁-C₆) alkylsulfonylamino group; a mono halo (C₁-C₆) alkylsulfonylamino group; a phenyl group; a substituted phenyl group having one or more substituents selected from group Z substituents on the ring; a phenoxy group; a substituted phenoxy group having one or more substituents selected from group Z substituents on the ring; a heterocyclic group; a substituted heterocyclic group having one or more substituents selected from group Z substituents on the ring; a heterocycloxy group; a substituted heterocycloxy group having one or more substituents selected from group Z substituents on the ring, the group Z substituents are a halogen atom; a cyano group; a nitro group; a (C₁-C₆) alkyl group; a halo (C₁-C₆) alkyl group; a (C₂-C₆) alkenyl group; a halo (C₂-C₆) alkenyl group; a (C₂-C₆) alkynyl group; a halo (C₂-C₆) alkynyl group; a (C₁-C₆) alkoxy group; a halo (C₁-C₆) alkoxy group; a (C₂-C₆) haloalkoxy group; a halo (C₂-C₆) haloalkoxy group; a (C₁-C₆) alkylthio group; a halo (C₁-C₆) alkylthio group; a (C₁-C₆) alkylsulfinyl group; a halo (C₁-C₆) alkylsulfinyl group; a (C₁-C₆) alkylsulfonyl group; a halo (C₁-C₆) alkylsulfonyl group; a (C₁-C₆) alkoxycarbonyl group; and a (C₁-C₆) alkoxyimino (C₁-C₃) alkyl group, Y¹ represents a (C₁-C₆) alkyl group, n represents an integer of 0 to 5, with the proviso that when n is an integer of 2 to 5, two adjacent Y groups may join together to form a (C₃₋₂₀) alkylene group; a (C₃₋₂₀) alkenylene group; a (C₂₋₂₀) alkyleneoxy group; a (C₁₋₂₀) alkenyleneoxy group; or a halo (C₁₋₂₀) alkenyleneoxy group, and the numbers on each ring represent positions where the ring can be substituted by Y and the free bond extending from each ring is a bond between A and B), or

2. The endoparasite control agent according to claim 1, wherein Het is any moiety selected from the following Het1 to Het17:

![Diagram of compounds](image)
10

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3. The endoparasite control agent according to claim 2, wherein Het is Het1, Het2, Het4, Het14 or Het15.

4. The endoparasite control agent according to any one of claims 1 to 3, wherein A is a (C₁-C₆) alkylene group; or a substituted (C₁-C₆) alkylene group having one or more substituents selected from a halogen atom, a (C₁-C₆) alkyl group and a (C₃-C₆) cycloalkyl group.

5. The endoparasite control agent according to any one of claims 1 to 4, wherein B is B₁, B₂ or B₅.

6. The endoparasite control agent according to claim 2, wherein Het is Het1, Het2, Het4, Het14 or Het15,

35 each X may be the same or different, and is a halogen atom; a (C₁-C₆) alkyl group; or a halo (C₁-C₆) alkyl group, m is 1 or 2,

A is a (C₁-C₆) alkylene group; or a (C₁-C₆) alkylene group substituted by a (C₁-C₆) alkyl group,

E is a hydrogen atom,

B is B₁, B₂ or B₅,

40 each Y may be the same or different, and is a halogen atom; a (C₁-C₆) alkyl group; a halo (C₁-C₆) alkyl group; a phenyl group; a substituted phenyl group having one or more substituents selected from a halogen atom, a (C₁-C₆) alkyl group, a halo (C₁-C₆) alkyl group, a (C₁-C₆) alkoxy group and a halo (C₁-C₆) alkoxy group on the ring; a phenoxy group; a substituted phenoxy group having one or more substituents selected from a halogen atom, a (C₁-C₆) alkyl group, a halo (C₁-C₆) alkyl group, a (C₁-C₆) alkoxy group and a halo (C₁-C₆) alkoxy group on the ring; a pyridyl group; a substituted pyridyl group having one or more substituents selected from a halogen atom, a (C₁-C₆) alkyl group, a halo (C₁-C₆) alkyl group, a (C₁-C₆) alkoxy group and a halo (C₁-C₆) alkoxy group on the ring; a pyridyloxy group; or a substituted pyridyloxy group having one or more or more substituents selected from a halogen atom, a (C₁-C₆) alkyl group, a halo (C₁-C₆) alkyl group, a (C₁-C₆) alkoxy group and a halo (C₁-C₆) alkoxy group on the ring, and

n is an integer of 1 to 3.

7. The endoparasite control agent according to claim 2, wherein Het is Het1, Het2, Het4, Het14 or Het15,

55 each X may be the same or different, and is a halogen atom; a (C₁-C₆) alkyl group; or a halo (C₁-C₆) alkyl group, m is 1 or 2,

A is a (C₁-C₆) alkylene group; or a (C₁-C₆) alkylene group substituted by a (C₁-C₆) alkyl group,

E is a hydrogen atom,

B is B₁,
each Y may be the same or different, and is a halogen atom; a (C<sub>1</sub>-C<sub>6</sub> alkyl group; a halo (C<sub>1</sub>-C<sub>6</sub>) alkyl group; a phenyl group; a substituted phenyl group having one or more substituents selected from a halogen atom, a (C<sub>1</sub>-C<sub>6</sub>) alkyl group, a halo (C<sub>1</sub>-C<sub>6</sub>) alkyl group, a (C<sub>1</sub>-C<sub>6</sub>) alkoxy group and a halo (C<sub>1</sub>-C<sub>6</sub>) alkoxy group on the ring; a phenoxy group; a substituted phenoxy group having one or more substituents selected from a halogen atom, a (C<sub>1</sub>-C<sub>6</sub>) alkyl group, a halo (C<sub>1</sub>-C<sub>6</sub>) alkyl group, a (C<sub>1</sub>-C<sub>6</sub>) alkoxy group and a halo (C<sub>1</sub>-C<sub>6</sub>) alkoxy group on the ring; a pyridyl group; a substituted pyridyl group having one or more substituents selected from a halogen atom, a (C<sub>1</sub>-C<sub>6</sub>) alkyl group, a halo (C<sub>1</sub>-C<sub>6</sub>) alkyl group, a (C<sub>1</sub>-C<sub>6</sub>) alkoxy group and a halo (C<sub>1</sub>-C<sub>6</sub>) alkoxy group on the ring; a pyridyloxy group; or a substituted pyridyloxy group having one or more substituents selected from a halogen atom, a (C<sub>1</sub>-C<sub>6</sub>) alkyl group, a halo (C<sub>1</sub>-C<sub>6</sub>) alkyl group, a (C<sub>1</sub>-C<sub>6</sub>) alkoxy group and a halo (C<sub>1</sub>-C<sub>6</sub>) alkoxy group on the ring, and

n is an integer of 1 to 3.

8. A method for controlling endoparasites, comprising orally or parenterally administering an effective amount of the endoparasite control agent according to any one of claims 1 to 7 to a non-human mammal or a bird.

9. A method for controlling endoparasites, comprising orally or parenterally administering an effective amount of the endoparasite control agent according to any one of claims 1 to 7 to a non-human mammal.

10. The method according to claim 9, wherein the non-human mammal is a domestic animal.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**
A61K31/44(2006.01)i, A61K31/38i(2006.01)i, A61K31/39(2006.01)i,
A61K31/415(2006.01)i, A61K31/426(2006.01)i, A61K31/4965(2006.01)i,
A61K31/505(2006.01)i, A61P33/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**
Minimum documentation searched (classification system followed by classification symbols)
A61K31/505, A61P33/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996
Jitsuyo Shinan Toroku Koho 1996-2013
Kokai Jitsuyo Shinan Koho 1971-2013
Toroku Jitsuyo Shinan Koho 1994-2013

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAplus/REGISTRY/MEDLINE/EMBASE/BIOSIS(STN)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<th>Category*</th>
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<td>Y</td>
<td>WO 01/14340 A1 (Ishihara Sangyo Kaisha, Ltd.), 01 March 2001 (01.03.2001), claims; examples &amp; AU 6597300 A</td>
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**Date of the actual completion of the international search**
13 September, 2013 (13.09.13)

**Date of mailing of the international search report**
01 October, 2013 (01.10.13)

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